Technical report: Hybrid simulations in STEPS

Authors: Iain Hepburn, Haroon Anwar and Erik De Schutter

Hybrid Simulations in STEPS

Software design

The software design in STEPS (Hepburn et al., 2012) makes it possible to simulate the same model description on tetrahedral meshes using either a spatial deterministic or spatial stochastic method, and well-mixed solutions are also available. Spatial stochastic simulations are used to investigate systems in what is generally perceived to be the most realistic representation of their behavior possible in this framework. In addition to these methods, it is possible to combine a stochastic with a deterministic simulation in one Python script ('hybrid simulations'), and even though the stochastic and deterministic solvers are technically separate and solved in series, they can be coupled very closely with frequent communication between the two. Such simulations make it possible to isolate separate aspects of a model (e.g. membrane channels and calcium dynamics), simulate one stochastically while keeping the other deterministic and therefore determine the stochasticity of each aspect individually. While there were many obstacles to overcome in building such simulations, technically and conceptually, successful implementation of this method was crucial for a study of stochastic calcium spike generation (Anwar et al., 2013) .

Difficulties become apparent in hybrid simulations at the point where the deterministic and stochastic meet. In (Anwar et al., 2013) this point was at the interaction between calcium molecules near the membrane and channels within the membrane. In a sense calcium ions could exist as a whole number in stochastic calculations and a fractional number in deterministic calculations. The approach to dealing with this problem was to convert, tetrahedron by tetrahedron at the surface, the concentration used in the deterministic simulation to a whole number for use in the stochastic simulation, and vice-versa, at every simulation time-step. Not only, therefore, was the conversion an important consideration, but also the order in which calculations were processed during a time-step. Due to the choice of event order and the frequent conversion between integers and floating point numbers it was important to choose a small time-step that did not give discrepancies in results if lowered, but approximately the largest possible that gave accurate results for considerations of overall simulation time. The simulation time-step was chosen to be 20 μs in every simulation, for consistency, and found not to produce significantly different behavior when tested at lower time-steps (typically 5 μs or 2 μs). In addition it was tested that results did not significantly differ if the order that events were processed was reversed.

Stochastic model with Well-Mixed conditions and 1D diffusion

The stochastic model with well-mixed conditions and 1D diffusion in (Anwar et al., 2013) was constructed as a hybrid model. A cylinder with concentric shells (depth of submembrane shell was 0.1 μm, depth of all other shells was 0.2 μm) was used instead of the tetrahedral meshes used in the detailed calcium dynamics model simulations. For the dendrite well-mixed model the number of shells depended on the diameter of each compartment. Ion channels on the surface membrane and different species molecules in each of the concentric shells had no

spatial separation. Diffusion of molecules was permitted only in one dimension i.e. across the surface shared by any of two consecutive shells. At each time step, the resulting current across the membrane from the well-mixed model was injected uniformly over the surface triangles of the mesh to allow 'Tetexact' solver to compute the membrane potential. The sequence of steps involved in simulations of this hybrid model is briefly described in a flow chart in Figure A.

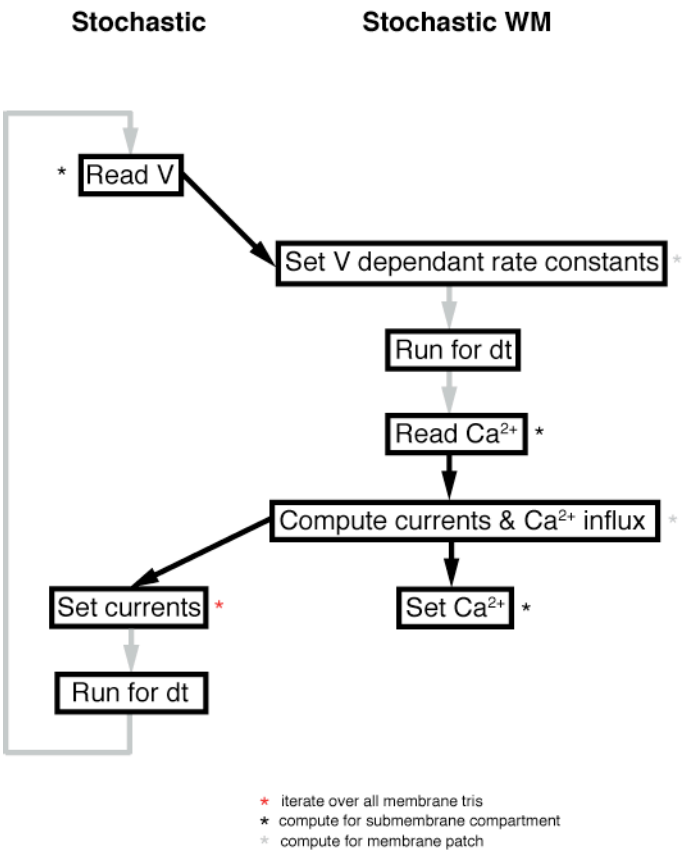

Figure A: Stochastic model with well-mixed conditions and 1D diffusion hybrid simulation flowchart.
Flow chart describing the sequence of steps executed during the simulations along with the communication between spatial stochastic solver ('Tetexact') and stochastic well-mixed solver ('Wmdirect'). The arrows in black show dependence whereas the arrows in gray show sequence of computations.

Deterministic channels, stochastic calcium

A hybrid model was constructed to show the effect of stochastic calcium in models of dendritic calcium spike generation in (Anwar et al., 2013). Although the ion channels were simulated deterministically, the distribution of these channels over the surface triangles of the mesh was kept discrete, matching the distribution recorded from the full stochastic model for each

compartment. The sequence of steps involved in simulations of this hybrid model is shown in a flow chart in Figure B.

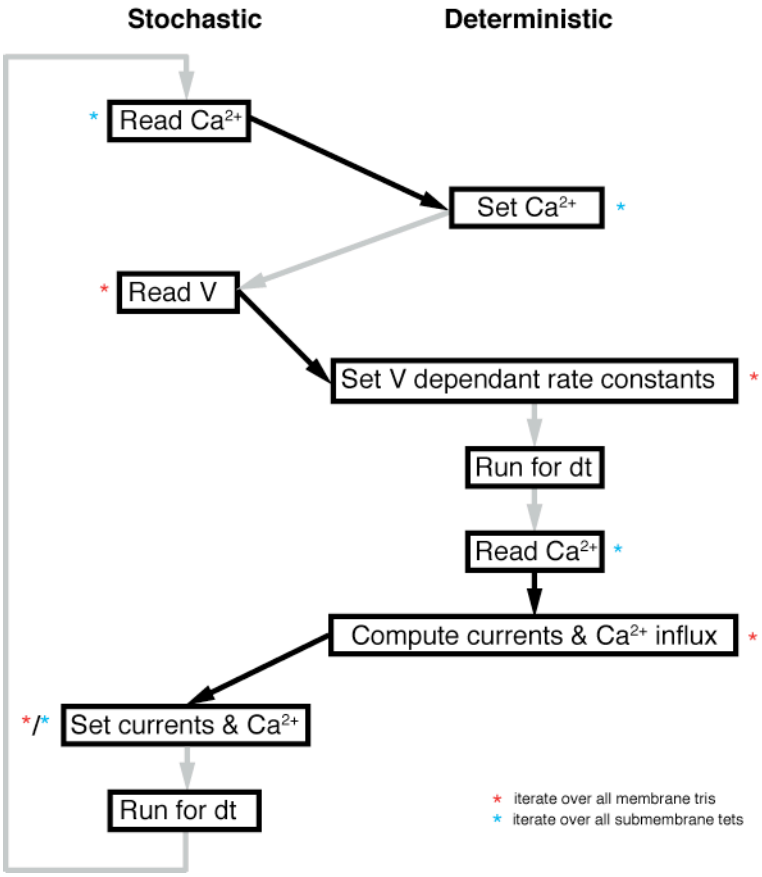

Figure B: Deterministic channels with stochastic component hybrid simulation flowchart.
Flow chart describing the sequence of steps executed during the simulations along with the communication between spatial stochastic solver ('Tetexact') and spatial deterministic well-mixed solver ('TetODE'). The arrows in black show dependance whereas the arrows in gray show sequence of computations.

It was not feasible to make only the calcium-activation of the calcium-activated channels stochastic, whilst simulating the voltage-dependent transitions deterministically, because approaches to this problem where found to affect channel activation detrimentally. When maintaining the full Markov chain, because stochastic activation requires discrete populations, any small deterministic continuous voltage-dependent activation for each channel during a time-step (increasing population of O states) would usually be 'reset' (to zero population of the O state) for the stochastic simulation, and so activation in the system was lost, or with a small chance of fully activating (1 population of O state), making the deterministic transitions in effect binary and stochastic. This problem was not fixed by altering simulation time-step. Attempts at combining C_n/O_n pairs into 'combined states' for the stochastic simulation, with continuous populations updated deterministically, was found to affect gating kinetics detrimentally and produced very unusual spike shapes. This was thought to be caused by a discrepancy in the

update of the continuous populations when stochastic jumps were made between combined states by adapted rate-constants compared to individual activation.

Deterministic model with individual stochastic component

Four hybrid models were constructed to estimate the effect of stochasticity of different channel types in isolation in (Anwar et al., 2013). In each of these models, one type of ion channels were simulated stochastically, all the other components of model were simulated deterministically. For the deterministic part of the model, the ion channels and intracellular molecules were considered non-discrete and were distributed uniformly over the surface triangles and tetrahedrons of the meshes. Only the mesh for a compartment with length 10 μm and diameter 2 μm was used for this model. The sequence of steps involved in simulations of these hybrid models is similar to hybrid model with deterministic channels and stochastic calcium shown in Figure B.

References

Anwar H, Hepburn I, Nedelescu H, Chen W, De Schutter E (2013) Stochastic calcium mechanisms cause dendritic calcium spike variability. submitted.

Hepburn I, Chen W, Wils S, De Schutter E (2012) STEPS: efficient simulation of stochastic reaction-diffusion models in realistic morphologies. BMC Syst Biol 6:36.