Global Sensitivity Analysis with SimBiology®

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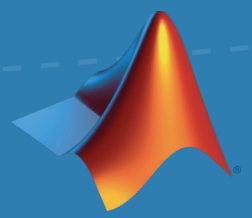
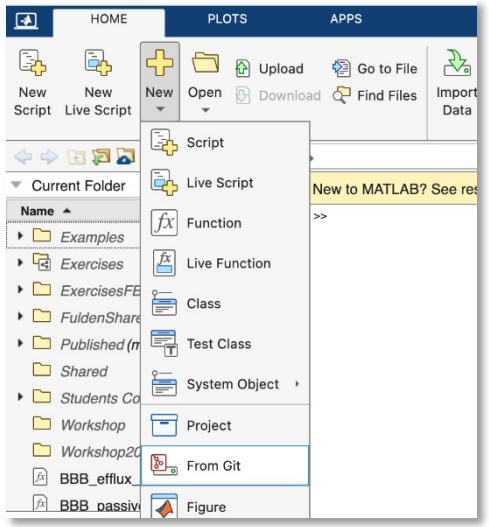


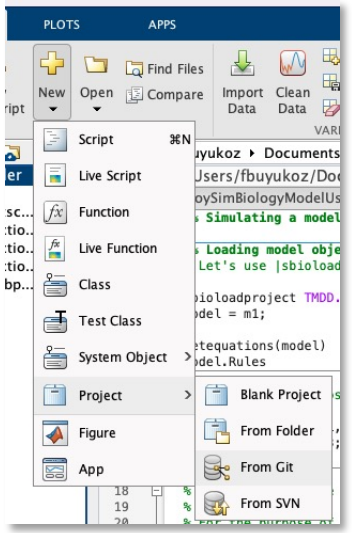
Set-Up Instructions

- **Step 1: Open MATLAB**
  - **Option 1**: Activate the workshop license and launch MATLAB Online
  - go to https://www.mathworks.com/licensecenter/classroom/4235453/
  - click ***Access MATLAB Online***
    - log in using your MathWorks account (or create one)

  - **Option 2**: Local MATLAB installation
    - Requirements: Statistics and Machine Learning Toolbox, Deep Learning Toolbox, SimBiology (optional)
    - Type `ver` in MATLAB command-line to confirm your installation contains these toolboxes

- **Step 2: Copy the materials via the Github repo**
  - once in MATLAB, click ***New>Folder***
  - name this folder **GSA_Workshop**
  - and double click on the folder to set it as your current folder
  - click ***New>From Git (New>Project>From Git** if local install)*
  - go to https://github.com/fuldenb/GSA_Workshop
  - workshop material is copied to the folder GSA_Workshop





Agenda

Time	Topic
8:00 am – 8:50 am	• **Introduction to Sensitivity Analysis (50 mins)** • Local Sensitivity Analysis (20 mins) • Global Sensitivity Analysis (20 mins) • GSA Settings in the PK/PD – QSP literature (10 mins)
8:50 am - 9:40 am	**Introduction to the Morris method (50 mins)** • What it is, how to interpret the results, pros and cons (30 mins) • Hands on exercise (20 mins)
9:40 am - 9:55 am	Break
9:55 am - 10:45 am	**Introduction to the Sobol method (50 mins)** • What it is, how to interpret the results, pros and cons (30 mins) • Hands on exercise (20 mins)
10:45 am -11:35 am	**Introduction Multiparametric GSA (50 mins)** • What it is, how to interpret the results, pros and cons (30 mins) • Hands on exercise (20 mins)
11:35 am - 11:50 am	Break
11:50am - 12:00 pm	**So which method do I use? (10 mins)** • Summary of pros and cons (5 mins) • Best practices (5 mins)

What is Sensitivity Analysis?

- From Saltelli's book: "The study of how uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input (Saltelli et al., 2004)".

- There are many sensitivity analysis methods available, each with their own measure of "model uncertainty", and particularly useful in certain scenarios. SimBiology has implemented three such methods:

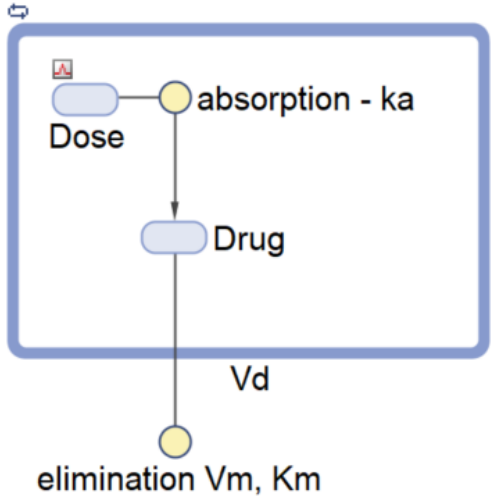
  - Local Sensitivity Analysis
  - Elementary effects method
  - Sobol method
  - Multiparametric GSA method

Concepts in Sensitivity Analysis

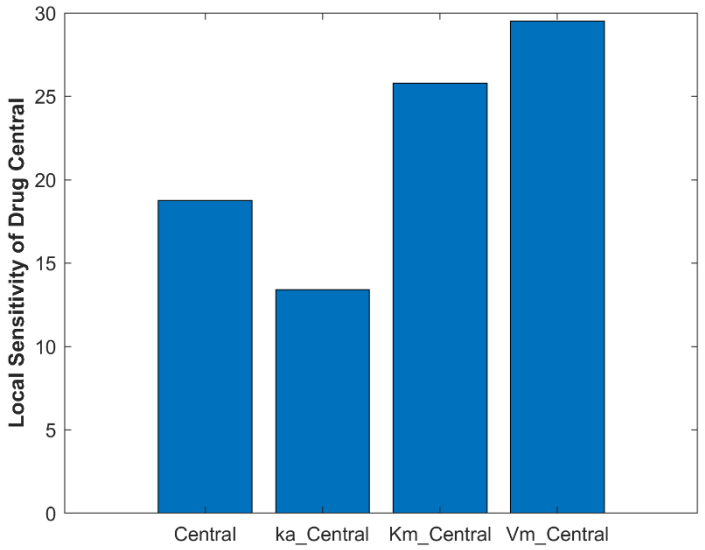
- Local or Global
  - Local: Analysis around a single operating point in parameter space
  - Global: Analysis across a defined domain in parameter space
- Sampling
  - One-at-a-time: change one parameter at a time to calculate sensitivity index
    - Unable to observe interactions between parameters from single analysis
  - All-at-a-time: take random samples from parameter space to calculate sensitivity index
    - Observe interactions between parameters
    - Multiple methods to sample parameter space – Sobol, Latin hypercube, uniform
- Calculating sensitivities: derivative, variance, or correlation-based

Example: Local versus Global Sensitivity Analysis

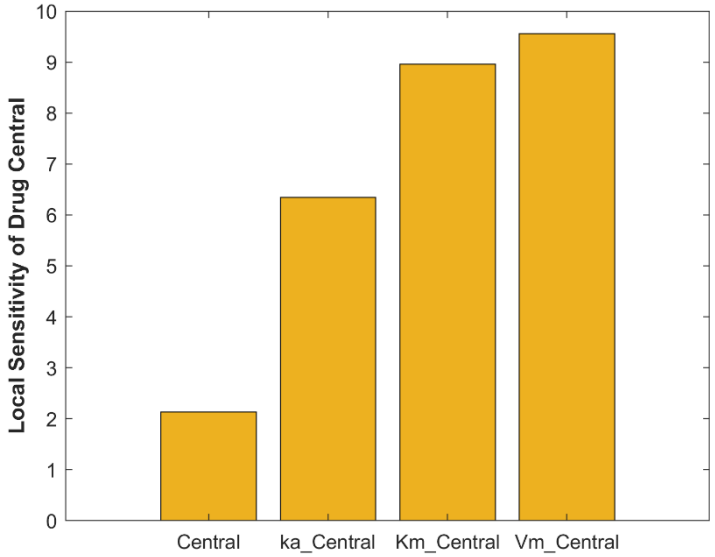
Example: 1-compartment model, oral dosing, enzymatic clearance



Local Sensitivity Analysis 1



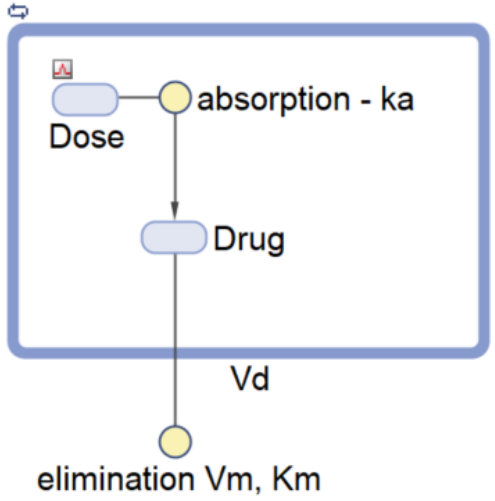
Local Sensitivity Analysis 2



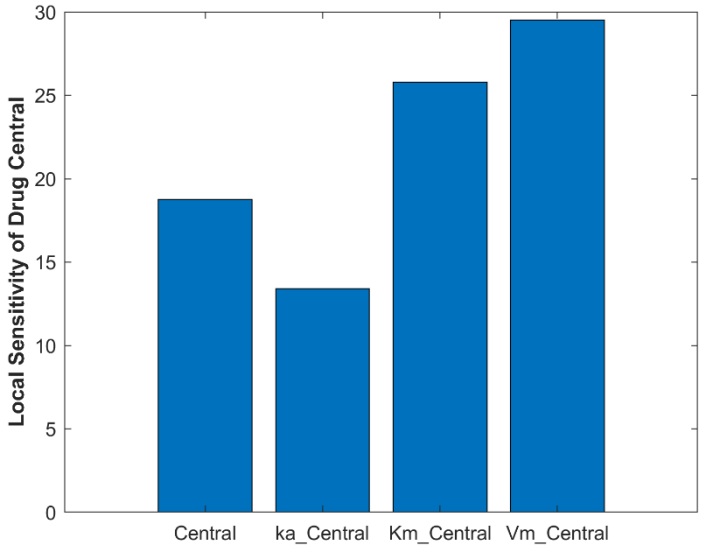
Local sensitivity analysis is very sensitive to the location in parameter space

Example: Local versus Global Sensitivity Analysis

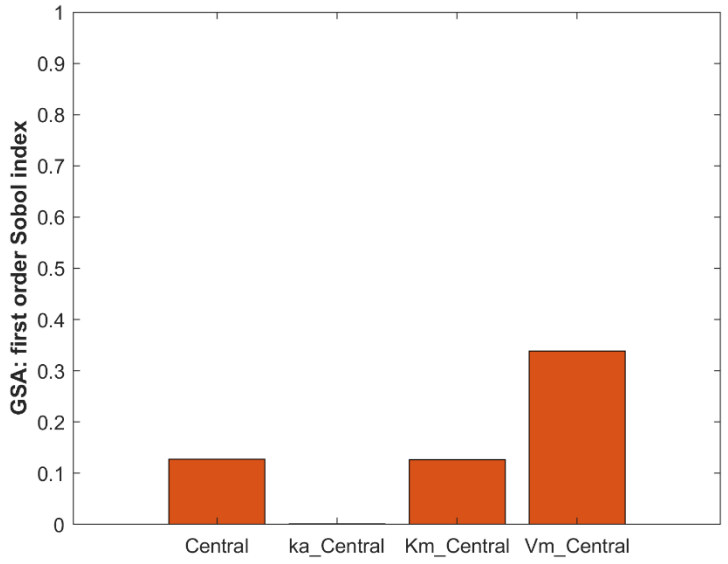
Example: 1-compartment model, oral dosing, enzymatic clearance



Local Sensitivity Analysis 1



Global Sensitivity Analysis



GSA is most appropriate when exploring sensitivities across a parameter domain

When to apply Local versus Global Sensitivity Analysis

- Local Sensitivity Analysis (LSA)
  - Target identification for specific model calibrations, e.g. for a kidney-impaired virtual patient
  - (Used in gradient-based optimization algorithms)

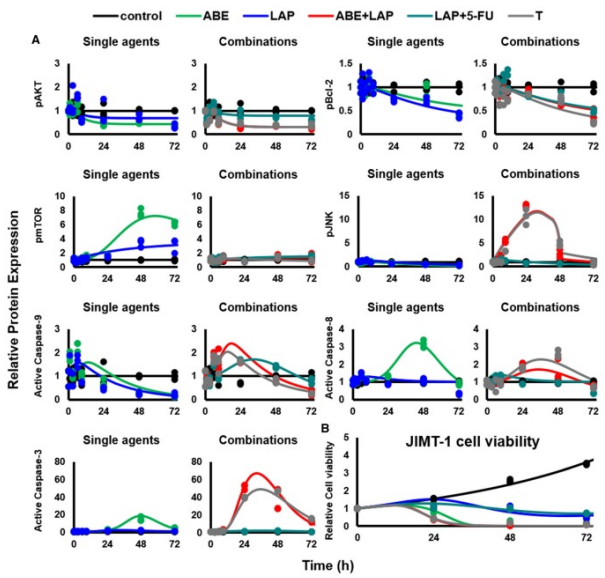
- Global Sensitivity Analysis (GSA)
  - Understand which model inputs drive model response or model-based decision metric
  - Inform parameter estimation strategy

Ultimately, the goal of any GSA method is to rank the model inputs rapidly and automatically in order of importance.

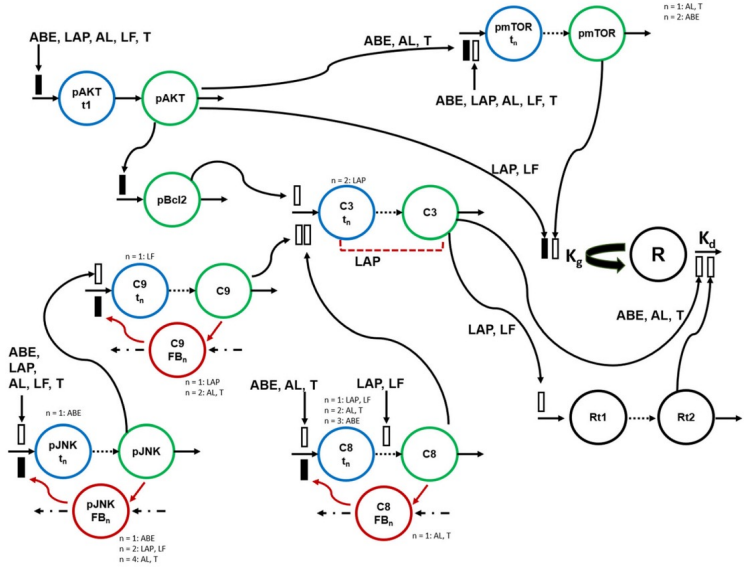
Schoeberl et al. (2017) Systems biology driving drug development …, *npj Systems Biology and Applications* 3(16034)

Test Case: Factor Prioritization

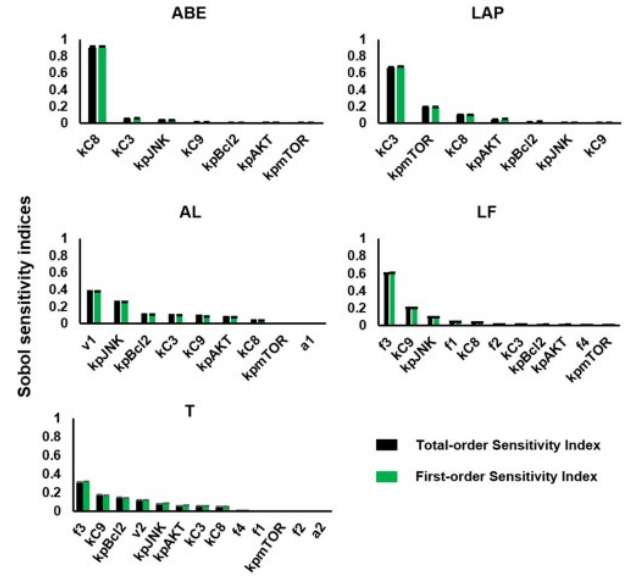
Data



Model



GSA Results

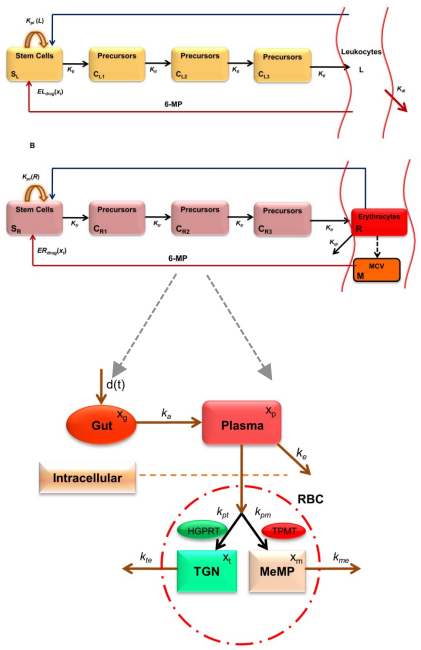


"The protein-signaling model and subsequent sensitivity analyses suggest that the activation of the stress pathway, through pJNK, may be an important driver of the observed declines in cellular viability."

Franco, Yesenia L., et al. "A quantitative systems pharmacological approach identified activation of JNK signaling pathway as a promising treatment strategy for refractory HER2 positive breast cancer." *Journal of Pharmacokinetics and Pharmacodynamics* 48 (2021): 273-293.

Test Case: Model reduction

Model

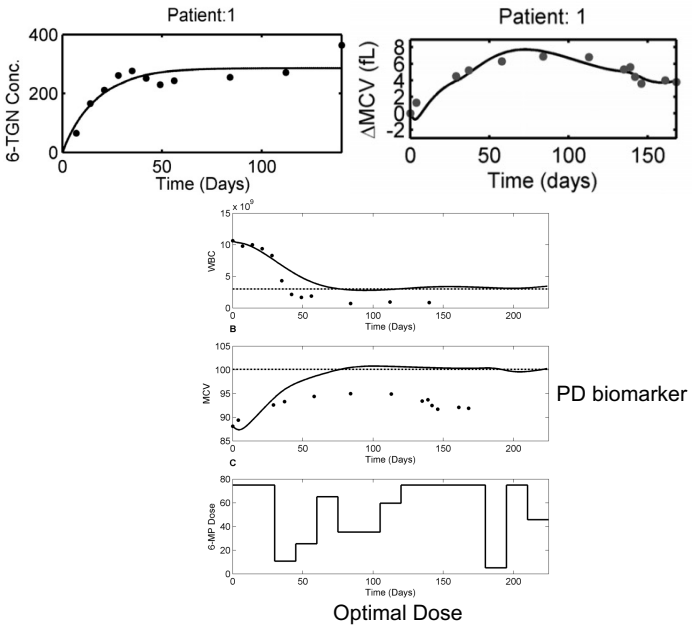


GSA Results

6-MP Model (Variable for GSA: x_t)

Parameters	$P\{\delta(\hat{\theta}_{(i)}) < (.)\}_j \geq 0.95$	% error(actual/maximum)
k_{pt}	**84.61**	**100**
k_{te}	**46.36**	**54.8**
K_t	0.0003	3.5×10^{-4}
k_e	0.0002	2.4×10^{-4}
k_a	4.0×10^{-5}	4.7×10^{-5}
k_{pm}	2.1×10^{-9}	2.5×10^{-9}
K_m	2.1×10^{-9}	2.5×10^{-9}
k_{me}	0	0
Leukopoiesis Model (Variable for GSA: L)		
k_{tl}	**65.54**	**100**
k_{pl}^{max}	**49.12**	**74.9**
k_{dl}	**39.02**	**59.5**
γ_l	**22.61**	**34.5**
Et_{max}	**17.60**	**26.9**
θ	2.18	3.32
ECL_{50}	0.25	0.38
MCV Model (Variable for GSA: M)		
k_{tr}	**76.48**	**100**
k_{pr}^{max}	**50.09**	**65.5**
k_{dr}	**20.71**	**27.1**
α	**11.00**	**14.4**
ER_{max}	**10.49**	**13.7**
γ_r	2.48	3.24
ψ	0.71	0.93
ECR_{50}	0.0034	0.004

Dose Optimization

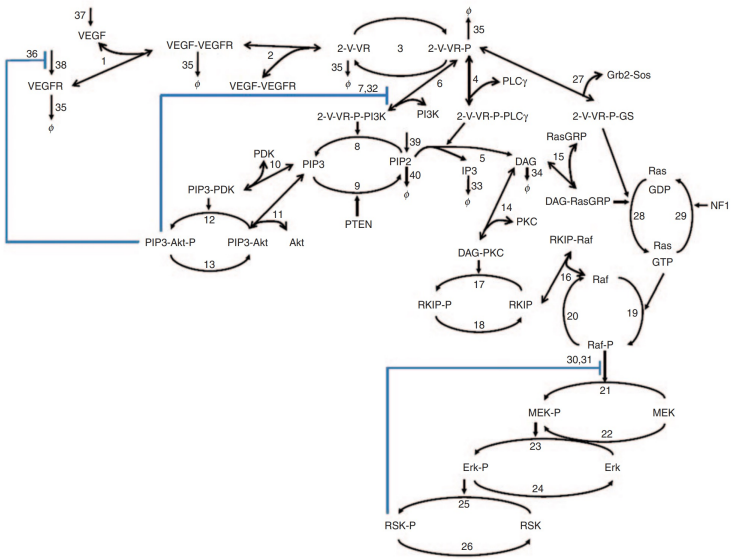


"For 6-TGN model, the important parameters are the ones closely related to production and elimination of the active metabolite of our interest…feedback mechanism and age-related death are important regulation steps during hematopoiesis… together with death rate due to drug have naturally come out to be the sensitive ones"

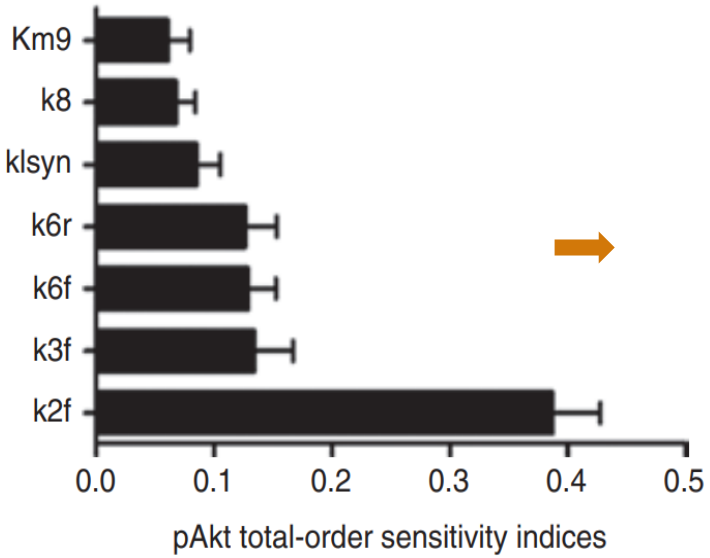
Jayachandran, Devaraj, et al. "Optimal chemotherapy for leukemia: a model-based strategy for individualized treatment." *PloS one* 9.10 (2014): e109623.

Test Case: Target Identification

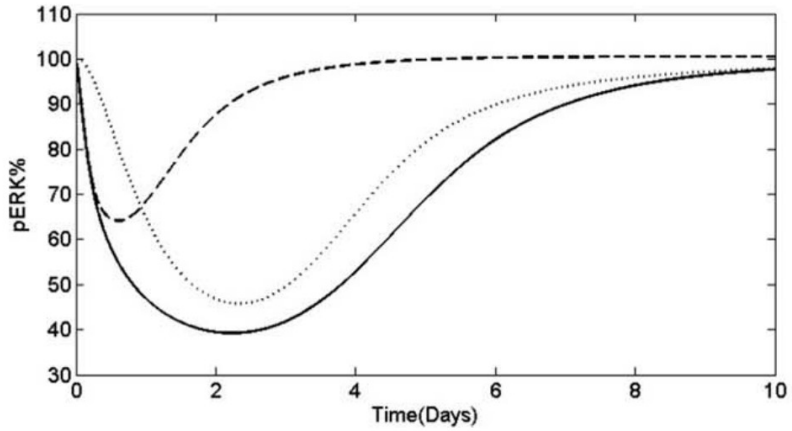
Model



GSA Results



GSA Results



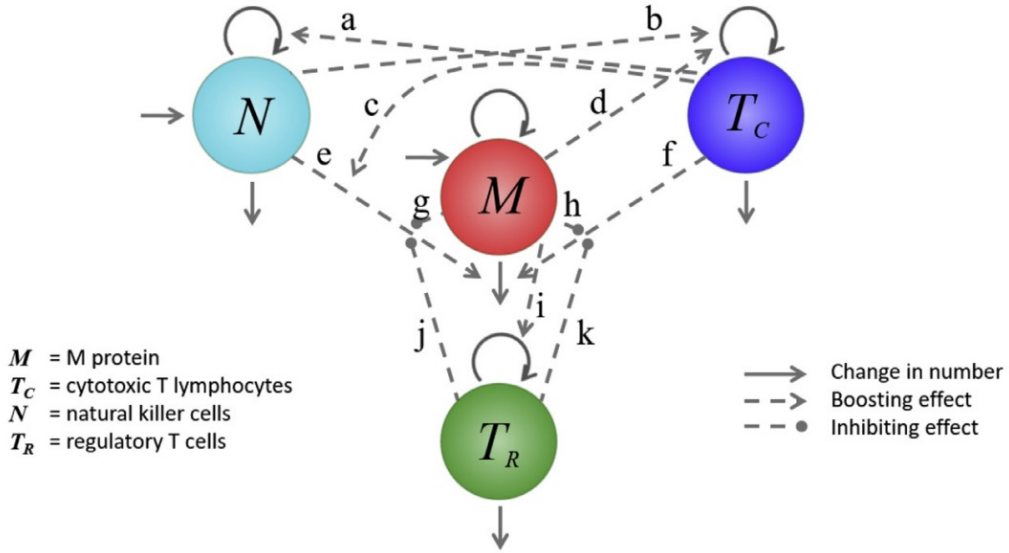
The model output pERK in presence of drug sunitinib (gray dotted lines), a PI3K inhibitor (black dashed lines), and sunitinib and a PI3K inhibitor used in combination (solid black lines).

"…there were seven important parameters and steps associated with pAkt inhibition by sunitinib. The PI3K-catalyzed PIP2 to PIP3 reaction (Km9, k8, k6f, and k6r) supported a PI3K inhibitor in enhancing sunitinib inhibition."

Zhang, X-Y., M. R. Birtwistle, and J. M. Gallo. "A general network pharmacodynamic model–based design pipeline for customized cancer therapy applied to the VEGFR pathway." *CPT: pharmacometrics & systems pharmacology* 3.1 (2014): 1-9.

Test Case: Factor Prioritization

Model



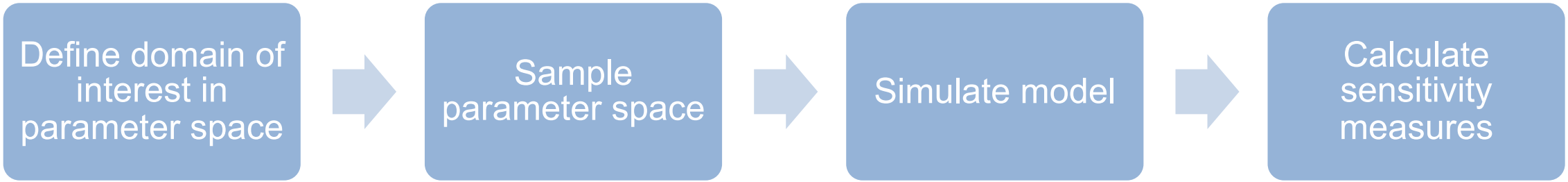
GSA Results

Number	Parameter	$E[\bar{S}_j]$	Number	Parameter	$E[\bar{S}_j]$
3	δ_M	28.610	8	a_{CNM}	3.610
1	r_M	25.603	16	a_{MC}	3.133
15	δ_C	20.691	11	a_{RM}	3.038
23	δ_N	19.232	20	s_N	2.392
13	r_C	17.877	17	b_{MC}	2.265
21	r_N	16.268	9	a_{MM}	2.047
4	a_{NM}	11.241	28	δ_R	2.012
22	K_N	10.451	26	r_R	1.860
14	K_C	9.077	12	b_{RM}	1.217
6	a_{CM}	8.426	27	K_R	1.216
5	b_{NM}	7.869	10	b_{MM}	0.931
18	a_{NC}	7.836	29	a_{MR}	0.303
24	a_{CN}	6.272	30	b_{MR}	0.234
7	b_{CM}	5.768	32	T_C^0	0.018
2	K_M	5.518	33	N^0	0.011
19	b_{NC}	5.178	31	M^0	0.006
25	b_{CN}	4.443	34	T_R^0	0.001

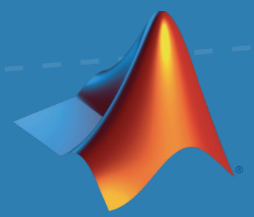
"We applied two different GSA methods, and found that the top ten sensitive parameters for each method have eight parameters in common…so we propose that this set of eight parameters is the maximum set of sensitive parameters to be considered for this model…work done here provides the necessary foundation for natural next steps: the prediction of optimal combination regimens for patients with MM, and the experimental validation of such a prediction"

Gallaher, Jill, et al. "Methods for determining key components in a mathematical model for tumor–immune dynamics in multiple myeloma." *Journal of Theoretical Biology* 458 (2018): 31-46.

Workflow for Global Sensitivity Analysis

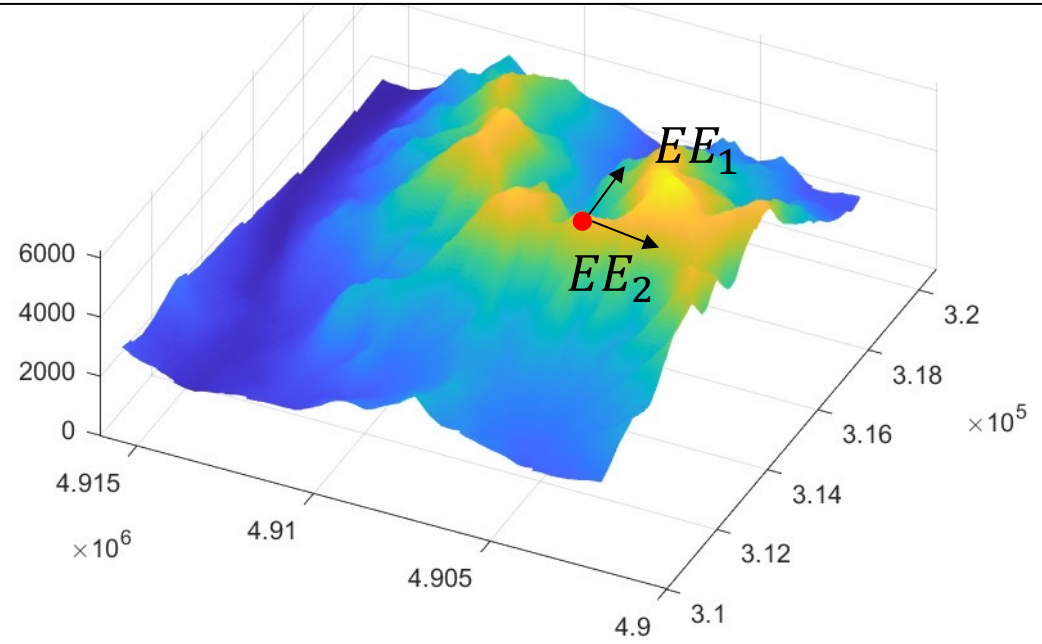


Morris method



The Morris method outputs the mean and variance of the elementary effects computed for each sampled point in the parameter domain

$$d_i(X) = \frac{y(x_1, \ldots, x_i + \Delta, \ldots, x_Q) - y(x_1, \ldots, x_i, \ldots, x_Q)}{\Delta}$$



Plot of the selected model output over a two-parameter domain.

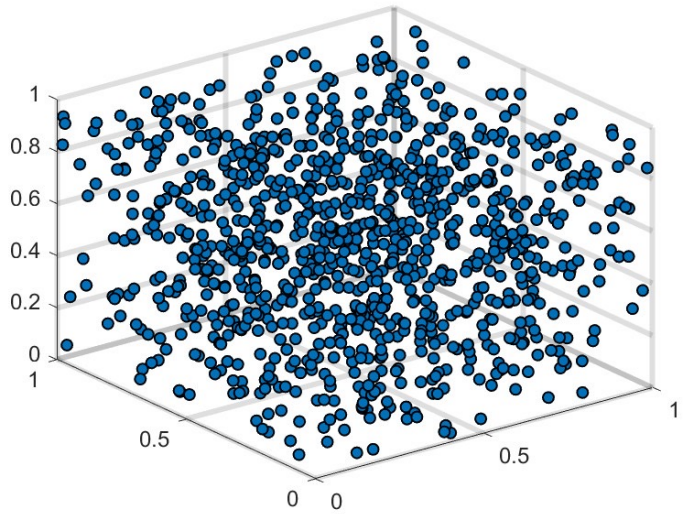
$$\mu_i = \frac{1}{r} \sum_{k=1}^{r} d_i^{(k)}$$

The mean μ assesses the overall influence of the parameter on the model output. μ^* which takes the average over the absolute value of the EE's is a better measure.

$$\sigma_i^2 = \frac{1}{r-1} \sum_{k=1}^{r} \left(d_i^{(k)} - \mu_i \right)^2$$

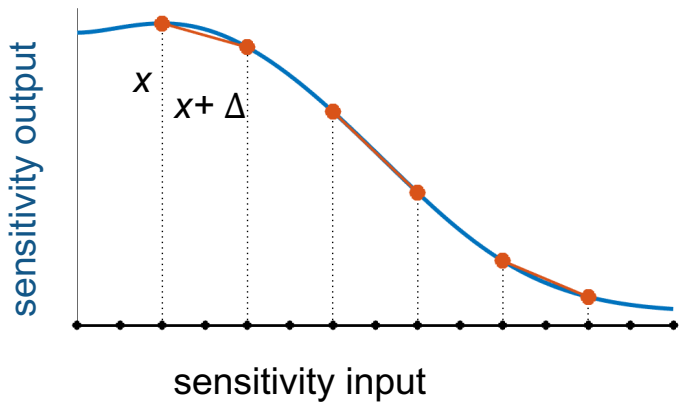
The standard deviation estimates σ estimates the ensemble of the factor's effects, whether due to its nonlinear response on the output and/or due to its interactions with other factors.

SimBiology requires setting four objects to compute the mean and variance of the elementary effects



Random sample of a three-parameter domain grid

$$d_i(X) = \frac{y(x_1, \ldots, x_i + \Delta, \ldots, x_Q) - y(x_1, \ldots, x_i, \ldots, x_Q)}{\Delta}$$



Compute elementary effects for each parameter input per sampled point

$$\mu_i = \frac{1}{r}\sum_{k=1}^{r} d_i^{(k)}$$

Mean

$$\sigma_i^2 = \frac{1}{r-1}\sum_{k=1}^{r}\left(d_i^{(k)} - \mu_i\right)^2$$

Standard Deviation

Estimate mean and variance per parameter input for sampled points

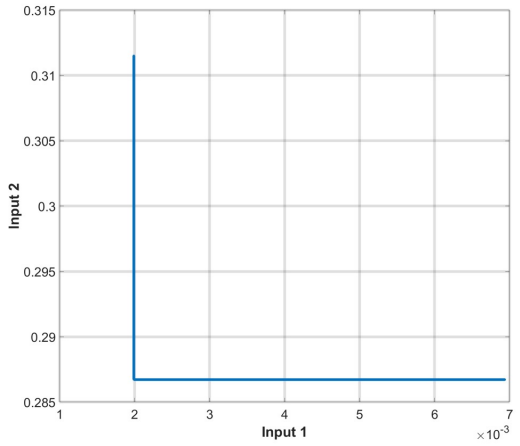
- Choose a parameter domain and discretization: bounds, GridLevel, GridDelta.
- Choose a sampling method of the parameter domain.
- Define a stencil type to compute elementary effects
- Absolute value of elementary effects?

Choose a parameter domain discretization

- Generalization: $EE_i(\vec{p}) = \frac{R(\vec{p}) - R(\vec{p} + \vec{e_i} \cdot \Delta_i)}{\Delta}$, where $\vec{e_i}$=[0,0,…,1,…,0]
- Define a grid for the sensitivity inputs

Name-value pair	Description
`Bounds`	Size of domain ([1e-3, 1e-2], [0.285, 0.315])
`GridLevel`	Discretization of domain, number of grid cells per sensitivity input
`GridDelta`	Delta of finite-difference in number of grid cells

GridLevel = 6, GridDelta = 2

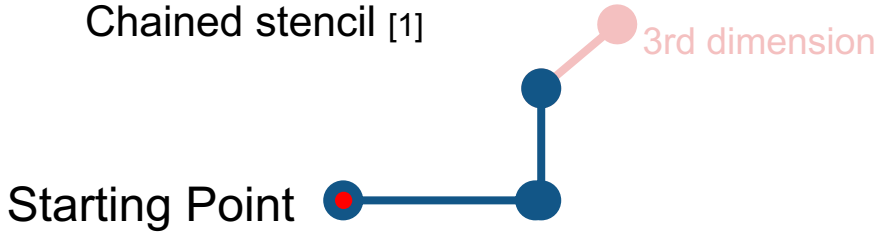


- GridLevel should be an even positive integer to guarantee accuracy.
- The finer the grid, the higher the number of samples to take to guarantee accuracy.

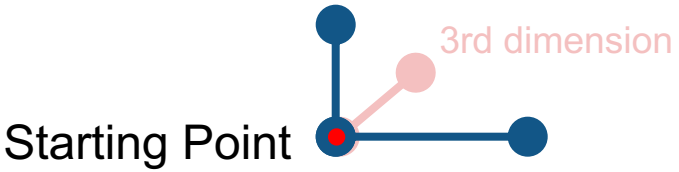
Choose a stencil to compute elementary effects

Name-value pair	Description
`PointSelection`	Type of stencil for finite differencing (`"radial"`, `"chain"`)

Chained stencil [1]



Radial stencil [2]



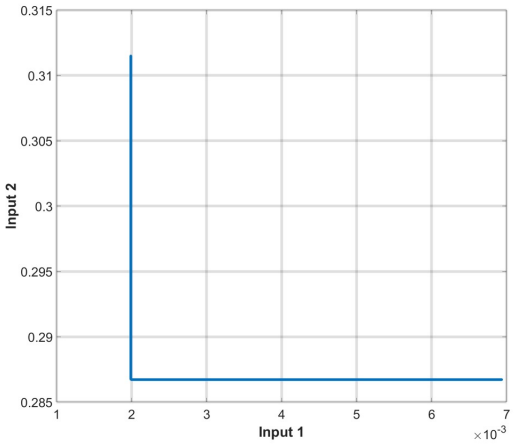
[1] Morris, M. “Factorial Sampling Plans for Preliminary Computational Experiments” Technometrics, 33(2), 1991, pp. 161-174
[2] Sohier H. et al. “Improvement of the Representativity of the Morris Method for Air-Launch-to-Orbit Separation” Proceedings of the International Federation of Automatic Control, Cape Town, South Africa, 2014

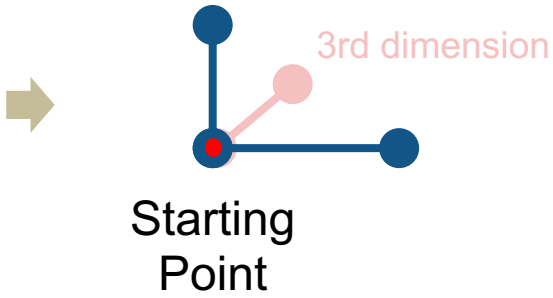
Choose a sampling method

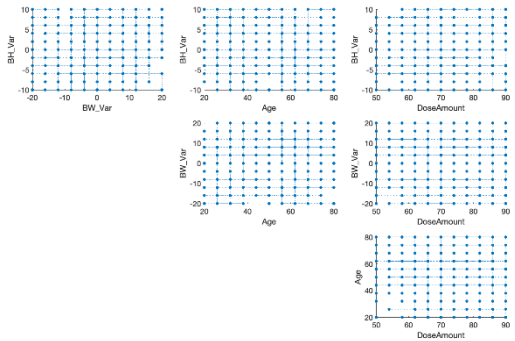
- Sample the grid

Name-value pair	Description
`SamplingMethod`	Sampling method to select start nodes for stencils (`"lhs"`, `"random"`)
`NumberSamples`	Number of start nodes in the grid

GridLevel = 6, GridDelta = 2



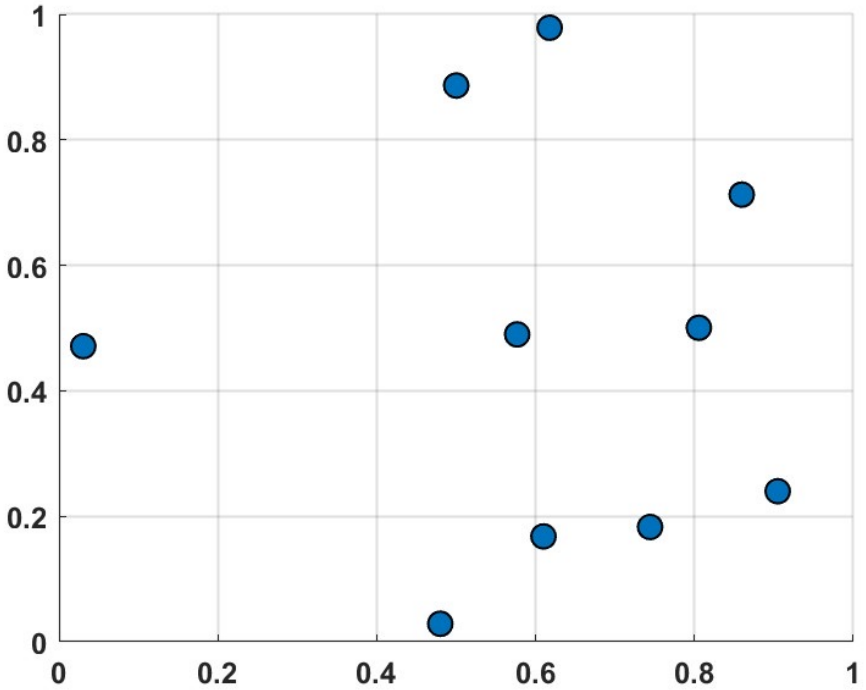




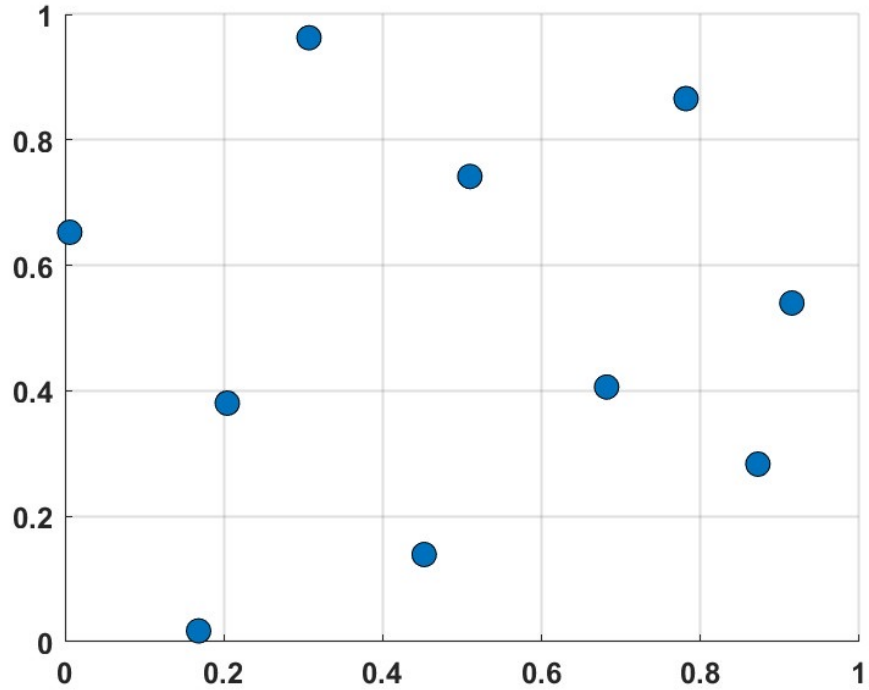
Choose a sampling method

Latin hypercube sampling ensures there is at least one point in each sub-interval of the parameter domain grid

Latin hypercube sampling is the default sampling method for performing a Morris method GSA



Random sampling



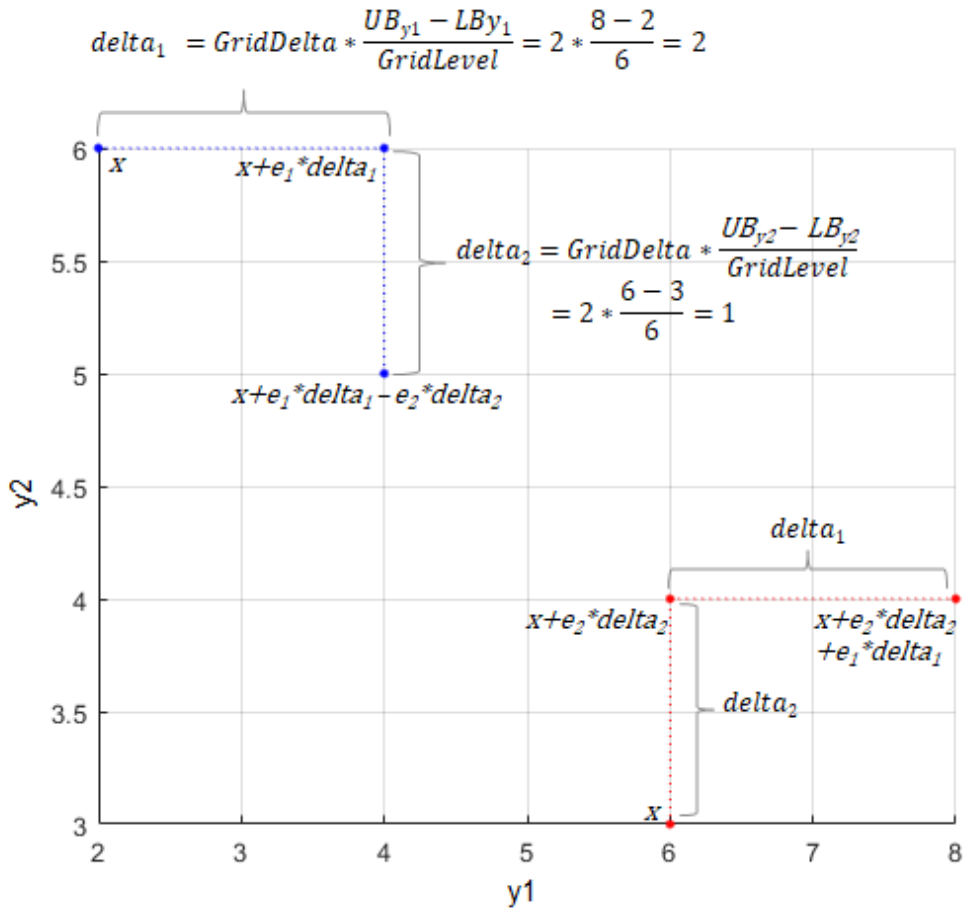
Latin hypercube sampling

Example of sample generation for Elementary effects

Example: k (# of sensitivity inputs) = 2, `NumberSamples` = 2, `GridLevel` = 6, `GridDelta` = 2

y1 Upper Bound (UBy_1) = 8
y1 Lower Bound (LBy_1) = 2

y2 Upper Bound (UBy_2) = 6
y2 Lower Bound (LBy_2) = 3



Parameter Samples

26
46
45

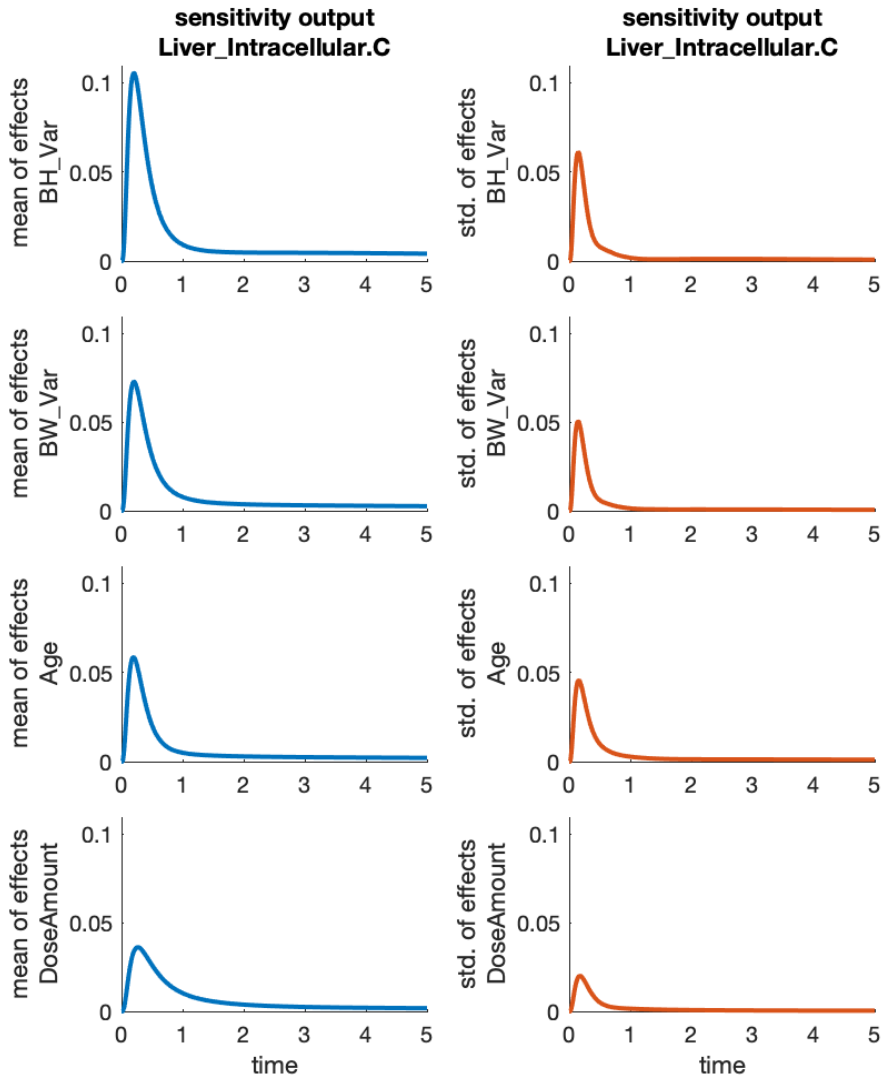
63
64
84

Interpreting the μ, μ*, σ, plots

Mean:
μ assesses the overall influence of the parameter on the model output.

Standard deviation:
estimates the ensemble of the factor's effects, due to its nonlinear response and/or due to interactions with other factors.

Absolute mean:
Switch to μ^* to avoid cancellations.



Cons/Can also be used for:

Mean
μ can fail to identify a factor with considerable influence on the model. These errors occur when positive and negative EE's cancel each other out.

Standard deviation:
It can be used to detect influential parameters with a low mean i.e. low μ but high σ.

Absolute mean:
Max information is extracted with all three measures. μ^*, μ provide info on the signs of the EE's.

Best practices for the Morris method

- How many samples (*N*) are required (as a function *P* = number of parameters) to gain confidence in estimated values? ~ $N > 2^P$. A representative sample of the parameter domain should have at least one point in each corner (2^P). Earlier work has provided empirical evidence that the Morris method requires lower number of samples to provide accurate results.
- Use LHS sampling scheme (default in SimBiology) for more accurate results.
- Choose GridDelta = GridLevel/2 to optimize equal sampling frequency between levels.
- Monitor the convergence of the measure as the sampling number increases.

Exercise 1: Global Sensitivity Analysis – Morris method

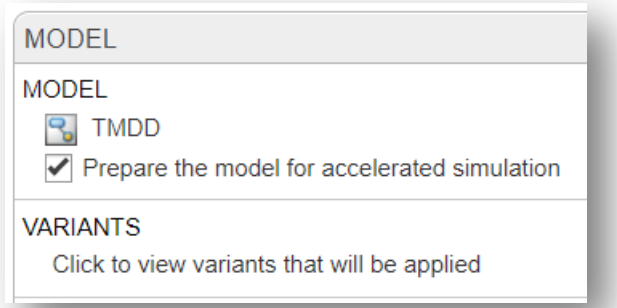
1. Open GSA_Exercise_Final, Open a new Global Sensitivity Analysis Program, choose Elementary Effects
2. Choose Gallaher2018 – Tumor Immune dynamics in multiple myeloma
3. Inputs = all from a uniform distribution, Number of samples = 2560, Stop time = 100000,
4. PointSelection=chain, SamplingMethod=lhs, GridLevel=100, GridDelta=10, Outputs: Steady_State, compartment.M

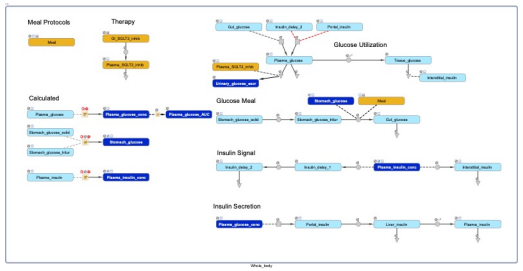
Name	Lower bound	Upper bound
rm	0.004	0.5
dm	1e-3	0.1
anm	0	20
acm	0	20
rc	0.01	0.5
dc	0.01	0.5
rn	0.01	0.5
dn	0.01	0.5

Strategies to speed up simulations

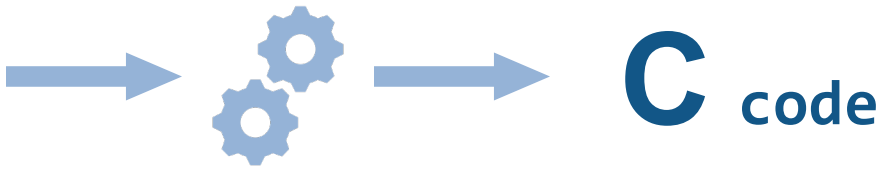
- **Model acceleration**
- Parallelization

Useful for multiple simulations (scan or GSA) or single, long simulations





Acceleration mode

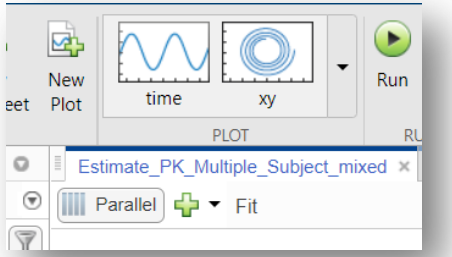


Hint: SimFunctions are accelerate automatically the first time they are used, unless you deactivate this feature when creating them

Strategies to speed up simulations

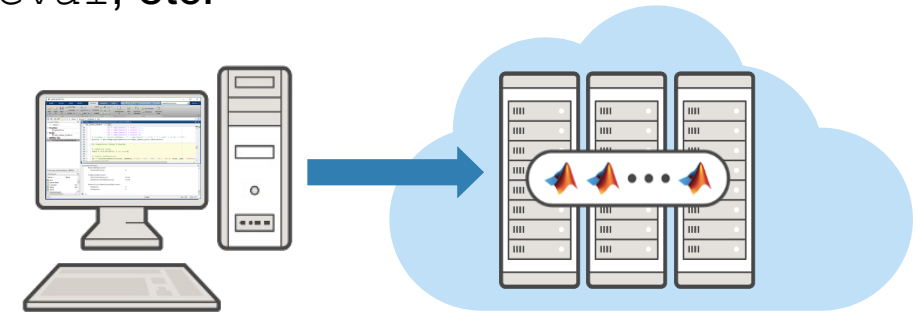
- Model acceleration
- **Parallelization**

SimBiology includes built-in support for Scans, Fits and GSA.

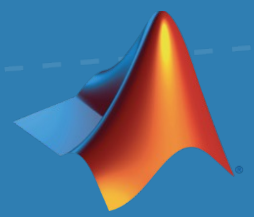


You can activate it in the Model analyzer for each program.
You can also use the `UseParallel` option in functions (for GSA: sbiosobol, sbiompgsa, sbioelementaryeffects).

Finally, you can all MATLAB constructs for parallel computing such as `parfor, parfeval`, etc.



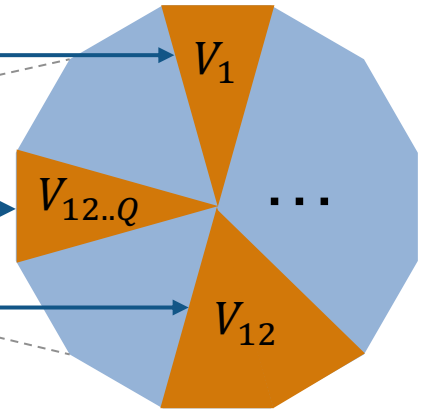
Sobol Method



The Sobol method decomposes the total output variance into contributions from each parameter and groups of parameters

- Variance of the output arises from the randomness of the model inputs.
- Relies on a mathematical result by Sobol that shows how to rewrite the variance of the output as the sum of the respective contribution of each subset of the entire set of model inputs.
- Each term $V_{i_1 i_2 \cdots i_j}$ represents the variance attributed to interaction of parameters $X_{i_1}, X_{i_2}, \ldots, X_{i_j}$.

$$V(Y) = \sum_{i=1}^{Q} V_i + \sum_{i=1}^{Q} \sum_{i<j}^{Q} V_{ij} + \cdots + V_{12\ldots k}$$



How many terms are in here?

$2^k - 1$, where *k* is the number of inputs.

Saltelli proposed two summary measures

- "The first-order index represents the **main effect contribution** of each input factor to the variance of the output."

- "The total effect index accounts for the total contribution to the output variation due to factor X_i, i.e. its **first-order effect plus all higher-order effects due to interactions**."

Dividing the variance decomposition above by V(Y) we get:

$$\sum_i S_i + \sum_i \sum_{j>i} S_{ij} + \sum_i \sum_{j>i} \sum_{l>j} S_{ijl} + \ldots + S_{123\ldots k} = 1$$

$$S_i = \frac{V_i}{V(Y)} = \frac{V[E(Y|X_i)]}{V(Y)}$$

First Order Index

To compute the values two variances must be approximated.

$$S_{T,i} = S_i + S_{i2} \cdots S_{1,2,\ldots i,\ldots k} = \frac{E[V(Y|\mathbf{X}_{\sim i})]}{V(Y)} = 1 - \frac{V[E(Y|\mathbf{X}_{\sim i})]}{V(Y)}$$

Total Order Index for model input X_i

Sobol sequences are designed to distribute points on the parameter domain uniformly to optimize convergence of the Sobol indices.

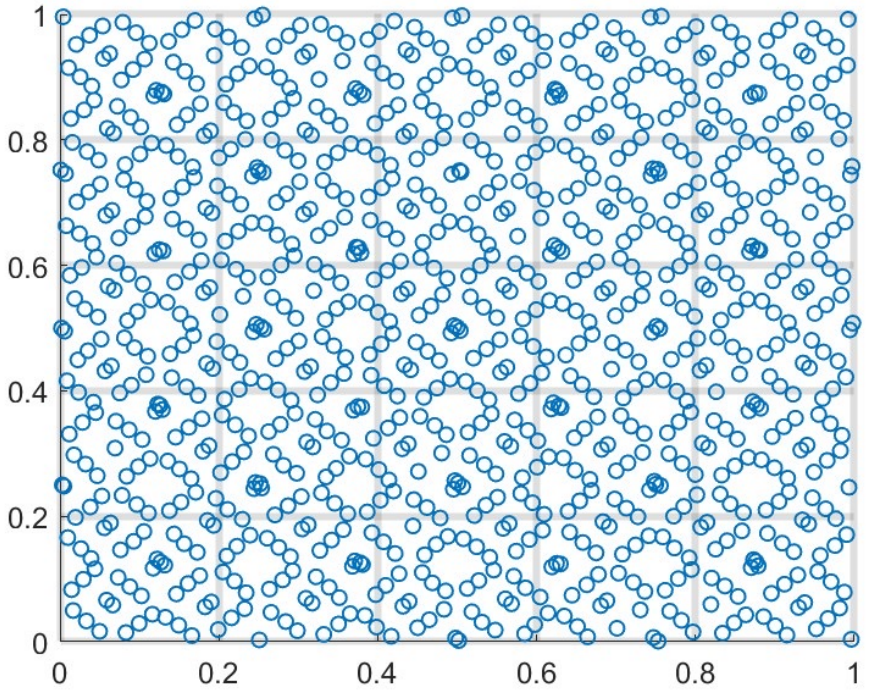
Sobol indices are computed as integrals. ***Sobol sequences are the default sampling method for performing a Sobol method GSA.***

$$S_i = \frac{V_i}{V(Y)} = \frac{V[E(Y|X_i)]}{V(Y)}$$

First Order Index

$$S_{T,i} = S_i + S_{i2} \cdots S_{1,2,\ldots i,\ldots k} = \frac{E[V(Y|\mathbf{X}_{\sim i})]}{V(Y)} = 1 - \frac{V[E(Y|\mathbf{X}_{\sim i})]}{V(Y)}$$

Total Order Index for model input X_i



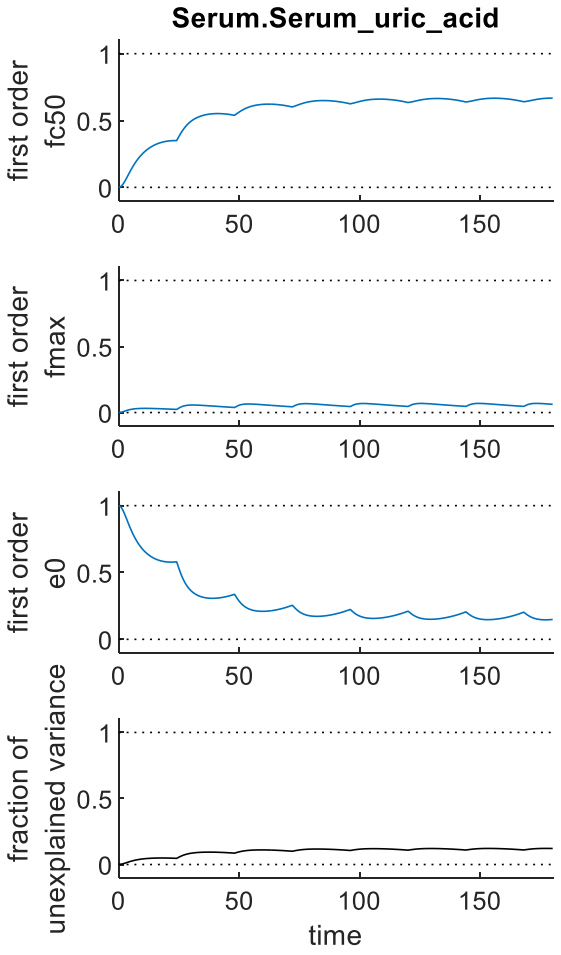
Sobol sequence

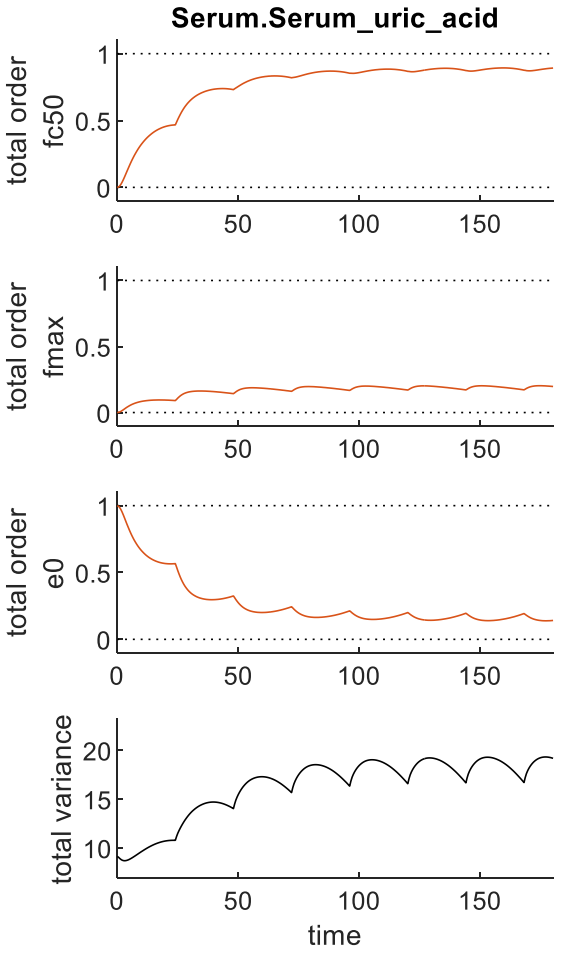
Interpreting Sobol indices plots

First order indices:
Indicates how much the variance could be reduced if a parameter could be fixed.

Total order indices:
Is a measure of contributions from both individual and group interactions involving a parameter to the variance.

Fraction unexplained indicates higher-order parameter interactions =1-sum(first-order indices)





The difference between total and first order is a measure of higher-order interactions between parameters e.g. e0 has no interactions with other parameters but fc50 and fmax do.

Best practices

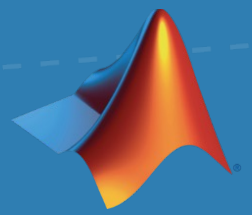
- How many samples (*N*) are required (as a function *P* = number of parameters) to gain confidence in estimated values? ~ $N > 2^P$. A representative sample of the parameter domain should have at least one point in each corner (2^P).
- Use Sobol sequences for sampling scheme as it is designed to optimize the accuracy of the approximation to the integral that is computed to obtain both S_i, S_T .
- Monitor the convergence of the indices as the sampling number increases.

Exercise 2: Global Sensitivity Analysis – Sobol method

1. Open GSA_Exercise_Final, Open a new Global Sensitivity Analysis Program, choose sobol
2. Inputs = all from a uniform distribution, Number of samples = 2560, Stop time = 100000,
3. SamplingMethod=sobol, Outputs: Steady_State, compartment.M

Name	Lower bound	Upper bound
rm	0.004	0.5
dm	1e-3	0.1
anm	0	20
acm	0	20
rc	0.01	0.5
dc	0.01	0.5
rn	0.01	0.5
dn	0.01	0.5

MPGSA

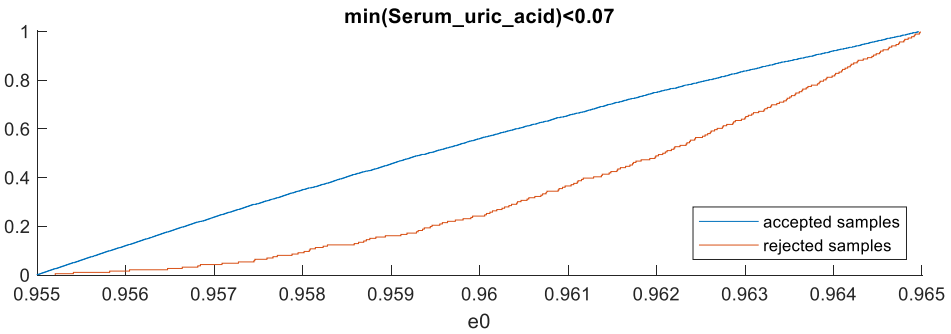


Global Sensitivity Analysis : Multi-Parametric GSA

- Relative importance of parameters wrt a classifier
- Classifier: a model-based decision metric
  - Based on model outputs; results in true/false outcome
  - *Effect > 70%,* $C_{end,i} > mean(C_{end,all})$ – can use more than one

Inputs		Output
k_{el}	IC50	Effect > 70%
0.29	30	Yes
0.18	21	No
0.41	23	No
0.03	26	Yes
0.12	20	Yes
0.25	39	No
0.17	14	Yes

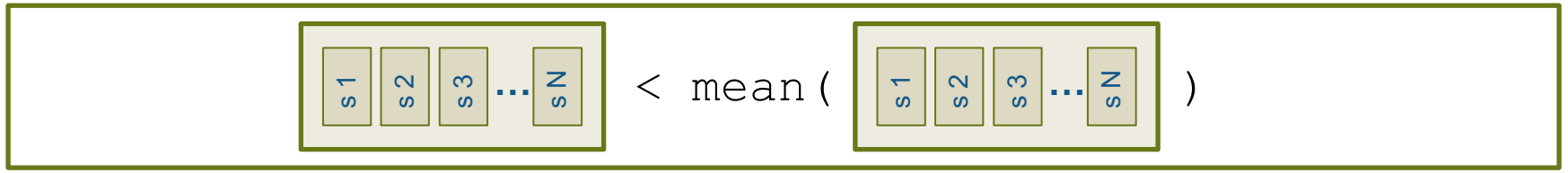
- Output measures:
  - Empirical Cumulative Distribution Function (eCDFs)
    - Accepted (yes) and rejected (no) samples
  - Calculate distances between eCDFs and significance using Kolmogorov-Smirnov Test



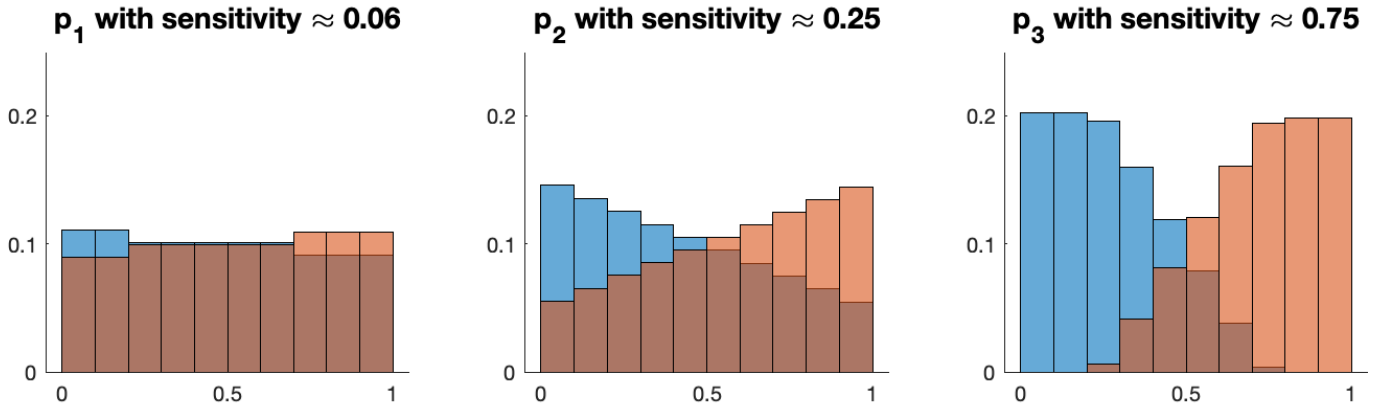
Tiemann et al. (2013) Parameter Trajectory Analysis to Identify Treatment Effects of Pharmacological Interventions, PLOS Comp Bio (SuppInfo T2)

Global Sensitivity Analysis : Multi-Parametric GSA

- A generic classifier for relative sensitivity analysis

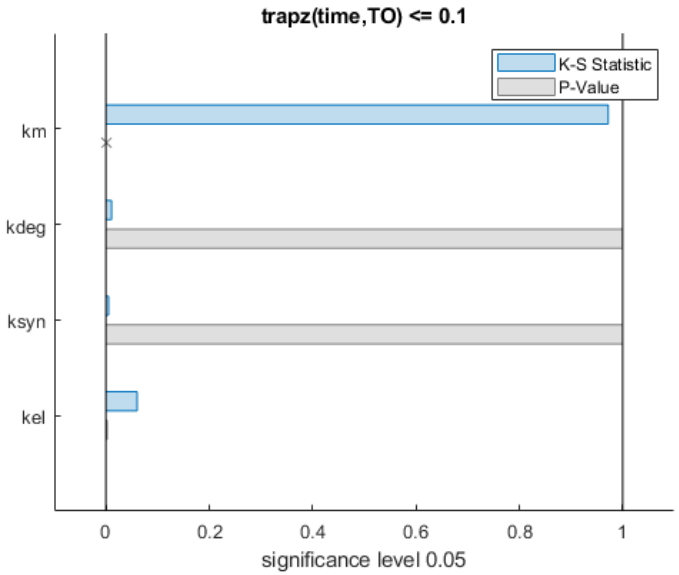


  - Example
    - Scalar observable: $s = p_1 + 5\,p_2 + 10\,p_3$
    - Parameters p_1, p_2, p_3 uniformly sampled in [0,1]

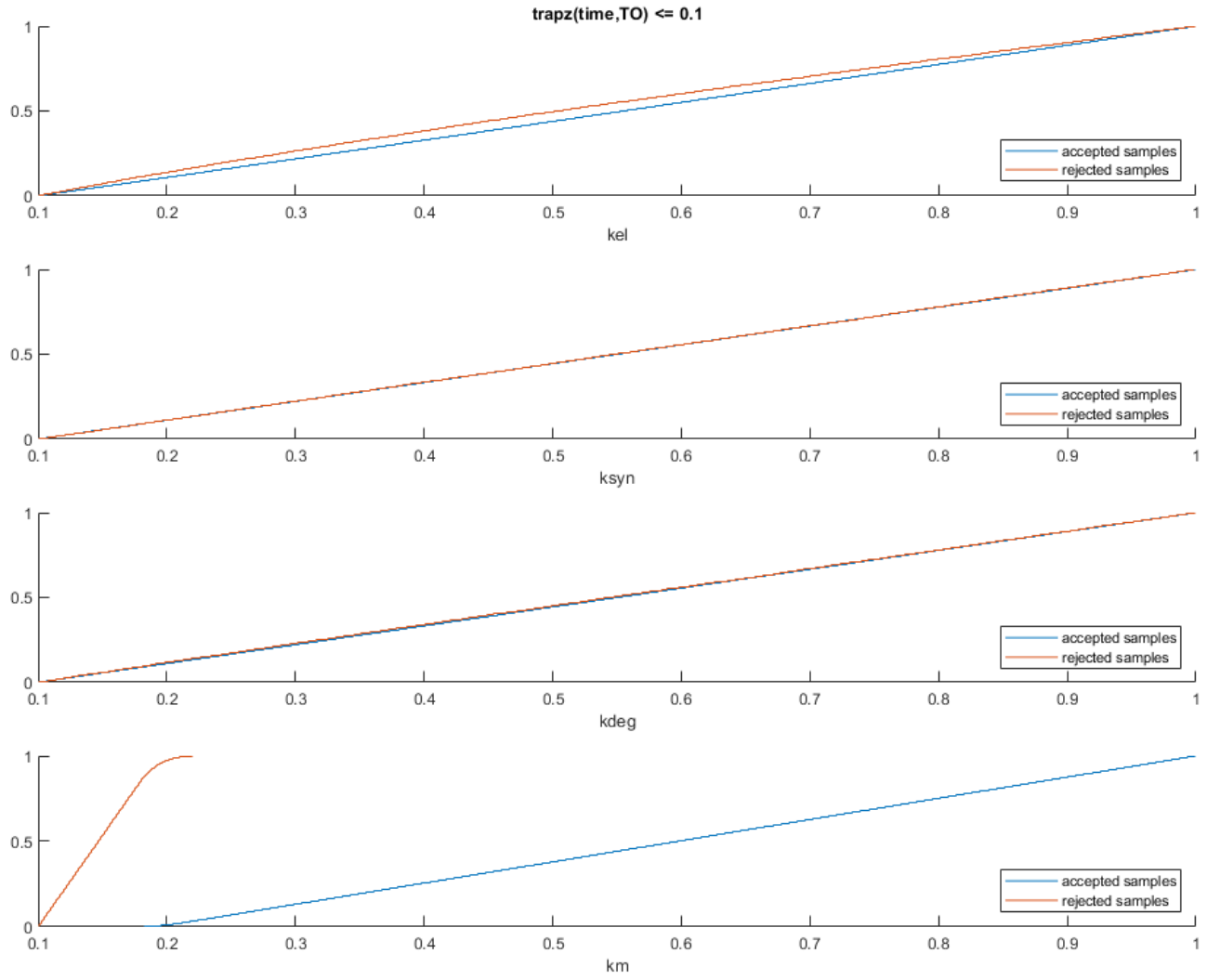


Interpreting MPGSA eCDF and K-S plots

- Are eCDFs different between accepted and rejected samples?
- If eCDFs are jagged/staircase: undersampled or violating assumptions
- Are p-values less than 0.05?



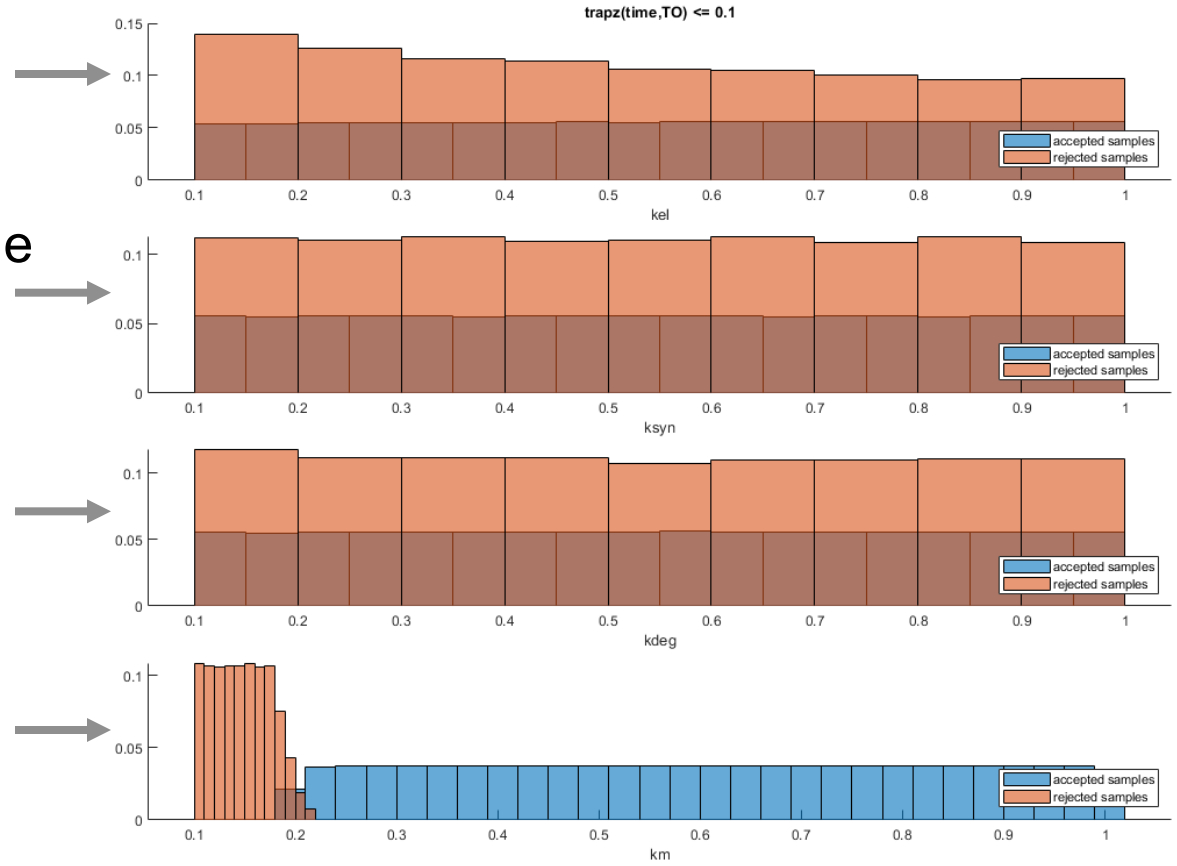
`bar(results)`



`plot(results)`

Interpreting the MPGSA histogram

1. Classification (ratio between accept/reject) changes if you change threshold value
2. Classification does not change if you change parameter value
3. No sensitivity if classification does not change over parameter range (for uniform samples here)
4. Clear separation here, shows the classification of the samples accumulated over all the other parameter dimensions



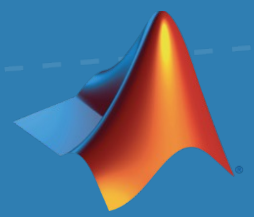

```
histogram(results)
```

Exercise 3: Global Sensitivity Analysis - MGPSA

1. Open `MPGSA_Exercise.sbproj`
2. Open Simulation program, add an Observable `maxTW = max(tumor_weight)`, run simulation
3. Add a GSA program to the current project
4. Choose MPGSA
5. Classifier `maxTW < mean(maxTW)`
6. Inputs = all from a uniform distribution

Name	Lower bound	Upper bound
k1	0.01	1
k12	0.01	0.05
k21	0.01	0.05
L1	0.01	1
L0	0.01	1
Cl_Central	0.2	1.5

Summary



Comparison of GSA methods

Method	Sensitivity Measure	Pro's and cons
Sobol indices sbiosobol	Computes the fractions of total variance of a model response (sensitivity output) that can be attributed to individual model parameters (sensitivity inputs). $V(Y) = \sum_{i=1}^{Q} V_i + \sum_{i=1}^{Q}\sum_{i<j}^{Q} V_{ij} + \cdots + V_{12\ldots Q}$ **Variance Decomposition** $S_i = \frac{V_i}{V(Y)}$ **First Order Index** $S_{Ti} = 1 - \frac{V_{X_{\tilde{i}}}\left[E_{x_i}\left(Y \mid X_{\tilde{i}}\right)\right]}{V(Y)}$ **Total Order Index**	• Variance-based method applicable to nonlinear and non-monotonic outputs. • Distinguishes both individual, and via interactions with other parameters to total variance. • Supports different distributions for sensitivity inputs. • Very computationally expensive because many samples may be required to achieve convergence.
Elementary Effects sbioelementaryeffects	Computes the means and standard deviations of elementary effects of sensitivity inputs with respect to a model response. Here each x_j is randomly selected from a grid of *p* uniformly distributed points in [0,1]. $\mu_i = \frac{1}{r}\sum_{k=1}^{r} d_i^{(k)}$ **Mean** $\sigma_i^2 = \frac{1}{r-1}\sum_{k=1}^{r}\left(d_i^{(k)} - \mu_i\right)^2$ **Standard Deviation** An elementary effect of a parameter x_i is defined as a linear approximation of a local sensitivity. $d_i(X) = \frac{y(x_1, \ldots, x_i + \Delta, \ldots, x_Q) - y(x_1, \ldots, x_i, \ldots, x_Q)}{\Delta}$ **Elementary Effect**	• Applicable to nonlinear and non-monotonic model outputs. • Yields global information on the impact of a parameter by averaging the individual elementary effects over a random sampling of the whole parameter range. • Least computationally-expensive GSA method. • Because the sensitivities are calculated one-at-a-time, it's not possible to distinguish results that may reflect interactions between parameters or nonlinearity of the output.

Evidence of good ranking accuracy at low sample number using the Morris method for large models is empirical

Influence of function with p=20 parameters all uniformly distributed in [0, 1]. Two sample sizes are taken W = 10 for a total cost of W*(P+1) = 210, and W = 1024 for a total cost of W*(P+1)=21504. Total indices are computed from W=1024 samples.

Ranking is similar for both sample sizes and does largely coincide with the ranking given by the values of the total order index, although the values of the absolute mean do differ.

Notice the ranking between X1, X2, X4 is shuffled in comparing both methods.

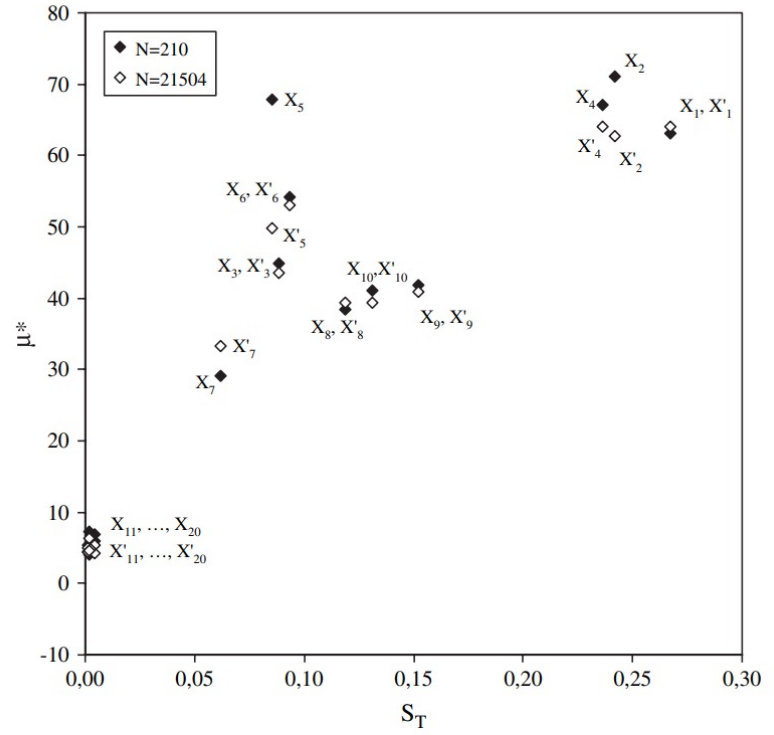


Fig. 2. Plots of μ^* versus S_T for the Morris test case. The Sobol' indices are estimated at the computational cost of $N = 21504$, while the EE values are computed at two different computational costs ($N = 21504$, apostrophed indices for the inputs, and $N = 210$, simple indices for the inputs).

Campolongo, F., Cariboni, J., & Saltelli, A. (2007). An effective screening design for sensitivity analysis of large models. *Environmental modelling & software*, *22*(10), 1509-1518.

Evidence of good ranking accuracy at low sample number using the Morris method for large models is empirical

Influence of function with p=12 parameters all uniformly distributed in [0, 1]. Two sample sizes are taken W = 10 for a total cost of W*(P+1) = 130, and W = 512 for a total cost of W*(P+1)=6656.

Ranking is similar for both sample sizes and does largely coincide with the ranking given by the analytical values of the total order index, although the values of the absolute mean do differ.

Notice the ranking between X8 and X5 is reversed in comparing both methods.

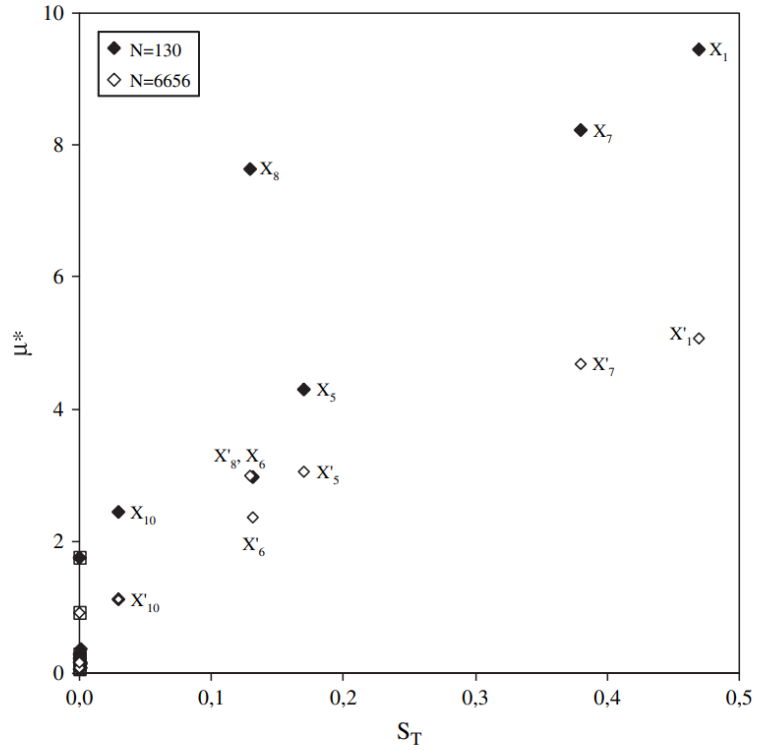


Fig. 7. Plots of μ^* versus S_T for the g-function test case. The Sobol' indices are estimated at the computational cost of $N = 6656$, while the EE values are computed at two different computational costs ($N = 6656$, apostrophed indices for the inputs, and $N = 130$, simple indices for the inputs).

Campolongo, F., Cariboni, J., & Saltelli, A. (2007). An effective screening design for sensitivity analysis of large models. *Environmental modelling & software*, *22*(10), 1509-1518.

Thank you!