

Multiscale Computational Methods for Silicon Cell

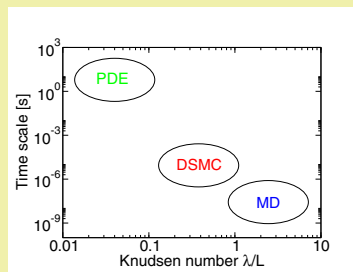
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Objective

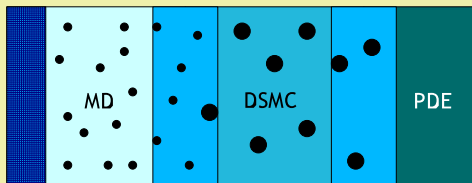
The biological phenomena occurring in a living cell span over 8-10 orders of magnitude in space and time. Particle-based simulation techniques such as molecular (MD) or Brownian dynamics (BD) are usually too computationally expensive for the scales we are interested in. Therefore, it is inevitable to develop *multi-scale* models, which could *couple* different approaches appropriate for their respective scales.

Atomistic-continuum coupling

In fluid dynamics the continuum description fails when the mean free path λ of molecules is comparable to the characteristic size of the system L .



Our aim. As a *proof of concept* for hybrid modeling of biological processes we will extend the model of Nedeia et al. [2] for one-dimensional heat flow in a nanochannel. The goal is to develop a coupled MD-DSMC-PDE method.



Chemical reaction

Intracellular phenomena such as gene regulation or bacterial chemotaxis often include a mixture of very small and large number of components (e.g. few copies of regulatory proteins compared to dozens of gene expression products). Multi-scale methods should be able to describe stochastic fluctuations and yet effectively simulate reasonable biological time scales.

The Stochastic Simulation Algorithm (SSA) from Gillespie [3] accounts for both stochasticity of chemical reactions and discreteness of reactants. It is a kinetic Monte Carlo scheme that solves numerically the Chemical Master Equation (CME). The system is characterized by the dynamical state $X(t) = (X_1(t), \dots, X_N(t))$ where:

- $X_i(t)$ = number of molecules S_i
- Propensity function a_j , where $a_j(X(t))dt$ = probability that given the state $X(t)$ the reaction of type j will occur in $[t, t + dt]$

The method does not include spatial information and assumes that the system is *well-mixed*. The timestep is taken such that only *one reaction* occurs in the time interval. Therefore the SSA is computationally inefficient when the number of molecules or the propensity function is large.

Multi-scale simulation of chemical reacting system can be built hierarchically based on the number of interacting species N and on the magnitude P of propensity function $a_i(X)$ [1].

Model	Discrete Cont.	Fluctuations	Technique	N	P	Comp. Time
CME	D	yes	SSA/ τ -leap	small		very long
CLE	C	yes	SDE	medium		medium
LMA	C	no	ODE	large		short

CME - Chemical Master Equation, CLE - Chemical Langevin Equation, LMA - Law of Mass Action

Hybrid model in space and time

The multi-scale methods for coupled chemical reactions as presented above do not account for spatial effects. Nor does the Particle-PDE coupled model include chemical reactions. For that coupling we consider:

- Green's Function Reaction Dynamics [4] - state parameters comparable to DSMC method,
- Lattice Gas Automata for diffusion with Gillespie-like simulation on lattice nodes for reactions,
- Reaction-diffusion PDE - a natural incorporation of reactions in continuum limit.

References

- [1] K. Burrage et al. A multi-scaled approach for simulating chemical reaction systems. *Progress in Biophysics & Molecular Biology*, 85:217-234, 2004.
- [2] S.V. Nedeia et al. Hybrid method coupling MD and MC simulations for the properties of a hard sphere gas in a micro-nanochannel. *in press*, 2004.
- [3] D.T. Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *J. Comp. Phys.*, 22:403-434, 1976.
- [4] J. van Zon and P.R. ten Wolde. Green's function reaction dynamics: a new approach to simulate biochemical networks at the particle level and in time and space. *q-bio.MN/0404002*, 2004.

CellMath: Mathematics and Computation for the Systems Biology of Cells

The aim of the project is to develop, implement, and validate mathematical and computational techniques for the systems biology of the cell. Biologists and mathematicians together will formulate realistic mathematical models of metabolic and regulatory networks including intrinsic spatial non-homogeneity. The planned outcome of the project are computational and mathematical algorithms, implemented in auto-adaptive computational models, and simulation results for the functioning of living cells.

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