Global sensitivity analysis for some stochastic epidemic compartmental models

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Outline

Compartmental modelling

- **A compartmental model** is composed with **compartments** and **arrows**.

Compartmental modelling

- **A compartmental model** is composed with **compartments** and **arrows**.
- Compartmental models are widely used:
  - Medicine, Physics, Chemistry, Ecology etc.
  - Epidemiology: spreading of disease among a population (humans, animals, plants)

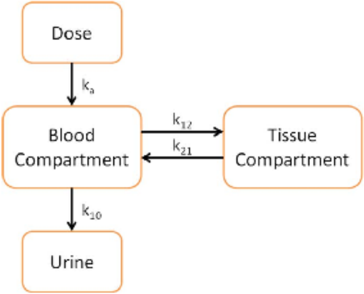


Figure 2: An example of compartmental model in medicine

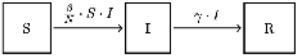


Figure 3: An example of epidemic model : SIR model

Continuous-time Markov chain

Consider a process $W = \{W(t); t \geq 0\}$ **that counts the number of individuals in the different compartments** for a closed population of constant size N.

- State space $\mathcal{E}$ composed of tuples of integers.
- Each type of transition is associated with a rate function depending on states and parameters of the studied phenomenon

Denote Θ the parameter space. W is parameterized by $\theta \in \Theta$.
Write $W(\theta; \cdot) = \{W(\theta; t), t \geq 0\}$ to highlight this parameterization.

For each θ, $W(\theta; \cdot)$ is assumed to be **a continuous-time Markov chain (CTMC)** with a generator that depends on rate functions.

The SIR model example:

$$\boxed{\mathrm{S}} \xrightarrow{\frac{\beta}{N}\cdot S \cdot I} \boxed{\mathrm{I}} \xrightarrow{\gamma \cdot I} \boxed{\mathrm{R}}$$

- Parameters: $\theta = (\beta, \gamma) \in (\mathbb{R}_+)^2$
- The SIR process $W(\theta; \cdot) = \{(S(t), I(t), R(t)); t \geq 0\}$ with generator Q:

$$Q_{(s,i,r),(s-1,i+1,r)} = \frac{\beta}{N} s \cdot i$$

$$Q_{(s,i,r),(s,i-1,r+1)} = \gamma \cdot i$$

Model and SA challenge

Consider a stochastic model $\mathcal{M} : \theta \longmapsto G(\theta; \cdot)$ with $G(\theta; \cdot)$ a random variable for each θ.

Methods in the literature

1. Methods for scalar output stochastic models (Mazo 2021; Hart, Alexanderian, and Gremaud 2017)
2. Meta-modelling based approaches (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. Da Veiga 2021, Fort, Klein, and Lagnoux 2020 considered stochastic simulators as probability distribution function valued computer codes.

In this work, the stochastic models are under the form $\theta \longmapsto F(W(\theta; \cdot))$ where F is a functional with scalar or functional values.

Main objectives

Assume X is a random variable on Θ. Consider a stochastic model with parameters sampled by X and output denoted Y.

A. **Objective:** to perform sensitivity analysis using existing methods without using meta-models.

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

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

Z stands for the intrinsic randomness.

Outline

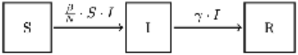
Link between compartmental models and graphs

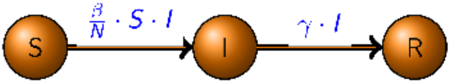
Consider any compartmental model. Assume that:

- each compartment is a vertex
- arrows between compartments are edges

Denote V the set of vertices and E the set of edges.
Any compartmental model can be considered as a directed graph $\mathscr{G} = (\mathrm{V}, \mathrm{E})$.

The SIR model example



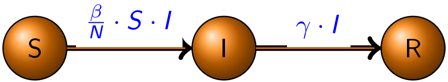


$\mathrm{V} = \{S, I, R\}$ $\quad$ $\mathrm{E} = \{(S, I), (I, R)\}$

Process description (1/2)

- Consider a closed population of constant size of N individuals.
- $W(\theta;\cdot) = \{W(\theta;t) = (W_\alpha(\theta;t))_{\alpha\in\mathrm{V}},\ t\geq 0\}$ where $W_\alpha(\theta;t)$ is the number of individuals in the compartment or vertex α at the time t.
- The process $W(\theta;\cdot)$: a continuous-time Markov chain on state space $\mathcal{E} = \{w\in\{0,\cdots,N\}^{|\mathrm{V}|} : \sum_{i=1}^{|\mathrm{V}|} w_i = N\}$ where $|\mathrm{V}|$ denotes the number of vertices.

The SIR model example



$\mathrm{V} = \{S, I, R\}$
$\mathrm{E} = \{(S,I),(I,R)\}$

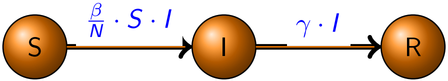
- $\mathcal{E} = \{w = (s,i,r) : s+i+r = N\}$
- $\theta = (\beta,\gamma)\in\mathbb{R}_+\times\mathbb{R}_+$
- $W(\theta,\cdot) = \{(S(t), I(t), R(t))\,;\,t\geq 0\}$

Process description (2/2)

- Assume $w \in \mathcal{E}$. The transitions of type $\alpha \to \beta$ are under the form: $w \to w + u_{\alpha,\beta}$, where $u_{\alpha,\beta} \in \{-1, 0, 1\}^{|V|}$
- To each transition of type $\alpha \to \beta$ corresponds a function $g_{\alpha,\beta} : (\theta, w) \mapsto g_{\alpha,\beta}(\theta, w)$ such that every transition $w \to w + u_{\alpha,\beta}$ occurs at rate $g_{\alpha,\beta}(\theta, w)$

The transitions of type $\alpha \to \beta$ are simply denoted by the edge $(\alpha, \beta) \in E$.

The SIR model example:



$$g_{(S,I)}(\theta, (s,i,r)) = \frac{\beta}{N} \cdot s \cdot i$$
$$u_{(S,I)} = (-1, 1, 0)$$

$$g_{(I,R)}(\theta, (s,i,r)) = \gamma \cdot i$$
$$u_{(I,R)} = (0, -1, 1)$$

Outline

Gillespie representation (1/2)

Let α, β be two vertices.

Denote $\lambda(t) = \sum_{(\alpha,\beta)\in \mathrm{E}} g_{(\alpha,\beta)}\left(\theta, W(\theta,t)\right)$

and $\mathrm{p}_{(\alpha,\beta)} = \dfrac{g_{(\alpha,\beta)}\left(\theta, W(\theta,t)\right)}{\lambda(t)}$

Gillespie Algorithm

1. Set θ, $t = 0$, $W(\theta, 0) = W_0$
2. Repeat until extinction
   - Draw $\tau \sim \exp(\lambda(t))$
   - Pick randomly a transition type (α, β) in E with probability $\left(\mathrm{p}_{(\alpha,\beta)}; (\alpha,\beta) \in E\right)$
   - $W(\theta, t+\tau) \leftarrow W(\theta, t) + u_{\alpha,\beta}$; $t \leftarrow t + \tau$

Objective

From Gillespie algorithm, find a function f_G and Z such that: $W(\theta, \cdot) = f_G(\theta, Z)$.

Strategy

- Modify the algorithm to be able to input all the random variables as uniform variables
- A number of 2 times the maximal number of jumps of the process $W(\theta, \cdot)$ i.i.d. standard uniform variables are needed.

Limitation

This is limited to the directed acyclic graph

Directed acyclic graphs

Directed Acyclic Graph

A directed acyclic graph (DAG) is a directed graph with no cycle.

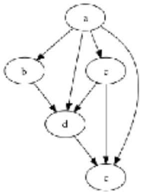


Figure 4: An example of DAG

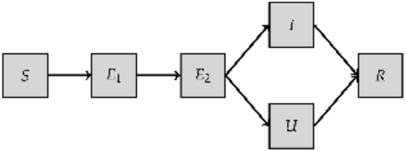


Figure 5: An example of DAG in epidemiology

Particularity of DAG in epidemiology

- Individuals cannot return to previous states
- The maximal number of jumps can be computed

Gillespie representation (2/2)

Assume the graph is acyclic and denote n_{jumps} the maximal number of jumps.

Gillespie Algorithm

1. Set θ, $t = 0$, $W(\theta, 0) = W_0$
2. Draw Z as a $(2, n_{\text{jumps}})$-matrix of i.i.d standard uniform variables
3. For $i = 1, \cdots, n_{\text{jumps}}$:
   - Pick ith row of Z and set $(u_1, u_2) \leftarrow Z[i,]$
   - Compute $\tau \leftarrow -\log(u_1)/\lambda(t)$
   - Using u_2, pick a transition type (α, β) in E with probability $\left(p_{(\alpha,\beta)}; (\alpha, \beta) \in E\right)$
   - $W(\theta, t+\tau) \leftarrow W(\theta, t) + u_{\alpha,\beta}$; $t \leftarrow t + \tau$

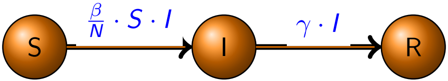
Pros

1. Easy construction
2. Available and well-studied algorithm

Cons

1. Not applicable to general directed graphs
2. Only for valid for markovian processes

The SIR model example



- Given $(S(0), I(0), R(0))$, $n_{\text{jumps}} = 2 \cdot S(0) + I(0)$

Kurtz representation (1/2)

Assume $\mathscr{G} = (\mathsf{V}, \mathsf{E})$ is a directed graph.

Theorem (Kurtz 1982,Ethier and Kurtz 1986)

For each $\theta \in \Theta$, the process $W(\theta; \cdot)$ satisfies almost surely:

$$\forall\, t \geq 0, \quad W(\theta; t) = W(\theta; 0) + \sum_{(\alpha,\beta)\in \mathsf{E}} P_{(\alpha,\beta)} \left(\int_0^t g_{\alpha,\beta}(\theta, W(\theta; s))\, \mathrm{d}s \right) \cdot u_{\alpha,\beta}$$

where $\{P_{(\alpha,\beta)}, (\alpha, \beta) \in \mathsf{E}\}$ are independent Poisson standard processes.

The SIR model example:

$$(S(t), I(t), R(t)) = (S(0), I(0), R(0)) +$$

$$P_{(S,I)} \left(\int_0^t \frac{\beta}{N} \cdot S(z) \cdot I(z)\mathrm{d}z \right) \cdot (-1, 1, 0) + P_{(I,R)} \left(\int_0^t \gamma \cdot I(z)\mathrm{d}z \right) \cdot (0, -1, 1)$$

Kurtz representation (2/2)

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

Assume X a random variable on the parameter space Θ. There exist f_K and Z' such that:

$$W(X,\cdot) \stackrel{\mathcal{L}}{=} f_K\left(\cdot, X; \underbrace{\left(P_{(\alpha,\beta)}, (\alpha,\beta) \in \mathrm{E}\right)}_{Z'}\right).$$

where $\{P_{(\alpha,\beta)}, (\alpha,\beta) \in \mathrm{E}\}$ are independent Poisson standard processes.

Z' stands for the intrinsic randomness of the model.

Pros

- Applicable to any directed graph

Cons

- Not applicable to non-markovian processes

Sellke representation (1/3)

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

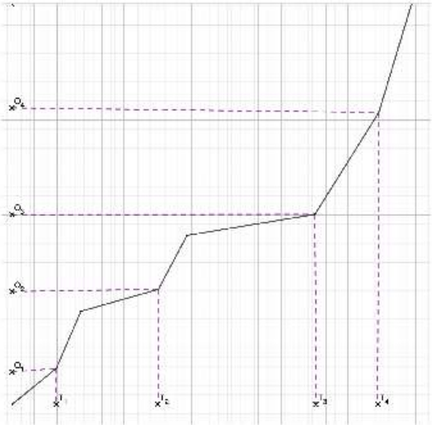


Figure 6: Example of evolution of infection pressure

- Infection transition depends on:
  - $P(t) = \frac{\beta}{N} \int_0^t I(u) \mathrm{d}u$

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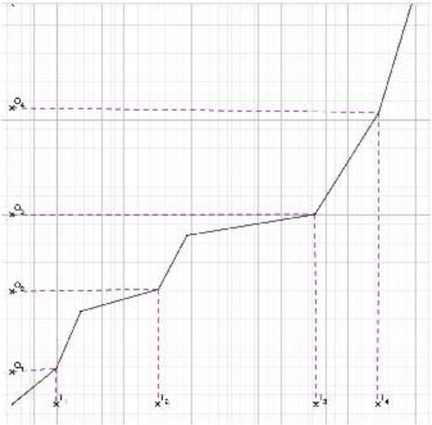

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- Infection transition depends on:
  - $P(t) = \frac{\beta}{N} \int_0^t I(u) \mathrm{d}u$
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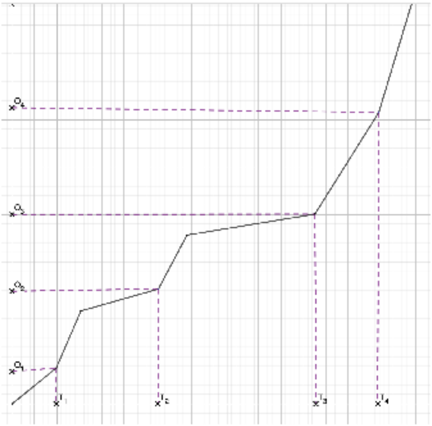

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  - $P(t) = \frac{\beta}{N} \int_0^t I(u) \mathrm{d}u$
  - $Q_1, Q_2, \cdots$ individual "resistance thresholds". As long as $Q_i > P(t)$, the ith individual is susceptible.
- Recovery transition: based on the sojourn time mechanism.

Objective: By generalizing Sellke construction, construct a stochastic process $W'(\theta;\cdot) = \{W'(\theta;t) = (W'_\alpha(\theta;t))_{\alpha\in\mathrm{V}},\ t \geq 0\},\ \theta \in \Theta$

- Root process $W'_\alpha(\theta,\cdot)$

Let α be a root and $Q_{\alpha,i}$, $i = 1,\dots,n_\alpha$ be i.i.d. exponential variables.

$$W'_\alpha(\theta,t) = \sum_{i\in\alpha} 1_{Q_{\alpha,i}>\zeta_\alpha(\theta,t)}$$

where

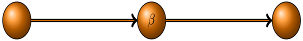
$$\zeta_\alpha(\theta,t) = \int_0^t \psi_\alpha(\theta, W'(\theta,s))\,\mathrm{d}s.$$

$Q_{\alpha,i}$, $i = 1,\dots,n_\alpha$ are called "resistance thresholds".

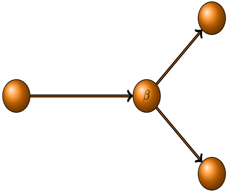
- Non-root process $W'_\beta(\theta,\cdot)$

Let β be a non-root vertex.

Duration mechanism:



Path choice mechanism:



$W'_\beta(\theta,\cdot)$ is entirely function of θ, the resistance thresholds, the sojourn time variables and uniform variables.

Sellke representation (3/3)

Assumption: All the sojourn time variables are independent with exponential distributions.

Theorem

1. *There exist f_S and Z such that:*

$$\forall\, t \geq 0, \forall\, \theta \in \Theta, \quad W'(\theta; t) = f_S\,(t, \theta, Z)$$

2. *Assume X is a random variable on the parameter space Θ. Under the assumption above:*

$$W(X, \cdot) \overset{\mathcal{L}}{=} f_S\,(\cdot, X, Z)$$

such that X and Z are independent.

Pros

- *Adaptable to markovian and non-markovian processes*

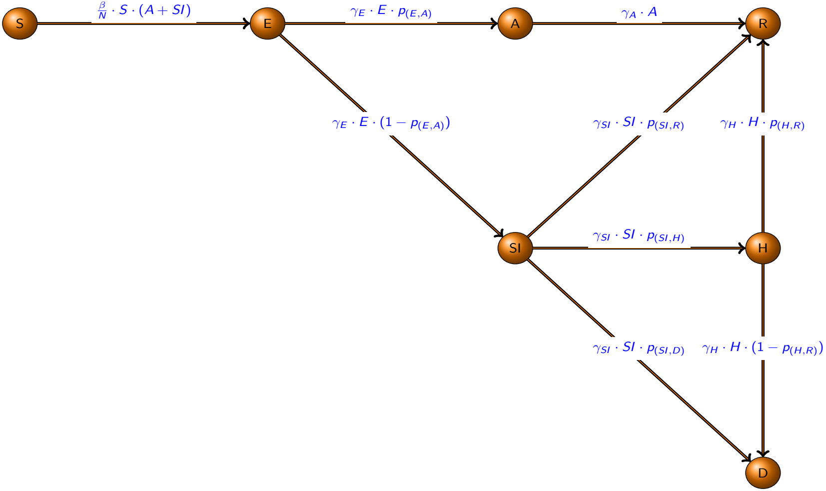
Cons

- *Only applicable to directed acyclic graphs*

Outline

SARS-CoV-2 model

Consider the following model for the spread of SARS-CoV-2 among a population with constant size N (Knock et al. 2021).



Sensitivity analysis (1/4)

The process $W(\theta, \cdot)$ depends on unknown parameters $\theta = \left(\beta, \gamma_E, \gamma_A, \gamma_{SI}, \gamma_H, p_{(E,A)}, p_{SI}, p_{(H,R)}\right)$ where $p_{SI} = \left(p_{(SI,R)}, p_{(SI,H)}, p_{(SI,D)}\right)$

- Model output: D_{tot} the total number of deaths during the epidemic.
- Computed indices: Sobol' indices
- Method: pick-freeze
- Number of explorations: $n = 1500$
- $N = 1003$ including 1000 susceptible and 3 exposed individuals at $t = 0$
- Uncertain parameter variation intervals are set according to Knock et al. 2021

Sensitivity analysis (2/4)

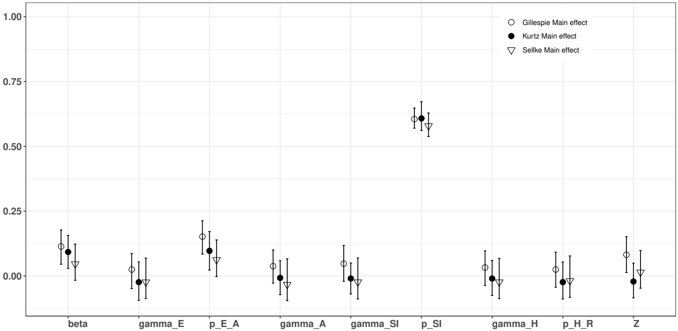


Figure 7: Main effects of parameters for D_{tot}

Conclusions

- Main effects show the importance of probabilities p_{SI} and $p_{(E,A)}$
- These probabilities influence the amount of individuals that will end up in the compartment D

Sensitivity analysis (3/4)

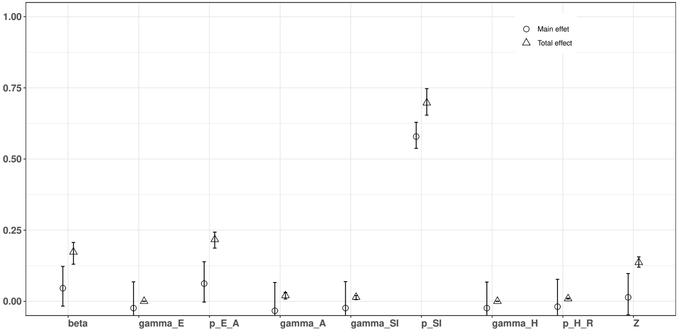


Figure 8: Main and Total effects of parameters for D_{tot} simulated by Sellke representation

Conclusions

- The total effects highlight the interactions of Z with the model parameters

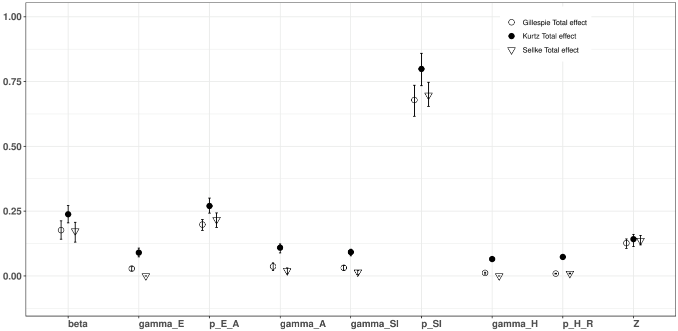


Figure 9: Total effects of parameters for D_{tot}

Conclusions

- Total effects point out the impact of $p_{SI}, p_{(E,A)}, \beta$ and Z.
- Significant differences can be observed in total effects of the parameters in the two representations.

Outline

Conclusion and Perspectives

Conclusion

Our approach:

- Provides additional information: intrinsic randomness contribution and its interactions with model parameters
- Is adaptable to most compartmental models used in epidemiology.

Perspectives

- Is the sensitivity analysis independent of the representations of the model?
- Comparison with representation-free methods based on sensitivity analysis of probability measures of the outputs.

Thanks for your attention !

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