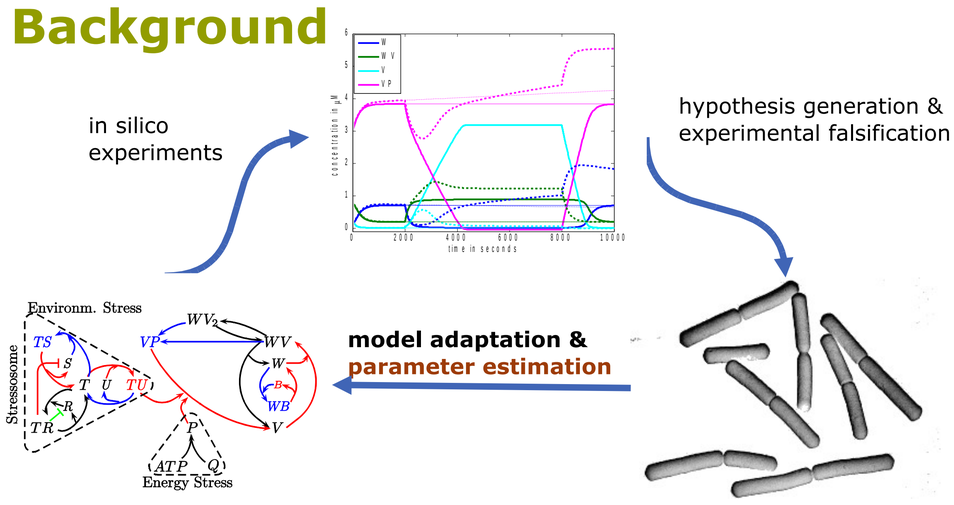
# Sensitivity Analysis based Adaptive Search-Space Reduction for Parameter Estimation Applications

**Ulf W. Liebal & Henning Schmidt**
University of Rostock, Systems Biology and Bioinformatics group

## Background




Modelling of biological systems is an iterative process. A common scenario is:

1. A model is built that reflects available experimental data.
2. New experimental data generated → the model is not able to explain the data.
3. Re-estimation of all parameters based on the new data?

Problems:
- many parameters
- different experiments and measurement data
- parameter unidentifiability

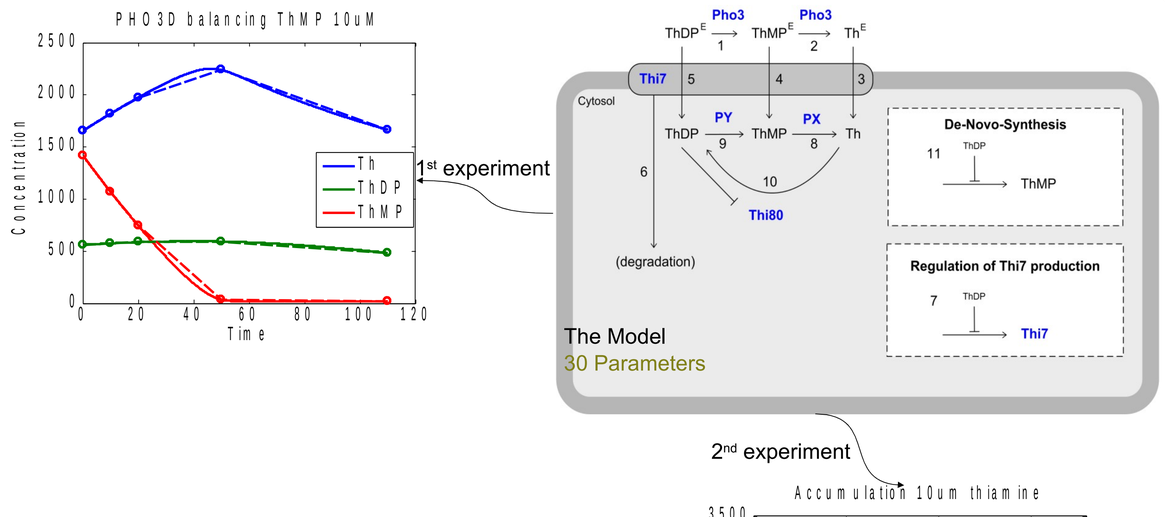
Current solutions use sensitivity based approaches for parameter selection:
- local SA, e.g. Dash et al.
- global SA, e.g. Jin et al.
- using SA with specific objective functions, e.g. Yue et al.

**Goal**: **Experiment specific adaptive identification of parameters responsible for divergent model-experiment behaviour!**
**R**esidual and **S**ensitivity aided **i**terative **S**earch space **R**eduction**: RSiSR**

## Method + Example

We consider a model of Thiamine uptake in *S. cerevisiae* (Ericson et al.). The example serves as a well known system; for the sake of demonstration of the method, simulated data is used with deviations in two parameters affecting Thiamine uptake.

Two exp. settings are investigated:
- 1st experiment: null-mutant for the Thiamine uptake
  →Experiment 1 - parameter estimation
- 2nd experiment: uptake of Thiamine is functional




### RSiSR procedure:

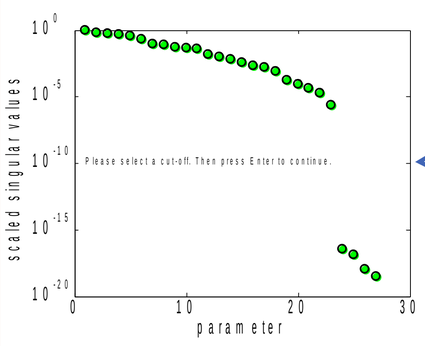
$$e(t,p) = y^m(t) - y(t,p) \quad \Rightarrow \quad \epsilon(p) = [e_1^1(t_1,p), e_1^1(t_2,p), ..., e_2^1(t_1,p), e_2^1(t_2,p), ..., e_1^2(t_1,p), ...]^T$$

residual — measured state (t) — model prediction (t) — stacked residuals vector

Taylor expansion for the error at $\Delta p$, assuming linear approximation and disregarding higher order terms.

$$\epsilon(p + \Delta p) = \epsilon(p) - \Omega \Delta p$$

$$-\frac{\partial}{\partial p}\epsilon(p) = \Omega = \begin{bmatrix} \frac{\partial y_1^1(t_1,p)}{\partial p_1} & \frac{\partial y_1^1(t_1,p)}{\partial p_2} & \cdots & \frac{\partial y_1^1(t_1,p)}{\partial p_n} \\ \vdots & \vdots & \vdots & \vdots \\ \frac{\partial y_1^1(t_{m_1},p)}{\partial p_1} & \frac{\partial y_1^1(t_{m_1},p)}{\partial p_2} & \cdots & \frac{\partial y_1^1(t_{m_1},p)}{\partial p_n} \\ \frac{\partial y_2^1(t_1,p)}{\partial p_1} & \frac{\partial y_2^1(t_1,p)}{\partial p_2} & \cdots & \frac{\partial y_2^1(t_1,p)}{\partial p_n} \\ \vdots & \vdots & \vdots & \vdots \\ \frac{\partial y_1^2(t_{m_1},p)}{\partial p_1} & \frac{\partial y_1^2(t_{m_1},p)}{\partial p_2} & \cdots & \frac{\partial y_1^2(t_{m_1},p)}{\partial p_n} \\ \vdots & \vdots & \vdots & \vdots \end{bmatrix}$$



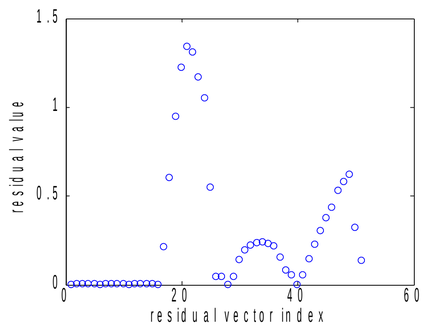

computing singular values of Ω allows identification of (almost) linearly dependent parameter sensitivities. These have to be eliminated to increase the information content of Ω.

Re-writing Taylor expansion for reduced sensitivity matrix and parameter vector.

$$\epsilon(p_{red} + \Delta p_{red}) \approx \epsilon(p_{red}) - \Omega_{red}\Delta p_{red}$$

setting l.h.s to zero and solving the equation for $\Delta p_{red}$ .

$$\Delta p_{red} = (\Omega_{red}^T W \Omega_{red})^{-1} \Omega_{red}^T W \epsilon(p_{red})$$

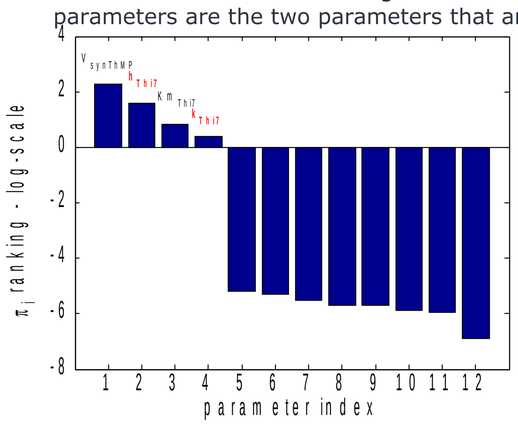



*W*, the weighting matrix, is user defined generated by choosing a threshold below which the significance of a residual increases the lower its value. This guarantees the conservation of already fitted experiments by raising their influence. The first 15 indices correspond to the well fitted experiment.

$\pi_i$ is a measure that reflects the relative parameter change that is required to minimize the residual error. $\pi_i$ forms the basis for a ranking for parameter estimation.

$$\pi_i = \Delta p_{red,i} \frac{1}{p_{red,i}}$$

The RSiSR ranking for weighted $\pi_i$ in **log scale** shows four parameters that strongly determine the discrepancy of model and observation. Among those four identified parameters are the two parameters that are perturbed.




In a following parameter estimation the four top-scoring parameters would be estimated. This speeds up the parameter determination process and renders it more precise.

## Conclusions

- Considerable reduction of search-space, identifying parameters important for un-fitted experiments
- Assumption of linearity => only an approximation
- Iterative use between different runs of parameter estimation
- Manual and eye inspection at the moment but can easily be automized
- Adaptable and improvable weight matrix
- Can be useful to determine parameters important for obtaining a desired response shape – potential use for drug target identification

**Method soon available in the SBTOOLBOX2**

## Literature

Dash, R.; et al. (2008); *IEEE Trans. on Biomedical Engineering*
Ericsson, A., et. Al. (2008); *Essays in Biochemistry - Systems Biology*
Jin, Y., et al. (2007); *American Control Conference*
Schmidt, H., et al. (2006); *Bioinformatics*
Yue, H ., et al. (2006); *Molecular BioSystems*

## Acknowledgments

**BMBF – BaCell-SysMO Project**
**BMBF – Forsys Partner**

SysMO Systems Biology of Microorganisms
FORSCHUNGSEINHEITEN FORSYS DER SYSTEMBIOLOGIE

## Contact

Henning Schmidt
FORSYS Research Group hIMOsYS
Systems Biology and Bioinformatics
University of Rostock
Albert Einstein Str. 21
18059 Rostock, Germany
henning.schmidt@uni-rostock.de