Orion: a spatial Multi Agent System framework for Computational Cellular Dynamics of metabolic pathways

Angeletti M (1), Baldoncini A (2), Cannata N (2), Corradini F (2), Culmone R (2), Forcato C (2),

Mattioni M (2), Merelli E (2), Piergallini R (2)

(1) Dipartimento Biologia Molecolare, Cellulare ed Animale, Università di Camerino

(2) Dipartimento di Matematica e Informatica, Università di Camerino

Motivation

Computational models that reproduce and predict the detailed behavior of cellular systems form the Holy Grail of systems biology [1]. Molecular Dynamics represents the most accurate and fundamental approach to cell simulation, taking into account the fundamental physical rules at the atomic level. Due to the incredible high number of atoms that must be considered, it cannot be practically used to simulate whole cell systems. A plethora of other mathematical and computational approaches are therefore applied -often experimentally- in systems biology, aiming at the modeling and simulation of cellular systems and processes (e.g. Ordinary Differential Equations, Partial Differential Equations, Petri Nets, UML, PI calculus, Multi Agent Systems, Dynamic Cellular Automata). Methods can be differentiated [2] according to the resolution levels adopted in space, scale and time representation, presence or absence of stochasticity, level of abstraction and to many other factors. The choice of the method implies critical consequences on the model's engineering cycle of life. Issues like accuracy, availability of formal methods to verify properties of the systems, modularity, questions that the model can answer, intuitiveness, scalability, practicability, usefulness for the biological community, existence of suitable experimental data, should all be accurately weighted when choosing a modeling and simulation framework.

Methods

Multiagent systems (MAS) are considered a suitable framework for modeling and engineering complex systems. Agents and agent society permit to intuitively describe a biological system as a set of active computational components interacting in a dynamic and often unpredictable environment [3]. The adoption of such an approach permits to describe the behavior of the individual components and the rules governing their interactions and to observe the emerging behavior of the running system. Our aim is to replicate in-silico the cell system, having the possibility to observe, perturb and inquire a controlled system in order to discover unknown or not too visible correlations between some causes and effects. The attention of systems biology community has been recently attracted by the importance of considering space in the modeling of cellular phenomena. Overcoming the current limitations of Molecular Dynamics, spatial simulation methods should be able to depict coarse grained shapes and size of molecules and their positions in three dimensional space [2]. In [1], Kitano defines Computational Cellular Dynamics (CCD) as the integration of interaction networks approaches with cell-system biophysics. Most interactionnetwork simulations use the Michaelis-Menten equation or a similar one that assumes a certain ideal condition. However, these assumptions might be unwarranted in a crowded molecular environment in which reactions and molecular movements are constrained in space. In ORION, we therefore propose to provide a physical dimension to the agents representing enzymes and metabolites involved in metabolic pathways. They are collocated and move in a virtual physical 3D space representing the cell cytoplasm. Each metabolic agent acts autonomously and move following Brownian Motion and other laws governing the meso-scale. Enzymes are able to recognize their possible counterparts in known metabolic reactions. The knowledge concerning metabolic pathways is mined from related databases and integrated into a developed domain-specific ontology. When an enzyme agent physically meet, in the space, a substrate agent involved in one of its possible reactions, both undergo to some planned destruction and a new specie of agent arose representing the intermediate complex. According to the related reaction simulation timing, the latter is also in turn subsequently destroyed to give birth to a product and enzyme agents.

Results

We developed an operational computational description of enzyme and metabolites behavior. Issues like movements, interactions and metabolic reactions have been described from the agent point of view. The implementation of the framework on the Hermes agent platform [4] is under development. Another important target of ORION is that of providing, in the context of the LITBIO virtual bioinformatics laboratory (http://www.litbio.org), a workbench to systems biologist on which to engineer, refine and validate models and simulations.

Contact email: nicola.cannata@unicam.it

References

1. Kitano H. Computational cellular dynamics: a network-physics integral. Nature Reviews Molecular Cell Biology. Vol 7, page 163, 2006
2. Takahashi K, Arjunan SN, Tomita M. Space in systems biology of signaling pathways--towards intracellular molecular crowding in silico. FEBS Lett. 579(8):1783-8. 2005.
3. N. Cannata, F. Corradini, E. Merelli, A. Omicini, and A. Ricci. An agent-oriented conceptual framework for systems biology. In T. Comp. Sys. Biology, volume 3737 of LNCS, pages 105-122, 2005.
4. F. Corradini and E. Merelli. Hermes: agent-based middleware for mobile computing. LNCS, 3465:234-270, 2005.

Supplementary informations

This work is supported by the FIRB project Laboratory of Interdisciplinary Technologies in Bioinformatics (LITBIO).