A MULTIDISCIPLINARY SURVEY OF MODELING TECHNIQUES FOR BIOCHEMICAL NETWORKS

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SIXTH FRAMEWORK PROGRAMME

ESIGNET

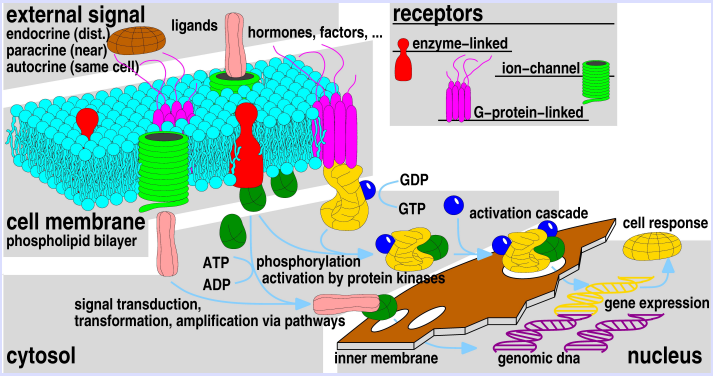
DCU

GOAL OF WORK PRESENTED IN THIS POSTER

The literature on modeling biochemical networks is growing rapidly and the motivations behind different modeling techniques are sometimes quite distant from each other. To clarify the current context, we present a systematic overview of the different philosophies to model biochemical networks.

INTRODUCTION

Cell Signaling networks (CSNs) are bio-chemical systems of interacting molecules in cells. Typically, these systems take as inputs chemical signals generated within the cell or communicated from outside. These trigger a cascade of chemical reactions that result in changes of the state of the cell and (or) generate some chemical output, such as prokaryotic chemotaxis or coordination of cellular division. The diagram below depicts the make-up of a simple signaling network:



MODELING BIOCHEMICAL NETWORKS

The **purpose** of modeling these networks is manifold. From a **theoretical point of view** it allows the exploration of network structures and dynamics, to find emergent properties or to explain the organization and evolution of networks. From a **practical point of view**, in silico experiments can be performed that would be very expensive or impossible to achieve in the laboratory, such as hypothesis-testing with regard to knock-out experiments or overexpression, or checking the validity of a proposed molecular mechanism.

THE DIFFERENT MODELING PHILOSOPHIES

Three modeling philosophies are distinguished and can be summarized as follows:

Mathematics

Some models: *Differential equations / difference equations*

Ideas/assumptions:
- State of CSN expressed in terms of concentrations of its molecular species without inner structure
- Concentrations, progress of time: positive real
- Statistically derived from reaction kinetics

Advantages:
- Efficient calculation at any given point in time
- Handling of fine granularity
- Well understood, analysis tools, software libraries

Statistics

Some models: *Bayesian networks / Stochastic simulation algorithm / Markov chains*

Ideas/assumptions:
- Considering standard deviations from average behaviour
- Introduction of probabilities to weight alternative behaviour
- Influence of nondeterminism to the model emphasised

Advantages:
- Explicitly address uncertainty in molecular processes
- Handling of probability distributions and interpretation
- Powerful analysis tools for systems without feedback`

Computer Science

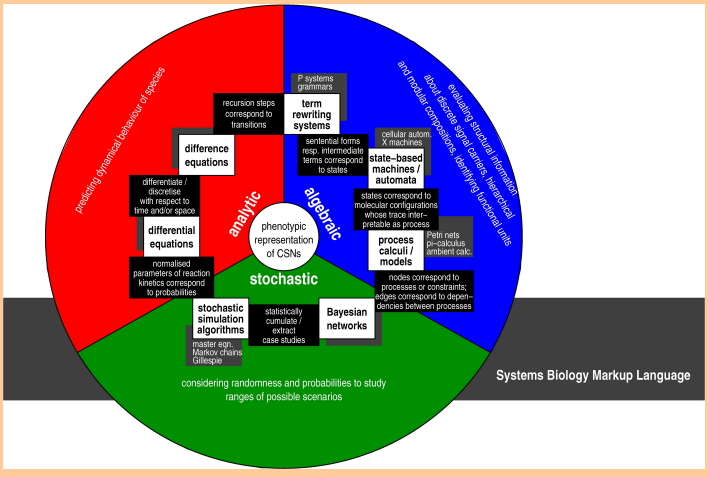
Some models: *Grammar systems, P-Systems / Petri nets, PI-calculus, Ambient-calculus / Abstract machines, Cellular Automata, X-machines*

Ideas/assumptions:
- Finite or recursive enumerable number of atomic objects
- Hierarchical composition of systems based on objects
- Interactions between objects/higher system components modelled explicitly (deterministic or non deterministic)

Advantages:
- Reflect discrete characteristics of cell signalling
- Small amounts of objects with substructures
- Molecular tracing
- Combine detailed tractability with powerful analysis tools

BRIDGES BETWEEN APPROACHES

The aforementioned approaches for representation of CSNs unify different aspects of the view to biological systems. Each approach is of particular interest to answer specific questions. Bridging tools and heterogeneous approaches allows one to combine some of those modeling techniques and thus to take advantages of their differing features. The diagram below presents a map of some of the available bridges and heterogeneous approaches:



NEXT STEP: MODELING THE EVOLUTION OF CSNs

This part of the research deals with the question of how artificial evolution of cellular signalling networks *in silico* can be achieved. So far, an experimental software package has been developed which evolves SBML models according to a given fitness function. Specific techniques based on evolutionary algorithms are currently being developed for this purpose.

THE ESIGNET PROJECT

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The overall goal of this project is to study the computational properties of CSNs by evolving them using methods from evolutionary computation, and to re-apply this understanding in developing new ways to model and predict real CSNs.

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Bibliography: **S. Eilenberg.** *Automata, Languages, and Machines.* Academic Press New York, 1976; **N.J. Eungdamrong, R. Iyengar.** *Modeling Cell Signaling Networks.* Biology of the Cell 96:355-362, 2004; **D.T. Gillespie.** *Exact stochastic simulation of coupled chemical reactions.* Journal of Physical Chemistry 22:403-434, 1977; **T. Hinze, T. Lenser, P. Dittrich.** *A Protein Substructure Based P System for Description and Analysis of Cell Signalling Networks.* In H.J. Hoogeboom et al., Proceedings Seventh Workshop on Membrane Computing, Lecture Notes in Computer Science 4361:409-423, Springer, 2006; **C.A.R. Hoare.** *Communicating Sequential Processes.* Prentice Hall International, 2004; **M. Hucka, A. Finney, B.J. Bornstein, S.M. Keating, B.E. Shapiro, J. Matthews, B.L. Kovitz, M.J. Schilstra, A. Funahashi, J.C. Doyle, H. Kitano.** *The Systems Biology Markup Language (SBML) Project.* Systems Biology 1(1):41-53, 2004; **R. Milner.** *Communicating and Mobile Systems: the Pi-Calculus.* Cambridge University Press, 1999; **G. Paun.** *Membrane Computing: An Introduction.* Natural Computing Series, Springer, 2002; **J.L. Peterson.** *Petri Net Theory and the Modelling of Systems.* Prentice Hall, 1961; **T.E. Turner, S. Schnell, K. Burrage.** *Stochastic approaches for modelling in vivo reactions.* Computational Biology and Chemistry 28:162-178, 2004