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Modeling intrinsic heterogeneity and growth of cancer cells

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HIGHLIGHTS

- Two mathematical models simulate the growth dynamics of cells in different states.
- These models predict variations in growth as a function of intrinsic heterogeneity.
- Duration and variation of the cell-cycle dramatically impact cancer-cell dynamics.
- The stochastic ABM can be approximated by efficient IDEs for high cell densities.

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ABSTRACT

Intratumoral heterogeneity has been found to be a major cause of drug resistance. Cell-to-cell variation increases as a result of cancer-related alterations, which are acquired by stochastic events and further induced by environmental signals. However, most cellular mechanisms include natural fluctuations that are closely regulated, and thus lead to asynchronization of the cells, which causes intrinsic heterogeneity in a given population. Here, we derive two novel mathematical models, a stochastic agent-based model and an integro-differential equation model, each of which describes the growth of cancer cells as a dynamic transition between proliferative and quiescent states. These models are designed to predict variations in growth as a function of the intrinsic heterogeneity emerging from the durations of the cell-cycle and apoptosis, and also include cellular density dependencies. By examining the role all parameters play in the evolution of intrinsic tumor heterogeneity, and the sensitivity of the population growth to parameter values, we show that the cell-cycle length has the most significant effect on the growth dynamics. In addition, we demonstrate that the agent-based model can be approximated well by the more computationally efficient integro-differential equations when the number of cells is large. This essential step in cancer growth modeling will allow us to revisit the mechanisms of multidrug resistance by examining spatiotemporal differences of cell growth while administering a drug among the different sub-populations in a single tumor, as well as the evolution of those mechanisms as a function of the resistance level.

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1. Introduction

1.1. Induced Heterogeneity

The development of a tumor is a complex evolutionary process that involves perturbations in many essential cellular mechanisms. Spatiotemporal cellular dynamics include various types of hallmark alterations that may be acquired through stochastic processes and induced by environmental signals, such as metabolic stress, inflammatory microenvironments, immune responses, and/or therapy. Combinations of these signals produce intratumoral heterogeneity. Many primary human tumors have been discovered to contain genetically and phenotypically distinct cellular subpopulations with different growth rates. This intratumoral heterogeneity has further been found to be a major contributor to drug resistance (Saunders et al., 2012). Resistance to chemotherapy is a major impediment to successful cancer treatment. Several central mechanisms have been identified as contributing to resistance; however, these do not

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necessarily account for tumor dynamics (Gillet and Gottesman, 2010). It is known that most patients that are diagnosed with cancer have already developed some level of drug resistance while the tumor is forming. Thus after therapy, they experience a relapse, where the disease could become intractable or even possibly untreatable. Various theoretical and empirical studies aim to predict the development of a tumor, mainly by assuming the existence of abnormal events that cause cancer-related alterations (Lavi et al., 2012). Understanding the course of malignancy and estimating cancer growth based on tumor cell responses to microenvironmental changes as an induced dynamic process may serve to identify new targets for therapy or methods of prevention.

1.2. Intrinsic heterogeneity

However, there is another side to this 'equation'; one that does not necessarily account for tumor heterogeneity that results exclusively from cancer-related irreversible processes. Instead, heterogeneity can arise via typical reversible biological processes that are stochastic, yet nevertheless tightly regulated, in nature. These natural intrinsic mechanisms add another layer of complexity to a cell's capacity to integrate information, particularly in cancer cells. One such cellular process is the cell-cycle. The cell-cycle is one of the most studied biological processes, and has obvious effects on cancer development, growth, and therapeutic resistance. Eukaryotic intracellular dynamics are mediated by many different molecular components (e.g. transcription factors, proteins, metabolites, RNA, etc.). Each such component operates at a different rate, often under different conditions, and responds to many dynamic inter- and intra-cellular signals, such as pH, temperature, and cellular density in the local environment. In order to maintain an ordered cell-cycle mechanism that would function consistently, despite a routinely noisy microenvironment, variations in gene expression (Pisco et al., 2013), cell-cycle period (Wang et al., 2010), cell size and age (Tzur et al., 2009), and cellular death period (Messam and Pittman, 1999; Spencer et al., 2009) of cells from the same clone must exist. Advances in methods to both study naturally intrinsic significant variations in tumor growth and characterize intratumoral heterogeneity would aid in determining natural fluctuations in cell growth, understanding how tumor development is affected by these natural fluctuations, detecting these types of tumors after treatment, and understanding how induced and intrinsic mechanisms can be found.

1.3. Self-organized dynamics

Two frameworks that are commonly used to design mathematical cancer models which predict cellular behavior are individual-based models and continuous deterministic models. Several different individual-based models of tumor growth have been developed recently (see review Anderson and Quaranta, 2008). Among them are agent-based models (ABMs). The ABM framework is a powerful simulation method that has seen a variety of applications, including bio-medical research (Piotrowska and Angus, 2009; Thorne et al., 2007; Zhang et al., 2009) and socio-economic modeling (Bonabeau, 2002). ABMs describe dynamic systems as collections of autonomous decision-making individuals called agents. Each agent assesses its state and makes decisions on the basis of a set of rules. Agents may execute various behaviors appropriate for the system they represent. ABMs are generally more flexible than deterministic models and may take into account virtually any biological phenomenon. Here, we present two mathematical approaches, the ABM and a corresponding integro-differential (IDE) model, to predict the growth of a single ovarian cell line, OVCAR-8, where the cells can be proliferating, dying, or in quiescence. The novelty of our methods lies in the description of cellular decision-making as a function of the global dynamic cell density, with intrinsic variations of the cell-cycle and death process lengths. Decisions concerning actions are based on how the cell senses its environment, in a probabilistic fashion. We study the robustness of cell growth despite noise in division and natural death rates. The entire system dynamic results from the decisions of individual entities that can cause transient or permanent heterogeneity, generate network effects, and potentially lead to significant deviations from stochastic to deterministic predictions. We demonstrate the existence of fluctuations in cell growth using data of proliferation rates as a function of cellular density. This fundamental framework of cellular growth dynamics is a necessary first step that will allow us to work on more complex co-cultured systems based on geometry, which includes a spatial mechanism of drug resistance that could shed light on the spatiotemporal evolution of intratumoral heterogeneity.

2. Agent-based model

The first model we introduce is an ABM, where each cell is distinguished by its own state and behavior. This framework permits a simple way to introduce an age structure into the model, which is a main focus of this work.

2.1. Model construction

The ABM consists of three compartments of cells: proliferative (P), apoptotic (A), and quiescent (Q). See Fig. 1 for an outline of the transitions between compartments. Q consists of cells that are neither dividing nor dying, and acts mainly as a reservoir for the other two compartments. P consists of cells that are currently in any stage of the cell-cycle. When a cell makes a transition from Q into P, a cell-cycle length, L_P, is chosen. L_P was assumed to be a random variable with normal distribution:

$$L_P \sim \mathcal{N}(\mu, \sigma^2), \tag{1}$$

where μ is the mean length of the cell-cycle, and σ is the standard deviation (Wang et al., 2010). The value of μ is taken as the doubling time of OVCAR-8 cells, which is estimated to be 24.4416 h (see

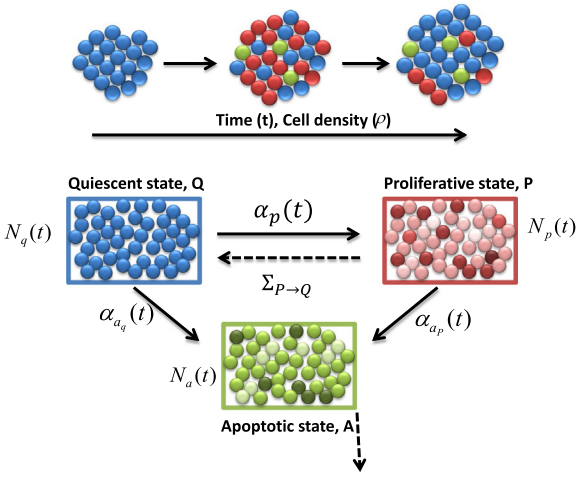

Fig. 1. Model dynamics. Diagram of transitions between the three cellular compartments in the ABM. Q denotes the quiescent compartment with $N_q(t)$ cells at time t, P denotes the proliferation compartment with $N_p(t)$ cells at time t, and A denotes the apoptosis compartment with $N_a(t)$ cells at time t. Note that $N_q(t), N_p(t)$, and $N_a(t)$ are all stochastic processes. The explicit transition rates between the compartments are shown in solid lines, and are labeled as $\alpha_p(t), \alpha_{a_p}(t)$, and $\alpha_{a_q}(t)$. The implicit transition rates, due to the completion of cellular cycles, are shown in dotted lines, and have no closed-form expression. For example, $\Sigma_{P\to Q}$ corresponds to the rate of cell-cycle completion. The line originating from compartment A indicates cells that are removed from the simulation.