A biased introduction to sensitivity analysis

joint work with:

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setup

model: \[ q = g(\theta_1, \ldots, \theta_p) \]

response
parameters

typically

- \( g \) is a computer code
- parameters are \textit{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 $\iff$ 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 $\Rightarrow$ GSA(surrogate) $\approx$ GSA(model)
\[ g(\theta_1, \theta_2) = \sin^2 \beta \theta_1 \sin^2 \theta_2 \]

\[ \theta_i \sim U(0, 2\pi), \ i = 1, 2 \]

- 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

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

Ilya Sobol’

- 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 $\sigma_q^2 = a^2 \sigma_1^2 + b^2 \sigma_2^2$

$$\Rightarrow 1 = \frac{a^2 \sigma_1^2}{a^2 \sigma_1^2 + b^2 \sigma_2^2} + \frac{b^2 \sigma_2^2}{a^2 \sigma_1^2 + b^2 \sigma_2^2}$$

- note the importance of the $\sigma_i$’s!
total Sobol’ indices

law of total variance

\[ \text{var}(\mathbb{E}[q|\theta \sim_i]) + \mathbb{E}[\text{var}(q|\theta \sim_i)] = \text{var}(q) \]

and thus

\[ \underbrace{\text{var}(q) - \text{var}(\mathbb{E}[q|\theta \sim_i])} = \mathbb{E}[\text{var}(q|\theta \sim_i)] \]

remaining variance if \( \theta \sim_i \) were known

- total index: \( T_i = \frac{\mathbb{E}[\text{var}(q|\theta \sim_i)]}{\text{var}(q)} = 1 - \frac{\text{var}(\mathbb{E}[q|\theta \sim_i])}{\text{var}(q)} \)
\[ T_i = 0 \iff \theta_i \text{ non-important} \]

\[
\iff:
\]

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

\[
\Rightarrow:
\]

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

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

\[
\operatorname{var}(q) = \int (g(\theta) - g_0)^2 \, d\theta = \int g(\theta)^2 \, d\theta - g_0^2
\]
\[
= \int g_1^2 \, d\theta + \int g_2^2 \, d\theta + \int g_{12}^2 \, d\theta
\]
\[
\underbrace{\operatorname{var}(g_1)} + \underbrace{\operatorname{var}(g_2)} + \underbrace{\operatorname{var}(g_{12})}
\]
another way to look at things

equivalent definition:

\[
T_i = \frac{\text{var}_i}{\text{var}(q)}; \quad S_i = \frac{\text{var}(g_i)}{\text{var}(q)}
\]

\[\text{total index} \quad \text{1st order index}\]

where \n
\[\text{var}_i = \text{var}(g_1) + \text{var}(g_{12}) = \text{total variance corresponding to } \theta_i\]

exercise:

\[
\text{var}_i = \frac{1}{2} \int \int \left( \frac{\partial g}{\partial \theta_i}(\hat{\theta})(\theta_i - \theta_i') \right)^2 d\theta d\theta_i'
\]

where \n
\[\theta' = (\theta_1, \ldots, \theta_{i-1}, \theta_i', \theta_{i+1}, \ldots, \theta_p)\].
GSA and surrogates

- $g =$ original model; $\hat{g}$ surrogate
- $S =$ sensitivity index
- question:
  
  \[ g \approx \hat{g} \implies S(g) \approx S(\hat{g}) \]

- would this help?

  \[ |S(g) - S(\hat{g})| \leq C \| g - \hat{g} \| \]
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)

\[ |S(g) - S(\hat{g})| \leq C \|g - \hat{g}\| \]

need to replace \(\|\cdot\|\) by weaker metric, more "aware of \(S\"

exercises:

▶ equivalence class of functions with same Sobol indices =?
▶ can we find something cheap to compute and useful to practitioners?
▶ 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:
  - intrinsic stochasticity
  - "indep." of randomness of \( \theta \)’s
  - aleatoric
  - epistemic

- example: chemical reaction networks
a question

▶ does this diagram commute?

\[
q = g(\theta, \omega) \xrightarrow{\text{GSA}} S(\omega)
\]

limiting process

\[
\hat{q} = \hat{g}(\theta) \xrightarrow{\text{GSA}} \hat{S}
\]

▶ in general, no it doesn’t

▶ if limiting process = thermodynamic limit, yes, it does

▶ possible "justification" of \(S(\hat{g}) \approx S(g)\)
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: \( N = 3, M = 1 \)

\[ S_1 + S_2 \rightarrow S_3 \Rightarrow X(t) = X(0) + \nu R(t) \]

where

- \( \nu = \begin{bmatrix} -1 & -1 & 1 \end{bmatrix}^T \) = stoichiometric vector

- \( R(t) = Y \begin{pmatrix} \int_0^t c X_1(s)X_2(s) \, ds \\ \text{propensity function} \end{pmatrix} \)
chemical reaction networks: general

\[
X(t) = X(0) + \sum_{j=1}^{M} \nu_j Y_j(\tau_j(t))
\]

\[
\tau_j(t) = \int_0^t a_j(X(s)) \, ds, \quad j = 1, \ldots, M.
\]

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 $\rightarrow \infty$

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

\[
\frac{dZ}{dt} = \sum_j \nu_j \bar{a}_j(Z(t)) + C.l..
\]

- $Z^V(t, \theta, \omega)$ 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 $\frac{1}{T} \int_0^T z(t) \, dt$
Theorem (Merritt, Alexanderian, G., 2020)

Under mild technical assumptions

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

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

$C \xrightarrow{k_2} S + E$

$C \xrightarrow{k_3} P + E$
Michaelis-Menten: histogram of Sobol indices
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another type of application: neuro-vascular models

- 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

picture from T. David et al.
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)