Multi-Resolution Spatial Simulation for Molecular Crowding

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1 INTRODUCTION

Recent findings emphasize the central role space plays in inter- and intracellular dynamics, for example that molecular crowding, i.e. a dense population of macromolecules, alters diffusion, hydration, and other properties of individual molecules.

The simulation of this type of phenomena is rather costly. To reduce the effort required in simulation, different approaches are already exploited in computational biology. One is to trade accuracy for efficiency. Among other approaches, this can be done by a combination of different simulation algorithms, e.g. a numerical integration algorithm and a stochastic discrete event approach [1]. In both cases temporal resolution forms the basis. The principal idea of this multi-resolution simulation can be adopted for the spatial variant. However, in this case time and space has to be taken into account.

When simulating macromolecular crowding it makes sense to simulate the larger molecules individually and the smaller ones with less detail, i.e. at population level. This combination of population, i.e. concentration-based, and individual-based approaches leads us to multi-level modeling and simulation.

2 MACROMOLECULAR CROWDING

Whereas interactions of macromolecular species within in-vitro experiments that are carried out in dilute solutions are not hampered by other macromolecules (e.g. actin filaments or ribosomes), in living cells macromolecules can occupy up to 30% - 40% of the available volume. This effect is called macromolecular crowding and can influence diffusion coefficients for species and effective rates for reactions taking place among species [2].

For diffusion coefficients, with increasing concentration of crowding molecules the movement of particles is perturbed and a reduction of the coefficients by a factor of ten is estimated [3]. In contrast, reaction constants increase as the particles are less randomly distributed compared to a solution without other macromolecules, resulting in a higher effective concentration and an increased probability for a reactive collision. However, it must be differentiated between reactions whose participating species diffuse fast enough that the rate limiting component is the reaction process itself and reactions including slowly diffusing species (diffusion-limited reactions). In the latter case the effective reaction constant can decrease under crowding conditions [3]. As also
mentioned by Ellis, the crowding effect on reaction activity only applies to entities of a specific size, whereas the change of the diffusion constant is present for all particles. For example, while an ion is too small for macromolecular crowding to exert effects on its activity the movement is still affected by the presence of other molecules that occupy space.

To simulate the effect of crowding on test solutes within experiments, background molecules in high concentrations are introduced that preferentially can only interact with the test particle via steric repulsion without undergoing a reaction, i.e. the interaction is limited to non-reactive collisions.

A good example for the effect of crowding conditions is the competition between protein folding and aggregation with molecular chaperones as studied in [4]. Chaperone proteins assist in the folding and unfolding process of other proteins by preventing the aggregation of these structures to non-functional units. Kinjo and Takeda show that crowding enhances the folding process of slow-folding proteins and inhibit their aggregation with the help of chaperones.

3 MULTI-ALGORITHM MULTI-RESOLUTION SIMULATION

The proposed multi-algorithm, multi-resolution simulator will focus on the combination of discrete-event with individual-based algorithms. Central to our approach is a coordinator responsible for the synchronization, but first let us introduce the two algorithms that we use in our case study. The algorithm for the lattice (population) level is based on the Next Subvolume Method (NSM) [5], whereas the algorithm used for the individual level is currently a rather simplistic one assuming random movements. Spherical macro objects move through space with position updates taking place in fixed time intervals. The model description for this abstraction level provides a movement function and a value representing the update interval for the individuals. The simulator uses this information to perform collision detection, update the position of the objects, and to calculate the new movement vectors and the next event times. As this implementation of the individual simulator is very basic, more complex algorithms are currently under development.

Both levels of abstraction can influence each other in numerous ways.

*Individual level → lattice level* Macromolecules occupy a certain amount of volume. With their movement through space, the volume that is available for the small molecules and their interactions changes. Thus, the density of the particles in a sub-volume is increased or decreased, which affect the reaction activity at population level because the free volume is taken into account when calculating reaction rates. As the available volume of a lattice cell decreases, particles that are currently inside the cell get distributed among its neighbors. This differs from normal diffusion as particles get ”pushed” out of the cell by the object. Furthermore, the location of the macromolecules will have an impact into which adjacent cell a particle is more likely to diffuse. Also reactions between macromolecules and particles can take place, thereby, those particles are no longer available within the sub-volume for other reactions.
Lattice level → individual level The population level can also influence the behavior of the macromolecules by, for example, providing reaction and binding partners. To determine the number of possible reaction partners is not trivial as a macromolecule might cover more than one sub-volume. It is also possible that, given different sub-volumes, the movement characteristics (speed and direction) of an individual might be influenced by the concentrations in these sub-volumes.

3.1 The Coordinator Component

The coordinator represents the connecting part between the different algorithms operating on distinct levels of abstraction and controls the simulation process. It keeps track of the next event times for the involved algorithms and schedules the simulation part with the least event time to process next. The coordinator also manages the interactions between the algorithms and updates the appropriate models dynamically to reflect changes made at another abstraction level.

Cell update at lattice level With the introduction of moving individual objects the spatial configuration at the lattice level changes with each update at the individual level. The volume of a lattice cell can increase or decrease depending on the movement of the macro objects. To dynamically change the available volume of a cell a subdivision algorithm based on an octree partitioning is introduced to determine the fraction of the total cell volume that is occupied by the individual object. The higher the subdivision depth is chosen, the finer the macro object can be approximated at the lattice level but this also increases the effort for the subdivision process. In the currently implemented NSM algorithm for the lattice level the volume of a cell is used to calculate both the diffusion and reaction rates whereas the rate is inversely proportional to the volume. Furthermore, the free area between two neighboring cells and the fraction of the cell that is occupied by an individual are taken into account when processing a diffusion event. In the basic NSM the probability for selecting a specific neighbor cell is $1/N$ with $N$ being the total number of neighbors. Now, collisions with the macro object must be taken into account. Therefore, the process for determining the diffusion target consists of two phases: First, a test if a collision occurs is performed; if this is not the case, a target cell is selected with respect to the fraction of the border between the source and each neighbor that is occupied by a macro object.

As mentioned before, an additional effect of a macro object entering a cell is a displacement of particles inside the cell and the lattice level algorithm has to account for this. Therefore, the NSM algorithm has been extended to handle this by distributing particles from cells that are completely occupied by the macro object among the cells at its "rim", i.e. among the cells partly occupied by the object.

Not only macro objects exclude space, but also elements at lattice level. To simulate crowding effects at this level, a parameter that represents the amount of volume an element occupies has been introduced. Thus, the volume of a cell is not only reduced by a macro object but also by the elements inside the cell. For now, this parameter is only considered during the diffusion step of the NSM algorithm. A particle can only diffuse into a neighboring cell if there is enough available space. Inside a cell the volume
of an element is assumed to be negligible compared to the volume of the cell, so this parameter does not influence the calculation of reaction and diffusion rates.

**Inter Reactions** Additionally to intra reactions at lattice level and individual level, reactions might also take place between elements of different levels. For example, a small cofactor can bind to an apoenzyme and assist during transformation of the enzyme to its active state (holoenzyme). The lattice level simulator should support this inter reactions by providing information about species concentration in cells that are partly occupied by a specific macro object. The coordinator can then determine whether and when a next interaction might take place between this macro object and an element of a species that is simulated at lattice level.

Furthermore, as an individual can occupy a number of cells it is possible to include orientation dependent reactions at the individual level by mapping a specific binding site of a macromolecule to a lattice cell.

### 4 First results

First experimental results show that reaction and diffusion activity inside crowded environments are altered under crowding conditions. Experiments were performed with varying numbers of crowding agents. With an excluded volume of approximately 30% the reaction activity is increased by factors of three and four. To observe the influence on diffusion activity, particles were initially placed at one corner of a grid and immobile reaction partners at the opposite corner. With this setup and an increasing number of crowders, the average time until the first reaction occurs inside the volume can increase by factors of two and three.

Performance comparisons with purely individual and lattice based simulation algorithm are part of the ongoing work. We expect that the presented approach is suitable for models that include a high number of background molecules that does not need to be simulated individually, but also few molecules of larger size or that have a specific movement pattern (e.g. active transportation along microtubuli). These molecules can then be simulated individually with high detail.

### References