Spatial behavioral modeling and simulation of metabolic pathways with Orion

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Motivation

With the omics revolution the focus of biomolecular research has shifted from single molecules to whole populations, taking into account the different kinds of molecules that determinate cell's development and behavior. The support of bioinformatics in managing and analyzing the astonishing amount of molecular data is indisputable. But now systems biology is establishing itself as the natural completion of the bioinformatics efforts, concentrating on the dynamic aspects of whole systems.

Putting together all the pieces, it is becoming possible to develop dynamic models of cellular processes. The classical mathematical approaches based on differential equations, even when successfully applied to limited simplified biomolecular systems cannot scale to higher levels of complexity. When more realistic sets of molecules are taken into account, new computational paradigms are requested. The cells as computation abstraction, which models a cell as the emergent behavior of interacting computational entities corresponding to the molecules is inherently compositional.

Multi Agent Systems, in particular, already proved to be a suitable method to model a complex system in which the behavior of the whole system emerges from the behavior and local interactions of a set of autonomous and reactive computational elements, able to perceive their surrounding environment and to react accordingly.

Methods

Orion is a Multi Agent System framework for modeling and simulation of metabolic pathways. Enzymes, metabolites and their complexes involved in metabolic pathways, are impersonated by software agents collocated in a three dimensional virtual space representing a portion of a cellular compartment. The molecules are represented as spheres with their molecular weight and a proportional radius estimated with Richards formula. We consider the molecules at mesoscale, abstracting from their 3D structure.

At this resolution the single atoms and their interactions disappear and the predominant law which drives the movement is considered the Brownian motion. The diffusion speed of molecules is calculated according to Stokes-Einstein relation, considering the temperature and viscosity of the medium and the radius of the molecule. The direction of movement, at every movement step performed by a molecule, is chosen randomly. When an enzyme or a complex, perceives the vicinity of an affine metabolite than they can interact in a biochemical reaction. Enzymes and complexes are the active entities of the system, whether metabolites are the passive ones. All the necessary knowledge concerning the reactions is collected from biochemical databases (e.g. Brenda, KEGG, BioModels) and organized into a XML database. Orion reads the list of molecules, their concentrations and the reactions in which they are involved from a SBML input file. The reactions are further detailed with the list of one-to-one interactions composing it, according to Michaelis-Menten kinetics. In each interaction the Km constant gives a measure of the probability that the interaction could actually take place. If the interaction is the final one of a reaction, which should give rise to the actual products and should free again the enzyme, then 1/Kcat indicates the number of simulation steps (ms) that must be waited before the reaction is completed.

Results

Orion has been written in Java and implemented on the Hermes MAS middleware. The XML database has been developed with the eXist XML databases management system. The consistency of the system is maintained thanks to a global clock managed by a Service agent, always compared from molecule agents with their inner clock to decide if they are allowed to perform a simulation step or they must wait that all the molecules have accomplished their previous step. The Service agent manages also the whole virtual space solving concurrency and coordination problems among the molecule agents and returning to actor molecules the list of molecules surrounding them.

Metabolite agents which have been chosen to take part in a reaction are locked and they are not able to move until a decision on their fate is actually taken. Regions of space already chosen as a destination of a movement step of molecules are not available to other molecules. The output of a simulation is a XML file with, for each time step, the list of all the existing species of molecules with their cardinality.

If the simulation is started in verbose mode, then for each time step it is provided also the position of all the

molecules. The output can be visualized as a time graph delineating the variations of the quantities of the molecular species. Another viewer takes as input the verbose results showing in the 3D virtual cell's space the molecules' spheres with different colors and dimensions in the various time points.
The first metabolic model developed with Orion describes a small cytoplasmatic portion of a yeast cell, in which it is simulated the glycolytic pathway.
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