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 [11] 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 inefficient to maintain homeostasis and leads to an unbounded cell growth. The potential biological implications are discussed.

Keywords: Cell production system; Regulatory mechanism; Global stability; Lyapunov function

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 [25]. 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 [19]. The relationship between cell-cycle progression and stem cell fate has been widely explored [13].

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 [15]. In [2, 10], using mathematical models formulated as delay differential equations, the authors explore biological mechanisms that cause oscillating circulating neutrophil count observed in a hematological disorder called cyclical neutropenia. From bifurcation analysis and numerical simulations the authors propose a destabilization mechanism via increasing the death rate of hematopoietic stem cell. See also [6] for a summary of related works. In [17] a single cell-based stochastic model is developed to explain constitution of stem cell pool as a self-organizing process. They assume that stem cells reside in two different signaling contexts characterizing the property of cell as either proliferating or quiescence. In [16], to overcome a time-consuming problem when simulating the agent-based model in [17], a structured population model is formulated as a system of partial differential equations. It is observed that the model captures the dynamics obtained by the agent-based model [17] in the context of modeling of disease and treatment dynamics with chronic myeloid leukemia. In [8] the authors investigate plausible controlling mechanisms of cell proliferation in mammalian olfactory epithelium with mathematical modeling. In particular, regulatory mechanisms for the length of cell cycle and for the replication probability of progenitor cells are discussed.

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The choice of regulatory mechanisms is an important modeling ingredient. It is known that the dynamics of cell proliferation and differentiation can be controlled by extracellular signaling molecules, 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 [11] a multi-compartment model of blood cell differentiation and hematopoietic reconstitution is 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 was assumed to be necessary to stabilize such a cell system [1]. Assuming short- and long-range feedbacks from either stem cells, mature cells or both populations, both normal homeostasis and oscillatory behavior were shown using linearized and global stability analysis. Numerical results in [11] showed that the positive equilibrium can be stable in the models with a single nonlinear feedback loop.

One aim of our research is to study analytical properties of the models proposed in [11] to understand better effects of different regulatory mechanisms. In this direction we analyzed local stability properties of two- and three-compartment models in [12]. It was found that the intermediate stage of differentiation is responsible for the emergence of an instability region in a parameter plane.In that paper it is assumed that the division rates of stem and progenitor cells are regulated. In the present paper we discuss two types of regulatory mechanisms, namely the mechanism of regulated division rate and of regulated fraction of self-renewal. Using two-compartmental models we show global stability of the positive steady state, where stem and mature cells coexist, for both regulatory mechanisms. Furthermore we develop another two-compartment model to investigate efficiency of the regulation of the fraction of differentiating cell instead of self-renewal fractions. The biological rationale behind the hypothesis is that overproduction of mature cells might switch on the inhibition of the differentiation process to avoid oversupply from stem cells. We show that this regulatory mechanism is inefficient and can lead to unbounded growth of stem cell population.

The remainder of the paper is organized as follows. In Section 2 we introduce two models of [11] that has two compartments. 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 the two models we respectively discuss the existence of equilibria and prove their global stability in terms of reproduction number of stem cells. We then show that at a positive equilibrium the system with the mechanism of regulated fraction of self-renewal admits less number of stem cells compared to the system with the mechanism of regulated division rate. We numerically show that different regulatory mechanisms cause different dynamical behavior of the cell population. In Section 4 we consider a model to test a new hypothesis in which the fraction of differentiation is regulated. In Section 5 we discuss and interpret our results.

2. Model formulation

First, we focus on the model which is a two-compartment version of the multi-compartment model established in [11]. The model describes the time evolution of the stem and mature cell populations. 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, by dividing, daughter cells that are stem cells, we refer to as self-renewal, the process of producing daughter cells that are mature cells, we refer to as differentiation. We here describe these processes by a per cell division rate and a fraction of self-renewal that gives the fraction of those "newborn" daughter cells that, like their mother, are stem cells. The remaining fraction of newborn cells are then those who have differentiated and become mature cells.

In [11] it is assumed that the extracellular signaling molecules are secreted by specialized cells and that this secretion is regulated by mechanisms sensitive to the amount of mature cells. By using a quasi steady state approximation of the plausible dynamics of the cytokine molecules, the signal intensity is given by

$$s(v) := \frac{1}{1+kv},$$

where k is a positive constant to take into account the sensitivity to the amount of mature cells and v is the number of mature cells. The expression reflects the heuristic assumption that the signal intensity achieves its maximum in absence of mature cells and decreases asymptotically to zero if the level of mature cells increases. Another qualitatively similar regulatory function is based on exponential dependence of signal intensity on mature cell counts, $s(v) = e^{-const \cdot v}$, similar to that in the well-known Lasota-Wazewska model [24].

Let p_w and a_w be positive constants with $a_w \in [0,1)$. We define the division rate of stem cells as

$$d_w(v) := p_w s(v) = \frac{p_w}{1+kv}.$$

The fraction of self-renewal is the fraction of progeny cells that are identical to the mother cells. It can also be interpreted as the probability that a daughter cell is of the same type as the mother cell. We define the fraction of self-renewal as

$$s_w(v) := a_w s(v) = \frac{a_w}{1+kv}.$$

Assuming that $\bar{v}$ is a level of mature cells in homeostasis, we define the corresponding constant cell division rate and the constant fraction of self-renewal by

$$\begin{aligned} \bar{p}_w := p_w s(\bar{v}) &= \frac{p_w}{1+k\bar{v}}, \\ \bar{a}_w := a_w s(\bar{v}) &= \frac{a_w}{1+k\bar{v}}. \end{aligned}$$

After perturbations of the system which are related to a drop in values of v below $\bar{v}$, the signal intensity is growing and consequently the model describes increase in the values of the regulated parameters above the values of those parameters in the homeostasis case. If the model parameters are unregulated, their values stay at the same level as during the homeostasis, i.e. in the healthy system. Consequently, one can interpret $\bar{p}_w$ as the unregulated division rate and $\bar{a}_w$ as the unregulated fraction of self-renewal. We denote by $w(t)$ the number of stem cells at time t. The expected flow of cells joining the stem cell pool at time t equals

$$(2s_w(v(t)) - 1)\, d_w(v(t))w(t).$$

On the other hand, the expected flow of cells into the pool of mature cells at time t due to differentiation of stem cells equals

$$2\,(1 - s_w(v(t)))\, d_w(v(t))w(t).$$

Then the dynamics of the two-compartment model can be formulated as

$$\begin{cases} w'(t) &= (2s_w(v(t)) - 1)d_w(v(t))w(t) - \mu_w w(t), \\ v'(t) &= 2(1 - s_w(v(t)))d_w(v(t))w(t) - \mu_v v(t), \end{cases}$$

where μ_w and μ_v are the death rates of stem and mature cells, respectively. We assume that $\mu_w > 0$ and $\mu_v > 0$. In Figure 1 we give a flow diagram for the mathematical model.

We introduce two different scenarios:

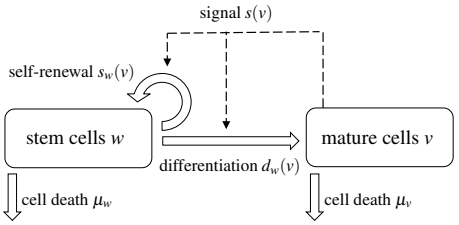


Figure 1: Compartmental diagram for stem and mature cell populations.

1. The division rate is regulated and the fraction of self-renewal is not regulated.
2. The division rate is not regulated and the fraction of self-renewal is regulated.

One has

$$\begin{cases} w'(t) &= (2\bar{a}_w - 1)d_w(v(t))w(t) - \mu_w w(t), \\ v'(t) &= 2(1 - \bar{a}_w)d_w(v(t))w(t) - \mu_v v(t) \end{cases} \tag{2.1}$$

for the first scenario whereas

$$\begin{cases} w'(t) &= (2s_w(v(t)) - 1)\bar{p}_w w(t) - \mu_w w(t), \\ v'(t) &= 2(1 - s_w(v(t)))\bar{p}_w w(t) - \mu_v v(t) \end{cases} \tag{2.2}$$

for the second scenario. For both models (2.1) and (2.2) we assume that

$$w(0) = w_0 \geq 0 \text{ and } v(0) = v_0 \geq 0 \tag{2.3}$$

as the initial conditions. Similar as in Lemma 4.1 in [22], one can prove that there exists a global nonnegative solution of (2.1) and (2.2) with initial conditions (2.3). If we take $w_0 = 0$, for both of (2.1) and (2.2), it follows that $w(t) = 0$ for $t > 0$ and that $\lim_{t\to\infty} v(t) = 0$. This implies that mature cell population can not grow without stem cells. To avoid this situation we assume that

$$w_0 > 0 \text{ and } v_0 \geq 0. \tag{2.4}$$

We define a set

$$\Sigma := \left\{(w,v) \in \mathbb{R}^2_+ | w > 0, v > 0\right\}. \tag{2.5}$$

It is easy to prove that $(w(t), v(t)) \in \Sigma$ for all $t > 0$. In particular, Σ is a positively invariant set i.e., if $(w_0, v_0) \in \Sigma$ then $(w(t), v(t)) \in \Sigma$ for all $t > 0$, see e.g. [21].

3. Stem and mature cell populations dynamics

In the following we consider global dynamics of the two models (2.1) and (2.2). For the different regulatory modes we respectively introduce (different) reproduction numbers for stem cells to characterize thresholds of existence and global stability of equilibria. In Section 3.2 we compare the amount of stem and mature cells at a positive equilibrium for each regulation mode. We discuss how the regulatory mechanisms are related to the amount of stem and mature cells at the positive equilibrium. In Section 3.2 we visualize dynamical behavior of stem and mature cell populations.

3.1. Global stability analysis

3.1.1. Regulated division rate

To analyze model (2.1) we define the *reproduction number of stem cells for regulated division rate* as

$$R_w := \frac{(2\bar{a}_w - 1)\, p_w}{\mu_w}. \tag{3.1}$$

We will interpret and discuss this number in Section 5. Using R_w the authors in [12] characterized the existence of equilibria and their local stability properties of (2.1). For the completeness of presentation, from [12] we quote the result on existence of equilibria in terms of R_w.

Theorem 3.1. *For the first model (2.1)*

1. *There always exists a trivial equilibrium.*
2. *There exists a positive equilibrium if and only if*

$$R_w > 1. \tag{3.2}$$

The positive equilibrium is given as

$$\left(\frac{(2\bar{a}_w - 1)\,\mu_v}{2\,(1-\bar{a}_w)\,\mu_w} \frac{1}{k} (R_w - 1), \frac{1}{k} (R_w - 1) \right). \tag{3.3}$$

One can see that, from the expression of equilibrium (3.3) and condition (3.1), strict positivity of model parameters is necessary for the existence of the positive equilibrium. In particular, in absence of the regulation mechanism such a positive equilibrium does not exist. The same result also holds for the second model (2.2), see (3.10) below for the expression of the equilibrium for the second model.

We have studied local stability of equilibria in [12]: the trivial equilibrium is locally asymptotically stable if $R_w < 1$ and unstable if $R_w > 1$ and the positive equilibrium is locally asymptotically stable for $R_w > 1$. In the following we show that similar threshold property holds for the global dynamics.

Theorem 3.2. *For the first model (2.1)*

1. *The trivial equilibrium is globally asymptotically stable if $R_w < 1$ and it is unstable if $R_w > 1$.*
2. *The positive equilibrium is globally asymptotically stable if and only if $R_w > 1$.*

PROOF. 1. By Theorem 3.2 in [12] the trivial equilibrium is locally asymptotically stable if $R_w < 1$ and it is unstable if $R_w > 1$. It remains to prove the global atractivity of the trivial equilibrium for $R_w < 1$. Let us assume that $R_w < 1$ holds. Then

$$w'(t) \le \mu_w (R_w - 1)\, w(t) < 0$$

and hence, $\lim_{t\to+\infty} w(t) = \lim_{t\to+\infty} v(t) = 0$ follows. Thus the trivial equilibrium is globally attractive.

2. Let us assume that $R_w > 1$. By Theorem 3.3 in [12] the positive equilibrium is locally asymptotically stable. To show the global attractivity, we employ the method of Lyapunov function. For $(w,v) \in \Sigma$, where Σ is defined in (2.5), we define the functions

$$L_{11}(w,v) := \frac{w}{w_1} - 1 - \ln \frac{w}{w_1},$$
$$L_{12}(w,v) := \frac{v}{v_1} - 1 - \frac{1}{v_1} \int_{v_1}^{v} \frac{d_w(\xi)}{d_w(v_1)} d\xi,$$

where (w_1, v_1) denotes the positive equilibrium of (2.1) which is given as (3.3). We consider the following Lyapunov function:

$$L_1(w,v) := \frac{1}{\mu_w} L_{11}(w,v) + \frac{1}{\mu_v} L_{12}(w,v). \tag{3.4}$$

To differentiate L_1 with respect to t along the system (2.1), we compute

$$\begin{aligned} &\frac{d}{dt} L_{11}(w(t), v(t)) \\ &= \left(\frac{1}{w_1} - \frac{1}{w(t)} \right) \left\{ (2\bar{a}_w - 1)\, d_w(v(t)) w(t) - \mu_w w(t) \right\}. \end{aligned}$$

Since it holds that $\mu_w = (2\bar{a}_w - 1)\, d_w(v_1)$, it follows that

$$\begin{aligned} &\frac{d}{dt} L_{11}(w(t), v(t)) \\ &= \mu_w \left(\frac{w(t)}{w_1} - 1 \right) \left(\frac{d_w(v(t))}{d_w(v_1)} - 1 \right) \\ &= \mu_w \left(\frac{w(t)}{w_1} \frac{d_w(v(t))}{d_w(v_1)} - \frac{w(t)}{w_1} - \frac{d_w(v(t))}{d_w(v_1)} + 1 \right). \end{aligned} \tag{3.5}$$

Next we compute

$$\begin{aligned} &\frac{d}{dt} L_{12}(w(t), v(t)) \\ &= \frac{1}{v_1} \left(1 - \frac{d_w(v(t))}{d_w(v_1)} \right) \left\{ 2\,(1-\bar{a}_w)\, d_w(v(t)) w(t) - \mu_v v(t) \right\}. \end{aligned}$$

Using the equality $\mu_v = 2(1-\bar{a}_w)\, d_w(v_1) w_1 \frac{1}{v_1}$, we obtain that

$$\begin{aligned}
&\frac{d}{dt} L_{12}(w(t), v(t)) \\
=&\mu_v \left(1 - \frac{d_w(v(t))}{d_w(v_1)}\right)\left(\frac{d_w(v(t))w(t)}{d_w(v_1)w_1} - \frac{v(t)}{v_1}\right) \\
=&\mu_v \left\{ \frac{d_w(v(t))w(t)}{d_w(v_1)w_1} - \frac{v(t)}{v_1} - \left(\frac{d_w(v(t))}{d_w(v_1)}\right)^2 \frac{w(t)}{w_1} \right. \\
&\left. + \frac{d_w(v(t))}{d_w(v_1)} \frac{v(t)}{v_1} \right\}. \qquad (3.6)
\end{aligned}$$

Using (3.5) and (3.6), we conclude that

$$\begin{aligned}
&\frac{d}{dt} L_1(w(t), v(t)) \\
=&-\frac{w(t)}{w_1}\left\{\left(\frac{d_w(v(t))}{d_w(v_1)}\right)^2 - 2\frac{d_w(v(t))}{d_w(v_1)} + 1\right\} \\
&+\left(-\frac{d_w(v(t))}{d_w(v_1)} + 1 - \frac{v(t)}{v_1} + \frac{d_w(v(t))}{d_w(v_1)}\frac{v(t)}{v_1}\right) \\
=&-\frac{w(t)}{w_1}\left(1 - \frac{d_w(v(t))}{d_w(v_1)}\right)^2 \\
&+\left(1 - \frac{d_w(v(t))}{d_w(v_1)}\right)\left(1 - \frac{v(t)}{v_1}\right).
\end{aligned}$$

By definition of $d_w(v)$, it holds that

$$\begin{aligned}
&\left(1 - \frac{d_w(v(t))}{d_w(v_1)}\right)\left(1 - \frac{v(t)}{v_1}\right) \\
=&\left(1 - \frac{1+kv_1}{1+kv(t)}\right)\left(1 - \frac{v(t)}{v_1}\right) \le 0.
\end{aligned}$$

Consequently, we obtain that

$$\frac{d}{dt} L_1(w(t), v(t)) \le 0. \qquad (3.7)$$

By (3.4) and (3.7) every solution in Σ is bounded. We denote by $\overline{\Sigma}$ the closure of Σ. Define

$$E := \left\{ (w(t), v(t)) \in \overline{\Sigma} \;\middle|\; \begin{array}{l} L_1(w(t), v(t)) < +\infty, \\ \frac{d}{dt} L_1(w(t), v(t)) = 0 \end{array} \right\}$$

and let M be the maximum invariant set in E. Then M consists of the positive equilibrium. By La Salle's invariance principle, see Theorem 2.1 in Chapter 2 in [21], we conclude that every solution in Σ tends to M. Thus the positive equilibrium is globally attractive.

□

3.1.2. Regulated fraction of self-renewal

For the second model (2.2) we introduce the *reproduction number of stem cells for regulated fraction of self-renewal* as

$$S_w := \frac{2a_w p_w}{\bar{p}_w + \mu_w}. \qquad (3.8)$$

We give the following result without proof, since it is straightforward.

Theorem 3.3. *For the second model (2.2)*

1. *There always exists a trivial equilibrium.*
2. *There exists a positive equilibrium if and only if*

$$S_w > 1. \qquad (3.9)$$

The positive equilibrium is given as

$$\left(\frac{(2a_w - S_w)\,\mu_v}{2(S_w - a_w)\,\mu_w}\frac{1}{k}(S_w - 1), \frac{1}{k}(S_w - 1)\right). \qquad (3.10)$$

In Theorem A.1 in the Appendix we show that the trivial equilibrium is locally asymptotically stable if $S_w < 1$ and unstable if $S_w > 1$. We prove that the positive equilibrium is locally asymptotically stable if $S_w > 1$ in Theorem A.3. In the following we show that similar threshold property holds for the global dynamics.

Theorem 3.4. *For the second model (2.2)*

1. *The trivial equilibrium is globally asymptotically stable if $S_w < 1$ and it is unstable if $S_w > 1$.*
2. *The positive equilibrium is globally asymptotically stable if and only if $S_w > 1$.*

PROOF. 1. By Theorem A.1 the trivial equilibrium is locally asymptotically stable if $S_w < 1$ and unstable if $S_w > 1$. Hence, it remains to show that the trivial equilibrium is globally stable for $S_w < 1$. Assuming that $S_w < 1$, we obtain

$$w'(t) \le (\bar{p}_w + \mu_w)(S_w - 1)\, w(t) < 0$$

and hence, $\lim_{t\to+\infty} w(t) = \lim_{t\to+\infty} v(t) = 0$ follows.

2. Let us assume that $S_w > 1$. By Theorem A.3 we have that the positive equilibrium is locally asymptotically stable. To show the global attractivity, we consider an equivalent system and then employ the method of Lyapunov function. We define

$$G(v) := 2(1 - s_w(v)) \text{ for } v \ge 0. \qquad (3.11)$$

Since we have $2s_w(v)-1=1-G(v)$, (2.2) is equivalent to the following system:

$$\begin{cases} w'(t) &= (\bar{p}_w-\mu_w)w(t)-\bar{p}_wG(v(t))w(t), \\ v'(t) &= \bar{p}_wG(v(t))w(t)-\mu_v v(t). \end{cases} \tag{3.12}$$

Now we denote by (w_2,v_2) the positive equilibrium of (2.2) which is given by (3.10). Obviously, (3.12) it has the same positive equilibrium (w_2,v_2) if (3.9) holds. Note that as $a_w<1$, $\bar{p}_w>\mu_w$ follows from (3.9). For $(w,v)\in\Sigma$, where Σ is defined in (2.5), we define the functions

$$\begin{aligned} L_{21}(w,v) &:= \frac{w}{w_2}-1-\ln\frac{w}{w_2}, \\ L_{22}(w,v) &:= \frac{v}{v_2}-1-\frac{1}{v_2}\int_{v_2}^{v}\frac{G(v_2)}{G(\xi)}d\xi \end{aligned}$$

Then we consider the following Lyapunov function:

$$L_2(w,v) := \frac{1}{\bar{p}_wG(v_2)}L_{21}(w,v)+\frac{1}{\mu_v}L_{22}(w,v). \tag{3.13}$$

To differentiate L_2 with respect to t along the system (2.2), we compute

$$\begin{aligned} &\frac{d}{dt}L_{21}(w(t),v(t)) \\ =&\left(\frac{1}{w_2}-\frac{1}{w(t)}\right)\left\{(\bar{p}_w-\mu_w)w(t)-\bar{p}_wG(v(t))w(t)\right\}. \end{aligned}$$

The equality $\bar{p}_w-\mu_w=\bar{p}_wG(v_2)$ yields

$$\begin{aligned} &\frac{d}{dt}L_{21}(w(t),v(t)) \\ =&\bar{p}_wG(v_2)\left(\frac{w(t)}{w_2}-1\right)\left(1-\frac{G(v(t))}{G(v_2)}\right) \\ =&\bar{p}_wG(v_2)\left(\frac{w(t)}{w_2}-1-\frac{w(t)}{w_2}\frac{G(v(t))}{G(v_2)}+\frac{G(v(t))}{G(v_2)}\right). \end{aligned} \tag{3.14}$$

Next, we compute

$$\begin{aligned} &\frac{d}{dt}L_{22}(w(t),v(t)) \\ =&\frac{1}{v_2}\left(1-\frac{G(v_2)}{G(v(t))}\right)\left(\bar{p}_wG(v(t))w(t)-\mu_v v(t)\right). \end{aligned}$$

Since we have $\mu_v=G(v_2)\bar{p}_ww_2\frac{1}{v_2}$, it follows that

$$\begin{aligned} &\frac{d}{dt}L_{22}(w(t),v(t)) \\ =&\mu_v\left(1-\frac{G(v_2)}{G(v(t))}\right)\left(\frac{G(v(t))}{G(v_2)}\frac{w(t)}{w_2}-\frac{v(t)}{v_2}\right) \\ =&\mu_v\left(\frac{G(v(t))}{G(v_2)}\frac{w(t)}{w_2}-\frac{v(t)}{v_2}-\frac{w(t)}{w_2}+\frac{G(v_2)}{G(v(t))}\frac{v(t)}{v_2}\right). \end{aligned} \tag{3.15}$$

Therefore, from (3.14) and (3.15), we obtain

$$\begin{aligned} &\frac{d}{dt}L_2(w(t),v(t)) \\ =&-1+\frac{G(v(t))}{G(v_2)}-\frac{v(t)}{v_2}+\frac{G(v_2)}{G(v(t))}\frac{v(t)}{v_2} \\ =&\left(1-\frac{G(v_2)}{G(v(t))}\right)\left(\frac{G(v(t))}{G(v_2)}-\frac{v(t)}{v_2}\right) \\ =&\frac{G(v(t))}{v_2}\left(1-\frac{G(v_2)}{G(v(t))}\right)\left(\frac{v_2}{G(v_2)}-\frac{v(t)}{G(v(t))}\right). \end{aligned}$$

By (3.11) the function $G(v)$ is monotone increasing for $v\geq 0$. If $\frac{v}{G(v)}$ is also monotone increasing for $v\geq 0$, then we obtain that $\frac{d}{dt}L_2(w(t),v(t))\leq 0$. From Proposition A.2 in the Appendix, we obtain

$$\begin{aligned} \frac{d}{dv}\left(\frac{v}{G(v)}\right) =&\frac{1}{G(v)}\left(1-\frac{G'(v)}{G(v)}v\right) \\ =&\frac{1}{G(v)}\left(1+\frac{s_w'(v)}{1-s_w(v)}v\right) \\ >&0. \end{aligned}$$

Thus, $\frac{v}{G(v)}$ is monotone increasing for $v\geq 0$. Hence, we obtain that

$$\frac{d}{dt}L_2(w(t),v(t))\leq 0. \tag{3.16}$$

By (3.13) and (3.16) every solution in Σ is bounded. We denote by $\overline{\Sigma}$ the closure of Σ. Define

$$E := \left\{(w(t),v(t))\in\overline{\Sigma}\;\middle|\; \begin{array}{l} L_2(w(t),v(t))<+\infty, \\ \frac{d}{dt}L_2(w(t),v(t))=0 \end{array}\right\}$$

and let M be the maximum invariant set in E. Then M consists of the positive equilibrium. By La Salle's invariance principle, see Theorem 2.1 in Chapter 2 in [21], we conclude that every solution in Σ tends to M. Thus the positive equilibrium is globally attractive.

□

3.2. The size of cell population at the positive equilibrium

It is not wrong what stands here but definitely it should be told from different perspective; I have to think about it

For the two regulation modes, regulated division rate and regulated fraction of self-renewal, we show that the sizes of both populations at the positive equilibrium are ordered independently of parameter values. We assume that $R_w>1$ and $S_w>1$ hold. We denote by (w_d,v_d) and (w_s,v_s) the sizes of stem and mature cell populations at the positive equilibrium for regulated division rate and for regulated fraction of self-renewal, respectively.

Theorem 3.5. *Let us assume that $R_w > 1$ and $S_w > 1$ hold. Then*

$$w_s < w_d \text{ and } v_s < v_d.$$

PROOF. Using respective definitions of R_w and S_w, (3.1) and (3.8), one obtains the following relation:

$$R_w - 1 > \frac{\mu_w}{\mu_w + p_w}(R_w - 1) = S_w - 1.$$

Thus $v_d > v_s$ holds from (3.3) and (3.10). From a direct calculation, it holds that

$$\frac{2a_w - 1}{2(1-a_w)} > \frac{2a_w - S_w}{2(S_w - a_w)}$$

if $S_w > 1$. Therefore, $w_d > w_s$ holds from (3.3) and (3.10).

□

At the equilibrium the cell production system with regulated division rate has more stem and mature cells than the system with the mechanism of regulated fraction of self-renewal. In the following we explain how different regulatory mechanisms cause the different sizes of both populations. We introduce two *regulated* reproduction numbers of stem cells for regulated division rate and for regulated fraction of self-renewal,

$$r_d(v) := \frac{(2a_w - 1)\, d_w(v)}{\mu_w}$$

and

$$r_s(v) := \frac{(2s_w(v) - 1)\, p_w}{\mu_w},$$

respectively. These reproduction numbers can be interpreted as the expected net number of stem cells coming into the stem cell compartment caused by one stem cell via self-renewal with regulation in a time that a stem cell would be expected to live without division. Then equilibrium conditions for the mature cells are defined via

$$r_d(v_d) = 1 \text{ and } r_s(v_s) = 1, \tag{3.17}$$

respectively. The form of the reproduction number for regulated fraction of self-renewal suggests that this mechanism reduces the influx of stem cells. One can see that $2a_w d_w(v) = 2s_w(v)p_w$ and that $d_w(v) < p_w$ for $v > 0$. This implies that the regulation of the division rate reduces the inflow as much as the mechanism of the regulated fraction of self-renewal, but the former additionally also reduces the outflow of stem cells. Thus

$$(2a_w - 1)\, d_w(v) > (2s_w(v) - 1)\, p_w, \tag{3.18}$$

which implies

$$r_d(v) > r_s(v). \tag{3.19}$$

Both of the regulated reproduction numbers decrease with respect to the number of mature cells. Hence there have to be more mature cells to obtain a higher reduction of the stem cells for regulated division rate to satisfy the condition (3.17). It holds that

$$v_d > v_s. \tag{3.20}$$

Next we consider the number of stem cells at the equilibrium point, which can be expressed as

$$w_d(v) := \frac{\mu_v v}{2\,(1-a_w)\, d_w(v)}$$

for regulated division rate and

$$w_s(v) = \frac{\mu_v v}{2\,(1 - s_w(v))\, p_w},$$

for regulated fraction of self-renewal. Similar to those discussed above one can prove

$$2\,(1 - s_w(v))\, p_w > 2\,(1-a_w)\, d_w(v), \tag{3.21}$$

which implies that the number of mature cells produced by one stem cell per unit of time for regulated fraction of self-renewal is bigger than that for regulated division rate. From (3.21), one can see

$$w_s(v) < w_d(v). \tag{3.22}$$

The size of the stem cell population at the equilibrium is given as $w_d(v_d)$ and $w_s(v_s)$ for regulated division rate and for regulated fraction of self-renewal, respectively. It is easy to see that w_d and w_s are increasing functions. This implies that if more mature cells exist, more stem cells are required to maintain mature cells. From (3.20) we can conclude that at the equilibrium the mechanism of regulated division rate has more stem cells than the mechanism of regulated fraction of self-renewal i.e.,

$$w_s(v_s) < w_d(v_d).$$

Finally, by a simple calculation, we can also compare the relative proportion of stem cells to mature cells when the sizes of both populations are at the positive equilibrium. We omit the proof since it is straightforward.

Theorem 3.6. *Let us assume that $R_w > 1$ and $S_w > 1$ hold. Then*

$$\frac{w_s}{v_s} < \frac{w_d}{v_d}.$$

One can see that, to supply a fixed number of mature cells, less stem cells are required in the mechanism of regulated fraction of self-renewal compared to the case of regulated division rate. It is suggested that the regulating the fraction of self-renewal is more efficient than regulating the division rate.

3.3. Simulations of solution behavior

In this subsection we show numerical simulations for the two models, regulated division rate (2.1) and regulated fraction of self-renewal (2.2). We choose two sets of parameters such that i) respective reproduction numbers exceed one and ii) are less than one. We present the parameter values and their interpretations in Tables 1 and 2.

In Figure 2 we plot two vector fields in the w-v- state space for both regulation modes where we set parameter values as in Table 1. Consider a situation in which there are a large number of mature cells such that they exceed the equilibrium level. In Figure 2-(a), for regulated division rate, v decreases to the equilibrium point if $w < w_d(v)$ holds. In Figure 2-(b), for regulated fraction of self-renewal, there are two possible behaviors of v: v increases if $w > w_s(v)$ whereas v decreases if $w < w_s(v)$. Since the number of mature cells can increase, even if it exceeds the equilibrium level, one may consider that the system does not react properly to the large quantity of mature cells. However, at the same time, the number of stem cells decreases due to the regulated fraction of self-renewal. Then small number of stem cells suppresses the supply of the mature cells. Finally, the number of mature cells decreases. Repeating this process, they approach the equilibrium point. Since $w_s(v) < w_d(v)$ holds from (3.22), this oscillatory-like behavior seems to easily occur in the mechanism of regulated fraction of self-renewal.

In Figure 3 we present the graph trajectory of w and v with respect to time for both regulation modes. For the case of regulated division rate, each solution trajectory takes at most one hump while, for the case of regulated fraction of self-renewal, there are two or three humps and each trajectory is damped oscillation to the equilibrium. Figure 3 suggests that solutions for regulated fraction of self-renewal reach the equilibrium faster than solutions for regulated division rate.

In Figures 4 and 5 we plot two vector fields and the corresponding graphs for time evolution of the solution of (2.1) and (2.2) when we fix parameters as in Table 2. Every solution converges to the trivial equilibrium.

4. Regulated fraction of differentiation

We consider a regulatory mechanism in which the fraction of cell differentiation is regulated by the amount of mature cells. The fraction of differentiation in absence of the regulation is given as $1-a_w$. As we derive the form of the regulated fraction of self-renewal in Section 2, we obtain

$$\tilde{s}_w(v) := (1-a_w)s(v) = \frac{1-a_w}{1+kv}$$

as the regulated fraction of differentiation. One can interpret $1-\tilde{s}_w(v)$ as the fraction of self-renewal. The population dynamics is then formulated as

$$\begin{cases} w'(t) &= \{2\,(1-\tilde{s}_w(v(t))) - 1\}\,\bar{p}_w w(t) - \mu_w w(t), \\ v'(t) &= 2\tilde{s}_w(v(t))\bar{p}_w w(t) - \mu_v v(t), \end{cases}$$

which can be rewritten as

$$\begin{cases} w'(t) &= (1-2\tilde{s}_w(v(t)))\,\bar{p}_w w(t) - \mu_w w(t), \\ v'(t) &= 2\tilde{s}_w(v(t))\bar{p}_w w(t) - \mu_v v(t). \end{cases} \tag{4.1}$$

We set (2.4) as the initial conditions of (4.1).

4.1. Stability analysis

First, we formulate the result on the existence of equilibria in terms of S_w.

Theorem 4.1. *For model (4.1)*

1. *There always exists a trivial equilibrium.*
2. *There exists a positive equilibrium if and only if*

$$S_w \in (a_w, 1)\,. \tag{4.2}$$

The positive equilibrium is given as

$$\left(\frac{2a_w - S_w}{2\,(S_w - a_w)}\frac{\mu_v}{\mu_w}\frac{1}{k}\frac{a_w\,(1-S_w)}{S_w - a_w}, \frac{1}{k}\frac{a_w\,(1-S_w)}{S_w - a_w}\right).$$

Next we formulate stability results for model (4.1) in terms of S_w. In Appendix we prove the following result.

Theorem 4.2. *For model (4.1)*

1. *The trivial equilibrium is locally asymptotically stable if $S_w < 1$ and unstable if $S_w > 1$.*
2. *Let us assume that (4.2) holds. Then the positive equilibrium is unstable.*

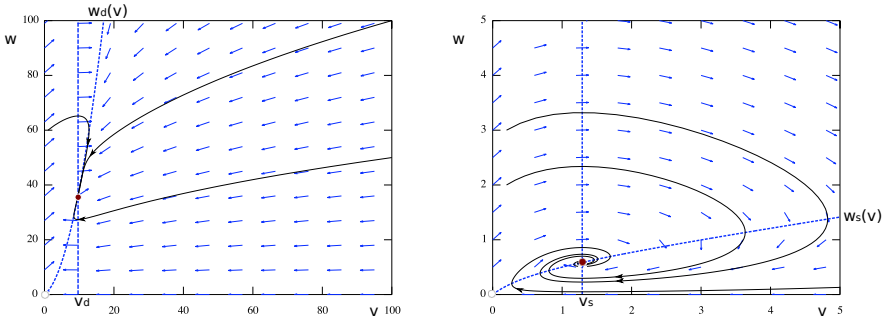
Finally we show that $w(t)$ and $v(t)$ tend to infinity if $S_w > 1$.

parameter	interpretation	value 1
a_w	fraction of self-renewal of the stem cells	0.8
p_w	division rate of the stem cells	1.3 per unit of time
k	regulation constant	0.3
μ_w	death rate of the stem cells	0.2 per unit of time
μ_v	death rate of the mature cells	0.5 per unit of time
S_w	reproduction number	1.30

Table 1: Parameters and their values. Respective reproduction numbers exceed one.

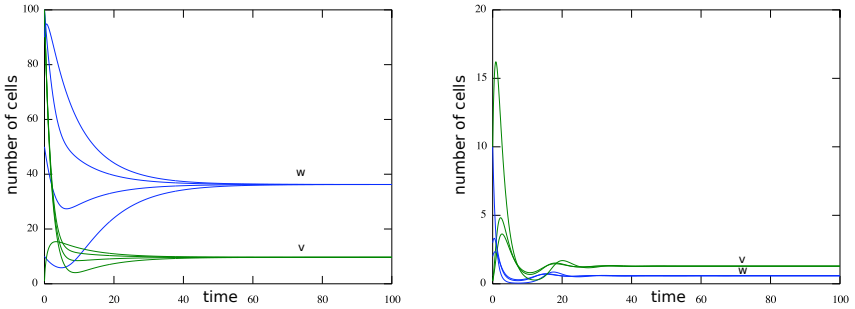
parameter	interpretation	value
a_w	fraction of self-renewal of the stem cells	0.4
p_w	division rate of the stem cells	1.3 per unit of time
k	regulation constant	0.3
μ_w	death rate of the stem cells	0.2 per unit of time
μ_v	death rate of the mature cells	0.5 per unit of time
S_w	reproduction number	0.65

Table 2: Parameters and their values. Respective reproduction numbers are less than one.



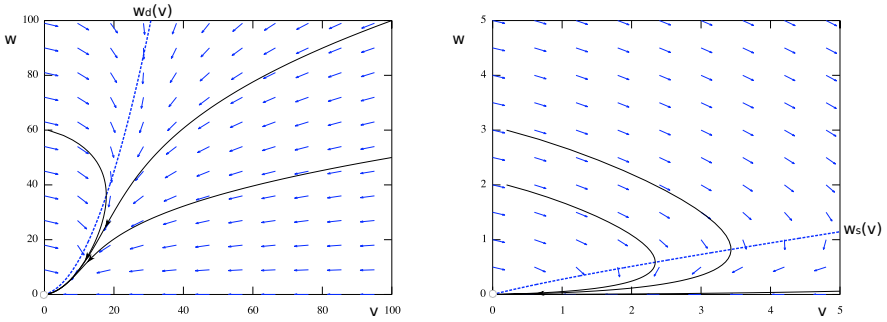
(a) regulated division rate (b) regulated fraction of self-renewal

Figure 2: Phase portrait of w, the amount of stem cells, and v, the amount of mature cells, for regulated division rate (a) and for regulated fraction of self-renewal (b) when the respective reproduction numbers exceed one. The respective vertical line and the dashed curve denote $v = v_{d,s}$ and $w = w_{d,s}(v)$, respectively. Each intersection of the vertical line and dashed curve is the positive equilibrium and the origin is the trivial equilibrium. In both figures (a) and (b) every solution converges to the positive equilibrium.



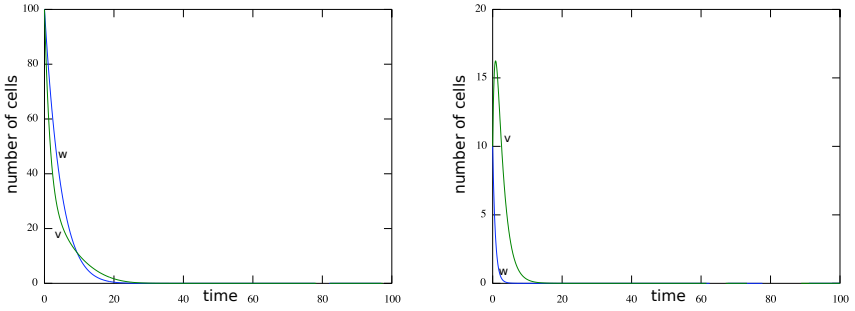
(a) regulated division rate (b) regulated fraction of self-renewal

Figure 3: Behavior of w, the amount of stem cells, and v, the amount of mature cells, with respect to time for regulated division rate (a) and for regulated fraction of self-renewal (b) when respective reproduction numbers exceed one. In both figures (a) and (b) every solution converges to the positive equilibrium.



(a) regulated division rate (b) regulated fraction of self-renewal

Figure 4: Phase portrait of w, the amount of stem cells, and v, the amount of mature cells, for regulated division rate (a) and for regulated fraction of self-renewal (b) when respective reproduction numbers are less than one. The respective dashed curve denotes $w = w_{s,d}(v)$. The origin is the trivial equilibrium. In both figures (a) and (b) every solution converges to the trivial equilibrium.



(a) regulated division rate (b) regulated fraction of self-renewal

Figure 5: Behavior of w, the amount of stem cells, and v, the amount of mature cells, with respect to time for the case of regulated division rate (a) and regulated fraction of self-renewal (b) when respective reproduction numbers are less than one. In both figures (a) and (b) every solution converges to the trivial equilibrium.

Theorem 4.3. *Let us assume that $S_w > 1$ holds. Then*

$$\lim_{t\to+\infty} w(t) = \lim_{t\to+\infty} v(t) = +\infty.$$

PROOF. Since we have

$$\begin{aligned} w(t) =& w_0 \exp\left[\int_0^t \left\{\left(1-2\tilde{s}_w(v(s))\right)\bar{p}_w - \mu_w\right\} ds\right] \\ >& w_0 \exp\left\{\left(\bar{p}_w + \mu_w\right)\left(S_w - 1\right) t\right\}, \end{aligned}$$

it holds that

$$\lim_{t\to+\infty} w(t) = +\infty.$$

Then $\lim_{t\to+\infty} v(t) = +\infty$ follows.

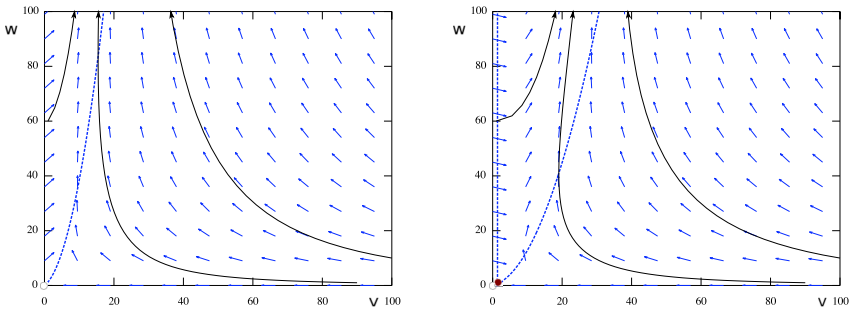
□

4.2. Simulations of solution behavior

Like in Section 3.3, we plot vector fields and corresponding graphs for time evolution of the solutions. We use the same parameter set given as in Tables 1 and 2. For $S_w > 1$ every solution tends to infinity (Figures 6-(a)). For $S_w < 1$ we numerically found that there exist solutions which tend to infinity, see Figure 6-(b). In Figure 7-(a) we focus on the vector field around the trivial equilibrium. One can see that there are two types of solutions depending on the initial conditions. Some solutions converge to the trivial equilibrium. However, there are solutions which do not approach the vicinity of the trivial equilibrium and tend to infinity.

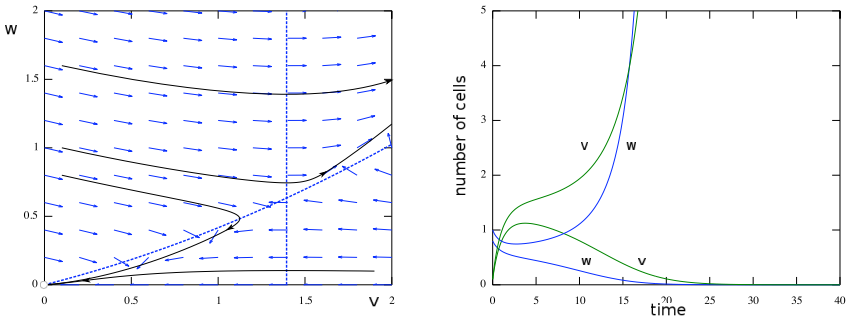
5. Discussion

We have analyzed two-compartmental models of [11] describing stem cell maturation that account for self-renewal, differentiation and cell death. In the mathematical models (2.1) and (2.2) different regulatory



(a) $S_w > 1$ (b) $S_w < 1$

Figure 6: Phase portrait of w, the amount of stem cells, and v, the amount of mature cells for regulated fraction of differentiation when the respective reproduction number exceeds one (a) and when the respective reproduction number is less than one (b). The respective dashed curve denotes the v-nullcline and the vertical line denotes the w-nullcline. In (a) the intersection of the dashed curve and the vertical line is the positive equilibrium. In both figures (a) and (b) every solution tend to infinity.



(a) Vector field (b) Time evolution of the solutions

Figure 7: Phase portrait of w, the amount of stem cells, and v, the amount of mature cells for regulated fraction of differentiation when the reproduction number is less than one (a). Solutions with four different initial conditions are illustrated. Two solutions approach to the trivial equilibrium while other solutions do not tends to the trivial equilibrium. The solution behavior with respect to time when the reproduction number is less than one (b). One solution tends to the trivial equilibrium while another solution tends to infinity.

mechanisms, namely regulated division rate and regulated fraction of self-renewal, are respectively featured. Stability analysis of basic models including different modes of regulation shall help understanding what mechanisms may be efficient to regulate homeostasis. In particular, global stability analysis may be a suitable way to explain the dynamics of the system after a big perturbation, such as chemotherapy treatment or bone marrow transplantation. In Section 3.1 we respectively analyzed the existence of equilibria and their global stability for models with regulated division rate and with regulated fraction of self-renewal. We compare the number of cell population for the two regulatory mechanisms in Section 3.2. The comparison result may suggest that the mechanism of regulated self-renewal is efficient to control the cell production system. We then numerically observe population dynamical behavior in Section 3.2.

To show the global stability we employed a method of Lyapunov function, which is widely used for analyzing stability properties of mathematical models [21]. In general, there is no unified method to construct Lyapunov functions. We have been inspired by Lyapunov functions introduced in [7] to analyze global stability of epidemiological models. However, since the cell population dynamics considered by us is based on significantly different type of interactions than in the infectious disease model, it is not straightforward to apply the same type of Lyapunov functions. For (2.1) and (2.2) we respectively find a suitable way to formulate Lyapunov functions and to compute the time derivatives. As a remark, we mention the difference of proofs for Theorems

3.2 and 3.4. In the proof of Theorem 3.4, we consider a different formulation of the model (3.12) that facillitates us to apply the Lyapunov function. We also use a specific property found in Proposition A.2 to compute the derivative of the Lyapunov function. We also note that it seems to be not straightforward to construct a Lyapunov function for the model that has both regulatory mechanisms, regulated division rate and regulated fraction of self-renewal.

We formulated global stability results using two different reproduction numbers. The first reproduction number R_w, which is defined as (3.1), can be interpreted as the expected net number of stem cells coming into the stem cell compartment due to one stem cell via self-renewal in the time that a stem cell would be expected to live given that it would not divide. This reproduction number is introduced in [12] to analyze the existence and local stability of equilibria of the first model (2.1). The analysis of local and global stability properties of the second model (2.2) for regulated fraction of self-renewal is new. The expression of the positive equilibrium, given in (3.10), motivates us to use the different reproduction number S_w which is defined as (3.8). This reproduction number can be interpreted as the expected number of stem cells produced by one cell through self-renewal during its expected lifetime. For the first and second models we prove that a positive equilibrium exists and that it is globally asymptotically stable, if and only if, respective reproduction numbers exceed one, i.e., if and only if, $R_w > 1$ or $S_w > 1$, see Theorems 3.2 and 3.4. The global stability of the positive equilibrium rules out the existence of periodic behavior of solutions. Thus our results indicate that the number of stem and mature cells from any initial state reaches the neighborhood of the equilibrium after sufficient time has elapsed. We also prove that the trivial equilibrium is globally asymptotically stable if the respective reproduction numbers are less than one.

Both threshold parameters, R_w and S_w, play the same role in the characterization of the dynamics of the first and second model, although their interpretations are different. It is easy to prove that $R_w > 1$ if and only if $S_w > 1$ and that both conditions are equivalent to

$$a_w > \frac{1}{2}\left(1 + \frac{\mu_w}{p_w}\right). \tag{5.1}$$

We see that (5.1) together with the consistency requirements $a_w < 1$, $\mu_w > 0$ and $p_w > 0$ imply that $p_w > \mu_w$, i.e., that the division rate should be greater than the mortality rate. Moreover, they imply that $a_w > \frac{1}{2}$, i.e., that fraction of self-renewal should exceeds $\frac{1}{2}$. The condition $S_w > 1$ says that the expected number of stem cells

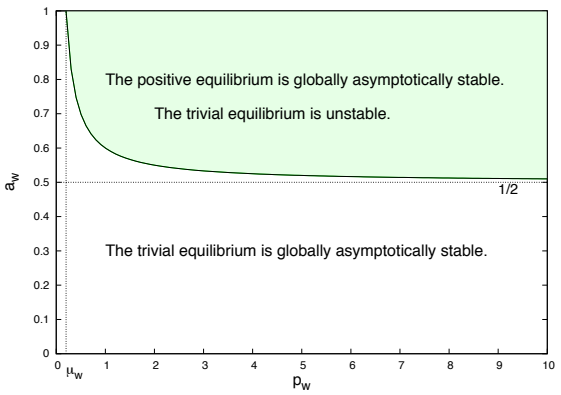


Figure 8: The stability boundary of the positive and trivial equilibrium in the (p_w, a_w)-parameter plane for regulated division rate and for regulated fraction of self-renewal. The shaded region is the stability region of the positive equilibrium. The vertical line represents $p_w = \mu_w$.

produced by one cell through self-renewal during its expected lifetime should exceed one. In the first two models, (2.1) and (2.2), as often in population dynamics [4], the equilibrium at the population level can be characterized by the requirement that every individual on average replaces itself, which in our case amounts to the requirement that $S_w > 1$. In Figure 8 we plot the stability region of both equilibria in the (p_w, a_w)-parameter space after fixing $\mu_w = 0.2$. The choice of p_w and a_w as free parameters allows a graphical representation of much of the discussed information.

To compare qualitative aspects of those regulatory modes, two-compartmental models seem to be a suitable setting due to the mathematical tractability, although the analysis of three-compartmental models is not impossible, see [12]. We found that the intermediate stage of differentiation is responsible for the emergence of an instability region in a parameter plane. For the same reason, some possible feedback mechanisms are not explicitly considered. For example, a quiescent phase of stem cells is not explicitly incorporated in the model. It is known that cell death is regulated by erythropoietin [3], which is not considered here.

In tissues that regenerate with certain frequency, homeostasis requires that the total number of stem and mature cells remains stable to avoid unrequested tissue expansion or extinction. This equilibrium may be achieved by exquisite regulation of the stem and mature cell populations. The molecular regulatory elements that control this equilibrium remain largely un-

resolved. However, in certain tissues, insights into the mechanisms of stem cell regulation and the signaling pathways involved are starting to be revealed. For example, *in vivo* and *in vitro* assays have shown the competition for contact between $Lgr5^{hi}$ cells with Paneth cell surface to have access to the signals that maintain stem cell competence in the intestine, such as Notch and Wnt [18]. In the mammary gland, estrogen can reduce the expression of key stem cell markers such as Nanog and Sox2 to influence stem cell fate [20]. Interestingly, the conclusions from our first and second models suggest that individual cells may be regulated by signals received from the environment and, independently of whether the main level of regulation occurs during the process of self-renewal or cell division rate, a steady state is reached. This may explain the possibility that most cells and organisms survive and manage to ignore many of the perturbations in their environment.

In Section 4, we developed a model (4.1), in which the regulation of the self-renewal fraction was replaced by the regulation of the fraction of cell differentiation. In this scenario, a large number of mature cells regulates the fraction of stem cell's differentiation to avoid the oversupply. Thus one may expect that homeostasis can be reached. However, contrary to one's expectation, we prove that the positive equilibrium is unstable, if it exists, and the number of stem and mature cells always tends to infinity if the reproduction number exceeds one, i.e., if $S_w > 1$. In this regulatory mechanism, the fraction of self-renewal increases as the size of mature cell population increases. Since the condition $S_w > 1$ implies that the stem cell population grows in absence of mature cells, the mature cell population gives a positive feedback to the growth of the stem cell population. Thus there is no positive equilibrium for the stem cell population and the number of stem cells tends to infinity. We also numerically found that this model can permit unbounded solutions even if the reproduction number is less than one. In Figure 9 we express parameter regions for unbounded growth of populations and stability of equilibria in the (p_w, a_w)-parameter space after fixing $\mu_w = 0.2$.

The elimination of the elaborated stem cell control and the exclusive regulation of the fraction of cell differentiation leads to unbounded growth, which may reflect the disturbed alterations of cell proliferation observed during tumorigenesis. Tumors are formed by heterogenous cell populations that include increased stem cell content and indiscriminated cell growth of more mature cells. In fact, the higher proportion of stem cells in a tumor correlates with the poorer prognosis of the cancer [14, 23]. Thus, this model may reveal the need for regulated control of the stem cell population, either at the self-renewal or cell division rate, to ensure cell homeostasis.

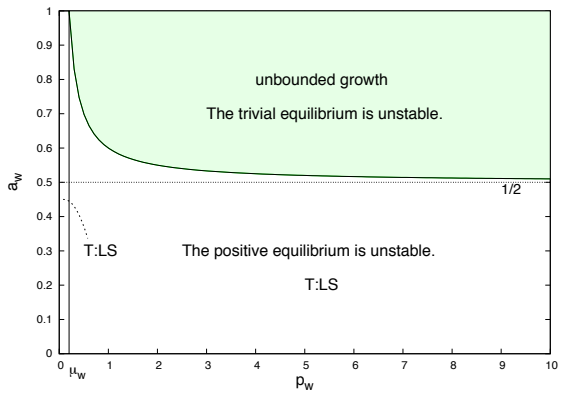


Figure 9: Parameter regions for unbounded growth of cell population and stability of the trivial and the positive equilibrium in the (p_w, a_w)-parameter plane for regulated fraction of differentiation. The curve represents the condition, $S_w = 1$. The vertical line represents $p_w = \mu_w$. T:LS denotes the local stability region of the trivial equilibrium.

Acknowledgement

Ph.G. and Y.N. were partially supported by the Grant MTM2010-18318 of the MICINN, Spanish Ministry of Science and Innovation. A.MC was supported by ERC Starting Grant "Biostruct" and Emmy Noether Programme of German Research Council (DFG). A.MC also would like to acknowledge Collaborative Research Center, SFB 873 "Maintenance and Differentiation of Stem Cells in Development and Disease". M.V. would like to thank the Institute of Health Carlos III, MICINN, and the Departments of Education and Health of the Government of the Autonomous Community of the Basque Country.

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A. Appendix

A.1. Asymptotic stability of equilibria of (2.2)

First, we present the stability of the trivial equilibrium without the proof.

Theorem A.1. *The trivial equilibrium of (2.2) has two real eigenvalues* $(\bar{p}_w+\mu_w)(S_w-1)$ *and* $-\mu_v$ *and is locally asymptotically stable if*

$$S_w < 1 \tag{A.1}$$

and it is unstable if (3.9) holds.

Next we study the stability of the positive equilibrium. We give the following proposition.

Proposition A.2. *It holds that*

$$1+\frac{s_w'(v)}{1-s_w(v)}v>0 \ \textit{for} \ v\geq 0. \tag{A.2}$$

PROOF. We denote by the second component of the positive equilibrium of (2.2), which is given as (3.10). It follows that

$$1+\frac{s_w'(v_2)}{1-s_w(v_2)}v_2 = 1-\frac{a_w}{S_w-a_w}\left(1-\frac{1}{S_w}\right)>0 \tag{A.3}$$

for $S_w>1$. The inequality $1-s_w(v)>0$ holds by definition. A direct computation yields

$$\begin{aligned}
&1-s_w(v)+vs_w'(v)\\
=&1-\frac{a_w}{1+kv}-\frac{a_wkv}{(1+kv)^2}\\
=&\frac{1}{(1+kv)^2}\left\{(1+kv)^2-a_w(1+kv)-a_wkv\right\}\\
=&\frac{1}{(1+kv)^2}\left\{(1-a_w)+2(1-a_w)kv+k^2v^2\right\}\\
>&0
\end{aligned}$$

for $v\geq 0$. Thus we obtain (A.2). Next we show (A.3). Since we have $1+kv_2=S_w$ from (3.10) in Theorem 3.3, we conclude

$$\begin{aligned}
\frac{s_w'(v_2)}{1-s_w(v_2)}v_2 &= -\frac{1}{1-\frac{a_w}{1+kv_2}}\left(\frac{a_w}{1+kv_2}\frac{kv_2}{1+kv_2}\right)\\
&= -\frac{a_w}{S_w-a_w}\left(1-\frac{1}{S_w}\right).
\end{aligned}$$

Hence, (A.3) follows.

□

Let us assume that (3.9) holds. For the eigenvalues associated to the positive equilibrium, we introduce the following positive constants

$$\zeta_1 := \mu_v \left\{ 1 - \frac{a_w}{S_w - a_w} \left(1 - \frac{1}{S_w} \right) \right\},$$
$$\zeta_2 := \frac{2a_w}{2a_w - S_w} \mu_w \mu_v \left(1 - \frac{1}{S_w} \right).$$

Theorem A.3. *Let us assume that (3.9) holds. The positive equilibrium of (2.2) has two eigenvalues $\lambda_i, i = 1,2$ where*

$$\lambda_{1,2} = \frac{1}{2} \left\{ -\zeta_1 \pm \left(\zeta_1^2 - 4\zeta_2 \right)^{\frac{1}{2}} \right\} \tag{A.4}$$

and $\lambda_{1,2}$ lie in the left half plane. Hence, the positive equilibrium is locally asymptotically stable.

PROOF. We introduce the following functions.

$$f_{w,1}(v) := (2s_w(v) - 1)\, \bar{p}_w,$$
$$f_{w,2}(v) := 2\,(1 - s_w(v))\, \bar{p}_w.$$

We denote by (w_2, v_2) the positive equilibrium of (2.2) which is given as (3.10). For the positive equilibrium it holds

$$f_{w,1}(v_2) - \mu_w = 0 \text{ and } w_2 = \frac{\mu_v v_2}{f_{w,2}(v_2)}.$$

By dropping the index of w_2 and v_2, we obtain the characteristic equation:

$$0 = \lambda \left\{ \lambda + \mu_v \left(1 - \frac{f'_{w,2}(v)}{f_{w,2}(v)} v \right) \right\} - f'_{w,1}(v) \mu_v v. \tag{A.5}$$

By a direct calculation and Proposition A.2, it follows that

$$1 - \frac{f'_{w,2}(v)}{f_{w,2}(v)} v = 1 + \frac{s'_w(v)}{1 - s_w(v)} v$$
$$= 1 - \frac{a_w}{S_w - a_w} \left(1 - \frac{1}{S_w} \right)$$

and that

$$-f'_{w,1}(v) v = (\bar{p}_w + \mu_w) \left(1 - \frac{1}{S_w} \right)$$
$$= \frac{2a_w}{2a_w - S_w} \mu_w \left(1 - \frac{1}{S_w} \right).$$

Hence, (A.5) becomes $0 = \lambda^2 + \zeta_1 \lambda + \zeta_2$. Therefore, $\lambda_{1,2}$ are as stated in (A.4) and lie in the left half plane.

□

A.2. Asymptotic stability of equilibria of (4.1)

Proof of Theorem 4.1 It is obvious that there always exists the trivial equilibrium. Assume that there exists a positive equilibrium (w_3, v_3). From the first equation of (4.1) it follows that

$$0 = \left(1 - 2\frac{1 - a_w}{1 + k v_3} \right) \bar{p}_w - \mu_w$$
$$= \left(1 - 2\frac{1 - a_w}{1 + k v_3} \right) \frac{S_w}{2a_w - S_w} \mu_w - \mu_w$$
$$= \frac{2\mu_w}{2a_w - S_w} \left\{ S_w - a_w - \frac{S_w (1 - a_w)}{1 + k v_3} \right\}.$$

Then we obtain

$$v_3 = \frac{1}{k} \left\{ \frac{S_w (1 - a_w)}{S_w - a_w} - 1 \right\} = \frac{1}{k} \frac{a_w}{S_w - a_w} (1 - S_w).$$

Now we have

$$\tilde{s}_w(v_3) = \frac{S_w - a_w}{S_w}.$$

From the second equation of (4.1) w_3 is given as

$$w_3 = \frac{\mu_v v_3}{2\tilde{s}_w(v_3) \bar{p}_w}$$
$$= \frac{S_w \mu_v}{2\,(S_w - a_w)} \left(\frac{S_w}{2a_w - S_w} \mu_w \right)^{-1} v_3$$
$$= \frac{2a_w - S_w}{2\,(S_w - a_w)} \frac{\mu_v}{\mu_w} v_3.$$

One can see that (4.2) if and only if $w_3 > 0$ and $v_3 > 0$.

□

Proof of Theorem 4.2 For the trivial equilibrium we obtain the characteristic equation as

$$\{ (2a_w - 1)\, \bar{p}_w - \mu_w - \lambda \} (-\mu_v - \lambda) = 0.$$

The characteristic equation has two roots $\lambda = -\mu_v$ and

$$\lambda = (2a_w - 1)\, \bar{p}_w - \mu_w = (\bar{p}_w + \mu_w)\, (S_w - 1).$$

Thus if $S_w < 1$ then every roots are negative and if $S_w > 1$ there exists a positive root from which we obtain the stability results for the trivial equilibrium. Next we consider the characteristic equation for the positive equilibrium. We introduce the following functions:

$$f_{w,1}(v) := (1 - 2\tilde{s}_w(v))\, \bar{p}_w,$$
$$f_{w,2}(v) := 2\tilde{s}_w(v) \bar{p}_w.$$

We denote by (w_3, v_3) the positive equilibrium. It holds

$$f_{w,1}(v_3) - \mu_w = 0 \text{ and } w_3 = \frac{\mu_v v_3}{f_{w,2}(v_3)}.$$

By dropping the index of w_3 and v_3, we obtain the characteristic equation:

$$0 = \lambda \left\{ \lambda + \mu_v \left(1 - \frac{f'_{w,2}(v)}{f_{w,2}(v)} v \right) \right\} - f'_{w,1}(v)\mu_v v. \quad \text{(A.6)}$$

By using an relation that

$$\bar{p}_w = \frac{\mu_w S_w}{2a_w - S_w},$$

it follows that

$$\begin{aligned} 1 - \frac{f'_{w,2}(v)}{f_{w,2}(v)} v &= 1 + \frac{s'_w(v)}{s_w(v)} = 1 + \frac{kv}{1+kv} \\ &= 1 + \frac{a_w(1-S_w)}{S_w(1-a_w)} \end{aligned}$$

and

$$\begin{aligned} -f'_{w,1}(v)v &= 2\bar{s}'_w(v)\bar{p}_w v \\ &= -\frac{2(1-a_w)}{1+kv}\frac{kv}{1+kv}\bar{p}_w \\ &= -\mu_w \frac{2a_w(1-S_w)(S_w-a_w)}{S_w(1-a_w)(2a_w-S_w)}. \end{aligned}$$

Hence, (A.6) becomes $0 = \lambda^2 + \zeta_1\lambda + \zeta_2$, where

$$\begin{aligned} \zeta_1 &:= \mu_v \left\{ 1 + \frac{a_w(1-S_w)}{S_w(1-a_w)} \right\}, \\ \zeta_2 &:= -\mu_w \frac{2a_w(1-S_w)(S_w-a_w)}{S_w(1-a_w)(2a_w-S_w)}. \end{aligned}$$

Therefore the characteristic equation has two roots $\lambda_i,\ i = 1,2$ given as

$$\lambda_{1,2} = \frac{1}{2}\left\{ -\zeta_1 \pm \left(\zeta_1^2 - 4\zeta_2\right)^{\frac{1}{2}} \right\}.$$

Since $\xi_2 < 0$, one root is positive. Hence the positive equilibrium is unstable.

□