Global sensitivity analysis for stochastic models based on continuous time Markov chains: application to epidemic models

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Outline

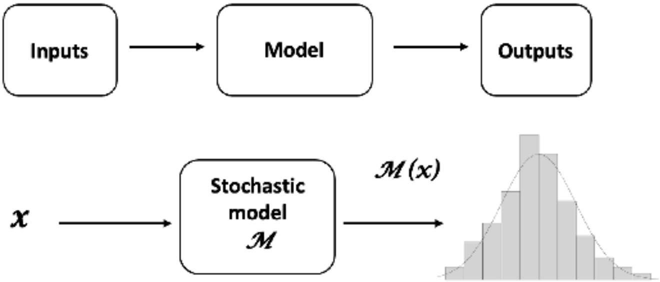
Introduction: context, state of art and objective

Stochastic model framework and sensitivity analysis

Application: SARS-CoV-2 model

Conclusion and Perspectives

SA for stochastic models is challenging!



- This kind of models is intrinsically random!
- How can global sensitivity analysis be performed on such model?

Methods in the literature

1. Methods for scalar output stochastic models (Mazo 2021; Hart, Alexanderian, and Gremaud 2017)
2. Meta-modelling based methods (Zhu and Sudret 2021; Etore et al. 2020; Jimenez, Le Maitre, and O. M. Knio 2017; Le Maitre and O. Knio 2015; Marrel et al. 2012)
3. Methods based on global sensitivity analysis for probability measures (Da Veiga 2021; Fort, Klein, and Lagnoux 2020)

Limitations

1. The computational cost of repetitions
2. Approximation errors issues that can arise from meta-modelling
3. Parameter estimations: contribution of intrinsic randomness and its interaction with parameters are useful.

Our approach: positioning and objective

Assume we have a stochastic model with entry X and output Y.

A. Objective: to perform sensitivity analysis using existing methods without making repetitions or using meta-models.

B. Approach: our approach aims to write Y as a deterministic function f of X and a random variable Z such as :

- $Y \overset{\mathcal{L}}{=} f(X, Z)$
- X and Z are independent
- f and Z distribution are explicit.

Stochastic model framework and sensitivity analysis

Stochastic models (1)

Consider $(\mathcal{X}, \mathfrak{B})$ and $(\mathcal{Y}, \mathfrak{F})$ two measurable spaces.

Definition

- A stochastic model $\mathcal{M}$ with input space $\mathcal{X}$ and output space $\mathcal{Y}$ is a family of distributions $(\mathcal{P}_x, x \in \mathcal{X})$ defined on $(\mathcal{Y}, \mathfrak{F})$.
  Each input $\in \mathcal{X}$ is associated with a distribution $\mathcal{P}_x$ such as for this input, the outputs of the model are distributed by $\mathcal{P}_x$.
- Let $(\mathcal{Z}, \mathfrak{G})$ be a measurable space, $f : \mathcal{X} \times \mathcal{Z} \longrightarrow \mathcal{Y}$ a measurable application and Z a random variable.
  (f, Z) is said to be a representation of $\mathcal{M}$ if Z is independent of inputs such as :

$$\forall x \in \mathcal{X}, f(x, Z) \overset{\mathcal{L}}{=} \mathcal{P}_x \tag{1}$$

From now on, we assume the existence of representations of a stochastic model $\mathcal{M}$.

Representations and sensitivity analysis (1)

- Assume there is an uncertainty on parameters
- Suppose parameter space $\mathcal{X} = (\mathcal{X}_1, \cdots, \mathcal{X}_d)$ is sampled with a random vector $X = (X_1, \cdots X_d)$ with a distribution P.

Let $X' = (X'_1, \cdots X'_d)$ be an independent copy of X.

Lemma

If (f, Z) and (f', Z') are two representations of the same stochastic model then :

$$(X, f(X, Z)) \stackrel{\mathcal{L}}{=} (X', f'(X', Z')) \tag{2}$$

Suppose $\mathbb{E}\left(|f(X, Z)|^2\right) < +\infty$.

Let $u \subset \{1, \cdots, d\}$ and denote by X_u the vector $(X_i, i \in u)$.
From the previous lemma, the following equality holds :

$$\mathbb{E}(f(X, Z) \mid X_u) \stackrel{\mathcal{L}}{=} \mathbb{E}(f'(X', Z') \mid X'_u) \tag{3}$$

But $\mathbb{E}[f(X, Z) \mid (X_u, Z)]$ and $\mathbb{E}[f'(X', Z') \mid (X'_u, Z')]$ are not necessarily equal.

Variance decomposition

Let $X_{d+1} = Z$.

Theorem (Sobol-Hoeffding decomposition)

Under the following conditions:

- $\mathcal{X} = \mathcal{X}_1 \times \mathcal{X}_2 \cdots \times \mathcal{X}_d$ *where* $\mathcal{X}_1, \mathcal{X}_2 \cdots, \mathcal{X}_d$ *are Polish spaces,*
- $\mathcal{Z}$ *and* $\mathcal{Y}$ *are Polish spaces,*
- $X_i, i = 1, \cdots, d+1$, *are independent random variables.*

Then:

$$Var(f(X, Z)) = Var(f(X, X_{d+1})) = \sum_{u \subset \{1, \cdots, d+1\}} V_u, \tag{4}$$

where

$$V_u = \sum_{v \subset u} (-1)^{|u|-|v|} \, Var(\mathbb{E}[f(X, X_{d+1}) \mid X_v]) \tag{5}$$

Application

Consider the following compartmental model for the spread of SARS-CoV-2 among a population with constant size N.

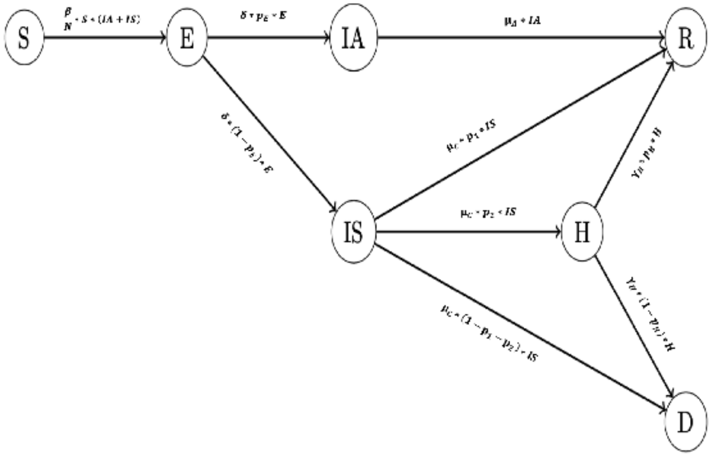


Figure 2: SARS-CoV-2 epidemic model

SARS-CoV-2 model: Presentation (2)

The process $W = \left\{ (S(t), E(t), IA(t), IS(t), H(t), R(t), D(t)) \,; t \geq 0 \right\}$ is described by a continuous time Markov chain whose generator is given by the transition rates mentioned on the figure above.

- The process W depends on unknown parameters $X = (\beta, \delta, \mu_A, \mu_C, p_E, p = (p_1, p_2), \gamma_H, p_H)$.

But

- W is a stochastic process, so there is an intrinsic randomness
- Repetitions to be avoided because of the cost of calculation
- There is a need to know the contribution of the intrinsic randomness and its interactions with parameters

Sellke construction (1)

Sellke 1983 introduced this construction detailed on the simple SIR model : $S \xrightarrow{\frac{\beta}{N} S * I} I \xrightarrow{\gamma I} R$

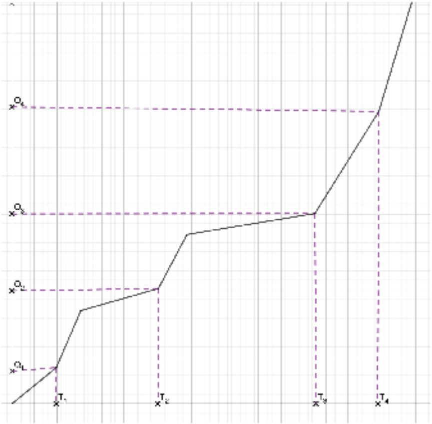


Figure 3: Example of evolution of infection pressure

- Infection transition depends on the infection pressure defined by : $P(t) = \frac{\beta}{N} \int_0^t (I(u))\,\mathrm{d}u$
- $Q_1, Q_2, \cdots$ define susceptible individual resistance thresholds. As long as $Q_i > P(t)$, the corresponding susceptible individual remains susceptible. Otherwise, this individual get infected at the time $T_i = \inf\{t \geq 0 : P(t) \geq Q_i\}$.
- Recovery transition is based on the duration of stay in compartment I.

Sellke construction (2)

Extension of Sellke construction to the SARS-CoV-2 model

- Infection mechanism depends on the evolution of infection pressure: $P(t) = \frac{\beta}{N} \int_0^t (IA(u) + IS(u))\,\mathrm{d}u$.
- Other transition mechanism: the other transitions are based on the duration of stay in the corresponding compartments.

With the mechanism transition above, we define a new process
$\widetilde{W} = \left\{ \left(\tilde{S}(t), \tilde{E}(t), \tilde{IA}(t), \tilde{IS}(t), \tilde{H}(t), \tilde{R}(t), \tilde{D}(t)\right); t \geq 0 \right\}$

Theorem (1)

Under distribution assumptions, there exist a random vector Z independent of X and a deterministic function F_S such as :

$$W \overset{f.d.d}{=} \widetilde{W} = F_S(\cdot, X, Z). \tag{6}$$

Moreover, F_S and Z are totally explicit.

Kurtz representation (1)

- Random Time change or Kurtz representation is studied by Ethier and Kurtz 1986 and applied to chemical reaction network models (Anderson and Kurtz 2011)

Consider $G = \{G(t), t \geq 0\}$ a continuous time Markov chain with M different transitions. Denote $\zeta_m, \lambda_m, m = 1, \cdots, M$ respectively the transition vectors and the intensity functions.

Theorem (Kurtz 1982)

There exist $Y_1, \cdots, Y_M$ Poisson independent processes with intensity 1 such as almost surely :

$$\forall\, t \geq 0, \quad G(t) = G(0) + \sum_{m=1}^{M} Y_i \left(\int_0^t \lambda_m (X, G(s))\, \mathrm{d}s \right) \cdot \zeta_m. \qquad (7)$$

- Use of this representation to perform global sensitivity analysis for chemical reaction network models (Le Maitre, O. M. Knio, and Moraes 2015; Navarro Jimenez, Le Maitre, and O. M. Knio 2016)

Kurtz representation (2)

Theorem (Navarro Jimenez, Le Maitre, and O. M. Knio 2016)

There exist $Y_1, \cdots, Y_M$ Poisson independent processes with intensity 1 and a deterministic function F_K such as almost surely :

$$G = F_K\left(\cdot, X, \underbrace{Y_1, \cdots, Y_M}_{Z'}\right) \tag{8}$$

Let adapt this technique to the SARS-CoV-2 model.
There are $M = 9$ different types of transitions.

- Each type of transition is under the form $x \longrightarrow x + \zeta_m$
- To each type of transition corresponds an intensity function λ_m such as the transition $x \longrightarrow w + \zeta_m$ rate is $\lambda_m(X, w)$.

Transitions	Transition vector	Intensity function
$S \rightarrow E$	$\zeta_1 = (-1, 1, 0, 0, 0, 0, 0)^t$	$\lambda_1(X, w) = \frac{\beta}{N} S \cdot (IA + IS)$
$E \rightarrow IA$	$\zeta_2 = (0, -1, +1, 0, 0, 0, 0)^t$	$\lambda_2(X, w) = \delta \cdot p_E \cdot E$
$\vdots$	$\vdots$	$\vdots$

Sensitivity analysis for the SARS-CoV-2 model (1)

Remind the process:
$W = \left\{ (S(t), E(t), IA(t), IS(t), H(t), R(t), D(t))\,;\, t \geq 0 \right\}$ dependent on unknown parameters $X = (\beta, \delta, \mu_A, \mu_C, p_E, p = (p_1, p_2), \gamma_H, p_H)$.

- Model output: $E = \{E(t); t \in [0, T]\}$ with $T = 50$
- Computed indices: dynamic Sobol indices, aggregated indices
- Method: pick-freeze
- Number of explorations: $n = 5000$
- Initial conditions: $S(0) = 100, E(0) = 1, IA(0) = 0, IS(0) = 0, H(0) = 0, R(0) = 0, D(0) = 0$
- Uncertain parameter variation intervals are set according to Knock et al. 2021

Sensitivity analysis for the SARS-CoV-2 model (2)

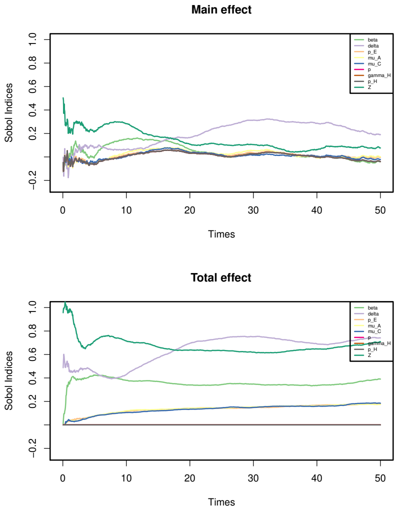


Figure 4: Dynamic of Sobol indices for Sellke representation

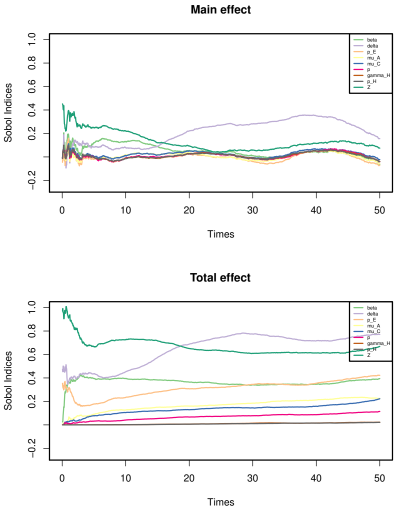


Figure 5: Dynamic of Sobol indices for Kurtz representation

Sensitivity analysis for the SARS-CoV-2 model (3)

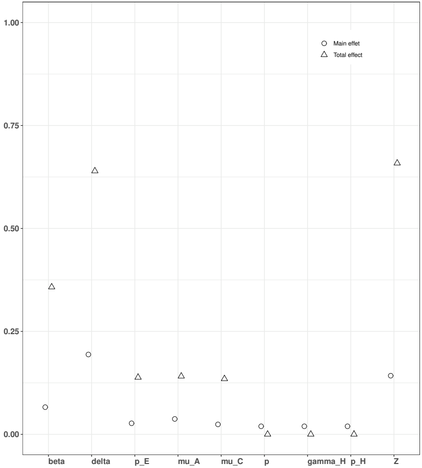


Figure 6: Aggregated indices for Sellke representation

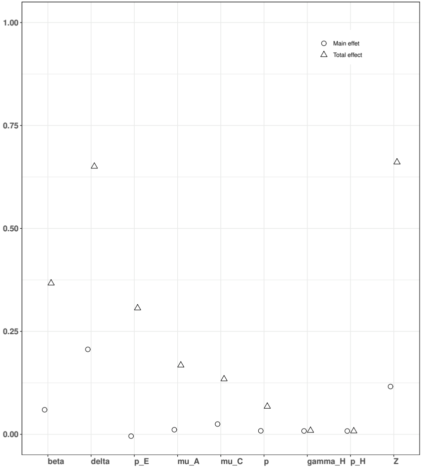


Figure 7: Aggregated indices for Kurtz representation

Sensitivity analysis for the SARS-CoV-2 model (4)

Zoom on the parameter p_E total effects

- Estimation of indices with $n = 5000$ explorations at instant $t = 20$
- 95% confidence intervals are computed by bootstrap using 100 replications.

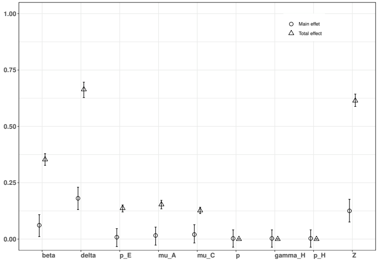


Figure 8: Indices for Sellke representation at instant $t = 20$

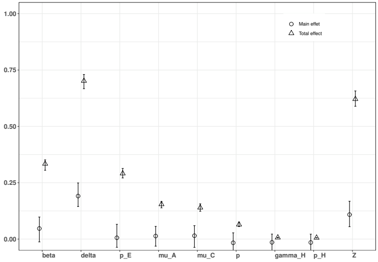


Figure 9: Indices for Kurtz representation at instant $t = 20$

Difference between p_E total effects for the two representations is due to difference in the distribution of the intrinsic randomness.

Conclusion

Our approach provides:

- Additional information: intrinsic randomness contribution and its interactions with model parameters
- Invariance of parameter main contributions with respect to representation
- A way to select a representation (or a computer code) based on the intrinsic randomness impact

Perspectives

- Study of the impact of the intrinsic randomness distribution on the conditional expectations of the form: $\mathbb{E}\left(f\left(X, Z\right) \mid \left(X_u, Z\right)\right)$
- Extension of Sellke construction to a larger class of compartmental models.
- Extension of our approach to non-markovian epidemic models using Sellke construction.
- Coupling this approach with other sensitivity analysis methods.
- Comparison with representation-free methods based on sensitivity analysis of probability measures of the outputs.

End

Thank you !

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