# A biased introduction to sensitivity analysis


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joint work with:

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# setup

model: $$\underbrace{q}_{\text{response}} = g(\underbrace{\theta_1, \ldots, \theta_p}_{\text{parameters}})$$

typically

- $g$ is a computer code
- parameters are uncertain
- $p$ is large[1]

[1] not necessarily in the "statistical" sense

# sensitivity analysis ($q = g(\theta)$)

we want to:

> *quantify how uncertainties in the model response can be apportioned to uncertainties in model inputs*

the larger the contribution, the more important the input

# rationale for SA (inspired by Saltelli)

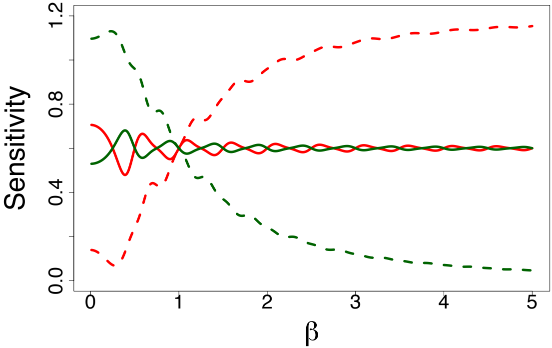
- model corroboration: is the inference robust?
- research prioritization: which factor most deserves further analysis/measurement?
- model simplification: can factors/compartments be fixed or simplified?
- model reliability: identify factors which interact and may lead to extreme values

# GSA challenges

- no agreement on the meaning of important
- one SA method $\Leftrightarrow$ one definition of "importance"
- inputs can be correlated
- GSA results depend on how parameter uncertainty is modeled; robustness?
- meaning of GSA for evolution pbs; causality?
- practical considerations $\Rightarrow$ use of surrogates (often):
  - surrogate $\approx$ model $\overset{?}{\Rightarrow}$ GSA(surrogate) $\approx$ GSA(model)

# importance?

- $g(\theta_1, \theta_2) = \sin^2 \beta\theta_1 \sin^2 \theta_2 \qquad \theta_i \sim U(0, 2\pi),\ i = 1, 2$




- dashed lines: partial derivative importance
- solid lines: total Sobol' indices
- only agree for $\beta = 1$!

# GSA: lots of choices

- regression based
- variance based (Sobol' indices)
- derivative based (Morris screening, . . . )
- game theoretic (Shapley values/effects)
- and many others. . .

this talk: (mostly) variance based

# variance based GSA

Ilya Sobol'

- considers $\theta_i$'s as random variables
- apportion to them their relative contribution to the variance of the response

- trivial example: $q = a\,\theta_1 + b\,\theta_2$, $\theta_i \sim N(0, \sigma_i^2)$, $a, b > 0$
- $q \sim N(0, \sigma_q^2)$ with $\sigma_q^2 = a^2\sigma_1^2 + b^2\sigma_2^2$

$$\Rightarrow 1 = \underbrace{\frac{a^2\sigma_1^2}{a^2\sigma_1^2 + b^2\sigma_2^2}}_{S_1} + \underbrace{\frac{b^2\sigma_2^2}{a^2\sigma_1^2 + b^2\sigma_2^2}}_{S_2}$$

- note the importance of the $\sigma_i$'s!

# total Sobol' indices

law of total variance

$$\mathrm{var}(\mathbb{E}[q|\theta_{\sim i}]) + \mathbb{E}[\mathrm{var}(q|\theta_{\sim i})] = \mathrm{var}(q)$$

and thus

$$\underbrace{\mathrm{var}(q) - \mathrm{var}(\mathbb{E}[q|\theta_{\sim i}])}_{\text{remaining variance if } \theta_{\sim i} \text{ were known}} = \mathbb{E}[\mathrm{var}(q|\theta_{\sim i})]$$

- total index: $T_i = \frac{\mathbb{E}[\mathrm{var}(q|\theta_{\sim i})]}{\mathrm{var}(q)} = 1 - \frac{\mathrm{var}(\mathbb{E}[q|\theta_{\sim i}])}{\mathrm{var}(q)}$

# $T_i = 0 \Leftrightarrow \theta_i$ non-important

$\Leftarrow$:

$\theta_i$ non-import. $\Rightarrow \mathrm{var}(q|\theta_{\sim i}) = 0 \Rightarrow \mathbb{E}[\mathrm{var}(q|\theta_{\sim i})] = 0 \Rightarrow T_i = 0$

$\Rightarrow$:

$T_i = 0 \Rightarrow \mathbb{E}[\mathrm{var}(q|\theta_{\sim i})] = 0 \underset{\mathrm{var}\geq 0}{\Rightarrow} \mathrm{var}(q|\theta_{\sim i}) = 0 \Rightarrow \theta_i$ not import.

Unimportance is important! (Art Owen)

- allows focus on key inputs
- potential for faster codes

# ANOVA (Reader's Digest version)

- assume $\theta_i$, iid, $\theta_i \sim U(0,1)$
- split $\theta = (\theta_i, \theta_{\sim i})$ and decompose $g$ as

$$g(\theta) = g_0 + g_1(\theta_i) + g_2(\theta_{\sim i}) + g_{12}(\theta_i, \theta_{\sim i})$$

  where
  - $g_0 = \int g(\theta)\, d\theta$,
  - $g_1(\theta_i) = \int (g - g_0)\, d\theta_{\sim i}, \quad g_2(\theta_{\sim i}) = \int (g - g_0)\, d\theta_i$
  - $g_{12} =$ remainder
- above functions have zero average $\Rightarrow \perp \Rightarrow$

$$\begin{aligned} \mathrm{var}(q) &= \int (g(\theta) - g_0)^2\, d\theta = \int g(\theta)^2\, d\theta - g_0^2 \\ &= \underbrace{\int g_1^2\, d\theta}_{\mathrm{var}(g_1)} + \underbrace{\int g_2^2\, d\theta}_{\mathrm{var}(g_2)} + \underbrace{\int g_{12}^2\, d\theta}_{\mathrm{var}(g_{12})} \end{aligned}$$

# another way to look at things

equivalent definition:

$$\underbrace{T_i = \frac{\mathrm{var}_i}{\mathrm{var}(q)}}_{\text{total index}}; \qquad \underbrace{S_i = \frac{\mathrm{var}(g_i)}{\mathrm{var}(q)}}_{\text{1st order index}}$$

where

$$\mathrm{var}_i = \mathrm{var}(g_1) + \mathrm{var}(g_{12}) = \text{ total variance corresponding to } \theta_i$$

**exercise:**

$$\mathrm{var}_i = \frac{1}{2} \iint (\overbrace{g(\theta) - g(\theta')}^{\frac{\partial g}{\partial \theta_i}(\hat{\theta})(\theta_i - \theta_i')})^2 \, d\theta \, d\theta_i'$$

where $\theta' = (\theta_1, \ldots, \theta_{i-1}, \theta_i', \theta_{i+1}, \ldots, \theta_p)$.

# GSA and surrogates

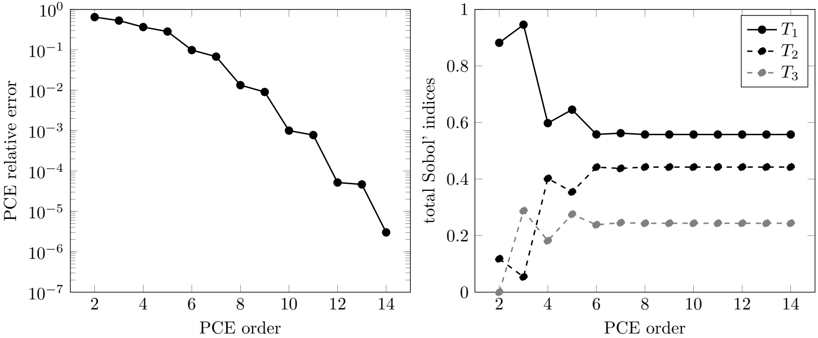
- $g$ = original model; $\hat{g}$ surrogate
- $\mathcal{S}$ = sensitivity index
- question:

$$g \approx \hat{g} \overset{?}{\Rightarrow} \mathcal{S}(g) \approx \mathcal{S}(\hat{g})$$

- would this help?

$$|\mathcal{S}(g) - \mathcal{S}(\hat{g})| \leq C \, \|g - \hat{g}\|$$

# not really...




Ishigami function

$$g(\theta) = \sin(\theta_1) + 7\sin^2(\theta_2) + 0.1\,\theta_3^4\,\sin(\theta_1)$$

$\theta_i$, $i = 1, 2, 3$, are independent, $\theta_i \sim U(-\pi, \pi)$

# GSA and surrogates (II)

In

$$|\mathcal{S}(g) - \mathcal{S}(\hat{g})| \leq C \, \|g - \hat{g}\|$$

need to replace $\|\cdot\|$ by weaker metric, more "aware of $\mathcal{S}$"

exercises:

- equivalence class of functions with same Sobol indices =?
- can we find something cheap to compute and useful to practioners?
- do it for $p = 2$...

# physically based surrogates

- high cost stochastic model: $q = g(\theta, \omega)$
- low cost deterministic surrogate: $\hat{q} = \hat{g}(\theta)$

$\omega$: intrinsic stochasticity of $g$

- assume:

$\underbrace{\text{intrinsic stochasticity}}_{\text{aleatoric}}$ "indep." of $\underbrace{\text{randomness of } \theta\text{'s}}_{\text{epistemic}}$

- example: chemical reaction networks

# a question

- does this diagram commute?

$$\begin{tikzcd} q = g(\theta, \omega) \arrow[r, "GSA"] \arrow[d, "\text{limiting process}"'] & \mathcal{S}(\omega) \arrow[d, "\text{limiting process}"] \\ \hat{q} = \hat{g}(\theta) \arrow[r, "GSA"'] & \hat{\mathcal{S}} \end{tikzcd}$$

- in general, no it doesn't
- if limiting process = thermodynamic limit, yes, it does
- possible "justification" of $\mathcal{S}(\hat{g}) \approx \mathcal{S}(g)$

# chemical reaction networks: notation

- $N$ reacting species, $M$ reactions
- state vector $X(t) = [X_1(t), \ldots, X_N(t)]^T$
- $X_i(t) = \#$ molecules of $i$-th species at time $t$

example: $N = 3$, $M = 1$

$$S_1 + S_2 \to S_3 \Rightarrow X(t) = X(0) + \nu R(t)$$

where

- $\nu = \begin{bmatrix} -1 & -1 & 1 \end{bmatrix}^T$ = stoichiometric vector
- $R(t) = Y\left( \int_0^t \underbrace{c\, X_1(s) X_2(s)}_{\text{propensity function}} ds \right)$

# chemical reaction networks: general

$$\begin{aligned} \mathbf{X}(t) &= \mathbf{X}(0) + \sum_{j=1}^{M} \boldsymbol{\nu}_j Y_j\big(\tau_j(t)\big) \\ \tau_j(t) &= \int_0^t a_j(\mathbf{X}(s))\, ds, \qquad j = 1, \ldots, M. \end{aligned}$$

where

- $\nu_j$: stoichiometric vector of $j$-th reaction
- $Y_j$: indep. unit rate Poisson processes
- $a_j$: propensity function of $j$-th reaction ($\Leftarrow$ Law of Mass Action)

# thermodynamic limit: system size $\to \infty$

- $V$ = size of system = volume $\times n_A$
- define $V$-dependent model in terms of concentrations (scaling!) $Z^V = X^V / V$
- $Z^V \overset{a.s.}{\to} Z$ where

$$\frac{dZ}{dt} = \sum_j \nu_j \bar{a}_j(Z(t)) + C.I..$$

- $Z^V(t, \theta, \omega)$ state vector of stochastic chemical system
- $Z(t, \theta)$ corresponding deterministic limit
- QoIs: $G(Z^V(t, \theta, \omega))$ and $G(Z(t, \theta))$ with $G(z(t)) = z(t^*)$ or $\frac{1}{T} \int_0^T z(t)\, dt$

# a result

**Theorem (Merritt, Alexanderian, G., 2020)**

*Under mild technical assumptions*

$$S_j(f_V(\cdot,\omega)) \to S_j(f), \qquad \text{as } V \to \infty, \nu - \text{almost surely}$$

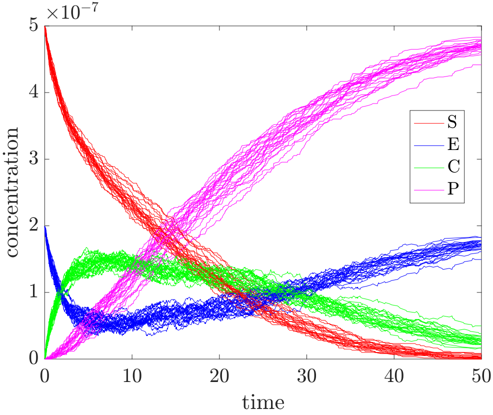
*where* $f_v(\theta,\omega) = G(Z^V(t,\theta,\omega))$, $f(\theta) = G(Z(t,\theta))$ *and* $(\Omega, \mathcal{F}, \nu)$ *is the probability space carrying the intrinsic stochasticity of the system*

# illustration: Michaelis-Menten

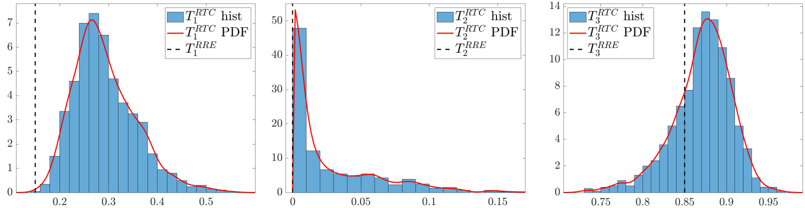
$$S + E \xrightarrow{k_1} C$$

$$C \xrightarrow{k_2} S + E$$

$$C \xrightarrow{k_3} P + E$$



# Michaelis-Menten: histogram of Sobol indices



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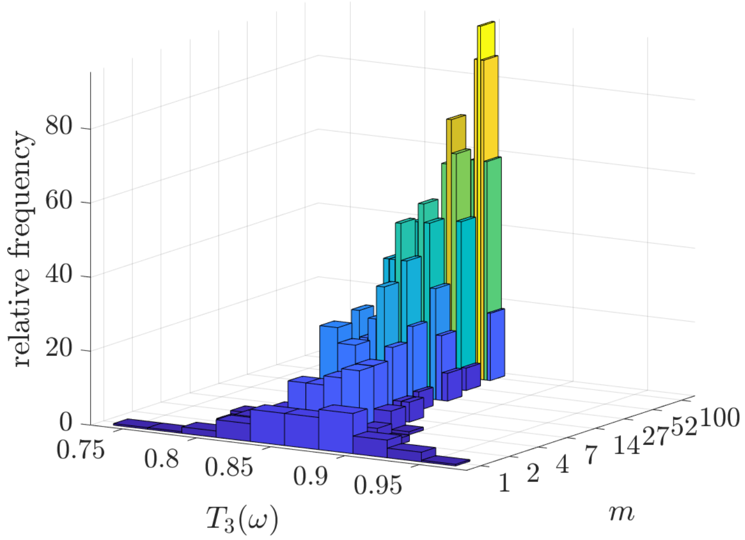
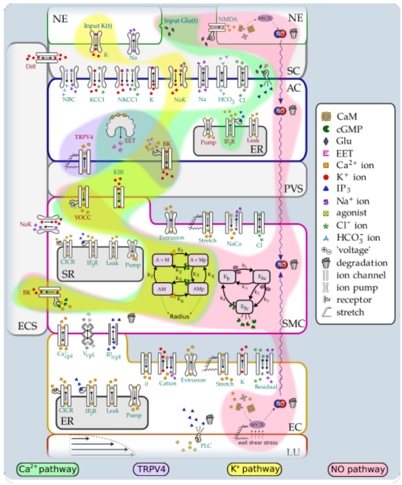


# another type of application: neuro-vascular models




picture from T. David et al.

- over-parametrized ODE models
- $\sim$ 100 state variables
- hundreds of uncertain parameters
- multiple time scales $\Rightarrow$ stiffness
- standard GSA methods may be too expensive out of the box $\Rightarrow$ screening
- "fuzzy" goals

# disciplinary goals

- physiology: understand dominant cellular mechanisms resulting in cerebral tissue perfusion after neuronal stimulation
- diagnostics (understanding) rather than prognostics (predictions)
- complexity: find the right balance between model discrepancy and error propagation to minimize model error

# method goals

- develop multi-level GSA approaches
- other notions of SA needed: see simplified kinetics (Petzold, Zhu, 1999)

# Perspectives and Conclusions

- here is the answer, what was the question?
- robustness and limitations of GSA
- lots of work to do in high dim approximation
- dimension reduction is key
- surrogate models: what to use?
- to solve a specific problem, quantitative experts and field experts have to work together
- "cultural issues" (not everyone is happy with a linear model with 10 parameters)