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Henri Mermoz Kouye

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Sensitivity analysis approaches for stochastic models. Application to compartmental models in epidemiology.

Approches d'analyse de sensibilité de modèles stochastiques. Application aux modèles compartimentaux en épidémiologie.

Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 574, Mathématique Hadamard (EDMH)
Spécialité de doctorat: Mathématiques aux interfaces
Graduate School : Mathématiques, Référent : Faculté des Sciences d'Orsay

Thèse préparée dans l'unité de recherche MaIAGE (Université Paris-Saclay, INRAE), sous la direction de Elisabeta VERGU, directrice de recherche, la co-direction de Clémentine PRIEUR, professeure des universités, le co-encadrement de Gildas MAZO, chargé de recherche.

Thèse soutenue à Paris-Saclay, le 02 décembre 2022, par

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Titre: Approches d'analyse de sensibilité de modèles stochastiques. Application aux modèles compartimentaux en épidémiologie.

Mots clés: Analyse de sensibilité, Indices de Sobol', Méthodes de Monte-Carlo, Processus stochastiques, Modèles épidémiologiques, Algorithmes de simulation exacte.

Résumé: Cette thèse traite de l'analyse de sensibilité des modèles stochastiques. Ces modèles sont souvent entachés d'incertitudes qui proviennent principalement de deux sources : l'incertitude paramétrique liée à la méconnaissance des paramètres et l'aléa intrinsèque qui représente le bruit inhérent au modèle provenant de la façon dont le hasard intervient dans la description du phénomène modélisé. La présence de l'aléa intrinsèque constitue un défi en analyse de sensibilité car, d'une part, il est en général caché et donc ne peut pas être caractérisé et, d'autre part, il agit comme un bruit lorsqu'on évalue l'impact des paramètres sur la sortie du modèle. Or, dans un domaine comme l'épidémiologie, les enjeux associés à la sensibilité d'un modèle peuvent être importants dans la gestion des épidémies car impactant les décisions prises sur la base de ce modèle. Cette thèse étudie des approches d'analyse de sensibilité des modèles stochastiques tels que les modèles épidémiologiques basés sur des processus stochastiques, dans le cadre de l'analyse basée sur la variance. Dans un contexte général, nous introduisons une méthode qui optimise le compromis entre le nombre de valeurs de paramètres des modèles et le nombre de répliques des évaluations en ces valeurs à considérer dans l'estimation des indices de sensibilité. Pour cette méthode, nous considérons la classe des quantités d'intérêt de la sortie des modèles stochastiques qui sont sous la forme d'espérances conditionnelles par rapport aux paramètres. Dans le cadre de l'estimation des indices de sensibilité par la méthode de Monte-Carlo, nous contrôlons le risque quadratique des estimateurs, montrons sa convergence et trouvons un compromis entre le biais lié à la présence de l'aléa intrinsèque et la variance. Dans le

contexte spécifique des modèles compartimentaux stochastiques en épidémiologie, nous caractérisons l'aléa intrinsèque associé aux processus stochastiques sur lesquels ces modèles sont basés. Ces processus stochastiques peuvent être Markoviens ou non-Markoviens. Pour les processus Markoviens, nous utilisons les algorithmes de Gillespie pour expliciter l'aléa intrinsèque et le séparer de l'aléa paramétrique. Et dans le cas des processus non-Markoviens, nous étendons à une classe large de modèles compartimentaux la construction de Sellke qui permettait à l'origine de décrire les dynamiques du modèle épidémiologique SIR dans un cadre non nécessairement Markovien. Cette extension a permis d'élaborer un algorithme de simulation permettant de générer des trajectoires exactes dans un cadre non-Markovien d'une large gamme de modèles compartimentaux mais aussi de pouvoir séparer l'aléa intrinsèque de l'aléa paramétrique dans la sortie de ces modèles. Ainsi, pour les deux types de processus, Markoviens et non-Markoviens, la séparation des deux sources d'aléas a été obtenue et elle permet d'écrire la sortie du modèle comme fonction déterministe des paramètres incertains et des variables représentant l'aléa intrinsèque. Lorsque l'incertitude sur les paramètres est supposée indépendante de l'aléa intrinsèque, cette représentation permet d'évaluer les contributions de l'aléa intrinsèque sur les sorties du modèle, en plus des contributions des paramètres. Il est également possible de caractériser les différentes interactions. Cette thèse a contribué à développer une approche d'estimation des indices de sensibilité et à évaluer la contribution de l'aléa intrinsèque dans les modèles compartimentaux en épidémiologie basés sur des processus stochastiques.

Title: Sensitivity analysis approaches for stochastic models. Application to compartmental models in epidemiology.

Keywords: Sensitivity analysis, Sobol' indices, Monte Carlo methods, Stochastic processes, Epidemic models, Exact simulation algorithms.

Abstract: This thesis focuses on the sensitivity analysis of stochastic models. These models include uncertainties that originate mainly from two sources: the parametric uncertainty due to the lack of knowledge of parameters and the intrinsic randomness that represents the noise inherent to the model coming from the way chance intervenes in the description of the modeled phenomenon. The presence of intrinsic randomness is a challenge in sensitivity analysis because, on the one hand, it is generally hidden and therefore cannot be characterized and, on the other hand, it acts as noise when evaluating the impact of the parameters on the model output. However, in epidemiology, the issues associated with the sensitivity of a model can be important in the control of epidemics because they impact the decisions made on the basis of this model. This thesis studies approaches for sensitivity analysis of stochastic models such as epidemiological models based on stochastic processes, in the framework of variance-based analysis. In a general context, we introduce a method for estimating sensitivity indices that optimizes the trade-off between the number of input parameter values of the model and the number of replications of model evaluation in each of these values. For this method, we consider the class of quantities of interest of stochastic model outputs that are in the form of conditional expectations with respect to uncertain parameters. In the context of estimation of sensitivity indices by the Monte Carlo method, we control the quadratic risk of the estimators, show its convergence and find a trade-off between the bias related to the presence of the intrinsic randomness and the variance. In the specific context

of stochastic compartmental models in epidemiology, we characterize the intrinsic randomness of the stochastic processes on which these models are based. These stochastic processes can be Markovian or non-Markovian. For Markovian processes, we use Gillespie algorithms to make explicit the intrinsic randomness and to separate it from uncertain parameters. Regarding non-Markovian processes, we extend to a large class of compartmental models the Sellke construction, which was originally introduced to describe epidemic dynamics of the SIR model in a framework that is not necessarily Markovian. This extension has allowed us to develop an algorithm that generates exact trajectories in a non-Markovian framework for a large class of compartmental models but also to be able to separate intrinsic randomness from parameter uncertainty in the output of these models. Thus, for both types of processes, Markovian and non-Markovian, the separation of the two sources of uncertainty has been obtained and it allows to represent model outputs as a deterministic function of the uncertain parameters and the variables representing the intrinsic randomness. When the uncertainty on the parameters is assumed to be independent of the intrinsic randomness, this representation allows to assess the contributions of the intrinsic randomness on the model outputs, in addition to the contributions of the parameters. It is also possible to characterize different interactions. This thesis has contributed to develop an approach to estimate sensitivity indices and to evaluate the contribution of intrinsic randomness in compartmental models in epidemiology based on stochastic processes.


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 **MaIAGE**
MATHÉMATIQUES ET INFORMATIQUE APPLIQUÉES DU GÉNOME À L'ENVIRONNEMENT

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CHAPTER 1

Introduction

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1.1 General considerations on modeling epidemic spread

Infectious diseases, whether they affect human, animal or plant populations can be associated with serious societal, economical and environmental issues which may directly concern human survival. Unfortunately, nowadays, it is not difficult to witness the potential costs of an epidemic. Indeed, the COVID-19 pandemic caused by SARS-CoV-2 is responsible of millions of deaths around the world according to World Health Organization (WHO). This pandemic resulted in food crisis, economic impact and recession and it led to huge social upheavals. This crisis highlighted the role and the relevance of analysis and prediction tools for infectious diseases. In particular, mathematical epidemic modeling has proven to be a valuable tool not only in understanding the spread of SARS-CoV-2 but also in decision-making and management policies. Long before the outbreak of the COVID-19 pandemic, the contribution of mathematical models in understanding and controlling epidemics was underlined. For example, [Becker \(1979\)](#), after a brief review of epidemic models, compared them and concluded to their usefulness. The question of usefulness was also discussed in the paper of [de Jong \(1995\)](#) which defends the use of these models despite criticisms of them. More recent studies highlighting the role of

mathematical modeling can be mentioned (Kao, 2002). When the COVID-19 pandemic occurred, the interest in mathematical models increased considerably and even far beyond the scientific sphere (Thompson, 2020; James et al., 2021).

Indeed, mathematical models provide useful insights into epidemic dynamics and enable to point out unsuspected phenomena such as, transmission ways or immunity duration... or underlying processes (e.g. temporal or spatial patterns) hidden behind observed dynamics. In addition to fields such as medicine, biology or microbiology which study pathogens, epidemic modeling enables to better understand the mechanisms by which pathogens spread within a population or between populations. The mathematical study of epidemics is not recent. It goes back at least to the 18th century with the study of smallpox by Bernoulli (1760). The development of this discipline has led to the emergence of different approaches for modeling the spread of epidemics, among which the ones relying on agent-based models or compartmental models are the most popular.

Agent-based models focus on the individuals in the population in which an infection spreads and it consists in tracking individual behaviors and interactions in order to infer the evolution of the epidemic dynamics, (for instance, see Perez and Dragicevic (2009); Hoertel et al. (2020)). Their construction relies on rules and characteristics of individuals to describe their behaviors and how these affect dynamics of the disease at population scale. Therefore, the great advantage of these models is that they provide a detailed description to understand the determinants of epidemic propagation on various aspects: environment, decisions, interactions, etc. However, they can easily get complex and their simulation can be computationally expensive in practice.

The compartmental approach took off from the work of Kermack et al. (1927). Today, it turns out to be the most widely used modeling method (Hethcote, 2000; Allen, 2008). Consider a population within which an infectious disease spreads. Moreover, suppose that, for such infection, different health statuses with respect to the disease are observed such as susceptible, infected and/or infectious, immunized, hospitalized, etc. These statuses are connected to each other according to the way the different stages of infection occur. Then, compartmental modeling consists in dividing individuals into usually disjoint classes with respect to their status and then in studying the evolution over time of the number or the proportion of individuals in the different classes considered. The resulting model is represented by compartments corresponding to classes of health statuses and arrows which schematize the different types of transitions that can occur between health statuses. A schematic representation of such models is proposed in Figure 1.1.

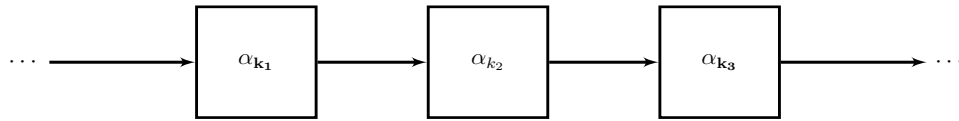


Figure 1.1 – Schematic representation of a compartmental model. α_{k_1} , α_{k_2} and α_{k_3} are three compartments corresponding to three different health statuses. Arrows represent transitions between compartments: for example, the arrow $\alpha_{k_1} \rightarrow \alpha_{k_2}$ means that individuals with status α_{k_1} can switch to status α_{k_2} .

This modeling approach can be refined or extended in various points. For example, structured population and meta-population approaches can be mentioned. The structured population approach is a refinement of compartmental modeling that consists in setting up categories or structures for individuals such as age (Gurtin and Maccamy, 1974; Castillo-Chavez et al., 1989; Balabdaoui and Mohr, 2020), predisposition to infection (Omame et al., 2021), social structures (Andersson, 1997; Pellis et al., 2012; Hilton and Keeling, 2019; Li et al., 2021) such as households, workplaces, transports... In this case, it is assumed that the infection characteristics differ with respect to the categories or structures considered. For example, in age-dependent models, infections or recoveries could depend on the range of ages of individuals. The meta-population approach is an extension of compartmental modeling to a group or a network of populations with different characteristics or located at different areas. Thus, this approach consists in studying not only the epidemic dynamics within each population using compartmental models but also the way the infectious disease spreads from a population to another as individual movement flows or contacts between individuals of different populations can occur within the network. This allows to take into account for example the spatial distribution of populations and enables to describe epidemics at larger scale (Sattenspiel and Dietz, 1995; Pastor-Satorras et al., 2015; Molina and Stone, 2012; Shao and Han, 2022; Ball et al., 2015).

1.2 Formal framework of the thesis

1.2.1 Compartmental models in epidemiology

Like any mathematical model, compartmental models can be classified into two categories according to the way they manage the hazard: there are deterministic and stochastic models.

Deterministic models rely on functions which depend only on epidemic parameters in order to describe dynamics. Let denote by θ the collection of epidemic parameters and by y the outputs of such models. Then, by disregarding the possible dynamic nature (e.g. time series, functional outputs) of

these model outputs for illustration purpose, y is under the form:

$$y = f(\theta), \quad (1.1)$$

where f is some deterministic function. Hence, the resulting outputs cannot vary unless initial conditions or epidemic parameters change. Among those models, ordinary differential equations (ODE) are widely used (Brauer et al., 2012). In that case, epidemic dynamics are ruled by some ODE system which depends only on parameters. Besides, there are also models based on integro-differential equations or partial differential equations (Chalub and Souza, 2011; Medlock and Kot, 2003).

Regarding stochastic compartmental models, even when initial conditions and epidemic parameters are set, transitions in health statuses of individuals are assumed to occur at random times. Therefore, the evolution over time of the epidemic dynamics is random, yielding stochastic processes (Allen, 2008; Britton et al., 2019). Let Z denote a random variable or a collection of random variables and $Z(\omega)$ a realization of Z where ω belongs to the measurable space on which Z is defined. Recall that θ denotes the collection of epidemic parameters. Therefore, for fixed value of θ , outputs of such models still vary at any evaluation. A realization $y(\omega)$ of model output is under the form:

$$y(\omega) = f(\theta, Z(\omega)), \quad (1.2)$$

where f is a deterministic function. Thus, two model evaluations at the same θ yield $f(\theta, Z(\omega_1))$ and $f(\theta, Z(\omega_2))$ where realizations $Z(\omega_1)$ and $Z(\omega_2)$ of Z are not necessarily equal. The stochasticity of outputs, regardless of variation of θ , is inherited from Z , hence Z is referred to as the *intrinsic randomness* of the model. Resulting processes belong to two main families: the Markovian processes and the non-Markovian processes (Gani, 1973; Anderson, 2012; Feng et al., 2019). The difference between those two families lies in the fact that for Markovian processes, future dynamic depends only on the current state of the process and not on past dynamic, which does not hold for non-Markovian processes.

1.2.2 Uncertainty quantification and sensitivity analysis in epidemic modeling

In practice, epidemic models are intended to address a certain number of questions including: are we able to predict epidemic trajectories? What are the key factors of the epidemic spread? What are the possible strategies to control the infectious disease spread? What are the potential impacts of these strategies? So many questions for which the accuracy of the answers strongly depends on the accuracy and reliability of the model. This requires knowing epidemic

parameters as accurately as possible. However, the true values of these parameters are generally unknown. Then, those models suffer from uncertainties. In order to improve their reliability and usefulness in decision-making or setting control and management policies, it is necessary to study and quantify uncertainties (Taghizadeh et al., 2020; Marion et al., 2022; Swallow et al., 2022). Uncertainties for stochastic models can be classified into two categories: the parameter uncertainty and the intrinsic randomness. Parameter uncertainty occurs when model parameters are unknown or poorly known. Regarding the intrinsic randomness, it is inherent to the model and it is responsible for the variability of the output of the model even when the parameters are perfectly known. As a part of uncertainty quantification (UQ), sensitivity analysis aims at evaluating the part due to each parameter or group of parameters in the variability of the model output. Such a study could have several objectives: identification of key parameters, model reduction, optimization, model calibration. Hence, sensitivity analysis provides a better understanding of the model regarding input-output relation. For instance, Wu et al. (2013) reviewed some sensitivity analysis methods for epidemic models. In Courcoul et al. (2011) and Rimbaud et al. (2018), sensitivity analysis was used to identify key parameters of disease propagation within animal and plant populations respectively. It has been naturally used in human epidemiology (Blower and Dowlatabadi, 1994) and especially in recent years to study epidemic models of COVID-19 (Lu and Borgonovo, 2021; Wang and Aydin, 2020; Da Veiga et al., 2021b).

Sensitivity analysis of deterministic models consists in varying model parameters and then quantifying the effects on the output in terms of variability. To assess the impact of a parameter or a set of parameters, the latter is varied and the corresponding variation of the output is measured. There are various ways to vary parameters and measure output variations, corresponding to various methods of sensitivity analysis. These methods belong to two main families: the so-called local methods and the so-called global methods. Local methods fix nominal or reference parameters θ^* , perturb these values with $\Delta\theta$ and evaluate the output at θ^* and $\theta^* + \Delta\theta$: $f(\theta^*)$ and $f(\theta^* + \Delta\theta)$. Depending on the choice of the perturbation, various indices can be constructed using differences $f(\theta^* + \Delta\theta) - f(\theta^*)$: derivative based indices (Capaldo and Pandis, 1997; Helton, 1993), Morris indices (Morris, 1991), derivative based global sensitivity measures (Sobol' and Kucherenko, 2010) which are globalized versions of local indices, etc. These methods allow to account locally for the influential parameters.

The so-called global methods are based on an exploration of the parameter space, unlike the local methods, to construct sensitivity indices. These methods include those based on Sobol' indices (Sobol', 1993), Shapley effects (Iooss and Prieur, 2019), moment-independent indices (Borgonovo, 2007; Da Veiga et al., 2021a) etc. Variations in outputs can be quantified using variance or

discriminant measures.

1.2.3 Brief overview of variance-based sensitivity analysis framework

A common way to measure variability is variance. The variance-based sensitivity analysis is an approach that measures the contribution of a parameter or group of parameters to the global variance of the output. This approach, which is one of the most widely used, was developed from the works of Sobol' and Saltelli (Sobol', 1993; Homma and Saltelli, 1996; Archer et al., 1997) and has its source in the work of Hoeffding (1948) on the representation of square integrable functions. The idea is to decompose the global variance of the output as a sum of variances related to the variation of each possible combination of model parameters. The higher the variance related to the variation of a parameter, the more this parameter is influential on the output of the model.

In stochastic model framework, i.e, models under the form (1.2), the correspondence $\theta \mapsto f(\theta, Z)$ is no longer a deterministic mapping because the output is no longer uniquely determined by θ but also by Z which is random. Two sets of parameters θ and $\tilde{\theta}$ respectively yield $f(\theta, Z(\omega))$ and $f(\tilde{\theta}, Z(\tilde{\omega}))$. Thus, when a parameter is varied, the resulting variation in output derives from both the variation in this parameter and the variation in the intrinsic randomness Z .

For variance-based sensitivity analysis, uncertainty is propagated in the model by sampling parameters using a random vector \mathbf{X} . Thus, output Y yields: $Y = f(\mathbf{X}, Z)$, where Z is the intrinsic randomness, given by a collection of hidden random variables and supposed independent of \mathbf{X} . Then, the variance of random variable Y obtained in output is then decomposed to separate the contributions of the parameters and the effects of their interactions. But here, $\text{Var}(f(\mathbf{X}, Z))$ also captures the effects of variation of Z . In most stochastic models used in practice, the intrinsic randomness Z is hidden and uncontrollable in the sense that it is not explicitly characterized and its distribution is unknown. Thus, contributions and interactions of the parameters or groups of parameters can be "corrupted" by effects of an uncontrolled noise, i.e. Z . Hence, the challenge is to assess the impact of parameters in presence of intrinsic randomness.

1.3 Main objectives and structure of the thesis

Faced with the challenge of intrinsic randomness of stochastic models, in particular those in epidemic modeling, several questions arise in the context of

sensitivity analysis.

- Q1.** How to accurately estimate variance-based indices for stochastic models despite the presence of intrinsic randomness?
- Q2.** How to separate effects of intrinsic randomness from those of uncertain parameters in variance-based sensitivity analysis for stochastic compartmental models?
- Q3.** How to assess contributions of intrinsic randomness to the global variance of stochastic compartmental models?

This PhD thesis addresses these issues. In the context of variance-based sensitivity analysis, the aim is to develop well-suited approaches to stochastic models, in particular the stochastic compartmental models used in epidemiology. This manuscript presents the different results according to the following plan. Chapter 2 reviews the state of the art around the two main themes of this thesis: compartmental modeling of epidemics and sensitivity analysis. A review of compartmental models is provided. In addition, simulation methods of stochastic models are discussed in both Markovian and non-Markovian contexts. Regarding sensitivity analysis, the framework of deterministic models is briefly presented in the univariate and multivariate cases: sensitivity indices and estimators. The framework of stochastic models, which is the focus of this work, is detailed according to current main approaches or techniques of sensitivity analysis. Finally, the problems studied in this thesis and our contributions are presented. In Chapter 3 (related to question Q1), the work carried out to control the quadratic risk of Monte Carlo estimators of Sobol' indices in the framework of stochastic models is presented. This chapter addresses the issue of accurate estimation of sensitivity indices for averaged quantities of interest in presence of intrinsic randomness. The problems of quadratic convergence of estimators and bias-variance trade-off encountered in estimation procedures are discussed. In Chapter 4 (related to questions Q2 and Q3), we address the issue of separating intrinsic randomness and parameter uncertainty in compartmental models based on continuous-time Markov chains. The procedure we propose consists in adapting exact simulation algorithms so that the intrinsic randomness becomes an input of the algorithms. Regarding Chapter 5 (related to questions Q2 and Q3), it deals with the same questions as Chapter 4 but in the framework of non-Markovian models. It describes a method for simulating compartmental models that are not necessarily Markovian, which allows to characterize the intrinsic randomness, to separate it from the parameter uncertainty and to evaluate its effects. In Chapter 6, a conclusion to this thesis as well as the perspectives opened by this work are presented.

CHAPTER 2

State of the art

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2.1 Compartmental modeling in epidemiology

Compartmental modeling of infectious diseases consists in describing a disease spread by defining classes or compartments of individuals with respect to different health statuses and then studying the dynamics over time of the number or proportion of individuals in these compartments. The definition of different compartments and connections between them is based on the knowledge of the different stages of infection or symptoms and how they are related to each other.

Several types of models can be built relying on what is known about the disease characteristics and dynamics (such as: rate of transmission of the infection, incubation periods, infectiousness periods...) and the characteristics of the population (like its size, its heterogeneity...) within which it spreads. Depending on modeling assumptions and context, models can be deterministic (i.e. predictions do not change from one simulation to another unless characteristics or initial conditions change) or stochastic (i.e. predicted dynamics incorporate randomness and can therefore change from one simulation to another).

2.1.1 Simple compartmental models in deterministic framework

This section aims at describing simple epidemic models corresponding to different basic constructions (different arrangement of compartments) in the literature. Throughout this section, a population of size N is considered. Individuals are supposed to mix perfectly so that the whole population is supposed homogeneous.

One of the most widely used method for describing epidemic dynamics in the deterministic framework relies on ordinary differential equations (ODE) (Kermack et al., 1927; Kermack and McKendrick, 1991; Hethcote, 2000, 1989) under the form:

$$\begin{cases} \frac{d}{dt}w(t) = F(w(t)) \\ w(0) = w_0 \\ t \geq 0 \end{cases} \quad (2.1)$$

where $w(t)$ represents the number or proportion of individuals in different compartments at time $t \geq 0$ and F is a function. In ODE epidemic modeling, to obtain the system (2.1), the principle is to describe and to quantify the interactions between the different compartments and their evolution over time. Depending on the number of compartments and of the nature and strength of interactions, different models can be obtained.

2.1.1.1 The simple SIR model

The SIR (Susceptible-Infected-Recovered) model is one of the first models studied (Kermack et al., 1927) and by far one of the most famous. This model assumes the existence of three health statuses: Susceptible (healthy individual who can contract the disease), Infected (infected and contagious individual) and Recovered (former infected individuals who are declared healed). Two types of events affect individual health statuses: an infection represented by the arrow $S \rightarrow I$ and a recovery represented by $I \rightarrow R$ (see Figure 5.1).

Infections depend on the capacity of the pathogen to spread and also on contacts between infected and susceptible individuals. The simple SIR model is schematized in Figure 5.1.

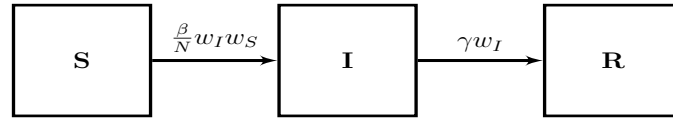


Figure 2.1 – The classical SIR model. Functions w_S and w_I denote the respective number of individuals in compartment S and I . Rates $\frac{\beta}{N}w_Iw_S$ and γw_I , with $\beta > 0$ and $\gamma > 0$, denote respectively the instantaneous proportion of individuals that are infected and recovered. Parameter β is the transmission rate and characterizes both the infectivity of the spreading pathogen and the propensity of a susceptible individual to become infected. Besides, parameter γ is such that $1/\gamma$ represents the average duration in infectious stage.

In the context of ODE modeling, epidemic dynamics of the simple SIR model $t \mapsto (w_S(t), w_I(t), w_R(t))$ are given by:

$$\begin{cases} \frac{d}{dt}w_S(t) &= -\frac{\beta}{N}w_S(t)w_I(t) \\ \frac{d}{dt}w_I(t) &= \frac{\beta}{N}w_S(t)w_I(t) - \gamma w_I(t) \\ \frac{d}{dt}w_R(t) &= \gamma w_I(t). \end{cases} \quad t \geq 0. \quad (2.2)$$

Notice that in this model, a recovered individual acquires long-life immunity. This model is therefore well-suited for epidemics for which recovering results in permanent immunity, as in the case of childhood diseases such as chickenpox, smallpox, mumps, measles (Giraldo and Palacia, 2008; Bjørnstad et al., 2002; Hethcote, 2000, 1989).

The SIR can be simplified into the simpler SI model in the case where recovery is not possible once an individual contracts the disease. This is the case for diseases such as AIDS, herpes, cytomegalovirus (Rana and Nitin Sharma, 2020; Han, 2007; Yadav and Akhter, 2021). This model is the simplest compartmental model that can be constructed in epidemiology. The ODE system of the SI model that governs epidemics is identical to that of the SIR model given by system (2.2) except that $\gamma = 0$.

2.1.1.2 The simple SEIR model

The SEIR (Susceptible-Exposed-Infected-Recovered) model is an extension of the SIR model that differentiates infected individuals into two classes: exposed individuals who are infected but not yet infectious and infectious individuals who are able to infect susceptible individuals. Thus, this model includes one more compartment than the SIR: the compartment E which contains exposed individuals. Such a generalization allows to take into account the incubation

or latency period of diseases in epidemic dynamics, that is, the period of multiplication phase of the pathogen within hosts.

Three types of events can change health statuses: infection $S \rightarrow E$, activation $E \rightarrow I$ and recovery $I \rightarrow R$. Infections induce transitions of individuals from susceptible to exposed whereas activations trigger switches from non-contagious to contagious for exposed individuals. And recoveries correspond to transitions from I to R (see Figure 2.2).

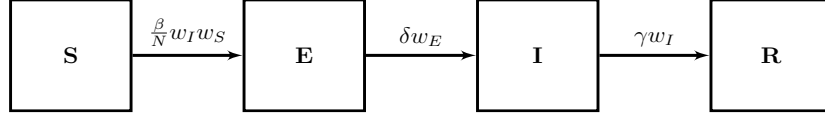


Figure 2.2 – The classical SEIR model. Functions w_S , w_E , w_I and w_R denote respectively the number of individuals in compartments S , E , I and R . Parameters β and γ have the same meaning as in the simple SIR model. The parameter δ is such that $1/\delta$ is the mean incubation time. Infections, activations and recoveries occur respectively at rates $(\beta/N)w_Sw_I$, δw_E and γw_I .

In such a model, epidemic dynamics $t \mapsto (w_S(t), w_E(t), w_I(t), w_R(t))$ with initial condition w_0 are described by:

$$\begin{cases} \frac{d}{dt}w_S(t) &= -\frac{\beta}{N}w_S(t)w_I(t) \\ \frac{d}{dt}w_E(t) &= \frac{\beta}{N}w_S(t)w_I(t) - \delta w_E(t) \\ \frac{d}{dt}w_I(t) &= \delta w_E(t) - \gamma w_I(t) \\ \frac{d}{dt}w_R(t) &= \gamma w_I(t) \end{cases} \quad t \geq 0. \quad (2.3)$$

This model is well-suited to study long incubation diseases such as tuberculosis (Das et al., 2021) and chronic hepatitis (Side et al., 2017).

2.1.1.3 The simple SEIAR model

The simple SEAIR model (Susceptible-Exposed-Asymptomatic infectious- symptomatic Infectious-Recovered) is a generalization the SEIR model that consists in categorizing infectious individuals into two groups: individuals who show symptoms (I) and those who do not (A). This differentiation implies that the two groups do not have the same characteristics such as the average duration in infectious stage. For example, in the model of Figure 2.3, symptomatic individuals spend an average duration of $1/\gamma_I$ units of times in I where asymptomatic individuals spend an average duration of $1/\gamma_A$. Moreover a proportion $p \in (0, 1)$ of exposed individuals is assumed to become symptomatic.

This model can also be used to describe an epidemic caused by a pathogen with two strains which are simultaneously spreading. In this case, compartments I and A would rather correspond to the compartments containing individuals infected by each strain.

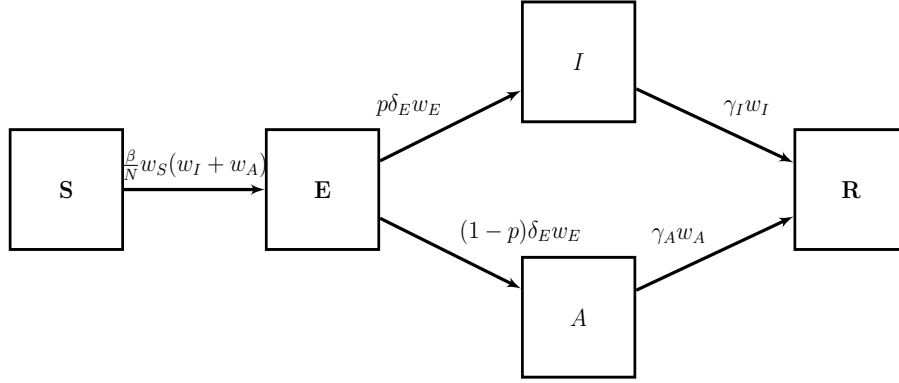


Figure 2.3 – The simple SEIAR model. This model includes five types of transitions: infection $S \rightarrow E$, activation to symptomatic $E \rightarrow I$ and asymptomatic $E \rightarrow A$, recovery of symptomatic $I \rightarrow R$ and asymptomatic $A \rightarrow R$. Asymptomatic and symptomatic individuals share the same transmission rate β but their infectious stage periods are different as stated above. A proportion p of exposed individuals becomes symptomatic and $1 - p$ asymptomatic.

Epidemic dynamics in this model are ruled by the following ODE with initial condition w_0 :

$$\begin{cases} \frac{d}{dt}w_S(t) &= -\frac{\beta}{N}w_S(t)(w_I(t) + w_A(t)) \\ \frac{d}{dt}w_E(t) &= \frac{\beta}{N}w_S(t)(w_I(t) + w_A(t)) - \delta_E w_E(t) \\ \frac{d}{dt}w_I(t) &= p\delta_E w_E(t) - \gamma_I w_I(t) \\ \frac{d}{dt}w_A(t) &= (1-p)\delta_E w_E(t) - \gamma_A w_A(t) \\ \frac{d}{dt}w_R(t) &= \gamma_I w_I(t) + \gamma_A w_A(t) \end{cases} \quad t \geq 0. \quad (2.4)$$

Such a model and its extensions have been widely used to model the COVID-19 epidemic since a significant proportion of people who contracted CoVID-19 had no symptoms (De la Sen et al., 2020; Jia and Chen, 2021; Basnarkov, 2021). It was also used to study other diseases like Influenza A (H1N1) (Jin et al., 2011).

2.1.2 Some extensions of classical compartmental models in deterministic framework

This section focuses on some extensions of simple compartmental models that allow to study epidemics under more realistic conditions as: loss of immunity, demographic dynamics and various cases of heterogeneity in the composition of the population or its spatial distribution (Bjørnstad et al., 2020).

2.1.2.1 Models with reinfection

In general, immunity induced by recovery is not permanent. Apart from a few exceptions such as childhood diseases, reinfections are possible. For example, loss of immunity occurred in tetanus, influenza or COVID-19 (WHO, 2017, 2018; Kojima and Klausner, 2022).

In compartmental modeling, the loss of immunity can be modeled by enabling recovered individuals to become susceptible again. Therefore, at least one arrow from a compartment of recovered individuals to a compartment of susceptible ones is included in the compartmental model. As an illustration, to allow reinfection in the simple SIR model, it suffices to add the type of transitions $R \rightarrow S$. Thus, the resulting model (SIRS) is schematized in Figure 2.4.

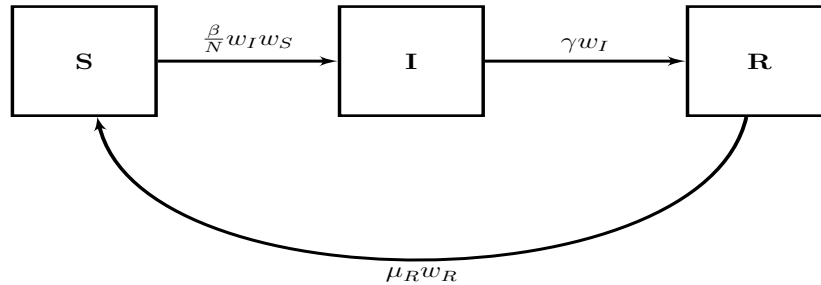


Figure 2.4 – The simple *SIRS* model.

Consider the simple SIRS model represented in Figure 2.4. In addition to infection and recovery transitions, a third type of transitions is included and corresponds to reinfection. Recovered individuals are assumed to be immunized only during $1/\mu_R$ units of time. This generates a flow of individuals from R to S with a rate denoted μ_R . Epidemic dynamics $t \mapsto (w_S(t), w_I(t), w_R(t))$ of this model can be described by the following ODE system:

$$\begin{cases} \frac{d}{dt} w_S(t) &= -\frac{\beta}{N} w_S(t) w_I(t) + \delta w_R(t) \\ \frac{d}{dt} w_I(t) &= \frac{\beta}{N} w_S(t) w_I(t) - \gamma w_I(t) \\ \frac{d}{dt} w_R(t) &= \gamma w_I(t) - \delta w_R(t) \end{cases} \quad t \geq 0.$$

This type of models enables to account for endemic diseases and to study persistence of epidemics, infection waves... (Kusmawati and Chandra, 2021; Li et al., 2009; Zhang and Zhou, 2019).

2.1.2.2 Models with demography

Populations are naturally subject to vital (or demographic) dynamics such as: births, deaths, migrations. These dynamics can affect their size and when an

epidemic spreads, they can change the number of individuals in the model compartments. So, those dynamics should be taken into account in order to better study epidemics especially regarding the issues of persistence or extinction of diseases (Cunniffe and Gilligan, 2010).

Under vital dynamics, the population is no longer closed. Its size becomes a function of time like the number of individuals in the compartments of the model under consideration. In the case of compartmental models, these dynamics can be modeled by adding demographic events in addition to events related to the infection spread. An example of a SIR model with demography is provided in Figure 2.5.

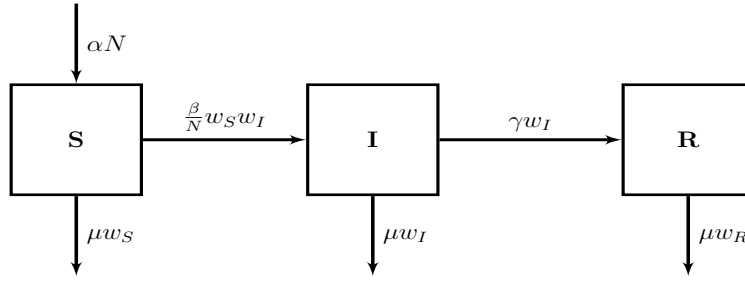


Figure 2.5 – A SIR model with demography.

A SIR model with demography is shown in Figure 2.5. Such a model considers that on the population scale, there is in average one birth every $1/\alpha$ units of time and one death every $1/\mu$ units of time. The size of the population is given by $N : t \mapsto N(t) := w_S(t) + w_I(t) + w_R(t)$. The epidemic dynamics are described by:

$$\begin{cases} \frac{d}{dt}w_S(t) &= -\frac{\beta}{N(t)}w_S(t)w_I(t) + \alpha N(t) - \mu w_S(t) \\ \frac{d}{dt}w_I(t) &= \frac{\beta}{N(t)}w_S(t)w_I(t) - \gamma w_I(t) - \mu w_I(t) \\ \frac{d}{dt}w_R(t) &= \gamma w_I(t) - \mu w_R(t) \end{cases} \quad t \geq 0.$$

Models with demographics have been widely used in the literature, for example to study smallpox in England (Duncan et al., 1994; Duncan and Duncan, 1997).

2.1.2.3 Models in structured-population

In general, a population is not homogeneous because individuals do not share the same characteristics. For instance, some groups of individuals may have a higher or lower risk of contracting a disease, or developing severe symptoms, etc. This can depend on different factors such as age, comorbidity, gender, sexual orientation or many other factors. Thus, individuals can be divided into

groups or classes according to different characteristics vis-à-vis the spreading epidemic or their behavior: this is called stratification. In compartmental modeling, in order to account for stratification, compartments of the model are subdivided into sub-compartments corresponding to the different classes and then the types of transitions between the sub-compartments are added regarding modeling hypotheses. This type of models is used to study diseases like: measles (Tudor, 1985), AIDS (Ghosh et al., 2018), COVID-19 (Bentout et al., 2021; Duan et al., 2022) etc.

One of the most used structuring feature is the age of individuals, leading to so-called age-dependent or age-structured models. For illustration, consider a SIR model with a population structured into two groups.

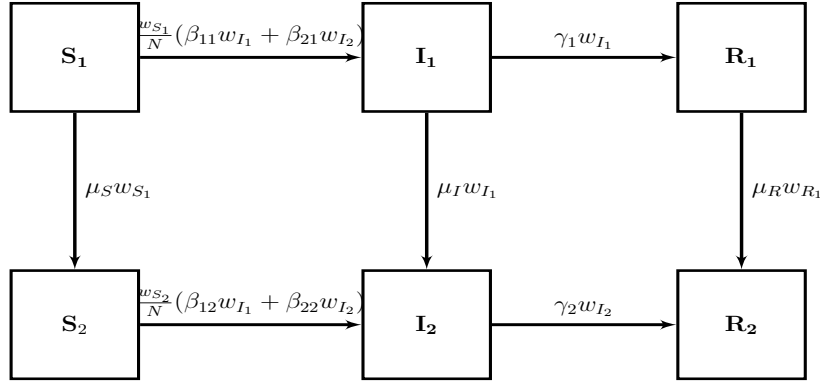


Figure 2.6 – An example of structured-population model with two classes.

The model presented in Figure 2.6 is a SIR model for a population divided into two classes 1 and 2 with transfers from class 1 to class 2. This model can be seen as an age-dependent model that categorizes the population into youth (pre-puberty) and adults (post-puberty) in a case study of sexually transmitted diseases. Parameters $\beta_{i,j}$ for $i, j \in \{1, 2\}$ define transmission rate in infection of individuals of class j due to individuals of class i . Parameters μ_S, μ_I, μ_R denote the rates at which individuals in compartment S_1, I_1 and R_1 moves to respective compartments in class 2. Epidemic dynamics of classes 1 and 2 are described by $(w_{S_1}, w_{I_1}, w_{R_1})$ and $(w_{S_2}, w_{I_2}, w_{R_2})$ respectively such that:

$$\begin{cases} \frac{d}{dt} w_{S_1}(t) &= -\frac{w_{S_1}(t)}{N} (\beta_{11}w_{I_1}(t) + \beta_{21}w_{I_2}(t)) - \mu_S w_{S_1}(t) \\ \frac{d}{dt} w_{I_1}(t) &= \frac{w_{S_1}(t)}{N} (\beta_{11}w_{I_1}(t) + \beta_{21}w_{I_2}(t)) - \gamma_1 w_{I_1}(t) - \mu_I w_{I_1}(t) \\ \frac{d}{dt} w_{R_1}(t) &= \gamma_1 w_{I_1}(t) - \mu_R w_{R_1}(t) \\ \frac{d}{dt} w_{S_2}(t) &= -\frac{w_{S_2}(t)}{N} (\beta_{12}w_{I_1}(t) + \beta_{22}w_{I_2}(t)) + \mu_S w_{S_1}(t) \\ \frac{d}{dt} w_{I_2}(t) &= \frac{w_{S_2}(t)}{N} (\beta_{12}w_{I_1}(t) + \beta_{22}w_{I_2}(t)) - \gamma_2 w_{I_2}(t) + \mu_I w_{I_1}(t) \\ \frac{d}{dt} w_{R_2}(t) &= \gamma_2 w_{I_2}(t) + \mu_R w_{R_1}(t) \end{cases} \quad t \geq 0. \quad (2.5)$$

2.1.2.4 Models in meta-populations

The metapopulation modeling meets the necessity to consider spatially fragmented populations in epidemic modeling. Fragmented population is composed of interacting homogeneous groups or patches located at different areas. The metapopulation approach proposes to study the spread of epidemics both within and between groups or patches. This enables to study epidemic spread at large scale: understanding the mechanisms of spatial spread of an infectious disease, the specificity of epidemic dynamics in a given subgroup, assessing global control measures, etc. In particular, this type of models enables to analyze the epidemic dynamics on networks through the movements of individuals within sub-populations and between them. The case of the spread of SARS-CoV-2 during the COVID-19 pandemic first in China and then in the rest of the world is an illustration of the usefulness of these models. Different levels can be used in this approach: individual level, community level, or larger levels. Such an approach was for instance studied by [Keeling et al. \(2004\)](#) and used by [Bolker and Grenfell \(1995\)](#) to model measles in England. It is also used in [Cristancho Fajardo et al. \(2021\)](#) to study epidemic dynamics in animal trade networks and provided as follows.

Consider J sub-populations noted P_1, \dots, P_J . In each sub-population, P_i , the epidemic dynamics $(w_{S_i}, w_{I_i}, w_{R_i})$ is described by a SIR model with demography (see Figure 2.5) where the birth rate is α_i , the death rate μ_i , and recovery rate γ_i . The rate at which individuals in P_i infect individuals in P_j is given by $\beta_{i,j}$. Between two distinct sub-populations P_i and P_j the movement of individuals takes place with a transfer rate of $\delta_{i,j}$. The resulting ODE system is given by:

$$\begin{cases} \frac{d}{dt} w_{S_i}(t) = \alpha_i N_i(t) - \frac{w_{S_i}(t)}{N_i(t)} \sum_{j=1}^J \beta_{i,j} w_{I_j}(t) - \mu_i w_{S_i}(t) - \sum_{j \neq i}^P \delta_{i,j} w_{S_i}(t) + \sum_{j=1}^J \delta_{j,i} w_{S_j}(t) \\ \frac{d}{dt} w_{I_i}(t) = \frac{w_{S_i}(t)}{N_i(t)} \sum_{j=1}^J \beta_{i,j} w_{I_j}(t) - \mu_i w_{I_i}(t) - \gamma_i w_{I_i}(t) - \sum_{j=1}^P \delta_{i,j} w_{I_i}(t) + \sum_{j=1}^J \delta_{j,i} w_{I_j}(t) \\ \frac{d}{dt} w_{R_i}(t) = \gamma_i w_{I_i}(t) - \mu_i w_{R_i}(t) - \sum_{j=1}^P \delta_{i,j} w_{R_i}(t) + \sum_{j=1}^J \delta_{j,i} w_{R_j}(t) \\ t \geq 0, \end{cases} \quad (2.6)$$

where $N_i(t) = w_{S_i}(t) + w_{I_i}(t) + w_{R_i}(t)$ for any $i = 1, \dots, J$.

2.1.3 Stochastic modeling of transitions between compartments

Stochastic modeling describes epidemic dynamics by accounting for the variability in individual characteristics with respect to infection, in their behaviors, environmental factors, etc. From this point of view, in practice, it can better account for the real dynamics of an epidemic because it includes randomness. With this approach, the health status of each individual is random, resulting in stochastic dynamics. In this section, a concise description of the stochastic processes obtained from compartmental models is proposed.

Consider a compartmental model with d compartments and define $W^\theta = (W_1^\theta, \dots, W_d^\theta)$ such that $W_i^\theta := \{W_i^\theta(t); t \geq 0\}$ describes over time the number of individuals in the i th compartment, where θ is the collection of epidemic parameters. Random elementary events induce the variation of the number of individuals in compartments so that for each i , the process $W_i^\theta := \{W_i^\theta(t); t \geq 0\}$ is stochastic. For a given compartment, each random event that occurs results in either the exit of an individual from the compartment or the entrance of an individual, unless the compartment is not involved. Therefore, for each process W_i^θ , at a given time t such that $W_i^\theta(t) = w_i \in \mathbb{N}$, a transition is always of the form $w_i \rightarrow w_i + \varepsilon_i$, where:

$$\varepsilon_i = \begin{cases} -1 & \text{if an individual leaves compartment } i \\ +1 & \text{if an individual enters compartment } i \\ 0 & \text{otherwise.} \end{cases}$$

Consequently, the process W^θ is stochastic such that at each time t , $W^\theta(t) \in \mathbb{N}^d$. Let $\mathcal{E} \subset \mathbb{N}^d$ be the state space of such a process. Due to the form of the transitions of processes $W_i, i = 1, \dots, d$, each transition of W^θ is under the form: $\xi \rightarrow \xi + \mathbf{u}$ where ξ belongs to \mathcal{E} and \mathbf{u} is under the form $\mathbf{u} = (\varepsilon_1, \dots, \varepsilon_d)$ such that $\xi + \mathbf{u}$ belong also to \mathcal{E} .

The different vectors \mathbf{u} characterize the types of transitions, i.e. the types of events that can induce a movement of an individual from a compartment to another. Let \mathcal{T} be the set of such vectors \mathbf{u} of the compartmental model. Note that any transition of W^θ is linked to the realization of a specific type of events.

The different types of events can affect individual health statuses (e.g. infection, immunization, recovering, hospitalization...). This is illustrated on the simple SIR model.

In the case of the simple SIR model, the epidemic process is given by $W^\theta = (W_S, W_I, W_R)$ where $\theta = (\beta, \gamma)$ and $W_S(t), W_I(t), W_R(t)$ denote respectively the number of individuals in S, I and R at time t . This model includes two types of events: infection and recovery. Assume W^θ is in a state (s, i, r) . An infection triggers a transition of the type $(s, i, r) \rightarrow (s-1, i+1, r) = (s, i, r) + (-1, +1, 0)$ because a susceptible individual becomes infected and switches to compartment I. A recovery results in a transition of type $(s, i, r) \rightarrow (s, i-1, r+1) = (s, i, r) + (0, -1, +1)$ because an infected individual recovers and moves from I to R.

Also, some types of events can be demographic such as births, deaths, migrations, so that they directly impact the number of individuals in compartments. They can originate from other sources depending on the model under study.

In the SIS model with demography, the epidemic process $W^\theta = (W_S, W_I)$ is ruled by five types of events:

- infection: $(s, i) \rightarrow (s - 1, i + 1) = (s, i) + (-1, +1)$
- recovery: $(s, i) \rightarrow (s + 1, i - 1) = (s, i) + (+1, -1)$
- birth in S : $(s, i) \rightarrow (s + 1, i) = (s, i) + (+1, 0)$
- death in S : $(s, i) \rightarrow (s - 1, i) = (s, i) + (-1, 0)$
- death in I : $(s, i) \rightarrow (s, i - 1) = (s, i) + (0, -1)$

The different types of events, depending on the order in which they occur and the times at which they take place, determine trajectories of the process W^θ . So, the process W^θ is characterized by the probabilities that a specific event happens at a given time. These probabilities can influence the process behaviors. For example, they may not depend on previous states of the process but only on the current state. In such a case, the process is said to be Markovian. Otherwise, it is a non-Markovian process.

2.1.4 Markovian process based models and their simulation

In this section, we discuss compartmental epidemic models based on Markov chains. For this, we briefly introduce Markov chains, then Markovian stochastic processes for epidemic modeling, and finally we discuss numerical algorithms for simulating epidemics in the Markovian framework.

2.1.4.1 Continuous-time Markov chains

Consider a stochastic process $H = \{H(t), t \geq 0\}$ defined on some probability space $(\Omega, \mathcal{B}, \mathbb{P})$ with states in $\mathcal{E} \subset \mathbb{N}^d$ (or some arbitrary discrete state space). The process H is said to be a continuous-time Markov chain (CTMC) if for any $p \in \mathbb{N}^*$, for any $t_0 := 0 \leq \dots \leq t_p$ and $\xi_0, \dots, \xi_p \in \mathcal{E}$ such that $\mathbb{P}(H(t_{p-1}) = \xi_{p-1}, \dots, H(t_0) = \xi_0) > 0$, it holds that:

$$\mathbb{P}(H(t_p) = \xi_p \mid H(t_{p-1}) = \xi_{p-1}, \dots, H(t_0) = \xi_0) = \mathbb{P}(H(t_p) = \xi_p \mid H(t_{p-1}) = \xi_{p-1}). \quad (2.7)$$

The property in Equation (2.7) is called Markov property and determines the finite-dimensional distributions of H , i.e. the probabilities

$\mathbb{P}(H(t_p) = \xi_p, \dots, H(t_1) = \xi_1)$. These probabilities are summarized with a family of matrices $\{P^t(h) = P_{\xi, \xi'}^t(h) : \xi, \xi' \in \mathcal{E}\}$ for $t, h \geq 0$ such that:

$$P_{\xi, \xi'}^t(h) = \mathbb{P}(H(t+h) = \xi' \mid H(t) = \xi)$$

and called the transition matrices of the process. Remark that for $h = 0$, the matrix $P^t(0)$ is the identity matrix on \mathcal{E} defined as $\mathbb{I} = (\mathbb{1}_{\xi=\xi'})_{\xi, \xi' \in \mathcal{E}}$. The

family of transition matrices is a family parameterized by time t except in the case of homogeneous CTMC where $P^t(h)$ is independent of t for any h , i.e., $P^t(h) = P^0(h) = \mathbb{P}(H(h) = \xi' \mid H(0) = \xi)$ for any $h \geq 0$ and $\xi, \xi' \in \mathcal{E}$.

Hereafter, assume H is homogeneous with transition matrix denoted by $P(h)$ for $h \geq 0$.

A fundamental property of the transition matrix follows: for any $h, h' \geq 0$, $P(h+h') = P(h) \cdot P(h') = P(h') \cdot P(h)$, where \cdot denotes the matrix multiplication. Such a property is known as Chapman-Kolmogorov equations. Note that for any $\omega \in \Omega$, for $h \geq 0$, transition matrices satisfy $P(h) \rightarrow \mathbb{I}$ as $h \rightarrow 0$ for any $t \geq 0$. Moreover, if $\mathcal{Q} := \lim_{h \rightarrow 0} \frac{P(h) - \mathbb{I}}{h}$ exists, then $\mathcal{Q} = (\mathcal{Q}(\xi, \xi'))_{\xi, \xi' \in \mathcal{E}}$ is called the generator or the infinitesimal matrix of H . Note that such a matrix is independent of h but enables to characterize the finite-dimensional distributions of H like the transition matrices because it satisfies:

$$\begin{cases} \frac{d}{dh} P(h) = \mathcal{Q} \cdot P(h) = P(h) \cdot \mathcal{Q} & h \geq 0, \\ P(0) = \mathbb{I} \end{cases}$$

and thereby defines completely the transition matrices. The entries of the matrix \mathcal{Q} are called the transition rates of H .

Since the state space of H is discrete, then the changes of states of H that are called state transitions correspond to jumps. As a continuous-time process on a discrete state space, two elements characterize trajectories $\{H(t, \omega), t \geq 0\}$ of H , for $\omega \in \Omega$: the jump times, i.e., instants at which the jumps occur and the jumps that are performed. The jump times are then state change times and thus given by the recurrent system:

$$\begin{cases} T_0 & = 0 \\ T_{n+1}(\omega) & = \inf\{t > T_n(\omega) \mid H(t) \neq H(T_n(\omega))\}. \end{cases}$$

Therefore, jump times $\{T_n, n \geq 1\}$ form a non-decreasing sequence of random variables. They are entirely determined by the random sequence $(\Delta_n)_{n \geq 1}$ defined by $\Delta_n := T_n - T_{n-1}$, with $n \geq 1$ and $T_0 = 0$. Note that each Δ_n is positive and represents the time it takes the process H to perform the transition $H(T_{n-1})$ to $H(T_n)$: it is called the waiting time or the holding time. The sequence of states described by H with respect to jump times $\{T_n, n \geq 1\}$ is given by $\{H_n := H(T_n), n \geq 0\}$. Such a sequence is a discrete Markov process called the embedded Markov chain of H . It is shown that the two sequences $\{H_n := H(T_n), n \geq 0\}$ and $(\Delta_n)_{n \geq 1}$ satisfy:

$$\mathbb{P}(H_{n+1} = \xi' \mid H_n = \xi) = \frac{\mathcal{Q}(\xi, \xi')}{|\mathcal{Q}(\xi, \xi)|}$$

Conditionally to H_n , $\Delta_{n+1} \sim \text{Exp}(|\mathcal{Q}(\xi, \xi)|)$,

where $\text{Exp}(|\mathcal{Q}(\xi, \xi)|)$ is the exponential distribution with mean $1/|\mathcal{Q}(\xi, \xi)|$.

The study of CTMCs and more generally of Markovian processes, whether in continuous or discrete time, with continuous or discrete state space, has been very prolific (Ethier and Kurtz, 2011). Numerous works allow to understand the behavior of these processes such as their convergence to limits in various modes, their links with other mathematical objects such as differential equations, partial differential equations or other stochastic processes such as stochastic differential equations. All these studies provide a wide range of tools to understand theoretically Markov chains but also various phenomena that are modeled using these processes. This explains the success of Markov chains in the mathematical modeling of epidemics.

2.1.4.2 Markovian epidemic models

Consider a compartmental model with d compartments such that W^θ , as defined in Section 2.1.3, counts over time the numbers of individuals in each compartment. In order to model the epidemic dynamics with a homogeneous continuous time Markov chain, one can define the transition probabilities related to each type of transition of the process, or equivalently, the transition rates associated to these transitions. This yields:

$$\mathbb{P}\left(W^\theta(s+h) = \xi + \mathbf{u} \mid W^\theta(s) = \xi\right) = q_{\mathbf{u}}(\xi)h + o(h) \quad (2.8)$$

and thus:

$$\mathbb{P}\left(W^\theta(s+h) \neq \xi \mid W^\theta(s) = \xi\right) = \left(\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi)\right)h + o(h), \quad (2.9)$$

where $q_{\mathbf{u}} : \mathcal{E} \rightarrow \mathbb{R}_+$ are positive functions and $o(h)$ is a negligible quantity as $h \rightarrow 0$. Therefore:

$$\begin{aligned} \lim_{h \rightarrow 0} \frac{\mathbb{P}\left(W^\theta(s+h) = \xi + \mathbf{u} \mid W^\theta(s) = \xi\right)}{h} &= q_{\mathbf{u}}(\xi) \\ \lim_{h \rightarrow 0} \frac{\mathbb{P}\left(W^\theta(s+h) \neq \xi \mid W^\theta(s) = \xi\right) - 1}{h} &= -\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi). \end{aligned}$$

Hence, the generator \mathcal{Q}_θ associated with the CTMC W^θ is defined as:

$$\mathcal{Q}_\theta(\xi, \xi') = \begin{cases} 0 & \text{if } \forall \mathbf{u} \in \mathcal{T}, \xi' \neq \xi + \mathbf{u} \\ -\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi) & \text{if } \xi' = \xi \\ q_{\mathbf{u}}(\xi) & \text{if } \exists \mathbf{u} \in \mathcal{T} : \xi' = \xi + \mathbf{u}. \end{cases}$$

Example 1. Consider the simple SIR model as given in Section 2.1.1.1. Let $\theta := (\beta, \gamma)$ and $\mathcal{E} = \{(s, i, r) \in \mathbb{N}^3 : s+i+r = N\}$. Dynamics can be modeled by

a CTMC $W^\theta := \{(W_S(t), W_I(t), W_R(t)) : t \geq 0\}$ with the following transition probabilities:

$$\begin{aligned}\mathbb{P}\left(W^\theta(t+h) = (s-1, i+1, r) \mid W^\theta(t) = (s, i, r)\right) &= \frac{\beta}{N}si \times h + o(h) \\ \mathbb{P}\left(W^\theta(t+h) = (s, i-1, r+1) \mid W^\theta(t) = (s, i, r)\right) &= \gamma i \times h + o(h),\end{aligned}$$

for $h > 0$ small enough. Then, the generator of such a CTMC is a parameterized matrix \mathcal{Q}_θ with entries:

$$\mathcal{Q}^\theta((s, i, r), (s', i', r')) = \begin{cases} \frac{\beta}{N}si & \text{if } (s', i', r') = (s-1, i+1, r) \\ \gamma i & \text{if } (s', i', r') = (s, i-1, r+1) \\ -\frac{\beta}{N}si - \gamma i & \text{if } (s', i', r') = (s, i, r) \\ 0 & \text{otherwise.} \end{cases}$$

However, it should be underlined that the modeling of epidemics using Markovian processes does not necessarily satisfy epidemiological relevance (e.g. assuming that recovery does not depend on the time since infection is not a realistic assumption). This approach remains a modeling choice and therefore an approximation. However, Markov processes facilitate theoretical studies and allow a better understanding of certain phenomena observed in epidemics, such as the endemic character, early extinction, etc.

2.1.4.3 Gillespie Stochastic Simulation Algorithms (SSA)

Markovian processes enable theoretical studies of epidemics, but in practice, it is necessary to predict trajectories of epidemic dynamics, to evaluate impacts of control measures, to anticipate worst-case scenarios of propagation, etc. All this requires numerical simulations and therefore methods or algorithms to simulate processes. If nowadays there are many methods to simulate Markovian processes, they are relatively recent, because these methods have been developed since late 70s with the works of D.T. Gillespie ([Gillespie, 1976](#), [1977](#)).

Gillespie Algorithm: Direct Method

Let $t \geq 0$ and suppose that $W^\theta(t) = \xi \in \mathcal{E}$. In order to simulate the next jump of W^θ , we have to determine the instant of the jump and the transition to execute. It is thus equivalent to find the waiting time of the system before the next jump and the type of transition which will take place at the end of the waiting time. We introduce τ the random waiting time or holding time from t and \mathbb{T} a random variable defined on the set of transition types \mathcal{T} whose value corresponds to the next type of transition to be performed. To characterize

the couple (τ, \mathbb{T}) , Gillespie (1977) proposed to compute their joint density conditionally to the current state of the system, i.e. $W^\theta(t) = \xi$.

Indeed, if τ is the waiting time then between instants t and $t + \tau$, the process W^θ does not make any transition. But for any infinitesimal quantity $d\tau$, between instants $t + \tau$ and $t + \tau + d\tau$, a jump occurs. Let $f_{(\tau, \mathbb{T})}$ be the joint density of (τ, \mathbb{T}) conditionally to $W^\theta(t) = \xi$. Thus:

$$\begin{aligned} f_{(\tau, \mathbb{T})}(s, \mathbf{u}) &= \lim_{ds \rightarrow 0} \frac{\mathbb{P}(\tau \in [s, s + ds[, \mathbb{T} = \mathbf{u} \mid W^\theta(t) = \xi)}{ds} \\ &= \lim_{ds \rightarrow 0} \frac{\mathbb{P}(W^\theta(t + s + ds) = \xi + \mathbf{u} \mid W^\theta(t + s) = \xi)}{ds} \\ &\quad \times \mathbb{P}(W^\theta(t + s) = \xi \mid W^\theta(t) = \xi) \\ &= q_{\mathbf{u}}(\xi) \mathbb{P}(W^\theta(t + s) = \xi \mid W^\theta(t) = \xi), \end{aligned}$$

using Equation (2.8). The explicit formula of $\mathbb{P}(W^\theta(t + s) = \xi \mid W^\theta(t) = \xi)$ remains to be found. For this intending, let us introduce the following result:

Proposition 1. *For any $\xi \in \mathcal{E}$ and for all $t, s \geq 0$:*

$$\mathbb{P}(W^\theta(t + s) = \xi \mid W^\theta(t) = \xi) = \exp\left(-s \sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi)\right).$$

Relying on Proposition 1 (refer to Gillespie (1977) for the proof), it holds that $f_{(\tau, \mathbb{T})}(s, \mathbf{u}) = q_{\mathbf{u}}(\xi) e^{-s \sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi)}$. By deducing the marginal densities, it appears that, conditionally to $W^\theta(t) = \xi$, τ follows an exponential distribution of mean $1/\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi)$ while \mathbb{T} is distributed under a multinomial distribution on \mathcal{T} with parameters

$\{q_{\mathbf{u}}(\xi)/\sum_{\mathbf{v} \in \mathcal{T}} q_{\mathbf{v}}(\xi), \mathbf{u} \in \mathcal{T}\}$. Thus, Gillespie introduced a method that simulates continuous-time Markov chain by sequentially generating waiting times with exponential distributions and transitions with multinomial distributions. This method is known as the Direct Method and is presented in Algorithm 1.

Gillespie Algorithm: First Reaction Method

Let us focus on the different types of transition or types of events $\mathbf{u} \in \mathcal{T}$ of the model. To each type of transition \mathbf{u} , there can be associated a counting process $N_{\mathbf{u}} := \{N_{\mathbf{u}}(t), t \geq 0\}$ where $N_{\mathbf{u}}(t)$ gives the number of times that the type of transition \mathbf{u} has been executed before time t . Since every transition of the system is of the form $\xi \rightarrow \xi + \mathbf{u}$ then W^θ can be fully described by processes $N_{\mathbf{u}}$ in the following way:

$$W^\theta(t) = W^\theta(0) + \sum_{\mathbf{u} \in \mathcal{T}} N_{\mathbf{u}}(t) \mathbf{u}. \quad (2.10)$$

Algorithm 1 Direct Method (Gillespie, 1977)**Require:** $\xi_0, T, \{q_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$

```

1:  $t \leftarrow 0$ 
2:  $\xi \leftarrow \xi_0$ 
3: while  $t < T$  do
4:   for  $\mathbf{u} \in \mathcal{T}$  do
5:     Compute proportion  $p_{\mathbf{u}} \leftarrow q_{\mathbf{u}}(\xi) / \sum_{\mathbf{v} \in \mathcal{T}} q_{\mathbf{v}}(\xi)$ 
6:   end for
7:   Draw  $\mathbf{u}_{next}$  with a multinomial with parameters  $\{p_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
8:   Draw  $\tau$  with exponential distribution with mean  $1 / \sum_{\mathbf{v} \in \mathcal{T}} q_{\mathbf{v}}(\xi)$ 
9:    $t \leftarrow t + \tau$ 
10:   $\xi \leftarrow \xi + \mathbf{u}_{next}$ 
11: end while

```

Let $t \geq 0$ and assume that $W^\theta(t) = \xi$. Equation (2.8) ensures that transitions $\xi \rightarrow \xi + \mathbf{u}$ occur at rate $q_{\mathbf{u}}(\xi)$, thus, conditionally to $W^\theta(t) = \xi$, it yields:

$$\mathbb{P}\left(N_{\mathbf{u}}(t+h) - N_{\mathbf{u}}(t) = 1 \mid W^\theta(t) = \xi\right) = q_{\mathbf{u}}(\xi)h + o(h), \quad (2.11)$$

for any sufficiently small $h > 0$.

If the set of transition types was a singleton: $\mathcal{T} = \{\mathbf{u}\}$, i.e., the compartmental model had only one transition type which is \mathbf{u} , then it would follow that:

$$W^\theta(t) = W^\theta(0) + N_{\mathbf{u}}(t) \mathbf{u}. \quad (2.12)$$

For example, this is the case of the simple SI model. Assuming that W^θ is under the form (2.12), then, using the same analysis as in Direct Method, it appears that, conditionally to $W^\theta(t) = \xi$, the waiting time $\tau_{\mathbf{u}}$ of the process $N_{\mathbf{u}}$ and thus of W^θ is distributed under an exponential distribution with mean $1/q_{\mathbf{u}}(\xi)$.

From such an observation, Gillespie proposed a second method of simulation by considering independently the processes $\{N_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$. The principle is to focus on each $N_{\mathbf{u}}$ and to assume that it is the only process able to perform the next transition. In other words, it is assumed that W^θ is reduced to $W^\theta(0) + N_{\mathbf{u}}(t) \mathbf{u}$. Thus, the waiting time corresponds to $\tau_{\mathbf{u}}$ with distribution given by the exponential with mean $1/q_{\mathbf{u}}(\xi)$. For the global process W^θ , this yields putative waiting times: $\tau_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}$. The actual waiting time of W^θ is defined as: $\tau_{\bar{\mathbf{u}}} := \min\{\tau_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$. Therefore, the type of transition to be performed is given by $\bar{\mathbf{u}}$ whose waiting time is $\tau_{\bar{\mathbf{u}}}$. Such a method is the so-called Gillespie First Reaction Method. It is provided in Algorithm 2.

Furthermore, Gillespie showed that the First Reaction Method and the Direct Method are both equivalent. Indeed, considering the First Reaction

Algorithm 2 First Reaction Method (Gillespie, 1977)**Require:** $\xi_0, T, \{q_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$

```

1:  $t \leftarrow 0$ 
2:  $\xi \leftarrow \xi_0$ 
3: while  $t < T$  do
4:   for  $\mathbf{u} \in \mathcal{T}$  do
5:     Draw  $\tau_{\mathbf{u}}$  with exponential distribution with mean  $1/q_{\mathbf{u}}(\xi)$ 
6:   end for
7:    $\tau \leftarrow \min\{\tau_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
8:    $\mathbf{u}_{next} \leftarrow \operatorname{argmin}\{\tau_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
9:    $t \leftarrow t + \tau$ 
10:   $\xi \leftarrow \xi + \mathbf{u}_{next}$ 
11: end while

```

Method, the density of the couple (τ, \mathbb{T}) conditionally to $W^\theta(t) = \xi$ as defined in Section 2.1.4.3 yields:

$$\begin{aligned}
f_{(\tau, \mathbb{T})}(s, \mathbf{u}) &= \lim_{ds \rightarrow 0} \frac{\mathbb{P}(\tau_{\mathbf{u}} \in [t+s, t+s+ds], \tau_{\mathbf{v}} > t+s, \text{ for all } \mathbf{v} \neq \mathbf{u} \mid W^\theta(t) = \xi)}{ds} \\
&= \frac{\mathbb{P}(\tau_{\mathbf{u}} \in (t+s, t+d+ds) \mid W^\theta(t) = \xi)}{ds} \\
&\quad \times \prod_{\mathbf{v} \neq \mathbf{u}} \mathbb{P}(\tau_{\mathbf{v}} > t+s \mid W^\theta(t) = \xi) \\
&= q_{\mathbf{u}}(\xi) \exp(-sq_{\mathbf{u}}(\xi)) \prod_{\mathbf{v} \neq \mathbf{u}} \exp(-sq_{\mathbf{v}}(\xi)) = q_{\mathbf{u}}(\xi) \exp\left(-s \sum_{\mathbf{v} \in \mathcal{T}} q_{\mathbf{v}}(\xi)\right),
\end{aligned}$$

which corresponds well to what is obtained with the Direct Method.

2.1.4.4 Other variants of Gillespie SSA

Since Gillespie's work, other studies have been carried out on the simulation of Markovian processes in order to develop more and more efficient methods. In this section, we will briefly present two of these methods which also enable to simulate exact trajectories for continuous-time Markov chains. These two methods are: the Next Reaction Method (Gibson and Bruck, 2000) and the Modified Next Reaction Method (Anderson, 2007).

The Next Reaction Method detailed in Algorithm 3 is an equivalent scheme to Gillespie's First Reaction Method from which it is in fact derived. The idea of this method is to avoid systematically simulating all the putative waiting times $\{\tau_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ at each iteration as it is the case in the First Reaction Method. For this purpose, Gibson and Bruck (2000) proposed to simulate only one random variable per iteration so that only the putative waiting time

of the type of transition executed in the current iteration is simulated to sample the corresponding next waiting time (refer to instructions 18-19 in Algorithm 3).

Algorithm 3 Next Reaction Method (Gibson and Bruck, 2000)

Require: $\xi_0, T, \{q_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$

```

1:  $t \leftarrow 0$ 
2:  $\xi \leftarrow \xi_0$ 
3: for  $\mathbf{u} \in \mathcal{T}$  do
4:   Compute  $a_{\mathbf{u}} \leftarrow q_{\mathbf{u}}(\xi)$ 
5:   Draw  $t_{\mathbf{u}}$  with exponential distribution with mean  $1/a_{\mathbf{u}}$ 
6: end for
7: while  $t < T$  do
8:    $\tau \leftarrow \min\{t_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
9:    $\mathbf{u}_{next} \leftarrow \operatorname{argmin}\{t_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
10:   $t \leftarrow \tau$ 
11:   $\xi \leftarrow \xi + \mathbf{u}_{next}$ 
12:  for  $\mathbf{u} \in \mathcal{T}$  do
13:    Compute  $\bar{a}_{\mathbf{u}} \leftarrow q_{\mathbf{u}}(\xi)$ 
14:  end for
15:  for  $\mathbf{u} \neq \mathbf{u}_{next}$  do
16:    Compute  $t_{\mathbf{u}} \leftarrow (a_{\mathbf{u}}/\bar{a}_{\mathbf{u}})(t_{\mathbf{u}} - \tau) + \tau$ 
17:  end for
18:  Draw  $r$  with exponential distribution with mean  $1/\bar{a}_{\mathbf{u}_{next}}$ 
19:  Compute  $\tau_{\mathbf{u}_{next}} \leftarrow \tau + r$ 
20:  for  $\mathbf{u} \in \mathcal{T}$  do
21:    Compute  $a_{\mathbf{u}} \leftarrow \bar{a}_{\mathbf{u}}$ 
22:  end for
23: end while

```

This method differs from the First Reaction Method in: storing rates $a_{\mathbf{u}}$ and putative jump times $t_{\mathbf{u}}$, reusing them and simulating only one random variable per transition. In this manner, Algorithm 3 is more efficient.

Before introducing the Modified Next Reaction Method, let us discuss first a representation of the W^θ process using Poisson processes. Consider the W^θ process under the form:

$$W^\theta(t) = W^\theta(0) + \sum_{\mathbf{u} \in \mathcal{T}} N_{\mathbf{u}}(t) \mathbf{u}.$$

Based on Equation (2.11) Kurtz (Ethier and Kurtz, 2011) showed that there exist independent unit-rate Poisson processes $\{P_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ such that:

$$W^\theta(t) = W^\theta(0) + \sum_{\mathbf{u} \in \mathcal{T}} P_{\mathbf{u}} \left(\int_0^t q_{\mathbf{u}}(W^\theta(s)) ds \right) \mathbf{u}, \quad (2.13)$$

provided that the functions $q_{\mathbf{u}}$ satisfy $\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi) < +\infty$, for all $\xi \in \mathcal{E}$. Such a condition ensures that the process W^θ does not perform an infinite number of jumps in finite time. Such a decomposition corresponds to a time change that allows to describe the processes $N_{\mathbf{u}}$ as inhomogeneous Poisson processes: it is called the random-time change (Ethier and Kurtz, 2011; Anderson and Kurtz, 2011). Then, each process $N_{\mathbf{u}}$ has its own internal clock that rules jump times and denoted $t_{\mathbf{u}}$. Let $(s_{\mathbf{u}})$ denote the process of jump times of the unit-rate Poisson process $P_{\mathbf{u}}$. Relying on decomposition (2.13), Anderson (2007) introduced a variant of the Next Reaction Method called the Modified Next Reaction Method and provided in Algorithm 4. This algorithm combines the jump times $(s_{\mathbf{u}})$ of unit-rate Poisson processes and the internal times $(t_{\mathbf{u}})$ to describe the jump times of W^θ . Note that, like the Next Reaction Method, it samples only one random variable per transition.

2.1.4.5 Link between Markovian models and ODE-based models

This section describes the link between Markovian and ODE-based models. Moreover, a comparison of deterministic and stochastic formalisms is proposed in order to highlight their advantages and their limitations in epidemic modeling.

Assume the population is closed and includes N individuals. Consider the process W^θ under the form:

$$W^\theta(t) = W^\theta(0) + \sum_{\mathbf{u} \in \mathcal{T}} P_{\mathbf{u}} \left(\int_0^t q_{\mathbf{u}}(W^\theta(s)) ds \right) \mathbf{u},$$

provided that $\sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(\xi) < +\infty$ for all $\xi \in \mathcal{E}$. Assume that positive functions $q_{\mathbf{u}}$ are defined over \mathbb{R}_+^d , with d the number of compartments of the model. Moreover, assume that W^θ is a density-dependent process, i.e., $q_{\mathbf{u}}(x) = N q_{\mathbf{u}}(\frac{x}{N})$. Define the process W_N^θ indexed by N , the size of the population such that $W_N^\theta(t) = \frac{1}{N} W^\theta$. Thus, W_N^θ satisfies:

$$W_N^\theta(t) = W_N^\theta(0) + \sum_{\mathbf{u} \in \mathcal{T}} P_{\mathbf{u}} \left(N \int_0^t q_{\mathbf{u}}(W_N^\theta(s)) ds \right) \mathbf{u}.$$

So, W_N^θ is a process of the same nature as W^θ but whose jumps are proportional to $1/N$. Thus, the larger N becomes, the smaller the amplitude of the jumps of W_N^θ gets. Heuristically, W_N^θ could tend to a potentially smooth limit when N becomes large. The mathematical study of the limit of W_N^θ with respect to different types of convergence and approximations was mainly carried out by Kurtz (1971, 1976, 1978); Barbour (1980); Ethier and Kurtz (2011).

Algorithm 4 Modified Next Reaction Method ([Anderson, 2007](#))

Require: $\xi_0, T, \{q_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$

```

1:  $t \leftarrow 0$ 
2:  $\xi \leftarrow \xi_0$ 
3: for  $\mathbf{u} \in \mathcal{T}$  do
4:   Compute  $t_{\mathbf{u}} \leftarrow 0$ 
5:   Compute  $s_{\mathbf{u}} \leftarrow 0$ 
6:   Compute  $a_{\mathbf{u}} \leftarrow q_{\mathbf{u}}(\xi)$ 
7: end for
8: for  $\mathbf{u} \in \mathcal{T}$  do
9:   Draw  $r_{\mathbf{u}}$  with exponential distribution with mean 1
10:  Compute  $s_{\mathbf{u}} \leftarrow r_{\mathbf{u}}$ 
11: end for
12: while  $t < T$  do
13:   for  $\mathbf{u} \in \mathcal{T}$  do
14:     Compute  $\Delta_{\mathbf{u}} \leftarrow (s_{\mathbf{u}} - t_{\mathbf{u}})/a_{\mathbf{u}}$ 
15:   end for
16:    $\Delta \leftarrow \min\{\Delta_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
17:    $\mathbf{u}_{next} \leftarrow \operatorname{argmin}\{\Delta_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ 
18:    $t \leftarrow t + \Delta$ 
19:    $\xi \leftarrow \xi + \mathbf{u}_{next}$ 
20:   for  $\mathbf{u} \in \mathcal{T}$  do
21:     Compute  $t_{\mathbf{u}} \leftarrow t_{\mathbf{u}} + \Delta a_{\mathbf{u}}$ 
22:   end for
23:   Draw  $r$  with exponential distribution with mean 1
24:   Compute  $s_{\mathbf{u}_{next}} \leftarrow s_{\mathbf{u}_{next}} + r$ 
25:   for  $\mathbf{u} \in \mathcal{T}$  do
26:     Compute  $a_{\mathbf{u}} \leftarrow q_{\mathbf{u}}(\xi)$ 
27:   end for
28: end while

```

If $F : x \mapsto F(x) = \sum_{\mathbf{u} \in \mathcal{T}} q_{\mathbf{u}}(x) \mathbf{u}$ is Lipschitz, let $w : t \mapsto w(t)$ be the solution of the ODE system:

$$\begin{cases} \frac{d}{dt} w(t) = F(w(t)) \\ w(0) = \lim_{N \rightarrow +\infty} W_N^\theta(0). \end{cases} \quad (2.14)$$

[Kurtz \(1978\)](#) proved that $\lim_{N \rightarrow +\infty} \sup_{s \leq t} \|W_N^\theta(s) - w(s)\| = 0$ almost surely for all $t \geq 0$. The function w solution of (2.14) is called the scale limit or the large population limit of W_N^θ .

Thus, it turns out that deterministic models based on ODE are limit models of Markovian models. These limits describe large-scale trends that emerge from individual behaviors and epidemic characteristics, regardless of effects of randomness. These limits therefore provide an approximation of epidemic dynamics when the population size is large enough. Moreover, they have the advantage of facilitating further theoretical analysis as there are numerous tools for studying ODE systems in the literature. This allows to study epidemic dynamic equilibrium (e.g. convergence to endemic equilibrium), characteristics of the epidemic such as the basic reproduction number R_0 (the average number of susceptible individuals that can be infected by one infectious individual in an entirely susceptible population), etc. However, approximating epidemic dynamics with ODEs can fail even when the population is large enough. Indeed, at the beginning of epidemics, the number of infected individuals is generally small. Then, the epidemic dynamics depend strongly on the behavior (contacts, interactions) of initial infected. For example, in the SIR model, the approximation of $(W_S(t)/N; W_I(t)/N; W_R(t)/N)$ by the SIR dynamic system is valid from a time which is random, complex and with approximate dominant term $\log(N)/(\beta - \gamma)$ ([Barbour and Reinert, 2013](#)), provided that $W_I(t) = O(N)$. So, the quality of the ODE approximation depends not only on the size of the population but also on the proportion of infected individuals at the beginning.

Conversely, Markovian models and more generally stochastic models allow a description of epidemic dynamics in both small and large populations. Unlike deterministic models, they allow to study questions related to the extinction of epidemics: the probability of such an event, the extinction time, the distribution of the final size of the epidemic (total number of infected individuals during the outbreak), etc. Indeed, stochastic models integrate chance and therefore allow the realization of events that cannot be described by deterministic models ([Dangerfield et al., 2009](#)). For example, they can explain early extinction of the epidemics. Furthermore, even when deterministic models predict a long-term equilibrium, extinctions can still occur due to chance. Through the theory of large deviations ([Kratz and Pardoux, 2018](#)), stochastic models can explain these phenomena. Nevertheless, these two modeling approaches are complementary. But as [Andersson and Britton \(2000a\)](#) pointed

out, "stochastic models should be preferred when their analysis is possible".

2.1.5 Non-Markovian process based models and their simulation

2.1.5.1 Non-Markovian processes

As mentioned before, modeling epidemics by Markovian processes is most of the time not realistic but only suitable for theoretical explorations. In contrast, using the non-Markovian framework is more realistic but often theoretically intractable. As pointed out in [van Kampen \(1998\)](#), "Non-Markov is the rule, Markov is the exception". Indeed, "most stochastic processes are non-Markovian" ([Gillespie, 2000](#)) and then challenging. This challenge already starts with the characterization of non-Markovian processes: all that can be said is that they do not satisfy the Markov property. There are various ways of not satisfying such a property. And so, there are various ways to build non-Markovian models. A direct implication of Markovian models is that the distributions of the sojourn times in the different compartments are necessarily exponential probability distributions. So, the simplest and by far the most used way to be in the non-Markovian framework is to consider sojourn times with general probability distributions other than exponential. This technique has been used several times in the literature. One could mention the use of Weibull distribution ([Van Mieghem and van de Bovenkamp, 2013](#)), lognormal distribution ([Nowzari et al., 2015](#)), the Gamma distributions ([Riaño, 2020](#)).

The challenge of models based on non-Markovian processes is also reflected in the difficulty of their simulation. If Equations (2.8) and (2.9) allow to deduce the probability distributions of waiting times and probability of transition types occurrence in the Markovian setting, it is not necessarily the case for non-Markovian processes for which equations of type (2.8) and (2.9) are not generally available. In order to simulate non-Markovian processes, methods proposed can be divided into two main approaches. Either Gillespie-type algorithms can be built in particular cases where one can take advantage of the knowledge of the mechanisms of transitions (knowledge of the underlying processes for each type of transitions, distributions of the sojourn times in the compartments etc.), or an individual-centered approach can be adopted in which the process is simulated from the evolution of the health states of each individual.

2.1.5.2 Gillespie-type simulators

Let $t \geq 0$ and suppose that $W^\theta(t) = \xi \in \mathcal{E}$. The idea of Gillespie algorithms and its variants in the Markovian framework is based on the principle of characterizing the distribution of waiting times. In non-Markovian setting, explicit

formula for the probability densities of waiting times cannot be obtained in general. But, as [Boguñá et al. \(2014\)](#) and [Masuda and Rocha \(2018\)](#) pointed out, if each process $N_{\mathbf{u}}$ as introduced in (2.10) is a renewal process, then simulation algorithms similar to those of Gillespie for the non-Markovian process can be deduced.

Assume that $\{N_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ are renewal processes, i.e. defined as $N_{\mathbf{u}} := \sup\{n \geq 1 \mid S_1^{\mathbf{u}} + \dots + S_n^{\mathbf{u}} \leq t\}$ with $S_1^{\mathbf{u}}, \dots, S_n^{\mathbf{u}}$ a sequence of i.i.d variables with finite variance. Moreover, for each type of transition $\mathbf{u} \in \mathcal{T}$, inter-event duration $S_1^{\mathbf{u}}, \dots, S_n^{\mathbf{u}}$ are assumed to be distributed under the probability distributions with density $\varphi_{\mathbf{u}}$ and survival function $\Psi_{\mathbf{u}}$, i.e. $\Psi_{\mathbf{u}}(s) = \mathbb{P}(S_1^{\mathbf{u}} > s)$, for $s \geq 0$.

Let $\lambda_{\mathbf{u}} : s \mapsto \varphi_{\mathbf{u}}(s)/\Psi_{\mathbf{u}}(s)$. Denote by $t_{\mathbf{u}}$ the time elapsed since the last transition of type \mathbf{u} . [Boguñá et al. \(2014\)](#) noted that conditionally to $\{t_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$, the waiting τ of W^θ admits the probability distribution function:

$$s \mapsto \prod_{\mathbf{v} \in \mathcal{T}} \frac{\Psi_{\mathbf{v}}(t_{\mathbf{v}} + s)}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})} \quad (2.15)$$

and moreover, at time s , the probability to perform a type of transition \mathbf{u} at the next transition conditionally to $\{t_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$, is given by:

$$\frac{\lambda_{\mathbf{u}}(t_{\mathbf{u}} + s)}{\sum_{\mathbf{v} \in \mathcal{T}} \lambda_{\mathbf{v}}(t_{\mathbf{v}} + s)}. \quad (2.16)$$

From Equation (2.15), it follows that $\prod_{\mathbf{v} \in \mathcal{T}} \frac{\Psi_{\mathbf{v}}(t_{\mathbf{v}} + \tau)}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})}$ is distributed under a standard uniform distribution over $[0, 1]$. Therefore, sampling τ at each transition of W^θ comes down to solve the problem:

$$\prod_{\mathbf{v} \in \mathcal{T}} \frac{\Psi_{\mathbf{v}}(t_{\mathbf{v}} + \tau)}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})} = u, \quad (2.17)$$

for $u \in (0, 1)$.

Notice that (2.17) defines a non-linear equation with functions $\Psi_{\mathbf{v}}$ which can be eventually complex. So, solving such a problem at each transition of W^θ can be analytically intractable and computationally expensive. To circumvent this challenge, [Boguñá et al. \(2014\)](#) proposed to compute approximate solutions of (2.17). For this purpose, the authors make the following approximation:

$$\begin{aligned} \prod_{\mathbf{v} \in \mathcal{T}} \frac{\Psi_{\mathbf{v}}(t_{\mathbf{v}} + \tau)}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})} &= \exp\left(-\sum_{\mathbf{v} \in \mathcal{T}} \log \frac{\Psi_{\mathbf{v}}(t_{\mathbf{v}})}{\Psi_{\mathbf{v}}(t_{\mathbf{v}} + \tau)}\right) \\ &\approx \exp\left(-\tau \sum_{\mathbf{v} \in \mathcal{T}} \frac{\varphi_{\mathbf{u}}(t_{\mathbf{v}})}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})}\right), \end{aligned}$$

Therefore, the problem (2.17) yields:

$$\tau = -\frac{\log(u)}{\sum_{\mathbf{v} \in \mathcal{T}} \frac{\varphi_{\mathbf{u}}(t_{\mathbf{v}})}{\Psi_{\mathbf{v}}(t_{\mathbf{v}})}} = -\frac{\log(u)}{\sum_{\mathbf{v} \in \mathcal{T}} \lambda_{\mathbf{v}}(t_{\mathbf{v}})} \quad (2.18)$$

Furthermore, [Boguñá et al. \(2014\)](#) derive Algorithm 5 to simulate non-Markovian processes. Note that Algorithm 5 generalizes the Direct Method of Gillespie

Algorithm 5 Non-Markovian Gillespie Algorithm

Require: $\xi_0, T, \{\varphi_{\mathbf{u}}, \Psi_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$

- 1: $t \leftarrow 0$
- 2: $\xi \leftarrow \xi_0$
- 3: **for** $\mathbf{u} \in \mathcal{T}$ **do**
- 4: $t_{\mathbf{u}} \leftarrow 0$
- 5: **end for**
- 6: **for** $\mathbf{u} \in \mathcal{T}$ **do**
- 7: Compute $\lambda_{\mathbf{u}}(t_{\mathbf{u}}) \leftarrow \varphi_{\mathbf{u}}(t_{\mathbf{u}})/\Psi_{\mathbf{u}}(t_{\mathbf{u}})$
- 8: **end for**
- 9: **while** $t < T$ **do**
- 10: Draw u with uniform distribution over $[0, 1]$
- 11: Compute $\tau \leftarrow -\frac{\log(u)}{\sum_{\mathbf{v} \in \mathcal{T}} \lambda_{\mathbf{v}}(t_{\mathbf{u}})}$
- 12: **for** $\mathbf{u} \in \mathcal{T}$ **do**
- 13: Compute $\lambda_{\mathbf{u}}(t_{\mathbf{u}} + \tau) \leftarrow \varphi_{\mathbf{u}}(t_{\mathbf{u}} + \tau)/\Psi_{\mathbf{u}}(t_{\mathbf{u}} + \tau)$
- 14: **end for**
- 15: **for** $\mathbf{u} \in \mathcal{T}$ **do**
- 16: Compute proportions $p_{\mathbf{u}} \leftarrow \lambda_{\mathbf{u}}(t_{\mathbf{u}} + \tau) / \sum_{\mathbf{v} \in \mathcal{T}} \lambda_{\mathbf{v}}(t_{\mathbf{v}} + \tau)$
- 17: **end for**
- 18: Draw \mathbf{u}_{next} with a multinomial with parameters $\{p_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$
- 19: $t \leftarrow t + \tau$
- 20: $\xi \leftarrow \xi + \mathbf{u}_{next}$
- 21: $t_{\mathbf{u}_{next}} \leftarrow 0$
- 22: **for** $\mathbf{u} \in \mathcal{T} \setminus \{\mathbf{u}_{next}\}$ **do**
- 23: $t_{\mathbf{u}} \leftarrow t_{\mathbf{u}} + \tau$
- 24: **end for**
- 25: **end while**

(Algorithm 1). Indeed, in Markovian setting, inter-events are distributed under exponential distributions and thus, ratios $\varphi_{\mathbf{u}}(t_{\mathbf{u}})/\Psi_{\mathbf{u}}(t_{\mathbf{u}})$ are given by parameters of exponential distributions.

However, the solution in (2.18) is not exact ([Masuda and Rocha, 2018](#)) and then Algorithm 5 is not exact in general. It only provides approximate trajectories of non-Markovian processes. [Masuda and Rocha \(2018\)](#) studied the cases where the approximate solution (2.18) is actually exact. The authors showed that if processes $\{N_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ are event-modulated Poisson processes, i.e. mixtures of Poisson processes of different rates, then (2.18) is exact. Furthermore, a variant of Algorithm 5 adapted to simulate event-modulated Poisson processes was introduced and it allows to generate statistically exact trajectories

in this particular setting.

2.1.5.3 An individual-based approach: Sellke construction

In order to overcome the difficulty of characterizing waiting time distributions, agent-based approaches offer an alternative for simulating non-Markovian processes. In this section, Sellke construction (Sellke, 1983), an approach to reconstructing epidemic dynamics based on characteristics of individuals in the population with respect to infection, is presented. This construction of the SIR model proposes a re-interpretation of infection mechanism.

Assume that the population considered is closed and includes N individuals. At the initial time ($t = 0$), each individual is labeled with a unique label which enables the identification throughout the study. Each initially susceptible individual (i.e. susceptible at time $t = 0$) is assigned with a tolerance threshold which gives the maximum level of exposure to the infection beyond which the individual becomes infected. If $W_I(t)$ denotes the number of individuals infected at time t and β the transmission rate, the level of exposure at time t is given by the infection pressure P defined as:

$$P(t) = \frac{\beta}{N} \int_0^t W_I(s) ds.$$

An initially susceptible individual with a tolerance threshold Q remains susceptible as long as $Q > P(t)$ for $t \geq 0$. He or she becomes infected at time t_{inf} such that $Q = P(t_{inf})$. Regarding recoveries, they are managed by a mechanism of sojourn times in the compartment I . Indeed, at the initial time, all susceptible and infected individuals are equipped with a sojourn time in the compartment I . These durations correspond to the time that each of these individuals will spend in the infectious state before recovery if he or she ever becomes infected. If an individual with sojourn time Δ is initially in I , i.e., at instant $t = 0$ or if he or she enters I at some instant $t > 0$, then it leaves this compartment at time $t + \Delta$ to reach R .

The characteristics of the individuals combined with the transition mechanisms allow to fully describe epidemic dynamics of the SIR model. In particular, when the tolerance thresholds are distributed independently according to an exponential distribution with parameter 1 and sojourn durations in I are independent and identically distributed according to a certain exponential distribution, then the resulting model is equivalent to the simple Markovian SIR model. This makes this construction a general approach to consider the SIR model in both Markovian and non-Markovian contexts.

Given the flexibility of this construction regarding the choice of distributions of individual tolerance thresholds and sojourn durations, it is used to study various non-Markovian formulations of the simple SIR model such as: dependence between tolerance thresholds and sojourn durations (Reinert,

1995), the use of the Weibull distribution for sojourn durations (Streftaris and Gibson, 2012), etc. It was also used in refinements of the SIR model such as: SIR-multitype epidemics (Andersson and Britton, 2000b), age-dependent SIR (Di Lauro et al., 2022) or SIR model with finite heterogeneous populations (House, 2014). However, to our knowledge, apart from the extension to the SEIR model (Britton et al., 2019), this construction has not been generalized to other types of compartmental models.

2.2 Global sensitivity analysis

This section presents and discusses some variance-based sensitivity analysis approaches with respect to both deterministic and stochastic model frameworks. Throughout this section, models whether they are deterministic or stochastic are assumed to include $p \in \mathbb{N}^*$ uncertain parameters. In addition, the parameter uncertainty is propagated through the model by modeling uncertain parameters with a random vector $\mathbf{X} := (X_1, \dots, X_p)$ distributed under $\mathbb{P}_{\mathbf{X}}$, a supposedly known probability distribution on the model input space. Finally, Assumption 1 is assumed in all what follows.

Assumption 1. *Random variables X_1, \dots, X_p are mutually independent.*

2.2.1 Variance-based sensitivity analysis for deterministic models

Let $(\mathcal{X}, \mathcal{B})$ and $(\mathcal{Y}, \mathcal{F})$ be two nonempty measurable spaces such that \mathbf{X} takes its values on \mathcal{X} . A deterministic model with inputs \mathbf{X} and output $Y \in \mathcal{Y}$ is defined as a deterministic function $f : \mathcal{X} \rightarrow \mathcal{Y}$ (i.e. to each $x \in \mathcal{X}$ corresponds a unique $y \in \mathcal{Y}$) such that $Y = f(\mathbf{X})$. Therefore, Y is random and depending on the type of output space \mathcal{Y} , Y can be scalar, multivariate or functional. In the following, \mathbf{X} can be referred to as inputs or parameters or even input parameters and the output of the model f can be denoted by Y or $f(\mathbf{X})$ depending on the convenience.

The variance-based sensitivity analysis aims at expanding the variance of Y into contributions of the different combinations $\mathbf{X}_u = \{X_j, j \in u\}$ of \mathbf{X} , where $u \subseteq \{1, \dots, p\}$. A way to obtain such a decomposition is to expand $f(\mathbf{X})$ into a sum of mutually uncorrelated functions $f_u(\mathbf{X}_u)$. Such an expansion is proposed in Hoeffding (1948), Efron and Stein (1981), Sobol' (1993) and known as the Sobol'-Hoeffding decomposition of f or the functional ANOVA decomposition. This decomposition is introduced in the following.

Assume that $f \in \mathbb{L}^2(\mathcal{X}, \mathbb{P}_{\mathbf{X}})$, i.e. f is square integrable. Then, there exists

a unique decomposition of $f(\mathbf{X})$ under the form:

$$f(\mathbf{X}) = \sum_{u \subseteq \{1, \dots, p\}} f_u(\mathbf{X}_u), \quad (2.19)$$

where f_u are functions of X_u , $u \subseteq \{1, \dots, p\}$ such that $\mathbb{E}[f_u(\mathbf{X}_u) | \mathbf{X}_v] = 0$ for any $u \subseteq \{1, \dots, p\}$ and $v \subsetneq u$. Moreover, the expansion (2.19) satisfies:

- i) $f_\emptyset = \mathbb{E}(f(\mathbf{X}))$,
- ii) $f_u(\mathbf{X}_u) = \mathbb{E}[f(\mathbf{X}) | \mathbf{X}_u] - \sum_{v \subsetneq u} f_v(\mathbf{X}_v)$.
- iii) $\mathbb{E}(f_u(\mathbf{X}_u) f_{u'}(\mathbf{X}_{u'})) = 0$, for any distinct subsets u and u' of $\{1, \dots, p\}$.

The univariate functions $f_1(X_1), \dots, f_p(X_p)$ are the so-called main effects of X_1, \dots, X_p respectively. The bivariate functions $f_{i,j}(X_i, X_j)$ for any distinct i and j in $\{1, \dots, p\}$ are second-order interactions whereas other multivariate functions are referred to as high order interactions. An illustration of Sobol'-Hoeffding decomposition is given in Example 2.

Example 2. Let $\mathbf{X} = (X_1, X_2)$ be distributed under a centered bivariate Gaussian distribution with variance-covariance matrix given by the identity matrix of dimension 2×2 . Let $f(\mathbf{X}) := X_1 + X_2 + X_1^2 X_2^2$. It holds that:

$$\begin{aligned} f_\emptyset &= \mathbb{E}(f(\mathbf{X})) = 1 \\ f_1(X_1) &= \mathbb{E}[f(\mathbf{X}) | X_1] - 1 = X_1 + X_1^2 - 1 \\ f_2(X_2) &= \mathbb{E}[f(\mathbf{X}) | X_2] - 1 = X_2 + X_2^2 - 1 \\ f_{1,2}(X_1, X_2) &= \mathbb{E}[f(\mathbf{X}) | X_1, X_2] - f_1(X_1) - f_2(X_2) - 1 = X_1^2 X_2^2 - X_1^2 - X_2^2 + 1. \end{aligned}$$

The decomposition (2.19) has the following characteristics. It is valid regardless the nature of the output of f : scalar, multivariate or functional. It is finite as it contains exactly 2^p terms. Moreover, its terms are orthogonal, referring to property iii) above.

2.2.1.1 Variance-based sensitivity indices

Assume that $f(\mathbf{X}) \in \mathbb{R}$ such that $\text{Var}(f(\mathbf{X})) > 0$. Based on decomposition (2.19), Sobol' (1993) introduced the so-called Sobol' indices. Indeed, the orthogonality of the terms in (2.19) yields:

$$\text{Var}(f(\mathbf{X})) = \sum_{u \subseteq \{1, \dots, p\}, u \neq \emptyset} \text{Var}(f_u(\mathbf{X}_u)). \quad (2.20)$$

The Sobol' index associated to a set of parameters \mathbf{X}_u for a non-empty subset u of $\{1, \dots, p\}$ is defined as:

$$S_u := \frac{\text{Var}(f_u(\mathbf{X}_u))}{\text{Var}(f(\mathbf{X}))}. \quad (2.21)$$

Notice that indices $S_u, u \subseteq \{1, \dots, p\} \setminus \emptyset$ sum up to one. In the case $u = \{i\}$ where $i \in \{1, \dots, p\}$, the corresponding index is given by

$$S_i = \frac{\text{Var}(f_i(\mathbf{X}_i))}{\text{Var}(f(\mathbf{X}))} = \frac{\text{Var}(\mathbb{E}[f(\mathbf{X}) | X_i])}{\text{Var}(f(\mathbf{X}))} \quad (2.22)$$

and known as the first-order Sobol' index associated to X_i (Sobol', 1993). This index measures the proportion of $\text{Var}(f(\mathbf{X}))$ due to the variation of the input X_i only. Thus, if $S_i = 1$, the global variance is entirely explained by the variation of X_i only. In fact, the higher the index S_i , the more X_i contributes to the model output uncertainty. So, first-order Sobol' indices allow to classify uncertain parameters according to their importance in the global variability of the output and thereby to identify key parameters of models: this is *factor prioritization*.

Furthermore, in the case $u = \{i, j\}$ with $i \neq j$, it yields that:

$$S_{i,j} = S_{j,i} = \frac{\text{Var}(f_{i,j}(X_i, X_j))}{\text{Var}(f(\mathbf{X}))} = \frac{\text{Var}(\mathbb{E}[f(\mathbf{X}) | X_i, X_j])}{\text{Var}(f(\mathbf{X}))} - S_i - S_j.$$

Index $S_{i,j}$ represents the second-order interaction of X_i, X_j , i.e. the combined effect of X_i and X_j on the model output excluding their main effects. Higher order interactions can be obtained by considering u with more inputs.

Note that the first-order Sobol' indices do not include interactions of $X_i, i = 1, \dots, p$ with other inputs $X_j, j \neq i$ although they also represent contributions of X_i to the variance of $f(\mathbf{X})$. In order to measure the total influence of X_i by itself or in interaction with other input parameters, Homma and Saltelli (1996) introduced the total Sobol' indices as follows:

$$ST_u = \sum_{v \subseteq \{1, \dots, p\}: u \cap v \neq \emptyset} \frac{\text{Var}(f_v(\mathbf{X}_v))}{\text{Var}(f(\mathbf{X}))}. \quad (2.23)$$

In the case where $u = \{i\}$ for any $i = 1, \dots, p$, the total Sobol' index of X_i is given by:

$$ST_i = 1 - \frac{\text{Var}(\mathbb{E}[f(\mathbf{X}) | \mathbf{X}_{\sim i}])}{\text{Var}(f(\mathbf{X}))},$$

where $\sim i$ denotes the set $\{1, \dots, p\} \setminus \{i\}$. This index aggregates all the Sobol' indices of sets of parameters of \mathbf{X} in which X_i is involved. Therefore, ST_i accounts for all the contributions of input X_i .

If $ST_i = 0$, then $\text{Var}(\mathbb{E}[f(\mathbf{X}) | \mathbf{X}_{\sim i}]) = \text{Var}(f(\mathbf{X}))$. The global variance is therefore totally due to $\mathbf{X}_{\sim i}$. This implies that X_i is not an influential parameter of the model since its main effect and any of its interactions with other parameters are null. Such a parameter can be frozen without modifying the variance of the model output: this is *factor fixing*. Hence, total indices can contribute to model reduction through factor fixing.

Now, let us assume that Y is multivariate, i.e. $Y \in \mathbb{R}^q$, with $q \geq 2$. The variance decomposition (2.20) still holds. In such a case, the variance-covariance matrix of Y , denoted $\Gamma := \text{Var}(f(\mathbf{X}))$ is a matrix of dimension $q \times q$ and can be decomposed as follows:

$$\Gamma = \sum_{u \subseteq \{1, \dots, p\}, u \neq \emptyset} \Gamma_u, \quad (2.24)$$

where $\Gamma_u = \text{Var}(f_u(\mathbf{X}_u))$ is a matrix since $f_u(\mathbf{X}_u)$ is a q -dimensional random vector. However, unlike the scalar case, sensitivity indices cannot be defined in unique way based on (2.24). Indeed, as pointed out by Gamboa et al. (2014), using Equation (2.24), different indices can be introduced because of particular properties of matrix calculus such as the non-commutativity of matrix multiplication operation.

Let M be any matrix of dimension $q \times q$ such that $\text{Trace}(M\Gamma) \neq 0$, where $\text{Trace}(\cdot)$ denotes the trace, i.e., the linear function that returns the sum of diagonal elements of matrices. Gamboa et al. (2014) introduced M -sensitivity measures S_u^M as:

$$S_u^M = \frac{\text{Trace}(M\Gamma_u)}{\text{Trace}(M\Gamma)}, \quad (2.25)$$

for $u \subseteq \{1, \dots, p\} \setminus \{\emptyset\}$. This index coincides with S_u in the scalar output framework. The particular choice of $M = Id$ leads to a sensitivity index invariant by isometric transformation (i.e. preserving the distance) of the model output. This index was first introduced in Lamboni et al. (2011) in the framework of a discretized functional model output.

Actually, in the case where the output of the model is functional, i.e., $Y = \{Y(t) := f(t, \mathbf{X}), t \in \mathbb{T}\}$, where \mathbb{T} is a non-empty set, sensitivity indices can be defined in several ways. Dynamical indices can be introduced by considering each $Y(t)$ with $t \in \mathbb{T}$ and using sensitivity indices defined in (2.21). Also, spectral methods can be used to reduce to the multivariate setting: Principal Component Analysis (Lamboni et al., 2011; Campbell et al., 2006), Vector projection (Xu et al., 2019), Polynomial Chaos Expansion (Garcia-Cabrejo and Valocchi, 2014), Karhunen-Loève decomposition (Li et al., 2020), wavelet decomposition (Xiao et al., 2018), etc. Then, Sobol' indices are defined from (2.25) on the vector coefficients in the multivariate decomposition.

2.2.1.2 Estimation of variance-based indices

In this section, Y is assumed to be scalar until further notice. In practice, function f that represents the deterministic model may not have simple analytical expression or even it may be given as computer code. In this case, analytical computation of sensitivity indices is impossible because moments of the model output are not tractable. Therefore, one can rely on estimation to assess sensitivity indices. In general, Monte Carlo methods are used to approximate

expectations of the model output, i.e. quantities under the form $\mathbb{E}(\phi(Y))$, where ϕ is an integrable function defined on \mathcal{Y} . This consists in sampling the input space \mathcal{X} using $\mathbb{P}_{\mathbf{X}}$ to generate samples: $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$, where $n \geq 1$, and then estimating $\mathbb{E}(\phi(Y))$ with empirical means: $\frac{1}{n} \sum_{l=1}^n \phi(f(\mathbf{X}^{(l)}))$. Several methods enable to sample spaces: Monte Carlo Sampling (Janssen, 2013), Quasi-Monte Carlo Sampling (Morokoff and Caffisch, 1995), Latin Hypercube Sampling (Michael Stein, 1987)...

Pick-freeze estimator

Consider the first-order Sobol' index S_i of input X_i for any $i = 1, \dots, p$. It holds that:

$$S_i = \frac{\mathbb{E} \left(\mathbb{E} [f(\mathbf{X}) | X_i]^2 \right) - (\mathbb{E} (f(\mathbf{X})))^2}{\mathbb{E} (f(\mathbf{X})^2) - (\mathbb{E} (f(\mathbf{X})))^2}.$$

Let $D_i := \mathbb{E} \left(\mathbb{E} [f(\mathbf{X}) | X_i]^2 \right)$ for any $i = 1, \dots, p$, $D := \mathbb{E} (f(\mathbf{X})^2)$ and $\mu := \mathbb{E} (f(\mathbf{X}))$. Then, it follows that $S_i = (D_i - \mu^2)/(D - \mu^2)$ for any $i = 1, \dots, p$. Note that D and μ can be estimated by the moment estimators given by empirical means of $f(\mathbf{X})$ and $f(\mathbf{X})^2$ respectively. Unlike, D_i includes the squared conditional expectation $\mathbb{E} [f(\mathbf{X}) | X_i]^2$ which makes estimation a little more complicated. To overcome this difficulty, $\mathbb{E} [f(\mathbf{X}) | X_i]^2$ is decoupled in the following way. Let $\tilde{\mathbf{X}}$ be an independent copy of \mathbf{X} , it appears that $\mathbb{E} [f(\mathbf{X}) | X_i]^2 = \mathbb{E} [f(\mathbf{X}) f(X_i, \tilde{\mathbf{X}}_{\sim i}) | X_i]$. Hence: $D_i = \mathbb{E} (f(\mathbf{X}) f(X_i, \tilde{\mathbf{X}}_{\sim i}))$ for any $i = 1, \dots, p$. Thus, D_i , μ and D can be respectively estimated by:

$$\begin{aligned} \hat{D}_i &:= \frac{1}{n} \sum_{j=1}^n f(\mathbf{X}^{(j)}) f \left(X_i^{(j)}, \tilde{\mathbf{X}}_{\sim i}^{(j)} \right) \\ \hat{\mu} &:= \frac{1}{n} \sum_{j=1}^n f(\mathbf{X}^{(j)}) \\ \hat{D} &:= \frac{1}{n} \sum_{j=1}^n f(\mathbf{X}^{(j)})^2 \end{aligned}$$

so that the first-order Sobol' index S_i is estimated by:

$$\hat{S}_i := \frac{\hat{D}_i - \hat{\mu}^2}{\hat{D} - \hat{\mu}^2} \quad (2.26)$$

for any $i \in \{1, \dots, p\}$. Estimator \hat{S}_i is the so-called pick-freeze estimator of S_i . Other forms of such an estimator can be considered. Noticing that $\text{Var}(\mathbb{E} [f(\mathbf{X}) | X_i])$ is also the covariance $\text{cov}(f(\mathbf{X}), f(X_i, \tilde{\mathbf{X}}_{\sim i}))$, then, S_i can be estimated by:

$$\tilde{S}_i^{(1)} := \frac{\hat{D}_i - \hat{\mu} \times \tilde{\mu}_i}{\hat{D} - \hat{\mu}^2}$$

where $\tilde{\mu}_i := \frac{1}{n} \sum_{j=1}^n f\left(X_i^{(j)}, \tilde{\mathbf{X}}_{\sim i}^{(j)}\right)$. Also:

$$\tilde{S}_i^{(2)} := \frac{\widehat{D}_i - \left(\frac{\widehat{\mu} + \tilde{\mu}_i}{2}\right)^2}{\left(\frac{\widehat{D} + \widehat{D}_i}{2}\right)^2 - \left(\frac{\widehat{\mu} + \tilde{\mu}_i}{2}\right)^2},$$

with $\widehat{D}_i := \frac{1}{n} \sum_{j=1}^n f\left(X_i^{(j)}, \tilde{\mathbf{X}}_{\sim i}^{(j)}\right)^2$, can be used to take advantage of available model evaluations in order to improve estimations. The two estimators were introduced in [Homma and Saltelli \(1996\)](#); [H. Monod \(2006\)](#) and studied by [Janon et al. \(2014a\)](#); [Gamboa et al. \(2016\)](#). Both are implemented in the R-package *sensitivity* ([Iooss et al., 2020](#)).

Statistical properties of estimators $\widehat{S}_i, i = 1, \dots, p$ were studied in [Homma and Saltelli \(1996\)](#) and are recalled in the following. Let $g : (x_1, x_2, x_3) \mapsto (x_3 - x_2^2)/(x_1 - x_2^2)$ defined over $\mathcal{D} = \{(x_1, x_2, x_3) : x_1 > x_2^2\}$. Denote $\theta_i = (D, \mu, D_i)$ and $\widehat{\theta}_i = (\widehat{D}, \widehat{\mu}, \widehat{D}_i)$ so that $S_i = g(\theta_i)$ and $\widehat{S}_i = g(\widehat{\theta}_i)$ for $i = 1, \dots, p$. Note that each $\widehat{\theta}_i$ is an empirical mean of i.i.d. square integrable random vectors such that $\mathbb{E}(\widehat{\theta}_i) = \theta_i$. Thus, the law of large numbers yields that $\widehat{\theta}_i$ converges in probability to θ_i . This implies that \widehat{S}_i converges in probability to S_i since g is continuous. Moreover, based on the central limit theorem, $\sqrt{n}(\widehat{\theta}_i - \theta_i)$ converges in distribution to $\mathcal{N}(0, V_i)$, for some matrix V_i . As g is differentiable such that $\nabla g(\theta_i) \neq 0$ then using the so-called delta-method, $\sqrt{n}(\widehat{S}_i - S_i)$ converges in distribution to $\mathcal{N}(0, \sigma_i^2)$, where $\sigma_i^2 = \nabla g(\theta_i)^T V_i \nabla g(\theta_i)$. Estimators $\tilde{S}_i^{(1)}$ and $\tilde{S}_i^{(2)}$ share also those properties of consistency and asymptotic normal distribution. Moreover, [Janon et al. \(2014a\)](#) showed that $\tilde{S}_i^{(2)}$ is asymptotically efficient.

For total Sobol' indices, following Equation (2.23), it is possible to derive an estimator similar to (2.26), by freezing all the inputs in $\mathbf{X}_{\sim i}$ ([Homma and Saltelli, 1996](#)). [Jansen \(1999\)](#) introduced later a new estimator using the identity: $\mathbb{E}(\text{Var}[f(\mathbf{X}) | \mathbf{X}_u]) = \mathbb{E}(f(\mathbf{X}) - f(\mathbf{X}_u, \tilde{\mathbf{X}}_{\sim u}))^2/2$. This estimator is later improved by [Saltelli et al. \(2010\)](#) and is given by:

$$\widehat{ST}_i := \frac{\frac{1}{2n} \sum_{j=1}^n \left(f(\mathbf{X}^{(j)}) - f(X_i^{(j)}, \tilde{\mathbf{X}}_{\sim i}^{(j)})\right)^2}{\frac{1}{n} \sum_{j=1}^n f(\mathbf{X}^{(j)})^2 - \left(\frac{1}{n} \sum_{j=1}^n f(\mathbf{X}^{(j)})\right)^2}, \quad i = 1, \dots, p.$$

Now, assume that Y is multivariate or functional. In such a case, [Gamboa et al. \(2014\)](#) introduced pick-freeze estimators generalizing those used in the scalar case ([Gamboa et al., 2016](#)) to estimate sensitivity indices defined in (2.25). In particular, their estimator generalizing $\tilde{S}_i^{(2)}$ is still consistent, asymptotically normally distributed and asymptotically efficient.

Overall, accurate estimation of sensitivity indices is an important issue in sensitivity analysis. Many studies have been conducted on this subject: [Sobol' and Myshetskaya \(2008\)](#); [Saltelli \(2002\)](#); [Azzini et al. \(2021\)](#). Aside,

non-parametric methods were introduced (Da Veiga and Gamboa, 2013; Solís, 2021; Heredia et al., 2021) in order to provide alternatives to Monte-Carlo methods. Also methods based on spectral tools for example in Cukier et al. (1978); Saltelli et al. (1999); Tissot and Prieur (2012) were used to improve rate of convergence under regularity assumptions on f .

Besides, it is possible to replace a model by a metamodel (see, e.g., Sudret (2008); Marrel et al. (2009)) to approximate indices. This approach allows either to compute analytically approximations of Sobol' indices or to estimate them with cheap surrogates using pick-freeze estimators.

2.2.2 Variance-based sensitivity analysis for stochastic models

Recall that $(\mathcal{X}, \mathcal{B})$ and $(\mathcal{Y}, \mathcal{F})$ are two nonempty measurable spaces. Let us introduce a new measurable space $(\mathcal{Z}, \mathcal{G})$ and define $f : \mathcal{X} \times \mathcal{Z} \rightarrow \mathcal{Y}$ a measurable function. In the following, we say that f is a stochastic model with inputs $\mathbf{X} = (X_1, \dots, X_p)$ and output Y if there exists a latent random variable or a collection of latent random variables denoted Z with values on \mathcal{Z} such that $Y = f(\mathbf{X}, Z)$. The random element Z is called the intrinsic randomness of the model. It should be noted that Z plays a role different from input vector \mathbf{X} as it is generally an uncontrolled latent variable. Hereafter, let us make the following assumption:

Assumption 2. \mathbf{X} and Z are independent.

Ideally, the input vector \mathbf{X} can be extended with Z , yielding $\mathbf{X}^{ext} := (\mathbf{X}, Z)$, so that the model defined by f with inputs \mathbf{X}^{ext} and output Y is deterministic. In such a case, using Assumptions 1 and 2, the Sobol'-Hoeffding decomposition holds:

$$f(\mathbf{X}, Z) = f(\mathbf{X}^{ext}) = \sum_{v \subseteq \{1, \dots, p+1\}} f_v(\mathbf{X}_v^{ext}), \quad (2.27)$$

where $\mathbf{X}_{p+1}^{ext} := Z$. Therefore, it is possible to decompose the variance of Y , to define and to assess Sobol' indices especially the first-order Sobol' index of the intrinsic randomness:

$$S_Z = \frac{\text{Var}(\mathbb{E}[f(\mathbf{X}, Z) | Z])}{\text{Var}(f(\mathbf{X}, Z))}$$

and interactions between intrinsic randomness and \mathbf{X}_u :

$$S_{\mathbf{X}_u, Z} = \frac{\text{Var}(\mathbb{E}[f(\mathbf{X}, Z) | \mathbf{X}_u, Z])}{\text{Var}(f(\mathbf{X}, Z))} - S_Z - S_{\mathbf{X}_u},$$

with $u \subseteq \{1, \dots, p\}$.

For many practical settings, it is possible to get realizations of $f(x, Z)$ for any $x \in \mathcal{X}$, however it is not possible to compute $f(x, z)$ for $(x, z) \in \mathcal{X} \times \mathcal{Z}$

and the probability distribution \mathbb{P}_Z is unknown. Then, decomposition (2.27) cannot be used in general. Hence, different methods have been introduced to perform sensitivity analysis of stochastic models. A review of these methods is proposed in the following.

2.2.2.1 Basic approach

Even though f cannot be decomposed as in (2.27), the law of total variance still provides a decomposition of the variance $\text{Var}(f(\mathbf{X}, Z))$:

$$\text{Var}(f(\mathbf{X}, Z)) = \text{Var}(\mathbb{E}[f(\mathbf{X}, Z) | \mathbf{X}]) + \mathbb{E}(\text{Var}[f(\mathbf{X}, Z) | \mathbf{X}]). \quad (2.28)$$

In practice, this leads to considering naturally the conditional mean $e(\mathbf{X}) = \mathbb{E}[f(\mathbf{X}, Z) | \mathbf{X}]$ and the conditional variance $v(\mathbf{X}) = \text{Var}[f(\mathbf{X}, Z) | \mathbf{X}]$ for the sensitivity analysis of f . Note that both e and v define deterministic models. Thus, such an approach amounts to assessing the Sobol' indices of the set of parameters \mathbf{X}_u , $u \subseteq \{1, \dots, p\} \setminus \{\emptyset\}$ for both e and v . This is illustrated in Example 3.

Example 3. Let be $\mathbf{X} = (X_1, X_2)$ distributed under the centered bivariate Gaussian distribution with variance-covariance matrix given by the identity matrix and Z distributed under the uniform distribution on $[-L, L]$, with $L > 0$ such that \mathbf{X} and Z are independent. Consider $f(\mathbf{X}, Z) = X_1 + X_2 Z$. Then: $e(\mathbf{X}) = X_1$ and $v(\mathbf{X}) = X_2^2 \mathbb{E}(Z^2)$.

Denote by S_1^e and S_1^v the Sobol' indices of X_1 for outputs $e(\mathbf{X})$ and $v(\mathbf{X})$ respectively and S_2^e and S_2^v those of X_2 . We get $S_1^e = 1$, $S_2^e = 0$, $S_1^v = 0$ and $S_2^v = 1$.

In general, $e(\mathbf{X})$ and $v(\mathbf{X})$ need to be estimated or metamodeled in order to estimate the variance of Y , as far as the influence of uncertain parameters on either $e(\mathbf{X})$ or $v(\mathbf{X})$. For example, [Iooss and Ribatet \(2009\)](#) and [Marrel et al. \(2012\)](#) estimate not only Sobol' indices of uncertain parameters but also the total Sobol' index of Z . However, their approach based on joint metamodeling of e and v , does not allow to estimate the main effect of Z on Y nor the interaction between \mathbf{X}_u and Z for a particular set $u \subseteq \{1, \dots, p\}$ such that $u \neq \emptyset$.

2.2.2.2 More general averaged quantities of interest

In Section 2.2.2.1, two quantities of interest (QoIs) were introduced: $e(\mathbf{X})$ and $v(\mathbf{X})$. More generally, one can consider QoIs under the form $Q(\mathbf{X}) = \mathbb{E}[\phi(f(\mathbf{X}, Z)) | \mathbf{X}]$, where ϕ is a measurable transformation. For example, we can have: conditional moments $Q(\mathbf{X}) = \mathbb{E}[f(\mathbf{X}, Z)^r | \mathbf{X}]$, $r \geq 1$, the probability $Q(\mathbf{X}) = \mathbb{E}[\mathbb{1}_{f(\mathbf{X}, Z) \in B} | \mathbf{X}]$ for a measurable set B , or other quantities such as

expectation of some exit time (Étoré et al., 2020), etc. Some examples in epidemiology are provided in Example 4.

Example 4. Consider a closed population with size N and the classical SIR model and $W^\theta = (W_S, W_I, W_R)$ the epidemic process with $\theta = (\beta, \gamma)$. We classically introduce the following QoIs:

- i. The extinction probability: $p_{ext} = \mathbb{P}(W_I(t) = 0), t > 0$.
- ii. The mean extinction time $\mathbb{E}(\tau_{ext} | \theta)$ where $\tau_{ext} = \inf\{t \geq 0 | W_I(t) = 0\}$.
- iii. The mean of the peak of infections: $\mathbb{E}(\tau_{max} | \theta)$ where $\tau_{max} = \max\{W_I(t), t \geq 0\}$.

Another example of QoI in uncertainty quantification is given by differential entropy. Assume that for each $x \in \mathcal{X}$, the output $f(x, Z)$ is a random variable with probability density function p_x . The differential entropy of $f(x, Z)$ is defined as:

$$H(x) = -\mathbb{E}(p_x(\log f(x, Z))), \quad (2.29)$$

and hence $H(\mathbf{X}) = -\mathbb{E}[p_{\mathbf{X}}(\log f(\mathbf{X}, Z)) | \mathbf{X}]$. The quantity (2.29) is a measure of uncertainty that informs about the way the output $f(x, Z)$ disperses the randomness, i.e., the way it is scattered on the output space \mathcal{Y} . Differential entropy was used in the place of the variance in sensitivity analysis of deterministic models, e.g. in Kala (2021); Auder and Iooss (2008); Hall (2006). More recently, Azzi et al. (2020) proposed to use (2.29) to perform the sensitivity analysis of stochastic models.

Overall, as function of \mathbf{X} only, Q defines a deterministic model. Then, sensitivity analysis can be handled based on the Sobol'-Hoeffding decomposition, provided that $\mathbb{E}(Q(\mathbf{X})^2) < +\infty$. As already said in Section 2.2.2.1, it is not always possible to compute explicitly $Q(\mathbf{X})$, thus estimation or metamodeling is needed. Estimating such conditional quantities requires having samples: $f(x, Z^{(1)}), \dots, f(x, Z^{(m)})$ with $m \geq 1$, given $\mathbf{X} = x$. This comes down to setting $\mathbf{X} = x$ and repeating m times the model evaluation at x . Therefore, estimation of Sobol' indices of $Q(\mathbf{X})$ needs not only exploration of parameter space to generate samples of \mathbf{X} but also repetitions of the model evaluations at each sample of \mathbf{X} . Since the estimation of $Q(\mathbf{X})$ can introduce bias, a bias-variance issue arises when estimating Sobol' indices. Such a problem can be all the more important as the computation budget is limited. To address this problem, Mazo (2021) proposed a bias-variance trade-off by studying the mean ranking error of Sobol' index estimators.

Anyway, with this manner of dealing with stochastic models, the intrinsic randomness is averaged. Unless this is relevant to the study being conducted, other approaches which would best preserve the intrinsic randomness of these models should be considered. One such approach introduced by Hart et al. (2017) is presented in the next section.

2.2.2.3 Parameterized Sobol'-Hoeffding decomposition

Recall that the intrinsic randomness Z of the stochastic model f takes values on \mathcal{Z} . To perform sensitivity analysis for f by leveraging available tools of the deterministic framework, Hart et al. (2017) suggested to change the way the stochastic model and its intrinsic randomness Z are viewed. Instead of dealing with Z as a noise, Hart et al. (2017) proposed to consider it as a parameter. The stochastic model is then a family of deterministic models parameterized by $z \in \mathcal{Z}$ so that for Z frozen at some z , the output of the deterministic model is given by:

$$Y(z) = f(\mathbf{X}, z) =: f_z(\mathbf{X}).$$

Therefore, f_z is a deterministic model with inputs \mathbf{X} such that f_z is square integrable. It follows that the Sobol'-Hoeffding decomposition (2.19) holds and thereby Sobol' indices can be defined. The parameterized first-order Sobol' index of parameter X_i is given by:

$$S_i(z) = \frac{\text{Var}(\mathbb{E}[f_z(\mathbf{X}) \mid X_i])}{\text{Var}(f_z(\mathbf{X}))},$$

for any $i = 1, \dots, p$. As Z is random, then so is $S_i(Z)$ random. Therefore, for $i = 1, \dots, p$, Hart et al. (2017) defined the first-order sensitivity index of parameter X_i as follows:

$$S_i^H = \mathbb{E}(S_i(Z)). \quad (2.30)$$

For illustration, consider the stochastic model given in Example 3 and let us compute sensitivity indices in (2.30):

Example 5. Consider the stochastic model f with inputs \mathbf{X} and intrinsic randomness Z as defined in Example 3, with $L > 0$. For $Z = z$, it holds that $f(\mathbf{X}, z) = X_1 + X_2 z$ and thus $\mathbb{E}[f(\mathbf{X}, z) \mid X_1] = X_1$, $\mathbb{E}[f(\mathbf{X}, z) \mid X_2] = zX_2$. Then, $S_1(z) = 1/(1 + z^2)$ and $S_2(z) = z^2/(1 + z^2)$. Therefore:

$$S_1^H = \mathbb{E}\left(\frac{1}{1 + Z^2}\right) = \frac{\arctan L}{L}$$

$$S_2^H = 1 - S_1^H = 1 - \frac{\arctan L}{L}.$$

It can be noticed that S_1^H and S_2^H depend on L which is proportional to the amplitude of the range of variation of Z . This helps to see how the noise may affect the effects of the parameters on model output.

Even if indices in (2.30) have the advantage of highlighting the link between the intrinsic randomness and the contributions of the uncertain parameters (refer to Example 5), they do not help in quantifying the influence of the intrinsic randomness on output.

2.2.3 Beyond the variance-based approach

More recently, stochastic models were re-interpreted as deterministic models, depending only on unknown parameters \mathbf{X} , with values in a set of probability distributions. In the following, we give an overview on the recent literature on the topic.

2.2.3.1 Probability distribution based approach

Let \mathcal{M} be the set of probability distribution functions (p.d.f) on the output space. In [Fort et al. \(2021\)](#), authors consider the function:

$$\begin{aligned}\varphi: \mathcal{X} &\longrightarrow \mathcal{M} \\ x &\longmapsto \varphi(x) = \mu_x,\end{aligned}$$

where μ_x is the p.d.f. of $f(x, Z)$. The function φ defines a deterministic model with values in \mathcal{M} . Thus, such a function allows to switch from the stochastic framework to the deterministic one. Note that the space \mathcal{M} is not Euclidean and is then a much more complex space than the usual space \mathbb{R}^q ($q \geq 1$). So, defining sensitivity indices for a model with outputs in \mathcal{M} can be challenging. But, this is addressed through different approaches. Two approaches are presented: the approach of [Fort et al. \(2021\)](#) which builds indices based on the Wasserstein metric and the kernel-based approach developed by [Da Veiga \(2021\)](#) using dependence measures on Hilbert spaces.

Sensitivity analysis based on test functions

In [Gamboa et al. \(2021, 2022\)](#), the authors considered a family of real-valued test functions parameterized by the output space, which is assumed to be a metric space. Then, they performed a Sobol'-Hoeffding decomposition on the parameterized test functions and integrated over parameters describing the test functions. Now, assume that \mathcal{M} is the Wasserstein space of probability measures on \mathbb{R} which have second order moment. The Wasserstein distance W_2 between two probability measures μ_1 and μ_2 is defined as:

$$W_2(\mu_1, \mu_2) = \mathbb{E} \left(F_{\mu_1}^{-1}(U) - F_{\mu_2}^{-1}(U) \right)^2,$$

where $F_{\mu_1}^{-1}$ and $F_{\mu_2}^{-1}$ are the quantile functions of μ_1 and μ_2 respectively and U is distributed under the uniform distribution over $[0, 1]$. In this framework, [Fort et al. \(2021\)](#) introduced the family of test functions $T_{\nu_1, \nu_2}(\mu) = \mathbb{1}_{W_2(\nu_1, \mu) \leq W_2(\nu_1, \nu_2)}$, for $\nu_1, \nu_2 \in \mathcal{M}$. Such a family, known as Wasserstein balls, characterizes the probability distribution of elements of \mathcal{M} ([Gamboa et al., 2018](#)). Consider the real-valued random variables $h_{\nu_1, \nu_2}(\mathbf{X}) := T_{\nu_1, \nu_2}(\varphi(\mathbf{X})) =$

$T_{\nu_1, \nu_2}(\mu_{\mathbf{X}})$, for $\nu_1, \nu_2 \in \mathcal{M}$. Note that $h_{\nu_1, \nu_2}(\mathbf{X})$ is bounded and then square integrable so that the Sobol'-Hoeffding decomposition yields:

$$\text{Var}(h_{\nu_1, \nu_2}(\mathbf{X})) = \sum_{u \subseteq \{1, \dots, p\}, u \neq \emptyset} \text{Var}(h_{\nu_1, \nu_2}^u(\mathbf{X}_u)).$$

Let us introduce μ_Y the p.d.f of the model output Y . In order to make this decomposition independent of the choice of ν_1 and ν_2 , expectation is taken with respect to μ_Y :

$$\mathbb{E}_{(\nu_1, \nu_2) \sim \mu_Y^{\otimes 2}} (\text{Var}(h_{\nu_1, \nu_2}(\mathbf{X}))) = \sum_{u \subseteq \{1, \dots, p\}, u \neq \emptyset} \mathbb{E}_{(\nu_1, \nu_2) \sim \mu_Y^{\otimes 2}} (\text{Var}(h_{\nu_1, \nu_2}^u(\mathbf{X}_u))).$$

Thus, for any $u \subseteq \{1, \dots, p\}$, the sensitivity index of \mathbf{X}_u is defined as:

$$S_u^G = \frac{\mathbb{E}_{(\nu_1, \nu_2) \sim \mu_Y^{\otimes 2}} (\text{Var}(h_{\nu_1, \nu_2}^u(\mathbf{X}_u)))}{\mathbb{E}_{(\nu_1, \nu_2) \sim \mu_Y^{\otimes 2}} (\text{Var}(h_{\nu_1, \nu_2}(\mathbf{X})))}. \quad (2.31)$$

Three different methods of estimation of indices S_u^G were discussed in [Fort et al. \(2021\)](#): pick-freeze procedure ([Janon et al., 2014a](#)), U-statistics ([Gamboa et al., 2021](#)) and rank-based estimators ([Gamboa et al., 2022](#)).

Kernel-based sensitivity analysis

In the following, we first consider the general framework with $\tilde{\mathcal{Y}}$ denoting any output space. Then we will specify the methodology for $\tilde{\mathcal{Y}} \subseteq \mathcal{M}$, the set of pdfs on \mathcal{Y} in the framework of stochastic models.

In [Da Veiga \(2021\)](#) (see also [Barr and Rabitz \(2022\)](#)), a kernel-based ANOVA decomposition is introduced using dependence measures in Reproducible Kernel Hilbert Space (RKHS). Recall that a Hilbert space \mathcal{H} of functions $g : \tilde{\mathcal{Y}} \rightarrow \mathbb{R}$ is said to be a RKHS with respect to $\tilde{\mathcal{Y}}$ if there exists a kernel function $k_{\tilde{\mathcal{Y}}} : \tilde{\mathcal{Y}} \times \tilde{\mathcal{Y}} \rightarrow \mathbb{R}$ such that for all $g \in \mathcal{H}$ and for all $y \in \tilde{\mathcal{Y}}$, $g(y) = \langle f(\cdot), k_{\tilde{\mathcal{Y}}}(\cdot, y) \rangle$.

Let P and Q be two pdfs on $\tilde{\mathcal{Y}}$. The idea used in [Da Veiga \(2021\)](#) is to measure the discrepancy between P and Q with the maximum mean discrepancy (MMD). For the RKHS \mathcal{H} , it is given by:

$$\text{MMD}(P, Q) = \|\mathbb{E}_{U \sim P} (k_{\tilde{\mathcal{Y}}}(U, \cdot)) - \mathbb{E}_{U \sim Q} (k_{\tilde{\mathcal{Y}}}(U, \cdot))\|_{\mathcal{H}},$$

with $\|\cdot\|_{\mathcal{H}}$ the Hilbert norm in the RKHS \mathcal{H} .

Consider $\mathbf{X}_u, u \subseteq \{1, \dots, p\}$ a set of parameters of a stochastic model f with output Y . Let us denote by μ_Y and $\mu_{Y|\mathbf{X}_u}$ the probability distribution of Y and the one of Y conditionally to \mathbf{X}_u respectively. Using the distance MMD, [Da Veiga \(2021\)](#) introduced the MMD-based sensitivity indices as follows:

$$S_u^{\text{MMD}} = \frac{\mathbb{E}_{\mathbf{X}_u} (\text{MMD}^2(\mu_Y, \mu_{Y|\mathbf{X}_u}))}{\sum_{v \subseteq \{1, \dots, p\}} \mathbb{E}_{\mathbf{X}_v} (\text{MMD}^2(\mu_Y, \mu_{Y|\mathbf{X}_v}))},$$

for $u \subseteq \{1, \dots, p\}$. These indices generalize Sobol' indices because the latter can be obtained by choosing as kernel $k_{\tilde{\mathcal{Y}}}(u, u') = uu'$. In addition, total Sobol' indices can be defined based on MMD distance as usual, i.e by adding contributions in which the considered parameter or set of parameters is involved.

A second type of kernel-based sensitivity indices is defined using the *Hilbert-Schmidt Independence Criterion* (HSIC) (Gretton et al., 2005). Considering a couple (\mathbf{X}_u, Y) , the HSIC criterion consists in evaluating the dissimilarity between the joint probability distribution $\mu_{(\mathbf{X}_u, Y)}$ of this couple and the product of their marginal probability distributions $\mu_{\mathbf{X}_u} \otimes \mu_Y$. This allows to assess how the output Y is dependent on \mathbf{X}_u . This criterion is defined as:

$$\text{HSIC}(\mathbf{X}_u, Y) = \text{MMD}^2(\mu_{(\mathbf{X}_u, Y)}, \mu_{\mathbf{X}_u} \otimes \mu_Y),$$

with MMD the maximum mean discrepancy associated to a RKHS \mathcal{H} of functions $g : \mathcal{X} \times \tilde{\mathcal{Y}} \rightarrow \mathbb{R}$. The resulting sensitivity index is given by:

$$S_u^{\text{HSIC}} = \frac{\text{HSIC}(\mathbf{X}_u, Y)}{\sum_{v \subseteq \{1, \dots, p\}} \text{HSIC}(\mathbf{X}_v, Y)}.$$

Kernel-based sensitivity analysis requires the choice of reproducible kernels: in the case of MMD-based indices, a kernel defined on $\tilde{\mathcal{Y}}$ is needed whereas for HSIC indices two kernels are required, one on \mathcal{X} and the other on $\tilde{\mathcal{Y}}$. Note that for stochastic models, $\tilde{\mathcal{Y}}$ is a subset of the set of pdfs on \mathcal{Y} . Da Veiga (2021) mentioned two kernels for stochastic models: $k(P, Q) = \sigma^2 e^{-\lambda \text{MMD}^2(P, Q)}$ and $k(P, Q) = \sigma^2 e^{-\lambda W_2^2(P, Q)}$, where λ, σ^2 are two positive quantities called hyperparameters, and with P and Q two pdfs on \mathcal{Y} , that is, with $P, Q \in \tilde{\mathcal{Y}}$.

The merit of probability distribution based approaches is that they deal with stochastic models in a suitable framework, which takes into account the stochastic nature of the output. However, these approaches may depend on choices that can affect the sensitivity analysis results. For example, the choice of a family of test functions in the approach of Gamboa et al. (2021) and the choice of kernels in the approach of Da Veiga (2021).

2.2.3.2 Metamodel-based approach

In the various approaches presented so far, sensitivity analysis requires numerous evaluations of a deterministic QoI defined from the stochastic model or of the stochastic model itself. The idea behind metamodeling is to replace evaluations of $Q(\mathbf{X}) = \mathbb{E}[\phi(f(\mathbf{X}, Z)) | \mathbf{X}]$ or $f(\mathbf{X}, Z)$ by a surrogate, much cheaper to evaluate. In the literature, there are various ways to build metamodels: Polynomial chaos expansion (Sudret, 2008), Gaussian processes (Marrel et al., 2012), Splines such as MARS (Hart et al., 2017), Machine learning: Support Vector Regression (Cheng et al., 2017), Neural Networks (Kala et al., 2019; Li et al., 2016), etc. Only two approaches, the most used in sensitivity analysis, are presented: PCE and Gaussian processes.

Polynomial Chaos Expansion

Consider the deterministic framework, with f a model with inputs $\mathbf{X} = (X_1, \dots, X_p)$ and output Y such that $Y = f(\mathbf{X})$ is a random variable of finite variance. Then, Y belongs to the Hilbert space of square-integrable variables and can be represented as:

$$Y = \sum_{\alpha \in \mathbb{N}^p} c_\alpha \Psi_\alpha(\mathbf{X}), \quad (2.32)$$

where $\Psi_\alpha(x) = \prod_{i=1}^p \varphi_{\alpha_i}^{(i)}(x_i)$ with $\{\varphi_j^{(i)}, j \in \mathbb{N}\}$ a family of univariate orthonormal polynomials (see [Sudret \(2008\)](#) for examples). Such a decomposition (2.32) was introduced by [Wiener \(1938\)](#) and known as the polynomial chaos expansion of Y .

Let \mathcal{A} be a finite subset of \mathbb{N}^p , in order to build the metamodel \tilde{f} (such that $Y = \tilde{f}(\mathbf{X}) + \varepsilon$), set:

$$Y = \sum_{\alpha \in \mathcal{A}} c_\alpha \Psi_\alpha(\mathbf{X}) + \varepsilon,$$

where $\varepsilon = \sum_{\alpha \notin \mathcal{A}} c_\alpha \Psi_\alpha(\mathbf{X})$. Then, the goal is to find coefficients c_α such that ε is minimal. This comes down to a classic regression problem:

$$\{\bar{c}_\alpha, \alpha \in \mathcal{A}\} = \underset{r_\alpha, \alpha \in \mathcal{A}}{\operatorname{argmin}} \mathbb{E} \left(Y - \sum_{\alpha \in \mathcal{A}} r_\alpha \Psi_\alpha(\mathbf{X}) \right)^2. \quad (2.33)$$

In practice, the problem (2.33) cannot be directly solved as theoretical quantities are generally unknown. Estimation is therefore required based on samples of \mathbf{X} . Solving yields approximate coefficients $\{\hat{c}_\alpha, \alpha \in \mathcal{A}\}$, hence, $\tilde{f} = \sum_{\alpha \in \mathcal{A}} \hat{c}_\alpha \Psi_\alpha(\mathbf{X})$.

Ultimately, computation of sensitivity indices is performed using the surrogate \tilde{f} . But, by combining the orthogonality of the terms of the Sobol'-Hoeffding decomposition and that of the terms of the PCE, analytical expressions of the Sobol' indices can be deduced and their computation can be performed without additional computational effort ([Sudret, 2008](#)).

PCE are commonly used in uncertainty quantification and sensitivity analysis. For deterministic models, the following works can be mentioned: [Sudret \(2008\)](#); [Le Gratiet et al. \(2017\)](#); [Mara and Becker \(2021\)](#). In the framework of stochastic models, it has been mainly studied for sensitivity analysis of models based on stochastic differential equations (SDE) (see, e.g., [Le Maître and Knio \(2015\)](#); [Jimenez et al. \(2017\)](#); [Étoré et al. \(2020\)](#)).

In the general case of models that are not necessarily based on SDEs, PCE can be coupled with other approaches to emulate the model output and perform sensitivity analysis. In [Zhu and Sudret \(2020, 2021a,b\)](#), it is proposed to build surrogates for stochastic models by relying on a family of distributions called generalized lambda distributions ([Freimer et al., 1988](#)).

with known quantile function Q parameterized by four functions $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ that control different characteristics of the distribution, so that for any input x , the original stochastic model $f(x, Z)$ is assumed to be distributed under $Q(U, \lambda_1(x), \lambda_2(x), \lambda_3(x), \lambda_4(x))$. In practice, characteristics $\lambda_1(x), \lambda_2(x), \lambda_3(x), \lambda_4(x)$ are approximated by using PCE. More recently in [Zhu and Sudret \(2022\)](#), an approach to perform sensitivity analysis with stochastic models with a stochastic version of PCE was introduced. The idea is to decompose model output $f(x, Z) = \sum_{\alpha \in \mathbb{N}^{p+1}} c_\alpha \Psi_\alpha(x, Z)$ and then to rely on a Gaussian approximation of the probability distribution of $f(x, Z) \approx \sum_{\alpha \in \mathcal{A}} c_\alpha \Psi_\alpha(x, Z) + \varepsilon$, where ε is a centered Gaussian distribution and \mathcal{A} is a finite set of \mathbb{N}^{p+1} . In practice, the metamodel is built by estimating coefficients using maximum likelihood estimator and Sobol' indices are deduced analytically.

Gaussian Process regression

Let \mathcal{W} be a nonempty set. A stochastic process $\{G(w), w \in \mathcal{W}\}$ is said to be Gaussian if for any finite set $J \subset \mathcal{W}$, the random vector $\{G(w), w \in J\}$ is distributed under some Gaussian distribution. Such a process is fully characterized by its mean $m(w) = \mathbb{E}(G(w))$ and its covariance function $C(w, w') := \mathbb{E}(G(w)G(w')) - m(w)m(w')$.

Consider a deterministic model f with input vector \mathbf{X} . Metamodeling by Gaussian processes consists in assuming that for any input x of the model, the output $f(x)$ is a response of a Gaussian process of the form: $f_0(x) + G(x)$ where f_0 is a known deterministic function and G is a centered Gaussian process of covariance function of the form $\sigma^2 R(x, x')$. The function R is often given as a function of the distance between points x and x' . In practice, one relies on samples of $X : \mathbf{X}^{(1)}, \dots, \mathbf{X}^{(N)}$ and their respective outputs $Y^{(1)}, \dots, Y^{(N)}$ to approximate the Gaussian process. Let x be an input of the model and denote $R_x := (R(x, \mathbf{X}^{(1)}, \dots, R(x, \mathbf{X}^{(N)}))^\top$, $\Sigma_N := (R(\mathbf{X}^{(i)}, \mathbf{X}^{(j)}))_{1 \leq i, j \leq N}$ and $\Delta_N := (Y^{(1)} - f_0(\mathbf{X}^{(1)}, \dots, Y^{(N)} - f_0(\mathbf{X}^{(N)}))^\top$. Then, the a posteriori probability distribution of $f(x)$ is:

$$f(x) \mid \{(X^{(1)}, Y^{(1)}), \dots, (X^{(N)}, Y^{(N)})\} \sim \mathcal{N}(m_N(x), V_N(x)), \quad (2.34)$$

where:

$$\begin{aligned} m_N(x) &= f_0(x) + R_x^\top \Sigma_N^{-1} \Delta_N \\ V_N(x) &= \sigma^2 \left(1 - R_x^\top \Sigma_N^{-1} R_x \right). \end{aligned}$$

Thus, in sensitivity analysis, the model f is substituted by the Gaussian process given in (2.34). The Gaussian character of the process facilitates the calculation of the conditional expectations and consequently estimation of Sobol' indices.

In the stochastic model framework, metamodels based on Gaussian processes can be obtained as in the deterministic case through a transformation of the covariance function. This transformation consists in adding some

Dirac function in order to take into account effects of the intrinsic randomness. Therefore, for a stochastic model f with inputs \mathbf{X} and intrinsic randomness Z , it holds that for any input x , $f(x, Z)$ is supposedly distributed under $f_0(x) + G(x)$, where f_0 is a known deterministic function and G is a centered Gaussian process with covariance function under the form $\text{Cov}(G(x), G(x')) = \sigma^2(R(x - x') + \varepsilon\delta(x - x'))$, where:

$$\delta(u) = \begin{cases} 1 & \text{if } u = 0 \\ 0 & \text{otherwise,} \end{cases}$$

and R a correlation function (Chiles and Delfiner, 2009). In Marrel et al. (2012), this approach is used to study the sensitivity of stochastic models by focusing on contributions of uncertain parameters to the variances of the quantities of interest given by the conditional expectation and variance. Browne et al. (2016) used Gaussian metamodel to emulate stochastic model and to perform sensitivity analysis for quantity of interest given by quantiles.

Metamodeling error

The metamodel-based approach replaces the original model f with a surrogate \tilde{f} up to some error ε and computes the sensitivity indices instead on the output of \tilde{f} . In general, by using techniques such as cross-validation, one can make sure that \tilde{f} is accurate enough in approximating f , and it holds that: $\tilde{f} \approx f$. But performing the sensitivity analysis on \tilde{f} suggests that the implication: $\tilde{f} \approx f \implies S_u(f) \approx S_u(\tilde{f})$, for $u \subseteq \{1, \dots, p\}$ holds, where $S_u(f)$ and $S_u(\tilde{f})$ denote respectively the Sobol' index of parameter or group of parameters \mathbf{X}_u with respect to models f and \tilde{f} .

Studies have been conducted to quantify metamodel errors impacts on sensitivity index estimations. We can mention: Janon et al. (2014a,b); Panin (2021). On the one hand, in Janon et al. (2014a), an approach to estimate the impact of the metamodel error ε on the indices is proposed when metamodel pointwise error bound is provided. On the other hand, Janon et al. (2014b) studied conditions on the metamodel error ε for which estimators of $S_u(\tilde{f})$ converge to $S_u(f)$ and satisfy a central limit theorem. In Panin (2021), bounds on the distance between $S_u(f)$ and $S_u(\tilde{f})$ have been obtained and the accuracy of estimators of Sobol' indices based on PCE or using polynomial interpolation techniques are reviewed.

However, even if metamodels can reduce computational costs, it is sometimes possible to work with the exact model, leading to a more accurate understanding of underlying phenomena.

2.2.4 Formulation of problems and contributions of the thesis

This PhD thesis is devoted to sensitivity analysis of stochastic models by leveraging variance-based sensitivity analysis tools for deterministic models with scalar or multivariate output.

In the first part (Chapter 3), our objective is to develop a method to accurately estimate Sobol' indices of parameters, in the general framework of stochastic models, for deterministic QoI under the form: $Q(\mathbf{X}) = \mathbb{E}(\phi(f(\mathbf{X}, Z)))$. Given $\mathbf{X} = x$, an estimator of Q is defined as: $\hat{Q}_m(x) := \frac{1}{m} \sum_{k=1}^m \phi(f(x, Z^{(k)}))$ and then depends on outputs $f(x, Z^{(1)}), \dots, f(x, Z^{(m)})$ with $m \geq 1$. Those outputs are obtained by repeating m times the model evaluation at input $\mathbf{X} = x$. Moreover, estimation of first-order Sobol' indices for Q requires to draw n samples $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$ from \mathbf{X} . At each sample $\mathbf{X}^{(i)}$, the model f is evaluated m times so that the first-order Sobol' index of X_j given by:

$$S_j = \frac{\text{Var}(\mathbb{E}[Q(\mathbf{X}) | X_j])}{\text{Var}(Q(\mathbf{X}))}$$

is estimated by:

$$\hat{S}_{j;n,m} = \frac{\frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)}) \hat{Q}_m(X_j^{(i)}, \tilde{\mathbf{X}}_{\sim j}^{(i)}) - \left(\frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)})\right)^2}{\frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)})^2 - \left(\frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)})\right)^2}$$

for any $j = 1, \dots, p$, with: $\hat{Q}_m(\mathbf{X}^{(i)}) = \frac{1}{m} \sum_{k=1}^m \phi(f(\mathbf{X}^{(i)}, Z^{(i,k)}))$ where $\{Z^{(i,k)}, i = 1, \dots, n; k = 1, \dots, m\}$ are i.i.d.

Note that estimating the first-order Sobol' indices of p inputs has a total cost of $n \times m \times (p + 1)$ multiplied by the computational cost of each call to f . The larger n and m are, the more precise the estimator is. But this is not a feasible strategy when each evaluation of f is expensive. So in a context of a limited total number of model evaluations, this PhD thesis studies what trade-off should be made between n and m to ensure that the mean squared error of the estimator $\hat{S}_{j;n,m}$ is small.

Contribution of the PhD thesis to the study of Sobol' index estimators for stochastic models

In this thesis, we study the bias-variance trade-off problem in estimating Sobol' indices for aforementioned quantities of interest Q . Our approach is based on a tractable bound for the mean squared error of sensitivity index estimator, leading to two main results. First, the convergence of mean squared error of estimator $\hat{S}_{j;n,m}$ is proved. This result extends de facto to the deterministic framework and ensures that the pick-freeze estimator converges in quadratic mean. On the other hand, under the constraint that the total number of calls to the model is fixed, i.e.

$nm = T$, we introduce a new strategy for choosing n and m allowing to reduce simultaneously both the bias and the variance. This is detailed in Chapter 3. This contribution is submitted for publication in an international peer-reviewed journal.

The other works carried out in this thesis concern compartmental epidemic models based on stochastic processes. These stochastic processes, whether they are Markovian or not, are under the form: $W^\theta(\omega) = \{W^\theta(t, \omega); t \in [0, T]\}$ where $T \in (0, +\infty)$, θ is a vector containing unknown or partially known epidemic parameters, $\omega \in (\Omega, \mathcal{F}, \mathbb{P})$ which is a probability space. It is assumed that for any $\omega \in \Omega$ and $t \in [0, T]$, $W^\theta(t, \omega) \in \mathcal{E} \subseteq \mathbb{N}^d$, with $d \geq 1$ and θ is a vector of dimension p such that $\theta \in \mathcal{X}$. To model the parametric uncertainty, we introduce a random vector $\mathbf{X} := (X_1, \dots, X_p)$ defined on $(\Omega, \mathcal{F}, \mathbb{P})$ with values in $(\mathcal{X}, \mathcal{B}(\mathcal{X}))$ a measurable space equipped with the Borel set $\mathcal{B}(\mathcal{X})$ and independent from the internal noise of the process. The resulting process is a random field $W^{\mathbf{X}}$.

For epidemic models, the internal noise is issued from various sources depending on the model considered: chance in the characteristics of individuals, in their behaviors, in their decisions and interactions, environmental factors, etc. This randomness has a well-defined meaning in epidemic models. Its effects can be detected in the variability of epidemic dynamics even when the initial conditions and epidemic parameters are fixed. It can explain the early extinction of epidemics even when the conditions for the explosion of infections are met. In sum, it impacts the model and it would therefore be important to measure its influence on model outputs.

In this PhD thesis, we want to assess the sensitivity of stochastic compartmental models with respect to both uncertain epidemic parameters and intrinsic randomness, without appealing to surrogate models, as metamodeling is not common practice in epidemiology. In order to achieve this goal, we seek for a representation of $W^{\mathbf{X}}$ under the form:

$$W^{\mathbf{X}} = f(\cdot, \mathbf{X}, Z) := \{f(t, \mathbf{X}, Z); t \in [0, T]\}, \quad (2.35)$$

where f is a deterministic function and Z is a random variable or group of random variables such that \mathbf{X} and Z are independent.

A representation under the form (2.35) was proposed and used by [Le Maître et al. \(2015\)](#); [Navarro Jimenez et al. \(2016\)](#). Indeed, based on the representation of continuous-time Markov chains with unit-rate independent Poisson processes $(P_{\mathbf{u}}, \mathbf{u} \in \mathcal{T})$, as introduced in Section 2.1.4.4, [Le Maître et al. \(2015\)](#) deduced that $W^{\mathbf{X}} = F(\cdot, \mathbf{X}, Z)$ where $Z = \{P_{\mathbf{u}}, \mathbf{u} \in \mathcal{T}\}$ and F is given by the decomposition (2.13).

In such a representation, Z is non-trivial and is independent of \mathbf{X} . Moreover, each component $P_{\mathbf{u}}$ represents the intrinsic randomness of the process associated with the type transitions \mathbf{u} . Thus $P_{\mathbf{u}}$ accounts for the stochasticity

characterizing the occurrence of transitions of \mathbf{u} in the dynamics of W^θ . Relying on this representation, [Le Maître et al. \(2015\)](#); [Navarro Jimenez et al. \(2016\)](#) obtained different contributions of Z and of its components in the global variance of $W^{\mathbf{X}}$. In their works, simulations of the Markov chains were performed via the Modified Next Reaction Method Algorithm (Algorithm 4). But in epidemiology, the widespread methods for simulating epidemic dynamics are the Gillespie algorithms (Algorithms 1 and 2). Besides, to our knowledge, no representation under the form (2.35) has been proposed so far in the non-Markovian setting.

Contribution of the PhD thesis to the sensitivity analysis for stochastic compartmental models based on continuous-time Markov chains

We propose in this PhD thesis two representations of compartmental epidemic models based on continuous-time Markov chain using the two Gillespie algorithms namely: Direct Method (Algorithm 1) and First Reaction Method (Algorithm 2). This allows to separate the intrinsic randomness from the parametric uncertainty and to put the model output under the form of a deterministic function of uncertain parameters and variables representing the intrinsic randomness. As a result, we can assess contributions of both uncertain parameters and intrinsic randomness. In addition, we propose a comparison between the representation based on the Gillespie algorithm and the representation used in [Le Maître et al. \(2015\)](#); [Navarro Jimenez et al. \(2016\)](#) which is based on the Modified Next Reaction Method Algorithm. It turns out that some results of the sensitivity analysis are different. This enables us to show that the choice of the representation influences the results of sensitivity analysis. All these results are detailed in Chapter 4 and in an article which is submitted for publication in an international peer-reviewed journal.

Contribution of the PhD thesis to the sensitivity analysis of non-Markovian epidemic models by extending the Sellke construction

In the non-Markovian framework, in order to compensate the lack of algorithms on which to rely to obtain a representation of $W^{\mathbf{X}}$, we extend the Sellke construction to closed population compartmental models. This construction, originally introduced for the SIR model, is generalized to models with an arbitrary number of compartments and arrows. We show that in the Markovian case, it coincides with the usual setting. We propose a new algorithm with R for exact simulation. Above all, from this construction, we deduce a representation of $W^{\mathbf{X}}$ that is used to perform sensitivity analysis, to evaluate various contributions of the intrinsic randomness and to make comparison between Markovian and non-Markovian models. All this is detailed in Chapter 5 and a corresponding paper is in preparation.

Asymptotic control of the mean-squared error for Monte-Carlo sensitivity index estimators in stochastic models

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This chapter deals with the general context of stochastic models and focuses on the problem of accurate estimation of sensitivity indices. This problem is treated for the widely used class of quantities of interest under the form of conditional expectations of functions of model outputs with respect to uncertain parameters. The goal is to study the mean-squared error of index estimators based on Monte-Carlo method, to find a bound for it and to exploit this bound to build accurate estimators.

3.1 Introduction

Sensitivity analysis (SA) provides useful insight into mathematical models. However, in SA, stochastic models are challenging. Indeed, such models include two sources of uncertainty: parameter uncertainty and intrinsic randomness. This intrinsic randomness is a collection of hidden random variables that can make challenging the definition of meaningful sensitivity indices and their efficient estimation.

Several methods have been introduced to deal with stochastic models. Apart from metamodel-based approach (Étoré et al., 2020; Jimenez et al., 2017; Fort et al., 2013; Zhu and Sudret, 2021a), usual SA methods for stochastic models may be divided into about three approaches. The first approach, proposed by Hart et al. (2017), considers random Sobol'-Hoeffding decompositions (Sobol', 1993) of stochastic model outputs and defines sensitivity indices of such models as expectations of the resulting random Sobol' indices. The second approach focuses on deterministic quantities of interest (QoIs) such as conditional expectations or conditional variances (Courcoul et al., 2011; Mazo, 2021). By conditioning with respect to the uncertain parameters, the aim is to smooth the intrinsic randomness out and hence to deal with quantities under the form of deterministic functions of the uncertain parameters only, so that SA methods for deterministic models can be applied. The third approach includes recently developed methods (Fort et al., 2021; Gamboa et al., 2021; Da Veiga, 2021) that see stochastic output models as deterministic function with values in probability distribution spaces. Various sensitivity indices are defined on such spaces in order to measure contributions of uncertain parameters.

For all these approaches, it appears that not only should the model be evaluated at many points in the input space (it is said that the input space is explored), but also it should be repeated at each of those explorations to estimate conditional expectations. In the first approach, these repetitions are performed when approximating the expectations of the random Sobol' indices. In the second and third approaches, model outputs are repeated when estimating the QoIs and the probability distributions, respectively. Therefore, the larger the number of explorations and the number of repetitions, the more

accurate the sensitivity index estimators. This leads to large numbers of runs of the model. However, in practice, models could be complex and a run could have a high computational cost so that computational issue could rise very quickly.

Therefore, the study of the choice of a number of explorations and a number of repetitions under the constraint of a computational cost or that of the precision of estimations, takes more and more importance beyond the sensitivity analysis but more globally in the fields which are interested in the stochastic simulators. It can be mentioned the works of [Chen and Zhou \(2014, 2017\)](#) which proposes various strategies of sequential design based on the Integrative Mean Squared Error (IMSE) for stochastic kriging. More recently still with metamodels based on Gaussian processes, [Binois et al. \(2018, 2019\)](#) explored different methods for optimal design also using IMSE criteria.

In [Mazo \(2021\)](#), the author studied this problem for estimation of sensitivity indices for stochastic models. In that paper, two QoIs were considered: the exact model output and its conditional expectation with respect to the uncertain parameters. Depending on the QoI, two types of Sobol' indices were defined and the so-called pick-freeze estimators [Gamboa et al. \(2016\)](#) were used. Those estimators are based on a double (or nested) Monte-Carlo sampling scheme and require the choice of the number of explorations, n , and the number of repetitions, m . Such procedure is the so-called Nested Monte Carlo. To better estimate such indices without increasing the computation cost, [Mazo \(2021\)](#) supposed that the total number of runs of the model is fixed and then proposed under such constraint a choice of n and m based on the minimization of some bound of the so-called mean ranking error (MRE) of the estimators. This error measures the gap between the ranks of the theoretical indices and those of the estimators. However, a small MRE does not necessarily imply that estimations are close to their theoretical values.

Accurate and efficient estimation of Sobol' indices is a major concern in SA . This is linked to the problem of accurately estimating expectation of functions of conditional moments, which is a problem that arises in wider framework than SA. Many studies have been conducted to address this issue. In global sensitivity analysis, [Da Veiga and Gamboa \(2013\)](#) addressed the problem with a semi-parametric estimation approach (see also [Da Veiga et al. \(2017\)](#)) in the case of deterministic models while [Mycek and De Lozzo \(2019\)](#) proposed methods based on Multilevel Monte-Carlo. In the case of metamodel based SA, [Janon et al. \(2014b\)](#); [Panin \(2021\)](#) studied the risk of estimators and provide error bounds. Regarding stochastic models, [Castellan et al. \(2020\)](#) discussed the accurate non-parametric estimation of first-order Sobol' indices for bounded stochastic models by relying on wavelet-based estimator approach. More generally, beyond SA, [Rainforth et al. \(2018\)](#) studied the nested Monte Carlo and its computational cost. [Giles and Haji-Ali \(2019\)](#); [Giorgi et al. \(2020\)](#)

discussed efficiency and convergence rates of Multilevel nested Monte-Carlo.

In this paper, we consider deterministic QoIs that are under the form of conditional expectations of some transformations of the stochastic model output with respect to the inputs. This class of QoIs includes the much used conditional expectation and conditional variance of the stochastic model output with respect to the inputs. We focus on variance-based indices such as first-order and total Sobol' indices for inputs or groups of inputs. The estimation of those indices is based on the pick-freeze method by using n explorations of the input space and m model repetitions. We study mean-squared errors (MSEs) of sensitivity index estimators and propose tractable upper bounds that depend on both n and m . Then, under the constraint that $n = T^{1-\eta}$ and $m = T^\eta$, $\eta \in [0, 1)$, with $T \rightarrow \infty$, the bias-variance trade-off is studied using those upper-bounds and the optimal allocation parameter η is deduced.

The main interest of this work lies in three points. First, up to some mild assumptions on the model outputs, pick-freeze estimators of first-order and total Sobol' indices are shown to converge in quadratic means. (We note that a byproduct of this result is the convergence in quadratic mean of the "usual" Sobol' index estimators for deterministic models.) Second, the scope of this study is large. It takes into account a large class of QoIs of stochastic model outputs and it includes two widely-used sensitivity indices. Finally, algorithms are provided for practical implementation of our results. These algorithms are expected to give better estimations of Sobol' indices.

This paper is organized as follows. Section 3.2 presents the general framework of stochastic models and QoI-based sensitivity indices. In Section 3.3, the MSE of a general class of estimators that contains our sensitivity indices is considered and its asymptotic behavior presented. Section 3.4 is dedicated to studying the MSE of some variance-based sensitivity indices. The bias-variance trade-off is discussed and the optimal allocation for m and n is given here. A practical procedure is implemented through two algorithms and illustrated on two toy models in Section 3.5. A conclusion closes the paper.

3.2 Sensitivity index estimators

A stochastic model with inputs $\mathbf{X} = (X_1, \dots, X_p) \in \mathbb{R}^p$ and output $Y \in \mathbb{R}$ is modeled as a function f of \mathbf{X} and some collection of random variables, denoted by Z , independent of \mathbf{X} such that

$$Y = f(\mathbf{X}, Z). \quad (3.1)$$

The stochasticity of the model originates from Z since the output of the model evaluated at an input $\mathbf{X} = x$ is a random variable $f(x, Z)$. The distribution of Z is generally unknown.

In the context of SA, a way to deal with stochastic models consists in carrying out SA for deterministic models given by deterministic QoIs. This allows to switch from a stochastic model to some deterministic models for which many SA methods are studied in the literature.

We consider QoIs of the form

$$Q(\mathbf{X}) = \mathbb{E}[\varphi(\mathbf{X}, Z) \mid \mathbf{X}], \quad (3.2)$$

where $\varphi(\mathbf{X}, Z)$ is a function of \mathbf{X} and Z as a transformation of f . For instance, if $\varphi = f$ then $Q(\mathbf{X})$ is the conditional expectation of the model and if $\varphi(\mathbf{X}, Z) = (f(\mathbf{X}, Z) - \mathbb{E}[f(\mathbf{X}, Z) \mid \mathbf{X}])^2$ then $Q(\mathbf{X})$ is the conditional variance, two common choices in practice.

If u is a subset of $\{1, \dots, p\}$, denote by \mathbf{X}_u the group of inputs $\{X_i, i \in u\}$ and $\mathbf{X}_{\sim u}$ the group of inputs $\{X_i, i \notin u\}$. The Sobol' and total indices of the input vector \mathbf{X}_u with respect to the function Q are defined as

$$S_u = \frac{\text{Var}(\mathbb{E}[Q(\mathbf{X}) \mid \mathbf{X}_u])}{\text{Var}(Q(\mathbf{X}))} \quad (3.3)$$

$$T_u = 1 - \frac{\text{Var}(\mathbb{E}[Q(\mathbf{X}) \mid \mathbf{X}_{\sim u}])}{\text{Var}(Q(\mathbf{X}))} = 1 - S_{\sim u}. \quad (3.4)$$

The sensitivity index S_u (and hence T_u) can be expressed in terms of a function g linking the components of some parameter vector. Let $\tilde{\mathbf{X}}$ be an independent copy of \mathbf{X} , independent of Z . Denote by $\tilde{\mathbf{X}}_{\sim u}$ the subvector of $\tilde{\mathbf{X}}$ whose components are those of $\tilde{\mathbf{X}}$ not indexed by u . (For instance, if $p = 4$ and $u = \{1, 4\}$ then $\tilde{\mathbf{X}}_{\sim u} = (\tilde{X}_2, \tilde{X}_3)$.) If $\theta = (\theta_1, \theta_2, \theta_3)$ with $\theta_1 = \mathbb{E}(Q(\mathbf{X})^2)$, $\theta_2 = \mathbb{E}(Q(\mathbf{X}))$ and $\theta_3 = \mathbb{E}(\mathbb{E}[Q(\mathbf{X}) \mid \mathbf{X}_u]^2) = \mathbb{E}(Q(\mathbf{X})Q(\tilde{\mathbf{X}}_{\sim u}, \mathbf{X}_u)) = \mathbb{E}(Q(\mathbf{X}_{\sim u}, \mathbf{X}_u)Q(\tilde{\mathbf{X}}_{\sim u}, \mathbf{X}_u))$ then

$$S_u = g(\theta) = \frac{\theta_3 - \theta_2^2}{\theta_1 - \theta_2^2}.$$

An estimator of S_u is built by the method-of-moments (pick-freeze procedure). Let $\{\mathbf{X}^{(i)}; i = 1, \dots, n\}$ and $\{\tilde{\mathbf{X}}^{(i)}; i = 1, \dots, n\}$ be independent Monte Carlo samples from the law of \mathbf{X} . For each i , denote by $\mathbf{X}_u^{(i)}$ the subvector of $\mathbf{X}^{(i)}$ whose components are those of $\mathbf{X}^{(i)}$ indexed by u . Likewise, denote by $\mathbf{X}_{\sim u}^{(i)}$ the subvector of $\mathbf{X}^{(i)}$ whose components are those of $\mathbf{X}^{(i)}$ not indexed by u , and denote by $\tilde{\mathbf{X}}_{\sim u}^{(i)}$ the subvector of $\tilde{\mathbf{X}}^{(i)}$ whose components are those of $\tilde{\mathbf{X}}^{(i)}$ not indexed by u . An estimator of S_u is given by

$$\hat{S}_u = g(\hat{\theta}) = \frac{\hat{\theta}_3 - \hat{\theta}_2^2}{\hat{\theta}_1 - \hat{\theta}_2^2}$$

where

$$\left. \begin{aligned} \hat{\theta}_1 &= \frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)})^2 \\ \hat{\theta}_2 &= \frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)}) \\ \hat{\theta}_3 &= \frac{1}{n} \sum_{i=1}^n \hat{Q}_m(\mathbf{X}^{(i)}) \tilde{Q}_m(\tilde{\mathbf{X}}_{\sim u}^{(i)}, \mathbf{X}_u^{(i)}) \end{aligned} \right\} \quad (3.5)$$

and

$$\begin{aligned}\widehat{Q}_m(\mathbf{X}^{(i)}) &= \frac{1}{m} \sum_{k=1}^m \varphi(\mathbf{X}^{(i)}, Z^{(i,k)}) \\ \widetilde{Q}_m(\widetilde{\mathbf{X}}_{\sim u}^{(i)}, \mathbf{X}_u^{(i)}) &= \frac{1}{m} \sum_{k=1}^m \varphi(\widetilde{\mathbf{X}}_{\sim u}^{(i)}, \mathbf{X}_u^{(i)}, \widetilde{Z}^{(i,k)}); \end{aligned}$$

here the objects $\{Z^{(i,k)}, \widetilde{Z}^{(i,k)}; k = 1, \dots, m; i = 1, \dots, n\}$, are independent and identically distributed random variables, independent of $\{\mathbf{X}^{(i)}, \widetilde{\mathbf{X}}^{(i)}; i = 1, \dots, n\}$, representing the randomness of the user's model. For more details, see [Mazo \(2021\)](#).

The estimator \widehat{S}_u may be asymptotically biased, depending on the rate at which m , the number of repetitions, increases with respect to n , the number of explorations. It was shown in [Mazo \(2021\)](#) that, if m is fixed, then

$$\sqrt{n} \left(\widehat{S}_u - S_u \left[1 - \frac{\mathbb{E} \operatorname{Var}(\varphi(\mathbf{X}, Z) | \mathbf{X})}{\mathbb{E} \operatorname{Var}(\varphi(\mathbf{X}, Z) | \mathbf{X}) + m \operatorname{Var} \mathbb{E}(\varphi(\mathbf{X}, Z) | \mathbf{X})} \right] \right)$$

converges to a centered normal distribution with some variance σ_m^2 depending on m . To get rid of the bias, it is needed that $m \rightarrow \infty$ such that $\sqrt{n}/m \rightarrow 0$, in which case $\sqrt{n}(\widehat{S}_u - S_u)$ goes to a centered normal distribution with variance $\lim_{m \rightarrow \infty} \sigma_m^2$.

The statistical performance of the estimator \widehat{S}_u goes hand in hand with the computation effort one is ready to spend. The computation of \widehat{S}_u requires a number of model evaluations proportional to mn . Given a fixed number of evaluations—and hence mn is fixed—it is of interest to find the couple (m, n) that most increases the estimator's performance. In [Mazo \(2021\)](#), a bound on an error that penalizes bad rankings of the sensitivity indices S_1, \dots, S_p was minimized, leading to a theoretically-guided choice for m and n . However, it is more natural to consider the MSE $\mathbb{E}((\widehat{S}_u - S_u)^2)$ as the quantity to be controlled.

3.3 Mean-squared error control for smooth functions

In this section, we study the MSEs of some estimators and give bounds and a rate of convergence. The aim is to characterize a class of estimators that include variance-based sensitivity index estimators and then to define conditions under which their MSEs admit tractable upper bounds.

For sake of generality, let us consider a convex domain $\mathcal{D} \subset \mathbb{R}^q$ with $q \geq 1$. For each $m \in \mathbb{N}^*$, let $\widetilde{\theta}_m^{(1)}, \dots, \widetilde{\theta}_m^{(n)}$ be n i.i.d. random vectors whose common

probability distribution depends only on m . Denote $\mu_m = \mathbb{E}(\tilde{\theta}_m^{(1)})$ and $\Sigma_m = \mathbb{E} \left((\tilde{\theta}_m^{(1)} - \mu_m)(\tilde{\theta}_m^{(1)} - \mu_m)^\top \right)$. Let $\theta \in \mathcal{D}$ and assume that

$$\hat{\theta}^{(n,m)} = \frac{1}{n} \sum_{i=1}^n \tilde{\theta}_m^{(i)} \quad (3.6)$$

is an estimator of θ . Let b_m be the bias of $\hat{\theta}^{(n,m)}$. Thus: $b_m = \mu_m - \theta$. For the sake of simplicity, hereafter, $\hat{\theta}^{(n,m)}$ is denoted $\hat{\theta}$. If m is fixed then $\mathbb{E}(\hat{\theta}) = \mu_m \neq \theta$ as soon as b_m is non-null. In particular, estimator $\hat{\theta}$ belongs to the class of Nested Monte-Carlo estimators if for $i = 1, \dots, n$, $\tilde{\theta}_m^{(i)}$ are under the form

$$\tilde{\theta}_m^{(i)} = \phi \left(\frac{1}{m} \sum_{k=1}^m \tilde{\eta}^{(i,k)} \right), \quad (3.7)$$

where ϕ is some measurable function with values on \mathcal{D} and $\{\tilde{\eta}^{(i,k)}; i = 1, \dots, n; k = 1, \dots, m\}$ is an array of identically distributed random vectors such that $\{\tilde{\eta}^{(i,k)}, k = 1, \dots, m\}$ and $\{\tilde{\eta}^{(j,k)}, k = 1, \dots, m\}$ are mutually independent as soon as $i \neq j$. The MSE of $\hat{\theta}$ is given by $\mathbb{E} \|\hat{\theta} - \theta\|^2$ and then, the variance bias decomposition yields:

$$\mathbb{E} \|\hat{\theta} - \theta\|^2 = \frac{1}{n} \text{Trace}(\Sigma_m) + \|b_m\|^2. \quad (3.8)$$

Make the following assumption:

Assumption 3. $b_m \rightarrow 0$ and $\Sigma_m \rightarrow \Sigma$ as $m \rightarrow +\infty$.

Under Assumption 3, it holds that $\lim_{n,m \rightarrow +\infty} \mathbb{E} \|\hat{\theta} - \theta\|^2 = 0$ and thereby $\hat{\theta}$ converges in quadratic means to θ . Mazo (2021) showed that Assumption 3 is satisfied by Sobol' index estimators introduced in Section 2. More generally, this assumption is fulfilled in the case Nested Monte Carlo estimators provided that $\theta = \mathbb{E}\phi(\tilde{\eta})$, with $\tilde{\eta}$ the limit (provided it exists) of $\sum_{k=1}^m \tilde{\eta}^{(1,k)}/m$, and that the function ϕ in Equation (3.7) has good properties such as boundedness and smoothness (Giorgi et al., 2020; Rainforth et al., 2018).

The form of the MSE in Equation (3.8) allows to control this error through the choice of n and m . Indeed, this enables to show convergence, to obtain convergence rates and to study optimal convergence strategies. For instance, in the framework of Nested Monte Carlo estimators, Hong and Juneja (2009) showed that for a real-valued function ϕ (introduced in (3.7)) at least third differentiable such that the third derivative is uniformly bounded, the MSE defined in (3.8) is of order $O(1/n + 1/m^2)$ and they deduced that the optimal convergence rate is $O(T^{-2/3})$ if $T = mn$ denotes the computational effort. Thus, it is useful to have either the mean-squared error or at least an upper bound of this error under the form in (3.8).

Now, given a non-constant function $g : \mathcal{D} \rightarrow \mathbb{R}$, assume that $\hat{\theta}$ is mapped to $g(\hat{\theta})$ so that $g(\hat{\theta})$ converges in probability to $g(\theta)$ as $n, m \rightarrow \infty$. Therefore, the main concern is to know if, as $\hat{\theta}$, the MSE of $g(\hat{\theta})$, i.e. $\mathbb{E}(g(\hat{\theta}) - g(\theta))^2$ converges to 0, or if it admits an upper bound under the form in (3.8) that converges to 0 as $n, m \rightarrow \infty$. Introducing g makes the study of the related MSE more challenging than the usual cases one could deal with, especially in the Nested Monte Carlo estimator framework (Giles, 2018; Giorgi et al., 2020). The obstacles to obtaining such upper bound for $\mathbb{E}(g(\hat{\theta}) - g(\theta))^2$ are multiple and involve both $\hat{\theta}$ and g : issues related to boundedness or smoothness of g , or to the probability distribution of $\hat{\theta}$ and its support, etc. Hence, responses to the main concern depend generally on both $\hat{\theta}$ and g . For instance, assume g is linear or more generally g is Lipschitz continuous, then there exists a constant L such that $|g(x') - g(x)| \leq L\|x' - x\|$, for all $x, x' \in \mathcal{D}$. Thus:

$$\mathbb{E} \left(g(\hat{\theta}) - g(\theta) \right)^2 \leq L^2 \mathbb{E} \|\hat{\theta} - \theta\|^2,$$

and thereby such MSE admits upper bound of the form in (3.8).

However, it can be difficult to get an exact upper bound in this form. Very often, in practice, the function g does not have good enough properties to obtain an exact bound. In this case, one could look for an approximate bound of the form (3.8), i.e. which is the sum of a quantity of the form (3.8) and a certain quantity negligible when n, m go to infinity. For example, let g be a twice continuously differentiable such that its Hessian matrix denoted $\nabla^2 g$ is uniformly bounded. Then, up to existence of some moments of $\hat{\theta}$, and combining Taylor-Lagrange expansion and convexity inequality yields:

$$\begin{aligned} \mathbb{E} \left(g(\hat{\theta}) - g(\theta) \right)^2 &\leq 2\mathbb{E} \left(\nabla g(\mu_m)^\top \left(\hat{\theta} - \mu_m \right) \right)^2 + 2(g(\mu_m) - g(\theta))^2 \\ &\quad + O \left(\mathbb{E} \|\hat{\theta} - \mu_m\|^4 \right). \end{aligned}$$

Thus, the MSE of $g(\hat{\theta})$ admits an upper bound. In addition, assume that the following condition is satisfied:

Assumption 4. As $n, m \rightarrow \infty$, it holds that:

$$\frac{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^8 \right)}{\left(\mathbb{E} \left(\nabla g(\mu_m)^\top \left(\hat{\theta} - \mu_m \right) \right)^2 \right)^2} = o(1).$$

Under Assumption 4, it appears that:

$$\mathbb{E} \left(g(\hat{\theta}) - g(\theta) \right)^2 \leq 2(1 + o(1)) \mathbb{E} \left(\nabla g(\mu_m)^\top \left(\hat{\theta} - \mu_m \right) \right)^2 + 2(g(\mu_m) - g(\theta))^2 \quad (3.9)$$

and therefore the $\mathbb{E}(g(\widehat{\theta}) - g(\theta))^2$ has approximately the form in (3.8) as $n, m \rightarrow \infty$. Though, the uniform boundedness of $\nabla^2 g$ is a very strong condition. A way to weaken such a condition consists in having:

$$\sup_{\lambda \in (0,1)} \mathbb{E} \left(\|\nabla^2 g(\lambda \widehat{\theta} + (1-\lambda)\mu_m)\|_F^4 \right) = O(1) \quad \text{as } n, m \rightarrow \infty, \quad (3.10)$$

where $\|\cdot\|_F$ denotes the Frobenius norm. Under condition in (3.10), the approximate decomposition (3.9) of the MSE into a sum of variance and squared bias holds. Therefore, the bias-variance trade-off problem can be likely addressed more easily since the terms of the upper bound are more tractable. Also, a well-informed choice for the (n, m) can be likely found to reduce the MSE.

Relying on Rosenthal inequality (Yuan and Li, 2015) and Marcinkiewicz–Zygmund inequality (Marcinkiewicz and Zygmund, 1937), Assumption 4 can be satisfied up to existence of moments of $\widehat{\theta}$. However, once again, even the condition provided in Equation (3.10) is still strong in general since this could impose a strong constraint on the probability distribution of $\widehat{\theta}$ which is generally unknown. For instance, in the case of Sobol’ index estimators defined in Section 3.2, condition (3.10) comes down to provide upper bounds for quantities under the form $\mathbb{E}[(\widehat{\theta}_1 - \widehat{\theta}_2^2)^{-\alpha}]$ with $\alpha > 0$ whereas the probability distribution of $\widehat{\theta}_1 - \widehat{\theta}_2^2$ is unknown and even the existence of such quantities is not guaranteed.

Faced with this issue, we propose a weaker condition than the one in Equation (3.10), which relaxes a little more the constraint on $\widehat{\theta}$. The idea is to introduce a "slight perturbation" g_h of the function g so that the condition of Equation (3.10) holds with $g = g_h$ and $\lim_{h \rightarrow 0} g_h(x) = g(x)$ pointwise. The advantage of having such a family of functions is that $\mathbb{E}(g_h(\widehat{\theta}) - g_h(\theta))^2$, the "perturbed MSE", could be bounded with an approximate upper bound in the form of Equation (3.9) with $g = g_h$. But the counterpart is that to control the "true" MSE, we also need to control $\Delta_{n,m}(h) := \mathbb{E}(g(\widehat{\theta}) - g_h(\widehat{\theta}))^2$ which measures the distance between the "true" estimator $g(\widehat{\theta})$ and its modified version $g_h(\widehat{\theta})$. Thus, the difficulty is to find such a family for which this gap $\Delta_{n,m}(h)$ can also be controlled.

Let us fix $\mathbf{u} \in \mathbb{R}^q$ such that $\|\mathbf{u}\| = 1$ and for all $x \in \mathcal{D}$, $x + h\mathbf{u} \in \mathcal{D}$ for any $h \in (0, 1)$. Henceforth, we shall focus on the family defined by functions $g_h(x) = g(x + h\mathbf{u})$ which enables to control $\Delta_{n,m}(h)$ under Assumption 5 as $n, m \rightarrow \infty$.

Assumption 5. *There exists a constant C independent of h such that, for all $h \in (0, 1)$:*

$$\limsup_{n, m \rightarrow \infty} \sup_{\lambda \in [0,1]} \mathbb{E} \left(\|\nabla^2 g(\lambda \widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4 \right) \leq C.$$

Introducing translations $x \mapsto x + h\mathbf{u}$ can be thought as a way to "transport" the original estimator $\widehat{\theta}$ to regions of \mathcal{D} where control of moments of $g(\widehat{\theta})$ is possible without additional conditions on $\widehat{\theta}$. Concretely, the goal of Assumption 5 is to "get away" from certain regions of the parameter space where the Hessian of g may explode. Notice that the supremum over λ is taken over the closed interval $[0, 1]$. The choice of h affects the approximation for the bound, as shown in Theorem 1. Recall that $\Delta_{n,m}(h) := \mathbb{E} \left(g(\widehat{\theta}) - g(\widehat{\theta} + h\mathbf{u}) \right)^2$ and let $V_{n,m}(h) := \mathbb{E}(\nabla g(\mu_m + h\mathbf{u})^\top (\widehat{\theta} - \mu_m))^2$ and $B_m(h) := g(\mu_m + h\mathbf{u}) - g(\theta)$.

Theorem 1. *Under Assumptions 3, 4 and 5, there exists $\tilde{C} > 0$ independent of h such that for every $h \in (0, 1)$:*

$$\mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 \leq 3(1 + p_{n,m}(h)) (\Delta_{n,m}(h) + V_{n,m}(h) + B_m(h)^2), \quad (3.11)$$

where $\limsup_{n,m \rightarrow \infty} p_{n,m}(h) = 0$ and

$$\Delta_{n,m}(h) \leq \tilde{p}_{n,m}(h)h^2, \quad (3.12)$$

where $\limsup_{n,m \rightarrow \infty} \tilde{p}_{n,m}(h) \leq \tilde{C}$.

Theorem 1 is the analog of (3.9), except that a term $\Delta_{n,m}(h)$ has appeared to control the gap between $g(\widehat{\theta} + h\mathbf{u})$ and $g(\widehat{\theta})$. The quantity $V_{n,m}(h) + B_m(h)^2$ can be rewritten to make the bias-variance trade-off appear. Indeed, $V_{n,m}(h) = n^{-1} \nabla g(\mu_m + h\mathbf{u})^\top \Sigma_m \nabla g(\mu_m + h\mathbf{u})$, which is of order $O(n^{-1})$ as $n, m \rightarrow \infty$, regardless of h . Moreover, we have $B_m(h)^2 = ((b_m + h\mathbf{u})^\top \nabla g(\bar{\theta}_{n,m}))^2$ for some $\bar{\theta}_{n,m}$ lying between θ and $\theta + b_m + h\mathbf{u}$, and hence $B_m(h)^2$ is bounded by $(\|b_m\| + h^2)$ times some universal constant. Therefore, up to a universal multiplicative constant, it holds that $\Delta_{n,m}(h) + V_{n,m}(h) + B_m(h)^2$ is bounded by $h^2(\tilde{p}_{n,m}(h) + 1) + 1/n + \|b_m\|^2$, where $1/n + \|b_m\|^2$ represents the bias-variance tradeoff, which is similar to (3.8).

Letting $n, m \rightarrow \infty$ and then $h \rightarrow 0$ in (3.11), the convergence of the MSE can be shown, as stated in Corollary 1.

Corollary 1. *Under the conditions of Theorem 1, it holds that:*

$$\lim_{n,m \rightarrow \infty} \mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 = 0.$$

3.4 Application to sensitivity index estimators

This section aims at studying the MSE of estimators of Sobol' indices introduced in Section 3.2. Let $\widehat{\theta} = (\widehat{\theta}_1, \widehat{\theta}_2, \widehat{\theta}_3)$ be as in (3.5) and (3.6), where $\widehat{\theta}_m^{(i)} =$

$(\widehat{\theta}_{m1}^{(i)}, \widehat{\theta}_{m2}^{(i)}, \widehat{\theta}_{m3}^{(i)}) = (\widehat{Q}_m(\mathbf{X}^{(i)})^2, \widehat{Q}_m(\mathbf{X}^{(i)}), \widehat{Q}_m(\mathbf{X}^{(i)})\widetilde{Q}_m(\widetilde{\mathbf{X}}_{\sim u}^{(i)}, \mathbf{X}_u^{(i)})$. Recall that $\theta_1 = \mathbb{E}(Q(\mathbf{X})^2)$, $\theta_2 = \mathbb{E}(Q(\mathbf{X}))$, $\theta_3 = \mathbb{E}(\mathbb{E}[Q(\mathbf{X}) | \mathbf{X}_u]^2) = \mathbb{E}(Q(\mathbf{X})Q(\widetilde{\mathbf{X}}_{\sim u}, \mathbf{X}_u))$, so that

$\mu_m = (\mu_{m1}, \mu_{m2}, \mu_{m3}) = (\theta_1 + b_{m1}, \theta_2 + b_{m2}, \theta_3 + b_{m3})$ and $b_m = (b_{m1}, b_{m2}, b_{m3}) = (\mathbb{E}\text{Var}[\varphi(\mathbf{X}, Z) | \mathbf{X}] / m, 0, 0)$. Recall that the function

$$g : (x_1, x_2, x_3) \mapsto (x_3 - x_2^2) / (x_1 - x_2^2) \quad (3.13)$$

is a twice-continuously differentiable function over its definition domain. But unfortunately, g is unbounded. The form of such a function makes the study of the MSE of Monte Carlo based Sobol index estimators almost impossible unless strong conditions are imposed on the output distribution of the model. This could explain why until now, to our knowledge, there is almost no study of the quadratic convergence of such estimators. The approach introduced in Section 3.3 allows to bypass the unbounded issue and thus, to establish the quadratic convergence of these estimators and to provide an approximate bound from which a strategy for optimizing convergence rate of the MSE is developed. Throughout this section, it is assumed that $\mathbb{E}(Q(\mathbf{X})^{16}) < +\infty$.

3.4.1 Control of the MSE

In order to provide an upper bound for $\mathbb{E}(g(\widehat{\theta}) - g(\theta))^2$ as in Theorem 1, it is necessary to fulfill Assumption 3, 4 and 5. Assumption 3 is trivially satisfied. Since the estimator $\widehat{\theta}$ is an empirical mean of i.i.d. random vectors, we can show that Assumption 4 is satisfied—see Theorem 2.

Theorem 2. *In the context of Section 3.4 with g given by (3.13), Assumption 4 is satisfied.*

To check Assumption 5, we need to find a direction \mathbf{u} that satisfies the required properties.

Theorem 3. *If $\mathbf{u} = (1, 0, 0)$, then, under the conditions of Theorem 1, Assumption 5 holds. Therefore, there is a constant \bar{C} independent of h such that, for every $h \in (0, 1)$,*

$$\mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 \leq \bar{p}_{n,m}(h) \left(\left(\frac{1}{n} + \left(\frac{\mathbb{E}(\text{Var}[\varphi(\mathbf{X}, Z) | \mathbf{X}])}{m} \right)^2 \right) + h^2 \bar{p}'_{n,m}(h) \right),$$

where the supremum limits of $\bar{p}_{n,m}(h)$ and $\bar{p}'_{n,m}(h)$ as $n, m \rightarrow \infty$ are less than \bar{C} .

Theorem 3 provides a bound for the MSE of the pick-freeze estimator $g(\widehat{\theta})$ of Sobol' indices. This bound allows an asymptotic control of the MSE in a general context. The interest of this result can be summarized in the following

points. First, the asymptotic bound of the MSE depends on tractable quantities, which enables analysis. Second, this result is also valid in the deterministic framework, in other words, it is a general control of the MSE of pick-freeze estimators of Sobol' indices in both the stochastic and the deterministic case where $m = 1$ and $\mathbb{E}(\text{Var}[\varphi(\mathbf{X}, Z) | \mathbf{X}]) = 0$. Finally, to our knowledge, this is the first result of this kind in sensitivity analysis. A direct consequence of the Theorem is the convergence in quadratic mean of the studied estimators. This is stated in Corollary 2.

Corollary 2. *Under the conditions of Theorem 2, we have $\lim_{n,m \rightarrow \infty} \mathbb{E}(g(\hat{\theta}) - g(\theta))^2 = 0$.*

Corollary 2 immediately follows from Corollary 1, Theorem 2 and Theorem 3.

3.4.2 Asymptotically optimal bias-variance tradeoff between repetitions and explorations

The Monte-Carlo estimation of sensitivity indices based on pick-freeze method requires a total number of model evaluations under the form: $nm \times (C_p + 1)$ where C_p is a constant that depends on p and the function φ only. Let $T \in \mathbb{N}^*$ and $\eta \in [0, 1]$ such that $m = T^\eta$ and $n = T^{1-\eta}$ and hence $T = mn$. So η allows to control the ratio between the number of exploration n and the number of repetitions m . It was shown in Corollary 2 and Theorem 3 that the MSE converges to zero as $n, m \rightarrow \infty$ and that the bias-variance tradeoff (BVT) is of order $T^{\eta-1} + T^{-2\eta}$.

Proposition 2. *As $T \rightarrow \infty$, the BVT convergence rate toward zero is optimal for $\eta = 1/3$.*

Thus, choosing m of order $T^{1/3}$ and n of order $T^{2/3}$ ensures that the BVT converges at a rate at least $T^{2/3}$ when $T \rightarrow \infty$.

Let us notice that the MSE cannot vanish at a faster rate than $T^{2/3}$ in general, as Proposition 3 shows.

Proposition 3. *If m is of order $T^{1/3}$ and n is of order $T^{2/3}$ then, under the constraint $mn = T$, there exist a random vector \mathbf{X} and a stochastic model f such that $\lim T^{2/3} \mathbb{E}(g(\hat{\theta}) - g(\theta))^2 > 0$ as $T \rightarrow \infty$.*

3.5 Practical algorithms

In Section 3.4, it turned out that the number of repetitions m should be of order $T^{1/3}$ under the constraint $nm = T$ in order to guarantee that the BVT converges at optimal rate.

However, an asymptotic order is not a specific value. To guide the choice of m in practice, notice that m should be linked to the intrinsic randomness of $\varphi(\mathbf{X}, Z)$, since the probability distribution of $Q(\mathbf{X})$ depends on that of Z . Therefore, we expect that the greater the intrinsic noise is, the larger m should be. Thus, in this section, the goal consists in proposing a value of m that takes into account the importance of the intrinsic randomness.

Under the constraint $nm = T$, the optimal convergence rate of the BVT is obtained when n_{opt} is of order $T^{2/3}$ and m_{opt} is of order $T^{1/3}$. Let $m_{opt} = \kappa T^{1/3}$ where $\kappa > 0$. Then, $n_{opt} = \kappa^{-1} T^{2/3}$. Thus:

$$\text{BVT} = \kappa T^{-2/3} + \frac{\mathbb{E}\text{Var}(\varphi(\mathbf{X}, Z))^2}{\kappa^2} T^{-2/3}.$$

Coefficient κ can be chosen such that $\kappa T^{-2/3} + \frac{\mathbb{E}\text{Var}(\varphi(\mathbf{X}, Z))^2}{\kappa^2} T^{-2/3}$ is the smallest over $\kappa > 0$. The minimum of such a quantity is reached at $\kappa_{opt} = (2 \mathbb{E}\text{Var}(\varphi(\mathbf{X}, Z))^2)^{1/3}$. Therefore:

$$\begin{aligned} m_{opt} &= \left(2 \mathbb{E}(\text{Var}[\varphi(\mathbf{X}, Z) | \mathbf{X}])^2 \right)^{1/3} T^{1/3} \\ &= \left(\frac{1}{\sqrt{2}} \mathbb{E} \left(\left[\varphi(\mathbf{X}, Z) - \varphi(\mathbf{X}, \tilde{Z}) \right]^2 \right) \right)^{2/3} T^{1/3}. \end{aligned} \quad (3.14)$$

Therefore, the number of repetitions suggested above ensures that the BVT converges at optimal rate and then it provides a good variance-bias trade-off so as not to have an imbalance in the rate of convergence of the variance and the bias that would reduce the global rate. Furthermore, it is noticeable that m_{opt} depends on $\mathbb{E}(\varphi(\mathbf{X}, Z) - \varphi(\mathbf{X}, \tilde{Z}))^2$. Relying on the law of total variance:

$$\text{Var}(\varphi(\mathbf{X}, Z)) = \text{Var}(\mathbb{E}[\varphi(\mathbf{X}, Z) | \mathbf{X}]) + \mathbb{E}(\text{Var}[\varphi(\mathbf{X}, Z) | \mathbf{X}]),$$

it follows that $\mathbb{E}(\varphi(\mathbf{X}, Z) - \varphi(\mathbf{X}, \tilde{Z}))^2$ quantifies the part of the total variance $\text{Var}(\varphi(\mathbf{X}, Z))$ that is not attributed to the inputs \mathbf{X} ; and so, that measures the influence of the intrinsic noise of the stochastic model $\varphi(\mathbf{X}, Z)$. Thus, $m_{opt}(T)$ takes into account the intensity of the intrinsic noise of the stochastic model so that the higher the intrinsic noise impact, the higher the number of repetitions should be, and therefore sufficient repetitions of the model are provided in order to reduce the bias b_m .

Finally, it also appears that $m_{opt}(T)$ depends on both T and the function φ . The dependence with respect to T guarantees that $m_{opt}(T)$ grows as T gets large. Besides, the dependence with respect to φ means that even if $m_{opt}(T)$ remains proportional to $T^{1/3}$, it also varies with respect to the chosen QoI of the stochastic model f .

3.5.1 Algorithms

This section is devoted to the practical implementation of the bias-variance trade-off strategy when performing SA for some QoI of a stochastic model. Recall that f is a stochastic model as in (3.1) and we are interested in carrying out SA of a QoI under the form (3.2), that is, $Q(\mathbf{X}) = \mathbb{E}[\varphi(\mathbf{X}, Z) \mid \mathbf{X}]$ in order to measure the impact of some groups of inputs $u_i \subset \{1, \dots, p\}$, $i = 1, \dots, l$. In other words, we are interested in estimating S_{u_1}, \dots, S_{u_l} . We shall use at most $T \times (l + 1)$ evaluations of $\varphi(\mathbf{X}, Z)$. Under the constraint $nm = T$, the number of repetitions m_{opt} found in 3.14 depends on $\rho := \mathbb{E}(\varphi(\mathbf{X}, Z) - \varphi(\mathbf{X}, \tilde{Z}))^2$. However, in practice, C is often unknown. So, before sensitivity index estimation, C needs to be estimated.

Consider r_0 i.i.d. samples of \mathbf{X} , denoted by $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(r_0)}$, and generate two outputs at each sample $\mathbf{X}^{(i)}$: $(\varphi(\mathbf{X}^{(1)}, Z^{(1,1)}), \varphi(\mathbf{X}^{(1)}, Z^{(1,2)})), \dots, (\varphi(\mathbf{X}^{(r_0)}, Z^{(r_0,1)}), \varphi(\mathbf{X}^{(r_0)}, Z^{(r_0,2)}))$. Thus:

$$\hat{\rho} = \frac{1}{r_0} \sum_{i=1}^{r_0} \left(\varphi(\mathbf{X}^{(i)}, Z^{(i,1)}) - \varphi(\mathbf{X}^{(i)}, Z^{(i,2)}) \right)^2$$

is a consistent and unbiased estimator of ρ . It appears that the estimation of C requires $2r_0$ evaluations of the model $\varphi(\mathbf{X}, Z)$. However, the maximal number of evaluations is $T \times (l + 1)$. So, for index estimation procedure, at most $T \times (l + 1) - 2r_0$ model evaluations are allowed.

Therefore, our strategy consists in leveraging the model outputs used to estimate ρ and then plugging and completing those outputs in order to compute sensitivity index estimates. This strategy relies on two algorithms: Algorithm 6 and Algorithm 7. Algorithm 6 enables to generate complementary outputs in addition to outputs already available after estimation of ρ . This allows to satisfy the constraint of the maximal number of model evaluations $T \times (l + 1)$. This part helps to optimize the whole estimation procedure by using the model outputs already generated. Regarding Algorithm 7, it effectively estimates indices in three steps based on pick-freeze procedure. First, it estimates ρ and thereby compute m_{opt} and $n_{opt} = T/m_{opt}$. Then, in the second step, by relying on Algorithm 6, complementary outputs required for estimations are generated. In the final step, sensitivity index estimates are computed with respect to inputs or groups of inputs specified by the user.

Algorithm 7 requires: r_0, T, φ, w and input samples. The transformation φ of the stochastic model is supplied as well as w the set of inputs or groups of inputs whose indices are estimated. In practice, r_0, T and c must be chosen. We recommend to take r_0 with respect to T so as not to waste a large part of the budget only in the first stage of Algorithm 7. Indeed, the estimator $\hat{\rho}$ has enough good statistical properties for efficient estimation of ρ with not too large value of r_0 . Regarding T , it follows T should be taken as large as possible depending on the computational cost of a run of both φ and the original model

Algorithm 6 Completing model evaluations

Inputs: $n, m, \varphi, l, (\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(T)})$
Data: $(\varphi(\mathbf{x}^{(1)}, Z^{(1,1)}), \varphi(\mathbf{x}^{(1)}, Z^{(1,2)})), \dots, (\varphi(\mathbf{x}^{(r_0)}, Z^{(r_0,1)}), \varphi(\mathbf{x}^{(r_0)}, Z^{(r_0,2)}))$

- 1: **if** $n \geq r_0$ **then**
- 2: **if** $m \geq 2$ **then**
- 3: **for** $i = 1, \dots, r_0$ **do**
- 4: **for** $k = 3, \dots, m$ **do**
- 5: Compute $\varphi(\mathbf{X}^{(i)}, Z^{(i,k)})$
- 6: **end for**
- 7: **end for**
- 8: **for** $i = r_0 + 1, \dots, n$ **do**
- 9: **for** $k = 1, \dots, m$ **do**
- 10: Compute $\varphi(\mathbf{X}^{(i)}, Z^{(i,k)})$
- 11: **end for**
- 12: **end for**
- 13: **end if**
- 14: **if** $m = 1$ **then**
- 15: **for** $i = r_0 + 1, \dots, n - r_0 - \lceil r_0 / (l + 1) \rceil$ **do**
- 16: Compute $\varphi(\mathbf{X}^{(i)}, Z^{(i,1)})$
- 17: **end for**
- 18: **end if**
- 19: **end if**
- 20: **if** $n < r_0$ **then**
- 21: **if** $m > 2 + 2\lceil 1 / (l + 1) \rceil * (-1 + r_0 / n)$ **then**
- 22: **for** $i = 1, \dots, n$ **do**
- 23: **for** $k = 3, \dots, m - 2\lceil 1 / (l + 1) \rceil * (-1 + r_0 / n)$ **do**
- 24: Compute $\varphi(\mathbf{X}^{(i)}, Z^{(i,k)})$
- 25: **end for**
- 26: **end for**
- 27: **end if**
- 28: **if** $m \leq 2 + 2\lceil 1 / (l + 1) \rceil * (-1 + r_0 / n)$ **then**
- 29: **Exit:** Budget already consumed
- 30: **end if**
- 31: **end if**

Algorithm 7 Estimation of Sobol' indices

- Inputs:** $r_0, T, \varphi, w = \{u_1, \dots, u_l\}, (\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(T)}), (\tilde{\mathbf{X}}^{(1)}, \dots, \tilde{\mathbf{X}}^{(T)})$
- 1: **for** $i = 1, \dots, r_0$ **do**
 - 2: **for** $k = 1, 2$ **do**
 - 3: Compute $\varphi(\mathbf{X}^{(i)}, Z^{(i,k)})$
 - 4: **end for**
 - 5: **end for**
 - 6: Compute $\hat{\rho} \leftarrow \frac{1}{r_0} \sum_{s=1}^{r_0} (\varphi(\mathbf{X}^{(i)}, Z^{(i,1)}) - \varphi(\mathbf{X}^{(i)}, Z^{(i,2)}))^2$
 - 7: Compute \hat{m}_{opt} according to Equation (3.14)
 - 8: $\hat{n}_{opt} \leftarrow \lfloor T/\hat{m}_{opt} \rfloor$
 - 9: Run Algorithm 6 with $m = \hat{m}_{opt}, n = \hat{n}_{opt}$ to complete samples $\varphi(\mathbf{X}^{(1)}, Z^{(1,1)}), \dots, \varphi(\mathbf{X}^{(r_0)}, Z^{(r_0,2)})$.
 - 10: **for** $j = 1, \dots, l$ **do**
 - 11: **for** $i = 1, \dots, \hat{n}_{opt}$ **do**
 - 12: **for** $k = 1, \dots, \hat{m}_{opt}$ **do**
 - 13: Compute $\varphi(\left(\tilde{\mathbf{X}}_{\sim u_j}^{(i)}, \mathbf{X}_{u_j}^{(i)}\right), \tilde{Z}^{(i,k)})$
 - 14: **end for**
 - 15: **end for**
 - 16: **end for**
 - 17: Compute sensitivity index estimates
-

f. Furthermore, to ensure that the MSE has a precision $\varepsilon \in (0, 1)$ with $h^2 \ll \varepsilon$, T must be roughly chosen larger than $\varepsilon^{-3/2}$ since the BVT is $O(T^{-2/3})$. This provides approximations for practical choice of T .

3.5.2 Illustrations

This subsection presents the performance of the estimators of first-order and total indices computed by Algorithm 7 in the case of two toy stochastic models for which analytical values of indices are known: a linear model $f(X_1, X_2, Z) = 1 + X_1 + 2X_2 + \sigma Z$ with $\sigma > 0$ and a stochastic version of the Ishigami function $f'(X_1, X_2, X_3, Z) = \sin X_1 + a \sin^2 X_2 + b X_3^4 \sin X_1 Z^2$ with $a, b > 0$ (Ishigami and Homma, 1990). For each value of $T = nm$, the estimators of Algorithm 7 are compared with two other arbitrary choices, namely, $(n, m) = (T/5, 5)$ and $(n, m) = (T^{1/2}, T^{1/2})$. For each choice of the couple (n, m) , $N = 100$ replications of estimations are carried out so that the global MSE $\sum_{j=1}^p \mathbb{E}(g(\hat{\theta}_{j,n,m}) - g(\theta_j))^2$ is estimated by using samples

$$\sum_{j=1}^p \left(g(\hat{\theta}_{j,n,m}^{(l)}) - g(\theta_j) \right)^2, l = 1, \dots, 100 \quad (3.15)$$

where $g(\hat{\theta}_{j,n,m}^{(l)})$ is the l th replication of estimator $g(\hat{\theta}_{j,n,m})$ of the j th input sensitivity index $g(\theta_j)$ and p is the number of inputs.

The two additional choices above represent two different situations. The choice $(n, m) = (T/5, 5)$ presents a case where the number of repetitions is constant and independent of T . This illustrates the situation where the bias does not get reduced so that it disturbs estimations no matter how large T is. Regarding $(n, m) = (T^{1/2}, T^{1/2})$, it shows that the case where the variance is not sufficiently reduced since there are not enough input samples. So, both choices enable to highlight the trade-off strategy implemented in Algorithm 7 and to confirm its performance regarding accuracy.

For illustrations, the product $T = mn$ is chosen in the set $T \in \{10^3, 10^4, \dots, 10^7\}$. The tuning parameter r_0 is set to 10. Thus, $2r_0 = 20$ model evaluations are used to get the estimates $\hat{\rho}, \hat{n}_{opt}, \hat{m}_{opt}$ in the first part of Algorithm 7, and then $T - 2r_0 \in \{10^3 - 20, 10^4 - 20, \dots, 10^7 - 20\}$ model evaluations are used to get the sensitivity index estimators with $n = \hat{n}_{opt}$ and $m = \hat{m}_{opt}$. For both toy stochastic models, the QoI considered is the conditional expectation so that $\varphi = f$ or $\varphi = f'$ depending on the model. For each value of T , the boxplots of the global MSE samples given by (3.15) for each of the three choices are plotted.

Linear model

Let $f(X_1, X_2, Z) = 1 + X_1 + 2X_2 + \sigma Z$ where $\sigma > 0$ and X_1, X_2 and Z are i.i.d. under the standard normal distribution. Such model includes two uncertain parameters X_1 and X_2 with respective first-order Sobol' indices $S_1 = 1/5$ and $S_2 = 4/5$. Two values of σ are considered: $\sigma = 1$ and $\sigma = 5$.

Figure 3.1 shows that the estimations obtained with Algorithm 7 are more accurate as T gets large because both bias and variance are efficiently reduced. Boxplots highlight that the strategies $m = 5$ and $m = T^{1/2}$ suffer respectively from bias and variance. Notice that in the case of the linear model under study, $\mathbb{E}(\text{Var}(f(X_1, X_2, Z) \mid (X_1, X_2))) = 2\sigma^2$; so the bias depends on σ . This explains why in the case $\sigma = 5$ (Figure 3.1), even for large value of T , estimations resulting of the choice $m = 5$ seem not to decrease but are rather concentrated around about 0.18 which is very large compared to what is obtained in the two other strategies. Focusing on strategies $m = m_{opt}$ and $m = T^{1/2}$, a zoom of the plot of Figure 3.1 for the case $\sigma = 5$, given in Figure 3.A.1 in Appendix 3.A, enables to compare them and then to confirm that the strategy implemented in Algorithm 7 provide more accurate estimations as T increases.

A stochastic Ishigami function

Let $f'(X_1, X_2, X_3, Z) = \sin X_1 + a \sin^2 X_2 + bX_3^4 \sin X_1 Z^2$ such that with $a, b > 0$, X_1, X_2, X_3 and Z are independent with X_1, X_2, X_3 distributed under $\mathcal{U}([-\pi, \pi])$ and $Z \sim \mathcal{N}(0, 1)$. The model f' is a modified version of benchmark function known as the Ishigami function in SA. For this model, first-order Sobol' indices of inputs X_1, X_2 , and X_3 for the QoI $\mathbb{E}(f'(X_1, X_2, X_3, Z) \mid X_1, X_2, X_3)$ are respectively given by $S_1 = \frac{1}{2} \frac{(1 + \frac{b\pi^4}{5})^2}{\frac{a^2}{8} + \frac{b\pi^4}{5} + \frac{b^2\pi^8}{18} + \frac{1}{2}}$, $S_2 = \frac{\frac{a^2}{8}}{\frac{a^2}{8} + \frac{b\pi^4}{5} + \frac{b^2\pi^8}{18} + \frac{1}{2}}$ and $S_3 = 0$. Parameters a and b are chosen with respect to Sobol' and Levitan (1999): $a = 7$, $b = 0.05$ and Marrel et al. (2009): $a = 7$, $b = 0.1$.

Figure 3.2 also reveals that estimations obtained by using Algorithm 7 are more accurate for large T . Besides, remark that the term $bX_3^4 \sin X_1$ that multiplies the intrinsic noise term Z^2 includes b so that $|bX_3^4 \sin X_1| \leq b\pi^4$. Then, b allows to control the magnitude of the intrinsic noise term of the model. This explains why estimations in the case $b = 0.1$ present much more variability compared to the case $b = 0.05$. Nonetheless, in both cases the strategy implemented in Algorithm 7 has better results.

Overall, Figures 3.1 and 3.2 lead to the same conclusion: the strategy of Algorithm 7 provides better estimations and its MSE estimates decrease faster and are generally smaller compared to those of the two other estimators. In the particular case of $m = 5$, it is noticeable that errors do not decrease when T gets larger but rather they are quite constant. This is explained by

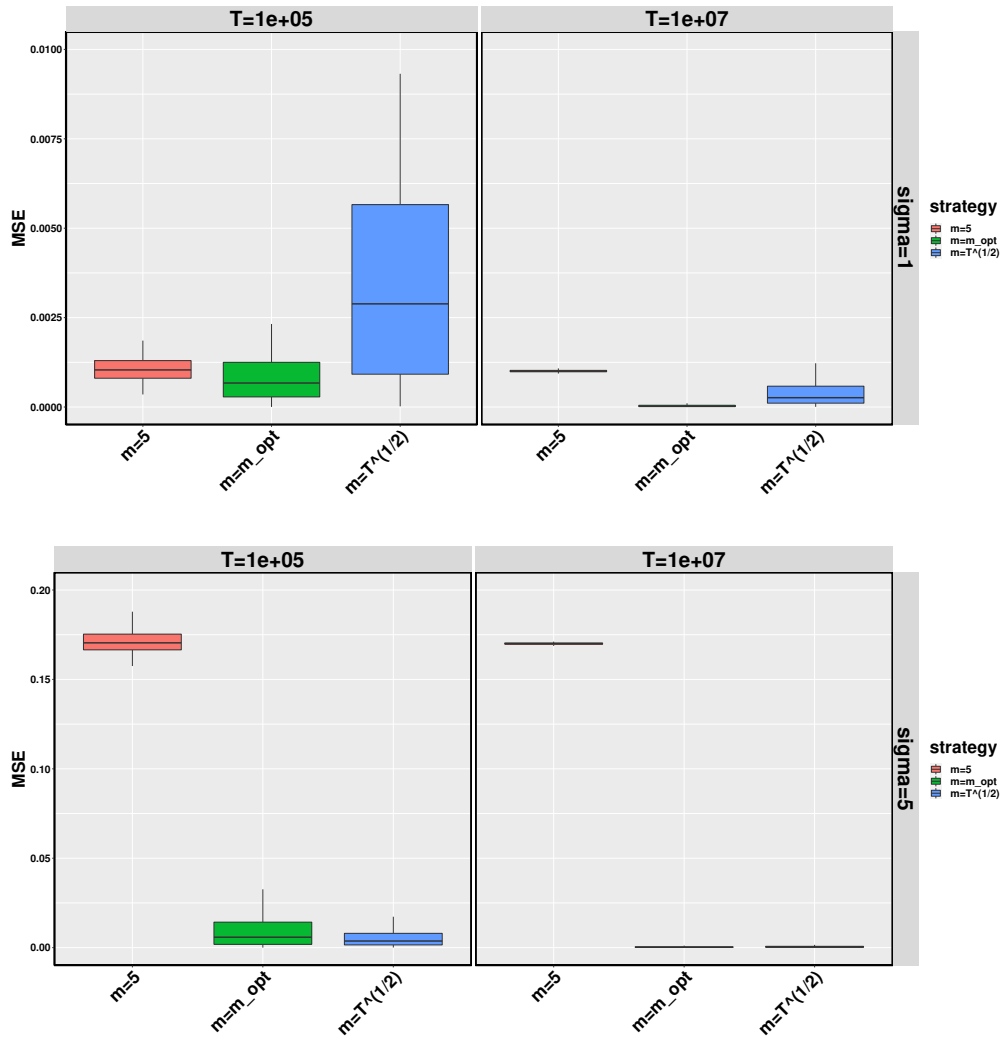


Figure 3.1 – Boxplots of global MSE estimates for the linear model for different values of T and σ . Three strategies of choice of m are compared: $m = 5$ (in red), $m = m_{opt}$ given by the trade-off strategy of Algorithm 7 (in green) and $m = T^{1/2}$ (in blue).

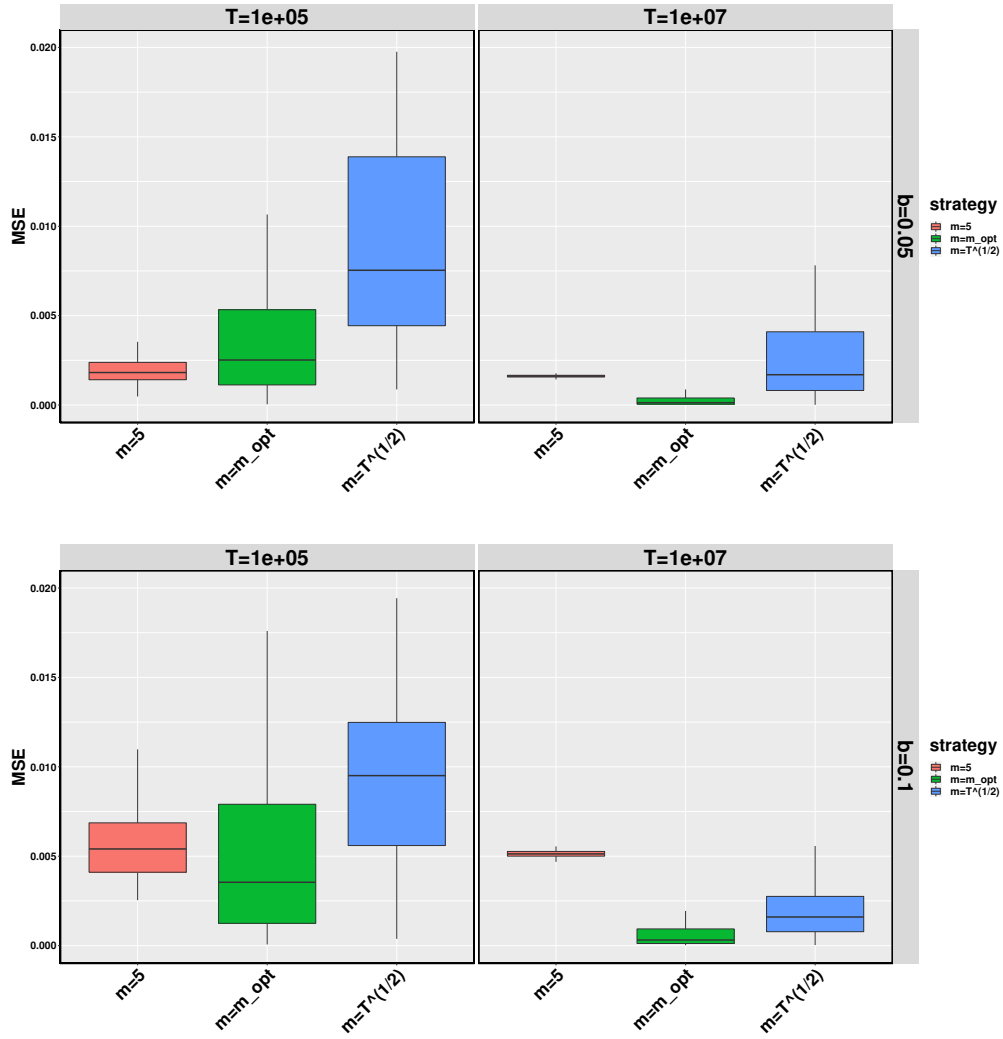


Figure 3.2 – Boxplots of global MSE estimates for the stochastic version of Ishigami function for different values of T and b . Three strategies of choice of m are compared: $m = 5$ (in red), $m = m_{opt}$ given by the trade-off strategy of Algorithm 7 (in green) and $m = T^{1/2}$ (in blue).

the fact that the bias is constant since m is constant. This illustrates the importance of varying the number of repetition when the total computational budget grows. Regarding the case $m = T^{1/2}$, it turns out that MSEs are not minimal compared to the case $m = m_{opt}$ due the variance part of those errors. Indeed, with $m = T^{1/2}$, the variance part of the BVT converges to 0 at rate $T^{1/2}$ while the squared-bias converges at rate T . Then, the global convergence rate of the BVT is $T^{1/2}$ that is slower than the rate $T^{2/3}$ of estimators built by Algorithm 7. These two cases clearly illustrate the bias-variance trade-off problem in Sobol' index estimation for stochastic models and they allow to show that the strategy proposed in this paper performs well.

3.6 Conclusion

This paper focuses on variance-based SA of stochastic models relying on the approach that consists in performing SA on some deterministic QoIs. Specifically, it deals with QoIs under the form of conditional expectations with respect to the uncertain parameters of some transformation of the original stochastic model output. For such deterministic quantities, estimation of Sobol' indices through Monte-Carlo methods (pick-freeze procedure) requires not only to sample the input space but also to estimate conditional expectations by making repetitions. Therefore, the resulting estimators depend on both the number of explorations n and the number of repetitions m . This study pointed out that the MSE of such estimators can be bounded by tractable quantities that depend on both n and m . This had two implications. First, the bounds enable to ensure that the MSE converges to zero when both $n, m \rightarrow +\infty$. Straightforwardly, this establishes that the estimators of Sobol' indices converge in quadratic mean. Secondly, A strategy can be developed for controlling the bias-variance trade-off that arises when the product nm is fixed. Indeed, the bias and the variance decrease respectively when $m \rightarrow +\infty$ and $n \rightarrow +\infty$. Under the constraint $nm = T$ and $T \rightarrow +\infty$, the numbers m and n should be chosen such that both the variance and the bias vanish at the fastest rate possible. This problem is discussed and this study showed that taking m of order $T^{1/3}$ and n of order $T^{2/3}$ guarantees that quantity BVT representing the bias-variance tradeoff in the MSE converges at rate at least $T^{2/3}$. Furthermore, the minimization of some upper bounds of the MSE under the constraint $nm = T$ provides a choice of m and n that adapts to the intrinsic randomness of the stochastic model. This strategy is implemented through two algorithms dedicated to Sobol' index estimation based on the pick-freeze procedure. The comparison of this strategy to two others was carried out using two toy stochastic models. It turned out that the strategy proposed in this paper performs well.

For further works, it could be interesting to couple the iterative estimation

approach of [Gilquin et al. \(2021\)](#) to the algorithms implemented in this study in order to build an adaptive version which could perform estimation with respect to a given precision. Furthermore, it would be interesting to compare the optimal BVT convergence rate of sensitivity index estimators based on basic Monte Carlo sampling with the rates one could get with other approaches, such as multilevel Monte Carlo methods ([Mycek and De Lozzo \(2019\)](#); [Giles and Haji-Ali \(2019\)](#)). Finally, although a convergence rate for the BVT has been found, that of the whole MSE remains an open problem.

Appendix

3.A Boxplot

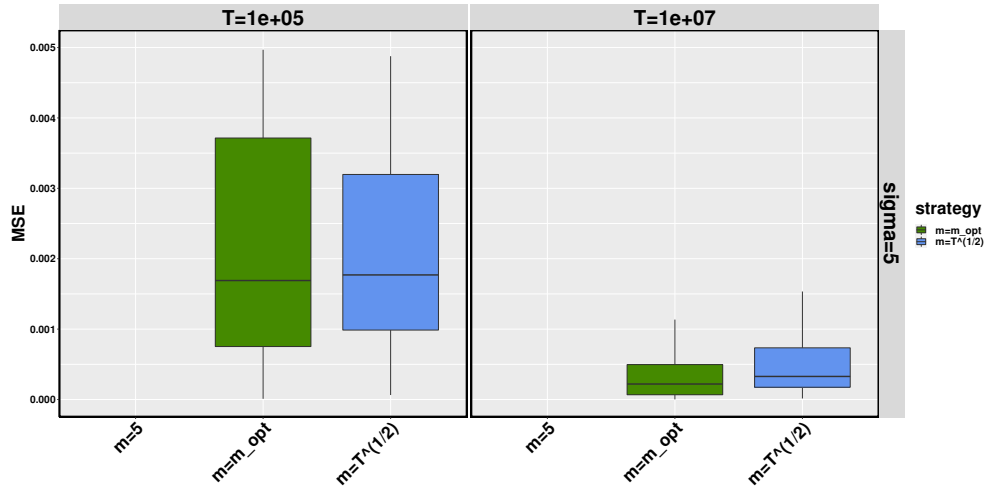


Figure 3.A.1 – Zoom of boxplots of Figure 3.1 .

3.B Proof of Theorem 1

Using convexity inequality, for all $h \in (0, 1)$ and $m \geq 1$, it holds:

$$\mathbb{E} \left(g \left(\hat{\theta} \right) - g \left(\theta \right) \right)^2 \leq 3 \mathbb{E} \left(g \left(\hat{\theta} \right) - g \left(\hat{\theta} + h \mathbf{u} \right) \right)^2 + 3 \mathbb{E} \left(g \left(\hat{\theta} + h \mathbf{u} \right) - g \left(\mu_m + h \mathbf{u} \right) \right)^2 + 3 \left(g \left(\mu_m + h \mathbf{u} \right) - g \left(\theta \right) \right)^2 .$$

Applying a Taylor-Lagrange expansion to g at points $\widehat{\theta} + h\mathbf{u}$ and $\mu_m + h\mathbf{u}$ yields:

$$\begin{aligned}
& \mathbb{E} \left(g \left(\widehat{\theta} + h\mathbf{u} \right) - g \left(\mu_m + h\mathbf{u} \right) \right)^2 \\
&= \mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) + \frac{1}{2} \left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2 \\
&\leq \mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2 \\
&\quad + \frac{1}{4} \mathbb{E} \left(\left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2 \\
&\quad + \sqrt{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2} \\
&\quad \times \sqrt{\mathbb{E} \left(\left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2}
\end{aligned}$$

for some $\lambda \in (0, 1)$. Thus:

$$\begin{aligned}
& \frac{\mathbb{E} \left(g \left(\widehat{\theta} + h\mathbf{u} \right) - g \left(\mu_m + h\mathbf{u} \right) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2} \\
&\leq 1 + \frac{1}{4} \frac{\mathbb{E} \left(\left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2} \\
&\quad + \sqrt{\frac{\mathbb{E} \left(\left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2}}.
\end{aligned}$$

Let $\phi : x \mapsto x/4 + \sqrt{x}$ and

$$p_{n,m}(h) := \phi \left(\sup_{\lambda \in [0,1]} \frac{\mathbb{E} \left(\left(\widehat{\theta} - \mu_m \right)^\top \nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h\mathbf{u} \right) \left(\widehat{\theta} - \mu_m \right) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\widehat{\theta} - \mu_m \right) \right)^2} \right). \tag{3.16}$$

then the ratio $\mathbb{E} \left(g \left(\hat{\theta} + h\mathbf{u} \right) - g \left(\mu_m + h\mathbf{u} \right) \right)^2 / \mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\hat{\theta} - \mu_m \right) \right)^2$ is bounded by $1 + p_{n,m}(h)$. Therefore:

$$\begin{aligned} \mathbb{E} \left(g \left(\hat{\theta} + h\mathbf{u} \right) - g \left(\mu_m + h\mathbf{u} \right) \right)^2 &= \frac{\mathbb{E} \left(g \left(\hat{\theta} + h\mathbf{u} \right) - g \left(\mu_m + h\mathbf{u} \right) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\hat{\theta} - \mu_m \right) \right)^2} \\ &\quad \times \mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top \left(\hat{\theta} - \mu_m \right) \right)^2 \\ &\leq (1 + p_{n,m}(h)) V_{n,m}(h). \end{aligned}$$

Now, let us show that $p_{n,m}(h) \rightarrow 0$ as $n, m \rightarrow \infty$. For this purpose, it is sufficient to have that $\sup_{\lambda \in [0,1]} \frac{\mathbb{E} \left((\hat{\theta} - \mu_m)^\top \nabla^2 g \left(\lambda \hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u} \right) (\hat{\theta} - \mu_m) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top (\hat{\theta} - \mu_m) \right)^2} = o(1)$ as $n, m \rightarrow +\infty$. A first use of Cauchy-Schwarz inequality yields that:

$$\begin{aligned} \left((\hat{\theta} - \mu_m)^\top \nabla^2 g \left(\lambda \hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u} \right) (\hat{\theta} - \mu_m) \right)^2 &\leq \|\nabla^2 g \left(\lambda \hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u} \right)\|_F^2 \\ &\quad \times \|\hat{\theta} - \mu_m\|^4. \end{aligned}$$

By a second use of Cauchy-Schwarz inequality, the argument of ϕ in Equation (3.16) is bounded by

$$\sqrt{\sup_{\lambda \in [0,1]} \mathbb{E} \left(\|\nabla^2 g \left(\lambda \hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u} \right)\|_F^4 \right)} \times \frac{\sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^8 \right)}}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top (\hat{\theta} - \mu_m) \right)^2}.$$

As $n, m \rightarrow \infty$, the first term of the product above is bounded by a constant independent of h , uniformly in λ , by Assumption 5. The second term is given by:

$$\begin{aligned} \frac{\sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^8 \right)}}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top (\hat{\theta} - \mu_m) \right)^2} &= \frac{\sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^8 \right)}}{\mathbb{E} \left(\nabla g \left(\mu_m \right)^\top (\hat{\theta} - \mu_m) \right)^2} \\ &\quad \times \frac{\mathbb{E} \left(\nabla g \left(\mu_m \right)^\top (\hat{\theta} - \mu_m) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top (\hat{\theta} - \mu_m) \right)^2} \\ &\leq \frac{\sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^8 \right)}}{\mathbb{E} \left(\nabla g \left(\mu_m \right)^\top (\hat{\theta} - \mu_m) \right)^2} \\ &\quad \times \sup_{h \in (0,1)} \frac{\mathbb{E} \left(\nabla g \left(\mu_m \right)^\top (\hat{\theta} - \mu_m) \right)^2}{\mathbb{E} \left(\nabla g \left(\mu_m + h\mathbf{u} \right)^\top (\hat{\theta} - \mu_m) \right)^2}. \end{aligned} \tag{3.17}$$

The first term in the right-hand side in (3.17) is of order $o(1)$ by Assumption 4 and does not depend on h . Moreover, since ∇g is continuous, we have $\sup_{h \in (0,1)} \frac{\mathbb{E}(\nabla g(\mu_m)^\top (\hat{\theta} - \mu_m))^2}{\mathbb{E}(\nabla g(\mu_m + h\mathbf{u})^\top (\hat{\theta} - \mu_m))^2} = O(1)$ as $n, m \rightarrow \infty$. Therefore, the quantity in (3.16) is of order $\phi(o(1)) = o(1)$, and hence

$$\mathbb{E} \left(g(\hat{\theta}) - g(\theta) \right)^2 \leq 3(1 + p_{n,m}(h)) (\Delta_{n,m}(h) + V_{n,m}(h) + B_m(h)^2),$$

where $\lim_{n,m \rightarrow +\infty} p_{n,m}(h) = 0$.

Let us focus on $\Delta_{n,m}(h) = \mathbb{E} \left(g(\hat{\theta}) - g(\hat{\theta} + h\mathbf{u}) \right)^2$. For this purpose, let $h \in (0, 1)$. Using convexity inequality, the Taylor-Lagrange expansion provides that:

$$\begin{aligned} g(\hat{\theta}) - g(\hat{\theta} + h\mathbf{u}) &= h \nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u} + \frac{1}{2} h^2 \mathbf{u}^\top \nabla^2 g(\hat{\theta} + h\lambda\mathbf{u}) \mathbf{u}, \\ \mathbb{E} \left(g(\hat{\theta}) - g(\hat{\theta} + h\mathbf{u}) \right)^2 &\leq 2h^2 \left(\mathbb{E} \left(\nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u} \right)^2 + \frac{h^2}{4} \mathbb{E} \left(\mathbf{u}^\top \nabla^2 g(\hat{\theta} + h\lambda\mathbf{u}) \mathbf{u} \right)^2 \right), \end{aligned}$$

for some $\lambda \in (0, 1)$. It appears that:

$$\mathbb{E} \left(\mathbf{u}^\top \nabla^2 g(\hat{\theta} + h\lambda\mathbf{u}) \mathbf{u} \right)^2 \leq \|\mathbf{u}\|^4 \mathbb{E} \left(\|\nabla^2 g(\hat{\theta} + h\lambda\mathbf{u})\|_F^2 \right).$$

Since $h\lambda \in (0, 1)$, the right-hand side is bounded by a constant independent of h and λ , as $n, m \rightarrow \infty$ (by Assumption 5). Regarding $\mathbb{E} \left(\nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u} \right)^2$, an additional Taylor-Lagrange expansion of $\nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u}$ yields:

$$\begin{aligned} \nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u} &= \nabla g(\mu_m + h\mathbf{u})^\top \mathbf{u} + (\hat{\theta} - \mu_m)^\top \nabla^2 g(\lambda\hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u}) \mathbf{u} \\ \mathbb{E} \left(\nabla g(\hat{\theta} + h\mathbf{u})^\top \mathbf{u} \right)^2 &\leq \left(\nabla g(\mu_m + h\mathbf{u})^\top \mathbf{u} \right)^2 + \|\mathbf{u}\|^2 \sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^4 \right)} \times \\ &\quad \sqrt{\sup_{\lambda \in [0,1]} \mathbb{E} \left(\|\nabla^2 g(\lambda\hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4 \right)} \end{aligned}$$

Then:

$$\mathbb{E} \left(g(\hat{\theta}) - g(\hat{\theta} + h\mathbf{u}) \right)^2 \leq \tilde{p}_{n,m}(h) h^2,$$

where:

$$\begin{aligned} \tilde{p}_{n,m}(h) &= 2 \left(\sqrt{\sup_{\lambda \in [0,1]} \mathbb{E} \left(\|\nabla^2 g(\lambda\hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4 \right)} + \left(\nabla g(\mu_m + h\mathbf{u})^\top \mathbf{u} \right)^2 + \right. \\ &\quad \left. \sqrt{\mathbb{E} \left(\|\hat{\theta} - \mu_m\|^4 \right)} \times \sqrt{\sup_{\lambda \in [0,1]} \mathbb{E} \left(\|\nabla^2 g(\lambda\hat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4 \right)} \right). \end{aligned}$$

Note that:

$$\limsup_{n,m \rightarrow \infty} \tilde{p}_{n,m}(h) \leq 2 \left(\sqrt{C} + \sup_{h \in (0,1)} \|\nabla g(\theta + h\mathbf{u})\|^2 \right) =: \tilde{C} < +\infty.$$

3.C Proof of Theorem 2

To prove Theorem 2, the following result is required.

Lemma 3.C.1. *Let $\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)}$ be n i.i.d. copies of \mathbf{X} and $Z^{(1,1)}, \dots, Z^{(n,m)}$ be $n \times m$ i.i.d. copies of Z such that $(\mathbf{X}^{(1)}, \dots, \mathbf{X}^{(n)})$ and $(Z^{(1,1)}, \dots, Z^{(n,m)})$ are independent. Then, for all $q \in \mathbb{N}$: $m^{-q} \mathbb{E} \left(\sum_{k=1}^m \varphi(\mathbf{X}^{(1)}, Z^{(1,k)}) \right)^q$ is polynomial in m^{-1} of degree $q - 1$ with constant $\mathbb{E} \left(\mathbb{E} [\varphi(\mathbf{X}, Z) \mid \mathbf{X}] \right)^q$.*

First, let us bound the numerator of the ratio in Assumption 4; we have

$$\mathbb{E} \left(\|\widehat{\theta} - \mu_m\|^8 \right) \leq 27 \sum_{j=1}^3 \mathbb{E} \left(\|\widehat{\theta}_j - \mu_{mj}\|^8 \right),$$

where $\widehat{\theta}_j$ and μ_{mj} denote the j th component of $\widehat{\theta}$ and μ_m , respectively. By Marcinkiewicz and Zygmund (1937) and Jensen inequalities, we have for every j that

$$\mathbb{E} \left(\|\widehat{\theta}_j - \mu_{mj}\|^8 \right) \leq \frac{B_8}{n^4} \mathbb{E} \left(\left| \widehat{\theta}_{mj}^{(1)} - \mu_{mj} \right|^8 \right),$$

where here B_8 is a universal constant.

The case $j = 2$ is the simplest. Notice that μ_{m2} does not depend on m , then the expansion of $\mathbb{E}(|\widehat{Q}_m(\mathbf{X}^{(1)}) - \mu_{m2}|^8)$ through Newton formula yields terms of the form $\mu_{m2}^k \mathbb{E}(\widehat{Q}_m^{8-k})$, $k = 0, \dots, 8$. Using Lemma 3.C.1 provides that those terms are polynomial in m^{-1} .

Let us deal with the case $j = 1$. Expanding the power 8 through Newton's formula and bounding its terms yields

$$\mathbb{E} \left(\left| \widehat{Q}_m(\mathbf{X}^{(1)})^2 - \mu_{m1} \right|^8 \right) \leq (\mu_{m1}^8 \vee 1) \binom{8}{4} \left(\mathbb{E} \left(\widehat{Q}_m(\mathbf{X}^{(1)})^{16} \right) + 1 \right). \quad (3.18)$$

Denoting $\varphi(\mathbf{X}^{(1)}, Z^{(1,k)}) = Y^{(1,k)}$, we have

$$\begin{aligned} \mathbb{E} \left(\left| \widehat{Q}_m(\mathbf{X}^{(1)}) \right|^{16} \right) &= \mathbb{E} \left(\left| \frac{1}{m} \sum_{k=1}^m Y^{(1,k)} \right|^{16} \right) \\ &= \frac{1}{m^{16}} \sum_{k_1, \dots, k_{16}=1}^m \mathbb{E} \left(Y^{(1,k_1)} \dots Y^{(1,k_{16})} \right). \end{aligned}$$

The expectation in the right-hand side is symmetric in k_1, \dots, k_{16} , and hence, from Lemma 3.C.1, the sum is a polynomial in m of degree 16. Therefore, the right-hand side in (3.18) is bounded uniformly in m .

Let us deal with the case $j = 3$. Proceeding as in (3.18), we have

$$\begin{aligned} & \mathbb{E} \left(\left| \widehat{Q}_m(\mathbf{X}^{(1)}) \widetilde{Q}_m(\widetilde{\mathbf{X}}_{\sim u}^{(1)}, \mathbf{X}_u^{(1)}) - \mu_{m3} \right|^8 \right) \\ & \leq (\mu_{m3}^8 \vee 1) \binom{8}{4} \left(\mathbb{E} \left(\left| \widehat{Q}_m(\mathbf{X}^{(1)}) \widetilde{Q}_m(\widetilde{\mathbf{X}}_{\sim u}^{(1)}, \mathbf{X}_u^{(1)}) \right|^8 \right) + 1 \right) \\ & \leq (\mu_{m3}^8 \vee 1) \binom{8}{4} \left(\mathbb{E} \left(\frac{1}{2} \widehat{Q}_m(\mathbf{X}^{(1)})^{16} + \frac{1}{2} \widetilde{Q}_m(\widetilde{\mathbf{X}}_{\sim u}^{(1)}, \mathbf{X}_u^{(1)})^{16} \right) + 1 \right), \end{aligned}$$

and this is also bounded uniformly in m . (Again by Lemma 3.C.1.)

We now deal with the root of the denominator of the ratio in Assumption 4. We have

$$\begin{aligned} & \mathbb{E} \left(\nabla g(\mu_m)^T (\widehat{\theta} - \mu_m) \right)^2 \\ & = \sum_{j_1, j_2=1}^3 \nabla g(\mu_m)_{j_1} \nabla g(\mu_m)_{j_2} \mathbb{E} (\widehat{\theta} - \mu_m)_{j_1} (\widehat{\theta} - \mu_m)_{j_2} \\ & = \frac{1}{n} \sum_{j_1, j_2=1}^3 \nabla g(\mu_m)_{j_1} \nabla g(\mu_m)_{j_2} \left(\mathbb{E} \widehat{\theta}_{mj_1}^{(1)} \widehat{\theta}_{mj_2}^{(1)} - \mu_{mj_1} \mu_{mj_2} \right). \end{aligned} \quad (3.19)$$

The infimum of the sum in (3.19) is reached for some m and greater than zero. Therefore, the numerator in Assumption 4 is less than $1/n^4$ times a constant not depending on m or n and the denominator is equal to $1/n^2$ times a quantity greater than zero. Therefore, the supremum over m of the ratio in Assumption 4 is of order $O(n^{-2})$. The proof is complete.

Proof of Lemma 3.C.1

It holds that:

$$\begin{aligned} \mathbb{E} \left(\frac{1}{m} \sum_{k=1}^m \varphi(\mathbf{X}^{(1)}, Z^{(1,k)}) \right)^q & = \frac{1}{m^q} \mathbb{E} \left(\sum_{k_1=1}^m \cdots \sum_{k_q=1}^m \varphi(\mathbf{X}^{(1)}, Z^{(1,k_1)}) \cdots \varphi(\mathbf{X}^{(1)}, Z^{(1,k_q)}) \right) \\ & = \frac{1}{m^q} \sum_{k_1=1}^m \cdots \sum_{k_q=1}^m \mathbb{E} \left(\varphi(\mathbf{X}^{(1)}, Z^{(1,k_1)}) \cdots \varphi(\mathbf{X}^{(1)}, Z^{(1,k_q)}) \right). \end{aligned}$$

Denote by $\lambda : \{1, \dots, m\}^q \rightarrow \mathbb{N}$ the map which with each $\mathbf{k} := (k_1, \dots, k_q)$ associates the number of distinct indices among k_1, \dots, k_q . If $1 \leq l \leq q$ then denote by $\rho_l : \lambda^{-1}(l) \rightarrow \{1, \dots, q\}^l$ the map which with each $\mathbf{k} \in \lambda^{-1}(l)$ associates (r_1, \dots, r_l) , where $r_i = |\{j : k_j = k_{j_i}\}|$ for every $i = 1, \dots, l$ and k_{j_1}, \dots, k_{j_l} are the distinct indices found among k_1, \dots, k_q . Obviously, $r_1 +$

$\dots + r_l = q$. We have

$$\begin{aligned}
& \sum_{k_1=1}^m \dots \sum_{k_q=1}^m \mathbb{E} \left(\varphi(\mathbf{X}^{(1)}, Z^{(1,k_1)}) \dots \varphi(\mathbf{X}^{(1)}, Z^{(1,k_q)}) \right) \\
&= \sum_{k_1=1}^m \dots \sum_{k_q=1}^m f(\mathbf{k}) \\
&= \sum_{l=1}^q \left(\sum_{(r_1, \dots, r_l) \in \{1, \dots, q\}^l: r_1 + \dots + r_l = q} \left(\sum_{\mathbf{k} \in \lambda^{-1}(l): \rho_l(\mathbf{k}) = (r_1, \dots, r_l)} f(\mathbf{k}) \right) \right). \quad (3.20)
\end{aligned}$$

Now, since

$$\begin{aligned}
& \mathbb{E} \left(\varphi(\mathbf{X}^{(1)}, Z^{(1,k_1)}) \dots \varphi(\mathbf{X}^{(1)}, Z^{(1,k_q)}) \right) \\
&= \mathbb{E} \left(\varphi(\mathbf{X}^{(1)}, Z^{(1,k_{j_1})})^{r_1} \dots \varphi(\mathbf{X}^{(1)}, Z^{(1,k_{j_l})})^{r_l} \right) \\
&= \mathbb{E} \left(\prod_{s=1}^l \mathbb{E} \left[\varphi(\mathbf{X}^{(1)}, Z^{(1,k_{j_s})})^{r_s} \mid \mathbf{X}^{(1)} \right] \right)
\end{aligned}$$

is symmetric in r_1, \dots, r_l , it holds that

$$\begin{aligned}
& \sum_{(r_1, \dots, r_l) \in \{1, \dots, q\}^l: r_1 + \dots + r_l = q} \left(\sum_{\mathbf{k} \in \lambda^{-1}(l): \rho_l(\mathbf{k}) = (r_1, \dots, r_l)} f(\mathbf{k}) \right) \\
&= c(l, (r_1, \dots, r_l), m) \mathbb{E} \left(\prod_{s=1}^l \mathbb{E} \left[\varphi(\mathbf{X}^{(1)}, Z^{(1,k_{j_s})})^{r_s} \mid \mathbf{X}^{(1)} \right] \right)
\end{aligned}$$

where

$$c(l, (r_1, \dots, r_l), m) = \binom{q}{r_1} \binom{q-r_1}{r_2} \dots \binom{q-r_1-\dots-r_{l-1}}{r_l} m(m-1) \dots (m-l+1). \quad (3.21)$$

Notice that the expression in the right-hand side of (3.21) is invariant by permutation of r_1, \dots, r_l . Therefore, the sum (3.20) is a polynomial in m of degree q with constant zero and hence $\mathbb{E} \left(\frac{1}{m} \sum_{k=1}^m \varphi(\mathbf{X}^{(1)}, Z^{(1,k)})^q \right)$ is a polynomial in $\frac{1}{m}$ of degree $q-1$ with constant $\lim_{m \rightarrow +\infty} \mathbb{E} \left(\frac{1}{m} \sum_{k=1}^m \varphi(\mathbf{X}^{(1)}, Z^{(1,k)})^q \right) = \mathbb{E} \left(\mathbb{E}[\varphi(\mathbf{X}, Z) \mid \mathbf{X}]^q \right)$.

3.D Proof of Theorem 3

The following lemma will be needed:

Lemma 3.D.1. For all $\alpha > 0$ and all $h \in (0, 1)$,

$$\lim_{n,m \rightarrow +\infty} \mathbb{E} \left[\frac{1}{(h + \widehat{\theta}_1 - \widehat{\theta}_2^\alpha)^\alpha} \right] = \frac{1}{(h + \text{Var}(Q(\mathbf{X})))^\alpha} \leq \text{Var}(Q(\mathbf{X}))^{-\alpha}. \quad (3.22)$$

Note that the function g is infinitely differentiable over its domain \mathcal{D} and then its gradient is given by:

$$\nabla g(\theta_1, \theta_2, \theta_3) = \left(-\frac{\theta_3 - \theta_2^2}{(\theta_1 - \theta_2^2)^2}, \frac{2\theta_2(\theta_3 - \theta_1)}{(\theta_1 - \theta_2^2)^2}, \frac{1}{\theta_1 - \theta_2^2} \right)^\top.$$

Furthermore, the hessian matrix of g yields:

$$\nabla^2 g(\theta_1, \theta_2, \theta_3) = \begin{pmatrix} \frac{2(\theta_3 - \theta_2^2)}{(\theta_1 - \theta_2^2)^3} & \frac{2\theta_2(\theta_1 - 2\theta_3 + \theta_2^2)}{(\theta_1 - \theta_2^2)^3} & \frac{-1}{(\theta_1 - \theta_2^2)^2} \\ \frac{2\theta_2(\theta_1 - 2\theta_3 + \theta_2^2)}{(\theta_1 - \theta_2^2)^3} & \frac{2(\theta_3 - \theta_1)(\theta_1 + 3\theta_2^2)}{(\theta_1 - \theta_2^2)^3} & \frac{2\theta_2}{(\theta_1 - \theta_2^2)^2} \\ \frac{-1}{(\theta_1 - \theta_2^2)^2} & \frac{2\theta_2}{(\theta_1 - \theta_2^2)^2} & 0 \end{pmatrix}.$$

For any $(\theta_1, \theta_2, \theta_3) \in \mathcal{D}$, the matrix $\nabla^2 g(\theta_1, \theta_2, \theta_3)$ is under the form $\nabla^2 g(\theta_1, \theta_2, \theta_3) = B(\theta_1, \theta_2, \theta_3)/(\theta_1 - \theta_2^2)^3$ where $B(\theta_1, \theta_2, \theta_3)$ is the matrix:

$$B(\theta_1, \theta_2, \theta_3) = \begin{pmatrix} 2(\theta_3 - \theta_2^2) & 2\theta_2(\theta_1 - 2\theta_3 + \theta_2^2) & -(\theta_1 - \theta_2^2) \\ 2\theta_2(\theta_1 - 2\theta_3 + \theta_2^2) & 2(\theta_3 - \theta_1)(\theta_1 + 3\theta_2^2) & 2\theta_2(\theta_1 - \theta_2^2) \\ -(\theta_1 - \theta_2^2) & 2\theta_2(\theta_1 - \theta_2^2) & 0 \end{pmatrix}.$$

Notice that $B(\theta_1, \theta_2, \theta_3)$ includes only multivariate polynomials of variables θ_1, θ_2 and θ_3 .

Let us check Assumption 5. Let $\lambda \in [0, 1]$ and $h \in (0, 1)$. We have

$$\begin{aligned} \nabla^2 g(\lambda\widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u}) &= \frac{B(\lambda\widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})}{\left(h + \lambda\widehat{\theta}_1 + (1-\lambda)\mu_{m1} - (\lambda\widehat{\theta}_2 + (1-\lambda)\mu_{m2})^2\right)^3} \\ &\mathbb{E} \left(\|\nabla^2 g(\lambda\widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4 \right) \\ &= \mathbb{E} \left(\frac{\|B(\lambda\widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^4}{\left(h + \lambda\widehat{\theta}_1 + (1-\lambda)\mu_{m1} - (\lambda\widehat{\theta}_2 + (1-\lambda)\mu_{m2})^2\right)^{12}} \right) \\ &\leq \sqrt{\mathbb{E} \left(\frac{1}{\left(h + \lambda\widehat{\theta}_1 + (1-\lambda)\mu_{m1} - (\lambda\widehat{\theta}_2 + (1-\lambda)\mu_{m2})^2\right)^{24}} \right)} \\ &\quad \times \sqrt{\mathbb{E} \left(\|B(\lambda\widehat{\theta} + (1-\lambda)\mu_m + h\mathbf{u})\|_F^8 \right)} \end{aligned}$$

$$\begin{aligned}
\nabla^2 g \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right) &\leq \sqrt{\mathbb{E} \left(\frac{1}{\left(h + \lambda \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 \right) + (1 - \lambda) (\mu_{m1} - \mu_{m1}^2) \right)^{24}} \right)} \\
&\quad \times \sqrt{\mathbb{E} \left(\|B \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right)\|_F^8 \right)} \quad (\text{convexity}) \\
&\leq \sqrt{\mathbb{E} \left(\frac{\lambda}{\left(h + \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 \right) \right)^{24}} \right) + \frac{1 - \lambda}{\left(h + \mu_{m1} - \mu_{m1}^2 \right)^{24}}} \\
&\quad \times \sqrt{\mathbb{E} \left(\|B \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right)\|_F^8 \right)} \quad (\text{convexity}) \\
&\leq \sqrt{\mathbb{E} \left(\frac{1}{\left(h + \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 \right) \right)^{24}} \right) + \frac{1}{\left(h + \mu_{m1} - \mu_{m1}^2 \right)^{24}}} \\
&\quad \times \sqrt{\sup_{\lambda \in [0,1]} \mathbb{E} \left(\|B \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right)\|_F^8 \right)} \\
&\leq \sqrt{\mathbb{E} \left(\frac{1}{\left(h + \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 \right) \right)^{24}} \right) + \sup_{h \in (0,1)} \frac{1}{\left(h + \mu_{m1} - \mu_{m1}^2 \right)^{24}}} \\
&\quad \times \sqrt{\sup_{h \in (0,1)} \sup_{\lambda \in [0,1]} \mathbb{E} \left(\|B \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right)\|_F^8 \right)}.
\end{aligned}$$

One should remark that $\sup_{h \in (0,1)} \frac{1}{\left(h + \mu_{m1} - \mu_{m1}^2 \right)^{24}} \leq \frac{1}{\left(\text{Var}(\mathbb{E}[\varphi(\mathbf{X}, Z) | \mathbf{X}]) \right)^{24}} < +\infty$. Moreover, the matrix B is composed with polynomials of three variables. Since $\mathbb{E} \left(Q(\mathbf{X})^{16} \right) < +\infty$ then by using Lemma 3.C.1 and by continuity of polynomial functions, it yields that $\sup_{h \in (0,1)} \sup_{\lambda \in [0,1]} \mathbb{E} \left(\|B \left(\lambda \widehat{\theta} + (1 - \lambda) \mu_m + h \mathbf{u} \right)\|_F^8 \right)$ is bounded. Finally, by relying on Lemma 3.D.1, $\mathbb{E} \left(h + \widehat{\theta}_1 - \widehat{\theta}_2^2 \right)^{-24}$ is a bounded by $\frac{1}{\left(\text{Var}(\mathbb{E}[\varphi(\mathbf{X}, Z) | \mathbf{X}]) \right)^{24}}$ as $n, m \rightarrow +\infty$. Therefore, Assumption 5 is satisfied.

Proof of Lemma 3.D.1

Let $h \in (0, 1)$ be fixed. The function $\beta_h : x \mapsto 1/(h + x)^\alpha$ is continuously differentiable such that its first derivative is uniformly bounded on \mathbb{R}_+ by $1/h^{\alpha+1}$ then it is Lipschitz. Therefore:

$$\begin{aligned}
\mathbb{E} \left(\beta_h \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 \right) - \beta_h \left(\theta_1 - \theta_2^2 \right) \right)^2 &\leq \frac{1}{h^{2\alpha+2}} \mathbb{E} \left(\widehat{\theta}_1 - \widehat{\theta}_2^2 - \theta_1 + \theta_2^2 \right)^2 \\
&\leq \frac{2}{h^{2\alpha+2}} \left(\text{Var}(\widehat{\theta}_1) + \text{Var}(\widehat{\theta}_2^2) + \left(\mathbb{E}(\widehat{\theta}_2^2) - \theta_2^2 \right)^2 \right),
\end{aligned}$$

using convexity inequality. Based on Marcinkiewicz-Zygmund inequality (see Theorem 3.H.1) and Lemma 3.C.1, it follows that

$$\lim_{n,m \rightarrow \infty} \left((\text{Var}(\widehat{\theta}_1) + \text{Var}(\widehat{\theta}_2^2) + (\mathbb{E}(\widehat{\theta}_2^2) - \theta_2^2)^2 \right) = 0.$$

Straightforwardly:

$$\lim_{n,m \rightarrow \infty} \mathbb{E} \left(\frac{1}{(h + (\widehat{\theta}_1 - \widehat{\theta}_2^2)^\alpha)} \right) = \frac{1}{(h + \theta_1 - \theta_2^2)^\alpha} \leq \frac{1}{\text{Var}(Q(\mathbf{X}))^\alpha}.$$

3.E Proof of Corollary 1

Relying on Theorem 1 , it holds that:

$$\begin{aligned} \limsup_{n,m \rightarrow \infty} \mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 &\leq 3 \limsup_{n,m \rightarrow \infty} (1 + p_{n,m}(h)) (\Delta_{n,m}(h) + V_{n,m}(h) + B_m(h)^2) \\ &\leq 3 \left(\tilde{C}h^2 + (g(\theta + h\mathbf{u}) - g(\theta))^2 \right). \end{aligned}$$

Notice that the MSE is independent of h . Moreover, \tilde{C} is also independent of h . Thus, relying on the continuity of g and taking the limit as $h \rightarrow 0$ yields that:

$$\limsup_{n,m \rightarrow \infty} \mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 = 0.$$

Hence $\lim_{n,m \rightarrow \infty} \mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 = 0$.

3.F Proof of Proposition 2

The problem of optimal rate comes down to find $\beta_{max} = \max\{\beta \geq 0 \mid T^\beta \text{BVT} = O(1)\}$. Using $\text{BVT} = O(T^{\eta-1} + T^{-2\eta})$ yields $T^\beta \text{BVT} = O(T^{\beta+\eta-1} + T^{\beta-2\eta})$. Thus, to obtain condition $T^\beta \text{BVT} = O(1)$, it suffices that:

$$\begin{cases} \beta + \eta - 1 \leq 0 \\ \beta - 2\eta \leq 0 \end{cases} \quad (3.23)$$

The maximal value of β that satisfies the system (3.23) is $\beta_{max} = 2/3$. This maximal value corresponds to $\eta = 1/3$. Therefore, m and n are respectively of order $T^{1/3}$ and $T^{2/3}$.

3.G Proof of Proposition 3

Choose f , φ and a law for \mathbf{X} such that $\varphi(\mathbf{X}, Z) \in (a, b)$ almost surely, where $0 < a < b$. Thus, there exists $C > 0$ such that $\widehat{\theta}_1 - \widehat{\theta}_2^2 \leq \frac{1}{C}$. Hence:

$$\mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 \geq C \mathbb{E} \left(\widehat{\theta}_3 - \widehat{\theta}_2^2 - g(\theta)(\widehat{\theta}_1 - \widehat{\theta}_2^2) \right)^2 \quad (3.24)$$

Let:

$$\begin{cases} \widehat{\varepsilon}_1 = \widehat{\theta}_1 - \theta_1 \\ \widehat{\varepsilon}_2 = \widehat{\theta}_2^2 - \theta_2^2 \\ \widehat{\varepsilon}_3 = \widehat{\theta}_3 - \theta_3 \end{cases}$$

Using the definition of g , Equation (3.24) leads to:

$$\mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 \geq C \mathbb{E} \left(-g(\theta)\widehat{\varepsilon}_1 - (1 - g(\theta))\widehat{\varepsilon}_2 + \widehat{\varepsilon}_3 \right)^2. \quad (3.25)$$

Tedious but standard calculations show that

$$\begin{aligned} \mathbb{E}(\widehat{\varepsilon}_1)^2 &= \frac{P_1(\frac{1}{m})}{n} + \left(\frac{cste}{m} \right)^2 \\ \mathbb{E}(\widehat{\varepsilon}_2\widehat{\varepsilon}_1) &= \frac{P_2^{(1)}(\frac{1}{m})}{n^2} + \frac{P_2^{(2)}(\frac{1}{m})}{n} \\ \mathbb{E}(\widehat{\varepsilon}_3\widehat{\varepsilon}_1) &= \frac{P_3(\frac{1}{m})}{n} \\ \mathbb{E}((1 - g(\theta))\widehat{\varepsilon}_2 - \widehat{\varepsilon}_3)^2 &= \frac{P_4^{(1)}(\frac{1}{m})}{n^2} + \frac{P_4^{(2)}(\frac{1}{m})}{n} \end{aligned}$$

where $P_i^{(j)}(\frac{1}{m})$, $i = 1, \dots, 4$, $j = 1, 2$, are polynomials in $\frac{1}{m}$ of degree at most 3. Hence, letting $R(\frac{1}{m})$ be a polynomial in $\frac{1}{m}$ of degree at most 3, the MSE satisfies:

$$\mathbb{E} \left(g(\widehat{\theta}) - g(\theta) \right)^2 \geq \frac{R(\frac{1}{m})}{n} + \left(\frac{cste}{m} \right)^2 + O(n^{-2}).$$

Since the lower bound has rate $T^{2/3}$ with $m = T^{1/3}$ and $n = T^{2/3}$, it follows that, under the constraint $nm = T$ and for $T \rightarrow \infty$, the rate of the MSE is at least $T^{2/3}$.

3.H The Marcinkiewicz-Zygmund inequality

Theorem 3.H.1 (Marcinkiewicz and Zygmund (1937)). *Let U_1, \dots, U_n be i.i.d. random variables such that $\mathbb{E}(U_1) = 0$ and $\mathbb{E}|U_1|^q < +\infty$, where $1 \leq q < +\infty$. There exist A_q and B_q depending only on q such that:*

$$A_q \mathbb{E} \left(\left(\sum_{i=1}^n |U_i|^2 \right)^{\frac{q}{2}} \right) \leq \mathbb{E} \left(\left| \sum_{i=1}^n U_i \right|^q \right) \leq B_q \mathbb{E} \left(\left(\sum_{i=1}^n |U_i|^2 \right)^{\frac{q}{2}} \right)$$

Furthermore, there exists C_q independent from n such that:

$$\mathbb{E} \left(\left| \frac{1}{n} \sum_{i=1}^n U_i \right|^q \right) \leq \frac{C_q}{n^{\frac{q}{2}}}. \quad (3.26)$$

Exploiting deterministic algorithms to perform global sensitivity analysis for continuous-time Markov chain compartmental models with application to epidemiology

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This chapter discusses the specific context of stochastic models in epidemiology. It is devoted to compartmental epidemic models based on continuous-time Markov chains. The pursued goal is to evaluate the contributions of both uncertain parameters and intrinsic randomness. In order to do so, an approach that allows to separate the intrinsic randomness from uncertain parameters using Gillespie algorithms is presented.

4.1 Introduction

The increasing use of mathematical modeling leads to an enhanced complexity of computational models. These models can be seen as mappings which take inputs and return random or deterministic outputs. If the output is random, two evaluations of the model at the same input generate different realizations: the model is said to be stochastic. Otherwise, the model is deterministic.

Stochastic models are often used in epidemiology. Indeed, in order to study and control the spread of infectious diseases in populations (humans, animals or plants), stochastic compartmental models enable to describe epidemic dynamics by incorporating randomness associated with biological and contact events. They consist in dividing the population into disjoint groups with respect to the different health statuses that are considered. The groups form the compartments of the model. As health statuses of individuals change over time, there are transitions between compartments. These transitions occur at random times and depend on numerous uncertain parameters (also called the input hereafter). Even by fixing uncertain parameters, the number of individuals in each compartment varies randomly over time. Therefore, the corresponding process is stochastic and under some modeling assumptions it is a continuous-time Markov chain (CTMC).

Very often, transition parameters of CTMC are poorly known. In order to better characterize and predict epidemic spread and assess corresponding control strategies, it is important to identify key parameters of the infection spread accounting parameter uncertainty. For this purpose, global sensitivity analysis (GSA) can be used. GSA enables to assess influence of uncertain parameters on the model output. However, performing GSA for stochastic model output is challenging. Unlike deterministic models, stochastic models include two sources of uncertainty: parameter uncertainty and intrinsic randomness. Indeed, intrinsic randomness originates from latent random variables that are generally assimilated to noise when performing sensitivity analysis. So far, several approaches have been introduced.

The pragmatic approach for this purpose consists in performing GSA on both conditional expectation and conditional variance of the model output with respect to uncertain parameters. Both quantities are averaged quantities

over the intrinsic randomness of the stochastic model. In practice, this comes down to estimate Sobol' indices (Sobol', 1993) for two deterministic models. This approach is often used in practice in various applications, for instance in: Courcoul et al. (2011) to identify key parameters of a model describing the spread of an animal disease in a cattle herd; Rimbaud et al. (2018) for a model describing the spatio-temporal spread of plant pathogens; Richard et al. (2021) for a SARS-CoV-2 spread model, Cristancho Fajardo et al. (2021) for a theoretical metapopulation model. However, this approach can suffer from inconsistent conclusions. Since GSA is performed separately on conditional mean and conditional variance, a parameter can appear to be important for a quantity and not for the other one. One can check this on the toy example given by $Y = X_1 + X_2 Z$ with X_1, X_2, Z i.i.d. under standard normal distribution such that X_1, X_2 are the inputs and Z stands for the intrinsic randomness variable. In this example, the first-order indices of X_1 and X_2 of the conditional expectation are respectively $S_{X_1} = 1$ and $S_{X_2} = 0$ whereas those of the conditional variance are $S_{X_1} = 0$ and $S_{X_2} = 1$. Moreover, in Mazo (2021) it is shown that the Monte-Carlo estimator of first order Sobol' indices for conditional mean with respect to input is biased. So, estimation accuracy issues arise.

In addition, conditional expectations with respect to inputs require an averaging over the intrinsic randomness variable since the law of the latter is unknown. This induces a loss of information as this averaging affects inputs that interact with intrinsic randomness. In order to avoid this loss, Hart et al. (2017) introduced new sensitivity indices. For this purpose, Sobol'-Hoeffding decomposition is interpreted as a random decomposition, where the randomness is due to the intrinsic noise; corresponding Sobol' indices can also be considered as random. The sensitivity indices proposed by Hart et al. (2017) are then defined as expectations of the random Sobol' indices. However, they do not fully reflect interactions between intrinsic randomness and uncertain parameters.

Recently, new methods have been developed for stochastic models. They rely on a paradigm shift in the way of dealing with intrinsic stochasticity. The stochastic model is interpreted as a deterministic model with values in the set of probability distributions on the original output space. Fort et al. (2021) and Da Veiga (2021) consider this approach and define new sensitivity indices well-suited to deterministic models with output valued in a set of probability distributions. This approach has the advantage of setting a framework in which stochastic output models are deterministic but it does not allow to assess the interactions between the intrinsic randomness and uncertain parameters.

Furthermore, it should be noted that even though stochastic models are less studied than deterministic ones, not all types of stochastic models have received the same attention from the sensitivity analysis community. The most

studied stochastic models are based on stochastic differential equation (see, e.g. [Le Maître and Knio \(2015\)](#), [Jimenez et al. \(2017\)](#), [Étoré et al. \(2020\)](#)). For these types of models, methods based on Polynomial Chaos Expansion meta-modeling have been proposed. Conversely, there are few GSA methods for models based on jump processes (Poisson processes, Markov chains, piecewise-deterministic jump processes). Generally, for these models, black-box or meta-model based GSA are proposed (e.g. [Marrel et al. \(2012\)](#), [Zhu and Sudret \(2021a\)](#)).

In this paper, we focus on continuous-time Markov based models. We develop an approach for performing GSA for such models. This approach consists first in representing the model outputs as deterministic functions of a random vector of uncertain parameters and intrinsic randomness with known probability distribution and then in exploiting the resulting representation for GSA. This enables to put model output under a deterministic form so that contribution of uncertain parameters and intrinsic randomness as well as interaction of both can be assessed. Concretely, we study the continuous-time Markov chain given by the stochastic process that counts over time the number of individuals in each compartment of epidemic compartmental models. We rely on Gillespie Stochastic Simulation Algorithm ([Gillespie, 1977](#)) allowing exact simulation of Markov chains from which we derive a new representation. Furthermore, we include a second representation, the random time change introduced by ([Kurtz, 1982](#)) and studied in [Navarro Jimenez et al. \(2016\)](#) so as to achieve comparison of GSA results between the two representations. We apply the two approaches to a SARS-CoV-2 spread model.

The paper is organized as follows. In Section [4.2](#) we set the framework of stochastic models and associated representations. The definition of Sobol' indices is reminded and dependence of GSA results on the choice of the representation is discussed. Section [4.3](#) is dedicated to the description of representations of continuous-time Markov chains. For this purpose, we describe compartmental models and we discuss two different representations: Gillespie and Kurtz. In Section [4.4](#), we present the application of our approach to a SARS-CoV-2 spread model. This section includes a description of the model, the GSA results and comparison elements between the results obtained with the two different representations of the model introduced in Section [4.3](#).

4.2 The general approach

This section is devoted to introducing (Subsection [4.2.2](#)) the concept of stochastic model representation under a deterministic form. Under such a form, GSA methods for deterministic models can be applied to perform sensitivity analysis. For this, the definition of the so-called Sobol' indices is briefly reminded in Subsection [4.2.1](#) in the context of deterministic models with scalar or func-

tional outputs. In Subsection 4.2.3, we discuss the question of the dependence of GSA results to the choice of the representation of the stochastic model.

4.2.1 Global sensitivity analysis for deterministic functions

Let us consider a deterministic model g with input $\mathbf{X} = (X_1, \dots, X_m)$ and output $Y = g(\mathbf{X})$ so that $\mathbb{E}[\|g(\mathbf{X})\|^2] < +\infty$ and X_1, \dots, X_m are mutually independent. For such a model, the definition of first-order and total Sobol' indices (Homma and Saltelli, 1996) is reminded according to two frameworks: a scalar output $Y = g(\mathbf{X}) \in \mathbb{R}$ and a functional output $g(\mathbf{X}) = (q(t, \mathbf{X}); t \in \{t_0, \dots, T\})$ for which dynamical and aggregated Sobol' indices are introduced.

In scalar case, first-order and total Sobol' indices (Sobol', 1993) associated to each input $X_j, j = 1, \dots, m$ are defined as:

$$S_{X_j} = \frac{\text{Var}(\mathbb{E}[g(\mathbf{X}) | X_j])}{\text{Var}(g(\mathbf{X}))},$$

$$S_{X_j}^T = 1 - \frac{\text{Var}(\mathbb{E}[g(\mathbf{X}) | X_1, \dots, X_{j-1}, X_{j+1}, \dots, X_m])}{\text{Var}(g(\mathbf{X}))}.$$

In the functional case, we focus on two types of indices: dynamical Sobol' indices and aggregated Sobol' indices. Considering each random variable $q(t, \mathbf{X})$, sensitivity indices such as first-order Sobol' indices and total Sobol' indices can be obtained as in scalar case for each time t as $\mathbb{E}[q(t, \mathbf{X})^2]$ is finite. Regarding aggregated Sobol' indices, note that output $g(\mathbf{X})$ is multidimensional so that according to Lamboni et al. (2011) and Gamboa et al. (2014), first-order and total Sobol' indices associated to each input $X_j, j = 1, \dots, m$ are respectively given by:

$$GSI_{X_j} = \frac{\text{Trace}[\text{Var}(\mathbb{E}[g(\mathbf{X}) | X_j])]}{\text{Trace}[\text{Var}(g(\mathbf{X}))]},$$

$$GSI_{X_j}^T = 1 - \frac{\text{Trace}[\text{Var}(\mathbb{E}[g(\mathbf{X}) | X_1, \dots, X_{j-1}, X_{j+1}, \dots, X_m])]}{\text{Trace}[\text{Var}(g(\mathbf{X}))]},$$

where $\text{Var}(\mathbb{E}[g(\mathbf{X}) | X_j])$ and $\text{Var}(g(\mathbf{X}))$ are the variance-covariance matrices of the random vectors $\mathbb{E}[g(\mathbf{X}) | X_j]$ and $g(\mathbf{X})$, respectively.

4.2.2 Deterministic representations of stochastic models

In the following, a stochastic model g is defined as a random function taking $\theta \in \Theta \subset \mathbb{R}^p$ as input and producing an output $g(\theta)$ which is a random variable with values in a set \mathcal{Y} . If $f : \Theta \times \mathcal{Z} \rightarrow \mathcal{Y}$ is a deterministic function and Z

is a random element valued in a set \mathcal{Z} such that $(\mathbf{X}, g(\mathbf{X}))$ and $(\mathbf{X}, f(\mathbf{X}, Z))$ are identically distributed, then the couple (f, Z) is said to be a deterministic representation of the stochastic model g . An example of stochastic model with two representations is provided in Example 6.

Example 6 (Toy example). Let $U \sim \mathcal{U}([0, 1])$ independent of $(\mathbf{X}, Z, Z_1, Z_2) \sim \mathcal{N}(0_{\mathbb{R}^4}, Id_4)$. Consider the stochastic model g with input \mathbf{X} and output $g(\mathbf{X}) = \mathbf{X} + Z$. This model can be represented by using $f(\mathbf{X}, Z_1, Z_2) = \mathbf{X} + \frac{1}{\sqrt{2}}(Z_1 + Z_2)$ or $f'(\mathbf{X}, U) = \mathbf{X} + \Phi^{-1}(U)$, where Φ is the cumulative distribution function of the standard normal distribution.

The function f is not necessarily explicit. It can correspond to an algorithm. Proposition 4 (see Appendix 4.B for the proof) provides a sufficient condition for a couple (f, Z) to be a representation of a stochastic model g .

Proposition 4. Assume that \mathbf{X} and Z are independent. Moreover, assume that for all $\theta \in \Theta$, $g(\theta)$ and \mathbf{X} are independent and the probability distributions of $g(\theta)$ and $f(\theta, Z)$ are identical. Then (f, Z) is a deterministic representation of the stochastic model g .

Representing stochastic models under deterministic form is useful in GSA. If both the probability distribution of Z and the function f are known, then the stochastic model becomes a deterministic model with inputs (\mathbf{X}, Z) . Hence, all the standard methods of GSA such as those presented in Subsection 4.2.1 can be applied. Therefore, contribution of Z and its interaction with uncertain parameters can be assessed.

However, as already discussed (see Example 6), a stochastic model may admit several representations. Indeed, the way to simulate a random variable is not unique, leading to different stochastic simulators. Considering two distinct representations (f, Z) and (f', Z') of the same stochastic model necessarily yields that the joint probability distributions of $(\mathbf{X}, f(\mathbf{X}, Z))$ and $(\mathbf{X}, f'(\mathbf{X}, Z'))$ are identical. However, the intrinsic randomness elements Z and Z' and functions f and f' may differ from one representation to the other. A natural question is then whether GSA results depend on the chosen representation. The answer is yes; this point is discussed in Subsection 4.2.3.

4.2.3 Dependence of global sensitivity analysis on model representation

In Subsection 4.2.2, it appears that representation always preserves the probability distribution of $(\mathbf{X}, g(\mathbf{X}))$. Our aim in this section is to prove that the results of GSA depends on the choice of representation.

Let us consider (f, Z) and (f', Z') two distinct representations of the stochastic model g with input $\mathbf{X} = (X_1, \dots, X_m)$ and output $g(\mathbf{X})$. By definition,

$(\mathbf{X}, g(\mathbf{X})) \sim (\mathbf{X}, f(\mathbf{X}, Z)) \sim (\mathbf{X}, f'(\mathbf{X}, Z'))$. If u is a subset of $\{1, \dots, m\}$, then:

$\mathbb{E}[f(\mathbf{X}, Z) | \mathbf{X}_u] = \mathbb{E}[f'(\mathbf{X}, Z') | \mathbf{X}_u]$ almost surely with $\mathbf{X}_u = \{X_j, j \in u\}$ (see Mazo (2021)). So, it yields:

$$\frac{\text{Var}(\mathbb{E}[f(\mathbf{X}, Z) | \mathbf{X}_u])}{\text{Var}(f(\mathbf{X}, Z))} = \frac{\text{Var}(\mathbb{E}[f'(\mathbf{X}, Z') | \mathbf{X}_u])}{\text{Var}(f'(\mathbf{X}, Z'))}.$$

It implies that closed Sobol' indices associated to $\mathbf{X}_u, u \subseteq \{1, \dots, m\}$ are representation-free, i.e. they do not depend on the chosen representation. A straightforward consequence is the invariance of first-order Sobol' indices associated to each $X_j, j = 1, \dots, m$, and of the total Sobol' index associated to Z with respect to the choice of the representation.

However, $\mathbb{E}[f(\mathbf{X}, Z) | (\mathbf{X}_u, Z)]$ and $\mathbb{E}[f'(\mathbf{X}, Z') | (\mathbf{X}_u, Z')]$ may have different probability distributions. Indeed, since $(f, Z) \neq (f', Z')$, the way each function f or f' combines its relative intrinsic randomness variable with input \mathbf{X} to generate outputs is different. So, differences can appear on some quantities such as conditional expectations with respect to a group of random variables that includes the intrinsic randomness variable. This is illustrated in Example 7.

Example 7. Let X be a random variable independent of Z and Z' where Z and Z' are i.i.d. under $\mathcal{N}(0, 1)$. Define two functions: $f(X, Z) = XZ$ and $f'(X, Z') = X^2Z'$. If X is distributed such that $\mathbb{P}(X = -1) = \mathbb{P}(X = 1) = \frac{1}{2}$ then $(X, f(X, Z)) \sim (X, f'(X, Z'))$. So (f, Z) and (f', Z') represent the same stochastic model but:

$$\mathbb{E}[f(X, Z) | Z] = 0 \quad \mathbb{E}[f'(X, Z') | Z'] = Z'.$$

First-order Sobol' indices of intrinsic randomness in the two representations are given by: $S_Z(f) := \frac{\text{Var}(\mathbb{E}[f(X, Z) | Z])}{\text{Var}(f(X, Z))} = 0$ while $S_Z(f') := \frac{\text{Var}(\mathbb{E}[f'(X, Z') | Z'])}{\text{Var}(f'(X, Z'))} = 1$. And total Sobol' indices of X in the two representations are different: $S_X^T(f) = 1 - S_Z(f) = 1$ and $S_X^T(f') = 1 - S_Z(f') = 0$. Consequently, first-order Sobol' index associated to intrinsic randomness depends on the choice of the representation.

Via a counter-example (see Example 7) and theoretical elements, we showed that GSA results depend on the choice of the representation. This point is illustrated in Section 4.4 in the context of GSA of continuous-time Markov chain based models, which are the models of interest in this paper.

4.3 Deterministic representations of CTMC stochastic compartmental models

In this section, we discuss two different representations for CTMC stochastic compartmental models. The section is organized as follows. In Subsection 4.3.1, we provide a description of the CTMC under study by using graph formalism to represent compartmental models. In Subsection 4.3.2, we present the representation detailed in Navarro Jimenez et al. (2016) and then we introduce a new representation based on Gillespie Stochastic Simulation Algorithm (SSA).

4.3.1 CTMC stochastic compartmental models

Consider a closed population that includes N individuals (i.e. N remains constant over time). Assume that an epidemic outbreaks within this population. Individuals can be susceptible or at various stages of infections. So, at each time, each individual is in a certain health status. Then, individuals are grouped according to their health status. The resulting groups form a partition (compartment). Let \mathbf{V} be the set of compartments. As health status of each individual can change over time, transitions can take place between compartments. A transition always involves two different compartments, say $\alpha, \beta \in \mathbf{V}$ such that $\alpha \neq \beta$. A pair of compartments (α, β) between which transitions are possible defines a type of transition occurring in the direction $\alpha \rightarrow \beta$. So, the pair (α, β) forms an arrow. An individual can move from a compartment α to another β only if there is an arrow from α to β . To each arrow is associated a vector $\mathbf{u}_{\alpha, \beta} \in \{-1, 0, +1\}^{\text{card } \mathbf{V}}$ whose components are zero except at the components corresponding to α and β which are equal to -1 and $+1$ respectively. Denote \mathbf{E} the set of arrows and n_E its cardinal. The couple $\mathcal{G} = (\mathbf{V}, \mathbf{E})$ is a directed graph with vertices \mathbf{V} and edges \mathbf{E} .

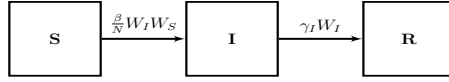
The intensities of transitions between compartments depend on the specific parameters θ of the epidemic. As θ is generally unknown, let $\Theta \subset \mathbb{R}^d$ be the set of all possible parameters θ . We are interested in the dynamics of the number of individuals in each compartment over time, which are stochastic since transitions occur at random times. Let $W_\alpha^\theta(t)$ denote the number of individuals in compartment α at time t and suppose that the initial state $\xi_0 \in \{0, \dots, N\}^{\text{card } \mathbf{V}}$ of the process $W^\theta := \{(W_\alpha^\theta(t))_{\alpha \in \mathbf{V}}; t \geq 0\}$ is known. Assume that for each $\theta \in \Theta$, the stochastic process W^θ is a homogeneous continuous-time Markov chain with state space \mathcal{E} defined as the smallest subset of $\{0, \dots, N\}^{\text{card } \mathbf{V}}$ that contains all the vectors of the form $\xi_0 + \sum_{i=1}^n \mathbf{u}_{\alpha^{(i)}, \beta^{(i)}}$ where $n \in \mathbb{N}$ and $(\alpha^{(i)}, \beta^{(i)}) \in \mathbf{E}$ for all $i = 1, \dots, n$. The generator \mathcal{Q}_θ of W^θ is characterized by nonnegative rate functions $g_{\alpha, \beta}$ defined by:

$g_{\alpha,\beta}(\theta, \xi) = \lim_{\varepsilon \rightarrow 0} \frac{1}{\varepsilon} \mathbb{P}(W^\theta(s + \varepsilon) = \xi + \mathbf{u}_{\alpha,\beta} \mid W^\theta(s) = \xi)$ for $\xi \in \mathcal{E}$ and $s \geq 0$ so that the element of the generator at the row corresponding to $\xi \in \mathcal{E}$ and column corresponding to $\xi' \in \mathcal{E}$ is given by:

$$Q_\theta(\xi, \xi') = \begin{cases} g_{\alpha,\beta}(\theta, \xi) & \text{if } \xi' = \xi + \mathbf{u}_{\alpha,\beta} \\ -\sum_{(\alpha',\beta') \in \mathbf{E}} g_{\alpha',\beta'}(\theta, \xi) & \text{if } \xi' = \xi \\ 0 & \text{otherwise.} \end{cases}$$

Every transition $\xi \rightarrow \xi + \mathbf{u}_{\alpha,\beta}$ of type $(\alpha, \beta) \in \mathbf{E}$ occurs at rate $g_{\alpha,\beta}(\theta, \xi)$.

Example 8. Let us consider the classical SIR model:



There are three compartments $\mathbf{V} = \{S, I, R\}$ and two types of transitions: infection (S, I) and removal (I, R) so that $\mathbf{E} = \{(S, I), (I, R)\}$. Infection is characterized by transition vector $\mathbf{u}_{S,I} = (-1, +1, 0)$ and rate function $g_{S,I} = \frac{\beta}{N} W_I W_S$. Removal has transition vector $\mathbf{u}_{I,R} = (0, -1, +1)$ and rate function $g_{I,R} = \gamma_I W_I$.

Commonly, Gillespie direct method is used to simulate continuous-time Markov chains. Algorithm 8 provides instructions intended to simulating paths of the process W^θ for a given $\theta \in \Theta$.

Algorithm 8 Gillespie SSA (direct method)

Inputs: θ

Require: $\xi_0, T, \{g_{\alpha^{(j)},\beta^{(j)}}, \mathbf{u}_{\alpha^{(j)},\beta^{(j)}}; j = 1, \dots, n_E\}$

- 1: $t \leftarrow 0, W(t) \leftarrow \xi_0$
 - 2: **while** $t < T$ **do**
 - 3: $\lambda \leftarrow \sum_{j=1}^{n_E} g_{\alpha^{(j)},\beta^{(j)}}(\theta, W(t))$
 - 4: Draw τ with exponential distribution with mean $1/\lambda$
 - 5: **for** $j = 1 \dots n_E$ **do**
 - 6: $p_j \leftarrow g_{\alpha^{(j)},\beta^{(j)}}(W(t), \theta) / \lambda$
 - 7: **end for**
 - 8: Draw U with standard uniform distribution
 - 9: Pick $l \in \{1, \dots, n_E\}$ with distribution (p_1, \dots, p_{n_E}) using U
 - 10: $W(t + \tau) \leftarrow W(t) + \mathbf{u}_{\alpha^{(l)},\beta^{(l)}}$
 - 11: $t \leftarrow t + \tau$
 - 12: **end while**
-

4.3.2 Deterministic representations

Assume that the random vector \mathbf{X} models the parameter uncertainty. Then, consider the stochastic model $(\mathbf{X}, W^{\mathbf{X}})$. For simplicity, let denote $W^{\mathbf{X}}$ by \mathbf{W} . We seek deterministic representations (f, Z) of (\mathbf{X}, \mathbf{W}) , i.e. such that the probability distribution of Z is known. For this aim, thanks to Proposition 4, it is sufficient to find Z independent of \mathbf{X} and f such that: for all $\theta \in \Theta$, $W^\theta \sim f(\cdot, \theta, Z) = \{f(t, \theta, Z); t \in [0, T]\}$. In the following, we discuss two representations of (\mathbf{X}, \mathbf{W}) . We present the random-time change representation studied in [Le Maître et al. \(2015\)](#) and [Navarro Jimenez et al. \(2016\)](#) and introduce the new representation based on Gillespie algorithm.

4.3.2.1 Random time change representation

The random time change representation is based on the random time change decomposition of the process W^θ for each $\theta \in \Theta$. This decomposition has been introduced by [Ethier and Kurtz \(1986\)](#). Consider the vector $Z^K = (Z_{\alpha, \beta})_{(\alpha, \beta) \in \mathbf{E}}$ of independent unit-rate Poisson processes $Z_{\alpha, \beta}(\cdot)$. [Kurtz \(1982\)](#) showed that there exists a function f_K satisfying

$$f_K(t, \theta, Z^K) = \xi_0 + \sum_{(\alpha, \beta) \in \mathbf{E}} Z_{\alpha, \beta} \left(\int_0^t g_{\alpha, \beta}(\theta, f_K(s, \theta, z^K)) ds \right) \mathbf{u}_{\alpha, \beta},$$

which defines a continuous-time Markov chain with initial state ξ_0 and generator \mathcal{Q}_θ . So, $f_K(\cdot, \theta, Z^K) \sim W^\theta$ for all $\theta \in \Theta$. In addition, Z^K does not depend on Θ . By construction, \mathbf{X} and Z^K are independent. Hence (f_K, Z^K) defines a representation of (\mathbf{X}, \mathbf{W}) .

For each $(\alpha, \beta) \in \mathbf{E}$, $Z_{\alpha, \beta}$ stands for the intrinsic noise of the reaction or type of transition (α, β) . So, Z^K includes intrinsic noise of each reaction channel or type of transition. Since the Poisson processes $Z_{\alpha, \beta}$, $(\alpha, \beta) \in \mathbf{E}$ that compose Z^K are mutually independent, then this representation enables to assess contribution of intrinsic noise of each reaction channel or type of transition as well as that of the whole intrinsic randomness Z^K . [Le Maître et al. \(2015\)](#) and [Navarro Jimenez et al. \(2016\)](#) used this representation to perform GSA for chemical reaction network models in order to estimate contribution of uncertain parameters and reaction channel intrinsic noises. In practice, simulation of this representation relies on the Modified Next Reaction Method (MNRM) developed by [Anderson \(2007\)](#) and provided in Algorithm 9 ([Navarro Jimenez et al., 2016](#)).

Algorithm 9 Modified Next Reaction Method

Inputs: θ

Require: $\xi_0, T, \{g_{\alpha^{(j)}, \beta^{(j)}}, \mathbf{u}_{\alpha^{(j)}, \beta^{(j)}}; j = 1, \dots, n_E\}$

- 1: **for** $j = 1 \dots n_E$ **do**
- 2: Draw r_j from RG_j
- 3: $t_j \leftarrow 0, t_j^+ \leftarrow -\log(r_j)$
- 4: **end for**
- 5: $t \leftarrow 0, W(t) \leftarrow \xi_0$
- 6: **while** $t < T$ **do**
- 7: **for** $j = 1 \dots n_E$ **do**
- 8: Evaluate $a_j = g_{\alpha^{(j)}, \beta^{(j)}}(\theta, W(t))$ and $dt_j = \frac{t_j^+ - t_j}{a_j}$
- 9: **end for**
- 10: $s \leftarrow \operatorname{argmin}_j dt_j$
- 11: $W(t + dt_s) \leftarrow W(t) + \mathbf{u}_{\alpha^{(s)}, \beta^{(s)}}$
- 12: $t \leftarrow t + dt_s$
- 13: **for** $j = 1 \dots n_E$ **do**
- 14: $t_j \leftarrow t_j + a_j \cdot dt_s$
- 15: **end for**
- 16: Get r_s from RG_s and set $t_s^+ \leftarrow t_s^+ - \log(r_s)$
- 17: **end while**

4.3.2.2 Gillespie representation

Gillespie SSA is widely used to simulate Markov chains. Especially, in epidemiology, many CTMC model simulators are based on this algorithm. Both Gillespie SSA and the Modified Next Reaction Method generate statistically exact paths of CTMC including W^θ : they are stochastically equivalent. However, representations of (\mathbf{X}, \mathbf{W}) derived from these two algorithms can lead to different sensitivity analysis results corresponding to different information as the interpretation of intrinsic noise is not the same for both representations. In the following, we introduce a representation of (\mathbf{X}, \mathbf{W}) based on Gillespie SSA.

Gillespie SSA simulates two processes: the jump process that provides the jump times of W^θ and the embedded chain that describes successive states of W^θ . Given two independent sequences of i.i.d. standard uniform variables $\mathbf{U}^1 = (U_1^1, U_2^1, \dots)$ and $\mathbf{U}^2 = (U_1^2, U_2^2, \dots)$, assume that the jump process is simulated from \mathbf{U}^1 and the embedded chain from \mathbf{U}^2 . In practice, \mathbf{U}^1 and \mathbf{U}^2 are respectively assimilated to two numbers RG_1 and RG_2 which are used as a seed for the random number generator so that setting seed to a value enables to stream random numbers. The resulting algorithm that is detailed in Algorithm 10 is a modification of the Gillespie SSA provided in Algorithm 8:

Algorithm 10

Inputs: $\theta, Z = (RG_1, RG_2)$

Require: $\xi_0, T, \{g_{\alpha^{(j)}, \beta^{(j)}}, \mathbf{u}_{\alpha^{(j)}, \beta^{(j)}}; j = 1, \dots, n_E\}$

- 1: $t \leftarrow 0, W(t) \leftarrow \xi_0, i \leftarrow 1$
- 2: **while** $t < T$ **do**
- 3: **for** $k = 1 \dots 2$ **do**
- 4: Pick U_i^k from RG_k
- 5: **end for**
- 6: $\lambda \leftarrow \sum_{j=1}^{n_E} g_{\alpha^{(j)}, \beta^{(j)}}(\theta, W(t))$
- 7: $t^* \leftarrow -\log(U_i^1)/\lambda$
- 8: **for** $j = 1 \dots n_E$ **do**
- 9: $p_j \leftarrow g_{\alpha^{(j)}, \beta^{(j)}}(W(t), \theta)/\lambda$
- 10: **end for**
- 11: Pick l such that $\sum_{j=1}^{l-1} p_j \leq U_i^2 < \sum_{j=1}^l p_j$
- 12: $W(t+t^*) \leftarrow W(t) + \mathbf{u}_{\alpha^{(l)}, \beta^{(l)}}$
- 13: $t \leftarrow t + t^*$
- 14: $i \leftarrow i + 1$
- 15: **end while**

Let Z^G be the vector $(\mathbf{U}^1, \mathbf{U}^2)$. If $f_G(t, \theta, Z^G)$ denotes the output of Algorithm 10 at time t for input (θ, Z^G) , then the following result holds:

Proposition 5. *Denote $\mathcal{L}([0, 1])$ the space of sequences on $[0, 1]$. The function:*

$$f_G : \mathbb{R}_+ \times \Theta \times \mathcal{L}([0, 1])^2 \longrightarrow \mathcal{E}$$

$$(t, \theta, z^G) \longmapsto f_G(t, \theta, z^G)$$

is such that the continuous-time Markov chains W^θ and $f_G(\cdot, \theta, Z^G) := \{f_G(t, \theta, Z^G); t \geq 0\}$ have the same finite-dimensional distributions.

The proof of Proposition 5 is detailed in Appendix 4.B. Note that Z^G does not depend on θ so that Z^G and \mathbf{X} are independent. Therefore, Propositions 4 and 5 ensure that (f_G, Z^G) is a representation of (\mathbf{X}, \mathbf{W}) . The random vector $Z^G = (\mathbf{U}^1, \mathbf{U}^2)$ stands for the intrinsic randomness variable. Z^G includes two intrinsic noises \mathbf{U}^1 and \mathbf{U}^2 that correspond to intrinsic noises of the jump time process and the embedded discrete chain.

Algorithm 10 aggregates all the types of transition processes to generate the sequence of jump times and the discrete chain. So, intrinsic noise associated to each type of transition $(\alpha, \beta) \in \mathbf{E}$ cannot be identified with this algorithm. Therefore, it is not possible to assess contribution of intrinsic noises of type of transition processes. To overcome this insufficiency, we can rely on the first

reaction method studied by Gillespie (1977) to build a representation allowing to separate the intrinsic noises associated to each type of transition processes.

For this purpose, let Z^G be the random vector $(\mathbf{U}_{\alpha,\beta}, (\alpha, \beta) \in \mathbf{E})$ where each $\mathbf{U}_{\alpha,\beta}$ is a sequence of i.i.d. standard uniform variables and assume that each component of Z^G is identified to a number RG_j with $j = 1, \dots, n_E$. A modification of Gillespie first reaction method algorithm in a similar way as Gillespie direct method yields Algorithm 11:

Algorithm 11

Inputs: $\theta, Z = (RG_1, \dots, RG_{n_E})$

Require: $\xi_0, T, \theta, \{g_{\alpha^{(j)}, \beta^{(j)}}, \mathbf{u}_{\alpha^{(j)}, \beta^{(j)}}; j = 1, \dots, n_E\}$

- 1: $t \leftarrow 0, W(t) \leftarrow \xi_0, i \leftarrow 1$
 - 2: **while** $t < T$ **do**
 - 3: **for** $j = 1 \dots n_E$ **do**
 - 4: Pick $U_{\alpha^{(j)}, \beta^{(j)}}^i$ from RG_j
 - 5: Evaluate $dt_j = \frac{-\log(U_{\alpha^{(j)}, \beta^{(j)}}^i)}{g_{\alpha^{(j)}, \beta^{(j)}}(\theta, W(t))}$
 - 6: **end for**
 - 7: **end while**
 - 8: $l = \operatorname{argmin}_j dt_j$
 - 9: $W(t + dt_l) \leftarrow W(t) + \mathbf{u}_{\alpha^{(l)}, \beta^{(l)}}$
 - 10: $t \leftarrow t + dt_l$
 - 11: $i \leftarrow i + 1$
-

If $f_G(t, \theta, Z^G)$ denotes the output of Algorithm 11 at time t and input (θ, Z^G) , it yields:

Proposition 6. Denote $\mathcal{L}([0, 1])$ the space of sequences on $[0, 1]$. The function:

$$f_G : \mathbb{R}_+ \times \Theta \times \mathcal{L}([0, 1])^{n_E} \longrightarrow \mathcal{E}$$

$$(t, \theta, z^G) \longmapsto f_G(t, \theta, z^G)$$

is such that the continuous-time Markov chains W^θ and $f_G(\cdot, \theta, Z^G) := \{f_G(t, \theta, Z^G); t \geq 0\}$ have the same finite-dimensional distributions.

Proposition 6 provides a new representation of (\mathbf{X}, \mathbf{W}) since \mathbf{X} and Z^G are independent. This representation allows to separate intrinsic randomness into independent intrinsic noises of type of transition processes. The proof of Proposition 6 is detailed in Appendix 4.B.

The intrinsic randomness captures all the variability of the model which does not depend on epidemic parameters. From an epidemiological point of

view, it encompasses the random behavior of individuals and their social interactions, as well as the biological variability between individuals with respect to infection.

4.4 Application to an epidemic model

In this section, we implement our method on a parsimonious SARS-CoV-2 spread model inspired by the literature (Cazelles et al., 2021). We perform variance-based GSA using the two representations: the one analyzed in Navarro Jimenez et al. (2016) and based on the random time change (described in Section 4.3.2.1) and the new one we introduced in Section 4.3.2.2 based on the modification of Gillespie algorithm provided in Proposition 6. The model considered in this section, although not necessarily the most refined from the point of view of application, remains very relevant. Moreover, it should be noted that our approach is generic and can therefore be applied to any other compartmental model.

4.4.1 Description of the model of SARS-CoV-2 spread

The compartmental model in Figure 4.1 is used to describe the spread of SARS-CoV-2 within a closed population with size N . This model includes seven compartments corresponding to seven health states and nine transitions between these states. Indeed, in this model, an individual can be susceptible (S), exposed (E) (i.e. infected but not yet infectious), asymptomatic infectious (A), symptomatic infectious (I), hospitalized (H), recovered (R) or dead (D). Two modeling assumptions can be mentioned. First, infection is neglected within hospitals so that hospitalized individuals cannot infect. Secondly, it is assumed that recovered individuals get perfectly immunized, so they cannot be susceptible after recovering. This assumption is valid on short time intervals.

We are interested in the process $\{(W_S(t), W_E(t), W_A(t), W_I(t), W_H(t), W_R(t), W_D(t)); t \in [0, T]\}$ that takes values in $\mathcal{E} \subset \{0, \dots, N\}^7$ and counts over time the number of individuals in each compartment, where N is the size of the population and $T \in (0, +\infty]$ is the final time of the study. The set of compartments is given by $\mathbf{V} = \{S, E, A, I, H, R, D\}$. The different types of transitions and their characteristics (rate function $g_{\alpha, \alpha'}$ and transition vector $\mathbf{u}_{\alpha, \alpha'}$, where (α, α') denotes a type of transition of the model) are described in Table 4.1.

Rate functions depend on the vector parameter $\theta = (\beta, \gamma_E, \gamma_A, \gamma_I, \gamma_H, p_{(E,A)}, p_{(I,H)}, p_{(I,D)}, p_{(H,D)})$. The interpretation of each of these parameters and their ranges of variation in the sensitivity analysis are provided in Table 5.2.

The process under study is: $W^\theta = \{(W_\alpha(t))_{\alpha \in \mathbf{V}}; t \in [0, T]\}$. Let Θ be the set of all possible values of θ . For all $\theta \in \Theta$, W^θ is assumed to be a

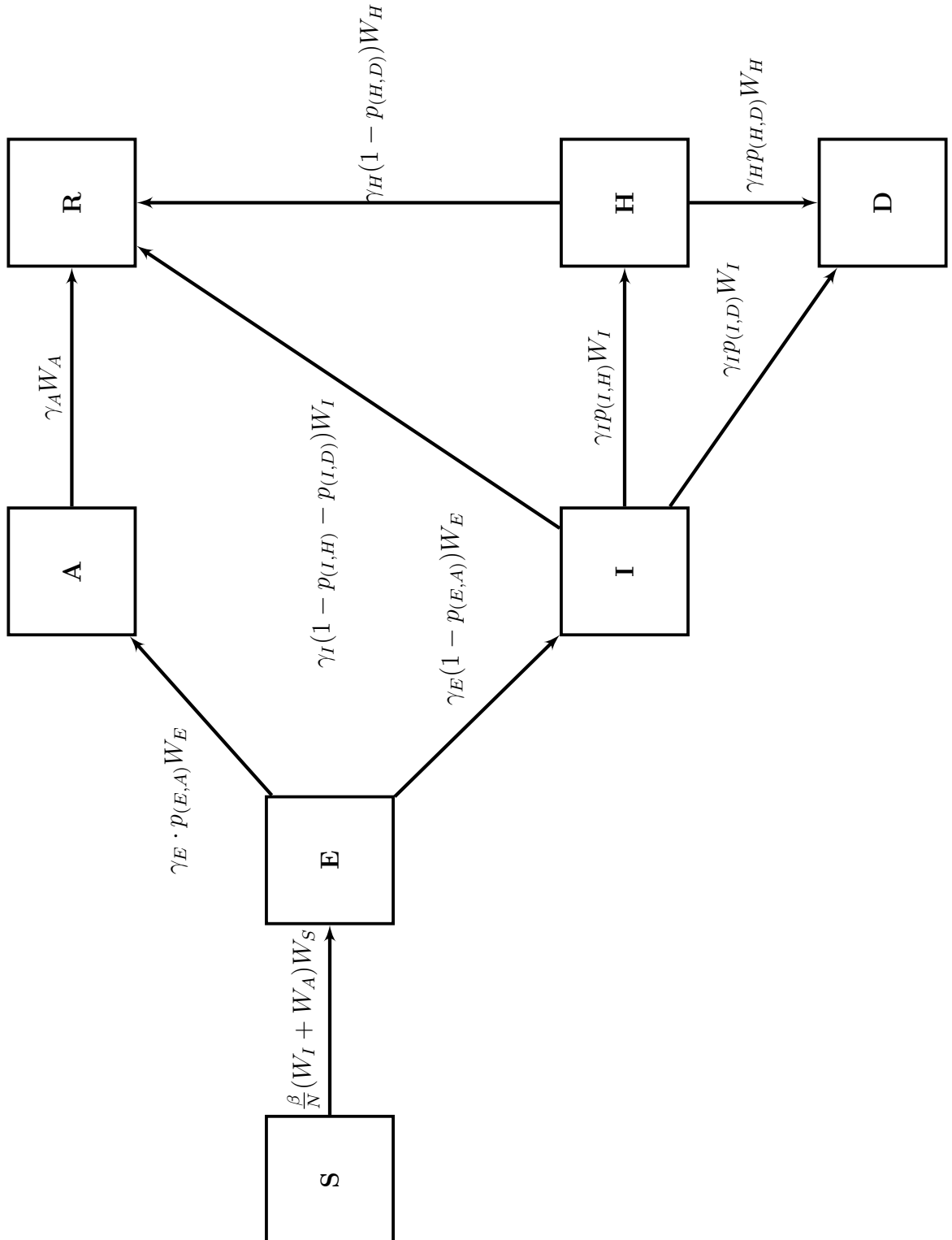


Figure 4.1 – Compartmental model of the spread of SARS-CoV-2 within a population, comprising seven health states (S,E,A,I,H,R,D) and corresponding transition rates. W_α with $\alpha \in \{S, E, A, I, H, R, D\}$ denotes the number of individuals in compartment α .

Type of transition (α, α')	Type	Rate function $(g_{\alpha, \alpha'})$	Transition vector $(\mathbf{u}_{\alpha, \alpha'})$
(S, E)	infection	$\frac{\beta}{N} \cdot W_S \cdot (W_A + W_I)$	$(-1, 1, 0, 0, 0, 0, 0)$
(E, A)	asymptomatic infection activation	$\gamma_E \cdot p_{(E,A)} \cdot W_E$	$(0, -1, +1, 0, 0, 0, 0)$
(E, I)	symptomatic infection activation	$\gamma_E \cdot (1 - p_{(E,A)}) \cdot W_E$	$(0, -1, 0, +1, 0, 0, 0)$
(A, R)	recovery of an asymptomatic	$\gamma_A \cdot W_A$	$(0, 0, -1, 0, 0, +1, 0)$
(I, R)	recovery of a symptomatic	$\gamma_I \cdot (1 - p_{(I,H)} - p_{(I,D)}) \cdot W_I$	$(0, 0, 0, -1, 0, +1, 0)$
(I, H)	hospitalization of a symptomatic	$\gamma_I \cdot p_{(I,H)} \cdot W_I$	$(0, 0, 0, -1, +1, 0, 0)$
(I, D)	death of a symptomatic	$\gamma_I \cdot p_{(I,D)} \cdot W_I$	$(0, 0, 0, -1, 0, 0, +1)$
(H, R)	recovery of a hospitalized	$\gamma_H \cdot (1 - p_{(H,D)}) \cdot W_H$	$(0, 0, 0, 0, -1, +1, 0)$
(H, D)	death of a hospitalized	$\gamma_H \cdot p_{(H,D)} \cdot W_H$	$(0, 0, 0, 0, -1, 0, +1)$

Table 4.1 – Description of the model transitions between states $\{S, E, A, I, H, R, D\}$.

Parameter Name	Parameter Role	Nominal value	Range of variation
β	transmission rate	2	(0.35, 4)
$1/\gamma_E$	mean sojourn duration in E	4.6 days	(2, 7)
$1/\gamma_A$	mean sojourn duration in A	2.1 days	(1, 3)
$1/\gamma_I$	mean sojourn duration in I	4 days	(3, 5)
$1/\gamma_H$	mean sojourn duration in H	10 days	(7, 12)
$p_{(E,A)}$	probability for an exposed to become asymptomatic	0.6	(0.3, 0.7)
$p_{(I,H)}$	probability for a symptomatic to be hospitalized	0.15	(10^{-3} , 0.2)
$p_{(I,D)}$	probability for a symptomatic to die	0.05	(10^{-3} , 0.1)
$p_{(H,D)}$	probability for a hospitalized to die	0.08	(0.001, 0.1)

Table 4.2 – Model parameter nominal values and their range of variation in the sensitivity analysis (values are plausible with current knowledge e.g. [Knock et al. \(2021\)](#)).

continuous-time Markov chain.

Let denote p_I the vector $(p_{(I,H)}, p_{(I,D)})$. For GSA purposes, we focus on the group of inputs p_I instead of $p_{(I,H)}$ and $p_{(I,D)}$ separately for two reasons. The first reason is related to the assumption of mutual independence of inputs that is necessary for Sobol'-Hoeffding decomposition. Since $p_{(I,H)}$ and $p_{(I,D)}$ are correlated, they are grouped as one input in order to ensure input independence. The second reason is that we are interested in the global influence of the probability distribution $(p_{(I,H)}, p_{(I,D)}, 1 - p_{(I,H)} - p_{(I,D)})$ that is represented by p_I . Therefore, in the context of sensitivity analysis, there are eight parameter inputs considered: $\beta, \gamma_E, \gamma_A, \gamma_I, \gamma_H, p_{(E,A)}, p_I, p_{(H,D)}$. Let us model the uncertainty by introducing the random vector $\mathbf{X} = (\beta, \gamma_E, \gamma_A, \gamma_I, \gamma_H, \mathbf{P}_{(E,A)}, \mathbf{P}_I, \mathbf{P}_{(H,D)})$ such that components are mutually independent with uniform distributions on intervals specified in Table 4.2. Specifically, the vector input \mathbf{p}_I is drawn from a multidimensional uniform on $[10^{-3}, 0.2] \times [10^{-3}, 0.1]$.

We study two types of outputs that are our quantities of interest (QoIs): a scalar QoI and a functional one. The scalar QoI considered is the extinction time Y_{ext} of the epidemic. Y_{ext} is defined as the first time when there are no more individuals E able to get infected or individuals A or I able to maintain infection by infecting new susceptible individuals:

$$Y_{ext} = \inf\{t \geq 0 : W_E(t) + W_A(t) + W_I(t) = 0\}.$$

Note that for all $\theta \in \Theta$, Y_{ext} is well-defined, i.e. $Y_{ext} < +\infty$. Indeed, by considering the compartmental model described in Figure 4.1, after a finite number of transitions, the stochastic process will necessarily reach an absorbing state where there is no individual in compartments E, A and I . A boxplot of $n = 2000$ simulations of Y_{ext} with parameter inputs set to nominal values given in Table 4.2 is showed in Figure 4.A.1.

The functional QoI is given by the dynamic of the number of symptomatic infectious individuals:

$$Y_I = \{W_I(t), t \in [0, T]\}.$$

The quantities Y_{ext} and Y_I are functions of the random field $\mathbf{W} = \{W^{\mathbf{X}}(t), t \in [0, T]\}$, so they inherit its representations.

By relying on Subsection 4.3.2, we obtained two representations of \mathbf{W} : the Gillespie representation $(\mathbf{X}, \mathbf{W}) \sim (\mathbf{X}, f_G(\mathbf{X}, Z^G))$ where $Z^G = (\mathbf{U}^1, \dots, \mathbf{U}^9)$ is a vector of nine independent sequences (one for each type of transition) of i.i.d. standard uniform variables and the Random time change representation $(\mathbf{X}, \mathbf{W}) \sim (\mathbf{X}, f_K(\mathbf{X}, Z^K))$ where $Z^K = (Z^1, \dots, Z^9)$ is a vector of nine independent unit-rate Poisson processes. For sensitivity analysis, intrinsic randomness variables Z^G and Z^K are treated as one input each. We are interested in the global influence of (\mathbf{X}, Z) where Z denotes Z^G or Z^K depending on the representation.

4.4.2 Numerical setting for sensitivity analysis

We consider a population of $N = 2005$ individuals including five exposed individuals at the start of the epidemics $t = 0$, so that for all $\theta \in \Theta$ the CTMC W^θ has the initial state:

$$\xi_0 = (W_S(0) = 2000, W_E(0) = 5, W_A(0) = 0, W_I(0) = 0, \\ W_H(0) = 0, W_R(0) = 0, W_D(0) = 0).$$

For the quantity of interest Y_{ext} , the final time T of the study is set to $T = +\infty$. In practice, this means that trajectories of W^θ are simulated until they reach absorbing states, i.e. extinction. Concerning Y_I , T is set to $T = 60$ days. This choice is motivated by the outputs of Y_I obtained with the nominal values of parameters and displayed in Figure 4.A.2. This figure shows that trajectories do not much vary after 60 days and about two-thirds of them reach extinction right after $T = 60$ days which is the 32th percentile of extinction times (see boxplot of Figure 4.A.1). Therefore, Y_I is studied on the interval $[0, 60]$ that is discretized into 1000 equidistant time points for GSA purposes.

Regarding sensitivity index estimation, we draw $n = 2000$ samples of each input with respect to uniform distributions over ranges specified in Table 4.2. The parameter space exploration is performed by using Latin Hypercube Sampling as the dimension of Θ is quite large. We simulate W^θ through Algorithm 9 for random time change representation and Algorithm 11 for Gillespie representation. In both cases, the intrinsic randomness variable is a vector of nine components. Nine integers are drawn independently and uniformly in $\{1, \dots, 10^9\}$ to serve as seeds for the random number generator with the aim to stream random numbers.

In practice, simulations are carried out with *R*. We use the *R* package *DiceDesign* (Dupuy et al. (2015)) for Latin Hypercube Sampling. Sensitivity indices are estimated by using functions *soboljansen* and *sobol2007* of the *R* package *sensitivity* (Iooss et al. (2020)). The function *soboljansen* is used for total Sobol' index estimation while *sobol2007* is used for first-order Sobol' index estimation.

4.4.3 Sensitivity index estimation

GSA is performed for the two outputs. For Y_{ext} , first-order and total Sobol' indices of the nine inputs are estimated. For each representation, 50 replications of these indices are provided. Regarding Y_I , dynamical and aggregated Sobol' indices are estimated.

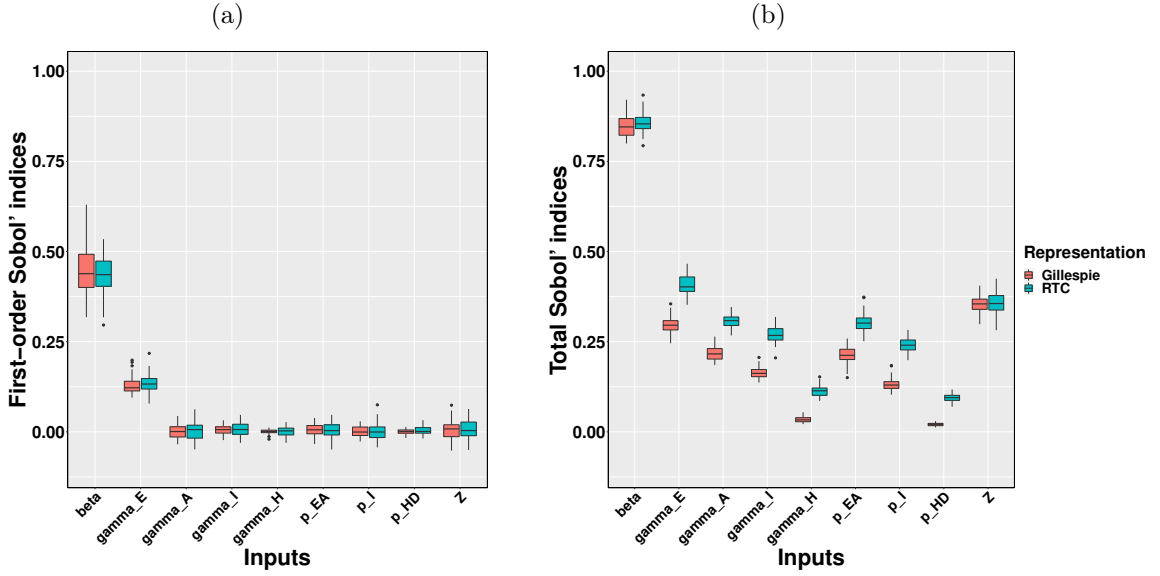


Figure 4.2 – Boxplots of 50 replications of first-order Sobol' indices (a) and total Sobol' indices (b) for Y_{ext} with respect to Gillespie representation (red) and Random time change representation (RTC) (blue). Each index estimation is obtained with $n = 2000$ samples of inputs.

4.4.3.1 Sensitivity analysis results for Y_{ext}

Figure 4.2 suggests that, considering first-order indices, only two parameters influence the variability of Y_{ext} : β and γ_E . Also, there is no significant difference in the input sensitivity indices between the two model representations. Regarding total indices, results point out strong interactions between inputs. Thus, one can notice that almost all the inputs have non-zero total effects except $p_{(H,D)}$ in the case of the Gillespie representation. Two main points can be emphasized: first, the total Sobol' index estimations of Z for the two representations are very close. Indeed, the total Sobol' index of Z is theoretically the same for the two representations (see Section 4.2.3). That is why estimations are equal up to sampling errors. Secondly, there are significant differences between the estimations for Gillespie and Random time change representations, and the three most influential inputs (more than 25% of variance each) are: β , γ_E and Z . The intrinsic randomness interacts strongly with uncertain parameters. This explains the difference that appears between main and total effects.

The ranking of inputs with respect to total Sobol' indices for Gillespie representation yields $\beta, Z, \gamma_E, \gamma_A, \gamma_I, p_{(E,A)}, p_I, \gamma_H, p_{(H,D)}$ while that of Random time change representation is $\beta, \gamma_E, Z, \gamma_A, p_{(E,A)}, \gamma_I, p_I, \gamma_H, p_{(H,D)}$. From one representation to another, rankings of inputs $\gamma_E, Z, \gamma_I, p_{(E,A)}$ have switched.

So, in practice, GSA conclusions relative to ranking depend on representation.

In order to confirm statistically the difference between indices, we carry out asymptotic statistical tests of comparison of means of two samples. For each input, the test consists in comparing the total Sobol' indices renormalized by the total variance (i.e. numerator of total Sobol' index formula defined in Subsection 4.2.1) obtained for the two representations. The samples derive from the total Sobol' index samples used for the boxplots in Figure 4.2.

The null hypothesis (H_0) is rejected for inputs $\gamma_E, \gamma_A, \gamma_I, \gamma_H, p_{EA}, p_I$ and p_{HD} with p-values less than 2.2×10^{-16} but not for inputs β and Z as their corresponding p-values 0.75 and 0.85 are greater than 5%. There is no surprise that the test for β is inconclusive since boxplots overlap (see Figure 4.2b).

Results provided in Subsection 4.4.3 reveal that differences can occur between GSA responses for the two representations. In particular, for total Sobol' indices of uncertain parameters, intrinsic randomness distributions are explicitly involved in formulas and consequently estimations for the two representations do not seem to be distributed around the same theoretical value. Even though these differences may legitimately exist, they can have significant repercussions in practice. For this model, we could indeed choose to adopt Gillespie representation as interactions with intrinsic noise are much less important for this representation. However, the most important message to keep in mind is that the intrinsic randomness varies from one representation to another, thus different representations yield different information. And in practice, this can impact GSA conclusions and even resulting decisions.

4.4.3.2 Sensitivity analysis results for Y_I

Dynamical Sobol' indices

As showed in Figure 4.3, both dynamical first-order and total Sobol' index estimation indicate that the most important input over time is β , followed by γ_E , and $p_{(E,A)}$, except at the very beginning of the epidemic where γ_E is the most important parameter. These conclusions are valid for both representations. First-order and total Sobol' indices of Z are the highest from the start until day 5, meaning that the intrinsic stochasticity influence exceeds that of uncertain parameters at the beginning of epidemics. This reflects the fact that intrinsic stochasticity rules the dynamics especially at the beginning of outbreaks when the number of infectious is low.

Aggregated Sobol' indices

The aggregated Sobol' indices enable to summarize over the whole time interval the impact of inputs. So, for both first-order and total indices, the transmission parameter β remains the most important input, followed by $\gamma_E, p_{(E,A)}$ and Z .

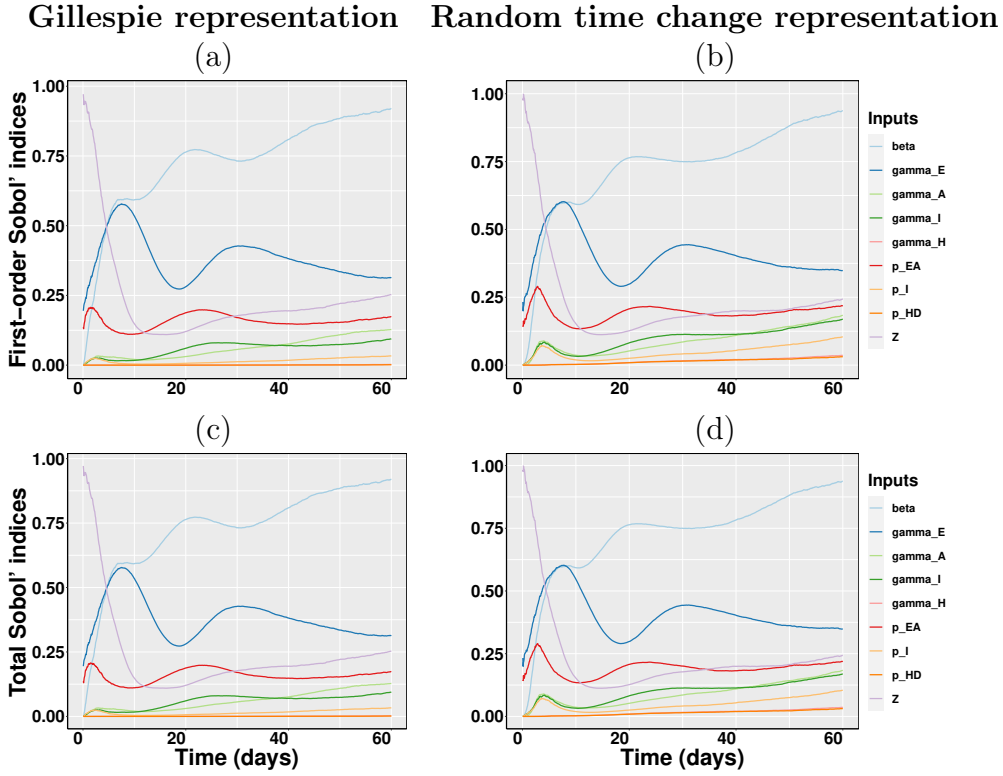


Figure 4.3 – Dynamical first-order and total Sobol' indices for Y_I with respect to Gillespie representation (a) & (c) and Random time change representation (b) & (d). At each of the 1000 discretization time points in $[0, 60]$, first-order Sobol' indices are estimated with $n = 2000$ samples of inputs.

The impact of Z is again noticeable when considering total effects, due to its interactions with other inputs.

With the aim of validating the differences between total Sobol' indices for the two representations, statistical tests are carried out as in the case of the scalar output Y_{ext} by using samples that allowed to generate boxplots of Figure 4.4. The null hypothesis that states the equality between total Sobol' indices of input parameters for the two representations is rejected with p-values smaller than 2.2×10^{-16} except parameters β and γ_E for which the p-values are respectively 2.24×10^{-4} and 2.6×10^{-14} . The test for Z does not reject the null hypothesis with a p-value of 0.76. Overall, the conclusions of these tests perfectly match with the theoretical analysis detailed in Subsection 4.2.3.

4.5 Conclusions

In this work, we developed an approach of sensitivity analysis for stochastic compartmental models described by continuous-time Markov chains. This

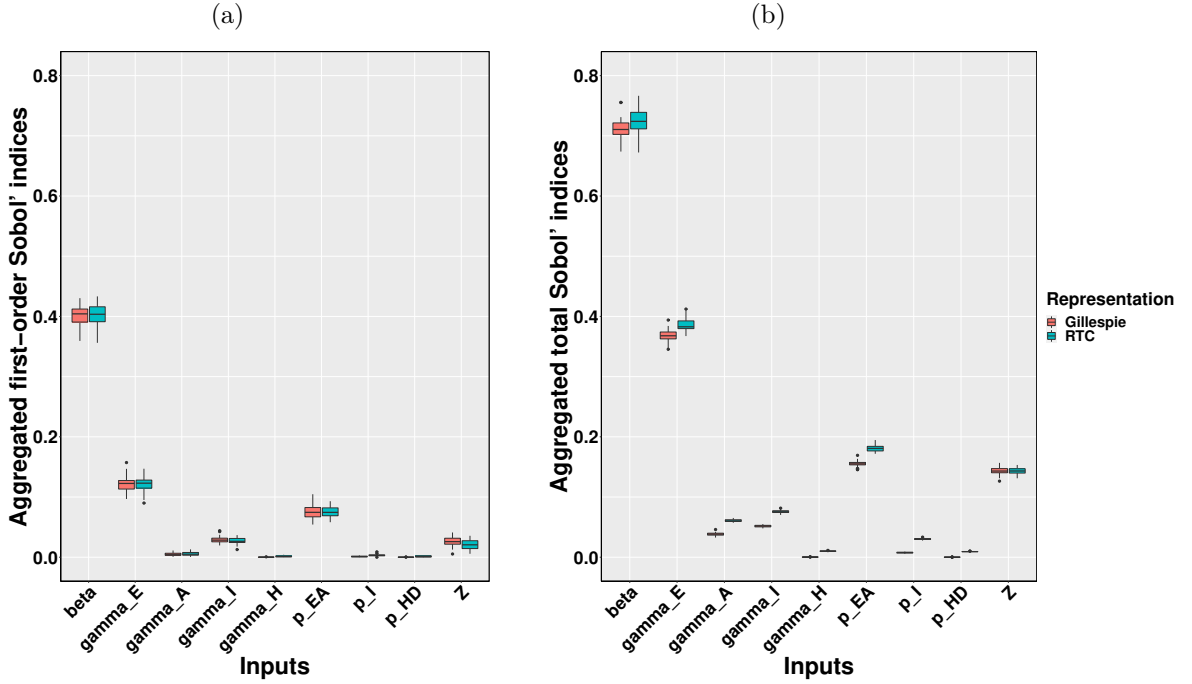


Figure 4.4 – Aggregated first-order (a) and total (b) Sobol' indices for Y_I with respect to Gillespie representation (red) and Random time change representation (blue). Indices are obtained with the 1000 discretization time points in $[0, 60]$ and $n = 2000$ samples of inputs.

approach consists in separating intrinsic randomness from parameter uncertainty by building exact deterministic representations of the model outputs as functions of uncertain parameters and explicit intrinsic randomness. For this purpose, we rely on Gillespie SSA to propose a deterministic representation of continuous-time Markov chains. We present two versions of the new Gillespie SSA based representation: the direct method (see Proposition 5) and the first reaction method (see Proposition 6). The latter representation enables to highlight the impact of intrinsic noise of each type of transition or reaction channel of the model. Regarding the representation based on direct method, it has the advantage to be computationally faster and most commonly used in practice.

This approach is applied to a stochastic compartmental model of SARS-CoV-2 spread and is compared to an approach based on random time change analyzed in Navarro Jimenez et al. (2016). GSA is performed for two quantities of interest. The first QoI studied is the extinction time of epidemics. The Gillespie and random time change representations reveal that the transmission parameter (β) is the most important input and that the intrinsic randomness (Z) much interacts with uncertain parameters. The second QoI is functional and given by the dynamics of number of symptomatic infectious individuals.

For both representations, sensitivity analysis highlights again the main role of transmission parameter (β) and incubation mean duration parameter (γ_E) and the slight influence of the intrinsic randomness (Z), except at the very beginning of the epidemic. Estimating Sobol' indices of intrinsic randomness allowed to point out not only the different phases of the epidemic, regarding the influence of the intrinsic randomness, but also its global influence on the whole epidemic dynamic.

Overall, our approach allows to estimate sensitivity indices for the main effect of intrinsic randomness as well as for its interactions with uncertain parameters. This additional information is complementary to the one on the influence of uncertain parameters. We also highlighted the fact that GSA results depend on the chosen representation. In practice, this impacts conclusions resulting from GSA. Nevertheless, the different results between the representations provide interesting information; for instance, choosing a representation which has lower interaction between the intrinsic randomness and the uncertain parameters. This may allow to estimate uncertain parameter values with a better accuracy.

In future research, the approach proposed in this study could be extended to compartmental models based on non-Markovian stochastic processes based on Sellke construction (Sellke, 1983).

Appendix

4.A Some simulations of QoIs Y_{ext} and Y_I

Case of Y_{ext}

For uncertain parameters set to nominal values (see Table 4.2), we simulate $n = 2000$ outputs of Y_{ext} . The outcomes are presented under the form of boxplot in Figure 4.A.1.

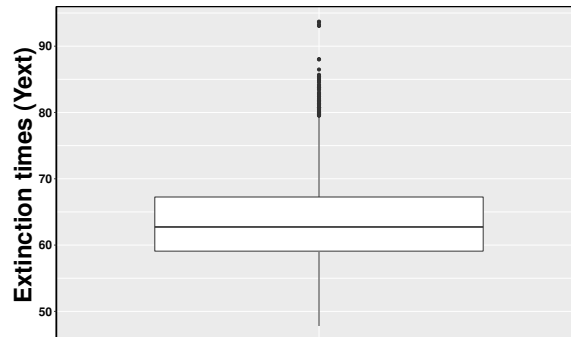


Figure 4.A.1 – Boxplot of $n = 2000$ outputs of Y_{ext}

Case of Y_I

Figure 4.A.2 shows 20 trajectories of the number of symptomatic infectious individuals corresponding to 20 outputs of the model for parameters set to nominal values (see Table 4.2).

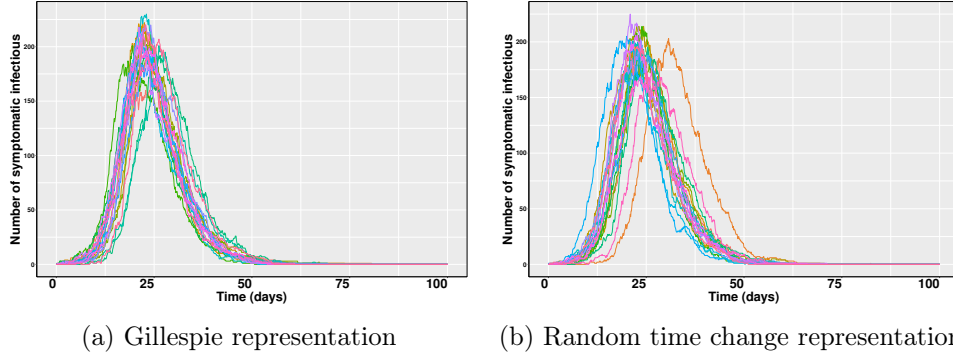


Figure 4.A.2 – 20 trajectories of number of symptomatic infectious per representations

4.B Proofs

Proof of Proposition 4

The proof is provided for a case of stochastic process so that it can be adapted to real or multidimensional output stochastic models. Assume that for all $\theta \in \Theta$, $g(\theta)$ is a stochastic process $\{g(\theta, t), t \geq 0\}$ over a discrete state space \mathcal{E} and independent of \mathbf{X} . Let A_1, \dots, A_d and B be Borel sets. Assume \mathbf{X} has a probability distribution μ . Consider $0 \leq t_1 \leq \dots \leq t_d$. Note that $\mathbb{P}(\mathbf{X} \in B, g(\mathbf{X}, t_1) \in A_1, \dots, g(\mathbf{X}, t_d) \in A_d)$ yields:

$$\begin{aligned} & \mathbb{E} \left[\mathbb{1}_{\mathbf{X} \in B} \mathbb{E} \left[\prod_{i=1}^d \mathbb{1}_{g(\mathbf{X}, t_i) \in A_i} \mid \mathbf{X} \right] \right] \\ &= \mathbb{P}(\mathbf{X} \in B, f(t_1, \mathbf{X}, Z) \in A_1, \dots, f(t_d, \mathbf{X}, Z) \in A_d) \end{aligned}$$

since $\mathbb{E} \left[\mathbb{1}_{\mathbf{X} \in B} \mathbb{E} \left[\prod_{i=1}^d \mathbb{1}_{g(\mathbf{X}, t_i) \in A_i} \mid \mathbf{X} \right] \right] = \int_B \mathbb{E} \left[\prod_{i=1}^d \mathbb{1}_{f(t_i, \theta, Z) \in A_i} \right] \mu(d\theta)$.

Construction of Gillespie representation and Proof of Proposition 5

For all $\theta \in \Theta$, W^θ is a CTMC on the finite state space \mathcal{E} with generator \mathcal{Q}_θ . The jump sequence $\{T_n; n \geq 0\}$ of W^θ is defined as:

$$\begin{cases} T_0 = 0 \\ T_{n+1} - T_n \sim \text{Exp} \left(\sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, W^\theta(T_n)) \right) \\ \text{Conditionally to } \{W^\theta(T_n), n \geq 0\}, (T_{n+1} - T_n) \text{ are mutually independent} \end{cases}$$

The sequence $\{W^\theta(T_n); n \geq 0\}$ is the embedded chain of W^θ i.e. a discrete-time Markov chain on \mathcal{E} with initial state ξ_0 and transition probabilities given by:

$$\begin{aligned} \forall \xi, \xi' \in \mathcal{E}, p_{\xi, \xi'} &= \mathbb{P} \left(W^\theta(T_{n+1} = \xi' \mid W^\theta(T_n) = \xi) \right) \\ &= \begin{cases} \frac{g_{\alpha', \beta'}(\theta, \xi)}{\sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, \xi)} & \text{if } \exists (\alpha', \beta') \in \mathbf{E} : \xi' - \xi = \mathbf{u}_{\alpha', \beta'} \\ 0 & \text{otherwise.} \end{cases} \end{aligned} \quad (4.1)$$

Therefore, W^θ can be rewritten under the form:

$$W^\theta(t) = \sum_{n=0}^{+\infty} W^\theta(T_n) \cdot \mathbb{1}_{[T_n, T_{n+1}[}(t).$$

Consider a discrete-time Markov chain $D^\theta = \{D_n^\theta; n \geq 0\}$ with transition probabilities $(p_{\xi, \xi'})_{(\xi, \xi') \in \mathcal{E} \times \mathcal{E}}$ defined in Eq. (4.1) and initial state ξ_0 . If the sequence $\{\tau_n; n \geq 0\}$ satisfies:

$$\begin{cases} \tau_0 = 0 \\ \tau_{n+1} - \tau_n \sim \text{Exp} \left(\sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, D_n^\theta) \right) \\ \text{Conditionally to } D^\theta, (\tau_{n+1} - \tau_n) \text{ are mutually independent} \end{cases} \quad (4.2)$$

then the stochastic process $H^\theta = \left\{ \sum_{n=0}^{+\infty} D_n^\theta \cdot \mathbb{1}_{[\tau_n, \tau_{n+1}[}(t); t \geq 0 \right\}$ defines a continuous-time Markov chain with generator \mathcal{Q}_θ , state space \mathcal{E} and initial state ξ_0 . Since \mathcal{E} is finite then:

$$\forall \theta \in \Theta, \quad W^\theta \stackrel{f.d.d.}{=} H^\theta. \quad (4.3)$$

Equation (4.3) implies that the two processes are stochastically equivalent. The discrete chain D^θ and sequence $\{\tau_n; n \geq 0\}$ can be arbitrarily chosen. Let us construct an example of D^θ and sequence $\{\tau_n; n \geq 0\}$ using two independent sequences $\mathbf{U}^1 = (U_1^1, U_2^1, \dots)$ and $\mathbf{U}^2 = (U_1^2, U_2^2, \dots)$ of i.i.d. standard uniform variables.

Note that \mathbf{E} is finite as \mathbf{V} is finite. Recall that n_E the cardinal of \mathbf{E} . So, we order the elements of \mathbf{E} with respect to an arbitrary order: $\mathbf{E} = \{(\alpha^{(1)}, \beta^{(1)}), \dots, (\alpha^{(n_E)}, \beta^{(n_E)})\}$. Let us introduce the function:

$$\begin{aligned} \phi^\theta : \mathcal{E} \times [0, 1] &\longrightarrow \mathcal{E} \\ (\xi, v) &\longmapsto \xi + \sum_{k=1}^{n_E} \mathbf{u}_{\alpha^{(k)}, \beta^{(k)}} \times \mathbb{1}_{v \in \left[\sum_{j=1}^{k-1} p_{\xi, \xi + \mathbf{u}_{\alpha^{(j)}, \beta^{(j)}}}, \sum_{j=1}^k p_{\xi, \xi + \mathbf{u}_{\alpha^{(j)}, \beta^{(j)}}} \right]} \end{aligned} \quad (4.4)$$

The discrete chain built by the recursion:

$$\begin{cases} D_0 = \xi_0 \\ D_n^\theta = \phi^\theta(D_{n-1}^\theta, U_n^1), n \geq 1 \end{cases} \quad (4.5)$$

is a Markov chain with transition probabilities $(p_{\xi, \xi'})_{(\xi, \xi') \in \mathcal{E} \times \mathcal{E}}$. Furthermore, the sequence:

$$\begin{cases} \tau_0 = 0 \\ \tau_{n+1} - \tau_n = -\frac{\log(U_n^2)}{\sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, D_n^\theta)} \end{cases} \quad (4.6)$$

satisfies conditions of Eq. (4.2.) Therefore the discrete chain in Eq. (4.5) and the sequence in Eq. (4.6) define a CTMC stochastically equivalent to W^θ in the sense of finite dimensional distributions.

Let define the function:

$$\begin{aligned} \Phi^\theta : \mathcal{L}([0, 1]) &\longrightarrow \mathcal{E}^{\mathbb{N}} \\ u = (u_1, u_2, \dots) &\longmapsto \Phi^\theta(u) = \left(\xi_0, \phi^\theta(\xi_0, u_1), \phi^\theta(\phi^\theta(\xi_0, u_1), u_2), \dots \right) \end{aligned}$$

By construction $\Phi^\theta(\mathbf{U}^1) = \{\Phi_n^\theta(\mathbf{U}^1) = D_n^\theta, n \geq 0\}$. If $\lambda_n = \sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, \Phi_n^\theta(\mathbf{U}^1))$ then the following function:

$$\begin{aligned} f_G : \mathbb{R}_+ \times \Theta \times \mathcal{L}([0, 1])^2 &\longrightarrow \mathcal{E} \\ (t, \theta, z_1, z_2) &\longmapsto f_G(t, \theta, z_1, z_2) = \sum_{n=0}^{\infty} \Phi_n^\theta(z_1) \mathbb{1}_{t \in \left[\sum_{j=1}^n \frac{-\log(z_2, j)}{\lambda_{j-1}}, \sum_{j=1}^{n+1} \frac{-\log(z_2, j)}{\lambda_{j-1}} \right]} \end{aligned}$$

is such that $f_G(\cdot, \theta, Z^G)$ is stochastically equivalent to W^θ with $Z^G = (\mathbf{U}^1, \mathbf{U}^2)$.

Moreover, since \mathbf{X} and Z^G are independent and $f_G(\cdot, \theta, Z^G) \sim W^\theta$ then the equivalence $(\mathbf{X}, \mathbf{W}) \sim (\mathbf{X}, f_G(\cdot, \mathbf{X}, Z^G))$ is proved in the same way as in Proposition 1.

Second construction of Gillespie representation and Proof of Proposition 6

We consider the vector of sequences of i.i.d. standard random variables: $(\mathbf{U}_{\alpha,\beta}, (\alpha, \beta) \in \mathbf{E})$ where $\mathbf{U}_{\alpha,\beta} = (U_{\alpha,\beta}^1, U_{\alpha,\beta}^2, \dots)$. Given the following recursive system:

$$\begin{cases} D_0^\theta = \xi_0 \\ s_{\alpha,\beta}^n = -\frac{\log(U_{\alpha,\beta}^n)}{g_{\alpha,\beta}(\theta, D_{n-1}^\theta)} \quad \forall (\alpha, \beta) \in \mathbf{E} \\ D_n^\theta = D_{n-1}^\theta + \mathbf{u}_{\alpha,\beta} \mathbb{1}_{s_{\alpha,\beta}^n = \min\{s_{\alpha,\beta}^n; (\alpha,\beta) \in \mathbf{E}\}} \end{cases} \quad (4.7)$$

$(\mathbf{U}_{\alpha,\beta}, (\alpha, \beta) \in \mathbf{E})$ is a vector of sequences of i.i.d. standard random variables where $\mathbf{U}_{\alpha,\beta} = (U_{\alpha,\beta}^1, U_{\alpha,\beta}^2, \dots)$. We have the following system:

$$\begin{cases} D_0^\theta = \xi_0 \\ s_{\alpha,\beta}^n = -\frac{\log(U_{\alpha,\beta}^n)}{g_{\alpha,\beta}(\theta, D_{n-1}^\theta)} \quad \forall (\alpha, \beta) \in \mathbf{E} \\ D_n^\theta = D_{n-1}^\theta + \mathbf{u}_{\alpha,\beta} \mathbb{1}_{s_{\alpha,\beta}^n = \min\{s_{\alpha,\beta}^n; (\alpha,\beta) \in \mathbf{E}\}} \end{cases}$$

1. Set $U_n = \{U_{\alpha,\beta}^n; (\alpha, \beta) \in \mathbf{E}\}$. $\{U_n; n \geq 1\}$ is a sequence of i.i.d. random vectors with distribution $\bigotimes_{i=1}^{nE} \mathcal{U}([0, 1])$. Given the function:

$$\begin{aligned} \varphi^\theta : \mathcal{E} \times [0, 1]^{nE} &\longrightarrow \mathcal{E} \\ (\xi, u = u_{\alpha,\beta}^n; (\alpha, \beta) \in \mathbf{E}) &\longmapsto \xi + \mathbf{u}_{\alpha,\beta} \mathbb{1}_{s_{\alpha,\beta}^n = \min\{-\frac{\log(u_{\alpha,\beta}^n)}{g_{\alpha,\beta}(\theta, \xi)}; (\alpha,\beta) \in \mathbf{E}\}} \end{aligned}$$

it yields $D_n = \varphi^\theta(D_{n-1}, U_n)$. So, $\{D_n^\theta, n \geq 0\}$ defines a Markov chain with initial state ξ_0 . Let us find the transition probabilities of this chain. Let ξ' and ξ be two states such that $\xi' \neq \xi$. We shall discuss two cases.

- Case 1: $\xi' \neq \xi + \mathbf{u}_{\alpha,\beta}$ for all $(\alpha, \beta) \in \mathbf{E}$. In this case, we have:

$$\begin{aligned} \mathbb{P}(D_{n+1}^\theta = \xi' \mid D_n^\theta = \xi) &= \mathbb{P}\left(\xi' = \xi + \mathbf{u}_{\alpha,\beta} \mathbb{1}_{s_{\alpha,\beta}^n = \min\{s_{\alpha,\beta}^n; (\alpha,\beta) \in \mathbf{E}\}} \mid D_n^\theta = \xi\right) \\ &= \mathbb{P}\left(\xi' = \xi + \mathbf{u}_{\alpha,\beta} \mathbb{1}_{s_{\alpha,\beta}^n = \min\{s_{\alpha,\beta}^n; (\alpha,\beta) \in \mathbf{E}\}}\right) \\ &= 0 \end{aligned}$$

- Case 2: $\exists (\hat{\alpha}, \hat{\beta}) \in \mathbf{E}$ such that $\xi' = \xi + \mathbf{u}_{\hat{\alpha}, \hat{\beta}}$. In this case, we have:

$$\begin{aligned}
\mathbb{P}\left(D_n^\theta = \xi' \mid D_{n-1}^\theta = \xi\right) &= \mathbb{P}\left(\xi' = \xi + \mathbf{u}_{\hat{\alpha}, \hat{\beta}} \mathbf{1}_{s_{\hat{\alpha}, \hat{\beta}}^n = \min\{s_{\alpha, \beta}^n; (\alpha, \beta) \in \mathbf{E}\}} \mid D_{n-1}^\theta = \xi\right) \\
&= \mathbb{P}\left(\mathbf{u}_{\hat{\alpha}, \hat{\beta}} = \mathbf{u}_{\hat{\alpha}, \hat{\beta}} \mathbf{1}_{s_{\hat{\alpha}, \hat{\beta}}^n = \min\{s_{\alpha, \beta}^n; (\alpha, \beta) \in \mathbf{E}\}} \mid D_{n-1}^\theta = \xi\right) \\
&= \mathbb{P}\left(s_{\hat{\alpha}, \hat{\beta}}^n = \min\{s_{\alpha, \beta}^n; (\alpha, \beta) \in \mathbf{E}\} \mid D_{n-1}^\theta = \xi\right) \\
&= \mathbb{P}\left(s_{\hat{\alpha}, \hat{\beta}}^n \leq s_{\alpha, \beta}^n; (\alpha, \beta) \in \mathbf{E} \setminus (\hat{\alpha}, \hat{\beta}) \mid D_{n-1}^\theta = \xi\right) \\
&= \mathbb{E}\left[\exp\left(-s_{\hat{\alpha}, \hat{\beta}}^n \times \sum_{(\alpha, \beta) \in \mathbf{E} \setminus (\hat{\alpha}, \hat{\beta})} g_{\alpha, \beta}(\theta, \xi)\right) \mid D_{n-1}^\theta = \xi\right] \\
&= \frac{g_{\hat{\alpha}, \hat{\beta}}(\theta, \xi)}{\sum_{(\alpha, \beta) \in \mathbf{E}} g_{\alpha, \beta}(\theta, \xi)}.
\end{aligned}$$

It turns out that $\{D_n^\theta, n \geq 0\}$ has transition matrix $(p_{\xi, \xi'})_{(\xi, \xi') \in \mathcal{E} \times \mathcal{E}}$.

2. It is straightforward since $\{U_{\alpha, \beta}^n; (\alpha, \beta) \in \mathbf{E}\}$ are i.i.d. and $s_{\alpha, \beta}^n$ are exponential variables.
3. The construction of f_G is similar to the one of the proof of Proposition 2 by using $Z^G = (\mathbf{U}_{\alpha, \beta}, (\alpha, \beta) \in \mathbf{E})$ and $\phi^\theta = \varphi^\theta$.

An extension of Sellke construction and application to sensitivity analysis for non-Markovian epidemic models

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This chapter deals with compartmental models based on non-Markovian processes. It is also related to the context of epidemic models and completes the study started in Chapter 4 concerning models based on continuous time Markov chains. In this context, the goal is still to find an approach allowing to evaluate various contributions of parameters and of the intrinsic randomness. Here, to

achieve this, we will rely on Sellke construction which we will generalize. The generalized construction allows to separate the intrinsic randomness from the uncertain parameters for a large class of compartmental models.

5.1 Introduction

The last two years, COVID-19 pandemic has shown the importance of mathematical epidemic modeling. Mathematical models in epidemiology, as complex as they are varied, have been proposed to predict the evolution of the pandemic and guide policy-making. However, the potential impact of decisions made based on these models highlights the necessity to understand these models in their diversity and complexity. Among the epidemic models, one of the most used categories is the stochastic compartmental models. These models are based on a simple principle: a group of health statuses is defined so that individuals in the population are divided into compartments with respect to their health status and then random changes in health statuses that may occur during the epidemic are ruled by mechanistic rules. Epidemic dynamics are then described by stochastic processes that track over time the number of individuals in the different compartments considered. Depending on the modeling choices, these continuous-time stochastic processes can be Markovian (in particular continuous-time Markov chains) or non-Markovian. In the Markovian case, the future dynamics of the stochastic process only depends on its current state and not on the past; this does not hold for non-Markovian processes where there is a memory effect. Markovian processes and the resulting ordinary differential equations are less complex to study and simulate. In addition, they provide good approximations in epidemic modeling, but they have limitations in practice because of the lack-of-memory property. For example, they fail to account for temporal characteristics of real epidemics, memory effects or when delays are involved (Nowzari et al., 2015; Großmann et al., 2021; Sofonea et al., 2021; Saeedian et al., 2017), etc. Thus, models based on non-Markovian processes turn out to be more general class of model. They can be obtained in multiple ways: using non-exponential distributions (Van Mieghem and van de Bovenkamp, 2013; Streftaris and Gibson, 2012), using systems with delays (Brett and Galla, 2013), etc. Sellke (1983) introduced a construction of the classical SIR (Susceptible-Infectious-Recovered) model, a new way to simulate SIR epidemic process. This enabled to approximate the final size of epidemics, i.e. the total number of individuals who have ever contracted the infection during outbreak. This construction relies on an individual-based approach and it has the advantage to enable the simulation of SIR epidemic process in both Markovian and non-Markovian frameworks. Since then, it has been studied and extended in many ways.

Reinert (1995) studied Sellke construction in the case where tolerance thresholds to infection and sojourn time variables in compartment I of susceptible individuals are not independent and provided convergence results for the resulting stochastic process. Andersson and Britton (2000b) extended Sellke approach to SIR-multitype epidemics. In Streftaris and Gibson (2012), the unit-rate exponential distribution of thresholds is changed to Weibul distribution. Moreover, still in the case of SIR model, House (2014) generalized the construction to the case of finite heterogeneous population while Di Lauro et al. (2022) focused on age-dependent SIR model. An extension to the classical SEIR (Susceptible-Exposed-Infectious-Recovered) model was detailed in Britton et al. (2019). This extension is straightforward because on one hand the jumps from the compartment E follow the same transition mechanism as those from compartment I and on the other hand individuals in compartment E are not infectious. However, in the view of all these works, it appears that so far, various uses or generalizations of the construction focus mainly on SIR model but under different modeling assumptions. For example, none of these works consider models with reinfection and more generally compartmental models that include branching compartments (like SEIAR: Susceptible-Exposed-Infectious-Asymptomatic-Recovered) or such that their corresponding graph includes cycles (or loops) like the classical SIS (Susceptible-Infectious-Susceptible).

This study proposes an extension of Sellke construction to a more general class of compartmental models for closed populations. This class includes SIR-type models (a series of compartments in one row), SEIAR-type (a series of compartments in several rows), models with cycles etc. This new construction proposes a reformulation of epidemic processes with respect to Sellke construction. The extended construction yields non-Markovian stochastic processes. Furthermore, as in the case of the original Sellke construction, the extended one we propose is equivalent to corresponding Markovian model under certain conditions on probability distributions of construction variables. This paper aims at modeling and simulating epidemics using this new construction and is not intended to provide a probabilistic study of resulting stochastic processes. Thus, we provide an algorithm to simulate epidemic based on such construction.

One of the advantages of this construction and also of the one of Sellke is that they enable to clearly identify the intrinsic randomness of epidemic processes through the behaviors and the characteristics of individuals. This allows us to investigate the impact of intrinsic randomness for non-Markovian epidemic processes. For this, we deduce a representation of epidemic processes in the form of a deterministic function of uncertain epidemic parameters and intrinsic randomness. In a previous work (Kouye et al., 2022), such a representation was derived for Markovian epidemic processes simulated by Gillespie

algorithm (Gillespie, 1977). Therefore, in addition to non-Markovian epidemic processes, the new construction investigated in this document provides also an alternative way to represent Markovian processes obtained with stochastic compartmental models. An application is proposed for the SEI_1I_2RS model.

This document is structured as follows. Section 5.2 discusses the extended construction that we propose. For this intending, the original Sellke construction is reminded in Subsection 5.2.1. Subsection 5.2.2 describes the class of compartmental models to which this construction detailed later in Subsection 5.2.3 is intended. Section 5.3 presents our algorithm for simulating epidemic processes and also gives some illustrations on the SEI_1I_2RS model. Regarding Section 5.4, it deals with the deterministic representation of epidemic processes based on the extended construction and presents an application to the SEI_1I_2RS . This application consists in estimating some variance-based sensitivity indices of both uncertain epidemic parameters and intrinsic randomness in the view of assessing impact of the intrinsic randomness in non-Markovian modeling framework.

5.2 Extending Sellke construction

This section introduces an extension of Sellke construction. It is divided into three subsections intended to present the original construction, to define the class of compartmental models we are interested in and to detail mechanisms of the extension we propose.

5.2.1 Sellke construction

Consider the classical SIR model (see Figure 5.1) and assume that the population is closed and comprises N individuals.

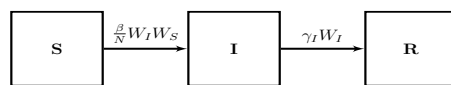


Figure 5.1 – The classical SIR model. $W_S(t)$ and $W_I(t)$ denote the respective number of individuals in compartment S and I at time $t \geq 0$.

In order to describe general epidemic dynamics corresponding to the model, Sellke proposed an individual-based construction. For this construction, at the start of the epidemic ($t = 0$), each individual of the population of size N is labeled ($i = 1, \dots, N$) and depending on his or her initial health status, he or she is given a set of variables that characterize individual behavior toward infection. Indeed, if the individual with label i is initially susceptible, then he or she is given a threshold $Q_i > 0$ and a sojourn duration $L_i > 0$ in I . If this

individual is initially infectious, then only sojourn duration L_i in compartment I is attributed.

The evolution of health status depends on two kinds of events: an infection or a recovering (or removal). Infection events depend on the dynamic of a function called the infection pressure and defined as $P(t) = \frac{\beta}{N} \int_0^t W_I(s) ds$ so that if the individual with label i is initially susceptible, he or she remains susceptible as long as $Q_i > P(t)$ for $t \geq 0$. This function is proportional to the cumulative number of infectious individuals and accounts for the pressure exerted on susceptible individuals. Thus, as soon as $Q_i \leq P(t)$ he or she gets infected and moves to compartment I (see Figure 5.2). Individuals with thresholds which remain greater than the value of the infection pressure escape infection.

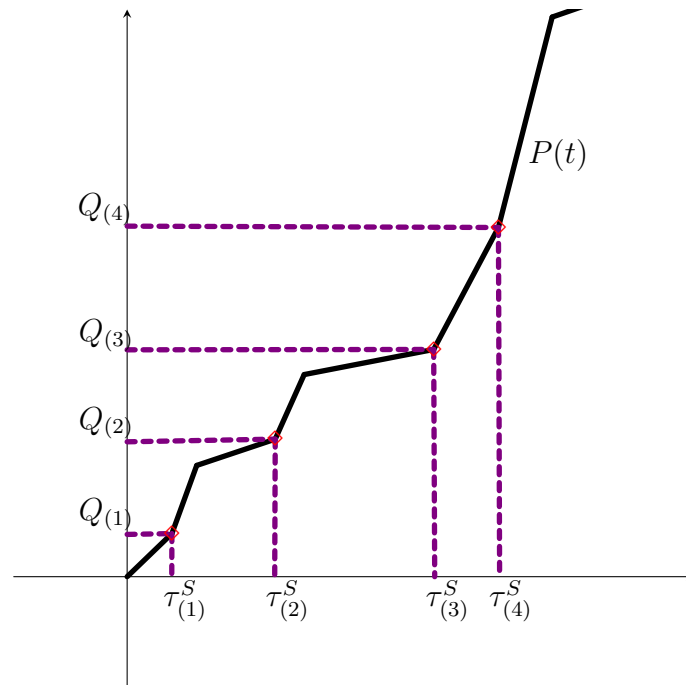


Figure 5.2 – An illustration of evolution of infection pressure $t \mapsto P(t)$. Marks \diamond denote points where infections have occurred. Quantities $0 \leq Q_{(1)} < Q_{(2)} < Q_{(3)} < Q_{(4)}$ are tolerance thresholds. Instants $\tau_{(1)}^S, \dots, \tau_{(4)}^S$ denote respectively infection times of susceptible individuals with thresholds $Q_{(1)}, \dots, Q_{(4)}$.

Regarding recovery events, they are based on sojourn duration of individuals. Suppose the individual with label i is initially infected ($t = 0$) or enters compartment I at time $t > 0$. If he has a sojourn duration in I equals to L_i , then at time $t + L_i$ he leaves I and move to R where he will stay forever.

This construction was originally introduced to study the distribution of the final size of epidemics modeled by the SIR model. Therefore, the approach is specific to the simple SIR model.

5.2.2 Description of general compartmental models

This subsection aims at presenting compartmental models in more generality. Modeling assumptions and notation necessary in the following are introduced.

Assume given a closed population of N individuals among which an epidemic outbreaks at time $t = 0$. Individuals present various health statuses that are listed in a set denoted \mathbf{V} . Health statuses partition the population into distinct groups. Individuals with health status $\alpha \in \mathbf{V}$ belong to the group or compartment α . Hereafter, we shall refer to health status α as compartment α and vice-versa. If individuals with health status α can switch from α to a different health status β , then compartments α and β are linked. This link defines the type of transition (α, β) in the direction $\alpha \rightarrow \beta$, which means that individuals of compartment α can jump to β . Denote \mathbf{E} the set of all types of transitions between compartments of \mathbf{V} . General compartmental models are under the form of a directed graph $\mathcal{G} = (\mathbf{V}, \mathbf{E})$ where \mathbf{V} stands for the set of vertices and \mathbf{E} represents the set of edges.

Over time, the health status of an individual can change, which defines a transition. Assume that each of the N individuals of the population is labeled: $1, 2, \dots, N$ at time $t = 0$. Consider the individual with label i and denote $X_i(t)$ his health status at time t . Transitions occur randomly so that for each $t > 0$, $X_i(t)$ is a random variable on the set \mathbf{V} . The evolution of $X_i(t)$ over time depends on some intrinsic characteristics of the individual i and also on epidemic parameters that are denoted θ . Let $\alpha \in \mathbf{V}$. For a time $t \geq 0$, $W_\alpha^\theta(t) = \sum_{i=1}^N \mathbb{1}_{X_i(t)=\alpha}$ defines the number of individuals with health status α , i.e. the number of individuals in compartment α . The global configuration of the population at time t is given by $W^\theta(t) = (W_\alpha^\theta(t))_{\alpha \in \mathbf{V}}$. Thus, $W^\theta = \{W^\theta(t), t \in [0, T]\}$ is a stochastic process that describes the epidemic dynamic in the population from the initial time 0 to a final time $T \in (0, +\infty]$. From the definition of W_α^θ , the global process W^θ takes values on the set $\mathcal{E} = \{w = (w_\alpha)_{\alpha \in \mathbf{V}} \in \mathbb{N}^{\text{card}\mathbf{V}} \mid \sum_{\alpha \in \mathbf{V}} w_\alpha = N\}$. The set \mathcal{E} is called the state space of process W^θ . Henceforth, assume that W^θ is càdlàg.

Let $\beta \in \mathbf{V}$ such that $(\alpha, \beta) \in \mathbf{E}$. Assume that the transition of type (α, β) occurs at time $\tau > 0$, i.e. an individual exits α and ends up in β . Denote τ^- the instant right before τ . Then, the following equations hold:

$$\begin{cases} W_\alpha^\theta(\tau) &= W_\alpha^\theta(\tau^-) - 1 \\ W_\beta^\theta(\tau) &= W_\beta^\theta(\tau^-) + 1 \\ W_\gamma^\theta(\tau) &= W_\gamma^\theta(\tau^-) \quad \forall \gamma \in \mathbf{V} \setminus \{\alpha, \beta\}. \end{cases} \quad (5.1)$$

Thus, from Equation (5.1) it yields that $W^\theta(\tau) = W^\theta(\tau^-) + \mathbf{u}_{\alpha, \beta}$ where $\mathbf{u}_{\alpha, \beta}$ is a vector with $\text{card}\mathbf{V}$ elements that includes -1 and +1 at positions corresponding respectively to α and β and 0 anywhere else. The vector $\mathbf{u}_{\alpha, \beta}$ is called a transition vector and characterizes transitions of type (α, β) , i.e. any transition of type (α, β) is under the form: $w \rightarrow w + \mathbf{u}_{\alpha, \beta}$ for $w \in \mathcal{E}$.

For $\alpha \in \mathbf{V}$, define the following sets: $\mathcal{P}_\alpha = \{\gamma \in \mathbf{V} \mid (\gamma, \alpha) \in \mathbf{E}\}$ and $\mathcal{C}_\alpha = \{\gamma \in \mathbf{V} \mid (\alpha, \gamma) \in \mathbf{E}\}$. Compartments $\alpha \in \mathbf{V}$ can be classified into three categories depending on whether corresponding sets \mathcal{P}_α and \mathcal{C}_α are empty or not: source compartments ($\mathcal{P}_\alpha = \emptyset, \mathcal{C}_\alpha \neq \emptyset$), transient compartments ($\mathcal{P}_\alpha \neq \emptyset, \mathcal{C}_\alpha \neq \emptyset$) and sink compartments ($\mathcal{P}_\alpha \neq \emptyset, \mathcal{C}_\alpha = \emptyset$). Notice that the category ($\mathcal{P}_\alpha = \emptyset, \mathcal{C}_\alpha = \emptyset$) is excluded because such compartments are completely isolated from others and thus irrelevant in modeling the epidemic dynamic.

Example 9. The SEI_1I_2RS model includes 5 compartments and 6 types of transitions such that: $\mathbf{V} = \{S, E, I_1, I_2, R\}$ and $\mathbf{E} = \{(S, E), (E, I_1), (E, I_2), (I_1, R), (I_2, R), (R, S)\}$. For instance, the transition vector of the type of transition $S \rightarrow E$ is $(-1, +1, 0, 0, 0)$ while that of $E \rightarrow I_2$ is $(0, -1, 0, +1, 0)$. Moreover $\mathcal{P}_E = \{S\}, \mathcal{C}_E = \{I_1, I_2\}$ etc.

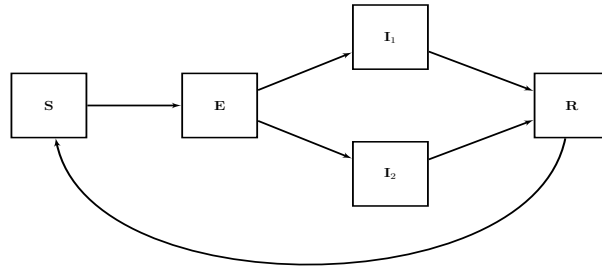


Figure 5.3 – An example of compartmental model: SEI_1I_2RS model

5.2.3 Extension of Sellke construction to general compartmental models

This subsection details a Sellke-type construction which extends the original Sellke construction to general compartmental models as described in Subsection 5.2.2. Like the original construction, the transition mechanisms of this approach depend on the type of compartments involved. But in addition, these mechanisms are now formulated in a more general way so as to address larger class of models such that: models with multitype health statuses (multiple compartments of susceptibles, infected or infectious etc.), models with "branching compartments" from which more than 2 types of transitions are possible (e.g. compartment E in the SEI_1I_2RS model in Figure 5.3, models with loops (e.g. models with reinfection $SIS, SIRS, SEI_1I_2RS, \dots$).

A transition consists in a switch from a health status to another one for an individual within the population. At the level of compartmental models, this results in a jump from a compartment to another. The jumps are ruled by

transition mechanisms which are supposed to be of two types: infection mechanism and sojourn duration mechanism. These two mechanisms are detailed in the following.

5.2.3.1 Infection mechanism

Let $\alpha \in \mathbf{V}$ such that α is a compartment composed of susceptible individuals (i.e. individuals who can contract the disease). Then infection events from α are driven by a function P_α called infection pressure defined as:

$$t \mapsto P_\alpha(t) = \int_0^t \psi_\alpha(\theta, W^\theta(s)) \, ds,$$

where ψ_α is a non-negative function so that P_α is a non-decreasing function. For example, in the original Sellke construction, $\psi_I(\theta, W^\theta(t)) = (\beta/N) \times W_I(t)$.

Infection pressure can be seen as a measure of the level of exposure to infection over time. With respect to the level of exposure, each individual present in the compartment has a tolerance (or resistance). This tolerance is given by a positive number. Assume that the individual with label i enters the compartment α at time $\eta_i^\alpha > 0$ or is initially present in α , i.e. $\eta_i^\alpha = 0$. Then, he or she is systematically assigned a positive value $Q_i^\alpha > 0$ called tolerance threshold. The thresholds $Q_i^\alpha, i = 1, \dots, N$ for any compartment α of susceptible individuals are drawn with positive continuous probability distributions (e.g. exponential distributions, Weibul distributions etc.). Individual with label i leaves α as soon as:

$$P_\alpha(t) \geq P_\alpha(\eta_i^\alpha) + Q_i^\alpha, \quad t \geq \eta_i^\alpha. \quad (5.2)$$

In particular, if the individual with label i is initially present in α (i.e. at time 0, this individual belongs to α), then $\eta_i^\alpha = 0$ and the condition of jump from α in Equation (5.2) yields:

$$P_\alpha(t) \geq Q_i^\alpha, \quad t \geq 0. \quad (5.3)$$

To better understand Equation (5.2), note that an individual who becomes susceptible at η_i^α has necessarily tolerance threshold greater than the infection pressure level at this time. Hence, the exit time of the individual with label i from compartment α is given by:

$$\tau_i^\alpha = \inf\{t \geq 0 \mid P_\alpha(t) \geq P_\alpha(\eta_i^\alpha) + Q_i^\alpha\}. \quad (5.4)$$

Since P_α is a non-decreasing function, then τ_i^α is well-defined in $[0, +\infty]$ and satisfies:

$$\tau_i^\alpha \geq t \iff P_\alpha(\eta_i^\alpha) + Q_i^\alpha \geq P_\alpha(t), \quad t \geq 0. \quad (5.5)$$

Straightforwardly, if $\eta_i^\alpha \leq t < \tau_i^\alpha$, then $X_i(t) = \alpha$.

It appears that this infection mechanism generalizes the one used in the original Sellke construction since the latter corresponds to the particular case $\eta_i^\alpha = 0$ given in Equation (5.3). This case implies that individuals can only leave the compartment of susceptibles. This new mechanism suggests to assign a threshold to an individual with respect to the pressure level at the time he or she becomes susceptible.

Furthermore, a compartment of susceptibles may have several pressure functions. This can appear when several pathogens or different strains of a pathogen are simultaneously spreading within a population. In such case, modelers could assume that each pathogen or each strain has a specific pressure function. Therefore, susceptible individuals are given tolerance thresholds with respect to each spreading pathogen or strain. An illustration of such mechanism is provided in Example 10.

Let us focus on models containing at least one loop, i.e. in such models, it is possible for an individual to leave a compartment and return back to it later after a finite number of transitions. In this case, for a given individual with label i and a given compartment α , the variable η_i^α which gives the entry time of the individual i in α can take different values over time, depending on the number of times the individual returns to the compartment. So, it defines a function $\eta_i^\alpha : t \mapsto \eta_i^\alpha(t) := \sup\{s \leq t \mid X_i(s) = \alpha\}$ of the time when $\eta_i^\alpha(t)$ gives the more recent instant when the individual i was in α . Notice that by construction, it is an increasing and piecewise-constant function. In the specific case of models with reinfections, the return to a compartment of susceptible individuals means that the individual has a new tolerance threshold, i.e. a new value Q_i^α . Thus, Q_i^α is variable over time, that makes it a function of time. Such a function is positive and piecewise-constant. Therefore, when the model contains loops, then construction variables for each individual can vary over time. As a consequence, it is not generally possible to know in advance for an individual the number of values of construction variables to use except in the case of models without loops.

5.2.3.2 Sojourn duration mechanism

Let $\alpha \in \mathbf{V}$ and suppose that the individual with label i enters α at time $\eta_i^\alpha \geq 0$. Then, he or she is automatically assigned a sojourn duration variable $L_i^\alpha > 0$ so that he or she leaves α at time $\eta_i^\alpha + L_i^\alpha$, where L_i^α is distributed with respect to a positive continuous probability distribution. Thus, individual i remains in α during time interval $[\eta_i^\alpha, \eta_i^\alpha + L_i^\alpha]$. Hence:

$$\forall t \in [\eta_i^\alpha, \eta_i^\alpha + L_i^\alpha], X_i(t) = \alpha, \quad (5.6)$$

and the exit time of i from α is $\tau_i^\alpha = \eta_i^\alpha + L_i^\alpha$.

In particular, if α is a sink compartment ($\mathcal{C}_\alpha = \emptyset$), then any individual that enters α is "trapped" indefinitely. Indeed, since $\mathcal{C}_\alpha = \emptyset$, no transition from α is possible. Therefore, if the individual with label i enters α at time $\eta_i^\alpha \geq 0$, then the sojourn duration of i in α is $+\infty$ so that the exit time of individual i from α is: $\tau_i^\alpha = +\infty$.

5.2.3.3 Transition choice mechanism

Let $\alpha \in \mathbf{V}$ such that $\text{card } \mathcal{C}_\alpha \geq 2$ (α is said to be a "branching" compartment). This means that at least two types of transitions from compartment α are possible. For example, in the SEI_1I_2RS model, one has $\text{card } \mathcal{C}_E = 2$.

Assume that the individual with label i jumps from α . Thus, $\text{card } \mathcal{C}_\alpha$ types of transitions can be performed. Let $p_{\alpha,\gamma} \in (0, 1)$ such that $\sum_{\gamma \in \mathcal{C}_\alpha} p_{\alpha,\gamma} = 1$ be the probability to choose the type of transitions (α, γ) among the $\text{card } \mathcal{C}_\alpha$ possibilities during a transition from α . Thus, in order to define the type of transition to execute during a transition of the individual with label i from compartment α , a variable M_i^α distributed under a multinomial distribution M^α valued on $\{(\alpha, \gamma), \gamma \in \mathcal{C}_\alpha\}$ with parameters $(p_{\alpha,\gamma})_{\gamma \in \mathcal{C}_\alpha}$ is simulated, where $p_{\alpha,\gamma} = \mathbb{P}(M^\alpha = (\alpha, \gamma))$. This mechanism enables to deal with models with "branching" compartments in our construction. Therefore, a larger class of compartmental models can be described compared to the original Sellke approach.

It should be noted that in the particular case of compartments of susceptible individuals, specific transition choice mechanism can be introduced depending on the epidemic modeling. For instance, consider the following model:

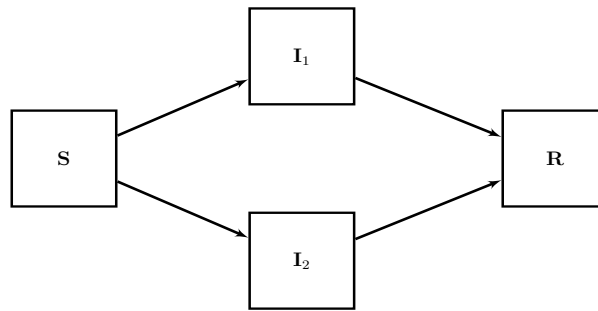


Figure 5.4 – Example of compartmental model: SI_1I_2R model

Example 10. In this model, $\mathcal{C}_S = \{I_1, I_2\}$ so that two kinds of infectious individuals are considered. Two types of infection mechanism can be considered:

- Mechanism based on global pressure

If infection events are ruled by one infection pressure P_S then each individual in compartment S is assigned with one tolerance threshold. When infection occurs, the choice between (S, I_1) and (S, I_2) is made by simulating a Bernoulli variable with parameter p_1 , where p_1 denotes the probability that an infected individual ends up in I_1 .

- Mechanism based on two pressure functions

Consider that infection events are driven by two infection pressures $P_S^{(1)}$ and $P_S^{(2)}$ so that susceptible individuals are given two tolerance thresholds. Assume that the individual with label i is susceptible and has tolerance thresholds $Q_i^{(1)}$ and $Q_i^{(2)}$ with respect to $P_S^{(1)}$ and $P_S^{(2)}$ respectively. If this individual gets infected at time t , the type of transition (S, I_1) is executed if $P_S^{(1)}(t) = Q_i^{(1)}$ and $Q_i^{(2)} > P_S^{(2)}$ and in the same way (S, I_2) is chosen if $P_S^{(2)}(t) = Q_i^{(2)}$ and $Q_i^{(1)} > P_S^{(1)}$. Hence, the type of transition to perform is given by the infection whose corresponding infection function reaches first the associated tolerance.

5.2.3.4 Description of the underlying stochastic process

Suppose that the following assumption holds:

Assumption 6. *Tolerance thresholds and sojourn time variables are distributed with respect to continuous nonnegative probability distributions.*

At the start of the epidemic ($t = 0$), in each compartment $\alpha \in \mathbf{V}$, the number of individuals is given by:

$$W_\alpha^\theta(0) = \sum_{i=1}^N \mathbb{1}_{X_i(0)=\alpha}$$

At time $t > 0$, each compartment $\alpha \in \mathbf{V}$ contains at most two categories of individuals: initially present individuals who have never left α and individuals that have ended up in α by jumping from a compartment $\gamma \in \mathcal{P}_\alpha$. The second category corresponds to individuals whose health status has switched from a previous status to α . Assume that the individual with label i is in α . Recall that τ_i^α denotes the exit time of i from compartment α . Then, the number of individuals $W_\alpha^\theta(t)$ in compartment α at time $t \geq 0$ is given by:

$$W_\alpha^\theta(t) = \sum_{i=1}^N \mathbb{1}_{\tau_i^\alpha > t, X_i(0)=\alpha} + \sum_{i=1}^N \sum_{\gamma \in \mathcal{P}_\alpha} \mathbb{1}_{\tau_i^\gamma \leq t < \tau_i^\alpha, M_i^\alpha = (\gamma, \alpha)} \quad (5.7)$$

Example 11. *Consider the classical SIR-model presented in Figure 5.1. We have $\theta = (\beta, \gamma_I)$, $\mathcal{P}_S = \emptyset$, $\mathcal{P}_I = \{S\}$ and $\mathcal{P}_R = \{I\}$ and $\mathcal{C}_R = \emptyset$. Assume the size of the population is N such that $W_S(0) + W_I(0) = N$. For an individual*

with label i , instants τ_i^S and τ_i^I denote exit times from compartments S and I respectively. Note that if $X_i(0) = I$, $\tau_i^S = 0$. Thus, the number of individuals in each compartment at time $t \geq 0$ is given by:

$$\begin{aligned} W_S(t) &= \sum_{i=1}^N \mathbb{1}_{\tau_i^S > t, X_i(0)=S} \\ W_I(t) &= \sum_{i=1}^N \mathbb{1}_{\tau_i^I > t, X_i(0)=I} + \sum_{i=1}^N \mathbb{1}_{\tau_i^S \leq t < \tau_i^I} \\ W_R(t) &= \sum_{i=1}^N \mathbb{1}_{\tau_i^I \leq t} \end{aligned}$$

By splitting $W_R(t)$ into two sums, it could be noted that $W_S(t) + W_I(t) + W_R(t)$ yields:

$$\begin{aligned} \sum_{i=1}^N \mathbb{1}_{\tau_i^S > t, X_i(0)=S} + \left(\sum_{i=1}^N \mathbb{1}_{\tau_i^I \leq t, X_i(0)=S} + \sum_{i=1}^N \mathbb{1}_{\tau_i^S \leq t < \tau_i^I} \right) \\ + \left(\sum_{i=1}^N \mathbb{1}_{\tau_i^I > t, X_i(0)=I} + \sum_{i=1}^N \mathbb{1}_{\tau_i^I \leq t, X_i(0)=I} \right) = N, \end{aligned}$$

because the second term of the sum in the left hand side yields $\sum_{i=1}^N \mathbb{1}_{\tau_i^I \leq t, X_i(0)=S} + \sum_{i=1}^N \mathbb{1}_{\tau_i^S \leq t < \tau_i^I} = \sum_{i=1}^N \mathbb{1}_{\tau_i^S \leq t, X_i(0)=S}$.

Each process W_α^θ defined as the number of individuals in compartment α at time $t \geq 0$ is a stochastic jump process with jumps -1 and $+1$. Jumps -1 and $+1$ occur when an individual leaves or enters α respectively. Let focus on the jump -1 from some compartment distinct of α . Let $t \geq 0$ and assume that the individual with label i is such that $X_i(t) = \alpha$. Let τ_i^α be its exit time from α . Therefore, the time at which an individual exits α is given $\min\{\tau_i^\alpha \mid X_i(t) = \alpha, i = 1, \dots, N\}$. This corresponds to the smallest exit time among exit times of individuals present in the compartment α at time t .

Therefore, relying on Equation (5.7), the global stochastic process W^θ is entirely described by tolerance thresholds, sojourn times and multinomial variables. For such a jump process, the following recursive system describes the sequence of jump times $(T_n)_{n \geq 0}$ of the process W^θ :

$$\begin{cases} T_0 = 0 \\ T_{n+1} := \min_{\alpha \in \mathbf{V}} \{ \min\{\tau_i^\alpha, i = 1, \dots, N \mid X_i(T_n) = \alpha\} \} \end{cases} \quad (5.8)$$

Equation (5.8) states that conditionally to T_n , the next jump time of the process W^θ is given by the smallest exit time from all the compartments. Notice that the sequence $(T_n)_{n \geq 0}$ is non-decreasing since for any compartment

$\alpha \in \mathbf{V}$ and any individual with label $i = 1, \dots, N$ such that $X_i(T_n) = \alpha$, it holds: $\tau_i^\alpha \geq T_n$.

Under specific probabilistic conditions, the process W^θ is a continuous-time Markov chain. This result is detailed in Proposition 7.

Proposition 7. *Recall that for a compartment α of susceptible individuals, infection pressure function is under the form $P_\alpha(t) = \int_0^t \psi_\alpha(\theta, W^\theta(s)) ds$ where ψ is a nonnegative function. Assume that:*

- i. the tolerance thresholds variables, the sojourn time variables and the multinomial variables are independent,*
- ii. the tolerance thresholds are i.i.d. variables distributed under an exponential distribution with mean 1,*
- iii. the sojourn times are i.i.d. variables distributed under some exponential distribution,*
- iv. the multinomial variables are iid,*

In the context of Markovian epidemic modeling, for any epidemic parameter θ , the extended Sellke construction yields a homogeneous continuous-time Markov chain W^θ characterized by the generator $\mathcal{Q}(\xi, \xi')_{\xi, \xi' \in \mathcal{E}}$ defined as follows:

$$\mathcal{Q}(\xi, \xi') = \begin{cases} \mathcal{Q}(\xi, \xi + \mathbf{u}_{\alpha, \beta}) & \text{if } \exists (\alpha, \beta) \in \mathbf{E} : \xi' = \xi + \mathbf{u}_{\alpha, \beta} \\ -\sum_{(\alpha, \beta) \in \mathbf{E}} \mathcal{Q}(\xi, \xi + \mathbf{u}_{\alpha, \beta}) & \text{if } \xi' = \xi \\ \mathcal{Q}(\xi, \xi') = 0 & \text{otherwise} \end{cases} \quad (5.9)$$

where:

$$\begin{aligned} \mathcal{Q}(\xi, \xi + \mathbf{u}_{\alpha, \beta}) &= \lim_{\varepsilon \rightarrow 0} \frac{\mathbb{P}(W^\theta(s + \varepsilon) = \xi + \mathbf{u}_{\alpha, \beta} \mid W^\theta(s) = \xi)}{\varepsilon} \\ &= \begin{cases} p_{\alpha, \beta} \cdot \xi_\alpha \cdot \psi_\alpha(\theta, \xi) & \text{if } (\alpha, \beta) \text{ is an infection transition} \\ p_{\alpha, \beta} \cdot \xi_\alpha \cdot \lambda_\alpha & \text{otherwise} \end{cases} \end{aligned} \quad (5.11)$$

and $s \geq 0$, $\xi = (\xi_\alpha)_{\alpha \in \mathbf{V}} \in \mathcal{E}$, λ_α is the mean sojourn duration in compartment α and $p_{\alpha, \beta}$ denotes the probability to perform the type of transitions (α, β) .

Proposition 7 ensures that when conditions are fulfilled, the resulting model of Sellke construction is a Markovian model with rates given in Equation (5.11). Note that these conditions regarding independence and exponential distributions as specified above, are necessary to obtain Markovian processes. For example, it is sufficient that a sojourn variable is not distributed under exponential distribution for the resulting process to be non-Markovian.

5.3 Simulation algorithm based on extended Sellke construction

This section is devoted to building an algorithm to simulate the process $W^\theta = \{W^\theta(t), 0 \leq t \leq T\}$ for a given final time $T > 0$. For this purpose, in Subsection 5.3.1, we provide a recursive description of dynamics of W^θ and then derive an algorithm. In Subsection 5.3.2, some simulations of dynamics for an SEI_1I_2RS model are carried out in order to illustrate our method.

5.3.1 Algorithm

Let $t \geq 0$ and $\xi_0 \in \mathcal{E}$. Recall that $(T_n)_{n \geq 1}$ denotes the sequence of jump times of the process W^θ and τ_i^α the exit time of an individual with label i from compartment α . Let $(\alpha^{(n+1)}, \beta^{(n+1)})$ be the type of transitions performed at jump time T_{n+1} for $n \geq 0$. Finally, let M_i^α be a sample of a multinomial distribution M^α with parameters $(\text{card } \mathcal{C}_\alpha = k; p_{\alpha, \gamma_1}, \dots, p_{\alpha, \gamma_k})$ such that $p_{\alpha, \gamma_l} > 0$ for all $l = 1, \dots, k$ and $\sum_{l=1}^k p_{\alpha, \gamma_l} = 1$.

Then, the dynamic of the process W^θ is entirely described by the following recursive system:

$$\left\{ \begin{array}{l} T_0 = 0 \\ W^\theta(T_0) = \xi_0 \\ T_{n+1} = \min_{\alpha \in \mathbf{V}} \{ \min\{\tau_i^\alpha, i = 1, \dots, N \mid X_i(T_n) = \alpha\} \} \\ \alpha^{(n+1)} = \underset{\alpha \in \mathbf{V}}{\text{argmin}} \{ \min\{\tau_i^\alpha, i = 1, \dots, N \mid X_i(T_n) = \alpha\} \} \\ i^* = \underset{i: X_i(T_n) = \alpha^{(n+1)}}{\text{argmin}} \tau_i^{\alpha^{(n+1)}} \\ \beta^{(n+1)} = \underset{\beta \in \mathcal{C}_{\alpha^{(n+1)}}}{\text{argmax}} \mathbb{1}_{M_{\alpha^{(n+1)}}^{i^*} = (\alpha^{(n+1)}, \beta)} \\ W^\theta(T_{n+1}) = W^\theta(T_n) + \mathbf{u}_{\alpha^{(n+1)}, \beta^{(n+1)}} \end{array} \right. \quad \text{for } n \geq 0. \quad (5.12)$$

Let $\alpha \in \mathbf{V}$. To describe the simulation of multinomial variables, let us suppose that $\mathcal{C}_\alpha \neq \emptyset$ with $\mathcal{C}_\alpha = \{\gamma_1, \dots, \gamma_k\}$ where $k = \text{card } \mathcal{C}_\alpha \geq 1$. Denote p_{α, γ_j} the probability to pick the type of transitions (α, γ_j) where $j = 1, \dots, k$. Let U be standard uniform variable, then M_α^i is simulated by:

$$\sum_{j=1}^k \gamma_j \mathbb{1}_{U \in [\sum_{l=1}^{j-1} p_{\alpha, \gamma_l}, \sum_{l=1}^j p_{\alpha, \gamma_l}]}$$

Regarding the computation of next exit times from a compartment $\alpha \in \mathbf{V}$, let assume that the process is in state $W^\theta(T_n)$ at time $t \geq T_n$. The way of computing next exit times depends on the type of compartment. Let κ^α denote

the next exit time from compartment α conditionally that the current state of the system $(T_n, W^\theta(T_n))$ remains unchanged.

Assume that α is not a compartment of susceptible individuals. Thus, the transition mechanism is based on sojourn time and $\kappa^\alpha = \min\{\tau_i^\alpha, i = 1, \dots, N \mid X_i(T_n) = \alpha\}$. Otherwise, if α is a compartment of susceptible individuals, then α is characterized by a pressure function P_α . Conditionally to the current state of the system $(T_n, W^\theta(T_n))$, the function P_α is affine on $[T_n, \kappa^\alpha[$ and satisfies:

$$P_\alpha(s) = P_\alpha(T_n) + \psi_\alpha(\theta, W^\theta(T_n)) \cdot (s - T_n), \quad (5.13)$$

for all $s \in [T_n, \kappa^\alpha[$.

Denote Q_i^α the tolerance threshold of individual i such that $X_i(T_n) = \alpha$ and let $Q_{min}^\alpha = \min\{Q_i^\alpha, i = 1, \dots, N \mid X_i(T_n) = \alpha\}$. According to the infection mechanism, the transition occurs when P_α reaches the resistance Q^α . The putative next exit time from α (i.e. not necessarily the true next exit time) is the exit time of the individual with tolerance Q_{min}^α :

$$\kappa^\alpha = \begin{cases} T_n + \frac{Q_{min}^\alpha - P_\alpha(T_n)}{\psi_\alpha(\theta, W^\theta(T_n))} & \text{if } \psi_\alpha(\theta, W^\theta(T_n)) > 0 \\ +\infty & \text{otherwise.} \end{cases} \quad (5.14)$$

Note that $\kappa^\alpha \geq T_n$ since $Q_{min}^\alpha > P_\alpha(T_n)$. Therefore Equation (5.14) provides a recursive equation that enables to compute the next exit time from a susceptible status compartment α conditionally to the current time and state of the process, i.e. $(T_n, W^\theta(T_n))$. Let T be the final time of the study. Note that T is chosen may not necessarily be the extinction time of the epidemic.

Before showing the algorithm, let us introduce some notation.

Notation:

- \mathcal{S} denotes the set of all compartments of susceptible individuals
- \mathcal{T} is the set of all compartments which are not sink compartments and which do not contain susceptible individuals
- Q_i^α denotes the tolerance of individual i in $\alpha \in \mathcal{S}$. Assume Q_i^α are distributed under a nonnegative continuous distribution Q^α .
- L_i^α is the sojourn time of individual i in $\alpha \in \mathcal{T}$. Assume L_i^α are distributed under a nonnegative continuous distribution L^α .

Algorithm 12 is based on the following principle. At each transition, putative exit times of the compartments are computed and the transition to be performed is given by the one associated with the minimum exit time at the scale of the whole system. This principle is that of the Gillespie First Reaction Method Algorithm 2. Moreover, this algorithm only considers the exit times

Algorithm 12 Simulation algorithm**Inputs:** θ **Require:** $\xi_0, \{\psi_\alpha, \alpha \in \mathcal{S}\}, \{\mathbf{u}_{\alpha,\beta}, (\alpha, \beta) \in \mathbf{E}\}, T$

```

1:  $t \leftarrow 0, w(t) \leftarrow \xi_0$ 
2:  $P_\alpha(t) \leftarrow 0$ 
3: for  $i$  such that  $X_i(0) = \alpha$  do
4:   Draw  $Q_i^\alpha$  under  $Q^\alpha$ 
5: end for
6: for  $\alpha \in \mathcal{T}$  do
7:   Draw  $L_i^\alpha$  under  $L^\alpha$ 
8:    $\tau_i^\alpha \leftarrow L_i^\alpha$ 
9: end for
10: while  $t < T$  do
11:   for  $\alpha \in \mathcal{S}$  do
12:      $Q_{min}^\alpha \leftarrow \min\{Q_i^\alpha, i = 1, \dots, N \mid X_i(t) = \alpha\}$ 
13:      $A_\alpha \leftarrow \psi_\alpha(\theta, w(t))$ 
14:      $\kappa^\alpha \leftarrow t + (Q_{min}^\alpha - P_\alpha(t)) / A_\alpha$ 
15:   end for
16:   for  $\alpha \in \mathcal{T}$  do
17:      $\kappa^\alpha \leftarrow \min\{\tau_i^\alpha, i = 1, \dots, N \mid X_i(t) = \alpha\}$ 
18:   end for
19:    $\kappa \leftarrow \min\{\kappa^\alpha, \alpha \in \mathcal{S} \cup \mathcal{T}\}$ 
20:    $\alpha^* \leftarrow \operatorname{argmin}_{\alpha \in \mathcal{S} \cup \mathcal{T}} \kappa^\alpha$ 
21:   for  $\alpha \in \mathcal{T}$  do
22:      $P_\alpha(\kappa) \leftarrow P_\alpha(t) + A_\alpha \times (\kappa - t)$ 
23:   end for
24:   if  $\alpha^* \in \mathcal{S}$  then
25:      $i^* \leftarrow \operatorname{argmin}_{\{i \mid X_i(t) = \alpha^*\}} Q_i^{\alpha^*}$ 
26:     Remove  $Q_{i^*}^{\alpha^*}$ 
27:   end if
28:   if  $\alpha^* \in \mathcal{T}$  then
29:      $i^* \leftarrow \operatorname{argmin}_{\{i \mid X_i(t) = \alpha^*\}} \tau_i^{\alpha^*}$ 
30:     Remove  $\tau_{i^*}^{\alpha^*}$ 
31:   end if
32:   Draw  $U$  under  $\mathcal{U}([0, 1])$ 
33:    $\beta^* \leftarrow \operatorname{argmax}_{\gamma_j \in \mathcal{C}_{\alpha^*}} \mathbb{1}_{U \in [\sum_{l=1}^{j-1} p_{\alpha^*, \gamma_l}, \sum_{l=1}^j p_{\alpha^*, \gamma_l}]}$ 
34:    $w(\kappa) \leftarrow w(t) + \mathbf{u}_{\alpha^*, \beta^*}$ 
35:    $t \leftarrow \kappa$ 
36:   if  $\beta^* \in \mathcal{S}$  then
37:     Draw  $Q_{\text{new}}$  under  $Q^{\beta^*}$ 
38:      $Q_{i^*}^{\beta^*} \leftarrow P_{\beta^*}(t) + Q_{\text{new}}$ 
39:   end if
40:   if  $\beta^* \in \mathcal{T}$  then
41:     Draw  $L_{\text{new}}$  under  $L^{\beta^*}$ 
42:      $\tau_{i^*}^{\beta^*} \leftarrow t + L_{\text{new}}$ 
43:   end if
44: end while

```

of the individuals. At a given time, it is not possible to know the compartment in which a given individual is located. This makes it more computationally efficient. Actually, Algorithm 12 is not an agent-based algorithm because it does not track individuals. The related complexity that is between the complexity of Gillespie First Reaction Method Algorithm associated to the compartmental model and that of the associated agent-based algorithm.

5.3.2 Simulations

In this subsection, Algorithm 12 is used to simulate dynamics of an SEI_1I_2RS model (see Figure 5.3). This model enables to describe the propagation of an epidemic within a population with the following characteristics: existence of an incubation period for the infected individuals, the presence of two categories of infectious individuals and the absence of total immunity (possible reinfection). For instance, it could allow to model the spread of SARS-CoV-2 by considering individuals in compartment I_1 as symptomatic people and those in compartment I_2 as asymptomatic people. Such a model includes six types of transitions detailed in Table 5.1.

Type of transition	Type	Transition vector
(S, E)	infection	$(-1, 1, 0, 0, 0)$
(E, I_1)	first type infection activation	$(0, -1, 1, 0, 0)$
(E, I_2)	second type infection activation	$(0, -1, 0, 1, 0)$
(I_1, R)	first type recovery	$(0, 0, -1, 0, 1)$
(I_2, R)	second type recovery	$(0, 0, 0, -1, 1)$
(R, S)	reinfection	$(1, 0, 0, 0, -1)$

Table 5.1 – Description of the model transitions between states $\{S, E, I_1, I_2, R\}$.

Model dynamics depend on six epidemic parameters provided in Table 5.2. Let us denote θ the vector of all parameters and choose $T \in (0, +\infty)$. We study the process $W^\theta = \{(W_S(t), W_E(t), W_{I_1}(t), W_{I_2}(t), W_R(t)), t \in [0, T]\}$ that counts over time in each compartment the number of individuals. In this modeling, it is assumed that only one pathogen agent is spreading. In addition, the transmission parameter β is assumed to be the same for individuals in compartment I_1 and I_2 so that the infection pressure is given by:

$$P_S(t) = \frac{\beta}{N} \int_0^t (W_{I_1}(s) + W_{I_2}(s)) ds.$$

Parameter Name	Parameter Role	Nominal value	Range of variation
β	transmission rate	0.2	$\mathcal{U}([0.01, 0.25])$
$1/\mu_E$	mean sojourn duration in E	5 days	$\mathcal{U}([0.4, 9.5])$
p	probability for an exposed to move to I_1	0.6	$\mathcal{U}([0.3, 0.7])$
$1/\mu_1$	mean sojourn time in I_1	8 days	$\mathcal{U}([0.1, 10.6])$
$1/\mu_2$	mean sojourn time in I_2	5 days	$\mathcal{U}([0.1, 7.9])$
$1/\delta$	mean sojourn time in R	120 days	$\mathcal{U}([60, 180])$

Table 5.2 – Model parameter nominal values and their probability distributions with ranges of variation (Knock et al., 2021)

Moreover, it is assumed that tolerance thresholds towards P_S are distributed under exponential with mean 1.

For illustration purpose, parameters are set to their nominal values (see Table 5.2) and simulations are carried out with respect to two cases: Markovian and non-Markovian. The difference between the two cases lies in the fact that the probability distributions of tolerance thresholds, sojourn time variables are exponential or not. The two cases are presented in the following.

5.3.2.1 Markovian case

In Markovian case, sojourn times in E, I_1, I_2 and R are respectively distributed under exponential distributions with mean $1/\mu_E, 1/\mu_1, 1/\mu_2$ and $1/\delta$. Moreover, tolerance thresholds are drawn from an exponential distribution with mean 1. The associated model is a continuous-time Markov chain with rates given in Table 5.3.

Type of transition	Rates
(S, E)	$\frac{\beta}{N} \cdot W_S \cdot (W_{I_1} + W_{I_2})$
(E, I_1)	$p \cdot \mu_E \cdot W_E$
(E, I_2)	$(1 - p) \cdot \mu_E \cdot W_E$
(I_1, R)	$\mu_1 \cdot W_{I_1}$
(I_2, R)	$\mu_2 \cdot W_{I_2}$
(R, S)	$\delta \cdot W_R$

Table 5.3 – Transition rates for the Markovian model.

The scale limit of such a model as $N \rightarrow \infty$ is an ODE system which is nothing but the corresponding SEI_1I_2RS deterministic model given in Equation (5.15):

$$\begin{cases} \frac{d}{dt}w_S(t) &= \delta w_R(t) - \frac{\beta}{N}w_S(t) \times (w_{I_1}(t) + w_{I_2}(t)) \\ \frac{d}{dt}w_E(t) &= \frac{\beta}{N}w_S(t) \times (w_{I_1}(t) + w_{I_2}(t)) - \mu_E w_E(t) \\ \frac{d}{dt}w_{I_1}(t) &= p \times \mu_E \times w_E(t) - \mu_1 w_{I_1}(t) \\ \frac{d}{dt}w_{I_2}(t) &= (1 - p) \times \mu_E \times w_E(t) - \mu_2 w_{I_2}(t) \\ \frac{d}{dt}w_R(t) &= \mu_1 w_{I_1}(t) + \mu_2 w_{I_2}(t) - \delta w_R(t) \end{cases} \quad (5.15)$$

In order to compare fluctuations of paths generated by Algorithm 12 to the theoretical mean trajectories in Markovian case, the ODE system is solved and solutions $(w_S, w_E, w_{I_1}, w_{I_2}, w_R)$ are displayed together with Algorithm 1 outputs.

5.3.2.2 Non-Markovian case

The non-Markovian character of the model originates from the use of Gamma distributions with shapes distinct of 1 to simulate sojourn time variables in compartments E, I_1 and I_2 . Indeed, if shapes were equal to 1, Gamma distributions would actually coincide with exponential distributions. Therefore, from Proposition 7, it follows that the resulting model would be Markovian. The use of Gamma distributions including Erlang distributions to describe sojourn in compartments is common in non-Markovian epidemic modeling. One could refer to Pellis et al. (2015); Rost et al. (2016); Vajdi et al. (2021); Di Lauro et al. (2022), etc. Here, the probability distributions used in the non-Markovian case are listed in Table 5.4.

Variables	Probability distributions
Tolerance thresholds	Exponential with mean 1
Sojourn time in E	Gamma with shape ρ_E and rate $\rho_E \times \mu_E$
Sojourn time in I_1	Gamma with shape ρ_1 and rate $\rho_1 \times \mu_1$
Sojourn time in I_2	Gamma with shape ρ_2 and rate $\rho_2 \times \mu_2$
Sojourn time in R	Gamma with shape ρ_R and rate $\rho_R \times \delta$

Table 5.4 – Probability distributions of thresholds and sojourn times. It should be noted that gamma distribution shapes: ρ_E, ρ_1, ρ_2 and ρ_R are arbitrarily chosen.

Note that the mean sojourn times in compartments E, I_1, I_2 and R remain the same in both Markovian and non-Markovian cases. Indeed, given $\rho > 0$ and $\mu > 0$, the Gamma distribution with shape ρ and rate $\rho \times \mu$ (denoted $\mathcal{G}(\rho, \rho \times \mu)$) and the Exponential distribution with mean $1/\mu$ (denoted $Exp(\mu)$) share the same mean, that is, $\rho/(\rho \times \mu) = 1/\mu$. However, variances of these two distributions are different if $\rho \neq 1$. It appears that the variance of $\mathcal{G}(\rho, \rho \times \mu)$ is $V_G = 1/(\rho \times \mu^2)$ while that of $Exp(\mu)$ is $V_E = 1/\mu^2$. Therefore, if $\rho < 1$, $V_G > V_E$ and conversely, if $\rho > 1$ then $V_G < V_E$. Hence, depending on the choice of shape ρ , different behavior of the process W^θ could be expected.

For this non-Markovian model, the scale limit when $N \rightarrow \infty$ is no longer an ODE system but rather a system of integrodifferential equations (IDE) as studied in Pang and Pardoux (2022); Forien et al. (2021a). It turns out that the IDE system is complex so that even a numerical solving was not considered. Instead, the empirical mean of a set of trajectories is used to heuristically illustrate the limit.

5.3.2.3 Numerical setting and simulations

For simulation purposes, a population of $N = 2005$ individuals is considered. At $t = 0$, it is assumed that 5 individuals are exposed while the 2000 remaining

individuals are all susceptible. Epidemic dynamic is observed over the interval $[0, 500]$ (i.e. $T = 500$ days) and in addition epidemic parameters are set to nominal values provided in Table 5.2.

Figure 5.5 shows epidemic dynamics in Markovian case (this corresponds to the case where every shape of various sojourn time distributions is equal to 1). One could note that trajectories fluctuate well around the theoretical mean given by the solution of the ODE system in Equation 5.15. This ensures that up to randomness, our stochastic simulator returns correct process realizations. The dynamics shown in this figure are emergent trajectories, i.e. trajectories obtained conditionally to non-extinction of the epidemic. By relying on extinction time defined as the first time when $W_E = 0$, $W_{I_1} = 0$ and $W_{I_2} = 0$ (here empirically defined here as extinction before day 125), it occurs that the proportion of early extinction of epidemics among 50 epidemic dynamics reaches 20%, i.e., empirically, one epidemic scenario out of 5 leads to early extinction.

In the non-Markovian framework, two cases are considered regarding Gamma distribution shapes: $\rho_E = 50$ and $\rho_E = 1/50$. This means that only the sojourn durations in compartment E are not distributed under exponential laws. Note that the choice of shape parameters are not necessarily realistic (Forien et al., 2021b). They are simply used for illustration purposes.

The main point that arises when analyzing Figure 5.6 is that each output W_E , W_{I_1} and W_R , dynamics are different from one case to another. On average, the model with $\rho_E = 50$ predicts more expositions to infection than that of shapes equal to $\rho_E = 1/50$. It also occurs that the proportion of early extinction of epidemics rises to 80% before day 125 in the case $\rho_E = 1/50$ whereas it is below 10% in the case $\rho_E = 50$. This is in agreement with previous findings in modeling of infectious diseases, where the level of extinction was shown to be higher when variance of the sojourn time distribution was also higher (see for instance Keeling and Grenfell (2002)).

To understand why in the case $\rho_E = 1/50$, the model predicts fewer number of exposed, consider densities of the Gamma distributions (refer to Figure 5.A.1). One could notice that when the shape parameter of a Gamma distribution is lower than 1, its density is decreasing and maximal at point 0. This means that the distribution is such that small values have larger weights. Thus, when drawing the sojourn duration in compartment E with such a distribution, a large proportion of samples are close to 0 (refer to Figure 5.A.2). As a result, individuals only have short stays in E . This explains the low number of exposed individuals since they do not accumulate in E .

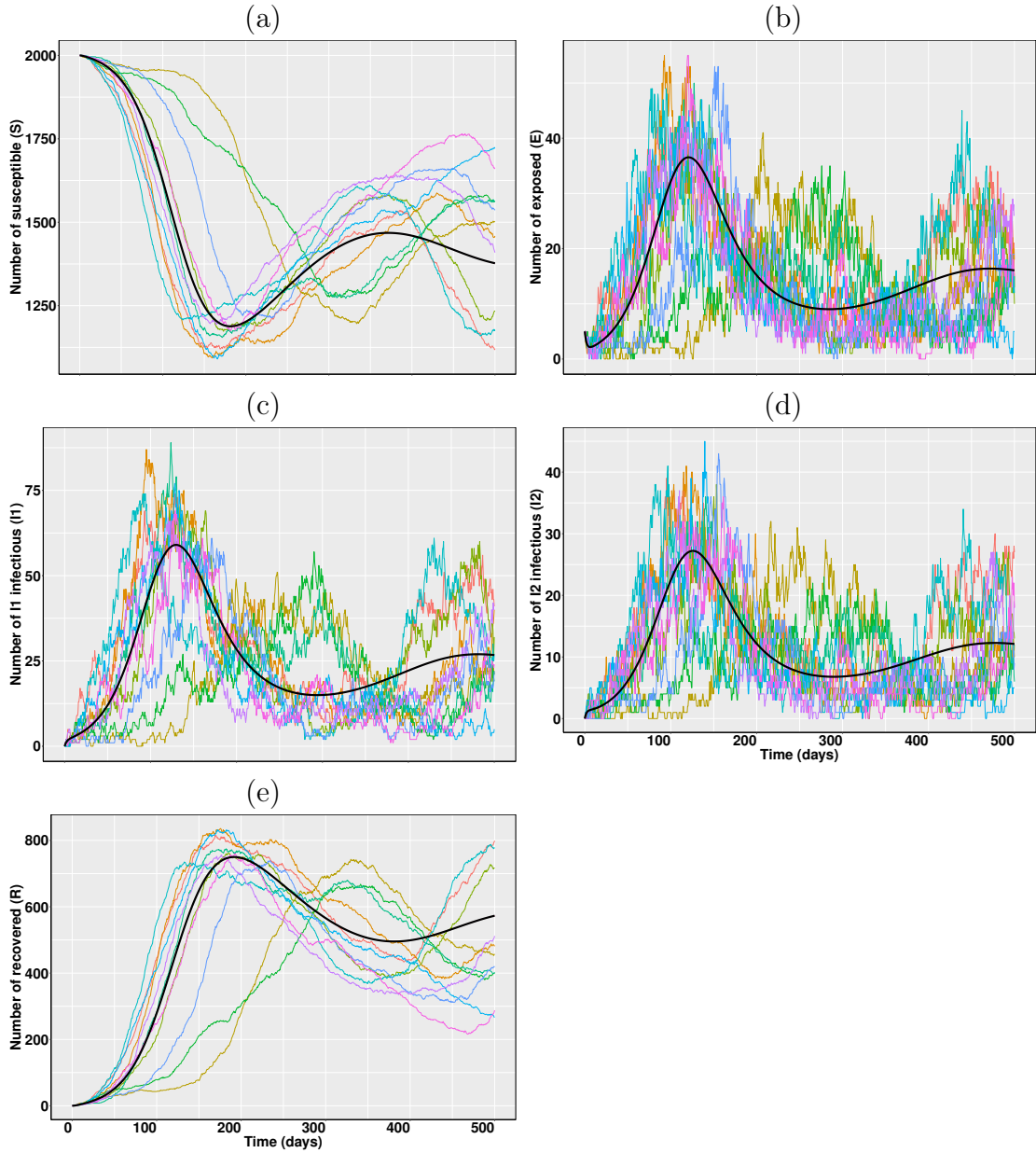


Figure 5.5 – 15 trajectories over $[0, 500]$ of number of individuals in compartments S, E, I_1, I_2 and R in the given Markovian case. The black curve corresponds to the solutions of the ODE defined in Equation (5.15). Epidemic parameters are equal and set to nominal values in Table 5.2.

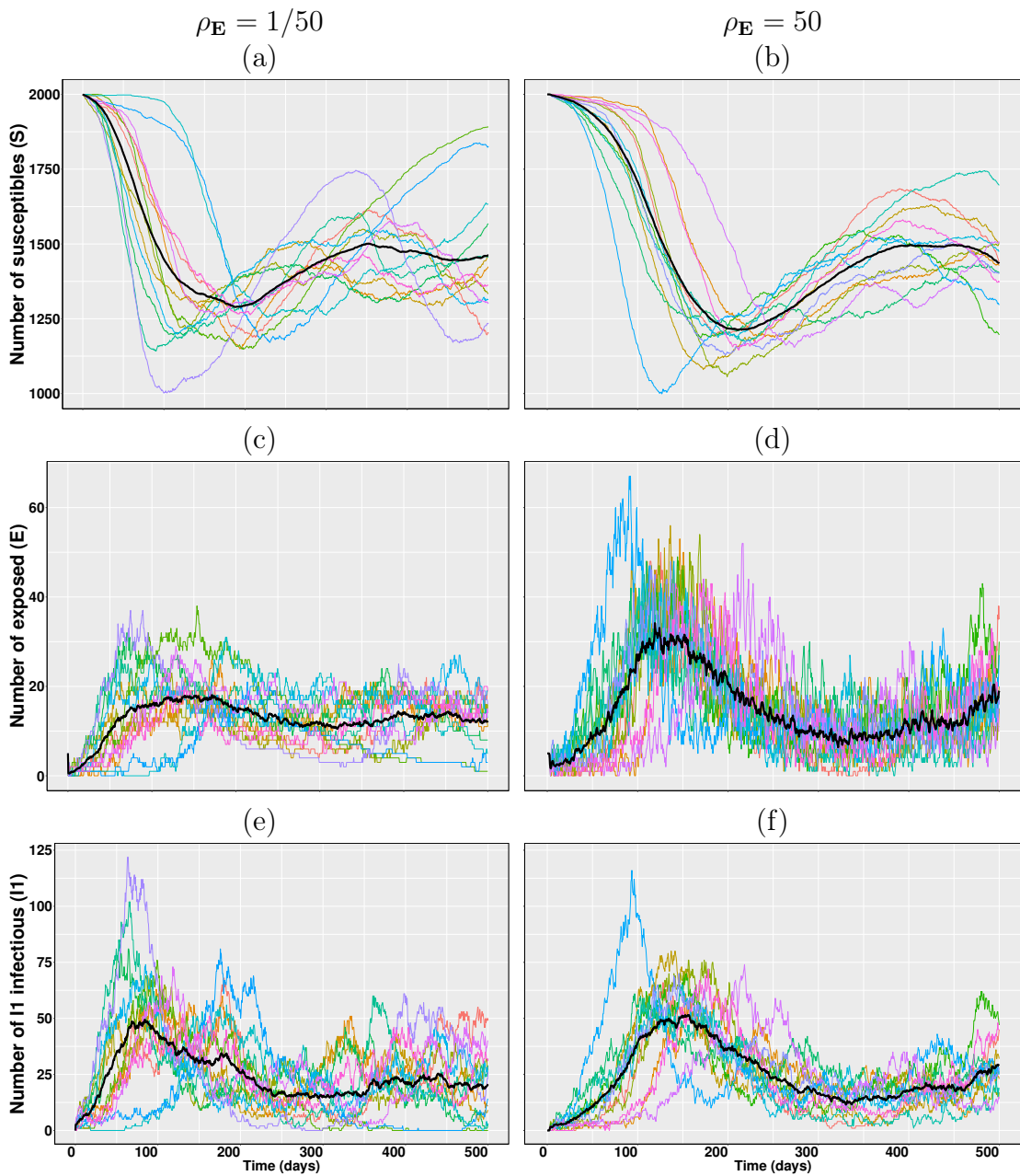


Figure 5.6 – 15 trajectories over $[0, 500]$ of number of individuals in compartments S , I_1 and R in the non-Markovian case, where $\rho_E = 1/50$, $\rho_1 = \rho_2 = \rho_R = 1$ (a,c,e) and the case $\rho_E = 50$, $\rho_1 = \rho_2 = \rho_R = 1$ (b, d, f). For both cases, epidemic parameters are equal and set to nominal values provided in Table 5.2. The black curve corresponds to empirical time-wise mean over the 15 trajectories.

5.4 Sensitivity analysis

This section aims at performing global sensitivity analysis of some quantities of interest defined from outputs of W^θ . In particular, we are interested in contributions of the intrinsic randomness of the non-Markovian process W^θ under different conditions. For this purpose, we introduce a deterministic representation of W^θ as in Kouye et al. (2022), that is, W^θ is put under the form of a deterministic function of θ and of a collection of random variables with known distributions that models the intrinsic randomness.

5.4.1 Deterministic representation

Let $\alpha \in \mathbf{V}$ and $t \geq 0$. Based on Equation (5.7), the number of individuals in compartment α at time t , $W_\alpha^\theta(t)$, is a function of exit times of individuals and multinomial variables. However, exit times of individuals can be written as sums of sojourn time variables and some functions of tolerance thresholds. More precisely, latter functions are defined as generalized inverses of pressure functions. Let us illustrate statements above through an example.

Example 12. *Consider the SEI_1I_2RS model. Then, health statuses are: S, E, I_1, I_2 and R . Assume that the individual with label i is initially susceptible, i.e., that $X_i(0) = S$. In addition, suppose that this individual will transit through the compartment I_1 . For such an individual, let us denote $Q_i^S, L_i^E, L_i^{I_1}, L_i^R$ his or her tolerance threshold, sojourn time variable in E and I_1 respectively. Thus, the first four exit times of individual with label i are given by:*

$$\begin{cases} \tau_i^S &= \inf\{s \geq 0 \mid P_S(s) \geq Q_i^S\} = P_S^{(-1)}(Q_i^S) \\ \tau_i^E &= \tau_i^S + L_i^E = P_S^{(-1)}(Q_i^S) + L_i^E \\ \tau_i^{I_1} &= \tau_i^S + L_i^E + L_i^{I_1} = P_S^{(-1)}(Q_i^S) + L_i^E + L_i^{I_1} \\ \tau_i^R &= \tau_i^S + L_i^E + L_i^{I_1} + L_i^R = P_S^{(-1)}(Q_i^S) + L_i^E + L_i^{I_1} + L_i^R \end{cases}$$

Therefore, it appears that any exit time is entirely function of multinomial variables, tolerance thresholds and sojourn time variables. Assume that this collection is simulated by using a sequence U of i.i.d. standard uniform variables. Let denote by $(\mathcal{L}([0,1]), \Omega)$ a measurable space of sequences on $[0,1]$. Let Θ the set of all parameters and $(\Theta, \mathcal{B}(\Theta))$ a measurable space. Thus, for all $i = 1, \dots, N$ and for $\alpha \in \mathbf{V}$, there exists a function $g_\alpha^{(i)} : (\theta, u) \in \Theta \times \mathcal{L}([0,1]) \mapsto g_\alpha^{(i)}(\theta, u)$ such that $\tau_i^\alpha = g_\alpha^{(i)}(\theta, u)$ for some $u \in \mathcal{L}([0,1])$. From Equation (5.7), it is straightforward that, for all $t \geq 0$:

$$\begin{aligned} W_\alpha^\theta(t) &= \sum_{i=1}^N \mathbb{1}_{g_\alpha^{(i)}(\theta, U) > t, X_i(0) = \alpha} + \sum_{i=1}^N \sum_{\gamma \in \mathcal{P}_\alpha} \mathbb{1}_{g_\gamma^{(i)}(\theta, U) \leq t < g_\alpha^{(i)}(\theta, U), F_{M\alpha}^{-1}(U_i) = (\gamma, \alpha)} \\ &:= f_\alpha(t, \theta, Z), \end{aligned}$$

where U_1, \dots, U_N are i.i.d. standard uniform variables independent from U , $Z = (U_1, \dots, U_N, U)$ and $F_{M^\alpha}^{-1}$ is the quantile function of the multinomial distribution M^α , where M^α is independent of any other random variable. Hence $W^\theta(t)$ can be seen as a function f of (t, θ, Z) where $f(t, \theta, Z) = ((f_\alpha(t, \theta, Z))_{\alpha \in \mathbf{V}})$.

To understand from a practical point of view what the function f represents, assume that Algorithm 12 is modified so that instead of simulating the variables during executions, a sequence Z of i.i.d. uniform variables is given as input. Then, the elements in this sequence are used sequentially to simulate any required random variables within the algorithm. Hence, $f(t, \theta, Z)$ can be seen as outputs of such modified version of Algorithm 12. Such modification is purely algorithmic so that the probability distribution of W^θ is preserved. The advantage of such representation lies in the fact that if parameters $\theta \in \Theta$ are uncertain and drawn from a random vector \mathbf{X} such that \mathbf{X} and Z are independent, then the resulting random field $W^{\mathbf{X}}$ satisfies:

$$W^{\mathbf{X}} = \{f(t, \mathbf{X}, Z), t \in [0, T]\}, \quad (5.16)$$

Therefore, the couple (f, Z) is said to be a representation of $W^{\mathbf{X}}$ in the sense of Kouye et al. (2022). Notice that if θ is fixed and Z is set to z , then the corresponding trajectory $\{f(t, \theta, z), t \in [0, T]\}$ is no longer random but deterministic. Hence (f, Z) is said to be a deterministic representation. If θ is fixed, the randomness of the process is entirely due to Z . Then, Z represents the intrinsic randomness of W^θ .

5.4.2 Results of sensitivity analysis

Assume that the components of \mathbf{X} are mutually independent. Thus, the Sobol'-Hoeffding decomposition (Sobol', 1993) allows to point out contributions of both parameter inputs \mathbf{X} and intrinsic randomness Z . Relying on such a representation, variance-based sensitivity indices of inputs \mathbf{X} and Z of some outputs of the epidemic process are assessed under different conditions. In particular, in this study, we focus on total indices (Homma and Saltelli, 1996). This kind of variance-based indices accounts for global impact of inputs, that is, both main contributions to the global variance and interactions with other inputs are taken into account.

For the SEI_1I_2RS model, we consider two types of quantities of interest (QoIs): a scalar QoI given by $\max\{W_E(t), t \in [0, 250]\}$ and dynamical outputs $W_S, W_E, W_{I_1}, W_{I_2}, W_R$ over $[0, 250]$. Regarding dynamical outputs, two total variance-based indices are introduced: dynamical total indices and aggregated indices (Lamboni et al., 2011). Dynamical total indices are actually total indices computed over time so that they define functions of time. Besides, aggregated indices are positive numbers in $[0, 1]$ given by ratios of sum over

time of weighted contributions and sum over time of global variances. Those indices are estimated using pick-freeze procedure (Jansen, 1999).

We estimate indices for epidemic inputs and intrinsic randomness: $\beta, p, \mu_E, \mu_1, \mu_2, \delta, \rho_E, \rho_1, \rho_2, \rho_R$ and Z . Recall that epidemic inputs are sampled with uniform distributions. The ranges of variations of $\beta, p, \mu_E, \mu_1, \mu_2, \delta$ are given in Table 5.2 where parameters $\rho_E, \rho_1, \rho_2, \rho_R$ are supposed to vary on either $[0, 1]$ or $[4, 5]$ depending on the case considered. For estimations, we consider $n = 1500$ samples of inputs. Notice that each sample of Z is a sequence of i.i.d. standard uniform variables. In practice, each sample of Z is associated with an integer that is used to set the random number generator seed so that as the seed is fixed, then it is possible to simulate an arbitrary number of uniform variables. In addition, estimations are performed by invoking the function *soboljansen* of the R-package *sensitivity* (Iooss et al., 2020). Each estimation is replicated $N = 50$ times in order to build 50 i.i.d. samples. Those index samples enable to show boxplots of total indices (see Figure 5.7) and aggregated total indices (refer to Figure 5.9).

5.4.2.1 Scalar output

Figure 5.7 shows boxplots of total indices of epidemic parameters and intrinsic randomness in three cases: the Markovian case and two non-Markovian cases depending on whether shapes are inferior to 1 or superior to 1. It appears that, except for the Markovian case for which the shape parameters have a null total contribution as expected, the results are consistent between the cases because input rankings are globally the same. However, in the case where shapes superior to 1, the total indices are globally higher than those in the two other cases. Either when the shape parameters are superior to 1, interactions are more pronounced, or as the shape parameters become smaller, there is more extinction and thus less variability. Anyhow, the results of the sensitivity analysis are different.

5.4.2.2 Dynamical outputs

Figure 5.8 shows the evolution over time of dynamical total indices. It follows that differences appear between the two cases. For instance, until day 50, the total indices of β, μ_1 and δ in the case shapes where inferior to 1 show faster growth than those in the case of shapes superior to 1. The most noticeable difference is observed in the intrinsic randomness (Z) dynamical indices. Thus, with respect to our numerical setting, the sensitivity analysis reveals the influence of Z decreases between days 0 and 250 unlike that of uncertain epidemic parameters. But, even when the impact of Z decreases in both cases, the decrease rate is much greater in the case of shapes inferior to 1.

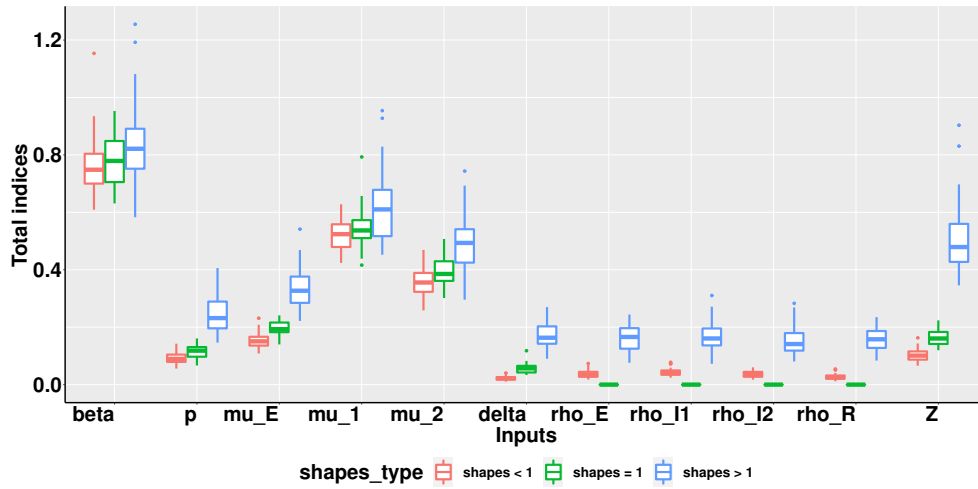


Figure 5.7 – Total indices of $\max W_E$. In both cases, boxplots are obtained with 50 samples.

The boxplots displayed in Figure 5.9 confirm the conclusion drawn from Figure 5.8. Better, they show a clear difference in the global impact of Z and shape parameters $\rho_E, \rho_1, \rho_2, \rho_R$ between the two cases. Indeed, for each process $W_S, W_E, W_{I_1}, W_{I_2}$ and W_R , the aggregated indices of Z are at least twice greater in the case of shapes superior to 1 and those of shape parameters are globally twice high.

By analyzing main contributions of inputs (see Figure 5.B.1), it follows that the high values of total indices are also due to interactions. This implies that the intrinsic randomness and the shape parameters interact with other inputs much more in the case where shapes are superior to 1. Overall, GSA results enable to conclude that depending on the choice of those shapes, influence of the intrinsic randomness of epidemic process can get reduced or magnified. Indeed, since non-Markovian processes have memory, the choice of shapes could modulate the memory of the process (Forien et al., 2021b). All of these results are consistent with studies in the literature which show that differences appear when the distributions of sojourn times change (Wilkinson and Sharkey, 2018).

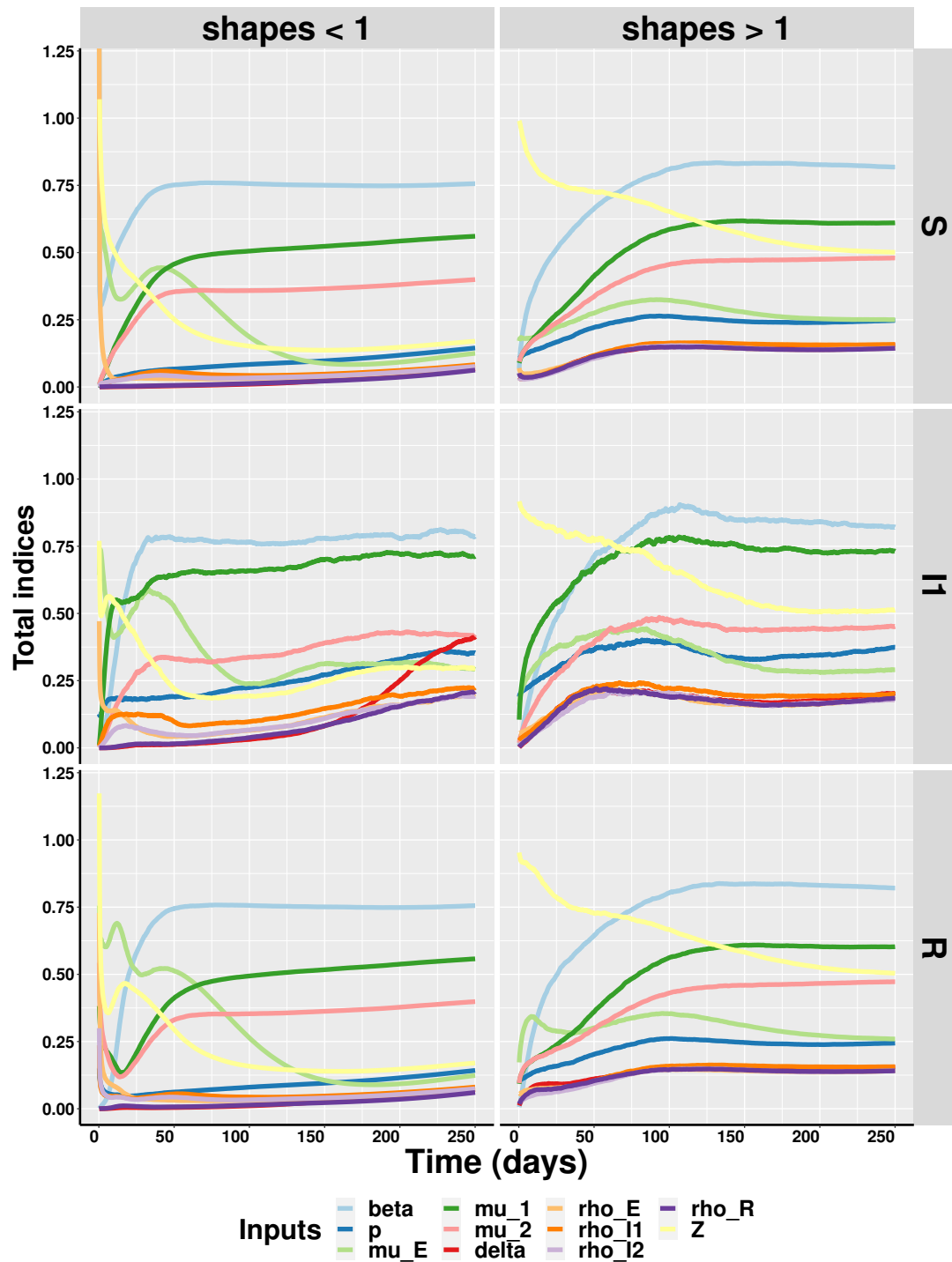


Figure 5.8 – Dynamical total indices of W_S, W_{I_1} and W_R over $[0, 250]$.

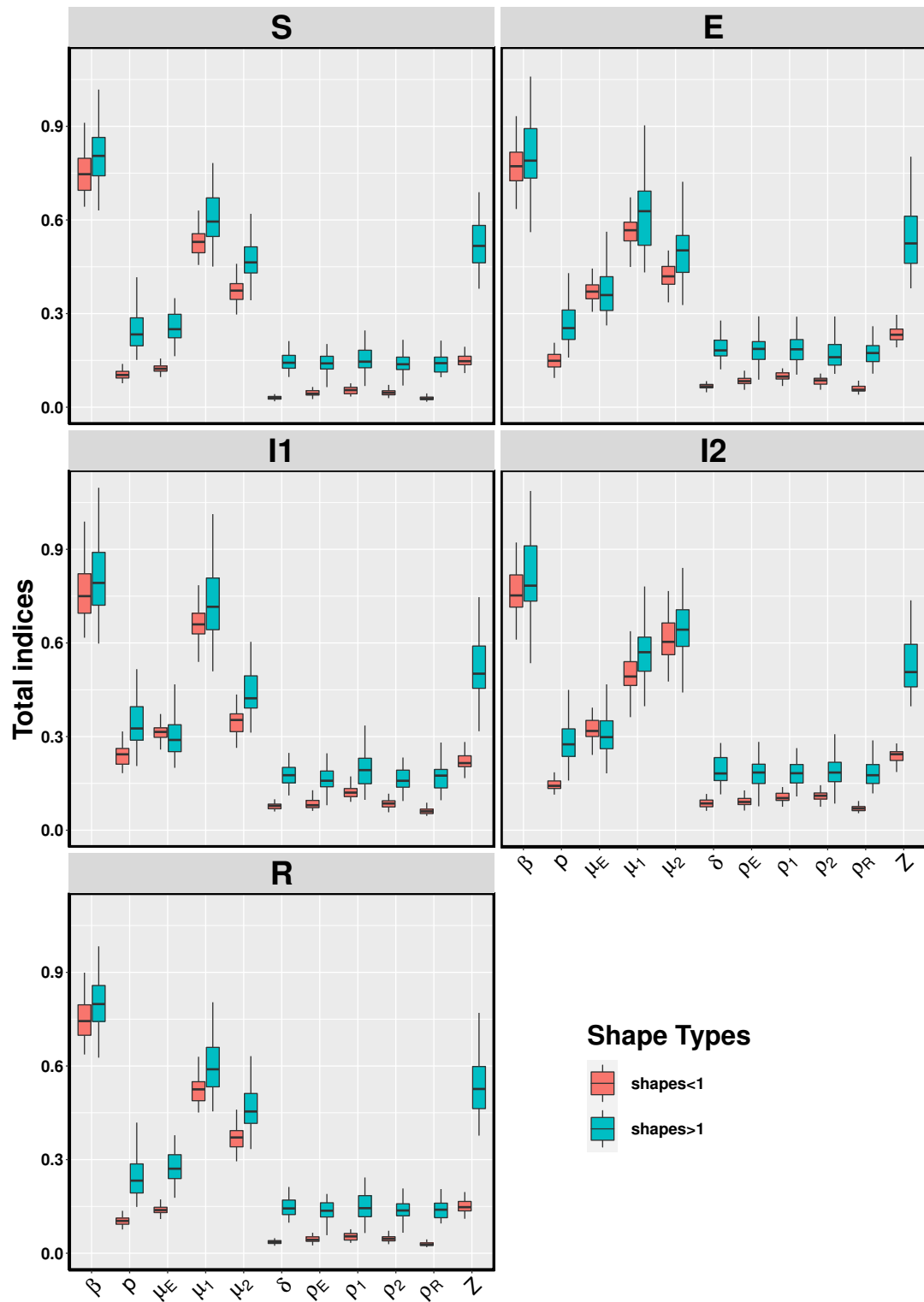


Figure 5.9 – Aggregated total indices of $W_S, W_E, W_{I_1}, W_{I_2}, W_R$. In both cases, boxplots are obtained with 50 samples.

5.5 Conclusion

This work extended the Sellke construction to more complex models. Like the original construction, the proposed one is also an individual-based approach that allows to describe epidemic models in both Markovian and non-Markovian frameworks. An algorithm is derived and allows to generate exact paths of stochastic epidemic processes. In addition, separating intrinsic randomness of such processes from uncertain epidemic parameters is then possible because, as a consequence of the use of individual-based approach, the intrinsic randomness can be characterized. The intrinsic randomness originates from noises due to individual particularities toward infections and their behaviors or choices and furthermore this makes dynamics of epidemics random even when epidemic parameters are totally known. This separation of uncertainties leads to see model outputs as deterministic functions of uncertain epidemic parameters and intrinsic randomness. In practice, such function is provided by Algorithm 12 up to slight modification.

Through a global sensitivity analysis, the impact of this intrinsic randomness in non-Markovian framework has been quantified on different versions of the SEI_1I_2RS model. The non-Markovian SEI_1I_2RS was obtained by considering that sojourn times in compartments E , I_1 , I_2 and R are distributed under Gamma distributions with shapes distinct of 1. The first case considers that all the shapes are inferior to 1 whereas the second case assumes that all the shapes are superior to 1. Estimation of total indices reveals that the impact of the intrinsic randomness is sensitive to the range of variation of shapes. This impact gets reduced or magnified depending on whether shapes are inferior to 1 or not. Note that the study non-Markovian models with shapes inferior 1 versus shapes superior to 1 was performed to understand the impact of this choice on epidemic dynamics and on sensitivity indices, but in practice the choice of shapes inferior to 1 is not realistic (Forien et al., 2021b). Indeed, for such a choice, the variance of the sojourn times in the different compartments would be greater than for the exponential distribution. But this is not what data suggest (Manica et al., 2022). In future work, interactions between inputs could be estimated in order to identify or confirm which uncertain parameters much interact with intrinsic randomness and shape inputs. Also, the non-Markovian models derived from the extended Sellke construction could be compared to other non-Markovian models (e.g. Vestergaard and Génois (2015); Boguñá et al. (2014); Masuda and Rocha (2018)). Since those algorithms are different, the results of variance-based sensitivity analysis can be different as well, as it is shown in Kouye et al. (2022). Therefore, it could be interesting to point out in the non-Markovian case, how the difference in simulation algorithms affects outputs and also the influence of both uncertain parameters and intrinsic randomness.

Appendix

5.A Reminder

Gamma distributions

A gamma distribution $\mathcal{G}(\rho, \rho \times \mu)$ with shape ρ and rate $\rho \times \mu$ is the probability distribution with density $f_{\rho, \mu}(x) = \frac{(\rho\mu)^\rho}{\Gamma(\rho)} x^{\rho-1} \exp(-\rho\mu x)$. The trivial case $\rho = 1$ is an exponential distribution with mean $1/\mu$. In addition, the mean of $\mathcal{G}(\rho, \rho\mu)$ is $1/\mu$, i.e. it is the same expectation as an exponential distribution with mean $1/\mu$. Figure 5.A.1 shows density curves of some gamma distributions and highlights the effect of the shape on the density.

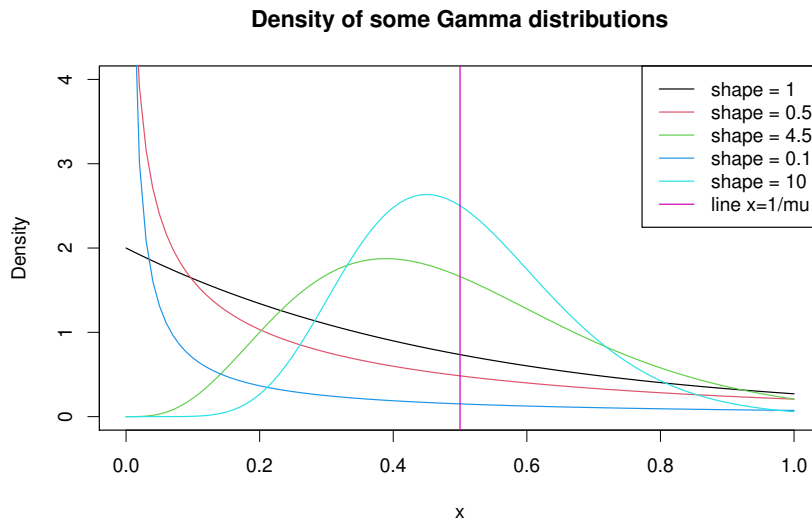


Figure 5.A.1 – Density of gamma distributions in the case $\rho = 0.1, 0.5, 1, 4.5, 10$ and $\mu = 2$. The vertical line corresponds to $x = 1/\mu$ the theoretical mean of those distributions.

5.B Plots

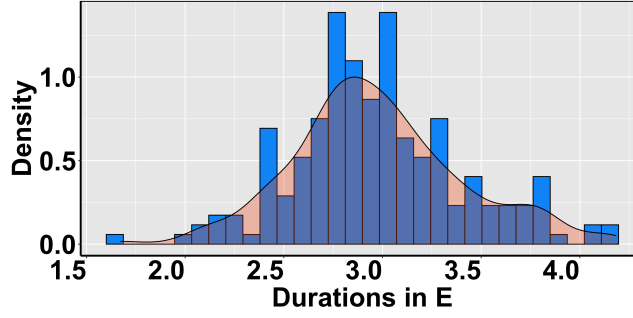
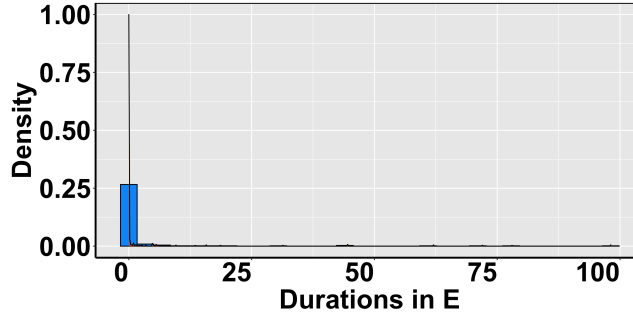

 (a) Case $\rho_E = 50$

 (b) Case $\rho_E = 1/50$

 Figure 5.A.2 – Histograms of durations in compartment E

5.C Proof of Proposition

Proof of Proposition 7

Under assumptions of Proposition 7, independence of sojourn variables and resistance thresholds and the loss of memory property of exponential distributions ensure that the resulting process is a continuous-time Markov chain.

Let $\xi = (\xi_\gamma)_{\gamma \in \mathbf{V}}$. Denote $\mathbf{p}(\varepsilon) = \mathbb{P}(W^\theta(\varepsilon) = \xi + \mathbf{u}_{\alpha,\beta} \mid W^\theta(0) = \xi)$. We aim to compute $\lim_{\varepsilon \rightarrow 0} \frac{\mathbf{p}(\varepsilon)}{\varepsilon}$. For this, remark that:

$$\begin{aligned} \mathbf{p}(\varepsilon) &= \mathbb{P} \left(\bigcup_{i: X_i(0)=\alpha} \{\tau_i^\alpha \leq \varepsilon, M_i^\alpha = (\alpha, \beta)\} \cap \bigcap_{j \neq i: X_j(0)=\gamma} \{\tau_j^\gamma > \varepsilon\} \right) \\ &= \sum_{i: X_i(0)=\alpha} \mathbb{P}(M_i^\alpha = (\alpha, \beta)) \mathbb{P} \left(\{\tau_i^\alpha \leq \varepsilon\} \cap \bigcap_{j \neq i: X_j(0)=\gamma} \{\tau_j^\gamma > \varepsilon\} \right) \\ \mathbf{p}(\varepsilon) &= p_{\alpha,\beta} \times \sum_{i: X_i(0)=\alpha} \mathbb{P}(\tau_i^\alpha \leq \varepsilon) \prod_{\gamma \in \mathbf{V}} \prod_{j \neq i: X_j(0)=\gamma} \mathbb{P}(\tau_j^\gamma > \varepsilon) \end{aligned}$$

Two cases are studied with respect to the type of compartment α .

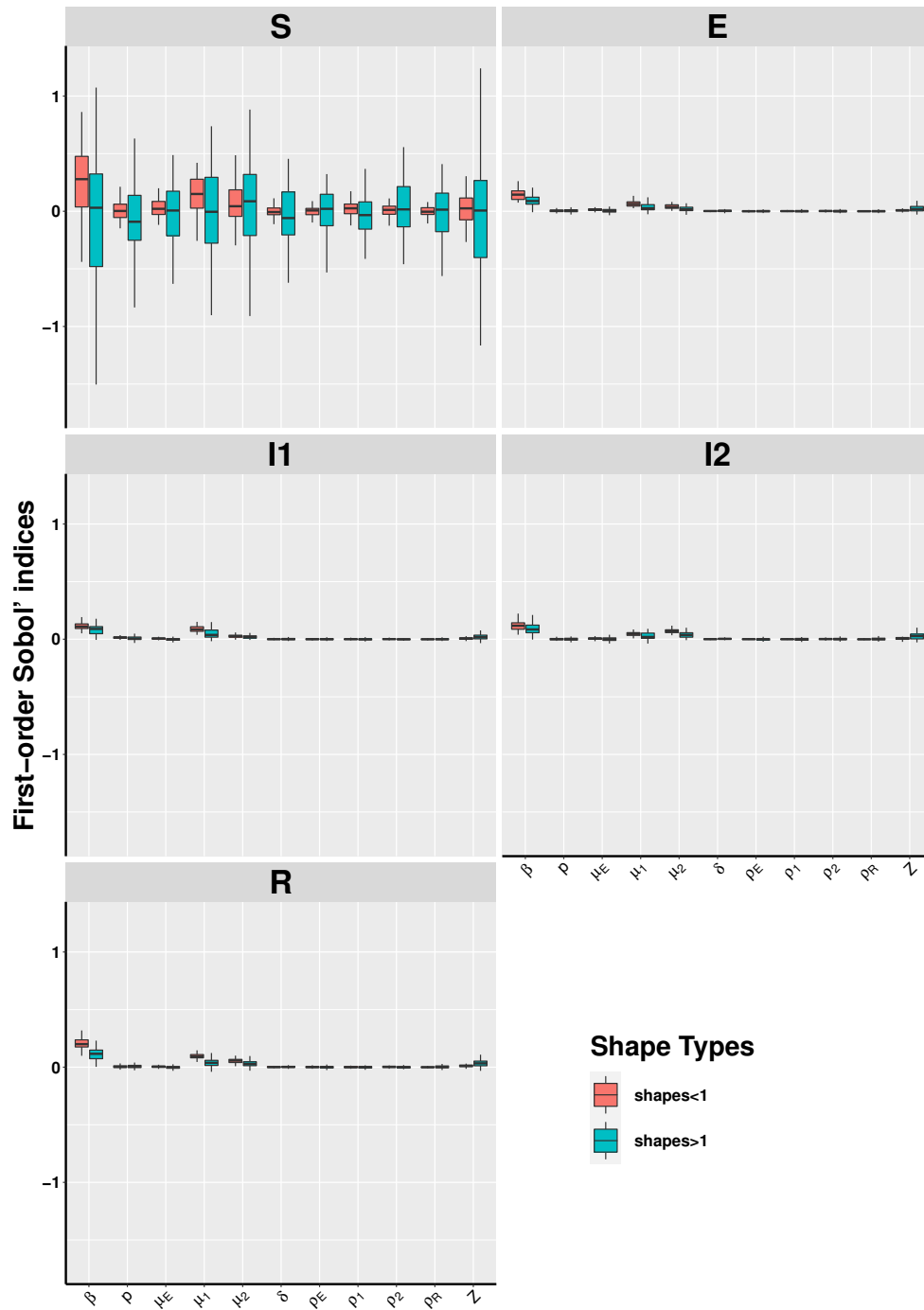


Figure 5.B.1 – Aggregated main indices of $W_S, W_E, W_{I_1}, W_{I_2}, W_R$

- If α is a compartment of susceptible individuals, then:

$\mathbb{P}(\tau_i^\alpha \leq \varepsilon) = \mathbb{P}(Q_i \leq P_\alpha(\varepsilon))$. So:

$$\mathbf{p}(\varepsilon) = p_{\alpha,\beta} \times (1 - \exp[-P_\alpha(\varepsilon)]) \sum_{i: X_i(0)=\alpha} \prod_{\gamma \in \mathbf{V}} \prod_{j \neq i: X_j(0)=\gamma} \mathbb{P}(\tau_j^\gamma > \varepsilon)$$

Thus, $\lim_{\varepsilon \rightarrow 0} \frac{\mathbb{P}(W^\theta(\varepsilon)=\xi+\mathbf{u}_{\alpha,\beta}|W^\theta(0)=\xi)}{\varepsilon}$ yields:

$$p_{\alpha,\beta} \times \lim_{\varepsilon \rightarrow 0} \frac{(1 - \exp[-P_\alpha(\varepsilon)])}{\varepsilon} \times \lim_{\varepsilon \rightarrow 0} \sum_{i: X_i(0)=\alpha} \prod_{\gamma \in \mathbf{V}} \prod_{j \neq i: X_j(0)=\gamma} \mathbb{P}(\tau_j^\gamma > \varepsilon).$$

Hence $\lim_{\varepsilon \rightarrow 0} \frac{\mathbb{P}(W^\theta(\varepsilon)=\xi+\mathbf{u}_{\alpha,\beta}|W^\theta(0)=\xi)}{\varepsilon} = p_{\alpha,\beta} \times \psi_\alpha(\theta, \xi) \times \text{card}(\{i : X_i(0) = \alpha\}) = p_{\alpha,\beta} \times \psi_\alpha(\theta, \xi) \times \xi_\alpha$.

- If α is not a compartment of susceptible individuals, then exit time from α for the individual with label i is under the form:

$$\tau_i^\alpha = \begin{cases} L_i^\alpha + \tau_i^\gamma & \text{if } \mathcal{P}_\alpha \neq \emptyset \\ L_i^\alpha & \text{if } \mathcal{P}_\alpha = \emptyset \\ +\infty & \text{if } \mathcal{C}_\alpha = \emptyset, \end{cases}$$

where $\gamma \in \mathcal{P}_\alpha$, τ_i^γ is the exit time of the individual with label i from γ and L_i^α is distributed under the exponential distribution with mean $1/\lambda_\alpha$. Therefore: $\mathbb{P}(\tau_i^\alpha \leq \varepsilon) = \mathbb{P}(L_i^\alpha \leq \varepsilon) = 1 - e^{-\lambda_\alpha \varepsilon}$.

It yields:

$$\mathbf{p}(\varepsilon) = p_{\alpha,\beta} \times (1 - e^{-\lambda_\alpha \varepsilon}) \sum_{i \in \alpha_s} \prod_{\gamma \in \mathbf{V}} \prod_{j \neq i: X_j(s)=\gamma} \mathbb{P}(\tau_j^\gamma > \varepsilon).$$

It follows that $\lim_{\varepsilon \rightarrow 0} \frac{\mathbb{P}(W^\theta(\varepsilon)=\xi+\mathbf{u}_{\alpha,\beta}|W^\theta(0)=\xi)}{\varepsilon} = p_{\alpha,\beta} \times \lambda_\alpha \times \text{card}(\{i : X_i(0) = \alpha\}) = p_{\alpha,\beta} \times \lambda_\alpha \times \xi_\alpha$.

Conclusion and Perspectives

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This thesis studies the sensitivity analysis of stochastic models. Indeed, unlike deterministic models which only include parametric uncertainty, stochastic models include an additional source of uncertainty given by intrinsic randomness. The intrinsic randomness that characterizes this type of models is responsible for the randomness of outputs even when parameters are perfectly known.

In epidemiology where stochastic models are commonly used as they provide useful insights of disease spread, sensitivity analysis is crucial because it is associated with reliability issue. Sensitivity analysis helps to better understand models, to highlight the role of uncertain epidemic parameters, to make decisions, etc.

During this thesis, we developed sensitivity analysis approaches to deal with the influence of intrinsic randomness in stochastic models in general and in compartmental epidemic models based on stochastic processes in particular. Precisely, the goal was to find methods to manage more efficiently the noise

originating from the intrinsic randomness in the estimation of sensitivity indices and to build approaches to deal with stochastic models in a paradigm where intrinsic randomness is no longer a noise but an input of models to be taken into account. The works carried out led to different main contributions discussed in the following.

6.1 Main contributions

6.1.1 Bias-variance trade-off in estimation of Sobol' indices for averaged quantities of interest

The first contribution of this thesis, detailed in Chapter 3, concerns the estimation of Sobol' indices for quantities of interest (QoIs) of stochastic models defined as averages with respect to the intrinsic randomness. Our contribution consisted in developing a strategy based on the mean squared error of estimators of sensitivity indices that helps to find a new trade-off between the number of repetitions of model evaluations and the number of input samples to consider. On one hand, the study of this error, which accounts for estimator accuracy, led to convergence results in the mean-squared sense as both number of repetitions and number of input samples increase. On the other hand, relying on an upper bound of the error, we deduced a trade-off of numbers of input sample and number of repetitions. Finally, an algorithm based on this trade-off was proposed to estimate Sobol' indices, which adapts to the magnitude of the intrinsic randomness of the considered stochastic model.

6.1.2 Deterministic representation for compartmental models based on continuous-time Markov chains

The second contribution discussed in Chapter 4 aims at performing the global sensitivity analysis of continuous-time Markov chain based models so that the contribution of both uncertain parameters and intrinsic randomness can be assessed. For this, we investigated the deterministic representation of such model outputs. This consisted in writing outputs as deterministic functions of uncertain parameters and intrinsic randomness. To obtain this representation for CTMC based models, we separated uncertain epidemic parameters from the variables involved in the simulation of chain jumps and those of jump times. Indeed, these variables are responsible for the randomness of outputs. To do that, we modified Gillespie algorithms (Gillespie, 1977) for simulation of CTMCs: Direct Method (see Algorithm 1) and First Reaction Method (refer to Algorithm 2). It was then possible to represent CTMCs under determinis-

tic form and to estimate the contributions of both uncertain parameters and intrinsic randomness in the case of an epidemic model of SARS-CoV-2 spread as an application. Finally, we compared this approach to an equivalent approach proposed in the literature (Le Maître et al., 2015; Navarro Jimenez et al., 2016). This led to highlight that the choice of the deterministic function and the random variables representing the intrinsic randomness influences the results of sensitivity analysis of stochastic models.

6.1.3 Extension of Sellke construction to perform the sensitivity analysis for non-Markovian epidemic models

The third contribution presented in Chapter 5 is related to the sensitivity analysis of compartmental models based on non-Markovian processes. For this category of models, the chosen approach is similar to the one used for models based on continuous time Markov chains. In other words, we wrote the outputs of these models as deterministic functions of uncertain parameters and variables representing the intrinsic randomness. While the availability of a wide range of analysis and simulation tools facilitates the sensitivity analysis approach we chose for Markov chain models, this is not the case for non-Markovian models. To bypass this issue, we described the epidemic models using a Sellke-type construction (Sellke, 1983). To our knowledge, Sellke construction was focused mainly on the simulation of SIR based models so far.

In this thesis, we extended it to more complex compartmental models with an arbitrary number of compartments and transitions in a non-Markovian framework with the size of the population assumed to remain constant. We showed that this construction leads to the Markovian model under specific assumptions and we developed an algorithm to simulate in practice epidemic dynamics based on such an approach. Finally, we performed sensitivity analysis and assessed contributions of the intrinsic randomness in a Markovian and non-Markovian frameworks based on Sellke extension. An application was carried out for the SEI_1I_2RS model.

6.2 Perspectives

This thesis and the contributions therein raised several points that could be addressed in future works.

6.2.1 About the bias-variance trade-off in estimation of Sobol' indices

Rate of convergence of the mean squared error

In this work, we considered the function $g : (x_1, x_2, x_3) \mapsto (x_3 - x_2^2)/(x_1 - x_2^2)$ to define first-order Sobol' indices and their estimators respectively under the form $g(\theta)$ and $g(\hat{\theta}_{n,m})$, where n denotes the number of input samples and m represents the number of repetitions of model evaluations at each input sample. In order to get tractable upper bound for the MSE given by $\mathbb{E}(g(\hat{\theta}_{n,m}) - g(\theta))^2$, we introduced a family of functions g_h parameterized by $h \in (0, 1)$ defined as $g_h : (x_1, x_2, x_3) \mapsto (x_3 - x_2^2)/(h + x_1 - x_2^2)$. For fixed h , we deduced upper bound of the MSE. However, this bound provides only an asymptotic control, i.e. when $n, m \rightarrow \infty$. Moreover, because of the dependence of n and m on the choice of h , we were not able to deduce the rate of convergence of the MSE. So, it would be interesting to conduct further investigation regarding the convergence rate and to compare it to the optimal rate in $(nm)^{2/3}$ suggested by the bias-variance trade-off on the bound. Furthermore, one could look for a non-asymptotic control of the MSE.

Sequential adaptive algorithm

The scheme we proposed to simulate the Sobol' indices using the bias-variance trade-off is for a fixed computational budget T , i.e, the total number of model evaluations allowed. One perspective to consider is to introduce an accuracy criterion on the MSE in combination with the total number of model evaluations. In that case, a desired precision on estimation could be fixed and then, required number of inputs and number of repetitions are performed until the total budget is reached or the precision is reached. Moreover, a sequential algorithm could be developed as in (Binois et al., 2019). This sequential algorithm would choose at each step either to consider a new input sample or to repeat an evaluation according to what enables to reduce more the MSE.

Multilevel Monte-Carlo for Nested simulation

In Chapter 3, estimation of moments of stochastic model outputs is based on a double Monte-Carlo procedure called Nested Monte-Carlo . On the one hand, in Giles (2018), authors developed a multilevel approach to estimate the moments of the form $\mathbb{E}(\varphi(\mathbb{E}[h(Y | X)]))$ where φ and h are two functions and X, Y are two random variables. This approach consists in using a sequence of estimators with increasing accuracy and computational cost. On the other hand, in Mycek and De Lozzo (2019) , the multilevel approach is applied to covariance estimators. Thus, considering Sobol' indices as ratios of covariances,

authors deduced a multilevel approach for estimating Sobol' indices. Hence, it would be of interest to combine these two approaches to estimate Sobol' indices in the case of stochastic models. This would take advantage of computation efficiency and accuracy of multilevel estimators.

6.2.2 About the deterministic representation of continuous-time Markov chains

Considering other indices

In Chapter 4, we represented under deterministic form the output of a continuous-time Markov chain from compartmental epidemic models. The sensitivity analysis method used is that based on the variance, that is, the Sobol' indices. However, the use of the variance as a measure of uncertainty can be subject to criticism as the variance only characterizes the moment of order 2 of a distribution and not even the higher moments. In this sense, it does not fully characterize distributions. For this, other types of indices can be used: moment-independent indices (Borgonovo, 2007; Borgonovo and Tarantola, 2008), Kernel-based indices (Da Veiga, 2021; Barr and Rabitz, 2022), etc. depending on what is possible given the model under consideration. It would be of interest to extend the scope of use of the deterministic representation to other sensitivity analysis methods in order to see from other perspectives the way the intrinsic randomness affects model output.

Studying the dependence on representation

An important point that emerges from this study is that the results of sensitivity analysis depend on the choice of the deterministic representation, i.e., the choice of the deterministic function and the random variables representing the intrinsic randomness. This makes equivocal sensitivity indices for stochastic models in the framework of variance-based analysis since they could depend on simulation algorithms. It would be interesting to investigate, given a model, which simulation algorithm should be preferred depending on which characteristics of the underlying process one wishes to better understand.

6.2.3 About the extension of Sellke construction

All the perspectives mentioned in Section 6.2.2 regarding the deterministic representation of continuous-time Markov chains are also valid in the case of deterministic representation of non-Markovian processes resulting from compartmental models. But in addition, we could mention some specific perspectives on the Sellke extension and its simulation.

Extension to open population models

In Chapter 5, the construction that extends Sellke's assumes that the population is closed, that is, the total number of individuals remains constant over time. This assumption simplifies the construction because phenomena such as population vital dynamics are not taken into account. Therefore, only transitions between compartments related to the infection are modeled. But it would be interesting to extend the framework of this construction to more realistic models such as models with demography and metapopulation models. This could increase the scope of this construction and thereby that of the related algorithm because the latter would enable to simulate a wide range of compartmental models within both Markovian and non-Markovian frameworks.

Improving algorithms

The algorithm related to the generalized construction is based on the following principle: at each transition, every type of transitions is considered and the putative jump times are computed and then compared in order to determine transition to be executed. Hence, the complexity of this algorithm increases if at least one of the following parameters increases: the size of population, the number of types of transitions or the number of compartments of the model. Then, either a more efficient algorithm should be introduced or the current algorithm should be optimized. One way to optimize the current algorithm would be to consider parallel implementation techniques.

6.3 Conclusion

This thesis studied approaches to perform sensitivity analysis of stochastic models by taking advantage of sensitivity analysis tools for deterministic models. For this, two main axes were considered: the estimation of Sobol' indices for averaged quantities of interest with respect to intrinsic noise and the representation under deterministic form of stochastic compartmental epidemic models by modeling explicitly intrinsic randomness. Concerning the first axis, we stated theoretical results leading to an estimation strategy based on a new trade-off between exploration and repetition. Regarding the second axis, we proposed new algorithms to perform sensitivity analysis of Markovian and non-Markovian compartmental models, assessing in particular the influence of the intrinsic randomness, by itself or in interaction with any subset of input parameters on model outputs. The results of this PhD thesis are theoretical (study of the mean squared errors of estimators and quadratic convergence), methodological (approaches of sensitivity analysis of stochastic models) and computational (algorithms for simulation of epidemiological models and sensitivity analysis).

Résumé long

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7.1 Introduction à la modélisation en épidémiologie

Les maladies infectieuses, qu'elles surviennent dans les populations humaines, animales ou végétales, peuvent avoir de graves conséquences sociétales (crise sanitaire, alimentaire, etc.), économiques (récession, etc.) ou environnementales (destruction d'écosystèmes, pollutions environnementales, etc.). Malheureusement, de nos jours, la pandémie de la COVID-19 causée par le SARS-CoV-2, qui a frappé le monde entier en 2019, a montré combien les dégâts suite à la propagation d'un agent pathogène, nouveau de surcroît, peuvent être énormes. Durant cette crise, les outils de modélisation mathématique de la propagation des épidémies se sont illustrés comme des instruments de choix pour comprendre la propagation, prédire les dynamiques d'infections, analyser les scénarios épidémiques, aider à prendre des décisions pour la gestion de l'épidémie.

En effet, les modèles mathématiques facilitent la compréhension de la dynamique des épidémies et permettent de mettre en évidence de nouveaux phénomènes en lien, par exemple, avec les modes de transmission ou la durée de l'immunité... ou des processus sous-jacents à la dynamique observée. En complément aux domaines tels que la médecine, la biologie ou la microbiologie qui étudient les agents pathogènes, la modélisation épidémique permet de mieux comprendre les mécanismes par lesquels les agents pathogènes se propagent au sein d'une population ou entre les populations. Le développement

de cette discipline a conduit à l'émergence de différentes approches pour la modélisation de la propagation des épidémies, parmi lesquelles la modélisation compartimentale (Kermack et al., 1927). Le principe de cette approche est le suivant. Considérons une population au sein de laquelle se propage une maladie infectieuse. De plus, supposons que, pour cette infection, différents états de santé vis-à-vis de la maladie sont observés, tels que : sensible (sain), infecté et/ou infectieux, immunisé, hospitalisé, etc. Ces états sont reliés entre eux en fonction de la manière dont se déroulent les différentes phases de l'infection. La modélisation compartimentale consiste alors à diviser les individus en classes généralement disjointes suivant leur statut, puis à étudier l'évolution au cours du temps du nombre ou de la proportion d'individus dans les différentes classes considérées. Le modèle résultant est schématisé par des compartiments donnés par des classes d'état de santé et des flèches qui représentent les différents types de transitions qui peuvent se produire entre les états de santé.

7.2 Contexte de l'analyse de sensibilité de modèles stochastiques, en particulier en épidémiologie et objectifs

Du point de vue de la manière dont ils considèrent l'aléa, les modèles compartimentaux peuvent être classés en deux catégories: les modèles déterministes et les modèles stochastiques. Les modèles déterministes (Brauer et al., 2012; Chalub and Souza, 2011; Medlock and Kot, 2003) reposent sur des fonctions déterministes qui ne dépendent que des paramètres épidémiques pour décrire la dynamique. Quant aux modèles stochastiques à compartiments, même lorsque les conditions initiales et les paramètres épidémiques sont fixés, les transitions dans les états de santé des individus sont supposées se produire à des temps aléatoires. Par conséquent, l'évolution dans le temps de la dynamique épidémique est aléatoire, ce qui génère en sortie des processus stochastiques (Allen, 2008; Britton et al., 2019). Ces processus peuvent être Markoviens ou non-Markoviens (Gani, 1973; Feng et al., 2019) selon que leurs évolutions dépendent du passé ou non.

En pratique, les modèles épidémiologiques visent à répondre à un certain nombre de questions, notamment : comment prédire la dynamique épidémique ? Quels sont les facteurs clés de la propagation de l'épidémie ? Quelles sont les stratégies possibles pour contrôler la propagation ? Quels sont les impacts potentiels de ces stratégies ? Autant de questions pour lesquelles la précision des réponses dépend fortement de la précision et de la fiabilité du modèle. Pour cela, il faut parfaitement connaître les paramètres de l'épidémie. Or, les vraies valeurs de ces paramètres sont généralement inconnues. Ces modèles souffrent alors d'incertitudes. Afin d'améliorer la fiabilité de ces modèles, il est

nécessaire d'étudier et de quantifier les incertitudes (Taghizadeh et al., 2020; Marion et al., 2022; Swallow et al., 2022).

Les incertitudes dans les modèles stochastiques peuvent être classées en deux catégories : incertitude sur les paramètres et aléa intrinsèque. L'incertitude sur les paramètres survient lorsque les paramètres du modèle sont inconnus ou mal connus. Quant à l'aléa intrinsèque, il est inhérent au modèle et il est responsable de la variabilité de la sortie du modèle même lorsque les paramètres sont parfaitement connus. Dans le cadre de la quantification des incertitudes, l'analyse de sensibilité des modèles vise à évaluer la part de chaque paramètre ou groupe de paramètres dans la variabilité de la sortie du modèle. Une telle étude peut viser plusieurs objectifs : l'identification des paramètres influents, la réduction de modèle, l'optimisation, le calibrage de modèle, etc. L'analyse de sensibilité permet donc de mieux comprendre le modèle en ce qui concerne la relation entre les entrées et les sorties.

Pour les modèles déterministes, la relation entre les entrées notées θ et la sortie notée y est donnée par $y = f(\theta)$ où f est une fonction déterministe. L'analyse de sensibilité de ces modèles consiste à faire varier θ , puis à quantifier les effets sur la sortie y . Plus la variation d'un paramètre induit une grande variation de la sortie, plus ce paramètre est influent. Diverses méthodes ont été élaborées pour mesurer les impacts des paramètres: des méthodes locales où l'on considère de petites perturbations des paramètres autour de valeurs nominales (Helton, 1993; Morris, 1991) ou des méthodes globales où l'on quantifie la variation de la sortie en considérant l'ensemble des valeurs possibles des paramètres (Sobol', 1993; Iooss and Prieur, 2019).

Dans le cadre des modèles stochastiques, c'est-à-dire sous la forme : $\theta \mapsto f(\theta, Z)$, où Z est aléatoire, la sortie n'est plus déterminée uniquement par θ mais aussi par Z . Deux entrées du modèle θ et $\tilde{\theta}$ donnent respectivement $f(\theta, Z(\omega))$ et $f(\tilde{\theta}, Z(\tilde{\omega}))$, avec $Z(\omega)$ et $Z(\tilde{\omega})$ deux réalisations de Z . Ainsi, lorsqu'on fait varier un paramètre, la variation de la sortie qui en résulte provient à la fois de la variation de ce paramètre et celle de l'aléa intrinsèque Z . Cependant, dans la plupart des modèles stochastiques utilisés en pratique, l'aléa intrinsèque Z est caché et incontrôlable dans le sens où il n'est pas explicitement caractérisé et où sa distribution de probabilité est inconnue. Ainsi, le défi est d'évaluer l'impact des paramètres en présence de l'aléa intrinsèque.

Face au défi de l'aléa intrinsèque des modèles stochastiques, notamment en modélisation des épidémies, plusieurs questions se posent dans le cadre de l'analyse de sensibilité. Comment estimer avec précision les indices basés sur la variance pour les modèles stochastiques malgré la présence de l'aléa intrinsèque ? Comment séparer les effets de l'aléa intrinsèque de ceux des paramètres incertains dans l'analyse de sensibilité des modèles stochastiques compartimentaux ? Comment évaluer les contributions de l'aléa intrinsèque à la variance globale de ces modèles ? Dans le contexte de l'analyse de sensibilité

basée sur la variance, cette thèse aborde ces questions et vise à développer des approches adaptées aux modèles stochastiques, en particulier les modèles stochastiques à compartiments utilisés en épidémiologie.

7.3 Contributions à l'analyse de sensibilité de modèles stochastiques

Contribution à l'estimation d'indices de paramètres de quantités d'intérêt

La première contribution de cette thèse, détaillée dans le Chapitre 3, concerne l'estimation des indices de Sobol' pour des quantités d'intérêt (QoIs) de modèles stochastiques. Pour cette étude, les QoIs considérées sont des espérances conditionnelles par rapport aux paramètres incertains de fonctions de la sortie de modèle stochastique. Pour de telles quantités, l'estimation des indices de Sobol' est précédée de l'estimation des QoIs, étant donné que les expressions analytiques sont généralement inconnues. L'estimation de ces espérances conditionnelles par Monte-Carlo requiert pour chaque jeu de paramètres du modèle stochastique un certain nombre de répétitions de l'évaluation du modèle. Par la suite, les estimateurs ainsi construits remplacent les quantités théoriques dans l'estimation des indices. Pour estimer ces indices, on se donne un certain nombre d'échantillons de valeurs paramètres du modèle et on approche les différentes variances encore par Monte-Carlo. Ainsi, pour cette procédure double Monte-Carlo, le nombre total d'évaluations du modèle est proportionnel au produit du nombre de répétitions et du nombre d'échantillons de valeurs de paramètres du modèle. Donc, plus on cherche à être précis dans les estimations, plus ce produit est élevé; ce qui peut devenir très vite insoutenable sur le plan de calcul. Une solution est de limiter le nombre total d'évaluations du modèle et de chercher pour un budget de calcul T donné les nombres de répétitions et d'échantillons d'entrées optimaux permettant d'avoir une meilleure précision dans les estimations. Un tel problème renvoie à un problème classique de compromis biais-variance. Ici, le biais est généré par l'erreur commise en remplaçant les quantités d'intérêt par des estimateurs, alors que la variance vient des estimateurs des indices.

Notre contribution a consisté à mettre au point une stratégie basée sur l'erreur quadratique des estimateurs des indices permettant de trouver un compromis entre le nombre de répétitions et le nombre d'échantillons à considérer. L'étude de cette erreur, qui mesure la précision des estimations, nous a permis, d'une part, de montrer qu'elle converge vers 0. C'est dire qu'en moyenne les estimateurs considérés s'approchent des vraies valeurs des indices lorsque les nombres de répétitions et d'échantillons augmentent. D'autre part, à par-

tir d'une borne de l'erreur que nous avons calculée, nous avons déduit une stratégie en minimisant une somme de biais au carré et de variance dans cette borne pour trouver les nombres associés qui permettent de réduire l'erreur quadratique. Il en ressort que le nombre optimal d'échantillons est de l'ordre de $T^{2/3}$ et le nombre optimal de répétitions de $T^{1/3}$ lorsqu'on considère un budget total T . Enfin, un algorithme basé sur cette stratégie a été proposé. Cet algorithme permet d'estimer les indices de Sobol' en utilisant la stratégie mise au point et en s'adaptant à l'amplitude de l'aléa intrinsèque du modèle stochastique considéré.

Contribution à l'analyse de sensibilité de modèles basés sur des chaînes de Markov à temps continu

La deuxième contribution présentée dans le Chapitre 4 traite de l'analyse de sensibilité des modèles épidémiologiques compartimentaux stochastiques basés sur des chaînes de Markov à temps continu. Pour gérer l'aléa intrinsèque de ces modèles et faire l'analyse de sensibilité, l'approche que nous proposons est d'écrire la sortie stochastique de ces modèles comme des fonctions déterministes de paramètres incertains et des variables aléatoires représentant l'aléa intrinsèque. Mettre la sortie sous cette forme a de nombreux avantages. Premièrement, cela permet d'utiliser les nombreux outils d'analyse de sensibilité disponibles dans le cadre des modèles déterministes. Deuxièmement, cette écriture permet de caractériser l'aléa intrinsèque et de le considérer comme une entrée du modèle de sorte que ses contributions telles que les effets principaux sur la variance et les interactions avec les paramètres incertains peuvent être évaluées. De telles informations permettent de mieux comprendre le rôle de l'aléa dans le modèle et ses relations avec les paramètres incertains.

Pour obtenir une telle représentation pour les modèles basés sur les chaînes de Markov à temps continu, nous avons réécrit les chaînes de façon à séparer les paramètres incertains des variables qui interviennent dans la simulation des sauts et des instants de sauts, responsables du caractère aléatoire des sorties. Par ailleurs, nous avons modifié les algorithmes de Gillespie (Gillespie, 1977): Direct Method (voir Algorithme 1) and First Reaction Method (voir Algorithme 2) qui permettent de réaliser des simulations exactes des chaînes de sorte à tenir compte de la séparation entre les paramètres incertains et des variables relatives à l'aléa intrinsèque. Ainsi, il a été possible de représenter les chaînes de Markov à temps continu sous forme déterministe et d'évaluer les contributions des paramètres incertains et de l'aléa intrinsèque dans le cas d'un modèle épidémiologique de propagation du SARS-CoV-2. Enfin, nous avons comparé cette approche à une approche équivalente proposée dans la littérature (Le Maître et al., 2015; Navarro Jimenez et al., 2016). Cela nous a permis de mettre en évidence que dans la représentation déterministe, le choix de la

fonction déterministe et des variables aléatoires représentant l'aléa intrinsèque influence les résultats d'analyse de sensibilité.

Contribution à l'analyse de sensibilité de modèles compartimentaux basés sur des processus non-Markoviens

La troisième contribution présentée au Chapitre 5 concerne l'analyse de sensibilité des modèles compartimentaux basés sur des processus non-Markoviens. Pour cette catégorie de modèles, l'approche choisie est identique à celle utilisée pour les modèles basés sur les chaînes de Markov à temps continu. Autrement dit, nous avons cherché à écrire les sorties de ces modèles sous la forme de fonctions déterministes de paramètres incertains et de variables représentant l'aléa intrinsèque. Si pour les modèles basés sur les chaînes de Markov la disponibilité d'une gamme variée d'outils d'analyse et de simulation facilite l'approche d'analyse de sensibilité que nous avons choisie, ce n'est pas le cas des modèles non-Markoviens. Pour contourner cette difficulté, nous avons décrit les modèles épidémiologiques à l'aide d'une construction de type Sellke. Cette construction est introduite dans (Sellke, 1983) pour décrire le modèle SIR (Sain-Infecté-Remis) avec une approche centrée sur les individus de la population. Cela consiste à affecter à chaque individu et selon son état de santé au temps initial des variables qui décrivent son seuil de tolérance à l'infection, sa durée d'infection s'il devient infecté. La description du nombre d'individus dans chaque compartiment du modèle en fonction du temps et des variables caractéristiques des individus permet d'écrire la sortie du modèle comme une fonction déterministe des paramètres incertains et des variables représentant l'aléa intrinsèque. Nous avons donc étendu cette construction aux modèles compartimentaux plus complexes avec un nombre arbitraire de compartiments et de transitions entre compartiments. Cela a permis de décrire les modèles stochastiques compartimentaux dans un cadre non-Markovien en population fermée (dont la taille est constante). Par la suite, nous avons montré que cette construction est équivalente au modèle Markovien sous certaines conditions et nous avons élaboré un algorithme permettant de simuler les dynamiques épidémiques en se basant sur une telle approche. Enfin, cela a permis de faire l'analyse de sensibilité et d'évaluer les contributions de l'aléa intrinsèque aussi bien dans un cadre Markovien que non-Markovien. Une application a été faite sur le modèle SEI_1I_2RS .

7.4 Conclusion

Cette thèse propose les approches permettant de réaliser des analyses de sensibilité de modèles stochastiques en tirant avantage des outils d'analyse de sensibilité pour les modèles déterministes. Pour ce faire, deux axes principaux

ont été considérés : l'estimation des indices de sensibilité pour des quantités d'intérêt déterministes et la représentation sous forme déterministe des sorties stochastiques des modèles épidémiques compartimentaux.

Ces travaux ont contribué à développer une approche d'estimation d'indices de sensibilité et à évaluer les contributions de l'aléa intrinsèque dans les modèles compartimentaux basés sur des processus stochastiques. Ils mettent en avant une nouvelle façon d'étudier la sensibilité des modèles stochastiques. Les retombées de ce travail sont d'ordre théorique (étude du risque quadratique des estimateurs et de la convergence quadratique), méthodologique (approches d'analyse de sensibilité de modèles stochastiques) et computationnel (algorithmes de simulation de modèles épidémiologiques et d'estimation d'indices de sensibilité).

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