AN INFORMATION-THEORETIC FRAMEWORK FOR GLOBAL SENSITIVITY ANALYSIS

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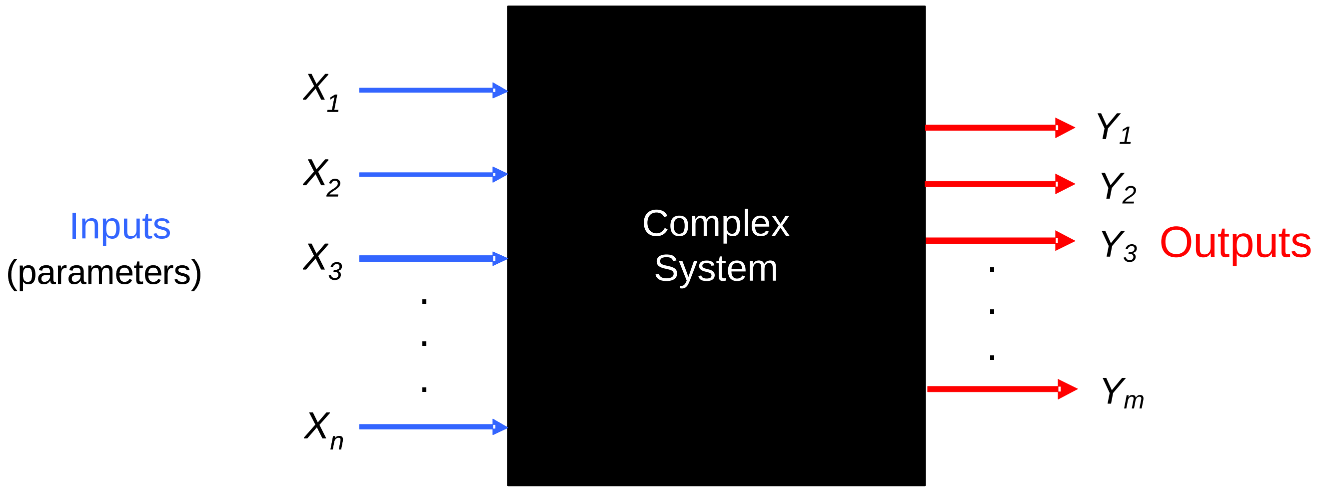
Parameter Sensitivity Analysis

- Pathway model as 'black box':



- Input-output mapping not explicit (e.g. ODE system)
- Which parameters are important?
- Do they interact?

Global Sensitivity Analysis

- Perturbing *all* inputs/parameters simultaneously => randomisation

- Inputs and outputs become random variables with pdfs $p(x_i)$ and $p(y)$.

Defining Sensitivity

- Result of repeated simulation:

$$\begin{pmatrix} x_1(1) \\ x_1(2) \\ \vdots \\ x_1(m) \end{pmatrix} \begin{pmatrix} x_2(1) \\ x_2(2) \\ \vdots \\ x_2(m) \end{pmatrix} \begin{matrix} \ldots \\ \ldots \\ \\ \ldots \end{matrix} \begin{pmatrix} x_n(1) \\ x_n(2) \\ \vdots \\ x_n(m) \end{pmatrix} \begin{matrix} \longrightarrow \\ \longrightarrow \\ \\ \longrightarrow \end{matrix} \begin{pmatrix} y(1) \\ y(2) \\ \vdots \\ y(m) \end{pmatrix}$$

- Sensitivity defined in terms of *associations* between sequences of random values (*columns*).

Information Theory

- Relates uncertainty and association ('correlation'):

  - Random parameter sampling creates output uncertainty, measured by *entropy* $H(Y)$

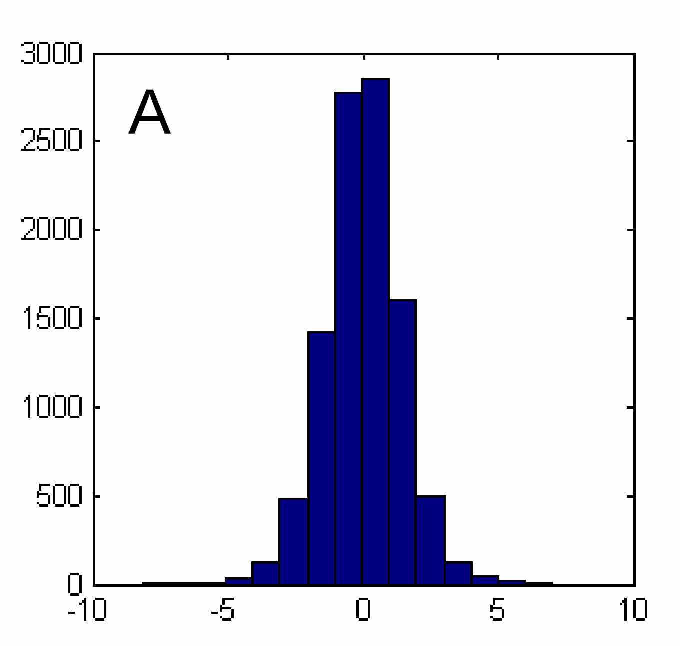
  - Input-output associations measured by *mutual information* $I(X;Y)$

- Complex system as a '*communication channel*'.
  How much information does X_i provide about Y?

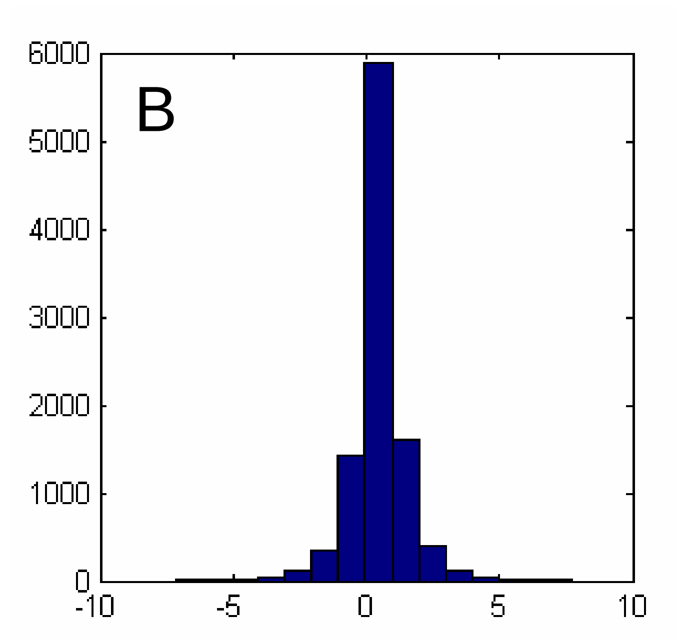
Answer: $I(X_i;Y) = H(Y) - H(Y \mid X_i)$.

Example: $y = x_1 * x_2 + x_3$ (x_1, x_2, x_3 normally distributed)

Unconditional output histogram



Output histogram for fixed $x_3 = 0.5$



- Conditioning (fixing parameters) reduces output entropy (uncertainty): $H(Y|X_i) \leq H(Y)$

First-order Sensitivity

- Normalised mutual information (Critchfield et al. 1986)

$$s_i = \frac{I(X_i;Y)}{H(Y)},$$

where we choose to *discretise* variables:

$$H(Y) = -\sum_{y} p(y)\log_2 p(y)$$

$$I(X_i;Y) = \sum_{x_i}\sum_{y} p(x_i,y)\log_2 \frac{p(x_i,y)}{p(x_i)\,p(y)}.$$

Second-order Interactions

- Captured by the conditional mutual information

$$I(X_i;X_j|Y) = \sum_F p(y) \sum_{k_i,k_j} p(x_i,x_j|y) \log_2 \frac{p(x_i,x_j|y)}{p(x_i|y)\,p(x_j|y)}$$

Requirement: parameters sampled independently

General form:

$$\underbrace{I\left(\{X_i,X_j\};Y\right)}_{\text{1st+2nd-order}} - \underbrace{I(X_i;Y) - I(X_j;Y)}_{\text{1st-order}} = \underbrace{I(X_i;X_j|Y) \quad - \quad \underbrace{I(X_i,X_j)}_{\text{input 'correlation'}}}_{\text{2nd-order}} \quad .$$

Third-order Interactions

- Decomposition for 3 independent variables yields:

$$I(\{X_1, X_2, X_3\};Y) = \underbrace{I(X_1;Y) + I(X_2;Y) + I(X_3;Y)}_{1st-order}$$

$$+\underbrace{I(X_1;X_2\,|\,Y) + I(X_1;X_3\,|\,Y) + I(X_2;X_3\,|\,Y)}_{\text{2nd-order}}$$

$$+\underbrace{I(X_2;X_3\,|\,X_1,Y) - I(X_2;X_3\,|\,Y)}_{\text{3rd-order}}.$$

- We define as third-order measure:

$$I_3(X_1;X_2;X_3\,|\,Y) \stackrel{\text{def}}{=} I(X_2;X_3\,|\,X_1,Y) - I(X_2;X_3\,|\,Y).$$

Conditional 'Interaction Information'

$$I_3(X_1;X_2;X_3\,|\,Y) \stackrel{\text{def}}{=} I(X_2;X_3\,|\,X_1,Y) - I(X_2;X_3\,|\,Y).$$

- Unconditional form introduced by McGill (1954)
- Captures genuine 3-way interaction
- Symmetrical in X_i
- Non-negative except for systems with extreme antisymmetry (*very rare*)

General Information Balance

- *n* parameters $X_1,\ldots,X_n$ and one output Y:

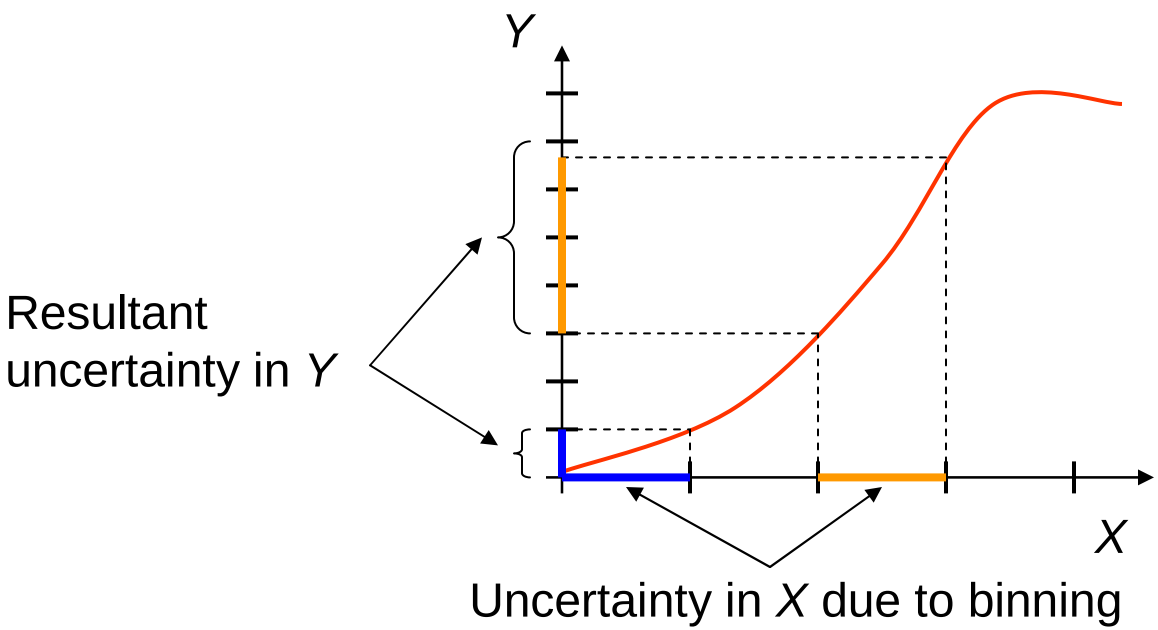
$$I\left(\{X_1,\ldots,X_n\};Y\right) = H(Y) - H(Y \mid X_1,\ldots,X_n)$$

Total output uncertainty

All Input-output associations, 1st order + interactions

Uncertainty due to discretisation and intrinsic stochasticity (if present)

Discretisation Effects



- If all parameters are known with *finite* precision, there can still be a *residual uncertainty* in *Y*, the *discretisation entropy:*

$$H_{\Delta} = H(Y \mid X_1, \ldots, X_n) \geq 0$$

Information Decomposition

$$I(X_1,...,X_n;Y) = H(Y) - H(Y \mid X_1,...,X_n)$$

- Total information can be written as sum of all information-theoretic sensitivity measures:

$$I(X_1,...,X_n;Y) = \sum_{i=1}^{n} I(X_i;Y) + \sum_{i<j}^{n} I(X_i;X_j \mid Y) + \sum_{i<j<l}^{n} I_3(X_i;X_j;X_l \mid Y) + \dots$$

$$= H(Y) - H(Y \mid X_1,...,X_n)$$

General Summation Theorem

$$\frac{1}{H(Y)-H_{\Delta}}\left\{\sum_{i=1}^{n} I(X_i;Y)+\sum_{\substack{i,j=1\\ i<j}}^{n}\left[I(X_i;X_j\,|\,Y)-I(X_i;X_j)\right]+\right.$$

$$\left.+\sum_{\substack{i,j,k=1\\ i<j<k}}^{n}\left[I_3(X_i;X_j;X_k\,|\,Y)-I_3(X_i;X_j;X_k)\right]+\ldots\right\}=1$$

- Correction terms account for input correlations.
  con: more computation time.
  pro: greater flexibility for sampling; higher orders?

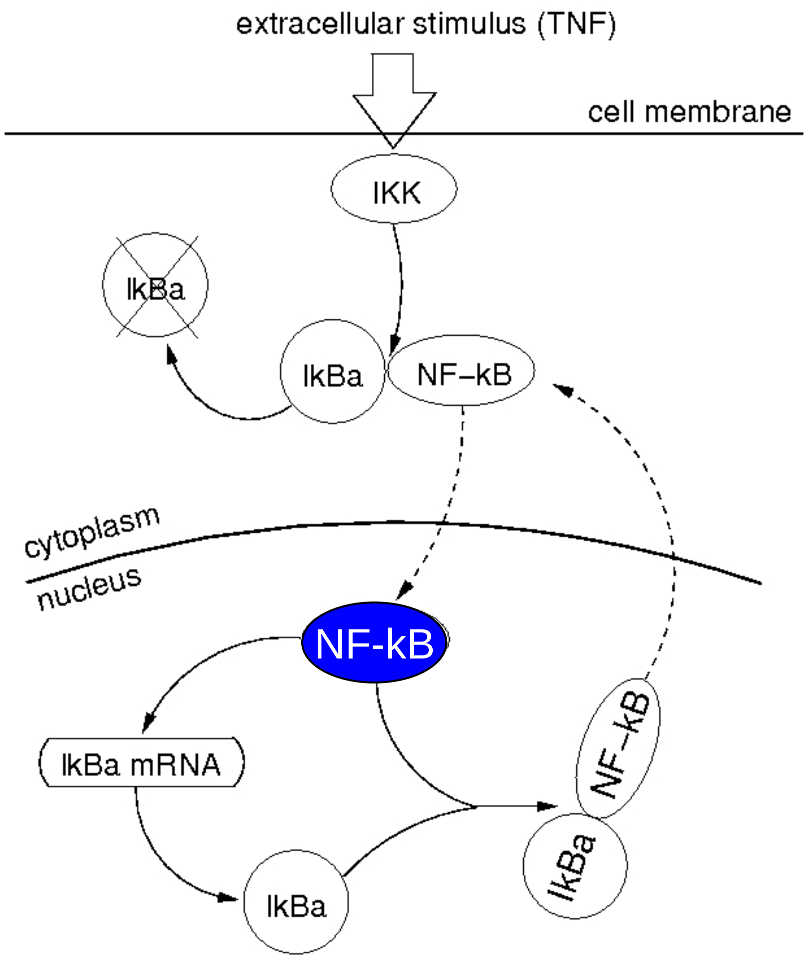
The Total Sensitivity Index

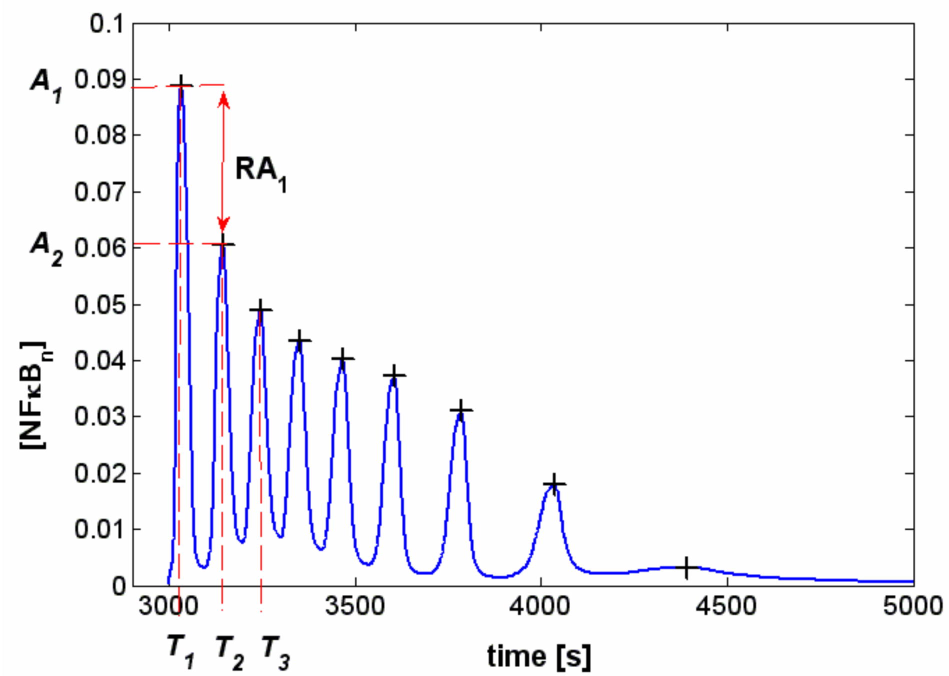
- Originally defined in variance-based method
- Captures the fraction of variance removed by a particular parameter and *all* its interactions.
- Information-theoretic equivalent:

$$s_{total,\, i} = \frac{H\left(Y \,\middle|\, \{X_1, \ldots, X_n\} \setminus X_i\right)}{H(Y) - H_{\Delta}}$$

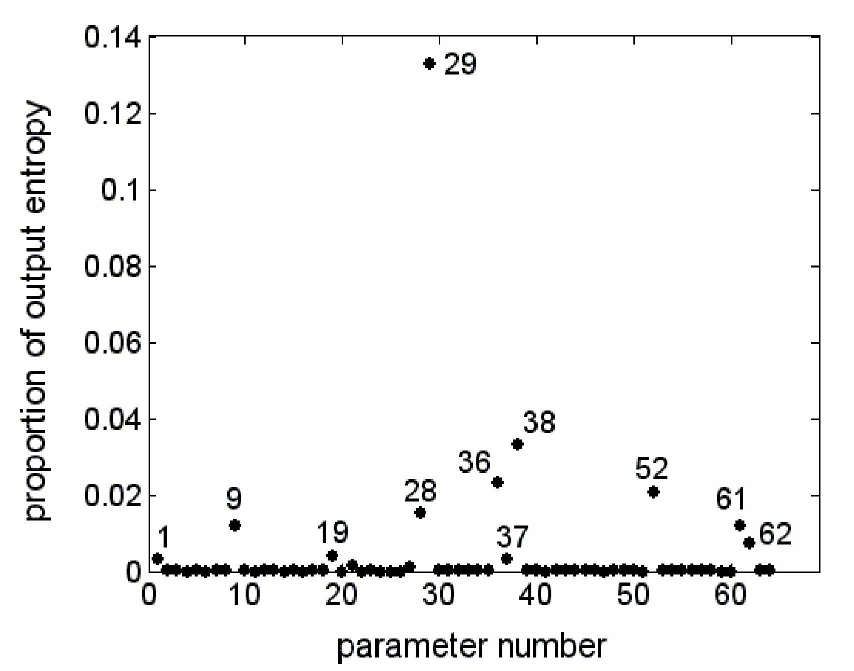
- Equals sum of all sensitivity indices containing parameter X_i but is calculated via Monte Carlo.

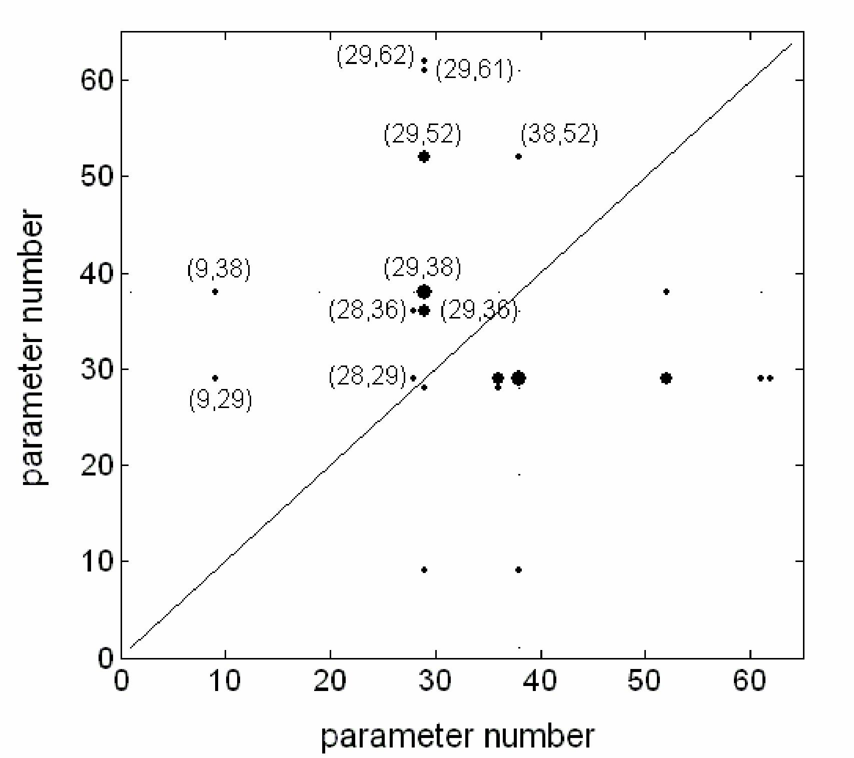
Example: (IκB)NF-κB pathway



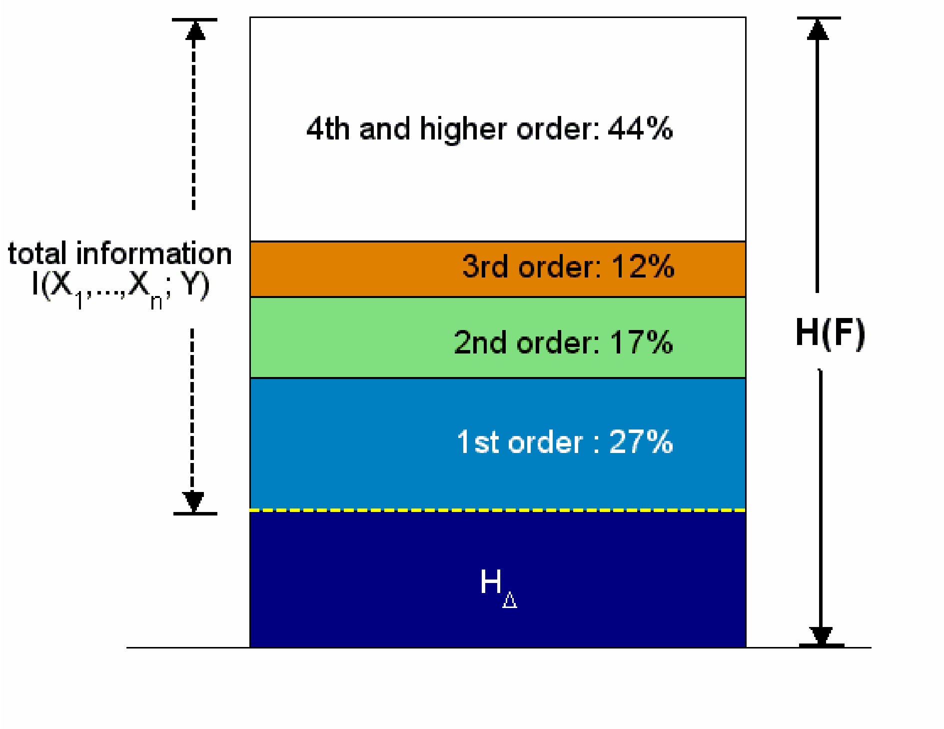


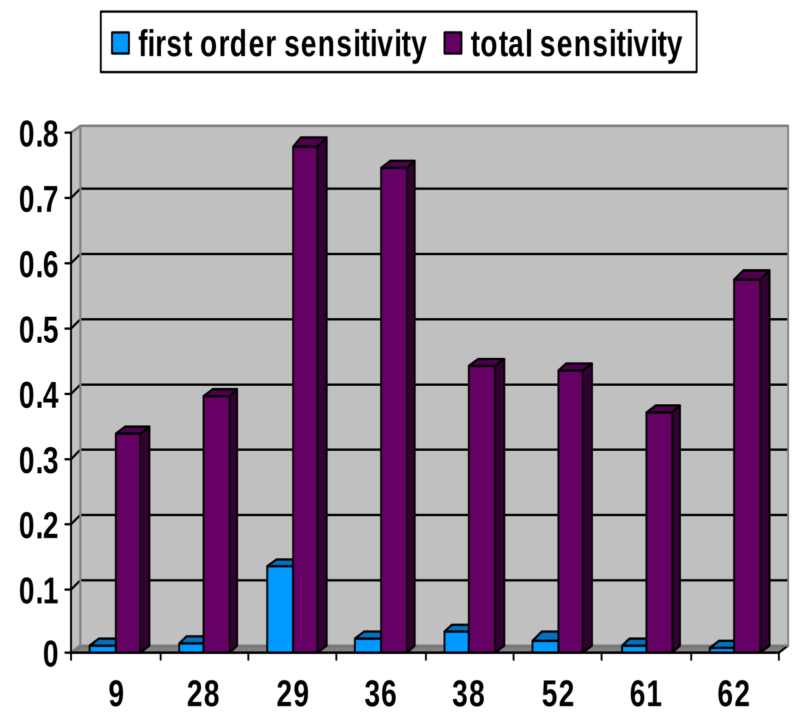
First and Second Order





Visualisation of Sensitivity Analysis





- Interactions are very prominent
- 4th and higher-order interactions contribute significantly!

Conclusions

- Novel framework for global sensitivity analysis based on information theory
- Systems Biology: reveals parameter interactions in complex non-linear system (NF-kB pathway)
- Method can incorporate correlated inputs
- Applicable to deterministic and stochastic systems
- Publication: Ludtke et al. (2007), **Information-theoretic Sensitivity Analysis: a general method for credit assignment in complex networks** *J. Royal Soc. Interface*, in print
- Email Niklas.Ludtke@manchester.ac.uk for preprints

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