Computer Simulation System for Modeling of Reaction-Diffusion of Biochemical Pathways

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1 Introduction

We have been developing a computer simulation system for an efficient modeling and analysis of intracellular processes involving transportation of molecules. Recently, many experimental studies focus on spatio-temporal dynamics of molecules that contribute to functions of biological pathways such as signal transduction pathways. A number of these studies reported localization of molecules. However, conventional modeling techniques which are based on simulations of ordinary differential equations (ODE) could only describe averaged dynamics since they assume that molecules are uniformly distributed. To improve the treatment of spatial information, partial differential equation (PDE) [3] and stochastic simulation methods [1, 4] were developed. Here we present our method and technology for stochastic simulation of reaction-diffusion problems of biochemical pathways. In particular, we introduce a plan to develop a special purpose computer which enables us to simulate reaction-diffusion problems involving more than 10^7 molecules.

2 Method and Results

2.1 Method

We developed computer simulation software for modeling and analyses of biochemical systems. In this simulation system, spatial arrangement and motion of molecules are explicitly considered.

The outline of simulation algorithm is as follows. First, every molecule undergoes a trial where a site for the next time step is chosen among neighboring sites. Second, then every molecule undergoes a trial where a reaction proceeds with a certain probability. Third, association and dissociation rate are calculated.

In Figure 1, we show an example that demonstrates movements and reactions of molecules obtained in a 3-D space by simulating a model for cell cycle control system [2]. Here the line plots show tracks of stochastic movements of molecules. During this simulation, an inactive ubiquitin (UbE) molecule is activated and becomes

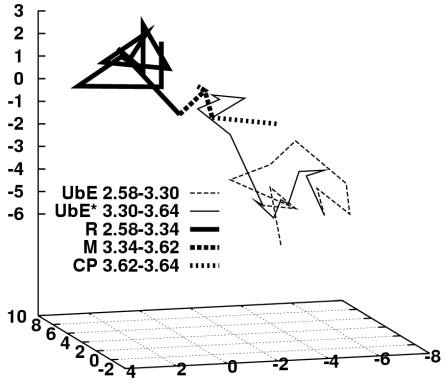

Figure 1: Tracks of molecules in space during a simulation of the cell cycle control system. UbE: inactive ubiquitin, UbE*: active UbE, R: inactive MPF, M: active MPF, CP: Cdc2 with threonine-167 phosphorylation. Here the unit of x, y, and z axes corresponds to μm, while the unit of time corresponds to one second.

a UbE* molecule and thereafter this UbE* molecule associates with a M molecule. This association of UbE* with M then caused a degradation of M. We then show in Figure 2 snapshot images of spatial arrangements of molecules obtained from the same simulation. The cell cycle control system model studied here consists of 17 species of molecules and the number of reactions defined in the model amounts to 33. Typical computation time required for a simulation with 36657 molecules was around 2 hours to reach its steady state (Pentium III 1GHz).

It is always important to carry out analyses of ensemble quantities (such as the mean value, standard deviation, etc) for systems with stochastic character. The ensemble is often obtained by performing simulations with independent (random) initial conditions. By processing these independent simulations simultaneously in multiple computers, the computation time is approximately proportional to reciprocal of the number of the processors.

The purpose of the present simulation analysis of cell cycling control system is to obtain the cyclic behavior. All of the results obtained so far, however, seem to be dominated by noise even if we observe a single simulation. We are now trying intensely to find region of parameter space where the system exhibits the oscillatory behavior.

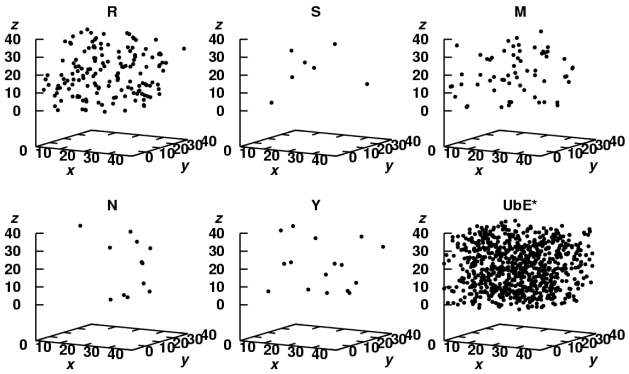

Figure 2: Snapshot images displaying spatial arrangements of particles representing molecules of cell cycle control system. R: inactive MPF, S: inactive MPF with tyrosine-15 phosphorylation, M: active MPF with threonine-167 phosphorylation, Y: free cyclin, UbE*: active ubiquitin.

2.2 Special Purpose Hardware

Our goal is to carry out a whole cell simulation involving more than 10^7 molecules. Here, we propose a high speed computation system with Field Programmable Gate Arrays (FPGAs). This system is estimated to enable simulations with 10^7 molecules and furthermore, achieve 10 to 100-fold speedup of processing rate as compared to a PC cluster (64×dual PentiumIII, 1GB memory/PC). In addition to this, the system has scalability (Figure 3). Using multiple units of the system, an exploration of huge simulation which thought to have more than 10^9 molecules is progressing.

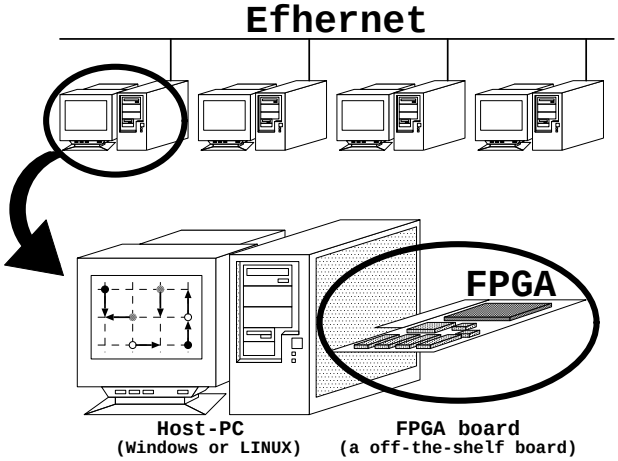

Figure 3: A simulation system with single FPGA and multiple simulation system connected by the Ethernet.

References

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