4DiCeS: Four-Dimensional Cell Simulation and Visualization

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Keywords. Stochastic Cell Simulation, Signal Transduction, Systems Biology, CAVE, Visualization

Introduction

Cells must be able to sense and respond to their environment, in particular to communicate with other cells. The exchange of information, called signal transduction, between and inside cells is essential for their survival. Modelling of cellular processes, such as signal transduction often involves the representation of biochemical reactions with very small numbers of molecules. Deterministic approaches to a continuous-variation in the concentrations of molecular species by using systems of coupled ordinary differential equations (ODE) fail. In order to correctly model the dynamics of cellular signalling, stochastic effects have to be taken into account. Stochastic simulations try to imitate biophysically and biochemically realistic processes by using computational methods. There have been already several attempts to use Monte Carlo simulations for the study of biochemical kinetics. However, these approaches possess a major problem. Although these algorithms are elegant and strait forward, the understanding of a model and its transformation to the simulation both become rather complicated. The user here has to handle with abstract parameters not easily found in the lab. In our computational approach we examine the important means by which cells communicate and work, using modelling and simulation of cellular behaviour, the interpretation of information transferred in as well as between cells, and the interpretation of signals they receive.

Signal Transduction

Signal reception starts at the point where an extra-cellular signal (first messenger) binds to a target molecule in the cellular membrane or within the cell. In many cases, the target molecule is a receptor protein, and is typically triggered by just one specific type of signal. It carries out the primary transduction step: receiving the external signal, and creating a new intracellular signal in response. This is only the beginning result in a subsequent chain of intracellular signal transduction processes. The information is passed and amplified from one set of intracellular signalling molecules to another, each set causing the production of the next. The final outcome is a cellular response, as e.g. the activation of a metabolic enzyme, gene expression, or changes within the cytoskeleton. Signal transduction is based on dynamic spatio-temporal networks which can not be understood any more intuitively without the help of computational modelling and simulation.

Four-Dimensional Cell Simulator (4DiCeS)

In our approach [1] the cell is divided into a three dimensional grid of sub volumes, called volume elements (VE)s. To simulate signal transduction of whole cells, cellular and sub-cellular structures have to be considered. All cellular boundaries are membranes – motional lipid bi-layers with bound reactive and transductive enzymes. Therefore, a two dimensional diffusion of molecules on the membranes and a three dimensional one in free solution exists. Especially for small numbers of particles, Random Walk [2] simulations show their benefits in realistically reflecting biophysical and biochemical behaviour. To simulate random walk, each particle has to be assigned either one angle in two dimensions or two angles in three dimensions, a diffusion distance and coordinates in space. The angles and the diffusion distance are calculated from random numbers [3] and during a defined time step they transform the old coordinates into the new ones. This Random Walk algorithm will scale to $O(M)$, where M is the number of molecules.

For large M a different Random Walk approach is used, to make the computation more efficient. In this approach equations [4] determine how many particles stay in their "home" VE or spread over to all the neighbouring VEs. This takes $O(V)$ time for V sub-volumes. The problem with this procedure is the assumption of equally distributed particles in every VE and the loss of distinct coordinates for every molecule, if the VE size is not adjusted appropriately to the mean diffusion distance of a particle species.

Reactions then take place with a well known Monte-Carlo method on simulating chemical reactions [5]. Instead of computing the whole cell at once, this approach uses the three dimensional grid and simulates signal

transduction processes on every single VE. A controlling function passes the amount of particles per VE to a linked chemical reaction processor, which then returns the resulting amounts of particles within the origin VE and its neighbours.
After an initial parsing process of the reaction equations and spatial information on the amount of every particle over all species within all VEs, the simulation starts by alternating diffusion and reaction processes over finite time-steps.

Visualization

After every finite time step the current cellular representation is stored for further processing. Since the modelling and simulation environment is three-dimensional, the information representation has also three dimensions. Currently, the visualization output can be viewed as a grid of boxes (Fig. 1), representing every VE of the cellular volume. The colour of every box is a mixture of different colours for different particle species and their amount, coded as shades of the specific used particle colour. The whole system can be transformed and rotated, whiles it is possible to use cutting planes to look inside the cell and to switch every particle species on or off.

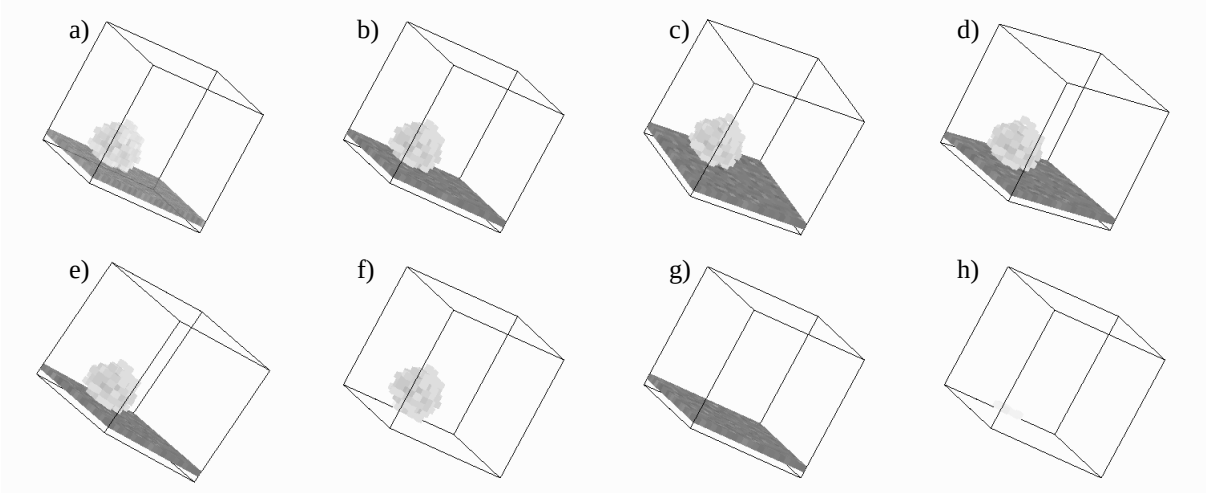

Fig. 1: Six snapshots from the three dimensional 4DiCeS viewer. The pictures show a) a transparent, b-e) different viewing angles and f-h) switching between different particle species.

Future Work

The project in progress consists of stand-alone modules at present. These modules have to be embedded in an overall processing environment, which ought to be able to parse commonly used cellular simulation input formats and store the results within a to be build data-base. Currently, we are including an output interface for the high-end visualization in the fully immersive (walk in) automatic virtual display environment (CAVE) [6].

Acknowledgements

This work is supported by a grant from the Ministry of Science and Research of North-Rhine Westphalia (NRW) to the International NRW Graduate School in Bioinformatics and Genome Research.

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