

436s Stochastic Simulations of Cell Population Dynamics

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Each individual cell of a population undergoes the so-called cell cycle during which it grows and then at a certain point it divides and partitions its cellular material into two daughter cells, each of which enters its own cell cycle. As a result of typically unequal partitioning at cell division, the operation of the cell cycle, and the fact that the single-cell growth rates, division rates and partitioning mechanisms depend on cellular content, each cell contains different quantities of proteins, DNA, RNA, and other cell properties at any given point in time. Consequently, cell properties are distributed among the cells of the population, and hence, a cell population is a heterogeneous system. The aforementioned single-cell processes are characterized by inherent stochasticity. Therefore, the accurate prediction of cell growth processes requires explicit incorporation of the stochastic and heterogeneous nature of cell population dynamics.

Several efforts to simulate stochastic cell population dynamics for a large number of systems have been presented in the literature. Despite offering valuable insights into various aspects of system behavior the vast majority of the aforementioned approaches, neglect the fact that cells are growing and dividing their cellular material in a typically unequal fashion. The few approaches which account for unequal partitioning at cell division refer to special cases where expressions for the time where the next division occurs can be obtained analytically. Thus, despite their predictive power, these algorithms are of limited applicability. Moreover, the computational burden of simulating the dynamics of large numbers of cells typically prevents a complete prediction of cell population dynamics from the initial condition until the system reaches time-invariant behavior.

Motivated by these challenges, we developed a stochastic Monte Carlo modeling approach describing the distribution dynamics of dividing cell populations comprised of cells where intracellular reactions are occurring. The model explicitly accounts for the stochastic nature of cell division, can simulate the dynamics of cell populations starting from one cell and can be used for a variety of single-cell reaction rate expressions as well as different division and partitioning mechanisms. Moreover, to address the heavy computational requirements, the presented algorithm consists of a hybrid constant-volume/constant-number approach. The validity of the stochastic model was verified through comparison with a deterministic cell population balance model in situations where stochastic division effects are expected to be negligible. We will first present results for a simple linear, single-cell reaction rate where analytical expressions for the times where each division event is occurring can be obtained. The results of the general algorithm with those when the analytical expressions are used were found to be in excellent agreement. We will also present simulation studies in a system where each individual cell follows nonlinear bistable dynamics and hence analytical expressions for the division times are not possible. Situations where the stochastic nature of cell division has a significant effect on the distribution dynamics will be discussed and presented for both cases of single-cell reaction rate expressions. The sensitivity of system behavior to division and partitioning mechanisms will also be quantitatively elucidated. Finally, through comparison of the stochastic algorithm with models treating the cell population as a homogeneous entity, the importance of accounting for cell population heterogeneity effects will be illustrated as a function of the molecular characteristics of the model bistable network.