Commun. Comput. Phys.
doi: 10.4208/cicp.130612.121012a

Vol. **14**, No. 2, pp. 461-476
August 2013

An Accelerated Method for Simulating Population Dynamics

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Received 13 June 2012; Accepted (in revised version) 12 October 2012

Available online 4 January 2013

Abstract. We present an accelerated method for stochastically simulating the dynamics of heterogeneous cell populations. The algorithm combines a Monte Carlo approach for simulating the biochemical kinetics in single cells with a constant-number Monte Carlo method for simulating the reproductive fitness and the statistical characteristics of growing cell populations. To benchmark accuracy and performance, we compare simulation results with those generated from a previously validated population dynamics algorithm. The comparison demonstrates that the accelerated method accurately simulates population dynamics with significant reductions in runtime under commonly invoked steady-state and symmetric cell division assumptions. Considering the increasing complexity of cell population models, the method is an important addition to the arsenal of existing algorithms for simulating cellular and population dynamics that enables efficient, coarse-grained exploration of parameter space.

PACS: 87.10.Mn, 87.10.Rt, 87.16.Yc, 87.17.Ee

Key words: Accelerated stochastic simulation algorithm, constant-number Monte Carlo, gene expression, population dynamics and fitness.

1 Introduction

Cell populations are heterogeneous entities. Part of this heterogeneity arises from the stochasticity inherently present in the process of gene expression, which can result in

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significant variability even among cells with identical genotypes in identical environments [7, 15, 16, 20, 26, 29, 35]. This variability can in turn have significant impact on the overall reproductive fitness of a cell population [1, 2, 5, 9, 41, 42].

In some cases it is possible to derive analytical solutions for the statistical characteristics of gene expression for simple models (e.g., [25, 27, 30, 31, 36]). However, for more biologically realistic models, these characteristics are available only through numerical simulations. To permit investigations, we previously developed an algorithm for the stochastic simulation of heterogeneous population dynamics at a single-cell resolution [4]. This Population Dynamics Algorithm (PDA) combines the Gillespie stochastic simulation algorithm (SSA) [10, 11] to simulate gene expression in individual cells and a constant-number Monte Carlo (MC) method [17, 21, 22, 28, 34] for simulating population dynamics.

To benchmark the performance and accuracy of the method, we compared simulation results from the PDA with steady-state and time-dependent analytical solutions for several scenarios, including steady-state and time-dependent gene expression, and the effects on population heterogeneity of cell growth, division, and DNA replication [4]. Additionally, we used the PDA to model gene expression dynamics within bet-hedging cell populations during their adaption to environmental stress. Later, in [5] the PDA and analytical solutions developed for determining the first-passage time dependent fitness of a cell population exposed to a drug over a single generation were found to be in agreement. We refer the reader to these papers for details on the analytical work. These comparisons demonstrated that the PDA accurately captures how complex biological features influence gene expression and population dynamics. However, simulation runtimes can be extensive when the biochemical reaction kinetics that take place within a large number of individual cells are simulated using conventional MC approaches.

To address this problem, we have developed an accelerated method for simulating population dynamics (AMSPD). We first demonstrate that the AMSPD algorithm is numerically accurate and provides a significant speedup compared to the PDA. We then use the AMSPD to perform a parameter scan of a simple model for the development of non-genetic drug resistance to illustrate that it can be advantageous to use the AMSPD and PDA in combination to find an optimal balance between efficiency and accuracy.

2 Algorithm

In this section we present the AMSPD algorithm. The stochastic simulation algorithm [10, 11] and the constant-number MC method [17, 21, 22, 28, 34] are also described for completeness.

2.1 Accelerated method for simulating population dynamics

The first step in the AMSPD algorithm is to generate a single stationary time series (such that the moments of the corresponding distribution are not changing) for each biochemical variable in the system using an appropriate simulation method (e.g. the SSA [10, 11]