Highly Scalable Computational Cell Microphysiology

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Simulating cellular processes is a computational challenge owing to the presence of multi-scale phenomena. We have implemented a highly scalable variant of the MCell microphysiology cell simulator called MCell-K. MCell employs Monte Carlo algorithms to simulate simultaneous diffusion and chemical reaction of individual molecules in arbitrary 3-D spaces. Diffusion is handled using optimized 3-D random walk methods, and this introduces challenges to efficient parallelization: how to efficiently detect termination, and how to maintain physical behavior.

MCell-K was implemented using the KeLP infrastructure. The MCell-K simulator currently scales to about 100 processors of an IBM SP-3 system located at the San Diego Supercomputer Center, but will soon be running on thousands of processors. MCell-K also runs on Blue Gene/L. For large-scale simulations with complex geometry, MCell-K allows each processor to handle one part of the geometry in a highly efficient way. The simulation algorithm is stochastic, and thus many hundreds to thousands of runs are typically conducted for each set of input conditions. Obtaining allocations of sufficient size to meet this demand remains a challenge, as one study could consume hundreds of thousands of CPU-hours. Since there is a worldwide MCell user community, MCell-K could have a significant influence on cell modeling. The latest version of MCell (version 3), employs an event driven strategy in lieu of time steps. To this end, the *Tarragon* project is investigating support for asynchronous flow control, to support the self-timed behavior of the algorithm. Included will be an automatic load balancer, which will respond to simulator dynamics.

We are interested in using MCell-K to solve some challenging simulation problems. We recently used this simulator to explore the release of neurotransmitter from the chick ciliary ganglion. Throughout the nervous system, the release of synaptic vesicles from presynaptic nerve terminals is thought to be associated with pre- and postsynaptic specializations, including active zones, where vesicles are docked to the membrane, and postsynaptic densities, where neurotransmitter receptors and other proteins are clustered. At the chick ciliary ganglion, where acetylcholine is released from presynaptic terminals, there are extrasynaptic receptors and vesicles docked outside the active zone. We explored ectopic neurotransmission at the ciliary ganglion by simulating the release of single vesicles from many different locations in a 3-D model reconstructed from high-resolution serial electron microscopic tomography. The distribution of amplitudes of the simulated synaptic activity was consistent with experimental recordings of miniature excitatory postsynaptic currents only when ectopic transmission was included in the model. Extrasynaptic receptors are also found on neurons in the central nervous system, which raises the possibility that neurons may communicate through sites outside the classically defined synaptic release zones, as we have found in the ciliary ganglion.

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