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Analysis of stochastic stem cell models with control

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ABSTRACT

Understanding the dynamics of stem cell lineages is of central importance both for healthy and cancerous tissues. We study stochastic population dynamics of stem cells and differentiated cells, where cell decisions, such as proliferation vs. differentiation decisions, or division and death decisions, are under regulation from surrounding cells. The goal is to understand how different types of control mechanisms affect the means and variances of cell numbers. We use the assumption of weak dependencies of the regulatory functions (the controls) on the cell populations near the equilibrium to formulate moment equations. We then study three different methods of closure, showing that they all lead to the same results for the highest order terms in the expressions for the moments. We derive simple explicit expressions for the means and the variances of stem cell and differentiated cell numbers. It turns out that the variance is expressed as an algebraic function of partial derivatives of the controls with respect to the population sizes at the equilibrium. We demonstrate that these findings are consistent with the results previously obtained in the context of particular systems, and also present two novel examples with negative and positive control of division and differentiation decisions. This methodology is formulated without any specific assumptions on the functional form of the controls, and thus can be used for any biological system.

1. Introduction

Tissue turnover dynamics, especially in the context of stem cell regulation, have attracted the attention of many researchers. Cell populations are assumed to possess a hierarchical structure, where different classes of cells can interact in intricate ways. In the simplest case, there are stem cells capable of self-renewing and regenerating the tissue, and differentiated cells which can perform the tissue's specific functions.

Differentiated cells are subject to relatively frequent cell death and need to be replenished by stem cell divisions. These divisions can be of several types. Specifically, a stem cell can differentiate by dividing into two differentiated cells, or it can proliferate, by dividing into two stem cells. Differentiation/proliferation decisions are thought to be under regulation coming from surrounding cells in the tissue. Various control loops help maintain a roughly constant overall tissue size, and keep variations in the numbers of stem and differentiated cells to a minimum.

There is significant theoretical literature exploring various aspects of stem cell dynamics. Conceptual theoretical issues for the studies of stem cells have been identified in [1–3]. Discrete and continuous models relevant for carcinogenesis have been studied [4–15]. Evolutionary modeling of stem cells in systems other than cancer was introduced in [16]. Modeling of stem cells in the hematopoietic system was proposed by several authors [17–21]. In these and other papers, both deterministic and stochastic models have been introduced and studied (see a great review of many modeling approaches provided in [22]). The deterministic (ODE) approach provides useful analytical insights into the dynamics and long-term behavior of cell lineages. Two- and multi-compartment models with several types of the regulation function have been studied in [23,24], where the authors discuss important conceptual issues about stem cell regulation from the engineering prospective. A systematic linear stability analysis of two- and three-compartment models with regulation of self-renewal fractions or regulation of proliferation rates was performed in [25]. Another type of regulation was studied in two-compartment models by [26]. Analysis of the structure of stationary solutions in the n-compartment version of the model was presented in [27].

The stochastic approach allows to quantify the role of fluctuations in the behavior of the system of interest [28–31]. Apart from several exceptions [32,33], most of the literature is devoted to numerical explorations of stochastic stem cell systems. Recently, we performed analytical studies of two stochastic stem cell systems involving nonlinear control [34,35] and found how the strength of control determines the amount of stochastic fluctuations in the numbers of stem and differentiated cells. This was done for several particular types of control functions. Unfortunately, the methods used in those papers cannot be extended to study other types of control loops.

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In the present paper we develop a general, analytical methodology for studying the behavior of hierarchical, two-compartment (stem and differentiated cells) systems with nonlinear control. We assume that division, death, and differentiation/proliferation decisions are given by some (unspecified) functions of the numbers of stem and differentiated cells, and provide tools to calculate the moments of the cell numbers, and importantly, the means and the variances of the numbers of cells.

It turns out that under some general assumptions, the amount of variation in the system is a function of the local behavior of the control functions near the equilibrium. For example, in the simplest case of the constant total population systems, the variance in the number of stem cells is inversely proportional to the derivative of the control function with respect to the number of stem cells, evaluated at the equilibrium. For non-constant populations, we develop similarly general methods and provide explicit formulas approximating cell number means and variances.

The method developed here is algorithmically different, and simpler, than the linear noise approximation [36]. We studied the connection between the two methods and proved that they give the same result to all orders of accuracy. Therefore, our method could be considered a short-cut compared with the Van Kampen power series expansion. We developed a computer program (written for *Mathematica* and presented in a supplement) which allows to apply our method to any system of stem and differentiated cells with given control functions. In other words, if we assign the rates of divisions, differentiation/proliferation, and death to be some functions of the numbers of stem and differentiated cells, our tools allow to calculate analytically the means and the variances of the stem and differentiated cell numbers as functions of the system parameters, and to study stability and robustness of the system.

The rest of this paper is organized as follows. In Section 2 we discuss systems with constant total populations, where only differentiation/proliferation decisions are under nonlinear regulation. In Section 3 we generalize this methodology to non-constant populations, where three types of processes (divisions, deaths, and differentiation/proliferation decisions) are under nonlinear regulation. In Section 4, the results are illustrated by using previously solved regulation problems as well as two novel examples. In the first example, both division and differentiation decisions are under negative control from the population sizes. In the second example, divisions are negatively regulated while differentiation decisions are under a positive control loop. Section 5 compares and contrasts our new method with the power series expansion method of Van Kampen. Discussion is provided in Section 6.

2. Modeling constant total cell populations

In the first set of models we will assume that the population consists of I stem cells and J differentiated cells, and that the total population size remains constant, $I+J=N$. This corresponds to a generalization of the well-known Moran process [37] in the presence of two sub-populations of different properties. In the classical Moran process, each update consists of a division event followed by a death event. All cells have an equal probability to die, and any cell has a chance to divide. A division event is a replacement of the dividing parent cell with two cells, which in the absence of mutations are both identical to the parent cell.

In the processes considered here, only differentiated cells die (with equal probabilities), and only stem cells divide (also with equal probabilities), see Fig. 1. Moreover, there are two types of stem cell divisions. A *proliferation event* results in two daughter cells which are both stem cells. A *differentiation event* leads to the creation of two differentiated cells. The probability of differentiation, p, is assumed to be under some regulatory loops from the stem and/or differentiated cell

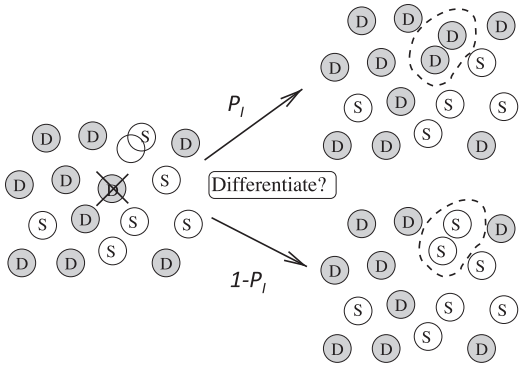

Fig. 1. A schematic showing one step of the update for the constant total population model. Circles represent stem cells ("S") and differentiated cells ("D"). Following a death of a randomly chosen differentiated cells, one of the stem cells is chosen for division. With probability p_I (where I is the current number of stem cells in the system) it will differentiate, that is, divide into two daughter differentiated cells. With probability $1-p_I$, it will proliferate, that is, divide into two stem cells.

populations. Since $J=N-I$, we can simply say that $p=p_I$, a function of the number of stem cells, I.

The above model gives rise to a 1D Markov process with $\text{Prob}(I\to I-1)=p_I$ and $\text{Prob}(I\to I+1)=1-p_I$. Denoting by $\varphi_I(t)$ the probability to find the system at state I at time t, we can write down the following Kolmogorov forward equation:

$$\dot{\varphi}_I=\varphi_{I-1}(1-p_{I-1})+\varphi_{I+1}p_{I+1}-\varphi_I. \tag{1}$$

Depending on the functional form of the differentiation probability p_I, the system can exhibit different types of behavior, from oscillating around an equilibrium, to an unstable behavior resulting in extinction/overflow.

2.1. Previous results for specific cases

In [34], several types of the differentiation probability p_I have been studied.

- **No control.** It was shown that for $p_I=p=\text{const}$, the system rapidly drifts to one of the two extinction states: either the $I=0$ state with no stem cells, or the $I=N$ state with no differentiated cells. This case corresponds to the absence of stem cell regulation.
- **A hyperbolic law.** In this case, we assume the following functional dependence:

$$p_I=\frac{\beta}{1-hI}, \tag{2}$$

where β and h are parameters. The magnitude of h defines the degree of control, and the case $h=0$ corresponds to the constant probability model. We obtained the following results for the mean and the variance of the stem cell numbers in this case:

$$E[I]=\frac{1-2\beta}{h}-\frac{1}{2},\quad \text{Var}[I]=\frac{\beta}{h}+\frac{1}{4}. \tag{3}$$

- **A Hill-type law.** Consider the following functional form of differentiation probability:

$$p_I=\frac{I^\alpha}{k^\alpha+I^\alpha}, \tag{4}$$

with $0<k<N$ and $\alpha\geq 0$. Here, $\alpha=0$ is the constant-p model, and $\alpha\to\infty$ corresponds to the Heaviside function. If we assume that $k\gg 1$, then the following approximations for the mean and the variance of the stem cell number have been obtained:

$$E[I]=k+\frac{1}{2\alpha}+O(1/k),\quad \text{Var}[I]=\frac{k}{\alpha}+\frac{2\alpha-1}{4\alpha^2}+O(1/k). \tag{5}$$