Variance Decomposition Techniques for Sensitivity Analysis in Stochastic / Noisy Models with Uncertain Parameters

Olivier Le Maître\(^1,2,3\), Omar Knio\(^1,2\)

1- Duke University, Durham, North Carolina
2- KAUST, Saudi-Arabia
3- LIMSI CNRS, Orsay, France

UNCECOMP, Crete
Variance-Based Sensitivity Analysis for SODE's
- Variance decomposition
- Galerkin approximation
- Examples

Stochastic Simulations
- Stochastic simulators
- Variance Decomposition
- Examples

Conclusion
**Stochastic models**

Physical systems with

- complex *small scale* dynamics (MD, chemical systems, ...)
- *random forcing* and source terms (finance, wind-load, ...)
- *unresolved scales* (turbulence, climate modeling, ...)

are often tackled by means of *stochastic modeling* where complex / unknown / unresolved phenomenons are accounted for by the introduction of noisy dynamics.

In addition to the effect of the noise, the model may involve *unknown parameters*: *e.g.* noise level, physical constants and parameters, initial conditions, ...

Our general objective is to *propagate / assess the impact of parameters uncertainty* within such stochastic models while characterizing the effect of *inherent noise*: 

*global sensitivity analysis & analysis of the variance*
Stochastic ODEs
We consider a simple systems driven by random noise (Ito equation) : for
$t \in [0, T] \equiv T$

$$dX(t) = C(X(t))dt + D(X(t))dW(t), \quad X(t = 0) = X_0,$$

where
- $X(t) \in \mathbb{R}$ is the solution,
- $W(t)$ is the Wiener process,
- $C(\cdot)$ is the drift function,
- and $D(\cdot)$ is the diffusion coefficient.

The solution can be computed through MC simulation, solving (e.g.)

$$X_{i+1} = X_i + C(X_i)\Delta t + D(X_i)\Delta W_i, \quad X_i \approx X(i\Delta t),$$

drawing iid random variables $\Delta W_i \sim \mathcal{N}(0, \Delta t)$.

Sample estimate expectation, moments, quantiles, probability law, . . . , of the stochastic process $X(t)$ :

$$\mathbb{E} \{g(X(i\Delta t))\} \approx \frac{1}{M} \sum_{l=1}^{M} g(X^{l}_i).$$
Stochastic ODEs with parametric uncertainty
The drift function and diffusion coefficient can involve some uncertain parameters $Q$:

$$dX(t) = C(X(t); Q)dt + D(X(t); Q)dW(t), \quad X(t = 0) = X_0.$$ 

We consider that:

- $Q$ random with known probability law,
- $Q$ and $W$ are assumed independent.

The solution can be seen as a functional of $W(t)$ and $Q$:

$$X(t) = X(t, W, Q).$$

We shall assume, $\forall t \in \mathcal{T}$,

1. $E\{X^2\} < \infty$,

2. $E\left\{E\{X|W\}^2\right\} = E\left\{X^2|W\right\} < \infty$,

3. $E\left\{E\{X|Q\}^2\right\} = E\left\{X^2|Q\right\} < \infty$.

We want to investigate the respective impact of $Q$, $W$ on the dynamics.
Classical sensitivity analysis

Focusing on the two first moments, global SA for the random parameters $Q$ is based on:

1. approximating the mean and variance of $X|Q$

$$\mathbb{E}\{X|Q\} = \mu_X(Q), \quad \mathbb{V}\{X|Q\} = \Sigma^2_X(Q),$$

2. perform a GSA of $\mu_X(Q)$ and $\Sigma^2_X(Q)$ with respect to the input parameters in $Q$.

In particular, for independent parameters $Q$, Polynomial Chaos approximations:

$$\mu_X(Q) \approx \sum_\alpha \mu_\alpha \Psi_\alpha(Q), \quad \Sigma^2_X(Q) \approx \sum_\alpha \Sigma^2_\alpha \Psi_\alpha(Q).$$

PC expansion coefficients can be computed / estimated by means of Non-Intrusive Spectral Projection, Bayesian identification, . . . .

This approach characterizes the dependence of the first moments with respect to the parameters $Q$. 
Another approach of GSA
Here, we exploit the structure of the model to take an alternative approach, inspired from the hierarchical orthogonal Sobol-Hoeffding decomposition of $X$:

$$X(W, Q) = \overline{X} + X_W(W) + X_Q(Q) + X_{W,Q}(W, Q), \quad \forall t \in T,$$

where the functionals in the SH decomposition are mutually orthogonal.
In fact, the decomposition is unique and given by

- $\overline{X}(t) \doteq \mathbb{E} \{X(t)\}$,
- $X_W(t, W) \doteq \mathbb{E} \{X(t)|W\} - \mathbb{E} \{X(t)\} = X|_W(t) - \overline{X}(t)$,
- $X_Q(t, Q) \doteq \mathbb{E} \{X(t)|Q\} - \mathbb{E} \{X(t)\} = X|_Q(t) - \overline{X}(t)$.

Owing to the orthogonality of the SH decomposition, we have

$$\nabla \{X\} = \nabla \{X_W\} + \nabla \{X_Q\} + \nabla \{X_{W,Q}\},$$

from which follow the definitions of the sensitivity indices

$$S_W = \frac{\nabla \{X_W\}}{\nabla \{X\}}, \quad S_Q = \frac{\nabla \{X_Q\}}{\nabla \{X\}}, \quad S_{W,Q} = \frac{\nabla \{X_{W,Q}\}}{\nabla \{X\}}.$$
Sensitivity indices
The sensitivity indices

\[ S_W = \frac{\text{Var} \{X_W\}}{\text{Var} \{X\}} \quad , \quad S_Q = \frac{\text{Var} \{X_Q\}}{\text{Var} \{X\}} \quad , \quad S_{W,Q} = \frac{\text{Var} \{X_{W,Q}\}}{\text{Var} \{X\}} , \]

then measure the fraction of the variance due to

- the Wiener noise only, or intrinsic randomness (\( S_W \)),
- the parameters only, or parametric randomness (\( S_Q \)),
- the combined effect of intrinsic and parametric randomness (\( S_{W,Q} \)).

In particular, \( S_W \) measure the part of the variance that cannot be reduced through a better knowledge of the parameters.

In addition,

\[ \frac{\text{Var} \{\mu_X(Q)\}}{\text{Var} \{X\}} = S_Q \quad \text{but} \quad \frac{\mathbb{E}_Q \{\Sigma^2(Q)\}}{\text{Var} \{X\}} = S_W + S_{W,Q} . \]

From \( \Sigma^2(Q) \), one cannot distinguish the intrinsic and mixed randomness effects.
**Polynomial Chaos expansion**
We express the dependence of $X$ on $Q$ as a PC expansion

$$X(t, W, Q) = \sum_{\alpha} X_\alpha(t, W) \psi_\alpha(Q),$$

where
- $\{\psi_\alpha\}$ is a CONS of $L^2(Q, p_Q)$,
- the expansion coefficients $X_\alpha$ are random processes.

The random processes $X_\alpha(t)$ are the solutions of the coupled system of SODEs

$$dX_\beta(t) = \left\langle F \left( \sum_\alpha X_\alpha(t) \psi_\alpha; QX \right), \psi_\beta \right\rangle dt + \left\langle G \left( \sum_\alpha X_\alpha(t) \psi_\alpha; Q \right), \psi_\beta \right\rangle dW,$$

where $\langle \cdot, \cdot \rangle$ denotes the inner product in $L^2(Q, p_Q)$.
This system can be solved by MC simulation (upon truncation).
PC expansion
Assuming $\Psi_0 = 1$, it comes

$$
\mathbb{E}\{X\} = \mathbb{E}\{X_0\}, \quad X_Q(Q) = \sum_{\alpha \neq 0} \mathbb{E}\{X_\alpha\} \Psi_\alpha(Q), \quad X_W(W) = X_0(W) - \mathbb{E}\{X_0\},
$$

and

$$
X_{W,Q}(W, Q) = \sum_{\alpha \neq 0} (X_\alpha(W) - \mathbb{E}\{X_\alpha\}) \Psi_\alpha(Q).
$$

Finally, the partial variances have for expression:

$$
\forall \{X_Q\} = \sum_{\alpha \neq 0} \mathbb{E}\{X_\alpha\}^2, \quad \forall \{X_W\} = \forall \{X_0\}, \quad \forall \{X_{W,Q}\} = \sum_{\alpha \neq 0} \forall \{X_\alpha\}.
$$

Observe:

1. $X_Q(Q) + \mathbb{E}\{X\} = \mu_X(Q),$
2. $\sum_\alpha \forall \{X_\alpha\} = \sum_\alpha \mathbb{E}\{X_\alpha^2\} - \mathbb{E}\{X_\alpha\}^2 = \mathbb{E}_Q\{\Sigma_X^2\}.$
Linear additive system

- Consider SODE with drift and diffusion terms given by:

\[ C(X, Q) = Q_1 - X \quad D(X, Q) = (\nu X + 1)Q_2 \]

where \( Q_1 \) and \( Q_2 \) are independent, uniformly-distributed, random variables with mean \( \mu_{1,2} \) and standard deviation \( \sigma_{1,2} \).

- The orthonormal PC basis consists of tensorized Legendre polynomials.

- We use for initial condition \( X(t = 0) = 0 \) almost surely.
Additive noise model \( (\nu = 0) \) with \( \mu_1 = 1, \mu_2 = 0.1, \sigma_1 = \sigma_2 = 0.05 \): 

\[
dX(Q) = (Q_1 - X(Q))dt + Q_2dW,
\]

a first-order expansion suffices to exactly represent \( X(Q) \).

Selected trajectories and variability ranges for \( [X_k](t, W) \). The plots correspond to \( k = 0, 1 \) and \( 2 \), arranged from left to right.
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Multiplicative Noise – I

Multiplicative noise: $Q_1 \sim \mathcal{U}[1, 0.05]$, $Q_2 \sim \mathcal{U}[0.1, 0.05]$, $\nu = 0.2$

Sample trajectories of $[X_k]$, $0 \leq k \leq 2$. Top row: order 0, bottom row: order 1 with and decreasing order in $Q_1$ from left to right.
Multiplicative noise: $Q_1 \sim \mathcal{U}[1, 0.05], Q_2 \sim \mathcal{U}[0.1, 0.05], \nu = 0.2$

Sample trajectories of $[X_k], 3 \leq k \leq 14$. The total order ranges from 2 (top row) to 4 (bottom row), with and decreasing order in $Q_1$ from left to right.
Multiplicative noise: $Q_1 \sim U[1, 0.05]$, $Q_2 \sim U[0.1, 0.05]$, $\nu = 0.2$

Probability density functions of the modes $[X_k]$ at $t = 10$. The modes have been centered and normalized to facilitate the comparison; the standard Gaussian distribution is also reported for reference.
Mode correlations

Projections in the planes \([X_k, X_{k'}]\) of realizations of the centered and normalized solution vector \(X\) at time \(t = 10\), for selected indices

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Left: trajectories for samples of $Q$ and a *fixed* realization of $W$
Right: trajectories for samples of $W$ at a *fixed* value of the parameters.
Selected trajectories of $X$ and its SH functions.
Effect of $Q_1$ and $Q_2$ of the (centered) conditional mean $\mu_X(Q) = \mathbb{E} \{ X \mid Q \} - \mathbb{E} \{ X \}$ and variance $\Sigma_X^2(Q) = \mathbb{V} \{ X \mid Q \}$ at time $t = 10$
Evolution of the components of the total variance. Shown are variance decompositions obtained for different values of $\sigma_1$ and $\sigma_2$. 
Consider a system with additive noise and non-linear drift

\[ dX = F(X)dt + \delta dW = -\gamma (X - a)(X - b)(X - c)dt + \delta dW \]

where \( \delta > 0 \) is an additional parameter controlling the noise level, and as before \( W \) is a Wiener process. Again the IC is \( X_0 = X(t = 0) \).

Sample trajectories with \( a = 10, b = 20, c = 30, \gamma = 0.01, \) and \( \delta = 1 \). In all cases, the initial condition coincides with \( x^0 = b \).
Consider an uncertain initial condition, $Q_1 \sim \mathcal{R}[17.5, 22.5]$, and forcing amplitude, $Q_2 \sim \mathcal{R}[0.5, 1.5]$.

\[ dX = F(X)dt + Q_1 dW \quad X_0 = Q_2. \]

- $Q_1$ and $Q_2$ independent.
- The PC representation is based on an adaptive multiwavelet basis expansion, which enables us to accommodate for bifurcation(s).
- The use of a non polynomial basis complicates the sensitivity analysis, but the framework is essentially unaltered.
Sample trajectories

Left plots: sample set of realizations of $W$, the trajectories of $X$ (time running up) for different initial conditions and two noise levels $Q_2 = 0.65$ (top plot) and $Q_2 = 1.35$ (bottom).

Right plots show for two realizations of $W$ (top and bottom), the trajectories of $X$ for a random sample set of values of $Q_10$ and $Q_2$. 
MW expansion

Left: partitions of the parametric domain and surface plots for $X(t = 6, W)$ as a function of $Q$. 
Variance decomposition

Variance-based SA

Partial variances of $X(t)$
Effect of Noise amplitude

Left : comparison of the total variances $\nabla \{X\}$ and total noise contributions $V_{\text{noise}} + V_{\text{mix}}$ to the variance, for two expected values of $\mathbb{E}\{\delta\} = 1$ and 2.

Right : partial variances of the stochastic process $X(t)$ for the case $\mathbb{E}\{\delta\} = 2$. 
Stochastic Systems

Stochastic Simulator

Work with Omar Knio and Alvaro Moraes (KAUST)
Stochastic Systems

Stochastic systems

governed by probabilistic evolution rules expresses by the master equation

\[
\frac{\partial P(x, t|x_0, t_0)}{\partial t} = \sum_{j=1}^{K_r} \left[ a_j(x - \nu_j)P(x - \nu_j, t|x_0, t_0) - a_j(x)P(x, t|x_0, t_0) \right],
\]

- \(P(x, t|x_0, t_0)\): probability of \(X = x\) at time \(t\), given \(X = x_0\) at time \(t_0\),
- general form \(\partial P(x, t|x_0, t_0)/\partial t = f(P(\cdot, t|x_0, t_0))\) (Markov process),
- \(x(t)\): state of the system at time \(t\),
- \(K_r\) reactions channels,
- propensity functions \(a_j\) and state-change vectors \(\nu_j \in \mathbb{Z}^{M_s}\).

Examples includes Reactive Networks (chemistry, biology), social networks, …

- Direct resolution of the master equation is usually not an option,
- Simulations of trajectories of \(X(t) \sim P(x, t|x_0, t_0)\), using a stochastic simulator.
Gillespie’s Algorithm

Given $X(t) = x$, the probability of the next reaction to occur in the $[t, t + dt]$ is

$$a_0(x) dt = dt \sum_{j=1}^{K_r} a_j(x).$$

The time to the next reaction, $\tau$, follows an exponential distribution with mean $1/a_0(x)$.

Gillespie’s Algorithm:

1. Set $t = t_0$, $X = x_0$.
2. Repeat until $t > T$
   - Draw $\tau \sim \text{exp} a_0(X)$
   - Pick randomly $k \in \{1 \ldots K_r\}$ with relative probability $p_k(a_k)$
   - update $t \leftarrow t + \tau$, $X \leftarrow X + \nu_k$
3. Return $X(T) \sim P(x, t|x_0, t_0)$.

From a sample set of trajectory, estimate expectation of functionals $\mathbb{E}\{g(X)\}$. 
For a given output $X(t)$ of a stochastic simulator, and a functional $g$, we would like:

assess the contributions of different channels (or group of channels) on the variability of $g(X)$

That is: which channel(s) is (are) responsible for most of the variance in $g(X)$?

This is **not to be confused with parametric sensitivity analyses** where one wants to estimate the sensitivity of $\mathbb{E}\{g(X)\}$ with respect to some parameters $q$ in the definition of the dynamics (e.g. propensity functions).
Sobol Analysis of the variance

- $\mathbf{N}(\omega) = (N_1, \cdots, N_D)$ a set of $D$ independent random inputs $N_i$,
- $F(\mathbf{N})$ a (second-order) random functional in $\mathbf{N}$,

$F(\mathbf{N})$ has a unique orthogonal decomposition

$$F(\mathbf{N}) = \sum_{\mathbf{u} \in \mathcal{D}} F_{\mathbf{u}}(\mathbf{N}_{\mathbf{u}}),$$

where $\mathcal{D}$ is the power set of $\{1, \cdots, D\}$ and $\mathbf{N}_{\mathbf{u}} = (N_{u_1}, \cdots, N_{u_{|\mathbf{u}|}})$. The orthogonality condition reads

$$\mathbb{E}\{F_{\mathbf{u}} F_{\mathbf{s}}\} = \int_{\Omega} F_{\mathbf{u}}(\mathbf{N}_{\mathbf{u}}(\omega)) F_{\mathbf{s}}(\mathbf{N}_{\mathbf{s}}(\omega)) d\mu(\omega) = 0,$$

so

$$\nabla\{F\} = \sum_{\mathbf{u} \in \mathcal{D} \setminus \emptyset} \nabla\{F_{\mathbf{u}}\},$$

where $\nabla\{F_{\mathbf{u}}\}$ are called partial variances.
Sobol Analysis of the variance (cont. . .)

From the variance decomposition,

\[ \mathbb{V} \{ F \} = \sum_{u \in \mathcal{D} \setminus \emptyset} \mathbb{V} \{ F_u \}, \]

- **First order sensitivity indices** \( S_u \): fraction of the variance caused by the random inputs \( N_u \) only

\[ \mathbb{V} \{ F \} S_u = \sum_{s \supseteq u} \mathbb{V} \{ F_s \} \]

- **Total order sensitivity indices** \( T_u \): fraction of the variance caused by the random inputs \( N_u \) and interaction

\[ \mathbb{V} \{ F \} T_u \sum_{s \in \mathcal{D} \setminus \emptyset} \mathbb{V} \{ F_s \} \]

The partial variances \( \mathbb{V} \{ F_u \} \) can be expressed as **conditional variances**:

\[ \mathbb{V} \{ F_u \} = \mathbb{V} \{ \mathbb{E} \{ F | N_u \} \} - \sum_{s \in \mathcal{D} \setminus \emptyset} \mathbb{V} \{ F_s \}, \]

or

\[ \mathbb{V} \{ F \} S_u = \mathbb{V} \{ \mathbb{E} \{ F | N_u \} \}, \quad \mathbb{V} \{ F \} T_u = \mathbb{V} \{ F \} - \mathbb{V} \{ \mathbb{E} \{ F | N_{u \sim} \} \} = \mathbb{V} \{ F \} (1 - S_{u \sim}), \]

where \( u \sim = \{1, \ldots, D\} \setminus u \).

**Decomposition of the Variance = Estimation of conditional variances**
Monte-Carlo estimation of the sensitivity indices

Consider two independent sample sets $\mathcal{N}^I$ and $\mathcal{N}^{II}$ of $M$ realizations of $\mathbf{N}$. The conditional variance $\mathbb{V} \{ \mathbb{E} \{ F \mid \mathbf{N}_u \} \}$ can be estimated as

$$\mathbb{V} \{ \mathbb{E} \{ F \mid \mathbf{N}_u \} \} + \mathbb{E} \{ F \}^2 = \lim_{M \to \infty} \frac{1}{M} \sum_{i=1}^{M} F(\mathbf{N}_u^I, (i)) F(\mathbf{N}_u^{II}, (i)) F(\mathbf{N}_u^I, (i)) F(\mathbf{N}_u^{II}, (i)),$$

such that

$$\hat{S}_u = \frac{1}{M} \sum_{i=1}^{M} F(\mathbf{N}_u^I, (i)) F(\mathbf{N}_u^{II}, (i)) - \mathbb{E} \{ F \}^2 \frac{\mathbb{V} \{ F \}}{\mathbb{V} \{ F \}^2},$$

and

$$\hat{T}_u = 1 - \frac{1}{M} \sum_{i=1}^{M} F(\mathbf{N}_u^I, (i)) F(\mathbf{N}_u^{II}, (i)) - \mathbb{E} \{ F \}^2 \frac{\mathbb{V} \{ F \}}{\mathbb{V} \{ F \}^2},$$

where $\mathbb{E} \{ F \}$ and $\mathbb{V} \{ F \}$ are the classical MC estimators for the mean and variance. The computational complexity scales linearly with the number of indices to be computed.
**Application to Stochastic Simulators**

To assess the respective impacts of different reaction channels through Sobol’s decomposition of $\nabla \{ g(X) \}$, when $X$ is the output of a stochastic simulator, we need to condition $X$ on the channels dynamics:

*What is a particular realization of a channel dynamics?*

Gillespie’s algorithm is not suited, and we have to recast the stochastic algorithm in terms of independent processes associated to each channel.

**Next Reaction Formulation.** [Ethier & Kurtz, 2005, Gibson & Bruck, 2000]

$$X(t) = X(t_0) + \sum_{j=1}^{K_r} \nu_j N_j(t_j),$$

where the $N_j(t)$ are independent standard (unit rate) Poisson processes, and the scaled times $t_j$ are given by

$$t_j = \int_{t_0}^t a_j(X(\tau))d\tau, \quad j = 1, \ldots, K_r.$$

Then, $g(X)$ can be seen as

$$g(X) = F(N_1, \ldots, N_{K_r}).$$
The random functional $g(\mathbf{X}) = F(N_1, \ldots, N_{K_r})$ can then be decomposed à la Sobol. A particular realization of a channel dynamic is identified with a realization of the underlying standard Poisson processes.

For instance, the conditional variance writes

$$
\mathbb{E} \{ g(\mathbf{X}) \mid N_u = n_u \} = \mathbb{E} \left\{ g \left( \mathbf{X}(t_0) + \sum_{j \in u} \nu_j n_j(t_j) + \sum_{j \in u} \sim \nu_j N_j(t_j) \right) \right\},
$$

with $t_j = \int_{t_0}^{t} a_j(\mathbf{X}(\tau)) d\tau$.

Note that

- in general, for fixed $n_u(t)$ the physical firing times $t_j$ remain random and depend on $N_u \sim$, even for $j \in u$
- in practice, the standard Poisson processes $N_j$ are entirely specified by their random seeds and pseudo-random number generator:

  the Poisson processes don't have to be stored but are computed on the fly
The birth-death (BD) process

Single species $S (M_s = 1)$ and $K_r = 2$ reaction channels:

$$
\emptyset \xrightarrow{b} S, \quad S \xrightarrow{d} \emptyset,
$$

with propensity functions

$$ a_1(x) = b, \quad a_2(x) = d \times x. $$

We set $b = 200$, $d = 1$, and use $M = 1,000,000$ Monte Carlo samples to compute the estimates.

**Figure:** Left: Selected trajectories of $X(t)$ generated using Next Reaction Algorithm. Right: histogram of $X(t = 8)$. 
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B-D process. Variance decomposition of $g(X) = X(t)$

Left: scaled first-order and total sensitivity indices (scaled by the variance) of the birth-death model and $t \in [0, 8]$. Right: long-time evolution of the first-order sensitivity indices, and of the mixed interaction term.

- Variance in $X$ is predominantly caused by the birth channel stochasticity for early time $t < 1$
- For $1 \leq t \leq 4$, the variability induced by $R_d$ only continues to grow with the population size (first order reaction), while mixed effects develops
- Eventually, effect of $R_b$ stabilize (zero-order reaction, rate independent of $X$) while effect of $R_d$ only slowly decays to benefit the mixed term (stochasticity of $N_b$ affects more and more the death process).
System with $K_r = 4$ reaction channels:

$$B_1 + 2S \xrightleftharpoons[\frac{c_1}{c_2}]{\frac{c_3}{c_4}} 3S,$$

with $B_1$ and $B_2$ in large excess and constant population over time, $X_{B_1} = X_{B_2}/2 = 10^5$ and a single evolving species $S$ with $M_s = 1$. The propensity functions are given by

$$a_1(x) = \frac{c_1}{2} X_{B_1} x (x - 1), \quad a_2(x) = \frac{c_2}{6} x (x - 1)(x - 2), \quad a_3(x) = c_3 X_{B_2}, \quad a_4(x) = c_4 x.$$  

We set $c_1 = 3 \times 10^{-7}$, $c_2 = 10^{-4}$, $c_3 = 10^{-3}$, $c_4 = 3.5$ and deterministic initial condition $X(t = 0) = 250$. Results in a bi-modal dynamic.

Left: selected trajectories of $X(t)$ showing the bifurcation in the stochastic dynamics. Right: histogram of $X(t = 8)$.
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Schlögl model - Variance decomposition of $g(X) = X(t)$

First and total order partial variances.

Higher order partial variances.

Reaction channels $R_1$ and $R_4$ are the dominant sources of variance

Dynamic essentially additive up to $t \sim 2$
Analysis of the partial variance revealed that $R_1$ and $R_4$ are the main sources of stochasticity.

It suggests a **dominant role in selecting the bifurcation branch**, as illustrated below.

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<th>(a) Conditioned on $N_1$ and $N_4$</th>
<th>(b) Conditioned on $N_2$ and $N_3$</th>
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Trajectories of $X(t)$ **conditioned** on (a) $N_1(\omega) = n_1$ and $N_4(\omega) = n_4$, and (b) $N_2(\omega) = n_2$ and $N_3(\omega) = n_3$. Each sub-plot shows 10 conditionally random trajectories for fixed realizations $n_1$ and $n_4$ in (a), and $n_2$ and $n_3$ in (b).
**Michaelis-Menten system**

\( M_S = 4 \) species and \( K_r = 3 \) reaction channels:

\[
S_1 + S_2 \xrightleftharpoons[\frac{c_1}{c_2}]{c_2} S_3, \quad S_3 \xrightarrow[c_3]{c_3} S_4 + S_2
\]

with \( a_1(x) = c_1 x_1 x_2, \) \( a_2(x) = c_2 x_3, \) and \( c_3(x) = c_3 x_3. \)

We set \( c_1 = 0.0017, \) \( c_2 = 10^{-3}, \) and \( c_3 = 0.125, \) and initial conditions \( X_1(t=0) = 300, \) \( X_2(t=0) = 120 \) and \( X_3(t=0) = X_4(t=0) = 0.\)
Michaelis-Menten system - Variance decomposition of $g(X) = X_i(t)$

Note: $X_2 + X_3 = \text{const}$, the sensitivity indices for $S_2$ and $S_3$ are equal.

<table>
<thead>
<tr>
<th></th>
<th>(a) $S_1$</th>
<th>(b) $S_2$</th>
<th>(c) $S_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
<td><img src="image3" alt="Graph" /></td>
</tr>
</tbody>
</table>

Michaelis-Menten model: First-order and total sensitivity indices $S\{j\}$ and $T\{j\}$ for $j = 1, \ldots, 4$.

Plots are generated for (a) $X_1$, (b) $X_2$, and (c) $X_4$.

- Relative importance of $R_1$ and $R_3$ changes in time for $S_1$ and $S_2$.
- Stochastic dynamic of $S_4$ is essentially additive and dominated by $R_3$.
- Channel $R_2$ induces nearly no variance in $X(t)$: here the dissociation reaction $R_2$ can be simply disregarded without affecting significantly the dynamics.
On the contrary, increasing $c_2$ by an order of magnitude, the effect of $R_2$ on the variances becomes apparent:

(a) $S_1$

(b) $S_2$

(c) $S_4$
We have proposed

- Hybrid Galerkin / MC approach for noisy systems, can be extended to Non-Intrusive methods
- Parametric dependence assumes smoothness of the trajectories
- Development of methods and algorithms that enable variance decomposition for stochastic simulators output
- Identification of the channels dynamics with their underlying standard Poisson processes
- Assessment of the relative importance of different reaction channels on the variance

On-going and future works

- Application to more complex functional $g(X)$: exit-time, path integrals, ...(smoothness?)
- Account for parametric uncertainty in the definition of the propensity functions
- Improve stochastic simulators for computational complexity reduction, e.g. Tau-Leaping method and variance reduction methods.


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**Algorithm**

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**Algorithm 2. Next Reaction Algorithm.**

Procedure Compute_SI(M, X₀, T, {νᵢ}, {aⱼ}, g)

Require: Sample set dimension M, initial condition X₀, final time T, state-change vectors {νᵢ}, propensity functions {aⱼ} and functional g

1: μ ← 0, σ² ← 0 ▷ Ini. Mean and Variance
2: for j = 1 to Kᵦ do
3: S(j) ← 0, T(j) ← 0 ▷ Ini. first and total-order SIs
4: end for
5: for m = 1 to M do
6: Draw two independent set of seeds s' and s''
7: X ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
8: μ ← μ + g(X), σ² ← σ² + g(X)² ▷ Acc. mean and variance
9: for j = 1 to Kᵦ do
10: Xₛ ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
11: Xᵦ ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
12: S(j) ← S(j) + g(X) × g(Xₛ) ▷ Acc. 1-st order
13: T(j) ← T(j) + g(X) × g(Xᵦ) ▷ Acc. total order
14: end for
15: end for
16: μ ← μ/M, σ² ← σ²/(M-1) - μ²
17: for j = 1 to Kᵦ do
18: S(j) ← S(j) / (M-1)σ² - μ²/σ² ▷ Estim. 1-st order
19: T(j) ← 1 - (T(j) / (M-1)σ² + μ²/σ²) ▷ Estim. total order
20: end for
21: Return S(j) and T(j), j = 1,..., Kᵦ ▷ First and total-order sensitivity indices S(j) and T(j) of g(X(T))

---

**Procedure NRA** implement the Next Reaction Algorithm

**Poisson processes defined by two independent sets of seeds and RNG**

**Obvious parallelization**

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**Algorithm 3. Computation of the first and total-order sensitivity indices S(J) and T(J) of g(X(T)).**

Procedure Compute_SI(M, X₀, T, {νᵢ}, {aⱼ}, g)

Require: Sample set dimension M, initial condition X₀, final time T, state-change vectors {νᵢ}, propensity functions {aⱼ} and functional g

1: μ ← 0, σ² ← 0 ▷ Ini. Mean and Variance
2: for j = 1 to Kᵦ do
3: S(j) ← 0, T(j) ← 0 ▷ Ini. first and total-order SIs
4: end for
5: for m = 1 to M do
6: Draw two independent set of seeds s' and s''
7: X ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
8: μ ← μ + g(X), σ² ← σ² + g(X)² ▷ Acc. mean and variance
9: for j = 1 to Kᵦ do
10: Xₛ ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
11: Xᵦ ← NRA(X₀, T, {νᵢ}, {aⱼ}, RG₁(s₁),..., RGₖ,sₖ₁))
12: S(j) ← S(j) + g(X) × g(Xₛ) ▷ Acc. 1-st order
13: T(j) ← T(j) + g(X) × g(Xᵦ) ▷ Acc. total order
14: end for
15: end for
16: μ ← μ/M, σ² ← σ²/(M-1) - μ²
17: for j = 1 to Kᵦ do
18: S(j) ← S(j) / (M-1)σ² - μ²/σ² ▷ Estim. 1-st order
19: T(j) ← 1 - (T(j) / (M-1)σ² + μ²/σ²) ▷ Estim. total order
20: end for
21: Return S(j) and T(j), j = 1,..., Kᵦ ▷ First and total-order sensitivity indices S(j) and T(j) of g(X(T))