Nonlinear Modeling: Sensitivity Analysis

Introduction to Statistical Modelling

Prof. Joris Vankerschaver

Sensitivity Analysis

Why sensitivity analysis?

- Verify what *sources of uncertainty* contribute most to variance (uncertainty) of model output.
- Sources of uncertainty in model can be
  - Model parameters, initial conditions, inputs
  - Model structure
- Better understand changes in model predictions due to the above

Why sensitivity analysis?

- Detect what *model parameters* contribute most to model output uncertainty
- Want to reduce model uncertainty, so best to focus on most influential parameters
- Gives idea of correlation between parameters
- Helps in choice of what parameters to estimate (in parameter estimation)

Why sensitivity analysis?

- Gives information about interesting location, time, ... to collect experimental data
- Basis for experimental design
- Gives information on insensitive model parameters
- Useful in model reduction of overparametrized models

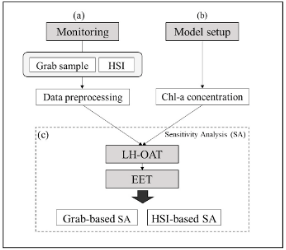
Local vs global

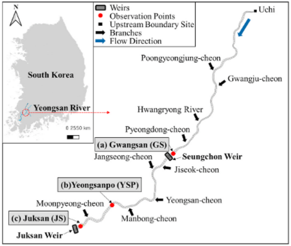
1. Local sensitivity analysis
   - Determine sensitivity at **one certain point** in parameter space
   - Not very computationally intensive
2. Global sensitivity analysis
   - Determine sensitivity in **delimited area** of parameter space
   - Usually gives a mean sensitivity
   - Can become extremely computationally intensive

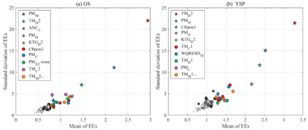
- Each technique has advantages and disadvantages
- Each technique gives different type of information

Examples of sensitivity analysis: water quality model

- Hundreds of parameters
- Each model simulation takes days to run
- Identifying highly sensitive parameters is critical





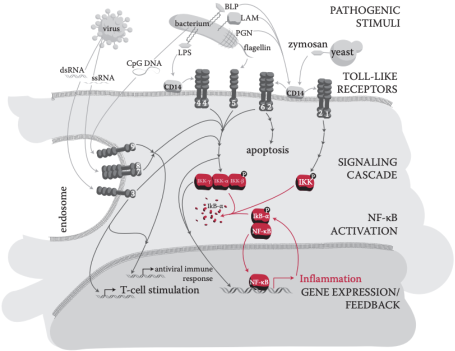


Source: *Developing a cloud-based toolbox for sensitivity analysis of a water quality model* (S. Kim et al, Environmental Modeling and Software, 2021)

Examples of sensitivity analysis: cell signaling

Toll-like signaling pathway:

- Cellular response to external stimuli (e.g. infection)
- Central role for NF-κB transcription factor
- Shuttles back and forth between cytoplasm and nucleus



Source: Images from *Fundamentals of Systems Biology*, M. Covert, CRC Press, 2014.

Examples of sensitivity analysis: cell signaling

Hoffmann-Levchenko (2005): Computational model for NF-κB

- 25 ODEs, 36 parameters
- Models protein production, degradation, transport
- Important role for **parameter estimation** and **sensitivity analysis**

$$\frac{d[NFkB]}{dt} = \underbrace{-a4\cdot[IkBa]\cdot[NFkB] - a4\cdot[IKK\_IkBa]\cdot[NFkB] - a5\cdot[IkBb]\cdot[NFkB]}_{association}$$

$$\underbrace{-a5\cdot[IKK\_IkBb]\cdot[NFkB] - a6\cdot[IkBe]\cdot[NFkB] - a6\cdot[IKK\_IkBe]\cdot[NFkB]}_{association}$$

$$\underbrace{+d4\cdot[IkBa\_NFkB] + d4\cdot[IKK\_IkBa\_NFkB] + d5\cdot[IkBb\_NFkB]}_{dissociation}$$

$$\underbrace{+d5\cdot[IKK\_IkBb\_NFkB] + d6\cdot[IkBe\_NFkB] + d6\cdot[IKK\_IkBe\_NFkB]}_{dissociation}$$

$$\underbrace{+r4\cdot[IKK\_IkBa\_NFkB] + r5\cdot[IKK\_IkBb\_NFkB] + r6\cdot[IKK\_IkBe\_NFkB]}_{IKK\ reaction\ degradation}$$

$$\underbrace{+deg4\cdot[IkBa\_NFkB] + deg4\cdot[IkBb\_NFkB] + deg4\cdot[IkBe\_NFkB]}_{spontaneous\ degradation}$$

$$\underbrace{-k1\cdot[NFkB] + k01\cdot[NFkBn]}_{nuclear\ translocation}$$

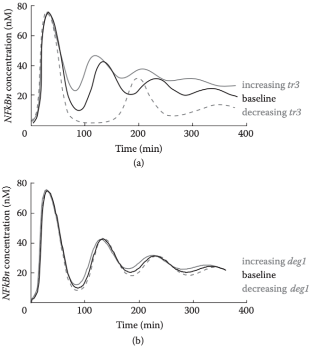
Source: Images from *Fundamentals of Systems Biology*, M. Covert, CRC Press, 2014.

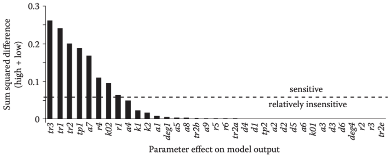
Examples of sensitivity analysis: cell signaling

Sensitivity analysis: which parameters affect the model the most?

- Transcription rate: affects output a lot (**sensitive**)
- Degradation rate: relatively **insensitive**

Gives rough idea, needs to be corroborated with full model.





Source: Images from *Fundamentals of Systems Biology*, M. Covert, CRC Press, 2014.

Local sensitivity analysis

Local sensitivity analysis

How sensitive is model output (y) to changes of model parameter (θ) *at one single point* in parameter space?

- **(Absolute) local sensitivity**: partial derivative of variable with respect to parameter at single point in parameter space

$$S(\theta, x) = \frac{\partial y}{\partial \theta}(\theta, x)$$

- If k parameters, then also k sensitivity functions:

$$S_i(\theta, x) = \frac{\partial y}{\partial \theta_i}(\theta, x), \quad i = 1, \ldots, k.$$

Local sensitivity analysis: absolute sensitivity

Problem: often very hard to compute partial derivative analytically.

Solution: compute derivative **numerically** through finite difference method:

- Forward difference:

$$\left.\frac{\Delta y}{\Delta \theta_j}\right|_{+} = \frac{y(x, \theta_j + \Delta\theta_j) - y(x, \theta_j)}{\Delta \theta_j}$$

- Backward difference:

$$\left.\frac{\Delta y}{\Delta \theta_j}\right|_{-} = \frac{y(x, \theta_j) - y(x, \theta_j - \Delta\theta_j)}{\Delta \theta_j}$$

Local sensitivity analysis: absolute sensitivity

- How to choose perturbation $\Delta\theta_j$?
  - Too large: approximation is not good
  - Too small: numerical instabilities.
- In practice, choose $\Delta\theta_j$ **small** and **fixed**, e.g.

$$\Delta\theta_j = 10^{-6}.$$

Convergence

Both the forward and the backward difference agree with the derivative up to **first order** in $\Delta\theta_j$:

$$\frac{\partial y(x)}{\partial \theta_j} = \left.\frac{\Delta y(x)}{\Delta\theta_j}\right|_{+} + \mathcal{O}(\Delta\theta_j), \quad \frac{\partial y(x)}{\partial \theta_j} = \left.\frac{\Delta y(x)}{\Delta\theta_j}\right|_{-} + \mathcal{O}(\Delta\theta_j).$$

Local sensitivity analysis: absolute sensitivity

- Third option: central difference

$$\frac{\Delta y(x)}{\Delta\theta_j} = \frac{y(x, \theta_j + \Delta\theta_j) - y(x, \theta_j - \Delta\theta_j)}{2\Delta\theta_j}$$

Convergence

The central difference agrees with the derivative up to **second order** in $\Delta\theta_j$:

$$\frac{\partial y(x)}{\partial\theta_j} = \frac{\Delta y(x)}{\Delta\theta_j} + \mathcal{O}((\Delta\theta_j)^2).$$

Local sensitivity analysis: relative sensitivity

Absolute sensitivity is influenced by magnitude of variable and parameter.

- Problematic if we want to compare sensitivities of different combinations of outputs and parameters
- Use **relative sensitivity**.

Local sensitivity analysis: relative sensitivity

Different definitions, depending on what's important:

1. Relative sensitivity w.r.t. parameter:

$$\frac{\partial y(t)}{\partial \theta_j} \cdot \theta_j$$

   Compare sensitivity of same variable w.r.t. *different parameters*

2. Relative sensitivity w.r.t. variable

$$\frac{\partial y_i(t)}{\partial \theta} \cdot \frac{1}{y_i}$$

   Compare sensitivity of *different variables* w.r.t. same parameter

Local sensitivity analysis: relative sensitivity

3. Total relative sensitivity

$$\frac{\partial y_i(t)}{\partial \theta_j} \cdot \frac{\theta_j}{y_i}$$

Compare all sensitivities (of *different variables* w.r.t. *different parameters*)

Local sensitivity analysis

- Relative sensitivities allow to **rank sensitivities**. Important for:
  - Choice parameters for parameter estimation
  - Choice parameters for model reduction
  - Choice for additional measurement or experimental determination of parameter (reduce sources of uncertainty)
- Ranking **depends on value of parameter**, can be different at different position in parameter space
- How to compare continuous sensitivity functions?
- Interest in specific values of independent variable
  - Where measurements are available
  - Where measurements will be collected

Local sensitivity analysis

- Create generic model with
  - Time t as independent variable
  - Outputs y_i, $i = 1, \ldots, v$
  - Parameters θ_j, $j = 1, \ldots, p$
  - Moments of measurements t_k, $k = 1, \ldots, N$
- Total relative sensitivity of variable y_i w.r.t. parameter θ_j at moment t_k

$$S_{i,j,k} = \frac{\partial y_i(t_k)}{\partial \theta_j} \cdot \frac{\theta_j}{y_i}$$

Local sensitivity analysis

Importance parameter is determined by its impact on *all* variables
$\rightarrow$ sum and average over all variables
$\rightarrow$ take sign into account (square and root)
root mean square sensitivity for parameter θ_j

$$\delta_{j,k}^{rmsq} = \sqrt{\frac{\sum_{i=1}^{v} S_{i,j,k}^2}{v}}$$

$\delta_{j,k}^{rmsq}$ can be very variable from moment to moment
$\rightarrow$ sum and average over all time points
time mean root mean square sensitivity for parameter θ_j

$$\delta_{j}^{rmsq} = \frac{1}{N} \sum_{k=1}^{N} \delta_{j,k}^{rmsq}$$

Local sensitivity analysis

- Gives one single measure for sensitivity of parameter
- Use this measure to determine importance of parameter
- Obtained value depends on
  - nominal parameter value: nonlinear models give different values at different location in parameter space (see also global sensitivity analysis)
  - choice of time points is arbitrary: this can lead to different set of parameters that are best estimated using dataset (see also identifiability)
- Modifications can be defined based on application/goal

Side track: Monte Carlo simulation

Monte Carlo simulation technique

- Computational algorithm, based on
  - Large number of simulations (thousands to millions)
  - Repeated random sampling
- Used for modeling of
  - Climate and environment
  - Nuclear reactions
  - Financial systems
  - Molecular dynamics
  - ...
- In this course:
  - Global sensitivity analysis
  - Uncertainty analysis

LE CASINO
MONTE·CARLO

Front view of Casino de Monte-Carlo

Principles behind Monte Carlo

Algorithm:

1. Draw random parameter samples
2. For each sample, run simulation
3. Aggregate results of simulations into quantity of interest (e.g. mean)

Advantages:

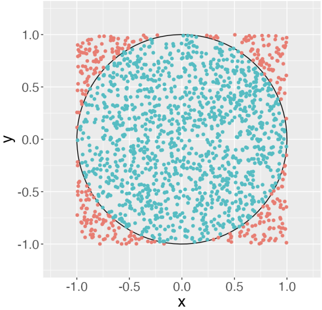
- Easy to implement/understand
- Applicable to wide range of problems (model-agnostic)

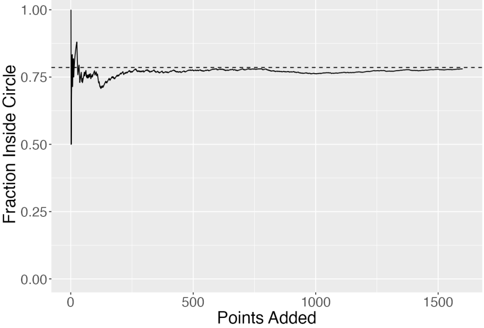
Disadvantages:

- Relatively slow convergence (many simulations needed)
- Requires information about parameter distributions

Example: computing π

- Drop points uniformly at random in the square $[-1, 1] \times [-1, 1]$
- Count fraction for which $x^2 + y^2 < 1$
- As $N \to \infty$, gives approximation for $\pi/4$.





App available at https://shiny-stats.fly.dev/monte-carlo/.

Global sensitivity analysis (GSA)

Global sensitivity analysis (GSA)

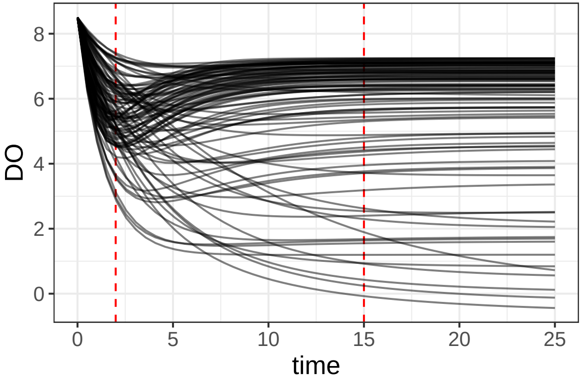
- Measure for sensitivity in delimited area in parameter space
- PDFs for parameters need to be chosen/found (same as for uncertainty analysis)

3 techniques will be discussed:

- Standardized regression coefficients
- Screening techniques
- Variance decomposition

GSA: Standardized regression coefficients

- Linear regression of Monte Carlo simulations
- Each line is simulation of variable y for different parameter set Θ, i.e., other point in parameter space



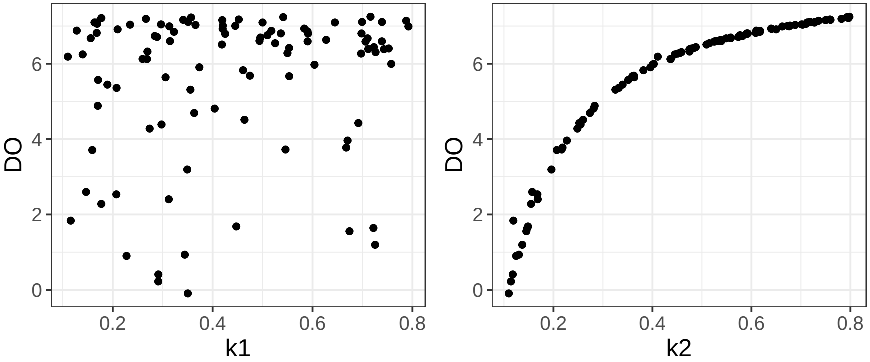
- Figure: 100 simulations of dissolved oxygen, with k_1, k_2 sampled uniformly between 0.1 and 0.8.

GSA: Standardized regression coefficients

- Consider outcomes at fixed time T
- Quantify effect of parameters $\theta_1, \dots \theta_p$ through linear model

$$y_{t=T} = b_1\theta_1 + \cdots + b_p\theta_p + \epsilon$$

- Regression coefficient b_i gives contribution of parameter θ_i in explaining variance of $y_{t=T}$



GSA: Standardized regression coefficients

- Correct for spread on both parameter and output
- Recalculate coefficients b_i to SRCs

$$SRC_{\theta_i} = b_i \cdot \frac{\sigma_{\theta_i}}{\sigma_y}$$

- Sample standard deviations from
  - vector $y_{t=T}$ for output
  - parameter samples for parameter θ_i.

GSA: Standardized regression coefficients

- For linear model in parameters that were examined, the total variance is explained by SRCs

$$\sum_i SRC_{\theta_i}^2 = 1$$

- For nonlinear models (in the parameters) *not* all variance will be explained. The part that is explained is given by determination coefficient

$$R^2 = \sum_{i=1}^{n} \frac{(\hat{y}_i - \overline{y})^2}{(y_i - \overline{y})^2}$$

- $\hat{y}_i$: prediction by regression model
- Technique only valid if $R^2 > 0.7$

GSA: Screening techniques

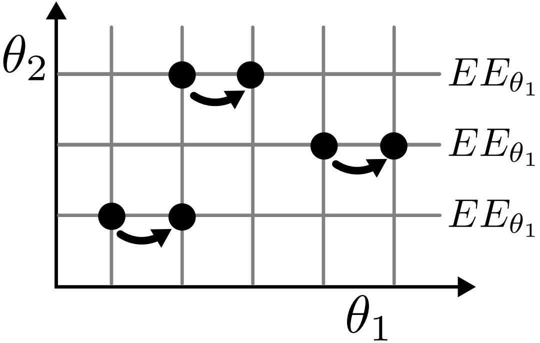
- Goal: obtain idea of importance of model parameters using only a limited number of simulations
- Example of technique: Morris screening
- Calculation of *elementary effect* for θ_i

$$EE_{\theta_i} = \frac{y(\theta_i + \Delta) - y(\theta)}{\Delta}$$

- Δ is a predetermined step size in parameter
- Remark analogy with local sensitivity, however, step size much larger

GSA: Morris screening

- Assume 2 parameters θ_1 and θ_2
- Choose regions in parameter space to compute elementary effects
- Summarize EE using mean and variance

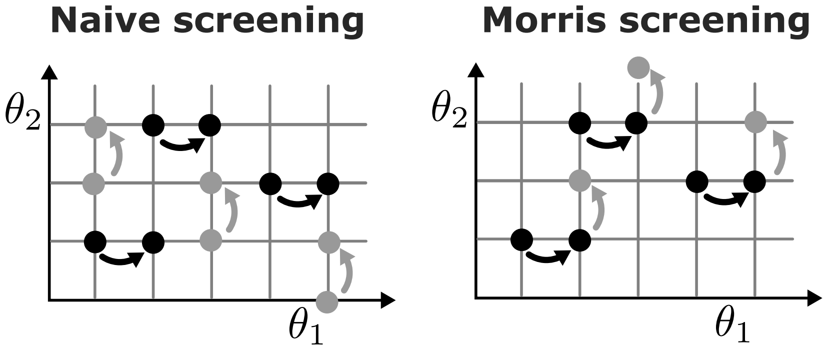


GSA: Morris screening

- Vector of EE (in this case 3)
- Statistical analysis of this vector
  - $\mu_{EE_{\theta_i}}$: indication on average effect of this parameter over entire parameter space; large value means important parameter and vice versa
  - $\sigma_{EE_{\theta_i}}$: information about linear behavior of parameter; large value means nonlinear parameter or parameter involved in interactions with other parameters
- Do same for θ_2

GSA: Morris screening

- Normally 2 simulations needed per EE
- 1991: Morris introduced more efficient way
- Number of simulations needed for p parameters:
  - Naive: $(2 \times \#\mathrm{EE})^p$
  - Morris: $(p + 1) \times \#\mathrm{EE}$



GSA: Variance decomposition

- Goal: find share of each model parameter in variance of model output
- Used for models that are strongly nonlinear or nonmonotonous
- Example of model with 3 paramaters:

$$\sigma_y^2 = \sigma_1^2 + \sigma_2^2 + \sigma_3^2 + \sigma_{12}^2 + \sigma_{13}^2 + \sigma_{23}^2 + \sigma_{123}^2$$

- Normalisation (i.e., divide by σ_y^2) gives *sensitivity indices*

$$1 = S_1 + S_2 + S_3 + S_{12} + S_{13} + S_{23} + S_{123}$$

- Indicate which fraction of total variance is determined by certain parameter or parameter combination

GSA: Variance decomposition

- *Total sensitivity indices*

$$
\begin{aligned}
S_{T1} &= S_1 + S_{12} + S_{13} + S_{123} \\
S_{T2} &= S_2 + S_{12} + S_{23} + S_{123} \\
S_{T3} &= S_3 + S_{13} + S_{23} + S_{123}
\end{aligned}
$$

- Give total contribution of a certain parameter, including interaction effects
- Watch out: some contributions are counted multiple times, hence sum of all total sensitivity indices is no longer 1

GSA: Variance decomposition

- Two techniques:
  - FAST (Fourier Amplitude Sensitivity Test): uses Fourier decomposition of model output; can determine first order effects (total effects $\rightarrow$ extendedFAST); computationally intensive ((ten) thousands of simulations)
  - Sobol indices: uses multiple integrals, both first order and higher order effects; computationally expensive; less efficient than FAST