In Vitro and in Silico approach of continuous subcutaneous insulin infusion system reliability

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Augmented *In Vitro* approach of continuous subcutaneous insulin infusion system reliability

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« D'aucuns te diront d'être le premier, jamais d'être heureux.
Premiers sont ceux qui ont besoin d'une note, ceux qui n'ont pas confiance en eux »

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Outlines

Abbrevations

DM: Diabetes Mellitus

IP: Insulin Pump

CSII : Continuous Subcutaneous Insulin Infusion

ICIJ: Internation Consortium of Investigative Journalists

T1D : Type I Diabetes

IDDM : insulin-dependent diabetes mellitus

T2D : Type II Diabetes

APS: Artificial Pancreas System

MD: Medical device

MDI: Multi Daily Injection

GV: Glycemic Variability

BGM: Blood Glucose Meter

CGMS: Continuous Glucose Monitoring System

SCT: Subcutaneous Tissue

MDR: Medical Device Regulation

DKA: Diabetes Ketoacidosis

MDC: Micro Delivery Chamber

CLS: Closed-Loop System

TIR: Time in Range

IEC: International Electrotechnical Commission

PK: Pharmacokinetic

PD: Pharmacodynamic

MT: Mettler Toledo®

ISO: International Standardization Organization

HHC: home healthcare

KF: Kalman Filter

MARD: Mean Absolute Relative Dispersion

RMSE: Root Mean Square Error

TV: Temperature Variations

BMI: Body Mass Index

SB: Skin Breakpoint

Abstract

Type 1 diabetes (T1D) treatment and the components of an artificial pancreas (AP) often include an insulin pump (IP) or continuous subcutaneous insulin infusion (CSII) device. The accuracy of CSII is essential for proper glycemic control, however, the metrics used to assess such devices have not been given sufficient study, especially at the lowest basal-rates. A few studies deal with CSII assessment accuracy, but are based on an indirect and limited measurement of insulin flow rate. Moreover, product testing is in large part detached from conditions encountered in daily actual patient usage. Importantly, too few studies discuss accuracy from a clinical point of view. Our study presents a novel "*in vitro*" methodology to assess CSII accuracy in conditions similar to that encountered by patients with actual use. A new measurement method was developed here based on insulin flow rate and volume double-measurement optimized by a Kalman filter algorithm. Unlike existing methods, insulin flow rate was measured continuously and at very low basal rates with reasonable uncertainties. The methodology and results indicating validity were published in July 2019 (Girardot et al, 2019). In-lab tools and specific protocols were also developed to assess CSII under daily life conditions that may alter delivery precision. Namely, pumps were tested under various temperatures, motion, hydrostatic pressure and skin endpoint conditions. Four off-the-shelf CSII systems, Medtronic® Minimed™ 640G, Omnipod™, Ypsopump™ and Tandem® t:slimX2™, were assessed at four set basal rates, 2 UI/h, 1 UI/h, 0.5 UI/h, 0.1 UI/h, using the proposed novel methodology. Accuracy was assessed using newly-designed mathematical indicators and graphical representations that support clinical interpretation. The continuous measurement approach allowed for a detailed insulin peak-wise analysis. Minimed™ 640G, Ypsopump™ and Tandem® t:slimX2™ were then tested under various hydrostatic pressure, temperature variation and motion conditions. Finally, Ypsopump™ and Minimed™ 640G insulin delivery were briefly investigated for subcutaneous endpoint conditions. CSII accuracy was model and basal rate dependent. The lowest insulin delivery ranges were associated with the highest inaccuracies and peak-wise analysis partly explained global errors as well as influences from manufacturing choices. Hydrostatic pressure and motion did not influence CSII accuracy, while temperature variations unexpectedly caused important CSII delivery alterations. In-water delivery was not associated with lower accuracy than in-skin infusion, however, pressure analysis between in-skin and in-water diffusion provided precious insights that deserve further investigation. The highest error range in CSII accuracy might question glycemic variability for

CSII users with the most insulin sensitivity. The link between delivery errors and GI have to be strengthened. CSII accuracy assessment under models that reflect actual-use conditions need further study to be generalized. Clinically-oriented CSII assessment protocols and new measurement methods should be established by industry and relevant regulatory agencies to better address CSII user safety and comfort.

Foreword

Diabetes mellitus (DM) is a chronic disease characterized by constant hyperglycemia resulting from a decrease in insulin secretion. It is diagnosed when the fasting blood glucose value is above 1.26 g/l on two separate occasions. The prevalence of DM is one of the highest for chronic conditions and continues to rise in modern society [1]. The oldest description of DM goes back to ancient Egypt. A papyrus record from Thebes dating back to 1550 B.C describes people suffering from high quantity of urine flow and thirst [2].

Prior to the discovery of insulin, there was no specific treatment to improve insulin-dependent diabetic conditions. Patients would suffer constantly until an untimely death. Over the past number of decades, numerous treatments and new technologies have emerged to improve management and quality of life for patients [3].

Despite many significant improvements, glycemic variability (GV) remains high for a large population and there is no definitive cure [4], [5]. Patients continue to have decreased quality of life with a shorter life expectancy [6]. These outcomes are driven by chronic complications, which can be due to constant glycemic variations [6].

For all these reasons, diabetes constitutes a major public health issue and there is a need to improve the general knowledge about its physiology as well as current treatment. Two current technologies are utilized for treatment, an insulin pump (IP) or continuous subcutaneous insulin infusion (CSII). These technologies, however, have some shortcomings in terms of assessment and efficiency. Accordingly, this work aims to address these issues and propose new assessment methods.

This research examines in-depth how insulin pumps and CSII are measured and tested. Unfortunately, many common assumptions about these devices and even clinical application are not thoroughly evidence-based for clinical application. Howard Zisser, director of clinical research and diabetes technology at the University of California, Santa Barbara, declared, “Once something makes it into the cannon of scientific literature, it is thought of as gospel and is often used by industry to differentiate their products.” In fact, insulin pump performance claims were often made without robust scientific evidence.

More recently, physicians and researchers in the scientific community have identified a need to look more closely at the data and performance of insulin devices. The International Consortium of Investigative Journalists (ICIJ) and recent publications have noted the need to get beyond current knowledge on insulin pump performance. Regarding such research, a congress chairman communication noted, "You open our eyes on a relevant and 'not so known' topic that might bring a lot to patients." *(European Association for Study of Diabetes Congress, Berlin, 2018)*.

Introduction

Context and motivation

Type I diabetes (T1D), also called immune-mediated diabetes mellitus (IDDM) is characterized by a destruction of pancreatic β-cells, which are responsible for insulin secretion, due to an auto-immune process [7]. Type II diabetes (T2D) is caused by a relative decrease in insulin secretion, associated with a defect in insulin sensitivity [8]. The lack of insulin or insulin resistance induces a decrease of the uptake and utilization of glucose by most of the cells in the body, though mainly in the skeletal muscles [9]. There is also an increase of the hepatic production of glucose, resulting in abnormally high blood sugar levels (hyperglycemia) [10]. Sustained hyperglycemia over several years results in long-term complications, such as nephropathy, retinopathy, neuropathy and damage to the cardiovascular system [11].

DM is one of the most prevalent diseases in society today. It has risen from 108 million in 1980 to 422 million in 2014 ("WHO | *Global Report on Diabetes*," n.d.) [12] and caused 4.8 million deaths in 2012 (ranking fifth by cause-specific mortality in most high-income countries). It is undoubtedly one of the most challenging health problems of the 21st century. The diabetes epidemic is expected to increase [13]. Treatment efficiency is key to improving quality of life and decreasing complications [14].

Currently, there is no cure, but many treatments are available for T1D diabetic patients to maintain normoglycemia (normal glycaemia ranges from 70 to 140 mg/dL) and to prevent chronic complications [15]. Among the plethora of available solutions, CSII allows for exogenous insulin intake and remains one of the best ways to achieve optimal glucose control [16]–[18]. CSII is also one of the main components for an automatic insulin delivery system, also known as an artificial pancreas system (APS) [12]. Treatment outcomes of APS has been successfully applied in multiple clinical trials [19]–[21]. Unfortunately, achieving recommended glycemic control still remains challenging in the T1D population [16].

Problem statement

CSII provides an exogenous method for insulin infusion through a subcutaneous route with an aim to compensate for the lack of endogenous insulin production of β-cells in diabetic patients.

CSII efficacy is key to patient safety and optimal glucose control [22]. The current standard method to assess CSII delivery precision is suboptimal for many reasons [23]. Several independent studies have investigated CSII precision, especially for specific delivery modes, such as for low basal rates [24]–[28]. The literature also indicates some potential bias introduced by subcutaneous infusion compared to an endogenous or peritoneal route [29]. These concerns warrant further investigation to guarantee CSII as an absolute efficient treatment or at minimum to reinforce knowledge and adapt good practices.

This thesis explains the current limitations of CSII assessment and the need for further investigation regarding device precision for several delivery modes and device performance reflecting conditions in actual clinical application. A novel leading-edge methodology is applied to test CSII under several in-lab models that reflect actual clinical and daily-life conditions. Finally, this work also paves the way for the investigation of a potential existing bias of the subcutaneous route within insulin administration.

Objectives

State-of-the art analysis and consideration of actual-use conditions are necessary for medical device (MD) assessment. Clinical studies remain the best way to assess MD in “real-life” conditions, however, these are costly and time-consuming. Meanwhile, “in-lab” instruments are increasingly precise and can model human behavior or physiology. One might also argue that human physiology and parameters in clinical trials are subject to many variations providing only an overview of MD performance. In comparison, in-lab tests cannot directly consider MD clinical impact, but does provide detailed analysis of functional performance. Hence, clinical trials and in-lab tests are two complementary and necessary approaches for MD assessment.

Current in-lab assessment methods for insulin pumps have been used for many years without major changes. However, the lowest basal rates have not been systematically studied and the test protocols are not always clinically relevant. The link between CSII delivery precision and potential clinical consequences remain unclear.

Based on these considerations, we defined the main objectives for the present study, as presented below:

➔ **Show that technology is available to increase "in-lab" CSII assessment consistency.**

New measure instruments and informatic tools can be applied to improve precision in CSII assessment. Our aim is to increase measurement accuracy and observe direct pump behavior.

➔ **Study CSII performance for the most challenging basal rates and clarify indicators that describe CSII performance in a clinically relevant way.**

Off-the-shelf CSII systems will be tested at several basal rates (including the lowest). New indicators and graphical representations will be developed to provide concise and clinically-relevant metrics for CSII performance.

➔ **Mimic human behavior with "in lab" (or *in vitro*) tools, that are likely to reflect actual conditions for insulin delivery.**

In-lab tools can be used to reproduce some human behavior and test CSII accuracy under various conditions. As an example, skin back pressure may impact CSII performance and will be studied.

➔ **Discuss insulin delivery accuracy results and potential clinical consequences.**

The accuracy and relevance of results are discussed considering a clinical perspective.

Thesis outline

An outline of this thesis and a summary of each contribution is presented hereunder:

Chapter 1: Background

This chapter provides background material on diabetes care, a panel of off-the-shelf CSII devices and various technologies, along with current CSII assessment methods and a discussion regarding limitations. CSII assessment involved in APS is also described.

Chapter 2: Development of a new Kalman-filter-based methodology

A leading-edge bench test for insulin pump accuracy assessment is proposed. The technical development, advantages, limitations as well as a method validation are introduced. This methodology has been presented in an already-published paper [30] and constitutes the core

and the foundation of this thesis. After raising concern regarding insufficient “in lab” CSII assessment methods, this thesis aims to benchmark, develop and qualify this new protocol.

Chapter 3: Off-the-shelf insulin pump assessment

The previously introduced method for CSII delivery assessment was applied to assess the precision of an off-the-shelf CSII panel. Four pumps were tested at four different set basal rates: 0.1 UI/h, 0.5 UI/h, 1 UI/h and 2 UI/h. New performance indicators are introduced and the results are discussed with an emphasis on being clinically relevant. This work has been submitted as a scientific publication.

Chapter 4: Insulin pump assessment: closer to patient

This chapter introduces CSII assessment within an ecological environment. We present “in lab” elements likely to reproduce patients “daily-life conditions” and introduce some CSII performance indicators in that context. The subcutaneous route and its effect on CSII infusion are also explored and presented.

Chapter 5: Discussion

Per the developed tools and the results obtained regarding CSII accuracy, we discuss implications of the present research and applicability to future research, such as for skin tissue, results integration on an AP system, and required clinical studies.

Chapter 1: Background and context

1.1 Diabetes

Diabetes affects a wide range of the population [31]. Patients can be old as well as young, overweight or thin [32]. Diabetes can have a genetic or behavioral cause [33]. The disease can be progressive and silent or emerge suddenly and viciously requiring urgent hospitalization [33]. Treatment is also heterogeneous, starting from a simple diet and hygiene care up to invasive insulin-therapy [34]. This extended range of phenotypes expresses as different forms of diabetes. Schematically, there are three forms of diabetes: T1D, T2D and the other [35]. The present research briefly defines T2D while specifically focusing on the T1D population due to its association with CSII therapy [36].

1.1.1 Type I diabetes

Type 1 diabetes (T1D) results from a total absence of insulin secretion. Two different forms of T1D are defined by the American Diabetes Association classification: immune-mediated diabetes and idiopathic diabetes [35].

Immune-mediated diabetes

Immune-mediated T1D (previously called "insulin-dependent diabetes" or "juvenile-onset diabetes") has the highest prevalence among T1D forms and accounts for 5 to 10% of all types of diabetes [31]. This specific type of the pathology is caused by cellular-mediated autoimmune destruction of the pancreatic β-cells, which are the cells responsible for insulin secretion and partly shape the Langerhans islet structure within the pancreas [37].

Many autoimmune markers such as islet cell autoantibodies, autoantibodies to insulin (or other markers involved in insulin secretion mechanism) are related to the disease [38]. The presence of one or several of these markers is sufficient to diagnose immune-mediated T1D [35].

The evolution of the pathology depends on β-cell destruction rate and is variable among individuals. It is commonly rapid for infants or children and slower for adults. This disease often declares itself with ketoacidosis in children and adolescent. This complication happens when the body produces high levels of blood acids (ketones) linked with an inability to produce

enough insulin. The disease may also reveal itself with fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. In better cases and most likely with adults, sufficient β-cell function may remain to prevent ketoacidosis for many years. Immune-mediate diabetes is most likely to occur during childhood or adolescence, but is still sometimes diagnosed later, even in the 8^{th} or 9^{th} decades of life [39].

To date, T1D patients can only be treated with a subcutaneous insulin infusion to compensate for the lack of endogenous insulin production [40]. Multi-daily injection (MDI) is provided through a pen or syringe or external CSII. In CSII, fast-acting insulin is infused permanently into the patient's body [41], [42].

These two treatment methods give imperfect metabolic consequences. Often, glycaemia remains unstable with sequences of hypo and hyper glycaemia [4], [5]. Subcutaneous tissue (SCT) is not a proper physiologic administration path and could partly explain glycemic instability (GI) associated with CSII or pen infusion. An intraperitoneal insulin pump provides better glycemic stability due to a more "straight-to-blood" mode of insulin infusion [43]. These exogenous insulin intake treatments, especially CSII, are the main focus of the present study.

Idiopathic diabetes

Some other forms of diabetes have no known etiologies. Patients have a constant insulinopenia and are predisposed to ketoacidosis without any auto-immune markers. The prevalence of these T1D forms is much smaller compared to immune-mediated diabetes [44]. Idiopathic diabetes patients are likely to suffer from episodic ketoacidosis and will show different amounts in their insulin deficiency. These forms of diabetes are highly hereditary [35].

1.1.2 Type II diabetes

Type II diabetes (T2D) was previously called 'non insulin-dependent' diabetes and affects patients with a metabolism resistant to insulin and a partial (or less commonly, total) insulinopenia. The prevalence for this disease represents 90 to 95% of all forms of diabetes. T2D does not systematically involve exogenous insulin intake [45], [46]. Nevertheless, we will describe this form of diabetes since this disease has a high and constantly growing prevalence,

and hence could one day may benefits from the present work. (NB: some publications have already highlighted the positive outcomes of CSII use for T2D [47]–[49]).

In the most common situation, patient obesity (or increase in fat tissue in the abdominal region) leads to a resistance of insulin action. This form of diabetes is often unknown to patients for many years due to its progressive evolution [50]. Despite its asymptomatic character, patients are prone to developing serious complications, notably micro or macrovascular aggravation [51]. The risk to develop T2D is associated with age, obesity and a lack of physical activity [52]. Hyperglycemia in T2D cases is generally associated with a hyperinsulinemia due to a compensation by the β-cells for the insulin-resistance [53].

T2D compared to T1D has a high genetic predisposition [54], [55]. Patients with a family background have greater chances to develop the disease. Many different genes have been identified as associated with T2D and thus characterize the disease as a genetic polymorphism.

T2D is most ideally and commonly treated with a proper diet and active lifestyle. Oral anti-diabetic agents and incretin mimetic agents can also be prescribed to improve normoglycemia in case lifestyle adaptation methods fail. In fewer occasions, exogenous insulin can also be added to the treatment to refine or replace drug-based treatment [56], [57].

1.1.3 Other forms of diabetes

Other forms of the disease are not classified as type 1 or type 2 diabetes because of their physiological causes such as monogenic diabetes [58], exocrine pancreas disease [59] and so on [60]. We do not address these forms.

1.1.4 Glycemic variability

Whatever the forms of diabetes, many patients still experience daily glycemic variability (GV) [61]–[63]. GV refers to swings in blood glucose levels and remain highly persistent in the T1D population, including patients treated with CSII [64], [65]. T1D experience daily life important glycemic variability whatever the adopted behavior (see **Fig. 1**).

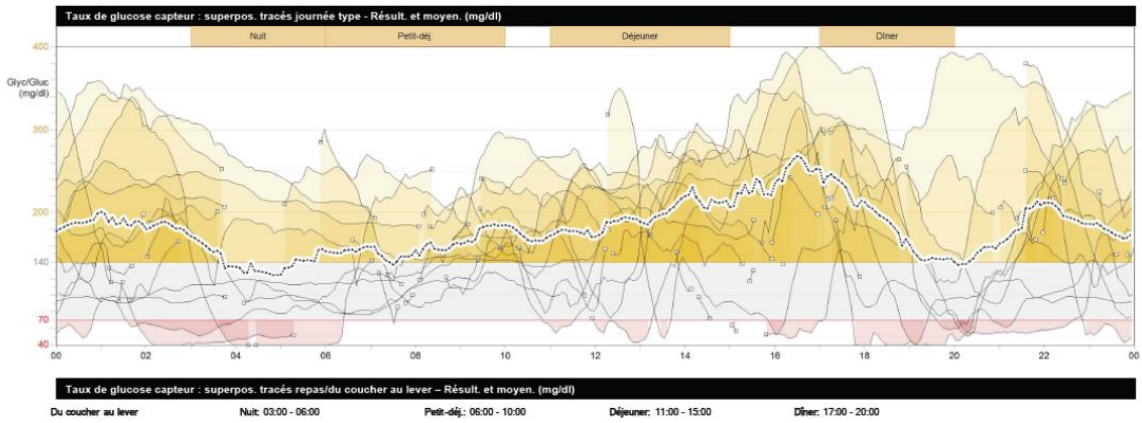

Figure 1: CSII user inter-day glycaemic variability. Multiple days combined CGM data highlighting important glycaemic instailbity over days.

GV have been related to many causes. External causes such as adrenal insufficiency [66], [67], internal causes such as gastroparesis [68], [69] or even patients' habits. Patients daily-life was indeed related to a variability index taking account of criteria such as eating out or buying ready-to-eat food, snacking between meals, alcohol consumption, and exercise level or even work schedules [70]. As highlighted in **Fig. 2** from Mori H *et al. (2016)*, glycemic mean of daily differences (or GV) are significantly influenced by life changes, but remains high without daily variability.

1.2 Treatment for diabetes and different technologies

To date, no treatment exists to get eliminate any form of diabetes. It is a chronic disease and treatments are required life-long to deal with symptoms and glycemic control. Progress in techniques and recent innovations may significantly reducing the physical and psychological burden [71] of patients managing normo-glycaemia [72], [73].

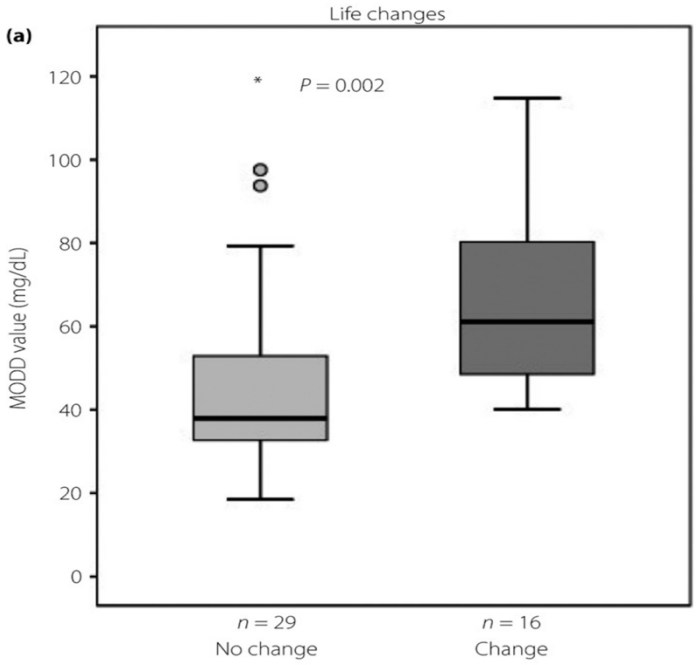

Figure 2: Relationship between mean of daily differences (MODD) in blood glucose levels and life variability. Difference in mean MODD value between patients with lifestyle changes and those without. Between- group comparisons were tested by unpaired Mann–Whitney U test. (Source: Mori H et al, doi:10.1111/jdi.12551)

1.2.1 Reading glycaemia

Diabetic patients, treated with insulin or not, have to monitor blood glucose to manage glycemic variations. For decades, a blood glucose meter (BGM) was the gold standard for glucose measurement. Around the 2000s, continuous measurement systems became able to evaluate glucose concentration within interstitial tissue liquid and health coverage in France became available in June 2017 [74], [75]. Reading glycemic technologies is left to other research and is not addressed here.

1.2.2 Controlling glycaemia by exogenous insulin intake

Diabetic patients treated with insulin have to continuously monitor blood glucose. Patients with T1D, and some with T2D, require exogenous insulin intake to compensate for the lack of endogenous production. Some T2D patients will also need exogenous insulin. Two main options are available for insulin uptake: MDI or CSII.

Multi-daily injection

Multi daily injection (MDI), also known as multi-dose injection is an exogenous insulin infusion treatment by means of a pen **(Fig. 3B)** or syringe **(Fig. 3A)**. This usually involves two injection types: long-acting insulin (also called "basal" insulin) and fast-acting insulin to metabolize meal uptake. Such a combination is called a "basal-bolus" regimen. Worldwide, a majority of T1D patients still uses [76]. MDI as insulin intake treatment. To illustrate, in the UK, MDI use is one of the highest with 90% of T1D under this practice [77], while in the US, 40% of T1D use MDI over CSII [78].

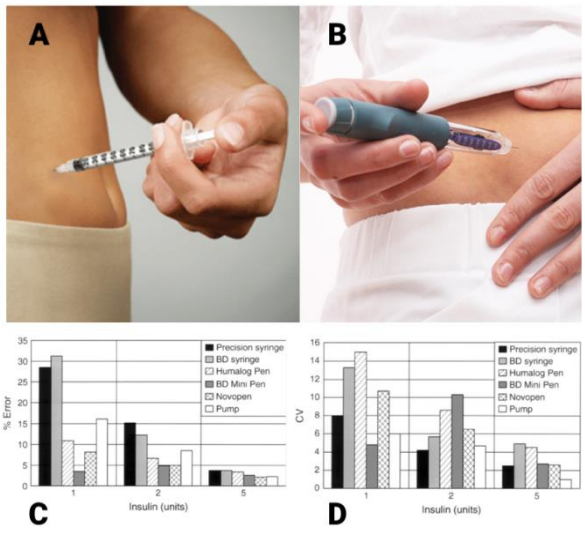

Figure 3: MDI illustration and precision assessment. Syringe (A) and pen (B) common use. % of delivery error (C) and reproducibility (D) of a panel of syringe, pens and CSII on single dose. (Sources: Keith et al, 2004 / https://hcp.medtronic-diabetes.co.uk)

Delivery precision of a panel of pens and syringes used for MDI treatment have been assessed in 2004 by Keith *et al.* The precision of single shots of 1 UI, 2 UI and 5 UI were compared for two syringe models, four pen models and one CSII model. At 1 UI, they conclude that syringes were relatively inaccurate with mean errors reaching 30% (Fig. 3C). Pens were globally more accurate, but less reproducible in terms of error (Fig. 3D) [79]. Therefore, in this study, CSII was measured as more accurate than MDI devices.

Continuous sub-cutaneous insulin-infusion

Continuous subcutaneous insulin infusion is insulin-therapy using an insulin pump [80]. This is a class IIb medical device according to the Medical Devices Regulation (MDR) 93/42/EEC. It subcutaneously and continuously perfuses through a catheter a defined amount of rapid insulin, usually an analog of insulin (Lispro, Aspart or Glusilin). The injection speed is called basal rate, and is measured in units of insulin (UI) per hour (UI/h). One UI corresponds to 10 µL of insulin at its standard concentration, namely U 100 for 100 units insulin per ml.

Several basal rates can be set in the day and are intended for the metabolization of hepatic glucose. In addition, the patient must trigger the delivery of a bolus (immediate delivery of a certain volume of insulin) prior to a glucose uptake from a meal, or in case of hyperglycemia [80].

CSII is a widely-adopted treatment for T1D and is also used in T2D. In 2015, one million people worldwide were estimated to be using CSII including 400,000 T1D patients in the U.S. [81]. For many studies, CSII treatment showed better efficiency in stabilizing glycaemia compared to MDI for T1D patients [16], [17]. As shown in **Fig. 4**, a plethora of studies over the past years highlighted a significant improvement of HbA1c for CSII users compared to MDI users.

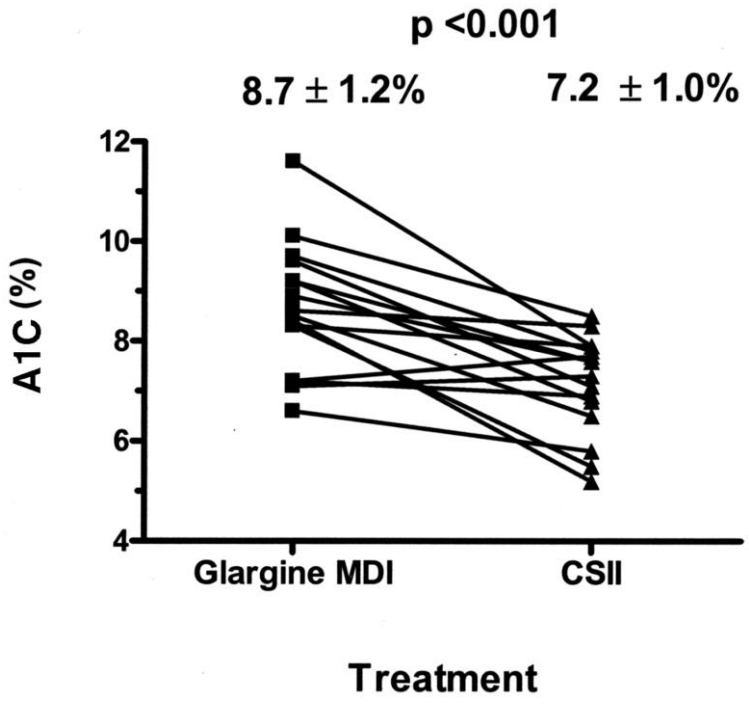

Figure 4: CSII vs MDI efficiency to improve HbA1c.

Several meta-analysis highlight CSII treatment as significantly more effective to improve HbA1c compared to glargine-based MDI treatment (source: John C. Pickup, Diabetes Care 2008).

CSII use has been associated with several drawbacks. Pump malfunction or absorption problems expose patients to diabetic ketoacidosis (DKA). Numerous CSII-involved adverse events have previously been listed by Heinemann *et al.* [82]. Skin infections or chronic pain at the catheter site are frequent and also constitute a limitation of CSII adoption [83], [84], [85].

The most feared side-effect of insulin therapy, especially using CSII, is iatrogenic hypoglycemia due to an unintended over-dosing [86]. Therefore, effective and safe use of CSII requires technophile candidates or good training to make efficient use of the device [87].

Figure 5: Insulin pump panel and use. External insulin pump delivering subcutaneously in the abdomen of a patient (up). A representative panel of off-the-shelves insulin pump (down). Omnipod®, Minimed™ 640G, Ypsopump™, Tandem t-slimX2™ (from left to right).

CSII delivery technologies

The last decade has seen a plethora of new technologies including several leading-edge-based IP. We briefly describe insulin delivery technologies of four off-the-shelf systems:

- Ypsopump™ and Medtronic® Minimed™ 640G delivery are based on an endless screw. As shown in **Fig. 6A**, a syringe reservoir (cartridge) filled with insulin is placed within the pump and the screw pushes the syringe according to the set command.
- Insulet® Omnipod™ uses a different technology called "SMA wire." According to device command and for each increment, the lever moves back and forth due to an independent movement and pushes a piston inside a reservoir that expulses 0.05 UI for each step (see **Fig. 6 (B1-B2)**).
- Tandem® t:slimX2™ chose a different technology based on a micro delivery chamber (MDC) that translates and can adapts insulin volume to the set command by modifying translation amplitude. As seen in **Fig. 6 (C1-C4)**, insulin is sucked up from the reservoir

to the bucket chamber when MDC translates forward. The given amount of insulin is then infused to the patient's body when MDC moves backward.

To date, no link has been established between model accuracy and its delivery technology.

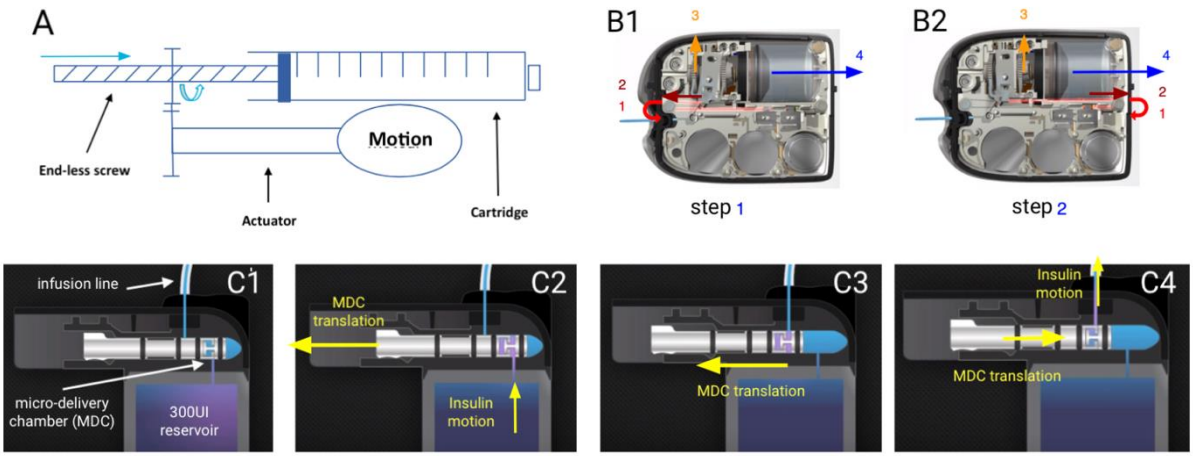

Figure 6: CSII delivery technologies. Ypsopump™ and Minimed™ 640G™ end-less screw delivery technology scheme. An actuator activates an endless screw motion which pushes the piston of a cartridge to expulse insulin out of the pump (A). The so called "SMA wire" delivery technology relative to Omnipod™ patch pump: at each step, a lever (2) moves back (B1) or forth (B2) due to independent actuators (1). Lever motions activate a nut (3) that trigger a piston translation (4) to expulse insulin (source: https://www.youtube.com/watch?v=rCjcZ6QXfSc). The micro-delivery chamber (MDC) based delivery technology of Tandem® t:slimX2™ pump (C1): MDC follows a two-step forward translation to suck up a given insulin volume (C2 and C3), MDC backward translation pushes this amount of insulin within the infusion line. (Source: https://www.youtube.com/watch?v=IHHdZdVds8I)

Beside stand-alone use, CSII can be integrated to more recent and complex systems able to automatically deliver insulin: the APS.

Closed-loop systems

An artificial pancreas system (APS), also called a closed-loop system (CLS), combines a CSII and a continuous glucose monitoring system (CGMS), using a control algorithm **(Fig. 7).** The algorithm allows the basal rate to be set and changed automatically, according to the needs of the patient and uses the input from the glucose sensor as well as physiological features [88],[89]. Such systems are highly beneficial to the patient as it releases some of the constant burden and attention needed to address fluctuations in glycemia.

APS effectiveness has greatly improved over the years. The time in range (TIR) constitutes a new standardized indicator representing time spent in normoglycemia (within 70 and 180

mg/dl). Recent clinical studies assessed leading-edge APS systems at above 70% TIR when using the best systems [90], [91].

Despite drastic improvement over the past decades, the 70% TIR threshold is not always reached [20], [92] and clinical studies do not systematically include the most challenging patients (i.e.: such as those with critical HbA1c, weakness with new technologies or even comorbidities [20],[91]). Having a closed loop system that is able to manage normoglycemia for the widest patient typology would be a huge gain for society [93].

Several paths to improve CLS efficiency are currently under investigation. Some believe in adding supplementary physiological data as input to the algorithm [94], [95], others have investigated various algorithm types [96], [97]. CLS technology choices are also being investigated such as dual-hormone (insulin and glucagon). The efficiency of these systems showed high performance for controlling glycaemia, but practical-use conditions remain to be addressed [98].

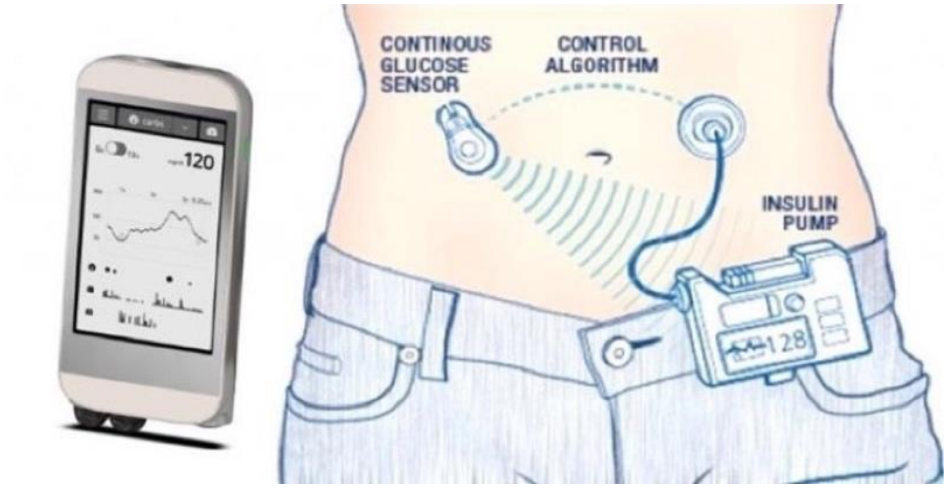

Figure 7: Artificial pancreas system description. CGMS and CSII plugged in subcutaneous tissue and combined with a control algorithm that automatically calculate insulin dose to inject. (Source: https://www.medgadget.com/)

By their very nature, the feedback control of a CLS will ignore a large amplitude of actuator error (i.e., CSII). Precision in injection is likely to be much more important in non-feedback systems (i.e., regular pump therapy). However, CSII usage within a CLS context is specific and might induce higher errors: for instance, a CSII model is "asked" by the control algorithm to importantly modify the basal rate value every 5 to 15 minutes [20]. Thus, delivery precision is likely to be impacted by such behavior. This is an interesting perspective within the present research and reinforces the need to learn more about CSII delivery behavior.

1.3 CSII assessment: state-of-the-art

Ensuring CSII efficiency over the entire basal and bolus range is essential to guaranteeing patient well-being and glucose control [99]. CSII delivery precision assessment have been the focus of some studies in the past decades [24]–[28], [100]. Nevertheless, no current method renders a continuous observation of CSII accuracy and data on lowest basal rates are rare. Many questions regarding potential clinical impact of delivery errors remain unknown. Moreover, some official recommendations recently claimed insulin infusion set use and subcutaneous infusion and require deeper investigation [84], [101], [102], [103]. In addition to scientific studies, many socio-technical-medico economic commentators have insisted on a need for a better understanding of CSII.

1.3.1 CSII assessment

The first marketed CSII systems were released in the late seventies and were promoted as improving patient comfort and physiology [104]–[107]. At the time, too few technical details were provided around pump precision [106]–[108]. The first study assessing the precision of a specific peristaltic pump was done by Jackman *et al.* (1980). The device was evaluated as precise with delivery errors < 1%, but the infusion test flow rate was tested with an equivalent basal rate of 600 UI/h. Such an insulin flow rate remains far from the usual doses used by patients and is not readily translatable to the accuracy of CSII real-life use [104]. This 30-year old evaluation method was based on an

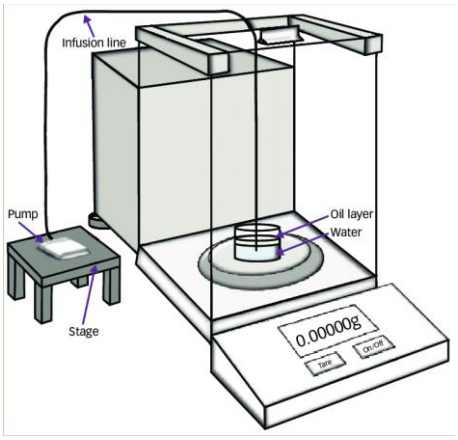

Figure 8: IEC 60601-2-24 standard protocol setup. Indirect insulin flow rate measurement based on a time-stamp micro gravimetic method. (Source: Bowen et al, 2016)

indirect measurement of flow rate through a weighing scale measurement over time. This method is still commonly used [27].

IEC 60601-2-24 gold-standard

Currently, the gold standard for CSII assessment precision is based on the International Electrotechnical Commission (IEC) (the international standards and conformity assessment for all electrical, electronic and related technologies) 60601-2-24:2012 standard [109]. Many authorities based their investigations on this method to authorize placing a medical device on the market. Despite consistent improvements in weighing technology, this current standard is based on the same principle as the previously described assessment method. This so-called "time-stamped microgravimetric method" describes a CSII set to deliver at a constant flow rate within a weighing scale through a standardized needle plunged into an initial liquid volume (see **Fig. 8**). The procedure removes evaporation (often with an oil layer or with tube sealed with parafilm) and the pump is also set at the same height as the meniscus of the liquid reservoir. After a 24 h start-up phase during which accuracy data is not considered, insulin volume is measured every 15-minutes over the whole experiment and changed into an "instantaneous" flowrate.

CSII precision is then analyzed through a trumpet curve and mean of error over the whole test. A trumpet curve represents the evolution of CSII delivery and mean error over an observation interval. Delivery mean error is calculated on a given time observation interval that slides along the whole-time experiment. The maximum and the minimum of this "time-based slides mean matrix" will constitute a single point that shapes the trumpet curve corresponding to the time interval size (see **Fig. 9**). Trumpet curve is not the simplest manner to render CSII accuracy on a wide heterogenous population. That is why, in common use, mean error became the gold standard to render CSII accuracy at a glance. Nevertheless, one might argue that global mean delivery error may compensate a positive error with a negative error. For instance, a pump that delivers with +200% error during the first half of a 24-hours test and with -200% error the next half will appear as highly accurate according to the mean error indicator.

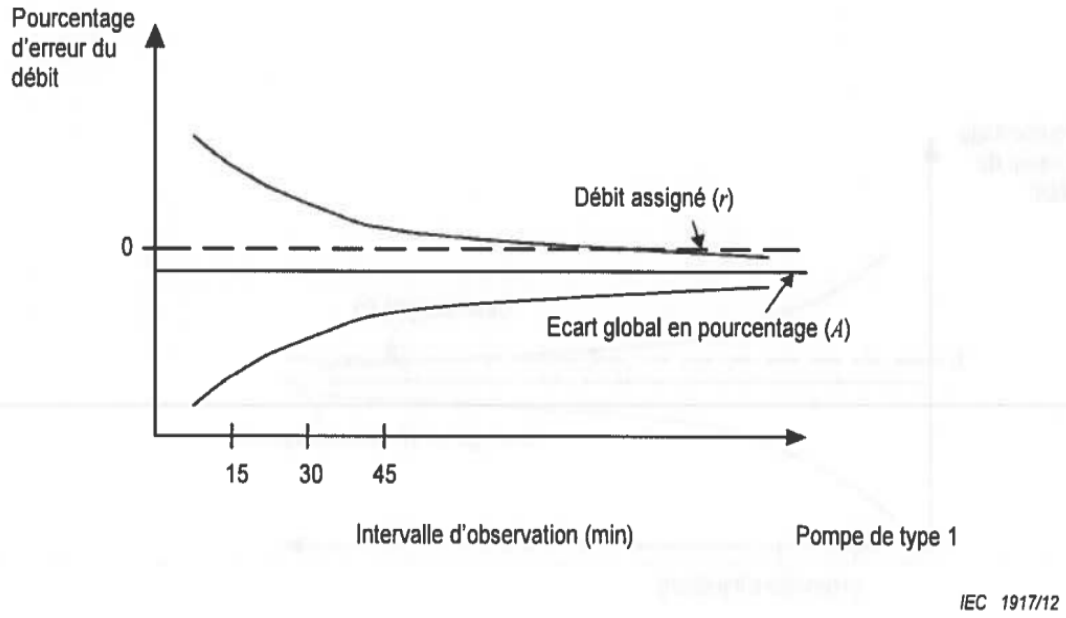

Figure 9: CSII assessment trumpet curve. Pump flow rate percentage error consider over several observation windows.

Literature and CSII assessment methods

Recent scientific studies dealing with *in vitro* CSII assessment were mostly inspired by the 60601-2-24 protocol [24]–[26], [28], [100], [104]. None of those studies include a start-up phase, since as mentioned by Laubner *et al.*, "In real life, patients program basal rate to immediately deliver after the placement of catheters." A low basal rate or "insulin pulse" measurement was performed by Borot *et al.*, Bowen *et al.* and Laubner *et al.* Accuracy analysis was done using different graphical or indicators than the standard trumpet curve. CSII accuracy was considered regarding dose percentage outside several acceptable ranges [24], [25], [100], [110].

Most recent studies, such as Kamecke *et al.* and Laubner *et al.* in 2019, discussed the clinical relevance of delivery precision. Kamecke *et al.* suggested a general protocol to analyze "for the first time" and interpret the results in a clinically relevant way [27]. Laubner *et al.* established a link with pharmacodynamic (PD) and pharmacokinetic (PK) studies and tries to make a conclusion on patient typology that could suffer from identified CSII delivery errors. These two studies also used a weighing method to assess CSII delivery. Table 1 sums up literature that focuses on CSII delivery assessment methods and compares the different studies on various criteria.

	Measurement method (Instrument model)/ Type of test (rate)	Pump tested (reproducibility)	Graphs	Clinical discussion	Funding	Main conclusions	Additional comments
Zisser et al., 2011	Imaging analysis (NA)	Omnipod™ (20)	Trumpet curve Table and histogram of overall errors	No	Independent	Omnipod is highly accurate. A new and simple technique have been designed to assess CSII accuracy	
Jahn et al., 2013	Weighing-based (Sartorius ME-5) Basal test (0.5UI/h)	One Touch Ping™ (30) Accu-check Combo™ (30) Paradigme Veo ™ (30) Omnipod™ (30)	Cloud shape of dose error over time experiment Error percentage of dose outside error zone Averaged flow rate	No	Animas corporation	Omnipod dose accuracy was lower and Animas one touch ping better than durable pumps Average dose and single dose analysis give different analysis results	Dose to dose analysis
Borot et al., 2014	Weighing-based (Sartorius MC-5) Basal test (0.1 UI/h, 1 UI/h) Occlusion alarm test	Minimed Paradigm™ 712 (3) Accucheck Combo™ (3) Omnipod™ (3) Animas vibe™ (3) Jewel Pump™ (3)	Trumpet curve Percentage of absolute flow error	Yes	Independent	Jewel pump is more precise over short-term period No 24h-accuracy differences between model	Combined with a clinical trial and quality of life survey
Bowen et al., 2016	Weighing-based (Discovery DV215CD) Basal rate (undetailed values)	Cellnovo™ (30) Omnipod™ (30)	Cloud shape of dose error over time experiment Trumpet curve Averaged flow rate	No	Cellnovo Ltd	Not all patch pumps are the same Pumping mechanism play a key role in accuracy Cellnovo more accurate than Omnipod	Dose to dose analysis
Laubner et al., 2019	Weighing-based (Sartorius AG BP121 S) Basal rate (0.2, 0.6, 1.8 UI/h) Bolus (0.5, 1,5, 10 UI)	Omnipod™ (33) Minimed 640G™ (15)	Boxplot of overall error dose distribution Percentage of correct dose (< 5% error)	Yes	Independent	CSII accuracy is model and basal rate dependent Low accuracy of pump at low bolus/basal rates	Accuracy tested on: long-period volume delivery
Kamecke et al., 2019	Weighing-based (General protocol)	NA	(Recommended) Cloud shape of dose error over time experiment Boxplot of each 1-hour interval overall error	Yes	Independent	NA	Publication only presenting a protocol and guidelines for relevant analysis
Freckman et al., 2019	Weighing-based (not detailed) Basal rate (1 UI/h) Bolus (1 UI, 2 UI)	Accu-check Insight™ (9) Accu-Check Spirit Combo™ (9) Animas Vibe™ (9) Minimed 640G ™ (9) Omnipod™ (9) Paradigm VEO™ (9)	Cloud shape of dose error over time experiment Boxplot of each 1-hour interval overall error	Yes	Independent	General similar level of accuracy Differences between patch and durable pump	Different setup for patch and durable pump

Table 1: Brief CSII literature review of accuracy and summary of some criteria

Only Zisser *et al.* published in 2011 a different method based on imaging to assess insulin going out of the device [111]. The purpose of this publication was to observe with a high-resolution camera, the insulin volume going out of a pump and through a graduated tube that shaped an insulin droplet at the extremity of the tube. The volume was then deduced from observed graduation and droplet size. This innovative protocol was favorably received by Ochoa *et al.,* which highlighted the limitations of the current gold-standard method and the persistent challenge in measuring insulin mass/flowrate with leading-edge analytic hardware [112].

1.3.1 Stakes for CSII assessment

CSII assessment gold-standard

The current gold standard for CSII assessment methods based on the IEC 60601-2-24 standard have some limitations regarding its protocol, which are often qualified as "not in phase with reality" by the literature [23], [27]. Indeed, the standard method guidelines do not require CSII assessment at the lowest basal rate range, and the overall device evaluation is most often based on typical average flow rate (usually 1 and 2 UI/h). The results obtained for these basal rates do not guarantee pump accuracy for the lowest basal rates (down to 0.025 UI/h, i.e., 0.25 microliter/h), which of concern are usually used in the pediatric population [113]. Additionally, the start-up phase previously described asks to run the CSII "for a time equivalent to empty half the container volume" or 24 h and then to calculate the CSII accuracy over the stabilization period. This requirement remains quite detached from parameters appropriate to a patient's daily life. Moreover, CSII flow rate is considered with volume acquisition gathered every 15-minutes and cannot provide fine information on delivery behavior. As mentioned earlier, manufacturers are solely asked to provide accuracy results following this protocol prior to being certified to enter the market.

Weighing-method measurement limitations

Despite systematic use as a measurement method, insulin weighing is limited. Indirect flow rate measurement using micro analytic balance instrument has the advantage of being able to consider an increasingly small volume delivery, relative to insulin needs for diabetic patients. However, many drawbacks are associated with this method. First of all, microanalytic scales are really sensitive to environment: a low-vibration table and a perfectly controlled room (temperature and pressure) are mandatory to minimize measurement error. Stabilization time between consecutive measurement imposes low temporal resolution (i.e., 15-minute sample

rate as indicated in the IEC standard protocol), evaporation effects during an experiment must also be controled and other less known phenomenon such as electrostatic effect [114] could introduce important and vicious drift in measurement (see example **Fig. 10**). Hence, many precautions have to be taken to minimize risks and ensure accurate measurement. Howard Zisser questioned Jahn *et al.* regarding its setup and the results for an CSII panel accuracy assessment [115]: "The Omnipod™ was actually placed inside of the measuring chamber.[…] I realized they were not necessarily measuring what they thought they were measuring […] These large noise spikes occurred with a regular periodicity every 3 hours. I believe what they were actually measuring was an episodic change in environmental conditions. […] Another possibility was that they were measuring the movement or vibration of the pump during delivery and not the actual volume of the insulin being delivered."

Howard Zisser has done considerable research into CSII assessment, and in particular developed the imaging-based method, explained in a white paper "using a precision balance is not an appropriate method to measure dose-to-dose accuracy at the lowest limit of a pump's dosing range" [115]. In 2011, Ochoa *et al.* went further saying that, "Even the most precise commercially available analytical scales with readabilities as low as 1 µg may be inadequate for characterizing dosages smaller than 1 U". Current leading-edge weighing technology has the ability to measure insulin volume increment of 0.1 UI/h basal rate with a 30 sec temporal resolution. Metrological analysis of the Mettler Toledo (MT) XPE56 (see Supplementary Data 1) highlights the theoretical capability of the instrument to measure such a low volume. Nevertheless, while supported by weighing and microfluidic experts, we indeed faced many phenomena over the course of a year looking at total control of measurement.

The method also has some limitations. Most scientific studies focused on CSII assessment based their measurement on weighing methods. Except for more recent studies [25], [27], no systematic metrological studies prove measurement relevance. Metrology is the science of measurement and ensures with mathematical proof that measurement methods and instruments are sufficiently relevant to give consistent results. The IEC 60601-2-24 protocol guidelines only require a five-digit reading capability for weighing scale measurement performance. Most publications only provide an instrument name and load limit and resolution without any concern regarding essential measurement performance criteria such as linearity, reproducibility, repeatability, eccentricity or sensitivity [116], [117].

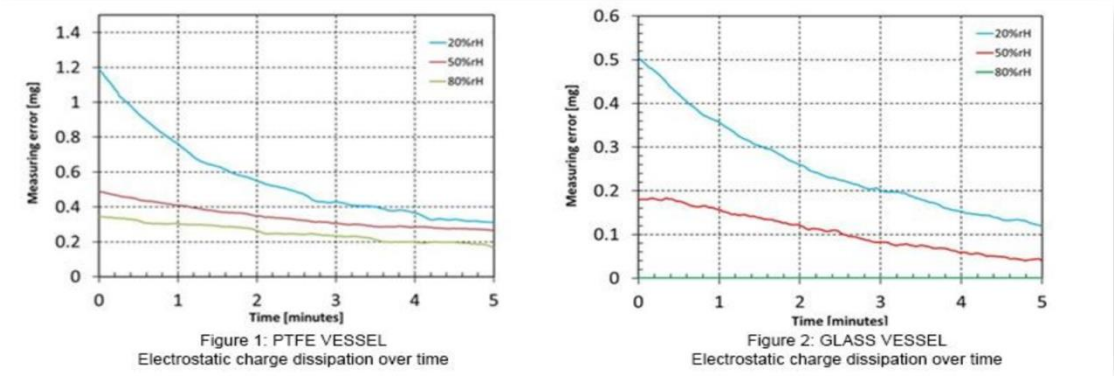

Figure 10: Electrostatic weighing disruption phenomenon. Electrostatic charge dissipation over the time likely to cause vicious and hardy detectable measurement drift. (Source: https://www.mt.com/in/en/home/library/collections/laboratory-weighing/electrostatic-and-weighing.html)

The time-stamp gravimetric method to assess infusion pump has existed from the early 80s and the original version of IEC 60601-2-24 is from 1998. An update of this standard was not done until 2012, which actually did not have any major changes [23]. The latest version of this standard was not adopted in practice: the European commission provides to manufacturers a list of harmonized standards that they have to refer to when designing a new product. The guidelines relative to each standard are supposed to guarantee product safety and performance. For infusion pumps, IEC 60601-2-24 is recommended/provided as the 1998 version [118].

After 40 years of using the weighing method, only the Zisser *et al.* protocol provides an alternative measurement to assess CSII device thru its intra-tubing delivery and imaging method [119]. However, this simple and cost-effective method is based on a one-shot delivery and is also limited to for observing the overall delivery behavior of CSII system, such as for insulin peak analysis.

Clinical consequences

One of the most challenging end points of CSII accuracy remains the lack of evidence between CSII errors and potential clinical consequences. Howard Zisser discussed this point saying [115], “The only true way to determine whether or not these micro-differences in insulin delivery have a clinical impact would be to do detailed PK/PD studies to show whether or not any of these differences directly impact insulin absorption or action in any clinically significant way.” As he mentioned, detailed PK/PD studies appear to be the only way to link CSII errors

and clinical consequences. Nevertheless, approaching CSII delivery behavior on a relevant way could constitutes a first step to understanding whether some cases are likely to be hazardous for users.

Some studies dealing with CSII assessment have discussed clinical consequences. Borot *et al.* compared results [100] with Heinemann *et al.* conclusions on systemic modifications for CSII infusion rate change during an euglycemic clamp [120]. Indeed, they found, "in an adult with a normal insulin requirement (0.12 UI/kg), changing basal rate from 1 UI/h to 2 UI/h had an effect on glucose infusion rate after 30-60 minutes. For the same patient type, a basal rate from 0.1 UI/h to 0.5 UI/h did not reveal any particular systemic consequences. However, observed pump errors raised the question for patients with lower insulin sensitivity" [100]. More recently, Laubner *et al.* demonstrated low accuracy for a panel of CSII and established the same conclusion [25].

Also, Kamecke *et al.* interpreted bolus accuracy results from a clinical perspective, where the authors observed a sequence of over- and sub-delivery that "may lead to very different glycemic outcomes after the given bolus without being comprehensible for the patient." He also observed that the majority of pump under-delivered the first 12 hours on basal rates mode. He related this to the fact that "patients often anecdotally report changes in their glycemic control immediately after a change of the insulin pump system."

Recent studies that pointed out that the lack of clinical studies evaluating the systemic impact of insulin dose, used an indirect method to gather some insights on the topic. For example, based on glucose measurement errors [121], [122] and clinical trials for carbohydrates count errors, they estimated that dosing errors > 15%, 20% could have a clinical impact [123], [124]. A more recent simulation study [125] also demonstrated that a variation of 0.1 UI/h in basal rate or 0.3 UI in bolus within a 4-hour time span also had a systemic incidence. Hence, despite the lack of clinical evidence, research is increasingly suggesting a need to reinforce knowledge on CSII delivery behavior and its potential clinical impact.

From a more general point of view, we raise the question of CSII errors impact on general glycemic instability. MDI tools have been proven to be less accurate than CSII, especially for low-dose [79]. CSII has also been proven to improve GI compare to MDI treatment [126]. Although GI appears to be multi-factorial, we hypothesized than treatment accuracy could also

play a key role in GI. In any case, ensuring treatment accuracy assessment is an asset to improve CSII efficiency or ruling out that it is not involved in overall persistent GI.

Subsistent errors in diabetes management

As with many technologies applied to in diabetes, CSII system usage has drastically increased over the past years, especially for babies where utilization increased by 50% from 2007 to 2017 **(Fig. 11)** [127]. At the same time, general diabetes outcomes appeared to relapse as shown by Foster *et al.* where HbA1c of a cohort of more than 22,000 patients was higher in 2018 than it was in 2012 [128]. Furthermore, as mentioned earlier, subsistent GV remain in CSII users and recent trials showed that GV improvement cannot be attributed to CSII therapy [129]–[131]. Hence, despite an increase in CSII use, important errors remain in diabetes management. Due to the inherent lack of data regarding CSII accuracy and the importance of CSII therapy within glycemic control, we raise the question of whether eventual delivery errors could participate to unperfect diabetes management. Further, could delivery instability could influence subsistent GV. The first step before answering such questions lie in more precise study of CSII delivery behavior.

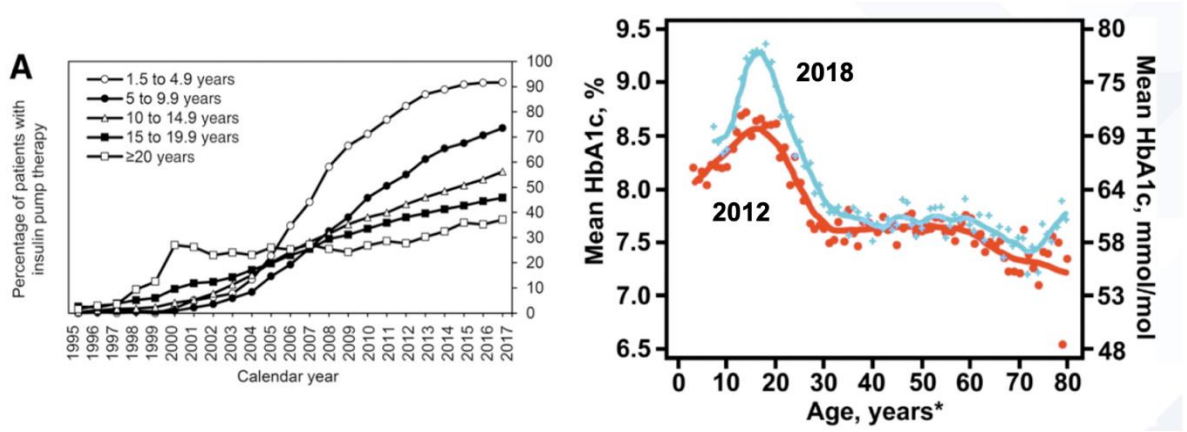

Figure 11: CSII usage and HbA1c evolution over the last decades. Evolution of insulin pump users percentage classified by age group from 1995 to 2017 (left). (Source: Louisa Van den Boom et al, Diabetes Care 2019)**.** Mean HbA1c percentage of a 22.000 patients cohort in 2012 and in 2018 (right) (Source: Foster NC et al. Diabetes Technology & Therapeutics 2019).

Socio-medico-economic context

A review of the literature and consideration of current socio-medical context also suggest that it is necessary to improve the general technical knowledge around CSII to prevent hazardous situations and to improve treatment efficiency. Early 2015, Heinemann *et al.* concluded that in

general, medical devices should be much more regulated to reduce adverse events [82]. A 10-year retrospective study of adverse events reported 1.594 cases related to insulin pumps, including 13 deaths from 1996 to 2005. These numbers rose by about 17% per year between 2001 and 2009 [132]. The Heinemann *et al*. statement was largely disseminated in the public realm through the *Medical Devices Investigation* report published by the ICIJ in 2018 [133]. CSII by itself is ranked third in terms of declared events with 305,000 cases even though ICIJ noted that the raw reports of each case were not rigorously assessed to identify specific issues caused by medical devices. In any event, the number of events points to the need to improve the regulatory processes for pre- and post-clinical studies.

At a national public health level, most countries are continuously adapting to economic conditions and reducing health care costs are typically a significant consideration. For instance, the home healthcare (HHC) budget from French payers (Securité Sociale) has been declining for many years [134]. One argument to defend this activity is to prove that investments on HHC will bring mid/long-term savings to the payer. In 2018, the French state endorsed a spend based on sleep disorders patients telemonitoring for follow up to reimburse HHC based on performance. More generally, a medico-economic study assessed the long-term profitability of innovative MD reimbursement [135]. The reimbursement for the CGM Abbot® Freestyle Libre™ in May 2017 led to an improvement in patients' outcomes for HbA1c and improved quality of life, which is likely to reduce complication costs. In the coming years, the efficiency of all medical treatments, including those using medical devices will be questioned for economic reasons. As such, improving laboratory-based MD assessment is a relevant cost- and time-effective solution to improve MD knowledge that is complementary to clinical trials.

Currently, a lack of data is inherent to CSII delivery assessment and thus its eventual clinical impact. Our ultimate goal would be to generate more information regarding CSII accuracy in order to infirm or confirm an eventual causality link with clinical application. Accordingly, our first work in the current study was to propose a novel measurement method with improved temporal resolution and higher precision at a low flow rate to assess CSII accuracy while tackling the previously identified limitations. This new method was illustrated by testing a current off-the-shelf insulin pump at several basal rates, including at the lowest range level. The results were published in July 2019 in *Diabetes Technology and Therapeutics*. The next chapter is a summary and somehow an extension of this paper. The complete study can be found in **Supplementary Data 1**.

Chapter 2: Novel Kalman-filter-based methodology for insulin pump assessment

Article 1 (Published): Kalman filter-based novel methodology to assess insulin pump accuracy.
Sylvain Girardot, Flavien Mousin, Jeremy Vezinet, Pauline Jacquemier, Sébastien Hardy, Jean-Pierre Riveline.
Published online: 23 Jul 2019, https://doi.org/10.1089/dia.2019.0147

2.1 Introduction

NB: A short description and main results of the published article are provided below. We invite the reader to refer to ***Supplementary Data 1*** *for complete details regarding the newly developed method and results. Some concepts such as the Kalman filter and MARD indicators are better introduced and argued in the full article.*

CSII has been a widely adopted treatment for T1D, sometimes for T2D, and it is a major component for APS systems. The efficacy of CSII has been proven over the past decades to improve normoglycemia compared to MDI [16]. Against all odds, GI overall has been maintained over the past decades [136]. This statement is undoubtedly the consequence of many factors and we address the question of CSII involvement. As previously detailed, in-lab CSII assessment has not had sufficient independent studies and current assessment methods are limited. Nowadays, many actors could benefit from an improved knowledge on CSII delivery accuracy and potential clinical consequences. This study provides a critical investigation of CSII accuracy using a new measurement method, which is more robust and likely to give more information regarding CSII precision.

2.2 New assessment method development

We developed a brand-new accuracy assessment method for CSII systems based on a double measurement approach, measuring on the one hand insulin flow rate and on the other hand insulin volume, combined with a Bayesian-based mathematical filter (Kalman). CSII is set to deliver within the flow meter and downstream insulin goes into a weighing scale setup (**Fig. 12**). Data from both instruments are combined offline through the Kalman filter (KF) for

optimization. Flow meter measurement uncertainties are improved for the lowest basal rates and weighing data are enriched regarding temporal resolution.

Our method displays instantaneous insulin flow rate for the first time and allows on to read the lowest basal rate with high confidence. Performance of the method was illustrated while testing an off-the-shelf CSII at several basal rates (2 UI/h, 1 UI/h, 0.5 UI/h and 0.1 UI/h). This CSII was tested for 8-hours with a single replica. Delivery accuracy was analyzed with mean error and mean absolute relative dispersion (MARD) indicators.

A significant amount of time was also dedicated to method qualification to ensure confidence in the results. Mathematical conditions for which KF is efficient were well respected. Mathematical indicators were used to verify *posteriori* that algorithms parameters guaranteed quality in the analyzed data (**see Supplementary Data 1**).

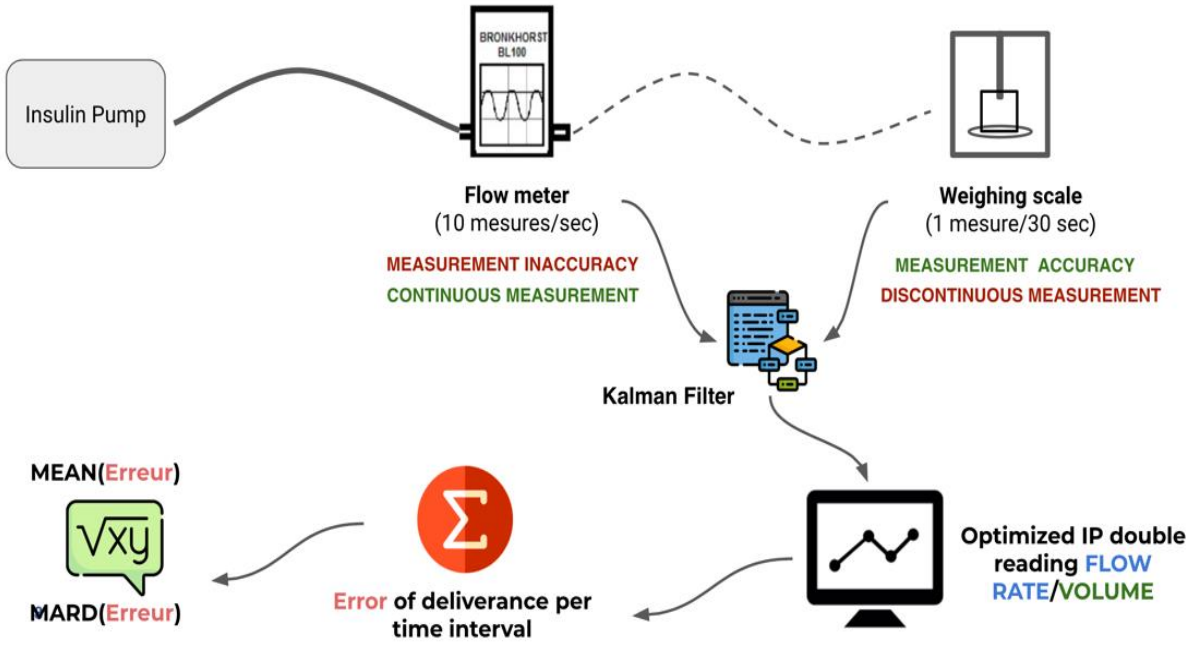

Figure 12: Novel methodology setup. Kalman filter-based double reading of insulin volume and flow rate using. CSII errors are then analyzed using MARD and mean indicators.

2.3 Main results of the study

2.3.1 Method building

Our KF was built according to several choices to provide a double frequency, standard, multivariate with linear estimator. Multivariate character refers to the several variables (included flow rate and volume) that are re-estimated. The linear estimator refers to the process model equations that are linear. Double frequency describes how the KF receives raw volume data each 30 seconds, while raw flow rate input frequency is established at 10 Hz. The KF was built to receive raw information with an interpolation process.

Moreover, instruments uncertainties are considered by the KF along matrix R. Uncertainties of the Bronkhorst BL100 flow meter were highly dependent on the measured value. Hence, we consider R as a dynamic matrix likely to adapt to flow meter values.
Finally, another important choice was the use of a drift (d(t)) as a third state variable. A drift phenomenon was observed on the Bronkhorst BL100 flow meter during the preliminary test phase. Hence, "d(t)" was added to preserve the flow-rate re-estimation from an eventual drift.

2.3.2 Method validation

Proper validation of our KF-based test bench should be ideally built on an external setup protocol. For instance, the use of a standardized infusion pump upstream to the test bench could assess whether the KF re-estimation remains close enough to the input. Unfortunately, despite an intensive benchmark, such a standardized infusion pump does not exist due to the low flow and volume ranges.

Facing this lack of materials, we approached validation of KF measurement re-estimation by another manner. Firstly, we respected the usual conditions of KF validity: process equations were verified to be linear and their noise were measured to have a Gaussian distribution. (*Erratum Article 1*: normality tests of process noise were performed using the d'Agostino and Pearson method. Such a test would make the false assumption that q(t) and V(t) variables are independent. Hence, a Shapiro-Wilk normality test were performed *a posterori* of the article publication. Normality was also confirmed by such tests (Table 2).

Flow rate value (UI/h)	2	0.5	0.1
p-value Eq. (1)	$<< 10^{-10}$	$<< 10^{-5}$	$<< 10^{-5}$
p-value Eq. (2)	$< 10^{-5}$	$< 10^{-3}$	$< 10^{-3}$

Table 2: Shapiro-Wilk normality test results for KF process noise

Secondly, arbitrary chosen mathematical indicators were allowed to validate output flow rate and volume. The auto-estimation of the process variance showed a convergence of KF estimation uncertainties (with a confidence interval at 99.7%), meaning that the estimator "feels comfortable" in its calculation. Then, a comparison of initial and re-estimated weighing scale data (using root mean square error (RMSE) remained at around $\sim 10^{-5}$ for 0.1 UI/h) (For details, see **Supplementary Data 1).** Since the initial weighing scale data were considered as highly accurate, this last result means that the KF properly re-estimate insulin volume.

2.3.3 Application of the method

The proposed novel method was used to test the accuracy and the delivery behavior of an Insulet® Omnipod system at 2 UI/h, 1 UI/h, 0.5 UI/h and 0.1 UI/h. For the first time, our method is able to consider insulin flow rate with a 10 Hz frequency display. It allows for the first time the capability to observe disparities in delivery between CSII models.

For all tests, the mean **(1)** and MARD **(2)** errors in insulin delivery were computed over the whole 8 h-test. For the mean, the difference between actual insulin dose (AID) and expected insulin dose (EID) was considered for each i-th interval upon the total n time intervals. For the MARD, the absolute value of errors is considered.

$$Mean(Error) = \sum_{i=1}^{n} [\frac{AID_i - EID_i}{EID_i}.100]. \frac{1}{n} \quad (1)$$

$$MARD(Error) = \sum_{i=1}^{n} [\frac{|AID_i - EID_i|}{EID_i}.100]. \frac{1}{n} \quad (2)$$

The MARD indicator, unlike mean error, does not compensate for sub- and over delivery during a given test, and thus, take into account "delivery instability."

The reactivity of the method allows for observation of any irregular stroke-based delivery for every basal rate value. MARD and mean indicators of pump errors highlighted an overall imprecision (> 5%) of delivery (Mean% (2 UI/h) = 8.16, MARD% (2 UI/h) = 12.7, Mean% (0.5 UI/h) = 18.16, MARD% (0.5 UI/h) = 20.4), especially at the lowest basal rate Mean% (0.1 UI/h) = 17, MARD% (0.1 UI/h) = 65.7).

2.4 Discussion

2.4.1 KF Validation

As mentioned, it was impossible to validate our double measurement bench test with an external method, which is a limitation. However, the use of well-chosen mathematical indicators provides a higher measure of confidence for our KF re-estimation. A majority of the hereunder presented CSII accuracy results have been analyzed from weighing scale data. Hence, we advance a full metrology confidence for the presented results.

2.4.2 Technical choices justification

Several choices oriented our solution toward our double measurement bench test setup and the use of this specific KF. A leading-edge flow meter allowed for the first time the consideration of insulin flow rate with a 10 Hz temporal resolution, but a metrological analysis revealed this measurement as too uncertain to obtain relevant data. Conversely, the usual weighing scale measurement considered insulin flow rate indirectly and discontinuously, but with a high accuracy. KF is usually used in many industrial domains to combine the advantages of several sensors and gather maximum available information in order to improve measurement. Intuitively, we chose to combine the temporal resolution of a flow meter and the accuracy of weighing scale through this algorithm.

There are other possible alternatives that could have been considered. Beside using a KF, a model of insulin volume could have made to increase temporal resolution of the weighing scale. Then, uncertainties of flow rate could be re-estimated with a Bayesian filter based on enriched volume. However, this alternative starts from the assumption that we know the behavior of insulin volume. Thus, we preferred to re-estimate insulin volume based on flow rate rather than model on a false assumption, even if this estimation was somehow based on uncertain flow rate measurement.

A particle filter or an extended Kalman filter could have also been used. However, the same results would have required increased computing power in the first case, and was not justified due to the linearity of our process model in the second case.

2.5 Study conclusions

A new method for CSII system assessment was developed and validated that provides measurement of direct flow rate and precisely assess CSII delivery accuracy and direct behavior using a 10 Hz time resolution. This improvement is particularly important for evaluating CSII performance, especially at a low flow rate or in the context of an APS. This method will be applied to assess a panel of off-the-shelf CSII devices at four basal rates (2 UI/h, 1 UI/h, 0.5 UI/h and 0.1 UI/h).

Chapter 3: Off-the-shelf insulin pump assessment

Article 2 (Accepted) All insulin pumps are not equivalent: a bench test assessment for several basal rates.
Sylvain Girardot, Pauline Jacquemier, Flavien Mousin, Carine Rendekeu, Sébastien Hardy, Jean-Pierre Riveline.

3.1 Introduction

NB: Here again, we only provide the main material describing the accepted publication and we invite the reader to refer to Supplementary Data 2 for detailed information.

Numerous innovations have emerged in the diabetes field in the past recent years. Several CSII devices with different core technologies have entered the market. The majority are already or will be soon be involved in APS projects. As mentioned, off-the-shelf CSII device accuracy has not been given sufficient study especially at the lowest basal rates. The weighing-based measurement method also limits the analysis of CSII delivery behavior.

3.2 Method

In this article, we used our novel CSII accuracy assessment method to test four CSII systems, namely Ypsopump™, Omnipod™, Minimed™ 640G and Tandem t:slimX2™ at four basal rates: 2 UI/h, 1 UI/h, 0.5 UI/h and 0.1 UI/h). Each test lasted 8 hours and was reproduced four times for consistency. CSII accuracy were evaluated using mean of dose error. MARD of error was calculated at different observation windows over the whole test.

MARD indicators have the advantage of considering the global error of an accuracy test without compensating for over and sub-delivery errors that could potentially encourage GI. However, one might argue that a cluster sequence of positive and negative errors could be physiologically compensated with no clinical consequences. Peak-wise insulin delivery was also assessed regarding stroke regularity in terms of frequency and volume.

3.3 Main study results

MARD of error showed discrepancies for each pump model and each basal-rate with an overall tendency to under deliver. Also, the largest errors and a lack of reproducibility was associated with the lowest basal rate values (see Supplementary data 2). For instance, Omnipod™ mean MARD reaches 61.3% at 0.1 UI/h while t:slimX2™ shows the smallest mean MARD results with a mean MARD at 22.7%.

Hence, we studied the evolution of MARD over several time observation windows and observed that MARD values could plummet when time interval got wider: Omnipod™ at 0.1 UI/h had 68% error at 15-min observation windows vs. 19% at a 60-min time interval. On the contrary MARD remain stable: Omnipod™ 0.5 UI/h 23% error at 15-min interval windows vs. 21% error at a 60-min time interval. Analysis of those different "error behaviors" and the eventual impact on GI is discussed in Supplementary Data 2.

Peak-wise analysis gave more insights on CSII accuracy. The Omnipod™ model appears to adapt peak frequency, t:slimX2™ volume, and both for Ypsopump™ and 640G™. Several strategies from each CSII manufacturer were observed for basal-rate adaptation. Peak volume and frequency reproducibility features are also given visibility. The 0.1 UI/h tests highlights insulin stroke overall poor volume reproducibility ($SD_{Omnipod}$ = 0.024, $SD_{ypsopump}$ = 0.015, SD640G=0.0092), except for Tandem™ (SD_{tandem} = 0.0045). Supplementary Data 2 displays a comparison of delivery choices (inter stroke times and micro bolus volumes) for the different CSII devices. This particular result can be linked with the overall observed MARD error. Peak-wise analysis has tremendous potential to accurately assess CSII delivery. We could now for instance establish a link with highlighted global delivery errors or CSII model behavior. This key point from our unique continuous measurement method is discussed later.

3.4 Study conclusion

We concluded that the accuracy of four off-the-shelf CSII systems was observed as model and basal-rate dependent. Our results suggest that CSII imprecision could be due to the overall variability of volume and/or frequency of strokes for every pump. Some models appear more adapted for the smallest insulin needs, or for inclusion in a CLS. The implication of these delivery errors on GI must be evaluated.

Chapter 4: Insulin pump assessment: closer to patients

Beyond the need to strengthen the CSII assessment method and understand CSII performance, it appears essential to evaluate CSII accuracy under (or closer to) real-life conditions. As previously mentioned, the IEC 60601-2-24 standard methodology as well as majority of published CSII assessment studies consider pump performance under "ideal conditions," where the device is motionless, placed at the same height as the injection site, and at ideal room temperature and pressure. In actuality, various conditions can influence a microfluidic-based device and disrupt efficiency. Zisser *et al.* studied the hydrostatic pressure effect on CSII delivery and noticed up to 123% in delivery errors [137]. Other external constraints such as motion or temperature variations might also have an influence on delivery accuracy and have never been explored. Additionally, the influence of injection site features (skin resistance, type of tissue, etc.) is also a key factor that could influence CSII treatment efficiency and which has never been considered in accuracy assessment. Despite the numerous studies related to insulin PK and PD, the influence of SCT features on insulin treatment efficiency remain unclear [101], [102].

We assessed CSII delivery under hydrostatic pressure, motion and temperature variations, and present the results. To further provide perspective, we reviewed current knowledge and preliminary results regarding the impact of SCT resistance on insulin delivery.

4.1 Hydrostatic pressure

4.1.1 Context

In common practice, wired CSII users usually wear the device around the waist or in the pocket while the injection site is preferred to be on the arm, abdomen, thigh or backside (see **Fig. 13**). Hence, a CSII device is rarely at the same height as the injection site in actual use. Hydrostatic pressure is the pressure that is exerted by a fluid at equilibrium at a given point within the fluid, due to the force of gravity. Similar to a reservoir/tubing situation (see **Fig. 14**), as in a water tower, an upstream reservoir is likely to exert a pressure downstream and move fluid forward.

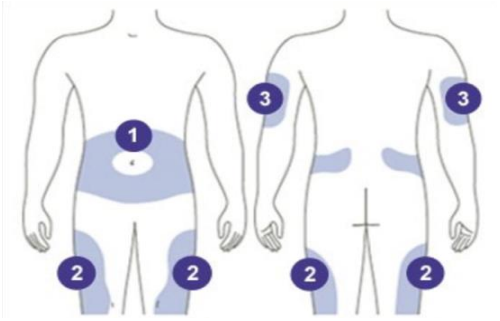

Figure 13: Usual injection sites for CSII use. Abdomen (1), thigh (2), arm (3) (Source : http://www.santeprendrelatete.com/)

Bernoulli's equation in fluid mechanic represents energy conservation among two points along a flow line (see **(3)** and **Fig. 14**). Considering when a reservoir is placed at the same pressure as the outside pressure of the catheter, the velocity of the downstream insulin will be a function of the height. In an CSII device, the interior pressure of the reservoir will determine the impact of hydrostatic pressure on CSII efficiency.

$$P_1 + \frac{1}{2}\rho {V_1}^2 + \rho g z_1 = P_2 + \frac{1}{2}\rho {V_2}^2 + \rho g z_2 \qquad (3)$$

With: $P_1 = P_2 = P_0$,
V_1 considered as negligible from V_2 due to a section of the reservoir compared to a section of the catheter.
$z_1 - z_2 = h$

$$\rho g h = \frac{1}{2}\rho {V_2}^2 \qquad (4)$$

$$V_2 = \sqrt{2gh} \qquad (5)$$

Therefore, in this situation, the action of the pump could be accompanied by a hydrostatic pressure induced fluid velocity of V_2. However, inside a syringe reservoir, $P_1 = P_{piston} \neq P_0$. In such a case, fluid stays at equilibrium, since at resting state, the only pressure that exerts on a fluid is P_0 pushing fluid from the tubing end point (see **Fig. 13**).

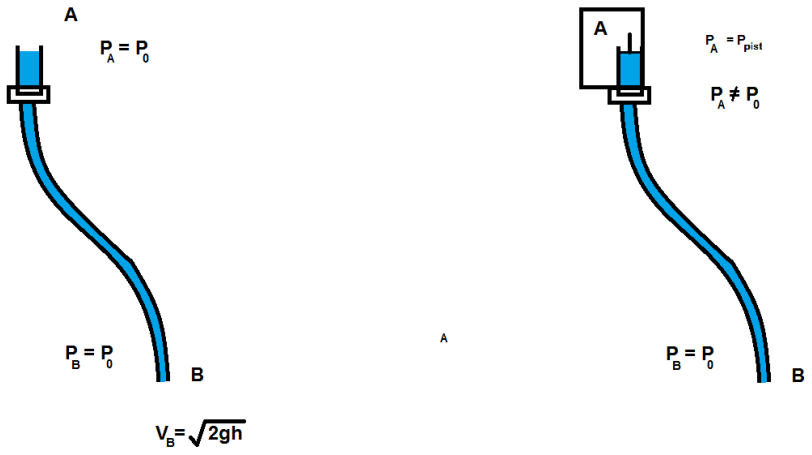

Figure 14: Siphon effect phenomenon adapted to CSII. Hydrostatic effect situation with an open reservoir (left) and with reservoir inside an CSII (left).

NB: At a resting state, rising a pre-filled CSII system above the tubing endpoint does not drive any flow or droplets out.

When a pump is active, flow is not stationery and Bernoulli's equation as presented in **(3)** becomes inapplicable. However, after each insulin stroke, the resting state inside the reservoir is back and V_2 is supposed to be back at 0. Therefore, in terms of this simplistic theoretical approach, nothing indicates that hydrostatic pressure could induce over or sub-delivery.

Zisser *et al.* previously highlighted significant errors when in wired CSII delivery related to height between the pump and the injection site [137]. The authors concluded, "the so-called siphon effect could lead to an over-delivery of up to 74.5% of the expected dose when the pumps were pumping upward and under-delivery up to 123.3% when the pumps were pumping downward." There are currently no other scientific publication confirming or counter to this statement. Subsequently, King *et al.* noticed that the ascent phase of an airplane could lead to a maximum 1.4 UI over-delivery due to cabin pressurization [138]. This supplementary information could indicate that environmental pressure is likely to disrupt CSII performance.

4.1.2 Main goal

Using our novel CSII assessment methodology, we aimed to confirm or identify potential CSII delivery bias driven by the height difference between injection site and the device.

4.1.3 Materials & methods

Delivery accuracy of a Tandem® t:slimX2™ and Ypsopump™ was assessed at several height differences. The catheter end-point of the CSII was placed at either the same height of the injection site (condition H^0/control) or 30 cm above the injection site height (H^1 condition) or 45 cm below the injection site height (H^{-1} condition) (see **Fig. 15**). Height values were chosen arbitrarily based on a typical CSII device use. We integrated the preliminary results of Medtronic® Minimed™ 640G based on the same protocol, but with a measurement method. This specific model assessment only benefited from volume measurement using the MT XPE56 weighing scale.

The Ypsopump™ and Tandem t:slimX2™ test time from from 1 h to 3 h (see **Table**), which were assessed using a double reading and KF-based bench test. The Minimed™ 640G test lasted

24 hours. The programmed basal rate was 1 UI/h and the pump was filled with colored grade III medical water (degasified, purified) instead of insulin. Grade III water is a standardized purified water recommended for laboratory testing protocols including the IEC 60601-2-24 standard [139]. Its physical properties are close to insulin (see **4.2.4**).

Global mean% errors for overall test was considered to render pump accuracy. A boxplot for each CSII system compares mean% errors regarding height conditions.

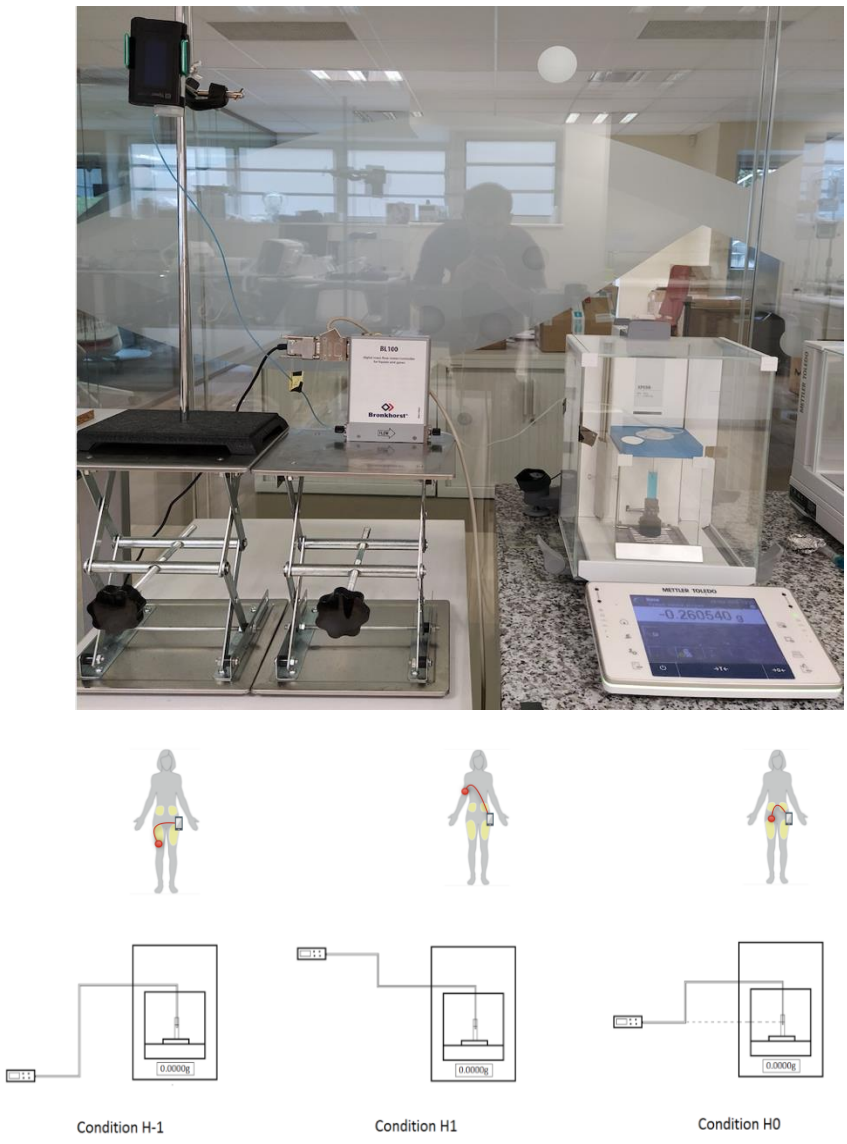

Figure 15: Setup relative to each height conditions. Photo setup example in configuration H1 (up) and scheme describing test conditions with: condition H-1 model pump upward situation (left), condition H1 model pump downward situation (center) and condition H0 model control situation with no height difference (right).

Hydrostatic Pressure Results		640G – 1UI/h			Ypsopump – 1UI/h			Tandem t:slim – 1UI/h		
		Mean% (time(h))	MARD %	p-values	Mean% (time (h))	MARD%	p-values	Mean% (time (h))	MARD%	p-values
Hydrostatic downward (H1)		1.26 (24) 1.73 (24) 2.62 (24) 2.45 (24) 5.23 (24) 2.38 (24) -0.41 (24) 0.39 (24)	NA	0.13	-18.13 (1) -3.57 (1) 4.49 (1) 7.65 (1)	32.735 1.496 4.234 14.127	0.73	-1.09 (1) -3.31 (1) 0.75 (1) -0.38 (1) -1.15 (1) -6.03 (1)	1.709 7.435 21.768 22.877 9.602 10.15	0.58
	O_Mean (SD)	**1.9 (1.6)**	NA		**-2.39 (9.9)**	**13.0 (12.2)**		**-1.8 (2.2)**	**12.2(7.6)**	
Control H0		1.28 (24) 0.8 (24) 1.6 (24) 0.6 (24) 1.72 (24) 1.28 (24) -1.76 (24)	NA	0.61	-1.5 (8) -1.6 (8) 3.5 (8) -1.5 (8)	12.2 8.9 9.0 8.0	0.70	2.45 (8) -5.1 (8) -1.2 (8) 0.4 (8)	19.9 7.2 15.7 7.9	0.14
	O_Mean (SD)	**-0.78 (1.10)**	NA		**-0.2 (2.2)**	**9.5 (1.6)**		**-0.9 (3.2)**	**12.7 (6.2)**	
Hydrostatic upward (H-1)		-4.6 (24) -2.23 (24) 3.02 (24) -1.3 (24) -0.61 (24)	NA		-13.54 (1.5) 2.48 (1.5) 7.03 (1.5) 6.15 (1.5) 5.50 (1.5)	15.3 8.5 21.9 12.8 10.7		-4.37 -2.85 -3.15 -3.90	13.68 8.095 6.894 29.054	
	O_Mean (SD)	**-1.1 (2.4)**	NA		**1.5 (7.7)**	**13.8 (4.6)**		**-3.5 (0.6)**	**14.4 (8.8)**	

Table 3: Overall data for CSII accuracy under hydrostatic pressure condition. Each model is tested under hydrostatic pressure conditions (H1, H-1, H0 (control)) along several replicas. Individual means and MARDs (except for 640G) errors of each replica are calculated. Overall mean (O_Mean) and standard deviation (SD) of the replicas mean and MARD for a given pump/condition is then considered. P_values comparing control and H1/H-1 mean errors distribution are also displayed.

4.1.4 Results

For all CSII systems (Minimed™ 640G, Tandem t:slimX2™, Ypsopump™) the boxplot representation of mean error distribution for each replica in each condition highlighted a **non-significant difference between control group and H^1, H^{-1} height conditions**. Individual data, p-values and test settings are shown in **Table** .

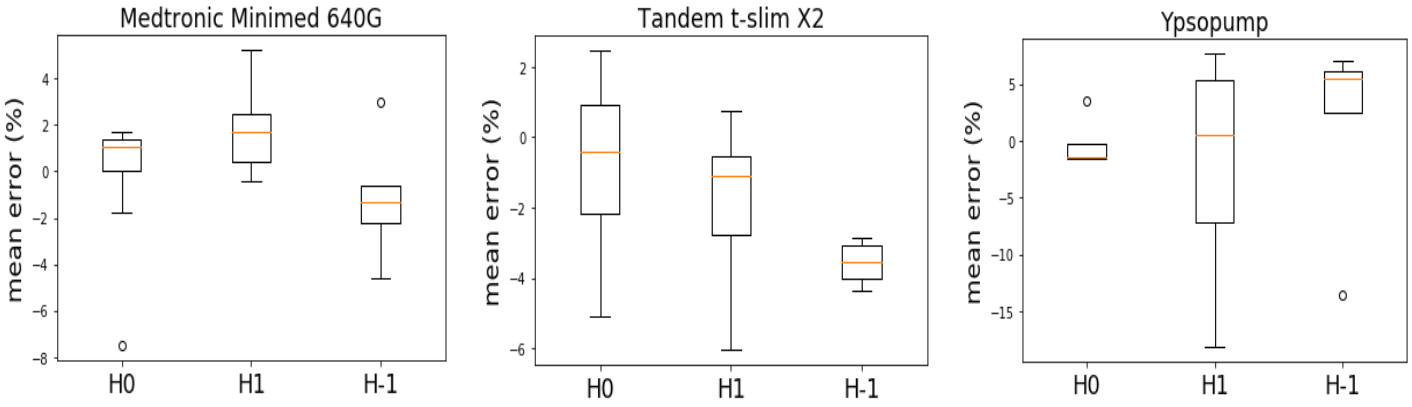

Figure 16: CSII delivery error under hydrostatic pressure constraint. Pourcentage of each test's mean error for Tandem t:slimX2™, Ypsopump™ and Minimed™ 640G at each height conditions (H0, H1,H-1)

Results for Minimed™ 640G are in accordance with Zisser *et al.* results since H^1 et H^{-1} conditions suggest respectively a tendency to over-/sub-deliver (see **Fig. 16**). However, p-values for these results as not significant (see **Table 3**).

There were no significant differences in insulin strokes (frequency and volume units) noticed for peak-wise analysis on hydrostatic conditions intrinsically to Tandem t:slimX2® and Ypsopump™ ($p_{peak\_vol}(ypsopump\_H^1\_H^0)$ = 0.1, $p_{peak\_vol}(ypsopump\_H^{-1}\_H^0)$ = 0.4, $p_{peak\_vol}(tandem\_H^1\_H^0)$ = 0.2, $p_{peak\_vol}(ypsopump\_H^{-1}\_H^0)$ = 0.05) (**Fig. 17**).

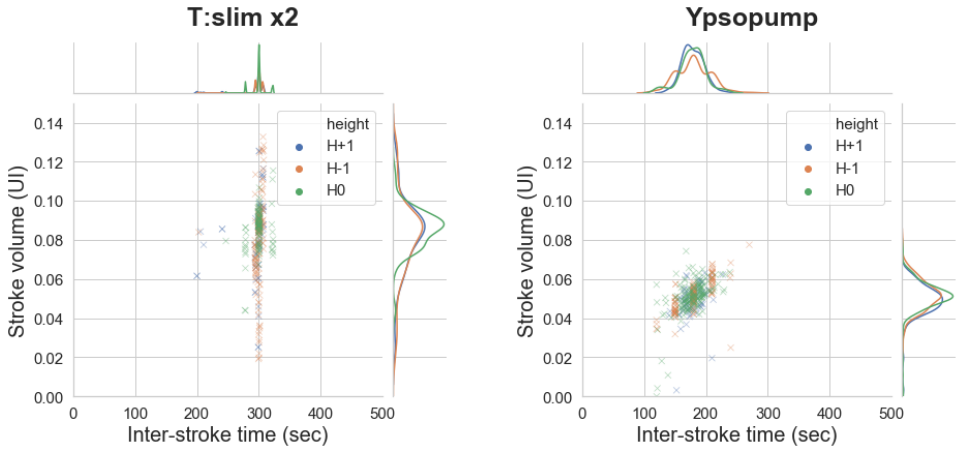

Figure 17: Peak-wise analysis of pump precision for hydrostatic pressure conditions. Tandem t:slimX2™ (right) and Ypsopump™ (left) insulin stroke delivery parameters (volume and frequency) were compared for each hydrostatic pressure conditions.

4.1.4 Discussion/Conclusion

It is worth noticing that the Medtronic® assessment was done without a KF-based test bench due to preliminary results. However, 0.5 minutes weighing scale measurement is totally sufficient to obtain a global mean error for each test measurement. Moreover, the KF-filter test bench mean error analysis is also based on optimized weighing scale volume. Hence the mean error results from Medtronic® 640G, Ypsopump™ and Tandem are based on the same measurement and are totally comparable.

Despite a slight similarity with Zisser *et al.* results for Minimed™ 640G, our results suggest that hydrostatic pressure does not have any significant effect on Ypsopump™, Tandem and Minimed™ 640G CSII accuracy ($p\ (640G\_H^{1}) = 0.13$, $p\ (640G\_H^{-1}) = 0.61$). It is worth noticing that the Minimed™ 640G testing campaign was performed with a high consistency: respectively 5, 7, 8 replicas for H^{-1}, H^{0}, H^{1} for 24 hours each.

Reconsidering the pressure airplane phenomenon studied by King *et al.*, their scenario deals with a high pressure change in a few minutes (ascent and descent phase). A change from 750 to 560 mmHg in an air cabin is not comparable with our situation at below 1 meter and constant. As such, a T1D alpinist or hikers would probably not experience "error doses" since our results suggest that local hydrostatic pressure has no effect on CSII accuracy and actually King *et al.* did not observe that phenomenon along the whole "modeled flight" (only for quick pressure changes).

4.2 Influence of temperature

Over the course of this three-year project, the influence of temperature on CSII delivery performance has been investigated several times. In the literature, the stability of an insulin analogue has been questioned regarding temperature variations (TV) [140], high summer temperature has been associated with hospitalizations in T1D [141], and intra-dermal temperature has also been related to insulin absorption [142]. Hence, TV may play a role in

insulin-treatment success. However, no existing literature has confirmed or excluded that CSII delivery in itself could be altered by TV.

CSII users are constantly subject to TV. Herr *et al.* studied CSII reservoir TV during different seasons. The average temperature was around 30°C regardless of season. Herr measured extremal reservoir temperatures at 36.8°C and 16.5°C when outside temperatures were respectively 43.8°C and 2.2°C [143]. This crucial information was gathered in a single place (North Carolina, USA) and seasonal data collection lasted 7 to 14 days with 3 to 5 volunteers.

Nowadays diabetic patients, especially young CSII users, have expressed a strong desire to live a normal life and control their diabetes while pursuing worldwide adventures (i.e., the hashtag tslim in the wild for the Tandem t:slim users community #tsliminthewild) [144] and numerous blogs that highlight these needs of the diabetes community [145]–[147]). We imagine that in the coming years, CSII systems will be utilized in increasingly extreme temperature conditions, such as at 2.2°C. Indeed, hiking or alpinism experiences could rapidly encounter conditions from -10°C (outside) and 40°C (close to the body within da own sleeping bag) and thus expose the device to large temperature changes. Accordingly, we investigated whether temperature changes affect CSII accuracy.

4.2.1 Main goal

We tested CSII delivery accuracy under a specific case temperature condition with cyclic variation from 5°C to 35°C.

4.2.2 Materials & methods

A “freezing oven” (Hettich Hettcube 200R) also called an incubator was programmed to change its inside temperature from 5°C to 35°C. The test pump was placed inside the incubator and near the measurement instruments (see **Fig. 18**).

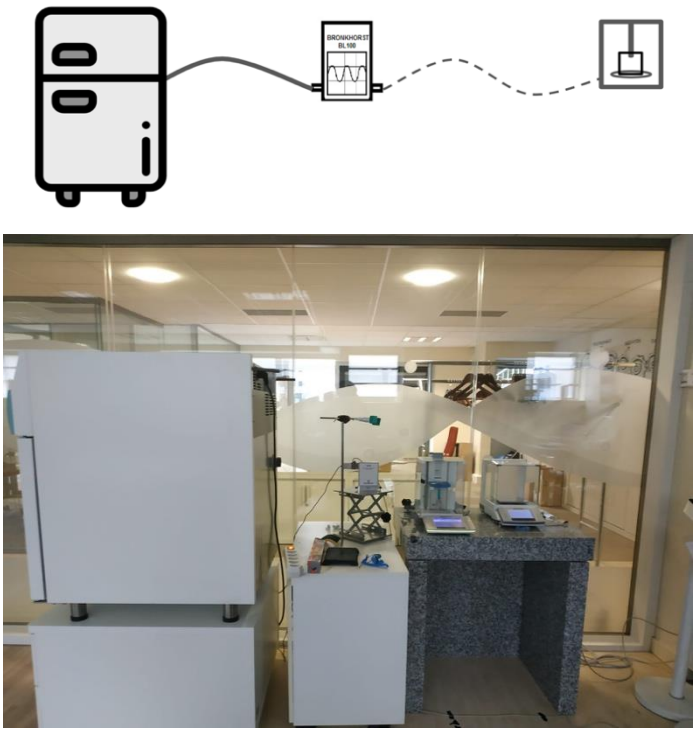

Figure 18: Testing setup for CSII precision assessment under temperature constraint. CSII is placed inside a programmed incubator that change temperature from 5°C to 15°C every hour. CSII flow rate is assessed using the KF-based double reading bench test.

Ypsopump™, Tandem® t:slimX2™ and Minimed™ 640G were tested for 8 hours with three replicas at 1 UI/h (4 replicas were performed for Minimed™ 640G) under these conditions. For practical reasons, only wired pumps were tested. The temperature inside the incubator was also measured using a temperature probe (Testo® 175-H1). Colored-water was used for the majority of tests to only focus on CSII system alteration. Other 1 x 12 hour tests was performed with insulin using Minimed™ 640G and Tandem® t:slimX2™ to compare insulin and water delivery.

4.2.3 Results

Delivery flow rate and volume were highly associated with TV for Medtronic® 640G and Ypsopump™ (**Fig. 19**)**.** The overall flow rate follow TV with respectively smaller and higher delivery for the lowest and the highest temperatures. Stroke amplitude was also significantly different with TV (p_value (640G) << 10^{-5}) (**Fig. 22**). This mis-delivery has a direct impact on error during the experiment (see **Fig. 20**) and global errors. The MARD error is significantly

higher with temperature change for the two tested pumps (p_value (640G) < 10^{-3}, p-value (Ypsopump) < 10^{-3}), while the global mean error over an 8-hour experiment were not significantly different than control (p_value (640G) = 0.78, p-value (Ypsopump) = 0.56) (See general results in **Table 4**). The Tandem® t:slimX2™ had non-significant differences in accuracy for TV (p_value (Tandem, MARD) = 0.16 , p-value (Tandem, mean) = 0.02). The insulin versus colored-water test had no significant impact on delivery accuracy (see **Fig. 21**).

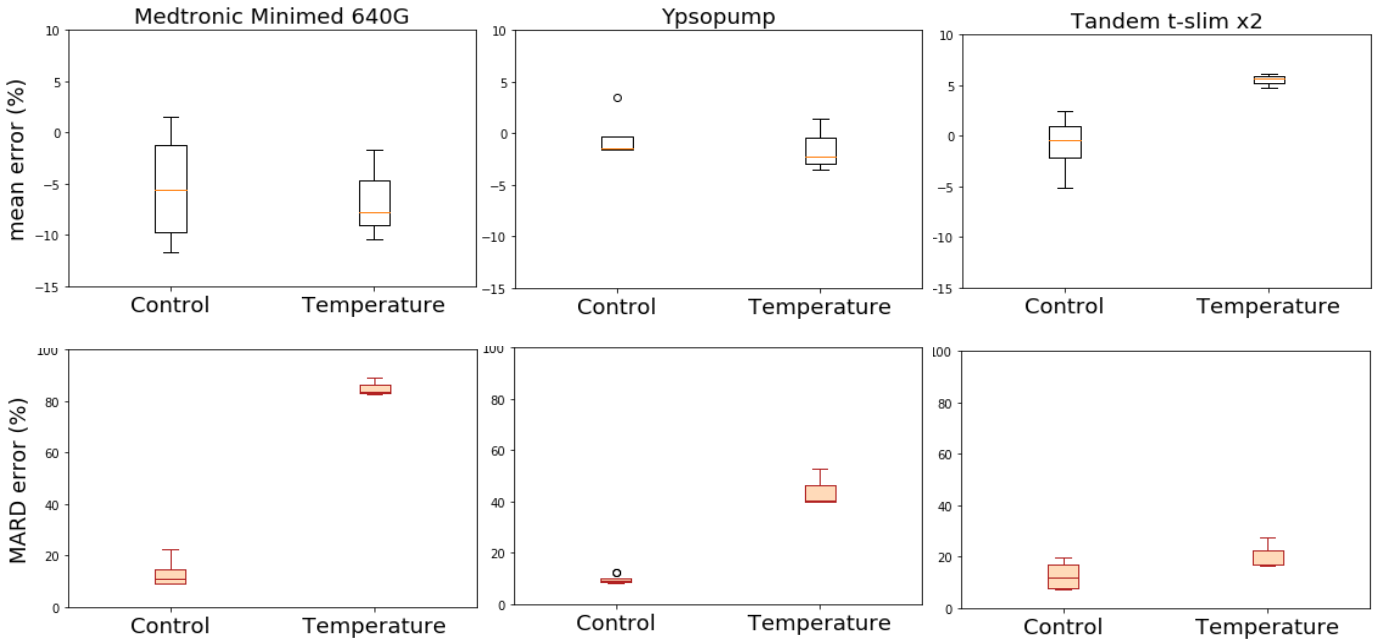

Figure 19: Pump delivery error for temperature variations. MARD (down) et mean (up) delivery error boxplot for Medtronic® Minimed™ 640G (left), Ypsopump™ (middle) and t:slimX2™ (right).

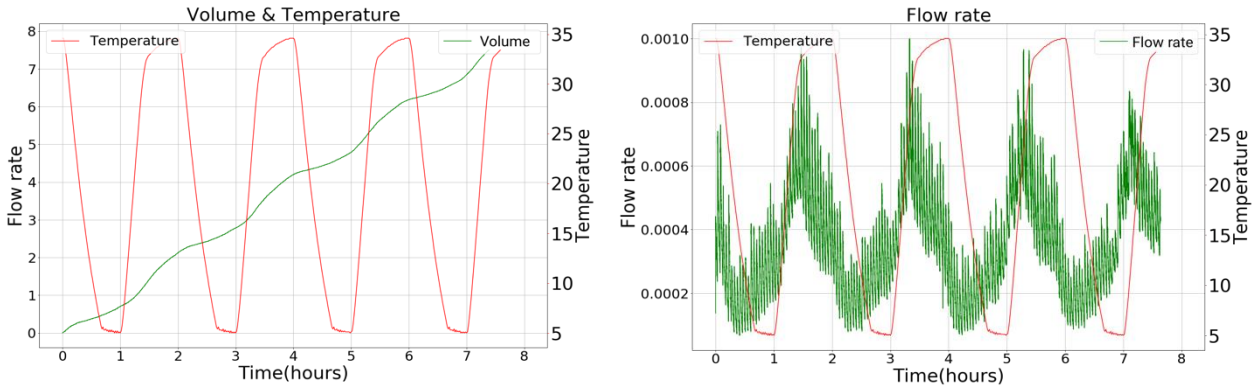

Figure 20: Flow rate and volume of CSII delivery following temperature variations. Temperature variations (red) from 5°C to 35°C is correlated with volume (green – left) and flow rate (green - right) CSII delivery.

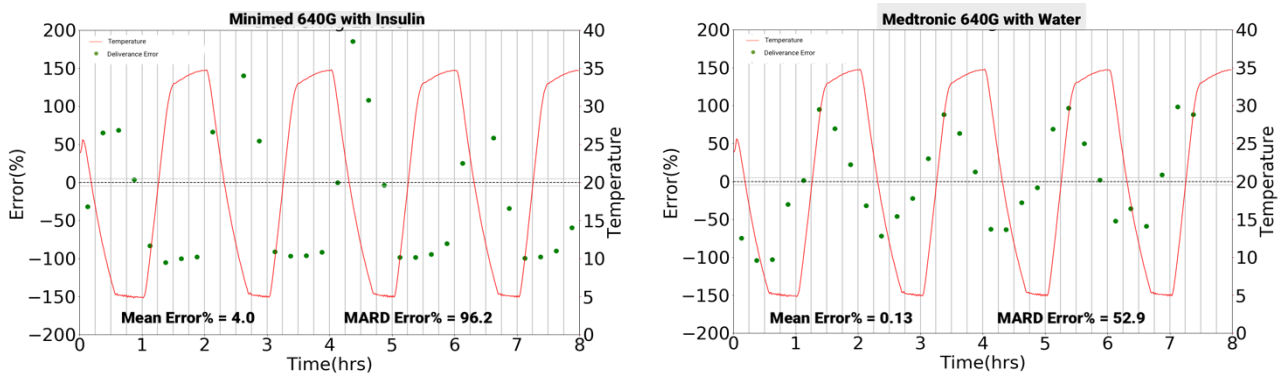

Figure 21: CSII delivery error under temperature constraints with insulin versus water. 15-minutes time interval delivery errors are calculated along experiment. Based on examples of Minimed™ 640G tests, we compare temperature variations constraint on CSII accuracy using water (right) and insulin (left).

Temperature Variation (TV) Results		640G – 1 UI/h			Ypsopump 640G – 1 UI/h			Tandem t-slim 640G – 1 UI/h		
		Mean% (time (h))	MARD%	P_value	Mean% (time (h))	MARD %	P_value	Mean% (time (h))	MARD %	P_value
Control		-1.5 -9.1 -2.3 -11.7	12.2 9.1 9.4 22.5	**0.13**	-1.5 -1.6 3.5 -1.5	12.2 8.9 9.0 8.	**0.73**	2.45 -5.1 -1.2 0.4	19.9 7.2 15.7 7.9	**0.58**
	O_Mean (SD)	**-6.1 (4.3)**	**13.3 (5.4)**		**-0.2 (2.2)**	**9.5 (1.6)**		**-0.9 (3.2)**	**12.2 (7.6)**	
T° variations		-10.41 -2.68 -7.76	83.54 89.32 82.87		-3.55 -2.31 1.43	52.9 40.0 40.2		4.7 6.1 5.6	27.7 16.9 16.5	
	0_Mean (SD)	**-6.9 (3.9)**	**85.2 (3.5)**		**-2.43 (1.06)**	**44.4 (7.4)**		**5.4 (0.6)**	**20.4 (5.2)**	

Table 4: Overall data for CSII accuracy under TV. Ypsopump™, 640G and Tandem t:slimX2™ model were tested with and without TV conditions along several replicas. Individual means and MARDs (Errors of each replica are

calculated. Overall mean (O_Mean) and standard deviation (SD) of replica mean and MARD for a given pump/condition is then considered. P-values comparing control and TV mean error distribution are also displayed.

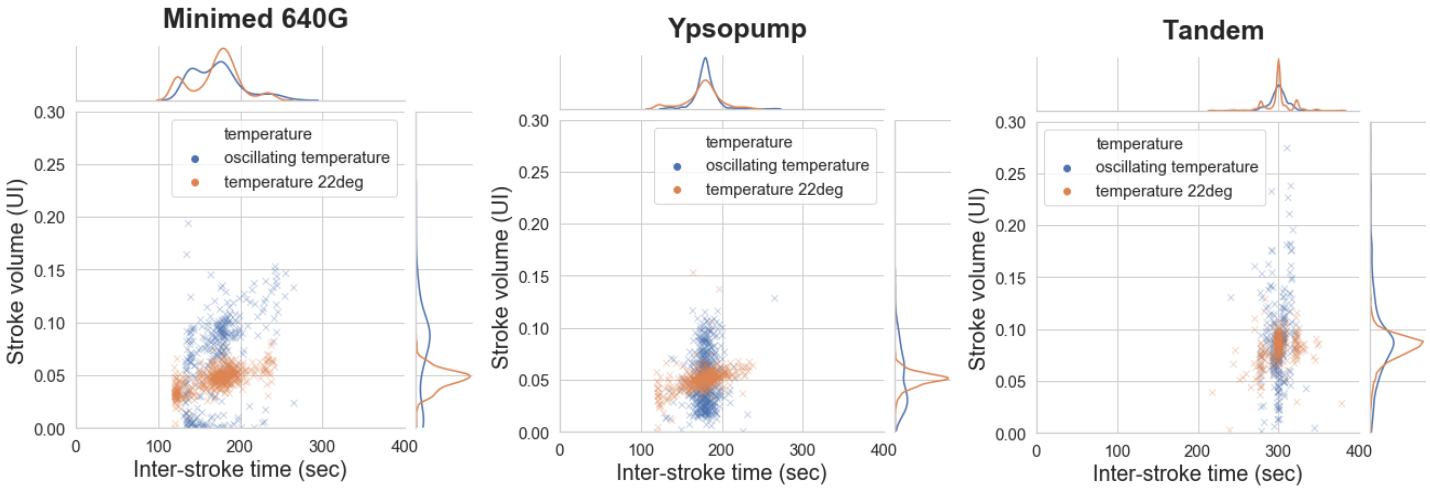

Figure 22: CSII delivery stroke analysis under TV conditions. Volume delivered for each stroke as well as time between each stroke is compared for CSII with (red) and without (blue) TV constraint for Minmed® 640G (left), Ypsopump™ (middle) and Tandem t:slimX2™ (right).

4.2.4 Discussion

TV has an unexpected and important effect on CSII accuracy. For two out of three pumps and along several replicas, flow rate amplitude strictly followed TV. This variation has an important effect on MARD errors due to the high variations and might drive to GV. Nonetheless, our TV scenario was designed as a worse-case situation and it is unlikely that CSII users experience such drastic situations. However, it is worth being aware of CSII performance under TV and a situation with some similarities to this extreme scenario may be applicable in certain specific life situations.

Despite some slightly higher inaccuracies, Tandem® t:slimX2™ was not as impacted by TV as Ypsopump™ and Minimed™ 640G. The mechanism of Ypsopump™ and Minimed™ are both based on an endless screw that drives a syringe cartridge. The Tandem® t:slimX2™ uses a infusion chamber trolley technology. This difference raises the possibility of a link between delivery mechanism and enhanced TV inaccuracy.

When considering various conditions, the infused liquid itself could impact delivery. However, our results suggest no differences in CSII performance between insulin and water. Moreover, insulin and water viscosities that could impact delivery are comparable and do not change considerably in terms of TV. Insulin analogue viscosity have been determined at 20°C around 1.1 mPa s [148]. This value remains highly equivalent to water viscosity, which oscillates

between 1.5 and 0.7 mPa s from 5°C to 35°C. As a comparison, olive oil dynamic viscosity is around 56 mPa s.

The causes of this insulin delivery inaccuracy require additional real-life studies to relate this phenomenon to clinical consequences. For example, a retrospective data analysis of seasonal GI related issues for pump users could reinforce evidence that large winter or summer temperature variations might be associated with higher GI.

More importantly, the place of temperature for in-lab CSII assessment could also be re-considered. A majority of tests (published work as well as IEC 60601-2-24 standard) based their tests on a standard lab temperature (i.e.: 22°C). Nevertheless, as already mentioned, Kerr *et al.* showed an average of 30°C in the surrounding temperature for CSII in daily life use and our results showed accuracy differences for TV. Hence, CSII accuracy has to be compared at fixed temperature (including 22°C and 30°C) and a general protocol should be adjusted accordingly with the results.

The insulin flow rate in advance from temperature measured within the "freezing oven" is shown in **Fig. 20**. Note that the flow rate curve is not in advance, but more than one period after the temperature is measured. This observation is explained by the fact that this 8-hour test is extracted from the largest sequence of the test. Thus, the displayed time of "0-hours" is not the absolute starting time of the experiment. This phenomenon of phase delay should be validated with a smaller frequency in temperature change.

4.2.5 Conclusion

TV unexpectedly affects CSII delivery for some pump models and drives errors likely to induce GI. Causes that result from a particular device mechanism require further investigation and general in-lab CSII assessment could be reconsidered regarding lab temperature in order to assess devices that are closer to actual-use conditions.

4.3 Influence of motion

The constant motion that patients experience on a daily basis may alter CSII delivery, and as such, motion was investigated. CSII users wear the device permanently, and accordingly, there is constant motion. Rising from and lying on bed, getting up from a sofa, or running after a subway are all typical situations likely to be experienced by CSII users and devices need to

operate under such conditions. Intuitively, microfluidic systems may be altered by external motion. An observational study of CSII accuracy under motion conditions has never been performed.

4.3.1 Main goal

This investigation aimed to show whether or not CSII delivery precision is influenced by external motion.

4.3.2 Materials & methods

A 6-axis robot arm was bespoke-designed with an Arduino® Uno electronic card to reproduce simple human motions. We placed each CSII at the extremity of the robot arm and set a basal rate before initiating measurements (see **Fig. 23**). The robot arm was programmed to adopt a single vertical or horizontal translation trajectory repetitively. A catheter was cautiously fixed with a vice to stop vibration induced by robot motion in order not to affect flow measurement.

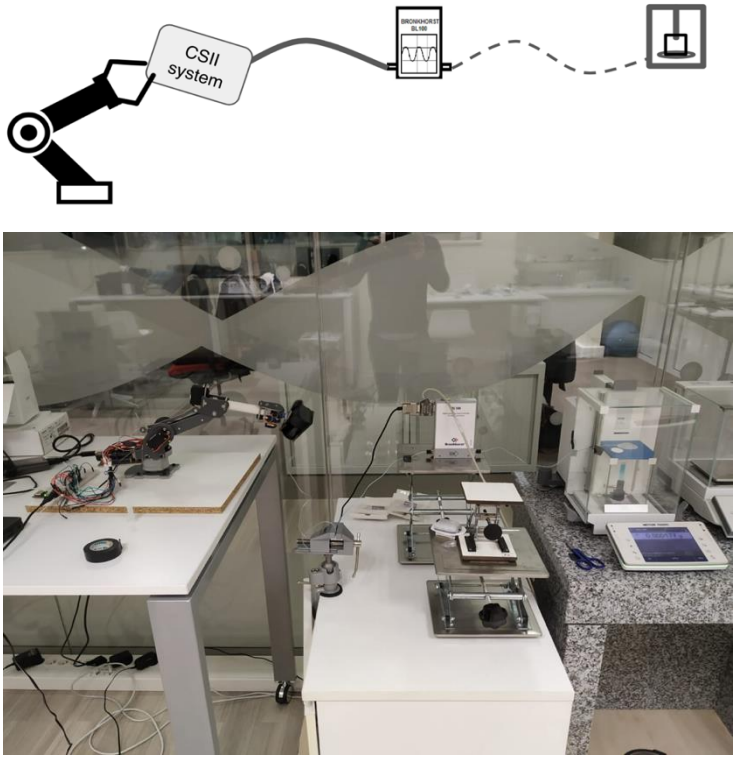

Figure 23: Testing setup for CSII precision assessment under motion constraint. CSII is stuck to an Arduino-based 6-axis robot arm that moved according to pre-programmed motions. CSII

The Medtronic® Minimed™ 640G, Ypsopump™ and Tandem® t:slimX2™ were tested for two hours at 1 UI/h along 3 replicas (8 instances for Ypsopump™). A two-hour test duration was test only for wired pump models due to practical reasons.

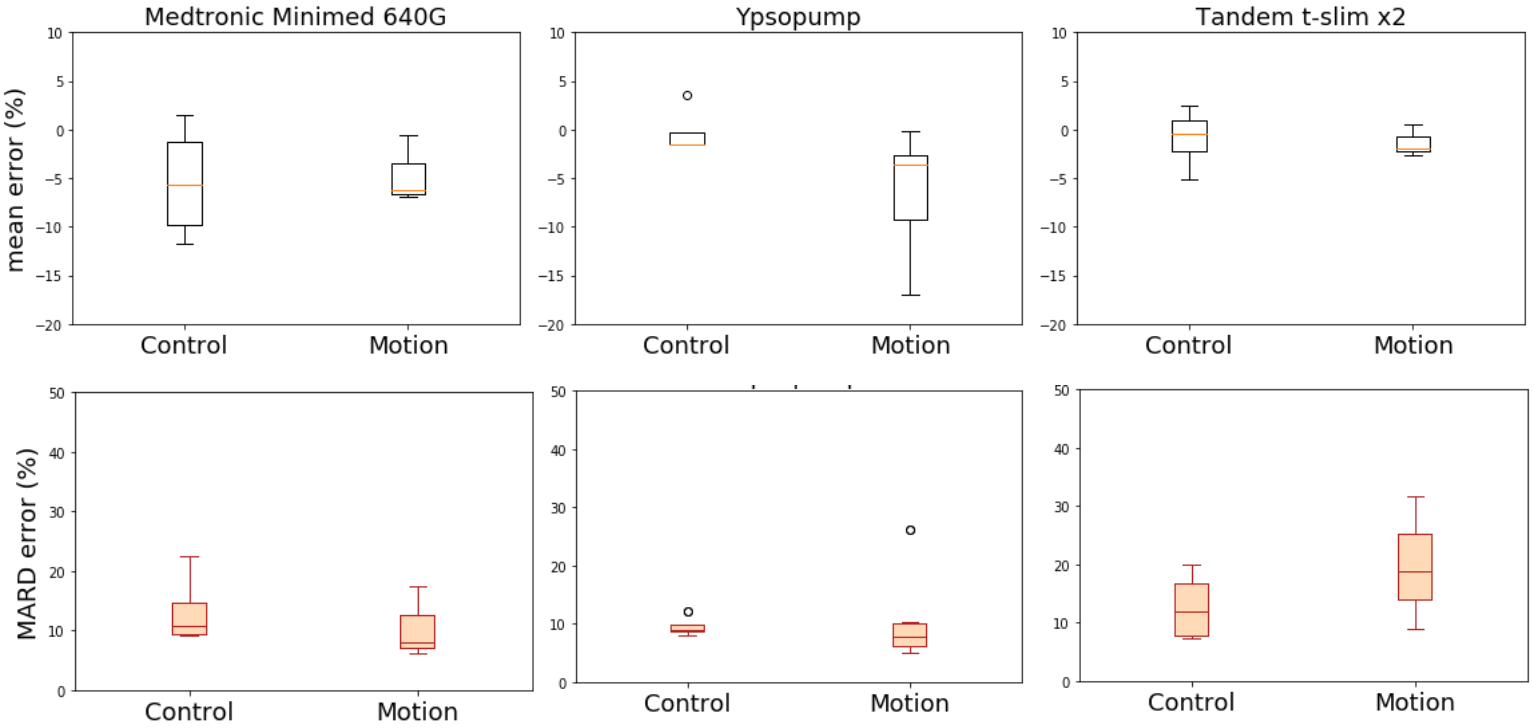

Figure 24: CSII global error delivery under motion constraint. MARD (down) and mean (up) distribution of Medtronic® Minimed™ 640G (left), Ypsopump™ (middle) and Tandem t:slimX2™ (right). Comparison of MARD error distribution without motion (control) versus with motion.

4.3.3 Results

There were no significant differences in CSII accuracy between motion and control groups for all pump models (**Fig. 24**). (p_value_mean (640G) = 0.85, p_value_mean (Ypsopump) = 0.08; p-value_mean (Tandem®) = 0.82). There were also no significant differences for global mean error or MARD error.

4.3.4 Conclusion

Simple horizontal and vertical motions of Ypsopump™, 640G and Tandem t:slimX2™ have no effect on their delivery accuracy. It is worth noticing that the vertical motions induced by dynamic height differences and present results are in accordance with hydrostatic pressure tests. These results can be generalized to all CSII models and for overall motion conditions, nevertheless, more complex motions and other CSII models might be require further studies to confirm this statement.

Chapter 5: An introduction to insulin injection into subcutaneous tissue

Our previously exposed “in lab” CSII assessment went beyond current method protocols and attempted to model daily-life conditions to render a more relevant CSII accuracy assessment approach. Nevertheless, SCT appears to be a central element of insulin infusion and has not been considered in any “in bench” CSII assessment.

5.1 Statement

Insulin SCT absorption, diffusion or even pressure at the injection site could importantly influence CSII performance or at influence CSII imprecision and GI.

SCT diffusion of a bolus of insulin differs according to the initial physiology of the skin [149], age, sex, ethnicity, body mass index (BMI), and also according to the chosen injection site (thighs, abdomen, arms) [150], [151]. Insulin frequently passing through subcutaneous fat tissue can alter the local physiology of the skin and can cause inflammation, immune alterations and lipodystrophies [152], which can ultimately locally modify the mechanical characteristics of the skin and is therefore likely to also affect the behavior of the injected bolus. Finally, the patient daily habits also modify the interaction between the injected insulin and the SC tissue: the micro vascularization of the hypodermis is modified by temperature changes, sports activity, smoking [153] or pressing on the injection site during sleep.

This variability in the behavior of the injected insulin (speed of diffusion, shape of depot) may cause changes in the resulting glycaemia of a particular patient, but could also mean a fluctuating resistance/opposition to the flow from the pump itself, and therefore cause a variability in the pump’s behavior. The impact of the stroke-based delivery of insulin on the SCT absorption, SCT depot formation and ultimately, insulin passage to the bloodstream and metabolization is unknown.

5.2 State of the art

5.2.1 Subcutaneous injection of insulin

Several studies have focused on the SCT injection site of insulin. They all used porcine tissue for testing and are centered on the impact of the injection parameters on the morphology of the injected bolus (injection speed, needle length [154], [155] injected tissue [155], injected volume [156]). However, none of the chosen values for these parameters are representative of the specific injection parameters of CSII delivery, and actually apply to other insulin delivery systems such as a pen or syringe.

These studies constitute however a thorough resource for imaging methods and exploitation of the acquired data. Depending on which imaging method was chosen, the acquired data can either be static, and is then used to characterize the state of the bolus at the end of the injection [156], [157], or dynamic throughout the injection [155].

Only one of these studies focuses on a delivery by CSII [156], but a bolus is injected, rather than a basal delivery, which is more specific to common CSII use. The study used histological cuts as an imaging method, and therefore, does not allow a temporal follow up of the injection. Injected volume varies, and the region is or is not massaged, to see the impact on the final shape of the depot.

It is necessary to study effects on human skin tissue rather than porcine tissue, with continuous data acquisition throughout the injection. The absence of blood flow in the *ex vivo* samples are also a major limitation in previous studies of insulin diffusion.

5.2.2 Impact of catheters on SCT

Studies carried out on catheters and their impact on the SCT cell state [158], [159] used CSII as an injection device, and injection was performed *in vivo*. These are the major assets of these studies. They implemented histopathological analysis for several choices of catheter, and after several days of use, on swine. The impact of parameters such as material or shape of the cannula were linked the evolution of the PK of insulin throughout the days to the state of skin tissue around the injection site.

Finally, Hofman's work [160], [161] studied the impact of length and canula characteristics on particular skin tissue (epidermis, dermis, hypodermis or muscle) when actually injected, depending on age, sex and BMI. These considerations underline the fact that the hypodermis is not always the only targeted tissue for injection. When it is not, the diffusion of insulin can be hindered, and this phenomenon is an additional factor for variability in insulin absorption.

5.3 Goal

Whether back pressure is involved in skin end-point and the influence on insulin delivery was investigated. Pressure profiles were also studied for when CSII is or is not delivered with a skin end point. This work paves the way for future studies on overall skin tissue delivery features regarding CSII delivery performance.

5.4 Materials & methods

As described in **Fig. 25**, a CSII system was set to deliver within a fresh piece of swine tail. For a Minimed™ 640G and an Ypsopump™ CSII model, 15 boluses of 2 UI were injected within the skin (3 boluses within 5 different injection sites) and 15 within a water reservoir. Water reservoir infusion constitutes the control test since the usual standard protocol uses in-water delivery. Mainly for practical purposes due to the weighing scale measurement instrument, the setup for control was similar to **Fig. 25** with a reservoir of water instead of skin tissue. Colored grade III water was infused instead of insulin for practical purposes.

We measured pressure profiles out of the pump (P1) and close to the injection site (P2). The pressure sensors are Microfluidic Pressure Sensors from Elveflow Co. A full-scale implementation of the instrument provide 1 psi (70 mbar) with an accuracy of 0.2% of full scale value. Flow rate was measured by a Bronkhorst BL100 apparatus. Only a bolus was injected in this study. For instance, a 2 UI bolus (injected within approximately 2 min) represents a flow rate value of 300 microliter/h. Metrological considerations resulted in a 0.3% error in reading value for that range (see **Supplemental Data 1**).

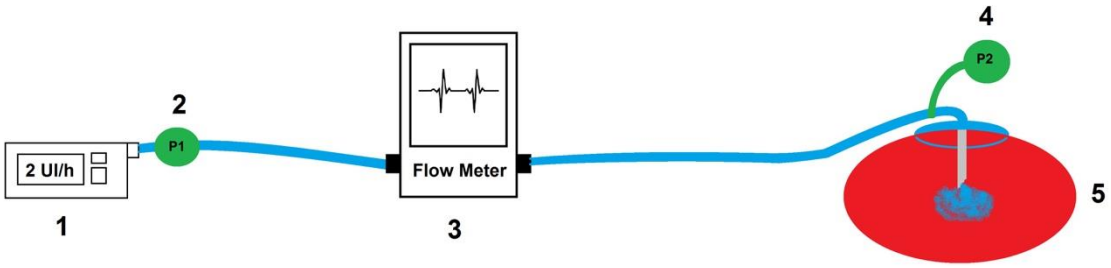

Figure 25: Back pressure distribution for CSII delivery setup. An CSII (1) delivers within a swine skin tissue (5). Pressure profiles is measured out of the pump (2) and before injection site (4). Flow rate is also considered (3).

5.5 Results

Insulin pressure differential between CSII and infusion site was noticed as a simple offset of a few millibars (~10 mbar). This correspond to pressure losses induced by the fluid path and flowmeter.

Within the swine skin, pressure became significantly higher for each insulin stroke infusion and reached a plateau (see asymptotic behavior). Sometimes, and exclusively for new injection sites, pressure collapses at some point during delivery to reach a lower plateau (see skin break-point phenomenon **Fig. 26**). We will refer to this phenomenon as a "skin breakpoint" (SB).

The pressure profile and values of CSII infusing in the water reservoir (control), were significantly different that those delivering in skin tissue (see **Fig. 26** and **Fig. 28**). However, these results did not reveal a significant impact on delivery error (see **Fig. 26**).

Additionally, we observed significantly different pressure profile delivery distribution within skin tissue between the Minimed™ 640G and Ypsopump™ (see **Fig. 28** middle). Renewing the injection site had also a significant effect on pressure profile distribution (see **Fig. 28** right).

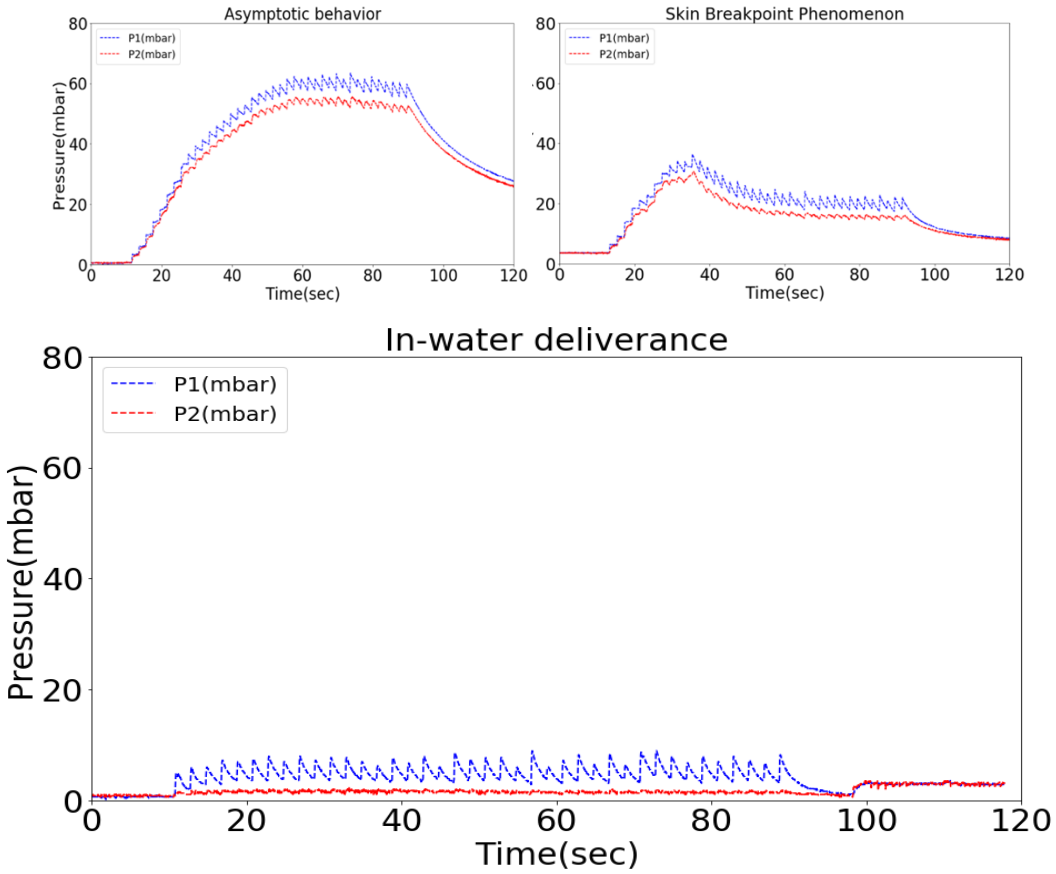

Figure 26: Up stream and down stream pressure time-series example of CSII infusion within skin tissue (up) and within water reservoir (down). Identification of two intra-skin pressure delivery: asymptotic pressure behavior (up left) and skin breakpoint phenomenon (up right).

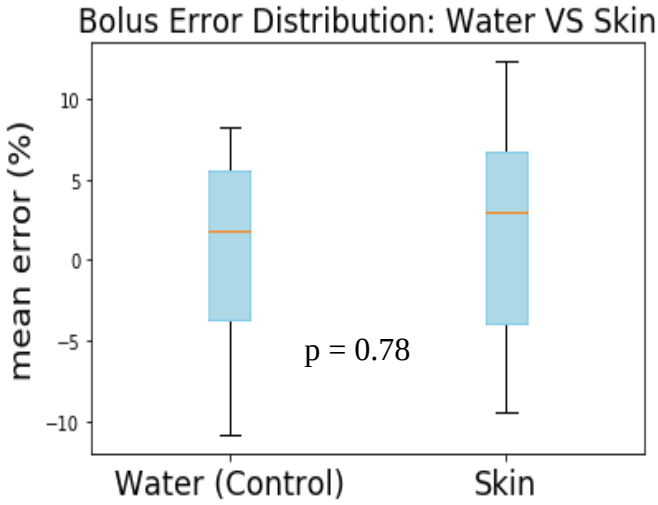

Figure 27: Bolus error distribution: skin injection vs in-water injection. 2UI boluses were infused within skin tissue (right) and water reservoir (left) end points. Delivery error distribution for each situation based on flow rate measurement integration were compared.

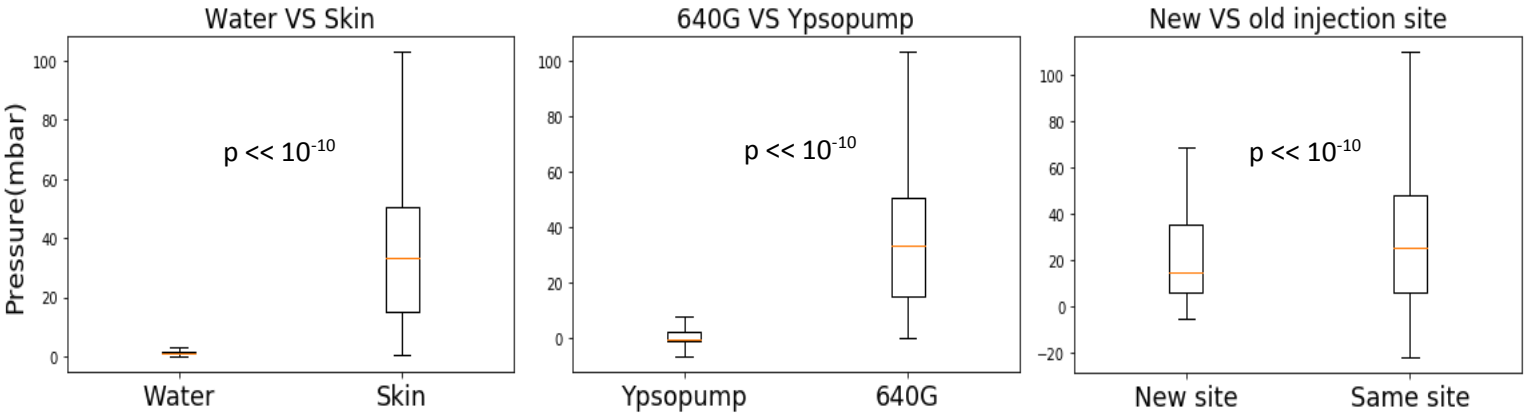

Figure 28: Down Stream pressure distribution. Pressure distribution comparison between an intra-skin and in-water reservoir (left), 640G and Ypsopump™ CSII model (middle) and within a novel injection

5.6 Discussion

Global errors in delivery within skin were not significantly different than in-water delivery and overall errors were in accordance with previous studies [28]. Regarding pressure distribution (**Fig. 28**) and the pressure time-series (**Fig. 26**), the previously defined skin-breakpoint phenomenon suggests that for some place within SCT, insulin pressure could accumulate within a SCT depot, thus increasing local pressure, which suddenly drops due to a tissue straining. This hypothesis has already been described and observed by Kim *et al.* [155].

The skin breakpoint for a 2 UI bolus occurs after only 100 seconds. We hypothesize that a patient with low insulin requirements such as 0.1 UI/h could wait longer to reach that same threshold pressure, which is likely to release pressure and create a fluid path within the tissue. If so, could an insulin depot increase SCT pressure and be mis-metabolized due to limited vascular penetration and then suddenly, in a single shot, spread into the tissue to reach systemic circulation? Hence, could SB be responsible for an eventual GI? Freckman *et al.* already mentioned that patients with low insulin requirements may experience GI after each new injection site [28]. However, the skin breakpoint pressure threshold is tissue-type dependent and could highly differ from one individual to another, or even from “lab swine” to human testing. Accordingly, this topic requires further investigation.

Tissue resistance pressure with CSII infusion was previously studied by Patte *et al*. on a real diabetic population and with normal subjects. A constant volume of 0.3 mL was infused at four different infusion rates (0.01, 0.05, 0.1 and 0.5 ml/min) using a Medfusion® 3500 model infusion pump. For bolus infusion, depending on CSII model, the flow rate is around 1 UI/min (0.01 ml/h). Hence, in their study, only the first bolus variation is comparable with the infusion rate experienced by CSII users. Moreover, pulsatile flow rate was not precise. For a 0.01 ml/min case, the authors noticed a 0-50 mbar pressure distribution which is in accordance with our results. However, no phenomenon relative to SB was mentioned [162].

5.7 Conclusion

Insulin delivery within SCT influences fluid behavior. The infusion end-point type – water or skin tissue – did not modify Minimed™ 640G or Ypsopump™ accuracy for 2 UI boluses. CSII in-lab assessment may include *in vitro* or *in silico* tools to more closely approximate a real-life evaluation. The SB phenomenon, likely to occur at each catheter change, could partly explain the GI issue for the first hours of delivery. This phenomenon requires further investigation and only insights and possible hypotheses are mentioned here.

Chapter 6: Discussion

Throughout this research, “in lab” CSII accuracy assessment with a specific care has been investigate to gain a closer approximation to real-life clinical usage. The initial objectives were met and the results and key findings are reviewed below.

6.1 Objectives achieved

Current CSII assessment standard limitations was discussed to elucidate the availability of recent technology to improve measurement accuracy in CSII insulin delivery. A KF-based double measurement optimization method was provided as an example of a solution among many others that could be developed in coming years. The novel method allows for the first time the measurement of continuous delivery at the lowest flow rate with acceptable measurement uncertainties.

This solution was essential to consider the most challenging flow range for an infusion mechanism, namely the flow range that is used by patients with the lowest insulin needs and what happens in such cases to give rise to delivery errors. Our results associated the biggest errors to the smallest basal rate range. As previously shown, the importance of the errors were also noticed to be device-model dependant.

Continous measurement allowed for the first time, a fine insulin peak-wise analysis to decipher manufacturing choices for insulin infusion as well as partial deduction of delivery causes for global errors. For instance, we confirmed that for the smallest basal rate, in some CSII models, such as Omnipod®, keep the same stroke-unit volume and adapt the frequency of peak delivery. This manufacturing choice might have clinical consequences since a “high” insulin volume unfrequently delivered to the patient could induce over-dose and under-dose sequences.

Accordingly, there may be clinical impacts associated with technical issues in some manufacturing choices. APS adapts CSII dose order every 5 to 15 minutes and such an unfrequent-stroke delivery mechanism could not be modified. Hence, it is vital to precisely analyze CSII accuracy to gathering insights and anticipate treatement efficiency.

Beyond improving measurement performances, the limits and extent that the current gold standard methodology reflects conditions experienced by patients on a daily basis was clarified. We developed in-lab tools and simple protocols to test CSII accuracy under such conditions. For example, a 6-axis robot arm was developed to place the device under typical human motion conditions and an incubator was used to mimic daily-life temperature variations. Hydrostatic pressure and skin endpoint back pressure effects were also tested. Hydrostatic pressure and motions were found not to influence CSII accuracy. The bolus-based skin end-point assessment found that this did not alter CSII accuracy. TV unexpectedly caused important CSII delivery alterations. It is important to raise awareness regarding daily-life conditions that are likely to alter CSII delivery. Such consideration is essential for patient safety and comfort, and reduce overall GI. In the literature, there are only a limited number of studies looking at CSII assessment with in-lab models of real-life conditions.

Graphical representation of CSII accuracy results is also important for many reasons. Such data has to be understood at a glance by an heterogenous population and provide accurate information that supports clinical interpretation. Further discussion and collaboration between physicians and engineers can raise awareness about the importance of CSII accuracy and potential clinical consequences.

As previously explained, indicators such as overall mean of delivery or trumpet curve are limited or do not represent CSII accuracy from a clinical point of view (see **1.3.1**). In the same manner as Kamecke *et al.*, we proposed indicators such as MARD or evolutional MARD, which are more likely to inform about clinical consequences related to delivery accuracy. Since glycaemic excursions are likely driven by delivery error and will undoubtebly be different for two given patients, it is key to represent CSII error with several interpretations.

Evolutional MARD provides information regarding general CSII delivery instability over several metabolization time windows. Using this graphical representation shows that some CSII devices, especially at the lowest basal rates, smooth errors rapidly, which could be compensated by metabolization time. Meanwhile, other devices experience more long-term errors that are more likely to participate to GI. Similarly, Kamecke *et al.* proposed a 1 h boxplot error distribution to render errors that could drive to GI. This representation may be more accessible since boxplots are commonly used by the scientific community. However, our evolutional MARD has the advantage of providing a global time representation of CSII innacuracies. This

research introduces the response of real-life constraint consequences on CSII delivery that are likely to cause GI. However, more research is necessary to determine the most clinically helpful graphical representations of CSII accuracy.

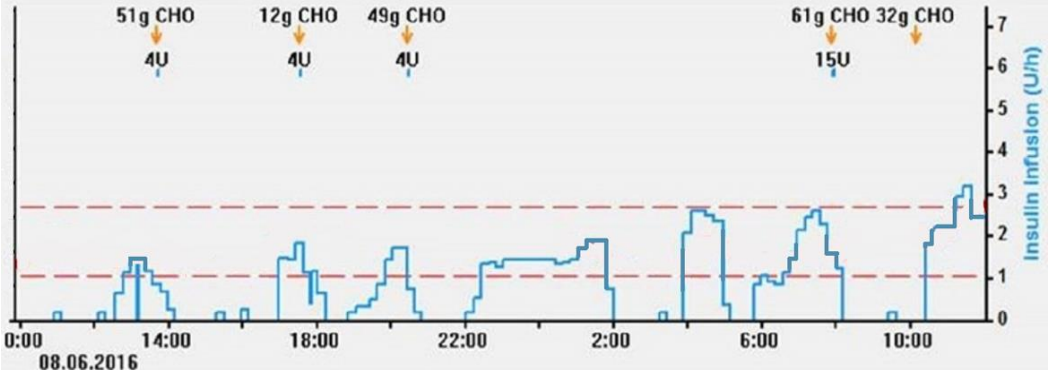

Figure 29: APS insulin delivery profile. APS constantly adapt insulin order of CSII. (Source: Bally L & al, Int J Pharm. 2018 Jun 15;544(2):309-318).

6.2 Results discussion

In the following discussion, we comment in-depth and contextualize some of our findings to provide a broader context and to support future research.

6.2.1 Peak-wise analysis

Zisser *et al.* showed that a 30-minute CSII interruption has a significant impact on glycemic excursions [163]. As previously mentioned, our peak-wise analysis showed that some pump mechanisms have the potential of experiencing difficulties with low-dose infusion. Some devices would have made the choice to adapt insulin frequency with the same stroke dose volume. Hence many mechanisms, when programmed at 0.1 UI/h infuse a single unit of 0.05 UI each single half hour. Following the same idea, a 0.05 UI/h basal rate should give a single dose every hour.

Patients with low insulin needs are likely to be more sensitive and metabolize the hormone faster than other diabetic populations [164]. A 1 UI injection was shown to be half-metabolized

within 30 minutes by a “normal” diabetic population [165], suggesting that 0.1 UI could be faster**.** Hence, receiving “strong” insulin volumes within small amount of time with long breaks in-between might encourage glycemic instability on a specific T1D population. Some CSII device mechanisms for the lowest basal rates infusion do not adequately adapted to these specific patients.

Several specific manufacturing choices also raised questions regarding APS system adaptation. In regards to the delivery behavior, APS algorithms adapt the dose to inject from every 5 minutes to every 15 minutes depending on the system [166]. As shown in **Fig. 29**, the lowest basal rates are frequent in an APS insulin delivery profile. Without any mechanism adaptation, the interval with the lowest insulin delivery will be free of insulin since it will only be delivered at a low frequency (“once in a while”).

6.2.2 Error range

The error ranges we obtained lead to numerous reflections once recontextualized in state-of-the-art literature or CSII use in general practice. There were MARD errors of 61% for Omnipod® at a 0.1 UI/h basal rate over 8 h tests with 15-minute intervals (see **3.3 – Supplementary Data 2**). For an isolated 15-minute time-interval, there was a 200% MARD error (**see Supplementary Data 2 - Article 2**) and up to 25% of MARD errors were observed for errors smoothed over a 1-hour time interval.

Freckman *et al.* mentioned an overall CSII delivery error of around 10% MARD and around 20% for Omnipod® at a 1 UI/h basal rate (see boxplots Fig.4 article Freckman *et al.*, 2019 [28]) We confirmed these results in Chapter 3 (see Fig. 3 Supplementary Data 2 – Article 2).

These observed error ranges give information regarding “basal variation” of actual patients. Indeed, physicians often mentioned that most patients are likely to set their pump with a main basal rate and numerous slight fluctuations around this main value. For instance, a main insulin need of a 1 UI/h basal rate will drive to a 1.0 UI/h pump setting the first hour, then become 1.05 UI/h the next hour, 0.95 UI/h the following and so on. Off-the-shelf CSII devices allow basal rate modification with 0.01 UI/h increments (for the last software version of Ypsopump™). In regard to our error findings, a 1 UI/h basal rate will actually deliver between 0.85 UI/h and 1.15% for the best CSII and between 0.75 UI/h and 1.25 UI/h for the less precise. Therefore,

apart from having a psychological or a random positive effect, this usual practice may not have the relevant assumed effect due to the noted overall CSII delivery errors.

Chan *et al.* studied an *in silico* model for the pulsatile nature of insulin infusion on plasma concentration. The authors described their insulin transport system as a combination of a first order and second order low-pass filter. Consequently, the system filters out most high-frequency variations and only carries on information contained in the low frequencies. Their simulation concluded that insulin oscillations under 15-min period have no significant impact compared to continuous-infusion variations. The rapid changes in the injections are smoothed out by the transport system. Nevertheless, the pulsatile nature of insulin delivery above 15-min starts to have a significant effect on plasmatic insulin (see **fig. 30**). Our results, and specifically our peak-wise analysis suggests that some CSII models deliver in a pulsatile way at around 30 minutes. The Omnipod at 0.05 UI/h has not been tested, but following the same logic could even deliver one stroke every hour. Moreover, the 15-minutes cutoff period established by the authors is an approximated mean and could vary in real-life from one patient to another. It is necessary to pursue further clinical investigation to confirm or exclude systemic consequences from long-term pulsatile insulin infusion.

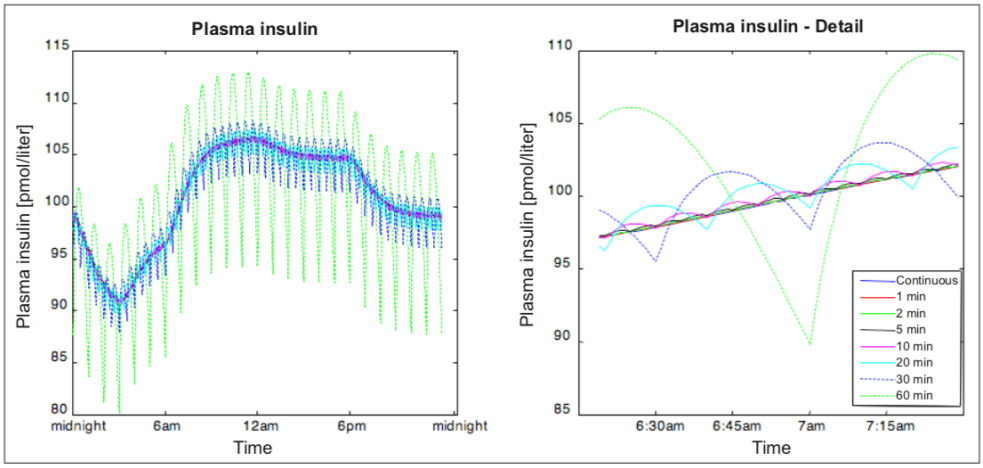

Figure 30: Simulated effect of pulsatile insulin injections.
Plasma insulin levels over 24h (left) and over 1h (right) (Source: Chan et al, 2008)

The same paper by Chan *et al.* also studies the impact of pulse error to plasmatic insulin. They add white and pink noise from 1% to 10% of insulin peak standard deviations. Important consequences of plasmatic insulin were found for 10% of errors, but only for high frequency

peak situations. The authors state, “the robustness of the cutoff value to pump errors containing a high amount of low frequencies and the low-pass filter nature of the insulin system provide strong basis to state that the 15 minutes cutoff is robust to most types of pump noise.” In other words, the 10% error of the insulin peak would be totally smoothed by the skin and insulin transport system with no systemic consequences. As already mentioned, our results suggest the highest error for 15-minute doses, which reach 200%, and errors that are smoothed over a 1 h-period reaching 20%. An increasingly interesting simulating approach as performed by Chan *et al.* could be updated will real-life measurement of CSII errors to check for potential systemic impacts.

In a pumping tube fluidic system, there are multiple resistive phenomenon such as frictional forces, gravity, or curving of the pipe that can result in fluid pressure loss along its pathway. Such tubing conditions in durable pump may alter delivery due to pressure losses induced by the tube. However, our results do not confirm a higher imprecision for durable pump compared to a patch pump.

Despite the different setup for each device [115], Freckman *et al.* noticed better overall accuracy for a durable pump compared to a patch pump [28]. Our findings confirmed a similar result using the same setup for both CSII types. Moreover, pressure losses measured along durable pump tubing does not seem significant enough to induce over delivery (see time series **Fig. 26**).

Some important insulin pulse delivery scenarios are associated with a loss of accuracy in the Omnipod® pump by *Jahn et al* in their dose-to-dose accuracy analysis [110]. Zisser *et al.* argue against this result highlighting the lack of relevance in their setup, since they used a different one for patch and durable pump testing [115]. However, Bowen *et al.* also exposed the same variation in the Omnipod® pump, but this time, using the same setup for a patch and durable pump [24]. Our results also came to the same conclusion as Bowen *et al.*, which is that the Omnipod® pump had variability with seasonality between over and sub delivery.

6.2.3 Clinical consequences

As described in chapter 1, potential clinical consequences induced by CSII errors constitute the most important end point of the present research. Most recent studies that focus on CSII accuracy indicate a wish to provide results that take clinical consequences into account [25], [27], [28]. As previously explained, MARD and evolutional MARD over various observation

windows aim at proposing quick and easy interpretation of CSII error. As shown in Fig. 3 of Supplementary Data 2, some CSII models maintain the MARD over various time-windows suggesting that inaccuracy continues for a long period of time, especially at the lowest basal rates. Hence, our results combined with the literature strongly suggests that for a certain T1D population, namely those with very low insulin needs, could be affected from inaccurate CSII delivery. Furthermore, could low dose highlighted delivery instability participate to GV?

Our results need further investigation and confirmation thru clinical studies. Glycemic stability measured with CGMS could be an example to compare among several periods with different CSII devices. A retrospective data analysis could also compare the overall link between seasons and GI or with patients practicing alpinism or trekking in extreme conditions for a few days. Finally, glycemic excursions could be related to moments after catheter renewals.

6.3 Broader perspectives

There are broader implications and perspectives that arise from the present work. We address some limitations, broader implications and suggestions for future research.

6.3.1 Limitations of the method

There are several limitations in our study. Our tests only focused on basal rates and did not consider bolus assessment. Indeed, our method was more suited to investigate lowest dose delivery that are more represented by basal rate and we had to make a choice due to timing. Our wish to investigate a low basal rate was also motivated by literature review since to date a few has been testing of a basal rate under 0.5 UI/h.

Our first approach which was to get rid of the weighing scale measurement and use a flow meter. Apart from removing practical limitations involved in using a weighing scale, the end-point of the catheter was exploited to add elements mimicking SCT tissue back pressure.

After almost one year of flow meter benchmarking and validation, no flowmeter exists today to assess CSII stand-alone regarding its metrology at the lowest basal rates. A micro-analytic weighing scale remains necessary to guarantee proper measurement. Future flow meter innovations could one day provide stand-alone measurement of CSII flow rate.

Skin tissue studies was possible only with bolus for metrological consistency. A basal rate study with a skin endpoint was not possible with our method when adopting measurement of flow rate without a weighing scale.

The metrology performance of our MT XPE56 weighing scale as well as Bronkhorst flow meter were consistently determined and the KF model was validated with a mathematical assessment. To the best of our knowledge, there is currently no standardized infusion pump likely to deliver the equivalent of 0.1 UI/h with controlled uncertainties. It would have been beneficial to have an experimental validation protocol in which KF optimized flow rate and volume were related to standardized pump volume.

5.3.2 APS and in-silico patients

The APS control algorithm only considers a theoretical CSII delivered dose [167], and as such does not take into account previously observed errors. Despite this, devices achieve 70% in TIR performance. As improvements in control algorithms reach a plateau, taking error delivery into account could be a plus to improve overall system performance. A new generation of APS algorithms could one day benefit from CSII error analysis input in order to increase TIR and reach a larger patient population.

An FDA-approved T1D patient simulator, UVA/Padova, has been used for years to assess numerous APS [96], [125], [168], [169]. This simulator is based on a complex insulin-glucose system model that reproduces a simplification of systemic insulin and glycaemia of a virtual patient in reaction to insulin and glucose incomes [170]. The model was updated in 2012 and includes some modifications such as selection of hardware for CSII: a generic represented by Omnipod® and One Touch Ping for a virtual CSII (see **Fig. 31**). However, the structural differences in the virtual devices are blind to the user and the simulation does not take into account variations in CSII efficiency under daily-life conditions or error handling. The results in our study could enrich this patient simulator to make it a more robust tool that is closer to reality.

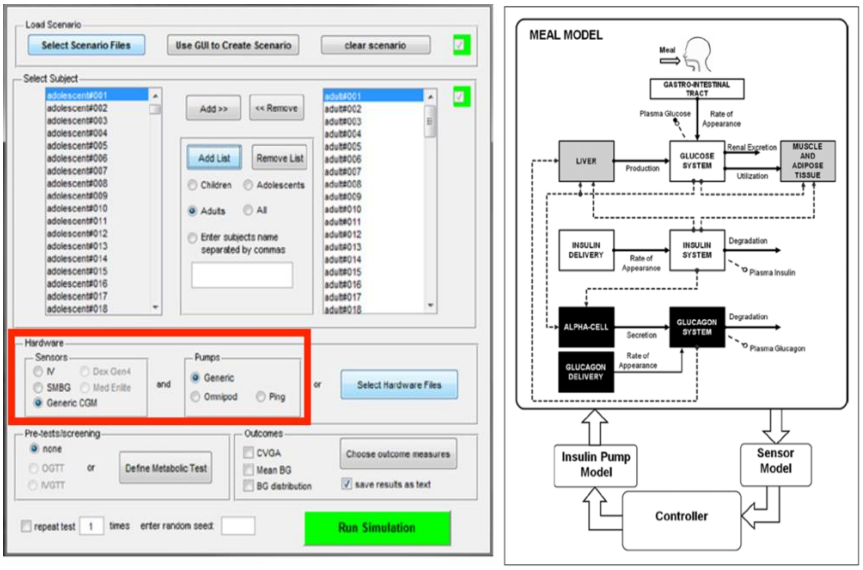

Figure 31: UVA/Padova simulator features.
Simulator model scheme (right) and user panel (left)

5.3.4 Future directions

Future directions of the present work have already been envisaged by the Explor Center and IMMEDIAB lab teams.

AP-like delivery accuracy assessment

Aside from considering that CSII delivery technology sometimes is not adapted to an AP algorithm, for instance due to rare stroke at the lowest basal rates, we have been thinking about the reactivity of the basal rate change in itself. Indeed, since an AP system adapts the basal rate every 5 to 15 minutes, is CSII reactive enough to provide the right dose with frequent basal rate changes? Work in the literature highlights that the start-up phase for each CSII delivery are less accurate in the first hour [28]. We also can confirm that observation. Hence, we already started the process of using our novel test bench to assess CSII delivery accuracy with a variable basal rate changing brutally in each given time interval.

Skin studies

CSII insulin delivery errors related to subcutaneous tissue (SCT) properties have only been lightly addressed. CSII accuracy and skin insulin diffusion are likely to be influenced by SCT tissue type. Deeper investigation on insulin interaction with SCT tissue could strengthen knowledge regarding CSII errors and clinical consequences. Pettis *et al.* recently noted the need to further investigate this topic [102]. This subject constitutes the upcoming work of a 3-year PhD endeavor realized by Pauline Jacquemier directed by Pr. Jean Pierre Riveline (Lariboisère hospital, Immediab lab, Inserm U1138) and Sébastien Hardy (Explor Center, Air Liquide Healthcare).

Results from different scenarios of SCT/insulin from CSII interaction could enrich the development of an improved CSII assessment method (see **Supplementary Data 1**). Indeed, *in silico* add-ons that can simulate skin resistance or skin behavior could be added. A computer-piloted mechanical counter-pressure valve might also be used to simulate end-point pressure loss induced by SCT tissue.

Personalized medicine treatment

Personalized medicine is increasingly being used to tailor treatment to individual needs. Better knowledge of CSII technology and delivery in regard to patient phenotypes would facilitate making a specific choice of devices. This task is already performed at the Explor center by our diabetes engineer expert, Carine Rendekeu, who established a comparison of off-the-shelf CSII models. This features-based device comparison aims at guiding physicians in the choice of the device in terms of a patient's phenotype. Reinforcing knowledge about the technology of each model thru our new assessment method will improve such personalization.

Moreover, a massive data set generated for CSII under many models of daily-life conditions could drive a more descriptive and predictive *in silico* model of CSII behavior. This could lead to an even more robust CSII technical knowledge and treatment individualization.

Communication and standardization of the method

The proposed innovative method (**Supplementary Data 1**) as well as "daily-life" model conditions need to be recognized by a standardized body to generally assess CSII. Insight from

Kamecke *et al.* regarding a general protocol and the representation of results are also key to improving CSII assessment [27].

Scientific evidence also has to be strengthened around this research topic. Two years ago, studying CSII accuracy was a "not-so-important" research topic. Too few independent studies dealt with this topic and both physicians and manufacturers expressed a lack of interest during discussions. Nowadays, several independent actors have taken the lead and have expressed interest in taking a closer look. Currently, many questions remain open and can be addressed in future research. A massive promotional effort and direct communication around this topic must be pursued to encourage further investigation. More conditions that are likely to alter CSII delivery accuracy have to be investigated, and importantly, independent actors have to strengthen results and reinforce knowledge on the link between CSII errors and clinical consequences. There is an old saying, "scientific evidence cannot come from one single result. Evidence is admitted when many studies agree for 10 years."

Team up!

Finally, this research highlights the importance of collaboration between engineers and physicians in biomedical research. Physicians are experts in diseases and patient treatment. Meanwhile, engineers master new technologies and techniques. A strong combination of expertise between these two skillsets is vital for driving forward the biomedical field, especially for medicine. The richness of the present work is due a collaboration between engineers and a physician, and many things would have been impossible without this combined effort.

Conclusion

CSII is a widely-adopted treatment for T1D and delivery accuracy is key to treatment efficiency. This work addressed limitations of current in-lab CSII assessment methods.

A novel methodology was developed to measure insulin flow rate continuously and at very low basal rates, namely 1 micro liter per hour. Tools were also modeled to reproduce conditions found in actual patient use. The presentation of CSII accuracy results were designed to support clinical interpretation. Four off-the-shelf systems were tested: CSII model (Minimed™ 640G, Ypsopump™, Omnipod™ and Tandem t:slimX2™) at four basal rates (2 UI/h, 1 UI/h, 0.5 UI/h, 0.1 UI/h). CSII accuracy was also tested under several in-lab reproduced daily life conditions such as temperature variation, motion and hydrostatic pressure. Finally, CSII accuracy and pressure profiles were measured with skin infusion endpoints.

The novel methodology was described and published in July 2019 [30]. This was the first time that CSII accuracy was measured at such a low flow rate. In accordance with previous studies, CSII accuracy was found to be model and basal rate dependent. Delivery accuracy decreases sharply for the lowest ranges. Model inaccuracies were party identified by studying insulin delivery manufacturing choices with peak-wise analysis. Hydrostatic pressure and motions did not influence CSII accuracy. Oppositely, temperature variations unexpectedly caused important CSII delivery alterations. CSII errors were not significantly higher when delivering within water than within skin, but pressure analysis provided interesting insights on skin diffusion that deserve further investigation.

The highest error range at the lowest basal rate or under temperture variations are likely to be hazardous for a specific CSII user population, namely those with high insulin sensitivity. The link between delivery error and potential cause of GI remains to be further elucidated. CSII accuracy assessment that models daily life conditions needs to generalized and our results require further confirmation.

In conclusion, it is important for manufacturers and relevant regulators to utilize a clinically-oriented CSII assessment protocol, such as our method or that by Kamecke *et al.*, to improve patient comfort and safety.

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Figure list

Table list

Résumé - [Français]

Étude *in vitro* et *in silico* de la variabilité d'administration des systèmes d'injection d'insuline

Introduction

Contexte générale

Le diabète

Le diabète est une maladie métabolique qui se définit par une hyperglycémie chronique due à une diminution de la sécrétion en insuline ou une réduction de son action. Cette hyperglycémie se doit d'être contrôlée afin d'éviter des complications à court terme (acidocétose diabétique) ou à long terme (anomalies cardio-vasculaires, neuropathie périphériques, …).
A ce jour, plus de 380 millions de personnes sont victimes du diabète dans le monde. Ce chiffre pourrait atteindre 550 millions d'ici 2030. Cette prévalence constitue selon l'OMS, la première pandémie de l'histoire non-causée par un virus. Elle constitue donc un enjeu médical et socio-économique majeur.
Il existe principalement trois formes de diabète de causes physiologiques différentes : le diabète de type 1, le diabète de type 2 et les autres formes de diabète. Certaines formes, principalement le type 1, nécessitent un apport exogène en insuline par le biais de multi-injections (seringue ou stylo) ou d'une pompe à insuline. Tout l'objectif d'un patient diabétique réside dans la régulation de sa glycémie au plus proche de la cible (70-140 mg/dl) par apport exogène d'insuline, en tenant compte de tous les évènements capables de faire varier son glucose sanguin (nourriture, activités physiques, émotions, …). De nouvelles technologies ne cessent d'émerger depuis plusieurs décennies et tentent avec plus ou moins de succès, de faciliter cette tâche au diabétique. C'est le cas des nombreuses générations de pompe à insuline ayant vu le jour depuis les années 1970.

Le traitement

Une pompe à insuline est un moteur qui perfuse en permanence et à débit constant, par voie sous-cutanée, une quantité prédéfinie d'insuline rapide, classiquement un analogue rapide de

l'insuline (Lispro, Aspart ou Glulisine), par l'intermédiaire d'un cathéter. La vitesse de perfusion s'appelle le « débit de base » et s'exprime en unité par heure. Plusieurs débits de base peuvent être programmés dans la journée. Le patient doit, avant chaque repas, et dès qu'une hyperglycémie l'exige, programmer un « bolus », lequel consiste en l'administration immédiate d'un supplément d'insuline. Les débits de base métabolisent le glucose d'origine hépatique, les bolus métabolisent le glucose provenant des aliments. La pompe à insuline est également un composant essentiel d'une délivrance automatique d'insuline appelé « pancréas artificiel ». Cet appareil est donc composé, d'une pompe à insuline, d'une mesure de glycémie interstitielle en continue ainsi que d'un algorithme de contrôle permettant de calculer la dose à injecter par rapport aux données d'entrée. **Au vu des quantités infimes d'insuline délivrées par une pompe, sa précision d'administration semble clé dans l'atteinte d'un équilibre glycémique ainsi que pour l'efficacité des systèmes de pancréas artificiel.**

Les méthodes d'évaluations

La pompe à insuline a largement montré son efficacité dans l'amélioration générale de l'équilibre glycémique par rapport à d'autre méthode comme la « multi-daily injection » par seringue ou stylo. Cependant, l'équilibre glycémique reste souvent instable chez les patients diabétiques de type 1. **Cette instabilité glycémique est sans nul doute la conséquence de plusieurs facteurs mais pourrait également être due à une mauvaise reproductibilité de l'administration d'insuline.**

État de l'art

La norme internationale IEC 60601-2-24 évalue la fiabilité d'administration des pompes à perfusion, notamment les pompes à insuline. Les fabricants de tels dispositifs médicaux doivent fournir des résultats de test conforme basés sur le protocole de cette norme afin d'obtenir le marquage CE médical. Cette méthode est aujourd'hui le « gold standard » de l'évaluation des pompes à insuline. Cependant, pour plusieurs raisons, ces méthodes sont limitées. La mesure en elle-même considère tout d'abord le débit de manière indirect par le biais d'une pesée au cours du temps. Cette technique à l'avantage de pouvoir mesurer des quantités infimes correspondantes à celles délivrées par les pompes, cependant, la mesure par micro balance d'analyse est très difficile à maitriser tant de nombreux phénomènes extérieurs peuvent venir perturber son utilisation. D'autre part, le protocole de la norme IEC évalue la pompe dans des conditions très éloignées de la réalité du patient au quotidien : les débits les plus faibles ne sont

par exemple pas obligatoirement testés, la pompe est placée au repos sans aucune contraintes extérieurs pouvant perturber son fonctionnement et l'analyse des résultats ne tient pas compte des premières 24 heures de fonctionnement.

La précision des pompes à insuline fait l'objet de peu d'études indépendantes, notamment à faible débit basal. Elles montrent globalement une précision générale liée au modèle et à la gamme de débit. Les débits les plus faibles étant les débits pour lesquels les pompes sont généralement les plus challengées. Hormis la méthode imaginée par Howard Zisser en 2011 qui considère de très faibles quantités d'insuline injectées dans un tube et mesurées par méthode d'imagerie, les études actuelles se basent principalement sur une méthode similaire à la norme IEC 60601-2-24. La méthode de Zisser, bien que simple et efficace, ne permet pas une analyse du comportement général de la pompe à insuline. Les études existantes adaptent tout de même leurs protocoles de manière à se placer davantage en phase avec la réalité d'un patient sous pompe. Par exemple, la période de stabilisation des 24 premières heures d'absence de test n'est pas considérée. Une seule étude a testé la pompe dans une contrainte de vie réelle pouvant altérer la délivrance : *Zisser et al* ont montré que des différences de hauteurs entre la pompe et le site d'injection pouvait entrainer des sur- sous- délivrances significatives due à un effet de pression hydrostatique.

D'autre part, les résultats de précision des études actuelles des pompes restent trop peu souvent intégrés dans une perspective clinique. Les études les plus récentes ainsi que *Borot et al* discutent des éventuels effets cliniques pour une population à faible besoin en insuline. **Trop peu d'éléments permettent aujourd'hui d'obtenir des réponses précises sur d'éventuels impacts cliniques liés aux erreurs de délivrance des pompes à insuline.** Ceci est notamment due à une grande variabilité phénotypique et à la difficulté technique d'évaluer précisément les pompes à insuline.

En 2019, plusieurs études indépendantes ont mis en avant l'intérêt de renforcer la connaissance autour de ce sujet. *Kamecke et al* ont proposé un protocole de test basé sur de nouvelles représentations graphiques des résultats orientées vers la clinique. Leur protocole de test se base cependant toujours sur une méthode de pesée inspirée de la norme IEC 60601-2-24.

On note ainsi le besoin de renforcer les méthodes d'évaluation de précision de la délivrance des pompes à insuline ainsi que de comprendre le lien entre les erreurs de délivrance et les éventuels impacts clinique.

Contexte social

Le contexte médico-social a également montré un intérêt dans le renforcement de la connaissance de la pompe à insuline. En 2015, une étude rétrospective dévoile 1594 incidents dans l'utilisation de la pompe à insuline dont 13 morts entre 1996 et 2005. Ce nombre augmenta de 17% par an entre 2001 et 2009. Plus récemment, le consortium international des journalistes d'investigation (ICIJ) présente la pompe à insuline comme un dispositif à risque avec plus de 305.000 incidents déclarés. Bien que la fiabilité de la base de données de l'ICIJ ait été remis en doute, ces éléments soulignent la nécessité de renforcer l'évaluation des dispositifs médicaux, notamment la pompe à insuline. Dans de nombreux pays, les systèmes de santé remboursent de plus en plus à la performance du traitement. Ces pratiques vont à l'avenir davantage nécessiter une connaissance technique accrue des dispositifs médicaux ainsi que de leur impact physiologique.

Objectif

Face aux différents constats, notre travail a été de développer des méthodes de mesure plus robustes et un protocole plus complet afin de permettre l'évaluation de la précision des pompes à insuline au plus proche de la réalité des patients diabétiques.

Principales méthodes et résultats

Article scientifique #1

Nouvelle méthode d'évaluation des pompes à insuline

L'objectif premier de nos travaux fut le développement d'une nouvelle méthode d'évaluation de la précision des pompes. Cette dernière se base sur une double mesure, débit et volume, de la quantité d'insuline délivrée par la pompe et optimisée par un filtre mathématique bayésien

(filtre de Kalman). Cette nouvelle méthode de mesure nous permet d'obtenir pour la première fois le débit d'insuline en continue (acquisition à 10Hz) tout en considérant les débits les plus faibles avec une incertitude de mesure acceptable, notamment jusqu'à 0.1UI/h (correspondant à 1 microlitre par heure). La description de cette méthode ainsi que sa validation a fait l'objet d'une publication scientifique en Juillet 2019 dans la revue *Diabetes Technology and Therapeutics.*

Article scientifique #2

Étude de la précision de pompes à insuline

Un panel de 4 pompes présentes sur le marché fut ensuite évaluées à l'aide de la méthode précédemment décrite. Les pompes Minimed™ 640G, Omnipod™, Ypsopump™ et Tandem t:slimX2™ furent testées à 4 débits de base : 2UI/h, 1UI/h, 0.5UI/h et 0.1UI/h, pendant 8h selon 4 réplicas. La performance des pompes fut évaluée selon plusieurs indicateurs : la moyenne globale d'erreur de délivrance ainsi que l'écart moyen des erreurs absolues (aussi appelé MARD pour « mean absolute relative dispersion) ont été déterminés pour chaque test. Au niveau graphique, une représentation en nuages de points donnant l'erreur de dose d'insuline sur chaque intervalle de 15-minutes a été obtenue pour chaque test. L'évolution de la MARD a également été représentée pour des erreurs de dose calculées sur des intervalles allant de 15 minutes à 2h. Une analyse de la reproductibilité (fréquence et volume unitaire) des pulses de délivrance d'insuline a également été rendu possible grâce à la mesure continue.

Les résultats de précision des pompes testées sont en accord avec la littérature et indiquent que leur précision de délivrance est dépendante du débit et du modèle. Une légère tendance globale à la sous délivrance a été observée. La précision et la reproductibilité des erreurs chutent globalement pour les débits les plus faibles et pour la plupart des modèles, bien que les résultats restent hétérogènes d'un modèle à l'autre. La moyenne des MARD d'erreur pour Omnipod™ atteint par exemple 61.3% à 0.1UI/h alors que la t:slimX2™ se maintient avec une moyenne de MARD à 22.7% pour le même débit. Contrairement à la moyenne, l'indicateur MARD possède l'avantage de rendre compte d'une erreur de délivrance globale sans compenser les erreurs positives par les erreurs négatives. Elle rend ainsi plus facilement compte des erreurs capables d'influencer l'instabilité glycémique par longues successions de sur- et sous- délivrance.

L’analyse de la reproductibilité des pulses d’insuline nous permet d’observer la stratégie de délivrance des différentes technologies de pompes. Certaines comme la Minimed™ 640G ou l’Ypsopump™ adaptent le volume unitaire de chaque pulse plutôt que leur fréquence lorsque les basaux sont sur des ranges élevés puis adaptent leur fréquence en fixant le volume unitaire pour les basaux les plus faibles. Omnipod adapte seulement ses fréquences pour un unique volume unitaire sur toute la gamme de débits alors que la t:slimX2™ adapte uniquement ses volumes. Cette analyse de pulses permet également d’observer la variabilité de précision pour les débits les plus faibles : à 0.1UI/h une mauvaise reproductibilité des volumes unitaires est généralement observée.

Études complémentaires

Évaluation de la précision : au plus proche du patient

Comme décrit précédemment, le protocole de la norme 60601-2-24 ainsi que les études publiées jusqu’alors se limitent à évaluer la pompe à insuline dans des conditions idéales : l’appareil est testé au repos et sans subir de contraintes extérieures, pourtant présentent dans le quotidien de des patients. Nous avons développé des outils ou des protocoles spécifiques capables de reproduire certaines de ces conditions qui pourraient éventuellement venir perturber la précision de délivrance. Un bras robotisé 6-axes a été développé afin de reproduire des contraintes de mouvement et une étuve réfrigérée a permis de placer la pompe sous des contraintes de variations de températures. Nous avons également souhaité confirmer ou infirmer les résultats d’Howard Zisser en testant la précision de délivrance pour des différences de hauteurs entre la pompe et son site d’injection. Enfin, l’impact du type de site d’injection (peau ou réservoir d’eau) sur les erreurs de délivrance a été étudiée. En effet, pour des raisons pratiques évidentes, la majorité des tests en laboratoire utilisant une balance de précision programme la pompe pour qu’elle délivre dans un réservoir d’eau ou d’insuline. Or la délivrance sous cutanée pourrait avoir des effets sur la précision et entrainer un biais méthodologique. Nous avons voulu vérifier cette hypothèse. Tous ces tests sous contraintes utilisent la méthode de double mesure optimisée par le filtre de Kalman.

Pression hydrostatique

Suite aux travaux de *Zisser et al*, précédemment évoqués, nous avons mesuré l’impact de la différence de hauteur entre la pompe et le site d’injection sur la précision de délivrance. Les

pompes Medtronic® 640G, Ypsopump™ et Tandem t:slimX2™ ont été programmées pour délivrer un débit basal de 1UI/h pendant 24h pour Medtronic® et 3h pour Ypsopump™ et Tandem. La précision des pompes a été testée sous trois conditions : la pompe infuse vers le haut (H1), la pompe infuse vers le bas (H-1), la pompe est le site d'injection sont à la même hauteur (H0). Malgré la consistance des réplicas de tests (notamment pour la pompe Medtronic® 640G), aucune différence significative n'a été observée pour la précision de délivrance entre les différentes conditions de hauteur. L'analyse de la régularité des pulses d'insulines et la précision globale (moyenne et MARD d'erreur) ne montrent aucune différence. **Ainsi, nos résultats infirment ceux de *Zisser et al* qui considérait que la différence de hauteur entre pompe et site d'injection entrainait des erreurs de délivrances significatives.**

Mouvements

Les mouvements de pompes à insuline, très présents chez le patient au quotidien pourraient intuitivement venir perturber la performance de délivrance. Une Medtronic® 640G, Ypsopump™ et Tandem t:slim™ ont été placées sur un bras robotisé 6 axes programmé pour effectuer des mouvements de translation verticale et horizontale pendant toute la durée des tests. Chaque pompe a été testée pendant 2h à un débit basal programmé de 1UI/h, et selon 3 réplicas. La performance de délivrance a été évaluée selon la moyenne et la MARD globale des erreurs de délivrance. Une analyse de la reproductibilité des pulses d'insuline a également été réalisée.

Là encore, **aucune différence significative de précision de délivrance n'a été observée entre des conditions de mouvement et des conditions de repos pour les 3 modèles de pompe à insuline.** Au vu des différences de hauteur dynamique induites par les mouvements de translation verticale, ces résultats sont en phase avec nos résultats précédents.

Variation de température

Les écarts de température extérieurs pourraient également rendre sensibles la performance des appareils électro-médicaux. De récents travaux montrent les différences de température que subit une pompe à insuline au quotidien. Aucun travail n'a, à ce jour, lié ces résultats avec d'éventuelles altérations de leur précision. Une Ypsopump™, une Medtronic® 640G et une Tandem t:slimX2™ ont été placées dans une étuve réfrigérée programmée pour effectuer des variations de températures cycliques de 5°C à 35°C. Chaque pompe a été programmée à un débit de 1UI/h et testée pendant 8h selon 3 réplicas. Les résultats sous conditions de variations

de températures ont été comparés à une situation de contrôle ne subissant aucune contrainte extérieure. La performance de délivrance a été évaluée selon la moyenne et la MARD globale des erreurs de délivrance. Une analyse de la reproductibilité des pulses d'insuline a également été réalisée.

Les moyennes d'erreurs de délivrance sur la globalité du test entre les variations de températures et la situation ne montrent pas de différences significatives. En revanche, les MARD de délivrance sont très fortement supérieures sous conditions de variations de température. En effet, les courbes d'erreurs de doses calculées sur chaque intervalle de 15-minutes et représentées sur la totalité du test montre une importante corrélation entre l'évolution de la température et les erreurs de délivrance. L'analyse des pulses d'insuline montre également des différences significatives dans la reproductibilité du volume unitaire. Ce phénomène a été largement plus observé chez Ypsopump™ et Minimed™ 640G que pour la pompe tandem t:slimX2™.

Injection sous cutanée

Les méthodes qui évaluent la précision de délivrance des pompes à insuline utilisent un réservoir dans lequel l'eau ou l'insuline vient s'écouler, notamment dans le but d'y être pesé. En situation réelle, la pompe délivre dans un tissue sous cutanée. L'étude de la précision de la pompe en fonction de la nature du site d'injection pourrait fournir davantage d'information sur l'évaluation de la pompe en situation de vie réelle ainsi qu'enrichir la connaissance sur le lien entre impact clinique et erreur de pompe. Nous avons étudié pour l'Ypsopump™ et la Minimed™ 640G l'erreur de délivrance ainsi que le profil des pressions au niveau du site d'injection pour une infusion dans un réservoir d'eau ou dans de la peau (queue de porc). Pour l'injection dans la peau, chaque pompe a été programmée pour délivrer 15 bolus (volume unitaire d'insuline) de 2UI en changeant de site d'injection toutes les 3 injections. Pour l'injection dans l'eau, la pompe a été programmée pour délivrer 15 bolus de 2UI dans un réservoir d'eau. Pour chaque situation, le volume globale d'insuline délivré est comparé ainsi que la distribution du profil de pression.

Aucune différence significative n'a été observée pour les erreurs de délivrance entre les conditions de délivrance dans la peau contre celle de délivrance dans l'eau. Cependant, la comparaison des distributions des valeurs de pressions est significativement différente pour une diffusion dans la peau en comparaison avec une diffusion dans de la peau. Plusieurs formes de

distribution ont également été observées pour « l'injection dans un nouveau site d'injection » et pourraient expliquer des phénomènes de diffusion sous cutanée déjà mentionnés dans la littérature. Ces phénomènes doivent être davantage étudiés car ils pourraient expliquer certains cas d'instabilité glycémique.

Discussion

Tout au long de cette recherche nous avons taché de renforcer la connaissance autour de l'évaluation de la précision de la pompe à insuline. Une nouvelle méthode de mesure permettant de considérer de manière plus performante le comportement de délivrance des pompes, notamment par le biais d'une analyse des pulses d'insuline, a été conçue. De nouveaux protocoles ainsi que des outils supplémentaires ont également permis d'évaluer la pompe dans des conditions plus proche des contraintes que subit le patient au quotidien, tels que variations de températures, de mouvements, la différence de hauteur entre la pompe et son site d'injection ou bien la différence structurelle du site d'injection. Un soin particulier a enfin été apporté à la manière de présenter les résultats, de manière à pouvoir lier le plus aisément possible la précision des pompes avec ses éventuelles impacts cliniques.

Nos travaux ont permis de confirmer que la précision de délivrance dépend du modèle de pompe et reste généralement moins précise pour les gammes de débits les plus faibles. Notre mesure inédite d'évaluation a permis pour la première fois d'évaluer les pompes pour un débit basal de 0.1UI/h. Une forte imprécision et un manque accru de répétabilité dans les erreurs a été observés. Notre analyse spécifique des pulses d'insuline a également permis de discriminer les choix de constructeurs de pompe à insuline en lien avec les erreurs observées pour chacun des modèles et des situations.

Nos résultats montrent par ailleurs que les contraintes de mouvements ainsi que la différence de hauteur entre le site d'injection et la pompe n'accentuent pas les erreurs de délivrance. Les variations de températures ont en revanche un effet important sur la précision de pompes. La nature du site d'injection, pour des bolus de 2UI et sur deux modèles de pompe, n'a pas entrainé d'erreurs de délivrance. Cependant, davantage d'investigations sont nécessaires afin de comprendre des phénomènes de distribution des pressions en lien avec d'éventuelles effets de diffusion/absorption de l'insuline. Ceci enrichirait grandement la connaissance sur la délivrance sous cutanée d'insuline ainsi que son passage au niveau systémique.

Les potentiels impacts cliniques des erreurs de délivrance constituent une finalité essentielle de ce projet de recherche. Ainsi, nous avons fait le choix de représenter nos résultats de manière à être tournés au maximum vers une interprétation clinique avec des indicateurs tels que la MARD ou son évolution en fonction d'une fenêtre temporelle « métabolique ».

Nous contextualisons ci-dessous certains de nos résultats afin de montrer au lecteur leurs potentiels impact et orienter les futurs chercheurs sur d'éventuelles perspectives intéressantes.

NB : une partie de la discussion est intégrée à ce résumé. La discussion générale se trouve dans le manuscrit ci-dessus.

Discussion des résultats

Nos résultats de précisons de délivrance sont globalement en accord avec la littérature. Notre méthode permet pour la première fois d'explorer des gammes de débits très faible à 0.1UI/h et les erreurs observées permettent de démarquer les modèles les plus précis des modèles davantage mis en difficulté.

Notre analyse des pulses d'insuline nous permet également d'observer le choix des technologies dans le comportement de délivrance des pompes. Certains modèles font par exemple le choix pour des débits basaux les plus faibles de conserver le volume unitaire de chaque pulse et d'abaisser la fréquence de délivrance. Ce choix pourrait avoir un impact clinique chez les patients à faible besoin d'insuline dans la mesure ou le volume d'insuline due en une heure est délivré en moins d'une seconde. En effet, le comportement pulsatile des pompes à insuline a été étudiée de manière *in silico* et des effets systémiques se feraient ressentir lorsque que la fréquence des pulses atteint une période de 15 minutes. Nos résultats vérifient que dans certains cas, la délivrance s'opère toutes les 30-minutes et ces comportements de délivrance pourraient ainsi avoir des conséquences cliniques.

De manière plus générale, nos résultats confirment que les erreurs de pompe, notamment à faible débit pourraient avoir des conséquences cliniques. Les populations les plus sensible à l'insuline sont celles qui utilisent les débits pour lesquelles la pompe est la moins précise et pour les comportements de délivrances « peu fréquentes » précédemment décrites sont les plus probables. Des investigations en vie réelle doivent dans tous les cas être menées afin de confirmer la pertinence clinique de nos résultats.

Perspectives futures

Nos résultats sur les précisions des pompes pourraient permettre à moyen terme de mieux appréhender le comportement de délivrance des pompes à insuline. Les algorithmes de contrôle des pancréas artificiels ne tiennent aujourd'hui pas compte des erreurs de pompes et l'intégration de nos résultats dans une nouvelle génération d'algorithmes pourrait être discutée. De la même manière, des simulateurs *in silico* de patients diabétiques, de pompes à insuline et de capteurs sont grandement utilisés par la communauté scientifique pour évaluer les pancréas artificiels. Les pompes virtuelles qui les composent pourraient également bénéficier d'un meilleur modèle en se basant sur nos résultats. Enfin, une meilleure connaissance technique de la pompe à insuline pourrait permettre de connaître les atouts et limites de chaque modèle. Une personnalisation des dispositifs en fonction des différents phénotypes s'avèrerait être un plus pour l'efficacité du traitement.

Par ailleurs, la force de notre méthode de mesure, de nos protocoles ainsi qu'une récente analyse des résultats proposé *Kamecke et al* sont à mettre en avant pour renforcer la connaissance générale dans l'évaluation de la précision des pompes à insuline. Nos protocoles se rapprochent de la réalité du patient et comprennent des indicateurs plus faciles à comprendre et plus proche d'une finalité clinique. Les organismes notifiés ainsi que les industrielles pourraient se baser officiellement sur ces protocoles afin de gagner en pertinence dans l'analyse de leurs dispositifs.

Conclusion

La pompe à insuline est un traitement majeur du diabète de type 1 et un acteur clé du pancréas artificiel. Elle a prouvé son efficacité dans l'amélioration de l'équilibre glycémique en comparaison à d'autres techniques d'administration d'insuline. Cependant, l'équilibre glycémique reste difficile à obtenir chez certains patients. La précision de la pompe insuline reste peu étudiée aujourd'hui et le lien entre erreurs de délivrance et potentielle instabilité glycémique reste incertain.

Une nouvelle méthode d'évaluation en laboratoire de la pompe à insuline ainsi que des protocoles davantage tournés vers la vie réelle du patient ont été développés tout au long de la présente recherche. Nous avons évalué pour la première fois la précision de la délivrance à très faible débit basal, sous contrainte de mouvements, de variations de températures, de différences de hauteur entre le site d'injection et la pompe et en changeant la nature structurelle du site

d’injection. Notre méthode permet également pour la première fois de considérer de manière continue le débit délivré par la pompe et ainsi d’étudier les caractéristiques des pulses d’insuline.

La précision d'administration des pompes s’est montrée dépendante du type de dispositif et de la gamme du débit basal. Une forte variabilité de la fréquence des impulsions d’insuline et du volume émis pour chacune d’entre elles a été observée pour les faibles débits. Des variations de températures extrémales ont par ailleurs montrées un lien étroit avec une imprécision de délivrance. En revanche, les différences de hauteur ainsi que les contraintes de mouvements n’ont montré aucun impact

Certains modèles de pompes semblent ainsi plus adaptés aux faibles besoins en insuline ou à une inclusion future dans un système en boucle fermée. Le comportement de délivrance d’insuline dans les différents sites d’injection ainsi que l’impact clinique des erreurs de délivrance observées restent à confirmer.

Mieux appréhender techniquement le comportement de délivrance des pompes à insuline constitue un enjeu majeur dans le contexte médico-social actuel et de nouvelles méthodes d’évaluation et de caractérisation des résultats sont nécessaires pour y arriver.

Supplementary data

Supplementary data 1: Article 1 – Kalman filter novel methodology to assess insulin pump accuracy

Erratum:

Affiliations

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Supplementary data 2: Article 2 – All insulin pumps are not equivalent: a bench test assessment for several basal rates.

All insulin pumps are not equivalent: A bench test assessment for several basal rates

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Abstract:

Background: Insulin pump or continuous subcutaneous insulin infusion (CSII) system is a widely-adopted contemporary treatment for type 1 diabetes and is a major component of the artificial pancreas (AP). CSII accuracy is essential for glycaemic control and to-date such metric has not been given sufficient study, especially at the range of the lowest basal rates (BR). Our study presents accuracy results of four off-the-shelves CSII systems using a new accurate and reactive method for CSII system evaluation based on direct insulin flow and volume measurement.

Methods: CSII systems accuracy was assessed by a double measurement approach utilizing a direct mass flow meter and a time-stamped micro-gravimetric test bench combined with a Bayesian-based mathematical filter (Kalman). Volume and direct flow rate measurement were gathered. CSII dose errors were evaluated using mean and mean absolute relative dispersion (MARD) for dose error calculated at different observation windows over the whole test. Peak-wise insulin delivery was also assessed regarding stroke regularity in terms of frequency and volume.

Results:
MARD of error shows very wide results for each pump and each basal-rate from 7.3%(2U/h) to 61.3%(0.1U/h). Peak-wise analysis shows several strategies for basal-rate adaptation (frequency for Omnipod, volume for Tandem, both for Ysopump and Minimed640G). 0.1UI/h tests highlights insulin stroke overall bad volume reproducibility (SDomnipod=0.024, SDypsopump=0.015, SD640G=0.0092) except for Tandem (SDtandem = 0.0045).

Conclusion:
Accuracy assessment of four off-the-shelves CSII systems showed that system precision is model dependant. A global tendency to under deliver was observed. Accuracy generally decreases for smaller BR. Depending on observed delivery typology, some models look to be more adapted for the smallest insulin needs or for AP systems. Further investigations are required to study potential clinical consequences of CSII delivery.

Introduction:

Continuous subcutaneous insulin infusion (CSII) is one of the gold standards to achieve glucose control in patients with type one diabetes (DT1) (1–3). CSII is also a key component of closed loop systems (CLS) (4). It allows insulin administration to be automatically adapted each 5 to 15-minutes according to several variables such as continuous glucose measurement (CGM), insulin-on-board and physiologic parameters (5,6). However, glucose control in patients treated with traditional CSII remains imperfect (7,8) and normoglycemia in patients using CLS (i.e. TIR(70-180mg/dl) >70%) is not always reached (6,9).
This statement can find many explanations, such as continuous glucose monitoring (CGM) imprecision, erratic insulin SC absorption, unstable lifestyle etc. (10,11). CSII

imprecision could also be one of these factors and to date, too few independent studies have evaluated insulin administration system accuracies.
There are several pumps on the market, all of them able to deliver insulin at various basal rates (BRs). Despite consistent improvements over the years, the international gold standard for the assessment of CSII, recognized by many authorities for their introduction on various markets, do have some limitations. Shortly, this standard is far from the daily life constraints, tests rely on indirect means of measurement with low frequency of data acquisition, and do not include compulsory testing for the tiniest BR (10), (12–15).

In this context, as previously suggested by *Heinemann et al* (12), the available evidence on the safety and efficacy of CSII remains limited. Hence, due to this lack of evidence, the accuracy of insulin administration of pumps available on the market require deeper evaluation, especially at different BR. Moreover, CSII mis-precision could be a potential factor of GV in T1D patients.

We recently introduced a new method able to reach high precision measurement of insulin administration at several BR (13) including the lowest ones commonly used in both pediatric population (14,15) and CLS (16,17). This new method provides both continuous measurements of insulin flow rate and insulin volume with good uncertainties (13). In the present study, four off-the-shelves insulin pumps were tested at several BR (2UI/h, 1UI/h, 0.5UI/h and 0.1UI/h) using that new method: a Medtronic® Minimed 640 G, an Ypsomed® Ypsopump, an Insulet® Omnipod and a Tandem® t:slim x2.

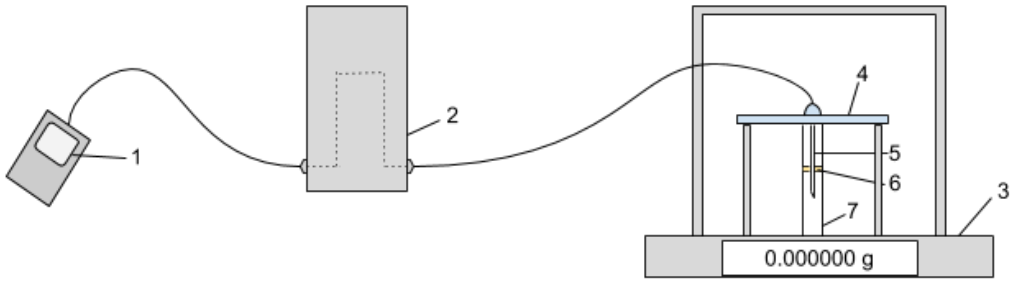

Fig. 1: Test bench setup
1: Insulin pump, 2: Bronkhorst BL100 flow meter, 3: Weighing scale, 4: infusion plate, 5: transition needle, 6: Oil layer, 7: End-point reservoir.

Measurements methods:

These methods have been precisely described in reference 13.

Direct mass flow meter BL100 and XPE56:

The measuring devices used are a Mettler Toledo® XPE56 weighing scale and a BL100 direct mass flowmeter by Bronkhorst® according to the setup designed and described in a previously published article (13). Briefly, the CSII under study is connected to the flowmeter by standard catheter tubing as shown in **fig. 1**. The flowmeter's exit is connected to similar tubing that plugs hermetically to a 18G, 1.2mm, ISO 7864 needle immersed in a test tube on the weighing scale. A thin oil layer prevents any evaporation to occur inside the tube during the several hours of test. As described in the previous article, the numerous microfluidic phenomena as well as environment constraints relative to measurement were controlled prior to each test.

Kalman filter based assessment method

A Kalman filtering method combining signals from both devices is implemented, as detailed in a previously published study (13). Here, the Kalman filter minimizes the mean square error of the two measured parameters. This step allows the high accuracy of the weighing scale to compensate for the uncertainty of the Flowmeter measure for the very low flowrates under study. Similarly, the low acquisition frequency of the balance is compensated by the high frequency of the Flowmeter acquisition. The output of the Kalman filter is composed of two signals: a corrected cumulated mass signal and a corrected flow rate signal.

Design of experiment

Three wired pumps: Minimed 640G (Medtronic®), Ypsopump (Ypsomed®), t:Slim x2 (Tandem®) and one patch pump: Omnipod (Insulet®) were assessed. All four were tested under four BRs, namely 2UI/h, 1UI/h, 0.5UI/h and 0.1 UI/h. Each test lasted for eight hours at constant BR, and was reproduced 4 times each. Overall, results of 64 8-hour tests are presented hereunder.

Numerical indicators

Mean error

For all tests, the mean error in insulin delivery was computed over the whole 8h-test (Eq.1). The difference between actual insulin dose (AID) and expected insulin dose was considered (EID).

$$Mean(Error) = \sum_{i=1}^{n} [\frac{AID_i - EID_i}{EID_i}.100]. \frac{1}{n}$$

(Eq. 1)

MARD error

Also, the mean absolute relative difference (MARD) between AID and EID was computed (**Eq. 2**), such that successive under-delivery and over-delivery do not compensate each other, as they do for simple mean computations.

Graphs plotting boxplot MARD errors replicas of each insulin pump model for each BR was displayed for 15-minute observation windows.

$$MARD(Error) = \sum_{i=1}^{n} [\frac{|AID_i - EID_i|}{EID_i}.100]. \frac{1}{n}$$

(Eq. 2)

MARD was also computed for different observation windows (30min, 60min, 120min, 240min) over the duration of the whole experiments. The resulting MARD was plotted according to the size of the considered time window for each pump and BR to evaluate if errors were being compensated for larger observation windows.

Insulin stroke analysis

In order to decipher more precisely the mechanism of insulin pump accuracy, we evaluated insulin stroke frequency and amplitude reproducibility. From the Kalman-filtered flowrate signal, local maxima of insulin flow rate were spotted, allowing to identify the stroke's positions, this using an algorithm detailed in supplementary data. This allowed to compute for each stroke the injected volume and the inter-stroke time in order to evaluate the intrinsic variability of insulin administration.

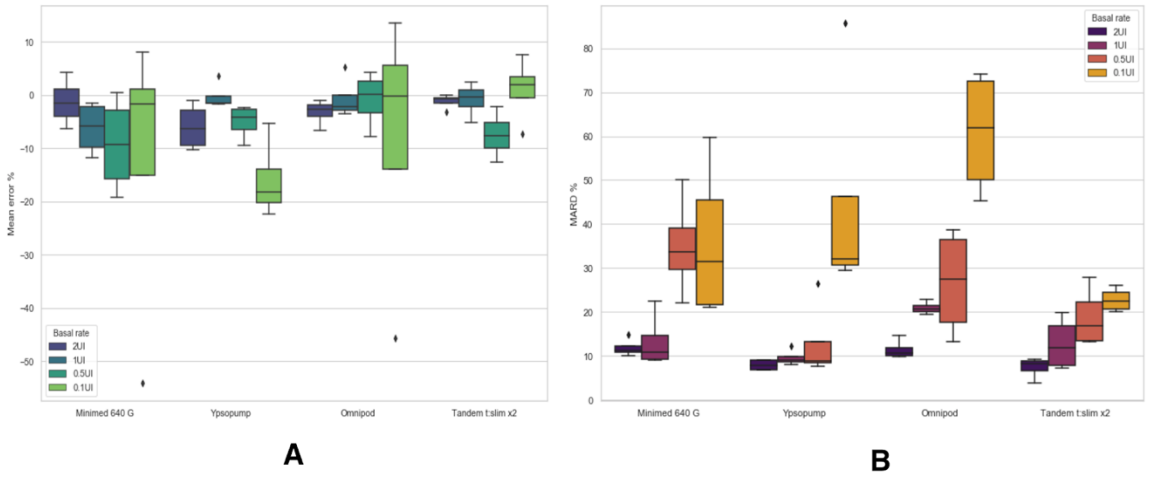

Fig. 2: Boxplot of mean error and MARD.
CSII system accuracy results for each BR with mean (A) and 15-minutes observation windows MARD errors (B) grouped by pump model.

Results:

Global error assessment:

The mean error and MARD were different according to BR and according to the pump as shown by boxplots in **fig. 2**. The values of mean error percentage showed **in Fig. 2A** are mostly negative and suggest a tendency to under delivery. Values for the 15 minutes observation windows MARD presented in fig. 2B highly increase as BR drops exhibiting a very high difference between setpoint and actual injected volume. Some important differences were observed between pumps. For 15 minutes observation windows, Omnipod mean MARD reaches 61.3% at 0.1UI/h while t:slimx2 shows the smallest mean MARD results with a mean MARD at 22.7% **(fig. 2B**). A table of these values can be found in **supplementary data.**

	Minimed 640 G		Omnipod		Ypsopump		t:slim x2	
	Volume per stroke (UI) mean (SD)	Stroke period (min) mean (SD)	Volume per stroke (UI) mean (SD)	Stroke period (min) mean (SD)	Volume per stroke (UI) mean (SD)	Stroke period (min) mean (SD)	Volume per stroke (UI) mean (SD)	Stroke period (min) mean (SD)
2 UI/h	0.28 (0.086)	8.54 (1.67)	0.049 (0.011)	1.50 (0.079)	0.095 (0.018)	2.99 (0.18)	0.17 (0.035)	4.99 (0.32)
1 UI/h	0.046 (0.014)	2.82 (0.50)	0.050 (0.014)	2.99 (0.15)	0.050 (0.011)	2.95 (0.37)	0.084 (0.031)	5.00 (0.29)
0.5 UI/h	0.024 (0.017)	3.05 (0.47)	0.050 (0.040)	5.98 (0.33)	0.048 (0.008)	5.99 (0.34)	0.039 (0.013)	4.92 (0.54)
0.1 UI/h	0.024 (0.0092)	14.6 (1.89)	0.045 (0.023)	29.7 (1.38)	0.041 (0.015)	29.6 (1.7)	0.0084 (0.0039)	4.94 (0.37)

Table 1 : Insulin stroke features
Insulin stroke regularity is calculated for each pump model at each BR regarding inter-stroke time and stroke volume regularity.

Evolution of MARD for different observation windows (15min, 30min, 60min, 120min and 240min), presented in **fig. 3,** differs between pump models and BR values. Overall, we observed two distinct behaviors. Firstly, when positive errors immediately compensate negative errors, the resulting MARD decreases when observations windows get wider.

This explains why some MARD evolution plots quickly plummet. For instance, error of Omnipod at 0.1UI/h was 68% error at 15-min observation windows vs 19% at 60-min time interval. We will later refer to this phenomenon as short-term inaccuracy in our discussion.

Secondly, some errors, either positive or negative, are maintained over longer time windows, sometimes even over the whole 8-hour test. Then, MARD does not evolve much when the observation window gets wider, making the MARD evolution plot nearly flat (**fig. 3**: Omnipod 0.5UI/h 23% error at 15-min interval windows against 21% error at 60-min time interval). This behaviour will be later referred to as long-term inaccuracy.

Evaluation of stroke amplitude and frequency in each pump

In order to decipher the cause for the inaccuracies, we evaluated the volume and frequency of each stroke according to BR and pump. As observed in **fig. 4**, pump models adopt different strategies to adjust BR. Omnipod made the choice to maintain stroke volume and to adapt inter-stroke time. Oppositely, t:slim x2 adjusted stroke volume keeping the same inter-stroke value for each set BR. Others, such as Minimed 640G and Ypsopump adopted both strategies changing either inter-stroke time value or insulin stroke volume depending on BR range. Also, **fig. 4** highlights overall imprecision of different mechanism: every model pump show approximately the same intrinsic stroke volume variability except for Minimed 640G at 2 U/h. However, this model had unclearly delimited strokes, allowing a less precise discrimination between strokes, whether segmentation was performed by the human eye or by use of our algorithm (see supplementary data). A good reproducibility for inter-stroke time at all BR was observed except for Ypsopump and Minimed 640G at 0.1UI/h BR.

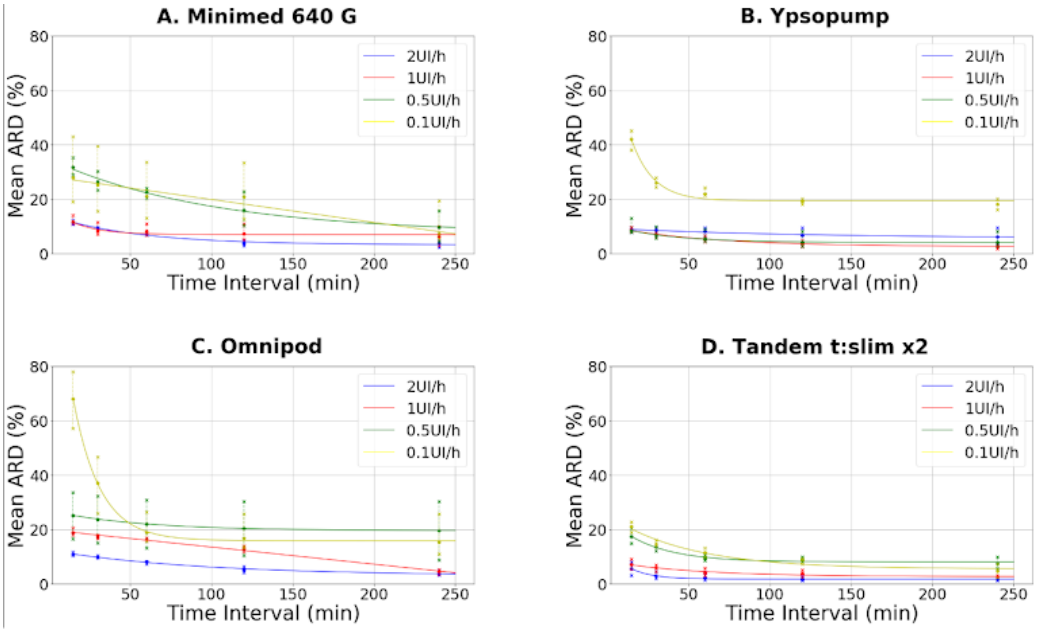

Fig. 3: Evolutive MARD.
For each pump model and each set BR, MARD error results is calculated for several time-windows intervals along the four replicas. Evolutive MARD is the graphic representation of MARD for several observation windows in each situation.

Discussion

This study evaluates for the first time, off-the-shelves CSII accuracy results at several BRs, from 0.1 to 2 UI/h, using a high precision and reactive method (13). Overall, our results showed a general tendency to under-delivery with up to -16% of the announced insulin volume delivered over 8h. We also demonstrated a huge heterogeneity of CSII accuracy according to BR and CSII model. Using usual BRs (1 to 2 UI/h), MARD goes from 8% (Ypsopump and t:slim x2) to 21% (Omnipod). At lowest BRs, MARD errors become commonly higher, from 22% for t:slimx2 until 61.3% for Omnipod at 0.1 UI/h. We also generally observed an overall less reproducible error for lower BRs. A few cases of over-delivery were even observed (Omnipod at 0.1 UI/h instance 3, and 0.5 UI/h instance 2, t:slimx2 at 0.1 UI/h).

CSII accuracy has been previously evaluated by independent (18, 20, 22) and dependent (19, 11, 23) teams testing several CSII models with numerous methodologies. Results generally agreed on a CSII lower precision for the smallest BRs and on the fact that accuracy is model dependent. However, some major differences between results remain in the literature: Omnipod overall precision is for example found highly accurate by Zisser et al (18) while inaccurate by others (11,19,20). However, our results remain unique for several reasons: some CSII model had not been yet assessed such as t:slimx2 and Ypsopump; accuracy using BR below 0.5 had never been tested and above all, a leading edge method of measurement able to measure insulin flow precisely and continuously was used here (13).

Testing at lowest BRs such as 0.1UI/h is essential, as the smallest flowrates remain intuitively the hardest to deliver correctly for CSII-based microfluidic systems. Yet, low BRs are commonly used in type 1 diabetes, especially in children (15) and by AP systems (16,21). CSII inaccuracy at low BRs could partly explain the fact that glucose targets are not always reached in these specific populations (7,9). Clinical studies have to be implemented in order to test this hypothesis.

The origins of these observed inaccuracies remain unknown. The analysis and the comparison of insulin stroke delivery parameters, such as frequencies and stroke volumes, for each CSII models at several BRs, could bring a piece of the response. Our method provides a continuous measurement able to study for the first time peak-wise CSII accuracy.

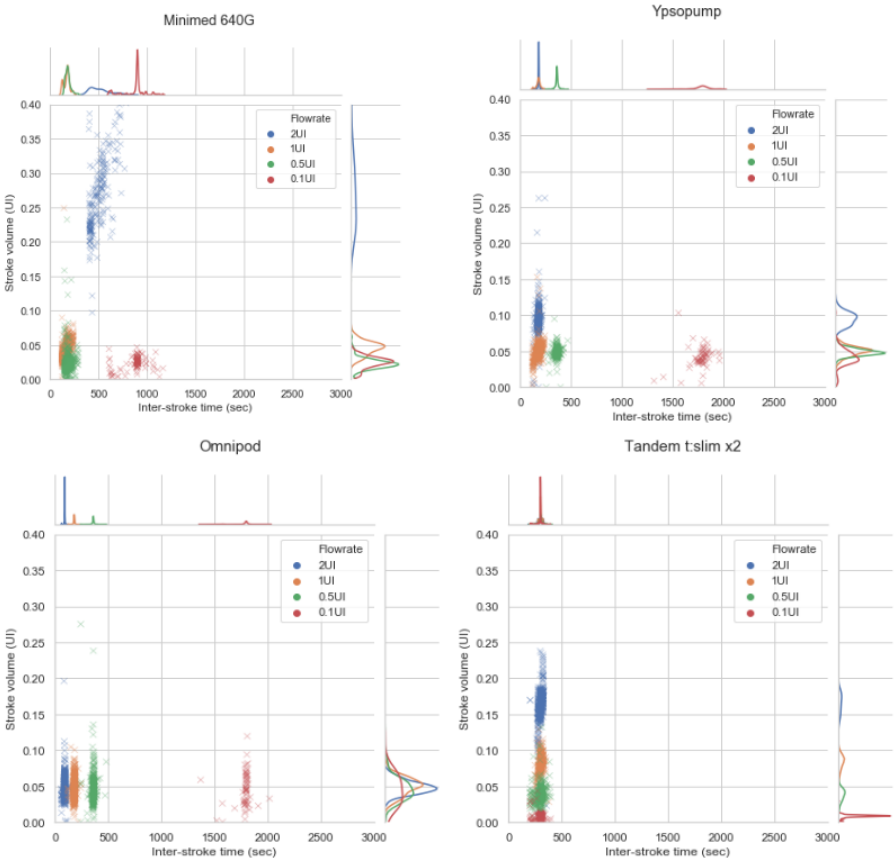

Fig. 4: Insulin stroke regularity.
The stroke unit volume is displayed according to its corresponding inter-stroke time, for all observed strokes. The uni-axial distributions of each test situation is represented with gaussians.

Insulin stroke analysis (**fig.4**) shows that CSII imprecisions appear to come from a variability of insulin strokes frequency. This phenomenon is accentuated when BR is reduced and of various significance depending on pump model. Indeed, inter stroke time are observed as more spread for smaller BRs, especially for Minimed 640G and Ypsopump at 0.1UI/h. Oppositely, t:slimx2 showed the lowest variability in inter-stroke time for the same BR. Variabilities of stroke volumes appear to be similarly spread whatever the BR. In the specific case of Minimed 640G at 2UI/h, the stroke volume appears to be exceptionally spread. At 2 UI/h, this model showed unclearly delimited strokes (see supplementary data), and its flow rate oscillates around an average value. However, it presents no extensive delivery error, looking at both the 15min MARD and the mean error (see fig.2). Therefore, we have no element to say its delivery isn't clinically adapted.

Figure 4 also points to the choice each manufacturer made, regarding the key parameter used to modulate BR. For instance, Omnipod clearly seems to use a variation in stroke frequency with constant stroke volume to modify BR, whereas t:slim

x2 apparently chose to keep a constant stroke frequency and to change the stroke volume to achieve this. Ypsopump and Minimed 640G seem to use a combination of both strategies, using stroke volume adaptation for the highest range of BRs and inter stroke adaptation for the lowest. These observations are made clear by looking at the relative positions of each cloud of points for each pump model on figure 4.

Manufacturer choices and CSII accuracy might have clinical consequences. Reducing BR by acting on stroke frequency implicates that in this situation, strokes as rare as one every thirty minutes could be observed. This discontinuous way to deliver insulin could promote glucose instability and leads to another consequence, concerning the usability of the CSII for artificial pancreas. As AP algorithms could potentially set a low BR order for only 5 to 15 minute (4), it is conceivable that no insulin at all would be delivered within that time window. For this reason Tandem manufacturers appear to have made the most adapted choice by keeping constant frequency and only changing its strokes amplitude to modulate BRs which seems to better suit the constraints of closed loop systems.

In the results section, we introduced two behaviours as regards to how MARD plots evolve according to time, namely short-term instability (Ypsopump and Omnipod at 0.1 U/h; t:slim x2 at all BRs) and long-term instability (Minimed640G; Ypsopump and Omnipod at higher BRs). To date, no evidence has established a causality between insulin administration errors and GV, whether short-term or long-term. One might indeed argue that under-delivery and over-delivery lasting less than 15 minutes (short-term instability) could physiologically have no clinical impact at all. On the opposite, long-term instability could foster overall GV, as it implies long exposures to either higher doses or lower doses of insulin, and naturally lead to a succession of hypoglycemia and hyperglycemia.
Besides, the only certainty we have is that CSII short-term instability would appear acceptable compared to long-term as far as that the global mean error remains low and the plateau shape is reached as fast as possible. On the opposite case, long term instability could be acceptable since a constant error makes it easier for the patient to adapt his treatment [22], provided of course no major changes from under to over delivery occur, but rather a simple and stable long-lasting error. In the context of AP systems, this last kind of predictable error could be integrated in an AP algorithm in order to correct these inaccuracies. By contrast, short-term instability, which corresponds to a high 15-min time interval MARD, could be seen as problematic since control algorithms adapt the dose frequently and could base their calculations on frequent errors.

Conclusion

In conclusion, we demonstrated that a more precise evaluation of CSII shows a slight global tendency to under-delivery, important errors in delivery over 15 minutes time intervals, and errors that are enhanced with the diminution of BR. Defects in reproducibility of the delivery of CSII have also been highlighted by identifying strokes characteristics. It appears necessary to qualify the characteristics of inaccuracies according to CSII models to develop closed loop algorithms that take these inaccuracies into account, specifically for the CSII they have been associated with.

Further investigation is required to specifically assess the clinical effect of the observed short-time mis deliveries on patients.

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Supplementary data:

CSII delivery typology:

Our new assessment method for CSII accuracy showed for the first time a direct flow measurement with a high precision resolution. The assessment of four off-the-shelves CSII
systems with all four core delivering technologies reveal different flow rate typologies.

Tandem t:slim x2 shows well drawn insulin stroke with a null inter-stroke value. On the opposite, Minimed 640G has a more diffusive signal oscillating around an average value. Omnipod and Ypsopump delivery behavior appear to be in-between with well-drawn insulin strokes but with a more diffusive system.

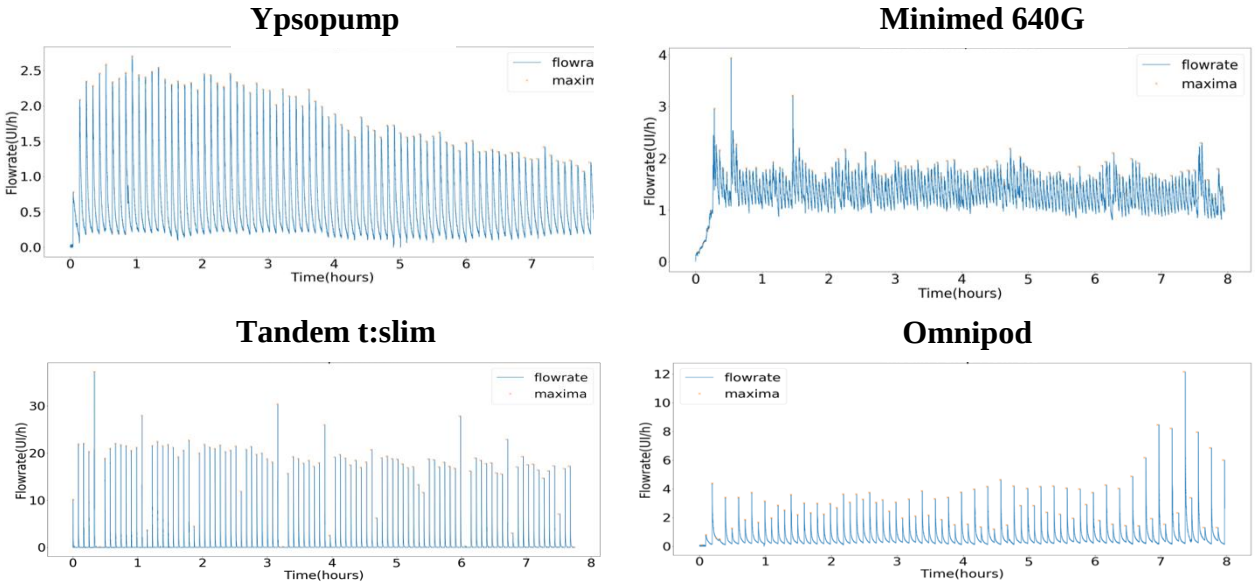

Fig. 1: Insulin delivery behavior regarding pump model.
Delivery behavior is different regarding device CSII technology. From Ypsopump (up left), to Omnipod (down right) passing by Minimed 640G (right up) and tandem t:slim x2 (left down).

Evolution of MARD as a function of time observation windows

Evolution of MARD for different observation windows (15min, 30min, 60min, 120min and 240min) represents the absolute error of CSII delivery for several time intervals in which error is calculated. We present here the correspondence between MARD evolution points and delivery error time series corresponding to each interval.

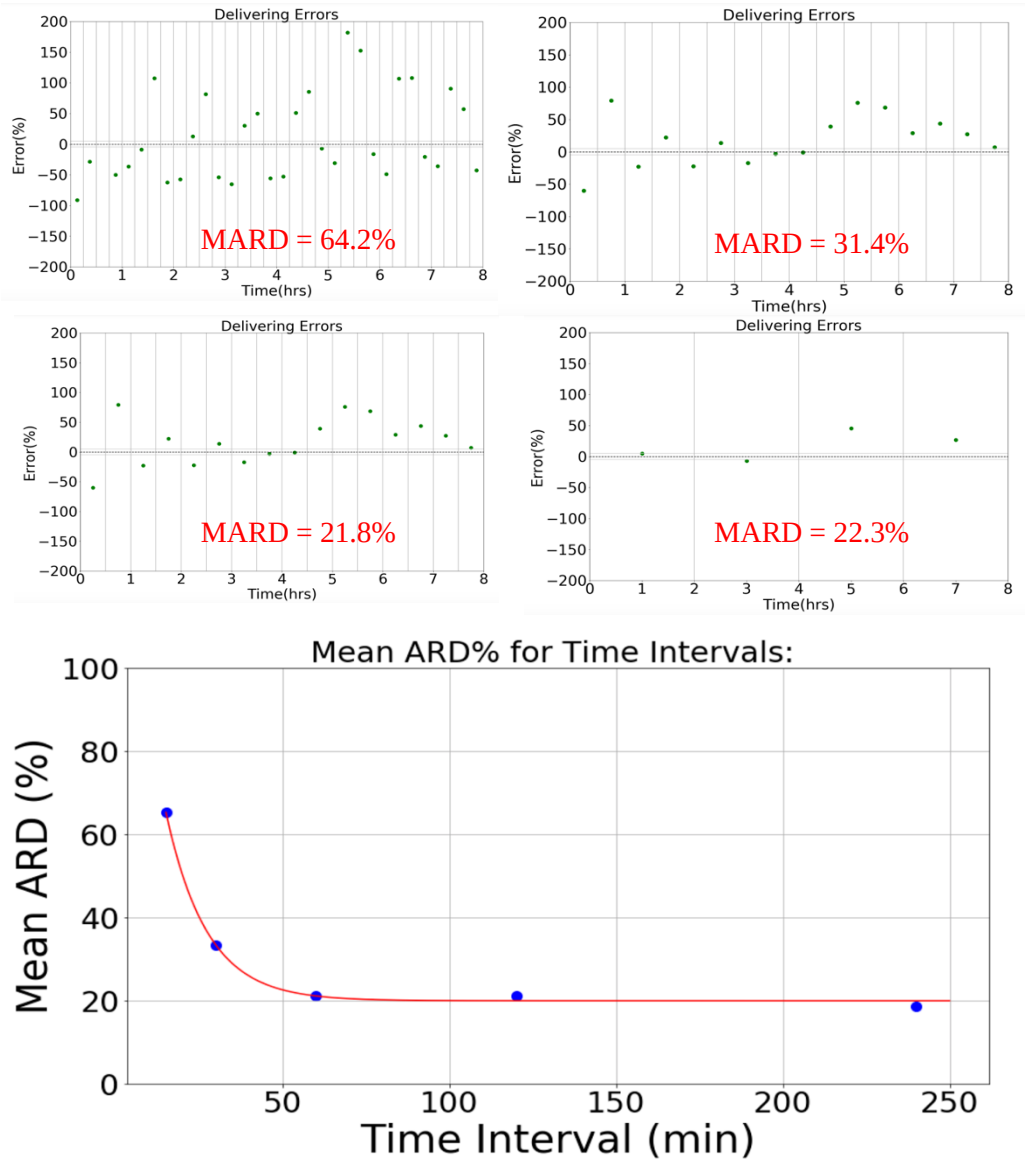

Fig. 2: Evolutive MARD building principle.
For a test results, error MARD is calculated at several time window. The more dose error is calculated for wide time interval, the more the error is smoothed over the total time experiment. Evolutive MARD is the evolution of that smoothness along time interval opening.

Minimed 640G peak detection

We observed that our algorithm visually detects all strokes efficiently, once provided with a parameter corresponding to the minimal distance under which two consecutive peaks should not be detected. This parameter, for each pump and BR combination, was determined by frequential analysis.

The entire pump model at all BRs had efficient peak detection except for Minimed 640G at the highest BR (2UI/h). As shown hereunder in the figure, delivery type looks too random (due to system inertia) to give a steady peak delivery. This explain the spread could shape of figure 4 for Minimed 640G at 2UI/h.

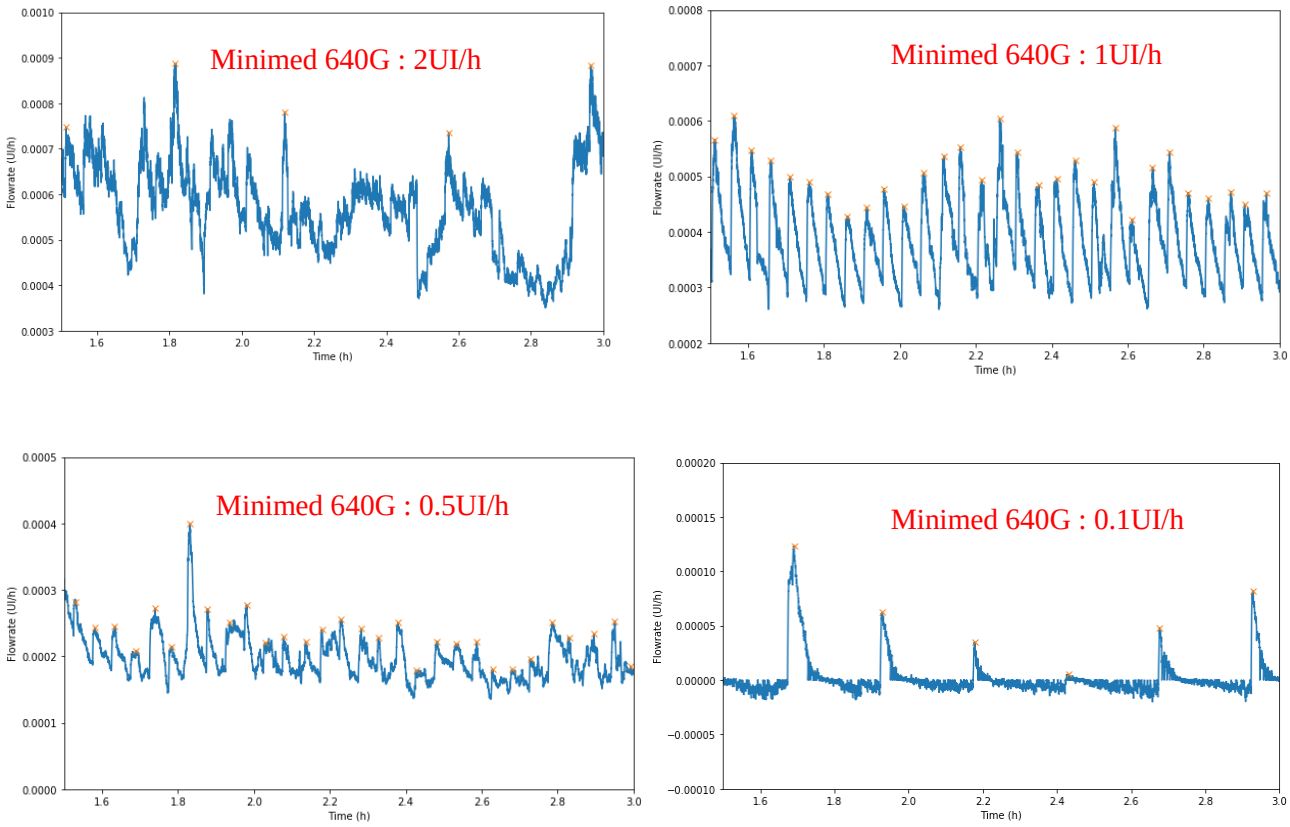

Fig. 3: Peak detection particularity illustration for Minimed 640G.
Peak detection at 2UI/h is more difficult for our peak algorithm due to the random oscillating delivery behavior.

General results table error:

Furthermore, we share the general results of mean and MARD error (with mean and standard deviation indicators) for the entire tests.

Results		640G		Omnipod		Ypsopump		t:slim x2	
		Mean%	MARD%	Mean%	MARD%	Mean%	MARD%	Mean%	MARD%
2UI	n =1 n = 2 n = 3 n = 4	-6.3 4.2 -3.1 0.005	10.1 14.9 11.2 11.3	-3.1 -1.0 -6.6 -2.2	9.8 10.0 11.0 14,5	-3.3 -1.1 -10.3 -9.1	9.1 6.8 8.93 6.7	-0.61 -3.2 -0.9 -0.07	8.7 9.3 7.6 3.9
	mean (SD)	**-1.3 (3.9)**	**11.8 (1.8)**	**-3.2 (2.4)**	**10.3 (0.64)**	**-5.9 (4.5)**	**7.9 (1.3)**	**-1.2 (1.4)**	**7.4 (2.4)**
1UI	n =1 n = 2 n = 3 n = 4	-1.5 -9.1 -2.3 -11.7	12.2 9.1 9.4 22.5	-2.6 -1.7 -3.6 5.2	22.8 21.1 20.3 19.4	-1.5 -1.6 3.5 -1.5	12.2 8.9 9.0 8.0	2.45 -5.1 -1.2 0.4	19.9 7.2 15.7 7.9
	mean (SD)	**-6.1 (4.3)**	**13.3 (5.4)**	**-0.6 (3.4)**	**21.6 (1.4)**	**-0.2 (2.2)**	**9.5 (1.6)**	**-0.9 (3.2)**	**12.7 (6.2)**
0.5UI	n =1 n = 2 n = 3 n = 4	-19.2 0.4 -3.8 0.1	35.4 32.1 22.1 50	-7.7 4.2 -1.8 -2.1	13.3 35.7 19.2 38,6	-5.6 -2.3 -9.5 -2.8	9.0 8.7 26.4 7.7	-12.6 -6.1 -9.1 -2.2	27.9 13.2 13.4 20.4
	mean (SD)	**-5.6 (8.0)**	**35.0 (10.0)**	**-1.85 (4.9)**	**22.7 (11.6)**	**-5.0 (2.9)**	**12.9 (7.8)**	**-7.5 (4.4)**	**18.7 (7.0)**
0.1UI	n =1 n = 2 n = 3 n = 4	-1.27 8.04 -54.0 -1.97	21.98 21.05 59.8 40.9	-45.6 -3.7 13.5 3.0	45.2 74.1 72.0 51.8	-19.6 -16.8 -5.2 -22.4	29.5 30.9 33.1 85.7	-5.6 1.9 7.8 2.1	26.0 20.1 24.0 20.8
	mean (SD)	**-12.3 (28.2)**	**35.9 (18.4)**	**-8.2 (25.9)**	**61.3 (13.8)**	**-16 (7.6)**	**44.8 (27.3)**	**1.55 (5.5)**	**22.7 (2.8)**

Table 1: General results of CSII accuracy
All tested CSII model are represented and mean/mard of each replicas are represented Mean(mean) and mean (MARD) for all replicas of a given model at a given basal rate is also represented.