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Global dynamics of two-compartment models for cell production systems with regulatory mechanisms

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ABSTRACT

We present a global stability analysis of two-compartment models of a hierarchical cell production system with a nonlinear regulatory feedback loop. The models describe cell differentiation processes with the stem cell division rate or the self-renewal fraction regulated by the number of mature cells. The two-compartment systems constitute a basic version of the multicompartment models proposed recently by Marciniak-Czochra and collaborators [25] to investigate the dynamics of the hematopoietic system. Using global stability analysis, we compare different regulatory mechanisms. For both models, we show that there exists a unique positive equilibrium that is globally asymptotically stable if and only if the respective reproduction numbers exceed one. The proof is based on constructing Lyapunov functions, which are appropriate to handle the specific nonlinearities of the model. Additionally, we propose a new model to test biological hypothesis on the regulation of the fraction of differentiating cells. We show that such regulatory mechanism is incapable of maintaining homeostasis and leads to unbounded cell growth. Potential biological implications are discussed.

1. Introduction

Adult stem cells, which give rise to differentiated cells of living organisms, have been identified in most tissues. They maintain and repair the host tissue function by replacing the mature cells through differentiation. They also repopulate the stem cell pool through self-renewal [42]. Under homeostatic conditions the system keeps the balance between maintaining the stem cell pool and providing differentiated cells when needed. The mechanisms underlying the cell production system have been a central issue in stem cell biology [35]. The relationship between cell-cycle progression and stem cell fate has been widely explored [28].

There is a long history for application of mathematical models built to understand processes of cell differentiation and tissue regeneration, especially in the case of hematopoiesis and its disorders [30]. Depending on the question of interest, different mathematical approaches can be chosen. One established method of modeling of multistage cell systems is to use a discrete collection of ordinary differential equations, each of which describes dynamics of cells at a single maturation stage, e.g. [4,19,25,21]. Describing cell differentiation as a continuous process leads to models based on partial differential equations of the transport type [32,10,1] or delay differential equations, e.g. [22,6,3,2,31]. For example, in papers [22,6], using mathematical models formulated as delay differential equations, the authors explore biological mechanisms that cause oscillating circulating neutrophil counts observed in a hematological disorder called cyclical neutropenia. From bifurcation analysis and numerical simulations a destabilization mechanism via an increase of the death rate of stem cells has been proposed. See also [12] for a summary of related works. Another group of models addresses the effects of stochasticity in the cell fate decisions or in the regulation of cell quiescence. For example, in [33] a single cell-based stochastic model has been developed to explain the constitution of the stem cell pool as a self-organizing process. This model assumes that stem cells reside in two different signaling contexts characterizing the property of cells as either proliferating or quiescent. In [32], to overcome a time-consuming problem of simulating the agent-based model in [33], a structured population model is formulated as a system of partial differential equations. It is observed that the model captures disease and treatment dynamics of chronic myeloid leukemia.

The choice of regulatory mechanisms is an important modeling element. It is known that the dynamics of cell proliferation and differentiation can be controlled by extracellular signaling molecules,

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such as cytokines. However, the precise nature of these processes remains to be fully elucidated. Different plausible regulatory feedback mechanisms lead to different types of nonlinearities in the model equations.

In [25] a multi-compartment model of blood cell differentiation and hematopoietic reconstitution has been developed to investigate two hypotheses concerning the regulatory mechanism based on a single negative regulatory feedback between the level of mature cells and the proliferation rate or the fraction of cell self-renewal. Previously, a regulatory mechanism based on two simultaneous feedback loops, i.e. short- and long-range feedbacks from stem cells and mature cells, was assumed to be necessary to stabilize such cell system [4]. Numerical results in [25] as well as linearized stability analysis in [27] indicated that stable regulation of the cell differentiation system can be achieved through a single nonlinear feedback loop. The models in [25] have been calibrated based on the data obtained from patients with multiple myeloma after high-dose chemotherapy and stem cell transplantation and also validated based on large patient groups [24]. They have been later extended in different directions, among other to address the role of continuous transitions in cell differentiation [3,10], to study effects of replicative senescence [26], or to approach the question of the mechanism of leukemia development [39]. Similar regulatory mechanism has been proposed in [19] to describe cell proliferation in mammalian olfactory epithelium.

The aim of the present work is to study analytical properties of the models proposed in [25] to better understand effects of different regulatory mechanisms. Following a parsimonious approach to modeling in which comprehensive models are better understood in view of simpler models, in the present paper we focus on a basic version of the model, consisting of two equations describing coupled dynamics of undifferentiated and mature cells. We provide a rigorous analysis of models with different types of regulation.

First, we focus on mechanisms proposed in [25], including a regulated division rate and a regulated fraction of self-renewal. Using two-compartment models for both regulatory mechanisms, we show global stability of the positive steady state where undifferentiated and differentiated cells coexist. Stability analysis of basic models including different modes of regulation will help understanding what mechanisms may be efficient to regulate homeostasis. Global stability analysis seems to be a suitable way to explain the dynamics of the system after a large perturbation, such as chemotherapy treatment or bone marrow transplantation. The proof is based on constructing Lyapunov functions, suited to specific nonlinearities of the model. The form of nonlinear feedbacks is significantly different from that in existing models and therefore the constructed Lyapunov functions are original, although inspired by those found for the models from epidemiology of infectious diseases [18].

Additionally, we develop a new model with a feedback loop from the level of mature cells to the fraction of differentiating cells. Using this model we test a biological hypothesis proposing that overproduction of mature cells might cause inhibition of differentiation to avoid oversupply from stem cell compartment. We show that this control mechanism, although intuitively plausible, is inefficient and can lead to the unbounded growth of the stem cell population.

Analysis of the model that has two compartments is a necessary step to investigate the role of the number of differentiation stages. In [27] we studied local stability properties of two- and three-compartment models with regulated division rates of stem and progenitor cells. It was found that the intermediate stage of differentiation may lead to the emergence of an instability region in the parameter space.

The remainder of the paper is organized as follows. In Section 2 we describe two-compartment versions of the models introduced in [25]. In the first model the division rate is regulated whereas in the second model the fraction of self-renewal is regulated. In Section 3, for both models, we interpret the existence of equilibria in the terms of reproduction number of cells and prove global stability of the positive equilibrium. In Section 4 we develop the model variant to test the new hypothesis in which the fraction of differentiation is regulated. Section 5 provides numerical simulations of the model solutions illustrating stable and unstable scenarios as well as showing differences in the dynamics of the models with different regulatory mechanisms. Finally, Section 6 is devoted to biological interpretations and implications of the mathematical results of this paper.

2. Model formulation

We focus on a two-compartment version of the multi-compartment system established in [25]. The model describes time evolution of two interacting populations, undifferentiated cells and mature cells. Since the considered model is a reduction of the multicompartment architecture, the first compartment describes all dividing cells (undifferentiated cells) which are located in the bone marrow, while the second compartment is related to the post-mitotic cells which are located in the blood. In the remainder of this paper we refer to them as *stem cells* and *mature cells*, respectively.

A basic assumption is that the differentiation process takes place during cell division. A stem cell divides and gives rise to two daughter cells, each of which is either a stem cell or a mature cell. The process of producing daughter cells that remain stem cells is referred to as *self-renewal*, while the process of producing daughter cells that are mature cells is referred to as *differentiation*. We describe these processes by a per cell division rate and a fraction of self-renewal that gives the fraction of stem cells in the population of "newborn" daughter cells. The remaining fraction of newborn cells are then those who have differentiated and become mature cells, see Fig. 1.

As in [25] we assume that the extracellular signaling molecules, e.g. G-CSF cytokine, are secreted by specialized cells at a constant rate and degraded by receptor mediated endocytosis. Since the density of G-CSF receptors is maximal on mature cells, the effect of immature stages on cytokine clearance can be neglected. We assume additionally constant in time cytokine degradation by a cell-independent mechanism, e.g. by liver or kidney. Then it leads to the following equation for the cytokine concentration c,

$$c'(t) = \alpha - \beta c(t) v(t) - \gamma c(t),$$

where α, β, γ are positive constants and v is the number of mature cells. Based on studies of cytokine kinetics during infections or injuries, we assume that the time scale of cytokine dynamics is much shorter than that of the cell cycle. Applying a quasi steady state approximation, after rescaling, yields the signal intensity given by

$$c(v) := \frac{1}{1 + kv}, \tag{2.1}$$

where k is a positive constant which depends on the rates of cell dependent and cell independent degradation. The above expression reflects the heuristic assumption that the signal intensity achieves its

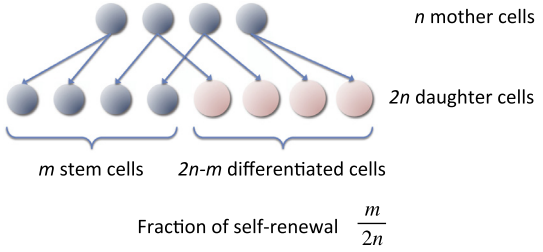

Fig. 1. Division, self-renewal and differentiation of stem cells.