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?

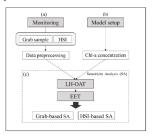
- Gives information about interesting location, time, ... to collect experimental data
- Basis for experimental design
- Gives information on insensitive model parameters
- Useful in model reduction of overparametrized models

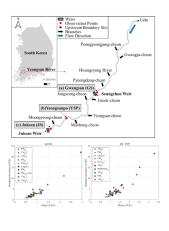
Local vs global

- 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



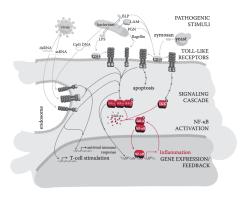


Source: Developing a cloud-based toolbox for sensitivity analysis of a water quality model (S. Kim et al, Environmental Modeling and Software, 2021)

Examples of sensitivity analysis: cell signaling

Toll-like signaling pathway:

- Cellular response to external stimuli (e.g. infection)
- Central role for NF- κ B 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- κ B

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

$$\frac{d\left[NFkB\right]}{dt} = -a4 \cdot \left[IkBa\right] \left[NFkB\right] - a4 \cdot \left[IKK_IkBa\right] \left[NFkB\right] - a5 \cdot \left[IkBb\right] \left[NFkB\right]$$

$$-a5 \cdot \left[IKK_IkBb\right] \left[NFkB\right] - a6 \cdot \left[IkBe\right] \left[NFkB\right] - a6 \cdot \left[IKK_IkBe\right] \left[NFkB\right]$$

$$+ d4 \cdot \left[IkBa_NFkB\right] + d4 \cdot \left[IKK_IkBa_NFkB\right] + d5 \cdot \left[IkBb_NFkB\right]$$

$$+ d5 \cdot \left[IKK_IkBb_NFkB\right] + d6 \cdot \left[IkBe_NFkB\right] + d6 \cdot \left[IkBe_NFkB\right] + d6 \cdot \left[IKK_IkBe_NFkB\right]$$

$$+ d6 \cdot \left[IKK_IkBb_NFkB\right] + r6 \cdot \left[IKK_IkBb_NFkB\right] + r6 \cdot \left[IKK_IkBe_NFkB\right]$$

$$+ r4 \cdot \left[IKK_IkBa_NFkB\right] + r6 \cdot \left[IKK_IkBb_NFkB\right] + r6 \cdot \left[IKK_IkBe_NFkB\right]$$

$$+ deg4 \cdot \left[IkBa_NFkB\right] + deg4 \cdot \left[IkBb_NFkB\right] + deg4 \cdot \left[IkBe_NFkB\right]$$

$$- k1 \cdot \left[NFkB\right] + k01 \cdot \left[NFkBn\right]$$

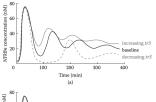
Source: Images from Fundamentals of Systems Biology, M. Covert, CRC Press, 2014.

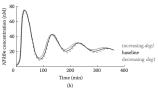
Examples of sensitivity analysis: cell signaling

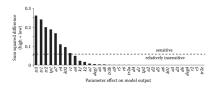
Sensitivity analysis: which parameters affect the model the most?

- 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.

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:

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

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 $\Delta\theta_j$:

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

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 ${\bf second}$ ${\bf order}$ 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)

- 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

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

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

Importance parameter is determined by its impact on all variables

- ightarrow sum and average over all variables
- \rightarrow take sign into account (square and root)

root mean square sensitivity for parameter $\boldsymbol{\theta}_j$

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

 $\delta_{j,k}^{rmsq}$ can be very variable from moment to moment

 \rightarrow sum and average over all time points

time mean root mean square sensitivity for parameter $\boldsymbol{\theta}_j$

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

- 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



Front view of Casino de Monte-Carlo



Principles behind Monte Carlo

Algorithm:

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

Advantages:

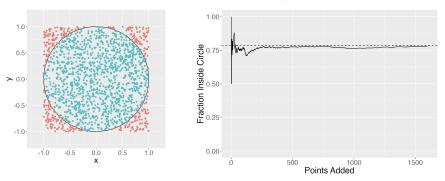
- Easy to implement/understand
- Applicable to wide range of problems (model-agnostic)

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)

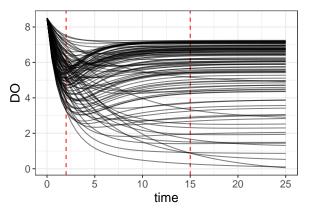
Global sensitivity analysis (GSA)

- 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

- 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

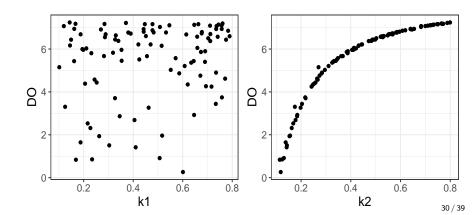


• Figure: 100 simulations of dissolved oxygen, with k_1, k_2 sampled uniformly between 0.1 and 0.8.

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

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

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



- 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 .

 \bullet For linear model in parameters that were examined, the total variance is explained by $SRC{\rm s}$

$$\sum_{i} SRC_{\theta_i}^2 = 1$$

 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

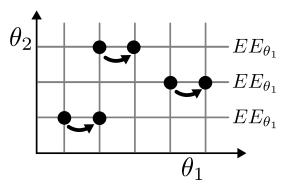
- Goal: obtain idea of importance of model parameters using only a limited number of simulations
- Example of technique: Morris screening
- Calculation of elementary effect for θ_i

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

- ullet 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
- ullet Do same for $heta_2$

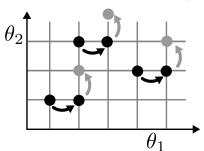
GSA: Morris screening

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

Naive screening

θ_2 θ_1

Morris screening



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

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

- 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 → 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