AN EFFICIENT HYBRID STOCHASTIC-DETERMINISTIC SIMULATION TECHNIQUE FOR LIVING CELLS

EXECUTIVE SUMMARY

Stochasticity in gene expression is an important source of noise that can have profound effects on the fate of a living cell. The reactions for gene expression, feedback loops, and transport occurring within cells are typically described by Chemical Master Equations (CME). Sampling the CME using the Stochastic Simulation Algorithm (SSA) results in large computational costs as each reaction event is evaluated explicitly. To improve the computational efficiency of cell simulations involving high-particle-number systems, the authors have implemented a hybrid stochastic–deterministic (CME/ODE) method to the publicly available, GPU-based lattice microschemes (LM) software suite, providing a convenient way to simulate complex cellular systems and interface with high-performance CME/RDME/ODE solvers. As a test of the implementation, the authors apply the hybrid CME–ODE method to the galactose switch in Saccharomyces cerevisiae, gaining a 10–50× speedup.

METHODS & CODES

The galactose switch system, with its four feedback loops and millimolar galactose concentration, is separated into a regime of species whose reactions will be simulated stochastically and another whose reactions will be simulated deterministically (see Fig. 1). At the beginning of each timestep, the LSODA differential equation solver is updated with the species counts obtained from the stochastic regime (transcription, translation) simulated via the SSA, and then takes adaptive timesteps to evolve the high particle number species through time in the deterministic regime. At the conclusion of a timestep, the stochastic rates of reactions involving low particle number species interacting with high particle number species are updated with the species counts found by the ODE solver. The hybrid algorithm also communicates updated species counts generated from reactions in the CME regime to the ODE regime at this time. The optimal communication times between the stochastic and deterministic descriptions, as well as the timesteps for each method, need to be assessed to verify that the hybrid description accurately describes the stochastic dynamics, which often have great impact on the cell’s behavior.

WHY BLUE WATERS

Blue Waters was essential to generate thousands of replicate hybrid simulations over the simulation time of 750 minutes and a range of concentrations. Only then did we have sufficient data to make the results statistically reliable and to determine the optimal communication time. In the worst case scenario, the full CME simulations take nearly two days of wall-clock time, while the hybrid CME–ODE implementation often requires approximately 40 minutes. The response of the switch guided the setup for much more computationally costly RDME–ODE simulations on Blue Waters, which account for the spatial heterogeneous environment (nucleus, cytoplasm, membrane, etc.) of a cell.

PUBLICATIONS & DATA SETS
