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NOVEL MODELING FORMALISMS AND SIMULATION TOOLS IN COMPUTATIONAL BIOSYSTEMS

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ABSTRACT

Living organisms are complex systems that emerge from the fundamental building blocks of life. Systems Biology is a recent field of science that studies these complex phenomena at the cellular level (Kitano 2002). Understanding the mechanisms of the cell is essential for research and development in several areas such as drug discovery and biotechnological production. In the latter, metabolic engineering is used for building mutant microbial strains with increased productivity of compounds with industrial interest, such as biofuels (Stephanopoulos 1998). Using computational models of cellular metabolism, it is possible to systematically test and predict the optimal manipulations, such as gene knockouts, that produce the ideal phenotype for a specific application. These models are typically built in an iterative cycle of experiment and refinement, by multidisciplinary research teams that include biologists, engineers and computer scientists.

The interconnection between different cellular processes, such as metabolism and genetic regulation, reflects the importance of the holistic approach claimed by the Systems Biology paradigm in replacement of traditional reductionist methods. Although most cellular components have been studied individually, the behavior of the cell emerges from the network-level interaction and requires an integrative analysis. Recent high–throughput methods have generated the so- called omics data (e.g.: genomics, transcriptomics, proteomics, metabolomics, fluxomics) that have allowed the reconstruction of biological networks (Palsson 2006). However, despite the great advances in the area, we are still far from a whole-cell computational model that is able to simulate all the components of a living cell. Due to the enormous size and complexity of intracellular biological networks, computational cell models tend to be partial and focused on the application of interest. Also, due to the multidisciplinarity of the field, these models are based on several different kinds of formalisms. Therefore, it is important to develop a framework with common modeling formalisms, analysis and simulation methods, that is able to accommodate different kinds biological networks, with different types of entities and their interactions, into genome-scale integrated models. Cells are composed by thousands of components that interact in myriad ways. Despite this intricate interconnection it is usual to divide and classify these networks according to biological function. The main types of networks are signaling, gene regulatory and metabolic. Signal transduction is a process for cellular communication where the cell receives and responds to external stimuli through signaling cascades (Gomperts et al. 2009; Albert and Wang 2009). These cascades affect gene regulation, which is the method for controlling gene expression, and consequently several cellular functions (Schlittand and Brazma 2007; Karlebach and Sgamir 2008). Many genes encode enzymes which are responsible for catalyzing biochemical reactions. The complex network of these reactions forms the cellular metabolism that sustains the cell's growth and energy requirements (Steuer and Junker 2009; Palsson 2006).

The objectives of this work, in the context of a PhD thesis, consist in re-search and selection of an appropriate modeling formalism to develop a framework for integration of different biological networks, with focus on regulatory and metabolic networks, and the implementation of suitable analysis, simulation and optimization methods. To achieve these goals, it is necessary to resolve many modeling issues, such as the integration of discrete and continuous events, representation of network topology, support for different levels of abstraction, lack of parameters and model complexity. This framework will be used for the implementation of an integrated model of *E. coli*, a widely used organism for industrial application.

REFERENCES

R. Albert and R.S. Wang. Discrete dynamic modeling of cellular signaling networks. Methods in enzymology, pages 281–306, 2009.
B.D. Gomperts, I.M. Kramer, and P.E.R. Tatham. Signal transduction. Academic Press, 2009.

G. Karlebach and R. Shamir. Modelling and analysis of gene regulatory networks. Nature Reviews Molecular Cell Biology, 9(10):770–780, 2008.
H. Kitano. Systems Biology: A Brief Overview. Science, 295(5560):1662, 2002.
B.O. Palsson. Systems Biology: Properties of Reconstructed Networks. Cambridge University Press, 2006.
T. Schlittand and A. Brazma. Current approaches to gene regulatory network modelling. BMC Bioinformatics, 8(Suppl 6):S9, 2007.
G. Stephanopoulos. Metabolic engineering. Biotechnology and Bioengineering, 58, 1998.
R. Steuer and B.H. Junker. Computational models of metabolism: Stability and regulation in metabolic networks. Advances in Chemical Physics, 142, 2009.