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 kinetic 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

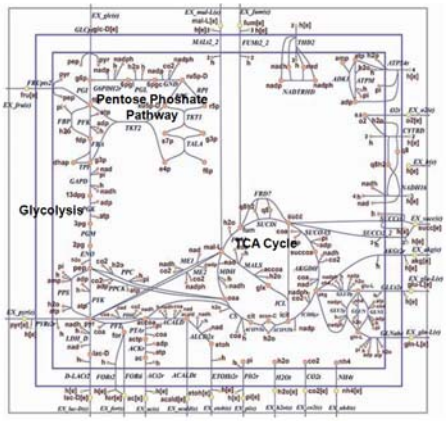
Metabolic Network of the *E. coli* metabolism

Condensed Genome-Scale Core Model includes:

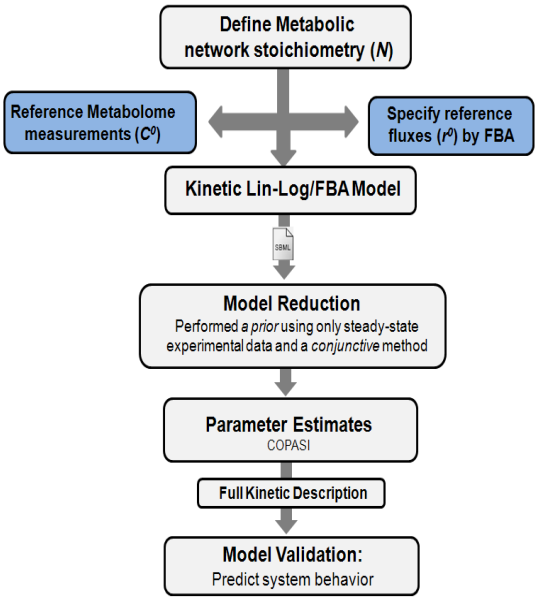
- Glycolysis, TCA cycle and Pentose Phosphate Pathway
- 62 Internal Reactions
- 14 Exchange Reactions
- 63 Metabolites

Available at:

http://gcrg.ucsd.edu/In_Silico_Organisms/E_coli/E_coli_SBML

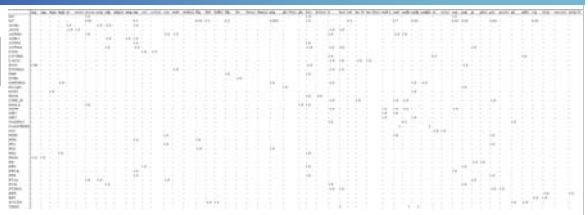


Flow Chart Ilustrating the Methodology Used



RESULTS

1. Reduced Initial Elasticity matrix



2. Comparison of Simulated Dynamics for the reduced metabolic network

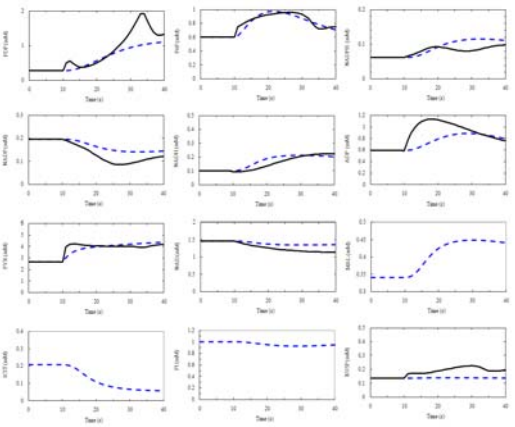


Figure 1. Comparison of simulated metabolite concentrations over time course produced by the reduced lin-log model (dashed blue line) and the mechanistic model (**black solid line**) of some metabolites after a glucose impulse (1.67mM) of the reduced core *E. coli* dynamic metabolic network. For MAL,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

3. Model Validation New Input

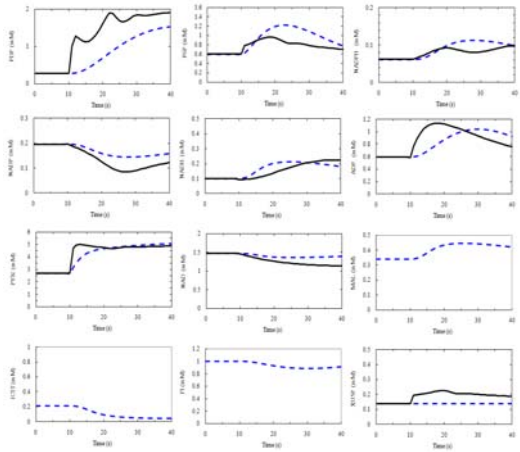


Figure 2. Comparison of simulated metabolite concentrations over time course produced by the reduced lin-log model (dashed blue line) and the mechanistic model (**black solid line**) of some metabolites after a glucose impulse (6mM) of the core *E. coli* dynamic metabolic network. For the MAL, ICIT and PI metabolites, only simulation results for the core 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

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Machado D, Costa RS, Rocha M, Rocha I, Tidor B, Ferreira EC (2010) BioPPN10 Proceedings, 101-115
Smallbone K, Simeonidis E, Swainston N, Mendes P (2010) BMC Systems Biology 4: 6

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