MODELING ENZYMATIC REGULATION IN METABOLIC NETWORKS

DANIEL MACHADO*
Supervisors: Eugénio C. Ferreira, Isabel Rocha, Bruce Tidor
* dmachado@deb.uminho.pt

University of Minho
School of Engineering
Centre of Biological Engineering

Introduction

➔ Systems Biology aims to understand and predict cellular behavior through the creation of computational cell models.

➔ Constraint-based modeling has been used to model metabolic networks at the genome scale [4]. Its simplicity provides scalability but ignores kinetic behavior and enzymatic regulation.

➔ Kinetic models at the genome scale are being recently built, adding approximative kinetic rate laws to constraint-based models [3,6]. However, they still lack enzymatic regulation.

➔ Petri nets are a graphical and mathematical formalism used to model all kinds of biological networks [5].

➔ Extended Petri nets are an extension that include special types of arcs able to model different kinds of interactions.

Objectives

➔ Use Extended Petri nets to model metabolic networks in order to account for regulatory interactions.

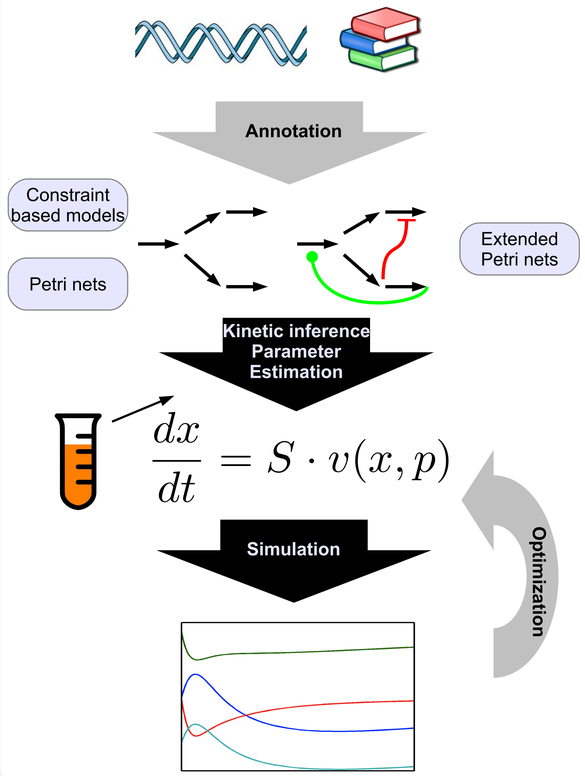
➔ Develop a framework for kinetic inference that generates kinetic models from the underlying topology.

➔ Build an Extended Petri net model of the central carbon metabolism of *E. coli*, based on the available dynamic model [1], and generate kinetic models (with and without enzymatic regulation).

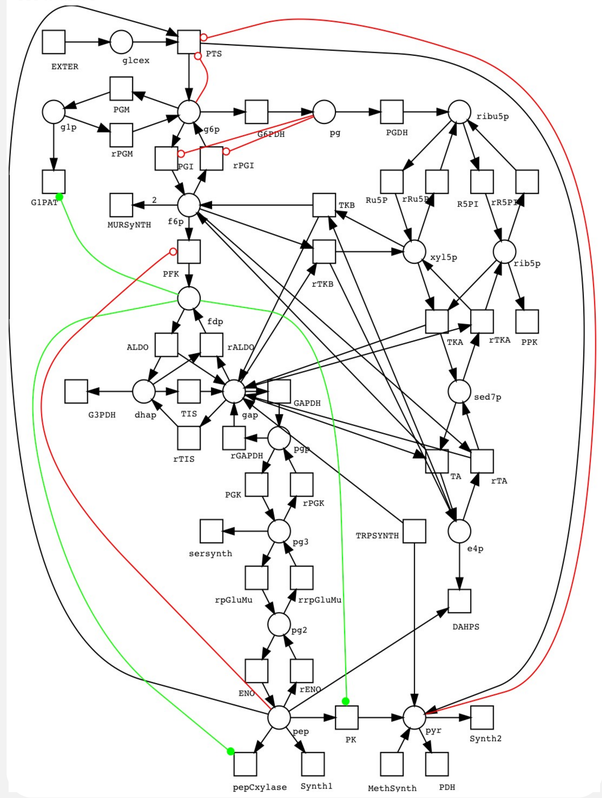
➔ Simulate the metabolic phenotype of mutant strains upon gene knockout and adjustment of enzyme expression levels.

➔ Evaluate the impact of accounting for enzymatic regulation by comparing the results with those obtained with the original model.

Methods



Model



Results

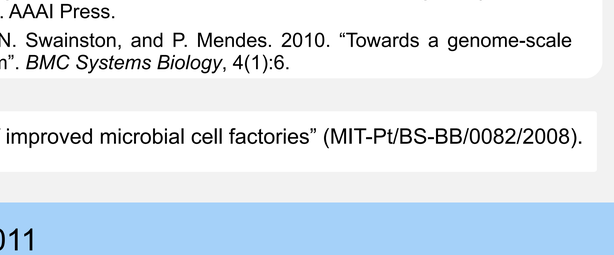
➔ Kinetic models generated with GMA kinetics [2].

➔ Parameters fitted to wild-type steady-state.

➔ New models predicted the mutant phenotypes.

➔ Regulatory effects can only be predicted by the model with regulation.

➔ Example: 5-fold underexpression of *pepCxylase* – only the model with regulation correctly predicted the flux shift confirmed by the original model.



Conclusions

➔ Enzymatic regulatory effects can influence the metabolic flux distribution.

➔ Extended Petri nets can model such effects with activation and inhibition arcs.

➔ They provide a better scaffold to generate large-scale kinetic models.

➔ These models may reveal new targets for rational strain design.

Future work...

➔ Parameter estimation is still the main bottleneck of this process.

➔ The framework can be extended to include transcriptional regulation.

References

[1] C. Chassagnole, N. Noisommit-Rizzi, J.W. Schmid, K. Mauch, and M. Reuss. 2002. "Dynamic modeling of the central carbon metabolism of Escherichia coli". *Biotechnology and Bioengineering,* 79(1):53–73.

[2] F. Horn and R. Jackson. 1972. "General mass action kinetics". *Archive for Rational Mechanics and Analysis*, 47(2):81–116.

[3] N. Jamshidi and B.O. Palsson. 2010. "Mass action stoichiometric simulation models: Incorporating kinetics and regulation into stoichiometric models". *Biophysical Journal*, 98:175–185.

[4] N.D. Price, J.A. Papin, C.H. Schilling, and B.O. Palsson. 2003. "Genome-scale microbial in silico models: the constraints-based approach". *Trends in Biotechnology*, 21(4):162–169.

[5] V.N. Reddy, M.L. Mavrovouniotis, and M.N. Liebman. 1993. "Petri Net Representations in Metabolic Pathways". *In Proceedings of the 1st International Conference on Intelligent Systems for Molecular Biology*, pages 328–336. AAAI Press.

[6] K. Smallbone, E. Simeonidis, N. Swainston, and P. Mendes. 2010. "Towards a genome-scale kinetic model of cellular metabolism". *BMC Systems Biology*, 4(1):6.

Acknowledgments: Research supported by PhD grant SFRH/BD/35215/2007 from FCT and MIT-Portugal Program through the project "Bridging Systems and Synthetic Biology for the development of improved microbial cell factories" (MIT-Pt/BS-BB/0082/2008).