Towards a genome-scale kinetic modeling of *Escherichia coli* metabolism

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OVERVIEW

Introduction

In the last times, a great effort has been carried out by researchers to develop different approaches for large-scale kinetic metabolic networks. To reduce the large number of kinetic parameters required by a mechanistic model, approximated kinetic equations are often employed. For example, in (Jamshidi and Palsson, 2008) the authors proposed a approximate modeling approach composed of mass-action kinetics by integration of genomic, proteomic, metabolomic and fluxomic data. One disadvantage of this approach is the need of concentrations of a large number of reaction intermediates. Another approach was developed by Smallbone and co-workers (2010) proposed a method combining two modeling approaches (approximated lin-log kinetics and constraint-based modeling), in which the parameters (elasticities) are given by the negative stoichiometric coefficient for the respective metabolites and/or derived from available kinetic models within online Biomodels database. The reference steady state fluxes are estimated by the FBA approach. However, using the negative stoichiometric coefficient values as parameter and the parameters taken from yeast or other species models are a rough estimation and may result in false predictions. Developing computational approaches of dynamic large-scale metabolic networks is hence a major challenge.

Aims

In the present work, we test an alternative strategy with a relatively small number of kinetic parameters composed by the approximated lin-log kinetics, coupled with a constraint-based method and a priori model reduction based on time scale analysis and a conjunctive fusion approach (Machado et al. 2010), for building a genome-scale kinetic model of *Escherichia coli* metabolism. This workflow was evaluated for the condensed version of a genome-scale network of *E. coli* (Orth et al., 2010).

The presented approach appears to be a promising mechanism for detailed kinetic modeling at the genome-scale of the metabolism of other organisms.

METHODOLOGY

**Metabolic Network of the *E. coli* metabolism**

*Condensed Genome-Scale Core Model includes:*  
- Glycolysis, TCA cycle and Pentose Phosphate Pathway  
- 62 Internal Reactions  
- 14 Exchange Reactions  
- 63 Metabolites

*Available at:*  
http://gcrg.ucsd.edu/In_Silico_Organisms/E_coli/E_coli_SBML

**Flow Chart Illustrating the Methodology Used**

1. Define Metabolic network stoichiometry (N)  
2. Reference Metabolite measurements (C°)  
3. Specify reference fluxes (α°) by FBA  
4. Kinetic Lin-Log/FBA Model  
5. Model Reduction  
6. Parameter Estimates  
7. Full Kinetic Description  
8. Model Validation

RESULTS

**Figure 1.** Comparison of simulated metabolite concentrations over time course produced by the reduced lin-log model (dashed blue line) and the mechanistic model (black solid line) of some metabolites after a glucose impulse (1.67mM) of the reduced core *E. coli* dynamic metabolic network. For MAL, ICT and PI, only simulation results for the model are shown. The prediction relative error for all the metabolites in the network is 23.22%.

**Figure 2.** Comparison of simulated metabolite concentrations over time course produced by the reduced lin-log model (dashed blue line) and the mechanistic model (black solid line) of some metabolites after a glucose impulse (1.67mM) of the reduced core *E. coli* dynamic metabolic network. For MAL, ICT and PI, only simulation results for the model are shown. The prediction relative error for all the metabolites in the network is 31.69%.

SUMMARY AND CONCLUSIONS

- **Automatic tool to help the modeler to create all the rate equations in large-scale kinetic metabolic models is created**
- **A new approach for dynamic modeling of genome-scale *E. coli* metabolic network is presented**
- **Makes this approach scalable to large and even genome-scale metabolic networks**
- **Presented approach appears a promising mechanism to detailed kinetic modeling at the genome-scale of other metabolic networks.**

References


