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A MODEL FOR STEM CELL POPULATION DYNAMICS WITH REGULATED MATURATION DELAY

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Abstract. We develop a structured population model for the maturation process of stem cells in the form of a state-dependent delay differential equation. Moreover, results on existence, uniqueness and positivity of solutions as well as conditions of existence for equilibria and representations of these are established. We give biological interpretations for the conditions of existence of equilibria.

1. **Introduction.** Stem cells are key players during development and tissue regeneration. They are defined by their ability to self-renew and produce more stem cells and their ability to differentiate [24]. During the development from stem cells to fully mature cells various processes at the cellular level drive the dynamics of the cell population. These include division, self-renewal, differentiation and mortality (apoptosis). Self-renewal means that after a division one or both daughter cells are of the same cell-type as the mother, whereas differentiation means that one or both daughters are of a type different from that of the mother, see Figure 1. In certain tissues, e.g. the hematopoietic system [23], the steps involved in this maturation process are well defined, while in others, such as the mammary gland, it is uncertain through how many stages cells differentiate and thus how many subpopulations of progenitors exist [12]. Regulation of cell fate decisions in the stem cell pool is critical to influence the production of mature cells, both, during homeostasis and to enable rapid responses when required. Even though different

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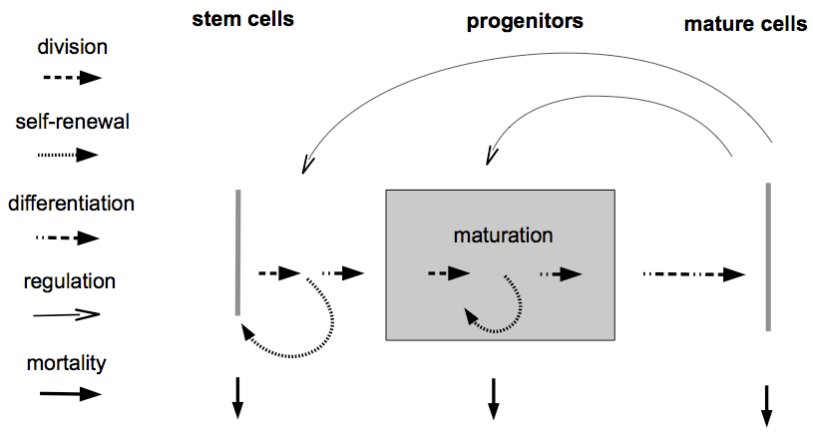

FIGURE 1. Stem cell population dynamics: After division daughter cells may be of the same cell type as the mother (self-renewal) or of a different type (differentiation). Processes related to division are regulated by the level of the mature cell population.

molecular mediators to control stem cell decisions have been identified [19] the exact nature of these processes is not fully understood. A multi-compartmental model for cytokine-regulated cell differentiation incorporating a discrete finite number of populations at different stages of maturity has been recently proposed in [16]. The model is based on the hypothesis that in each step of maturation, the percentage of self-renewal versus differentiation is regulated by a single external feedback mechanism dependent on the level of mature cells, Figure 1. Modeling results show that the proposed mechanism is able to regulate the dynamics of a hierarchical cell population after strong perturbation and to stabilize it at the desired level [16, 21]. Multi-compartmental models are based on the traditional understanding that the process of cell maturation takes place only during divisions, and therefore, there exists a discrete chain of maturation stages. However, there are indications that the differentiation process involves transitions that are continuous, a scenario that suggests application of continuous structured modeling [17]. Comparing the dynamics of the two types of models will help to elucidate the role of discrete and continuous transitions in the differentiation process as well as their regulation. In the framework of structured models, a range of mathematical results have been obtained (such as stability criteria), some of which are applicable to the stem cells system, e.g., [1, 2, 3, 6, 5, 10, 11, 13]. The existing models of cell differentiation are based on the assumption that when cells enter the progenitor phase, maturation takes place with a constant speed, what leads to age-structured models. However, taking into consideration regulation of cell maturation, as proposed in [16], leads to a model with a nonlinear state-dependent maturation speed. See [7, 9] for the effects of a regulated rate of individual development on the population dynamics for Daphnia. In the present paper we formulate a model of cell differentiation as a state-dependent delay differential equation. This approach not only includes regulated maturation speeds, but also allows to incorporate a wider class of smoothly regulated maturation delays. Moreover for delay equations strong analytical [15] and numerical [7] results have become available. In Section 2 we modify the model of [16] by incorporating a delay regulated by the mature cell population. This also

allows to incorporate continuous maturation of progenitor cells. We describe the dynamics of stem and mature cell population by means of a differential equation with state dependent delay, where the latter expresses the fact that the maturation delay depends on the history of the mature cell population and thus on one component of the population, which is the state of the system. State dependence leads to an increase in mathematical complexity and the theory of such equations is a modern and challenging field of mathematics [15]. In Section 4 we prove global existence and uniqueness of solutions, which provide the basis for a numerical approximation of solutions. Moreover, we show that nonnegative initial data remain nonnegative for all times. In Section 5 we elaborate conditions of existence for a unique positive equilibrium and compute a representation for it.

2. **The cell population model.** In this Section we develop a model for the interactions of stem-, progenitor and mature cell populations and show that this model can be formulated by the pair of equations

$$w'(t) = q(v(t))w(t), \tag{1}$$
$$v'(t) = \beta(v(t-\tau(v_t)))w(t-\tau(v_t))\mathcal{F}(v_t) - \mu_v v(t). \tag{2}$$

Here, w and v represent the time development of concentrations of stem cells and mature cells respectively. In (1-2) w, v are functions of time, whereas below w and v will denote - depending on the context- either functions of time or values of these functions. For a given concentration of mature cells v, equation (1) describes stem cell dynamics as in [16]. We define $q(v) := [2s_w(v) - 1]d_w(v) - \mu_w$ as the *stem cell population net growth rate*, where

$$d_w(v) := \frac{p_w}{1 + k_p v} \tag{3}$$

is the *regulated rate of stem cell division* and

$$s_w(v) := \frac{a_w}{1 + k_a v} \tag{4}$$

the *regulated fraction of self-renewal of dividing stem cells*. By μ_w we denote the *mortality rate of stem cells*. We assume that the parameters μ_w, p_w, k_p, a_w and k_a are given nonnegative values and that $a_w < 1$, which leads to $s_w(v) < 1$. The parameter p_w reflects the stem cell division rate in the absence of mature cells, a_w the fraction of self-renewal in the absence of mature cells and k_p and k_a are regulation constants. Now we have introduced all ingredients for the first equation. Our next step is to model the progenitor phase. We define the *flow of cells* at some level of maturity as the amount of progenitor cells passing through this level *per time unit*. Then, the flow of cells into the progenitor compartment at time t is given as

$$\beta(v(t))w(t) \tag{5}$$

with $\beta(v) := 2[1 - s_w(v)]d_w(v)$ the rate of inflow. Next, we call a *history* a function defined on a negative time interval $[-h, 0]$, where $h > 0$, or $(-\infty, 0]$. Moreover, for our functions of time v and w, we use the notation

$$v_t(a) := v(t + a), \quad t \geq 0, \quad a \in (-\infty, 0],$$

and similarly for w, as usual in Functional Differential Equations [14]. Then, if t denotes the present, v_t denotes the history of the concentration of mature cells at time t. Now, we model the inflow into the mature cell population. We assume that

a cell that has just entered the progenitor phase and does neither divide nor die, fully matures in a finite time, which we call *maturation delay*. As maturation is regulated by mature cells, the maturation delay depends on the history of mature cells. We denote the maturation delay as $\tau(\psi)$, if ψ describes the history of the concentration of mature cells. Hence $\tau(\psi)$ represents the length of the progenitor

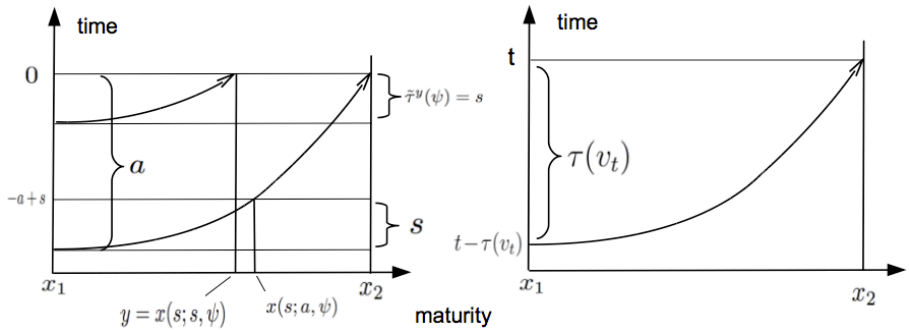

FIGURE 2. *Left:* $x(s; a, \psi)$ denotes the maturity level a cell has reached s time units after it entered the progenitor phase given that after a time units in the progenitor phase it is time zero and the cell has experienced history ψ. Time span $\tilde{\tau}^y(\psi)$ defined via $x(s; s, \psi) = y$ as the time to mature from x_1 to y given that upon reaching y at time zero history ψ is experienced. *Right:* Cells that mature at time t have experienced history of regulation by mature cells v_t, have a maturation delay of $\tau(v_t)$ and thus entered the progenitor phase at $t - \tau(v_t)$.

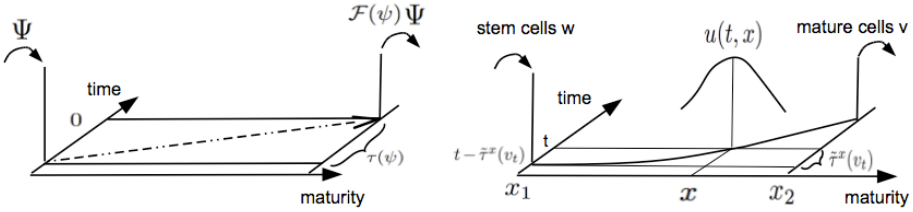

FIGURE 3. *Left:* Cells that mature at time zero and have experienced regulation of mature cells ψ have a maturation delay of $\tau(\psi)$. In this time their numbers change by a factor $\mathcal{F}(\psi)$. *Right:* Density $u(t, x)$ of progenitor cells of maturity x at time t. At time t these cells have experienced history v_t and they have entered the progenitor phase at time $t - \tilde{\tau}^x(v_t)$.

phase provided full maturity is reached at time zero, see Figure 3 (left), $\tau(v_t)$ is the length of the progenitor phase, given that full maturity is reached at time t and $t - \tau(v_t)$ is the moment when the progenitor phase is entered, see Figure 2 (right). Then we can use (5) to compute

$$\beta(v(t - \tau(v_t)))w(t - \tau(v_t)) \tag{6}$$

as the inflow of stem cells into the progenitor phase that corresponds to those cells that fully mature at time t (note that t now denotes a point in time different from the one in (5)), or the number of cells that would fully mature per unit of time at time t if during the progenitor phase cell numbers would not change. To take into account the actual change in numbers, we assume that the inflow into the mature cell population can be computed from the outflow of the stem cell population via a *progenitor net population growth factor* $\mathcal{F}(\psi)$ that depends on the history ψ of mature cells via regulation. If Ψ is the inflow into the progenitor cell population due to differentiation of stem cells, we define $\mathcal{F}(\psi)$ such that $\mathcal{F}(\psi)\Psi$ is the inflow of mature cells $\tau(\psi)$ time units later, see Figure 3 (left). Then, we can deduce from (6) that the inflow of mature cells at time t is

$$\beta(v(t-\tau(v_t)))w(t-\tau(v_t))\mathcal{F}(v_t) \tag{7}$$

and the equation for mature cells becomes indeed (2). Equation (2) is a Delay Differential Equation (DDE) with state-dependent delay and (1) and (2) together are a closed system. We are going to interpret (1,2) as a two-component autonomous DDE with state-dependent delay. In Subsection 2.1 we specify a setting in which the delay is defined only implicitly.

2.1. **Maturation.** In the following section we specify a submodel for the progenitor phase. We assume that there is an interval of possible maturity levels $[x_1, x_2]$, such that at x_1 stem cells enter the phase and at x_2 cells become mature cells. Next, suppose that we can compute the maturity level $x(s; a, \psi) \in [x_1, x_2]$ that a cell has s time units after it entered the progenitor phase given that after a time units in the progenitor phase it is time zero and the cell has experienced history ψ, see Figure 2 (left). Moreover, assume that for given y and ψ we can define a time span $\tilde{\tau}^y(\psi) := s$, where s is the solution of

$$x(s; s, \psi) = y,$$

that denotes the time to mature from x_1 to y given that upon reaching y at time zero history ψ is experienced, Figure 2 (left). Then we define $\tau(\psi) := \tilde{\tau}^{x_2}(\psi)$ and $\tau(\psi)$ has the same interpretation as before. As a further specification, we assume that at a given maturity level $x \in [x_1, x_2]$ and mature cell concentration v we can describe the *regulated maturation speed of a progenitor cell* as

$$g(x, v) := \frac{\gamma(x)}{1 + k_g v}, \tag{8}$$

where $\gamma(x)$ is the *unregulated maturation speed* and k_g is the regulation constant of maturation. This function describes the phenomenon that an increase of the level of mature cells leads to a decrease of the velocity of maturation. Then we can define $x(s; a, \psi) := \tilde{x}(s)$, where $\tilde{x}(s)$ is the solution of

$$\tilde{x}'(s) = g(\tilde{x}(s), \psi(-a + s)), \ s > 0, \ \ \tilde{x}(0) = x_1, \tag{9}$$

if it exists, see again Figure 2 (left).

2.2. **Population net growth factor during maturation.** In the following we specify the progenitor population growth factor. First, recall that maturation from stem to progenitor cells was modeled as a discrete random event. *Within* the progenitor compartment, however, we assume maturation to be a continuous process, independent of cell divisions. We hence assume that division of a progenitor cell

is an instantaneous process and that maturity does not change upon division. We introduce the *regulated proliferation rate* of a progenitor cell as

$$a(x,v) := \frac{\alpha(x)}{1+k_\alpha v}. \tag{10}$$

The rate $a(x,v)$ also equals the rate of inflow at maturity level x. Finally let $\mu(x)$ denote the mortality rate of progenitor cells. Then $d(x,v) := a(x,v) - \mu(x)$ is the population *net* growth rate. Hence

$$d(x(\sigma;\tau(\psi),\psi),\psi(-\tau(\psi)+\sigma))$$

is the population growth rate σ time units after entering the progenitor phase, given that at the time of full maturity (if this is reached) history ψ has been experienced. Then the population net growth factor can be defined as

$$\mathcal{F}(\psi) = e^{\int_0^{\tau(\psi)} d(x(\sigma;\tau(\psi),\psi),\psi(-\tau(\psi)+\sigma))d\sigma}. \tag{11}$$

A way to compute $\mathcal{F}$ numerically would be to integrate in parallel (9) and the ODE

$$\tilde{\mathcal{F}}'(s) = d(\tilde{x}(s),\psi(-a+s))\tilde{\mathcal{F}}(s), \quad s>0, \quad \tilde{\mathcal{F}}(0)=1$$

and then define $\mathcal{F}(\psi) := \tilde{\mathcal{F}}(\tau(\psi))$. Supposed we can solve (1,2), we can modify (7) and compute the density $u(t,x)$ of progenitor cells at level x at time t from the equality of flows

$$g(x,v(t))u(t,x) = \beta(v(t-\tilde{\tau}^x(v_t)))w(t-\tilde{\tau}^x(v_t))\tilde{\mathcal{F}}(\tilde{\tau}^x(v_t)), \tag{12}$$

see Figure 3 (right). In this sense, we can speak of a structured population model, see e.g. [18], with maturity as the structuring variable.

3. Existence and uniqueness.

3.1. Theoretical results.

In this subsection we summarize some theory for state-dependent DDE that can be found in [15]. For some $h>0$, $n\in\mathbb{N}$ we will use the Banach spaces $C := C([-h,0],\mathbb{R}^n)$ and $C^1 := C^1([-h,0],\mathbb{R}^n)$ equipped with their usual norms. Then we can define solutions for DDE:

Definition 3.1. (Solution) Let $U\subset C^1$ open, $F: U\to\mathbb{R}^n$ continuously differentiable. A *solution* is a continuously differentiable function $x:[-h,t_*)$ for some $t_*\in(0,\infty]$, which satisfies $x_t\in U$ for all $t\in[0,t_*)$ and

$$x_0=\varphi, \quad x'(t)=F(x_t), \quad 0<t<t_*. \tag{13}$$

Appropriate conditions for the unique solvability of (13) are initial data restricted to the closed set

$$X_F := \{\varphi\in U : \varphi'(0)=F(\varphi)\}, \quad U\subset C^1 \text{ open} \tag{14}$$

as well as the following smoothness condition, an adaptation of condition (S) in 3.2 in [15].

Hypothesis 3.2. Let $U\subset C^1$ open, $F: U\to\mathbb{R}^n$, then

(i) F is continuously differentiable on $U\subset C^1$,
(ii) each derivative $DF(\varphi): C^1\to\mathbb{R}^n$, $\varphi\in U$ extends to a linear map $D_eF(\varphi): C\to\mathbb{R}^n$ and
(iii) the following map is continuous

$$U\times C\to\mathbb{R}^n, \quad (\varphi,\chi)\mapsto (D_eF)(\varphi)\chi\in\mathbb{R}^n.$$

To show the existence result we will apply Theorem 3.2.1 in [15]:

Theorem 3.3. (Existence and Uniqueness) *Let $U \subset C^1$ open and suppose that $F : U \to \mathbb{R}$ satisfies Hypothesis 3.2 and that X_F defined by (14) is nonempty. Then X_F is a continuously differentiable submanifold of U with codimension n and each $\varphi \in X_F$ uniquely defines a noncontinuable solution $x^\varphi : [-h, t_+(\varphi)) \to \mathbb{R}$ of the IVP (13). All segments x^φ_t, $0 \le t < t_+(\varphi)$, belong to X_F and the relations*

$$S(t, \varphi) := x^\varphi_t, \ \varphi \in X_F, \ 0 \le t < t_+(\varphi)$$

define a domain $\Omega \subset \mathbb{R} \times X_F$ and a continuous semiflow $S : \Omega \to X_F$.

3.2. **Well-posedness, global existence and nonnegativity.** In the following we establish existence and uniqueness in the setting of Section 2. We should first define an appropriate set U on which we can define a map F, such that (1,2) can be written in the form (13). First note that if the maturation delay is modeled with g defined as in (8), we cannot expect $v \mapsto \tau(v)$ to be uniformly bounded. We thus first restrict the set of initial conditions by choosing some $R > 0$, such that for any biologically meaningful amount v of mature cells one has that $v < R$. Next, note that U should be open and contain the zero function and thus we have to allow functions to take negative values. To exclude the singularities in (3) and (4) for negative v values, we introduce

$$R_- := \max\{-\frac{1}{2k_a}, -\frac{1}{2k_p}\} \in [-\infty, 0), \quad I := (R_-, R).$$

If τ is defined via g, we will show below that the following hypothesis holds.

Hypothesis 3.4. There exists some $h = h(R)$, such that, if $\psi \in C^1([-h, 0], \mathbb{R})$ is such that $\psi(\theta) \in I$ for all $\theta \in [-h, 0]$, then $\tau(\psi) \in [0, h]$.

Now we can define

$$C^1 := C^1([-h, 0], \mathbb{R}), \quad M := \{\psi \in C^1 : \ \psi(\theta) \in I, \ \forall \theta \in [-h, 0]\}, \quad U := C^1 \times M$$

and obtain that $\tau(\psi) \in [0, h]$ for every $\psi \in M$. We then get

Lemma 3.5. *The functions $\beta, q : I \to \mathbb{R}$ are continuously differentiable.*

Next, we prove

Proposition 1. *Suppose that the maps $M \to \mathbb{R}$; $\psi \mapsto \tau(\psi)$ and $\psi \mapsto \mathcal{F}(\psi)$ satisfy Hypothesis 3.2, then so does the map $U \to \mathbb{R}^2$*

$$(w, v) \quad \mapsto \quad F(w, v) = \begin{pmatrix} q(v(0))w(0) \\ \beta(v(-\tau(v)))w(-\tau(v))\mathcal{F}(v) - \mu_v v(0) \end{pmatrix}. \tag{15}$$

Proof. The continuous differentiability follows from Lemma 3.5 and the assumed differentiability properties of τ and $\mathcal{F}$. In particular, one has

$$\begin{aligned} &DF(w, v)(\varphi, \psi) \\ =&(q'(v(0))w(0)\psi(0) + q(v(0))\varphi(0), \\ &w(-\tau(v))\{\mathcal{F}(v)\beta'(v(-\tau(v)))[\psi(-\tau(v)) - v'(-\tau(v))D\tau(v)\psi] \\ &+ \beta(v(-\tau(v)))D\mathcal{F}(v)\psi\} \\ &+ \beta(v(-\tau(v)))\mathcal{F}(v)[\varphi(-\tau(v)) - w'(-\tau(v))D\tau(v)\psi] - \mu_v\psi(0))^T. \end{aligned} \tag{16}$$

The required extension $D_eF(w, v)$ is given by the right hand side of (16), if one replaces $D\tau(v)$ and $D\mathcal{F}(v)$ by the respective extensions $D_e\tau(v)$ and $D_e\mathcal{F}(v)$. □

To better understand the set X_F, we define equilibria: (Nonnegative) equilibria of (13) are constant functions with values in $(\mathbb{R}_+ \cup \{0\}) \times [0, R)$ that are zeros of F. For F defined in (15), there is a trivial equilibrium $(0, 0)$, which lies in X_F and thus $X_F \neq \emptyset$. Moreover, if there exist nontrivial equilibria they also lie in X_F. Proposition 1 yields

Theorem 3.6. *Suppose that the maps $M \to \mathbb{R}$; $\varphi \mapsto \tau(\varphi)$ and $\varphi \mapsto \mathcal{F}(\varphi)$ satisfy Hypothesis 3.2, then for F defined by (15) the conclusions of Theorem 3.3 hold.*

The proof of global existence is rather standard:

Lemma 3.7. *(Global existence) Suppose that there exist $c_1, c_2 \geq 0$, such that for every $s \geq 0$, if $x_s \in X_F$ and $x_s = (w_s, v_s)$ one has $\mathcal{F}(v_s) \leq c_1 e^{c_2 s}$. Then $t_+(\varphi) = \infty$ for any $\varphi \in X_F$.*

Proof. Denote by $x^\varphi := (w, v)$ the solution on $[-h, t_+(\varphi))$ that exists according to Theorem 3.6. Suppose that $t_+(\varphi) < \infty$. If the trajectories

$$\{w(t) : \ t \in [0, t_+(\varphi))\} \text{ and } \{v(t) : \ t \in [0, t_+(\varphi))\} \tag{17}$$

are bounded, then by Proposition VII 2.2 in [8] it follows that $t_+(\varphi) = \infty$, which yields global existence. Integrating the first equation yields

$$w(t) = w(0) e^{\int_0^t q(v(s))ds}, \tag{18}$$

which is exponentially bounded, since q is uniformly bounded. The variation of constants formula applied to (2) yields

$$v(t) = e^{-\mu_v t}[v(0) + \int_0^t e^{\mu_v s} \beta(v(s - \tau(v_s)))\mathcal{F}(v_s) w(s - \tau(v_s))ds]. \tag{19}$$

Since β is uniformly bounded, we deduce exponential boundedness of v from (19), the exponential boundednes of w and the assumed boundedness property of $\mathcal{F}$. Hence, also the v-trajectory is bounded. □

Next, we show invariance of the set of nonnegative values.

Lemma 3.8. *(Nonnegativity) Suppose that the conditions of Theorem 3.6 and Lemma 3.7 are satisfied. Then for the solution (w, v) for some nonnegative initial data in X_F, one has that $w(t) \geq 0$ and $v(t) \geq 0$ for all $t \geq 0$.*

Proof. Continuity in zero implies that $w(0)$ is nonnegative for nonnegative initial conditions and hence w is nonnegative by (18). Next, for nonnegative initial conditions the nonnegativity of v follows via (19) from the continuity of v in zero. □

Next, we specify the results for the setting of Subsection 2.1. First, we exclude the singularity of g by redefining

$$R_- \quad := \quad \max\{-\frac{1}{2k_g}, -\frac{1}{2k_\alpha}, -\frac{1}{2k_p}\} \in [-\infty, 0).$$

Assumption 3.9. The function γ is continuous and $\gamma(x) \geq \varepsilon$ for some $\varepsilon > 0$ and all $x \in [x_1, x_2]$.

To guarantee Hypothesis 3.4 with $h := (1 + k_g R) \int_{x_1}^{x_2} \frac{1}{\gamma(x)} dx$ we rewrite (9) as

$$\int_{x_1}^{\tilde{x}(s)} \frac{1}{\gamma(x)} dx = \int_0^s \frac{1}{1 + k_g \psi(-a + \sigma)} d\sigma. \tag{20}$$

Lemma 3.10. *Suppose that $\psi \in M$ and $a \in [0, h]$, then*

(a) there exists a unique continuously differentiable function

$$[0, a'(a,\psi)] \to [x_1, x_2]; \quad s \mapsto x(s; a, \psi)$$

that fulfills (20) as well as (9), where

$$a'(a,\psi) := \begin{cases} a, & \text{if } \int_0^a \frac{1}{1+k_g\psi(-a+\alpha)}d\alpha \leq \int_{x_1}^{x_2} \frac{1}{\gamma(x)}dx \\ \tau(a,\psi), & \text{if } \int_0^a \frac{1}{1+k_g\psi(-a+\alpha)}d\alpha > \int_{x_1}^{x_2} \frac{1}{\gamma(x)}dx \end{cases}$$

with $\tau(a,\psi) =: \tau$ and τ the unique solution of

$$\int_0^\tau \frac{1}{1+k_g\psi(-a+\alpha)}d\alpha = \int_{x_1}^{x_2} \frac{1}{\gamma(x)}dx,$$

(b) there exists a unique $\tau = \tau(\psi) \in [\frac{1}{2}\int_{x_1}^{x_2} \frac{1}{\gamma(x)}dx, h]$, such that

$$\int_0^\tau \frac{1}{1+k_g\psi(-\tau+\alpha)}d\alpha = \int_{x_1}^{x_2} \frac{1}{\gamma(x)}dx \tag{21}$$

and there exists a unique continuously differentiable function

$$[0, \tau(\psi)] \to [x_1, x_2]; \quad \sigma \mapsto x(\sigma; \tau(\psi), \psi)$$

that fulfills (20) as well as (9) and for which $x(\tau(\psi); \tau(\psi), \psi) = x_2$.

Now, by the implicit function theorem applied to (21), τ satisfies Hypothesis 3.2 and we can give a more specific version of Theorem 3.6.

Theorem 3.11. *Suppose that g is as in (8) and that $M \to \mathbb{R}$; $\psi \mapsto \mathcal{F}(\psi)$ satisfies Hypothesis 3.2, then the conclusions of Theorem 3.3 hold.*

In the following, we outline how it can be guaranteed that the map $\psi \mapsto \mathcal{F}(\psi)$ satisfies Hypothesis 3.2. First, we redefine

$$R_- := \max\{-\frac{1}{2k_a}, -\frac{1}{2k_g}, -\frac{1}{2k_\alpha}, -\frac{1}{2k_p}\} \in [-\infty, 0).$$

Then, we suppose smoothness of α and μ:

Assumption 3.12. The functions α and μ are continuously differentiable.

Now, note that it is sufficient to show that the maps $M \to \mathbb{R}$

$$v \mapsto \int_0^{\tau(v)} \frac{\alpha(x(\sigma, \tau(v), v))}{1+k_\alpha v(-\tau(v)+\sigma)}d\sigma, \quad v \mapsto \int_0^{\tau(v)} \mu(x(\sigma, \tau(v), v))d\sigma$$

satisfy Hypothesis 3.2. As α and μ are assumed smooth it remains to elaborate a sufficient differentiability condition for x and to show that this condition is guaranteed, if x is defined via the ODE. One can proceed similarly as in [9]: First, one can formally linearize the right hand side of (9) and define a solution of the resulting ODE with a variation of constants formula. This solution defines the derivative of x with respect to v. Next, note that d is uniformally bounded, so is τ and hence, so is $\mathcal{F}$. Thus the boundedness property of $\mathcal{F}$ that was required in Lemma 3.7 is satisfied and we also obtain global existence.

4. **Equilibrium analysis.** The conditions for nontrivial equilibria are

$$[2s_w(v) - 1]d_w(v) = \mu_w, \tag{22}$$

$$w = \frac{\mu_v v}{\beta(v)\mathcal{F}(v)}. \tag{23}$$

They can (for any equilibrium) be supplemented by

$$u(x) = \frac{\mu_v v \tilde{\mathcal{F}}(\tilde{\tau}^x(v); \tilde{\tau}^x(v), v)}{g(x, v)\mathcal{F}(v)}. \tag{24}$$

If the v-component is positive, then so are the w and u - components. From (22) one can deduce the following result in a straightforward computation.

Lemma 4.1. *If $k_a = k_p = 0$, then in general there exists no positive equilibrium. If at least one of the two, k_a or k_p, is greater than zero, then there exists a positive equilibrium if and only if*

$$\frac{(2a_w - 1)p_w}{\mu_w} > 1. \tag{25}$$

In this case, we obtain

$$\begin{aligned}
v &= \frac{1}{k_p}\left[\frac{(2a_w - 1)p_w}{\mu_w} - 1\right], \quad k_a = 0,\ k_p > 0,\\
v &= \frac{1}{k_a}\left[\frac{2a_w p_w}{p_w + \mu_w} - 1\right], \quad k_a > 0,\ k_p = 0,\\
v &= -\frac{1}{2}\frac{\mu_w(k_a + k_p) + k_a p_w}{\mu_w k_a k_p}\\
&\quad + \sqrt{\frac{1}{4}\left[\frac{\mu_w(k_a + k_p) + k_a p_w}{\mu_w k_a k_p}\right]^2 - \frac{\mu_w + p_w - 2a_w p_w}{\mu_w k_a k_p}}, \quad k_a > 0,\ k_p > 0.
\end{aligned}$$

5. **Discussion.** On the basis of an existing two compartment model we have developed a structured population model to describe and analyze the maturation of stem cells as a continuous process. We have formulated the model as a differential equation with state-dependent delay and established existence and uniqueness, global existence and positivity results. We have analyzed the existence of equilibria and computed expression for these.

From Lemma 4.1 it is obvious that regulation of division processes is a condition for persistence of cell populations at equilibrium, a conclusion that was drawn in [16] for multi-compartment models. Note that (25) says that the stem cells' net reproduction number in the absence of regulation should exceed one, which is a classical condition for the existence of population dynamical equilibria [18].

We have designed our model to be applicable to many situations in which regulated stem cell maturation plays a role and believe that the main conclusions of this paper hold for a large class of models. For some modeling ingredients, we chose to give examples, where an alternative would have been to use more general ingredients: E.g., instead of specifying the division rate in the way we did, we could have formulated the results for a class of division rates that, as a function of the mature cell population, fulfills some standard smoothness, positivity and monotonicity properties.

In relation to cancer, our approach could be relevant, since the continuous maturity structure considered here can easily accommodate the heterogeneity observed

in cancer cell populations [4]. In particular, the molecular complexity of breast cancer entails many challenges for the development of effective treatments. Furthermore, there is increasing evidence that many cancers, including breast cancer, contain populations of cells that display stem-cell properties [12, 20]. The cancer stem cell hypothesis proposes that tumors originate in stem/progenitor cells, which has provided a new vision of this disease. The breast cancer stem cells retain key stem cell properties, including self-renewal, which initiates and drives tumorigenesis, and differentiation that contributes to the heterogeneity found in the tumor. Thus, breast cancer may develop through dysregulation of stem cell self-renewal pathways, resulting in an increased number of cancer stem cells that is associated with poorly differentiated and highly aggressive tumors [22]. In addition, cancer stem cells appear to be more resistant to radiation and cytotoxic chemotherapy, which may contribute to treatment resistance and relapse. Therefore, our model could be extended to analyze the effect of therapy on the cancer stem cell pool. Combining conventional therapies with the effective targeting of cancer stem cells may improve outcome for cancer patients.

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