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Quantification, reduction and management of kinematic variability in clinical gait analysis

Mickael Cardoso Fonseca

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Quantification, reduction and management of kinematic variability in clinical gait analysis

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Geneva, 15th September 2022

Mickael Cardoso Fonseca

PREAMBLE

Measurement instruments are widely used in many fields but are prone to errors. In the clinical field, measurement instruments serve the purpose of diagnosing and planning treatments. Therefore, measurement errors in clinics affect the quality of diagnosis and possibly the outcome of treatments, the quality of life of patients as well as higher cost of treatments. The biomedical engineering field addresses those problems by developing new improved instruments and measurement methodologies as well as validating and improving reliability. The assessment of motor disorders, such as cerebral palsy, often relies on three-dimensional gait analysis system which provides a complete set of gait data. However, measurement error is also inherent to measured gait data and arises from many sources. Biomedical researcher is constantly supporting clinicians by evaluating and improving diagnosis, prognosis as well as treatment methods and technologies.

The present thesis work is inserted into a multidisciplinary project, designed as SimGait (<https://p3.snf.ch/project-177179>) supported by the Swiss National Science Foundation. This project is divided between three laboratories: The Kinesiology laboratory at the University of Geneva (UNIGE) and Geneva University Hospitals (HUG) led by Prof. Stéphane Armand; the BIOROB laboratory at École Polytechnique Fédérale de Lausanne (EPFL) led by Prof. Auke Ijspeert; and the Data Mining and Machine Learning (DMML) group at the University of Applied Sciences, Western Switzerland led by the Prof. Alexandros Kalousis. This four-year project began in September 2018. It aims to develop pathological gait simulators and be used to support the decision of treatment by predicting the outcome gait patterns of different treatments. While the BIOROB laboratory is sensed to develop a simulative tool based on the musculoskeletal models, the DMML group aims to develop the same simulation tool based on machine learning algorithms. The main roles of the Kinesiology laboratory are 1) to provide a clean database containing mainly gait data from pathological subjects that have been acquired mostly from patients visiting the laboratory for clinical gait analysis; 2) to evaluate the intrinsic and extrinsic variability of this data.

Considering that gait data is subject to variability due to measurement errors, the performance of these simulating tools is prone to be affected. Thus, one of the aims of my doctoral work was to provide information concerning variability arising from measurement error as well as minimizing its effect on the output kinematics and consequently improve the quality of the database provided. The second aim of my doctoral work within the project was to develop metrics to evaluate and compare the performance of both simulators developed.

Throughout the development of this project, I was based in the Kinesiology Laboratory, where a team of researchers focuses their work on different aspects of the musculoskeletal system applied to several disorders and with a close link to the clinical level. The constant interchange of information between me and my colleagues, during laboratory meetings and everyday discussions, as well as short term collaborations was important for my doctoral work and to improve my knowledge in the field. Additionally, the close involvement of Dr. Geraldo De Coulon in the laboratory and regular clinical interpretation session helped me to bridge my background in biomedical engineering and biomechanics to the clinical aspect.

Finally, all the above mentioned was the basis for the present study which allowed me to develop and publish four peer-reviewed articles, one submitted and three currently under preparation for submission. It also provided me with the opportunity to communicate regularly those studies at French and European conferences during the development of my PhD thesis.

ABSTRACT

Gait is the most repeated motor function of humans and a key factor for a healthy and satisfactory quality of life. However, motor disorders, such as cerebral palsy, lead to musculoskeletal impairments resulting often in gait abnormalities as well as limitations in other functional tasks. Patients with motor disorders often require single or multiple medical therapies at the musculoskeletal level for improving their mobility and consequently quality of life. Therefore, treatment decision planning requires a complex set of gait data for identifying motor disorders and possibly their causes. In recent years, three-dimensional gait analysis has been widely used to measure gait data such as kinematics, kinetics, muscular activity or spatio-temporal parameters. Measured gait data is then transmitted to clinicians in a form of a report describing all measured gait data. However, and similarly to every type of measurement system, gait analysis data are prone to measurement errors that can arise from different sources, being marker placement the highest source of measurement variability. Consequently, those errors may impact the interpretation of the results and lead to erroneous treatment decisions impacting, the efficiency of treatments costs.

The doctoral work here presented intends to improve the quality of measured gait data directed to the application in clinical gait analysis and is divided into three main aims.

The first aim is to quantify the variability caused by measurement error. Within this goal, and since marker placement is considered as the main source of variability, the first two studies evaluated the impact of simulated marker displacement in the output kinematics. Results showed that a marker placement precision within 1 cm results in kinematic variability within 5°, with the exception of the hip, knee and ankle rotation where variability was observed over 5° in more than 40% of the combinations of marker displacement simulated. Complementarily, a third study evaluated experimentally the precision of marker placement among different evaluators as well as the associated variability on the kinematic data. On the one hand, results showed no statistically significant correlation between marker variability and kinematic variability, possibly because the effect of marker misplacement in the output kinematic data results from the combination of the overall markers misplaced. On the other hand, significant differences between the evaluator's experience and kinematic variability were observed, showing that experience has a positive effect on gait data reliability. Finally, the fourth study reported an analytical model that was also developed to understand the propagation of error when defining the axes of the joint coordinate system and to separate intrinsic and extrinsic variabilities (i.e. axes of the joint coordinate system versus helical axis of the movement). The results showed that the emblematic cross-talk phenomenon (i.e. erroneous amplitude of knee adduction-abduction during swing phase) can be attributed to both intrinsic and extrinsic variabilities.

The second aim of this thesis focused on reducing the variability caused by measurement error. Within this, one study compared the variability calculated within the test-retest experimental protocol when applying different biomechanical models and two calibration methods. The results showed that by applying additional calibration methods the variability of hip rotation was reduced as well as the crosstalk phenomenon. Additionally, another study proposed a new developed method to accurately estimate gait events based on auto-correlation and auto-selection among concurrent models. The proposed method used the vertical force from the force platform to detect gait events, when gait events are valid on the platform (single foot completely within the limits of the platform during the complete gait cycle), and take those events to create several algorithms based on auto-correlation as well as to automatically select the method that best performs from all methods

implemented. The results demonstrated an excellent accuracy, outperforming all existing methods previously reported.

Finally, the third main aim was to evaluate new possibilities to improve the management of the variability in clinical gait analysis. After reducing and quantifying the variability associated with measurement error, it is important to bridge this information with the clinical interpretation. Thus, the goal was to incorporate expected measurement variability into the gait data reports. Related to this aim, two studies are currently under preparation. Firstly, one study proposed a metric to collect marker placement confidence in a qualitatively way. Quality of this metrics in terms of validity and reliability has been made with the support of two test-retest experimental protocols. Therefore, correlation between marker placement confidence and output kinematic variability have been evaluated. It was hypothesized that the confidence of marker placement is associated with reliability of output kinematics and could potentially use to predict extrinsic variability. Even though the metrics demonstrated good validity and reliability, no correlation was observed between confidence and extrinsic kinematic variability. Finally, the preliminary work on the development of a new gait score considering clinically relevant features of kinematics and expected variability is presented.

During this doctoral work, the high complexity of the link between the sources of measurement error and the kinematic variability were a big challenge. However, the work developed brought up a better quantification and understanding of how measurement error as marker placement or axes definition is translated to the output kinematic data variability. Therefore, this information has the potential to be integrated within clinical interpretation in order to provide higher confidence in the identification and interpretation of gait deviations. Finally, the Conventional Gait Model was the base model for the work developed during the complete thesis due to the fact that it is the most accepted model in the clinical context. However, most of results can be reproduced using different biomechanical models.

Keywords: gait, clinical gait analysis, measurement error, kinematics, variability, conventional gait model

RÉSUMÉ

La marche est la fonction motrice la plus répétée chez l'homme et est une fonction primordiale pour avoir une bonne qualité de vie. Cependant, les troubles moteurs, tels que ceux associés à la paralysie cérébrale, entraînent souvent des troubles de la marche ainsi que des limitations d'autres tâches fonctionnelles. Les patients atteints de troubles moteurs ont souvent besoin d'un ou de plusieurs traitements médicaux pour améliorer leur mobilité et par conséquent leur qualité de vie. Par conséquent, la planification des décisions thérapeutiques nécessite un ensemble complexe de données sur la marche pour identifier les troubles moteurs et éventuellement leurs causes. Ces dernières décennies, l'analyse quantifiée de la marche (AQM) a été largement utilisée pour mesurer la marche, avec des données cinématique, cinétique, d'activité musculaire ou des paramètres spatio-temporels. L'ensemble de ces données de marche sont ensuite transmises aux cliniciens sous la forme d'un rapport qui permettra d'identifier et comprendre les troubles de la marche de leurs patients. Cependant, et comme pour tout type de système de mesure, les données de l'AQM sont sujettes à des erreurs de mesure qui peuvent provenir de plusieurs sources. Le placement des marqueurs est la source la plus importante de variabilité de cette mesure. Par conséquent, ces erreurs peuvent avoir un impact sur l'interprétation des résultats et conduire à des décisions de traitement erronées. En conséquence, l'efficacité des traitements peut être réduite et le coût thérapeutique augmenté.

Le travail de doctorat présenté ici vise à améliorer la qualité des données de marche mesurées en vue de leur application dans l'AQM. Il est divisé en trois objectifs principaux.

Le premier objectif était de quantifier la variabilité causée par l'erreur de mesure. Dans le cadre de cet objectif, et compte tenu du fait que le placement des marqueurs est considéré comme la principale source de variabilité, les deux premières études ont évalué l'impact du déplacement simulé des marqueurs sur le calcul de la cinématique. Les résultats ont montré que l'impact d'un mauvais placement varie selon les différents marqueurs du membre inférieur et selon les différentes directions de déplacement de chaque marqueur. Une troisième étude a évalué expérimentalement la précision du placement des marqueurs chez des évaluateurs avec différents niveaux d'expérience ainsi que son impact sur les données cinématiques. D'une part, les résultats n'ont montré aucune corrélation statistiquement significative entre la variabilité des marqueurs et la variabilité cinématique, peut-être parce que l'effet du mauvais placement des marqueurs dans les données cinématiques résulte de la combinaison de l'ensemble des marqueurs mal placés. D'autre part, des différences significatives ont été observées entre l'expérience de l'évaluateur et la variabilité cinématique, ce qui montre que l'expérience a un effet positif sur la fiabilité des données de la marche. Enfin, la quatrième étude présente un modèle analytique qui a été développé pour comprendre la propagation de l'erreur lors de la définition des axes du système de coordonnées articulaires et pour séparer les variabilités intrinsèques et extrinsèques (c'est-à-dire les axes du système de coordonnées articulaires par rapport à l'axe hélicoïdal du mouvement). Les résultats montrent que le phénomène emblématique de diaphonie (i.e. amplitude erronée de l'adduction-abduction du genou pendant la phase d'oscillation) peut être attribué à la fois aux variabilités intrinsèques et extrinsèques.

Le deuxième objectif de cette thèse était de réduire la variabilité causée par l'erreur de mesure. Dans ce cadre, une étude a comparé la variabilité calculée dans le protocole expérimental test-retest en appliquant différents modèles biomécaniques et deux méthodes de calibration. Les résultats ont montré qu'en appliquant des méthodes de calibration qui se basent uniquement sur les essais de marche, la variabilité de la rotation de la hanche pouvait être réduite. Une autre étude s'est intéressée à améliorer la détection des événements de la marche. Une approche basée sur

l'autocorrélation et l'auto-sélection parmi des méthodes concurrentes a été développée. L'approche proposée utilise la force verticale de la plate-forme de force pour détecter les événements de la marche, lorsque les événements de la marche sont valides sur la plate-forme (uniquement un pied complètement dans les limites de la plate-forme pendant le cycle de marche complet). Ces événements sont utilisés comme données de référence dans plusieurs algorithmes basés sur l'autocorrélation ainsi que pour sélectionner automatiquement la méthode la plus performante. Les résultats ont démontré une excellente précision, surpassant toutes les approches existantes précédemment rapportées.

Enfin, le troisième objectif était d'évaluer de nouvelles possibilités pour améliorer la gestion de la variabilité dans l'AQM. Après avoir réduit et quantifié la variabilité associée à l'erreur de mesure, il est important de faire le lien entre cette information et l'interprétation clinique. Ainsi, l'objectif était d'incorporer la variabilité de mesure attendue dans les rapports de données de marche. Associées à cet objectif, deux études sont actuellement en cours de préparation. Tout d'abord, une étude a proposé un questionnaire pour collecter la confiance dans le pl en termes de validité et de fiabilité a été établie à l'aide de deux protocoles expérimentaux de test-retest. La corrélation entre la confiance dans le placement du marqueur et la variabilité cinématique de la sortie a été évaluée. Nous avons émis l'hypothèse que la confiance dans le placement des marqueurs est associée à la fiabilité de la cinématique de sortie et pourrait potentiellement être utilisée pour prédire la variabilité extrinsèque. Bien que les mesures aient démontré une bonne validité et fiabilité, aucune corrélation n'a été observée entre la confiance et la variabilité cinématique extrinsèque. Enfin, un travail préliminaire sur le développement d'un nouveau score de marche prenant en compte les caractéristiques cliniquement pertinentes de la cinématique et la variabilité attendue est présenté.

Ce travail de doctorat a permis de mieux quantifier et comprendre les erreurs de mesure, notamment l'influence du placement des marqueurs ou la définition des axes sur la variabilité des données cinématiques de la marche. Par conséquent, ces connaissances pourront être intégrées dans l'interprétation clinique de l'AQM afin de mieux identifier des troubles de la marche. Enfin, le modèle de marche conventionnelle a été le modèle de base pour les travaux développés au cours de la thèse complète car c'est le modèle le plus accepté dans le contexte clinique. Cependant, la plupart des résultats peuvent être reproduits à l'aide de différents modèles biomécaniques.

Mots clés : marche, analyse clinique de la marche, erreur de mesure, cinématique, variabilité, modèle conventionnel de la marche

GLOSSARY

BMI – Body mass index

CGM – Conventional Gait Model (biomechanical model)

PiG – Plut-in-Gait (biomechanical model)

CP – Cerebral palsy

TDC – Typically developing children

3DGA – three dimensional gait analysis

3D – Three dimensional

CGA – Clinical gait analysis

OSS – Optoeletronic system

DoF – Degrees of freedom

GMFCS – Gross Motor Function Classification System

EMG –Electromyographic sensors

CAST – ‘*calibrated anatomical systems technique*’ (biomechanical model)

HBM - Human Body Model (biomechanical model)

IOR – ‘*Instituti Ortopedici Rizzoli*’ (biomechanical model)

SEM – Standard error of a measurement

MDC – Minimal detectable change

SD – Standard deviation

RMSD – Root mean square deviation

ICC – Intraclass correlation

CMC – Coefficient of multiple correlation

CV – Coefficient of variance

CMP – Confidence in marker placement

GPS – Gait Profile Score

GVS – Gait Variable Score

GDI – Gait Deviation Index

IQR – Interquartile range

GRF – Ground Reaction Force

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Chapter 1 - INTRODUCTION AND OUTLINE OF THE THESIS

1.1. Human locomotion

1.1.1. Basics of Locomotion

Locomotion plays an elementary role in animal life. The ability to move is essential for species to survive through the conditions of their environment. Thus, the anatomy of species is adapted for the conditions required to adjust to their environment. The first documented theoretical consideration about the movement of species was primarily reported by Aristotle (384 – 322 BC) in his 'Theories on the movement of humans and animals' (Baker 2007). He stated that in nature the different species are constituted by a different physiognomy, adapted to the different environments and tasks associated with the life of each one of these. All forms of locomotion adopted naturally by animals and humans, including swimming, running, hopping, flying, climbing, soaring, gliding or walking allow them to move through their environment. The capacity of locomotion is essential for the basic activities of a species such as, moving toward food, escaping from predators, migrating or finding a partner to mate. Walking is, for humans, the most repeated movement performed on a daily basis. Most of the activities performed by humans require walking and different health benefits are associated with walking activity (I-Min and David 2008).

1.1.2. Importance of normal gait

Despite the new recently developed technologies to assist displacement, walking is still the most natural and practical way of moving for short distances. Although often taken for granted, such ability is considered essential for maintaining a good quality of life as it guarantees a functional independence and therefore, integration of an individual in society (Hausdorff and Alexander 2005). Thus, it is important that an individual is able to walk or run in an efficient way, with respect to energy consumption. Moreover, it is also essential that an individual can stand and move on a stable, comfortable, painless and aesthetical way.

1.1.3. Physiology of locomotion

Equally to all types of movements, referred above, adopted by animals, walking is considered as a complex motor behavior characterized as a sequential activity actuated by the limbs and body muscles in a precise repetitive rhythm and pattern (Kiehn and Dougherty 2013). Gait itself involves a complex synergic operation concerning various organ systems. Several mammals are able to walk within the first minutes of their life. However, that is not the case for human beings. A typically developing child (TDC) starts walking, on average, at about fifteen months and keeps being developed until reaches a fully matured gait pattern around seven years of age (Sutherland 1980, Samson *et al.* 2013). At elderly ages, due to deterioration of neurological and musculoskeletal systems, the gait capacity is also decreased.

The locomotor system can be divided into different sub-systems such as skeletal, joint articulations, muscular, neurologic, vestibular, visual and proprioceptive systems (Bonney-Mazure and Armand 2015). The skeletal system in humans is constituted by 206 bones and their main role in

the human body is to provide shape and support for the body. Therefore, they are also important in locomotion as essentially the skeleton of the trunk and lower limbs play an active role for stability and weight support. The role of the joint articulations in locomotion is to connect the different segments of the pelvis and lower limb segments, constrain and allow a smooth motion between connected segments. In addition, the motion of the articular joints is limited by passive structures as the articular surfaces and ligaments. While the hip behaves as a spherical joint, permitting three rotational degrees-of-freedom (DoF), knee and ankle joints behaves more like a hinge, allowing mainly motion in one DoF (flexion-extension) even though the knee allows a small internal-external rotation (Koopman 2010). Finally, the ankle joint (considering both talocrural and subtalar joints) resembles a universal joint, having two intersecting rotational axes. One of the basic assumptions in rigid body dynamics is that movement only occurs in the joints.

Skeletal muscles are also a key mechanism for locomotion. The body is composed by approximately 650 skeletal muscles that are responsible for allowing a wide range of movements and functions. When contracting, agonist skeletal muscles produce a force that creates a controlled motion between connected segments allowing an individual to move (Saunders *et al.* 1953, Koopman 2010). The sensory system (e.g. visual, auditory, vestibular, somatosensory) is responsible for capturing stimuli from the surrounding environment such as visual or auditory information or forces and movements sensed by muscles and skin. This information is sent to the central nervous system through excitatory and inhibitory neural junctions and processed either by the cerebral areas or by an interneuron (arc reflex). The treated information triggers a response that is transmitted through the spinal cord to the actuator muscles. Circuits in the spinal cord, called the central pattern generators are also responsible for orchestrating a precise phasing and timing through the repeated patterns of locomotion. They receive an input from the brain from which they are able to set this rhythmic activity that is posteriorly transferred to the motor neurons and then to the muscles for controlled contraction (Kiehn and Dougherty 2013). The Figure 1 illustrates how the different systems aforementioned are connected and interact with the mechanism of locomotion.

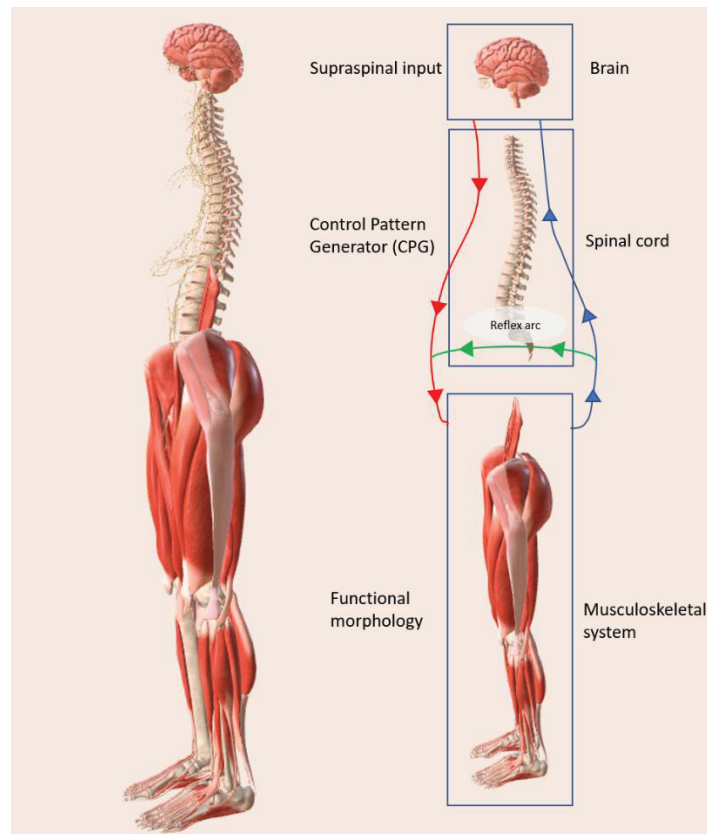


Figure 1 - Illustration of the connection from the brain to the muscles. Information is conducted from the brain to the actuator muscles on a descendent pathway (red line) through the spinal cord. On contrary, sensory information is sent through the CNS (blue line) to the brain for a posterior response or to a sensory mechanism known as reflex arc (green line) which consist in a simple arrangement between the receptor, an interneuron (responsible for adjusting the input) and finally the motor neuron that transmit the response to the muscles (actuator). (source: www.biodigital.com)

The slow development of the central nervous system allied with the unique difficulties of a bipedal balance control is believed to be the cause of the late maturation of gait in humans (Sutherland 1980, Ivanenko *et al.* 2007). Due to the high number of systems involved in gait, a precise understanding of the causes of an altered gait can be challenging (Armand *et al.* 2016). A single alteration due to injuries or other pathologies at any of the above-described sub-systems may result in gait deficits (Kuo and Donelan 2010).

1.1.4. Mechanics of gait

Gait characteristics are influenced by the morphology and function of the neuromuscular and musculoskeletal systems. Human gait is naturally adapted, as any other system of the human body, to strategies of minimizing the cost of energy consumption and efficiently in terms of stability (Zhao *et al.* 2021). Thus, the typically adopted gait strategy consists of forward bipedal locomotion, known as walking. “The adoption of the concept that fundamentally locomotion is the translation of the center of gravity through space along a pathway requiring the least expenditure of energy possible” (Saunders *et al.* 1953). Taking this idea into account, gait can be described by an inverted pendulum model. This model has the advantage that it conserves mechanical energy, and it reduces the energy consumption to produce motion of the leg through a sagittal arc in the stance phase. In physics, the energy of a body is considered as the sum of potential and kinetic energies (Uchida and Delp 2020). Thus, in a

pendulum model, the loss of potential energy is compensated by the gain in kinetic energy through motion and vice-versa. Contrarily, during running, the phase of double support is replaced by a phase of flight (no support), the pendulum model is thought to be less dominant and higher energy is required to produce motion (Kuo and Donelan 2010). Thus, instead of an exchange between forward kinetic and potential energy, the lower limbs work similarly to a spring storing and releasing potential energy within muscles and tendons as they stretch and recoil (Uchida and Delp 2020).

Therefore, as walking is characterized by a cyclic pattern, it is naturally decomposed in different phases of a cycle, defined as the motion between two consecutive repeated events during gait (Figure 2 -). For convenience, a gait cycle is typically cropped between the moment a foot hits the ground and the next moment the same foot repeats such action. The gait cycle is divided primarily into two main phases: stance phase, relative to the part of the gait cycle where one considered foot (left or right) strikes on the ground, typically known as foot strike (FS) (about 60% of the cycle); and swing phase, that occurs when the contact between the same foot and the ground is ended until the next FS, typically known as foot off (FO) (about 40% of the cycle). Within each of those phases, several sub-phases are also defined for a complete understanding of the gait. The gait cycle has been commonly divided into five stance and three swing phase periods (Harris *et al.* 1994). Additionally, we can also divide gait between periods of loading and unloading of the limbs, where single support refers to the period in which one limb is in contact with the ground and double support the period both limbs are in contact with the ground and supporting the body (Kirtley 2006).

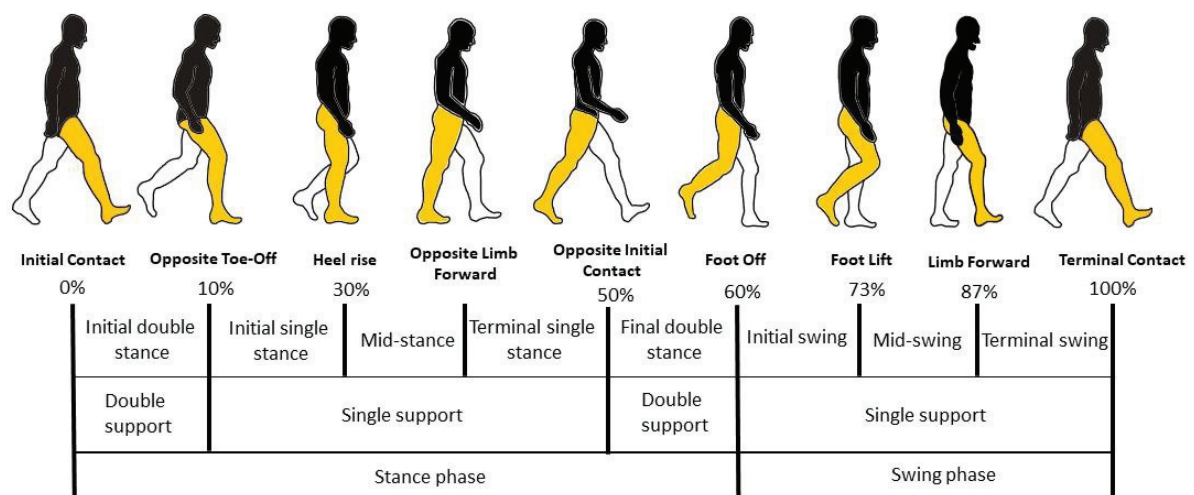


Figure 2 - Phases and events of the walking gait cycle.

1.2. Movement disorders

Movement disorders are chronic conditions that affect the optimal functional motor system of an individual (Arif *et al.* 2011). Those disorders can occur at neurological, muscular, joint articulation or bone levels and appear during the fetal development or at any moment of life. Those can be then classified based on their cause as neurological disorders (e.g. cerebral palsy, stroke, Parkinson), joint diseases (e.g. osteoarthritis), muscle disease (e.g. muscular dystrophia, sarcopenia), and lesions of the musculoskeletal system (e.g. trauma caused by accident). In this section, one type of neurological disorder, more specifically cerebral palsy (CP), will be addressed in more detail as it was the motor disorder mostly evaluated within this doctoral work.

1.2.1. Neurological disorders

Neurological disorders are attributed to lesions of the brain which consequently affect the peripheral or central nervous system, which comprises both motor neurons and sensory nerves, responsible for connecting the spinal cord and the brain to the musculoskeletal system (Stone and Carson 2015). The most common neurological disorders associated with musculoskeletal impairments are CP, Parkinson's disease, stroke and multiple sclerosis. Contrarily to the other above-mentioned neurological disorders, CP is caused by a brain lesion during its development, affecting subsequently the neurological and musculoskeletal development of the child. CP is among all, the most common cause of gait impairments in children, with an actual prevalence estimated approximately 1.77 cases per thousand of life births in Europe (Sellier *et al.* 2016).

1.2.1.1. Cerebral palsy

1.2.1.1.1. Definition, description and prevalence

CP is a neurological irreversible condition that is linked to a brain injury during its development. Approximately 92% of cases relate to brain injuries traced to the perinatal period and the most common risk factors are preterm birth, perinatal infection, intrauterine growth restriction, use of preterm antibiotics, acidosis or asphyxia, and multiple gestations. Fewer than 10% of the cases are related to the intrapartum hypoxia. Despite the identification of several risk factors, approximately 80% of the cases have no clear cause and are considered idiopathic (Vitrikas *et al.* 2020). CP leads to a loss of motor control and abnormal musculoskeletal development (Armand *et al.* 2016; Bax *et al.* 2017; Durkin *et al.* 2016). Encephalic lesions encountered in patients with CP can be located in different regions of the brain and some of the observed sources of those non-progressive injuries are related to hypoxia, stroke, hypertension, infection, or asphyxia at pre- and post-neonatal levels (Wimalasundera and Stevenson 2016). Babies with low birth weight are more likely to have CP, increasing the probability to up to 4.2% (Sellier *et al.* 2016). However, the improvement of obstetric care over the years failed to eliminate it entirely and, so to speak, it shows that there some background factors as well. Additionally, CP is often accompanied by several disturbances at the level of sensation, perception, cognition, communication, behavior, increased probability of epilepsy and secondary musculoskeletal problems (Bax *et al.* 2017). Patients with CP can present a wide variety of impairments such as muscle spasticity, muscle weakness, muscle contracture, dystonia, abnormal bone growth, lack of muscle control selectivity and lack of balance (Durkin *et al.* 2016). About 40% of the patients with CP are not able to walk independently or without the aid of external devices (Morgan and Mcginley 2018).

1.2.1.1.2. Associated motor disorders

CP is characterized by a wide range of motor disorders altering, typically, muscular activity and motor function, which impacts directly the development of the musculoskeletal system. The type of motor disorders varies with the location and type of brain lesion. Therefore, CP can be classified as spastic, dyskinetic, ataxic or mixed types (Graham *et al.* 2016). Spastic CP is caused by lesion of the motor cortex and accounts for 90% of the cases while dyskinetic and ataxic types are caused by damage of the basal ganglia and cerebellum, respectively.

Lesions of the neurological system can directly affect the muscular level in different ways. Muscle alterations observed in patients with CP are mostly joint stiffness, abnormal length, and tone. The most abnormal muscle tone observed within CP populations is spasticity and it's caused by the lack of inhibition of the spinal reflexes, typically induced by damage in the motor cortex or corticospinal tract (Gracies *et al.* 2010, Graham *et al.* 2016, Vitrikas *et al.* 2020). Moreover, at the skeletal level, as a consequence of muscle overactivity, can induce bone deformation such as torsion, angulation, or abnormal bone length (Armand *et al.* 2016; Gracies *et al.* 2010). The gait of patients with CP is commonly characterized by an imbalance between both sides of the lower limb, decreased range of motion of some joints (which induce an increase of other joint's motion as a consequence of compensatory movements), and muscle weakness (Graham *et al.* 2016). Even though patients with CP are reported to have a normal life expectancy, the related motor impairments are normally associated with pain during gait, higher levels of energy consumption, limited actions, and aesthetical gait. Those consequences may be, as in any other movement disorder, a limitation on the social and professional integration of patients. A study evaluating the social integration of adults with CP in Denmark reported a decrease in independence at a young adult age, with 68% of patients with CP (aged 29-35 years) living independently compared to the 92% observed in the comparison group (same age interval). Additionally, only 15% of the same inquired group were living as couples and with children compared to 52% of the comparison group (Michelsen 2006). Physical activity, known to be a positive stimulus for good health is also inhibited or reduced for patients with CP (Michelsen 2006, World Health Organization 2020).

Topographically, patients with CP can be sub-classified by the affected limb as unilateral and bilateral (Morgan and Mcginley 2018). Unilateral CP refers to patients affected on one lower limb, and it is considered monoplegia if only the lower limb is affected and hemiplegia if both lower and upper limbs are affected. In contrast, bilateral CP refers to patients affected on the two lower limbs and being described as diplegia if only the lower limbs are affected or triplegia and quadriplegia if one or two upper limbs (Graham *et al.* 2016).

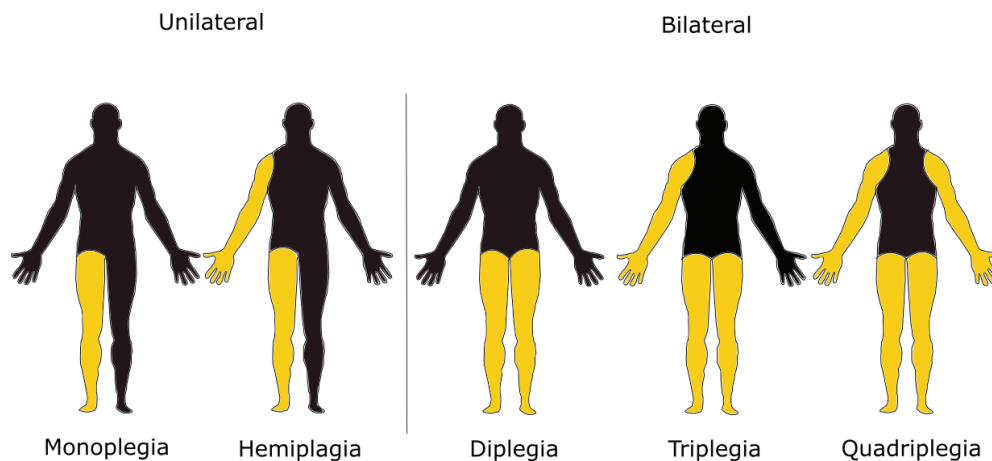


Figure 3 - Topography classification of CP.

A patient with CP can be classified according to the level of motor impairment by a 5-level classification system (Gross Motor Function Classification System) that is based on the physical abilities and limitations (Palisano *et al.* 1997). The GMFCS was developed as a method for standardizing the classification of CP according to the concepts of disability and functional limitations. It classifies children with CP into five levels as follows Figure 4:

GMFCS level 1: Children can walk indoors and outdoors and can climb stairs without using the hands for support. Can perform normal daily life activities (e.g. run, jump). Has decreased speed, balance and coordination.

GMFCS level 2: Children can walk indoors and outdoors and can climb stairs using the hands as support on the railing. Has difficulty with uneven surfaces, inclines or in crowds. Has minimal ability to run or jump.

GMFCS level 3: Children can walk only if using an assistive mobility device indoors and outdoors on level surfaces. May be able to climb stairs using a railing. May propel a manual wheelchair for short distances on an even surface.

GMFCS level 4: Children present severe limitation in walking even with assistive devices. Uses wheelchairs most of the time and may propel their own power wheelchair. May participate in standing transfers.

GMFCS level 5: Children can be transported on a wheelchair with head and trunk support propelled by a tertiary person.

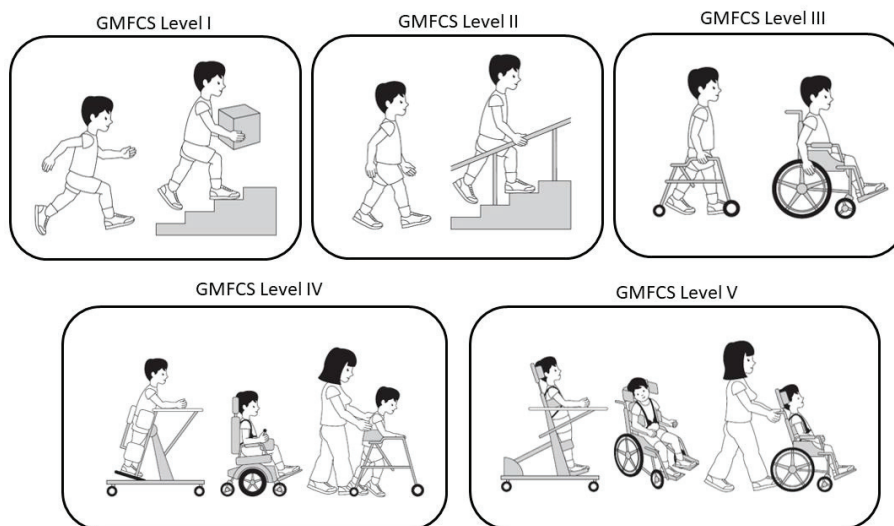


Figure 4 - GMFCS levels for children (adapted from (Rutz et al. 2018))

The GMFCS is a useful classification to classify patients with CP in terms of motor function. However, the associated motor disorders are complex and can affect different levels of the musculoskeletal system, not only for patient with CP but for every type of motor disorders. Clinicians require a more complete set of information relative to the gait of patients in order to assess correctly the causes of motor impairments (at a musculoskeletal level) and plan the adequate treatments. The following section describes the state-of-the art gait analysis.

1.3. Gait analysis

Although the primary goal of locomotion may be simply stated as the translation of the body from one point to another by means of a bipedal gait, its analysis requires the collection of an enormous amount of data in order to follow the entire cycle of events. It is evident that a complete description of locomotion involves consideration of both the kinematics and kinetics of the extremities in all their manifold details; but such knowledge, even if complete, would be of little value to the

orthopaedic surgeon unless it was integrated to evolve as a concept of locomotion from which deductions can be drawn and applied to the analysis of the clinical problems which are part of his/her daily issues. (Saunders *et al.* 1953).

Due to the known complexity of the gait mechanism in humans, it is important to fully understand the interrelationships existing between the various segments of the locomotor system in order to analyze disorders of locomotion with greater precision (Saunders *et al.* 1953).

1.4. History of gait analysis

Similarly, to any scientific field, knowledge is always dependent on the technology available at a determined time as well as the cultural environment. Technology brought the capacity to perform experimental analysis to support theories. In the history of science, many were the conclusions drawn based on theoretic observations that were later discredited with the help of experimental trials. The evolution of gait analysis was not different. Furthermore, the evolution of gait analysis, as it will be demonstrated during this section, was possible due to the involvement of different areas of expertise, from physical to life sciences (Blanc and Dimanico 2014).

The analysis of human gait is ancient and its development has gradually accompanied scientific, mathematics and technological developments over the years. The locomotion of humans and animals has been firstly depicted in early cave art, a few thousand years BCE and followed by the first basic theoretical observations reported by Aristotle (384-322 BCE).

Until the development of new technologies, several theoretical considerations were added on this topic until the 19th century (Baker 2007). Some of those theories were later key concepts/tools for gait analysis. In the 16th and 17th centuries, Cardan and Euler, respectively, reported theories to describe the movement of an object in space. They introduced a set of equations to describe the orientation in space, divided into a set of three different angles. Nowadays, the three-dimensional angles, globally used in biomechanics, are still known as Euler or Cardan angles (Chao 1980, Grood and Suntay 1983, Ramakrishnan and Kadaba 1991). Also, in the 17th century, Rene Descartes, by watching a fly on the ceiling over his room, described the coordinate system, so called, cartesian system that allows the positioning of a point with respect to a reference point by a set of three coordinates (Ariew *et al.* 2015). Those two theories are today used to describe motion of a body with respect to a reference frame. In early 1830s, the Weber brothers reported for the first-time measurements of spatial-temporal parameters of gait (Baker 2007). Descartes, was also the first to describe the motion in humans as controlled by muscular activity under the influence of nerves connected to the brain, which is now a basic concept in human movement analysis and essential to understand the cause and consequential effects of several motor disorders (Ariew *et al.* 2015). The famous Leonardo Da Vinci also contributed to the anatomical understanding of the musculoskeletal system as well as some mechanical concepts during different movements describing lines of action and center of gravity trajectories (Borelli 1680).

Fortunately, in 1878, Edward Muybridge invented a system for photographing a galloping horse (Muybridge 1985). He set up 24 large cameras alongside a racetrack, obtaining a series of photographs, breaking down each movement of the horses. This contribution led Marey to develop photographic systems that could represent, by a means of several superposed photos per second, the motion of humans and animals. Those inventions were primarily used in sports research for the study and identification of the most optimal movements that lead to the best performance like high jumps in the Olympic games. However, the movements described by Marey were purely on the sagittal plane, in

other words, on the two-dimensional plane. At the end of the 19th century, Otto Fischer and Wilhelm Braune were responsible for the first human three-dimensional gait analysis, using Geissler tubes strapped to each segment and interfering them with an electrical circuit. The set-up was very complicated and time consuming. The processing of recorded data took them several months (Rosenbaum and Brandes 2008). They were the first to track the three-dimensional coordinates of anatomical points during walking and posteriorly reconstruction of body segments by estimation of joint centers (Baker 2007). Additionally, they were also able to track the joint moments of the lower limbs during swing phase of gait by inverse dynamic methods.

Marey and Gaston Carlet were one of the pioneers in kinetic analysis by developing a shoe containing a set of three transducers and recorded (Uchida and Delp 2020) for the first time, the forces applied from the foot to the floor during movement in the vertical direction. The breakthroughs reported in the 20th are related to the technological development as well as the high number of injured soldiers from the wars. In early 1900s, the first force platform, to measure not only the vertical component of the ground reaction force but all three components, was developed (Baker 2007). Nowadays, the same principles are used in the construction of more sophisticated force platforms that are built essentially with more pressure sensors.

One important feature of gait analysis is the tracking of muscular activity. Linked with the discovery of electricity, the first observations regarding the animal production of electricity were noted. Luigi Galvani observed, by accident, that electricity was stimulating contraction in frog muscles. After that, many studies have been performed on the understanding of the relationship between electrical activity and muscular contraction (Kazamel and Warren 2017). The development of devices with the ability to track the electrical activity of a muscle, known as electromyography (EMG), soon highlighted its importance in the understanding of the gait complex system and posteriorly its importance to compare patterns under pathological gait to diverse diagnoses of motor disorders. In 1927, Scherb and his team reported muscle activity through gait on a treadmill measured by identifying the time of contraction with palpation (Baker 2007). In 1945, at Berkley, study concerning the use of EMG for tracking gait of a human was first reported (Blanc and Dimanico 2014). The principles of EMG remained similar to our days, however, the technology used has been developed and nowadays the system is wireless, and activity is registered digitally, contrary to the huge number of wires and paper sheets required in the past.

Saunders et al. highlighted six determinants of the gait with higher importance for analyzing gait cycle such as: pelvic rotation; pelvic tilt; knee flexion in stance phase; foot mechanics; knee mechanics; and lateral displacement of the pelvis (Saunders *et al.* 1953). However, at such time the analysis was still merely qualitative and in late 1980s, researchers started to measure and quantify kinematic features and soon his claims were discredited (Kuo and Donelan 2010).

In 1972, the Vanguard Motion analyzer was introduced. It was composed by a set of cameras that operate at 50 frames/second. It was the first time that instrumented gait analysis could be made without an apparatus attached to the subject and allowed the tracking of multiple information simultaneously. For instance, EMG data could be superposed to motion data. Not long after, in 1976, the first camera-based 3-D motion analysis system was developed and reported as SELSPOT (Woltring and Marsolais 1980). It consisted of an observation of a sequence of pulsed LEDs placed over anatomical landmarks of a subject and used a set of 1-16 cameras calibrated with a force platform. One of the disadvantages of this system was the wired characteristic of the mounted LEDs that required a power source to be carried by the subject. This limitation stimulated further development and the VICON motion analysis system (Oxford Metrics Limited) replaced the LEDs by passive reflective markers that are illuminated stroboscopically. Infra-red light was reflected by those markers and tracked by cameras. This system was promising, however, some technical limitations regarding the

camera resolution to track passive markers and the need for constant calibration, were pointed out. During the past years, many motion tracking systems using passive reflective markers were developed such as: MacReflex (Sweden), Kinemetrix (Medical Research Ltd., Wortley Moor Road, Leeds, United Kingdom), Expert Vision and Orthotrak (Motion analysis corporation, Santa Rosa, CA), Peak Performance (Peak Performance Technologies Inc., Englewood, CO), Primas (Netherlands), Qualisys Inc (USA), Qualisys AB (Sweden), Elite (Bioengineering Technology and systems, Milan, Italy) and Ariel Dynamics (Life Systems Inc. La Jolla, CA) (Al-Zahrani and Bakheit 2008). In addition, alternative technologies have been recently proposed as marker-less tracking (Colyer *et al.* 2018) and using inertial sensors (Muro-de-la-Herran *et al.* 2014). While markerless techniques calculate the joint angles from videos based on deep learning algorithms, inertial sensors-based technology calculates joint angles based on sensors attached to the segments (Lanovaz *et al.* 2017, Park and Yoon 2021). Both techniques have not yet been proven with higher reliability than the stereophotogrammetric systems above mentioned.

The application of gait analysis in a clinical context arose in the 1960s by Perry and Sutherland. Willy Taillard founded the first gait laboratory in Basel, Switzerland. Due to its easier implementation, electromyography was initially used over three-dimensional analysis but soon was concluded that alone was not enough for a complete evaluation of motor disorders. One of the first reported laboratories using a stereo photogrammetric system for evaluating gait of patients with motor disorders was the Gait Analysis Laboratory at Newington Children's Hospital using a set of three cameras (Davis *et al.* 1991). Since then, the methodology has not been much altered with respect to the biomechanical models used. Since then, despite some improvements added to the biomechanical model used at that time, in relation to the location and number of markers used, the basis of this model remains the same. Whilst the basic principles of the stereo-photogrammetric system also remain the same nowadays, the development of more sophisticated technologies allowed the improvement of the speed, accuracy and reliability of the system. For instance, features such as calibration time, precision of the cameras, frequency of acquisition and automation of the system as labelling of the markers are examples of considerable upgrades observed in gait analysis. Until this day, gait analysis is the topic of many research projects. A search in PubMed for the scientific articles reported in 2022 that include "*gait analysis*" in the title shows more than six thousand publications (Figure 5).

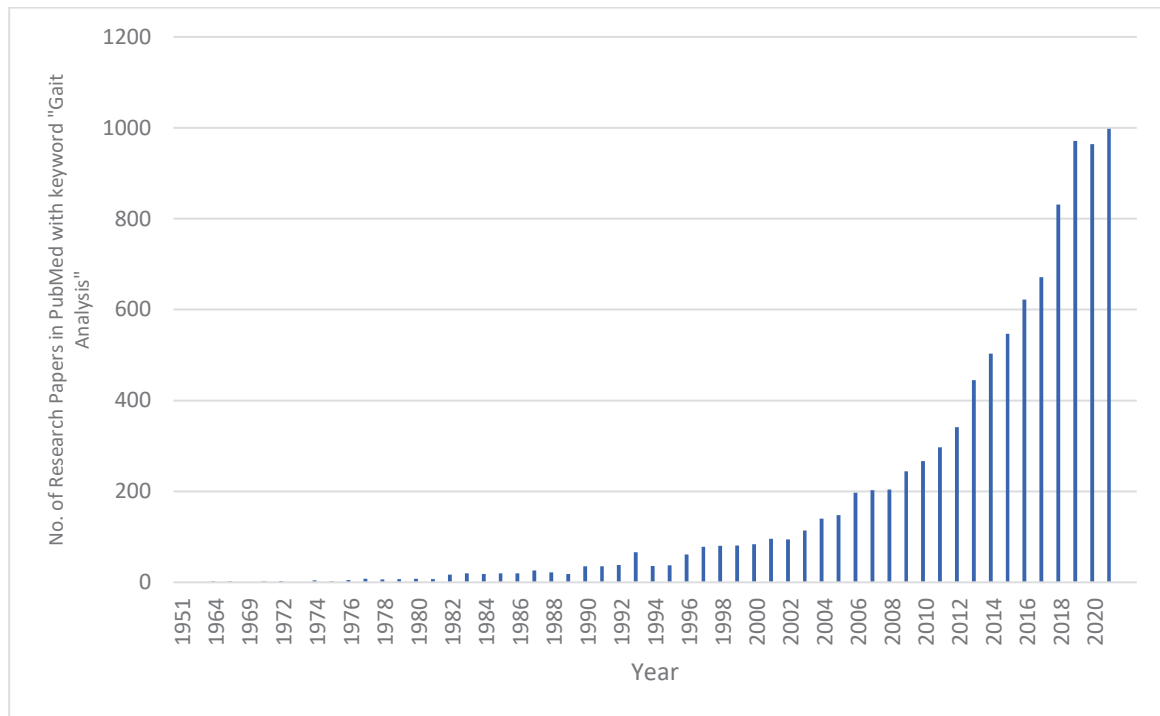


Figure 5 - Distribution of research effort regarding gait analysis from 1951 to 2021.

1.5. Instrumented gait analysis

Gait analysis corresponds to a series of systematic measurements of a group of dynamic parameters that combined serve to characterize human locomotion. Its importance has been reportedly increasing in different fields apart from evaluation of pathological gait as for example clinical research or analysis of sport performance. Instrumented gait analysis can be divided into different applications such as: clinical gait analysis (CGA), gait research and sports research. There is some overlap between those fields as, for instance, data acquired from clinical routine may end up serving as a basis for research studies.

1.5.1. Clinical gait analysis

The aim of CGA is to evaluate the motor capacity of a subject and serve as support for clinicians to decide the best treatment for correcting movement disorders and improving gait at all levels. This is generally accepted as the gold standard measure in clinical practice, for decision-making prior to intervention planning.

1.5.1.1. Methodology for gait analysis – state of the art

Before the development of bioengineering tools, the analysis of gait by clinicians was merely observational. Hence, only features that clearly differ visually from normal gait were qualitatively highlighted and much relevant information was not accessed. Thus, the clinical assessment was incomplete and optimal decision-making for treatments was compromised. The combination of new

technology such as pressure or force sensors, electromyography sensors, infra-red cameras, computers, and other devices, allied with all theoretical knowledge acquired in the past relative to different fields of science such as physics, mechanics, and anatomy (Baker 2007) allowed the development of a complete system to track gait pattern. The following section describes each of the elements used in a gait laboratory as well as its importance in gait analysis.

1.5.1.2. Typical gait laboratory – materials and set-up

The minimum set of measurement systems required for a CGA examination is: an optoelectronic stereophotogrammetric system (OSS), force platforms, and EMG sensors (Benedetti *et al.* 2017). Therefore, a typical modern gait analysis laboratory is constituted by a series of essential features (Figure 6):

- **OSS system**, also typically known as optoelectronic system, is equipped with a set of infrared cameras. Several commercial systems are nowadays available for CGA. Infrared cameras are used to track the three-dimensional coordinates of the markers over time. Usually, a gait analysis system has mounted a number with a minimum of 6 cameras. In gait analysis, tracking a marker in space requires that a marker is visible, at each frame, by at least two cameras, with known position and orientation. Typically, optoelectronic systems acquire marker coordinates at 100Hz.
- **Reflective markers.** The passive reflective markers are shaped as spheres and typically have diameters of 9-25 mm.
- **Video cameras.** Commonly, a few cameras are fixed strategically to record the motion of a subject in the three different planes during the gait trials (coronal, sagittal and transversal). Those are used for qualitative analysis
- **Walkway.** A gait laboratory requires a clean path where the subjects perform the gait trials. It is important that the environment created helps the patient to walk as normally as possible. Typically, the acquisition walkway, in gait laboratories, measures approximately 10 meters.
- **Force platforms** are dynamometric instruments centered in the middle of the walkway. They are capable of measuring forces and moments in three dimensions in synchronization with the motion capture system. Its presence is hidden from subjects to avoid influencing their steps over it.
- **Electromyographic system.** Electromyographic sensors (EMG) are synchronized with the OSS and capture the muscular activity during gait. Those sensors are equipped with electrodes that can sense the sum of the action potentials created by muscle contraction. EMG sensors are typically placed on the surface of the muscle but can be also transcutaneously implanted into the muscle with fine wires. The latter is used mostly to track the muscular activity of muscles located deeply and can avoid noise caused by underlying soft tissues. The placement of the EMG follows guidelines recommended by the SENIAM project (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles, www.seniam.org) for better-measured precision.

Possible additional assessment:

- **Foot pressure.** A baropodometric evaluation, also known as a plantar pressure mat, is typically included in clinical gait analysis set up to collect information on the pressure distribution under the foot as well as the center of motion pattern stance phase. It is constituted by a series of sensors mounted evenly within the mat or treadmill.

- **Oxygen consumption.** The oxygen consumption (VO_2) is tracked in some laboratories to measure indirectly the energy expenditure which represents the net chemical energy consumed by the muscles during physical activity. This measurement is performed using a ergospirometer device. The net metabolic cost is calculated over walking speed and the efficiency is then calculated by the ratio between the total mechanical work and the net metabolic cost (Lobet *et al.* 2013, Gjellesvik *et al.* 2017).

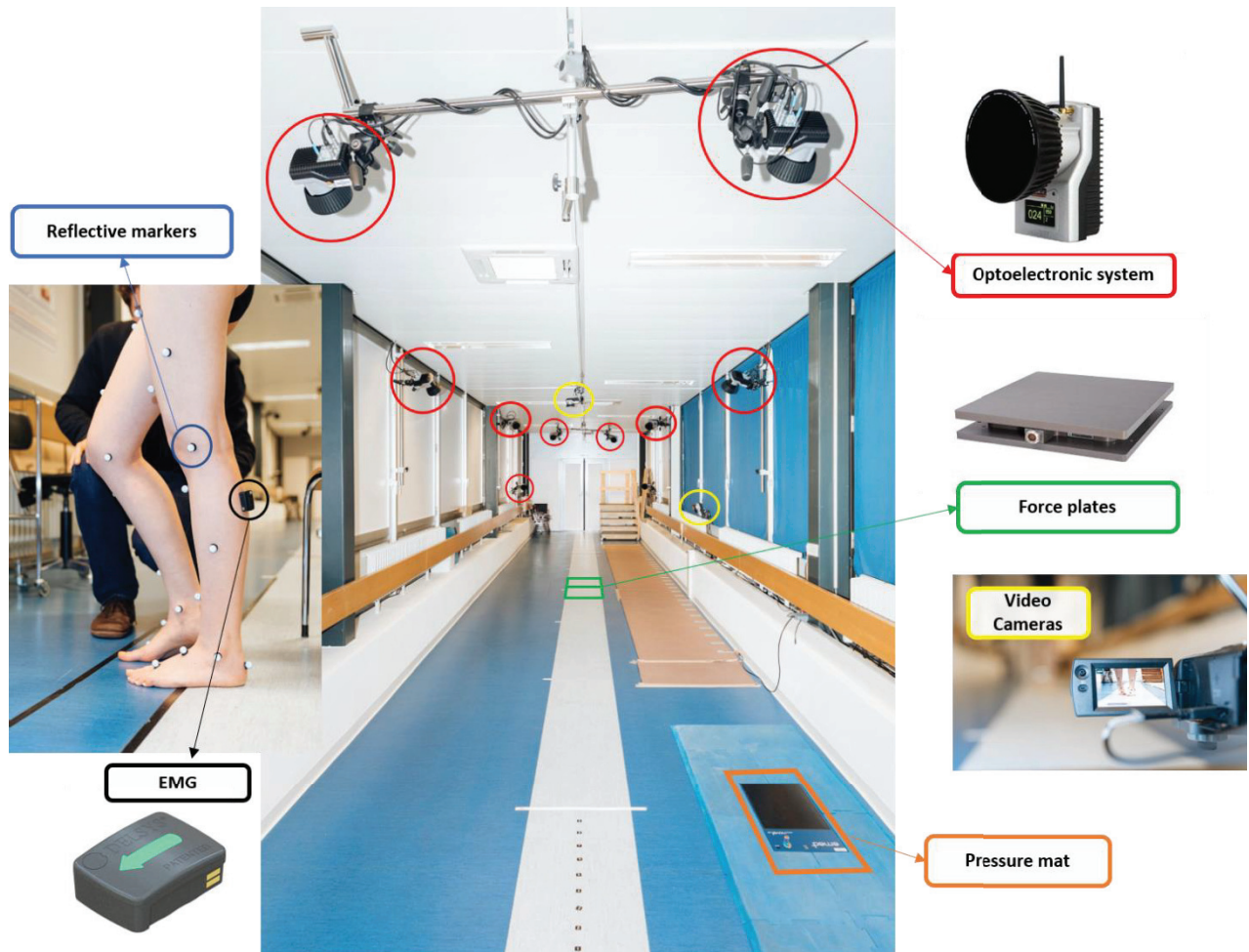


Figure 6. Gait analysis components.

1.5.1.3. Biomechanical models – marker set

A gait analysis protocol defines a biomechanical model through a set of markers, and procedures for data collection, processing, analysis and reporting of the results. Gait analysis protocols are intended to provide kinematic and kinetic data clinically interpretable (Ferrari *et al.* 2008). Reflective markers are used in gait analysis to represent the musculoskeletal system by a simpler reconstructed multi-segment model. Therefore, those need to be placed by a trained evaluator, also commonly referred as a rater, tester or examiner, following palpation guidelines (Van Sint Jan 2007) and knowledge of the biomechanical model used. Those can be used for different purposes such as estimating joint centers, defining directly the segment coordinate systems or supporting optimization or calibration procedures. Several biomechanical models have been proposed and implemented in gait analysis (Cappozzo *et al.* 1995; Davis *et al.* 1991; Leardini *et al.* 2007; Rabuffetti *et al.* 2019). Many

relevant differences exist in the biomechanical models adopted between the current gait analysis protocols which include the degrees of freedom assigned to the joints, anatomical and technical reference frames, measured variables, joint rotation conventions, and terminology. Notwithstanding, gait analysis data are exchangeable irrespective of the protocol adopted. However, the considerable methodological differences may result in inconsistent results, and consequently affect substantially the clinical interpretation, it is still unknown how close the different protocols used worldwide compare to each other. Among the existing models, the Conventional Gait Model (CGM) is the most used model in CGA (Baker 2013). The most commonly used skin markers and anatomical landmarks are illustrated and described in Figure 7 and Table 1.

Also known as Newington, Davis, Gage, Helen Hayes, Kadaba, Vicon Clinical Manager (VCM) or Plug-in-Gait (PiG), CGM can present various alterations on the reflective markers used. However, the basic principles for its construction remain the same through the years (Baker 2013; Davis et al. 1991; Kadaba and Ramakrishnan 1990; Kadaba et al. 1989). The lower limb model is constituted by a set of 7 rigid segments (the pelvis and two thighs, shanks and feet) linked by joints assumed to be ball and socket joints with three degrees of freedom (3DoF). Additionally, CGM is a top-down hierarchical model and so, a segment is defined with respect to its proximal segment. This constitutes a limitation for the models as a misalignment of proximal segments coordinate system may be amplified on the distally located segments coordinate system definitions (Kainz *et al.* 2017). Each segment is defined based on the measured positions of three markers (reflective or virtual). Virtual markers correspond to inaccessible anatomical landmarks and are estimated by reflective markers and mathematical considerations. On the other hand, reflective markers can be divided into two sub-groups considering their utility: anatomical or technical markers. Anatomical markers are the markers used to define the biomechanical model during static and dynamic trials. Technical markers are intended to support only the calibration of additional anatomical landmarks and/or to help to position the segment in other methods as inverse kinematics. Technical markers are generally placed such as the underlying soft tissue artefacts are minimal, not aligned and sufficiently distant with respect to the technical markers.

Alternatively, other models commonly used in CGA altering not only the marker configuration (Figure 7) but also mechanical considerations. The Human Body Model (HBM) is an optimized model for the real-time computing of kinematics (Van Den Bogert *et al.* 2013). The CAST, which stands for 'calibrated anatomical systems technique', differs from the CGM mainly by using cluster markers, calibrated with bony landmarks without joint constraints and by a different definition of the foot segment (Cappozzo *et al.* 1995), as calibration of some anatomical landmarks is done via instrumented pointers. The IOR model, which stands for Istituto Ortopedici Rizzoli, has been proposed as a development of the CAST. The main difference is due to the replacement of the location of technical markers using the instrumented pointer by the use of direct skin-mounted markers. Additionally, the LAMB protocol (Rabuffetti *et al.* 2019) differ slightly in the choice of markers and uses different equations for estimating the hip joint center (Ferrari *et al.* 2008).

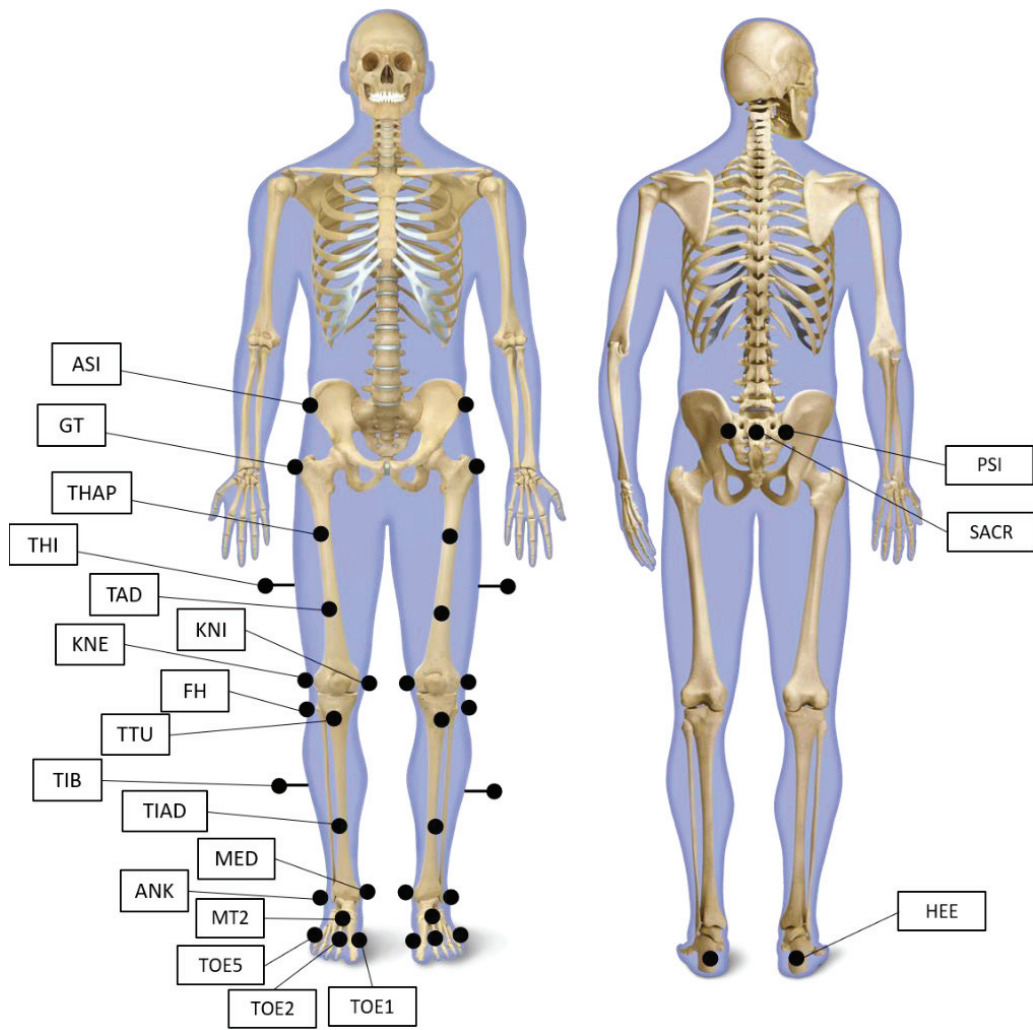


Figure 7. Illustration of the most used skin markers in biomechanical models. Image source: res.cloudinary.com.

Table 1. Configuration of the most used marker sets. CGM (Davis, Tyburski, et al. 1991); CGM2 (Leboeuf et al. 2019); LAMB (Rabuffetti et al. 2019); CAST (Cappozzo et al. 1995); IOR (A. Leardini et al. 2007); Clev (Horsak et al. 2018; M. P. Kadaba et al. 1989)

Abbreviation	Placement	Required for protocol
ASI	Anterior Superior Iliac Spine	All protocols
PSI	Posterior Superior Iliac Spine	CGM, CGM2, CAST, IOR, HBM
SACR	Mid-point between the posterior superior iliac spines	LAMB, Clev., HBM
GT	Prominence of greater trochanter (external surface)	LAMB, CAST, IOR, HBM
THI (wand)	50-70% of distance from hip to knee, lateral	CGM, CGM2
THAP	≈33% from hip joint center to knee joint center, anterior	CGM2, LAMB, HBM
TAD	≈66% from hip joint center to knee joint center, anterior	CGM2
KNE	Lateral femoral epicondyle	All protocols
KNI	Medial femoral epicondyle	CGM2, LAMB, CAST, IOR, Clev.
FH	Prominence of tibial tuberosity	LAMB, CAST, IOR
TTU	Tibial tubercle (most prominent part)	CGM2, CAST, IOR
TIAD	Shin bone – halfway between the TTU and ankle joint	CGM2, LAMB, HBM
TIB (wand)	Mid-point between knee and ankle, lateral	CGM, CGM2
ANK	Lateral tibial malleolus	All protocols
MED	Medial tibial malleolus	CGM2, LAMB, CAST, IOR, Clev.
HEE	Upper ridge of calcaneus posterior surface	All protocols
TOE1	Head of 1 st metatarsal bone	LAMB
TOE2	Head of 2 nd metatarsal bone	CGM, CGM2, CAST, IOR, Clev., HBM
TOE5	Head of 5 th metatarsal bone	CGM, CGM2, LAMB, CAST, IOR
MT2	Base of 2 nd metatarsal bone	CGM2
MT3	Base of 3 rd metatarsal bone	HBM
MT5	Base of 5 th metatarsal bone	HBM

1.5.1.4. Computational models – The Conventional Gait Model

In biomechanical modeling, a segment is defined by an orthogonal coordinate system composed by three axes. Typically, the segment coordinate system is defined by one primary axis linking the two joints (at which it is attached to the adjacent segment), a secondary axis, orthogonal to the primary axis and defined by a specific anatomical landmark that serves as a reference point for the definition of the rotation about the primary axis and a tertiary axis, orthogonal to the other two axes. The definition of segmental coordinate systems following the CGM (Figure 8) is explained below.

Pelvis. The principal axis of the pelvis is defined by the axis that joins the two anterior superior iliac spines (ASIS). A pelvic plane is defined by the plane that joins the ASIS markers with the virtual marker of the sacrum (estimated in the mid-point between the two reflective markers placed on the posterior superior iliac spines). The secondary axis of the pelvis is orthogonal to the defined plane. Finally, the tertiary axis represents the pelvic rotation and is defined as the orthogonal between the primary and secondary axes.

Thigh and Shank. The primary axis of the thigh and shank are the axis that joins the hip joint center with the knee joint center and the latter with the ankle joint center, respectively. The secondary axis of the thigh is calculated as the axis from the knee joint center to the lateral femoral epicondyle marker and the tertiary axis the orthogonal to the primary and secondary axes. On the other hand, the secondary axis of the shank is estimated as the axis from the ankle joint center to the lateral malleolus while the tertiary axis the orthogonal to the primary and secondary axes. Additionally, two different approaches have been applied for estimating the knee and ankle joint center. In the absence of a medial femoral_epicondyle marker, the primitive CGM calculates the knee joint center through a dynamic knee joint center calculation, also known as a modified “*chord*” function. From the global position of the hip joint center, the thigh wand marker and the lateral knee marker allied with the knee width and wand angle offset (from the subject measurement). Therefore, the knee joint center is determined such as is at half distance of the knee width from the lateral knee marker and the line connecting both markers is perpendicular to the primary axis. Additionally, the angle between the knee joint center and lateral knee line and the knee joint center and thigh wand, projected onto a plane perpendicular to the primary axis, is the same as the thigh wand offset angle. A similar process can be used to estimate the ankle joint center. On the other hand, with the inclusion of medial markers (knee and ankle) on newer variants of CGM, the knee and ankle joint centers are calculated by simply estimating the midpoint between the bilateral knee and ankle markers, respectively (Leboeuf *et al.* 2019).

Foot. In CGM, the foot is defined as a single axis. A longitudinal axis of the foot is calculated as the axis from the heel and second metatarsal markers. For calibration, the foot rotation and plantarflexion offsets, calculated between the ankle joint center to the second metatarsal markers and the longitudinal_axis, are removed. Those offsets removed from the longitudinal axis, on the horizontal and sagittal planes, resulting in the primary axis of the foot (Baker 2013)

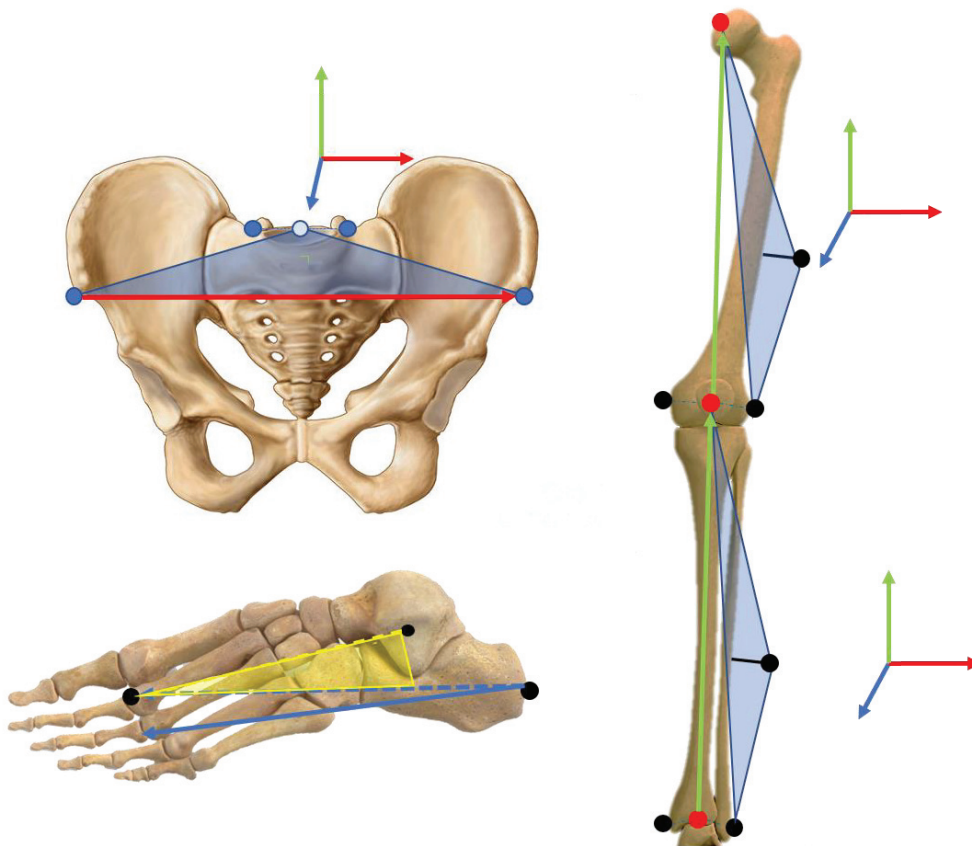


Figure 8 - Definition of segmental reference frames following the CGM. Image source: images.fineartamerica.com

Since its creation, and despite several addressed weaknesses, few developments have been proposed. A second version of CGM, the CGM2, has been recently proposed as an update to the classic CGM, where strengths are preserved while being formulated to address its weaknesses (Leboeuf *et al.* 2019). It was designed to be transparent, a platform for future developments and backward compatible with the original CGM. The CGM 2, which is freely available as an open-source python package (pyCGM2: <https://pycgm2.github.io>), includes different technical advancements such as optimized hip joint center estimation (Hara *et al.* 2016), an inverse kinematic approach (Lu and O'Connor 1999), the use of a marker-cluster within an optimized marker set (Peters *et al.* 2009), among other implementations (Leboeuf *et al.* 2019).

1.5.1.5. Clinical gait analysis – Measurement Protocol

A typical gait analysis session is constituted by different measurement stages. In terms of professional personnel, it requires the presence of a technician to perform the gait analysis and a physician to perform a physical examination. The overall session lasts, generally, between 1-3 hours. Gait analysis is, usually, recommended before a scheduled surgery. The different stages defined in a gait analysis protocol are the following:

1.5.1.5.1. System Calibration

Active system calibration is required before each session to calibrate the environment of the tracking system (position and orientation of the complete system). This procedure locates the camera's optical coordinate frame with reference to a global coordinate frame (volume origin). The global coordinate system is defined by placing strategically a rigid calibration tool in the center of the measurement area, which defines where the center of the capture volume is and its orientation (x, y, and z axes). The laboratory space is calibrated by moving another wand around the laboratory during a certain period. Camera calibration describes the capture volume of the system enabling the motion capture system to estimate accurate three-dimensional data. Both tools are rigid and contain reflective markers strategically tapped over, with a known distance between markers. This process is generally performed in less than two minutes.

1.5.1.5.2. Subject set-up

Patients are equipped with passive reflective cutaneous markers or wand markers tapped on anatomical and technical landmarks according to the biomechanical model adopted by the laboratory. The EMG electrodes are equally tapped on the skin (over the muscles) to record the muscular activity of the lower limbs following the SENIAM recommendations (Hermens *et al.* 2000). Patients are tested barefoot and dressed in swimsuits or underwear so the reflective markers are directly placed on the skin and can be entirely visible by the cameras. An additional examination is often included where the patient is asked to perform gait trials with shoes and an orthotic device if the case. Thus, foot and shank markers are removed from the skin and mounted over the shoes and orthotic device. This is done to provide information relative to the gait of the patient with the orthotic device.

1.5.1.5.3. Data acquisition

The patient performs initially one static trial where stands in a static position for a few seconds, normally. This procedure requires the complete set of markers to be tracked simultaneously and it is used to calibrate the gait model posteriorly.

Patients walk at a self-selected speed on the walkway for several trials. Commonly between three to 20 trials depending on the capacity of the patient and the objective of the assessment. For tracking kinetic data, commonly a minimum of three clean steps over the platforms are detected per foot. A clean step refers to a step in which foot strike and foot off are observed with the entire foot within the limits of the platform and the contralateral foot completely out of it. The examination is finished when the evaluator decides that a sufficient number of gait cycles have been recorded and that the recorded data is representative of the patient's gait. (Armand *et al.* 2017). Additionally, other tasks can be performed as for example fast gait, slow gait, balance, run, etc.

1.6. Gait data

1.6.1. Spatiotemporal (SPT) parameters

Spatial and temporal parameters are linked with the cyclic characteristics of gait. They are computed from FO and FS events and marker trajectories of the foot. Alternatively, they can be calculated using data acquired by an instrumented mat (e.g. GaitRite® (Menz *et al.* 2004)). In a gait analysis report, SPT parameters such as walking speed, cadence (number of steps per minute), stride/step length and width as well as durations of different gait cycle phases are reported for each lower limb and compared with an asymptomatic reference database (Armand *et al.* 2017).

PARAMETRES	Gauche	Droite	Normal
Vitesse de marche	1.1 ± 0.05 m/s	1.09 ± 0.05 m/s	1.1–1.3
Vitesse de marche normalisée	1.18 ± 0.06 m.s-1/m	1.17 ± 0.05 m.s-1/m	1.3–1.7
Cadence	113.66 ± 2.48 pas/min	112.98 ± 3.13 pas/min	110–130
Longueur du pas	0.63 ± 0.01 m	0.53 ± 0.03 m	0.65–0.75
Largeur du pas	0.11 ± 0.02 m	0.11 ± 0.02 m	0.05–0.15
Phase d'appui	60.3 ± 1.36 %	67.34 ± 1.23 %	55–65
Durée du pas	0.6 ± 0.02 s	0.47 ± 0.02 s	0.45–0.55
Durée d'un cycle	1.06 ± 0.02 s	1.06 ± 0.03 s	0.9–1.1
Longueur d'un cycle	1.16 ± 0.03 m	1.16 ± 0.04 m	1.4–1.6
Simple appui	32.9 ± 1.89 %	39.69 ± 1.55 %	40–50
Double appui	27.4 ± 1.88 %	27.65 ± 1.69 %	10–20

Table 2. Example of the report of spatiotemporal parameters.

1.6.2. Kinematics

Kinematics is the branch of mechanics in charge of studying motion between objects without considering the forces applied. In gait analysis, the tracked markers during gait and static trials provide three-dimensional information regarding segment position with respect to the global reference frame of the laboratory. The markers are located over specific anatomical landmarks and are used to create virtual rigid segments representing the real segments such as the pelvis, thighs, shanks, and feet (for lower limb analysis). A transformation matrix is calculated for each segment at each frame. Therefore, the joint angles are calculated by the motion of an adjacent segment with respect to its anterior segment in a three-dimensional space. Typically, kinematics is normalized with respect to the percentage of the gait cycle. Thus, the superposition of gait cycles allows the calculation of statistical parameters such as mean and standard deviation as well as the visual comparison between identical curves (Armand *et al.* 2017). The three planes considered in gait analysis are defined as sagittal, coronal (frontal), and transversal. Indeed, even if the joint angles are computed about axes that are not all normal to any segment planes and even if the segment planes are not parallel to each other during the movement, the flexion-extension, adduction-abduction, and internal-external rotation are generally referred to as sagittal, frontal and transversal angles in clinical reports (Figure 9).

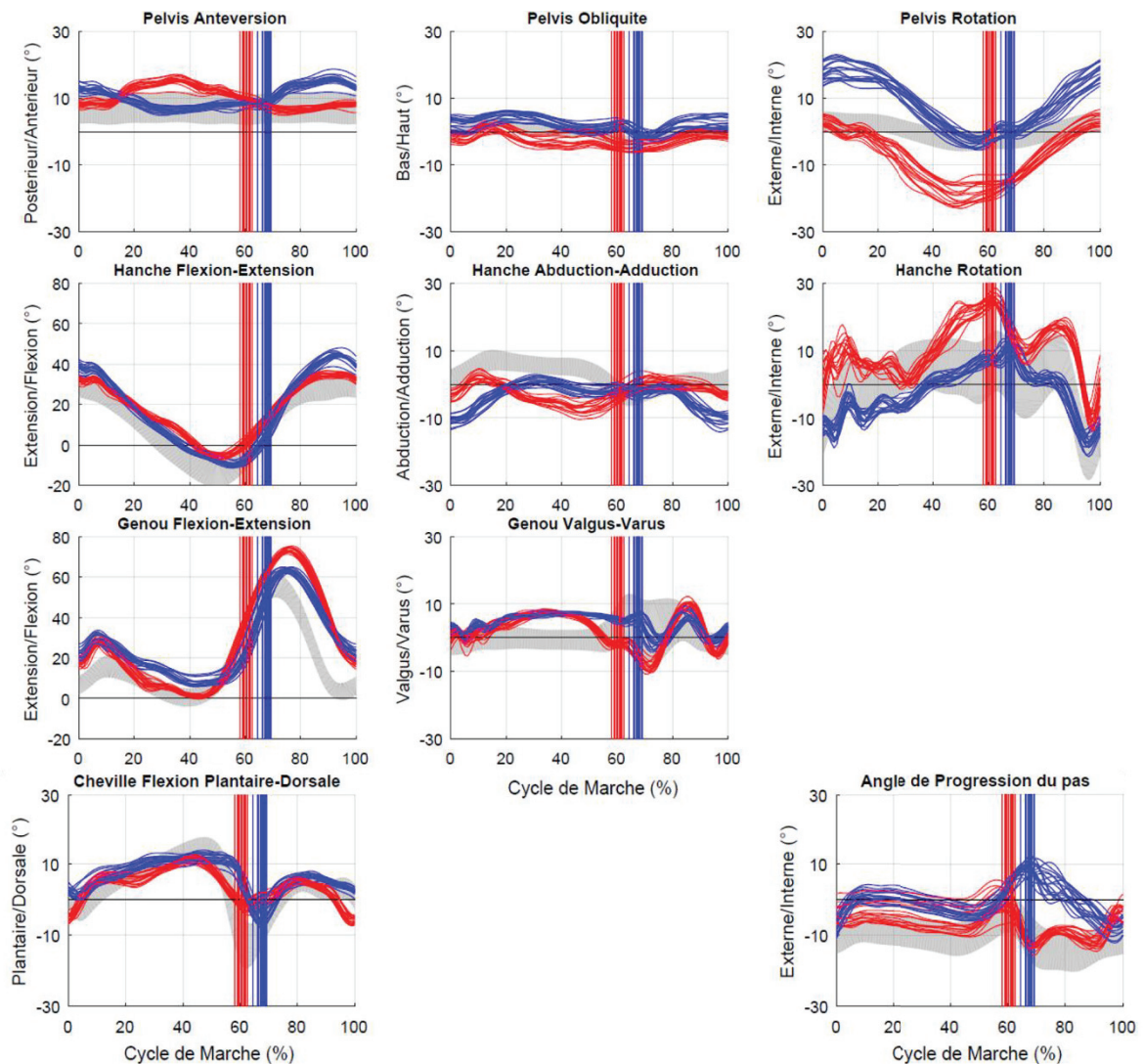


Figure 9. Example of reported kinematics. Kinematic data relative to the overall cycle for the left (red) and right (blue) sides, in comparison with a reference normative database (mean \pm standard deviation).

1.6.3. Kinetics

In gait analysis, kinetics is the study of the forces, power, and energy that affects the pattern in which a subject walks. Actual technologies applied in gait analysis for measuring kinetics rely on force platforms embedded in the ground which allow measuring the center of pressure, forces, and moments. They have the capacity to quantify ground reaction forces acting on the foot in the vertical, mediolateral, and anteroposterior directions (Dicharry 2010). Data measured by the force platforms allow, together with kinematic data, calculation of the inter-segmental forces and moments and powers on the three above-mentioned components, using the laws of physics, namely the Newton-Euler equations. Commonly known as inverse dynamics, this method allows the computation of the internal forces and moments based on kinematic data and the body's inertial properties through a kinematic chain of rigid bodies (segments) (Bae *et al.* 2009, Dicharry 2010). Their computation is also linked to the biomechanical model. Inter-segmental moments refer to the amount of force (multiplied by their lever arms) applied by the internal structure crossing the joint to perform the rotation of a segment around a specific axis of rotation (Sloot and van der Krogt 2018). Joint power refers to the energy generated or absorbed by the muscles or soft tissues per unit of time. In a simplistic view (one

joint axis driven by muscle forces), the power is positive when the concentric muscle activity within a joint generates energy, negative when the eccentric muscle activity absorbs energy and null when the isometric muscles provide no alterations in energy (Sloot and van der Krogt 2018). Analyzing kinetic data comparatively with a normative dataset, it is possible to investigate the parameters that influence a subject's gait (Figure 10).

Both kinematic and kinetic data are computed based on the biomechanical model defined. There are several different software and toolboxes used to compute this data (e.g., Nexus-Vicon, Visual 3D-CMotion, OpenMA, PyCGM2).

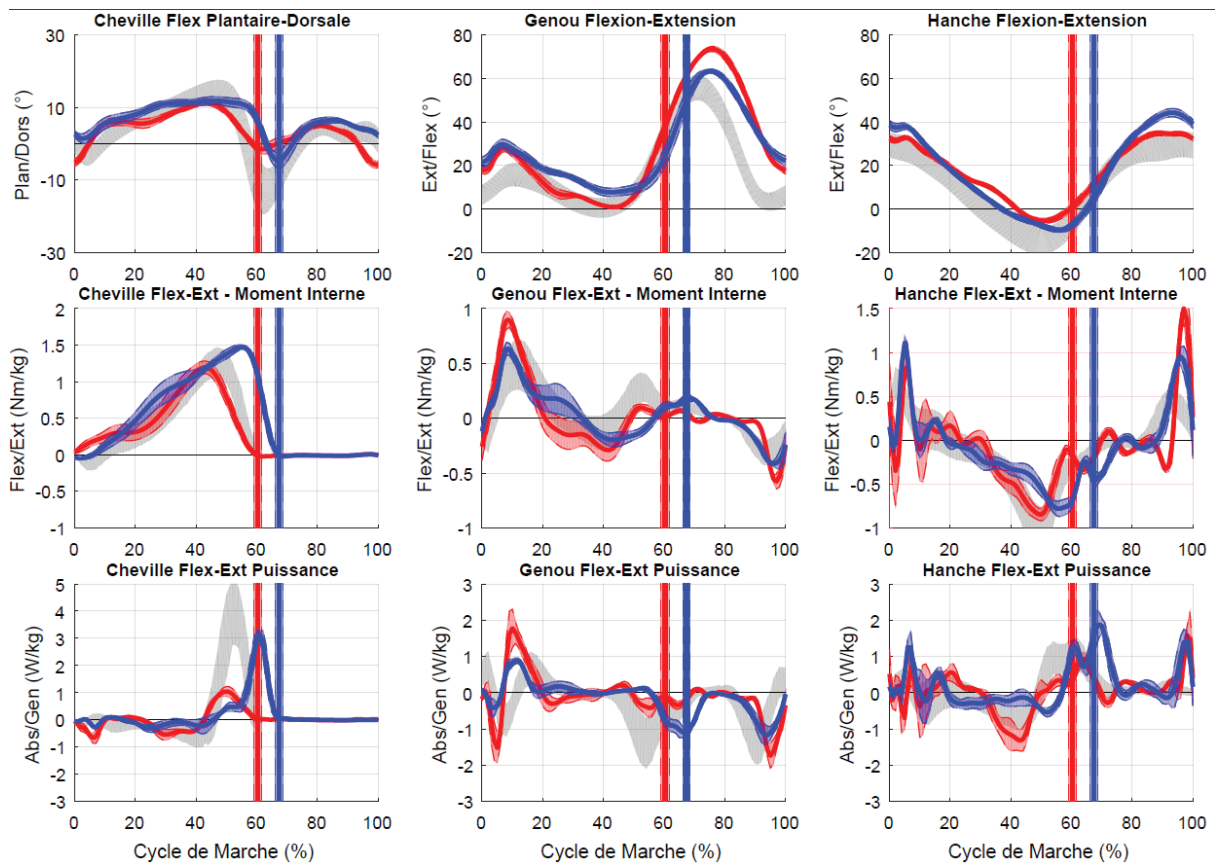


Figure 10. Example of reported kinetics. Kinetic data relative to the overall cycle for the left (red) and right (blue) sides, in comparison with a reference normative database (mean \pm standard deviation).

1.6.4. Electromyography

EMG data is recollected during a gait analysis session via electrodes that detect the sum of action potentials specific to each muscle of interest. It provides important information regarding the time of activation of each muscle of the lower limbs during gait. Moreover, the amplitude of muscle activation is another important parameter in accessing the capacity of a muscle to contract (Armand et al. 2017). The recommendation for the normalization of EMG signal is the maximum voluntary isometric force. However, this normalization is not adapted for pathological populations as patients with motor disorders are often unable to perform the required voluntary contraction. This is still a limitation and discussion topic in the CGA community and it is still typically excluded from clinical evaluations (Tabard-Fougère et al. 2018). Therefore, the main use of EMG in CGA is to identify the timing of muscular activations during the different phases of gait.

1.6.5. Foot Pressure Mapping

Foot pressure, measured with the aid of an instrumented mat or in-shoe pressure sensor, is another familiar tool in gait analysis. It provides useful information to quantify the pressure applied to the foot during the step. This information helps to identify asymmetries between both foot and provide information about the pressure distribution of the feet. Note that the trajectory of the center of pressure can be already analyzed from the force platforms. It is the point where the action of the ground on the foot (reaction) is generally interpreted. However, instrumented mats provide detailed information about the pressure (*i.e.* vertical load only) distribution under the foot. Force platforms and instrumented mats can be therefore considered complementary.

1.6.6. Gait scores

Clinicians, whose focus extends beyond the biomechanics of gait, can be frequently overwhelmed by the complexity of gait reports. Successful attempts have been made to address this problem by developing simplified summaries of gait results in the form of a single number or gait index, which represents the patient's global deviation from normality (Baker et al. 2009; Schutte et al. 2000; Schwartz and Rozumalski 2008).

Gait scores are used in the interpretation of CGA data to provide a general single classification of the kinematic gait pattern. More specifically, a gait score calculates the amounts by which gait kinematics of a patient deviates from an average normal pattern constituted by a reference normative database (Schutte *et al.* 2000, Baker *et al.* 2012a). The most accepted gait scores in CGA are the Gillette Gait Index (GGI) (Schutte *et al.* 2000), the Gait Deviation Index (GDI) (Schwartz and Rozumalski 2008) and the Gait Profile Score (GPS) (Baker *et al.* 2009). The GDI is calculated similarly to a scaled Euclidean distance between the average of the reference dataset with the average patient's gait and incorporates an evaluation of 459 discrete points (51 points per joint angle) acquired from 15 gait features (Schwartz and Rozumalski 2008). On the other hand, GPS is calculated based on the relative difference among the nine key kinematic parameters with the reference database. For each kinematic parameter, the root mean square difference with respect to the mean reference is calculated, the so-called Gait Variable Score (GVS). The GPS is then calculated as the mean of the overall GVS including the pelvis and the two lower limbs. However, their characteristics have induced a discussion among the clinical gait community regarding which one is more appropriate to use. While the GDI has the advantage of being a more intuitive measure for assessing clinical changes, the GPS provide a quantification of relative contributions from specific joints or planes of rotation (through the GVSs). Both GPS and GDI have been demonstrated to have a very strong exponential correlation (Baker *et al.* 2009).

1.6.7. Physical analysis

A systematic physical examination of the patient is usually conducted as part of gait analysis. It provides useful information regarding the passive and active characterization of clinical impairments. Contrary to gait analysis *per se*, physical examination is based on static responses. The association of gait analysis and physical examination data supports the notion that each one provides information

that is relevant to the evaluation of motor disorders. Several parameters are measured by a physical therapist or medical doctor and reported in proper measurement scales. A wide range of information is measured by the physician during a physical examination such as anthropometric data, joint range of motion, and muscle properties. The anthropometric data serves to posteriorly calibrate the biomechanical model and to evaluate the musculoskeletal morphology (e.g. symmetry). The joint range of motion, calculated with the aid of a goniometer, serves to investigate muscle contractures. Finally, the muscle properties, such as selectivity, muscle weakness, and spasticity help to provide a detailed description that can delineate the nature of the problem and its severity (Papageorgiou *et al.* 2019, Sarathy *et al.* 2019).

1.6.8. Clinical Interpretation

Clinical interpretation is where all aforementioned measured data is evaluated. A clinician, typically accompanied by a biomechanical expert, evaluate data with respect to the normative standard (reference database acquired from an asymptomatic population) and, if applicable, comparatively with previous data acquired from the subject. While the comparison with normative data is used to evaluate gait deviations (from healthy gait), the comparison with past data is generally done to assess its evolution and the effects of treatments. It is important to note that providing a rigorous interpretation of measured gait data is a difficult task and requires high expertise and knowledge as causes of gait deviations, at a musculoskeletal level, are generally identified by a combination of measured factors. Thus, the assessment of gait deviations requires the identification of all the 'clues' and pertinently connecting them. For that, different types of measured data need to be evaluated together as two complementary sources of information. In order to simplify this process, data is displayed in the most simplified way. There is little agreement as to what an ideal gait report should look like and how it should be produced (Baker 2013). For example, the display of data should be always the same among subjects, with colors differentiating sides, omitting less relevant graphs, and automatically highlighting abnormal data.

A particular technique for interpretation and reporting gait data, known as focused interpretation, has been evolving with the main focus on children with cerebral palsy prior to complex orthopaedical surgery. The aim of gait analysis is to support the identification of impairments, affecting the child's gait, and to support the decision treatment for removing or reducing those impairments. An impairment has already been defined by the World Health Organization as a problem in body structures or functions such as significant deviation or loss (WHO 2001). This is accomplished by highlighting features present in gait data and associating them to results reported through physical examination. A feature, in gait analysis, is defined as the "*specific aspect of the gait analysis that is considered clinically significant or, in other words, something that can be seen on one of the graphs.*" (Baker 2013). Those features can be marked up with associated symbols which are intuitive to the representing feature and combine information regarding the type of feature (i.e. increased range, reduced peak), side (left, right or bilateral), timing (with respect to phases of the gait cycle), and variable. Those marks can be useful to highlight and better describe gait deviations. The overall information is then summarized as a form of gait report containing all the findings concluded during clinical interpretation.

1.7. The importance of clinical gait analysis for treatment decision

During the past two decades, preoperative three-dimensional gait analysis has been recommended for assessing motor disorders such as CP (Armand et al. 2016; Bonnefoy-Mazure et al. 2013; Rozumalski and Schwartz 2009). The combination of gait analysis and clinical assessment can be a powerful tool for managing gait disorders (Armand et al. 2016). For instance, decision treatment for motor disorders is not an exact science, as, despite the information describing the condition of the patient, different clinicians will define their choice by personal experience. CGA is performed to support the decision treatment selection amongst available options (including the possibility of not intervening). The selection is based on several points such as: assessment of the severity, extent, or nature of a disease or injury; monitoring the progress in the presence or absence of an intervention, and prediction of the outcome of an intervention (Brand and Crowninshield 1981, Baker 2006). Despite the information provided by the CGA, decision treatment is done in a combination of CGA data with other data previous from medical history, medical imaging, and patient's expectation among other factors. Previous studies have shown that it makes a substantial impact on orthopedic decision-making (Lofterød and Terjesen 2008, Bonnefoy-Mazure *et al.* 2013, Wren *et al.* 2020). Lofterød et al. evaluated two groups of patients with CP, undergoing or not previous gait analysis. They have observed a 51% disagreement between the proposals for surgical procedures planned based on only clinical evaluation with the procedures planned based on preoperative gait analysis. In addition, they reported a 92% agreement among procedures planned based on gait analysis reports and subsequent surgery, indicating that the orthopedic surgeons followed the recommendations to a high degree (Lofterød and Terjesen 2008).

Before gait analysis, motor disorders were assessed by stages and the surgical interventions used to be done in different steps. Repeated surgical interventions and associated rehabilitation processes can be very disruptive to patients, interfering with daily life. Therefore, gait analysis provides a full assessment of motor disorders at multiple levels, and thus, surgeons are able to identify the causes of gait impairments and intervene at multiple levels simultaneously (multilevel surgery). By doing so, treatments have a lower impact on the patient's life as well as reduce the treatment costs significantly (surgical interventions are costly) (Wren *et al.* 2009). In a retrospective study between CP groups undergoing or not preliminary gait analysis, Wren et al. demonstrated that patients that didn't undergo CGA, reported a smaller number of procedures at first surgery (mean: 4.2 procedures) comparatively to the other group (mean: 5.8 procedures). Surgical planning without gait analysis required more additional surgeries than the comparative group, 32%, and 11%, respectively. Additionally, they have reported a different distribution regarding the type of surgery performed. They reported a significant reduction in the total costs for the CGA group due to a decrease in the number of additional surgeries, even though in the first year (of assessment using CGA) the costs were higher for the CGA group due to the addition of CGA. They also reported better improvement of the CGA group over the years (Wren *et al.* 2009). Regarding treatment costs, Öunpuu et al. have demonstrated that treatment-associated charges between single multilevel surgery based on comprehensive gait analysis were 20% to 47% reduced in comparison with multi-staged surgical approaches, referent to ambulatory children with CP (Öunpuu *et al.* 2022).

In conclusion, many studies have reported the benefits of using gait analysis for the assessment of motor disorders and as a support for treatment planning in the sense that the clinicians plan the treatment based on a significantly higher amount of information. Even though it is still not an exact science as it is dependent on the experience of the medical team, patient characteristics and reliability of acquired data, the proven advantages of gait analysis in a clinical context are: a higher agreement level between clinicians for identification and decision making for treatments; reduction of costs

associated with medical assessment at long term; and most importantly, a considerable improvement on treatment outcome (Simon 2004, Wren *et al.* 2009, Armand *et al.* 2017).

1.7.1. Requirements for a good gait analysis

In clinical practice, as above mentioned, measurements are central for diagnosis, prognosis, and evaluation of the outcomes of medical interventions (De Vet *et al.* 2011). However, in order to consider gait analysis as a valuable tool in a clinical context, it needs to fulfill some requirements in terms of quality and applicability. Kirtley *et al.* have reported the following eleven fundamental requirements for considering gait analysis as a tool to evaluate motor disorders (Kirtley 2006) (summarized in Table 3):

- **Ease.** The measurement should be not difficult for the intervenient.
- **Rapid.** The measurement process should be fast enough to minimize fatigue on the part of the patient. A gait analysis session that requires a considerable amount of time or a high number of tasks performed by the patient results in fatigue from the patient's side. This can result in alterations of the gait patterns measured.
- **Patient-friendly.** Allied with the two points above, it must be non-invasive, painful or dissatisfy the patients during measurement.
- **Free from error.** Measurements are always subject to errors. However, the measurement error should not interfere with the interpretation of the data and consequently decision making.
- **Validity.** It should measure what it claims to measure.
- **Accurate.** Gait analysis should result in a measured value representing the real gait of the patient.
- **Repeatability and reliability.** Results from measurements should be consistent between measurements performed by the same or different evaluator.
- **Must not significantly affect the gait of the patient.** The set-up and the environment should be propitious so that the patient can reproduce his/her normal walking.
- **Relevant information.** The information quantified through gait analysis actual system should not be quantified through other systems that present general advantages. There is no point in doing any gait analysis if the results could be obtained sufficiently well by simply observing the patient or by another simpler or more affordable system.
- **Able to distinguish between normal and abnormal.** The goal of gait analysis is the identification of gait impairments, and thus, the information prevenient from it should lead to its aim.
- **Reportable and clinically understandable.** Clinicians that are the receiver of gait information should understand every piece of information reported.
- **Cost-effective.** The benefit of performing the test must be worth the cost. This balance need not necessarily be determined in purely financial terms, but the financial cost of gait analysis is a significant factor.
- **Sensible to change.** It should detect alterations of gait patterns (Mokkink and Terwee 2010).
- **Positive impact.** The outcomes must be proven to positively impact the treatment decision for patients.

Fundamental Requirements for Clinical Gait Analysis

Data Acquisition	Measured Data	Data Interpretation
<ul style="list-style-type: none"> - Ease to be measured - Low time consuming (to minimize possible fatigue) 	<ul style="list-style-type: none"> - Free from errors - Valid (measure what is intended) - Accurate (measure real gait) - Repeatable and Reproducible 	<ul style="list-style-type: none"> - Discriminative - Reportable - Clinically understandable
Global value		
<ul style="list-style-type: none"> - Cost effective 		

Table 3. Fundamental requirements for Clinical Gait Analysis

Therefore, it is questionable if the actual gait analysis specifications and procedures fully meet those requirements. It is generally accepted that there has been a high improvement in most of these referred points during the years. For instance, the setup mounted on the patient is considerably low (reflective markers and EMGs) and rapidly mounted. The entire gait session is performed approximately during 21-3 hours but the patient is only required to stand and perform tasks for approximately 30 minutes. It is also proven that the information obtained by gait analysis is important and clinically understandable for improving clinical interpretation and decision-making for treatments. Additionally, even considering the high cost of mounting and maintaining a gait laboratory, the long-term reduction of costs associated with the management of motor disorders (Wren *et al.* 2009). In recent years, two main gait evaluation tools have been developed in complement to OSS: video-based motion tracking, known as markerless, that tracks the joint movement only based on video cameras and relies on machine learning techniques (Colyer *et al.* 2018) and method based on inertial sensors that have the advantage of tracking kinematics at any environment (Orlowski *et al.* 2017). Despite their advantages, none has been proven to provide more reliable and valid results than OSS (McGinley *et al.* 2009a, Orlowski *et al.* 2017, Colyer *et al.* 2018). However, gait analysis based on OSS, like any other gait measurement system, incorporates measurement errors that affect its reproducibility and reliability. Thus, there is a need for understanding and quantify the level of reproducibility and reliability of the measurements performed.

The role of gait analysis in supporting decision-making has been in discussion since its inclusion in clinical practice. During the first years, in which gait analysis started to be applied for the assessment of motor disorders, many authors rose the importance of obtaining satisfactory levels of reproducibility and reliability, so to speak, that do not significantly impact the clinical interpretation. *“The measurement must be accurate and reproducible”* (Brand and Crowninshield 1981). *“It is crucial to ask whether or not results from a single gait evaluation is representative of a subject’s overall gait performance and whether the data are consistent enough from day to day for making significant, clinical decisions”* (Kadaba *et al.* 1989a). Those considerations lead to the work of many researchers and in the last two decades about 66 thousand scientific articles were published concerning the terms *“gait analysis”* allied with the concepts of *“reproducibility”*, *“repeatability”* and *“reliability”*. Therefore, those considerations lead to the following contents of this thesis.

1.8. Analysis of the quality of measured gait data

In order to evaluate the quality of measurement techniques, it is important to first define the concepts used to do so. Terminology and definition often vary within the scientific community, leading to confusion in communication. Therefore, a consensus based on the expertise of several intervenients was developed for the selection of measurement instruments (Mokkink and Terwee 2010). This section is intended to describe and clarify relevant terms used within the scope of the present thesis.

1.8.1. Terminology and definitions

1.8.1.6. Agreement and Reliability

Reliability relates to the consistency of measurement (Figure 11). Mathematically, it represents a ratio of true variance over true variance plus error variance (Koo and Li 2016). A consistent measurement is a measurement that is performed several on the same subject (test-retest) and results in the same outcome data. The term reliability compares the measurement error with the inherent variability between measurands (subjects) and it is typically expressed as the standard deviation of those parameters (Bland and Altman 1986). As an example, if the inherent variability between measured individuals is hypothetically valued at 100 and the magnitude of the measurement error is 1, the measurement is considered reliable. However, when we consider the inherent variability between measured individuals as 2 and with the same magnitude of measurement error (1), the measurement is considered with low reliability. Thus, if reliability is high, measurement errors are small in comparison with the true differences between individuals to be measured. Additionally, reliability is dependent on the population in which measurements are performed and not just on the measurement errors associated with the measurement system (Bartlett and Frost 2008). Reliability can also be divided into absolute and relative reliability. Whereas absolute reliability refers to the degree of variation in measurements for individuals, relative reliability refers to the degree of variation in position among individuals for repeated measurements (Pini *et al.* 2022). The reliability is typically reported as Intraclass correlation (ICC) and can vary between 0 (no reliable) and 1 (extremely reliable).

Agreement quantifies how close two measurements performed on the same individual are. One common form for quantifying the level of agreement between two measurements is the estimation of the 95% limits of agreement (test-retest score) (Bland and Altman 1986). Another way to estimate agreement between measurements is by computing the standard error of measurement (Terwee *et al.* 2007).

1.8.1.7. Reproducibility and Repeatability

When evaluating the reliability of a measurement system, there are two terms that are often considered and evaluated by test-retest evaluation: reproducibility and repeatability. While **repeatability** refers to the variation of the measured data from repeated measurements performed under identical conditions (*i.e.* intra-evaluator), **reproducibility** refers to the variation of measured data under different conditions (*i.e.* inter-evaluator) (Bartlett and Frost 2008). In gait analysis, repeatability is quantified by repeating measurements of gait on the same subject within a short period of time between sessions, with the measurements performed in the same laboratory and by

the same evaluator. On the other hand, in gait analysis, reproducibility is obtained by reproducing the measurements of gait on the same subject but altering one or more conditions stated for a repeatability analysis (*i.e.* laboratory, gait analysis system, evaluator).

1.8.1.8. Validity and Responsiveness

Validity refers to the extent to which the measured gait data represents the real gait of an individual (De Vet *et al.* 2011). This concept differs from the reliability of a measurement as a reliable measurement that is consistent through different repetitions, it can, somehow, be not valid if the measurements do not represent the real gait. There are three sub-categories of validity considered: content validity; criterion validity and construct validity (Figure 11). Content validity refers to whether the content of the instrument corresponds with the construct that one intends to measure, with respect to comprehensiveness and relevance. Criterion validity refers to how a measurement instrument agrees with a measurement performed by a gold standard instrument. Contrarily, construct validity is applicable in the absence of a gold standard and relates to how close a measurement system can provide the expected measurements, taking into account knowledge about the parameter being measured (De Vet *et al.* 2011). The evaluation of validity in gait analysis is more complicated than reliability as there is no perfect gold standard. Some used approaches rely on the comparison of the reflective marker locations with anatomical landmark identification using imaging (*i.e.* fluoroscopy) or intracortical pins (Cereatti *et al.* 2017). However, even those approaches have to be validated and fail on their applicability.

Responsiveness is defined by the COSMIN study as the ability of an instrument to detect change over time in the construct to be measured (Figure 11). In other words, the responsiveness of an instrumented gait analysis system relates to how able is the system to track clinically important changes in a patient's gait, even if these changes are small. Whilst, instrumented gait analysis incorporates measurement error, the responsiveness of the system may be reduced (Terwee *et al.* 2007). It can be then tested by relating the smallest detectable change (SDC) with the minimal amount of change that is considered to be important (minimal important change). To be considered responsive, SDC is required to be smaller than the minimal important change (Terwee *et al.* 2007). Moreover, before using instrumented gait analysis, it is important to understand the general effects of motor disorders and treatments as well as the clinical relevance of those changes and the responsiveness of CGA to measure these changes.

The assessment of both validity and responsiveness is related. In fact, responsiveness is considered a measure of longitudinal validity (De Vet *et al.* 2011).

Validity and reliability are two complementary considerations to evaluate the quality of a measurement instrument. In Figure 12 (second row), an illustration represents the different possible outcomes when evaluating the quality of a measurement instrument with respect to reliability and validity. As an example, let us consider two evaluators in charge of detecting a specific anatomical landmark and consequently placing a reflective marker, multiple times (in Figure 12, measures performed by the two evaluators are distinguished by black and green dots), and the real anatomical landmark point lies in the center of the target represented in Figure 12. Here the analysis of reliability represents how dispersed the markers placed among and between the same evaluator are observed. On the other hand, validity evaluates how close the overall set of markers is to the real anatomical landmark.



Figure 11 - COSMIN taxonomy of relationships of measurement properties. Image source: (Mokkink and Terwee 2010)

1.8.1.9. Random and Systematic error

In statistics, the term error is generally applied to refer to the deviation of an observed measured value from its true value. Measurement error consists of random and systematic errors. **Random error**, in gait data, refers to the inherent variation of the patient to repeat cyclic gait or by the measurement system. Random errors are caused by sources that are not immediately obvious. Also called a 'statistical error', as it can be suppressed in measurement by statistical means due to its random nature. Contrarily, the **systematic error** or also denoted as bias, demonstrates a general trend for the measurements to deviate from the true value and cannot be predicted (Taylor *et al.* 2010).

1.8.1.10. Precision and Accuracy

Precision and accuracy are two concepts inherent to any measurement performed. **Precision** refers to the concept of agreement and repeatability, hence it is a measure of dispersion between measurements of the same measurand. **Accuracy** is related to the validity of a measurement as it is a measure of the difference between the measured quantity and its real value (Westgard and Lott 1981). A measurement that is both accurate and precise has low measurement error. Figure 12 illustrates a possible combination of precision and accuracy. The repeated measures result in a high dispersion of values (black dots) and measure far from the real value to be measured (smaller circle in the center of the target), both the precision and accuracy are low. In the case, measured values show high dispersion but are close to the value to be measured then the precision is low but accuracy is high. Finally, if the dispersion is observed low the precision is high and accuracy low if measured values are far from the real value and high if they are centered close to the real value. In gait analysis, evaluating the accuracy of a measurement is limited due to the lack of a reference (gold standard). Therefore precision and

reliability are similar concepts as they are measured based on the dispersion of the measured data, independently of how far it is from the actual value to be measured. On the other hand, validity is a close concept to accuracy as it measures how close the measurements are from the values to be measured. The better estimation of a reference to calculate accuracy is based on the use of intracortical pins, directly mounted on the anatomical landmarks. In some cases, a three-dimensional reconstruction based on bi-planar x-rays or fluoroscopy is used as a reference and so marker placement and axis orientation accuracy is estimated with respect to it (Assi *et al.* 2016, Gasparutto *et al.* 2020). However, measurement error is also inherent to the identification of anatomical landmarks by imaging and the 'ideal' location for the reflective marker is also dependent on the underlying adipose tissue. On the other hand, precision is typically calculated with test-retest studies.

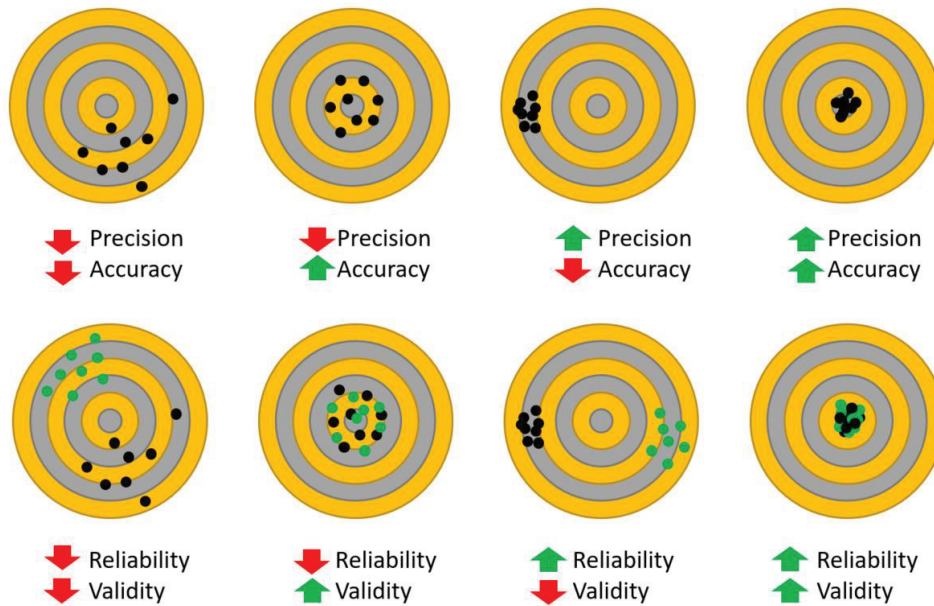


Figure 12 - Illustration of reliability, validity, precision, and accuracy.

1.8.1.11. Interpretability

Interpretability refers to the meaningfulness of the measured data by an instrument. Although not considered a measurement property, it is considered an important characteristic. This term is relevant for considering a measurement system in clinical practice and research.

When interpreting gait data, it is important to have an estimation of the associated measurement error in order to provide confidence in the interpretation of the output data. If the measurement errors conceal clinically relevant gait deviations, information may be lost. Additionally, if the limitations of the measurement error are not considered or understood, small deviations may be considered meaningful and consequently lead to over-interpretation.

1.9. Variability in gait analysis

Measurements are likely prone to various sort of errors, which may cause the measured value deviates from the true value (Bartlett and Frost 2008). Variability is here defined as the sum of variances from each independent source. In CGA, it is the origin of incertitude in the interpretation of gait data. It is described by the fluctuations of gait parameters (kinematic, kinetic, Spatio-temporal, and electromyographic measurements) of gait, and it can be divided into two main sub-groups: intrinsic variability and extrinsic variability.

1.9.1. Intrinsic variability

On the one hand, **intrinsic variability** (also referred to in gait analysis as within-subject, stride-to-stride, or internal variability) is related to the natural variance of a subject's gait or population and it is affected by several factors such as: demographic (age, BMI, gender); pathologic (motor disorders); current physiologic (fatigue, pregnancy); and psychologic state (general mood) (Stansfield *et al.* 2001, Schwartz *et al.* 2004). This variability is related to the subject's condition at the moment of the measurement and cannot be reduced. Intrinsic variability relates to the inherent capacity of an individual to reproduce the same gait pattern across gait cycles and is increased for sessions performed with a considerable gap of time. This variability is considered as an indicator of motor disorder and is important to characterize a specific pathology. For example, muscle spasticity tends to augment the intrinsic variability within-subject at kinematic and spatio-temporal parameters (Steinwender *et al.* 2000). Additionally, intrinsic variability can be associated with aging as well as diseases such as Parkinson's and be used as an indicator of risk of fall (Hausdorff *et al.* 2001). In gait analysis, intrinsic variability can be analyzed by the variability observed between cycles of the same session (Srinivasan and Mathiassen 2012). In order to summarize the overall kinematic variability, the GaitSD has been proposed (Sangeux *et al.* 2016). It represents an index of variance among superposed gait cycles for kinematic data. This index has been demonstrated to be correlated with age (gait maturity), GDI, or motor selectivity in patients with CP (Tabard-Fougère *et al.* 2022).

1.9.2. Extrinsic variability

Extrinsic variability is linked to the error associated with the measurement of gait data. It is affected by a combination of different factors such as: the precision of the cameras, in detecting the exact position of each marker; errors in the calculation of gait data; estimation of gait events; soft tissue artefacts (STA) (segments do not act like rigid bodies due to relative movement of the soft tissues with respect to the underlying bones); and precision and accuracy on marker placement. Extrinsic variability is, in clinical interpretation, observed as a negative source of variability that induces confusion and reduces the trust of clinicians in the source of gait deviations. In dynamic data reported with a high amount of extrinsic variability expected, its information is typically neglected by clinicians.

Ideally, extrinsic variability would be eliminated while the intrinsic variability would be kept intact and without interfering with the validity of measured gait data. However, such an ideal is not possible for the state of the art of CGA. Due to the extreme importance of planning the best treatment for correcting motor disorders, measurement errors resulting from gait analysis are required to be

minimal (Bartlett and Frost 2008). Thus, it is then important to measure the levels of variability in order to validate measured gait data and to avoid being negatively biased in decision-making for treatments. Extrinsic variability can be assessed, for instance, by performing repeatability and reproducibility studies. This variability cannot be completely eliminated but can be reduced through quality improvements.

The intrinsic variability may be of interest to compare between different cohorts as it is an indicator of motor dynamic instability (Tabard-Fougère et al. 2021). On the one hand, excluding intrinsic variability from the clinical interpretation may suppress important information in the evaluation of motor disorders. On the other hand, considering intrinsic variability in clinical interpretation, in the presence of extrinsic variability, may result in an overestimation of gait deviations. In both cases, the result is an increase in the risk of leading to non-significant findings that can be a real indicator of motor disorders.

1.10. Sources of measurement error

1.10.1. Instrumental error

An additional part of the measurement error is attributed to the OSS used in gait analysis. In static and dynamic trials, the detection of markers in space is subject to errors caused by the measuring system (Croce and Cappozzo 2000, Conconi *et al.* 2021). Consequently, error in positioning the markers in space causes errors in the position and orientation of the rigid segments constituting the musculoskeletal model relatively to the global reference frame (Chiari *et al.* 2005). Some steps in which the OSS can cause those errors to relate to the calibration procedures and camera resolution. Posteriorly, the processing of data acquired from the OSS such as filtering and smoothing of marker coordinates may also introduce errors (Chiari *et al.* 2005). The state of the art of OSS used to measure the positions of reflective markers is satisfactorily advanced that there is probably no longer a significant source of error in CGA (Baker 2006). The errors associated with the marker positioning with respect to the global reference frame of the laboratory are generally reported to be within 1mm for the actual OSS used (Chiari *et al.* 2005, Carse *et al.* 2013). Therefore, the number of cameras, their disposition around the laboratory, the frequency of acquisition, lighting conditions, measurement, and calibration volume, and camera resolution affect the output gait data (Morlock *et al.* 2008). Eichelberger et al. (Eichelberger *et al.* 2016) compared the trueness and uncertainty of measurements in static and dynamic conditions for 6, 8, and 10 cameras and found better results with an increased number of cameras. To conclude, periodic assessment of the quality of the OSS used is recommended for each gait laboratory by precision and accuracy evaluations (Chiari *et al.* 2005, Benedetti *et al.* 2017).

1.10.2. Model calibration

1.10.2.1. Marker placement

Marker placement has been reported to be the biggest source of extrinsic variability (Besier *et al.* 2003, Gorton *et al.* 2009a). It consists of the lack of precision or/and accuracy in placing the markers over the anatomical landmarks caused by different factors. First, the experience and sensitivity of the evaluator to perform the identification of those landmarks by palpation is important to identify correctly the points where the markers should be tapped. It is important to refer to the anatomical landmarks as bony surfaces and not points, sometimes large and irregular (Della Croce *et al.* 2005). Rigid clusters or wands, generally, tapped on the side of the thigh and shank are susceptible to mislocations by the absence of underlying anatomical landmarks. Its placement relies on a visual alignment considering other markers instead of palpation. Second, underlying soft tissue such as adipose tissue, muscles, or tendons induces a determined level of uncertainty on the palpation of the anatomical point. Third, even though the same soft tissues do not significantly interfere with the palpation, sometimes create a gap between the anatomical point and its best location (Della Croce *et al.* 2005). For instance, when placing the markers of the anterior iliac spines on a subject with high subcutaneous abdominal adipose tissue, the bony landmarks may be easily palpable, but the marker will be placed at a considerable distance from it (Horsak *et al.* 2018, Horsak *et al.* 2021). Additionally, bony deformations, often observed in patients with motor disorders, may also interfere with the correct palpation of bony landmarks. Lastly, the identification of landmarks is dependent on the guidelines followed for placing palpating and placing the markers (Della Croce *et al.* 2005).

Some methods have been proposed to correct the extrinsic variability caused by marker placement. One study has evaluated the fusion of motion capture and 3D medical imaging (bi-planar x-rays) for that purpose (Gasparutto *et al.* 2020). An average reduction of the root mean square deviation by $-78\pm 15\%$ and range of variability by $-80\pm 16\%$ for the pelvis and hip kinematics was reported. However, despite proven a significant reduction of the extrinsic variability and consequent increase of repeatability in gait data, the identification of anatomical landmarks via medical imaging introduced a new source of extrinsic variability and more assessment is required. Additionally, the inclusion of this technique in CGA would involve a discussion regarding the use of radiation (especially in children) as well as an increase in the cost and time of data processing to the CGA. Another study has reported the effects of real-time feedback to improve marker placement precision among novice evaluators (Macaulay *et al.* 2017). An average reduction of 27% of the 95% confidence interval range of kinematic parameters (except hip on the transversal plane) was observed within the first day of practice. However, this method has not been validated by expert evaluators.

In conclusion, many factors are related to variability caused by marker placement. Those can be referent to the evaluator and amplified by inherent characteristics of the subject as a high level of underlying adipose tissue or by bony deformities (Della Croce *et al.* 2005). Training of evaluators and experience may also play a role in the precision of marker placement. One study did not find a significant correlation between measurement error in gait data measured by two evaluators with different experiences and suggested that experience has no impact on the reliability of output gait data as long as the evaluators are properly trained in palpation (Leigh *et al.* 2014). Contrarily, other studies have observed lower reliability on kinematics performed by novice evaluators placing the markers in the lower limb (Sinclair *et al.* 2014) and foot (Reay *et al.* 2022).

1.10.2.2. Segmental axis definition

Joint kinematics can be represented by a single unique vector (attitude vector or helical axis) and angle (helical angle) (Woltring 1994) or by a set of different rotations (Chao 1980, Tupling and Pierrynowski 1987). For the purpose of interpretability, three-dimensional angular kinematics are obtained using the Euler/Cardan technique instead of a single angle for the representation of joint motion (Sinclair *et al.* 2013). However, the magnitude of the three orthogonal angles of rotation depends on the sequence of rotation defined (Ying and Kim 2002). Studies have reported a significant influence on the sequence of rotation used for several kinematic parameters (Sinclair *et al.* 2013). A non-orthogonal joint coordinate system has been proposed to overcome those limitations, by including two axes embedded in the fixed and moving segments while a third axis (floating axis) is perpendicular to the other two axes (Grood and Suntay 1983). However, the non-orthogonal nature of this system presents drawbacks to the determination of joint forces and moments (Dumas and Cheze 2014). Finally, the computation of the Euler angles may also amplify the variability associated with extrinsic factors (Growney *et al.* 1997).

The determination of the axis of rotation is also considered an important cause of variability in kinematic data mainly as a consequence of marker placement and joint center estimation lack of precision and accuracy. For instance, the low repeatability generally observed in hip rotation is attributed to the difficulties in defining the secondary axis of the femur (Passmore *et al.* 2018). To reduce the dependence on marker placement, several functional methods have been proposed to redefine a particular axis. Regarding the femur segment, the medial-lateral axis is recalculated using the movement between the femur and tibia segments to determine the axis of rotation (Baker *et al.* 1999, Ehrig *et al.* 2007, Sangeux *et al.* 2017a, Passmore *et al.* 2018, Naaim *et al.* 2019). Those methods are affected by soft tissue artefacts and the quality and range of the calibration movement (Sangeux *et al.* 2017a). The validation of those methods with subjects has been done with the use of imagery to define the reference axis based on biplanar radiographs or free-hand ultrasound (Passmore and Sangeux 2016).

1.10.2.3. Joint centers and axes estimation

An accurate definition of the joint centers and axis of rotation is important for the calculation of kinematics and kinetics in 3DGA and requires efforts from the gait analysis community concerning the development and validation of methodologies for application in CGA (Stagni *et al.* 2000, Besier *et al.* 2003). The definition of the musculoskeletal model of the lower limbs relies on, not only on the skin mounted markers but also, on virtual markers representing the joint centers such as the hip, knee, and ankle (as explained in section 1.4.2.2). Several methods have been proposed to determine the different joint centers as predictive, functional, and imaging (*i.e.* free-hand ultrasound, x-ray) based methods (Peters *et al.* 2010, Assi *et al.* 2016, Hara *et al.* 2016). Predictive methods, based on markers and regression equations are the actual commonly most used methodology for estimating joint centers (or commonly called centers of rotation). Knee and ankle joint centers are typically calculated by the mid-point between the two markers placed in the femoral epicondyles and tibial malleolus, respectively (Davis *et al.* 1991). Contrarily to knee and ankle joint centers, the estimation of the hip joint center is not so simple due to its location. Typically, in a clinical context, some predictive methods based on regression equations have been applied are used to estimate the location of the hip joint center based on anthropometric measurements and the position of the pelvic markers (Bell *et al.* 1989,

Davis *et al.* 1991, Harrington *et al.* 2007, Hara *et al.* 2016). Those equations were calculated based on radiographic imaging including different characteristics such as age and gender. Most of those equations were calculated based on short sample sizes, not exceeding 32 subjects (Bell *et al.* 1989, Davis *et al.* 1991, Harrington *et al.* 2007). With a larger cohort of subjects ($n=157$) and incorporating age and gender, Hara *et al.* reported an improved accuracy in the determination of the hip joint center. However, due to marker placement errors and the unique morphology of each subject, those estimations are susceptible to mislocations (Stagni *et al.* 2000, Keizer and Otten 2020).

The CGM has been demonstrated to be highly sensitive to hip joint center mislocations in the hip and knee kinematics and kinetics. For instance, a 3 cm mislocation of the HJC resulted in an approximately 50% difference in mean flexion-extension hip moment through the gait cycle as well as kinematic data with a range of propagated error of the mean up to 32° on the hip and knee joints (Stagni *et al.* 2000). The generalization of regression equations through age, gender and populations (pathological gait is not considered) has a limiting effect on the accuracy of hip joint center location (Sangeux *et al.* 2014). No documentation was found reporting whether either this methodology is valid for children with motor disorders, including cerebral palsy. For example, a commonly observed characteristic of children with CP is hip dysplasia or deformity of the pelvis, thus it is unlikely that any form of predictive method (regression equation), reported to the moment, could be used in these patients to determine HJC position (Baker 2006).

The alternative for estimating joint centers to regression equations is the so-called functional calibration, which estimates the joint centers based on functional movements and reports improved accuracy (Sangeux *et al.* 2014). Several methods have been developed using functional calibration (Cereatti *et al.* 2009; Chang and Pollard 2007; Leardini *et al.* 1999; Piazza *et al.* 2004). However, functional techniques require additional movements demanding an amplitude of range of motion, and patients with motor disorders are often unable to perform the required movements and its implementation in a clinical context is still limited (Klejman *et al.* 2010, Sangeux *et al.* 2014). Using low-dose biplanar x-rays (EOS[®]; EOS imaging, Paris, France) as a reference, functional calibration techniques have been demonstrated to perform better than regression equations for asymptomatic adults (Sangeux *et al.* 2014). Contrarily, additional comparisons demonstrated better accuracy of regression methods in typically developing children and children with CP (Assi *et al.* 2016).

1.10.3. Anthropometric measurements

Anthropometric measurements as for example height, weight or segment height, or width are used to calibrate the biomechanical model in gait analysis. Using this information, allied with previously reported anthropometric scales and the static calibration, it is possible to estimate the joint centers (*i.e.* HJC, KJC, and AJC) positions. Therefore, errors in the measurement of anthropometric data can result in inaccuracy in the calibration of the biomechanical model. One study reporting the evaluation of the effects of inconsistent anthropometric measurements observed a variation up to 1.6° in joint kinematics (Krumm *et al.* 2016).

1.10.4. Soft tissue artefacts

STA is considered another important cause of extrinsic variability (Leardini *et al.* 2005). STA is referent to the motion of the subcutaneous tissues such as adipose tissue, muscles, or tendons associated with muscular contraction during gait as the markers attached to the skin are not rigidly

fixed to the underlying bones (Camomilla, Dumas, and Cappozzo 2017). Variability caused by STA is also augmented by increased adipose tissue and its magnitude has been difficult to determine (Peters *et al.* 2010). Ideally, pin markers mounted directly on the anatomical landmarks would reduce the effects of STA, however, this a technique is invasive for the patient and normal gait is compromised (Benoit *et al.* 2006). Alternatively, imaging techniques have been proven to provide information regarding the effects of STA. The errors associated with the underlying movement of soft tissues can reach the order of the joint movement evaluated (Camomilla *et al.* 2017). In biomechanical models like CGM, STA typically results in segment length inconstancy which is not specifically studied. Its impact on joint kinematics (excluding joint displacements by construction) remains unclear. Despite the high efforts done to evaluate and compensate for the effects of STA in kinematics, it remains one of the biggest issues in gait analysis: *“Despite the numerous solutions proposed, the objective of reliable estimation of 3D skeletal system kinematics using skin markers has not yet been satisfactorily achieved and greatly limits the contribution of human movement analysis to clinical practice and biomechanical research”* (Leardini *et al.* 2005).

1.10.5. Gait event detection

Gait event detection, namely foot-strike and foot-off, in gait analysis is typically estimated automatically through methods based on the trajectories of specific markers during gait (Zeni *et al.* 2008, Desailly *et al.* 2009, Osis *et al.* 2016). Foot-strike is, generally, used to divide gait data in different cycles and posteriorly superposed and normalized for the purpose of statistical analysis and interpretation. Within the defined gait cycles, foot-off is also used to define the swing and stance phases. Additionally, gait cycles are important to calculate spatio-temporal parameters. Thus, errors in the incorrect time identification of the sequential gait events cause a temporal shift of the data and consequently lead to errors in the normalization of gait data and inaccurate estimation of spatio-temporal parameters (Visscher *et al.* 2021). Even though that gait events detection is not performed at the time of gait data measurement it can be considered a measurement error. Recently, machine learning-based algorithms have been proposed to improve the accuracy and precision of gait event detection but require high-computational power and the time of processing is high compared to traditional methods (Lempereur *et al.* 2020).

1.10.6. Temporal data alignment

As previously described, continuous gait data (kinematic, kinetic, or electromyographic) are presented not as a single curve but as a superposition of curves, representing a complete gait cycle where time is normalized as a percentage of the gait cycle. Due to stride-to-stride (spatio-temporal) variability, the cyclic representation varies among the group of superposed cycles in terms of both amplitude and phase. More specifically, a temporal misalignment (or shift) between curves is observed and consequently can lead to increased amplitude variation. As a result, when computing the cross-sectional averages (*i.e.* mean, SD) between a group of superposed gait curves can lead to the suppression of critical shape characteristics and landmarks (Kneip and Gasser 1992). The curve misalignment in gait analysis may induce an additional issue when summarizing gait data as a series of superposed cycles during interpretation. Despite the existing methods for temporal alignment such as curve registration, which efficiently reduce those problems (Kneip and Gasser 1992, Sadeghi *et al.*

2000, Helwig *et al.* 2011), their application in data processing is not common in CGA (Chau *et al.* 2005). Moreover, when comparing gait data from a patient with a normative reference database either visually or either on the calculation of gait scores, the natural temporal differences inherent to pathologic gait (*i.e.* walking speed) are exacerbated. Evaluating the influence of temporal normalization in the calculation of GPS on a CP population showed little influence on the clinical interpretation, with 99% of the results showing a difference lower than the 1.6° considered in GPS as minimal detectable change (Armand *et al.* 2015).

1.10.7. Data interpretation

Data interpretation does not account for measurement error but it can be considered another source of variability in CGA. There is considerable disagreement among clinicians on the follow-up treatments to be planned using gait data (Skaggs *et al.* 2000). It is mostly a consequence of differences in treatment philosophy and experience. However, the confounding effect of the measurement errors and the subjectivity in assessing gait deviations contribute to this inconsistency (Schwartz *et al.* 2004). Thus, it is vital to estimate the sources of errors.

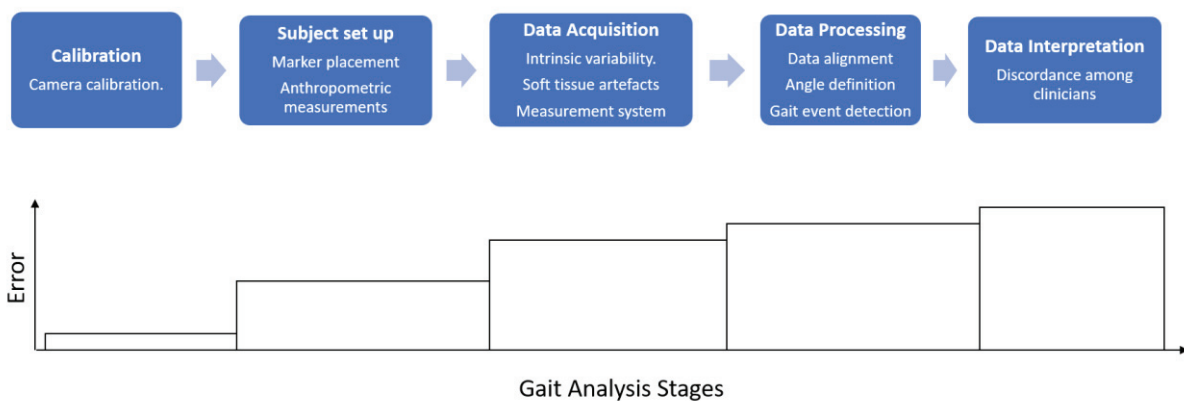


Figure 13. Cumulative sources of variability from calibration to data interpretation.

1.11. Quantification of measurement error in instrumented gait analysis

Three-dimensional (3D) CGA is considered a valuable tool in the assessment of gait disorders. However, following the concepts introduced in section 1.7.1, such an assumption needs to be sustained by several questions as: is the instrument used for measuring gait valid and reliable? Are the measurements performed by 3D CGA repeatable and reproducible? In order to answer to those considerations, several analyses are required to evaluate the reliability of the measurement system used. The most common strategy to evaluate it is by test-retest, which incorporates the repetition of 3D CGA under similar or different conditions. Thus, repeatability is generally quantified by repeating measurements on the same subject within a short amount of time (to reduce alteration of gait pattern), measurement system, and evaluator. In 3D CGA, if those measurements are not reliable, it is not possible to understand whether the data observed are the result of an intervention or instead

an error of measurement (Pini *et al.* 2022). Reproducibility is quantified by reproducing gait measurements by altering one of the conditions referred to for repeatability. The four main outcomes observed in literature for test-retest studies to quantify variability in 3D CGA are: 1) Intra-evaluator, commonly referred to as inter-session, is estimated by repeating 3D CGA under the same conditions and comparing the outcomes; 2) Inter-evaluator, estimated by reproducing 3D CGA under the same conditions by different evaluators and comparing the outcomes; 3) Intra-subject is estimated by comparing the outcomes resulting from the different trials/cycles within a session; 4) Inter-laboratory consists in the reproduction of 3DGA under the same conditions except for the measurement system used and comparing the resultant outcomes. By altering only one condition, it is possible to isolate and estimate the variation of those conditions. Here, it is important to consider the data curves obtained from gait kinematics or kinetics as divided into two components such as the true curve and an error component, where the error component consists of both systematic and random (Pini *et al.* 2022). Through test-retest situations, the error component can be evaluated by playing with the parameters that can induce a variation in the measurements. Taking into consideration that the variation can arise from intrinsic or extrinsic factors in the individual, Kottner *et al.* (Kottner *et al.* 2011) suggested that reliability should be defined as the ratio of variability between intrinsic variation (among individuals) to the total variability of all measurements in the sample.

Additionally, another relevant point for discussion when reporting test-retest measurements is the statistical metrics used and their relevancy for making conclusions regarding the reliability and errors of the 3D CGA measurements. Firstly, different approaches are required when evaluating curves or discrete parameters. For instance, the data relative to a curve are not independent and are treated as univariate data.

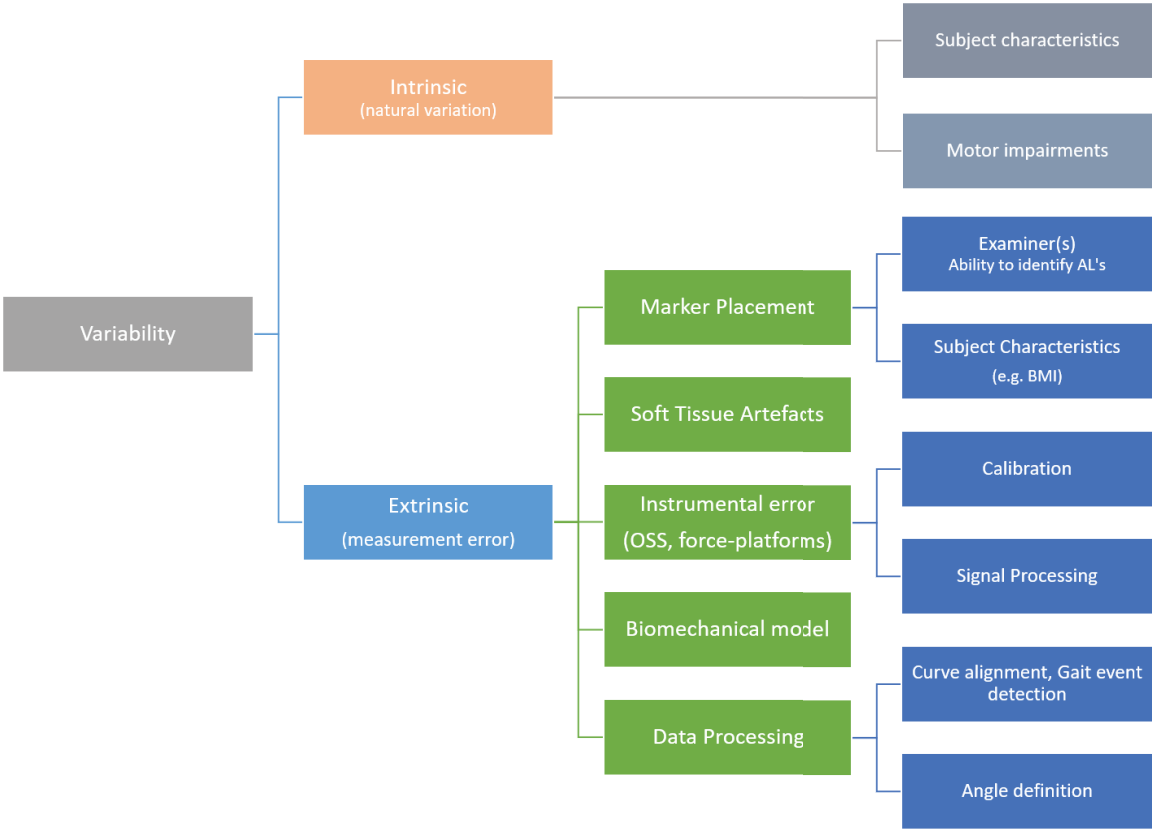


Figure 14. Sources of variability in empirical gait measurements.

1.11.1. Evaluate variability in gait analysis – Metrics

Several different analytical methods have been applied to estimate the variability in gait variables. The most used are the intra-class correlation (ICC), the coefficient of multiple correlation (CMC), standard deviation (SD), Root mean square difference (RMSD), standard error of measurement (SEM), smallest (or minimal) detectable change (SDC), coefficient of variation (CV) and limits of agreement. Moreover, an alternative to reporting a single number for reporting the variability is to define a prediction corridor to provide higher coverage than conventional standard deviation bands.

1.11.1.1. Intra-class correlation

Generally, ICC is the elected metric, among other correlation coefficients such as Pearson or Coefficient of multiple correlation, for calculating reliability in 3D CGA as it reflects both degrees of agreement and correlation between measurements. More specifically, it is used to evaluate inter-evaluator, intra-evaluator, and test-retest reliability (Koo and Li 2016). ICC ranges between zero and one, with one being the higher reliability. However, a high ICC does not necessarily mean lower variability as it can also be affected by various factors (Lee *et al.* 2012). ICC represents the part of the variance attributed to the inter-subject variance in comparison with the within-subject variance. Consequently, it is affected by the magnitude of the total variance calculated. For example, a cohort of healthy subjects show typically less between-subject variance, and thus ICC is expected to be lower than a pathological group of subjects that are expected to have higher between-subject variances (Meldrum *et al.* 2014). Thus, one of the limitations of ICC is attributed to the impossibility to compare the results obtained for different subject populations.

There are different formulas for calculating ICC and the choice of the appropriate form depends on different factors related to how the study is conducted and the number of measurements performed. Additionally, the proper form of ICC is required as an inappropriate selection of ICC perpetuates a risk that an incorrect level of reliability is estimated (Trevethan 2017). The majority of test-retest studies concerning 3D CGA provide insufficient or no details about the applied form of ICC (Lee *et al.* 2012). It can be determined using different models (one-way random, two-way random, or two-way mixed), forms (single or averaged measurements), and types (consistency or absolute agreement) (Lee *et al.* 2012, Koo and Li 2016, Trevethan 2017). The model and form of ICC defined should be represented when expressing this index, typically by two numbers within parenthesis (ICC(m,f), where m and f represent the model and form, respectively) (Koo and Li 2016, Trevethan 2017). The choice of the model depends on the sources of variability that interfere with the measurement. For example, when evaluating the intra-evaluator reliability, other sources of variability such as intra-subject variability are also inherent to the measurement.

Typically, the evaluation criteria and standard for ICC interpretation are accepted as: ICC from 0.75 represents excellent repeatability; from 0.4 to 0.74 represents adequate repeatability, and lower than 0.4 represents poor repeatability (Yavuzer *et al.* 2008). Those values may be altered considering the power of the ICC obtained, which is based on the sample size and number of repeated measurements performed (Bujang and Baharum 2017). The majority of the reliability studies insufficiently supported their decisions regarding the sample size and number of repetitions to ensure adequate power. Instead, most of those have considered a small sample size and thus the reliability estimates are prone to statistical error (Meldrum *et al.* 2014).

Table 4. ICC models and form selection.

Category	Research context and outcomes
Model	
1	A range of different subjects is assessed by different raters with no match between subjects and evaluators. This situation has not been observed in test-retest studies on gait measurement. This model typically produces lower ICCs than the other models.
2	Same evaluators assess all subjects and both are randomly selected. Thus, evaluators and subjects selected are representative of the population of not included evaluators and subjects. So to speak, the results represent a generalization of the measurement reliability through a different set of evaluators and subjects. This model is particularly appropriate to estimate the consistency of raters using the same measurement system.
3	Same evaluators assess all subjects. The difference with the Model 2 is that the evaluators selected are the only ones of interest for measurement purposes. The results represent a generalization of the measurement reliability through different sets of subjects. This model typically produces the highest ICCs than the other models.
Form	
1	On any occasion, only one measurement is performed by each evaluator from each subject for purposes of analysis.
2	Two measurements are performed for each subject, either two measurements performed by one evaluator or a single measurement performed by two evaluators. The results are averaged.
3	k measurements are performed for each subject, a single measurement performed by k evaluators. The results are averaged.

1.11.1.2. Coefficient of multiple correlation

The CMC examines the consistency of the measurements across the entire gait cycle and it is typically used in test-retest to evaluate the similarity between curves (Pini *et al.* 2022). Similarly to ICC, the range index of agreement is calculated for CMC between 0 (minimal agreement) and 1 (maximal agreement) (McGinley *et al.* 2009a). However, CMC has been proven to be strongly affected by several aspects such as the amplitude of movement (Steinwender *et al.* 2000, Mackey *et al.* 2005, Røislien *et al.* 2012). Thus, the interpretation of CMC is different for different dynamic data. Another reported drawback of the use of CMC is related to the dependency on gait cycle data which is not mitigated by its calculation. The result is that CMC increasingly underestimates the true variance as more sampling rate is defined on the measured data (Røislien *et al.* 2012). Considering those unfortunate conditions inherent to CMC calculation, many authors have discarded it for generalized reliability measurements of gait data. Additionally, a few authors considered the coefficient of multiple determination (CMD) for reliability analysis which can be also used to calculate the CMC by the positive square root of CMD (Steinwender *et al.* 2000). The coefficient of determination is a measure of how well the regression line represents the data. If the regression line passes exactly through every point on the gait cycle, it would be able to explain all of the variations. The further the line is away from the points, the less it is able to explain those. So higher the value better the model.

1.11.1.3. Standard error of a measurement (SEM) and minimal detectable change (MDC)

Information from ICC coefficients alone has limited utility in clinical practice, as it lacks in defining the magnitude of disagreement between different measurements as if the observed changes are due to actual change in performance. Thus, it is recommended the use more meaningful metrics that provide a magnitude of difference between two curves. Typically, ICC evaluations are accompanied by SEM and MDC.

Expressed as the actual units of measurements (*e.g.* angles in deg for kinematic data) SEM and MDC represent the indicator of absolute reliability. SEM is calculated as $SEM = SD\sqrt{1 - ICC}$, where SD represents the standard deviation of the measured sample. It represents an easy-interpretable value of the dispersion of measurement error around the mean (Klejman *et al.* 2010). A small value of SEM represents a high level of reliability. One of the advantages of considering the SEM for measuring the reliability of measurement is that it is not affected by the amplitude of the measured data (Atkinson and Nevill 1998).

MDC measures the amount of change between two repeated measurements and is considered as the minimal amount of change that is not likely to be due to measurement variation. Typically, MDC at 95% confidence is used to evaluate the minimal amount of change required to exceed the measurement error or to identify the gait parameters that are more sensitive to change in pathologic populations (Klejman *et al.* 2010, Hayakawa *et al.* 2020). However, the confidence interval (CI) used can vary, depending on the precision needed for the score estimate. The MDC is based on the SEM and is calculated as $MDC = CI * \sqrt{SEM}$ (Haley and Fragala-Pinkham 2006). Pathological populations are expected to have increased variation in performance over time and result in greater MDC. In case the MDC values of similar magnitude are observed when assessing non-pathologic populations, it would indicate limited usefulness for detecting all but the largest kinematic and kinetic changes (Wilken *et al.* 2012a).

1.11.1.4. Standard deviation (SD)

The standard deviation measures the amount of variability of a set of values. The standard deviation relies on an underlying normal distribution characterized by a “z-score” and is typically used to express how close the ‘next’ single measurement is likely to be to the mean of the underlying population. The term SD is often confused with SEM due to their similarity. As the SEM always gives lower values than SD for the same population, it is often tempting to use SEM to make the distribution of measurement better looking. The SD should be used to measure the variability within a group of individual measurements and to assess how close the next measurement is likely to fall to the mean of that population, the SEM should be used only to assess how the estimated means of groups of measurements relate to each other (Pleil 2016).

1.11.1.5. Coefficient of variation (CV)

The CV is another reported statistical tool applied in the literature to measure the reliability of a measurement. It can be calculated by dividing the SD by the mean and multiplying by a factor 100 (for CV%). However, and unlike SEM, CV applies to data in which the level of agreement between measurements depends on the magnitude of the measured parameters. Therefore, it assumes that the highest variation occurs in individuals with the largest measured parameters (Atkinson and Nevill 1998). Consequently, such a metric would be meaningless for that is measured around the zero level (including negative values of CV in some cases).

1.11.1.6. Limits of agreement

The limits of agreement, introduced by Bland and Altman (Bland and Altman 1986), is another indicator of absolute reliability (as SEM or CV). The advantage of using LoA is that it assumes a population of individual test-retest differences. The analysis of LoA incorporates an exploration of the test-retest data by a Bland-Altman plot, which plots the individual subject differences with the respective individual means (Bland and Altman 1986). In doing so, the direction and magnitude of the scatter data around the zero line provide insight into the systematic and measurement error, respectively (Atkinson and Nevill 1998). In case the correlation coefficient between the absolute differences and the individual means is close to zero and differences are normally distributed in the Bland and Altman plots, the LoA (95%) is calculated by simply computing the mean of the test-retest minus and plus $1.96 \times SD$. Thus, for 95% of CI, the calculated LoA should contain the difference between the measurements for 95% of future measurements (Atkinson and Nevill 1998).

1.12. Variability in gait analysis – state of the art

The general way for quantifying reliability and measurement error in 3DGA is by simply repeating the measurements on the same subjects on equal or altering conditions such as evaluator, measurement system, or biomechanical model. Table 5, describes the characteristics of a set of identified studies evaluating the reliability of 3D CGA to measure lower limb gait data. However, those studies presented high variability concerning inclusion criteria, protocol, measurement system, marker set, and statistical metrics applied. The magnitude of errors estimated also varied across gait variables and studies. This heterogeneity makes it difficult to compare all results and make objective conclusions.

1.12.1. Statistical metrics

One of the differences between studies is the statistical metrics used to calculate reliability vary among studies and as described above, their differences provide incomparable data and thus need to be considered differently. CMC and ICC are the most used indexes of reliability in clinical gait analysis studies. On the one hand, CMC is the preferred metric to evaluate waveform similarity for continuous data and its main limitation is its dimensionless nature and is affected by the magnitude of the

measurements. Thus, kinematic waveforms with a small range of values will show a small CMC and vice versa (Meldrum *et al.* 2014). On the other hand, ICC is usually applied for evaluating reliability on discrete points (*i.e.* at initial contact, mid stance, mid swing, toe-off, or minimal, maximal values and ROM) as points in the gait cycle are not independent (Noonan *et al.* 2003).

1.12.2. Variability related to the subject population

Approximately half of the reported studies included non-pathological population (M. P. Kadaba *et al.* 1989a, Growney *et al.* 1997, Della Croce *et al.* 1999, Steinwender *et al.* 2000, Ferber *et al.* 2002, Besier *et al.* 2003, Tsushima *et al.* 2003, Charlton *et al.* 2004, Schwartz and Rozumalski 2005, Monaghan *et al.* 2007, Leardini *et al.* 2007, Ferrari *et al.* 2008, McGinley *et al.* 2009a, Gorton *et al.* 2009a, Wilken *et al.* 2012b, Meldrum *et al.* 2014, Kainz *et al.* 2017, Rabuffetti *et al.* 2019). The majority of studies including pathological populations observed the reliability of patients with CP (Steinwender *et al.* 2000, Noonan *et al.* 2003, Mackey *et al.* 2005, Redekop *et al.* 2008, Klejman *et al.* 2010, Kainz *et al.* 2017, Ricardo *et al.* 2021) and some isolated studies included other pathologies such as scoliosis (Fortin *et al.* 2008), chronic low back pain (Fernandes *et al.* 2015), stroke (Yavuzer *et al.* 2008), osteoarthritis (Laroche *et al.* 2011) or knee prosthesis (Ferrari *et al.* 2008). Surprisingly, the inclusion criteria were typically not inclusive for patients with a need for assistive aids to walk (*i.e.* orthosis, canes). Information regarding the reliability of the system to measure gait data from those patients is of importance as it is commonly observed in CGA. Moreover, age and gender differences in reliability were also not addressed. Even though children may develop a mature gait pattern from 7 years of age (Sutherland 1980), they are associated with different morphology and anthropometric data (*i.e.* leg length), thus marker placement error may affect differently the level of misalignment of the segment coordinate systems. The palpation and marker placement may also be affected by the different characteristics of the subject's morphologies and genders, especially at the pelvis due to underlying adipose tissue (Moriguchi *et al.* 2009). However, no studies have been found with such analysis.

1.12.3. Instrumentation

The motion capture systems used are highly varied among authors. The most frequently OSS are constructed by VICON (Vicon Motion Systems, LA, USA), and the number of cameras varied from 2 (Della Croce *et al.* 1999) to 26 (Wilken *et al.* 2012a). Both camera definition, associated with the system used, frequency of acquisition, and number of cameras are prone to affect the reliability of the output kinematics and thus increase confusion in the comparison of test-retest outcome results (Eichelberger *et al.* 2016). No study was found evaluating the repeatability or reproducibility among different measurement systems.

1.12.4. Inter-trial variability

Intrinsic variability observed by many authors by the inter-trial (also commonly referred as intra-session) variation was demonstrated to be highly reliable for the overall data. The variance observed between different trials of the same gait session has been reported to be lower in comparison with

the variance between sessions which supports the observations that extrinsic variability has a major impact on the overall variability (Schwartz *et al.* 2004). Additionally, pathological subjects are associated with increased intrinsic variability for all dynamic parameters evaluated due to decreased ROM, reduced walking stability and motor control impairments, and adaptative strategies (Growney *et al.* 1997, Steinwender *et al.* 2000, Kainz *et al.* 2017). Moreover, Monaghan *et al.* (2007) observed reduced inter-trial variation when at least 10 trials were collected for kinematic and kinetic data. On the other hand, the reliability of spatio-temporal parameters was stabilized from two trials. Additionally, increasing walking speed reduced the level of reliability of several parameters (Fortin *et al.* 2008).

1.12.5. Intra- and inter-evaluator

One of the main general conclusions observed in the literature refers to marker placement as the biggest source of variability in CGA. One way of quantifying the measurement error resulting from marker placement is simply by repeating the measurement under the same conditions, including the evaluator (intra-evaluator), or by different evaluators (inter-evaluator). Consequently, the differences in mean data between the sessions provide information regarding the impact of marker placement inaccuracy or lack of precision in the output measured data. Results showed that repeated gait analysis sessions are typically more repeatable when the marker placement is performed by the same evaluator and both variabilities are lower than inter-trial reliability (intrinsic variability) (Schwartz *et al.* 2004). Additionally, SPT data are not significantly affected by marker placement and are generally associated with excellent reliability. The reliability to measure kinematic data with CGA is typically observed as very high for the sagittal plane while low to moderate is observed on the coronal plane and lower regarding the transversal plane (Charlton *et al.* 2004; Kadaba *et al.* 1989; Mackey *et al.* 2005; Schwartz *et al.* 2004; Tsushima *et al.* 2003). The explanation for supporting this observation may be the lower range of motion associated with those planes in walking (Growney *et al.* 1997, Steinwender *et al.* 2000). Moreover, marker placement variability typically translated to kinematic data as a vertical shift between the calculated gait curves but showed similar waveforms. Thus, using similarity indexes such as CMC may result in high levels of reliability (Røislien *et al.* 2012). For that reason, some authors decided to remove the offset when evaluating the reliability of the data (Growney *et al.* 1997; Leardini *et al.* 2007; Kadaba *et al.* 1989). However, removing the offset appears to make the calculation of reliability insensitive to apparent differences in gait (intrinsic variability) (Røislien *et al.* 2012).

The precision of marker placement for repeated measurements was also evaluated for intra-evaluator and inter-evaluator in two healthy adults (Della Croce *et al.* 1999). Their results showed a variance in the three-dimensional positioning of the markers in the pelvis and lower limb up to 21.0 and 24.8 mm for intra-evaluator and inter-evaluator, respectively. This precision translates into a variation of up to 10.9° in joint angles. Few studies have evaluated the effect of evaluators' experience in marker placement in kinematic variability. While one reported no difference between novice and expert evaluators (Leigh *et al.* 2014), another study showed significant differences in some discrete parameters in the coronal and transversal planes (Sinclair *et al.* 2014). Other studies evaluated the impact of marker placement error in calculated gait data by numerical simulations (Groen *et al.* 2012; Osis *et al.* 2016; Szczerbik and Kalinowska 2011). Kinematic values exceeding 10° for 10mm of misplacement were observed (Szczerbik and Kalinowska 2011a). Therefore, the impact of marker misplacement depends on the marker selected due to its role in the definition of segment coordinate systems and the direction of misplacements. For instance, the knee, shank and thigh markers in the

anterior-posterior direction showed the highest output kinematic variance. However, the identified studies did not apply the same evaluations on pathological gait and as marker placement-related variability results from the combination of the overall set of marker placement errors, an understanding of the impact of multi-marker misplacement is unknown. Finally, those results can serve to improve the understanding of how the placement of markers influences kinematics and consequently improve the precision of marker placement between evaluators by providing awareness in which markers and directions to pay additional verification and to direct the focus of future research to improve the correction of marker placement effect. Finally, a standardized procedure is globally applied for anatomical landmark palpation, following previously reported guidelines (Van Sint Jan 2007).

1.12.6. Inter-laboratory

Gait data acquired from different laboratories on the same subject are susceptible to several sources of variance such as the setup of the cameras and their resolution as well as other technical aspects, marker sets, methods for applying the markers, physical environment, and evaluators (Growney *et al.* 1997). Two studies evaluated the variability between laboratories (Noonan *et al.* 2003, Gorton *et al.* 2009a). In those cases, not only evaluators have altered but also the measurement system and biomechanical model. Apart from the high inter-laboratory variability observed by Noonan *et al.*, the differences between data did not only present an offset but also different gait patterns (Noonan *et al.* 2003). The analysis performed in different laboratories lead to a low to a fair level of agreement in final treatment recommendations with increased discordance with more severe impairments (Skaggs *et al.* 2000, Noonan *et al.* 2003). The low reliability and discordance reported initiated a debate regarding the usefulness of CGA for clinical applications since its cost-benefice is reduced if data is poorly reproducible. Gorton *et al.* showed that no standardization of the experimental protocols resulted in more than 75% of the total variance attributed to the marker placement (Gorton *et al.* 2009a). Guidelines for marker placement and perception of how the marker placement affects the segment coordinate system and how underlying soft tissues act during gait contributes to the majority of evaluator variance. By standardizing the experimental protocol, a decrease of up to 31% in the maximum difference was attributed to evaluators in kinematic data acquired from different laboratories (Gorton *et al.* 2009a). In conclusion, based on those results, the preferred recommendation is for acquiring gait data of a patient in the same laboratory and alternatively to standardize the methodology between the laboratories in which the patient undergoes gait analysis.

Table 5. Literature review on reliability studies by test-retest. A (Adults), C (Children), Y (Adolescents), H (Asymptomatic), KP (Knee prosthesis), AIS (Idiopathic scoliosis), OA (Osteoarthritis), KV (Knee varus), E(Evaluator), S(Session), D(Day), L (Laboratory), W (week), M (Month), NS (Not stated), IT (Inter-trial), IS (Intra-evaluator/inter-session), IE (Inter-evaluator), IL(inter-laboratory), IP (Inter-protocol), OptoSys. (Optoelectronic system used), Cam.(infra-red cameras).

First Author (year)	Population		Methodological		Gap time	Design						OptoSys (n°cam)	Biom. Model	Statistical tools
	n	Age	Pop.	E		IT	IS	IE	IL	IP				
Kadaba (1989)	40	A	H	1E, 3S, 3D	1	NS	x	x				Vicon (5)	CGM	Mean (SD), CV, CMC
Growney (1997)	5	A	H	1E, 1S, 3D	1	NS	x	x				ExpertVision (4)	CGM	Mean (SD), CV, CMC
Della Croce (1999)	2	A	H	IS:1E, 6S, 4L IE:6E, 1S	6	NS	x	x	x			Elite, B.T.S. Milan (2)	Cleveland	SD, RMS
Steinwender (2000)	40	C	H, CP	1E, 1S, 3D	1	< 1 W	x	x				MAC (6)	CGM	ROM, CMC, CV
Noonan (2003)	11	C, Y	CP	1S, 4L	4	6-20 W						Vicon370(3), HiRes(1)	CGM (3), Cleveland (1)	ICC, Vabs
Maynard (2003)	29	?	?	1E, 3S (n = 10) 3E, 3S (n = 10)	3	1 D, 1 W	x	x				CODA mpx30 (?)	NS	ICC, LoA, SEM
Tsushima (2003)	6	A	H	2E, 2S	2	2 W	x	x				Vicon 140 (4)	CGM	CMC
Besier (2003)	10	H	H	IS:1E, 2S; IE:1E, 1S	2	1 D	x	x	x			Vicon (6)	“Anatomical landmark”, FUN	CMD
Charlton (2004)	1	A	H	IE:2E, 1Sess.; IS:1E, 3S	3	NS	x	x	x			Vicon 512 (8)	CGM	Mean (SD)
Schwartz (2004)	2	A	H	4E, 3S.	4	NS	x	x	x			Vicon 512 (12)	CGM	SD
Mackey (2005)	10	C	CP	1E, 2S	1	1 W	x					MotionAnalysis (8)	Cleveland	CMC, MAD(°)
Monaghan (2007)	10	A	H	1E, 2S	1	1 W	x	x				CODA	Custom	ICC, LoA, Mean(SD), ROM(°)
Leardini (2007)	10	C	H	3E, 2S	3	NS	x	x	x			VICON 612 (8)	Total3Dg	Mean (SD), ROM
Ferrari (2008)	3	A	2H, 1KP	1E, 1S		NS				x		VICON 612 (8)	T3D, PiG, SAFLo, CAST, LAMB	MAV, Mean (SD)

Yazuver (2008)	20	A	S	1E, 2S.	1	1 D	x x	VICON 370 (5)	CGM	ICC, CV%, Mean(SD)
Fortin (2008)	20	Y	AIS	1E, 2S	1	5-10 D	x	Optotrak	Custom	SEM, Mean (SD)
Redekop (2008)	33	C	CP	1E, 1S.	1	NS	x	VICON MX (7)	CGM	ICC, SEM, ROM
Gorton (2009)	1	A	H	24E, 1S	24	3 M	x x	VICONx10(?),MACx2(?)	CGM	ANOVA
Klejman (2010)	20	C	CP	1E, 2S	1	3 W	x	VICON MX (?)	NS	ICC, MDC, SEM, Mean(SD)
Laroche (2011)	23	A	OA	1E, 2S.	1	2 W	x x	SMART (6)	NS	ICC
Wilken (2012)	29	A	H	2E, 2S	2	1W	x x x	MAC (26)	CGM	ICC, MDC, SEM
Stief (2013)										
	IT:									
		Y	IT: KV + H IS: H	IT: 1E, 1S IS: 1E, 2S	1	2 W	x	VICON (8)	Custom made, CGM	RMSD, ROM
	IS: 10									
Benedetti (2013)	1	A	H	1S, 7L.	7	1 M	x x	4xVicon, 3xBTS	4xCGM, 2xTotal3Dg, 1xCAS	Mean(SD), Pearson
Meldrum (2014)	30	A	H	1E, 2S	1	2 W	x	VICON (5)	CGM + KAD	ICC, LOA, MDC, Mean (SD), SEM
Kainz (2017)	11+7	C	CP + H	IS: 1E, 2 S; IE: 2E, 1S.	2	NS	x x x	VICON (8)	CGM, 6DoF-DK, 3-1-1DoF- IK, 3-3-2-DoF-IK	SEM, Mean (SD)
Rabuffetti (2019)	3	A	H	IS: 1E, 3S; IE: 6E, 1S.	6	NS	x x	LAMB	MAV	
Ricardo (2021)	8	C, Y	CP	1E, 2S	1	1 W	x	QTM (14)	CGM	ICC, SEM, Mean (SD), LOA

1.12.7. General considerations

In summary for the reliability of CGA data, spatio-temporal data are associated with excellent reliability. Kinetic data also showed good to excellent reliability. Therefore, the major problem resides in kinematics where reliability highly varies among studies and is reported from poor to excellent. In the sagittal plane, the reliability is generally reported as good to excellent while in the coronal and transversal plane the variability between gait sessions is considerably higher, especially for the transversal plane. Most of the studies reported SD of less than 5°, except for hip, knee, and ankle on the transversal plane (McGinley *et al.* 2009a). The main explanation for this reduced reliability is the effect of cross-talk and offset in kinematic computation (i.e. pelvis), whereby the inconsistent definition of the segment coordinate systems, the sagittal motion (that encompasses the major range of movement in the lower limbs) is translated to the other planes.

Based on the variability reported by test-retest studies, two maximum thresholds of variability were defined, for better confidence in the interpretation of kinematic data, to 2° and 5°, and defined as excellent and acceptable confidence, respectively (McGinley *et al.* 2009a). Thus, joint angle kinematics associated with variability over 5° should not be integrated into the gait reports, or from 2° to 5° should be considered with caution. This is the case for hip, knee, and ankle angles on the transversal plane. Therefore, hip rotation is generally included in the CGA to evaluate the gait of patients and is used to calculate gait scores. For instance, it is an important indicator of excessive femoral anteversion, often observed in patients with CP which supports and guides the decision for femoral derotation osteotomy (de Morais Filho *et al.* 2018). Removing hip rotation data from gait scores was shown to significantly improve gait scores on its ability to discriminate between patients from a control group due to its low reliability and high measurement error (Barton *et al.* 2019). An alternative to discarding information from gait data interpretation in clinical analysis, such as hip rotation is to adopt methods that are able to realign the segment coordinate systems based on *a priori* knowledge of the lower limb geometry and mobility.

1.13. Methods to reduce measurement error

We have seen above the current evaluation of the measurement errors in normal gait analysis as well as the main sources of such errors and their impact on output data as extrinsic variability. Therefore, this variability can be compensated or corrected. In the past years, several authors have proposed different types of methods to mitigate extrinsic variability. Those methods can vary on the application (*e.g.* marker positioning, joint center estimation, STA, axis definition, curve alignment, gait event detection) and methodology (*e.g.* optimization, functional or geometrical calibration, machine learning).

1.13.1. Biomechanical model calibration

In normal gait analysis, when one segment is calculated with respect to the coordinate system of another, artefacts linked with the motion of the markers due to STA or marker placement error can be amplified. Additional calibration of joint angles can mitigate those issues and reduce extrinsic variability. Those methods can be divided into: external devices; functional (Ehrig *et al.* 2007; Schache

et al. 2006; Schwartz and Rozumalski 2005); optimization (Reinbolt *et al.* 2005, Andersen *et al.* 2010); and fitting calibration techniques (Gamage and Lasenby 2002, Naa'im *et al.* 2019).

As previously described, the transversal plane is the least accurate and reliable parameter in kinematic data (Wren *et al.* 2013). It is mainly a result of the difficulty in correctly identifying the medial-lateral axis of the thigh and shank which is then considered a key factor to accurate measurement in gait analysis (Sangeux and Armand 2015). Error on the definition of the medial-lateral axis results in the translation of motion from the sagittal to the coronal plane, a phenomenon typically named as cross-talk effect. Thus, most of the corrective methods focus on the correction of the medial-lateral axis, more specifically relative to the thigh (Schache *et al.* 2006, Schwartz *et al.* 2014). Knee alignment device (KAD) is a rigid external device that is mounted on the subject's knee during the static trial and is constituted by three poles containing a reflective marker at the extremities of each pole. It is used to improve the definition of the thigh coordinate system and thus reduces errors in the definition of varus/valgus errors (Schache *et al.* 2006). Posteriorly, the origin of the KAD referential is replaced by the lateral femoral epicondyle marker for dynamic trials. The use of KAD may improve the reliability of gait data as it may decrease the impact of STA during knee flexion movement (Klejman *et al.* 2010).

Functional calibration corrects the orientation of a certain axis based on additional functional joint movement (Baker *et al.* 1999; Ehrig *et al.* 2007; Rivest 2005; Schache *et al.* 2006; Schwartz and Rozumalski 2005; Woltring *et al.* 1985). In the case of the correction of the medial-lateral axis of the thigh, a knee sagittal movement is tracked for calibration. An optimal flexion-extension axis is determined based on the calibration movement which is used to recalculate the anteroposterior axis (cross product with longitudinal axis), which is then used to calculate the medial-lateral axis (cross product with longitudinal axis) (Ehrig *et al.* 2007). One of the advantages of those techniques is that it does not rely on the location of the markers. Several limitations are attributed to functional methods with a special impact on clinical application. One of the limitations refers to the range of motion of the movement required for calibration may be not applicable in subjects with motor impairments and consequently limited range of motion on the sagittal plane (Besier *et al.* 2003). In addition, the existing methods consider the joint, to which the method is applied, as one (Woltring *et al.* 1985, Schwartz and Rozumalski 2005, Schache *et al.* 2006, Ehrig *et al.* 2007) or two (Baker *et al.* 1999, Rivest 2005) degree-of-freedom joint and consequently may mitigate intrinsic variability, an indicator of gait deviations (*e.g.* adduction-abduction and rotation mobility). The assumption of the joint as a hinge (1 DoF) makes it impossible to consider the crosstalk effect within the validation of the methods. Another limitation related to functional calibration methods refers to the fact that functional calibrations are still affected by STA (Peters *et al.* 2010). One study evaluated the performance of calibration methods with the simulation of marker placement error and STA, with Gaussian noise, and reported accuracy within 1° for a calibration movement above 45°, which is often not applicable in the clinical context (Ehrig *et al.* 2007). The identification of the position and orientation of the joint axes (together with other model parameters) can be also included in inverse kinematics procedures (Reinbolt *et al.* 2005, Andersen *et al.* 2010). One major drawback is the risk of overfitting. The joint parameters may be found out of physiological ranges to maximally reduce the tracking errors in the trajectories of the markers. It should, therefore, be verified that these tracking errors are matching the expected amount of STA (Begon *et al.* 2018).

Geometrical calibration is another type of axis correction which redefines *a-posteriori* as the segmental coordinate system based on segment geometry. One of the most recently reported methods redefines the medial-lateral axis of the thigh as the orthogonal to the mean plane joining the three joint centers (hip, knee, and ankle) during the phase of knee flexion over 20° (Naa'im *et al.* 2019).

This technique is also limited in clinical application due to the range of motion required for its applicability in patients with reduced knee flexion (*e.g.* stiff knee). An additional limitation to this type of approach is related to the fact that it considers segment geometry and thus it may be affected by skeletal deformities, also often observed in a clinical context. Results showed a reduction, but not completely, of the cross-talk effect on knee kinematics (Naaïm *et al.* 2019).

In sum, the application of numerical methods has proven to improve the determination of joint centers and axis of rotation and so decreasing the need for an accurate location of the anatomical landmarks by the skin markers (Besier *et al.* 2003). The application of such methods has been validated either *in-silico* (Ehrig *et al.* 2007) or *in-vivo* with the aid of mechanical devices (V. Camomilla *et al.* 2006) or by test-retest (Schache *et al.* 2006; Schwartz and Rozumalski 2005). The reference positions of markers and joint centers are typically considered with the aid of biplanar radiographs to allow the calculation of the method's accuracy (Sangeux *et al.* 2014, Sauret *et al.* 2016). Even considering its proven improvement on the biomechanical model calibration, its inclusion in CGA has been shortly reported due to the limitations presented above associated with intrinsic characteristics of the population with movement disorders.

1.13.2. Soft tissue artefacts

As previously described, STA refers to the relative movement between the skin markers and the underlying bone landmarks. Markers are used to define a segment as a rigid body but motion due to STA limits their riding nature (cluster). Consequently, the configuration of the markers used to define the segment coordinate system is altered inducing an error (deformation of the cluster of markers). The challenge in the gait analysis community is to use computational techniques to compensate for or reduce the effects of STA (Baker 2006, Camomilla *et al.* 2017). However, several methods that aim to compensate for the STA have been proposed (Camomilla *et al.* 2013; Leardini *et al.* 2017) but a globally accepted and validated solution remains unclear. Current methodologies applied in CGA do not incorporate any method that reduces or compensates for such an effect.

1.14. Thesis objectives and outline

3D CGA has proven to be an important tool for identification and follow-up for patients with movement disorders. Similarly to any other specialty concerning health care, an accurate functional diagnosis is essential for an optimized treatment decision to improve the quality of the patient's life allied with reduced treatment costs. In the case of gait analysis, an accurate treatment decision is associated with improvement of motor functions as well as a reduced number of interventions. However, measurement errors are inherent to gait analysis which increases the probability of misinterpretation of the outcome data and treatment decision-making. Thus, an extensive evaluation of the quality of measured gait data from current methodology and instrumentation is of great relevance for gait analysis as well as the implementation of methods to reduce measurement error.

The present thesis was conceived to address these issues. Three main goals were defined with the final goal of reducing the effect of measurement errors from CGA on clinical interpretation and consequently on the treatment decisions. The primary goal of this thesis was to extensively evaluate reliability and measurement error, with emphasis on the error associated with marker placement, as it was generally reported as the main source of variability in kinematic data from gait analysis. The second goal was to evaluate the application of new or existing methodologies for the reduction of variability. Lastly, the final aim was to apply the results obtained from the different studies performed to manage the variability of CGA in the report of gait data to improve clinical interpretation.

1.14.1. Outline

This thesis is organized into five main chapters (Figure 15).

The first chapter is merely introductory, intended to provide informative background and support for the contents presented in the thesis.

The second chapter is composed of a set of four studies aiming to quantify gait analysis variability and to evaluate the impact of different sources of variability, such as measurement error and joint axes definition. To evaluate the effect of marker placement, two studies based on numerical simulations (Articles 1 and 2) were performed with retrospective displacements of lower limb markers and a comparison of kinematics between original and simulated data. Complementarily, one experimental study evaluating the marker placement precision among four evaluators and its impact on kinematic data is presented. Finally, another study (Article 4) proposed an analytical model to evaluate the propagation of the error on the definition of the axis of the knee joint and estimate the effects of so-called "*crosstalk*" in kinematics.

The third chapter is composed of two studies intended to evaluate methods for reducing kinematic extrinsic variability. The first study presented (Article 5) evaluated the performance of different variations of the pyCGM2 toolbox as well as corrective methods to reduce the extrinsic variability in kinematics. The study was supported by an experimental protocol in pathological and asymptomatic populations. The second study (Article 6) describes a developed method to estimate gait events based on auto-selection among concurrent methods.

The fourth chapter is also composed of two different studies intended to apply variability to improve gait data interpretation. In the first study (Article 7), information acquired from the subjects

(i.e. anthropometric, age) and evaluators (i.e. experience, confidence in marker placement) were experimentally evaluated as an indicator of kinematic variability. To acquire marker placement confidence, one custom-made questionnaire has been proposed. The second study (Article 8), which is still in preparation, intends to develop a new gait score including variability as a weighting parameter for each input.

Finally, one general discussion is presented in the fifth chapter containing the main findings of the doctoral work, some limitations encountered as well as future perspectives.

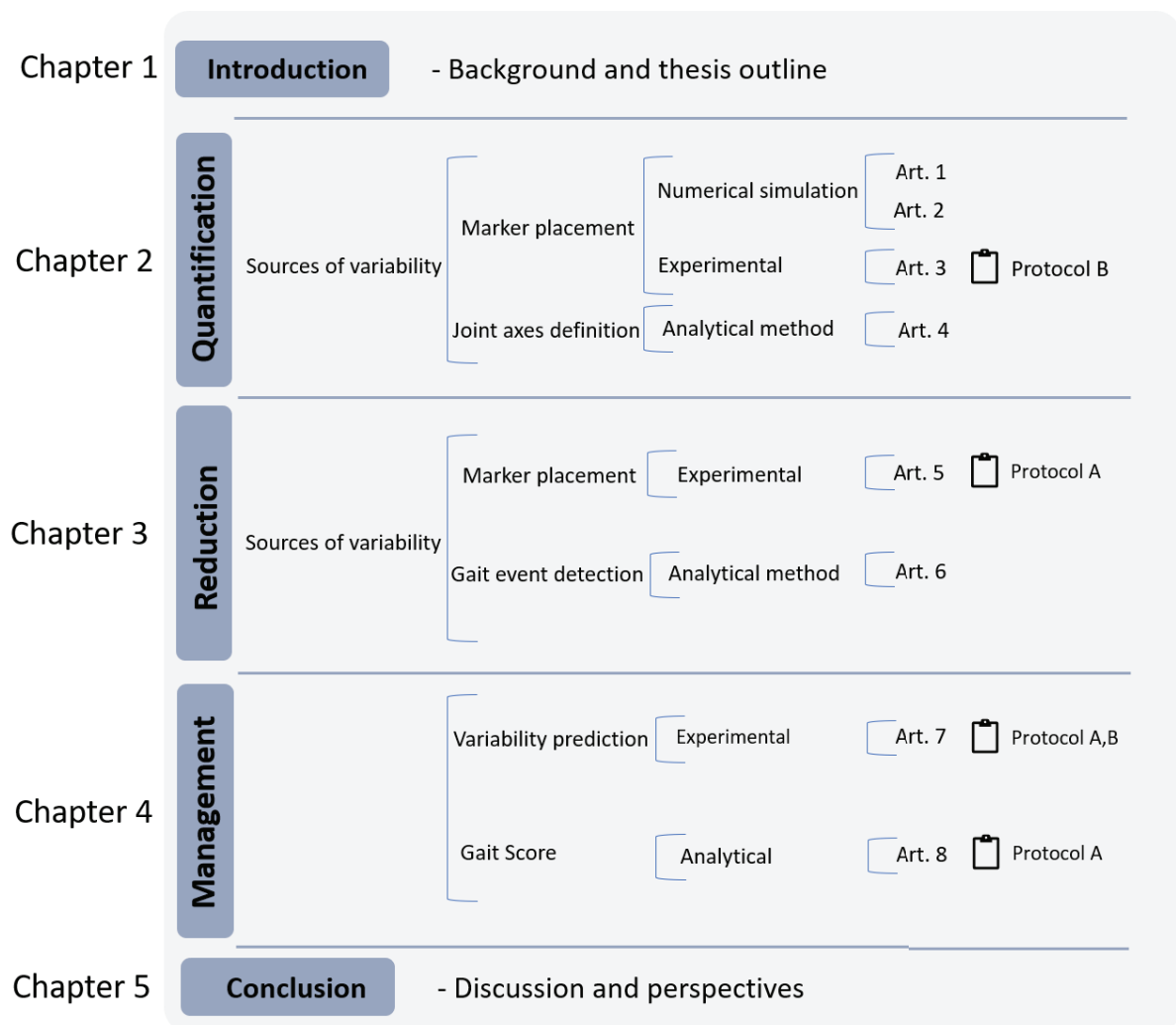


Figure 15. Graphic outline of the thesis.

1.14.2. Experimental protocols

Two experimental protocols have been designed, within the present doctoral work, to provide test-retest data to directly support three studies herein (Figure 16). A total of 64 participants were recruited for those protocols.

In **protocol A**, 54 participants were included, divided between patients with CP (n=24), asymptomatic participants (n=24), and patients with other motor diseases (n=8), (Figure 16, Protocol A). Protocol A was defined to support the findings of Article 5. Moreover, a heterogeneous population in terms of age was aimed (for CP and asymptomatic), and three sub-groups of eight participants were composed between children, adolescents, and adults. Additionally, the experimental protocol was composed of three sessions divided between two visits. Within the first visit, one evaluator (Figure 16, A1) was in charge of mounting the reflective markers on the participant as well as all the other steps of the gait analysis acquisition. The participant was then asked to perform static acquisition as well as walk barefoot on the walkway. Gait data acquisition was ended when at least five steps have been visually validated within the force platform, for each foot. The first visit, for the pathological population, coincided with a clinical analysis measurement. During the second visit (approximately one week apart), two gait analysis sessions were made. Within the first session, the same evaluator repeated the placement of markers followed by equal data acquisition. Finally, a second evaluator (Figure 16, A2) repeated the same process. Each session required approximately thirty minutes and only the evaluator in charge of the session was present, to limit familiarization with the subject.

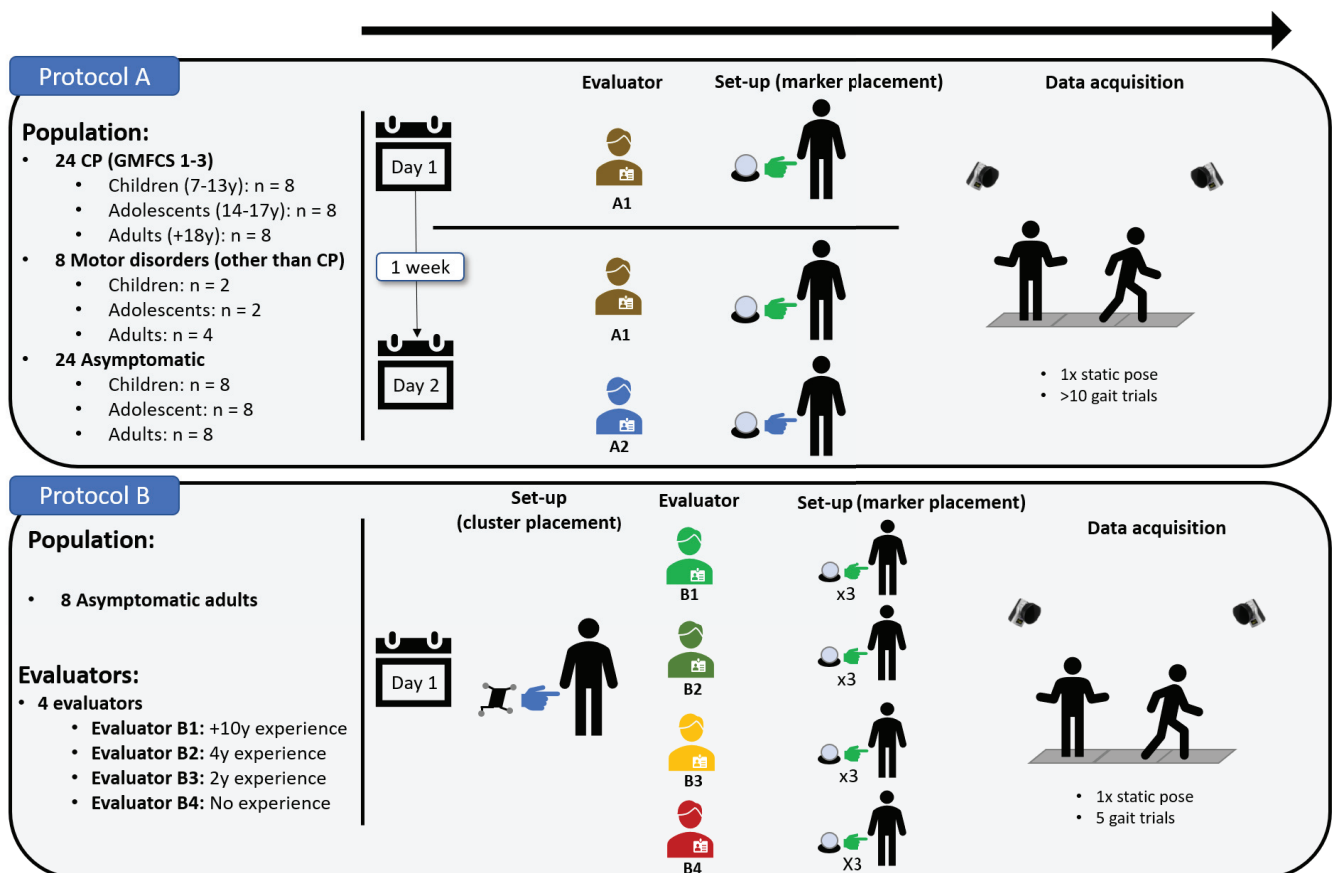


Figure 16 Graphical illustration of the two experimental protocols defined.

Protocol B was defined to support the findings of Articles 3 and 7. Eight asymptomatic adults and four evaluators were involved in the protocol. Evaluators were selected to form a group with different levels of experience. Thus, one experienced evaluator with more than ten years of regular experience in CGA, two evaluators with four and two years of experience in research practice, and one evaluator with no previous experience (but properly trained) were recruited for protocol B. Each participant visited the laboratory one time. Initially, anthropometric data were measured followed by the placement of clusters within each of the segments (pelvis, thigh, shank, and foot) and fixed with a bandage. After fixing the clusters, each evaluator performed, interspersed, three gait analyses each. Each gait analysis involved the placement of markers on the pelvis and the lower limbs, followed by one static pose acquisition and five gait trials. Between each session, the participant rested for 5 to 10 minutes, and no visible marks of previously placed markers were reported. The duration of each visit was approximately three hours.

Both protocols were done in the Kinesiology Laboratory Willy Taillard at the Geneva University Hospitals. The laboratory is equipped with a 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) to track marker trajectories and three force-platforms AccuGait, AMTI (Watertown, MA, USA) within a 10m walkway. All subjects were equipped with the CGM marker set (Davis *et al.* 1991) (14mm). Both protocols were approved by the “Commission cantonale d’éthique de la Recherche” of Geneva (CCER-2018-00229) and all participants provided written informed consent, signed by their legal guardian.

Chapter 2 - Quantification of Variability in Gait Analysis

When interpreting gait data, it is important to have an *a priori* estimation of how much can we trust the results. In order to do so, validity and reliability studies are required. Additionally, each of the sources of measurement error may impact differently the final output data. Therefore, it is also important to understand how the different sources of measurement error affect the gait curves. Different approaches can be applied to evaluate the outcomes under uncertain conditions. In gait analysis, those studies are generally performed experimentally, with a test-retest methodology and isolating parameters (*i.e.* evaluators, laboratories, instrumental system) which provide an estimation of the variability that can be attributed (expected) to those parameters. The advantage of this approach is the fact that it corresponds to a real representation of the outcomes. Alternatively, simulation (numerical) methods, such as Monte Carlo simulation (Banack et al. 2021), are based on the simulation of controlled uncertainties and evaluation of the outcomes. The main advantage of those methods is that it allows the simulation of a high number of situations (comparatively to experimental approaches) with a controlled input, which improves the robustness of the statistical analysis. However, some parameters associated with the simulated uncertainty may be suppressed. For example, if a simple displacement of a marker is simulated, the STA effect is not tracked. This chapter includes four articles that intend to quantify the variability in gait analysis as well as understand the impact of sources of measurement error such as marker placement and joint axes definition on kinematic variability.

Marker placement was previously described as the biggest source of gait data variability. Thus, the two first studies presented in this chapter aim to better understand how marker misplacement (or marker placement error) affects the reliability and validity of output kinematic data, calculated following the Conventional Gait Model. In order to do so, retrospective simulations were applied to induce error on marker location and compare the output with original kinematics. The first article, published in PLoS ONE (2020) presents the evaluation of simulated knee (lateral femoral epicondyle) marker displacements within a wide range of magnitudes and directions. The second article, published in Scientific Reports (2022), presents an evaluation of the impact of a combination of simultaneous displacement among eight markers of the pelvis and one lower limb, within the same magnitude and in four directions (the original position also considered), in a total of approximately 390 thousand different marker configurations. Both studies were supported by a set of gait data previously acquired on a cohort of ten typically developing children and ten children with CP. The third article aimed to evaluate, experimentally, the precision of marker placement among different evaluators, with different levels of experience as well as to link the evaluator's experience, precision in marker placement, and the output kinematic variability.

The highest reported variability in gait analysis is related to the definition of the medial-lateral axis of the femur, resulting in larger errors at the hip on the transversal plane. Therefore, the fourth article here presents an analytical model to quantify the impact of uncertainties, associated with the definition of the axes of the knee joint coordinate system.

[Additional note]

Article 1 refers to the simulation alteration of markers as “*marker misplacement*”. Despite the veracity of this term, it may lead to confusion with the error associated with marker placement. Thus, it was decided that “*marker displacement*” is more indicated to refer to the deliberate alteration of position. So, except for Article 1, all references to “*marker displacement*” are associated with intentional alteration of marker position, and “*marker misplacement*” refers to the unintentional error of the placement of markers.

2.1. **Article 1** - Impact of knee marker misplacement on gait kinematics of children with cerebral palsy using the Conventional Gait Model – A sensitivity study

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Communication:

Results presented at European Society for Movement Analysis in Adults and Children (ESMAC), September 2019 at Amsterdam, Netherlands, as podium presentation.

Keywords:

Marker placement; Gait analysis; Knee; Conventional Gait Model; Joint Angles; Kinematics; Sensitivity

2.1.3. Abstract

Clinical gait analysis is widely used in clinical routine to assess the function of patients with motor disorders. The proper assessment of the patient's function relies greatly on the repeatability between measurements. Marker misplacement has been reported as the largest source of variability between measurements and its impact on kinematics is not yet fully understood. Thus, the purpose of this study was: 1) to evaluate the impact of the misplacement of the lateral femoral epicondyle marker on lower limb kinematics, and 2) to evaluate if this impact can be predicted.

The kinematic data of 10 children with cerebral palsy and 10 aged-matched typical developing children were included. The lateral femoral epicondyle was virtually misplaced around its measured position at different magnitudes and directions. The outcome to represent the impact of each marker misplacement on the lower limb was the root mean square deviations between the resultant kinematics from each simulated misplacement and the originally calculated kinematics. Correlation and regression equations were estimated between the root mean square deviation and the magnitude of the misplacement expressed in the percentage of leg length.

Results indicated that the lower-limb kinematics is highly sensitive to the lateral femoral epicondyle marker misplacement in the anterior-posterior direction. The joint angles most impacted by the anterior-posterior misplacement were the hip internal-external rotation (5.3° per 10 mm), the ankle internal-external rotation (4.4° per 10 mm), and the knee flexion-extension (4.2° per 10 mm).

Finally, it was observed that the lower the leg length, the higher the impact of misplacement on kinematics. This impact was predicted by regression equations using the magnitude of misplacement expressed in percentage of leg length. An error below 5° on all joints requires a marker placement repeatability under 1.2% of the leg length.

In conclusion, the placement of the lateral femoral epicondyle marker in the antero-posterior direction plays a crucial role in the reliability of gait measurements with the Conventional Gait Model.

2.1.4. Introduction

Clinical gait analysis (CGA) is widely used in the clinical field to assess the functionality of the lower limbs in patients with motor disabilities such as cerebral palsy (CP) (Armand *et al.* 2016). This pathology is considered the most frequent cause of motor disabilities among children and CGA has been demonstrated to play an important role in supporting decision-making for treatment recommendations (Wren *et al.* 2011). In this examination, a set of skin mounted reflective markers is taped on specific bony landmarks on the skin. The three-dimensional coordinates of those markers are used to estimate the movement of the bones which constitutes the kinematic outcomes of gait analysis. An accurate assessment is essential to obtain appropriate outcomes and to make sound decisions for treatments. Thus, data arising from motion analysis needs to be reliable (McGinley *et al.* 2009b). The variability observed in gait data is a consequence of several factors including the measurement system (Chiari *et al.* 2005), the soft tissue artefacts (Leardini *et al.* 2005, Camomilla *et al.* 2017) and the marker placement (Della Croce *et al.* 2005b). The latter has been identified as one of the largest sources of variability in gait analysis and leads to an improper reconstruction of the local coordinate systems used to compute the outcomes of the assessment (Gorton *et al.* 2009a). More specifically, an average inter-therapist variability up to 9.8 mm on the anterior-posterior (AP) direction was found for the placement of the lateral femoral epicondyle (KNE) among two adults (Della Croce *et al.* 1999). Finally, to our knowledge, there is no published evaluation of uncertainty in marker placement in the population of children, whether they have CP or are typically developing.

Several reliability studies focused on evaluating the variability induced by marker misplacement over different conditions. Most of the studies (Schwartz and Rozumalski 2005, McGinley *et al.* 2009b, Wilken *et al.* 2012b) reported average kinematic errors of 6° (but up to 25°) in some peak angles among different testers which overcomes the 5° considered as the limit of acceptability by the gait analysis community (McGinley *et al.* 2009b). In addition, a few studies performed over different laboratories observed values of variability reaching up to 34° for hip rotation (Gorton *et al.* 2009a). However, the lack of standardized marker placement protocol and anatomical reconstruction was considered as the main factor for the high variability encountered between laboratories (Gorton *et al.* 2009a).

The Conventional Gait Model (CGM) (Davis *et al.* 1991) is one of the most used biomechanical models in clinical practice (Jensen *et al.* 2016). This model defines the lower limbs through a set of seven segments (pelvis, thighs, shanks, and feet). It is characterised by the computation of the kinematic output through a hierarchical top-down process (Baker *et al.* 2017). Specifically, the KNE marker is involved in the construction of both the thigh and shank longitudinal axis as it is used to define respectively the endpoint and origin of these two segments, i.e. the knee joint centre. It is also used to define the medial-lateral axis of the thigh. Thus, misplacement of KNE marker directly influences the hip, knee and ankle angles with the CGM settings.

Despite broad application in clinics, little has been published about the sensitivity of CGM to marker misplacement. Thus, understanding the influence of marker misplacement on kinematics is critical to obtain a proper interpretation of gait data. Thereby, a few authors studied the influence of marker misplacement on kinematics in adult populations, either by systematically changing a marker position between sessions (Szczerbik and Kalinowska 2011b, Groen *et al.* 2012) or by retrospectively simulating a virtual misplacement (Kadaba and Ramakrishnan 1990, Osis, Hettinga *et al.* 2016b). All those studies with the exception to one (Osis *et al.* 2016b) relied on the CGM. Kadaba *et al.* (Kadaba and Ramakrishnan 1990) evaluated the sensitivity of knee joint angles to the definition of the femoral mediolateral axis of the CGM in a group of 40 asymptomatic young adults. The authors analytically altered the orientation of this axis up to $\pm 15^\circ$ and observed that knee adduction-abduction and internal-external rotation were considerably affected (up to 15°). In an experimental study using CGM, Szczerbik and Kalinowska (Szczerbik and Kalinowska 2011b) applied systematically a bidirectional shift

of 14 mm in the anterior-posterior and proximal-distal direction on the KNE marker to an adult with knee hyperextension and a sixteen year old girl with CP. Their results showed a maximum of 25° of variation on joint angles, with more incidence on the internal-external rotation for the overall joint angles. Finally, sensitivity analysis by Baker (Baker *et al.* 2017) performed on the CGM showed errors up to -1.8° of hip internal rotation and 2.2° of knee flexion for a misplacement of the KNE marker 5 mm on the anterior and proximal direction. All other angles showed a variation lower than 0.4°, however, no information was provided regarding the methodology of their analysis. Using an alternative model based on the marker set reported by Pohl *et al.* (Pohl *et al.* 2010), Osis *et al.* [17] simulated a misplacement of several markers independently over a population of 411 adults with common running injuries. They observed errors up to 5.1° and 0.6° each 10 mm of KNE marker misplacement in the AP and proximal-distal (PD) directions respectively.

To better understand the relationship between KNE marker misplacement and kinematics, it is important to perform a complete analysis by considering the concomitant effect of direction and magnitude of marker misplacement with populations encountered in clinical practice. To our knowledge, no study using specifically the CGM has considered the impact of KNE misplacement combining both multiple directions and magnitudes of misplacement. Moreover, most of these studies were made with healthy adults. Due to skeletal deformities and altered gait patterns, the results from the studies performed on adult subjects cannot be generalized to children, especially with CP. It can also be anticipated (according to trigonometric rules and differences in size) that the errors in the kinematics would be amplified in children for a similar misplacement error. Thus, the aims of the present study were: 1) to evaluate the sensitivity of the CGM model to marker misplacement of the lateral epicondyle marker within children with CP and 2) to identify a potential correlation between root mean square deviation (RMSD) error and misplacement magnitude normalized by the anthropometric parameters of the patients.

2.1.5. Materials and Methods

Data Collection

This study was approved by the “Commission Cantonale d’Éthique de la Recherche” of Geneva (CCER-2018-00229) and all participants provided written informed consent. Gait data of ten children (6 males and 4 females, mean (standard deviations), [range]: 12.4 (4.7), [6-18] years; height: 150.0 (22.7), [119-187.5] cm and weight: 45.1 (26.4) [14.8-106] kg) with CP (GMFCS level I-II; five bilateral and five unilateral) acquired during clinical routine were retrospectively included. The height of the participants presented, intentionally, a large range with a stepwise increase of 7.7 ± 2.0 cm (mean \pm standard deviations) between participants. Ten typically developing children (8 males and 2 females, mean (standard deviations), [range]: 13.7 (3.16), [9-18] years; height: 160.8 (19.1), [127-191] cm and weight: 49.5 (17.7), [24-83] kg) was included as a control group. One experienced examiner with more than 10 years of regular practice in marker placement and that follows guidelines for marker placement and anatomical palpation (Van Sint Jan and Della Croce 2005) has performed the marker placement.

Testing Procedure

The workflow of the study is represented in Figure 17. The anthropometric data (leg length, knee and ankle width, height, and weight) were collected by experienced physiotherapists. Then, participants were equipped according to the CGM marker set (Davis *et al.* 1991) (12.5mm) and asked to walk barefoot at a self-selected speed. A 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) tracked the marker trajectories at 100Hz. Gait kinematic was processed with the Vicon PiG clone, provided as CGM1.1 by the open-source library PyCGM2, which requires a static trial for calibration (Leboeuf *et al.* 2019). In agreement with the original version of the CGM (Baker *et al.*

2017), the coronal plane of the femur was constructed from the hip joint centre, the KNE, and the lateral thigh wand mounted marker. A systematic offset was introduced to the KNE marker along the AP and PD axis of the thigh to create a virtual marker. Virtual markers were placed every 45° around the original position at five different magnitudes (distance from the original marker): 5, 10, 15, 20, and 30 mm leading to a total of 40 virtual misplacements of the KNE position for each patient. The equation (1) estimates the new position of the KNE marker (KNE_{misp}) as a result of the sum of the original position (KNE_{ori}) on the segment coordinate system with an error (E) defined in function of magnitude (ϵ) and direction (θ).

$$KNE_{misp} = KNE_{ori} + E(\epsilon, \theta) \quad (1)$$

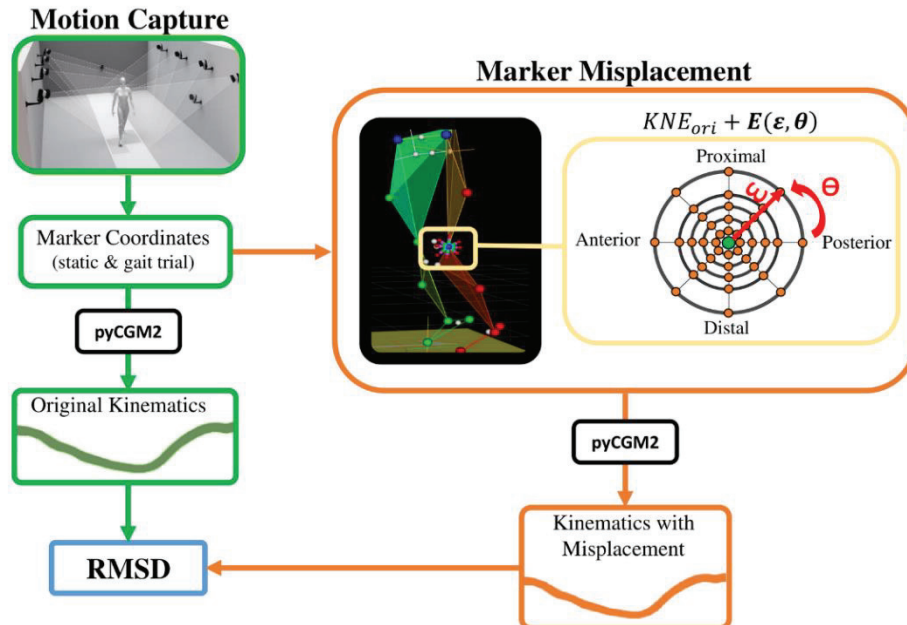


Figure 17. Workflow for sensitivity analysis. From gait measurement, one static and one gait trial were considered. The original marker set was used to calculate the reference kinematics (green path). Coordinates of KNE marker were systematically misplaced as a function of angle direction (θ) and magnitude (ϵ) and the kinematics was calculated for each misplacement (orange path). Finally, the RMSD was calculated as a function of each misplacement kinematics (Err_i) and the reference kinematics (O_i) (grey).

Statistical analysis

The quantification of the influence of each misplacement on the kinematics was assessed by the RMSD between the originally calculated angle value and the angle resultant from the misplaced KNE marker (2):

$$RMSD = \sqrt{\frac{\sum_{i=1}^n (Err_i - O_i)^2}{n}} \quad (2)$$

where n is the number of frames, O_i is the original angle and Err_i is the angle resultant from marker misplacement. Discrete and continuous parameters of the gait cycle were considered.

Values of error under 2° were considered as within the optimal value, errors between 2° and 5° were considered within the acceptable interval and errors above 5° were considered too high for

clinical interpretation as previously reported (McGinley *et al.* 2009b). Finally, the coefficient of correlation between the RMSD with the misplacement magnitude normalized by leg length and knee width was estimated by a Pearson correlation. Altman's guidelines were used to interpret the correlation as: poor if $R \leq 0.2$, fair if $0.2 < R \leq 0.4$, moderate if $0.4 < R \leq 0.6$, good if $0.6 < R \leq 0.8$, and very good, if $R > 0.8$ (Bland and Altman 1986). Slope (m) and y-intercept (b) were also calculated for each regression line between RMSD error and percentage of leg length (see Supporting information S1).

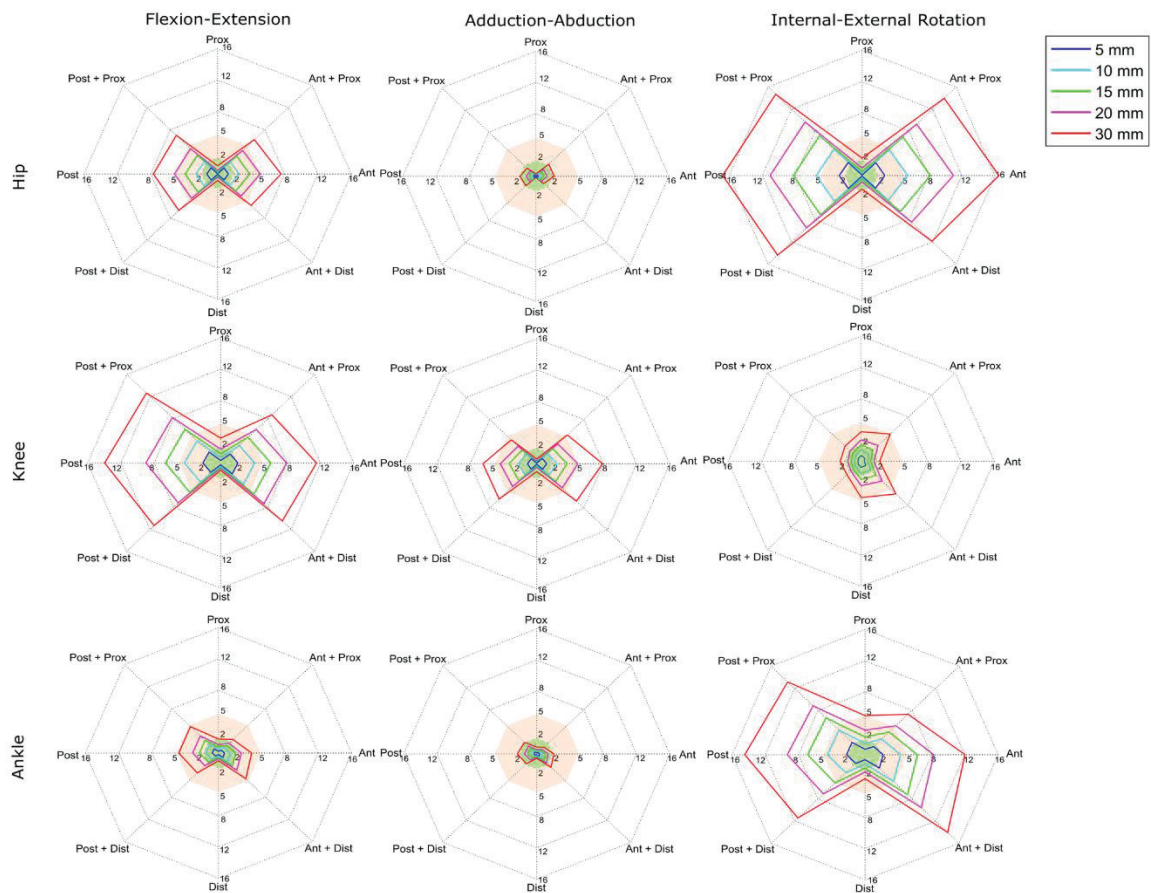
2.1.6. Results

Figure 18 and Table 6 report the RMSD of the kinematics according to each of the misplacements simulated for the whole group of patients. Figure 18 shows that the most affected joint angles are the ankle and hip internal-external rotation and knee flexion-extension as a result of a misplacement in the AP direction. Table 6 provides information relative to the errors resulting from a 10mm misplacement of the KNE marker for both CP and TD group. In the AP direction, hip internal-external rotation RMSD (5.5°) is above 5° while for a misplacement in the PD direction no joint angles were above this value. The lowest error for a misplacement in the AP direction was observed on the hip and ankle adduction-abduction with a RMSD up to 2.1° for a magnitude of misplacement of 30mm. RMSD differences between CP and TD groups were not statistically significant with an exception for the hip flexion-extension. Contrarily, the largest RMSD for the same magnitude, on the AP direction were observed for the hip and ankle internal-external rotation and knee flexion-extension angles with RMSD up to 16.4° , 14.1° , and 13.5° , respectively. Misplacement in the PD direction induced considerably less impact than in the AP direction except for the knee angle in the transversal plane (up to 6.5°).

Table 6. RMSD (standard deviations) representing kinematic impact after 10 mm KNE marker misplacement. Values of RMSD represent the mean difference observed among both populations considering the complete gait cycle and for the CP group considering. Bold fonts represent the values of RMSD over 2°. RMSD differences between CP and control group (TD) were evaluated by the p-value for AP and PD directions. Values with (*) indicate a significant difference between the two groups (p-value < 0.05). GC: Gait cycle, TD: Typically developed.

Joint	Angle	Anterior		Posterior		Proximal		Distal	
		CP	TD	CP	TD	CP	TD	CP	TD
Hip	Flexion peak	2.54 (0.5)*	2.29 (0.1)	2.58 (0.6)*	2.29 (0.1)	0.11 (0.1)*	0.04 (0.0)	0.10 (0.0)*	0.04 (0.0)
	Flexion-Extension GC	2.57 (0.5)*	2.26 (0.1)	2.59 (0.6)*	2.25 (0.1)	0.11 (0.1)*	0.04 (0.0)	0.10 (0.0)*	0.04 (0.0)
	Adduction peak	0.63 (0.4)	0.4 (0.2)	0.55 (0.4)	0.38 (0.2)	0.03 (0.0)	0.01 (0.0)	0.02 (0.0)	0.01 (0.0)
	Adduction-Abduction GC	0.63 (0.4)	0.4 (0.2)	0.56 (0.3)	0.39 (0.2)	0.03 (0.0)	0.01 (0.0)	0.02 (0.0)	0.01 (0.0)
	External Rotation peak	5.19 (1.4)	5.45 (0.2)	5.21 (1.3)	5.44 (0.2)	0.22 (0.1)	0.09 (0.0)	0.20 (0.1)	0.09 (0.0)
	Internal-External Rotation GC	5.46 (1.3)	5.61 (0.2)	5.48 (1.3)	5.55 (0.2)	0.23 (0.1)	0.1 (0.0)	0.21 (0.2)	0.09 (0.0)
Knee	Flexion peak	3.39 (0.4)	3.04 (0.3)	3.73 (0.5)	3.39 (0.4)	1.31 (0.3)	0.81 (0.4)	1.03 (0.3)	0.77 (0.3)
	Flexion-Extension GC	4.07 (0.7)	3.81 (0.4)	4.33 (0.8)	4.02 (0.4)	0.72 (0.2)	0.54 (0.3)	0.42 (0.1)	0.55 (0.3)
	Adduction peak	3.39 (1.3)	3.51 (1.6)	3.55 (1.4)	3.23 (1.5)	0.12 (0.1)	0.10 (0.1)	0.33 (0.2)	0.11 (0.1)
	Adduction - Abduction GC	2.42 (0.5)	2.52 (1.4)	2.23 (0.5)	1.97 (1.5)	0.14 (0.1)	0.10 (0.1)	0.15 (0.1)	0.1 (0.1)
	External-Rotation peak	0.60 (0.7)	0.42 (0.2)	0.62 (0.8)	0.42 (0.2)	2.21 (0.9)	2.20 (0.9)	2.16 (0.8)	2.19 (0.9)
	Internal-External Rotation GC	0.74 (0.6)	0.46 (0.2)	0.77 (0.7)	0.49 (0.2)	1.49 (0.4)	1.49 (0.9)	1.59 (0.4)	1.55 (0.9)
Ankle	Flexion peak	0.87 (0.3)	0.81 (0.3)	1.10 (0.2)	0.91 (0.3)	0.51 (0.3)	0.41 (0.2)	0.43 (0.3)	0.41 (0.2)
	Flexion-Extension GC	1.39 (0.3)	1.18 (0.4)	1.49 (0.4)	1.22 (0.3)	0.49 (0.2)	0.37 (0.2)	0.40 (0.2)	0.38 (0.2)
	Internal-External Rotation GC	4.25 (0.5)	3.86 (0.9)	4.51 (0.5)	4.05 (0.8)	1.03 (0.2)	1.26 (0.7)	1.23 (0.3)	1.32 (0.8)

Figure 18. Impact of KNE marker misplacement on kinematics. Polar plot representing mean RMSD between marker misplacement and the original position of the overall population of participants respective to each magnitude and direction of misplacement. Green and orange area represent the thresholds of $<2^\circ$ (Optimal) and $<5^\circ$ (Acceptable) respectively.



Offsets were observed between the curves representing different magnitudes of misplacement among the same directions for most of the joint angles (Figure 19). However, the knee adduction-abduction angle showed more of a change in amplitude than offset as a function of the KNE marker misplaced in the AP direction. Indeed, the differences were mainly in peak values between the curves (i.e. cross-talk phenomenon).

The correlation calculated between RMSD and misplacement magnitude expressed in percentage of leg length (Table 7) revealed a very good relationship ($R > 0.9$) for most of the angles with an exception for the ankle adduction-abduction and the knee internal-external rotation for which the correlations were moderated ($R < 0.61$) through AP direction.

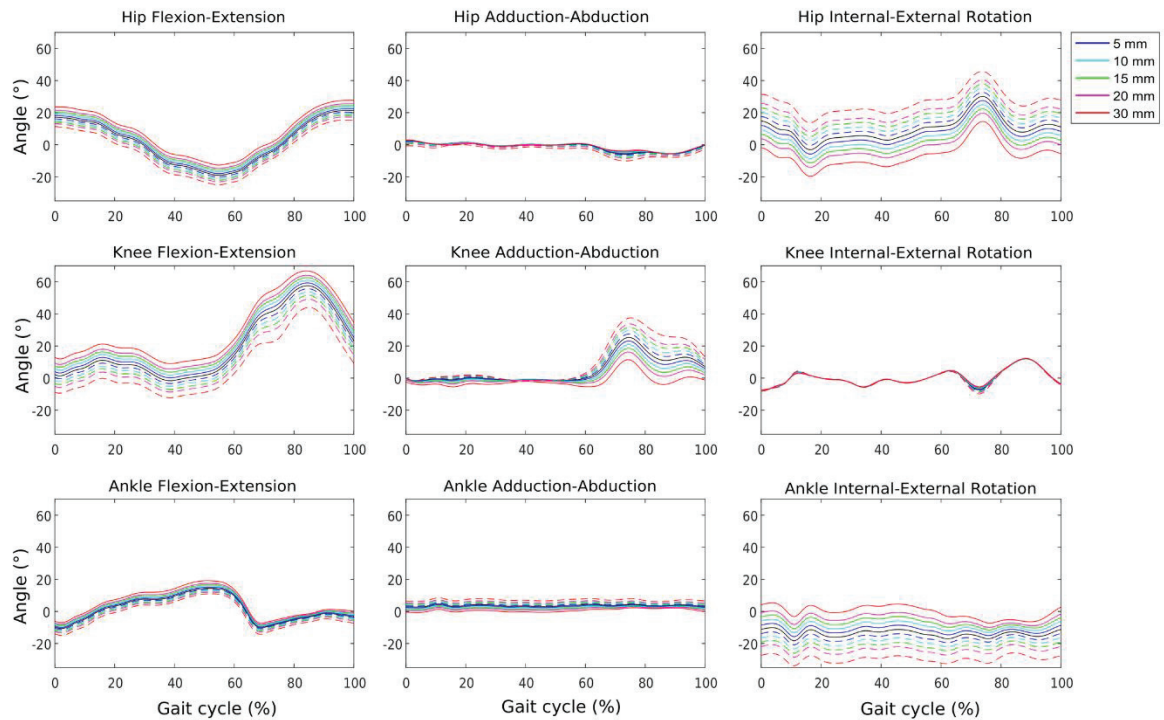


Figure 19. KNE marker misplacement on anterior-posterior direction. Kinematic deviations resultant from KNE marker misplacement on the anterior (solid lines) and posterior (dashed) directions at different magnitudes for one participant. One gait cycle is represented per condition.

Joint	Angle	Anterior		Posterior		Proximal		Distal	
		CP	TD	CP	TD	CP	TD	CP	TD
Hip	Flexion-Extension	0.99	0.99	0.98	0.99	0.95	0.96	0.95	0.97
	Adduction-Abduction	0.75	0.77	0.54	0.67	0.78	0.74	0.75	0.76
	Internal-External Rotation	0.91	0.94	0.90	0.94	0.91	0.95	0.91	0.96
Knee	Flexion-Extension	0.98	0.96	0.97	0.95	0.97	0.97	0.91	0.97
	Adduction-Abduction	0.90	0.87	0.90	0.83	0.84	0.78	0.82	0.77
	Internal-External Rotation	0.58	0.61	0.59	0.71	0.83	0.93	0.92	0.96
Ankle	Flexion-Extension	0.96	0.85	0.94	0.84	0.94	0.88	0.86	0.78
	Adduction-Abduction	0.61	0.64	0.59	0.57	0.67	0.61	0.59	0.64
	Internal-External Rotation	0.91	0.89	0.92	0.90	0.94	0.94	0.83	0.82

Table 7. Correlation coefficients R between RMSD and magnitude of misplacement in the percentage of leg length for both groups. All correlations resulted in a p -value < 0.001 . TD: Typically developed children.

2.1.7. Discussion

The objectives of this study were 1) to evaluate the sensitivity of the CGM model to marker misplacement of the lateral epicondyle marker within children with CP and 2) to identify a potential correlation between the error on kinematics and the misplacement magnitude expressed in the percentage of anthropometric parameters of the patients. Our results demonstrated that the largest error on the kinematics introduced by the KNE marker when misplaced in the AP direction (Figure 18 and Table 6), which is in agreement with previous studies (Della Croce *et al.* 1999, Szczerbik and

Kalinowska 2011b, Osis *et al.* 2016a, Baker *et al.* 2017). The most altered angles were the hip internal-external rotation, the ankle internal-external rotation, and the knee flexion-extension. These angles reached values over the 5° threshold for magnitudes of misplacement between 10 and 15 mm (Figure 18). Furthermore, knee adduction-abduction and hip flexion-extension were moderately affected as they presented an error over 5° only when the misplacement magnitude was above 20 mm. Finally, marker misplaced in the AP direction had a low influence on hip and ankle adduction-abduction, ankle flexion-extension and knee internal-external rotation as they did not present any error above 5° with any of the misplacements tested. Based on the results of *Table 7*, and being the maximal mean error obtained 5.5° (hip internal-external rotation) for a misplacement magnitude of 10 mm, we estimate that to ensure an error within 5° for all joint angles, a precision within approximately 1.2% of leg length on the AP direction needs to be assured. Thus, it is important to notice that repeatability of marker placement of this magnitude might be difficult to obtain in clinical practice (Della Croce *et al.* 2005b), especially for young children as they have a smaller morphology than adults

A few major differences can be found between our results and the results reported by Osis *et al.* (2016). The major discordance is relative to the knee internal-external rotation where they reported an error of 5.1° with a misplacement of 10 mm in the AP direction. Our study showed only 0.7° for the same condition, which is in agreement with the small error observed in previous studies with the CGM marker-set (Kadaba and Ramakrishnan 1990, Baker *et al.* 2017). More differences were found in hip abduction-adduction, knee flexion-extension, knee abduction-adduction and ankle internal-external rotation where Osis *et al.* (2016) reported errors of 2.9°, 1.6°, 0.6° and <0.5° respectively while we obtained 0.6°, 4.3°, 3.5° and 4.5° respectively. The explanation for this difference may be because they analysed subjects while running and with a different marker set and biomechanical model which differs especially in the definition of the frontal plane of the thigh and shank segments (Pohl *et al.* 2010). Thus, the generalization of the errors due to marker misplacement from one model to another is hazardous.

Kinematics were relatively unaffected by PD misplacement of the KNE marker as RMSD was generally presented to be under the 2° threshold, with the exception of the knee internal-external rotation that revealed a deviation up to 2.2° per 10 mm of misplacement. These results are in agreement with the results of Baker (Baker *et al.* 2017) that presented more sensitivity of the knee internal-external rotation angle to PD misplacement than to AP misplacement (+0.4° and <0.1° respectively for a magnitude of 5 mm misplacement).

Deviations observed on internal-external rotation and flexion-extension angles are mainly characterized by offsets. Contrarily, the amplitudes of the adduction-abduction and internal-external rotation angles of the knee are mainly altered during the swing phase, where the knee is more flexed. Kadaba *et al.* (1990) reported similar observations. Those alterations correspond to the well-known cross-talk phenomenon (Della Croce *et al.* 2005b) revealing a misorientation of the knee flexion axis (equal to the thigh medial-lateral axis).

The high sensitivity of the hip internal-external rotation angle to the misplacement of the KNE marker plays an important role in the clinical assessment of patients with CP. Indeed, this pathology frequently presents excessive femoral anteversion to which hip internal-external rotation angle is an indicator (Davids *et al.* 2002). An error on this angle could lead to an erroneous evaluation that could potentially affect, for instance, the decision-making for a derotation procedure (Boyer *et al.* 2016). Excessive hip external rotation and ankle internal rotation may be caused by anterior misplacement of KNE marker while excessive hip internal and ankle external rotation may be caused by a posterior misplacement (Figure 19). Furthermore, from our results, we can conclude that interpretation of gait data with KNE marker misplaced in the anterior and posterior directions may lead to a false interpretation of hyperflexion and hyperextension respectively on the sagittal plane.

The deviations due to marker misplacement have a very good positive correlation with the leg length, especially, hip internal-external rotation and all flexion-extension angles ($R > 0.9$). On the contrary, knee internal-external rotation and ankle adduction-abduction showed a moderate correlation with the magnitude of the misplacement expressed in the percentage of leg length ($R < 0.61$). Those results show that a model addressing the effect of marker misplacement on the kinematics could be developed and used in CGA to support the placement of the marker and the interpretation of data. The model presented in this study can estimate the kinematics for a misplacement considered in the percentage of leg length and could be added to the report of a specific patient.

Various optimization techniques were proposed in the past to reduce the impact of marker misplacement on the output kinematics (Baker et al. 1999; Besier et al. 2003; Marin et al. 2003; Naaim et al. 2019; Schache et al. 2006). Those methods were observed to reduce the effect of lack of marker placement precision and could be tested as a complement of the CGM in order to reduce the sensibility of this biomechanical model to marker misplacement (Schache *et al.* 2006). For instance, the calibration method proposed by Baker (Baker *et al.* 1999) aiming to compensate for the misalignment of thigh markers could be implemented, serving as checking for the placement of the markers and thus supporting the training of examiners. In addition, well-validated and standardized guidelines for the placement of the markers is crucial to produce in order to reduce the effects of incorrect anatomical landmark identification (Van Sint Jan and Della Croce 2005).

Additionally, the RMSD differences calculated between the CP and the TD group showed no significant difference except on the hip flexion-extension for misplacements in the AP and PD directions (Table 6) but the misplacement errors were of similar magnitude. The correlation between RMSD and magnitude of marker misplacement also did not present a significant difference between both groups (Table 7). We can conclude that the impact of KNE misplacement has a similar effect on gait kinematics in children who are typically developed and with CP ranging between GMFCS I and II. Nevertheless, we recommend including both CP and the TD groups in the upcoming studies on the impact of other marker misplacements or on the effect of the optimization techniques proposed to reduce this impact.

Several limitations can be detected in the present study. The first is that the reference position of the KNE marker is dependent on palpation and incorporates the subjectivity associated with marker placement precision. To limit this effect, all marker placements were performed by a single experienced operator. However, as the results showed mainly an offset of the kinematic curves due to marker misplacement for every patient and that every patient is likely to have different physical misplacement errors, we conclude that this inherent error added to the reference position has a low impact on the results of this study. The second limitation is that the influence on the kinematics of only one marker misplacement was assessed when, in practice, the variability is the result of the combination of misplacements on the whole marker set. For instance, an erroneous definition of the femur orientation due to a misplacement of the KNE marker can be mitigated or intensified by a misplacement of other markers, such as thigh markers (Baker et al. 1999; Della Croce et al. 2005) and pelvic markers (Osis et al. 2016). Nonetheless, only the KNE marker was introduced in this study due to its central place in the CGM and for the clarity of the analysis. Further study will analyse the effect of the interactions of simultaneous misplaced markers. The third limitation is that different soft tissue artefacts were not considered among different positions of the marker which constitutes another difference with a real experimental misplacement. Moreover, with only kinematic data incorporated, this study lacks information relative to the sensitivity of the kinetics of the CGM under marker misplacement conditions. Finally, the study used as a reference for the uncertainty of marker placement (Della Croce *et al.* 1999) was based on a small healthy adult population. A similar study on a young population would be of great interest to scale the range of misplacements introduced in this study.

2.1.8. Conclusion

This study demonstrated that the kinematics of the CGM is highly sensitive to KNE marker misplacement over the AP direction when performing gait analysis in children with CP. The most affected joint angles are the hip and ankle internal-external rotation, and the knee flexion-extension. In order to obtain an accuracy below 5° for the hip rotation profile, the misplacement of the KNE marker in the AP direction should be lower than 1.2% of the leg length. In clinical gait analysis, error may considerably impact the management of motor disorders, especially when considering the hip internal-external rotation profile. This study shows that a model of marker misplacement can be developed for the KNE marker. Indeed, its impact on kinematics is linear in the function of the magnitude expressed in percentage of the leg length, apart from the knee internal-external rotation and ankle adduction-abduction. This study also showed that CGM is equally sensitive to misplacement of KNE the marker on typically developing children and children with CP (GMFCS I and II). Moreover, we can conclude that there is a potential for the development of a general model of marker misplacement to add a margin of errors on reports of CGA and support the clinical decision.

2.1.9. Supplementary Information

Joint		Anterior		Posterior		Proximal		Distal	
		m	b	m	b	m	b	m	b
Hip	Flexion-Extension	1.90	0.09	2.00	-0.08	0.33	-0.32	0.26	-0.24
	Adduction-Abduction	0.68	-0.33	0.36	0.20	0.11	-0.13	0.05	-0.03
	Internal-External Rotation	3.91	0.57	4.02	0.42	0.68	-0.62	0.52	-0.43
Knee	Flexion-Extension	2.79	0.47	3.47	-0.09	0.89	-0.44	0.22	0.09
	Adduction-Abduction	1.89	0.07	1.50	0.34	0.20	-0.14	0.27	-0.17
	Internal-External Rotation	0.65	-0.16	0.73	-0.23	0.80	0.49	1.08	0.22
Ankle	Flexion-Extension	0.99	0.11	1.27	-0.18	0.49	-0.16	0.25	0.05
	Adduction-Abduction	0.36	0.35	0.41	0.33	0.17	0.09	0.10	0.13
	Internal-External Rotation	2.60	1.13	3.25	0.67	1.21	-0.03	0.66	0.39

Table 8. Regression equation parameters. Slope (m) and y -intercept (b) relatively to the regression equation defined between RMSD and magnitude of misplacement expressed in terms of percentage of leg length.



Figure 20. Correlation between RMSD and magnitude of misplacement in percentage of leg length. Scatter plot representing RMSD for all tested magnitudes to misplacement of the KNE marker on the AP direction considering the CP population. R (correlation coefficient).

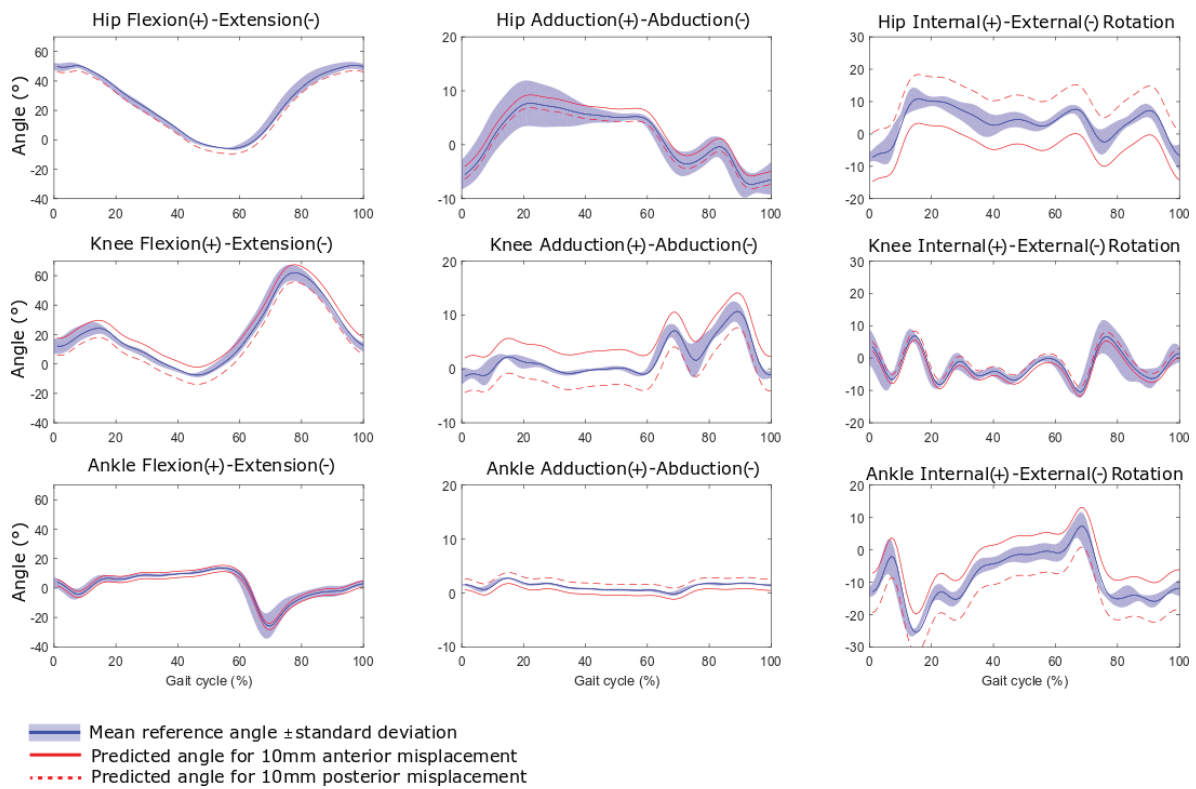


Figure 21. Prediction of kinematics based on misplacement magnitude from leg length. Representation of prediction based on the regression equation described in (Supplementary Information 2.1.7., Figure 20 and Table 8), for one patient and for a misplacement of the lateral epicondyle marker on the anterior-posterior direction. Mean and standard deviation of the reference kinematics (blue line and shadow, respectively). Predicted mean kinematics for a misplacement of 10 mm on the anterior (red solid line) and posterior (red dashed line) directions.

2.2. Article 2 – The Conventional Gait Model’s sensitivity to lower-limb marker placement

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Communication:

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- Société Francophone d’Analyse du Movement chez l’Adulte et l’Enfant (SOFAMEA), June 2022 in Marseille, France as podium presentation.

Keywords:

Skin-marker placement; Level walking; Conventional Gait Model; Reliability; Variability; Kinematics; Gait Profile Score; Misplacement

2.2.1. Abstract

Clinical gait analysis supports treatment decisions for patients with motor disorders. Measurement reproducibility is affected by extrinsic errors such as marker misplacement, which is considered the main factor in gait analysis variability. However, how marker placement affects output kinematics is not completely understood. The present study aimed to evaluate the Conventional Gait Model's sensitivity to marker placement. Using a dataset of kinematics for 20 children, eight lower-limb markers were virtually displaced by 10 mm in all four planes, and all the displacement combinations were recalculated. Root-mean-square deviation angles were calculated for each simulation with respect to the original kinematics. The marker movements with the greatest impact were for the femoral and tibial wands together with the lateral femoral epicondyle marker when displaced in the anterior–posterior axis. When displaced alone, the femoral wand was responsible for a deviation of $7.3^\circ (\pm 1.8^\circ)$ in hip rotation. Transversal plane measurements were affected most, with around 40% of simulations resulting in an effect greater than the acceptable limit of 5° . This study also provided insight into which markers need to be placed very carefully to obtain more reliable gait data.

2.2.2. Introduction

Three-dimensional gait analysis provides large amounts of information used to characterize motor disorders such as cerebral palsy (CP) and plays a demonstrated important role in supporting treatment decision-making (Wren *et al.* 2011, Armand *et al.* 2016). Reflective markers are attached to specific anatomical landmarks and used to build a biomechanical model for calculating patients' kinematics (anatomical segment motion with respect to the ground and other segments). One of the most used models in clinical practice is the Conventional Gait Model (CGM), also known as the Plug-in Gait model (Kadaba *et al.* 1989, Davis *et al.* 1991). The CGM defines lower-limb geometry via a set of seven anatomical segments and a hierarchical top-down process (Baker *et al.* 2016). The kinematic data are calculated from marker trajectories on a frame-by-frame basis (Baker *et al.* 2016). Any measurement errors in gait analysis introduce variability into the output data and negatively impact data interpretation (Chia and Sangeux 2017a). Marker placement has been reported as the primary cause of variability in gait analysis (Gorton *et al.* 2009, McGinley *et al.* 2009). Because of the CGM's process, wrongly placed markers will affect the definition of segment lengths and thus how far all other segments are from them.

Many studies have quantified the general variability caused by gait analysis marker placement by repeating measurements under identical conditions with either the same or different examiners (McGinley *et al.* 2009). Based on their results, 2° and 5° were defined as the optimal and acceptable thresholds for measurement differences, respectively. Moreover, the transversal plane was found to be the most sensitive to marker placement. For instance, hip joint rotation results have been reported to have a variability above acceptable limits (5°), and they should be considered with extreme caution (McGinley *et al.* 2009). Gait scores, such as the Gait Profile Score (GPS) or the Gait Deviation Index, are also used to evaluate motor disorders by providing an overall gait score with respect to reference asymptomatic data (Baker *et al.* 2009; Schwartz and Rozumalski 2008). As gait scores are calculated based on kinematics, they are also expected to be sensitive to marker placement. Estimating the expected errors resulting from marker misplacement is therefore important, as is its impact on both kinematic data and gait scores. To the best of our knowledge, gait score sensitivity to marker misplacement has never before been addressed.

One study has evaluated the precision with which investigators place markers (Della Croce *et al.* 1999). It reported average pelvic and lower marker placement errors of 6–21 mm and 13–25 mm for intra- and inter-examiner, respectively. *Mcfadden et al.* (2020) demonstrated that the CGM was more sensitive to poorly placed thigh, knee, and tibia markers in anterior–posterior movements. Another study evaluated the impact of different lateral femoral epicondyle marker placements on kinematics, and it reported differences of up to 5.3° per 10 mm of marker displacement in the anterior–posterior axis (Fonseca *et al.* 2020). However, little information is available concerning the sensitivity of kinematics to the placement of the complete set of CGM markers.

In practice, the variability resulting from imprecise marker placement is due to the combined imprecision of the placement of all markers together. Thus, this study aimed to evaluate the CGM's sensitivity to overall lower-limb marker placement. To do so, we simulated marker displacements over the results from CGM measurements made using its basic marker-set configuration. This study was an extension of our previous sensitivity analysis focusing on the knee's lateral epicondyle marker (Fonseca *et al.* 2020).

2.2.3. Methods

Data Collection

Original gait data were collected retrospectively from 20 children: 10 children with CP (6 males and 4 females, mean (standard deviation): age, 12.4 (4.7) years old; height, 150.0 (22.7) cm; and weight, 45.1 (26.4) kg), at Gross Motor Function Classification System levels I and II (five bilateral and five unilateral), and 10 typically developing children (TDC) (8 males and 2 females, mean (standard deviation): age, 13.7 (3.2) years; height, 160.8 (19.1) cm, and weight, 49.5 (17.7) kg). After anatomical palpation, markers were placed according to the guidelines by an investigator with over 10 years of continuous practice experience (Van Sint Jan 2007). All methods carried out in this study were in accordance with the guidelines for gait analysis in clinical practice. This study was approved by the “Commission cantonale d'éthique de la Recherche” of Geneva (CCER-2018-00229) and all participants provided written informed consent, signed by their legal guardian.

Testing Procedure

The present sensitivity analysis used a procedure similar to that of a previous study (Fonseca *et al.* 2020). All subjects were equipped with the CGM marker set (Davis *et al.* 1991) (14 mm) and walked barefoot at a self-selected speed along a 10 m walkway. Marker trajectories were tracked by a 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) at a frame rate of 100 Hz. Gait kinematics were processed using a Vicon Plug-in Gait software clone—provided as ‘CGM 1.1’ by the PyCGM2 open-source library—that uses a static trial for calibration (Leboeuf *et al.* 2019).

The analysis used the eight markers required to define one of the lower limbs. The present study only considered the left leg. For the pelvis, we calculated a virtual marker at the midpoint of the posterior iliac spine (SACR, for sacrum), between the right and left anterior iliac spine (RASI and LASI, respectively) markers. Then, we considered the lateral femoral epicondyle (LKNE, for lateral knee), lateral tibial malleolus (LANK, for lateral ankle), and the second metatarsal head of the foot (LTOE, for lateral toe). The medial femoral epicondyle and tibial malleolus markers were not used to calibrate the knee- and ankle-joint centers. However, the femoral and tibial wands were included (LTHI, for the left thigh, and LTIB, for the left tibia, respectively).

We added a specific offset to the segmental reference frames for each static and dynamic trial, thus creating a new virtual marker and new virtual marker trajectories. These offsets were a ‘displacement’ of 10 mm from each marker’s original position in four different directions (every 90° around the original position) and in their main plane of action. More specifically, as described in Figure 22, the pelvis markers were displaced in the coronal plane in the medial–lateral (0°, 180°) and proximal–distal (90°, 270°) axes. The foot marker was displaced in the transversal plane in the lateral–medial (0°, 180°) and anterior–posterior (90°, 270°) axes. Finally, the remaining markers (wands on tibia (LTIB) and thigh (LTHI), LANK and LKNE) were displaced in the sagittal plane in the anterior–posterior (0°, 180°) and proximal–distal (90°, 270°) axes. Each marker’s original position was also included, giving us five different virtual positions for each marker. Every possible combination of these marker positions was considered, resulting in 390,625 displacement simulations. This number (n_{sim}) was calculated as $n_{sim} = s^m$, where s represents the number of positions considered for each marker and m represents the number of markers considered. For each marker displacement simulation, every other marker position was defined and lower-limb kinematic data were computed together with the GPS. Due to the great computational resources required because of the high number of simulations planned (at around 10 s per simulation, or 45 days of computation per subject with a standard computer), calculations were performed using a high-performance, multi-core computing system suitable for parallel computation. The toolbox used for this study is available at <https://gitlab.unige.ch/KLab/multi-marker-misplacement.git>.

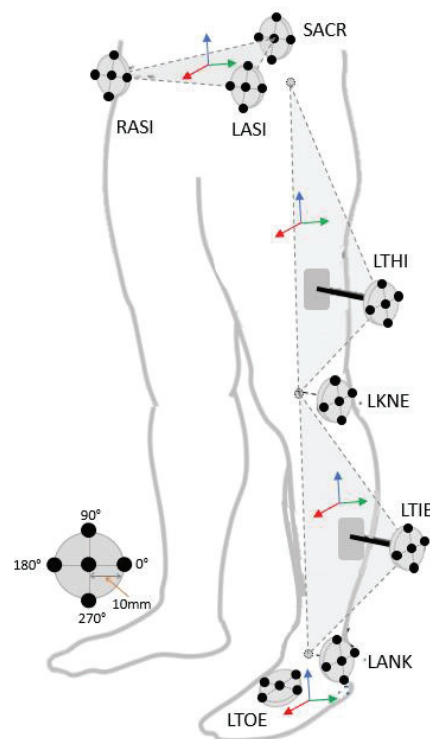


Figure 22. Marker displacement illustration for each marker. Each marker displacement occurred in a defined plane: LASI; RASI and SACR were displaced in the coronal plane; LTHI, LTIB, LKNE and LANK were displaced in the sagittal plane; and LTOE was displaced in the transversal plane.

Statistical analysis

For each simulation, a root-mean-square deviation (RMSD) angle was calculated between the original kinematics and simulated data kinematics. To better understand the impact of combined marker displacements, we separated the simulations into four categories of angle variability according to their mean RMSD. Therefore, each group's overall RMSD fell into the angle interval categories of: 1) lower than or equal to 2°; 2) higher than 2° and lower than or equal to 5°; 3) higher than 5° and lower than or equal to 10°; and 4) higher than 10° (McGinley *et al.* 2009b). The distribution of variability resulting from these displacement simulations was also extracted.

2.2.4. Results

Figure 23 illustrates the distributions (in percent) of displacement simulations with RMSDs in each of the four categories of angle variability for both groups of subjects. Multiple marker displacements (8% of all simulations) resulted in hip, knee, and ankle rotations of over 10° of RMSD, and over 40% of all simulations resulted in rotations over 5°. Nearly 10% of the hip, knee, and ankle flexion–extension and knee varus/valgus simulations resulted in rotations over 5°. All the displacement simulations on the other joint angles resulted in RMSDs less than 5°. No considerable differences were observed between the two populations. The combinations of displacements resulting in the ten highest overall RMSD are described in Figure 24a, as well as the kinematics resulting from the worst-case scenario (Figure 24b) and its representation on the lower limb definition in comparison with the original marker placement in Figure 24c. In all the displacement simulations referred to, the anterior iliac spines (RASI and LASI) were noted to be displaced in opposite directions in the vertical axis, and the SACR was displaced in the horizontal axis or, in some cases, was not displaced at all. The wands shifted in the anterior–posterior axis; the LKNE was displaced in the proximal–distal axis. Finally, the LANK was displaced either distally, anteriorly, and not at all, whereas the LTOE was displaced in the medial–lateral axis.

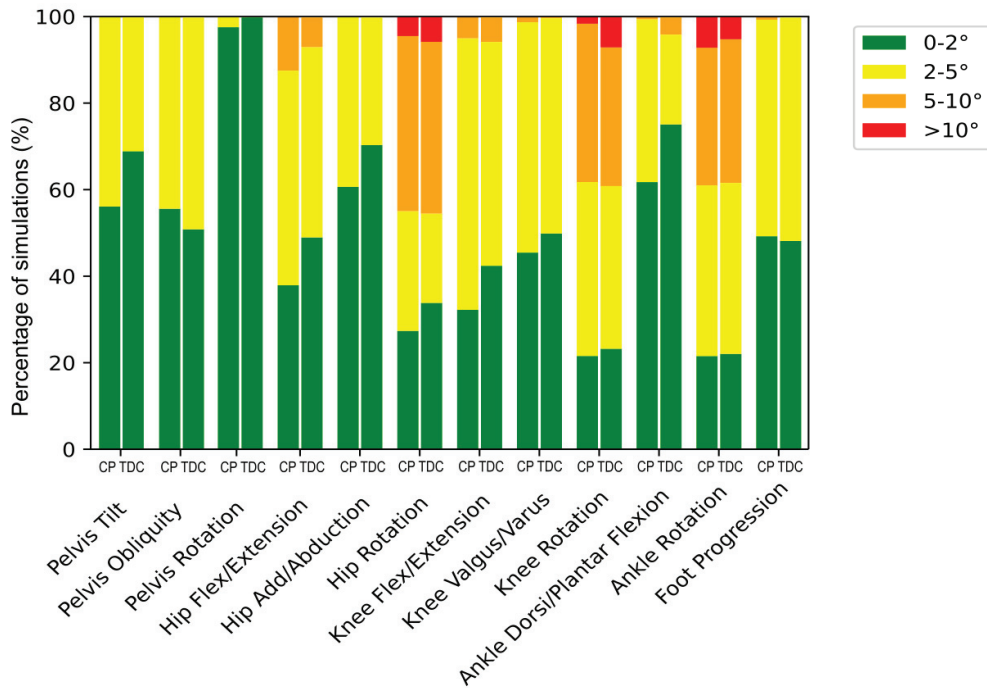


Figure 23. Distribution, in percent, of simulations with RMSDs within the four categories of angle variability (RMSD of 0-2°, >2-5°, 5-10° and >10°) for the two populations (cerebral palsy = CP, typically developed children = TDC).

The Figure 25 demonstrates the impact of a series of single marker displacements (vertical axis) on different joint kinematics (horizontal axis). Simulated displacements of the thigh and tibia wands (LTHI and LTIB) and the knee marker (LKNE) in the anterior–posterior axis resulted in the highest RMSD of all markers, with RMSD angles for hip, knee, and ankle of over 5° in the transversal plane. The highest mean RMSD angle calculated is relative to the displacement of the femoral wand marker in the anterior–posterior axis, with a hip rotation angle, with a mean RMSD of 7.3° (SD: 1.8°).

We also investigated the impact of marker displacement on each subject’s GPS, and their distributions are reported in Figure 26. The results showed a different variability among the population as the amplitude of scores for each subject varied from 2 to 7 points to its original calculated score. In general, the CP group had higher simulated gait profile scores. Finally, Figure 27 shows the original kinematics of one representative child with CP together with the corridors of simulated RMSD angles (using the maximum value calculated at each point in the gait cycle). The RMSD angle added by marker displacement was considerably higher than the inter-trial variability, except for the kinematics of pelvis rotation and foot progression angle.

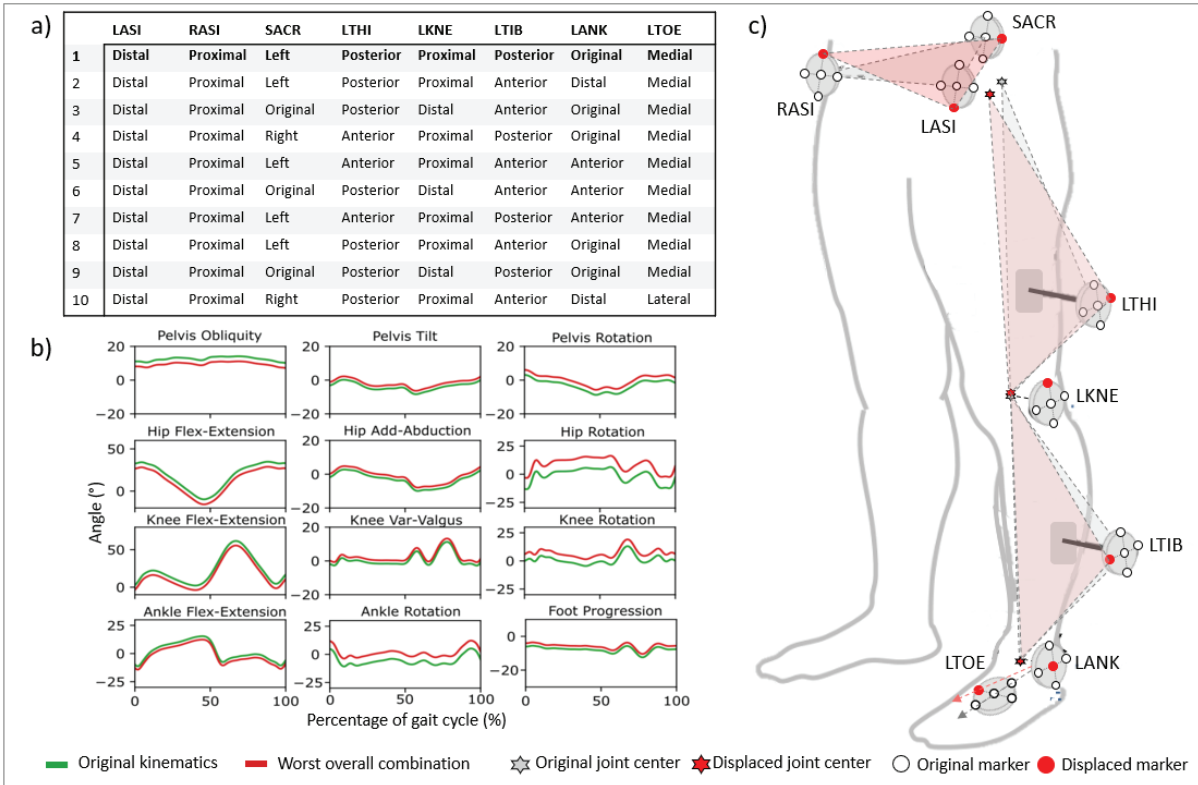


Figure 24. Overall worst-case scenario. a) The 10 simulations resulting in the highest overall RMSD angles in kinematics. Described the direction of displacement of the eight markers for each of the scenarios. b) Kinematics of overall worst-case scenarios (red) plotted against the original (green) kinematics of one CP patient. c) illustration of impact of the worst-case scenario (bold in the table).

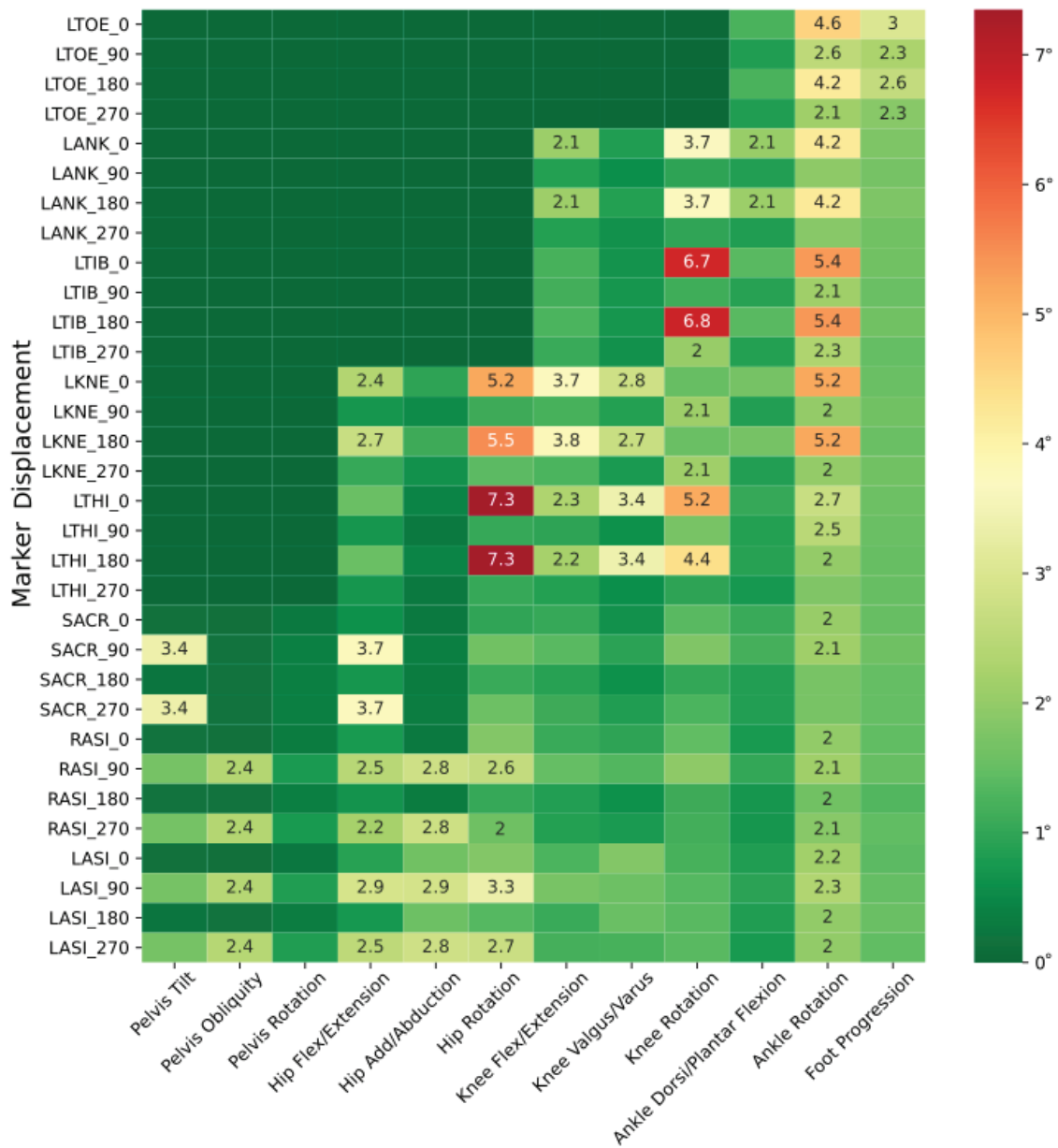


Figure 25. Impact of a single marker displacement on each of the angles across the entire group. Cells only indicate values when the RMSD angle was greater than 2° for the respective marker displaced.

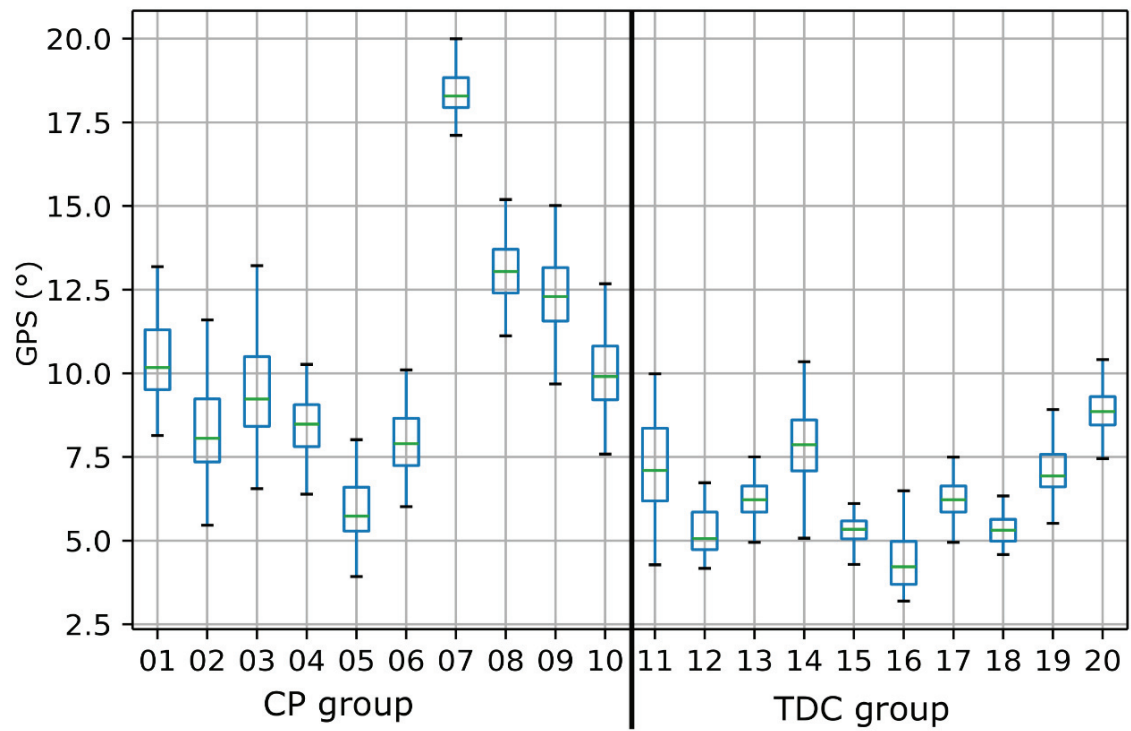


Figure 26. Distribution of Gait Profile Scores for each subject, calculated from their simulated displacement kinematic data.

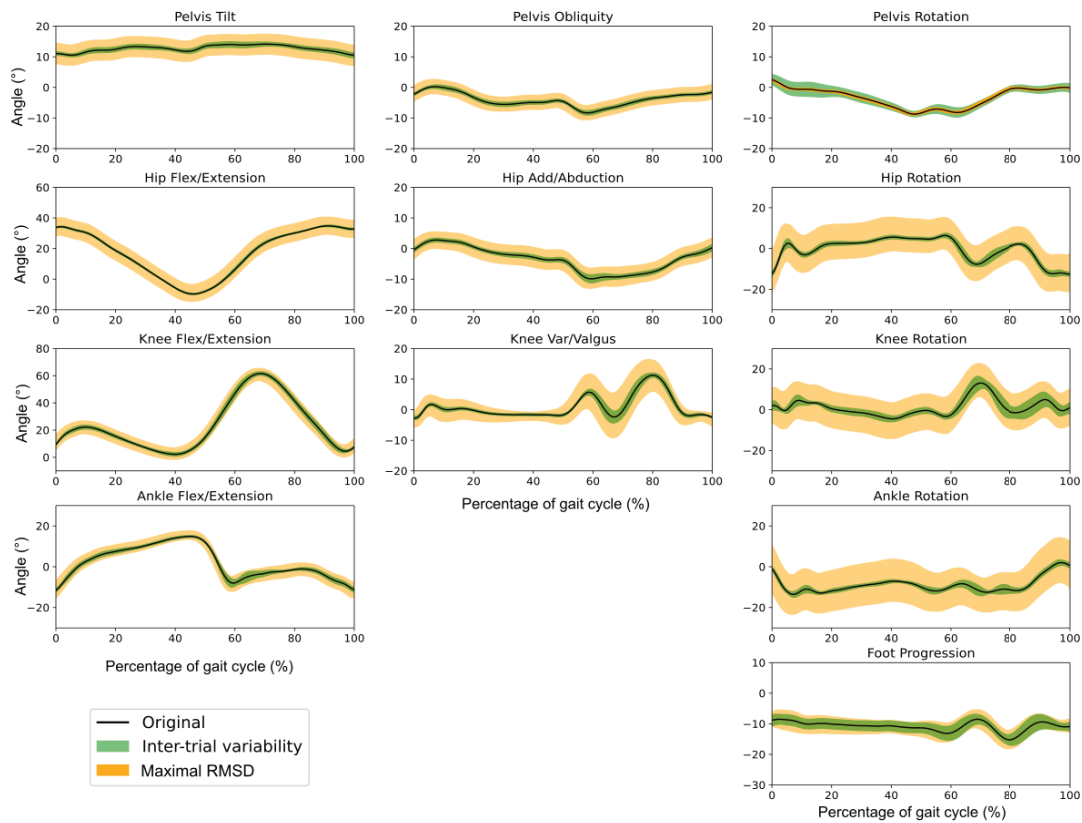


Figure 27. Variability induced by marker displacement. Original kinematics (solid line), inter-trial variability (green corridor), and maximal RMSD angle (yellow corridor) calculated for each point in the gait cycle for a representative child with cerebral palsy.

2.2.5. Discussion

This study's objective was to evaluate the CGM's sensitivity to marker placement. We simulated different combinations of markers on the lower-left limb, displaced in different directions by 10 mm. Overall, measurements in the transversal plane demonstrated the greatest sensitivity to marker displacement, whereas the markers displaced in the sagittal plane resulted in the highest RMSD angles in comparison to the original kinematics.

Pelvic kinematics showed very low sensitivity to marker displacement, with all their RMSD angles calculated to within an acceptable limit of 5° and the majority of their simulations resulting in RMSD angles within 2°. For the other joint angles calculated, the transversal plane was the most affected by marker displacement, with about 47% of simulations returning an error over the 5° limit of acceptability. These findings agreed with previous literature reporting that the transversal plane was the least reliable in gait analysis (Schwartz *et al.* 2004, Wren *et al.* 2011).

An analysis of the ten worst-case marker misplacement scenarios allowed us to better understand the effects of a combination of marker displacements on the lower-limb model. For instance, the 'worst' marker configuration for the pelvis was calculated when the anterior iliac spines markers were displaced in opposite directions on the vertical axis and the SACR was displaced in the horizontal axis. With this simulated marker configuration, the pelvis was both tilted and rotated with respect to its original definition. Because the CGM is a hierarchical, anatomical, top-down model, this

would be expected to affect the hip-joint centre estimation, hip kinematics, and all the distal joint angles. As illustrated in Figure 24, the CGM's thigh and tibia's flexion–extension axes are defined as orthogonal to the plane connecting the proximal and distal joint centres when the wand is placed along the segment. Thus, those segments' medial–lateral axes are estimated to be orthogonal to both the flexion–extension and proximal–distal axes. The simulated displacement of the femoral wand (LTHI) in the anterior–posterior axis directly affects the femur's coronal plane, thus altering the flexion–extension axis and the medial–lateral axis. As a consequence, the kinematics of the hip and knee joints will be directly affected, as will the knee joint centre that is defined along the femur's medial–lateral axis (in the absence of the medial femoral epicondyle marker). A similar impact was noted for the tibia. Finally, the medial displacement of the LTOE marker was responsible for a rotation of the foot's angle with respect to the direction of walking and for an impact on the foot progression angle.

Regarding displacements of individual markers, displacements of the thigh and tibia wands and the knee marker in the anterior–posterior axis had the largest calculated impact on kinematics, all with an RMSD angle of over 5° in the transversal plane (Figure 25). These findings confirmed previous results demonstrating the knee marker's high impact in the anterior–posterior axis in the transversal plane but its very low impact when displaced in the proximal–distal axis (Fonseca et al. 2020; McFadden, Daniels, and Strike 2020). Even though some studies have reported improvements in calibration methods, such as the Knee Alignment Device, marker placement reproducibility and reliability remain the CGM's most significant limitation (Baker et al. 2017). The CGM's high sensitivity to wand orientation is even more critical as the lack of an anatomical landmark makes its placement somewhat subjective. Current user manual specifications for wand placement are simply, “*Adjust the position of the marker so that it lies in the plane that contains the hip and knee-joint centers and the knee flexion/extension axis.*” (Fellinger et al. 2010).

The CGM is characterized by a hierarchical, anatomical, top-down approach; therefore, a displaced marker affects the kinematics of every joint located distally to the anatomical segment containing that marker and the joint most proximal to it (Leboeuf et al. 2019). Additionally, the slight impact that we calculated on the foot progression angle demonstrates that without the medial markers of the knee and ankle, defining the joint centers is affected by multiple marker displacements. Thus, an error in the placement of the knee-joint center marker impacts the definition of the ankle-joint center and consequently the foot progression angle. Overall, the calculated impact of a displaced marker could be noted in the two simulated displacements in opposite anatomical directions.

Gait scores, like the GPS, are very good at classifying a patient's gait by comparing it with a reference database of a general asymptomatic population. As the calculation uses kinematic data, the variability noted because of marker displacement also introduces variability into the final gait classification and thus may also have a considerable impact on gait data interpretation. We, therefore, investigated the impact of marker displacement on overall gait scores. Marker displacement in one leg resulted in GPS variations of up to 7°. This is comparatively much greater than the 1.6° rated as the minimal variation of clinical significance (Baker et al. 2012). As the GPS is calculated using the kinematics of both lower limbs, the variation expected if our simulations were applied to both sides would be even higher.

The impact of the variability of marker placement on our simulated gait kinematics is shown in Figure 26 by the corridors of maximal RMSD angle calculated per frame in the gait cycle added around one subject's original curve. We note that the error can be defined by an overall offset added to the original data. This finding agrees with previous results reporting that the impact of errors on axis definition was more like an offset to the kinematics than a change in their overall pattern (Kadaba et

al. 1989b). Those results may be useful for estimating the expected variability in kinematics when considering expected marker placement variability. To evaluate the impact of marker misplacement more accurately, our results could be used in combination with those from studies reporting on the precision of marker placement, such as Della Croce *et al.* (Della Croce *et al.* 1999). Thus, the magnitude of each marker's misplacement would be defined based on experimentally observed error.

Considering the overall results provided within this study, different solutions can be proposed to mediate the displacement of the markers. First, anatomical landmark identification should be followed carefully and with good training of the responsible evaluators. The guidelines used for marker placement in our data are recommended (Van Sint Jan 2007). Secondly, the referred evaluator should have additional attention to the markers and directions which have a large impact on the kinematics, as demonstrated in the Figure 25. In order to solve the high sensitivity observed on the wand, lateral femoral epicondyle and lateral tibial malleolus to anterior-posterior misplacement, Knee Alignment Device or the medial femoral and tibial markers could be a solution but specific studies are required to validate the possible solution (Baker *et al.* 2016; Motion Lab Systems 2011). Thirdly, in patients who have undergone 3D imaging, a fusion between medical imaging and motion capture system could limit the marker misplacement but seems difficult to apply to all patients who performed a clinical gait analysis (Gasparutto *et al.* 2015).

The present study had some limitations. Firstly, the lack of literature regarding gait analysis' sensitivity to marker placement makes comparisons with our results difficult. Secondly, marker displacement was done virtually, so the effects of soft tissue artifacts could not be considered. Different marker displacement distances and axes could also induce different soft tissue artifacts (Barré *et al.* 2015, Sangeux *et al.* 2017b). Moreover, our reference marker placements cannot be considered as 'true' references as they too were subject to the uncertainty of marker placement. We only applied displacements of 10 mm in only four directions, although that distance was defined according to Della Croce's results and to serve as a potential standard reference for future comparisons (Della Croce *et al.* 1999). Finally, the enormous amount of simulations required to compute every potential combination of marker displacement for the twenty subjects required enormous computing time. This imposed limits on the testing of numerous displacement distances and directions, as previously reported for single-marker displacements (Fonseca *et al.* 2020).

To conclude, we performed a very extensive sensitivity analysis combining 390,625 simulated marker placements. We successfully identified the most sensitive angles contributing to an overall marker displacement simulation measurement and quantified the RMSD angles associated with the displacements of the different lower-limb markers. We also identified and analyzed simulated worst-case marker displacement scenarios. Additionally, we reported on which markers and which axes caused the greatest variability in the angles measured. Greater accuracy in the placement of thigh and tibia wands (or markers) and lateral femoral epicondyle markers in the anterior–posterior axis are required to improve the reliability of gait analysis using the GCM.

2.2.6. Supplementary Information – Web application

The present study provides useful information regarding the markers that need to be placed with additional caution as well as knowledge relative to the impact of marker misplacements in the construction of the biomechanical model as well as the output kinematics. This information may be useful when training new gait analysis evaluators to marker placement. For that purpose, one interactive web application was developed and made freely available (<http://wmedapp723.unige.ch/>). One gait file of a patient with cerebral palsy was previously loaded. The user is asked to define the displacement of one or more markers in terms of direction and magnitude. Then the simulation is performed and the new configuration, as well as the kinematic data, is displayed together with the original configuration and data. One illustration of the application with (Figure 29) and without (Figure 28) simulated marker displacement is presented below.

Marker displacement simulator

DEFINE THE MISPLACEMENT TO BE ADDED TO EACH MARKER AND PRESS RUN

LASI (Left Anterior Iliac Spine)
 Original Medial Lateral Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

RASI (Right Anterior Iliac Spine)
 Original Medial Lateral Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

SACR (Sacrum)
 Original Medial Lateral Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

LTHI (Left Femoral Wand)
 Original Anterior Posterior Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

LKNE (Left Lateral Femoral Epicondyle)
 Original Anterior Posterior Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

LTIB (Left Tibial Wand)
 Original Anterior Posterior Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

LANK (Left Lateral Tibial Malleolus)
 Original Anterior Posterior Distal Proximal

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

LTOE (Left 2nd Metatarsal Head)
 Original Medial Lateral Anterior Posterior

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Press RUN for initialization of simulation!

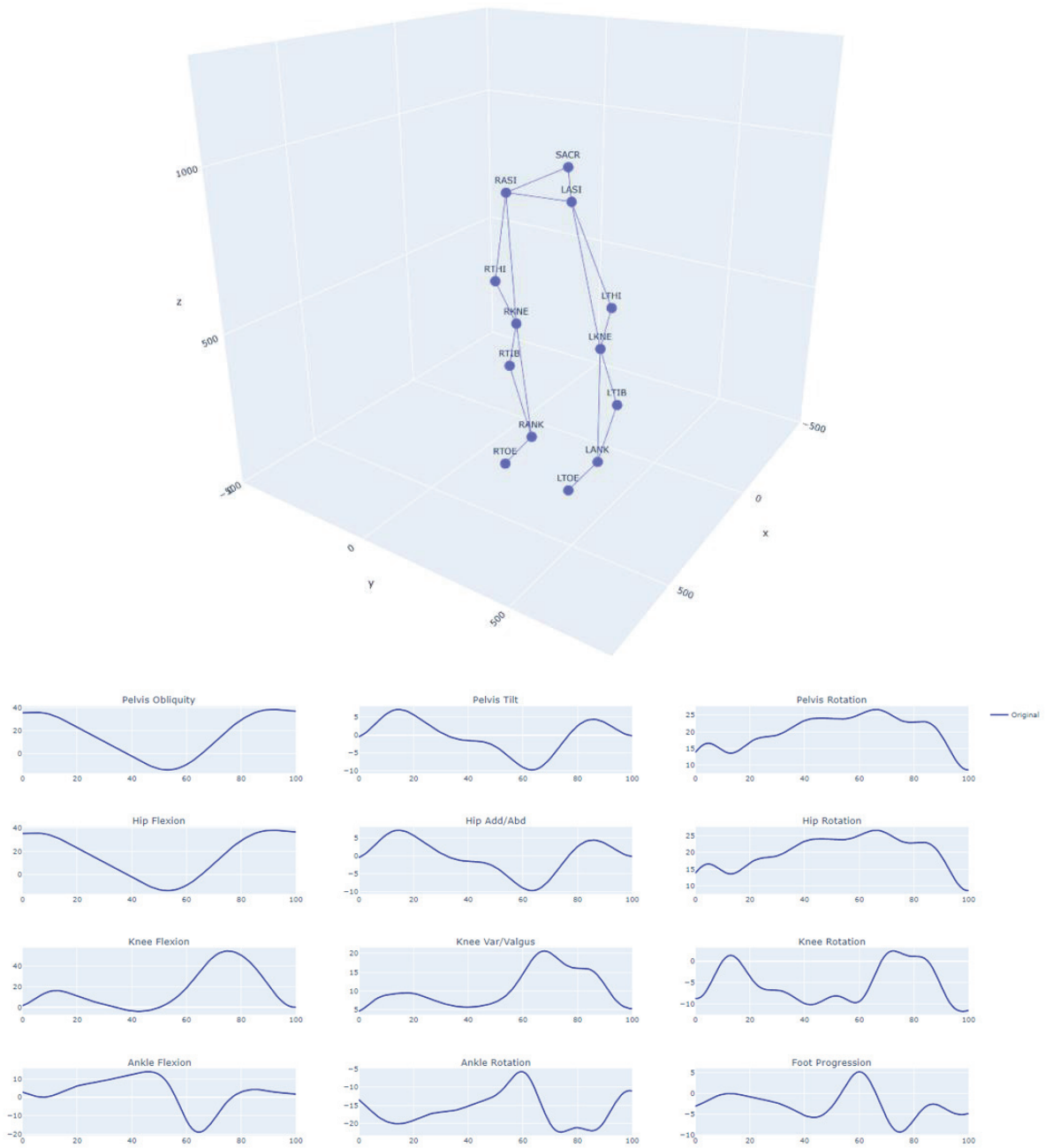


Figure 28. Illustration of the web application without any simulation performed. One panel (top) is used by the user to define the direction and magnitude of displacement for each marker. The second panel (mid) is an interactive 3D plot that shows the coordinates of the markers in space as well as the connection lines between markers used in the calculation of common segment coordinate systems. One panel (down) plots the original kinematics in percentage of gait cycle.

DEFINE THE MISPLACEMENT TO BE ADDED TO EACH MARKER AND PRESS RUN

LASI (Left Anterior Iliac Spine)

Original Medial Lateral Distal Proximal



RASI (Right Anterior Iliac Spine)

Original Medial Lateral Distal Proximal



SACR (Sacrum)

Original Medial Lateral Distal Proximal



LTHI (Left Femoral Wand)

Original Anterior Posterior Distal Proximal



LKNE (Left Lateral Femoral Epicondyle)

Original Anterior Posterior Distal Proximal



LTIB (Left Tibial Wand)

Original Anterior Posterior Distal Proximal



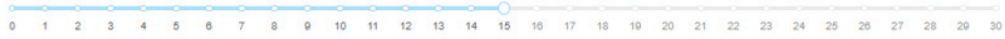
LANK (Left Lateral Tibial Malleolus)

Original Anterior Posterior Distal Proximal



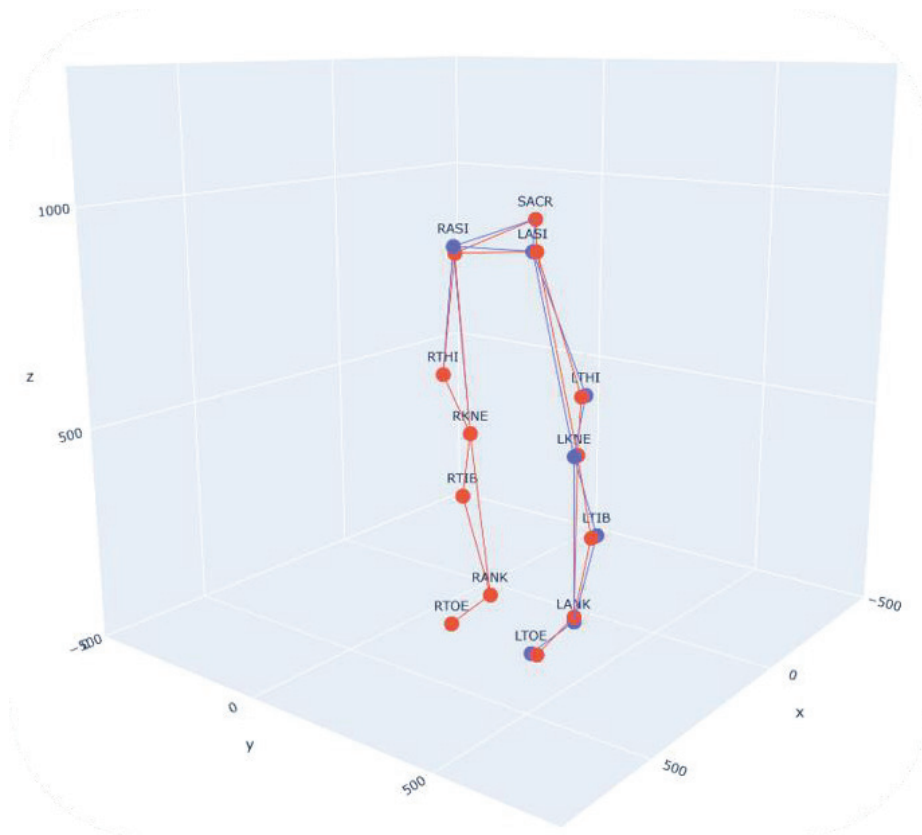
LTOE (Left 2nd Metatarsal Head)

Original Medial Lateral Anterior Posterior



Press RUN for initialization of simulation!

RUN



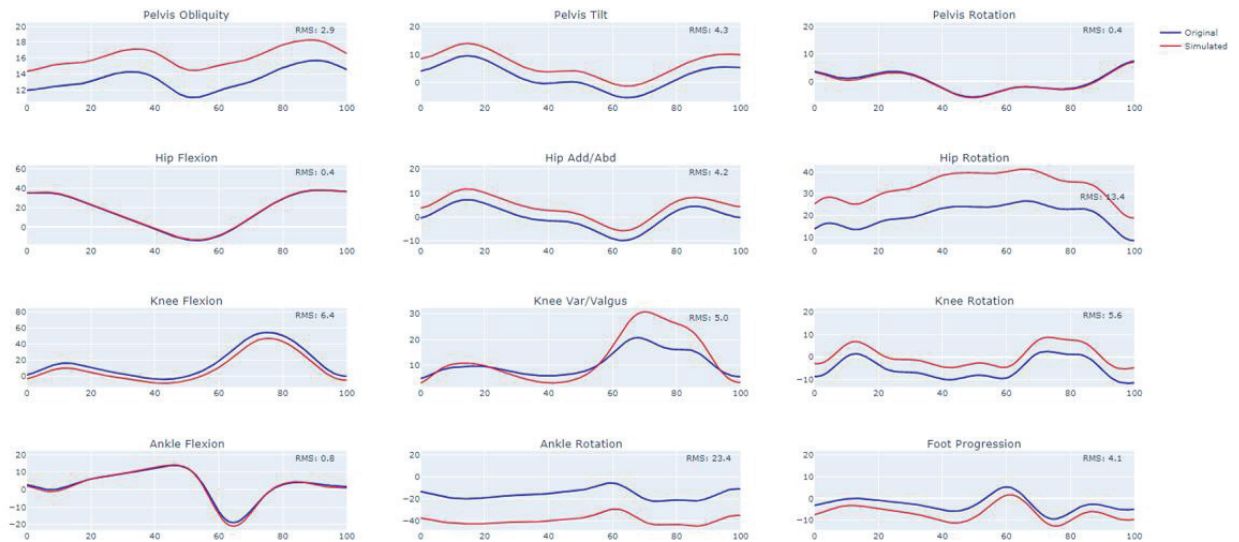


Figure 29. Illustration of the web application with one simulation performed. One panel (top) is used by the user to define the direction and magnitude of displacement for each marker. The second panel (mid) is an interactive 3D plot that shows the coordinates of the markers in space as well as the connection lines between markers used in the calculation of common segment coordinate systems for the original (blue) and simulated (red) configurations. One panel (down) plots the original (blue) and simulated (red) kinematics in the percentage of the gait cycle as well as the Root Mean Square between the two curves.

2.3. Article 3 – Evaluation of lower limb and pelvic marker placement precision among different evaluators and its impact on gait kinematics

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Communication:

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Keywords:

Marker placement; Gait analysis; Kinematics; Variability

2.3.1. Abstract

Gait analysis relies on the accurate and precise identification of anatomical landmarks to provide reliable and reproducible data. More specifically, the precision of marker placement among repeated measurements is responsible for increased variability in the output gait data.

The objective of this study was to quantify the precision of marker placement on the lower limbs by a test-retest procedure and to investigate its propagation to kinematic data.

The protocol was tested on a cohort of eight asymptomatic adults involving four evaluators, with different levels of experience. Each evaluator performed, three repeated marker placements for each participant. The standard deviation was used to calculate the precision of the marker placement, the precision of the orientation of the anatomical (segment) coordinate systems, and the precision of the lower limb kinematics. In addition, one-way ANOVA was used to compare the intra-evaluator marker placement precision and kinematic precisions among the different levels of the evaluator's experience. Finally, a Pearson correlation between marker placement precision and kinematic precision was analyzed.

Results have shown a precision of skin markers within 10 mm and 12 mm for intra-evaluator and inter-evaluator, respectively. Analysis of kinematic data showed good to moderate reliability for all parameters apart from hip and knee rotation that demonstrated poor intra- and inter-evaluator precision. Inter-trial variability was observed reduced than intra- and inter-evaluator variability. Moreover, experience had a positive impact on kinematic reliability since evaluators with higher experience showed a statistically significant increase in precision for most kinematic parameters. However, no correlation was observed between marker placement precision and kinematic precision which indicates that an error in the placement of one specific marker can be compensated or enhanced, in a non-linear way, by an error in the placement of other markers.

2.3.2. Introduction

Instrumented gait analysis is currently the most used tool for the clinical assessment of motor disorders, such as cerebral palsy. It provides a meaningful complex set of data to support the evaluation of motor function and treatment decision (Armand *et al.* 2016). However, by repeating or reproducing such procedure, the outcome data varies due to intrinsic factors, i.e. the natural variability of movement, and extrinsic factors, i.e. measurement error. Intrinsic factors are caused by the capacity of the subject to perform a repeated gait pattern and can be used as an indicator of pathology (Tabard-Fougère *et al.* 2022). Extrinsic factors, the largest source of measurement errors between sessions is the lack of precision in marker placement which leads to variations in the biomechanical model construction (Gorton *et al.* 2009, McGinley *et al.* 2009). The lack of precision in marker placement results from the difficulty in anatomical landmark identification and is affected by the morphology of the subject and ability of the evaluators (Page *et al.* 2006). While accuracy refers to how close skin markers are located from their true anatomical location, precision refers to the variability of repeated placements of markers.

Variability in gait analysis has been widely assessed (Kadaba *et al.* 1989, Schwartz *et al.* 2004, Gorton *et al.* 2009, McGinley *et al.* 2009). However, little understanding exists in the literature regarding the quantification of the marker placement precision among different gait analysis sessions

and its impact in the reliability of kinematic data. *Della Croce et al.* evaluated the precision of examiners in the placement of the markers in only two healthy subjects and reported a precision ranging up to almost 25mm (*Della Croce et al.* 1999). The propagation of the precision in marker placement to the definition of anatomical (segment) coordinate systems is critical and can result in joint angle differences over 10° in upright posture (*Della Croce et al.* 1999). Generally, precision under 2° is considered optimal and 5° is the threshold of acceptability in kinematic data (*McGinley et al.* 2009a). In *Della Croce et al.*'s study, contrarily to the current standard in clinical gait analysis, markers were pointed with a dedicated device and positioned concerning marker clusters through a calibration procedure (*Leboeuf et al.* 2019). Hence, such method does not fully represent a typical gait analysis session and the use of a laterally mounted marker cluster on the pelvis seemed to amplify the error on the pelvic markers of the contralateral side. The present study addresses those limitations: skin markers' precision was evaluated; the number of participants, sessions, and evaluators was increased; the pelvic cluster was symmetrical, and the development of motion capture systems technology over the past two decades has naturally improved.

Simulations of marker misplacements and their impact on kinematic data have also been evaluated (*Szczerbik and Kalinowska* 2011, *Osis et al.* 2016b, *Fonseca et al.* 2020). These studies reported a considerable impact of marker misplacement on kinematics as, in some markers, a misplacement of 10mm in a specific direction resulted in kinematics errors above the limit of acceptability (hip, knee, and ankle angles in the transverse plane). However, these studies are of limited use if the real precision of marker placement is not estimated.

Thus, the objective of this study was to quantify the precision of marker placement in lower-limb and to evaluate the impact of this precision on kinematics using gait data acquired from a cohort of eight asymptomatic adults. In addition, it was hypothesized that evaluators with more experience obtain better precision in marker placement and consequently in kinematic data. Thus, four evaluators with different levels of experience were included in the experimental protocol.

2.3.3. Materials and Methods

Data collection

This study was approved by the "Commission Cantonale d'Éthique de la Recherche Genève" (CCER-2020-00358) and all participants provided written informed consent. Gait data of eight asymptomatic participants (4 females and 4 males, mean [SD]: 31.2 [11.0] years; 171.2, [8.9] cm and 71.5, [16.1] kg), were acquired.

A set of rigid marker clusters was mounted on the lower limb segments and the lateral pelvis (Pcl, Figure 30). In addition, four markers were added on the iliac crests of the pelvis for five participants as a second pelvic cluster of markers (*P*, Figure 30). All markers' locations and definitions are detailed in Figure 1. Four evaluators placed three times the markers (14mm) according to the Conventional Gait Model (CGM) (*Leboeuf et al.* 2019) on the pelvis and lower limbs. All evaluators were properly trained and differed in the level of experience: evaluator A had more than ten years of experience in clinical practice, with over a hundred gait analysis sessions per year; evaluators B and C had approximately four and two years of experience in gait analysis, respectively, with nearly fifty sessions per year; evaluator D only received training in marker placement and had no previous experience in gait analysis. Anatomical landmark identification was performed based on reported palpation guidelines (*Van Sint Jan* 2007).

The time between consecutive marker placements (sub-sessions) for the same evaluator was approximately one hour to limit a familiarization effect. For the same reason, the other evaluators were not present during the marker placement. For each sub-session, one static and five gait trials at self-selected speeds were collected after marker placement. A 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) tracked the marker trajectories at 100Hz. The overall time for the complete acquisition was approximately two and a half hours.

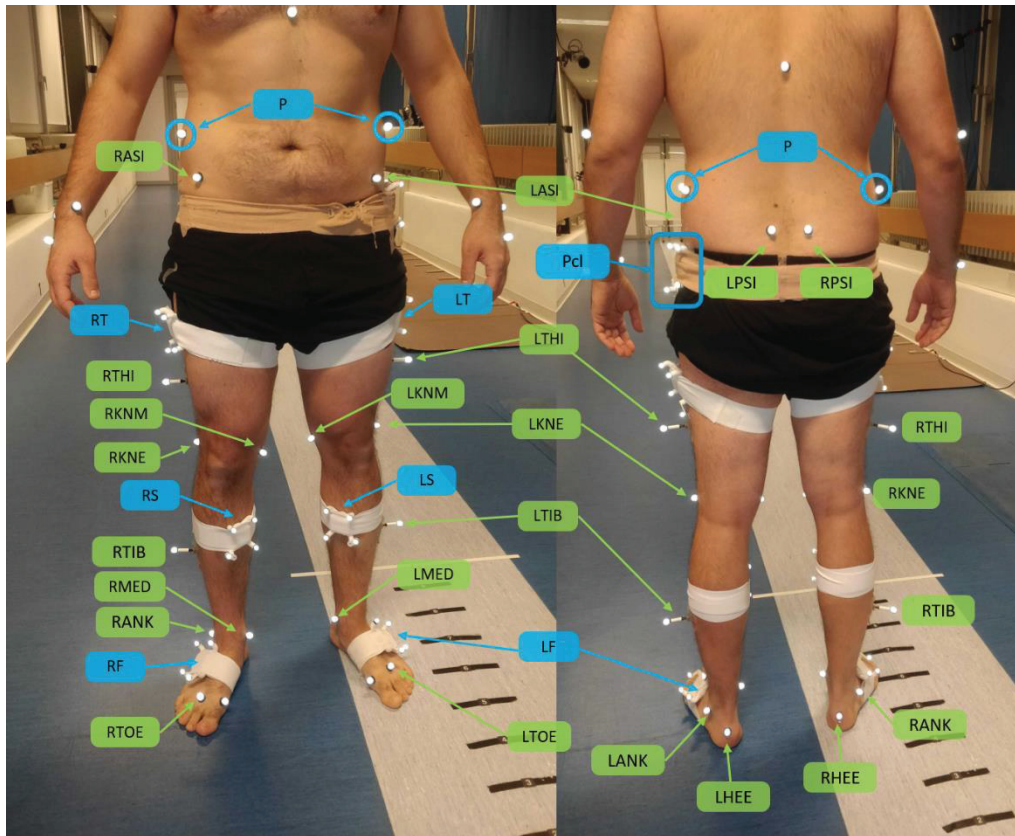


Figure 30. Marker-set used on the experimental protocol. Markers (green) and clusters (blue) setup.

Data processing

Gait data were processed with the Vicon PiG clone, provided as CGM1.1 by the open-source library PyCGM2 (Leboeuf *et al.* 2019) to estimate the joint centers of the hip (HJC), knee (KJC) and ankle (AJC) and, to compute the lower limb kinematics. Note that this model estimates the KJC and AJC as the midpoint between lateral and medial markers relative to the knee and ankle, respectively.

For each patient, during the static pose, skin marker and joint center positions were expressed in the technical (marker-cluster) coordinate system of the corresponding segment. Their mean position for all marker placements and segment orientations were computed and used to define a reference anatomical (segment) coordinate system for each segment. For the pelvis segment, this reference coordinate system was computed only for the five subjects with the four-marker cluster (P, Figure 30). Gait events were calculated with a previously reported method (Zeni *et al.* 2008).

Marker	Segment	Location
(L/R)ASI	Pelvis	Anterior superior iliac spine
(L/R)PSI	Pelvis	Posterior superior iliac spine
(L/R)THI	Thigh	50-70% distance from the hip joint center and lateral femoral epicondyle
(L/R)KNE	Thigh	Lateral femoral epicondyle
(L/R)KNM	Thigh	Medial femoral epicondyle
(L/R)TIB	Shank	50-70% lateral femoral epicondyle and tibial malleolus
(L/R)ANK	Shank	Lateral tibial malleolus
(L/R)MED	Shank	Medial tibial malleolus
(L/R)HEE	Foot	Upper ridge of calcaneus posterior surface
(L/R)TOE	Foot	Head of 2 nd metatarsal bone.
Joint Center		
HJC	Determined based on equations (Hara <i>et al.</i> 2016)	
KJC	Mid-point between femoral epicondyle markers	
AJC	Mid-point between tibial malleolus markers	
Cluster		
P	Pelvis	Non-rigid 4 marker cluster placed on the iliac crests
Pcl	Pelvis	Lateral side of pelvic, lower to the iliac spines
(L/R)T	Thigh	30-40% distance from the hip joint center and lateral femoral epicondyle
(L/R)S	Shank	30-40% distance from knee joint center and medial tibial malleolus
(L/R)F	Foot	Over 4 th and 5 th metatarsal bones

Table 9. Description of locations of markers and clusters.

Data Analysis

The standard deviation (SD) was calculated to evaluate the precision of the marker position and the corresponding anatomical (segment) orientation by measuring the difference between each measurement and the reference of each participant (Della Croce *et al.* 1999). Inter-class correlation (ICC) was not computed for these features since the inter-participant variance was removed by using an averaged reference coordinate system.

Regarding gait kinematic data, intra-evaluator precision was also assessed with the SD (Figure 31). Additionally, based on COSMIN recommendations (Weir 2005, Mokkink and Terwee 2010), the reliability was assessed with the ICC for the kinematic data for inter-trial, intra-evaluator and inter-evaluator conditions. A linear mixed model using the lme4 package (v1.1-27.1; (Bates *et al.* 2015)) available in R (R Core Team 2020) was used to assess the variance of class components. For the ICC calculation, we applied the ICC form previously described as ICC(2,1), also referred to as two-way with a random effect for absolute agreement (Shrout and Fleiss 1979, Van Lummel *et al.* 2016). The ICC was classified as: good ($ICC \geq 0.75$); moderate ($0.75 > ICC \geq 0.5$); and poor ($ICC < 0.5$) (Koo and Li 2016). An average of the reliability values over the gait cycle was calculated to provide a global outcome for each degree of freedom as well as peaks and range of motion for each parameter (Nieuwenhuys *et al.* 2016). The Pearson correlation coefficients were used to estimate the correlation between marker placement precision with segment orientation and kinematic variability with p -value < 0.05 defined as statistically significant. Finally, one-way ANOVA was used to compare the intra-evaluator variability among the different levels of experience of the evaluators, with statistical significance set at $p < 0.05$ (Chia and Sangeux 2017). The experience was evaluated as four ordinal variables. Additionally, a Tukey's post-hoc test was done to evaluate the differences among paired evaluators.

2.3.4. Results

Marker placement – Static data

The Table 10 presents the precision of the markers' position in three directions: anterior-posterior, proximal-distal, and medial-lateral. Generally, the precision was similar between matching markers from both sides. As expected, the intra-evaluator variability was reduced comparing with the inter-evaluator variability. Skin markers, wand markers and joint centers showed a precision of up to 9.3, 32.9 and 11.0mm, respectively. Except for wands in the proximal-distal direction, precision for all markers was observed within an SD of 10mm. **Error! Reference source not found.** represents the distribution of marker positions on the three planes concerning the reference position per evaluator. Wands were not included due to the lack of anatomical landmarks for palpation. The increased variability was observed on the lateral and medial femoral markers. Some differences between evaluators could be noted (Figure 31). For instance, evaluator D demonstrated a tendency to place the knee skin markers more distally than the other evaluators (Figure 31C). The evaluator A tended to place metatarsal markers more posteriorly than the other evaluators (Figure 31A). It can also be observed that evaluator D tends to place the anterior pelvic markers (LASI and RASI) considerably more distally and posteriorly, respectively, in comparison with the other evaluators. Finally, the results relative to the ANOVA and post-hoc analysis reporting the differences between marker placement precision and experience of the evaluators are presented in Supplementary Material (S3).

Direction	Antero-Posterior						Medial-Lateral						Proximal-Distal						
	Evaluator	A	B	C	D	Intra	Inter	A	B	C	D	Intra	Inter	A	B	C	D	Intra	Inter
Marker																			
LASI	3.6	3.5	3.4	3.0	3.4	4.2	4.8	2.5	2.6	3.4	3.7	4.5	5.0	3.3	4.6	4.5	3.1	5.6	
RASI	2.8	3.0	3.5	4.9	3.4	4.6	3.6	3.4	3.3	5.0	3.7	4.9	2.5	2.9	5.2	3.9	3.7	4.7	
LPSI	1.7	1.4	1.4	1.1	1.5	1.8	4.9	3.3	6.4	3.2	3.7	5.7	3.9	4.9	5.3	3.1	3.8	5.6	
RPSI	1.6	1.2	1.6	1.1	1.6	1.8	4.3	2.5	3.4	3.6	3.1	4.1	5.1	4.7	6.0	3.1	4.5	6.1	
LTHI	10.1	6.8	5.6	7.2	7.9	9.6	1.7	2.2	2.4	3.6	2.2	3.2	12.0	9.8	12.0	20.2	9.0	17.1	
RTHI	8.9	7.8	10.2	7.2	8.8	11.3	2.6	3.4	2.7	4.4	3.3	4.3	11.8	13.4	11.4	23.5	9.8	19.1	
LKNE	7.7	5.2	6.3	6.1	4.9	7.9	1.9	1.7	1.9	2.3	2.1	2.6	5.2	7.8	4.2	9.4	5.2	8.2	
RKNE	8.6	5.1	9.7	6.0	5.3	9.2	3.4	2.2	2.8	4.2	3.6	4.0	5.5	7.4	5.5	11.3	5.5	9.4	
LKNM	7.5	4.4	10.8	6.6	5.0	8.9	3.6	2.9	4.9	4.5	3.0	4.7	5.4	4.0	4.3	8.1	4.5	7.0	
RKNM	4.3	4.4	6.6	5.5	4.2	6.6	3.7	2.1	5.2	5.5	4.0	5.4	6.4	7.0	4.5	10.8	5.9	8.9	
LTIB	10.8	6.9	9.5	6.2	7.7	10.9	3.5	4.0	2.3	2.6	2.9	4.1	31.7	27.0	10.4	13.2	19.4	30.7	
RTIB	9.0	4.8	5.7	7.6	6.6	8.9	4.0	3.4	1.9	1.6	2.4	3.7	43.2	25.6	12.7	13.6	15.0	32.9	
LANK	2.4	2.2	2.2	2.8	2.2	3.0	3.2	4.2	4.8	2.2	3.2	4.6	4.2	3.6	4.4	4.1	3.6	5.1	
RANK	1.9	2.1	2.1	3.5	2.4	3.0	1.5	1.5	1.4	1.8	1.7	1.9	2.7	2.4	3.4	5.0	2.4	4.2	
LMED	3.4	2.6	2.2	4.0	2.8	3.9	1.1	1.4	1.6	2.3	1.8	2.0	2.9	1.3	2.8	2.6	2.4	3.2	
RMED	4.1	4.9	2.8	5.6	4.1	5.9	1.4	1.5	2.4	3.4	2.4	3.0	1.4	2.6	2.1	3.1	2.2	2.9	
LHEE	1.6	2.4	1.9	2.1	1.4	2.5	4.2	4.5	5.4	4.4	5.9	9.9	5.6	6.6	7.1	10.1	4.6	9.0	
RHEE	1.4	2.2	1.1	2.3	1.4	2.3	3.6	3.2	2.7	4.4	3.6	4.3	3.8	9.2	2.8	9.7	3.0	8.0	
LTOE	6.8	5.1	3.0	2.2	2.5	5.5	5.9	5.0	3.1	2.4	3.4	6.0	2.5	2.6	1.7	0.8	1.8	2.7	
RTOE	7.3	4.7	3.1	2.1	2.1	5.3	2.5	1.4	1.3	3.7	2.1	3.3	2.7	1.6	1.2	1.1	1.0	2.1	
Joint Center																			
LHJC	3.4	3.8	3.9	4.7	4.3	5.1	2.7	2.4	3.3	3.3	3.7	3.9	4.2	3.1	2.7	3.4	2.3	4.2	
RHJC	2.1	3.1	3.6	3.4	3.9	4.2	3.6	2.3	5.0	4.4	5.0	5.0	3.2	2.4	3.0	4.2	3.2	4.0	
LKJC	9.9	5.8	10.1	5.6	5.8	10.0	1.7	1.7	1.9	2.8	2.0	2.5	5.6	7.5	4.4	10.1	5.2	8.6	
RKJC	10.0	7.9	9.5	8.1	7.6	11.0	2.6	2.3	2.2	2.9	2.6	3.3	6.0	7.4	5.3	12.1	5.5	9.8	
LAJC	5.0	5.8	4.4	2.9	4.2	5.8	3.6	4.2	5.1	2.7	3.3	5.0	4.7	5.1	5.5	4.4	3.8	6.0	
RAJC	3.5	3.5	3.5	3.4	3.6	4.2	1.8	1.6	1.5	1.9	1.9	2.2	3.0	2.4	3.8	5.3	2.6	4.5	

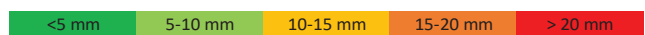


Table 10. Comparison of precision of marker position (SD, in mm) calculated for each evaluator (A-D), intra-evaluator (Intra) and inter-evaluator (Inter).

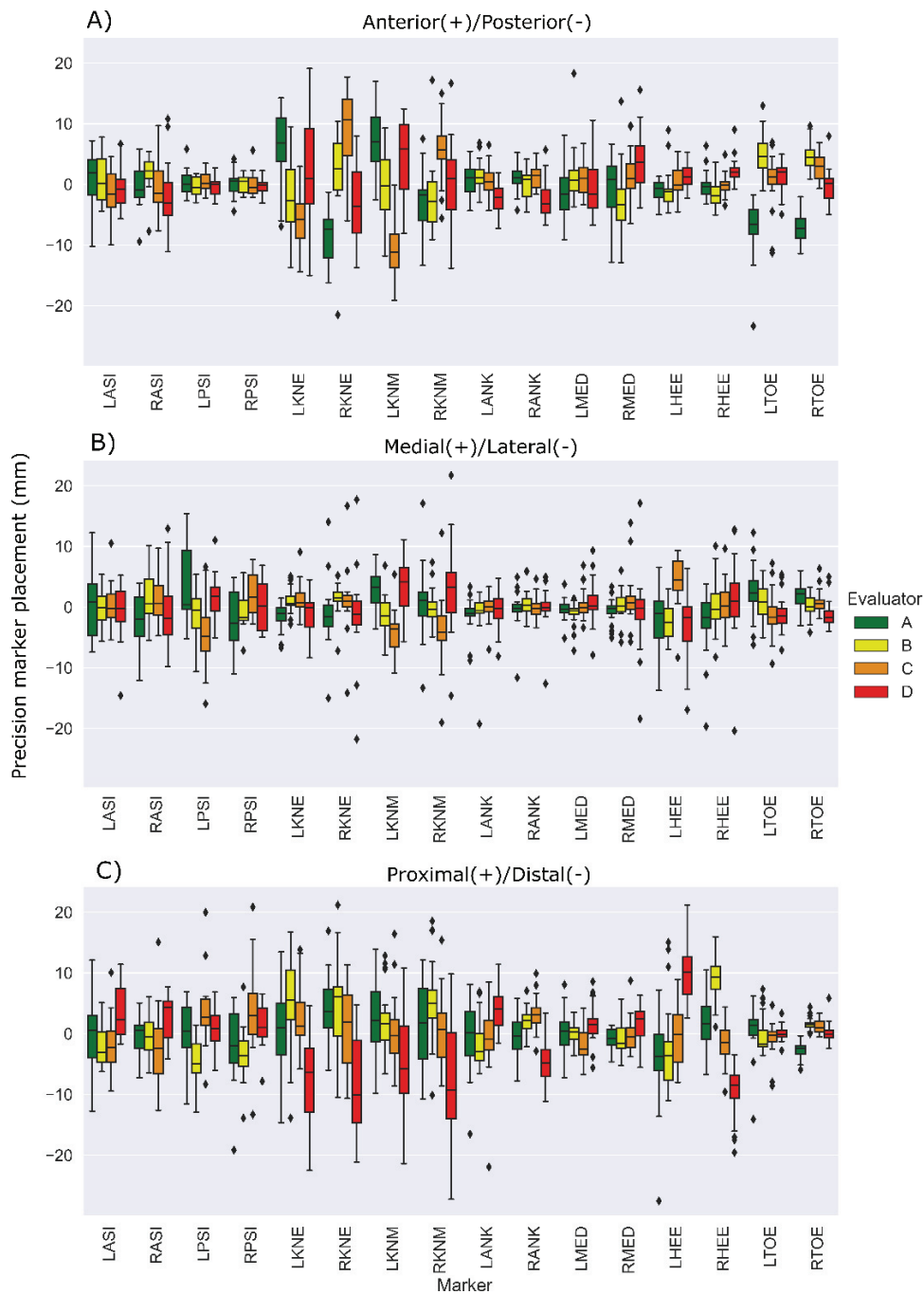


Figure 31. Difference of skin marker position with respect to the reference position, per evaluator, for the three different directions.

Orientation of anatomical coordinate systems – Static data

Table 11 reports the precision of the orientation of the anatomical (segment) coordinate systems. The definition of the sagittal and coronal planes showed all segments within 2.2° of precision while the transverse plane demonstrated higher variability for defining the thigh and shank, with differences up to approximately 6° of inter-evaluator precision and 4.5° of intra-evaluator precision.

Angles	Evaluator				Intra	Inter
	A	B	C	D		
Sagittal						
Pelvis	1.3	2.4	1.3	1.1	1.5	2.2
Thigh	1.3	1.2	1.2	1.5	1.3	1.7
Shank	1.3	1.3	1.0	1.6	1.3	1.8
Average	1.3	1.6	1.2	1.4	1.4	1.9
Coronal						
Pelvis	0.8	0.8	0.9	1.0	0.8	1.1
Thigh	0.8	0.5	0.9	1.3	0.9	0.9
Shank	0.5	0.5	0.5	0.9	0.6	0.7
Average	0.7	0.6	0.8	1.1	0.8	0.9
Transversal						
Pelvis	0.8	1.2	0.6	0.8	0.9	1.0
Thigh	6.2	4.3	3.6	3.7	4.5	5.6
Shank	5.1	3.8	5.4	3.6	4.5	5.8
Foot	2.5	1.4	1.9	1.8	1.9	3.0
Average	4.6	3.2	3.6	3.0	3.6	4.8

< 2°	2-5°	>5°
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Table 11. The precision of the orientation of anatomical (segment) coordinate systems (standard deviation in °) calculated for each evaluator (A-D), intra-evaluator (Intra), and inter-evaluator (Inter).

Kinematic variability – Gait data

Generally, good inter-trial and intra-evaluator reliability was observed among the joint angles. The SD ranged between 0.7° and 6.5°, with increased values associated with inter-evaluator variability (Table 12). Moreover, sagittal plane hip angle and foot progression angle showed the maximal variability (Table 12). The variability associated with each of the evaluators was similar among the joint angles. Additional reliability parameters are presented in Supplementary Material (S2). Moreover, the ANOVA analysis showed a statistically significant effect of the evaluators' experience on the precision of the following kinematic parameters: pelvic tilt, hip adduction-abduction, hip rotation, knee flexion-extension, knee varus-valgus, knee rotation, ankle flexion and foot progression angle (Table 13). The intra-evaluator variability was observed to increase in the hip and knee flexion-extension. Finally, the results relative to the post-hoc analysis reporting differences between the evaluators are presented in Supplementary Material (S4).

In addition, no statistically significant correlation ($p < 0.05$) was observed between the marker and kinematic precision calculated with the SD(°).

Variable	Plane	Parameter Feature	ICC			SD (°)		
			IT	IS	IE	IT	IS	IE
Pelvis	Sagittal	Mean cycle	0.85	0.82	0.73	1.5	1.7	2.0
		Max	0.41	0.35	0.40	0.7	0.7	0.7
		Min	0.87	0.84	0.75	1.4	1.6	1.9
		ROM	0.84	0.80	0.72	1.5	1.7	2.0
	Coronal	Mean cycle	0.76	0.74	0.62	0.9	1.0	1.2
		Max	0.90	0.88	0.87	0.9	1.0	1.0
		Min	0.80	0.78	0.72	0.9	1.0	1.1
		ROM	0.83	0.82	0.69	0.9	1.0	1.2
	Transversal	Mean cycle	0.51	0.41	0.38	1.6	1.8	2.1
		Max	0.73	0.69	0.72	1.8	1.9	2.5
		Min	0.62	0.53	0.46	1.4	1.5	2.2
		ROM	0.57	0.46	0.46	1.5	1.7	2.2
Hip	Sagittal	Mean cycle	0.85	0.81	0.77	1.9	2.7	3.1
		Max	0.88	0.82	0.86	1.4	1.8	1.9
		Min	0.82	0.79	0.72	1.9	2.0	2.3
		ROM	0.86	0.82	0.77	1.9	2.2	2.5
	Coronal	Mean cycle	0.77	0.75	0.61	1.2	1.3	2.0
		Max	0.91	0.89	0.89	1.2	1.3	1.9
		Min	0.86	0.84	0.77	1.3	1.7	2.6
		ROM	0.72	0.69	0.42	1.1	1.7	2.6
	Transversal	Mean cycle	0.81	0.73	0.61	2.2	4.8	6.5
		Max	0.83	0.80	0.70	2.7	3.8	5.5
		Min	0.83	0.78	0.68	2.2	3.6	5.3
		ROM	0.80	0.73	0.60	2.3	3.9	5.7
Knee	Sagittal	Mean cycle	0.81	0.77	0.58	2.0	2.2	2.9
		Max	0.65	0.59	0.62	1.8	1.9	2.4
		Min	0.62	0.54	0.22	1.8	2.0	3.6
		ROM	0.82	0.75	0.37	1.3	1.6	3.5
	Coronal	Mean cycle	0.93	0.92	0.88	0.8	0.8	1.0
		Max	0.78	0.76	0.65	2.0	2.4	3.0
		Min	0.88	0.85	0.76	1.6	1.8	2.3
		ROM	0.88	0.85	0.78	2.1	2.3	2.8
	Transversal	Mean cycle	0.77	0.66	0.62	3.6	4.4	5.7
		Max	0.75	0.73	0.68	2.7	3.8	4.5
		Min	0.75	0.65	0.54	3.3	4.9	5.5
		ROM	0.82	0.73	0.71	3.6	5.3	5.5
Ankle	Sagittal	Mean cycle	0.64	0.58	0.41	1.3	1.4	1.7
		Max	0.85	0.85	0.84	2.8	2.8	2.9
		Min	0.61	0.53	0.42	1.6	1.7	1.9
		ROM	0.90	0.88	0.87	2.6	2.9	3.1
Foot Progression	Transversal	Mean cycle	0.83	0.79	0.70	2.1	2.6	3.3
		Max	0.79	0.77	0.78	2.6	3.0	3.1
		Min	0.79	0.77	0.62	2.4	2.8	3.7
		ROM	0.87	0.84	0.78	2.2	2.7	3.3

Table 12. Reliability of kinematic data among three conditions: Inter-trial (IT); Intra-evaluator (IS); and Inter-evaluator (IE). Colors for ICC refer to good or excellent (ICC>0.75, green), moderate (0.75>ICC>0.5, yellow) and poor (ICC < 0.5, red). Colors for SD correspond to the generally applied cutoffs in clinical gait analysis as excellent (SD < 2°, green), acceptable (2° < SD < 5°, yellow) and unacceptable (SD > 5°, red) (McGinley et al. 2009a). Inter-trial (IT), intra-evaluator (IS) and inter-evaluator (IE) conditions analyzed.

Variable	Plane	Evaluator	ICC				SD (°)				ANOVA (F, p)
			A	B	C	D	A	B	C	D	
Pelvis	Sagittal	Mean cycle	0.82	0.75	0.72	0.65	4.0	4.0	4.2	3.5	2.25 (0.084)
		Max	0.85	0.76	0.76	0.67	3.9	3.9	4.2	3.5	3.08 (0.029)
		Min	0.82	0.72	0.67	0.62	3.8	3.8	4.1	3.4	1.85 (0.140)
		ROM	0.38	0.26	0.37	0.25	1.0	0.9	1.0	0.9	0.29 (0.833)
	Coronal	Mean cycle	0.57	0.76	0.59	0.72	1.6	1.9	1.9	2.0	0.81 (0.490)
		Max	0.72	0.78	0.69	0.79	2.0	2.1	2.2	2.4	0.53 (0.665)
		Min	0.73	0.79	0.69	0.79	2.0	2.2	2.2	2.4	0.93 (0.427)
		ROM	0.89	0.79	0.83	0.87	2.9	2.7	3.1	3.0	1.04 (0.375)
	Transversal	Mean cycle	0.38	0.43	0.40	0.40	2.2	2.4	2.3	2.3	0.68 (0.566)
		Max	0.47	0.54	0.45	0.39	2.3	2.5	2.3	2.3	0.35 (0.789)
		Min	0.39	0.45	0.38	0.30	2.2	2.4	2.3	2.2	0.38 (0.768)
		ROM	0.69	0.76	0.65	0.64	3.4	3.7	3.3	3.0	1.31 (0.273)
Hip	Sagittal	Mean cycle	0.80	0.73	0.68	0.77	5.4	5.5	5.4	5.2	0.86 (0.465)
		Max	0.83	0.70	0.72	0.78	5.3	4.9	5.1	5.0	0.94 (0.422)
		Min	0.78	0.62	0.59	0.67	3.9	4.0	4.2	3.9	0.41 (0.749)
		ROM	0.82	0.74	0.87	0.85	4.2	4.0	4.2	3.9	1.22 (0.303)
	Coronal	Mean cycle	0.73	0.82	0.70	0.77	3.0	3.0	3.0	3.3	1.50 (0.216)
		Max	0.81	0.88	0.80	0.84	3.7	3.5	3.6	4.0	2.67 (0.049)
		Min	0.70	0.72	0.48	0.70	2.7	2.8	2.5	2.9	0.79 (0.500)
		ROM	0.92	0.84	0.87	0.88	4.1	3.9	3.9	4.2	0.56 (0.642)
	Transversal	Mean cycle	0.79	0.70	0.71	0.59	7.4	8.0	7.4	6.7	4.07 (0.008)
		Max	0.83	0.72	0.68	0.67	7.5	7.5	7.0	6.9	0.95 (0.418)
		Min	0.85	0.64	0.70	0.65	8.2	8.5	8.2	7.4	4.80 (0.003)
		ROM	0.76	0.70	0.69	0.70	6.0	5.9	5.1	6.5	1.73 (0.162)
Knee	Sagittal	Mean cycle	0.71	0.72	0.72	0.72	4.0	4.5	4.0	4.1	1.45 (0.229)
		Max	0.45	0.31	0.36	0.34	2.5	2.6	2.3	3.0	3.95 (0.009)
		Min	0.60	0.64	0.61	0.55	2.4	2.8	2.8	2.8	9.93 (0.000)
		ROM	0.54	0.60	0.56	0.68	3.1	3.3	3.1	3.4	1.67 (0.174)
	Coronal	Mean cycle	0.91	0.92	0.94	0.89	3.4	3.0	3.1	3.5	1.61 (0.185)
		Max	0.84	0.70	0.69	0.86	5.1	4.1	4.0	5.8	2.54 (0.037)
		Min	0.92	0.78	0.85	0.90	7.4	6.9	7.1	6.2	0.87 (0.542)
		ROM	0.88	0.65	0.71	0.74	4.9	4.8	4.9	4.0	0.58 (0.652)
	Transversal	Mean cycle	0.60	0.43	0.60	0.30	7.7	6.4	6.7	6.0	3.58 (0.021)
		Max	0.64	0.37	0.63	0.23	7.2	5.5	6.6	5.5	1.12 (0.262)
		Min	0.74	0.56	0.70	0.48	8.5	7.1	7.4	7.2	3.12 (0.021)
		ROM	0.61	0.68	0.71	0.68	5.0	5.1	4.5	5.3	1.54 (0.111)
Ankle	Sagittal	Mean cycle	0.56	0.56	0.54	0.56	2.0	2.0	1.8	2.2	3.03 (0.031)
		Max	0.61	0.78	0.61	0.56	2.4	2.8	2.5	2.6	4.74 (0.003)
		Min	0.87	0.91	0.92	0.89	3.5	3.2	3.3	3.9	1.43 (0.235)
		ROM	0.87	0.88	0.90	0.87	3.8	3.6	4.3	4.1	0.96 (0.411)
Foot Progression	Transversal	Mean cycle	0.65	0.81	0.78	0.81	4.6	4.8	4.7	4.5	3.27 (0.022)
		Max	0.65	0.80	0.77	0.80	5.0	5.5	5.5	5.3	4.44 (0.005)
		Min	0.73	0.76	0.89	0.81	6.3	6.1	6.8	5.9	3.52 (0.016)
		ROM	0.70	0.73	0.81	0.77	6.2	6.6	6.8	6.4	0.83 (0.478)

Table 13. Reliability comparison of kinematic data between evaluators. Colors for ICC refer to good or excellent (ICC>0.75, green), moderate (0.75>ICC>0.5, yellow) and poor (ICC < 0.5, red). Colors in SD(°) correspond to SD within the three generally applied cutoffs in clinical gait analysis as excellent (SD < 2°, green), acceptable (2° < SD < 5°, yellow) and unacceptable (SD > 5°, red) (McGinley et al. 2009a). ANOVA demonstrates the differences between kinematics (SD(°)) among evaluators. F represents the F-statistics and p the p-value. Bold ANOVA (F,p) data in the table signify those data are statistically significant (p<0.05).

2.3.5. Discussion

This study aimed to evaluate the precision of marker placement among different evaluators and to evaluate its impact on the orientation of anatomical (segment) coordinate systems and kinematic data.

The protocol applied within this study was proven to be suitable for evaluating marker placement precision among evaluators as well as to evaluate its effect on the joint angle definition in static and gait trials. As expected, the evaluated precision on the marker position demonstrated that intra-

evaluator variability of marker placement is increased in comparison to the inter-evaluator. The least precise markers were the wands, especially in the proximal-distal direction. This is consistent with the fact that this marker is used to define only the frontal plane of the thigh and shank segments. Thus, its placement is not based on any anatomical bony landmark but rather on a visual alignment with other markers in the anterior-posterior direction and the wand can be placed in a range of positions within the segments for the proximal-distal direction. However, the processing of kinematic data following the CGM 1.1, estimates the knee joint center based on the femoral epicondyle markers and consequently the wand marker precision is less relevant for defining the thigh axes (Stief *et al.* 2013). A comparison between reliability of kinematic data computed with and without the use of medial femoral epicondyle markers (CGM 1.1 and CGM 1.0, respectively) is shown in Supplementary Material (S5). The impact of marker placement precision in kinematic variability is naturally dependent on the modeling specifications applied to processing of kinematic data. Thus, the results here presented cannot be generalized to other processing choices and it is expectable that the sensitivity to marker placement precision may vary as well.

In addition, the three joint centers demonstrated similar precision with maximal variability observed for the knee joint center, in anterior-posterior and proximal-distal directions (up to 11.0mm), which may arise from the fact that its estimation relies on the wand of the thigh. While the joint centers are defined based on multiple skin markers, it seems that there is no cumulative effect of the variability of markers used to estimate them. In general, the precision was comparable to the results reported by Della Croce *et al.* (Della Croce *et al.* 1999) but with slightly reduced variability. The increased sample size (participants and evaluators) and the use of skin markers instead of pointers may justify for such differences as well as advancements in technology used for recording gait analysis since then (1999).

In their results, Della Croce *et al.* showed high differences between the precision of the pelvic markers concerning their contra-lateral markers in anterior-posterior and medial-lateral directions (Della Croce *et al.* 1999). Such differences may be a consequence of placing the pelvic marker-cluster on the lateral side, as a slight displacement of the marker-cluster results in increased measurement error for markers placed further away from it. The abovementioned effect was slightly observed during our experiment (Supplementary Material, S1), where initially the lateral pelvic cluster was applied to the three first subjects. The definition of the cluster segment frame showed an amplified error on more distal markers. Such effect was suppressed with the use of a four-marker cluster added on the iliac crests. To ensure the quality of the analysis, the three participants initially mounted with rigid clusters were excluded from pelvic marker precision data. Consequently, the pelvic results are reported for only five patients and may explain the similarity among the results between contralateral pelvic markers.

Differences in the identification of the anatomical landmarks among evaluators were shown in Figure 31, with a clear difference in positioning. For instance, one of the evaluators (D) tended to place the knee and the anterior pelvic markers considerably more distally and posteriorly, respectively, in comparison with the other evaluators. Thus, this protocol could identify differences in marker placement practice between evaluators and could be used for quality assessment within a gait laboratory.

In static condition, the orientation of pelvis and lower limb anatomical (segment) coordinate systems showed good precision for the sagittal and coronal planes but increased variability for the transverse plane (**Error! Reference source not found.** 11). Those results are following those published previously (Della Croce *et al.* 1999) and demonstrate that the low reliability observed in the transverse

plane kinematics in gait analysis is considerably due to high variability in the placement of the skin markers.

Kinematic data had good reliability for the majority of the parameters evaluated (Table 12). The inter-evaluator reliability was poor for the knee and ankle on sagittal plane and the pelvis on transverse plane. The increased variability was observed for hip and knee rotation (SD up to 6.5 and 5.7°, respectively), supporting the consideration that these angles are the least reliable in three-dimensional gait analysis (McGinley *et al.* 2009). Moreover, the inter-trial variability was lower than the intra-evaluator variability, which was also reduced than the inter-evaluator variability for all parameters in accordance with previous reproducibility studies (Schwartz *et al.* 2004, Gorton *et al.* 2009, McGinley *et al.* 2009). This indicates that, for these participants, intrinsic variability is reduced than extrinsic variability due to marker misplacement.

Finally, the variability of kinematic data presented significant differences according to the level of experience of the evaluator (Table 13). Few studies have been identified in the literature reporting the influence of evaluator's experience on kinematic reliability (Leigh *et al.* 2014, Sinclair *et al.* 2014, Meng *et al.* 2020, Reay *et al.* 2022). A positive influence of experience in the reliability of kinematic data has also been demonstrated (Sinclair *et al.* 2014, Meng *et al.* 2020, Reay *et al.* 2022). Those findings suggest that the ability to identify anatomical landmarks and place the markers is improved with experience. This finding suggests the need for appropriate training for evaluators in clinical gait analysis.

Lastly, and contrarily to our hypothesis, the marker placement precision showed no significant correlation with the kinematic precision. This may arise from the fact that marker placement varies in a multidirectional way, with different magnitudes and that the resultant kinematic variability is the result of the complete set of markers. Thus, an error in the placement of one specific marker can be compensated or enhanced, in a non-linear way, by an error in the placement of other markers, as shown in a previous simulation study (Fonseca *et al.* 2022).

The main limitation of the present and similar studies (Leigh *et al.* 2014, Sinclair *et al.* 2014, Meng *et al.* 2020, Yeo and Park 2020, Reay *et al.* 2022) is the non-inclusion of a population with motor disorders, bone deformity, or high body mass index as it would be more representative of the precision obtained during clinical gait analysis. The inclusion of participants with increased body mass indexes could also provide better insight into the effect of soft tissue on the precision of marker placement. The inclusion of such characteristics would increase the robustness of the statistical evaluation of the influence of experience in measurement reliability. However, such a procedure requires the participant to be standing and walking for a considerable amount of time (two and a half hours), and so complicated for pathological participants. Finally, the low number of evaluators per level of experience is another limitation affecting the robustness in the evaluation of the influence of experience in marker placement. However, the increased time required for the experimental procedure has a low marge to increase the number of evaluators.

In sum, the results of this study provide quantitative information regarding the actual precision of marker placement of the CGM in a clinical gait analysis laboratory and its impact on the orientation of anatomical coordinate systems and kinematics. Such information, coupled with simulation tools can be used to estimate the variability of kinematics by implementing measured marker placement precision to set the magnitude of simulated displacements. This study showed that femoral and wand markers have increased variability, in both anterior-posterior and proximal-distal directions. Moreover, the hip and knee angles on transverse plane showed the least reliability. In addition, the experience of evaluators impacts significantly marker precision and kinematic variability. Finally, it was

demonstrated that no correlation exists between marker placement precision and kinematic variability. The authors recommend a periodical evaluation of the reliability of measurements of their evaluators by applying similar measurement procedures. These results could be used in a quality standard procedure for each clinical gait laboratory and could be extended to other biomechanical models. Furthermore, this protocol can also serve for the training of new evaluators.

2.3.6. Supplementary Material

2.3.6.1. S1 – Comparison between rigid and non-rigid pelvic cluster

Due to the morphology of the pelvic structure, the fixation of a rigid cluster was reported a difficult task. This is due to that the clusters should not interfere with the placement of pelvic markers. As a consequence, the most practical location for this cluster is on the lateral part of the pelvis and distally in comparison with the pelvic markers. However, if for any reason, the orientation of the cluster coordinate system is slightly altered, the contralateral markers will show a higher error due to the lever arm effect. Thus, we have added a non-rigid four-marker cluster placed on the iliac crests of the two sides of the pelvis. Therefore, the distance between all markers with respect to the origin of the coordinate system of the cluster was approximately the same among contralateral markers. Figure S1 illustrates the variation of the cluster coordinate system for both situations demonstrated. No clear differences can be observed between the orientation of the anatomical (segment) coordinate systems calculated by the rigid and non-rigid pelvic cluster. However, taking into account the aforementioned possible cause of the error and the differences presented by Della Croce (Della Croce *et al.* 1999) on the pelvic marker placement precision, we recommend the selection of a non-rigid cluster.

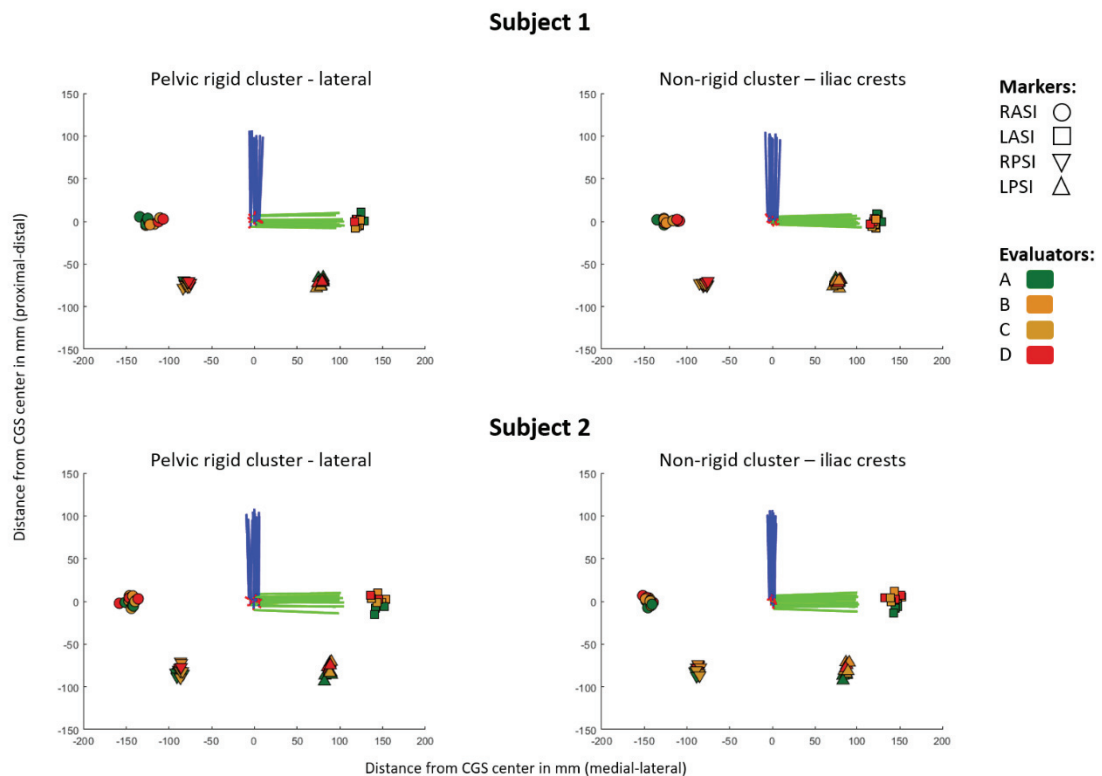


Figure 32. Comparison between the definition of the pelvic cluster coordinate system calculated from the rigid (left) and non-rigid four markers and estimation of marker coordinates. Medial-lateral axis (green), proximal-distal axis (blue), and anterior-posterior axis (red) are represented for each session relative to two subjects.

2.3.6.2. S2 – Reliability results for kinematic data

Variable	Plane	Feature	ICC (IT)	ICC (IS)	ICC (IE)	SEM (IT)	SEM (IS)	SEM (IE)	MDC (IT)	MDC (IS)	MDC (IE)
Pelvis	Sagittal	Mean cycle	0.85	0.82	0.73	1.5	1.7	2.0	4.2	4.6	5.6
		ROM	0.41	0.35	0.40	0.7	0.7	0.7	1.9	2.0	2.0
		Max	0.87	0.84	0.75	1.4	1.6	1.9	3.9	4.4	5.4
		Min	0.84	0.80	0.72	1.5	1.7	2.0	4.3	4.7	5.6
	Coronal	Mean cycle	0.76	0.74	0.62	0.9	1.0	1.2	2.6	2.7	3.3
		ROM	0.90	0.88	0.87	0.9	1.0	1.0	2.6	2.9	2.9
		Max	0.80	0.78	0.72	0.9	1.0	1.1	2.6	2.7	3.1
		Min	0.83	0.82	0.69	0.9	1.0	1.2	2.6	2.6	3.4
	Transversal	Mean cycle	0.51	0.41	0.38	1.6	1.7	1.8	4.3	4.8	4.9
		ROM	0.73	0.69	0.72	1.8	1.9	1.8	4.9	5.2	5.0
		Max	0.62	0.53	0.46	1.4	1.5	1.7	3.9	4.3	4.6
		Min	0.57	0.46	0.46	1.5	1.7	1.7	4.3	4.8	4.8
Hip	Sagittal	Mean cycle	0.85	0.81	0.77	2.2	2.4	2.6	6.0	6.8	7.3
		ROM	0.88	0.82	0.86	1.4	1.7	1.5	3.8	4.6	4.1
		Min	0.82	0.79	0.72	1.9	2.0	2.3	5.2	5.6	6.5
		Max	0.86	0.82	0.77	1.9	2.2	2.5	5.3	6.1	6.8
	Coronal	Mean cycle	0.77	0.75	0.61	1.2	1.3	1.6	3.4	3.6	4.5
		ROM	0.91	0.89	0.89	1.2	1.3	1.3	3.3	3.6	3.7
		Max	0.86	0.84	0.77	1.3	1.3	1.6	3.5	3.7	4.4
		Min	0.72	0.69	0.42	1.1	1.2	1.6	3.1	3.3	4.5
	Transversal	Mean cycle	0.81	0.73	0.61	3.2	3.8	4.5	9.0	10.6	12.6
		ROM	0.83	0.80	0.70	2.7	2.8	3.5	7.4	7.9	9.6
		Max	0.83	0.78	0.68	3.2	3.6	4.3	8.8	10.0	12.0
		Min	0.80	0.73	0.60	3.3	3.9	4.7	9.1	10.7	13.0
Knee	Sagittal	Mean cycle	0.81	0.77	0.58	2.0	2.2	2.9	5.4	6.2	7.9
		ROM	0.65	0.59	0.62	1.8	1.9	1.9	4.9	5.4	5.2
		Max	0.62	0.54	0.22	1.8	2.0	2.6	4.9	5.5	7.1
		Min	0.82	0.75	0.37	1.3	1.6	2.5	3.6	4.3	6.9
	Coronal	Mean cycle	0.93	0.92	0.88	0.8	0.8	1.0	2.1	2.3	2.8
		ROM	0.78	0.76	0.65	2.0	2.1	2.6	5.7	5.9	7.1
		Max	0.88	0.85	0.76	1.6	1.8	2.3	4.5	5.1	6.5
		Min	0.88	0.85	0.78	2.1	2.3	2.8	5.8	6.5	7.8
	Transversal	Mean cycle	0.77	0.66	0.62	3.6	4.4	4.7	10.0	12.1	13.0
		ROM	0.75	0.73	0.68	2.7	2.8	3.0	7.5	7.8	8.4
		Max	0.75	0.65	0.54	3.3	3.9	4.5	9.1	10.8	12.3
		Min	0.82	0.73	0.71	3.6	4.3	4.5	9.9	12.1	12.5
Ankle	Sagittal	Mean cycle	0.64	0.58	0.41	1.3	1.4	1.7	3.7	4.0	4.7
		ROM	0.85	0.85	0.84	2.8	2.8	2.9	7.7	7.9	8.1
		Max	0.61	0.53	0.42	1.6	1.7	1.9	4.3	4.7	5.2
		Min	0.90	0.88	0.87	2.6	2.9	3.1	7.3	8.0	8.6
Foot	Transversal	Mean cycle	0.83	0.79	0.70	2.1	2.3	2.8	5.8	6.4	7.7
		ROM	0.79	0.77	0.78	2.6	2.7	2.6	7.1	7.4	7.2
		Max	0.79	0.77	0.62	2.4	2.5	3.2	6.7	7.0	9.0
		Min	0.87	0.84	0.78	2.2	2.4	2.8	6.1	6.7	7.9

Table 14. S2.1. Reliability of kinematic data among three conditions: Inter-trial (IT); Intra-evaluator (IS); and Inter-evaluator (IE). Intra-class correlation (ICC); standard error of a measurement (SEM) and minimal detectable change (MDC) analyzed for continuous (Mean cycle) and discrete parameters (ROM – range of motion; Max – maximum peak; Min – minimum peak).

Variable	Plane	Feature	ICC(A)	ICC(B)	ICC(C)	ICC(D)	SEM(A)	SEM(B)	SEM(C)	SEM(D)	MDC(A)	MDC(B)	MDC(C)	MDC(D)	ANOVA (F,P)
Pelvis	Sagittal	Mean cycle	0.82	0.75	0.72	0.65	1.67	1.99	2.23	2.08	4.62	5.51	6.19	5.76	2.25 (0.084)
		Max	0.85	0.76	0.76	0.67	1.52	1.91	2.08	2.03	4.20	5.29	5.75	5.61	3.08 (0.029)
		Min	0.82	0.72	0.67	0.62	1.60	1.98	2.34	2.07	4.45	5.49	6.48	5.75	1.85 (0.140)
		ROM	0.38	0.26	0.37	0.25	0.82	0.80	0.76	0.77	2.28	2.21	2.10	2.12	0.29 (0.833)
	Coronal	Mean cycle	0.57	0.76	0.59	0.72	1.02	0.91	1.19	1.07	2.82	2.51	3.31	2.96	0.81 (0.490)
		Max	0.72	0.78	0.69	0.79	1.05	0.98	1.25	1.10	2.90	2.72	3.46	3.05	0.53 (0.665)
		Min	0.73	0.79	0.69	0.79	1.02	0.96	1.23	1.09	2.82	2.65	3.42	3.02	0.93 (0.427)
		ROM	0.89	0.79	0.83	0.87	0.94	1.26	1.28	1.10	2.61	3.49	3.54	3.06	1.04 (0.375)
	Transversal	Mean cycle	0.38	0.43	0.40	0.40	1.73	1.80	1.77	1.80	4.78	5.00	4.92	4.99	0.68 (0.566)
		Max	0.47	0.54	0.45	0.39	1.66	1.71	1.64	1.70	4.59	4.74	4.54	4.71	0.35 (0.789)
		Min	0.39	0.45	0.38	0.30	1.69	1.76	1.76	1.78	4.69	4.89	4.87	4.92	0.38 (0.768)
		ROM	0.69	0.76	0.65	0.64	1.88	1.81	1.98	1.81	5.20	5.02	5.50	5.02	1.31 (0.273)
Hip	Sagittal	Mean cycle	0.80	0.73	0.77	0.68	2.43	2.87	2.51	3.06	6.72	7.96	6.96	8.49	0.86 (0.465)
		Max	0.83	0.70	0.78	0.72	2.17	2.70	2.34	2.72	6.01	7.48	6.48	7.55	0.94 (0.422)
		Min	0.78	0.62	0.59	0.67	1.83	2.45	2.67	2.25	5.08	6.79	7.40	6.23	0.41 (0.749)
		ROM	0.82	0.74	0.87	0.85	1.81	2.03	1.51	1.48	5.03	5.63	4.17	4.09	1.22 (0.303)
	Coronal	Mean cycle	0.73	0.82	0.70	0.77	1.54	1.20	1.58	1.53	4.28	3.32	4.37	4.25	1.50 (0.216)
		Max	0.81	0.88	0.80	0.84	1.61	1.17	1.57	1.56	4.45	3.24	4.36	4.32	2.67 (0.049)
		Min	0.70	0.72	0.70	0.48	1.49	1.33	1.44	1.56	4.13	3.68	4.00	4.33	0.79 (0.500)
		ROM	0.92	0.84	0.87	0.88	1.18	1.56	1.41	1.42	3.26	4.33	3.92	3.94	0.56 (0.642)
	Transversal	Mean cycle	0.79	0.70	0.71	0.59	3.38	4.31	4.01	4.30	9.38	11.94	11.13	11.91	4.07 (0.008)
		Max	0.83	0.72	0.68	0.67	3.09	3.96	3.98	3.90	8.57	10.97	11.04	10.82	0.95 (0.418)
		Min	0.85	0.64	0.70	0.65	2.98	4.99	4.37	4.34	8.26	13.82	12.10	12.03	4.80 (0.003)
		ROM	0.76	0.70	0.69	0.70	2.87	3.22	2.78	3.19	7.96	8.92	7.72	8.85	1.73 (0.162)
Knee	Sagittal	Mean cycle	0.71	0.72	0.72	0.72	2.19	2.37	2.09	2.14	6.06	6.57	5.78	5.94	1.45 (0.229)
		Max	0.45	0.31	0.36	0.34	1.88	2.17	1.89	2.38	5.22	6.01	5.23	6.59	3.95 (0.009)
		Min	0.60	0.64	0.61	0.55	1.47	1.71	1.73	1.90	4.09	4.73	4.78	5.26	9.93 (0.000)
		ROM	0.54	0.60	0.56	0.68	2.07	2.12	2.05	1.92	5.73	5.89	5.68	5.32	1.67 (0.174)
	Coronal	Mean cycle	0.91	0.92	0.94	0.89	1.00	0.82	0.72	1.14	2.77	2.28	1.98	3.17	2.10 (0.101)
		Max	0.84	0.70	0.69	0.86	2.04	2.25	2.18	2.10	5.67	6.25	6.03	5.83	2.05 (0.108)
		Min	0.92	0.78	0.85	0.90	2.07	2.97	2.46	1.99	5.74	8.24	6.81	5.50	1.09 (0.356)
		ROM	0.88	0.65	0.71	0.74	1.66	2.62	2.51	1.96	4.59	7.26	6.96	5.43	0.36 (0.783)
	Transversal	Mean cycle	0.60	0.43	0.60	0.30	4.87	4.79	4.12	5.02	13.50	13.29	11.41	13.91	0.78 (0.506)
		Max	0.64	0.37	0.63	0.23	4.31	4.37	4.04	4.84	11.93	12.11	11.19	13.41	0.84 (0.472)
		Min	0.74	0.56	0.70	0.48	4.31	4.69	4.03	5.17	11.95	13.00	11.18	14.34	1.29 (0.280)
		ROM	0.61	0.68	0.71	0.68	3.00	2.91	2.40	2.81	8.30	8.06	6.65	7.80	0.30 (0.828)
Ankle	Sagittal	Mean cycle	0.56	0.56	0.54	0.56	1.36	1.32	1.24	1.47	3.76	3.66	3.43	4.08	3.03 (0.031)
		Max	0.61	0.78	0.61	0.56	1.46	1.30	1.53	1.60	4.04	3.59	4.23	4.44	4.74 (0.003)
		Min	0.87	0.91	0.92	0.89	2.88	2.68	2.64	2.92	7.97	7.42	7.31	8.08	1.43 (0.235)
		ROM	0.87	0.88	0.90	0.87	2.64	2.58	2.59	2.78	7.32	7.14	7.19	7.71	0.96 (0.411)
Foot	Transversal	Mean cycle	0.65	0.81	0.78	0.81	2.74	2.07	2.14	1.97	7.61	5.74	5.92	5.47	3.27 (0.022)
		Max	0.65	0.80	0.77	0.80	2.91	2.42	2.64	2.36	8.06	6.71	7.33	6.55	4.44 (0.005)
		Min	0.73	0.76	0.89	0.81	3.27	2.98	2.22	2.57	9.07	8.26	6.16	7.13	3.52 (0.016)
		ROM	0.70	0.73	0.81	0.77	3.42	3.51	2.85	3.11	9.49	9.72	7.91	8.63	0.83 (0.478)

Table 15. S2.2 Reliability comparison of kinematics data between evaluators. Intra-class correlation (ICC); standard error of a measurement (SEM) and minimal detectable change (MDC) analyzed for continuous (Mean cycle) and discrete parameters (ROM – range of motion; Max – maximum peak; Min – minimum peak). Bold ANOVA (F,p) data in the table signify those data are statistically significant.

Variable	Plane	Feature	ICC(A)	ICC(B)	ICC(C)	ICC(D)	SEM(A)	SEM(B)	SEM(C)	SEM(D)	MDC(A)	MDC(B)	MDC(C)	MDC(D)
Pelvis	Sagittal	Mean cycle	0.82	0.75	0.72	0.65	1.67	1.99	2.23	2.08	4.62	5.51	6.19	5.76
		Max	0.85	0.76	0.76	0.67	1.52	1.91	2.08	2.03	4.20	5.29	5.75	5.61
		Min	0.82	0.72	0.67	0.62	1.60	1.98	2.34	2.07	4.45	5.49	6.48	5.75
		ROM	0.38	0.26	0.37	0.25	0.82	0.80	0.76	0.77	2.28	2.21	2.10	2.12
	Coronal	Mean cycle	0.57	0.76	0.59	0.72	1.02	0.91	1.19	1.07	2.82	2.51	3.31	2.96
		Max	0.72	0.78	0.69	0.79	1.05	0.98	1.25	1.10	2.90	2.72	3.46	3.05
		Min	0.73	0.79	0.69	0.79	1.02	0.96	1.23	1.09	2.82	2.65	3.42	3.02
		ROM	0.89	0.79	0.83	0.87	0.94	1.26	1.28	1.10	2.61	3.49	3.54	3.06
	Transversal	Mean cycle	0.38	0.43	0.40	0.40	1.73	1.80	1.77	1.80	4.78	5.00	4.92	4.99
		Max	0.47	0.54	0.45	0.39	1.66	1.71	1.64	1.70	4.59	4.74	4.54	4.71
		Min	0.39	0.45	0.38	0.30	1.69	1.76	1.76	1.78	4.69	4.89	4.87	4.92
		ROM	0.69	0.76	0.65	0.64	1.88	1.81	1.98	1.81	5.20	5.02	5.50	5.02
Hip	Sagittal	Mean cycle	0.80	0.73	0.77	0.68	2.43	2.87	2.51	3.06	6.72	7.96	6.96	8.49
		Max	0.83	0.70	0.78	0.72	2.17	2.70	2.34	2.72	6.01	7.48	6.48	7.55
		Min	0.78	0.62	0.59	0.67	1.83	2.45	2.67	2.25	5.08	6.79	7.40	6.23
		ROM	0.82	0.74	0.87	0.85	1.81	2.03	1.51	1.48	5.03	5.63	4.17	4.09
	Coronal	Mean cycle	0.73	0.82	0.70	0.77	1.54	1.20	1.58	1.53	4.28	3.32	4.37	4.25
		Max	0.81	0.88	0.80	0.84	1.61	1.17	1.57	1.56	4.45	3.24	4.36	4.32
		Min	0.70	0.72	0.70	0.48	1.49	1.33	1.44	1.56	4.13	3.68	4.00	4.33
		ROM	0.92	0.84	0.87	0.88	1.18	1.56	1.41	1.42	3.26	4.33	3.92	3.94
	Transversal	Mean cycle	0.79	0.70	0.71	0.59	3.38	4.31	4.01	4.30	9.38	11.94	11.13	11.91
		Max	0.83	0.72	0.68	0.67	3.09	3.96	3.98	3.90	8.57	10.97	11.04	10.82
		Min	0.85	0.64	0.70	0.65	2.98	4.99	4.37	4.34	8.26	13.82	12.10	12.03
		ROM	0.76	0.70	0.69	0.70	2.87	3.22	2.78	3.19	7.96	8.92	7.72	8.85
Knee	Sagittal	Mean cycle	0.71	0.72	0.72	0.72	2.19	2.37	2.09	2.14	6.06	6.57	5.78	5.94
		Max	0.45	0.31	0.36	0.34	1.88	2.17	1.89	2.38	5.22	6.01	5.23	6.59
		Min	0.60	0.64	0.61	0.55	1.47	1.71	1.73	1.90	4.09	4.73	4.78	5.26
		ROM	0.54	0.60	0.56	0.68	2.07	2.12	2.05	1.92	5.73	5.89	5.68	5.32
	Coronal	Mean cycle	0.91	0.92	0.94	0.89	1.00	0.82	0.72	1.14	2.77	2.28	1.98	3.17
		Max	0.84	0.70	0.69	0.86	2.04	2.25	2.18	2.10	5.67	6.25	6.03	5.83
		Min	0.92	0.78	0.85	0.90	2.07	2.97	2.46	1.99	5.74	8.24	6.81	5.50
		ROM	0.88	0.65	0.71	0.74	1.66	2.62	2.51	1.96	4.59	7.26	6.96	5.43
	Transversal	Mean cycle	0.60	0.43	0.60	0.30	4.87	4.79	4.12	5.02	13.50	13.29	11.41	13.91
		Max	0.64	0.37	0.63	0.23	4.31	4.37	4.04	4.84	11.93	12.11	11.19	13.41
		Min	0.74	0.56	0.70	0.48	4.31	4.69	4.03	5.17	11.95	13.00	11.18	14.34
		ROM	0.61	0.68	0.71	0.68	3.00	2.91	2.40	2.81	8.30	8.06	6.65	7.80
Ankle	Sagittal	Mean cycle	0.56	0.56	0.54	0.56	1.36	1.32	1.24	1.47	3.76	3.66	3.43	4.08
		Max	0.61	0.78	0.61	0.56	1.46	1.30	1.53	1.60	4.04	3.59	4.23	4.44
		Min	0.87	0.91	0.92	0.89	2.88	2.68	2.64	2.92	7.97	7.42	7.31	8.08
		ROM	0.87	0.88	0.90	0.87	2.64	2.58	2.59	2.78	7.32	7.14	7.19	7.71
Foot	Transversal	Mean cycle	0.65	0.81	0.78	0.81	2.74	2.07	2.14	1.97	7.61	5.74	5.92	5.47
		Max	0.65	0.80	0.77	0.80	2.91	2.42	2.64	2.36	8.06	6.71	7.33	6.55
		Min	0.73	0.76	0.89	0.81	3.27	2.98	2.22	2.57	9.07	8.26	6.16	7.13
		ROM	0.70	0.73	0.81	0.77	3.42	3.51	2.85	3.11	9.49	9.72	7.91	8.63

Table 16. S2.3 Intra-evaluator reliability among the four evaluators. Intra-class correlation (ICC); standard error of a measurement (SEM) and minimal detectable change (MDC) analyzed for continuous (Mean cycle) and discrete parameters (ROM – range of motion; Max – maximum peak; Min – minimum peak).

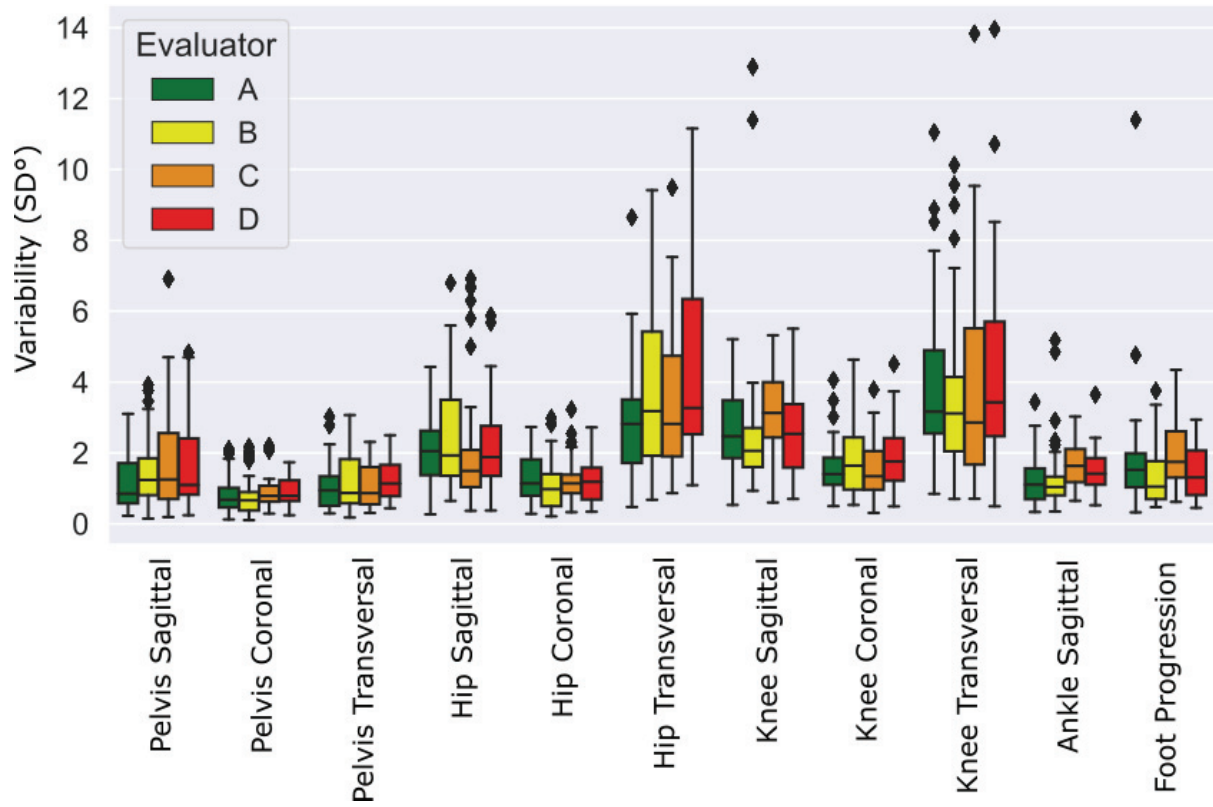


Figure 33. S3.4. Intra-evaluator kinematic variability (SD°).

2.3.6.3. S3 – Marker precision differences among evaluators.

Anterior-Posterior							
Marker	Anova (F, p)	Diff (p)					
		A-B	A-C	A-D	B-C	B-D	C-D
LASI	1.75 (0.162)	2.78 (0.818)	2.98 (0.785)	4.18 (0.585)	5.76 (0.317)	6.96 (0.166)	1.20 (0.900)
RASI	0.94 (0.426)	3.00 (0.900)	3.94 (0.900)	7.26 (0.665)	6.93 (0.693)	10.26 (0.405)	3.33 (0.900)
LPSI	0.32 (0.807)	0.42 (0.900)	6.24 (0.867)	5.84 (0.894)	5.82 (0.895)	5.42 (0.900)	0.40 (0.900)
RPSI	0.31 (0.816)	1.15 (0.900)	5.92 (0.856)	5.71 (0.871)	4.76 (0.900)	4.55 (0.900)	0.21 (0.900)
LTHI	2.72 (0.049)	7.09 (0.045)	1.13 (0.900)	2.75 (0.709)	5.96 (0.122)	4.35 (0.369)	1.61 (0.900)
RTHI	9.66 (0.000)	7.82 (0.055)	15.59 (0.001)	11.62 (0.001)	7.77 (0.057)	3.79 (0.583)	3.98 (0.550)
LKNE	17.12 (0.000)	8.16 (0.001)	12.38 (0.001)	4.69 (0.050)	4.22 (0.094)	3.46 (0.223)	7.69 (0.001)
RKNE	32.38 (0.000)	11.05 (0.001)	17.80 (0.001)	5.65 (0.019)	6.75 (0.003)	5.40 (0.027)	12.15 (0.001)
LKNM	7.61 (0.000)	7.63 (0.243)	17.83 (0.001)	2.48 (0.900)	10.20 (0.065)	5.15 (0.573)	15.35 (0.002)
RKNM	1.87 (0.142)	0.94 (0.900)	8.78 (0.149)	2.40 (0.900)	7.84 (0.231)	1.45 (0.900)	6.38 (0.410)
LTIB	9.37 (0.000)	13.58 (0.001)	10.45 (0.002)	10.81 (0.001)	3.14 (0.649)	2.77 (0.723)	0.37 (0.900)
RTIB	11.47 (0.000)	10.17 (0.001)	10.55 (0.001)	10.96 (0.001)	0.38 (0.900)	0.79 (0.900)	0.41 (0.900)
LANK	3.75 (0.014)	0.93 (0.857)	0.13 (0.900)	2.89 (0.091)	0.80 (0.900)	3.82 (0.012)	3.02 (0.072)
RANK	7.99 (0.000)	1.09 (0.608)	0.43 (0.900)	3.59 (0.001)	1.52 (0.337)	2.50 (0.034)	4.02 (0.001)
LMED	0.89 (0.451)	2.35 (0.497)	1.97 (0.626)	0.60 (0.900)	0.39 (0.900)	1.76 (0.697)	1.37 (0.825)
RMED	2.12 (0.103)	2.07 (0.777)	2.44 (0.686)	3.03 (0.541)	4.51 (0.204)	5.10 (0.121)	0.59 (0.900)
LHEE	0.67 (0.572)	0.14 (0.900)	1.58 (0.884)	2.71 (0.601)	1.43 (0.900)	2.56 (0.637)	1.13 (0.900)
RHEE	1.22 (0.308)	1.66 (0.831)	0.03 (0.900)	2.24 (0.673)	1.69 (0.822)	3.90 (0.235)	2.21 (0.683)
LTOE	6.03 (0.001)	11.80 (0.001)	7.41 (0.052)	8.08 (0.028)	4.39 (0.418)	3.72 (0.554)	0.67 (0.900)
RTOE	6.59 (0.000)	12.01 (0.001)	10.32 (0.004)	7.01 (0.085)	1.69 (0.900)	5.00 (0.325)	3.30 (0.653)
LHJC	1.40 (0.249)	2.46 (0.550)	1.22 (0.900)	0.24 (0.900)	3.68 (0.209)	2.70 (0.478)	0.98 (0.900)
RHJC	1.59 (0.199)	0.85 (0.900)	1.46 (0.807)	2.57 (0.440)	2.31 (0.529)	3.43 (0.194)	1.11 (0.900)
LKJC	23.26 (0.000)	6.73 (0.012)	17.70 (0.001)	6.82 (0.011)	10.97 (0.001)	0.09 (0.900)	10.88 (0.001)
RKJC	20.58 (0.000)	11.44 (0.001)	17.29 (0.001)	3.42 (0.500)	5.85 (0.084)	8.02 (0.008)	13.87 (0.001)
LAJC	13.39 (0.000)	8.02 (0.001)	1.06 (0.869)	1.10 (0.853)	6.96 (0.001)	6.92 (0.001)	0.04 (0.900)
RAJC	1.90 (0.135)	0.90 (0.867)	2.46 (0.181)	0.06 (0.900)	1.56 (0.561)	0.96 (0.838)	2.53 (0.164)

Table 17. S3.1. ANOVA analysis of marker precision difference among evaluators on the anterior-posterior direction. Bold entries represent values with statistically significant difference ($p < 0.05$). Comparison between differences in marker placement precision between paired evaluators with a Tukey's post-hoc difference (Diff) and p-value (p).

Medial-Lateral							
Marker	Anova (F, p)	Diff (p)					
		A-B	A-C	A-D	B-C	B-D	C-D
LASI	0.61 (0.610)	1.15 (0.900)	14.18 (0.726)	14.09 (0.729)	13.03 (0.771)	12.94 (0.774)	0.09 (0.900)
RASI	0.66 (0.579)	2.61 (0.900)	5.51 (0.900)	8.51 (0.745)	8.12 (0.769)	11.12 (0.580)	3.00 (0.900)
LPSI	2.41 (0.072)	3.73 (0.900)	14.52 (0.112)	12.76 (0.196)	10.80 (0.335)	9.04 (0.493)	1.76 (0.900)
RPSI	0.03 (0.993)	1.15 (0.900)	0.35 (0.900)	0.15 (0.900)	0.80 (0.900)	1.30 (0.900)	0.50 (0.900)
LTHI	0.83 (0.481)	0.17 (0.900)	0.08 (0.900)	2.98 (0.574)	0.25 (0.900)	3.16 (0.533)	2.91 (0.592)
RTHI	0.94 (0.425)	0.95 (0.900)	1.26 (0.900)	3.44 (0.672)	0.31 (0.900)	4.39 (0.504)	4.70 (0.447)
LKNE	3.04 (0.033)	2.65 (0.137)	2.86 (0.094)	0.34 (0.900)	0.21 (0.900)	2.31 (0.238)	2.52 (0.172)
RKNE	1.11 (0.349)	2.72 (0.507)	2.25 (0.640)	0.03 (0.900)	0.47 (0.900)	2.75 (0.498)	2.28 (0.631)
LKNM	13.30 (0.000)	4.28 (0.016)	7.18 (0.001)	0.39 (0.900)	2.89 (0.175)	4.67 (0.007)	7.57 (0.001)
RKNM	4.62 (0.005)	0.93 (0.900)	4.91 (0.059)	2.05 (0.688)	3.98 (0.172)	2.99 (0.413)	6.96 (0.003)
LTIB	2.46 (0.068)	2.69 (0.386)	1.67 (0.730)	0.68 (0.900)	4.36 (0.053)	3.37 (0.194)	0.99 (0.900)
RTIB	1.80 (0.153)	3.51 (0.127)	0.80 (0.900)	1.57 (0.729)	2.71 (0.324)	1.93 (0.602)	0.78 (0.900)
LANK	2.35 (0.078)	3.48 (0.527)	3.29 (0.568)	0.68 (0.900)	6.77 (0.048)	2.80 (0.675)	3.97 (0.416)
RANK	0.33 (0.800)	0.89 (0.799)	0.02 (0.900)	0.43 (0.900)	0.87 (0.810)	0.46 (0.900)	0.41 (0.900)
LMED	1.67 (0.179)	0.64 (0.891)	0.72 (0.847)	1.28 (0.505)	1.36 (0.453)	1.93 (0.162)	0.56 (0.900)
RMED	0.94 (0.425)	0.81 (0.900)	1.79 (0.509)	0.12 (0.900)	0.98 (0.860)	0.94 (0.877)	1.91 (0.453)
LHEE	6.56 (0.000)	8.28 (0.232)	10.33 (0.088)	3.27 (0.862)	18.61 (0.001)	5.01 (0.639)	13.60 (0.012)
RHEE	1.67 (0.178)	2.73 (0.396)	2.56 (0.454)	3.70 (0.148)	0.17 (0.900)	0.97 (0.900)	1.14 (0.900)
LTOE	3.50 (0.019)	6.66 (0.025)	5.84 (0.063)	5.69 (0.073)	0.82 (0.900)	0.96 (0.900)	0.14 (0.900)
RTOE	3.19 (0.027)	1.59 (0.713)	1.07 (0.898)	4.59 (0.021)	0.52 (0.900)	3.00 (0.224)	3.52 (0.115)
LHJC	0.48 (0.694)	1.04 (0.842)	0.68 (0.900)	0.39 (0.900)	0.35 (0.900)	1.43 (0.677)	1.07 (0.827)
RHJC	0.18 (0.907)	1.46 (0.900)	0.15 (0.900)	0.53 (0.900)	1.61 (0.900)	0.93 (0.900)	0.69 (0.900)
LKJC	3.70 (0.014)	0.88 (0.582)	1.07 (0.431)	1.02 (0.473)	0.19 (0.900)	1.90 (0.040)	2.08 (0.019)
RKJC	1.40 (0.248)	0.98 (0.720)	0.05 (0.900)	1.69 (0.307)	0.93 (0.748)	0.71 (0.872)	1.65 (0.333)
LAJC	2.72 (0.049)	4.31 (0.361)	3.11 (0.622)	1.10 (0.900)	7.42 (0.029)	3.22 (0.600)	4.21 (0.384)
RAJC	0.63 (0.596)	0.00 (0.900)	0.60 (0.870)	0.52 (0.900)	0.60 (0.867)	0.51 (0.900)	1.12 (0.516)

Table 18. S3.2 ANOVA analysis of marker precision difference among evaluators in the medial-lateral direction. Bold entries represent values with statistically significant differences ($p < 0.05$). Comparison between differences in marker placement precision between paired evaluators with a Tukey's post-hoc difference (Diff) and p-value (p).

Proximal-Distal							
Marker	Anova (F, p)	Diff (p)					
		A-B	A-C	A-D	B-C	B-D	C-D
LASI	6.98 (0.000)	1.98 (0.733)	1.61 (0.835)	6.78 (0.006)	3.59 (0.286)	8.76 (0.001)	5.17 (0.056)
RASI	1.12 (0.345)	3.46 (0.900)	15.38 (0.562)	18.27 (0.422)	11.92 (0.724)	14.81 (0.589)	2.89 (0.900)
LPSI	1.91 (0.134)	3.15 (0.900)	12.96 (0.382)	10.67 (0.546)	16.11 (0.198)	13.82 (0.324)	2.29 (0.900)
RPSI	1.60 (0.194)	0.50 (0.900)	19.42 (0.378)	17.31 (0.481)	19.92 (0.355)	17.82 (0.456)	2.11 (0.900)
LTHI	1.93 (0.130)	1.79 (0.900)	1.32 (0.900)	23.50 (0.209)	3.11 (0.900)	21.71 (0.273)	24.82 (0.169)
RTHI	3.04 (0.034)	0.74 (0.900)	2.11 (0.900)	26.48 (0.083)	2.84 (0.900)	25.75 (0.096)	28.59 (0.052)
LKNE	16.01 (0.000)	4.83 (0.095)	1.82 (0.788)	8.71 (0.001)	3.00 (0.466)	13.53 (0.001)	10.53 (0.001)
RKNE	17.64 (0.000)	1.13 (0.900)	2.99 (0.593)	14.52 (0.001)	4.11 (0.328)	15.65 (0.001)	11.53 (0.001)
LKNM	5.20 (0.002)	0.24 (0.900)	2.51 (0.678)	8.04 (0.005)	2.28 (0.735)	7.80 (0.006)	5.53 (0.088)
RKNM	9.12 (0.000)	3.59 (0.551)	1.65 (0.900)	10.17 (0.002)	5.24 (0.229)	13.76 (0.001)	8.52 (0.013)
LTIB	4.28 (0.007)	33.08 (0.004)	14.56 (0.415)	20.77 (0.128)	18.51 (0.208)	12.30 (0.553)	6.21 (0.900)
RTIB	8.90 (0.000)	44.93 (0.001)	39.29 (0.001)	35.90 (0.002)	5.64 (0.900)	9.03 (0.761)	3.39 (0.900)
LANK	6.44 (0.001)	1.13 (0.856)	1.20 (0.829)	4.41 (0.019)	0.07 (0.900)	5.55 (0.002)	5.62 (0.001)
RANK	32.22 (0.000)	2.64 (0.014)	3.72 (0.001)	3.99 (0.001)	1.08 (0.575)	6.62 (0.001)	7.71 (0.001)
LMED	1.93 (0.130)	0.10 (0.900)	2.30 (0.464)	1.44 (0.772)	2.21 (0.500)	1.54 (0.737)	3.75 (0.088)
RMED	1.71 (0.171)	0.05 (0.900)	0.46 (0.900)	2.47 (0.227)	0.51 (0.900)	2.52 (0.212)	2.01 (0.407)
LHEE	14.71 (0.000)	0.99 (0.900)	0.49 (0.900)	13.97 (0.001)	0.50 (0.900)	12.98 (0.001)	13.48 (0.001)
RHEE	70.54 (0.000)	7.02 (0.001)	3.73 (0.030)	11.84 (0.001)	10.75 (0.001)	18.86 (0.001)	8.11 (0.001)
LTOE	0.54 (0.658)	0.87 (0.887)	1.54 (0.580)	0.68 (0.900)	0.68 (0.900)	0.19 (0.900)	0.87 (0.889)
RTOE	13.75 (0.000)	4.29 (0.001)	3.79 (0.001)	2.72 (0.002)	0.50 (0.900)	1.56 (0.148)	1.07 (0.468)
LHJC	0.26 (0.853)	2.91 (0.900)	1.02 (0.900)	4.25 (0.900)	3.94 (0.900)	7.16 (0.794)	3.23 (0.900)
RHJC	0.15 (0.927)	2.44 (0.900)	0.52 (0.900)	2.89 (0.900)	2.95 (0.900)	5.32 (0.900)	2.37 (0.900)
LKJC	1.48 (0.225)	4.65 (0.900)	2.23 (0.900)	9.48 (0.547)	2.42 (0.900)	14.13 (0.208)	11.70 (0.368)
RKJC	2.08 (0.108)	0.31 (0.900)	2.87 (0.900)	16.14 (0.155)	3.18 (0.900)	16.45 (0.142)	13.27 (0.308)
LAJC	4.12 (0.009)	0.39 (0.900)	2.22 (0.689)	4.80 (0.106)	1.84 (0.792)	5.19 (0.069)	7.02 (0.006)
RAJC	24.59 (0.000)	3.21 (0.008)	4.43 (0.001)	3.25 (0.007)	1.22 (0.591)	6.46 (0.001)	7.68 (0.001)

Table 19. S3.3. ANOVA analysis of marker precision difference among evaluators in the proximal-distal direction. Bold entries represent values with statistically significant differences ($p < 0.05$). Comparison between differences in marker placement precision between paired evaluators with a Tukey's post-hoc difference (Diff) and p-value (p).

2.3.6.4. S4 -ANOVA – Kinematic variability differences among evaluators

Angle	Plane	Variable	ANOVA (F, p)	Diff (p)					
				A-B	A-C	A-D	B-C	B-D	C-D
Pelvis	Sagittal	Mean cycle	2.25 (0.084)	0.38 (0.410)	0.60 (0.068)	0.47 (0.219)	0.22 (0.771)	0.09 (0.900)	0.13 (0.900)
		Max	3.08 (0.029)	0.48 (0.183)	0.64 (0.038)	0.70 (0.049)	0.16 (0.900)	0.12 (0.900)	0.04 (0.900)
		Min	1.85 (0.140)	0.36 (0.488)	0.57 (0.115)	0.44 (0.311)	0.21 (0.823)	0.08 (0.900)	0.13 (0.900)
		ROM	0.29 (0.833)	0.04 (0.852)	0.00 (0.900)	0.03 (0.900)	0.04 (0.871)	0.01 (0.900)	0.03 (0.900)
	Coronal	Mean cycle	0.81 (0.490)	0.07 (0.891)	0.05 (0.900)	0.07 (0.872)	0.12 (0.611)	0.14 (0.477)	0.02 (0.900)
		Max	0.53 (0.665)	0.11 (0.778)	0.00 (0.900)	0.03 (0.900)	0.11 (0.774)	0.14 (0.629)	0.03 (0.900)
		Min	0.93 (0.427)	0.10 (0.794)	0.07 (0.900)	0.06 (0.900)	0.17 (0.451)	0.16 (0.499)	0.01 (0.900)
		ROM	1.04 (0.375)	0.18 (0.495)	0.13 (0.721)	0.21 (0.365)	0.05 (0.900)	0.03 (0.900)	0.08 (0.900)
	Transversal	Mean cycle	0.68 (0.566)	0.08 (0.900)	0.01 (0.900)	0.15 (0.642)	0.09 (0.894)	0.07 (0.900)	0.16 (0.578)
		Max	0.35 (0.789)	0.00 (0.900)	0.08 (0.900)	0.08 (0.900)	0.07 (0.900)	0.09 (0.900)	0.16 (0.712)
		Min	0.38 (0.768)	0.05 (0.900)	0.05 (0.900)	0.12 (0.873)	0.10 (0.900)	0.07 (0.900)	0.16 (0.717)
		ROM	1.31 (0.273)	0.08 (0.900)	0.14 (0.628)	0.08 (0.896)	0.06 (0.900)	0.16 (0.531)	0.22 (0.246)
Hip	Sagittal	Mean cycle	0.86 (0.465)	0.37 (0.541)	0.03 (0.900)	0.15 (0.900)	0.40 (0.483)	0.22 (0.842)	0.18 (0.900)
		Max	0.94 (0.422)	0.34 (0.636)	0.14 (0.900)	0.03 (0.900)	0.47 (0.368)	0.31 (0.695)	0.17 (0.900)
		Min	0.41 (0.749)	0.31 (0.683)	0.09 (0.900)	0.12 (0.900)	0.21 (0.865)	0.19 (0.900)	0.03 (0.900)
		ROM	1.22 (0.303)	0.15 (0.734)	0.12 (0.836)	0.08 (0.900)	0.27 (0.285)	0.23 (0.450)	0.05 (0.900)
	Coronal	Mean cycle	1.50 (0.216)	0.27 (0.166)	0.11 (0.803)	0.09 (0.900)	0.16 (0.605)	0.19 (0.485)	0.03 (0.900)
		Max	2.67 (0.049)	0.45 (0.027)	0.21 (0.543)	0.20 (0.578)	0.24 (0.441)	0.25 (0.405)	0.01 (0.900)
		Min	0.79 (0.500)	0.24 (0.444)	0.08 (0.900)	0.07 (0.900)	0.16 (0.731)	0.17 (0.706)	0.01 (0.900)
		ROM	0.56 (0.642)	0.11 (0.825)	0.02 (0.900)	0.14 (0.676)	0.09 (0.893)	0.04 (0.900)	0.13 (0.744)
	Transversal	Mean cycle	4.07 (0.008)	0.92 (0.171)	0.49 (0.666)	1.50 (0.005)	0.43 (0.750)	0.58 (0.556)	1.01 (0.112)
		Max	0.95 (0.418)	0.51 (0.701)	0.41 (0.821)	0.82 (0.344)	0.11 (0.900)	0.31 (0.900)	0.41 (0.813)
		Min	4.80 (0.003)	1.31 (0.042)	0.64 (0.609)	1.91 (0.002)	0.66 (0.589)	0.61 (0.648)	1.27 (0.049)
		ROM	1.73 (0.162)	0.17 (0.900)	0.14 (0.900)	0.76 (0.157)	0.03 (0.900)	0.59 (0.363)	0.63 (0.317)
Knee	Sagittal	Mean cycle	1.45 (0.229)	0.11 (0.900)	0.47 (0.408)	0.00 (0.900)	0.58 (0.230)	0.11 (0.900)	0.47 (0.406)
		Max	3.95 (0.009)	0.59 (0.070)	0.20 (0.822)	0.22 (0.777)	0.79 (0.007)	0.37 (0.410)	0.42 (0.311)
		Min	9.93 (0.000)	0.71 (0.019)	0.58 (0.085)	0.28 (0.636)	1.29 (0.001)	0.43 (0.285)	0.86 (0.003)
		ROM	1.67 (0.174)	0.07 (0.900)	0.05 (0.900)	0.21 (0.446)	0.02 (0.900)	0.28 (0.192)	0.26 (0.256)
	Coronal	Mean cycle	1.61 (0.185)	0.22 (0.604)	0.02 (0.900)	0.37 (0.179)	0.24 (0.547)	0.15 (0.825)	0.39 (0.145)
		Max	2.54 (0.037)	0.00 (0.900)	0.30 (0.753)	0.47 (0.439)	0.30 (0.753)	0.47 (0.439)	0.77 (0.031)
		Min	0.87 (0.542)	0.52 (0.310)	0.31 (0.707)	0.39 (0.553)	0.21 (0.892)	0.13 (0.900)	0.08 (0.900)
		ROM	0.58 (0.652)	0.08 (0.900)	0.19 (0.889)	0.05 (0.900)	0.27 (0.721)	0.13 (0.900)	0.13 (0.900)
Transversal	Mean cycle	3.58 (0.021)	0.42 (0.824)	0.02 (0.900)	0.36 (0.889)	0.40 (0.845)	0.78 (0.424)	0.38 (0.868)	
	Max	1.12 (0.262)	0.13 (0.900)	0.41 (0.855)	0.61 (0.642)	0.54 (0.719)	0.74 (0.507)	0.20 (0.900)	
	Min	3.12 (0.021)	0.81 (0.480)	0.33 (0.900)	0.24 (0.900)	0.48 (0.809)	1.04 (0.252)	0.56 (0.722)	
	ROM	1.54 (0.111)	0.14 (0.900)	0.22 (0.812)	0.04 (0.900)	0.08 (0.900)	0.11 (0.900)	0.19 (0.888)	
Ankle	Sagittal	Mean cycle	3.03 (0.031)	0.07 (0.900)	0.40 (0.035)	0.25 (0.340)	0.34 (0.108)	0.18 (0.599)	0.15 (0.698)
		Max	4.74 (0.003)	0.08 (0.900)	0.45 (0.020)	0.03 (0.900)	0.53 (0.004)	0.10 (0.900)	0.43 (0.033)
		Min	1.43 (0.235)	0.13 (0.900)	0.38 (0.452)	0.08 (0.900)	0.51 (0.193)	0.22 (0.815)	0.30 (0.637)
		ROM	0.96 (0.411)	0.28 (0.447)	0.11 (0.900)	0.25 (0.532)	0.17 (0.779)	0.03 (0.900)	0.14 (0.860)
Foot Progression	Transversal	Mean cycle	3.27 (0.022)	0.48 (0.137)	0.13 (0.900)	0.33 (0.430)	0.60 (0.034)	0.14 (0.900)	0.46 (0.159)
		Max	4.44 (0.005)	0.50 (0.249)	0.28 (0.693)	0.54 (0.185)	0.78 (0.021)	0.04 (0.900)	0.82 (0.013)
		Min	3.52 (0.016)	0.48 (0.208)	0.14 (0.900)	0.50 (0.192)	0.73 (0.049)	0.01 (0.900)	0.74 (0.043)
		ROM	0.83 (0.478)	0.17 (0.827)	0.03 (0.900)	0.25 (0.616)	0.20 (0.744)	0.08 (0.900)	0.28 (0.533)

Table 20. S4.1. ANOVA analysis of kinematic differences among evaluators. Bold entries represent values with statistically significant differences ($p < 0.05$). Comparison between differences in kinematic variability between paired evaluators with a Tukey's post-hoc difference (Diff) and p-value (p).

2.3.6.5. Comparison of kinematic reliability among different methodologies

The biomechanical model applied on the calculation of kinematics in the present study was the version CGM 1.1 (available in the pyCGM2 toolbox). The main difference between this version with its precedent (CGM 1.0) is the inclusion of a medial marker on the knee (femoral epicondyle). Such marker alters the estimation of the knee joint center. In the CGM 1.0 the knee joint center is calculated by a chord function and in the CGM 1.1 is estimated as the midpoint between medial and lateral knee markers. Therefore, the presence of this marker, in static, is used to estimate a new medial-lateral axis which allows the calculation of an offset to be removed from the same axis calculated as in CGM 1.0, during gait trials. Thus, the positioning of the wands have no effect on the orientation of such axis. On the table S5.1 the reliability has been calculated on the kinematic data extracted from the population among the twelve sessions of each participant, using both CGM 1.0 and CGM 1.1. The use of a medial

knee marker is here demonstrated to remove variability in kinematic data when applying the CGM 1.0. Such observation may be expected, taking into account that wand markers were demonstrated to be the markers with lowest marker placement precision.

Table 21. Inter-session reliability comparison among the two versions available at pyCGM2 referent to the CGM 1 (1.0 and 1.1).

Joint	Plane	ICC		SEM		MDC	
		CGM 1.0	CGM 1.1	CGM 1.0	CGM 1.1	CGM 1.0	CGM 1.1
Pelvis	sag	0.73	0.73	1.95	1.96	5.40	5.45
	cor	0.67	0.67	1.10	1.07	3.04	2.96
	tra	0.39	0.39	1.78	1.79	4.91	4.97
Hip	sag	0.69	0.70	3.04	2.96	8.42	8.20
	cor	0.71	0.71	1.49	1.49	4.13	4.13
	tra	0.57	0.68	5.01	4.10	13.89	11.38
Knee	sag	0.57	0.63	3.81	3.45	10.55	9.55
	cor	0.85	0.85	1.97	1.66	5.46	4.61
	tra	0.55	0.54	5.27	4.68	14.61	12.97
Ankle	sag	0.54	0.59	2.16	2.01	5.98	5.56
	cor	0.37	0.45	1.27	1.33	3.53	3.70
	tra	0.33	0.50	5.41	3.84	15.00	10.65
FootProgress	tra	0.76	0.76	2.53	2.56	7.01	7.10

2.4. Article 4 - An analytical model to quantify the impact of the propagation of uncertainty in knee joint angle computation

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Keywords:

Joint coordinate system, attitude vector, Euler and Cardan angles, knee kinematics, cross-talk, reproducibility

2.4.1. Abstract

Joint kinematics are typically described using Cardan angles or the attitude vector and its projection on the joint axes. Whichever the notation is used, the uncertainties present in gait measurements affect the computed kinematics, especially for the knee joint. One notation - the attitude vector - enables the derivation of an analytical model of the propagation of uncertainty. Thus, the objective of this study was to derive this analytical model and assess the propagation of uncertainty in knee joint angle computation. Multi-session gait data acquired from one asymptomatic adult participant was used as reference data (experimental mean curve and standard deviations). Findings showed that an input uncertainty of 5° in the attitude vector and joint axes parameters matched experimental standard deviations. Taking each uncertainty independently, the *cross-talk* effect could result from uncertainty in the orientation of either the attitude vector (intrinsic variability) or the first joint axis (extrinsic variability). We concluded that the model successfully estimated the propagation of input uncertainties on joint angles and enabled an investigation of how that propagation occurred. The analytical model could be used to *a priori* estimate the standard deviations of experimental kinematics curves based on expected intrinsic and extrinsic uncertainties.

2.4.2. Introduction

Reproducibility studies have been performed in the literature to evaluate different sources of variability in gait analysis (McGinley *et al.* 2009, Wren *et al.* 2011). Some studies have performed a sensitivity analysis on joint axes for a given type of joint motion (Della Croce *et al.* 1999, Fonseca *et al.* 2020). More specifically, knee joint kinematics is known to be prone to non-linear error propagation, which results in the well-known kinematic effect of *cross-talk* (Baudet *et al.* 2014, Pothrat *et al.* 2015).

Joint angles are computed by evaluating the continuous movement of one segment with respect to its adjacent segment. This motion has typically been expressed using two mathematical methods: the Cardan sequence of rotations (Chao 1980, Wu and Cavanagh 1995) and the attitude vector, also commonly referred to as the helical axis or screw axis (Woltring 1991). The Cardan sequence of rotations represents overall joint movement during a set of three rotations about three joint axes: one embedded in the proximal segment (\mathbf{e}_1), one *floating* (mutually orthogonal to the two others, \mathbf{e}_2), and one embedded in the distal segment with respect to the joint (\mathbf{e}_3). These three axes are referred to as the joint coordinate system. Due to its easy interpretability, the Cardan sequence of rotations has been recommended as the most adequate for measuring angles in gait analysis (Wu and Cavanagh 1995, Wu 2002). This recommendation was recently extended to the interpretation of joint (*i.e.* intersegmental) moments (Derrick *et al.* 2020). Comparisons of Cardan angles and attitude vectors projected (in a non-orthogonal way) on the three joint axes have demonstrated some differences in the kinematic curves and different sensitivities to experimental errors (Ramakrishnan and Kadaba 1991, Woltring 1994, Chéze 2000, Rouhani *et al.* 2012).

In terms of the propagation of uncertainty, the variability in kinematic curves can be understood to depend on the intrinsic variability of joint motion and on the extrinsic variability of the definition of the three joint axes. To the best of our knowledge, no previous attempts have been made to separate the intrinsic and extrinsic variabilities in the measurement of knee joint kinematics. Intrinsic variability is linked to the movement of the joint itself, independently of any coordinate system, and it can be assessed by looking at the dispersion of the knee's rotation angle θ and of the orientation of the rotation axis \mathbf{k} . In other words, intrinsic variability is dependent on the ability of the subject to perform a repetitive movement during gait. Intrinsic variability may be affected by the presence of motor disorders, so it is considered an indicator of gait deviations (Chau 2005). Extrinsic variability arises from the inaccurate measure the real movement of the subject (whether due to instrumentation, mathematical or human factors), which results in dispersion in the orientation of the joint axes \mathbf{e}_1 , \mathbf{e}_2

and \mathbf{e}_3 . In other words, it is characterised by the error in the definition of the three axes used to interpret the movement of the joint. The theoretical propagation of uncertainty in joint angle computation can be analysed based on the equations used to project the attitude vector onto the three joint axes. These equations only include dot and cross products, which enable the use of the additive rules for calculating uncertainty components through functional relationships (Farrance and Frenkel 2012).

The objective of this study was to define an analytical model to evaluate the propagation of uncertainty in knee joint angle computation and to investigate the origins of the *cross-talk* commonly observed in knee kinematics. We hypothesised that input uncertainties of 5° in the rotation angle θ , the orientation of the rotation axis \mathbf{k} , and the orientation of the joint axes \mathbf{e}_1 , \mathbf{e}_2 and \mathbf{e}_3 would match the experimental dispersion of knee joint angles. Secondly, we hypothesised that output uncertainty would be more dependent on extrinsic variability (orientation of joint axes) than on intrinsic variability (rotation angle, orientation of the rotation axis) when propagating each of them independently.

2.4.3. Methods

Data Collection

Data to assess typical gait analysis variabilities were collected from a single, healthy, asymptomatic adult male (29.3 years old) weighing 92 kg and 183 cm tall, over five sessions performed within two months by a single examiner. A minimum of eight trials was collected per session. The participant was equipped with 53 markers (14 mm) according to the Conventional Gait Model (Baker *et al.* 2017) and asked to walk barefoot at a self-selected speed. A 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) tracked the marker trajectories at 100 Hz. Gait kinematics was processed using the open-source library PyCGM2, CGM1.1 (Leboeuf *et al.* 2019).

Rotation angle θ and orientation of the rotation axis \mathbf{k} were computed using the rotation matrix from the thigh segment to the shank segment. Projections of the attitude vector $\mathbf{k}\theta$ onto the joint axes and Cardan angles (for the comparison of experimental variabilities) were computed from the same rotation matrix. Note that in this rotation matrix, the orientation of the third joint axis \mathbf{e}_3 corresponded to the second column, whereas the orientation of the first axis \mathbf{e}_1 was, by definition, $[0\ 0\ 1]^T$. Root-mean-square deviation (RMSD) was calculated to assess inter-session and intra-session variabilities.

Furthermore, typical mean values for the rotation angle θ and for components of the rotation and joint axes vectors (\mathbf{k} , \mathbf{e}_2 and \mathbf{e}_3) expressed in the thigh coordinate system, were also computed for all the gait trials. The mean duration of the stance phase was calculated from all the trials. It was 61.6% of the gait cycle, with the remaining percentage of the gait cycle referent to the swing phase.

Analytical model of the propagation of uncertainty

Equations (1–3) define the non-orthogonal projection of the attitude vector (rotation angle θ and rotation axis \mathbf{k}) onto the joint axes (flexion–extension \mathbf{e}_1 , adduction–abduction \mathbf{e}_2 and internal–external rotation \mathbf{e}_3). The symbols “ \times ” and “ \cdot ” designate cross products and dot products, respectively.

$$\theta_1 = \frac{(\mathbf{e}_2 \times \mathbf{e}_3) \cdot \mathbf{k}}{(\mathbf{e}_1 \times \mathbf{e}_2) \cdot \mathbf{e}_3} \theta \quad (1)$$

$$\theta_2 = \frac{(\mathbf{e}_3 \times \mathbf{e}_1) \cdot \mathbf{k}}{(\mathbf{e}_1 \times \mathbf{e}_2) \cdot \mathbf{e}_3} \theta \quad (2)$$

$$\theta_3 = \frac{(\mathbf{e}_1 \times \mathbf{e}_2) \cdot \mathbf{k}}{(\mathbf{e}_1 \times \mathbf{e}_2) \cdot \mathbf{e}_3} \theta \quad (3)$$

To apply the rules for calculating uncertainty components (Farrance and Frenkel 2012), independent variables must be considered. First, the second joint axis (\mathbf{e}_2) is defined as the mutually orthogonal vector to the two others, as described in equation (4).

$$\mathbf{e}_2 = \frac{\mathbf{e}_3 \times \mathbf{e}_1}{\|\mathbf{e}_3 \times \mathbf{e}_1\|} \quad (4)$$

Then, the fact that the different axes are normalised vectors is taken into account by considering two uncertain components only and computing the last one (corresponding to the main direction), as in equations (5–7).

$$k_z = \sqrt{1 - k_x^2 - k_y^2} \quad (5)$$

$$e_{1z} = \sqrt{1 - e_{1x}^2 - e_{1y}^2} \quad (6)$$

$$e_{3y} = \sqrt{1 - e_{3x}^2 - e_{3z}^2} \quad (7)$$

Therefore, the uncertain parameters used as inputs for equation (7) are θ , k_x , k_z , e_{1x} , e_{1y} , e_{3x} and e_{3z} . Equation (8) describes the squared standard uncertainty u^2 of $y = \{\theta_1, \theta_2, \theta_3\}$ by appropriately combining the squared standard uncertainties in the input quantities $x = \{\theta, k_x, k_z, e_{1x}, e_{1y}, e_{3x}$ and $e_{3z}\}$. Variables g and f represent the denominator and numerator of the equations defining the non-orthogonal projections of the attitude vector onto the joint axes in equations (1–3).

$$u^2(y) = (1/g)^4 \left[\left(\frac{g\partial f}{\partial x_1} - \frac{f\partial g}{\partial x_1} \right)^2 u^2(x_1) + \left(\frac{g\partial f}{\partial x_2} - \frac{f\partial g}{\partial x_2} \right)^2 u^2(x_2) + \dots + \left(\frac{g\partial f}{\partial x_7} - \frac{f\partial g}{\partial x_7} \right)^2 u^2(x_7) \right] \quad (8)$$

The partial derivatives with respect to x_i , $\frac{\partial f}{\partial x_i}$ and $\frac{\partial g}{\partial x_i}$ were computed using the Matlab® (R2016b) symbolic toolbox (The Mathworks, Inc, Massachusetts) and then replaced by the mean values of x and the targeted values of $u^2(x)$ to compute the output uncertainties $u^2(y)$. In this final step, the input uncertainties in the axes' orientations were described as a cone of solid angle α , as in equation 9, as an example for rotation axis \mathbf{k} .

$$k_x = k_y = \tan(\alpha_k) \quad (9)$$

Testing Procedure

To test the first hypothesis, the input uncertainties ($u(\theta)$, $u(\alpha_k)$, $u(\alpha_{e1})$, $u(\alpha_{e3})$) were set to 2°, 5° and 10°. The output uncertainties ($u(\theta_1)$, $u(\theta_2)$, $u(\theta_3)$) estimated using the analytical model of the propagation of uncertainty were compared to the experimental inter-session and intra-session variabilities. The best match discovered was designated as the reference value to be evaluated in the

second test, in which each input uncertainty was propagated independently to test the second hypothesis. The impact of each input uncertainty was analysed from a qualitative point of view to determine which joint angles were affected (i.e. overestimated or underestimated) during which phase of the gait cycle.

2.4.4. Results

Table 22 represents the RMSD for the experimental variabilities calculated from inter-session and intra-session data considering either rotation angles and Cardan angles of rotation or the attitude vector projected onto the joint axis of rotation. The projection of the attitude vector onto the three joint axes resulted in a variability slightly lower than the variability of the respective joint angles for the flexion–extension θ_1 and internal–external rotation θ_3 . Contrarily, the variability in the adduction–abduction angle θ_2 was observed to be comparatively lower than its respective attitude vector projection. The rotation axis orientation was the most variable parameter observed (6.35° relative to inter-session measurements). Overall, inter-session kinematic data were found to be more variable than intra-session data, with means (standard deviation) of 4.25° (1.29°) vs 1.78° (0.76°), respectively. Figure 34 compares the experimental variabilities and estimated theoretical uncertainties, using the 2°, 5° and 10° input values. Except for θ_1 during the swing phase and θ_3 during the stance phase, where the best matches with experimental variability were obtained with the input uncertainties of 2° and 10°, respectively, results obtained with an input uncertainty of 5° best matched experimental variability.

The qualitative analysis of the impact of a 5° input uncertainty in each parameter separately is shown in Table 23. Furthermore, Figure 35 demonstrates the impact of a 5° input uncertainty in each of the rotation angle θ , the orientation of the rotation axis \mathbf{k} , and the orientation of the joint axes \mathbf{e}_1 and \mathbf{e}_3 . The flexion–extension angle θ_1 was the most affected by the uncertainty in θ , whereas uncertainty in the other three parameters resulted in very low variability compared to the experimental variability. Moreover, the uncertainty in θ resulted in an overestimation of the variability of most of the stance phase (approximately 0%–55%), initial swing (approximately 65%–72% of the gait cycle) and terminal swing (approximately 95%–100% of the gait cycle). For the remaining sub-phases of the gait cycle (55%–65% and 72%–95%), the theoretical corridor matched the experimental corridor relatively well. The adduction–abduction angle θ_2 closely matched the corridors for uncertainty in the orientation of \mathbf{e}_1 and \mathbf{k} , except for the initial swing, where uncertainty in both parameters underestimated experimental variability. On the other hand, the uncertainty in θ and the orientation of \mathbf{e}_3 showed a general underestimation of the experimental variability of adduction–abduction angle θ_2 , with a higher difference on the corridors of swing phase. Finally, uncertainty in θ resulted in a noteworthy underestimation of experimental variability by half during the stance phase. Uncertainty in the orientation of \mathbf{e}_3 , however, had almost no impact, and uncertainty in the orientation \mathbf{e}_1 and \mathbf{k} showed an underestimation of experimental variability by approximately a quarter. For the internal–external rotation angle θ_3 , on the initial swing, the uncertainty in θ resulted in an almost inexistent corridor, the uncertainty in the orientation of \mathbf{e}_3 matched well, and the uncertainty in the orientation of \mathbf{e}_1 and \mathbf{k} overestimated the experimental variability. At mid-swing and terminal swing, the uncertainty in all the parameters resulted in very low theoretical variability.

	RMSD (in °)	
	Inter-session	Intra-session
Rotation angle	3.12	1.99
Orientation of the rotation axis	6.35	3.01
Flexion–extension angle (Cardan)	5.06	2.36
Projected attitude vector onto e_1	5.05	2.34
Adduction–abduction angle (Cardan)	2.21	0.59
Projected attitude vector onto e_2	2.87	0.85
Internal–external rotation angle (Cardan)	4.77	1.58
Projected attitude vector onto e_3	4.58	1.50

Table 22. Experimental variability of extracted rotational parameters for the knee joint during gait cycle experimental measures. RMSD for within sessions (intra-session) and between sessions (inter-session).

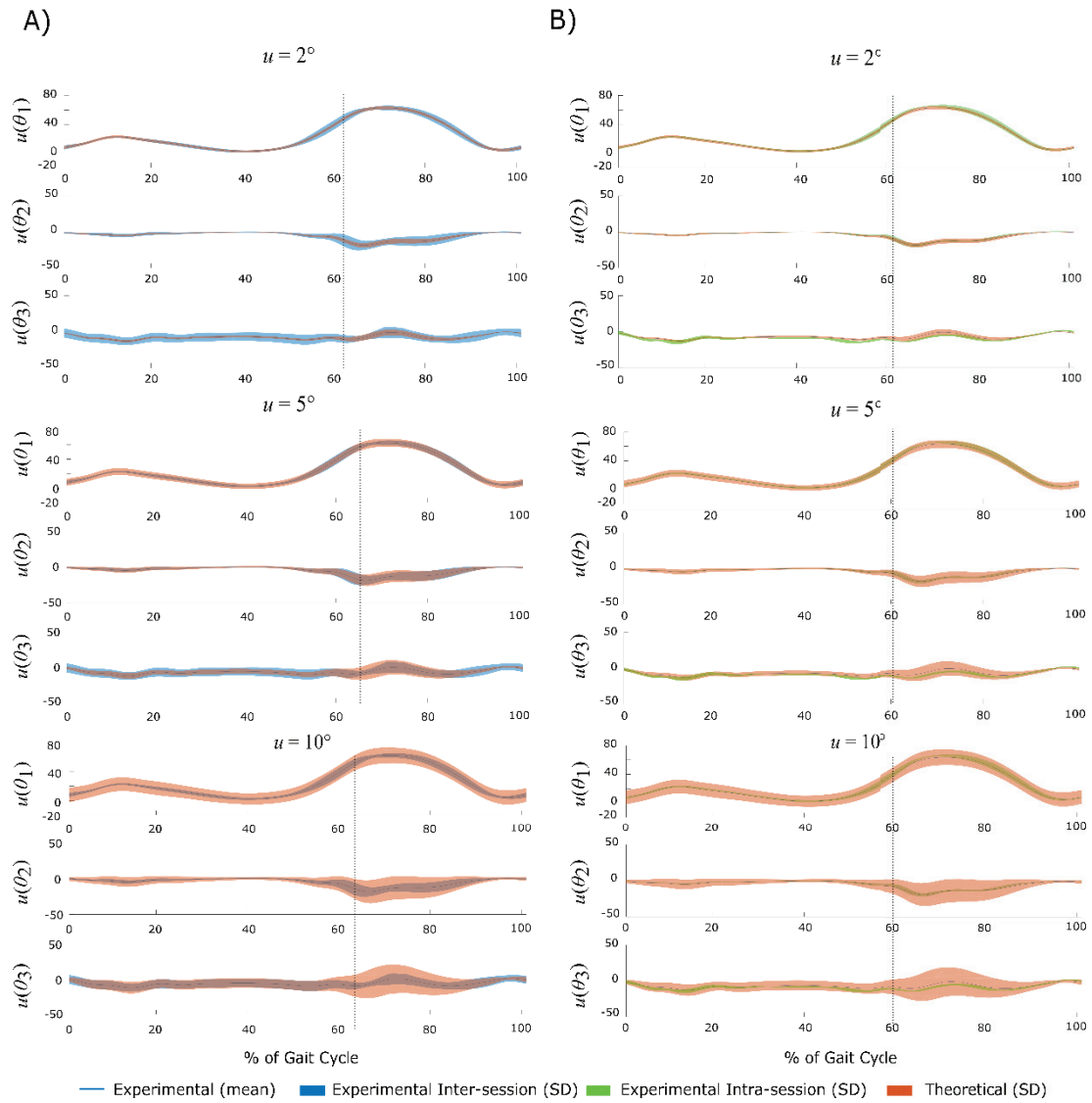


Figure 34. Comparison between the experimental variabilities and the theoretical standard uncertainties (u) corresponding to 2° , 5° and 10° of input uncertainty in rotation angle θ , the orientation of the rotation axis \mathbf{k} and in the orientation of joint axes \mathbf{e}_1 and \mathbf{e}_3 . The dotted blue line separates the stance and swing phases.

$u = 5^\circ$	θ_1		θ_2		θ_3		
	Stance	Swing	Stance	Swing	Stance	Swing	
						>61.8%–85%	>85%–100%
θ	++	0	-	--	-	--	--
\mathbf{k}	--	--	0	0	-	0	-
\mathbf{e}_1	--	--	0	0	-	0	-
\mathbf{e}_3	--	--	0	-	--	0	-

Table 23 Qualitative analysis relative to the impact of 5° uncertainty in each input variable for stance and swing phases. Experimental variability: highly overestimated (++), slightly overestimated (+), good match (0), slightly underestimated (-), and highly underestimated (--).

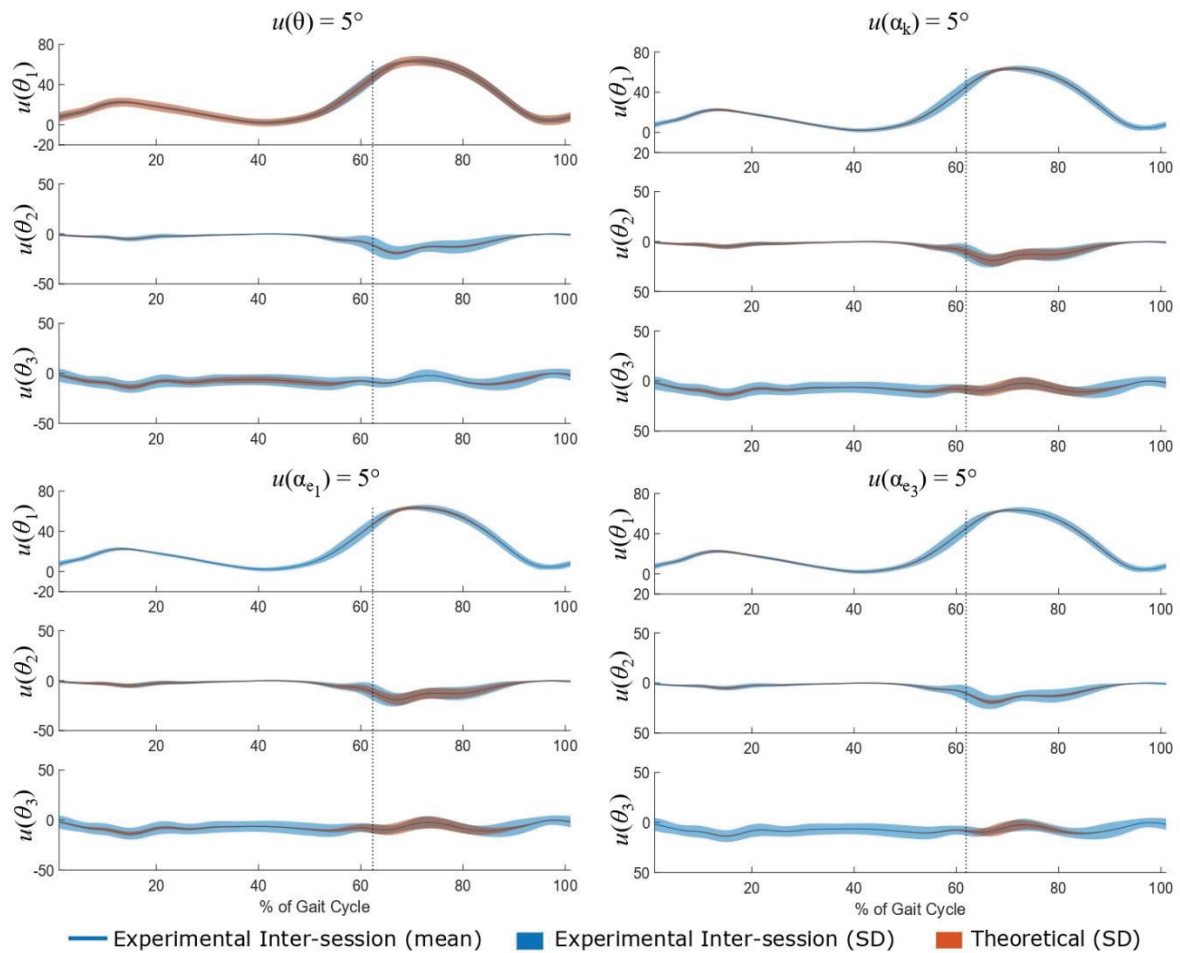


Figure 35 Impact of the standard input uncertainty (u) of 5° in the rotation angle θ , the in orientation of the rotation axis \mathbf{k} and in the orientation of joint axes \mathbf{e}_1 and \mathbf{e}_3 on knee joint angles. The solid blue line and the blue corridor represent the mean and standard deviation of inter-session experimental variability, respectively, and the red corridor represents the theoretical standard uncertainty (u). The dotted blue line separates the stance and swing phases.

2.4.5. Discussion

The main objective of this study was to define an analytical model to investigate the propagation of uncertainties in the computation of knee joint kinematics. Joint kinematics was expressed as the projection of the attitude vector onto the three joint axes of the knee because this enabled the application of the rules for calculating the components of uncertainty. Experimentally, intra-session and inter-session variabilities were verified as being comparable between the Cardan angles and these projections (Table 22). A slightly lower variability was found for the projection of the attitude vector onto the three knee joint axes as previously reported in the literature (Ramakrishnan and Kadaba 1991, Woltring 1994, Chéze 2000). Two hypotheses were made in this study.

The first hypothesis assumed that an uncertainty of 5° would closely match the experimental variabilities recorded in a gait analysis. This hypothesis was confirmed. Findings showed that an *a priori* input uncertainty of 5° in all the intrinsic and extrinsic parameters matched the experimental variability observed on the three joint angles (Figure 34). This was in accordance with previous studies

reporting on reliability in gait analysis (McGinley *et al.* 2009). An uncertainty of about 5° appears to be a generally accepted result in gait analysis. The knee joint, however, does not behave like a hinge with a fixed axis and the orientation of the knee's rotation axis \mathbf{k} also seemed to be in accordance, again, with a 5° variation (Van den Bogert *et al.* 2008). By dividing the analysis into stance and swing phases, we concluded that the match between our hypotheses and our experiment was not perfect everywhere, as the variability estimated experimentally was sometimes underestimated or overestimated. However, this finding led us to compare the different sources of uncertainty and their impacts on joint angles. It is important to note that the output uncertainties are not additive: the combined uncertainty is the square root of the sum of the squares of the individual uncertainties (and is less than the sum of them).

Our second hypothesis suggested that the output uncertainty was more dependent on extrinsic variability (the orientation of joint axes) than on intrinsic variability (rotation angle, orientation of the rotation axis), when each variability was propagated independently. This hypothesis was not confirmed. By analysing the propagation of uncertainties (set at 5°, according to our first hypothesis) independently (Table 23 and Figure 35), we found that the impact of the uncertainty in the rotation angle θ was significant on the flexion–extension angle θ_1 , and that the impact of the uncertainty in the orientation of the rotation axis \mathbf{k} was very similar to that in the first joint axis \mathbf{e}_1 . These similar impacts were greatest on the adduction–abduction angle θ_2 during the swing phase of gait, and this was a perfect illustration of the well-known *cross-talk* effect (Baudet *et al.* 2014). Cross-talk occurs when medial-lateral axis of the thigh does not match with the knee movement axis. In this case, both intrinsic and extrinsic variabilities play roles. In comparison, the orientation of the inferior–superior axis of the shank (joint axis \mathbf{e}_3) had the most limited impact. Moreover, as with the *cross-talk* effect, the impact of input uncertainties was not linear. Although the flexion–extension angle θ_1 only seemed to be affected by the intrinsic uncertainty in the rotation angle θ , the two other joint angles (θ_2 and θ_3) were affected by all the parameters, and their impact was amplified by higher values of θ , at approximately 16% and 70% of the gait cycle. As the first and third joint axes are not orthogonal, it can be inferred that input uncertainty in any of their orientations affects all three joint angles.

One limitation of this approach is the simplified view that it provides, as the theoretical error is estimated using an input uncertainty that is constant throughout the gait cycle. Secondly, this study presents a qualitative overview of the propagation of uncertainties (using the terms of overestimation and underestimation without giving further metrics). Assuming the same amount of uncertainty in both intrinsic (θ and \mathbf{k}) and extrinsic (\mathbf{e}_1 , \mathbf{e}_2 and \mathbf{e}_3) parameters, as well as constant uncertainty throughout the gait cycle, can only offer a simplified view. Therefore, this was purposely defined as the objective was limited to using a qualitative approach to demonstrate tendencies in the propagation of uncertainty relative to different input parameters. A final limitation was the study's population, as data came from a single participant who took part in five sessions with the same examiner, who was also responsible for the experimental setup. Nevertheless, the reference data (mean curve and standard deviations) could be considered as typical values for gait analysis. The propagation of uncertainties, which is assessed qualitatively, should therefore be generalisable in gait analysis.

In conclusion, the analytical model presented in this study helped to improve our understanding of the propagation of uncertainty on knee joint kinematics. Evaluating how variability propagates is important if we wish to understand why the calculation of some joint angles is more uncertain than others, for example. In a clinical context, this could be used to present any experimental joint angle curve with the estimated variabilities for given *a priori* levels of intrinsic and extrinsic uncertainty. Setting this level of uncertainty to 5° would seem appropriate. Due to their specific kinematics, this model may be more useful for investigating the propagation of uncertainty on the knee joint angles and, perhaps, the elbow joint angles than on another joint kinematics.

2.5. Chapter Discussion

The studies presented within this chapter aimed to better understand and quantify the effects of marker placement error in the output kinematic data. The well-known crosstalk phenomenon, affecting knee kinematics and the high variability reported in the hip rotation is associated with errors in the definition of the femoral axis. Therefore, the lateral femoral epicondyle marker plays a crucial role in the definition of this axis. Thus, the first study evaluated the sensitivity of the CGM to the lateral femoral marker displacement. The results presented in the first study, related to displacement of the lateral femoral epicondyle marker, demonstrated a high sensitivity of the Conventional Gait Model when displaced in the anterior-posterior direction. Hip and ankle rotation as well as the knee flexion-extension angles were the most sensitive joint angle with respect to such displacement, with a kinematic variation of 5.3°, 4.4° and 4.2° per 10mm of displacement, respectively. Taking that 5° is considered as the threshold of acceptable variability in CGA (McGinley et al. 2009), only by having a precision of placement of this particular marker of 10mm is enough to encounter hip rotation over this threshold. In addition, it was found that the impact of marker displacement could be predicted with regression equations using the magnitude of displacement expressed in percentage of leg length. An error within the limits of acceptability requires a precision within 1.2% of the leg length. In conclusion, this study is important to understand how the error in the lateral femoral epicondyle marker is translated to kinematics and suggests additional caution when placing this marker with respect to the anterior-posterior direction. However, the effects of marker placement are dependent on the positioning of other markers. Thus, the complete analysis of marker placement effect requires an analysis of simultaneous multi-marker displacements. This conclusion was the motivation for the second study, here presented.

The second article of this chapter follows a similar methodology related to the first article. However, instead of the impact of one marker, a combination of the displacement of eight markers of the lower limb was performed. The simulation of five positions per marker (four displaced and one original) resulted in over 390 thousand different combinations. Consequently, a high amount of time was required to simulate all the marker configurations and thus the number of displacement directions and magnitudes were kept to a minimum. The number of simulations provided a high amount of results and so its analysis was performed on a more global form, such as the amplitude of kinematic data. Approximately 40% of the total of simulations resulted in an error over the 5° limit of acceptability on the transversal plane. Gait Profile Score also showed high variance among the different simulations, with an IQR higher than the 1.6° considered as the minimal detectable change, for most of the subjects. Additionally, single marker displacements were also analyzed. Results of single marker displacements demonstrated that the sensitivity of the CGM to marker misplacement is highly dependent on the marker and direction of displacement. Thus, the classification of precision differs among markers and directions. In other words, 10mm precision of one marker may be considered as unacceptable in one direction and acceptable on another direction of misplacement. The single marker displacement analysis showed that the CGM is more sensitive to femoral epicondyle and wand marker displacement, on the anterior-posterior direction and for the transversal plane (hip, knee and ankle). The finding concerning the lower precision in the latter marker confirms *a posteriori* the choice made on the first study (Article 1). In conclusion, the effect of marker misplacement was proven to be a combination of a set of markers as initially hypothesized. In other words, the misplacement of one marker can be either enhanced or mitigated by the misplacement of other markers. Thus, the understanding of the marker misplacement effect is a very complex task due to the infinite set of possible configurations to be measured. Globally, results have showed that

measurement error associated with a global marker placement with a precision of 10mm is not enough to ensure a global acceptable kinematic variability and may impact negatively gait data interpretation. Finally, one study intended to be used for education purposes and contribute to the better understanding of the impact of specific marker displacement in kinematics. However, to simulate a set of configurations closer to the experimental error, one experimental quantification of the measured marker placement precision is required. This was one of the motivations for the third article of this chapter.

Among the limitations of simulated marker misplacement is the neglected effect of soft tissue artefacts that may differ according to the positioning of the markers. A second limitation is that the magnitudes applied may not be representative of the real precision associated to the placement of each marker. For instance, the magnitude was based on the only study found regarding precision of marker misplacement (Della Croce et al. 1999). Contrarily to what was defined in the second article, precision of marker placement varies among markers and direction. However, Della Croce et al. (1999) performed their precision estimation using pointers instead of skin markers, a small sample size and showed a high discrepancy among the precision calculated for the two sides of the pelvis. Thus, in order to overcome this limitation and feed future simulations with more realistic magnitudes of displacement as well as evaluating the impact of marker misplacement in real experimental procedure, the third (Article 3) study was developed.

The third article aimed to evaluate experimentally the precision of marker placement among different evaluators and its impact on anatomical (segment) coordinate system definition and output kinematic variability. Therefore, four different evaluators, with different level of experience, were responsible for performing, each and interspersed, three marker placement sessions per subject, on a population of eight asymptomatic adult subjects. Clusters of markers were used through the entire set of sub-sessions in order to estimate the position of markers in the local coordinate system of the segments. The results showed lower precision for the wand on the proximal-distal direction. Considering the results observed on the preceding article, we can conclude that misplacement of those markers in such direction have low impact of the output kinematics. Therefore, wands and femoral epicondyle markers (and consequently the knee joint center) showed an inter-evaluator precision varying from 6.6mm to 11.3mm, on the anterior-posterior direction. This low precision has been previously demonstrated (Article 1 and 2) to result in kinematic variability above the threshold of acceptability (5°), on the transversal plane. This result, aggregated to the high variability found on the angle orientation of the anatomical (segment) coordinate system on the transversal plane, supports the consideration of marker placement as the main source of kinematic variability (Gorton *et al.* 2009a). In addition, significant differences were observed among the evaluator's experience and the kinematic variability for some parameters. This observation demonstrates that experience can have a positive impact on the outcome kinematic variability, contrarily to previous findings (Leigh *et al.* 2014). One of the main limitations of the Article 3 is related to the cohort of participants included. First, the population included can be characterized as homogeneous and with normal BMI. A previous study reported higher discrepancy on the palpation on patients with high BMI (Moriguchi *et al.* 2009). Thus, lower precision would be expected for a population with increased BMI. Second, the integration of a population with motor disorders would be more representative of the marker placement precision practiced in clinical context. However, the experiment required the participant to stand for long period (approximately three hours), which is more difficult to achieve for subjects with motor disorders.

The higher variability, typically reported in the literature (McGinley et al. 2009) and supported by the abovementioned results, of the hip and knee angles on the coronal and transversal plane is

generally attributed to misalignment of the system of axes of the thigh segment. For instance, the well-known crosstalk effect, where the thigh flexion-extension axis is wrongly defined and consequently motion on such axis is translated to the other two axes (Baudet *et al.* 2014). Joint angles can be expressed by attitude vector or by the Cardan sequence of rotations. The main advantage of the Cardan angles is their easy interpretability. However, those angles are prone to the erroneous definition. Therefore, in order to understand the propagation of the uncertainties, due to measurement errors such as joint axes definition (based on marker placement), on the definition of Cardan angles of the knee, one analytical model was proposed on the Article 4. The projection of the attitude vector (not prone to crosstalk) was compared with the Cardan angles. Different input uncertainties were tested, and results showed that 5° of input uncertainty in the orientations of the attitude vector (i.e. intrinsic variability) and joint axes (i.e. extrinsic variability) matched the experimental variability, and so, proving the validity of the model. Thus, the model can serve as support for improving our understanding of the propagation of the measurement error through the gait curves and to explain how some angles are more uncertain than others. The applicability of this model could be an *a priori* estimate of the experimental kinematic variability based on expected levels of intrinsic and extrinsic variabilities. More specifically, the method could be used in a clinical context to estimate confidence intervals over the measured gait curves.

The main difficulty encountered when evaluating different sources of variability is to find a strategy that isolates those sources and at the same time keeps the measurement realistic. As an example, both Articles 1 and 2, managed to isolate the effect of markers and successfully provide knowledge of its impact in gait data. However, in practice, this is not completely accurate, as the placement of one marker in different locations is accompanied by a different underlying soft tissue motion through gait. In Article 3, variability associated to the different marker positions incorporated the effects of soft tissue artefacts.

In conclusion, this chapter provided not only a quantification of the variability expected in gait analysis measurements but a better understanding on the role of sources of measurement error, such as marker placement and joint axes definition, on the output kinematic variability. However, and as previously described, extrinsic variability is the result of a combination of different sources, which impact differently on the output data. This understanding can be helpful on the training of the evaluators but can also serve as baseline for the development and integration of new methodology associated with lower extrinsic variability. Finally, the knowledge provided within this chapter can therefore be potentially used for the management of variability during clinical interpretation of gait data.

Chapter 3 - Reduction of Variability in Gait Analysis

Taking into consideration the motto of the previous chapter, the quantification of variability is essential to understand and estimate the effect of sources of error in the output gait data and to predict the amount of variability in CGA. Therefore, after understanding and quantifying the measurement variability, the next step is to evaluate possible ways to improve the measurement process by reducing such errors. Thus, this part of the doctoral work intends to evaluate possible methodologies to reduce the effect of measurement error and two studies are presented.

The first study (Article 4) goes in line with the previous chapter as it aims to quantify the variability associated with measurement error through an experimental protocol including a cohort of symptomatic and asymptomatic populations. Moreover, this study intends to compare the resulting variability by computing kinematics, using different proposed variations of the CGM. Results showed that the implementation of calibration methods is effective in reducing the extrinsic variability of the hip rotation angle.

The second study presented within this chapter shows a newly developed and proposed methodology to estimate gait events. The methodology applied involves the incorporation of existing and newly developed algorithms for gait event detection and an automatic selection of the best methods for each gait session with the use of vertical components of the force. The methodology was tested with a database formed by pathological gait. Positive results were reported, where the proposed methodology outperformed all implemented methods, including one based on a machine learning model.

3.1. Article 5 – Estimation of gait analysis variability in test-retest analysis by the application of different modeling and processing choices

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3.1.1. Abstract

The Conventional Gait Model (CGM) is widely used in clinical gait analysis. Different modeling and processing choices exist to compute gait kinematics based on the CGM. However, no information is available that compares the reliability of those different choices in computing gait data from pathological populations.

Thus, the goal of the present study was to evaluate the reliability of different modeling and processing choices to compute gait data in participants with and without motor disorders through a test-retest protocol. Twenty-four patients diagnosed with cerebral palsy, eight patients diagnosed with other motor disorders and twenty-four asymptomatic participants underwent three gait analysis sessions divided by two evaluators during two visits. Data from static and gait trials were collected. Gait data were computed following five variants of CGM and two calibration methods (functional and geometrical).

All modeling and processing choices showed good intra-session reliability. Within-evaluator and between-evaluator showed good to moderate reliability to all kinematic parameters but hip rotation reliability was observed to be the lowest. Similar reliability was presented between all modeling and processing choices with the exception of hip rotation where the calibration methods have demonstrated to improve reliability within-evaluator and between-evaluator.

3.1.2. Introduction

Clinical gait analysis (CGA) has been widely used as a measurement tool for the evaluation of gait abnormalities and to assess the outcome of clinical interventions in patients with motor disabilities. It describes the gait by a set of biomechanical parameters, including kinematics, kinetics and spatio-temporal parameters (Baker *et al.* 2016). Therefore, the measured gait data are required to be reliable for a correct clinical assessment of gait deviations (Mokkink and Terwee 2010). However, variability in CGA data affects the reliability of the measurements and it is due to a combination of intrinsic and extrinsic factors (McGinley *et al.* 2009). Intrinsic factors are related to the natural ability of the subjects to repeat gait patterns throughout cycles and it is considered an indicator of motor disorders and a discriminative parameter between subjects (Schwartz *et al.* 2004, Monaghan *et al.* 2007, Laroche *et al.* 2011, Tabard-Fougère *et al.* 2022). Alternatively, the extrinsic factors correspond to measurement error and it is caused by different causes, such as instrumental errors, marker placement, soft tissue artefacts and data processing (Chiari *et al.* 2005, Della Croce *et al.* 2005, Leardini *et al.* 2005). From those, marker placement has been proved to be the main source of variability in CGA (Gorton *et al.* 2009). Confidence in gait data interpretation is supported by previous reliability studies that suggest that most of the measurement errors are clinically reasonable (extrinsic variability $< 5^\circ$), with the exception of the transversal plane, which is considered as the least reliable output of gait analysis (extrinsic variability $> 5^\circ$) (McGinley *et al.* 2009).

In the past years, several protocols have been proposed to calculate kinematic data (Davis *et al.* 1991, Cappozzo *et al.* 1995, Leardini *et al.* 2007, Rabuffetti *et al.* 2019). These protocols can differ on marker sets, collection procedures and biomechanical model, which includes segment definition, degrees of freedom assigned to the joints and joint rotation conventions. High waveform differences were previously reported between kinematic data estimated through different protocols and models,

more accentuated in the transversal plane (Ferrari *et al.* 2008). Among the existing protocols, the Conventional Gait Model (CGM), which refers to a family of similar models, is the most used in CGA (Baker 2006; Davis *et al.* 1991; Kadaba *et al.* 1990). In addition, different modeling and processing choices have been reported. For instance, several methods have been proposed to estimate joint centers. Typically, the hip joint center can be estimated based on a set of regression equations or by functional calibrations (Davis *et al.* 1991; Hara *et al.* 2016; Kainz *et al.* 2015). The knee joint center is morphologically more simple to estimate, generally by either applying a chord function, which uses the hip joint center allied with two other markers (thigh wand and knee) or by simply adding one marker internally on the knee and estimating the mid-point between the knee markers (Leboeuf *et al.* 2019). Other types of post-processing methods apply kinematic constraints to the joint kinematics blocking some degrees of freedom. These methods have been demonstrated to perform similarly to the typical methods (unconstrained inverse kinematics sometime called direct kinematics), except for the hip internal/external rotation for which constrained inverse kinematics (also named multibody kinematics optimization) was demonstrated to reduce the variability between sessions (Kainz *et al.* 2017). Other studies demonstrated clinically relevant differences when comparing processing models based on inverse kinematic frameworks (Mantovani and Lamontagne 2017) or between inverse kinematics and typical methods (Charlton *et al.* 2004). However, due to applied joint constraints, part of the intrinsic variability may be suppressed and useful clinical information lost (Duprey *et al.* 2010). Previous studies have demonstrated some advantages in the reduction of soft tissue artefacts (Lu and O'Connor 1999, Richard *et al.* 2017). Finally, several additional calibration methods have been proposed to make use of functional or geometrical considerations to correct the definition of the different segmental coordinate systems and thus, contribute to the reduction of sensitivity to measurement error, such as marker placement (Schache *et al.* 2006, Ehrig *et al.* 2007, Naaim *et al.* 2019). Those methods are typically added as additional calibration and use functional movement to re-calibrate either centers of rotation and/or axis of rotation. Both approaches have been demonstrated to improve the determination of segmental axes (Sauret *et al.* 2016) and consequently reduce the effect of marker placement error in gait data. One of the limitations of these methods for the inclusion in CGA is the required movement for calibration which may not be applicable for some patients.

To our knowledge, the reliability of these different modeling and processing choices has not yet been compared all together with a pathological population. The results will support the choice of a protocol for CGA that minimizes the extrinsic variability

Thus, the aim of this study is to compare the reliability of a set of different processing choices (joint center definition, joint constraints, calibration) through a test-retest experimental protocol including a cohort of pathological and asymptomatic subjects. Taking into account previous studies of reliability in CGA, we hypothesized that, whatever the modeling and processing choice is, a higher variability is observed in the transversal plane of kinematic data. Moreover, we hypothesized that a reduced variability is observed when using some of these choices.

3.1.3. Methods

a) Participants

Fifty-six participants were recruited for the present study, divided between pathological (PATH, n=32) and non-pathological (AP, n=24) subjects. The PATH group was constituted of two sub-groups based on the diagnostic, with one group being constituted of patients with CP (CP, n = 24) and another with distinct motor disorders (OMD, n = 8). Group age was divided within the age range: children (C) aged between 7 and 12 years old; adolescents (Y) aged between 13 and 17; and adults (A)

aged from 18 years old. Table 24 provides a complete description of the definition of population groups as well as participants' demographics. Of the 8 patients included in the OMD group, the diagnoses were reported as: bilateral femoral rotational troubles (n=2); unilateral lower-limb polytraumatism (n=1); bilateral muscular dystrophy (n=1); bilateral idiopathic toe walkers (n=3) and unilateral lower limb congenital malformation with ligament hyperlaxity (n=1). This study was approved by the "Commission Cantonale d'Éthique de la Recherche Genève" (CCER-2020-00358) and all participants provided written informed consent (legal tutors signed the consent for non-adult participants). The exclusion criteria for all groups were known pregnancy and no allergy to adhesive tape.

Table 24. Populations and mean (SD) of participant's characteristics. M - Male, F - Female, PATH – pathological population, CP – cerebral palsy group; OMD – Other motor disorders, AP – asymptomatic population, C – children (7-13 years), Y – adolescents (14-17 years), A – adults (+18 years). Height, lengths and widths are reported in cm, weight in kg and age in years.

Group	Sub-Group	Group Age	Population size	Height	Weight	Age	Leg Length	Knee Width	Ankle Width
PATH	CP	C	8 (M= 7, F = 1)	138.9 (8.1)	34.5 (8.2)	10.1 (1.8)	72.5 (5.5)	9.3 (0.7)	6.0 (0.0)
		Y	8 (M=5, F=3)	164.4 (10.8)	60.7 (13.4)	16.1 (0.7)	86.1 (7.4)	10.6 (1.2)	6.6 (0.5)
		A	8 (M=6, F=2)	172.4 (4.1)	64.5 (10.6)	28.3 (5.5)	90.6 (4.4)	10.3 (0.9)	6.8 (0.5)
	OMD	C	4 (M= 4, F = 0)	136.3 (9.6)	35.3 (11.9)	9.0 (1.7)	69.3 (4.5)	9.4 (0.7)	5.9 (0.6)
		Y	2 (M=2, F=0)	161.9 (9.7)	52.6 (2.2)	15.0 (0.0)	83.4 (5.7)	10.1 (0.4)	6.3 (0.4)
		A	2 (M=1, F=1)	171.6 (11.3)	80.0 (26.6)	32.0 (15.0)	89.6 (4.8)	10.9 (1.1)	6.9 (0.5)
AP	C	8 (M=5, F=3)	134.9 (11.1)	30.3 (7.8)	9.0 (1.5)	70.3 (7.2)	8.8 (0.8)	6.1 (0.5)	
	Y	8 (M=3, F=5)	166.8 (7.8)	57.0 (7.8)	15.6 (1.2)	88.4 (4.1)	9.8 (0.7)	6.4 (0.4)	
	A	8 (M=4, F=4)	167.4 (13.1)	64.6 (15.9)	32.9 (5.6)	86.9 (8.6)	10.0 (0.9)	6.7 (0.7)	

b) Experimental Protocol

All participants visited the gait laboratory on two occasions within 10 days apart to minimize possible modifications of gait due to the evolution of the disease or modifications of anthropometric characteristics. Two evaluators (A and B) were responsible for conducting the complete gait analysis sessions. Passive reflective markers were placed following the CGM described in (Leboeuf *et al.* 2019) (14mm) and palpation followed the guidelines previously proposed (Van Sint Jan 2007). On the first visit, each participant performed one gait analysis session conducted by the evaluator A, who was responsible for placing the reflective markers. Within the second visit, each participant underwent two new gait sessions conducted by each of the evaluators individually. Both evaluators underwent previous proper training on marker placement and gait analysis procedures. In order to avoid any bias from the marker placement, only the evaluator responsible for the respective gait analysis session was present at the time of marker placement. Moreover, participants were asked to perform, barefoot, one static and several walking trials, until at least five valid steps were recorded within the limits of the force platforms. Trials were validated by visual observation of the single foot within the limits of the force-platform during one complete cycle while the contra-lateral foot was completely outside those limits. A 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) tracked the marker trajectories at 100 Hz. For each of the visits, anthropometric data were measured by evaluator B.

c) Kinematics and data processing

Measured gait data was computed following, in parallel, seven different modeling and processing choices related to the CGM. The processing of all these variants has been implemented in the open-source “pyCGM2” library (<https://github.com/pyCGM2/pyCGM2>) as described in Table 25. To note that DynaKAD and Geometrical methods were added as an additional calibration to the CGM 2.1. and one gait trial was used for calibration.

Method	Description
CGM 1.0	Clone of the simplified Plug-inGait model (Davis, Tyburski, <i>et al.</i> 1991)
CGM 1.1	The knee joint center is calculated as the mid-point between the two knee markers (CGM 1.0 uses chord function).
CGM 2.1	Update to CGM 1.1 with respect to the estimation of the hip joint center where equations proposed by Davis <i>et al.</i> (1991) were replaced by regression equations proposed by Hara <i>et al.</i> (2016)
CGM 2.2	Calibration of rigid segment model to data captured during a static trial and inverse kinematics to use this model to track marker trajectories(cost function is the weighted root mean square distance between modeled and measured markers).
CGM 2.3	In comparison with CGM 2.2, wand markers were replaced by additional markers placed over the thigh and shank segments, and knee markers were excluded for inverse kinematics.
DynaKAD (CGM 2.1)	Additional functional calibration method (Baker <i>et al.</i> 1999) of the knee joint based upon a functional calibration trial (knee flexion-extension against gravity) conducted in addition to static calibration and gait trials.
Geometrical (CGM 2.1)	Geometrical calibration method (Naaim <i>et al.</i> 2019) of the medial-lateral axis of the thigh based on the normal axis to the mean plane defined between hip, knee, and ankle joint centers during one gait cycle.

Table 25. Respective description of modeling and processing choices used to compute gait data.

Additionally, to kinematic data, the Gait Variation Score (GVS) and Gait Profile Score (GPS) were calculated for each session from results obtained with each of the modeling and processing choice (Baker. *et al.* 2009).

d) Statistical analysis

Four types of variability were considered within our results. The inter-trial variability refers to the variance observed within the gait cycles of the same session. The intra-evaluator and inter-evaluator variability referred to the variance between the mean kinematics relative to the two sessions of evaluator A and between the two sessions of the second visit, respectively. Finally, the inter-session variability represents the variability among the three sessions for each participant. The relative reliability of the complete gait cycle, for inter-trial, intra-evaluator and inter-evaluator, was calculated with the interclass correlation (ICC) (model 2,1) using two-way mixed effects for absolute agreement (Shrout and Fleiss 1979). Moreover, the ICC were classified as ‘excellent’ (≥ 0.75), ‘good’ (0.60-0.74), ‘fair’ (0.40-0.59) and ‘poor’ (< 0.40) (Shrout and Fleiss 1979). The absolute reliability was calculated using the Standard Error of a Measurement (SEM) and Smallest Detectable Change

(SDC_{95%}). The SEM indicates the expected error in the measurement of data acquired from a participant and it was calculated as:

$$SEM = SD \times \sqrt{(1 - ICC)} \quad (1)$$

where SD is the standard deviation between gait sessions.

Reliability was calculated using the lme4 package (v1.1-27.1; (Bates *et al.* 2015)) available in R (R Core Team 2020)(Weir 2005). Additionally, SD was applied to calculate the inter-session variability relative to kinematics, gait scores and anthropometric measurements variability, which represents the overall variance of the data among the three sessions. Additionally, paired t-tests were performed on the variability of kinematic data among age groups (children, adolescents and adults) and between pathological and asymptomatic groups to test for statistically significant differences ($p < 0.05$).

3.1.4. Results

Table 26 shows the mean and confidence interval at 95% confidence (CI_{95%}) of the spatial and temporal parameters for description of walking characteristics of each population sub-group. The mean SEM across the gait cycle and discrete points such as maximum, minimum and range of motion among the modeling and processing choices and between AP and PATH groups are presented for inter-trial (Table 27), intra-evaluator (Table 28), and inter-evaluator (Table 29). The SEM is also plotted along the gait cycle for the AP (Figure 36) and PATH (Figure 37) populations to provide a better insight into the differences through the gait cycle. The SEM associated with foot progression and pelvic angles are not displayed for the calibration methods (DynaKAD and Geometrical) as they do not affect those values calculated with CGM 2.1. Matching ICC plots are available in Supplementary Information. SEM is generally similar among the different modeling and processing choices for the kinematic parameters. However, for the intra- and inter-evaluator conditions, the calibration methods (DynaKAD and Geometrical) showed a reduction of SEM in the transversal plane of the hip as well as the coronal plane of the knee.

Diagnostic	Cadence (steps/min)		Stride Length (m)		Walking Speed (m/s)		Percentage Stance	
	mean	CI _{95%}	mean	CI _{95%}	mean	CI _{95%}	mean	CI _{95%}
CP	115.86	[113.47,118.25]	1.15	[1.11,1.18]	1.11	[1.06,1.15]	65.05	[64.68,65.42]
OMD	118.20	[107.92,119.58]	1.28	[1.07,1.22]	1.25	[1.00,1.15]	64.33	[64.68,66.08]
AP	113.75	[115.85,120.55]	1.14	[1.23,1.32]	1.08	[1.21,1.29]	65.38	[64.14,64.53]

Table 26. Spatial and temporal parameters per group of subjects.

		Inter-trial SEM(°)													
CGM version		Asymptomatic							Pathologic						
		1.0	1.1	2.1	2.2	2.3	Dyna	Geo	1.0	1.1	2.1	2.2	2.3	Dyna	Geo
Sagittal															
Pelvis	Max	1.0	1.0	1.0	1.0	1.0			1.1	1.1	1.1	1.2	1.1		
	Min	1.1	1.0	1.0	1.0	1.1			1.1	1.1	1.1	1.2	1.1		
	ROM	1.0	0.9	0.9	0.9	1.0			1.1	1.1	1.1	1.3	1.1		
	Cycle	1.2	1.2	1.2	1.2	1.2			1.3	1.3	1.3	1.4	1.3		
Hip	Max	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Min	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.4	1.4	1.4	1.7	1.3	1.4	1.4
	ROM	1.9	1.9	1.9	1.9	1.9	1.9	1.9	2.0	2.0	1.9	2.2	2.0	1.9	2.0
	Cycle	2.1	2.1	2.1	2.1	2.0	2.1	2.1	2.6	2.6	2.5	2.6	2.5	2.5	2.6
Knee	Max	2.0	2.0	2.0	1.9	1.8	2.0	2.0	2.4	2.3	2.3	2.2	2.2	2.3	2.4
	Min	1.6	1.6	1.6	1.5	1.7	1.6	1.6	2.4	2.4	2.3	2.4	2.5	2.3	2.5
	ROM	2.5	2.5	2.5	2.4	2.5	2.5	2.5	3.1	3.1	3.1	3.0	3.1	3.0	3.4
	Cycle	3.4	3.4	3.4	3.4	3.5	3.4	3.4	4.1	4.1	4.1	4.3	4.3	4.1	4.2
Ankle	Max	1.5	1.5	1.5	1.4	1.4	1.5	2.8	1.4	1.5	1.5	1.8	1.3	1.5	2.7
	Min	2.8	2.9	2.8	3.0	3.1	2.8	1.6	2.8	2.9	2.9	2.7	2.9	2.8	1.5
	ROM	2.8	2.8	2.8	2.9	3.0	2.8	2.8	2.8	2.8	2.8	2.8	2.9	2.8	2.7
	Cycle	2.2	2.3	2.2	2.2	2.2	2.2	2.3	2.3	2.4	2.4	2.4	2.3	2.4	2.4
Coronal															
Pelvis	Max	0.9	0.8	0.8	0.8	0.8			1.2	1.0	1.0	1.2	1.0		
	Min	0.8	0.8	0.8	0.8	0.8			1.1	0.9	0.9	1.1	0.9		
	ROM	1.1	1.1	1.1	1.1	1.2			1.3	1.2	1.2	1.2	1.2		
	Cycle	0.9	0.8	0.8	0.9	0.9			1.2	1.0	1.0	1.3	1.2		
Hip	Max	1.1	1.1	1.1	1.0	1.0	1.1	1.1	1.3	1.3	1.3	1.4	1.3	1.3	1.3
	Min	1.1	1.1	1.1	1.2	1.2	1.1	1.1	1.3	1.3	1.2	1.3	1.2	1.2	1.3
	ROM	1.4	1.4	1.4	1.5	1.5	1.4	1.4	1.6	1.6	1.6	1.7	1.7	1.6	1.6
	Cycle	1.3	1.2	1.2	1.2	1.3	1.2	1.2	1.6	1.6	1.5	1.6	1.6	1.5	1.6
Knee	Max	1.2	1.2	1.2	0.7	0.8	1.1	1.1	1.5	1.5	1.4	1.4	1.2	1.3	1.3
	Min	1.1	1.1	1.1	1.0	1.0	1.4	1.4	1.2	1.6	1.6	1.3	1.4	1.5	1.3
	ROM	1.6	1.6	1.6	1.3	1.2	1.8	1.8	1.9	2.3	2.3	1.4	1.5	2.0	2.0
	Cycle	1.1	1.1	1.1	0.8	0.8	1.1	1.1	1.8	1.8	1.8	1.5	1.4	1.7	1.4
Transversal															
Pelvis	Max	1.8	1.8	1.8	1.8	1.8			2.1	2.2	2.2	2.2	2.2		
	Min	2.0	2.1	2.1	2.0	2.1			2.5	2.5	2.5	2.6	2.6		
	ROM	2.6	2.6	2.6	2.6	2.6			2.7	2.7	2.7	2.7	2.7		
	Cycle	2.1	2.1	2.1	2.1	2.1			2.7	2.8	2.8	2.8	2.8		
Hip	Max	1.6	1.6	1.6	1.4	1.4	1.6	1.9	1.8	1.8	1.8	1.7	1.5	1.8	1.8
	Min	2.3	2.3	2.3	2.1	1.7	2.3	2.4	2.2	2.2	2.2	2.3	1.7	2.1	2.2
	ROM	2.9	2.9	2.9	2.5	2.1	2.9	2.9	2.9	3.0	3.0	2.5	2.1	2.8	2.5
	Cycle	2.3	2.3	2.3	2.1	1.7	2.3	2.4	2.8	2.8	2.9	2.8	2.2	2.8	2.7
Knee	Max	1.7	1.7	1.6	1.6	1.4	1.7	1.6	1.7	1.7	1.7	1.6	1.3	1.6	2.5
	Min	1.7	1.7	1.7	1.7	1.7	1.7	1.8	2.0	1.8	1.8	1.5	1.6	2.2	2.8
	ROM	2.4	2.4	2.3	2.3	2.1	2.3	2.3	2.5	2.4	2.4	2.1	1.9	2.7	2.3
	Cycle	2.1	2.1	2.1	2.0	1.8	2.1	2.1	2.3	2.2	2.2	2.1	1.9	2.2	2.9
Foot	Max	2.6	2.6	2.6	2.7	2.6			3.0	3.0	3.0	3.0	3.0		
	Min	2.5	2.5	2.5	2.6	2.6			2.7	2.8	2.8	2.8	2.8		
	ROM	3.1	3.2	3.2	3.2	3.2			3.3	3.3	3.3	3.3	3.3		
	Cycle	2.8	2.8	2.8	2.8	2.8			3.5	3.5	3.5	3.5	3.5		

Table 27. Inter-trial reliability: standard error of measurement (SEM) of kinematic data with respect to discrete (Maximum (Max), Minimum (Min) and Range of Motion (ROM)) and mean SEM among the complete gait cycle (Cycle). Comparison of reliability among modeling and processing choices and between groups. AP – Asymptomatic population; PATH – pathologic population; Dyna– DynaKAD; Geo - Geometrical. Color code grading between the minimal value(0.8° observed in inter-trial) (green) and the maximal value error observed among the three conditions (inter-trial, intra-evaluator and inter-evaluator) tested (8.8° observed in the inter-evaluator) (red).

		Intra-evaluator SEM (°)													
		Asymptomatic							Pathologic						
CGM version		1.0	1.1	2.1	2.2	2.3	Dyna	Geo	1.0	1.1	2.1	2.2	2.3	Dyna	Geo
Sagittal															
Pelvis	Max	1.8	1.8	1.8	1.7	1.7			2.3	2.3	2.3	2.3	2.2		
	Min	1.8	1.8	1.8	1.8	1.8			2.4	2.4	2.4	2.5	2.4		
	ROM	1.1	1.0	1.0	1.0	1.1			1.4	1.4	1.4	1.8	1.4		
	Cycle	1.9	1.9	1.9	1.9	1.8			2.5	2.5	2.5	2.5	2.4		
Hip	Max	3.0	3.1	2.9	2.7	2.8	2.9	3.1	3.0	3.3	3.1	2.9	2.8	3.1	3.3
	Min	2.6	2.6	2.6	2.5	2.6	2.6	2.6	3.0	3.3	3.2	3.3	3.0	3.2	3.3
	ROM	3.1	3.1	3.0	3.1	3.1	3.0	3.1	2.6	2.6	2.5	2.9	2.5	2.5	2.6
	Cycle	3.6	3.6	3.4	3.4	3.4	3.4	3.6	4.5	4.7	4.5	4.5	4.3	4.5	4.7
Knee	Max	3.2	3.3	3.2	2.3	2.3	3.2	3.2	3.3	3.6	3.3	2.7	2.6	3.7	3.7
	Min	2.4	2.3	2.3	2.0	2.4	2.3	2.3	3.2	3.4	3.3	3.2	3.4	5.0	4.5
	ROM	3.2	3.1	3.1	2.8	3.2	3.1	3.1	3.5	3.6	3.5	3.5	3.5	3.8	5.5
	Cycle	5.1	5.1	5.0	4.9	5.1	5.1	5.1	6.2	6.2	6.1	6.2	6.4	7.1	6.6
Ankle	Max	2.2	1.9	1.9	1.7	1.7	1.9	3.5	2.3	2.2	2.2	2.5	1.8	2.2	3.2
	Min	3.3	3.4	3.3	3.5	3.5	3.3	2.8	3.6	3.4	3.4	3.1	3.3	3.3	2.2
	ROM	3.7	3.4	3.4	3.4	3.4	3.4	3.5	3.2	3.2	3.2	3.3	3.6	3.2	3.1
	Cycle	3.3	3.1	3.1	2.8	2.9	3.1	3.9	3.1	3.0	3.0	3.0	2.8	3.0	3.0
Coronal															
Pelvis	Max	1.3	1.2	1.2	1.2	1.2			1.6	1.5	1.5	2.0	1.8		
	Min	1.3	1.3	1.3	1.2	1.3			1.6	1.4	1.4	1.8	1.7		
	ROM	1.7	1.5	1.5	1.5	1.7			1.7	1.6	1.6	1.5	1.7		
	Cycle	1.3	1.3	1.3	1.3	1.4			1.7	1.6	1.6	2.1	2.0		
Hip	Max	2.0	2.0	1.8	1.6	1.6	1.8	2.0	2.7	2.7	2.3	2.6	2.4	2.3	2.7
	Min	2.0	1.9	1.6	1.7	1.8	1.6	1.9	2.9	2.9	2.6	2.7	2.9	2.6	2.9
	ROM	2.1	2.1	2.0	1.9	2.0	2.0	2.1	2.0	2.0	1.9	2.1	2.2	1.9	2.0
	Cycle	2.1	2.0	1.8	1.8	1.9	1.8	2.0	3.0	3.0	2.7	2.9	3.0	2.7	3.0
Knee	Max	3.0	4.0	4.0	2.5	2.8	2.8	1.7	5.7	6.0	6.0	4.5	4.4	4.2	3.9
	Min	3.2	3.1	2.8	3.0	4.6	2.4	1.7	4.2	4.3	4.4	4.2	4.7	3.8	1.9
	ROM	2.6	3.3	3.4	2.3	3.3	2.6	2.7	4.2	4.1	3.9	2.5	2.9	2.7	5.2
	Cycle	2.4	2.7	2.6	1.9	2.5	2.1	1.8	4.9	4.7	4.9	4.1	4.1	4.2	2.5
Transversal															
Pelvis	Max	2.3	2.3	2.3	2.3	2.3			2.5	2.6	2.6	2.6	2.6		
	Min	2.4	2.5	2.5	2.5	2.5			2.9	2.9	2.9	3.0	3.0		
	ROM	3.2	3.2	3.2	3.3	3.3			3.1	3.0	3.0	3.1	3.1		
	Cycle	2.5	2.5	2.5	2.5	2.4			3.1	3.1	3.1	3.2	3.1		
Hip	Max	4.0	5.4	5.5	4.6	6.4	4.9	3.3	6.7	6.0	6.1	6.2	5.8	3.7	2.9
	Min	5.4	5.9	5.7	5.4	6.5	4.6	3.8	7.8	6.4	6.5	6.7	6.2	4.8	3.5
	ROM	4.6	4.6	4.5	4.1	2.4	4.5	4.6	5.0	4.7	4.8	3.8	2.9	4.3	3.9
	Cycle	4.9	5.8	5.8	4.9	6.5	5.0	3.7	7.7	6.6	6.7	6.9	6.2	5.1	3.8
Knee	Max	4.4	4.6	4.4	4.9	5.9	4.4	5.6	5.5	5.2	5.2	5.2	4.8	4.8	5.2
	Min	4.7	4.8	4.5	5.1	5.2	5.0	6.4	6.2	5.3	5.3	4.8	4.4	5.2	5.8
	ROM	3.0	3.2	3.0	2.8	2.8	3.3	3.1	3.6	3.3	3.3	3.1	2.7	4.0	2.9
	Cycle	4.8	5.1	4.8	5.3	6.0	5.0	6.4	6.4	5.6	5.6	5.5	5.0	5.4	5.8
Foot	Max	5.3	3.8	3.7	3.9	3.8			3.3	3.3	3.3	3.4	3.4		
	Min	5.5	3.6	3.4	3.2	3.4			3.3	3.2	3.2	3.3	3.3		
	ROM	3.2	3.3	3.2	3.5	3.4			3.4	3.5	3.4	3.5	3.5		
	Cycle	5.7	4.1	4.0	3.6	3.7			4.0	4.0	4.0	4.0	4.0		

Table 28. Intra-evaluator reliability: standard error of measurement (SEM) of kinematic data concerning discrete (Maximum (Max), Minimum (Min) and Range of Motion (ROM)) and mean SEM among the complete gait cycle (Cycle). Comparison of reliability among modeling and processing choices and between groups. AP – Asymptomatic population; PATH – pathologic population; Dyna– DynaKAD; Geo - Geometric. Color code grading between the minimal value(0.8° observed in inter-trial)

(green) and the maximal value error observed among the three conditions (inter-trial, intra-evaluator and inter-evaluator) tested (8.8° observed in the inter-evaluator) (red).

CGM version	Inter-evaluator SEM (°)														
	AP							PATH							
	1.0	1.1	2.1	2.2	2.3	Dyna	Geo	1.0	1.1	2.1	2.2	2.3	Dyna	Geo	
Sagittal	Max	2.2	2.2	2.2	2.2	2.2		2.5	2.5	2.5	2.5	2.4			
	Min	2.3	2.3	2.3	2.2	2.1		2.4	2.5	2.5	2.5	2.3			
	ROM	1.1	1.0	1.0	1.0	1.1		1.2	1.2	1.2	1.5	1.3			
	Cycle	2.4	2.3	2.3	2.3	2.3		2.6	2.6	2.6	2.6	2.5			
Pelvis	Max	3.0	3.0	2.9	2.6	4.4	2.9	3.0	3.5	3.6	3.4	3.2	3.2	3.5	3.6
	Min	2.9	2.8	2.7	2.6	5.2	2.7	2.8	3.4	3.4	3.3	3.4	3.2	3.5	3.4
	ROM	2.6	2.5	2.5	2.7	3.1	2.5	2.5	2.2	2.2	2.2	2.8	2.4	2.2	2.2
	Cycle	3.6	3.5	3.4	3.3	5.2	3.4	3.5	4.4	4.4	4.3	4.2	4.1	4.4	4.4
Hip	Max	3.9	3.6	3.5	2.7	4.2	3.4	3.6	3.8	3.5	3.5	2.8	2.8	3.4	3.5
	Min	3.9	3.2	3.1	2.8	3.6	3.2	3.2	3.8	3.5	3.4	3.4	3.3	3.4	3.6
	ROM	2.7	2.7	2.7	3.1	5.1	2.7	2.7	3.5	3.6	3.5	3.7	3.5	3.3	4.0
	Cycle	5.3	4.9	4.8	4.7	5.3	4.9	4.9	5.8	5.6	5.5	5.5	5.7	5.5	5.6
Knee	Max	2.1	2.2	2.1	1.8	2.2	2.1	3.9	2.3	2.3	2.3	2.5	1.9	2.3	3.7
	Min	3.8	4.1	3.9	4.9	4.8	3.9	2.5	4.2	3.8	3.8	3.5	3.8	3.8	2.3
	ROM	3.3	3.6	3.5	4.9	4.6	3.5	3.6	3.5	3.3	3.3	3.3	3.6	3.3	3.3
	Cycle	3.0	3.1	3.0	2.8	3.1	3.0	3.7	3.4	3.3	3.3	3.2	3.1	3.3	3.4
Ankle	Max	1.4	1.4	1.4	1.4	2.3		2.0	2.0	2.0	2.4	2.2			
	Min	1.4	1.4	1.4	1.4	2.2		2.0	2.0	2.0	2.3	2.1			
	ROM	1.6	1.5	1.5	1.6	3.4		1.6	1.5	1.5	1.5	1.6			
	Cycle	1.4	1.4	1.4	1.5	2.4		2.1	2.1	2.1	2.5	2.3			
Coronal	Max	1.9	2.0	1.9	1.8	2.8	1.9	2.0	2.6	2.6	2.5	2.8	2.7	2.5	2.6
	Min	2.0	2.2	2.0	2.1	2.5	2.0	2.2	2.6	2.6	2.5	2.8	2.7	2.5	2.6
	ROM	1.8	1.9	1.8	2.1	2.5	1.8	1.9	1.9	1.9	1.8	2.1	2.2	1.8	1.8
	Cycle	2.0	2.1	1.9	2.1	2.6	1.9	2.1	2.8	2.8	2.7	3.0	3.0	2.7	2.8
Hip	Max	4.3	4.3	4.2	3.0	2.8	1.7	1.4	4.7	3.8	3.9	3.1	2.9	2.5	1.8
	Min	3.7	3.9	3.7	5.3	6.1	2.0	1.7	3.9	3.4	3.5	4.5	4.6	2.8	1.7
	ROM	3.3	3.5	3.3	3.8	4.6	2.2	2.4	3.6	3.8	3.8	3.3	3.7	2.8	2.6
	Cycle	2.6	2.8	2.7	2.6	3.3	1.8	1.6	3.8	3.1	3.1	3.2	2.8	2.8	1.7
Knee	Max	4.3	4.3	4.2	3.0	2.8	1.7	1.4	4.7	3.8	3.9	3.1	2.9	2.5	1.8
	Min	3.7	3.9	3.7	5.3	6.1	2.0	1.7	3.9	3.4	3.5	4.5	4.6	2.8	1.7
	ROM	3.3	3.5	3.3	3.8	4.6	2.2	2.4	3.6	3.8	3.8	3.3	3.7	2.8	2.6
	Cycle	2.6	2.8	2.7	2.6	3.3	1.8	1.6	3.8	3.1	3.1	3.2	2.8	2.8	1.7
Transversal	Max	2.4	2.3	2.3	2.3	3.8			2.6	2.6	2.6	2.6	2.6		
	Min	2.4	2.4	2.4	2.4	4.0			2.9	2.9	2.9	2.9	2.9		
	ROM	3.2	3.2	3.2	3.3	3.4			2.8	2.8	2.8	2.8	2.8		
	Cycle	2.5	2.4	2.4	2.4	4.0			3.1	3.1	3.1	3.1	3.1		
Pelvis	Max	5.4	6.9	6.4	6.0	8.0	3.6	3.3	7.0	7.5	7.3	6.0	6.5	4.2	4.8
	Min	7.4	7.6	7.1	6.8	7.8	4.8	3.9	7.9	8.0	7.8	6.7	6.2	5.1	5.4
	ROM	4.5	4.5	4.5	3.6	2.7	4.5	4.5	4.7	5.0	5.1	4.4	3.1	4.7	4.5
	Cycle	6.3	7.1	6.7	6.6	8.0	4.3	3.7	7.6	7.8	7.8	6.7	6.6	5.5	5.6
Hip	Max	4.5	8.0	7.9	7.3	7.5	5.7	5.5	7.0	6.7	6.6	5.9	5.7	4.6	5.5
	Min	4.4	8.4	7.7	6.8	6.4	6.1	5.6	7.7	7.5	7.4	6.7	6.5	4.6	6.6
	ROM	3.4	3.2	3.2	3.3	4.1	3.2	3.1	3.7	3.7	3.7	3.8	3.3	4.1	3.2
	Cycle	4.9	8.8	8.1	7.2	7.6	6.2	5.8	7.8	7.5	7.4	6.8	6.6	5.2	6.5
Knee	Max	4.5	8.0	7.9	7.3	7.5	5.7	5.5	7.0	6.7	6.6	5.9	5.7	4.6	5.5
	Min	4.4	8.4	7.7	6.8	6.4	6.1	5.6	7.7	7.5	7.4	6.7	6.5	4.6	6.6
	ROM	3.4	3.2	3.2	3.3	4.1	3.2	3.1	3.7	3.7	3.7	3.8	3.3	4.1	3.2
	Cycle	4.9	8.8	8.1	7.2	7.6	6.2	5.8	7.8	7.5	7.4	6.8	6.6	5.2	6.5
Foot	Max	5.4	5.3	5.4	5.4	5.6			3.8	3.8	3.7	3.7	3.8		
	Min	5.1	4.7	5.0	4.5	4.7			3.6	3.5	3.5	3.6	3.6		
	ROM	3.3	3.3	3.2	3.4	3.5			3.2	3.2	3.2	3.2	3.2		
	Cycle	5.3	5.2	5.3	4.8	5.0			4.2	4.2	4.2	4.2	4.2		

Table 29. Inter-evaluator reliability: standard error of measurement (SEM) of kinematic data concerning discrete (Maximum (Max), Minimum (Min) and Range of Motion (ROM)) and mean SEM among the complete gait cycle (Cycle). Comparison of reliability among modeling and processing choices and between groups. AP – Asymptomatic population; PATH – pathologic population; Dyna – DynaKAD; Geo - Geometric. Color code grading between the minimal value(0.8° observed in inter-trial) (green) and the maximal value error observed among the three conditions (inter-trial, intra-evaluator and inter-evaluator) tested (8.8° observed in the inter-evaluator) (red).

SEM - Pathological

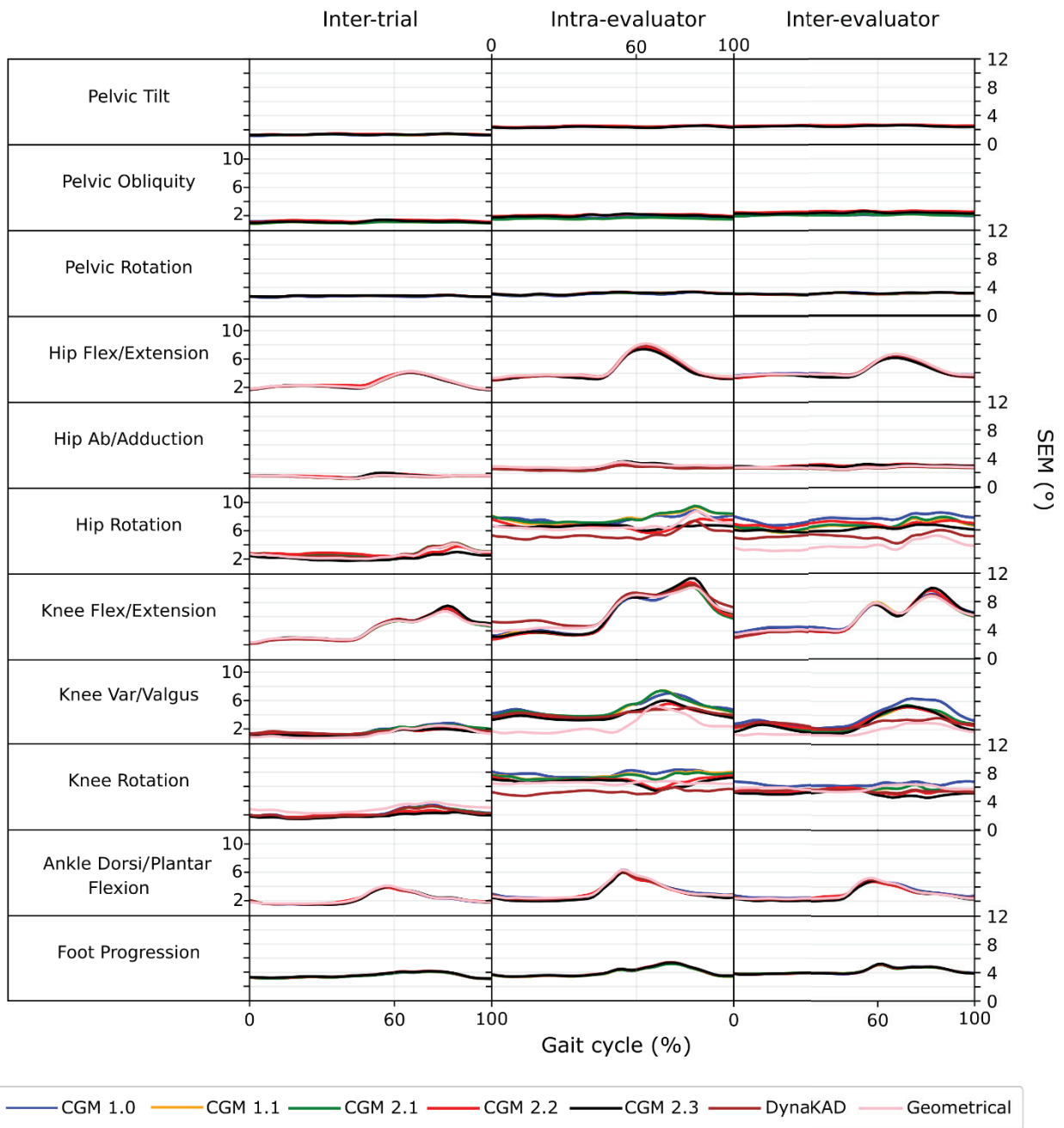


Figure 36. SEM (°) relative to the pathologic (PATH) group (CP and OMD) through the gait cycle and among modeling and processing choices.

SEM - Asymptomatic

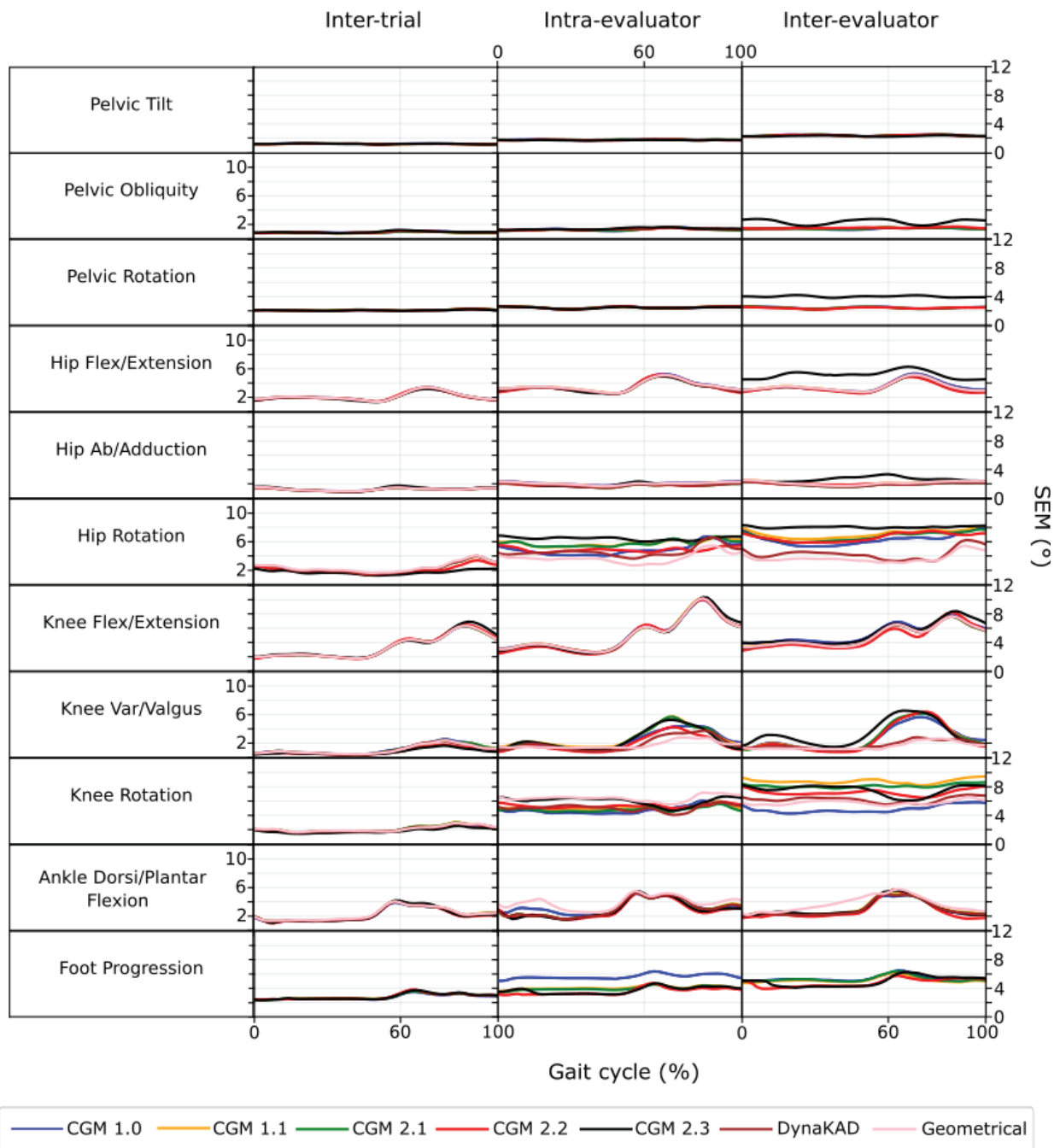


Figure 37. SEM(°) relative to the asymptomatic (AP) population through the gait cycle and among modeling and processing choices.

The analysis of the impact of test-retest gait measurements calculated by different modeling and processing choices in gait scores is demonstrated in the Figure 38.

Among the different angles, hip rotation score is the most variable and generally, AP group showed reduced GVS and MAP variance comparing with the PATH group. Additionally, DynaKAD and Geometrical calibrations demonstrated to result in less variability for the hip rotation.

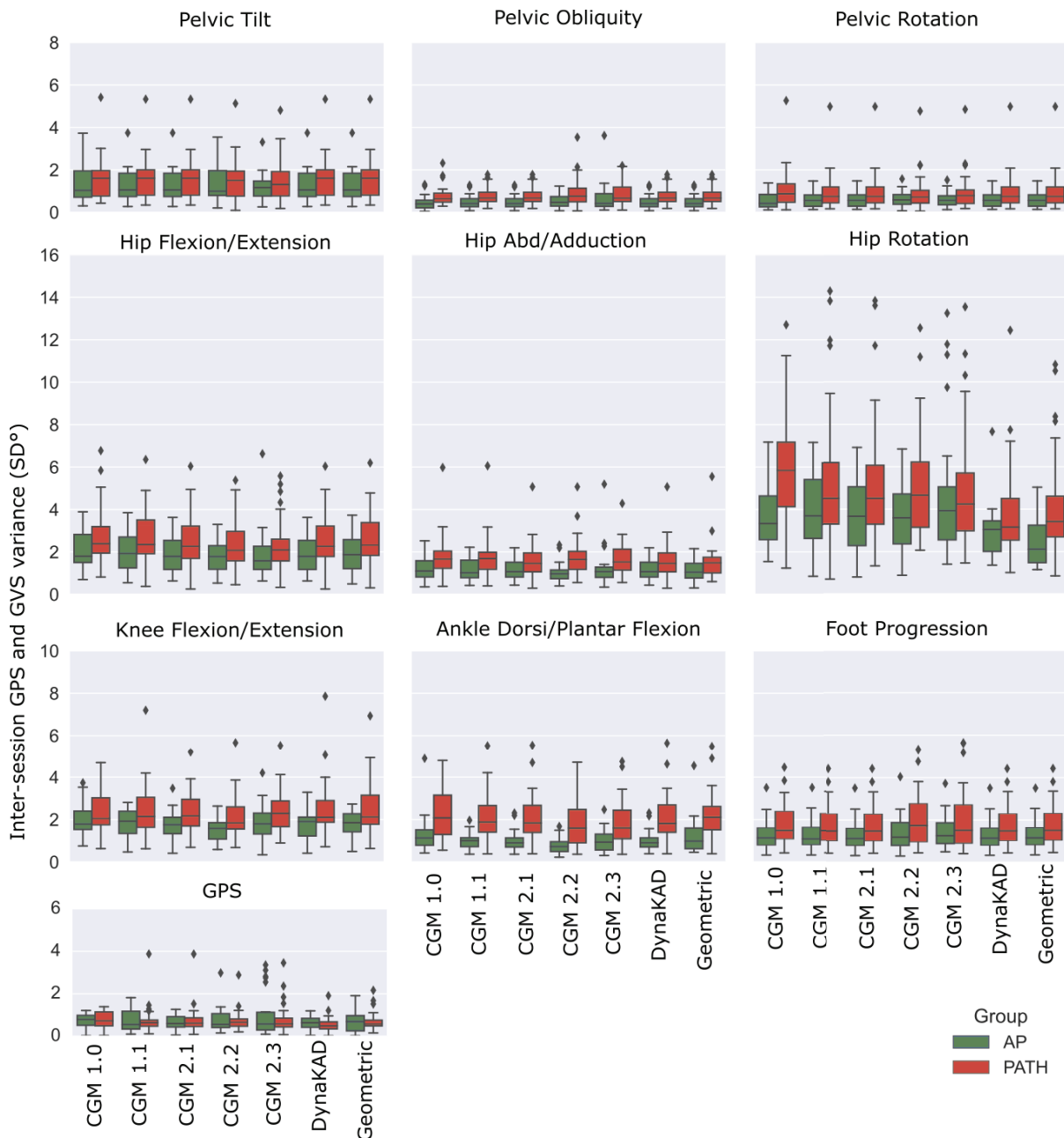


Figure 38. Inter-session variability relative to the mean of left and right sides of Gait Variable Score (GVS), and Gait Profile Score (GPS) among both populations.

Figure 39 illustrates the distribution of inter-session variability concerning the age group and population sub-group, respectively. In Figure 39 (left), apart from the pelvic tilt, which resulted in higher variability in adult participants (with respect to children and adolescents), few differences were observed. Regarding Figure 39 (right), comparing inter-session variability among the two groups (AP and PATH), demonstrated no statistically significant differences ($p < 0.05$) in any of the parameters evaluated for the PATH group for all kinematic parameters, except foot progression.

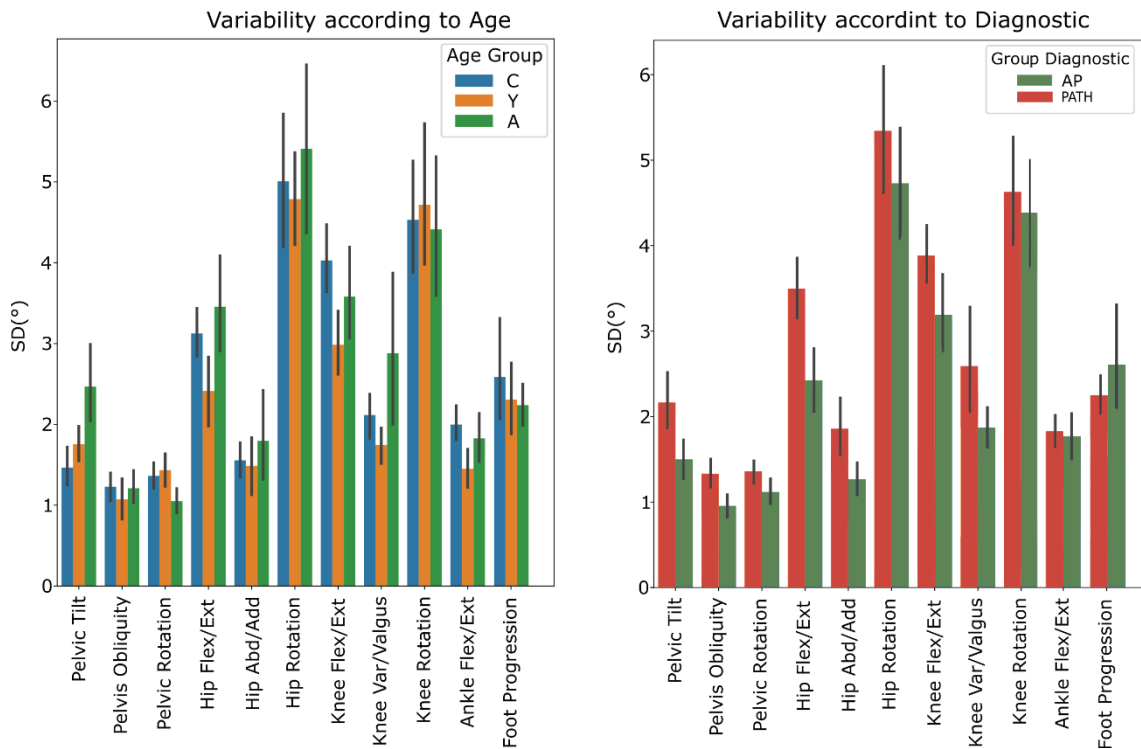


Figure 39. Inter-session kinematics variability (evaluated by SD, in degrees) per age sub-group (left) and between the two main groups. C – children, Y – adolescents, A – adults, AP – asymptomatic population, PATH – pathologic population.

Figure 40 compares the intrinsic (green) with extrinsic (red) variability for different variants of pyCGM2 and calibration models among the two populations. In the pelvic rotation, intrinsic variability (inter-trial) resulted higher than extrinsic with a ratio of approximately 2:1. Contrarily, the magnitude of extrinsic variability at the hip and knee rotation angles was higher than intrinsic variability. However, in the case of hip rotation, the calibration methods resulted in two almost similar variabilities. Generally, PATH showed higher extrinsic comparatively with the AP group but very similar levels of intrinsic variability.

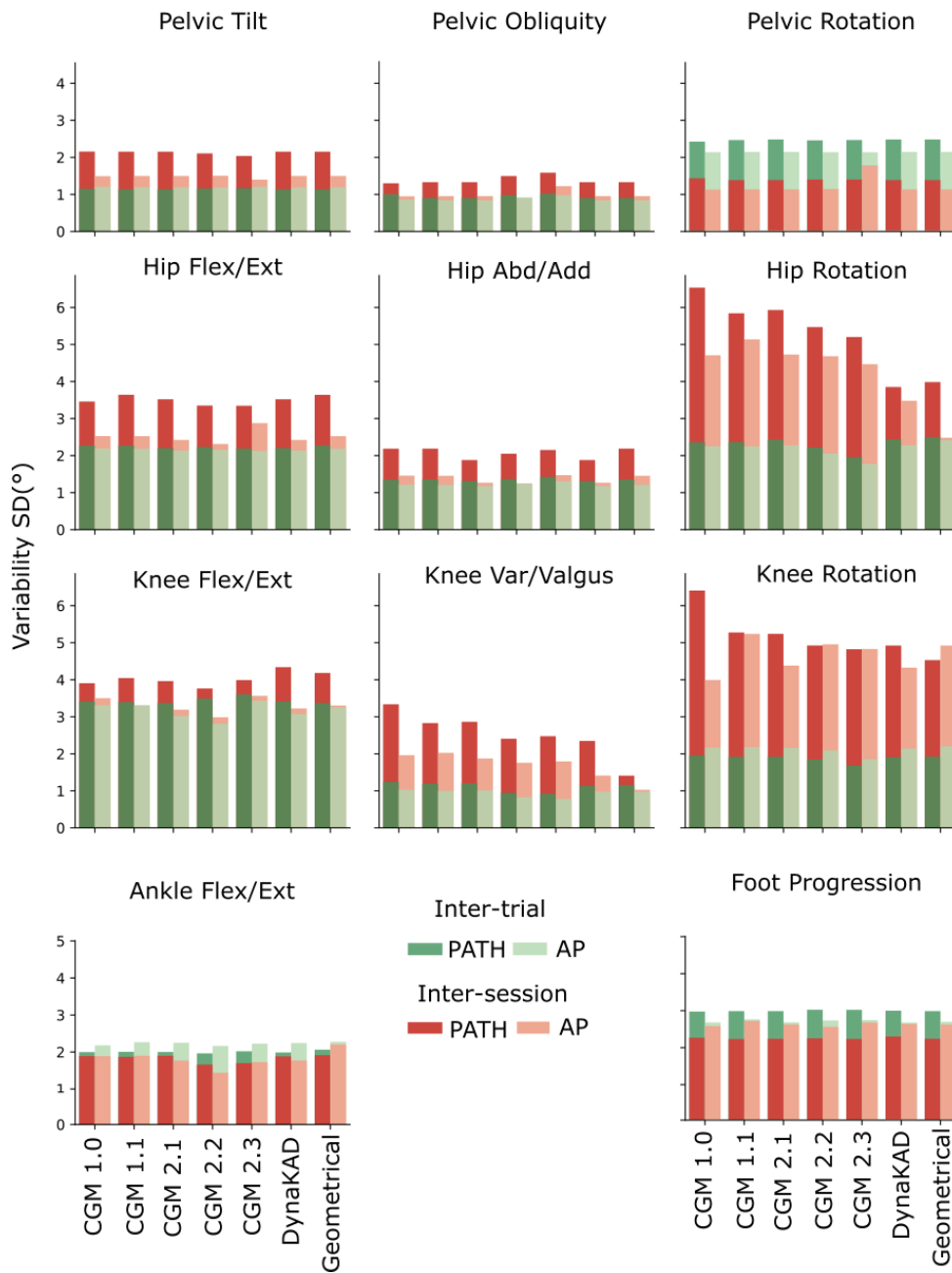


Figure 40. Comparison between inter-trial (intrinsic variability) in green and inter-session (extrinsic variability) in red kinematic variabilities (evaluated by SD, in degrees) between the two main populations and different modeling and processing choices.

3.1.5. Discussion

The main purpose of the present study was to compare the reliability of a set of seven modeling and processing choices through a test-retest study on a cohort of pathological and asymptomatic participants. Therefore, taking into consideration the nature of the different methods evaluated, we hypothesized that the kinematic variability observed among the different sessions would be affected. For instance, calibration methods (DynaKAD and Geometrical) are expected to reduce the effects of the crosstalk phenomenon (Naaïm *et al.* 2019) and improve the reliability of hip rotation. Both calibration methods have demonstrated improved variability of the knee varus-valgus at the swing phase, and thus demonstrating that by calibration of the knee axis, the crosstalk phenomenon can be reduced (Figure 36 and Figure 37), as previously demonstrated (Naaïm *et al.* 2019) and in agreement to the analytical model developed in Article 4. For those methods, also the hip rotation angle showed better reliability when computed with the addition of those methods. These observations go in line with previous sensitivity analysis who demonstrated that the knee varus-valgus and hip rotation angles are highly sensitive to the specification of the knee rotation axis (Baker *et al.* 1999; Kadaba *et al.* 1990; Piazza and Cavanagh 2000). Alternatively, the methods tested based on inverse-kinematics (CGM 2.2 and CGM 2.3) were expected to perform similarly to typically used methods except for hip rotation where it has been proven to improve reliability. This conclusion was not observed in our results (Figures 36 and 37) where those methods did not perform better than the rest of the tested methods. This observation may be explained by the fact that the kinematic constraints used stand for spherical joints only (the joint translations are limited). The final effect is merely to prevent the segment lengths to change which marginally affects joint kinematics. In addition, those modeling and processing choices resulted in similar reliability for the generality of kinematic data and showed that the replacement of wands for thigh and shank markers relative to the CGM 2.3 approach and the exclusion of the knee markers for the inverse kinematics have small effects on kinematic reliability. Additionally, the use of an internal knee marker to estimate the knee joint center (CGM 1.1) or the implementation of different regression equations to estimate the hip joint center (CGM 2.1) was not proven to have a general impact on kinematics reliability concerning the original clone of Plug-in-Gait (CGM 1.0).

In general, inter-trial reliability (Table 27) was better than intra-evaluator (Table 28), which was slightly more reliable than inter-evaluator (Table 29). This finding supports the idea that the same evaluator should be in charge of reproducing clinical gait analysis for the same patients. In addition, the transversal plane was the least reliable, especially for the hip and knee angles, with a SEM up to 6.8°. Reported reliability was similar to previous similar studies using the simplest methods (CGM 1.0 and CGM 1.1). Regarding the differences between the two groups, the reliability calculated for the pathological group was generally lower than for the asymptomatic group. This conclusion is supported by past studies reporting higher reliability in asymptomatic groups (Steinwender *et al.* 2000). However, the variance observed inside each group affects the output ICC calculated as the higher the variance among subjects of a group, the lower the variance associated with other measurement parameters. Thus, as the pathological population is expected to have higher variance among subjects, the difference between groups in terms of reliability may be higher than reported by ICC (Supplementary Information).

The hip rotation score calculated from the DynaKAD and Geometrical calibration methods showed lower variability among test-retest. However, GVS and GPS were not observed to be altered among those choices as those scores are calculated as the mean of GVS parameters, and variability in one parameter has a low impact on it. Additionally, the results provided showed that even though both

calibration methods reduce extrinsic variability, the intrinsic variability remains similar among all tested variants which is desirable as the intrinsic variability is of use in the characterization of gait deviations (Tabard-Fougère *et al.* 2022).

One of the limitations encountered in this study is the fact that only a few processing options were included. For instance, other different biomechanical models (Cappozzo *et al.* 1995, Leardini *et al.* 2007, Van Den Bogert *et al.* 2013), other inverse kinematic constraints, or different calibration models (Ehrig *et al.* 2007, Passmore *et al.* 2018) could improve the robustness of this study. However, for simplicity, we have only used the variants available in the pyCGM2 package. Another possible limitation is the fact that the test-retest protocol implemented was repeated only among three sessions. Additional sessions would also provide more power to the reliability analysis.

Contrarily, one of the strengths of the present study is the inclusion of a pathological population, including patients with CP and other different motor disorders. The heterogeneity of the populations in terms of age (three sub-groups) provides a more global overview of the reliability among gait reliability and also provides a comparative evaluation among those sub-groups.

In conclusion, all kinematic parameters demonstrated moderate to good reliability among and for all modeling and processing choices, except for the hip and knee rotation where variability was higher than the limit of acceptability. However, the integration of additional calibration methods, such as the Geometrical method, successfully improved the reliability of hip rotation, and thus, we recommend its integration in clinical practice.

3.1.6. Supplementary Information

S1. Intraclass correlation analysis

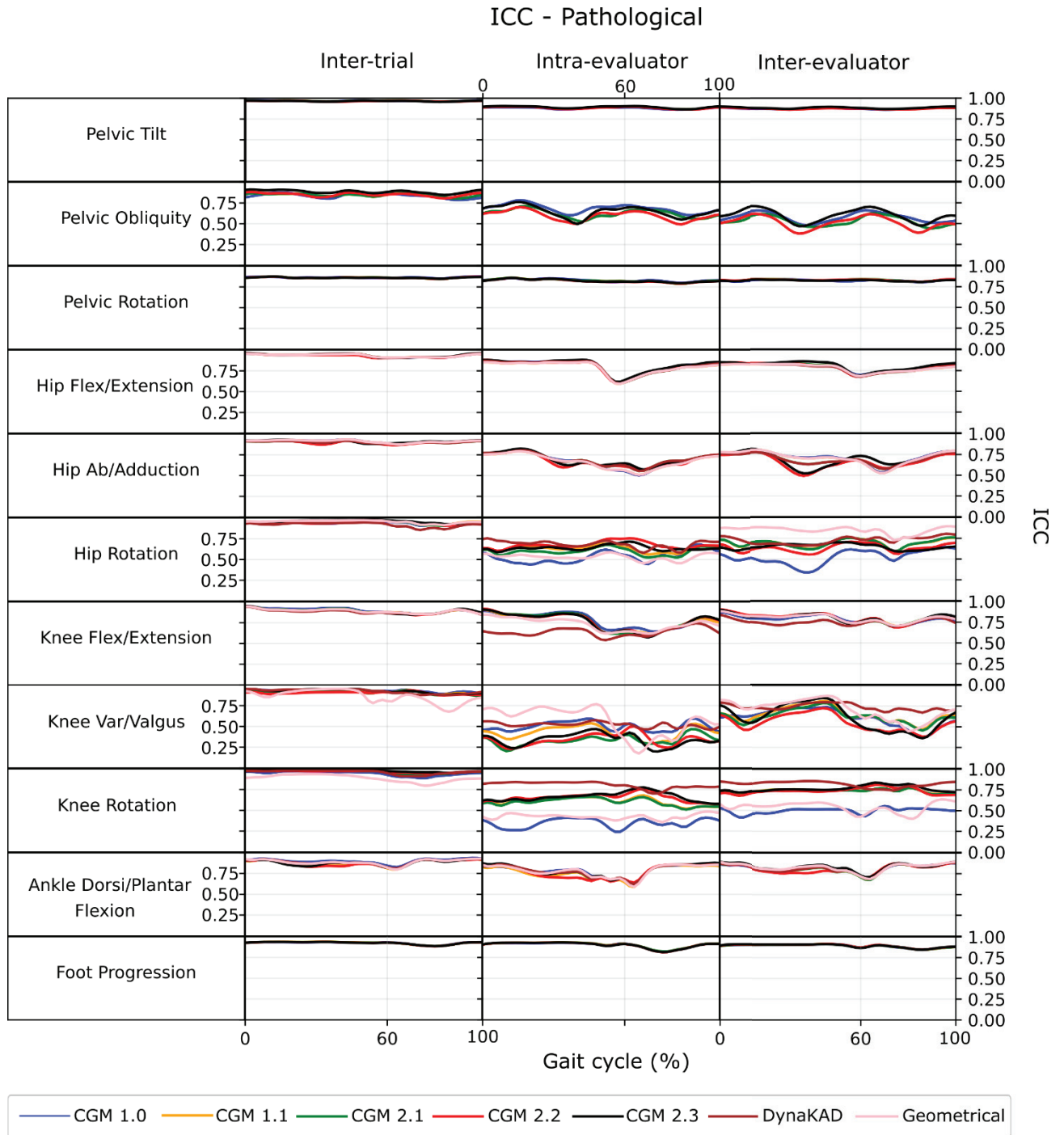


Figure 41. ICC values among the gait cycle relative to the pathological group through the gait cycle and among CGM modeling and processing choices.

ICC - Pathological

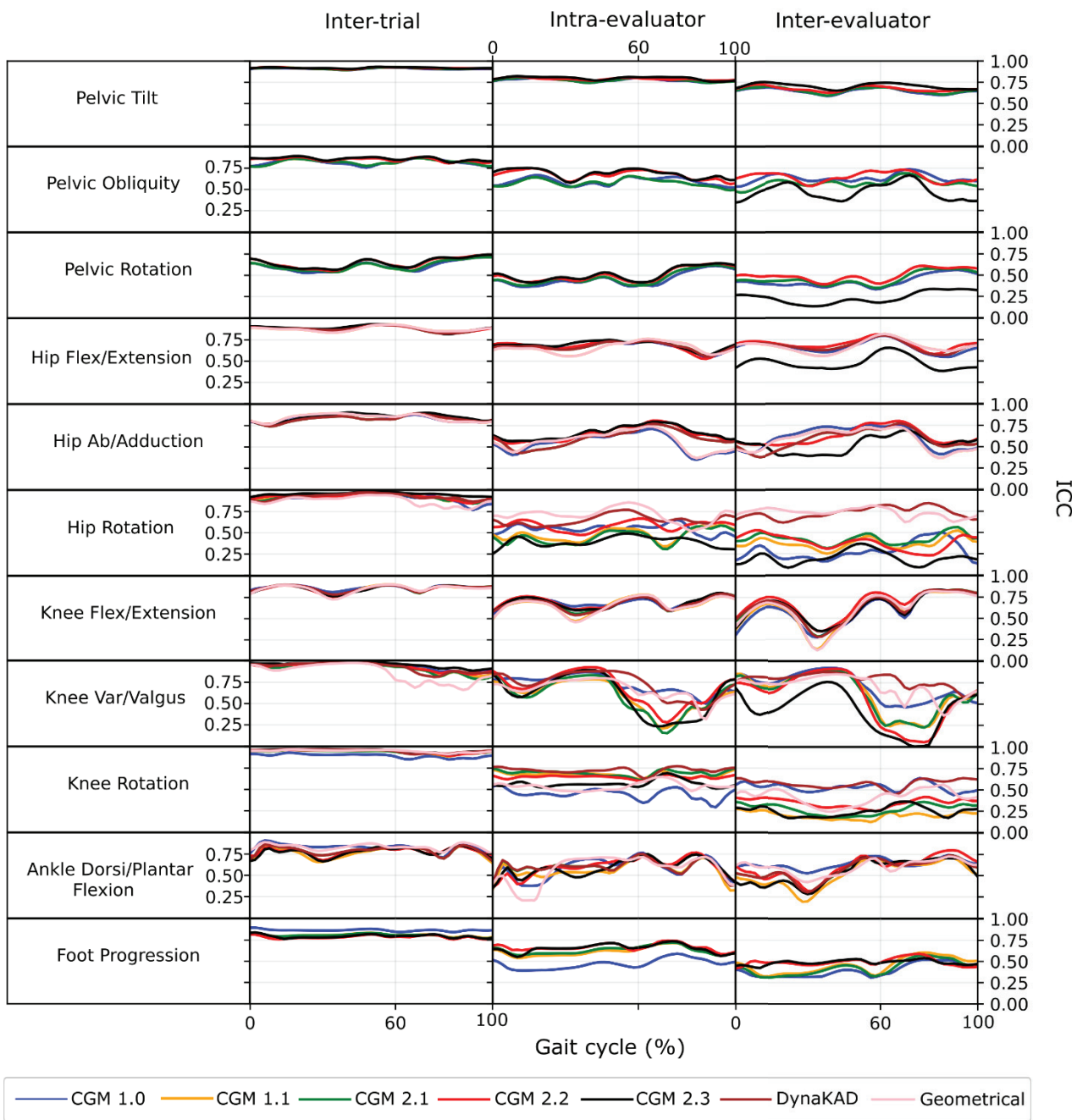


Figure 42. ICC values among the gait cycle relative to the asymptomatic group through the gait cycle and among CGM modeling and processing choices.

S2. Variability in anthropometric measurements

Figure 43 illustrates the variability in measuring the anthropometric data between both visits. Weight showed very low variability with an IQR within 1kg. Relatively to the measured lengths, leg length was the most variable parameter with a median over 5mm while the pelvis width showed a median value within 1mm.

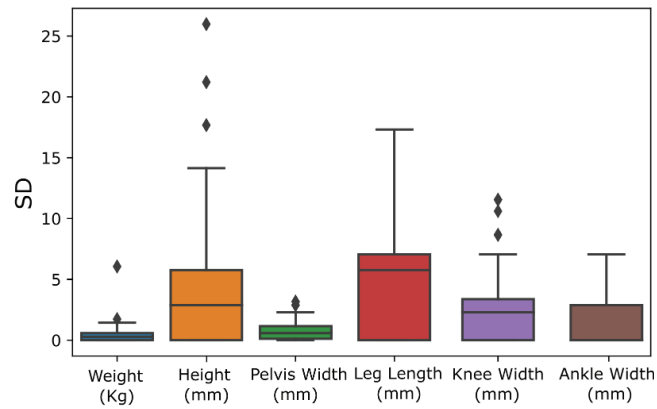


Figure 43. Variability (evaluated by SD) of anthropometric measurements between the two visits for all the participants.

3.2. Article 6 - Automatic gait event detection in pathologic gait using an auto-selection approach among concurrent methods

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Communication:

Results presented at European Society for Movement Analysis in Adults and Children (ESMAC), September 2021, virtual conference, as a poster communication.

Keywords: Gait; Events; Foot-off; Foot-strike; Kinematics; Auto-correlation

3.2.1. Abstract

Accurate gait event detection is crucial to analyze pathological gait data. Existing methods relying on marker trajectories were reported to be sensitive to different gait patterns, which is an inherent characteristic of pathologic gait.

We propose a new approach based on auto-selection among different methods, original and taken from the literature.

The auto-selection approach evaluates the accuracy of the implemented methods for both foot-strike and foot-off on all available events detected by the force platforms, independently, and automatically selects the most accurate one to be used on the whole gait session. Pathological gait data from 272 patients with cerebral palsy and idiopathic toe walking were used retrospectively to evaluate the accuracy of this approach. Three methods previously reported in literature together with original methods developed based on auto-correlation were implemented and constituted our auto-selection approach. The accuracy and precision were compared to a recently reported method based on deep events as it is the method that showed the best performance in literature.

Results showed that the proposed approach outperformed all implemented methods used alone, with an accuracy of -2.0ms and -0.9ms for foot strike and foot-off, respectively. Additionally, more than 99% and 93% of events detected were detected within 20ms and 10ms of accuracy, respectively.

The proposed methodology has been demonstrated to improve the accuracy and precision of gait event detection in gait analysis.

3.2.2. Introduction

Three-dimensional gait analysis requires accurate detection of events to align the different cycles and to identify their different phases. The gold standard for detecting events relies on the detection of a threshold on the vertical ground reaction force (GRF) measured by force-platforms (Hansen *et al.* 2002). However, this condition is generally applicable to a small number of steps during a gait session.

Several methods have been proposed to automatically estimate gait events based on kinematics (Hansen *et al.* 2002, Ghossein *et al.* 2004, O'Connor *et al.* 2007, Zeni *et al.* 2008, Desailly *et al.* 2009). However, none has yet been consensually accepted as the gold standard. The methods based on markers position, velocity or acceleration are highly sensitive to different gait patterns (Hansen *et al.* 2002, Visscher *et al.* 2021) and variations of walking speed (Zeni *et al.* 2008). Thus, their accuracy is reduced in a clinical context as pathological gait means higher heterogeneity at those levels (Armand *et al.* 2016).

The objective of this study is to design and evaluate an approach that automatically selects the best method for one gait session by concurrency of methods. Nine methods are implemented, six original methods based on auto-correlation between kinematic parameters and events detected by GRF and three methods from the literature.

3.2.3. Materials and Methods

Gait data

A total of 272 gait sessions collected from 184 patients, aged 13.0 (± 6.8) years, 129 diagnosed with cerebral palsy (CP) and 54 diagnosed with idiopathic toe-walking (ITW), were used retrospectively for this study. This study was approved by the "Comission Cantonale d'Éthique de la Recherche" (CCER-2018-00229). Two motion capture systems were used alternatively (Vicon MX3, Oxford Metrics, Oxford, UK and Oqus7+, Qualisys, Göteborg, Sweden) and two force platforms AccuGait, AMTI, (Watertown, MA, USA) with a sampling rate of 100Hz and 1000Hz, respectively. Participants were equipped with the conventional gait model marker set (Davis *et al.* 1991) and were asked to walk barefoot at self-selected speed. Marker trajectories and GRFs were filtered with a low-pass Butterworth filter at a cut-off frequency of 6Hz.

Auto-selection approach

The Figure 44 describes the workflow followed in the construction of the Auto-selection approach. The code was developed in Matlab (v2019a, Mathworks Inc., Natick, MA, USA) and is fully available (<https://gitlab.unige.ch/KLab/gev>).

Reference

For each gait session, events (foot-strike and foot-off) were automatically detected with GRFs using a generally accepted 20N threshold (Zeni *et al.* 2008), respectively. Steps without a unique and entire foot position on the force-platform were automatically excluded. The detected frames were stored for posterior accuracy calculation. For these events, foot and pelvic marker positions were extracted at foot-strike and foot-off and normalized (target values of the parameters).

Gait event detection

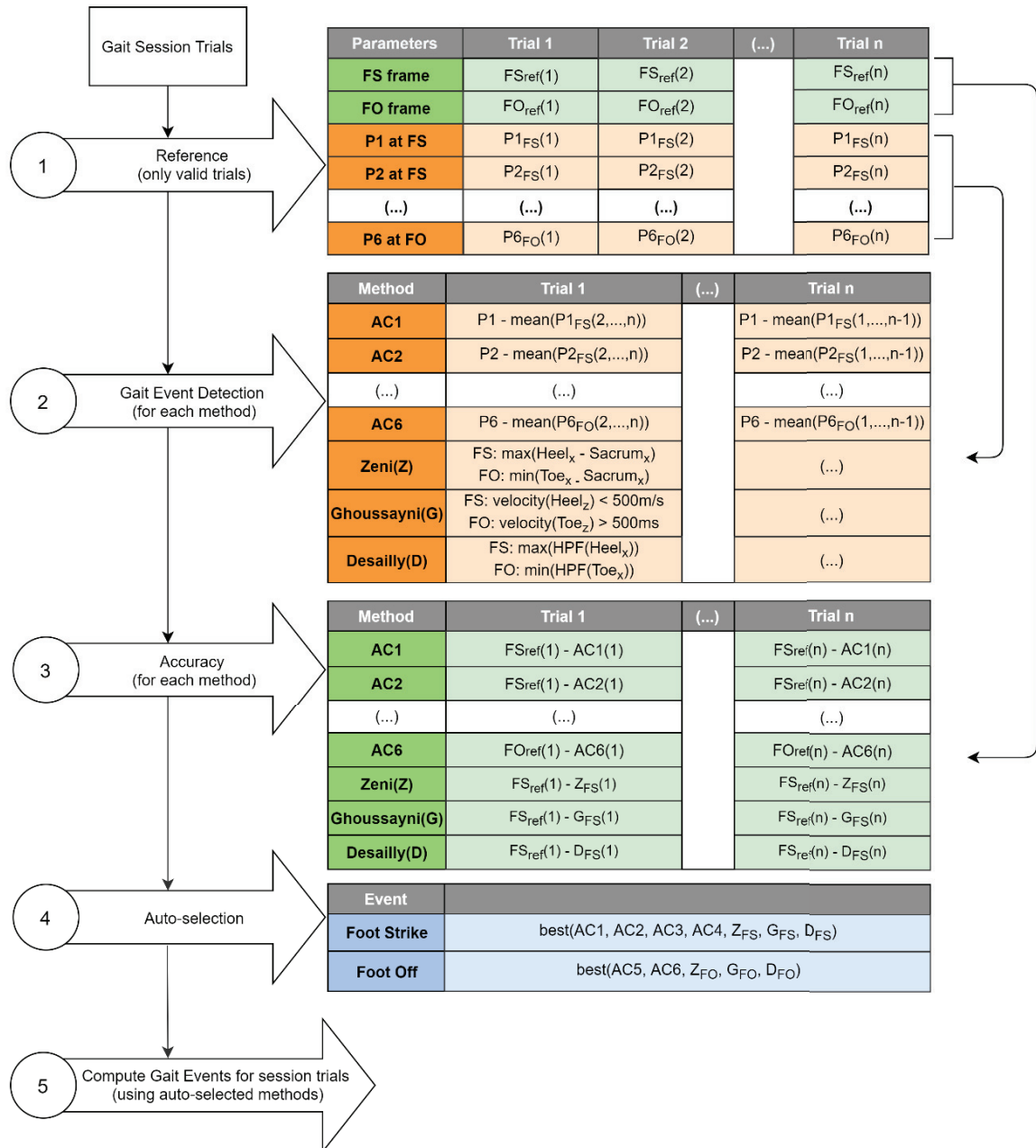
Normalized marker trajectories from each trial were extracted. The difference between those trajectories and the respective target values was calculated. Thus, different combinations of those parameters served to detect the event frames by minimum peak detection of this difference. Four auto-correlation methods were built for detecting foot-strike (AC1-AC4) and two for detecting foot-off (AC5-AC6). The description of the auto-correlation methods is fully described in Supplementary Information (S1). Additionally, three methods from the literature were implemented and used in the auto-selection approach: *Ghoussayni, Zeni, Desailly* (Ghoussayni *et al.* 2004, Zeni *et al.* 2008, Desailly *et al.* 2009).

Accuracy and auto-selection approach

The accuracy of each implemented method was calculated by the time difference between the reference and the predicted events for each trial and side. The overall session accuracy for each method was estimated by the mean accuracy among the session. The method with the lowest averaged time difference was selected, one method for each event (foot-strike and foot-off). No correlation was observed between the accuracy of the methods and the number of trained events used (Supplementary Information S2).

Validation

For the evaluation of each method and the auto-selection approach, the averaged time difference was completed by the confidence interval and compared to *DeepEvent* (Lempereur *et al.* 2020), which was not included in the auto-selection approach. The distribution of the methods selected by the auto-selection approach on the different patients and sessions was used to rank them.



FS - Foot Strike, FO - Foot Off, P - Predictor, AC - Auto-Correlation method, HPF - High Pass Filter, ref - Reference

Figure 44. Workflow of the Auto-selection approach. 1) Reference: Event frames are detected by GRF (green). Marker trajectories (P) are extracted at those events (orange). 2) Gait Event Detection: Marker trajectories stored at the Reference stage are used to build AC methods and calculate gait events for each trial. The P obtained at the same trial is not included. Methods Z, G, and D are also computed. 3) Accuracy: Event frames calculated in Reference are used to calculate the accuracy of each method outcome. 4) Auto-Selection: The method with higher accuracy for the entire session is selected, for FS and FO separately. 5) Compute Gait Events: The two methods selected in Auto-Selection are used to detect the event frames on the entire session.

3.2.4. Results

Validation

The auto-selection approach predicted foot-strike within a mean accuracy of -1.2ms and -2.0ms for CP and ITW groups, respectively (Table 30). Moreover, it predicted foot-off with a mean accuracy of -0.1ms and -0.9ms for both groups, respectively. The auto-selection approach resulted in better accuracy and precision (Figure 45). In general, most of the methods showed relatively good accuracy (median of accuracies close to zero) but poor precision (most have a wide range of dispersion). The auto-selection approach detected 99.3% of events within 20ms of accuracy and 93% within 10ms (Table 30).

Distribution of selected methods

For detecting foot-strike, AC1 was the most selected method for both groups. Contrarily, the methods implemented from the literature were generally less selected.

Regarding the detection of foot-off, *Zeni* method was the most selected method for both groups with a percentage of selection above 70%.

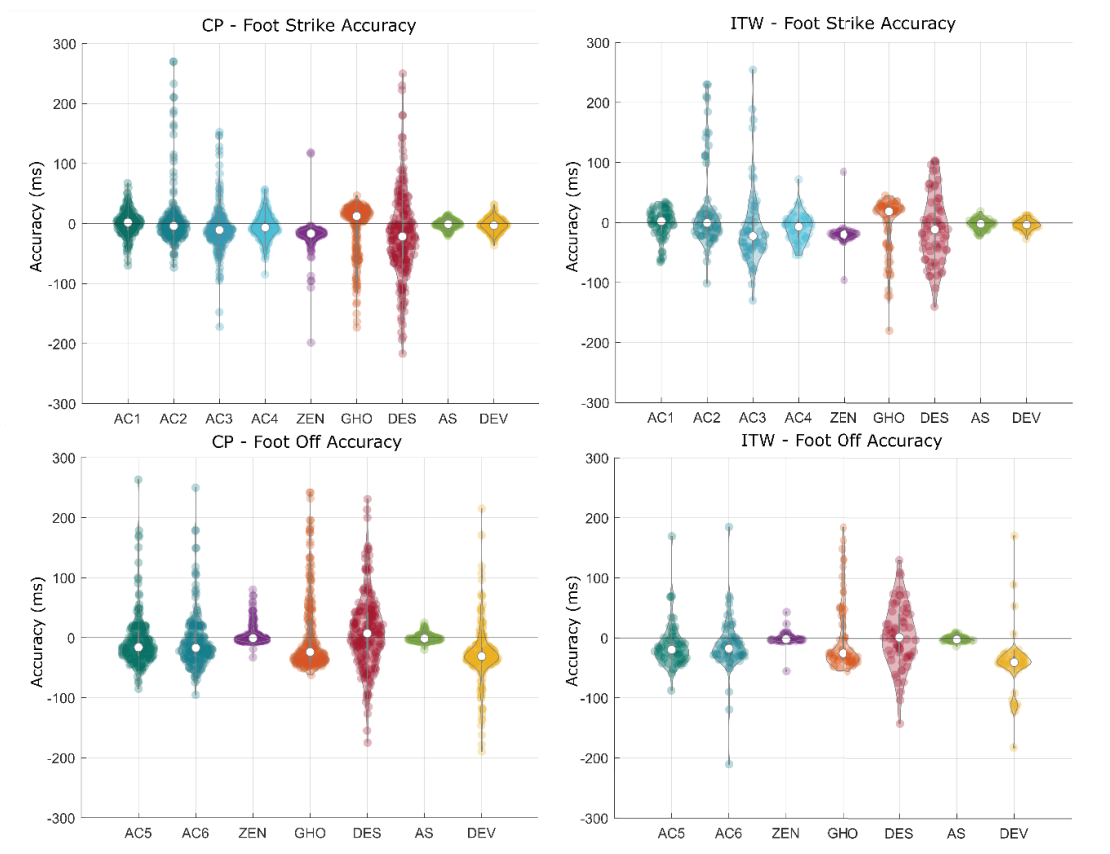


Figure 45. Violin plot for visualization of accuracy distribution for all sessions in milliseconds with respect to the two populations. The white point represents the median of the observations. Auto-correlation (AC[1-6]), *Zeni* (ZEN), *Ghoussayni* (GHO), *Desailly* (DES), *DeepEvent* (DEV) and Auto-selection (AS).

Method	Cerebral Palsy			Idiopathic Toe Walking			<20ms (%)	<10ms (%)
	Mean (ms)	CI (ms)	AS (%)	Mean (ms)	CI (ms)	AS (%)		
Foot Strike								
<i>AC1</i>	0.2	[-2.6; 3.0]	30.9	-0.9	[-6.9; 5.2]	36.9	84.2	71.7
<i>AC2</i>	8.1	[0.6; 20.5]	19.3	27.8	[13.5; 66.8]	12.3	78.3	71.3
<i>AC3</i>	-7.0	[-12.3; 0.2]	13.5	-6.6	[-23.1; 9.8]	7.7	82.0	76.1
<i>AC4</i>	-4.4	[-7.5; -1.3]	15	-8.4	[-14.2; -2.7]	24.6	87.5	77.6
<i>Zeni</i>	-17.8	[-20.2; -15.4]	6.3	-23.8	[-30.0; -17.7]	1.5	98.9	98.9
<i>Ghoussayni</i>	-3.1	[-8.5; 2.4]	9.7	-4.8	[-16.5; 6.9]	3.1	60.7	36.8
<i>Desailly</i>	-19.7	[-30.8; -10.7]	5.3	-9.5	[-23.3; 4.4]	13.8	76.1	71.7
Auto-selection	-1.2	[-2.2; -0.3]		-2.0	[-3.9; -0.1]		100.0	93.0
<i>DeepEvent</i>	-3.2	[-4.6; -1.7]		-3.3	[-5.3; -1.3]		98.5	90.1
Foot Off								
<i>AC5</i>	-6.0	[-12; 0.0]	6.3	-6.3	[-17.7; 5.1]	4.6	80.5	74.6
<i>AC6</i>	-5.2	[-11.3; 0.9]	3.9	-5.7	[-19.5; 8.1]	4.6	75.0	72.1
<i>Zeni</i>	4.7	[2.5; 6.9]	71	-0.7	[-3.2; 1.8]	80	89.0	83.8
<i>Ghoussayni</i>	3.0	[-5.6; 11.6]	15	2.4	[-11.8; 16.6]	3.1	75.4	74.3
<i>Desailly</i>	9.2	[1.2; 17.3]	3.9	7.3	[-4.8; 19.3]	7.7	59.9	51.1
Auto-selection	-0.1	[-0.9; 0.7]		-0.9	[-1.9; 0.1]		99.3	93.0
<i>DeepEvent</i>	-26.8	[-33.5; -20.2]		-43.2	[-55.0; -31.3]		90.4	88.2

Table 30. Performance evaluation among methods for the two groups of patients. Mean and CI (Confidence Interval) reported for the different methods and events, in ms. Distribution by percentage (AS(%)) of methods used to build AS method. Moreover, the percentage of accuracy was observed within 20 and 10 ms of error for each method and event (two right columns).

3.2.5. Discussion

The purpose of the present study was to define and evaluate an improved approach for gait event detection in pathological gait. Our approach proposed the implementation of existing methods, together with original ones based on auto-correlation and an auto-selection of the best predicting method within a gait session. After testing different combinations of parameters, we have proposed six methods for detecting foot-strike and foot-off. The parameters used on those methods (i.e. foot and pelvis marker positions with the exception of anterior iliac spine markers) were previously used (Visscher *et al.* 2021), which support them as indicators of gait events. Parameters based on velocity and acceleration of markers were not included as they showed higher sensitivity to gait velocity and patterns (Lempereur *et al.* 2020, Visscher *et al.* 2021). Most of the velocity-based or acceleration-based methods reported in the literature have only been validated for normal gait (Ghoussayni *et al.* 2004, Zeni *et al.* 2008, Desailly *et al.* 2009).

The performance of the implemented methods was observed similar to what was reported in the literature (Ghoussayni *et al.* 2004, Zeni *et al.* 2008, Desailly *et al.* 2009, Lempereur *et al.* 2020, Visscher

et al. 2021) but the auto-selection approach outperformed all tested methods. *Lempereur et al.* reported an absolute accuracy of 5.5ms and 10.7ms with a confidence interval of [0.9;10.2] and [5.4;15.9], for foot-strike and foot-off, respectively (*Lempereur et al.* 2020). In this study, *DeepEvents* resulted in considerably lower accuracy regarding foot-off, but *DeepEvent* was trained on their own entire database, acquired in a different laboratory, while our model is trained for each session. Our proposed approach requires considerably lower computation time than *DeepEvent* (approximately 70s by trial with *DeepEvent* compared to 0.2s with auto-selection). The considerably lower confidence interval and percentage of predicted events within 10ms and 20ms reported in Table 30 (99.3% and 93% of the predictions within one frame for foot-strike and foot-off, respectively) demonstrate the high performance of the auto-selection approach.

All methods used alone demonstrated high accuracy but low precision. All methods were selected in the auto-selection approach (Table 30), some methods were more often selected for foot-strike and others for foot-off, and with differences between CP and ITW. This observation reinforces the idea that existing methods are sensitive to heterogeneous gait. The Auto-selection approach allows finding the adjusted solution according to the patient's gait characteristics. demonstrating that all methods implemented have different performances for both gait events and that separating the selection by the type of event, results in more accurate detection. In addition, our proposed approach requires considerably lower computation time than *DeepEvent*.

In conclusion, the proposed approach has been demonstrated to improve the accuracy and precision of gait event detection in pathological gait. Thus, we propose its use in clinical practice. The implementation of additional existing methods is possible and expected to further improve its performance.

3.2.6. Supplementary Information

S1. Construction of methods

Marker trajectories were normalized relative to their amplitude, between 0 and 1 (0 corresponds to the minimum and 1 to the maximum values). Then, the normalized marker trajectories relative to each considered trial from one session were extracted. The proposed methods are based on an auto-correlation model. It aims to find the timings of a gait trial that represent the highest similarity between a marker trajectory value at known gait events. Four parameters were considered for the foot strike detection models and three for foot off as described in Table 30. The choice of parameters was based on those generally used in reported methods (Visscher *et al.* 2021). Equation 1 represents the estimation of the parameter function p , for each parameter, where the parameter value x at each instant of time, the mean of the target values obtained at the detected events x_{REF} was subtracted.

$$p = x - \text{mean}(x_{REF}), \quad \epsilon [-1,1] \quad (1)$$

This equation was applied to select the best parameters corresponding to the lower absolute values (close to zero) of the predictive functions and thus representing the highest similarity to the reference values. From several combinations of parameters tested, only the combinations that showed satisfactory similarity were considered. Thus, four different combinations were used for foot-strike detection: AC1, combines the prediction curve of Hz and StHx by summing both time series; AC2, adds the FOOT α to AC1; AC3, sums StHx and HIPx; AC4, sums all four parameters. On the other hand, two different methods were considered for foot-off: AC5, which combines Tz with StTx; and AC6, which combines all three parameters. Events were then extracted by detecting the minimal peaks for each one of the combined prediction curves. Table 30 summarizes the definition of each of the described methods based on auto-correlation, together with the three methods used in the literature.

Parameter	Gait Event Method	Description
H _z	Foot-strike	Vertical position of heel marker
StH _x	Foot-strike	Horizontal distance from the heel to the midpoint between the two posterior iliac spines
HIP _x	Foot-strike	Horizontal distance between the anterior iliac spine markers
FOOT α	Foot-strike; Foot-off	Foot angle relative to the floor
T _z	Foot-off	Vertical position of toe marker
StT _x	Foot-off	Horizontal distance between toe and mid point between the posterior iliac spines

Table 31. Definition of parameters used in the auto-correlation methods.

Method	Method construction
AC1	$\rho(\text{Hz}) + \rho(\text{StHx})$
AC2	$\rho(\text{Hz}) + \rho(\text{StHx}) + \rho(\text{FOOT}\alpha)$
AC3	$\rho(\text{StHx}) + \rho(\text{HIPx})$
AC4	$\rho(\text{Hz}) + \rho(\text{StHx}) + \rho(\text{FOOT}\alpha) + \rho(\text{HIPx})$
AC5	$\rho(\text{Tz}) + \rho(\text{StTx})$
AC6	$\rho(\text{Tz}) + \rho(\text{StTx}) + \rho(\text{FOOT}\alpha)$
<i>Zeni et al. (2007)</i>	Maximum distance between Heel and Sacrum (FS) and minimal distance between Toe and Sacrum (FO) markers in the horizontal plane
<i>Ghoussayni et al. (2004)</i>	Sagittal velocity of the Heel (FS) and Toe (FO) markers goes below and above a threshold of 500m/s, respectively
<i>Desailly et al. (2008)</i>	High pass filtered maximum horizontal Heel (FS) and minimal horizontal Toe (FO) markers, respectively.

Table 32. Description of the construction of each method. AC[1-6] - Auto-correlation methods, FS – Foot Strike, FO – Foot Off, ρ – parameter, Hz – vertical component of the heel markers; StHx – horizontal component of the distance from the heel to the anterior-posterior iliac spine markers; FOOT α – Foot angle concerning the ground, HIPx – horizontal component of the distance between the anterior iliac spine markers; StTx – horizontal component of the distance from the heel to the anterior-posterior iliac spine markers; Tz – vertical component of the toe marker.

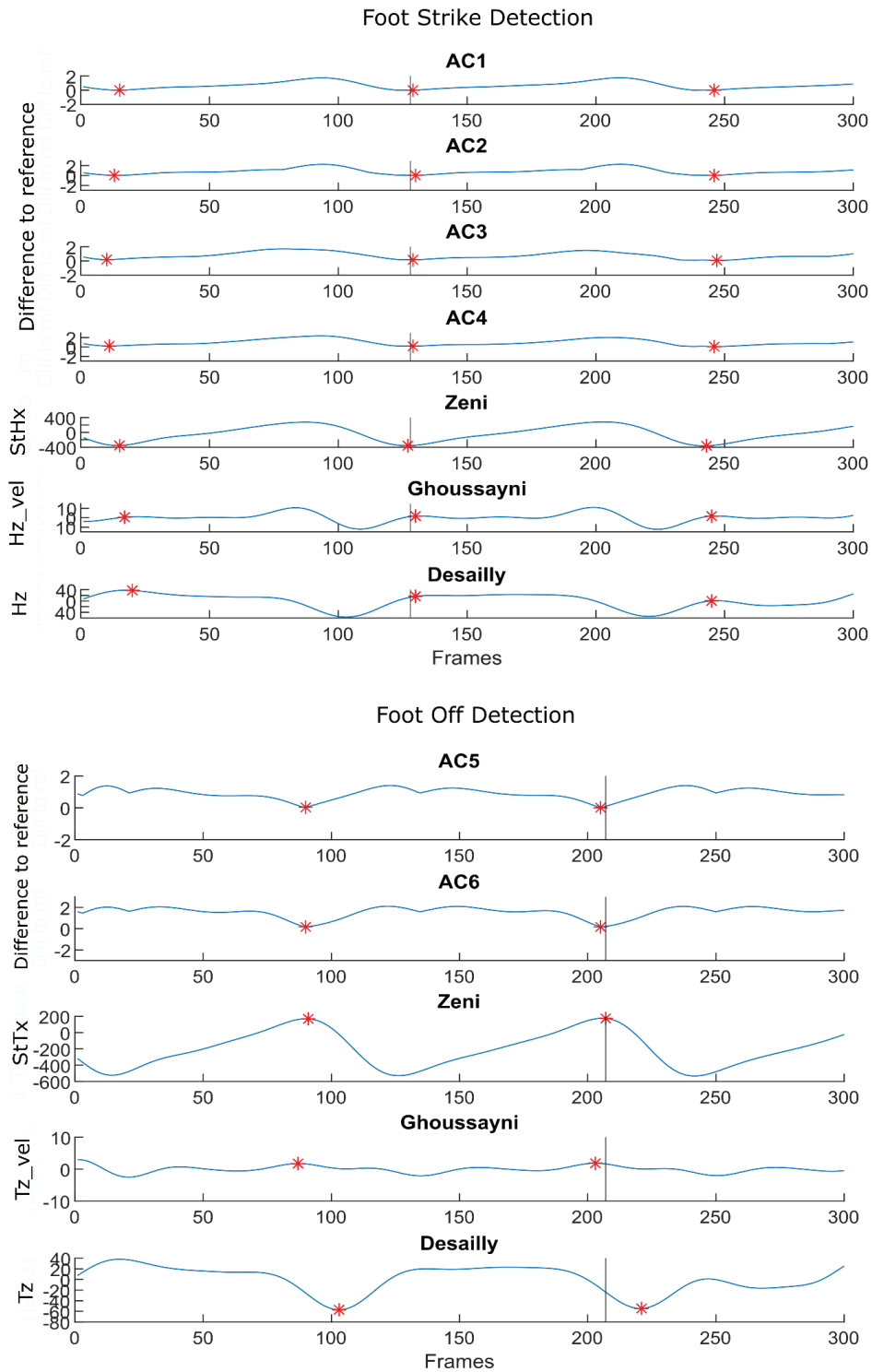


Figure 46. Gait event detection for each method. Example of foot strike detection for each of the implanted methods in the auto-selection approach. Blue line represents the parameter of detection, vertical black line represents the event detected by the ground reaction force, red mark represents the detected event times for each method. StHx, the distance between the sacrum (midpoint between posterior iliac spine markers) and heel marker in the horizontal direction; H_z_vel , heel marker velocity on the vertical direction; H_z , heel marker position in the vertical direction; T_z_vel , toe marker velocity on the vertical direction; T_z , toe marker position in the vertical direction; StTx, the distance between the sacrum (midpoint between posterior iliac spine markers) and toe marker in the horizontal direction.

S2. Required number of training events

The correlation between the accuracy of auto-correlation methods and the number of training events was not observed (Figure 47). The coefficient of Pearson correlation between the accuracy of auto-correlation methods proposed (AC [1-6]) with the number of training events was $R = 0.06$ ($p=0.42$) showing that the number of training events is not important for the accuracy of the AS approach. Therefore, as the reference data extracted in one specific trial is not used to build the AC models for estimating gait events in this particular trial, a minimum of two training events are required over the session.

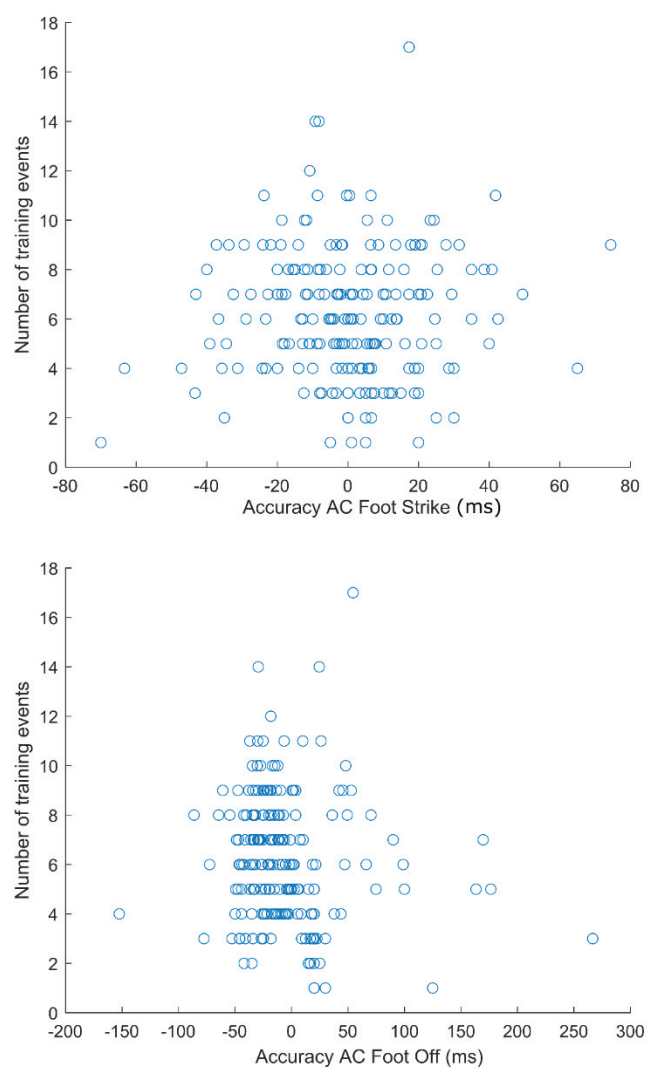


Figure 47 Correlation analysis between the accuracy of auto-correlation methods and the number of training events.

3.3. Chapter Discussion

Variability in gait analysis due to measurement error can affect the curves on a temporal level (and information is lost in the means when averaging several trials), amplitude (shift up/down), or curve shape. Different sources of variability impact the final result in a different way, some sources of variability such as marker placement may mainly induce an offset (as observed in Articles 1 and 2), while soft tissue artefacts may affect the shape of the curve and gait event detection may then temporally shift the superposed signals.

Article 5 was meant to evaluate the performance of different modeling and processing choices in reducing extrinsic variability. In particular, two calibration methods (DynaKAD and Geometrical), previously reported in the literature and implemented in the PyCGM2 package, were added as functional calibration of the CGM2.1 variant (Baker et al. 1999; Naa'im et al. 2019) to complete a series of 7 variations of the CGM. The CGM was the model chosen as it is the model most commonly applied in clinical routine and more validated in literature (McGinley et al. 2009). Results showed similar values of reliability among all the modeling and processing choices tested for most of the kinematic parameters. However, at the hip on the transversal plane, the DynaKAD and Geometrical calibration methods lead to an improvement of reliability, reminding that this is the angle associated with higher variability and so, with low trust from the clinicians during interpretation. Thus, such results support the need for the integration of calibration methods in the computation of gait kinematics in clinical routine. More tests may be necessary to assure that intrinsic variability is not mistakenly corrected.

The experimental protocol used followed previously reported studies designed for evaluating the reliability of gait analysis (Schwartz *et al.* 2004). Two evaluators were involved in the protocol within two sessions. On the first visit, one gait session was recorded by one evaluator who performed marker placement. Data collected from the pathological population during the first session coincided with the clinical visit. As the clinical evaluation is generally long (approximately three hours) and to avoid the fatigue of the patients, a second session (with the second evaluator) was not incorporated into the protocol. Therefore, on the second visit, the two evaluators performed, each, one gait analysis session. Moreover, the cerebral palsy and asymptomatic populations were selected to form three sub-groups of eight subjects in terms of age interval (children, adolescents and adults). The aim was to evaluate potential differences in terms of variability in terms of age. Additionally, eight patients with motor disorders different from cerebral palsy were included. Ideally, a wide range of BMI would be included in the recruitment process to evaluate possible differences of variability related to the difficulties associated with marker placement in participants with higher BMI (Moriguchi *et al.* 2009). However, difficulties in the recruitment process allied with the restrictions caused during the Covid-19 pandemic limited the selection of participants.

Another source of variability in gait analysis data is related to the estimation of gait events, used to crop the data temporally within gait cycles. Erroneous temporal cropping of the gait cycles affects mostly the spatial and temporal parameters as curve registration can compensate for part of the shift introduced (Sadeghi *et al.* 2000). Several methods have been proposed in the literature but their accuracy and precision vary among different types of gait (Bruening and Ridge 2014). Alternatively, algorithms based on deep-learning have been proposed and highly improved the detection of events. However, the computational time and requirements are considerable, making it difficult to apply in clinics. Article 6 presented a newly developed methodology for estimating the gait events based on an auto-selection approach among concurrent methods. Part of the implemented methods (4 to detect foot-strike and 2 to detect foot-off) have also been developed based on auto-

correlation with detection made using the vertical component of the force detected by the force platforms at valid gait cycles. Complementarily, three more methods have been added from literature. The auto-selection process is made by calculating the minimal distance between the predictions of the events by all methods included and the events detected by the force-platform data and then the best performing method, for each of the events, is applied to the overall gait session data. Results have demonstrated that the proposed method outperformed all methods applied, with an extremely satisfactory accuracy and precision, improving especially the detection of foot-off (where all proposed methods have been typically less efficient). In comparison with the deep-learning based method applied (Lempereur *et al.* 2020), our methodology showed better performance, and so overcoming the above limitations described for deep-learning based methods. In addition, it was demonstrated that all methods were selected (even in different proportions) for estimating events among the populations. This observation showed that no method can be chosen as the best for the general population and for both events when used alone. The difference in the observed proportion among the two groups (CP and ITW) and events (foot-strike and foot-off) also demonstrated that some methods tend to be more efficient than others in different types of gait and between events.

In sum, the methodology proposed is simple and mutable as new methods are easily integrated and tend surely to improve even more the efficiency of the detection. The toolbox has been shared in opensource with the article for free use by the gait analysis community. Another positive point associated with this methodology is the fact that previous work made by other researchers, who proposed methods, can be more valued and integrated together. The good accuracy reported suggests that fewer resources may be directed into improving the detection of events in gait analysis as compared to limiting the impact of marker misplacements. In perspective, the replication of the data processing performed on Article 5 with the integration of this new methodology would allow the comparison with the typically used method (Zeni *et al.* 2008) as well as to understand its impact on the variability of kinematic, SPT parameters and clinical interpretation of gait deviations. Another possibility for this tool would be to release it in another computational language such as Python (largely used by the gait analysis community).

In conclusion, both articles presented in this chapter intended to propose or apply a methodology for improving the reliability of clinical gait analysis.

Chapter 4 - Management of Variability in Clinical Gait Data Interpretation

In the previous chapter, we have demonstrated that the reliability of gait data can be reduced by applying calibration methodology, or even that there is a margin for developing new methods for improving the measurement of gait in terms of reliability. The third and final aim of this doctoral work proposes the application of the knowledge acquired in the two previous chapters referent to the variability of kinematic data on clinical interpretation. Thus, two studies have been designed to incorporate and manage variability in the interpretation of gait data.

Taking into consideration that marker placement is the main source of kinematic variability and the marker placement precision may be affected by the capacity and expertise of the evaluator in identifying anatomical landmarks, a hypothesis was formulated. This hypothesis suggests that confidence in marker placement is correlated with kinematic variability. In Article 7 (currently in the final stage of preparation), one metric was proposed to measure qualitatively the confidence in marker placement. The first objective of the study was to evaluate the validity and reliability of the proposed metrics. The second objective was to evaluate the relationship between measured confidence and output kinematic variability.

The second study within this chapter (Article 8, in an early stage of preparation) proposes a new gait score including clinically relevant features and integration of kinematic expected variability together with a more intuitive display, for patients with CP. In Article 2, it was observed that GPS was highly variable due to marker placement errors. In addition, the typical gait scores, such as GPS or GDI, consider all kinematic parameters equally. Therefore, it was hypothesized that a score focused on previously reported clinically relevant features and including the experimentally estimated variability would improve the interpretability of the gait score as well as reduce its sensitivity to kinematic variability. In addition, it was considered that a more visually and detailed display of the score would improve its interpretability and assessment of gait deviations. Thus, the primary focus of this study is to evaluate its validity for clinical application. This study is still in the early stages of preparation and no preliminary results are yet incorporated.

4.1. Article 7 – Can the evaluation of marker placement confidence be used as an indicator of kinematic variability?

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Keywords:

Marker placement; confidence; kinematics; variability; gait analysis

4.1.1. Abstract

Three-dimensional gait analysis is widely used for the clinical assessment of movement disorders. However, measurement error affects the reliability of kinematic data and consequently assessment of gait deviations. Therefore, the estimation of extrinsic variability in the analyses of kinematics could improve gait data interpretability. Moreover, marker placement error has been demonstrated to be the biggest source of variability in gait analysis and may be affected by factors intrinsic to the evaluators such as evaluator's experience or marker placement confidence.

In the present study, we hypothesized that confidence in marker placement is correlated with kinematic variability and has the potential to be used as a predictor factor. Therefore, we have proposed a questionnaire to evaluate qualitatively the confidence of evaluators in lower-limb marker placement. The primary aim of this study was to evaluate the reliability and validity of the presented questionnaire. The secondary objective was to test a possible relationship between marker placement confidence and kinematic variability.

To do so, test-retest gait data were acquired from two different experimental protocols. One protocol included data from a cohort of 32 pathological and 24 asymptomatic subjects where gait analysis was repeated three times, involving two evaluators. A second protocol included data from a cohort of 8 asymptomatic adults with gait analysis repeated 12 times, per participant, and involving four evaluators with a wider range of experience.

Results demonstrated that the questionnaire proposed is valid and reliable to evaluate qualitatively the confidence of evaluators in placing markers. Indeed, confidence scores were correlated with actual variability of marker placement and revealed the evaluator's experience and subjects' characteristics. However, no correlation was observed between confidence scores and kinematic variability and the formulated hypothesis was not proven.

4.1.2. Introduction

Three-dimensional gait analysis (3DGA) is widely used in the assessment of motor disorders and to support treatment decision-making. However, several studies reported variability within the measured data by reproducing gait data collection under the same conditions (McGinley *et al.* 2009). Variability in 3DGA is due to a combination of intrinsic and extrinsic factors. Intrinsic factors refer to the natural variability associated with the capacity of a subject to repeat the same gait movement across cycles, within or between days, and it is considered an indicator of gait impairments, typically described as intrinsic variability (Tabard-Fougère *et al.* 2022). On the other hand, extrinsic factors are associated with measurement error and are caused by a combination of parameters such as marker placement, instrumentation, soft tissue artifacts, and data processing (Chiari *et al.* 2005, Della Croce *et al.* 2005, Leardini *et al.* 2005, Camomilla *et al.* 2017). Variability associated with extrinsic factors reduces confidence when interpreting gait deviations. Moreover, marker placement has been reported as the biggest source of variability in 3DGA (Gorton *et al.* 2009). Marker placement relies on the correct palpation and identification of the subcutaneous anatomical landmarks (AL) and its precision and accuracy are sometimes difficulted by their large and curvy characteristics (Della Croce *et al.* 2005). The correct identification of ALs depends on the ability of the evaluator, allied with the anatomy of the subject since underlying adipose tissue or bony deformations may render difficult the palpation or correct positioning of the markers. For instance, a subject with high subcutaneous adipose tissue has been proven to be associated with higher difficulty in the palpation (Moriguchi *et al.* 2009, Horsak *et al.* 2021). Even if the AL is correctly identified for this subject, the accurate location of the skin marker will probably be reduced and consequently affects the definition of the segment coordinate systems. Therefore, we can expect that the difficulties encountered by the evaluator to place the marker (correct identification of the AL and presence of soft tissues) will impact his/her confidence in this placement.

The application of 3DGA in clinics requires the most reliable measurement setup possible, including the placement of markers by the evaluator. The most commonly applied biomechanical model in 3DGA is known as the Conventional Gait Model (CGM) and it has been proven to be highly sensitive to marker placement accuracy, and thus dependent on the ability of the evaluator (Osis *et al.* 2016, Baker *et al.* 2017, Fonseca *et al.* 2020). Therefore, the question of whether an evaluator should be well prepared and experienced to place markers in a gait analysis session was debated. Previous results have shown that the more experienced the experimenter, the greater the repeatability of marker placement (Sinclair *et al.* 2014). Thus, suitable training has proven to play a more important role than experience in gait analysis. However, the evaluation was performed between only two evaluators (one experienced and one novice) in a short sample size (10 asymptomatic subjects) and each evaluator collected one kinematic data per subject. In addition, the level and heterogeneity of the population observed in terms of BMI were low. Thus, due to these factors, the data collected in this previous study may not be sufficient for evaluating possible statistically significant differences between the evaluators and between the subjects.

Extrinsic variability is inherent to measuring gait data and negatively affects the assessment of gait deviations during the interpretation of the results (McGinley *et al.* 2009). Differences in data concerning the normative reference database are required to be higher than the estimated variability to be accepted as true gait deviations. Being so, the estimation of such variability could be important to improve the confidence in kinematic data.

Therefore, we hypothesized that the confidence of evaluators in placing markers may be related to measurement error in gait kinematics data and have the potential to be used as predictors of joint (hip, knee, ankle) and segment (pelvis, foot) angles variability. Thus, the first objective of this study is to evaluate the reliability and validity of a proposed custom-made questionnaire for reporting qualitatively the confidence in marker placement (CMP) from the evaluators. To do so, we intended to evaluate the relationships between CMP scores relative to other aspects of measurement gait such as the evaluator's experience, subject characteristics, and marker placement precision, and to characterize its distribution. The second objective is to evaluate the correlation between CMP scores and kinematic variability. We hypothesized that confidence in marker placement has the potential to be used as a predictor of kinematic variability.

Two test-retest experimental protocols were used. Firstly, we used an experimental protocol (A) with a test-retest methodology on a heterogeneous cohort, incorporating asymptomatic subjects and patients with motor disorders within different age groups. Data collection was repeated three times, for each subject among two evaluators. Secondly, we have defined an experimental protocol (B) composed of a test-retest methodology and including four evaluators with different levels of experience in marker placement. This protocol involved the participation of eight asymptomatic adults, and for each, data collection was repeated twelve times within a unique visit (three sessions per evaluator). As described in the methods section, both protocols helped to answer both objectives and include a custom-made questionnaire for collecting the confidence of evaluators in marker placement.

4.1.3. Methods

a) Subject populations

Two different protocols were used for the present study (Figure 48). The protocol A involved the recruitment of 56 subjects, of which 24 asymptomatic, ((mean (SD) age: 18.3 (9.6) years; height: 155.4 (21.7) cm; weight: 52.1 (19.2) kg; 12 males and 12 females), 32 patients (24 patients with CP and 8 patients with other motor disorders; mean (SD) age: 18.4 (9.7) years; height: 156.7 (17.5) cm; weight: 52.4 (19.2) kg; 25 males and 7 females). In protocol B, 8 asymptomatic adults were recruited, (mean (SD) age; 31.2 (11.0) years; height: 171.2 (8.9) cm; weight: 71.5 (16.1) kg; 4 males and 4 females) with no pathological condition affecting normal motor ability, were acquired. These protocols were approved by the "Commission Cantonale d'Éthique de la Recherche Genève" (CCER-2020-00358) and all subjects provided written informed consent (legal tutors signed the consent for non-adult subjects). The exclusion criteria for all groups were known pregnancy and no allergy to adhesive tape.

b) Experimental protocol A

In protocol A, subjects visited the laboratory on two occasions 10 days apart. Two evaluators with required training for AL identification were responsible for conducting the complete gait analysis sessions. On the first visit, evaluator A1 was responsible for placing the markers and each participant performed one gait analysis session, including one static and a minimum of ten barefoot walking trials. On the second visit, the subjects were asked to repeat two gait analysis sessions, conducted by evaluators A1 and A2, respectively. Reflective markers (14mm) were placed following the Conventional Gait Model described in (Leboeuf *et al.* 2019) and palpation followed the guidelines previously described (Van Sint Jan 2007) (description of marker locations in Supplementary Information S1). A 12-camera motion capture system (Oqus7+, Qualisys, Göteborg, Sweden) tracked the marker trajectories at 100Hz.

c) Experimental protocol B

In protocol B, the subjects visited the laboratory on one occasion. Four evaluators were responsible for conducting three different gait sessions each. All evaluators were properly trained and differed in level of experience: evaluator B1 with more than ten years of experience in clinical practice, with over a hundred gait analysis sessions per year; evaluators B2 and B3, have approximately four and two years of experience in gait analysis, respectively, with approximately fifty sessions per year; evaluator B4 had no previous experience in gait analysis. Reflective markers were placed following the same biomechanical model applied for protocol A. Moreover, the same equipment was used for both protocols.

Kinematic data for both protocols were calculated using the PyCGM2 open-source library (<https://github.com/pyCGM2/pyCGM2>).

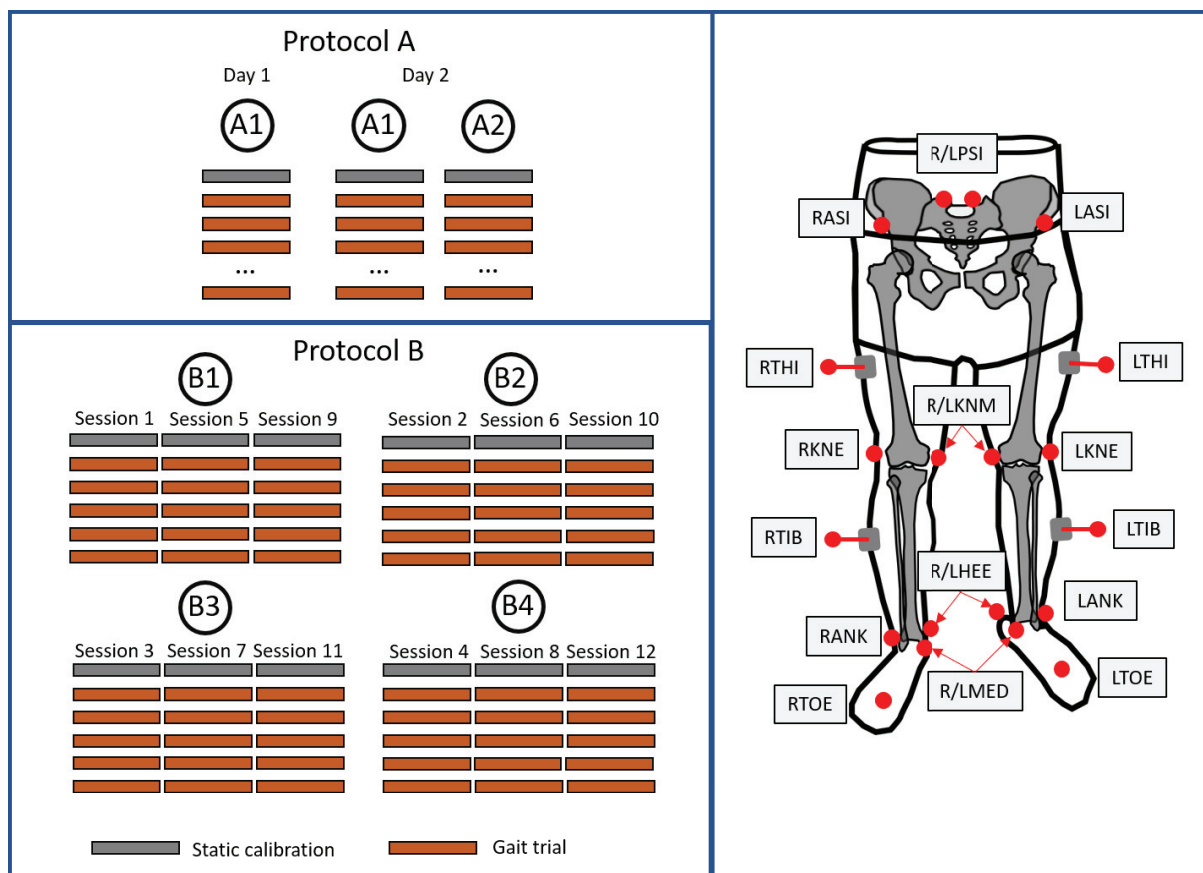


Figure 48. Illustration of the two protocols applied in the present study (left) and marker placement protocol applied on both protocols (right).

d) Marker placement confidence questionnaire

A custom-made questionnaire was designed to report qualitatively the confidence of evaluators in placing the markers (See Supplementary Information S2). For each marker, a scale of confidence is provided ranging from zero (extremely low confidence) to ten (extremely confident). Evaluators of each protocol filled out the questionnaire after each marker placement session.

e) Statistical analysis

Firstly, following the COSMIN guidelines for assessing the methodological quality of the measurement of CMP scores, reliability and validity were evaluated (Mokkink and Terwee 2010). To answer this first objective, the reliability of the CMP scores was evaluated in both protocols A and B using the interclass correlation (ICC) (3,1) (Shrout and Fleiss 1979), typically used in agreement studies with interval ratings (de Raadt *et al.* 2021).

Several relationships were then evaluated to analyze the validity of the CMP score. The statistical differences in CMP scores between the two populations (asymptomatic and pathologic) were tested with protocol A. Additionally, with protocol A, Spearman rank correlation coefficients between CMP scores among all markers were calculated, with alpha values of $p < .05$ regarded as significant. Markers were grouped by segments and correlations among the groups and between CMP scores and subject's characteristics such as weight, BMI, pelvis width, leg length, and age were analyzed. The statistical differences in CMP scores between the four evaluators were tested with protocol B for all markers and groups of markers. The validity of CMP was also evaluated relative to the marker precision estimation provided by protocol B with the Spearman rank correlations between the CMP score and marker precision, for each marker. In this analysis of the CMP score validity, statistical differences were tested and correlations were analyzed by Spearman rank correlation coefficients, with $p < 0.05$ considered significant. Marker placement precision for each session was calculated as the difference in the positioning of the markers concerning the mean location among all twelve sessions for each subject of the corresponding markers.

To answer the second objective, the correlation between mean CMP scores per group of markers and inter-session kinematics variability was evaluated with protocol A (Figure 49). A Spearman rank correlation coefficient was applied, with $p < 0.05$ considered statistically significant. Kinematics variability associated with protocol A was calculated as the standard deviation of the mean kinematics acquired among the three sessions of each participant.

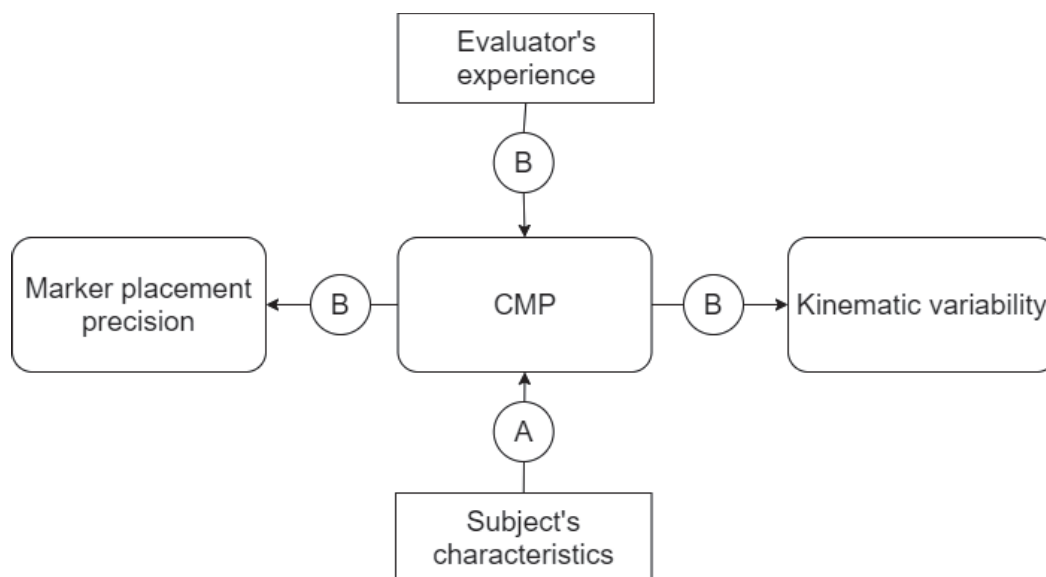


Figure 49. Diagram describing the relationships evaluated and experimental protocols (A or B) used for each relationship.

4.1.4. Results

The diagram represented in Figure 43 illustrates the relationships evaluated and the protocols used.

Reliability of CMP scores

The reliability evaluation, provided in Table 33, reported the ICC calculated among the CMP scores for the data of the two protocols separately. Very similar values were obtained between both lower limb sides. On the one hand, protocol A demonstrated high reliability ($ICC \geq 0.75$) for the CMP of pelvic markers and moderate reliability ($0.75 > ICC \geq 0.5$) for the remaining markers. On the other hand, CMP for all markers resulted in high reliability on protocol B.

Marker	Protocol A	Protocol B	Marker	Protocol A	Protocol B
LASI	0.90	0.85	RASI	0.90	0.82
LPSI	0.84	0.82	RPSI	0.84	0.83
LTHI	0.63	0.76	RTHI	0.70	0.77
LKNE	0.74	0.83	RKNE	0.76	0.83
LKNM	0.74	0.84	RKNM	0.76	0.84
LTIB	0.64	0.75	RTIB	0.71	0.75
LANK	0.59	0.77	RANK	0.59	0.76
LMED	0.59	0.76	RMED	0.59	0.76
LHEE	0.66	0.77	RHEE	0.66	0.78
LTOE	0.57	0.84	RTOE	0.57	0.84

Table 33. Inter-evaluator reliability (ICC) for CMP scores compared between both protocols.

Validity of CMP scores

Figure 50 reports the distribution of CMP scores through the different markers among both populations in protocol A. CMP score is observed widely variable across the pelvis, femoral epicondyles, and wands. It also shows a higher variance of CMP scores associated with patients, compared to the asymptomatic subjects with significant differences reported. On the other hand, very low variability was observed in the CMP score of the tibial malleolus and foot markers among all subjects from both populations.

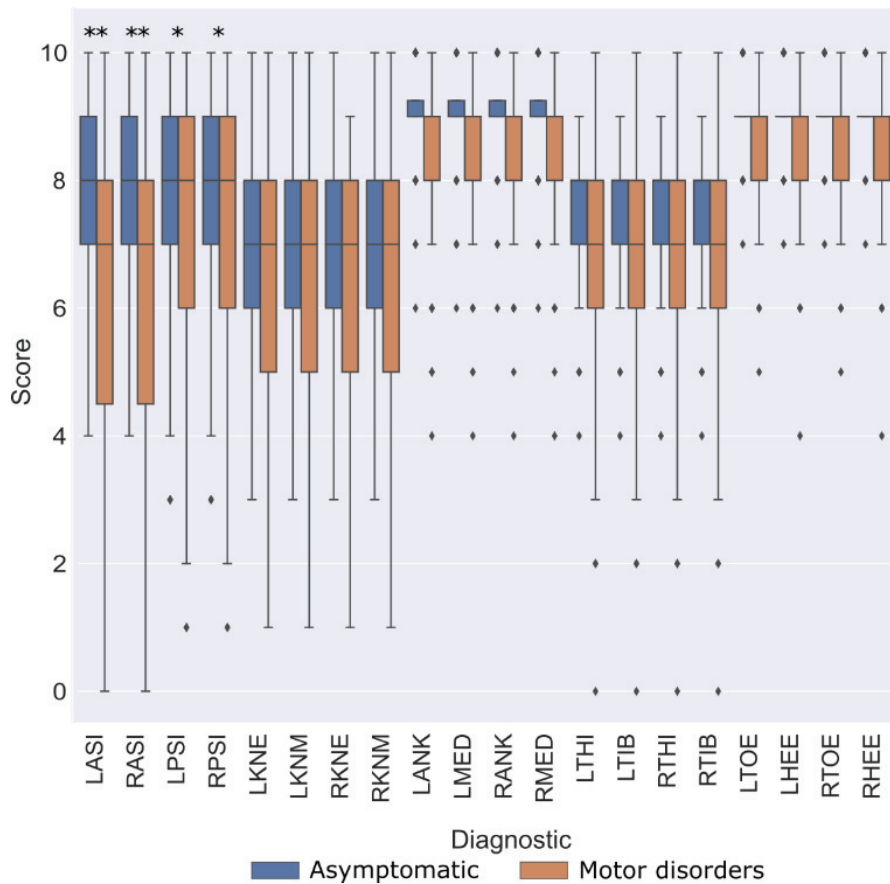


Figure 50. Comparison of CMP scores between asymptomatic subjects (blue) and patients with motor disorders (orange). Statistically significant differences among populations ($p < 0.05$ marked with *, and $p < 0.005$ marked with **).

The correlation between CMP scores among all markers is reported in Figure 51. CMP scores among markers are extremely correlated within the matching contra-lateral markers (*i.e.* LASI and RASI). Additionally, the results show that evaluators tend to be equally confident among groups of markers of the same typology (wands) and segment (pelvis, thigh, shank, and foot). Thus, a subset of markers was grouped as follows: Pelvis (L/RASI and L/RPSI); Knee (L/RKNE and L/RKNM); Ankle (L/RANK and L/RMED); and Foot (L/RHEE and L/RTOE); Wand (L/RTHI and L/RTIB). Correlations between CMP scores among groups of markers and between CMP scores and the subject's characteristics are presented in Figure 54. Some subjects' characteristics, such as BMI showed a good correlation with CMP scores of pelvic and thigh markers.

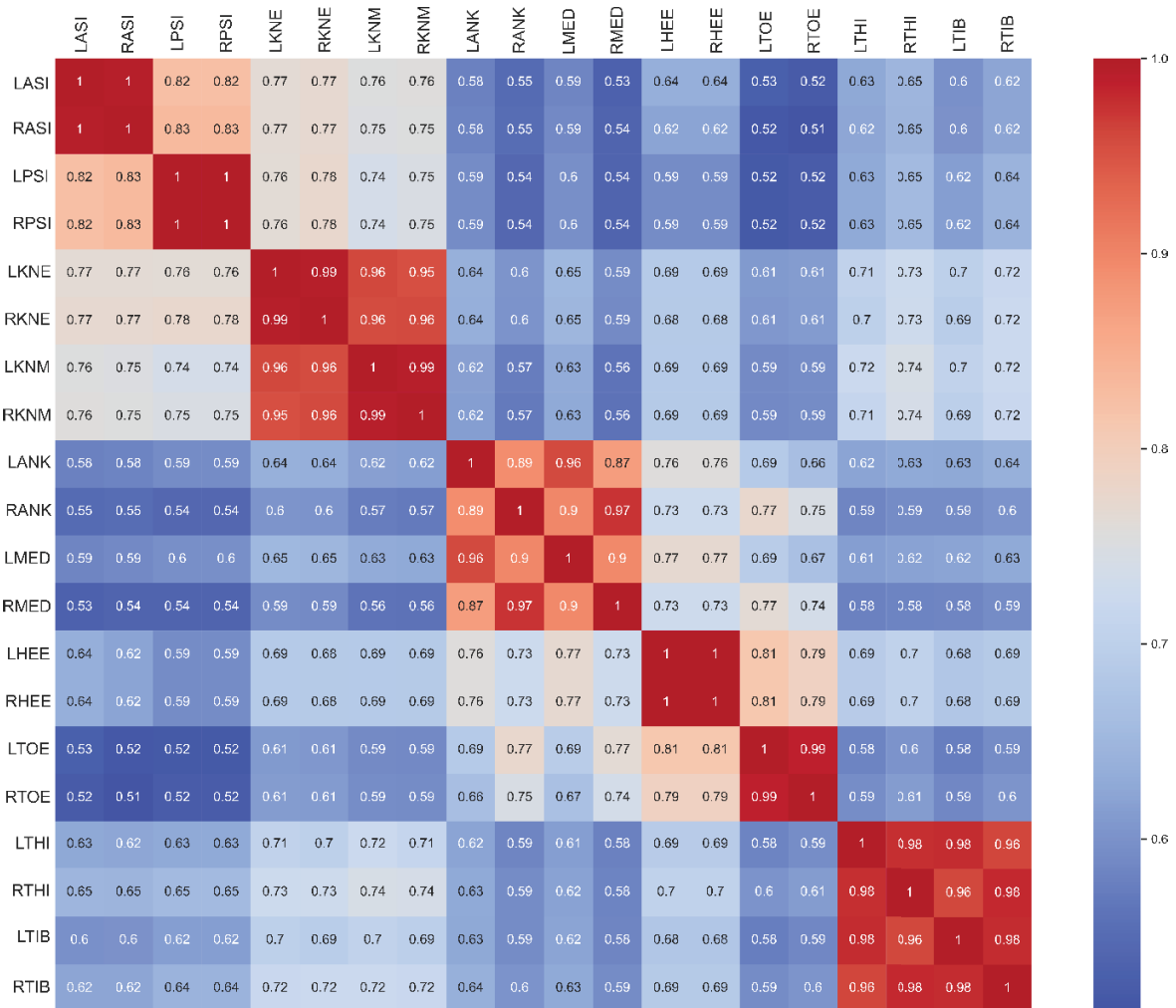
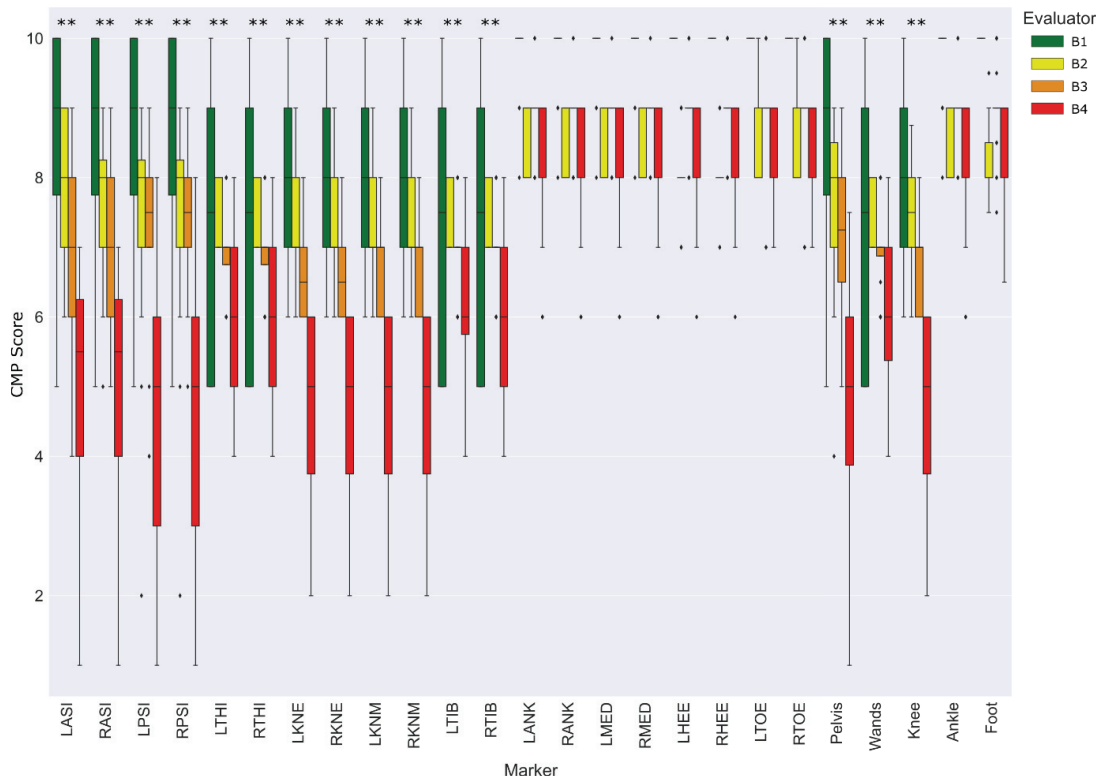


Figure 51. Correlation of CMP scores among markers.

The distribution of CMP scores for each marker and groups of markers among evaluators in protocol B is presented in Figure 52. The CMP scores for pelvic, thigh, shank, and wand groups of markers were significantly different according to the experience level of the evaluators. Similarly, to the results observed in Figure 50, ankle and foot markers showed very low variance while the remaining markers resulted in a wide range of CMP scores. Moreover, Table 33 represents the correlation analysis between the CMP scores of each marker with the precision, decomposed per direction (medial-lateral, anterior-posterior and proximal-distal) of the respective marker per session. Moderate correlations, with statistical significance, were observed for all pelvic, femoral, and wand markers in at least one of the directions.

Figure 52. Distribution of CMP scores per evaluator and marker among the entire population relative to protocol B. Statistically significant differences among evaluators ($p < 0.05$ marked with *, and $p < 0.005$ marked with **). The absence of colored boxes from the boxplot represents an IQR equal to the median, due to a very low variance of CMP scores estimated on that specific marker.



Marker	Anterior-Posterior		Medial-Lateral		Proximal-Distal	
	R	<i>p</i>	R	<i>p</i>	R	<i>p</i>
LASI	0.060	0.563	-0.411	0.000	-0.135	0.189
RASI	0.032	0.757	-0.369	0.008	-0.077	0.458
LPSI	-0.285	0.005	-0.399	0.000	-0.094	0.362
RPSI	-0.315	0.002	-0.359	0.022	-0.161	0.118
LTHI	-0.145	0.158	-0.316	0.002	-0.418	0.000
RTHI	-0.155	0.131	-0.177	0.084	-0.460	0.000
LKNE	-0.266	0.009	-0.105	0.307	-0.429	0.000
RKNE	-0.194	0.041	-0.039	0.709	-0.509	0.000
LKNM	0.048	0.639	0.055	0.596	-0.422	0.000
RKNM	0.059	0.570	0.041	0.695	-0.412	0.000
LTIB	0.069	0.506	-0.212	0.039	-0.179	0.081
RTIB	-0.011	0.918	-0.226	0.027	-0.326	0.001
LANK	-0.121	0.140	-0.062	0.546	-0.161	0.116
RANK	-0.369	0.000	-0.116	0.259	0.164	0.110
LMED	-0.259	0.011	-0.146	0.157	-0.024	0.820
RMED	-0.208	0.059	0.073	0.482	0.031	0.764
LHEE	0.127	0.218	0.086	0.404	-0.164	0.110
RHEE	0.126	0.220	-0.143	0.165	0.006	0.951
LTOE	-0.334	0.001	-0.292	0.004	0.000	0.997
RTOE	-0.230	0.024	-0.310	0.002	0.076	0.064

Table 34. Spearman's rank correlation between CMP scores and respective marker precision, in the three directions.

CMP vs Kinematic variability

The distribution of CMP scores for each marker and groups of markers among evaluators in protocol B is presented in Figure 53. The CMP scores for pelvic, thigh, shank, and wand groups of markers were significantly different according to the experience level of the evaluators. Similarly, to the results observed in Figure 54, ankle and foot markers showed very low variance while the remaining markers resulted in a wide range of CMP scores. Moreover, Table 44 represents the correlation analysis between the CMP scores of each marker with the precision, decomposed per direction (medial-lateral, anterior-posterior and proximal-distal) of the respective marker per session. Moderate correlations, with statistical significance, were observed for all pelvic, femoral, and wand markers in at least one of the directions.

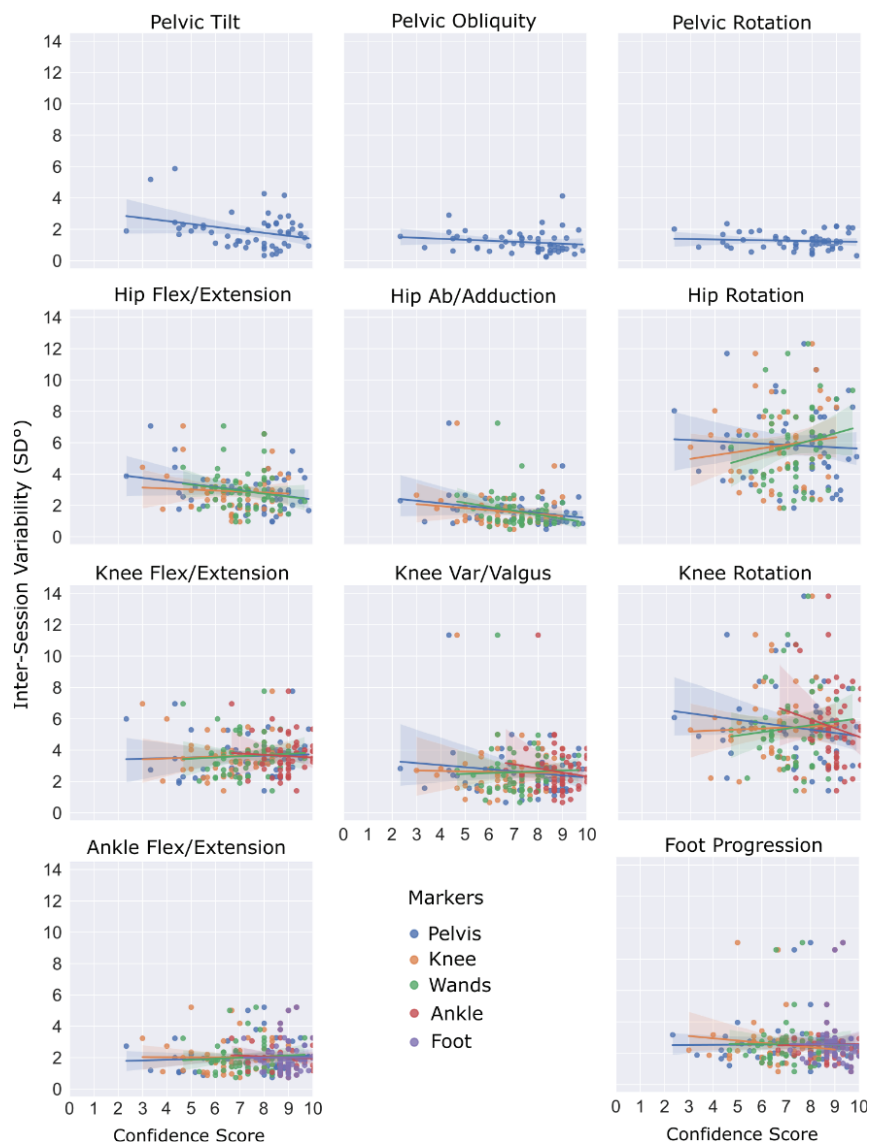
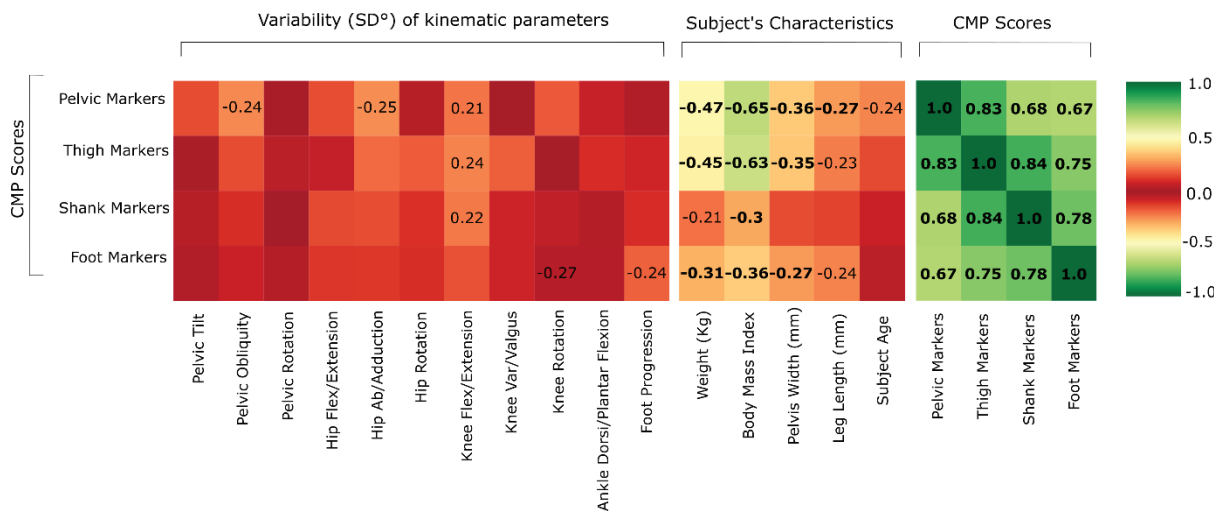


Figure 53. Relationship between inter-session kinematic variability and mean of CMP scores by groups of markers.

Figure 54. Correlation heatmap between CMP scores (grouped) with kinematic variability (SD°), subject's characteristics and the same CMP scores.



4.1.5. Discussion

In the present study, a questionnaire has been proposed to evaluate qualitatively the confidence in marker placement. The first aim was to evaluate the reliability and validity of CMP scores. The reliability of the proposed questionnaire was evaluated with ICC (Table 32) and showed good to moderate reliability for all markers. Moreover, the lower reliability observed in the tibial and foot skin markers may be explained by the low variance above mentioned. To evaluate its validity, we have analyzed how well the CMP scores transmit qualitatively the sensation of confidence from evaluators in placing markers on the lower limbs. The distribution of the CMP scores (Figures 51 and 52) demonstrated that the confidence related to the placement of some markers (pelvic, femoral, and wands) varies widely among subjects while others (tibial and foot) showed constant high confidence and with low variance. Lower confidence in the placement of pelvic, femoral, and wand markers in the pathological in comparison with the asymptomatic group was observed (Figure 52) with significant differences between the population for the pelvis markers. This may explain the higher variability observed for pathological subjects in the literature (Steinwender *et al.* 2000). In addition, significant differences between the confidence reported for those markers with the experience of the evaluator were observed (Figure 54). A significant correlation was also observed between CMP scores among skin markers located within the same segment (*i.e.* pelvis) and among the wands (Figure 53). In addition, CMP scores showed a significant correlation with BMI. Thus, it suggests that underlying adipose tissue negatively affects the palpation of anatomical landmarks, especially on the pelvis and thigh markers, and consequently is the cause of previously reported reduction of marker placement precision for subjects with higher BMI (Moriguchi *et al.* 2009). This finding goes following previously reported findings suggesting that underlying adipose tissue negatively impacts the marker placement precision. Finally, confidence was significantly correlated with marker placement precision in at least one direction, especially for the pelvic and femoral markers (Table 33). All these results suggest that the CMP scores can robustly reflect the difficulties to place markers on the pelvis and thigh segments of a specific population with pathology or more adipose tissues, especially for less experienced evaluators. These perceived difficulties, quantified by the questionnaire, are related to the actual marker precision. It is important to note that marker misplacement follows mostly a bi-planar direction (*i.e.* pelvic markers are misplaced mainly in the anterior-posterior or proximal-distal

directions). This may naturally explain why the correlation between CMP scores and marker placement precision (Table 32) is not found significant in one of the three directions for each marker.

The second goal of the study was to evaluate the correlation between the marker placement confidence reported subjectively with the output kinematics variability measured by test-retest. Considering the good correlation among markers previously described (Figure 53), we have considered the mean of correlated markers for simplification to evaluate the CMP scores with kinematics variability. Thus, the mean CMP scores reported on the markers of the pelvis, thigh, shank, foot, and wands were used, and no significant correlation has been observed. This observation may be explained by the complexity of the effect of marker placement on kinematics. As previously reported by another study with the CGM (Fonseca *et al.* 2022), the impact of one marker misplaced can be enhanced or mitigated by the misplacement of another marker.

In conclusion, the proposed questionnaire to evaluate marker placement confidence has been demonstrated to be valid and reliable. However, no significant correlation has been observed between confidence scores and kinematics variability in the specific case of CGM. The proposed questionnaire may be further tested with other gait analysis protocols and models in the perspective of managing uncertainty in the clinical assessment of movement disorders.

4.1.6. Supplementary Information

S1 . Marker set-up information

Table 35. Palpation guidelines and marker name list

Marker	Location
(L/R)ASI	Anterior superior iliac spine
(L/R)PSI	Posterior superior iliac spine
(L/R)THI	50-70% distance from the hip joint center and lateral femoral epicondyle
(L/R)KNE	Lateral femoral epicondyle
(L/R)KNM	Medial femoral epicondyle
(L/R)TIB	50% lateral femoral epicondyle and tibial malleolus
(L/R)ANK	Lateral tibial malleolus
(L/R)MED	Medial tibial malleolus
(L/R)HEE	Upper ridge of calcaneus posterior surface
(L/R)TOE	Head of 2 nd metatarsal bone.

S2. Confidence in marker placement score

		Low confidence → High confidence										
Pelvis	LASI	0	1	2	3	4	5	6	7	8	9	10
	RASI	0	1	2	3	4	5	6	7	8	9	10
	LPSI	0	1	2	3	4	5	6	7	8	9	10
	RPSI	0	1	2	3	4	5	6	7	8	9	10
Thigh	LTHI	0	1	2	3	4	5	6	7	8	9	10
	RTHI	0	1	2	3	4	5	6	7	8	9	10
	LKNE	0	1	2	3	4	5	6	7	8	9	10
	LKNM	0	1	2	3	4	5	6	7	8	9	10
	RKNE	0	1	2	3	4	5	6	7	8	9	10
	RKNM	0	1	2	3	4	5	6	7	8	9	10
Shank	LTIB	0	1	2	3	4	5	6	7	8	9	10
	RTIB	0	1	2	3	4	5	6	7	8	9	10
	LANK	0	1	2	3	4	5	6	7	8	9	10
	LMED	0	1	2	3	4	5	6	7	8	9	10
	RANK	0	1	2	3	4	5	6	7	8	9	10
	RMED	0	1	2	3	4	5	6	7	8	9	10
Foot	LTOE	0	1	2	3	4	5	6	7	8	9	10
	LHEE	0	1	2	3	4	5	6	7	8	9	10
	RTOE	0	1	2	3	4	5	6	7	8	9	10
	RHEE	0	1	2	3	4	5	6	7	8	9	10

Table 36. Illustration of confidence in marker placement score applied during the experimental protocols.

4.2. Article 8 -Feature base gait score including variability to summarize severity of gait deviations in patients with cerebral palsy

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Article in preparation.

Keywords:

Gait score; gait analysis; variability;

4.2.1. Abstract

Gait scores have been demonstrated utility in the clinical interpretation of gait analysis and follow-up of the evaluation of a patient by summarizing the severity of gait deviations. Traditional gait scores, such as the Gait Profile Score and Gait Deviation Index are the most commonly used scores for that purpose. Three weaknesses have been identified transversal to those gait scores. First, the scores rely equally on on the kinematic parameters, not highlighting clinically relevant parameters. Secondly, kinematic variability has been proven to impact the scores. Lastly, the interpretability can be improved with a more friendly display

The present study aims to propose a new gait score for summarizing gait deviations and addressing those identified weaknesses. Validation of the score is planned to involve a survey among experts for evaluating the feedback related to the score's interpretability in the clinical context. Therefore an evaluation of the sensitivity to kinematic variability is also planned to validate the integration of estimated variability as a parameter to calculate the score.

The study is in its preliminary stages and no results have been yet presented.

4.2.2. Introduction

Three-dimensional gait analysis (3DGA) is the currently most used exam for assessing gait deviations in patients with motor disorders. Of motor disorders, Cerebral Palsy (CP) is the most common condition assessed by this exam. The 3DGA provides a complex set of interdependent dynamic parameters that represent joint motion through different planes and need to be analyzed as the combinations of multiple joints and considering the multiple instants at the gait cycle. There is also the need to summarize the severity of gait deviations to follow the evolution of a patient after treatments or to evaluate the outcomes of clinical studies. Therefore, gait scores have been developed to provide an overall sense of gait pathology (Baker et al. 2009; Schwartz and Rozumalski 2008). Those scores estimate the differences between gait parameters referent to a patient concerning a reference data set previously acquired from a population of asymptomatic subjects.

The most commonly used scores in clinical gait analysis are the Gait Deviation Index (GDI) (Schwartz and Rozumalski 2008) and Gait Profile Score (GPS) (Baker et al. 2009). Both scores are estimated based on the complete gait cycle of nine kinematic parameters (pelvic and hip on the three planes, knee and ankle on the sagittal plane, and foot progression angle). More specifically, GDI is calculated as the distance of a subject's data with respect to the reference data set, posteriorly transformed and scaled to 100, such as every 10 values from it representing one standard deviation from the reference (Baker et al. 2009). GPS is calculated as the root mean square difference between the subject's data and the mean from the reference database and its unit of measure is degrees (Baker et al. 2009). Both, GDI and GPS have been demonstrated to be highly correlated since are based on the same nine kinematic parameters (Baker et al. 2009).

More recently, a Delphi consensus research for listing relevant kinematic patterns to the characterization of gait abnormalities in patients with CP was reported (Nieuwenhuys *et al.* 2016). This consensus showed that, within a gait cycle, some variables are more important than others for identifying gait abnormalities. This limits the use of the aforementioned gait scores since both GDI and GPS assign equal weight to every point in the normalized gait cycle and across all joint parameters.

Moreover, both scores are presented numerically as a segmental (Gait Variable Score) or global measure of deviation and thus, different gait deviations can lead to the same gait scores. This ambiguity limits the interpretability of the scores. Finally, potential offsets on the computed kinematics and kinetics may lead to an impact on the typically used gait scores (i.e. pelvis anteversion) (Armand et al. 2017).

In addition, measurement error is known to affect the reliability of 3DGA, and it is translated as variability of gait data measured among different gait sessions. According to results provided by previous test-retest studies, measurement error affects differently joints and planes (McGinley et al. 2009). Thus, kinematics and consequently gait scores are sensitive to gait variability which can affect the use of scores for clinical assessment and treatment decisions.

Thus, the objective of the present study is to propose a new gait score to evaluate gait deviations in patients with CP based on clinically relevant features, including previously estimated variability, and to improve its interpretability with a graphically presented layout. Additionally, we intend to evaluate the quality of the score proposed in terms of validity, reliability and interpretability. Therefore, one test-retest experimental protocol, including a cohort of patients with CP and asymptomatic subjects, was used to support such evaluation.

4.2.3. Materials and Methods

Feature-based score

The proposed gait score incorporated data from the same joint angles as GDI and GPS such as the three planes of the pelvis and hip (sagittal, coronal and transversal), the sagittal plane of the knee and ankle, and the foot progression angle. Additionally, and similar to those scores, kinematic data is normalized to 51 points, representatives of the gait cycle. The principle of the proposed gait score is not to quote the absolute difference between a given kinematic parameter and the reference value in the database but the relative difference concerning the standard deviation of the parameter in the database. Moreover, the score is based on several features following the Delphi consensus (Nieuwenhuys *et al.* 2016) The selected features are listed in (Table 37). Several features representing opposite conditions have been combined together. For each feature, the z-score (zF_{score}) of the relative difference between the value referent to the subject's feature ($Feature_{sub}$) with the mean reference ($Feature_{ref}$) is calculated and scaled by the standard deviation in the same way as a centered reduced variable as represented in Equation 1.

$$zF_{score} = \frac{Feature_{sub} - Mean(Feature_{ref})}{SD(Feature_{ref})} \quad (1)$$

The feature score (F_{score}) is then calculated as,

$$F_{score} = 100 - \varepsilon \times 10 \quad (2)$$

where ε represents the absolute rounded number of the scaled relative difference. To ensure the Fscore as a positive value, ε over 9 is considered as 9. The result is similar to the GDI score as a $F_{score}=100$ means that the feature is within 1 SD from the reference and every 10 values subtracted means 1 SD from the reference.

Table 37. Features included in gait score based on Delphi consensus.

Joint	Plane	Code	Description	Feature
Pelvis	Sagittal	Px1	Increased difference between sides (asymmetry)	Difference between sides
		Px2	Increased ROM	ROM
		Px3	Increased/Decreased motion	Mean angle
	Coronal	Py1	Increased/Decreased motion	Mean angle
		Py2	Increased ROM	ROM
		Py3	Continuous pelvic elevation (asymmetry)	Difference between sides
	Transversal	Pz1	Increased ROM	ROM
		Pz2	Increased/Decreased motion	Mean angle
		Pz3	Excessive rotation	Difference between sides
Hip	Sagittal	Hx1	Increased/Decreased motion	Mean angle
		Hx2	Extension deficit	ROM
		Hx3	Increased/Decreased peak (swing)	Peak in swing
		Hx4	Hyperflexion (stance)	Mean angle in stance
	Coronal	Hy1	Increased/Decreased motion (stance)	Mean angle in stance
		Hy2	Increased/Decreased motion (swing)	Mean angle in swing
	Transversal	Hx1	Increased/Decreased motion	Mean angle
Knee	Sagittal	Kx1	Increased/Decreased motion (stance)	Mean angle in stance
		Kx2	Increased/Decreased motion (swing)	Mean angle in swing
		Kx3	Increased motion at initial contact	Angle at initial contact
		Kx4	Decreased peak knee flexion	Peak angle
Ankle	Sagittal	Ax1	Increased/Decreased motion (stance)	Mean angle in stance
		Ax2	Horizontal or reversed 2 nd rocker	Angle at 10% gait cycle
		Ax3	Calcaneuous gait/Equinus	Angle in stance
		Ax4	Increased/Decreased motion (swing)	Mean angle in swing
		Ax5	Increased motion at end of gait cycle	Angle at last point of gait cycle
Foot Progression		FP1	Increased/Decreased motion	Mean angle in stance

Additionally, a joint score (J_{score}) relative to each joint rotation is calculated as described in the Equation (3), where n is the number of features per joint angle and α corresponds to the variability parameter and is used as a weighting parameter. The variability parameter is defined from previously experimentally estimated variability associated with each feature and normalized, between 0 and 1, with respect to the sum of all variability parameters relative to the features constituting the joint angle. The side scores (left and right) are calculated as the mean of the joint scores relative to each side (Equation 4). Finally, the global score is the mean of the joint scores (Equation 4).

$$J_{score} = \frac{\sum_{x=0}^n (F_{score\ x} \times \alpha_x)}{n}, \quad \alpha \in [0,1] \quad (3)$$

$$S_{score} = \frac{\sum_{x=0}^n (J_{score\ x})_{side}}{n} \quad (3)$$

$$G_{score} = \frac{\sum_{x=0}^n (J_{score\ x})}{n} \quad (4)$$

Results are then, graphically presented with a color code relative to the level of deviation of each feature for better interpretability. Joint, side and global scores are also plotted within the graphical representation as illustrated in Figure 55.

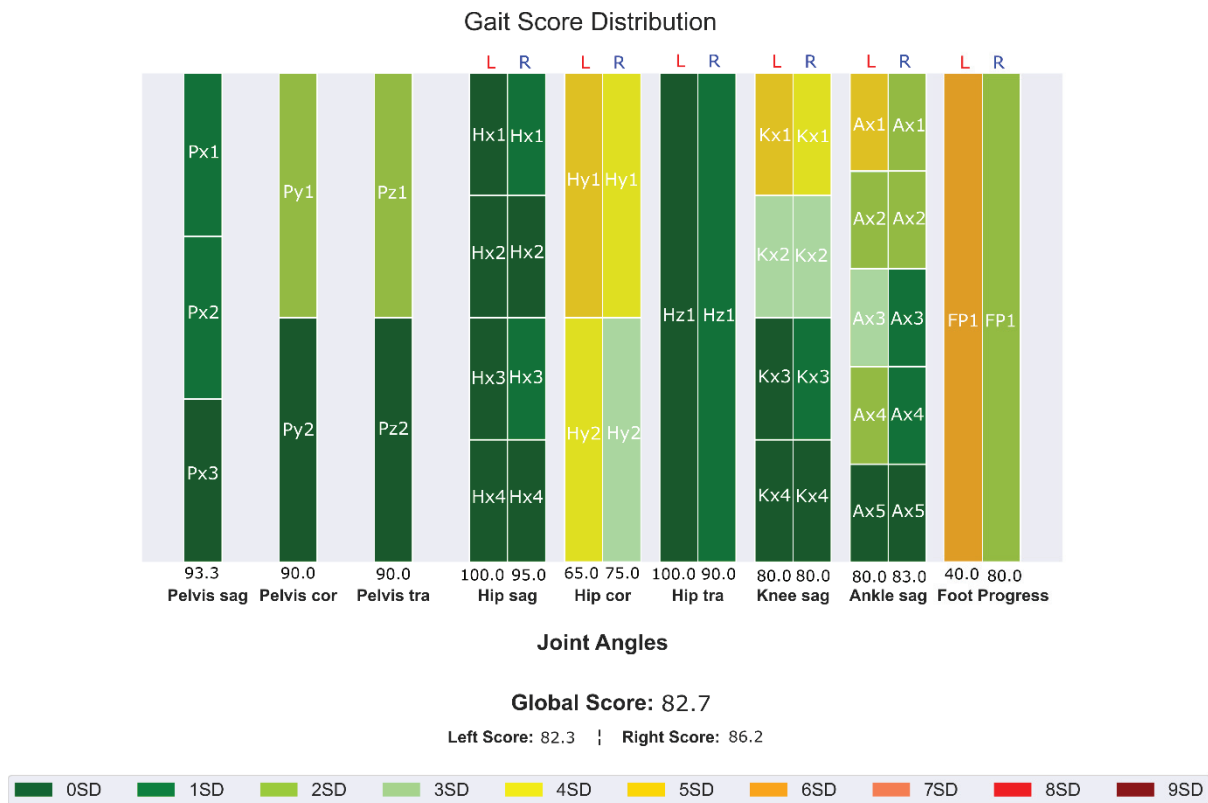


Figure 55. The proposition of layout for the Feature-based score. The score calculated for a CP patient.

Materials and methods

Experimental data acquired from protocol A described in Article 5 will be used to support the quality analysis relative to the presented score.

Statistical analysis

For the validation of the score, several analyses are planned. Firstly, evaluate its correlation with GPS as well as its sensitivity to kinematic variability induced by the test-retest experimental data.

4.2.4. Preliminary discussion

In the present study, we proposed a new feature-based gait score to improve gait data interpretability. The score is developed to overcome several limitations identified within generally used scores such as GPS or GDI. For instance, those scores give equal weight for all the 459 points (51 points for each of the 9 joint angles) included, thus, ignoring clinically relevant features listed by the gait analysis community as important for characterizing gait deviations in patients with CP (Baker al. 2009; Nieuwenhuys et al. 2016, 2017; Schwartz and Rozumalski 2008). One of the main advantages of

the proposed gait score is that evaluates gait kinematics only by reported features with clinical relevance. Secondly, the gait scores mentioned, characterize gait deviations by a single or a group of numerical scores, which are ambiguous (different deviations can provide the same score) and lack information. Therefore, the score here presented provides more information regarding the location of the gait deviations within each joint angle and feature. Finally, gait scores are affected by gait analysis variability. Considering that, for instance, extrinsic variability associated with the hip on the transversal plane has been estimated above 5°, a strong influence is expected on the resultant score. However, with the proposed score, an estimated variability parameter is added to weigh the level of confidence. It is expected that the sensitivity to extrinsic variability will be reduced with the inclusion of this weighting parameter. Another advantage of this method is that it can easily integrate new features, adapted for each type of pathology or gait deviation indicated.

The next steps for the present study will be to evaluate the quality of the proposed gait score in terms of validity, reliability and interpretability. Additionally, the layout is intended to be improved by the identification within each bar of the respective gait feature by specific symbols. In perspective, is also the addition of the same symbols within the gait curves, colored following the color code represented in the graphical illustration of the score.

4.3. Chapter Discussion

Within this final chapter, two studies have been proposed to incorporate and manage variability in the interpretation of gait data.

Taking into consideration that marker placement is the main source of kinematic variability and the marker placement precision may be affected by the capacity and expertise of the evaluator in identifying anatomical landmarks one hypothesis was formulated. Thus, it was hypothesized that confidence in marker placement is correlated with kinematic variability. In Article 7 one metric was proposed to measure qualitatively the confidence in marker placement. The first goal of the study was to evaluate the validity and reliability of the proposed metrics. Moderate to good reliability was demonstrated for the measured confidence. Furthermore, the validation was demonstrated by a statistically significant difference between the confidence scores among the two groups (pathological and asymptomatic) and the good correlation observed between the scores and parameters such as: marker placement precision, evaluator's experience, anthropometric data, and among markers of the same typology or segments. The second goal was to evaluate the correlation between the confidence scores and the kinematic variability. However, no correlation was proven and it may be explained by the complexity of the effect of marker placement into kinematics. As previously reported by another study (Fonseca *et al.* 2022), the impact of one marker misplaced can be enhanced or mitigated by the misplacement of another marker. In conclusion, the proposed questionnaire to evaluate marker placement confidence has been demonstrated to be valid and reliable. However, no correlation has been observed between confidence scores and kinematic variability. Thus, it is here demonstrated that this score has no proven potential to be used as a predictor of kinematic variability.

The second study, which is in the early stages of development, is integrated within this doctoral work more as a perspective for the next steps following the focus of the overall work developed. The objective was to develop a new gait score sustained on three main bases of improvement with respect to typically used scores in CGA (Baker *et al.* 2009; Schwartz and Rozumalski 2008). Firstly, gait scores provide the same importance to all kinematic points included, and so, hide clinically relevant information. Thus, the first basis of the developed score was to calculate a score with a focus on a Delphi consensus highlighting relevant features for evaluating gait deviations focused on children with CP (Nieuwenhuys *et al.* 2016, 2017). Secondly, the typical gait scores are affected by kinematic variability such as potential offsets on the computed kinematics. Thus, the developed gait score incorporates previously estimated variability calculated for each feature and inputs it within the score formula to turn the scoreless sensitive to kinematic variability. Finally, the third basis of the newly developed score was to provide a detailed but intuitive for improving gait deviations allied to each feature. For that, a set of bars representing each joint angle, which are divided equally by the number of features associated with each joint angle and formed with a color code representing, intuitively, each of the levels corresponding to the distance from the norm relative to each feature. Prospectively, a validation analysis is planned, involving a survey among clinicians to collect feedback about the use of the score in clinical interpretation. Finally, an evaluation regarding its sensitivity to kinematic variability will be performed, with a test-retest experimental protocol, to validate the integration of estimated variability.

Chapter 5 - General discussion and perspectives

Within each chapter presented before, one general discussion has been provided. Therefore, this chapter presents a global summary of how all different studies interconnect as well as main contributions, limitations and future perspectives.

5.1. Global overview and main contributions

Measurement error, in CGA, negatively affects the quality of the assessment of gait deviations and consequently the planning for treatment decisions. Thus, the focus of this doctoral work was directed to the improvement of gait data interpretation concerning extrinsic variability. In order to do so, some questions were initially defined such as: how much extrinsic variability is expected for each kinematic parameter; how the measurement error affects measured gait data; what can be done to reduce the extrinsic variability from the final output data; or how can gait data interpretation be improved considering the extrinsic variability. To answer those questions, several studies were proposed. Within this thesis, those studies were presented in three chapters relative to their objectives. Chapter 2 focused on the estimation and evaluation of the impact of measurement error in extrinsic kinematic variability. The focus of Chapter 3 was mainly to propose or evaluate methodologies to reduce the effect of measurement error, so to speak extrinsic variability, in gait data. Finally, Chapter 4 intended to apply the knowledge provided by the two previous chapters and define methodologies to improve the interpretability of gait analysis by the estimation or prediction of extrinsic variability. Figure 56 illustrates the interconnectivity of the different studies reported. At the center of this model is kinematic variability, a common concept within all studies.

Firstly, inside the dashed rectangle (Figure 56), several articles were defined to evaluate inter-relationships between several parameters associated with the measurement of gait data and aim to create a potential model to predict output kinematic variability (Figure 56, black arrow). In Chapter 1, two relationships are evaluated (Figure 56, green arrows). The first three articles (Articles 1-3) evaluated the relationship between the precision of marker placement with kinematic variability. To do so, two different approaches, each with advantages and limitations, were identified. Numerical approaches allow us to simulate a high number of marker placement conditions and better understand the propagation of the error into computed kinematics. However, they present some limitations such as the lack of a true referent position of the markers (the original location of the markers is subject to inaccuracies from the marker location) and do not exactly represent the real pattern during motion (since soft tissue artefacts differ according to the location of the marker concerning the underlying characteristics of the tissues). On the other hand, experimental approaches allow the real quantification of the precision of marker placement, which can also serve as complementary to define the simulations tested in numerical tools as magnitude and direction for each marker but are limited in terms of the number of configurations provided. Therefore, Articles 1 and 2, relied on a numerical approach to evaluate the impact of lower-limb marker displacement on kinematics. Results showed that the sensitivity of kinematics differs among markers and directions. For instance, wand and femoral epicondyle markers affect the most kinematics, when displaced in the anterior-posterior direction, with a variation of kinematics superior to 5° (when displaced alone). One of the main contributions provided by those studies is that understanding the impact of marker

displacement in kinematics can improve the awareness of the evaluators when placing specific markers. Additionally, one tool developed (2.2.6) within Article 2 allows the user to define a specific displacement (single or multiple markers) and to observe its impact on kinematics. This tool can contribute, not only to educational purposes but has the potential to create a confidence interval within the kinematic curves (for clinical interpretation) when set with experimentally estimated precision for each marker. Thus, the third article involved four examiners and eight adult asymptomatic subjects and, evaluated experimentally the precision of lower-limb marker placement. One of the main contributions of this study (Article 3) is the experimental quantification of lower-limb marker placement precision, which was previously and shortly addressed but included only two evaluators (Della Croce *et al.* 1999, Moriguchi *et al.* 2009). However, no correlation was observed between marker placement precision and kinematic variability which indicates that an error in the placement of one specific marker can be compensated or enhanced, in an unpredictable way, by an error in the placement of other markers.

The fourth article (Article 4) aimed to evaluate the relationships between the knee joint axes definition with kinematic variability by understanding how uncertainties (intrinsic and extrinsic variability) are propagated to the kinematics and explain the crosstalk *phenomenon*. The analytical model demonstrated that by inputting an uncertainty of 5° among the different parameters, the output error matched the experimentally estimated variability. The results showed also that the crosstalk phenomenon can be attributed to both intrinsic and extrinsic variability.

The two articles reported within Chapter 3 (CGM variants and additional corrective calibration methods, gait event algorithm), were intended to reduce the observed kinematic variability in the currently applied methodology for measuring gait data (Figure 56, purple arrows). Article 5 demonstrated that the integration of calibration methods helps to reduce extrinsic variability knee. Thus, the reliability of the angle most affected by extrinsic variability (hip rotation) was improved and the crosstalk phenomenon of the knee was reduced. By realigning the orientation of the femur medial-lateral axis, the output kinematic becomes less sensitive to errors caused by marker placement. Therefore, the integration of these calibration methods on actual kinematic computational routines improves the reliability of data and consequently could improve the quality of clinical data interpretation. In parallel, Article 6 promoted a newly developed methodology to estimate gait events, another source of variability which affects the reliability of data during the superposition of gait cycles. The methodology promotes the synergy between concurrently implemented methods, tested over a pathological data base (CP and idiopathic toe-walking), resulting in very high accuracy and precision, outperforming all reported methods found in the literature. Increased accuracy and precision of gait event detection are expected to improve the reliability not only of kinematic data but kinetic and SPT parameters. In sum, the combination of those two studies allows the improvement of the kinematic reliability and consequently the quality of clinical interpretation, by reducing the possible misinterpretation of extrinsic and intrinsic variability. However, such impact has not been evaluated during this doctoral work.

Kinematic variability varies across subjects due to their intrinsic characteristics, such as the presence of motor disorder (Steinwender *et al.* 2000). This was also observed in Article 5 where pathological groups demonstrated higher variability. Thereby, it is logical to assume that marker placement precision is affected by the subject's characteristics. For instance, Moriguchi *et al.* (2009) reported decreased marker placement precision in subjects with higher BMI. These effects may be related to the difficulty of evaluators in identifying anatomical landmarks during palpation for marker placement. Thus, it was hypothesized that marker placement precision is dependent on the confidence of the evaluators when placing each of the markers. By measuring qualitatively this

confidence it could be potentially used to estimate the output kinematic variability due to marker placement. A questionnaire was proposed to track qualitatively this marker placement confidence. The lower limb markers, except for the tibial and foot, showed a wide variance among the subjects tested. This confidence in marker placement score was validated by the significant correlation demonstrated among evaluator's experience, marker placement precision, and by significant differences among scores reported between pathological and asymptomatic groups. Moderate to good reliability was also observed on the marker placement confidence score among all markers. However, no correlation was observed with resultant kinematic variability. This finding can be justified by the absence of correlation observed in Article 3 between the marker placement precision and kinematic variability (both studies were developed simultaneously).

Finally, the last study (Article 8) intended to develop a new gait score based on clinically relevant parameters, with improved interpretability and incorporating an estimated kinematic variability. The main importance of including kinematic variability within the calculation of gait score is to reduce its sensitivity to extrinsic variability. The quality analysis of validity and reliability were not included in the present thesis and its possible contribution is in perspective.

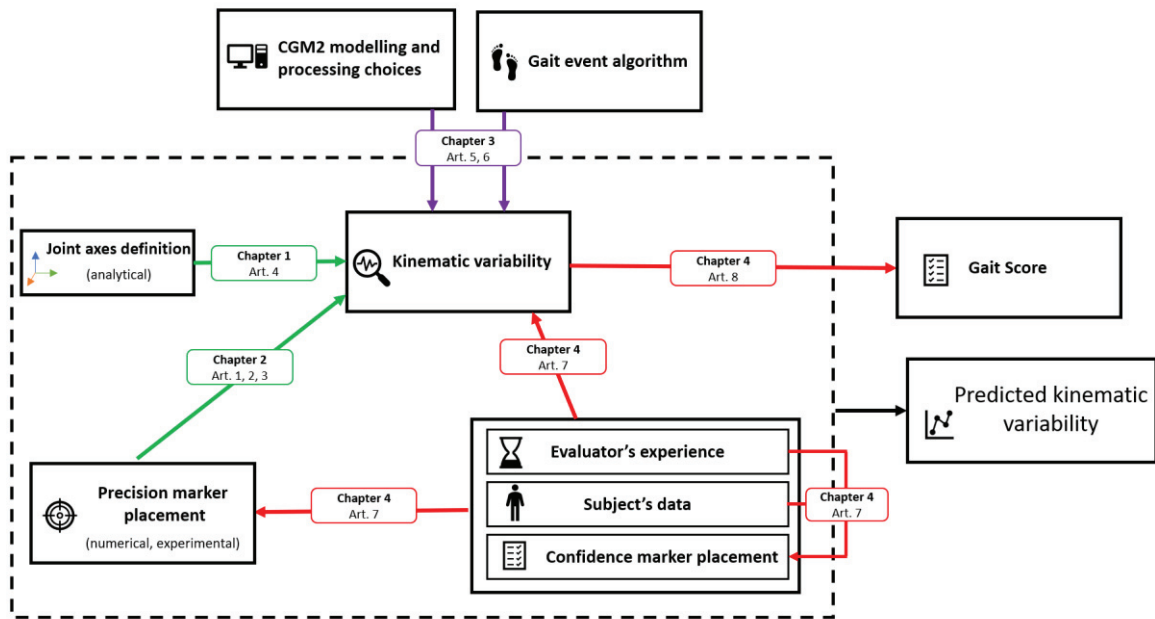


Figure 56 - Schematic representation of the interconnections between the studies reported.

5.2. Main limitations

Different limitations have been reported for each respective study and must be considered. The most global recurrent limitations as well as future possible solutions for improvement are formulated within this section.

5.2.1. Study participants

One of the most recurrent limitations present within this thesis relates to the sample size and characteristics of the recruited populations. For classical experimental evaluations, the sample size seems to be never enough as more subjects increase the robustness of the analysis. However, in the case of gait analysis, the recruitment is not always simple, especially for pathological populations. Within this doctoral work, the recruitment of pathological subjects for protocol A (Figure 16) was limited to the patients visiting the laboratory following a clinical gait analysis session. Another limitation factor was the inclusion criteria, where sub-groups of age were defined. Therefore, the inclusion of those patients in the experimental protocol was subject to the number of patients visiting the laboratory (which was limited by the restrictions caused by the worldwide pandemic situation), their acceptance, and the inclusion criteria. In the case of asymptomatic participants, the recruitment process was only accomplished by the public advertisement of the study. In sum, protocol A involved 56 participants (from those 32 patients and 24 asymptomatic) and was finalized within twenty-four months. However, the sample size was calculated for the calculation of reliability and based on statistical guidelines for the calculation of ICC at the initiation of the experimental protocol, and groups of a minimum of twenty-four subjects were considered (Bujang and Baharum 2017).

Another important factor involving the participants is associated with the heterogeneity of the populations within two factors. First, the imbalanced repartition across GMFCS levels regarding patients with CP limited the comparison of kinematic variability among those groups. (Palisano *et al.* 1997) Additionally, most pathological participants showed a low severity of gait deviations despite being classified as pathological, which consequently limited the comparison between those groups with asymptomatic populations. Secondly, the low level of heterogeneity observed within Article 7 relative to the anthropometric data constitutes another limitation when evaluating its effect on marker placement precision and kinematic variability. Thus, parameters such as body mass index, which may have an impact on the latter parameters (Moriguchi *et al.* 2009), were not addressed.

5.2.2. The high complexity of marker precision inter-relations

The outcome of this doctoral work was to develop a model to predict the impact of extrinsic variability inherent to CGA for improving the confidence of data interpretation. The expectation regarding the use of quantitative and qualitative measured information concerning the process of marker placement to predict a personalized confidence interval was not achieved. Even though a correlation between the confidence in marker placement and the precision of several markers, and the direct modeling of kinematic variation altering a specific configuration of marker positions was analyzed. The direct correlation between confidence and marker placement precision was partially observed. However, the direct correlation between confidence scores and kinematic variability was

not observed. As previously described, this is explained by the fact that error in marker placement is a combination of the positioning of several markers and it is translated into a much more complex formulation. However, by knowing the estimated precision for each marker concerning each of the directions among a reference population, it is possible to estimate an interval of confidence, as demonstrated in Article 2, which may be added to the kinematic curves during analyzed of gait data.

5.2.3. Different sources of measurement error

As previously described in this thesis (Chapter 1.10), measured gait data is affected by different sources. Those sources affect differently the quality of the output data. Marker placement has been considered the biggest source of variability in kinematic data. Thus, the focus in the doctoral work was mostly done concerning this particular source of measurement error (axis definition also addressed in Article 4 and gait event detection in Article 6). Alternatively, soft tissue artefacts have been also reported as a considerable source of measurement error, affecting mostly the validity of the output measured data (Camomilla *et al.* 2017). One of the limitations of this Ph.D. work was that it did not address soft tissue artifacts which is a major source of error in CGA. The lack of ground truth as a reference position limits the evaluation of the impact of soft tissue artefacts on CGA. The closer that has been identified as reference positioning of the markers was achieved with the application of intra-cortical pins or the use of radiographic images in asymptomatic adults (Peters *et al.* 2010, Cereatti *et al.* 2017). These approaches are invasive and thus limited in application for children populations. Therefore, it was not addressed within this thesis.

5.2.4. Validity of kinematics measurement

Within the present thesis, the term reliability was predominant for the evaluation of the data provided by 3DGA while criterium validity was not addressed. Models such as the CGM intend to represent the movement of bones during gait. In the absence of a true gold standard, there is no robust form of measuring the accuracy of this model to represent the motion of bones. This represents a limitation transversal to all known biomechanical models. The best-considered approximations to a gold standard rely on intra-cortical pins or imaging (i.e. fluoroscopy) (Cereatti *et al.* 2009, Sangeux *et al.* 2017a). However, and as previously described, intra-cortical pins are an invasive technique and imaging such as fluoroscopy involves ionizing radiation and is not applicable to research in children.

5.2.5. Results cannot be generalized to other models

The CGM was chosen as the model evaluated in the overall analysis here presented since it is the most applied model in CGA. Therefore, the results here presented cannot be generalized through other models. However, the methodology used can be applied to other models, including upper-body and multiple-foot rigid body models. As previously described (1.5.1.3), different models as the HBM, CAST, or IOR, are expected to differ with respect to kinematic variability due to their differences regarding marker setup and biomechanical considerations (i.e. constraints, joint axes definition) (Cappozzo *et al.* 1995, Leardini *et al.* 2007, Flux *et al.* 2020).

Similarly, the reliability was studied only for markers-based gait analysis while sensor-based (inertial measurement units) or marker-less gait analysis exist. Here, the methodology cannot be directly applied as the kinematic parameters result from a different process including, for instance, sensor data fusion and statistical inferences.

5.3. Perspectives

5.3.1. Kinetic, spatial and temporal parameters

3D CGA is affected by measurement error not only at a kinematic level. Even though kinematics has been proven to be the least reliable among the measured gait data (Wilken et al. 2012), Kinetics and SPT parameters are also affected by measurement error, which impacts its reliability and consequently interpretation. Therefore, one of the limitations but also a perspective of the present doctoral work is the reproduction of its main goals through these three types of gait data. For instance, a part of the instrumentation error associated with the force platforms, and kinetics are also affected by the estimation of joint centers (Camomilla *et al.* 2017). The impact of joint center displacement (Article 1 and 2), and precision of joint center estimation (Article 3) in the kinetic data would provide an insight into how such data is affected by measurement error. In line with this, gait event estimation also interferes with this data, especially with SPT parameters. The extension of the methodology proposed (Article 6) to its effect on those parameters would support its validation across more gait parameters by evaluating its impact with variability in comparison with other methods. Thus, the approach used to evaluate the marker placement in kinematics, addressed in Article 2, could be applied to kinetics by evaluating the impact of joint center displacement in measured kinetic data. Complementary, the quantification of the estimation of joint centers provided in Article 3 could be used to set the simulation of joint centers displacement in terms of amplitude and direction.

5.3.2. Estimate variability for data interpretation in CGA

Another perspective identified is associated with the analytical model proposed in Chapter 2 to understand the propagation of uncertainties in the definition of knee joint axis (Article 4). This model showed that by introducing 5° degrees of input uncertainty, the kinematic output matched the experimentally evaluated variability. Taking into account this validation, the application of this model could be extended to the gait data interpretation as a form of the interval of expected measured variability considering previously estimated variability. The extension and validation of this model to other joint angles could also provide new information regarding the propagation of uncertainties in the definition of the complete set of lower-limb kinematics. However, the main objective of the development of such a model was to evaluate the causes of knee crosstalk.

Similarly, the tool developed within Article 2 to simulate marker displacement, in association with the results from marker precision experimentally observed in Article 3 could be applied to estimate a corridor of expected variability. For instance, gait data is reported together with the corresponding data of a reference database (mean \pm SD). Thus, a corridor of expected extrinsic variability would be added around the kinematic curve. Figure 57 illustrates a possible application of the estimated extrinsic and intrinsic variability to support clinical interpretation and assessment of

gait deviations. An additional study based on questionnaires to evaluate qualitatively the impact of such extra information, among clinicians in charge of analyzing data from CGA, would be helpful to validate this integration.

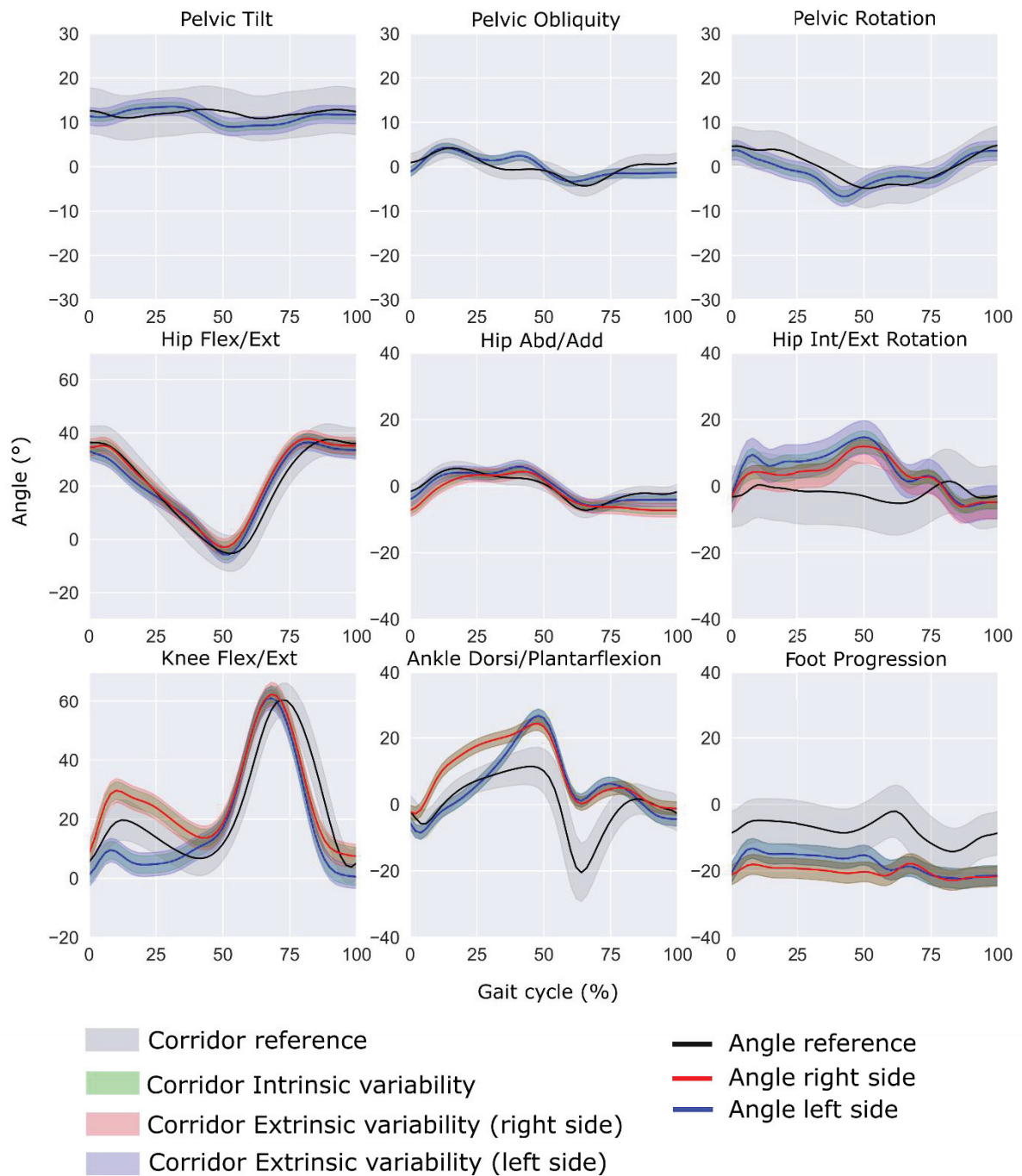


Figure 57. Illustration of application of extrinsic and intrinsic variability corridors for clinical interpretation. Amplitude is defined based on the results presented in Figure 40, reported for the pathological group, and processed with CGM 2.1.

5.3.3. Multibody foot models

In the previous section, one limitation was attributed to the fact that results were obtained using CGM and cannot be generalized among other models. The reasons for its selection, as previously explained, were due to its wider integration by the gait analysis community. However, one of the weaknesses addressed to CGM relates to the over-simplification of the foot, considering it as a single rigid body, and ignoring the motion between structures inside the foot. Several models have been proposed that divide the foot into multiple rigid bodies and allow the description of the inter-segmental kinematics of the foot (Leardini *et al.* 2019). Despite little information regarding its proven importance in the assessment of motor disorders, those models provide information potentially relevant for characterizing foot-associated pathologies (Rampal *et al.* 2020). Thus, all the methodologies described within this thesis would be applicable to the diverse foot models in order to evaluate their reliability.

5.3.4. Methods to correct marker placement position

One of the main results provided in Article 2 demonstrated that the most important kinematic variability is attributed to the precision of marker placement of knee and wand markers in the anterior-posterior direction. Article 3 demonstrated that those are also the markers that are the least precise in real experimentation. Considering these results, efforts should be canalized into this limitation. Some lines of development can be identified. One option is to identify a different marker model that can provide better accuracy and equally valid and reliable data. Another option can be to a-posteriorly recalibrate the axis of rotation defined as it was demonstrated in Article 5 with DynaKAD and Geometrical methods (Baker *et al.* 1999, Naaim *et al.* 2019). A final option identified is related to the calibration of marker positioning.

The use of 3D medical imaging could provide a possibility for correct marker placement. Gasparutto *et al.* (Gasparutto *et al.* 2020) have tested a fusion method to correct marker placement based on anatomical landmarks estimated by bi-planar x-rays. The fusion was proven to reduce the variability associated with marker placement. However, the identification of anatomical landmarks via medical imaging introduced a new source of extrinsic variability that needs to be therefore considered before considering this method for clinical applications (Gasparutto *et al.* 2020). Additionally, the use of medical imaging introduces an additional clinical examination which introduces a new inconvenience due to the use of radiographic images in patients. Consequently, an increase in terms of cost, radiation for the patients, and time of data processing would be another limitation of this method. In parallel, the use of 3D free-hand ultrasound has been evaluated to register anatomical landmarks and estimate the location of joint centers (Passmore and Sangeux 2016, Horsak *et al.* 2021). This technique, which is becoming increasingly popular to assist CGA mainly due to its non-radiation exposure and portability, has been demonstrated to improve the accuracy of anatomical landmark and joint center estimation, especially with obese patients (Horsak *et al.* 2021). In addition, the impact of the use of 3D free-hand ultrasound on the segmental axes definition has been evaluated, more, in particular, the medial-lateral axis of the femur (the cause of the high variability observed in hip rotation) (Passmore and Sangeux 2016). After registration in the motion capture system, anatomical landmarks and skin markers were tracked with high accuracy (1.3 mm and 0.4 mm, respectively), leading to the high accuracy of the medial-lateral axis of the femur, with respect to the axis defined by the bi-planar x-ray based reference (mean difference of 1°) (Passmore and Sangeux 2016). This

constitutes an improvement, with respect to the calibration methods (abovementioned), and signifies a lower sensitivity to marker misplacement (Sauret *et al.* 2016). In conclusion, the association of tools such as the 3D free-hand ultrasound or bi-planar x-rays has been proven to be promising to assist typical CGA but further progress seems to be needed in order to make it available for general implementation in clinical gait analysis.

5.3.5. Alternatives to marker-based gait analysis

During the current thesis, it was demonstrated that three-dimensional gait analysis relies on the accurate and precise marker placement on specific anatomical landmarks. Furthermore, securing markers to reduce noise resulting from skin and soft tissue artefacts is an additional challenge as the markers are not placed directly over the anatomical landmarks but rather over the skin. In the past years, alternatives have been proposed to the typically used three-dimensional gait analysis removing the need for marker placement and consequently eliminating marker placement as a source of measurement error. Some of the alternatives encountered are markerless motion capture and wearable inertial measurement units. However, new sources of error are associated with each one of the proposed alternatives.

Markerless motion capture systems consist of a series of synchronized video cameras, being the most used type of camera either RGB or depth. Those cameras collect two-dimensional images of the subject which are then transformed into three-dimensional images. Keypoints are identified, allowing the construction of a biomechanical model (similarly to the reflective markers used with the marker-based system) (Nakano *et al.* 2020). The identification of key points is done via deep-learning models previously trained from images of human poses. The main advantages of marker-less are the no dependency on accurate and precise marker placement, more comfortable for the subjects being measured as no markers are mounted, and faster to acquire data due to the absence of setup. Despite being able to qualitatively reproduce the subject's movements, the measurement error associated with joint positions is higher than the marker-based system, from a quantitative point of view (Nakano *et al.* 2020). The constant advancements in terms of computer vision based on deep-learning algorithms are promising with respect to the quality of gait data measured by markerless systems. For now and despite several authors have recommended its use for clinical applications, no study found in the literature reported an improved validity and reliability than the marker-based motion capture system in pathological populations (Liang *et al.* 2022, Riazati *et al.* 2022).

5.3.5.1. Wearable inertial measurement units (IMUs)

Alternatively, IMUs-based gait analysis have been developed. This system is based on the use of sensors such as gyroscopes, accelerometers, and magnetometers to estimate the orientation of segments and calculate joint rotations. The main advantages of IMUs-based gait analysis with respect to the traditional marker-based are: lower cost; no need for trained personnel in anatomical palpation; high applicability as it can be used to measure gait outside of the gait laboratories (Lanovaz *et al.* 2017). Marker-based CGA is not worldwide applied within the assessment of motor disorders due mainly to its high cost and need for a trained specialist to perform the measurement. Therefore, the advantages mentioned regarding the IMUs-based gait analysis have the potential for being applied in a wider number of laboratories as well as a more periodic assessment of patients for the follow-up for

treatments. However, several limitations are yet to be overcome. For instance, either type of sensor used has limitations. Accelerometers are affected by gravitational acceleration, gyroscopes are affected by noise and bias that induces error cumulatively during longer acquisitions, and magnetometers are also impacted by the presence of ferrous materials during measurement (Al Borno et al. 2022; Nazarahari and Rouhani 2021). The use of IMUs-based gait analysis does not suppress the effect of STA as sensors are placed on the segments (Zügner et al. 2019). Standardized guidelines with respect to the location of the IMU's sensors for minimization of STA are also required. Contrary to the marker-based gait analysis, sensors are not placed over specific anatomical landmarks. Additionally, other sources of error have been reported such as the calibration techniques which have not yet been standardized (Carcreff et al. 2022). Finally, most of the validation and reproducibility studies have focused on the SPTs where good quality data has been reported for pathological populations (mainly groups of patients with osteoarthritis). In sum, IMUs-based gait analysis seems promising and brings new advantages with respect to the traditional gait measurement system but developments are required for improving the reliability of the output data and to validate its use in the clinical application (typically done with respect to the marker-based gait analysis). For instance standardization of calibration methods. Also, more reproducibility studies evaluate its validity and reliability including cohorts of patients with motor disorders.

5.4. Final Conclusion

The main goal of the present doctoral work was to evaluate the effects of measurement error such as marker misplacement on the kinematics, with associated quantification and reduction of extrinsic variability. The main focus was to improve the gait data interpretability using extrinsic variability. Thus, extensive experimental and numerical analyses were performed to evaluate the effect of marker misplacement on kinematics. Different simulations of marker displacement were evaluated. Results showed the CGM is highly sensitive to anterior-posterior misplacement of the knee and wand markers, with an error over 7° for those markers displaced alone. The configuration of multiple marker displacements (amplitude of displacement of 1cm) showed a range of motion of kinematic data variability over 20° . Furthermore, to support the experimental analysis, two protocols have been defined including a test-retest methodology with heterogeneity at the level of age, including pathology and asymptomatic populations and the evaluator's experience. Based on these data, different processing methods were compared with respect to the estimated variability. Results demonstrated that hip rotation has been proven more reliable with the integration of additional calibration methods. Marker placement precision has also been evaluated experimentally and a partial correlation with experience's evaluator was observed. However, no correlation was observed with kinematic variability.

Finally, tools were developed to integrate extrinsic variability in the kinematics interpretation that can be possibly applied in clinical routine. One final note regarding the CGM, which has been proposed more than three decades ago, despite the more recently proposed technologies (i.e. markerless, IMU) or methodologies (i.e. alternative models), it seems to be the most trusted in the gait analysis community. However, there is always a margin for future developments and improvement.

5.5. References

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Scientific Publications

Accepted

Rampal, V., Pierre-Yves, R., Pillet, H., [Fonseca M.](#), Desailly, E., Wicart, P., Skalli, W. "Combined 3D analysis of lower-limb morphology and function in children with idiopathic equinovarus clubfoot" *Orthop Traumatol Surg Res.* (2020) 106(7):1333-1337

[Fonseca, M.](#), Gasparutto, X., Leboeuf, F., Dumas, R., Armand, S. "Impact of knee marker misplacement on gait kinematics of children with cerebral palsy using the Conventional Gait Model". *PLoS ONE*, (2020) 15(4), 1-12.

[Fonseca, M.](#), Dumas, R., Armand, S. "Automatic gait event detection in pathologic gait using an auto-selection approach among concurrent methods". *Gait & Posture*, (2022) 96: 271-274.

[Fonseca, M.](#), Armand, S., Dumas, R. "An analytical model to quantify the impact of the propagation of uncertainty in knee joint angle computation". *International Biomechanics*, (2022) 9:1, 10-18

[Fonseca, M.](#), Bergere, M., Candido, J., Leboeuf, F., Dumas, R., Armand, S. "The Conventional Gait Model's sensitivity to lower-limb marker placement". *Scientific Reports* (2022) 12:14207

Under review

[Fonseca, M.](#), Gasparutto, X., Grouvel G., Bonnefoy-Mazure, A., Dumas, R., Armand, S. "Evaluation of lower limb and pelvic marker placement precision among different evaluators and its impact on gait kinematics", in *Gait & Posture*, in August 2022

[Fonseca, M.](#), Gasparutto, X., Grouvel G., Carcreff, L., Bonnefoy-Mazure, A., Dumas, R., Armand, S. "Can the evaluation of marker placement confidence be used as an indicator of gait kinematic variability?", in *Frontiers in Rehabilitation Science*, in November 2022

Conferences

[Fonseca, M.](#), Gasparutto, X., Leboeuf, F., Dumas, R., Armand, S. "Impact of knee marker misplacement on gait kinematics of children with cerebral palsy using the Conventional Gait Model". Annual meeting of European Society of Movement Analysis in Children and Adults (ESMAC), Amsterdam, Netherlands, 2019

[Fonseca, M.](#), Bergere, M., Candido, J., Leboeuf, F., Dumas, R. "The Conventional Gait Model's sensitivity to lower-limb marker placement". Annual meeting of European Society of Movement Analysis in Children and Adults (ESMAC), virtual conference.

[Fonseca, M.](#), Dumas, R., Armand, S. "Automatic gait event detection in pathologic gait using an auto-selection approach among concurrent methods". Annual meeting of European Society of Movement Analysis in Children and Adults (ESMAC), virtual conference.

[Fonseca, M.](#), Armand, S., Dumas, R. "An analytical model to quantify the impact of the propagation of uncertainty in knee joint angle computation". Biannual symposium 3d Analysis of Human Movement (3d-ahm), virtual conference.

[Fonseca, M.](#), Bergere, M., Candido, J., Leboeuf, F., Dumas, R., Armand, S. "The Conventional Gait Model's sensitivity to lower-limb marker placement". Annual meeting of Société Francophone d'Analyse du Mouvement chez l'Adulte et l'Enfant (SOFAMEA), Marseille, France.

[Fonseca, M.](#), Gasparutto, X., Grouvel G., Bonnefoy-Mazure, A., Dumas, R., Armand, S. "Evaluation of lower limb and pelvic marker placement precision among different evaluators and its impact on gait kinematics", Annual meeting of European Society of Movement Analysis in Children and Adults (ESMAC), Dublin, Ireland, (September) 2022

