# Model Reduction based on dynamic sensitivity analysis: A systems biology case of study

**R. S. Costa, I. Rocha and E. C. Ferreira**

IBB-Institute for Biotechnology and Bioengineering, Centre of Biological Engineering,
Universidade do Minho, Campus de Gualtar, 4710-057, Braga, Portugal
(Email: {*rafacosta, irocha, ecferreira*} @deb.uminho.pt)

## OVERVIEW

### INTRODUCTION

The complexity of dynamic mathematical models due to large number of parameters is a major obstacle for their effective use in optimization and control processes. Furthermore, the experimental estimation of a great number of parameters is often an unfeasible task [1]. Therefore, model reduction represents a key step to eliminate unimportant parameters and to uncover the most important control pathways of the models. Several techniques for parameter model reduction exist, including methods based on sensitivity analysis [2].

### AIM

Here, the complex *E. coli* dynamic model describing the carbon central metabolism [3] which has 25 species participating in 30 reactions and with 116 parameters was used to:
• **Identify key parameters that have more impacts on the global systems.**
• **Study a model reduction strategy based on univariate analysis of the Euclidean-norm to consider the effect to all metabolites.**

## METHODOLOGY

### DYNAMIC MODEL OF CENTRAL CARBON METABOLISM
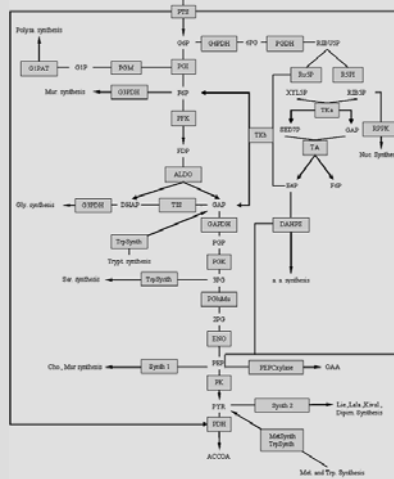


Complex Mechanistic Model:

- 25 Species

- 30 Enzyme Kinetics

- 116 Parameters

**Figure 1.** Metabolic network from the central carbon metabolism of *E. coli* (adapted from [3]).

### SENSITIVITY ANALYSIS

- **Nonlinear ODE model**

$$\frac{dX_i}{dt} = \sum_j v_{ij} r_j - \mu X_i \qquad X_i(t) = f(t, p_j, X_0)$$

- **Computing sensitivity analysis in Matlab**

$$S_{i,j}(t) = \frac{X_i(p_j + \Delta p_j) - X_i(p_j - \Delta p_j)}{2\Delta p_j} \times \frac{p_j}{X_i(p)} \approx \frac{\partial \ln X_i(t,p)}{\partial \ln p_j}$$

- **Dynamic sensitivity analysis based on Euclidean-norm**

$$OS_j = \frac{1}{n}\sqrt{\sum_{k=1}^{n}\sum_{i=1}^{p}\left|S_{i,j}(t)\right|^2}$$

## RESULTS

### COMPARISON ORIGINAL AND REDUCED MODEL

Of all the 116 parameters from the complex model analyzed, 41 (35.3%) parameters were rejected without significant changes on the model prediction. Further 24 (20.7%) parameters were found to have significant influence on the systems, although their overall sensitivity ($OS_j$) was low, and as such were also not considered in the model reduction. Although the metabolically structured model was affected by the model reduction, the dynamics of the network are generally well represented. By comparing the simulation results of the original and the reduced model, it can be showed that species trajectories did not change considerably with time (Figure 2) and also for the fluxes trajectories (Figure 3).
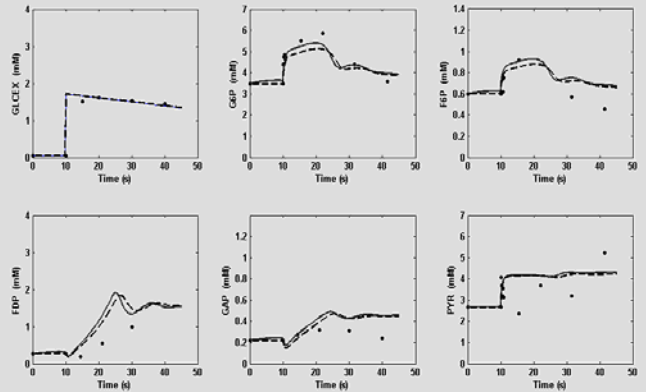


**Figure 2.** Comparison between experimental (symbols) and simulated data (gray solid line: reduced model based on local sensitivity and black dashed line: original model) of the main species: GLCEX (extracellular glucose), G6P (glucose-6-phospate), F6P (fructose-6-phospate), FDP (fructose-1,6-bisphosphate), GAP (glyceradehyde-3-phosphate) and PYR (pyruvate) variation with time in *E. coli*, after a glucose pulse (10 s). For GLCEX the lines are overlapped.
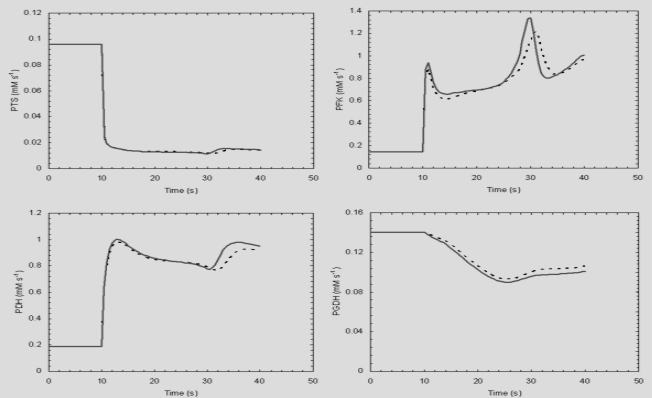


**Figure 3.** Time courses of PTS (phosphotransferase system), PFK (phoshofruuctokinase), PDH (pyruvate dehydrogenase) and PGDH (6-phophogluconate dehydrogenase) fluxes during steady-state conditions and after a glucose pulse (10 s). Comparison between simulated data, gray solid line: reduced model and black dashed line: original model

## CONCLUSIONS AND FUTURE WORK

✓ Dynamic sensitivity analysis was successful used for the complex model structure reduction

✓ Kinetic model parameters can be rejected from the rate expressions with very limited effect on the system behaviour

✓ Up to 41 of 116 parameters are rejected without significant changes in the main species and fluxes

✓ Different global sensitivity methods will be performed to compare with the local sensitivity

**References**

[1] F.R.Sidoli, A.Mantalaris, and S.P.Asprey, Industrial & Engineering Chemistry Research 44 (2005) 868-878.
[2] T.Turanyi, Journal of Mathematical Chemistry 5 (1990) 203-248.
[3] Chassagnole, C., et al. Biotechnology and Bioengineering 79 (2002) 53-73.