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Extinction models for cancer stem cell therapy

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ABSTRACT

Cells with stem cell-like properties are now viewed as initiating and sustaining many cancers. This suggests that cancer can be cured by driving these cancer stem cells to extinction. The problem with this strategy is that ordinary stem cells are apt to be killed in the process. This paper sets bounds on the killing differential (difference between death rates of cancer stem cells and normal stem cells) that must exist for the survival of an adequate number of normal stem cells. Our main tools are birth–death Markov chains in continuous time. In this framework, we investigate the extinction times of cancer stem cells and normal stem cells. Application of extreme value theory from mathematical statistics yields an accurate asymptotic distribution and corresponding moments for both extinction times. We compare these distributions for the two cell populations as a function of the killing rates. Perhaps a more telling comparison involves the number of normal stem cells N_H at the extinction time of the cancer stem cells. Conditioning on the asymptotic time to extinction of the cancer stem cells allows us to calculate the asymptotic mean and variance of N_H. The full distribution of N_H can be retrieved by the finite Fourier transform and, in some parameter regimes, by an eigenfunction expansion. Finally, we discuss the impact of quiescence (the resting state) on stem cell dynamics. Quiescence can act as a sanctuary for cancer stem cells and imperils the proposed therapy. We approach the complication of quiescence via multitype branching process models and stochastic simulation. Improvements to the τ-leaping method of stochastic simulation make it a versatile tool in this context. We conclude that the proposed therapy must target quiescent cancer stem cells as well as actively dividing cancer stem cells. The current cancer models demonstrate the virtue of attacking the same quantitative questions from a variety of modeling, mathematical, and computational perspectives.

1. Introduction

Cancer cells with stem cell-like properties represent a novel target of therapy that may revolutionize the treatment of cancer. Mathematical models sharpen our understanding of how cancer stem cell populations evolve and suggest optimal strategies to attack them. Because they undergo repeated divisions, stem cells accumulate mutations over time. Cells derived from stem cells start down differentiation pathways that involve a limited number of cell divisions. Once they reach the end of their pathways, differentiated cells no longer accumulate the mutations caused by faulty DNA replication during cell division. Thus, many oncologists contend that only cells with stem cell-like properties can drive cancer [2,4,5,13,17,21,41,46,49,51,52,54,55,57,59,64–66,68,71]. Because normal stem cells are vital for the maintenance and repair of tissues [58], safe eradication of cancer stem cells requires selectively targeting cancer stem cells while sparing normal stem cells. In the current paper we explore in depth this hypothetical strategy and discuss its implications for the design of the next generation of cancer therapeutics. In a related paper we apply and extend some of these results to address current challenges facing medical oncologists in targeting leukemic stem cells [61].

There are controversies about what is meant by a cancer stem cell. Some of the properties we describe may hold for some malignant progenitor cells. Some authors use the term stem-like cell and tumor initiating cell when referring to cells with the above properties. We use the term stem cell in this article in that sense.

Our point of departure is the stochastic theory of linear birth–death processes. This is well trod ground mathematically [18,28,31,39,40,42,45], but the current problems raise novel issues not encountered in the standard treatments. For instance, how can

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Nomenclature

CSC	cancer stem cell
HSC	hematopoietic stem cell
N_H	number of healthy stem cells at random time of extinction of cancer stem cells
M_n	time at which n clans of stem cells go extinct

Greek symbols

β	birth rate per stem cell
δ	death rate per stem cell
ϕ	rate of quiescence per actively dividing stem cell
α	rate of awakening per quiescent stem cell
ν	death rate per quiescent stem cell
β_C	birth rate per cancer stem cell
δ_C	death rate per cancer stem cell
β_H	birth rate per healthy stem cell
δ_H	death rate per healthy stem cell
ϕ_C	rate of quiescence per actively dividing cancer stem cell
α_C	rate of awakening per quiescent stem cancer cell
ν_C	death rate per quiescent stem cancer stem cell
ϕ_H	rate of quiescence per actively dividing healthy stem cell
α_H	rate of awakening per quiescent healthy stem cell
ν_H	death rate per quiescent healthy stem cell

one approximate the distribution of the extinction time for either population of stem cells? This brings in extreme-value theory from statistics, eigenfunction expansions, and the finite Fourier transform. We particularly fixate on three related questions: (a) What is the killing differential (difference between death rates of cancer stem cells and normal stem cells) that makes our hypothetical therapy viable? (b) What is the distribution of the number of normal stem cells at the random time of extinction of the cancer stem cells? (c) What implications does the phenomenon of quiescence have for the proposed therapy? To answer questions (a) and (b), we condition one birth–death process on the random extinction time of the other birth–death process. To answer question (c), we turn to multi-type branching processes, with stem cells of either kind divided into active and quiescent types. Because some of our answers are approximate, it helps to look at the same problem from multiple perspectives. This leads us to introduce the subject of stochastic simulation by τ-leaping [60]. Except for numerically unstable eigenfunction expansions, the different techniques discussed here reinforce one another and increase our confidence in the basic model.

Before presenting an overview of the rest of the paper, let us comment on the relevance of stochastic models in general and birth–death processes in particular. In a nutshell, stochastic models are ideal for studying stem cell dynamics because key events of interest, such as extinction of a population of stem cells, are probabilistic in nature. Stem cells occupy well defined niches in the body, and it is not too hard to imagine the stem cell clans behaving independently, at least in the short run. Thus, linear birth–death processes appear to offer a good vehicle for modeling [18,28,31,39,40,42,45].

In the next section, we provide a brief overview of stem cell biology. In Section 3 we start with the distribution of the extinction time for a subcritical birth–death process starting with a single cell. This classical result is inadequate for our purposes because we typically start with many cells and must track all clans issuing from them. Using extreme-value theory, we find an accurate asymptotic distribution for the time at which all clans go extinct. This result allows us to compare probability densities for the extinction times of two coexisting populations of stem cells: normal stem cells and cancer stem cells, dying at different rates under therapy. Convergence in distribution does not imply convergence of moments, so in Section 3.2 we verify convergence of the mean and variance of the extinction times to the mean and variance of the asymptotic distribution.

In Section 3.3, we study the number of normal stem cells N_H remaining at the random time all cancer stem cells go extinct. We derive the mean and variance for N_H by conditioning on the extinction time of cancer stem cells. These quantities are heavily dependent on the selectivity of a therapy. We also compute the full distribution of N_H using eigenvalue expansions and the finite Fourier transform. In Section 3.5 we discuss the quiescent (resting) state of the stem cell, and its impact on cancer stem cell dynamics under therapies that selectively eliminate actively dividing cells. Quiescence requires new models and a different set of numerical tools. We particularly focus on simulation and τ-leaping in Section 4. Our discussion summarizes all findings and comments on the role of mathematical modeling in cancer therapy.

2. Biological background

Let us begin by describing some biological features of stem cells that shape our birth–death process models. Two of the principal distinguishing features of stem cells are *self-renewal* and *potency* [48]. Self-renewal refers to the ability of a cell to indefinitely reproduce copies of itself at the same level of differentiation. In asymmetric cell division, a stem cell produces an identical daughter cell and a second more differentiated daughter cell. A stem cell can also divide symmetrically, generating two copies of itself in self-renewing symmetric division, or generating two partially differentiated daughter cells in differentiative symmetric division. Fig. 1 depicts the three modes of cell division.

Potency is the capacity of a stem cell to replenish all of the highly specialized cells of a tissue. For instance, hematopoietic stem cells can give rise to a closely related family of cells that circulate in the blood. Fig. 2 illustrates the ability of the hematopoietic stem cell to generate multipotent progenitors, which then begin the process of differentiation, either into the myeloid lineage or the lymphoid lineage. The cells of the myeloid lineage carry oxygen to tissues (erythrocytes), help with clot formation (platelets), and fight acute infection (granulocytes), while the cells of the lymphoid lineage populate the immune system (B and T lymphocytes). It is noteworthy that progenitor cells do have the ability to self-renew, but only for a limited time. Only stem cells have the capacity for indefinite self-renewal. (see Fig. 3)

Additional important features of stem cells include slow self-renewal and quiescence; these allow stem cells to maintain a long life span [48]. Different kinds of stem cells spend varying percentages of time in an actively dividing state and a quiescent (resting) state. For example, embryonic stem cells spend about 90% of the time in an actively dividing state, whereas hematopoietic stem cells are quiescent approximately 75% of the time [11]. Stem cells can enter the state of quiescence and later re-awaken.

3. Stem cell extinction times under therapy

In our simplified model of therapy, there are two populations of stem cells, normal stem cells and cancer stem cells. These coexisting