Spatial-dependant Pathways

In many pathways part of its species is transported across or through the cell’s membrane while the rest are located in the cytosol. This particular spatial organization might give rise to gradients in the cytosolic substances concentrations \[\tau^2\]. It is found that gradients are more significant for larger cells \[\tau\]. Moreover while some molecules are present in large quantities, others might be in low number increasing the fluctuations of the system. In some cases these might not be properly modelled by a system of PDEs, which are based on the mass action law reactive dynamics.

The Model

To tackle the different time and space scales involved we chose a Mesoscopic level of simulation to avoid unattainable molecular dynamics simulations yet still working at the particle level (in contrast to PDE models that work with concentrations).

- Space is discretised regularly in a Cartesian lattice (see Figure 2). The diffusion of particles is carried out according Chopard multiparticle diffusion method [1].
- On each lattice site, an stochastic mesoscopic reaction method is run. Our choice is Gillespie reaction algorithm [2].
- Reaction and Diffusion processes are executed alternately \[\tau^2\]. The duration of the reaction intervals are determined by the diffusion time step defined as: \(\tau^2 = (1/2d^2)\lambda^2\), where \(d\) is dimensionality, \(\lambda\) is lattice spacing and \(D\) the diffusion coefficient.

We have chosen Gillespie reaction algorithm because it is a computational feasible mesoscopic model of the Master Equation (ME) that describes the stochastic trajectory of a set of chemical reactions. First a reaction \(i\) is chosen following the probability distribution: \(P_R(i) = a_i/\sum a\), where \(a\) is the propensity function.

And then the virtual occurrence time \(t\) is assigned following the probability distribution:

\[P(t) = \sum a_i \exp(-\sum a)\ dt.

This method alone reproduces the ME results exactly, thus it can cope with any reaction system, provided it fulfills the requirements: reaction limited and well-stirred and initially homogeneous.

For the diffusion, Chopard multiparticle method enhances the diffusion of particles by partitioning the molecules into groups of particles present at a site \(i\) and moving them to its neighbours, provided enough particles are present, otherwise each particle is moved individually.

PTS case study

Phosphoenolpyruvate:glycose phosphotransferase (PTS) is a small pathway found in most of bacteria, such as E. coli, involved in the glucose metabolism.

External glucose (Glc) is transported to the interior of the cell by the membrane-bound protein IICB. The pathway (PTS) is initiated by a phosphoenolpyruvate (PEP), which is passed to the IICB protein through the PTS pathway.

Conclusions

We present a method to cope with spatial inhomogeneities as well as with stochastic fluctuations of reactions from a mesoscopic simulation point of view. The membrane is a principal source of inhomogeneity and error. Reaction processes on the membrane are only approximately simulated, due to homogeneity assumption on each lattice site implicit in Gillespie method, and diffusion also undergoes side effects from the fluxes through the membrane.

The lattice size effects, which affects accuracy and computational cost, and the membrane errors are two major issues to research in the near future.

Finally, in certain cases, especially with fast decay reaction, the diffusion time step \(\tau\) interferes with the reaction process.

Future Work

- Modify (diffusion) method to cope with stiff systems by varying \(\tau\) parameter.
- Combine non-planar surface and bulk diffusion using a cartesian grid, for membrane error.
- Study lattice granularity effects for diffusion limited systems and complex geometries.
- Hybridisation of the method: run best method at convenient site and time.
- Using a membrane-cytosolic pathway where stochastic effects become evident to validate the spatial and stochastic properties that PDE models cannot account for.

References


Figure 1. Gradients obtained with the deterministic PDE model by Blom (2). Membrane is located at \(x=1\), center of spherical cell at \(x=0\). Bottom-right figure are membrane-bound concentrations in time.

Figure 2. Gradient profile of a decay reaction where \(A\) is confined to the membrane. We notice two sources of errors:

1. The membrane-cytosol reaction have a different effective rate due to the homogeneous assumption of Gillespie algorithm (vertical shift).
2. The diffusion of released membrane particles causes the horizontal shift as particles diffuse on average from the center of the lattice site, not from the membrane surface.

Figure 3. Mass evolution in time per species in the PTS system. Mass is shown on y axis, time on x axis. Stochastic results are shown in solid lines, while Deterministic are the dashed lines. Notice how some proteins decay or increase at different rate. These shifts might be omitted on the membrane reactions.

Figure 4. Simple membrane-bound decay reaction. Notice the different decay rate at the membrane (\(\tau\)), and the horizontal shift as a result of the errors introduced by the membrane reactions.

Figure 5. Mass evolution in time per species in the PTS system. Mass is shown on y axis, time on x axis. Stochastic results are shown in solid lines, while Deterministic are the dashed lines. Notice how some proteins decay or increase at different rate. These shifts might be omitted on the membrane reactions.