A stochastic operator-splitting method for simulating the development of intratumor heterogeneity

Andrew Brettin[1,2*],

1 Department of Mathematics, University of Minnesota, Minneapolis, MN, United States
2 Center for Discrete Mathematics and Computer Science, Rutgers University, Piscataway Township, NJ, United States

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* brett057@umn.edu

Abstract

Cancer is a genetic disease which begins from a single aberrant progenitor cell, which successively divides into pairs of daughter cells with similar reproductive capacities. As the tumor grows, many distinct genetic lineages may proliferate throughout the neoplasm, resulting in significant intratumor heterogeneity. Such high levels of genetic diversity within tumors is associated with low survival rates for patients, as genetically-distinct cell variants have differential sensitivities to current therapies. Despite its importance, how intratumor heterogeneity develops is not well understood. However, mathematical models can provide insight into potential causes. This work applies a stochastic operator-splitting method developed for simulating chemical reaction-diffusion processes to model neoplastic growth. It is shown that high differential birth-rates, high diffusion rates and early onset of mutations can result in substantial levels of intratumor heterogeneity.

Author summary

In this analysis, I apply an existing framework for stochastically simulating reaction-diffusion processes to model neoplastic growth. Diffusion of cells is modeled using Brownian dynamics while reactions are modeled using the Gillespie stochastic simulation algorithm. An adaptive time-step is also used to improve algorithmic efficiency. From the output animations, it is evident that high mutant-cell birth rates, high diffusion rates, and early onset of mutations can result in significant intratumor heterogeneity.

Introduction

Cancer is a classification of genetic diseases characterized by abnormal and uncontrollable cell growth [1,2]. Globally, it is the second leading cause of death, taking the lives of 8.8 million people in 2015 [3], even as the incidence of cancer continues to

rise [4]. Roughly 40% of Americans will develop cancer at some point in their lifetimes [5]; worldwide, cancer is responsible for one out of every six deaths [3].

Cancer begins from a single aberrant progenitor cell [2]. The tumor grows as cells within it undergo mitosis, producing two new daughter cells with similar reproductive capability after some timespan. During each cell division, there is a nonzero probability that a daughter cell will acquire a mutation. The majority of these mutations are neutral or weakly deleterious, but some of these mutations are driver mutations which may increase the selective advantage of cells of that type.

Through random genetic drift or natural selection, certain subclonal mutations may proliferate and become more prevalent throughout the tumor. Due to this development process, tumors typically develop significant heterogeneity [6] from distinct cell lineages, as supported by substantial observational evidence [6–9]. Such heterogeneity has important implications. The presence of a broad variety of subclones permits a higher chance for genotypes resistant to prescribed therapies within the tumor. Numerous studies have shown that different subclones respond differently to chemotherapies [10,11], radiation therapies [12], and immunotherapies [13–15]. Indeed, high levels of intratumor heterogeneity (ITH) are associated with limited response to targeted therapies and poor survival rates for patients [16,17].

Although reducing the incidence of ITH can improve outcomes for a patient, little is understood about how intratumor heterogeneity develops. At the time of diagnosis, tumors are typically about 1 cm in diameter [18] and have acquired a population size on the order of 10^9 cells [19], providing a snapshot of the present tumor but not in itself revealing anything about the tumor's history.

Mathematical models can provide certain insights about pre-diagnostic neoplastic progression that other tools such as imaging or tissue sampling cannot. In particular, mathematical frameworks for studying chemical reaction-diffusion processes are quite well-developed and can be adapted to study tumor growth. Cells can be thought of as particles, whereas cell birth, cell death, and cell mutation of a cell type A are analogously represented by the chemical reactions

$$A \to 2A, \qquad A \to \emptyset, \qquad A \to B, \tag{1}$$

respectively. Furthermore, quantitative methods for measuring ecological diversity can be useful for assessing the level of heterogeneity within a tumor.

This paper describes how a stochastic operator-splitting algorithm for simulating chemical reaction-diffusion processes was applied to study how intratumor heterogeneity develops. In Materials and methods, some background on continuous and stochastic modeling approaches is provided, followed by a brief description of the operator-splitting method applied to this problem as well as an overview of the implementation of the algorithm in Python. See S2 File for a more in-depth explanation of the code. Factors found to influence intratumor heterogeneity are discussed in Results. Potential routes for further research are described in Discussion.

Materials and methods

Background

Reaction-diffusion processes are often modeled using reaction-diffusion partial differential equations. These models assume that the time evolution of the number of particles is a continuous, deterministic process. For M different chemical species, the time evolution of the local species counts $\{A_i(\boldsymbol{x}, t)\}_{i=1}^{M}$ is governed by

$$\frac{\partial A_i}{\partial t} = D_i \nabla^2 A_i + R_i(A_1, \ldots, A_M); \qquad i = 1, \ldots, M. \tag{2}$$