Commun. Comput. Phys.
doi: 10.4208/cicp.311009.100310a

Vol. **9**, No. 2, pp. 390-405
February 2011

Stochastic Simulation of the Cell Cycle Model for Budding Yeast

Di Liu*

Department of Mathematics, Michigan State University, East Lansing, MI 48824, USA.

Received 31 October 2009; Accepted (in revised version) 10 March 2010

Communicated by Gang Bao

Available online 27 August 2010

Abstract. We use the recently proposed Nested Stochastic Simulation Algorithm (Nested SSA) to simulate the cell cycle model for budding yeast. The results show that Nested SSA is able to significantly reduce the computational cost while capturing the essential dynamical features of the system.

AMS subject classifications: 65C05, 60G17, 74A25, 92C42

Key words: Stochastic simulation algorithm, stochastic process, bio-chemical reacting network, system biology.

1 Introduction

System biology, which studies integrated cellular reacting networks involving multiple levels of biological activities from gene expression, protein interaction, metabolism to signal transduction, has emerged as a new scientific discipline. Within such functional networks, many types of molecular processes take place on a wide range of time and population scales, under significant influence of random perturbations. From the point of view of modeling, Gene Regulatory Networks (GRNs), unlike protein and metabolic networks, involve fewer number of species and lower population of molecules in a small volume within a cell [1]; therefore stochastic effects have a significant impact on the system and stochastic models are particularly well suited to the study of the functionality of GRNs [2]. The Stochastic Simulation Algorithm (SSA) introduced by Gillespie in [3,4] has been the most successful and promising meso-scale bio-chemical reacting model, as well as an accurate simulation scheme that incorporates stochastic effects. Meanwhile, it is well known that bio-chemical reactions in intracellular networks involving gene expression occur on different time scales, e.g. the fast binding of RNA Polymerase to the DNA

*Corresponding author. *Email address:* richardl@math.msu.edu (D. Liu)

chain versus the relatively slower transcription process, which makes SSAs necessarily inefficient despite its accuracy.

In recent years, the stochastic simulation of intracellular bio-chemical reacting networks with multiple time scales has received a great deal of attention and important progress has been made. The main idea, pursued in different forms by many people, is to capture the effective dynamics on the slow time scale, by assuming the fast processes to be in a quasi-equilibrium distribution [5–11]. In [5], a scheme based on the quasi-equilibrium assumption was proposed supposing that the probability density of the fast species is known exactly as a function of the slow species or can be approximated, e.g. by a Gaussian. The same quasi-equilibrium assumption was used in [6,7], where the effective slow rates are obtained by solving a system of approximate algebraic equations, which are based on extra assumptions on both the reaction rates and the equilibrium distributions of the fast reactions. These limitations are removed in the recent work [8,9], in which stochastic simulation algorithms with nested structures are proposed to deal with the time scale issue. The Nested Stochastic Simulation Algorithm (Nested SSA, or NSSA) proposed in [8,9] relies only on the disparity of the rates, and makes no a priori assumption on the form of the slow and fast variables, nor upon the analytic form of the rate functions. Similar schemes are also proposed in [10,11], with different implementations on sampling the quasi-equilibrium of the fast reactions and time advancing of the slow reactions.

The purpose of the current paper is to test the Nested SSA on the cell cycle model for budding yeast [12]. The cell-division cycle is the sequence of events that take place in a eukaryotic cell leading to its replication. A growing cell replicates all its components and divides them into two daughter cells, so that each daughter has the information and machinery necessary to repeat the process. To account for random fluctuations in the molecular numbers of some major regulatory proteins, it is imperative to incorporate stochastic effects in the dynamics. A stochastic version of the budding yeast cell cycle model has been proposed in the framework of SSA [13,14], which consists of 55 reacting species involved in 82 reactions. Using Nested SSA, we are able to significantly speed up the simulation of the model without losing much accuracy in the key dynamical features of the system, such as the period of the cell cycle. In the following, we will first briefly introduce the Nested SSA and the stochastic cell cycle model for budding yeast. Then we will discuss in detail how NSSA can be applied to improve the efficiency of the stochastic simulation.

2 The nested stochastic simulation algorithm

2.1 Direct SSA

The Stochastic Simulation Algorithm [3,4] describes the time evolution of a spatially homogeneous mixture of chemically reacting molecules contained in a fixed volume V. The solution is assumed to be well mixed and iso-thermal so the details of the diffusion and