

STABILITY ANALYSIS OF A RENEWAL EQUATION FOR CELL POPULATION DYNAMICS WITH QUIESCENCE

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Abstract. We propose a model to analyze the dynamics of interacting proliferating and quiescent cell populations. The model includes age dependence of cell division, transitions between the two sub-populations and regulation of the recruitment of quiescent cells. We formulate the model as a pair of renewal equations and apply a rather recent general result to prove that (in-)stability of equilibria can be analyzed by locating roots of characteristic equations. We are led to a parameter plane analysis of a characteristic equation, which has not been analyzed in this way so far. We conclude how quiescence of cells as well as two sub-models for cell-division may influence the possibility of destabilization via oscillations.

Key words. quiescence, cell-population model, age structure, renewal equation, Hopf bifurcation, characteristic equation

AMS subject classifications. 37N25, 45D05, 45G15, 45M10, 92C37

1. Introduction. Cells in many types of tissue in the human body are in a quiescent state, i.e., they are under cell cycle arrest [11]. For blood cells the ability to enter and exit the quiescent state seems essential for preventing the supply of mature blood cells from becoming too large or too small [30]. In treatment of cancer a major obstacle is acquired resistance by cancer cells to chemotherapy [12]. It is an accepted hypothesis that cancer stem cells are the factory of cancer cells in solid tumors as well as in hematological disorder such as leukemia [32, 40]. The cancer stem cell hypothesis states that quiescent cells are far less sensitive to drugs and thus drive the increase of resistance [12, 9]. Based on the analysis of a mathematical model it is indeed suggested in [3] that the quiescent population provides a buffer for a hostile environment for the whole population, i.e., mediates the survival of the population.

Individual cells base appropriate responses, such as proliferation and cell death, largely on their processing of both, internal signals and signals from their environment [4]. A modeling technique used to describe these response-generating mechanisms is that of physiologically structured population modeling which incorporates the dynamics of the internal state of the cell. In general one also needs to take the environmental conditions into account as well as the way the population of cells does impact these conditions. This feedback cycle makes models nonlinear.

There is an abundance of interesting linear and nonlinear structured models that incorporate transitions between proliferating and quiescent cell populations and are

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formulated as partial differential equations, e.g. [5, 7, 8, 19, 21, 24, 33]. Many of these postulate regulation of one or both transition rates by the population. It is a common feature that a positive equilibrium is possible if and only if there is a strong enough regulation of the transition processes.

In the tumor model in [24] the behavior of both proliferating and cancer cells is dependent on cell size. The authors elaborate conditions for asynchronous exponential growth of the population (meaning roughly that population size grows exponentially while the cell-size distribution stabilizes) and for the stability of a trivial equilibrium, which means extinction of the tumor. In [33] the behavior of cells in both stages depends on a variable called “age”. The authors develop a numerical scheme and use this to compute the time development of the population density. In [5] a very general model that incorporates dependence of the cell’s behavior on age and cyclin content is developed. The paper contains a mathematical analysis of an unregulated variant of the model. Moreover it is shown that there exists a positive equilibrium for a regulated variant and convergence to this equilibrium is numerically simulated. In [7, 8] cyclin content structured versions of the model in [5] are considered. In [7] well-posedness is established and the existence of equilibria is studied. In [8] the authors show numerically that, apart from convergence to an equilibrium, oscillations are also possible. In [21] a general model for cell population dynamics, that includes cell size structure, spatial structure as well as density dependent transitions to and from quiescence is developed. The authors establish well-posedness for a porous media type single compartment model derived from the general model via a limiting process and simulate spatial dynamics.

In [19] the authors analyze the model developed in [33]. They use a (formally derived) characteristic equation to compute stability boundaries for a nontrivial equilibrium in a parameter plane. Stability of a nontrivial equilibrium means roughly that a population can be expected to persist. From an interpretation of the stability boundaries the authors conclude that both, increasing the growth rate of the stem cell population and decreasing the rate of differentiation, can be responsible for a destabilization of the equilibrium.

On the other hand there are many models [1, 6, 20, 22, 23, 29], in particular the work of Mackey and collaborators, that show the importance of modeling to explain the interplay of quiescence and clinically observed oscillations at the population level. Many of these use delay differential equations [18, 36] as the basic modeling tool. In [1, 20, 23] cell population models that include explicitly feedback, division and quiescence are analyzed and oscillations are detected and related to quiescence. Some of these models are very general, e.g. [20] incorporate interactions with a stem cell population and consider, additionally to age, maturity of cells.

One of our aims here is to show how (in)stability of a positive equilibrium can be analytically proven for models with explicitly incorporated cell cycle. We analyze possibilities for the emergence of oscillations at the population level and try to identify at the cell level some biological mechanisms that trigger the oscillations. These aims are facilitated by our formulation of the dynamics with renewal equations or Volterra functional equations. Linear Volterra equations have been used e.g. in [37] to analyze an epidemiological problem. The results in [14] provide our basis for proving linearized stability results and the Hopf bifurcation theorem for nonlinear Volterra functional equations. There are few linearized-stability results for structured proliferation-quiescence models and we hope to advertise renewal equations as a useful tool for related problems.

We start with a model where the cell cycle is incorporated via age-dependence as a continuous process. We consider transitions between quiescent and proliferating cell populations, with age dependence in division and mortality processes. As a result, one difference with the models in [1, 20, 23] is that we include the two mechanisms of dividing and going quiescent in a more probabilistic way. We incorporate a control of the recruitment from quiescence by the population with contributions weighted according to whether or not cells are quiescent. We keep the number of parameters low by fixing a point, age zero of the proliferation phase, in the cell cycle state space at which cells start after a transition. The flow of cells through this point can then be described as a population level “birth” rate. For the resulting model we elaborate sharp conditions for the stability of a positive equilibrium and its destabilization by way of growing oscillations. We explicitly verify conditions for some linearized stability theorems and find relations between (in)stability of the equilibrium and the different ways of modeling the division process. Moreover we relate (in)stability to the regulation mode of the recruitment process.

A key point is the analysis of characteristic equations. Such equations can be visualized by defining stability boundaries in planes of parameters. The characteristic equation that we find here has to our knowledge not been analyzed in a parameter plane before and also here we hope that our work can be useful for related problems in the future.

The remainder of the paper is organized as follows. In Section 2 we introduce assumptions and ingredients of the model and formulate the population dynamics as a renewal equation. In Section 3 we prove that for the renewal equation the principle of linearized stability holds for any equilibrium. In Section 4 we elaborate conditions for the behavior of an individual cell that lead to (in)stability of the zero equilibrium and conditions under which there exists a unique positive equilibrium. We also give a dissipativity result. In Section 5 we specify modeling ingredients in more detail and use these specifications to analyze the stability of the positive equilibrium. We also exploit the fact that we can allow for age dependence of the per capita division rate. In particular we introduce two parameterizations: one that describes cell division at a constant rate and one in which division is concentrated in a point of the age axis such that there is a fixed delay between two divisions in the absence of a quiescent phase. We show how different ways of modeling the control of recruitment influence stability and destabilization. In Section 6 we discuss the biological motivation of the model, comparisons with the literature, interpretations and mathematical results. Finally we refer to the appendix for proofs of our results.

2. Model formulation.

2.1. Biological ingredients. For the model we assume that cell division is a moment at which the cell dies and gives birth to two daughters. Immediately after birth, each daughter either goes into quiescence, with probability $1 - \alpha$, or commits itself to proliferation, with probability α , see also Figure 2.1, Table A.1 and Assumption 3.1. So in a sense we neglect the duration of the G_1 -phase, which is when cells usually go quiescent. By the *age* of a cell we mean the time elapsed since the cell was born, irrespective of whether or not it went quiescent. Quiescent cells can be recruited, which means that they become proliferating cells. By the *proliferation age* of a proliferating cell we mean the time it lived as proliferating cell. We define $\beta(a)$ as the *individual division rate* of a cell at proliferation age a . Next, we denote by $\mathcal{F}(a)$ the probability for a cell to survive in the proliferation age interval $[0, a)$, given that it does not divide and by $\tilde{\mathcal{F}}(a)$ the probability for a cell to survive in quiescence in

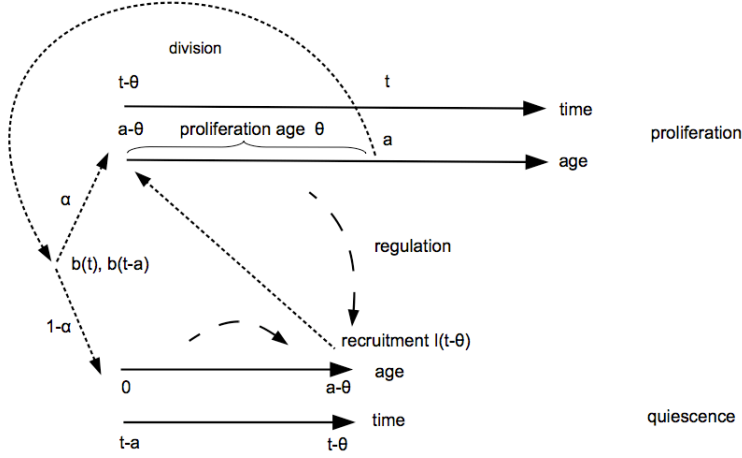


FIG. 2.1. Cycle of cells that enter proliferation directly or experience quiescence and recruitment before. Dashed lines refer to instantaneous events, straight lines to processes that take time.

the age interval $[0, a)$, given that it does not get recruited. The probability per unit of time that a quiescent cell is recruited we call the individual recruitment rate G . We assume that, at time t , G depends on the weighted total population, i.e.,

$$(2.1) \quad G = G(N(t)), \quad N(t) := (1 - q)P(t) + qQ(t),$$

where $P(t)$ and $Q(t)$ are the respective numbers of proliferating and quiescent cells and q and $1 - q$ are relative weights.

2.2. Individual dynamics and population bookkeeping. We denote by $\mathcal{F}_\beta(a) := \mathcal{F}(a)e^{-\int_0^a \beta(\alpha)d\alpha}$ the (unconditioned) survival probability for a cell in proliferation. We use the notation $x_t(\theta) := x(t + \theta)$, $\theta \leq 0$, as usual in the theory of functional differential equations, see e.g [26]. By $b(t)$ we denote the *population birth rate*. Moreover, we introduce $I(t) := G(N(t))$. We formulate the population dynamics by the system of renewal equations

$$(2.2) \quad b(t) = \int_0^\infty b(t - a)R(I_t)(a)da,$$

$$(2.3) \quad I(t) = G\left(\int_0^\infty b(t - a)S(I_t)(a)da\right), \quad \text{with}$$

$$(2.4)$$

$$(2.5) \quad \begin{aligned} R(\psi)(a) &:= 2\alpha\beta(a)\mathcal{F}_\beta(a) + 2(1 - \alpha) \int_0^a \tilde{\mathcal{F}}(a - \theta)\psi(-\theta)e^{-\int_\theta^a \psi(-\sigma)d\sigma} \beta(\theta)\mathcal{F}_\beta(\theta)d\theta, \\ S(\psi)(a) &:= (1 - \alpha)[(1 - q) \int_0^a \tilde{\mathcal{F}}(a - \theta)\psi(-\theta)e^{-\int_\theta^a \psi(-\sigma)d\sigma} \mathcal{F}_\beta(\theta)d\theta \\ &\quad + q\tilde{\mathcal{F}}(a)e^{-\int_0^a \psi(-\sigma)d\sigma}] + \alpha(1 - q)\mathcal{F}_\beta(a). \end{aligned}$$

In the following we explain how this system is constructed. First, $2\beta(a)\mathcal{F}_\beta(a)$ is the expected rate of giving birth of a mother at age a , given that she has not been

quiescent. Next, $e^{-\int_{\theta}^a I(t-\sigma)d\sigma}$ is the probability to not get recruited in the time interval $[t-a, t-\theta]$. Hence, $\tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma}$ for $0 < \theta < a$ is the expected rate of recruitment at age $a-\theta$ and time $t-\theta$ of a cell that has gone quiescent at time $t-a$, see Figure 2.1. Then

$$(2.6) \quad 2 \int_0^a \tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma} \beta(\theta)\mathcal{F}_{\beta}(\theta)d\theta$$

is the expected rate of giving birth of a mother at age a and time t , given that she has gone quiescent at time $t-a$ and was recruited at some time $t-\theta$ in $[t-a, t]$. From the definition of R it follows that

$$(2.7) \quad R(I_t)(a) = 2\alpha\beta(a)\mathcal{F}_{\beta}(a) + 2(1-\alpha) \int_0^a \tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma} \beta(\theta)\mathcal{F}_{\beta}(\theta)d\theta.$$

So we can interpret $R(I_t)(a)$ as the expected rate of giving birth by a mother cell at age a and time t . Since already a simple survival probability of the form $\mathcal{F}(a) = e^{-\mu a}$, $\mu > 0$, is nonzero for no matter how large a , we have to integrate up to infinity. Now (2.2) follows as a consistency relation from the interpretation of b . Next, $\alpha\mathcal{F}_{\beta}(a)$ is the probability for a newborn to become proliferating and survive to age a and

$$(2.8) \quad (1-\alpha) \int_0^a \tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma} \mathcal{F}_{\beta}(\theta)d\theta$$

is the probability for a newborn to become quiescent, get recruited and survive to age a at time t . Hence,

$$(2.9) \quad P(t) = \int_0^{\infty} b(t-a)[\alpha\mathcal{F}_{\beta}(a) + (1-\alpha) \int_0^a \tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma} \mathcal{F}_{\beta}(\theta)d\theta]da,$$

$$(2.10) \quad Q(t) = (1-\alpha) \int_0^{\infty} b(t-a)\tilde{\mathcal{F}}(a)e^{-\int_0^a I(t-\sigma)d\sigma} da.$$

By definition of S , one has

$$(2.11) \quad S(I_t)(a) = (1-\alpha)[(1-q) \int_0^a \tilde{\mathcal{F}}(a-\theta)I(t-\theta)e^{-\int_{\theta}^a I(t-\sigma)d\sigma} \mathcal{F}_{\beta}(\theta)d\theta + q\tilde{\mathcal{F}}(a)e^{-\int_0^a I(t-\sigma)d\sigma}] + \alpha(1-q)\mathcal{F}_{\beta}(a).$$

If we compute N via (2.1), (2.9) and (2.10) and use (2.11) we get

$$(2.12) \quad N(t) = \int_0^{\infty} b(t-a)S(I_t)(a)da.$$

Now, (2.3) follows as $I(t) = G(N(t))$. Moreover, $S(I_t)(a)$ in (2.11) can now be interpreted as the weighted probability for a newborn to survive to age a at time t , where “weighted” refers to whether at age a the cell is quiescent or proliferating. In summary we can interpret (2.2–2.3) as an equation for the reproduction of the population coupled to a law for the feedback via recruitment.

3. The principle of linearized stability. It is shown in [14, 15] that for equations of the type $x(t) = F(x_t)$ the principle of linearized stability holds if F is continuously Fréchet differentiable, for short C^1 . In the remainder of the section, we guarantee continuous Fréchet differentiability and conclude the principle of linearized stability.

3.1. Continuous differentiability. We here work with weighted L^1 -spaces. One reason for the weight is that a constant function, say $b > 0$, such as a steady state solution, is not integrable on $(-\infty, 0]$, but the weighted function $a \mapsto e^{-\rho a}b$, $\rho > 0$, is. We therefore define for some $\rho \geq 0$ to be specified

$$\|\varphi\|_{1,\rho} := \int_0^\infty e^{-\rho a} |\varphi(\theta)| d\theta,$$

whenever the integral converges. Note that if survival probabilities reach zero in finite time, one may simplify the setting by choosing $\rho = 0$. Then, for $m \in \mathbb{N}$

$$L_\rho^{1,m} := \{\varphi : \mathbb{R}_- \rightarrow \mathbb{R}^m \text{ measurable, } \|\varphi\|_{1,\rho} < \infty\}$$

becomes a Banach space with norm $\|\cdot\|_{1,\rho}$. Its dual space can be represented as

$$L_\rho^{\infty,m} := \{k : \mathbb{R}_+ \rightarrow \mathbb{R}^m, \|k\|_{\infty,\rho} < \infty\},$$

where

$$\|k\|_{\infty,\rho} := \sup \operatorname{ess}_{s \in \mathbb{R}_+} \{e^{\rho s} |k(s)| < \infty\},$$

via the pairing

$$\langle \varphi, k \rangle := \int_0^\infty \varphi(-\tau) k(\tau) d\tau, \quad \varphi \in L_\rho^{1,m}, \quad k \in L_\rho^{\infty,m}.$$

For $(\varphi, k) \in L_\rho^{1,1} \times L_\rho^{\infty,m}$ we introduce an m -vector via

$$\langle \varphi, k \rangle := (\langle \varphi, k_i \rangle)_{i=1 \dots m}.$$

ASSUMPTION 3.1. The survival probabilities are nonincreasing, nonnegative, $\mathcal{F}(0) = \tilde{\mathcal{F}}(0) = 1$ and

$$\exists \kappa, K > 0 \text{ such that } \mathcal{F}(a) \leq K e^{-\kappa a}, \quad \tilde{\mathcal{F}}(a) \leq K e^{-\kappa a}.$$

The division rate β is bounded and nonnegative. Moreover $\alpha, q \in [0, 1]$ and $G : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is continuous.

For κ given in this way we can specify ρ :

ASSUMPTION 3.2. $0 < 4\rho < \kappa$.

For the following result we use only $0 < 2\rho < \kappa$, but in the differentiability proof the full property will be used. Next, we define the positive cones

$$L_{\rho,+}^{1,m} := \{\varphi \in L_\rho^{1,m} : \varphi(\theta) \geq 0 \text{ for almost all } \theta \in (-\infty, 0]\}$$

and similarly $L_{\rho,+}^{\infty,m}$.

LEMMA 3.3. $R, S : L_{\rho,+}^{1,1} \rightarrow L_{\rho,+}^{\infty,1}$ are well-defined operators.

Proof. We show the statement for S , the statement for R can be shown similarly. First, $\alpha(1-q)\mathcal{F}_\beta \in L_{\rho,+}^{\infty,1}$ by Assumptions 3.1 and 3.2. Next, similarly, for $\psi \in L_{\rho,+}^{1,1}$ we have

$$e^{\rho a} |q\tilde{\mathcal{F}}(a)e^{-\int_0^a \psi(-\sigma)d\sigma}| \leq Ke^{-(\kappa-\rho)a} \leq K.$$

Hence, $a \mapsto q\tilde{\mathcal{F}}(a)e^{-\int_0^a \psi(-\sigma)d\sigma}$ is an element of $L_{\rho,+}^{\infty,1}$. Finally for some $K_1, K_2 \geq 0$

$$\begin{aligned} e^{\rho a} \int_0^a \tilde{\mathcal{F}}(a-\theta)\psi(-\theta)e^{-\int_\theta^a \psi(-\sigma)d\sigma} \mathcal{F}_\beta(\theta)d\theta &\leq K_1 e^{-(\kappa-\rho)a} \int_0^a \psi(-\theta)d\theta \\ &\leq K_1 e^{-(\kappa-2\rho)a} \int_0^a e^{-\rho\theta}\psi(-\theta)d\theta \leq K_1 e^{-(\kappa-2\rho)a} \|\psi\|_{1,\rho} \leq K_2 \|\psi\|_{1,\rho}. \end{aligned}$$

Thus

$$\sup \text{ess}_{a \in [0, \infty)} e^{\rho a} \left| \int_0^a \tilde{\mathcal{F}}(a-\theta)\psi(-\theta)e^{-\int_\theta^a \psi(-\sigma)d\sigma} \mathcal{F}_\beta(\theta)d\theta \right| < \infty.$$

Hence, the statement follows \square

Now we can define

$$(3.1) \quad F : L_{\rho,+}^{1,2} \rightarrow \mathbb{R}_+^2; \quad F(\varphi, \psi) = (\langle \varphi, R(\psi) \rangle, G(\langle \varphi, S(\psi) \rangle)),$$

set $x = (b, I)$ and rewrite (2.2-2.3) as

$$x(t) = F(x_t), \quad t > 0, \quad x(t) = (\varphi_0(t), \psi_0(t)), \quad t \in (-\infty, 0]$$

for given functions $\varphi_0, \psi_0 \in L_{\rho,+}^{1,1}$. Note, that as F is nonnegative, if there exists a solution for nonnegative initial conditions, it is necessarily nonnegative. Our next aim is to show that F is continuously Fréchet differentiable. As the domain of F is the positive cone we use the concept of relative Fréchet differentiability, where the point at which is differentiated and the perturbation are required to be elements of the domain (see e.g. Definition 2.1 in [35]), which here is the positive cone. The next result we prove in the appendix.

PROPOSITION 3.4. *The operators R and S are C^1 with*

$$(3.2) \quad \begin{aligned} DR(\bar{\psi})\psi(a) &= 2(1-\alpha) \int_0^a \tilde{\mathcal{F}}(a-\theta)\mathcal{F}_\beta(\theta)\beta(\theta)e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma} \\ &\cdot [\psi(-\theta) - \bar{\psi}(-\theta) \int_\theta^a \psi(-\sigma)d\sigma]d\theta, \end{aligned}$$

$$(3.3) \quad \begin{aligned} DS(\bar{\psi})\psi(a) &= (1-\alpha)\{(1-q) \int_0^a \tilde{\mathcal{F}}(a-\theta)\mathcal{F}_\beta(\theta)e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma} \\ &\cdot [\psi(-\theta) - \bar{\psi}(-\theta) \int_\theta^a \psi(-\sigma)d\sigma]d\theta - q\tilde{\mathcal{F}}(a)e^{-\int_0^a \bar{\psi}(-\sigma)d\sigma} \int_0^a \psi(-\sigma)d\sigma\}. \end{aligned}$$

Differentiability of F is now a straightforward combination of the previous result and the chain rule.

THEOREM 3.5. *Suppose that for an element $(\bar{\varphi}, \bar{\psi}) \in L_{\rho,+}^{1,2}$ the map G is C^1 in a neighborhood of $\langle \bar{\varphi}, S(\bar{\psi}) \rangle$, then F is C^1 in a neighborhood of $(\bar{\varphi}, \bar{\psi})$ with derivative $DF(\bar{\varphi}, \bar{\psi})(\varphi, \psi)^T = (D_1F(\bar{\varphi}, \bar{\psi})\varphi, D_2F(\bar{\varphi}, \bar{\psi})\psi)$, where*

$$(3.4) \quad D_1F(\bar{\varphi}, \bar{\psi})\varphi = \langle \varphi, (R(\bar{\psi}), G'(\langle \bar{\varphi}, S(\bar{\psi}) \rangle)S(\bar{\psi})) \rangle,$$

$$(3.5) \quad D_2F(\bar{\varphi}, \bar{\psi})\psi = \langle \bar{\varphi}, (DR(\bar{\psi}), G'(\langle \bar{\varphi}, S(\bar{\psi}) \rangle)DS(\bar{\psi}))\psi \rangle$$

with R and S defined in (2.4 - 2.5) and DR and DS as computed in (3.2 - 3.3).

3.2. Linearized stability and characteristic equation. To establish the principle of linearized stability we first specify derivatives for steady states. Let $(\bar{\varphi}, \bar{\psi})$ be a steady state, i.e., a constant solution of (3.1). Suppose moreover that G is invertible at $\bar{\psi}$ then it holds that $\langle \bar{\varphi}, S(\bar{\psi}) \rangle = G^{-1}(\bar{\psi})$ and if the function G is easy to invert, the right hand side may be easier to deal with than the left hand side. In particular the expressions given in (3.4 - 3.5) can then be simplified to

$$(3.6) \quad D_1 F(\bar{\varphi}, \bar{\psi})\varphi = \langle \varphi, (R(\bar{\psi}), G'(G^{-1}(\bar{\psi}))S(\bar{\psi})) \rangle,$$

$$(3.7) \quad D_2 F(\bar{\varphi}, \bar{\psi})\psi = \langle \bar{\varphi}, (DR(\bar{\psi}), G'(G^{-1}(\bar{\psi}))DS(\bar{\psi}))\psi \rangle.$$

Now we formulate a linearized stability result that is a corollary of Theorem 3.15 in [15].

THEOREM 3.6. *Suppose that there exists an equilibrium solution $(\bar{\varphi}, \bar{\psi})$ of (3.1) and that G is invertible at $\bar{\psi}$ and C^1 in a neighborhood of $G^{-1}(\bar{\psi})$, then the stability of $(\bar{\varphi}, \bar{\psi})$ is determined by the location of the roots of the characteristic equation*

$$(3.8) \quad \det(M(\lambda) - id) = 0, \quad \text{with } M(\lambda) := (m_{ij})_{1 \leq i, j \leq 2},$$

$$(3.9)$$

$$m_{11} := 2 \int_0^\infty e^{-\lambda a} \{ \alpha \beta(a) \mathcal{F}_\beta(a) + (1 - \alpha) \bar{\psi} \int_0^a e^{-(a-\theta)\bar{\psi}} \tilde{\mathcal{F}}(a-\theta) \beta(\theta) \mathcal{F}_\beta(\theta) d\theta \} da,$$

$$(3.10) \quad m_{12} := 2\bar{\varphi}(1 - \alpha)$$

$$\cdot \int_0^\infty \int_0^a \tilde{\mathcal{F}}(a-\theta) e^{-\bar{\psi}(a-\theta)} \left(1 - \bar{\psi} \frac{1 - e^{-\lambda(a-\theta)}}{\lambda} \right) \mathcal{F}_\beta(\theta) \beta(\theta) e^{-\lambda\theta} d\theta da,$$

$$(3.11) \quad m_{21} := G'(G^{-1}(\bar{\psi})) \{ (1 - q) [\alpha \int_0^\infty e^{-\lambda a} \mathcal{F}_\beta(a) da$$

$$+ (1 - \alpha) \bar{\psi} \int_0^\infty e^{-\lambda a} \int_0^a \tilde{\mathcal{F}}(a-\theta) e^{-\bar{\psi}(a-\theta)} \mathcal{F}_\beta(\theta) d\theta da] \\ + q(1 - \alpha) \int_0^\infty e^{-(\lambda + \bar{\psi})a} \tilde{\mathcal{F}}(a) da \},$$

$$(3.12) \quad m_{22} := G'(G^{-1}(\bar{\psi})) \bar{\varphi} (1 - \alpha) \{ (1 - q) \int_0^\infty \int_0^a \mathcal{F}_\beta(\theta)$$

$$\cdot e^{-\lambda\theta} \tilde{\mathcal{F}}(a-\theta) e^{-\bar{\psi}(a-\theta)} \left(1 - \bar{\psi} \frac{1 - e^{-\lambda(a-\theta)}}{\lambda} \right) d\theta da \\ - q \int_0^\infty \tilde{\mathcal{F}}(a) e^{-\bar{\psi}a} \frac{1 - e^{-\lambda a}}{\lambda} da \}.$$

In particular, if all roots have negative real parts, then $(\bar{\varphi}, \bar{\psi})$ is locally exponentially stable. If there exists a root with positive real part, then $(\bar{\varphi}, \bar{\psi})$ is unstable.

4. Linearized stability of the trivial equilibrium and existence of a positive equilibrium. To simplify the discussion of existence and stability of equilibria, the following notation is useful. A crucial role will play the compound parameter

$$r_0 := 2 \int_0^\infty \beta(a) \mathcal{F}_\beta(a) da$$

that gives the expected lifetime production of daughter cells of a cell, given that it has not been quiescent. Note that $r_0 < 2$ by what we have assumed. Moreover we define

$$(4.1) \quad R_0(I) := r_0[\alpha + (1 - \alpha)I \int_0^\infty \tilde{\mathcal{F}}(a)e^{-Ia}da]$$

as the expected lifetime reproduction number of a cell in constant environmental conditions as specified by I . The notion of reproduction number is widespread in the literature on analysis of population dynamical models [31, 16]. Next, we can derive equilibrium conditions as

$$(4.2) \quad b = b \int_0^\infty R(I)(a)da,$$

$$(4.3) \quad I = G(b \int_0^\infty S(I)(a)da).$$

If $b = 0$ there is exactly one equilibrium, $(b, I) = (0, G(0))$, which we call the trivial equilibrium. We give conditions for the (in)stability of this equilibrium with classical interpretations at the individual level. We will apply the well-known identity

$$(4.4) \quad \int_0^\infty e^{-\lambda a} \int_0^a f(\theta)g(a - \theta)d\theta da = \int_0^\infty e^{-\lambda\theta} f(\theta)d\theta \int_0^\infty e^{-\lambda a} g(a)da.$$

LEMMA 4.1. *If $R_0(G(0)) < 1$ holds, then the trivial equilibrium is stable, if $R_0(G(0)) > 1$, then the trivial equilibrium is unstable.*

Proof. If we incorporate λ into the notation, the characteristic equation for the trivial equilibrium becomes $m_{11}(\lambda) = 1$, where by (4.4)

$$m_{11}(\lambda) = 2\{\alpha + (1 - \alpha)G(0) \int_0^\infty e^{-\theta(\lambda + G(0))} \tilde{\mathcal{F}}(\theta)d\theta\} \int_0^\infty e^{-\lambda\theta} \beta(\theta)\mathcal{F}_\beta(\theta)d\theta.$$

Note that $m_{11}(0) = R_0(G(0))$. Suppose that $R_0(G(0)) < 1$ and that there is a root $\lambda = x + iy$, $x \geq 0$. Then $|m_{11}(\lambda)| \leq m_{11}(0) = R_0(G(0)) < 1$, which yields a contradiction, and stability follows. Next, suppose that $R_0(G(0)) > 1$, then $m_{11}(0) > 1$, $m_{11}(x) \downarrow 0$, $x \in \mathbb{R}$ as $x \uparrow \infty$. Hence there exists some $x > 0$ such that $m_{11}(x) = 1$ and instability follows. \square

Next note that we can apply (4.4) to see that $\int_0^\infty R(I)(a)da = R_0(I)$. If $b > 0$, and $I \geq 0$ we call the equilibrium *positive*. Hence, there exists a positive equilibrium if and only if there exists some (b, I) with $b > 0$ and $I \geq 0$ such that

$$(4.5) \quad 1 = R_0(I)$$

and (4.3) hold. An equivalent condition is the existence of a positive root N of

$$(4.6) \quad 1 = R_0(G(N)).$$

If $\alpha = 1$, then (2.2) is independent of I . Hence, the model is linear and in general only the trivial equilibrium exists. In the following we will ignore this case by assuming that $\alpha \in [0, 1)$. We will guarantee monotonicity of the function $N \mapsto R_0(G(N))$ via

ASSUMPTION 4.2. Either

- (i) the function G is strictly monotonously decreasing or

- (ii) there exists some $y \in (0, \infty)$, such that G is strictly monotonously decreasing on $[0, y)$ and constant on $[y, \infty)$.

Note that by the non-negativity property of G there exists a finite limit $G(\infty)$ and that in case (i) $G^{-1}(G(\infty))$ is empty and in case (ii) $G^{-1}(G(\infty)) = [y, \infty)$. We now elaborate sufficient conditions for the existence of a positive equilibrium.

THEOREM 4.3. *If $R_0(G(0)) < 1$, then there is no positive equilibrium. If $R_0(G(0)) > 1$ and $R_0(G(\infty)) < 1$ then there exists a unique positive equilibrium. In this case there exists a unique positive root I of (4.5), the I -component of the positive equilibrium, $G^{-1}(I)$ is uniquely defined and the b -component of the positive equilibrium has the representation*

$$(4.7) \quad b = \frac{r_0 I G^{-1}(I)}{(1-q)I \int_0^\infty \mathcal{F}_\beta(a) da + q(1-\alpha r_0)}.$$

Proof. First note that if $I \geq 0$, then

$$(4.8) \quad I \int_0^\infty \tilde{\mathcal{F}}(a) e^{-Ia} da = 1 + \int_0^\infty e^{-Ia} d\tilde{\mathcal{F}}(a),$$

where the right hand side should be understood as a Stieltjes integral. Now consider the quantity in (4.8) as a function of I . From the left hand side it follows that this function is zero in zero. Considering the right hand side, one sees that the derivative of the function with respect to I is positive, since $\tilde{\mathcal{F}}$ is non-increasing and non-constant. Hence, the function and thus $R_0(I)$ is strictly increasing in I . Then we can conclude that $N \mapsto R_0(G(N))$ is non-increasing. Hence it is clear that if $R_0(G(0)) < 1$ then there cannot be a positive equilibrium. Now suppose that $R_0(G(0)) > 1$ and that $R_0(G(\infty)) < 1$. Then there exists some $N > 0$, such that (4.6) holds and the existence of a positive equilibrium follows. Moreover there exists a root $I := G(N)$ of (4.5) and uniqueness and positivity of this root follow from the strict monotonicity of $R_0(I)$. To understand the uniqueness of the b -component, first assume that Assumption 4.2 (i) holds. Then there can be only one N satisfying $I = G(N)$. Now suppose that Assumption 4.2 (ii) holds and assume that there is some $N' \neq N$ such that $G(N') = I$. Then $G(N') = G(N)$, hence $y \leq N'$, thus $G(N') = G(\infty)$ and hence

$$1 > R_0(G(\infty)) = R_0(G(N')) = R_0(G(N)) = 1,$$

which is a contradiction. We can conclude that the b -component is uniquely defined by

$$b = \frac{G^{-1}(I)}{\int_0^\infty S(I)(a) da}.$$

If we use (2.5), (4.4) and (4.5), we can deduce that the b -component has the representation that is claimed. \square

Suppose now that $R_0(G(\infty)) < 1$ and, when some parameter is changed, $R_0(G(0))$ increases from below one to above one. From what we have shown so far, we know that at the critical value the trivial equilibrium loses its stability and the positive equilibrium emerges. We thus have a transcritical bifurcation and according to the principle of the exchange of stability [27] we can expect the positive equilibrium to be stable just above the critical value. That this is indeed the case, we will see below.

As soon as we identify two parameters we can use the equation $R_0(G(0)) = 1$ that corresponds to the transcritical bifurcation to define a curve in the two parameter plane. A picture of the curve yields biological insight: at a glance we can see how parameters influence the persistence of a cell population. In the following we specify the survival probability for quiescent cells as $\tilde{\mathcal{F}}(a) = e^{-\mu a}$, $\mu > 0$, and use μ as one of the two parameters. Note first of all that for this particular $\tilde{\mathcal{F}}$ we get

$$R_0(I) = r_0[\alpha + (1 - \alpha)\frac{I}{\mu + I}], \quad \text{sign}(R_0(I) - 1) = \text{sign}(I(r_0 - 1) - \mu(1 - \alpha r_0))$$

Moreover, we can solve $R_0(I) = 1$ with respect to I , which yields

$$(4.9) \quad I = \xi\mu, \quad \text{with } \xi = \xi(\alpha, r_0) := \frac{1 - \alpha r_0}{r_0 - 1}.$$

Note that $I > 0$ if and only if

$$(4.10) \quad r_0 \in (1, \min\{\frac{1}{\alpha}, 2\}).$$

Then, the statements of Lemma 4.1 and Theorem 4.3 lead to

COROLLARY 4.4. *If either $r_0 < 1$ or both (4.10) and $G(0) < \xi\mu$ hold, then the trivial equilibrium is stable and no positive equilibrium exists. If (4.10) holds but $G(0) > \xi\mu$ then the trivial equilibrium is unstable, if additionally $G(\infty) < \xi\mu$ then there exists a unique positive equilibrium with I given as in (4.9) and*

$$b = \frac{\mu r_0 G^{-1}(I)}{(1 - q)\mu \int_0^\infty \mathcal{F}_\beta(a) da + q(r_0 - 1)}.$$

In conclusion of the section, we prove that the system is dissipative i.e. there exists a bounded set that attracts solutions, when either the trivial equilibrium is locally asymptotically stable or the positive equilibrium exists.

THEOREM 4.5. *Assume that there exists M such that $G(N)N \leq M$ for any $N \in \mathbb{R}_+$. If $q \in (0, 1]$ and $\alpha r_0 < 1$, then*

$$\limsup_{t \rightarrow \infty} b(t) \leq \frac{M}{q} \frac{r_0}{1 - \alpha r_0}.$$

Proof. Recall that $I(t) = G((1 - q)P(t) + qQ(t))$. Since G is a decreasing function, one has an estimation for $q > 0$:

$$I(t)Q(t) \leq G(qQ(t))Q(t) \leq \frac{M}{q}.$$

It is now convenient to write

$$b(t) = 2 \int_0^\infty (\alpha b(t - a) + I(t - a)Q(t - a)) \beta(a) \mathcal{F}_\beta(a) da.$$

Thus,

$$b(t) \leq 2 \int_0^\infty \alpha b(t - a) \beta(a) \mathcal{F}_\beta(a) da + \frac{M}{q} r_0.$$

Assume that $\limsup_{t \rightarrow \infty} b(t) = \infty$. Then there exists a sequence $\{t_n\}_{n=1}^{\infty}$ such that

$$b(t) \leq b(t_n), \quad t \leq t_n \quad \text{and} \quad \lim_{n \rightarrow \infty} b(t_n) = \infty.$$

One obtains $b(t_n) \leq \alpha r_0 b(t_n) + \frac{M}{q} r_0$, which implies

$$b(t_n) \leq \frac{M}{q} \frac{r_0}{1 - \alpha r_0}$$

for each n . Thus we get a contradiction. It then holds that $\limsup_{t \rightarrow \infty} b(t) < \infty$. The same estimation shows the conclusion. \square

For the case $q = 0$ we need to consider the behavior of two components P and Q to estimate $IQ = G(P)Q$. Since, in general, this does not seem straightforward and analysis of the global behavior of solutions is not the scope in this manuscript, we here leave this as an open problem. We remark that, by a simple comparison argument, one can show that if $\alpha r_0 > 1$ then $b(t)$ tends to infinity.

5. Stability boundaries for the positive equilibrium. Our next aim is to study the stability of the positive equilibrium. We reduce the generality by assuming that $\mathcal{F}(a) := e^{-\mu a}$ or, in words, that also proliferating cells have age-independent mortality rate μ . The main benefit is parameter reduction. For this choice, we write in Lemma 5.2 below, as a first step, the characteristic equation such that the type of dependence on the complex variable is clearly visible. In this context it is useful to introduce two functions $l_1(q) := \frac{3q-1}{2}$ and $l_2(q) := 1-2q$. Note that $r_0 l_1(q) + l_2(q) > 0$, since the left hand side equals $(1-q)(1-\frac{1}{2}r_0) + q(r_0-1)$, which is positive as $q \in [0, 1]$ and $r_0 < 2$. In the following we shall often omit the argument q of l_1 and l_2 . To simplify representations we use the usual notation $\hat{f}(\lambda) = \int_0^{\infty} e^{-\lambda a} f(a) da$ for the Laplace transform of an appropriate function f . In the appendix we prove

PROPOSITION 5.1. *The characteristic equation for the positive equilibrium can be represented as*

$$(5.1) \quad 2\widehat{\beta\mathcal{F}}_{\beta}(\lambda) \left[\alpha\lambda + \frac{G'(G^{-1}(I))G^{-1}(I)l_1(r_0-1)}{r_0l_1+l_2} + \frac{\mu(1-\alpha)}{r_0-1} \right] \\ - \lambda + \frac{G'(G^{-1}(I))G^{-1}(I)l_2(r_0-1)}{r_0l_1+l_2} - \frac{\mu r_0(1-\alpha)}{r_0-1} = 0.$$

In the remainder of this paper, we specify $G(N) := \max\{c(1-N), 0\}$, where c is a positive parameter. Note that G , \mathcal{F} and $\widehat{\mathcal{F}}$ satisfy Assumptions 3.1 and 4.2. Moreover, $G(0) = c$ and $G(\infty) = 0$, such that Corollary 4.4 yields the line shown in Figure 5.1 (a). We now elaborate (5.1) for the specific recruitment function. The proof of the next result is straightforward and we omit it. The notation is designed to deduce stability boundaries in the μ - c -plane, which we shall do below.

LEMMA 5.2. *For $G(N) = c(1-N)$ the characteristic equation becomes*

$$2\widehat{\beta\mathcal{F}}_{\beta}(\lambda)(\alpha\lambda + a_1(\mu, c)^T) - \lambda + a_2(\mu, c)^T = 0, \quad a_i := (a_{i1}, a_{i2}), \quad i = 1, 2, \\ a_{11} := \frac{1-\alpha}{r_0-1} + \frac{(1-\alpha r_0)l_1}{l_1 r_0 + l_2}, \quad a_{12} := -\frac{(r_0-1)l_1}{l_1 r_0 + l_2}, \\ a_{21} := -\frac{(1-\alpha)r_0}{r_0-1} + \frac{(1-\alpha r_0)l_2}{l_1 r_0 + l_2}, \quad a_{22} := -\frac{(r_0-1)l_2}{l_1 r_0 + l_2}.$$

Below we would like to analyze a submodel where division is concentrated in a point in the cell cycle. Note first that we can not specify an essentially bounded β such that for division probability densities one has

$$\beta(a)e^{-\int_0^a \beta(\alpha)d\alpha} = B\delta_1(a),$$

where δ_1 is a Dirac-measure concentrated in one and $B \in [0, 1]$ denotes the probability that a cell that has reached one divides. We can however generalize the characteristic equation to

$$(5.2) \quad \widehat{m}_b(\lambda)(\alpha\lambda + a_1) - \lambda + a_2 = 0,$$

abbreviating $a_i = a_i(\mu, c)^T$, $i = 1, 2$, where $\widehat{m}_b(\lambda) = \int_0^\infty e^{-\lambda a} m_b(da)$ is a Laplace-transform generalized to (positive) measures. Then, with

$$(5.3) \quad \begin{aligned} m_\beta(\omega) &:= 2 \int_\omega \beta(a) \mathcal{F}_\beta(a) da, \\ m_D(\omega) &:= \delta_1(\omega) 2Be^{-\mu} \end{aligned}$$

we recover the old setting, i.e., $\widehat{m}_\beta(\lambda) = 2\widehat{\beta\mathcal{F}_\beta}(\lambda)$ as well as include concentrated division with $\widehat{m}_D(\lambda) = 2Be^{-(\lambda+\mu)}$. We remark that the case of division concentrated at arbitrary $\tau > 0$ can be scaled to $\tau = 1$. Note first that $r_0 = \widehat{m}_b(0)$ and in case of concentrated division

$$(5.4) \quad r_0 = \widehat{m}_D(0) = 2Be^{-\mu}.$$

In the following we will first analyze (5.2) for general m_b , then for m_D and finally combine the two results to conclude (in)stability properties for approximated concentration of division.

LEMMA 5.3.

- (i) $c = \xi\mu \Leftrightarrow (r_0 a_1 + a_2)(\mu, c)^T = 0$.
- (ii) If $c = \xi\mu$ then $\lambda = 0$ solves (5.2) and $a_1(\mu, c)^T > 0$.

Proof. (i) can be shown by filling in ξ , a_1 and a_2 . Next, (5.2) in $\lambda = 0$ is $(r_0 a_1 + a_2)(\mu, c)^T = 0$, which is true by (i). □

In the following let $x, y \in \mathbb{R}$.

LEMMA 5.4.

- (i) If $\lambda = x + iy$, $x \geq 0$ then $|\widehat{m}_b(\lambda)| \leq r_0$. If $x > 0$, then $|\widehat{m}_b(\lambda)| < r_0$.
- (ii) If $c = \xi\mu$ and $\lambda = x + iy$ solves (5.2), then $x > 0$ can not be and $x = 0$ iff $\lambda = 0$.

Hence, for $c = \xi\mu$ there are no roots in the right half plane and the only root on the imaginary axis is $\lambda = 0$.

LEMMA 5.5. *If at $c = \xi\mu$ for fixed μ the parameter c increases sufficiently little, then the root $\lambda = 0$ moves into the left half plane and there are no roots in the right half plane.*

Note that for absolutely continuous measures that can be expressed via (5.3) we have now shown that at $c = \xi\mu$ there is an exchange of stability such that for $c > \xi\mu$ locally the trivial equilibrium destabilizes and the nontrivial equilibrium stabilizes. The next result makes sure that roots can enter the right half plane only through a compact subset of the imaginary axis and not from infinity, see e.g. Chapter XI in [18].

LEMMA 5.6. *(A priori estimate) For any $K > 0$ there exists some $L = L(K) > 0$, such that if $\lambda = x + iy$, $x \geq 0$ solves (5.2) and $c, \mu \leq K$, then $x, y \leq L$.*

5.1. Stability boundary of the positive equilibrium. For an analysis in a parameter plane we consider μ and c as variable and q , α and r_0 as fixed. Now, in the μ - c -parameter plane the existence boundary for the positive equilibrium is defined as the straight line $c = \xi\mu$ and the existence region for the positive equilibrium is given as $\{(\mu, c) \mid c > \xi\mu \text{ for } \mu > 0\}$, see Figure 5.1 (a). In the following we present and analyze respective characteristic equations for the positive equilibrium for two sub-models of concentrated and constant cell division.

5.1.1. Concentrated cell division. For concentrated cell division, we have $\widehat{m}_b(\lambda) = e^{-\lambda}r_0$ and can derive the characteristic equation for the positive equilibrium as

$$(5.5) \quad H(\mu, c, \lambda) = 0 \text{ with } H(\mu, c, \lambda) := e^{-\lambda}r_0(\alpha\lambda + a_1(\mu, c)^T) - \lambda + a_2(\mu, c)^T.$$

In the following we will analyze (5.5) in the μ - c -plane. We have seen already, that there are no roots with positive real part slightly above the existence boundary. Next, we investigate the possibility that there are purely imaginary roots for parameter values in the interior of the existence region. For every nonnegative integer k we define a curve via

$$(5.6) \quad \begin{aligned} C_k &:= \{(\mu^*, c^*)(\nu) \mid \nu \in I_k\}, \quad I_k := (2k\pi, (2k+1)\pi), \\ \mu^*(\nu) &:= \frac{\nu}{\sin \nu} \frac{r_0 - 1}{(1 - \alpha)r_0} m(\nu), \end{aligned}$$

$$(5.7) \quad \begin{aligned} c^*(\nu) &:= \frac{\nu}{\sin \nu} \left\{ \frac{1 + \alpha r_0}{r_0 - 1} (1 - \cos \nu) + \frac{1 - \alpha r_0}{(1 - \alpha)r_0} m(\nu) \right\} \\ m(\nu) &:= \frac{\alpha r_0^2 l_1 - l_2}{l_1 r_0 + l_2} - \frac{l_1 r_0 - \alpha r_0 l_2}{l_1 r_0 + l_2} \cos \nu, \end{aligned}$$

see Figure 5.1 for numerical examples. Before we discuss how these curves relate to (5.5), we determine their location with respect to the existence region. First note that $\nu \in ((2k+1)\pi, (2k+2)\pi)$ would lead to $c^*(\nu) < \xi\mu^*(\nu)$, hence the restriction to the intervals I_k .

Introducing $\bar{q}(r_0) := \frac{r_0+2}{3r_0+4} \in (0, \frac{1}{2})$ one can easily prove

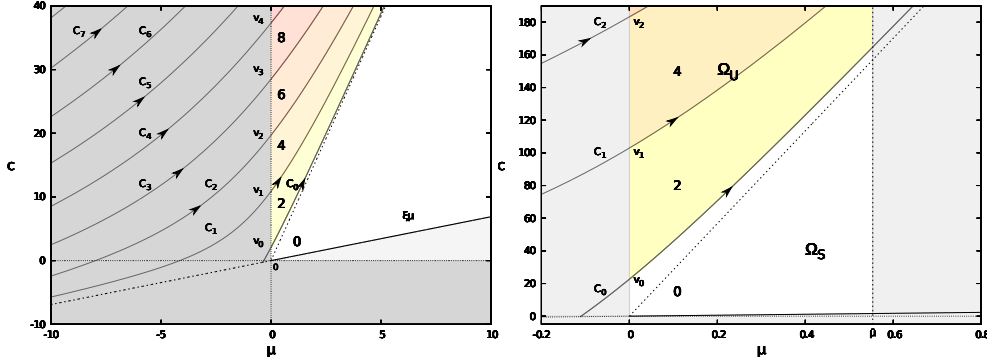
LEMMA 5.7. *It holds that $\text{sign}(l_1(q)r_0 - l_2(q)) = \text{sign}(q - \bar{q}(r_0))$. Hence, for $q \in (\bar{q}(r_0), 1]$ and $k \in \mathbb{N}_0$ we can define*

$$\begin{aligned} \rho(q) &:= \frac{\alpha r_0^2 l_1(q) - l_2(q)}{l_1(q)r_0 - \alpha r_0 l_2(q)} \in (-1, 1), \quad \nu_k := \arccos(\rho(q)) + 2k\pi \in I_k, \\ J_k &:= (\nu_k, (2k+1)\pi) \subset I_k. \end{aligned}$$

LEMMA 5.8. *For every k the following assertions hold. If $q \in [0, \bar{q}(r_0)]$ then the curve C_k lies outside the existence region. If $q \in (\bar{q}(r_0), 1]$ then $(\mu^*, c^*)(\nu)$ lies inside the existence region for $\nu \in J_k$ and not inside the existence region for $\nu \in I_k \setminus J_k$.*

Note that for the numerical examples plotted in Figure 5.1 it holds that $r_0 \in (1, \frac{1}{\alpha})$ and $q \in (\bar{q}(r_0), 1]$ such that there is consistency with Lemma 5.8. We will now use the C_k to describe the parameter set in the existence region at which the characteristic equation has purely imaginary roots.

PROPOSITION 5.9. *For $q \in [0, \bar{q}(r_0)]$ there are no roots on the imaginary axis for parameter values inside the existence region. For $q \in (\bar{q}(r_0), 1]$ and parameter values (μ, c) inside the existence region if there exists a $k \in \mathbb{N}_0$ and $\nu \in J_k$, such that*



(a) Bifurcation curves in the extended parameter plane (b) The admissible parameter region with $\bar{\mu}$ defined via $r_0 = 2$.

FIG. 5.1. Curves and numbers of roots with positive real part in the μ - c -plane. Arrows indicate the direction of increasing ν . The straight line denotes the existence boundary, dotted lines show the asymptotes. Parameter values are (a) $\alpha = 0.01$, $r_0 = 1.9$ and $q = 0.45$, (b) $\alpha = 0.49$, $r_0 = 1.15$ and $q = 0.438$.

$(\mu, c) = (\mu^*, c^*)(\nu)$ then there is (exactly) a pair of purely imaginary roots and else there are no purely imaginary roots.

In the following we focus on the case $q \in (\bar{q}(r_0), 1]$. Before we determine how the number of roots with positive real part changes upon crossing a curve C_k , we summarize more qualitative properties of the curves which can be proved analytically, see Figure 5.1 for visualization of some of these properties for numerical examples. The properties can be proven with similar techniques as in Chapter XI in [18], so that we omit some of the proofs here. First, one can prove that the intersection of the curves C_k with the c -axis is ordered from bottom to top with increasing k and that curves do not intersect one another.

LEMMA 5.10. *It holds that*

$$\lim_{\nu \downarrow 0} (\mu^*, c^*)(\nu) = \left(-\frac{(r_0 - 1)(1 - \alpha r_0)}{(1 - \alpha)r_0}, -\frac{(1 - \alpha r_0)^2}{(1 - \alpha)r_0} \right)$$

and this point lies on the (extended) existence boundary. For $k \geq 1$, as $\nu \downarrow 2k\pi$, the curve C_k parametrized by $(\mu^*, c^*)(\nu)$ converges to the existence boundary in the third quadrant, in particular $\lim_{\nu \downarrow 2k\pi} (\mu^*, c^*)(\nu) = (-\infty, -\infty)$. For every k , as $\nu \uparrow (2k + 1)\pi$, the curve C_k converges to the straight line

$$(5.8) \quad c = \xi\mu + 2 \frac{(1 - \alpha)r_0}{(r_0 - 1)^2} \frac{l_1 r_0 + l_2}{l_1 r_0 - l_2} \mu,$$

hence in particular $\lim_{\nu \uparrow (2k+1)\pi} (\mu^*, c^*)(\nu) = (\infty, \infty)$.

LEMMA 5.11. *For every k , it holds that $d_\nu \mu^*(\nu) > 0$, $d_\nu c^*(\nu) > 0$ for $\nu \in I_k$.*

Hence, none of the curves C_k can intersect itself. In the direction of increasing ν we agree on left and right of the curves C_k . We then can prove

PROPOSITION 5.12. *For every k upon crossing the curve C_k transversally from right to left two roots cross transversally into the right half plane and no other roots cross.*

It follows that in the existence region there are no roots with positive real part between the existence boundary and the curve C_0 . Moreover, upon crossing the curve C_0 from right to left, the characteristic equation gets exactly two roots with positive real part. Furthermore, for every k , upon crossing C_k from right to left, the number of roots with positive real part increases by two. Hence, the numbers of roots with positive real part are distributed as written in Figure 5.1. Next, we define

$$\begin{aligned}\Omega_S &:= \{(\mu^*(\nu), c) \mid \nu \in J_0, c \in (\xi\mu^*(\nu), c^*(\nu))\}, \\ \Omega_U &:= \{(\mu^*(\nu), c) \mid \nu \in J_0, c \in (c^*(\nu), \infty)\}.\end{aligned}$$

THEOREM 5.13. *If $q \in (\bar{q}(r_0), 1]$ then for $(\mu, c) \in \Omega_S$ there are no roots in the right half plane and for $(\mu, c) \in \Omega_U$ there are at least two roots in the right half plane.*

5.1.2. Approximated concentrated cell division. In the following we show that if the division process is sufficiently peaked around proliferation age one then for $q \in [0, \bar{q}(r_0)]$ the stability region of the positive equilibrium is given by $c > \xi\mu$ and for $q \in (\bar{q}(r_0), 1]$ regions of (in)stability are given by small modifications of Ω_S and Ω_U respectively. Here, small modifications will be defined in terms of arbitrarily small tubes around boundary curves in an arbitrarily large (compact) rectangle.

We first approximate the Dirac-measure by absolutely continuous measures. The proof of the following result is straightforward and we omit it.

LEMMA 5.14. *Let $B \in [0, 1]$, $\varepsilon > 0$. Define*

$$\beta_\varepsilon(a) := \chi_{[1-\varepsilon, \infty)}(a) \frac{1}{\varepsilon} \frac{B e^{-\frac{1}{\varepsilon}[a-(1-\varepsilon)]}}{1 - B[1 - e^{-\frac{1}{\varepsilon}[a-(1-\varepsilon)]}]}$$

Then $a \mapsto \beta_\varepsilon(a)$ is bounded on $[0, \infty)$ and

$$\beta_\varepsilon(a) e^{-\int_0^a \beta_\varepsilon(\alpha) d\alpha} = \frac{B}{\varepsilon} \chi_{[1-\varepsilon, \infty)}(a) e^{-\frac{1}{\varepsilon}[a-(1-\varepsilon)]}.$$

Next, we define $m_\varepsilon(\omega) := 2 \int_\omega \beta_\varepsilon(a) e^{-\int_0^a \beta_\varepsilon(\alpha) d\alpha} \mathcal{F}(a) da$. We then get

$$\hat{m}_\varepsilon(\lambda) = \frac{2B e^{-(\lambda+\mu)(1-\varepsilon)}}{(\lambda+\mu)\varepsilon+1} = \frac{r_0 e^{-\lambda(1-\varepsilon)+\varepsilon\mu}}{(\lambda+\mu)\varepsilon+1}.$$

We can extend the function $\varepsilon \mapsto \hat{m}_\varepsilon(\lambda)$ to a neighborhood of $\varepsilon = 0$. The resulting function is C^1 and

$$\hat{m}_0(\lambda) = r_0 e^{-\lambda} = \hat{m}_D(\lambda), \quad \hat{m}_0(0) = r_0 = \hat{m}_D(0).$$

Then the characteristic equation becomes

$$r_0 e^{-\lambda(1-\varepsilon)+\varepsilon\mu} (\alpha\lambda + a_1) - \lambda^2 \varepsilon + \lambda[\varepsilon(a_2 - \mu) - 1] + a_2(\varepsilon\mu + 1) = 0.$$

For $\lambda = x + iy$ the realification is

$$\begin{aligned}r_0 e^{\varepsilon\mu - x(1-\varepsilon)} [(\alpha x + a_1) \cos(y(1-\varepsilon)) + \alpha y \sin(y(1-\varepsilon))] \\ - (x^2 - y^2)\varepsilon + x[\varepsilon(a_2 - \mu) - 1] + a_2(\varepsilon\mu + 1) = 0, \\ r_0 e^{\varepsilon\mu - x(1-\varepsilon)} [\alpha y \cos(y(1-\varepsilon)) - (\alpha x + a_1) \sin(y(1-\varepsilon))] + y[\varepsilon(a_2 - \mu) - 1] = 0.\end{aligned}$$

This we can write as $g(\varepsilon, x, y, \mu, c) = 0$ with $g : U \times \mathbb{R}^4 \rightarrow \mathbb{R}^2$ a C^1 -map defined by the left hand side and U some open neighborhood of zero.

LEMMA 5.15. *Suppose that $g(0, \kappa, \nu, \bar{\mu}, \bar{c}) = 0$, for some $\kappa \geq 0$ and some $\nu \geq 0$. Then there exist neighborhoods $U_1^{\kappa, \nu}$ of zero, $U_2^{\kappa, \nu}$ of (κ, ν) and $U_3^{\kappa, \nu}$ of $(\bar{\mu}, \bar{c})$ and a C^1 -function $U_1^{\kappa, \nu} \times U_2^{\kappa, \nu} \rightarrow U_3^{\kappa, \nu}$, $(\varepsilon, x, y) \mapsto (\mu^\varepsilon, c^\varepsilon)(x, y)$ such that*

- (i) $g(\varepsilon, x, y, (\mu^\varepsilon, c^\varepsilon)(x, y)) = 0, \forall (\varepsilon, x, y) \in U_1^{\kappa, \nu} \times U_2^{\kappa, \nu},$
 (ii) $g(\varepsilon, x, y, \mu, c) = 0, (\varepsilon, x, y) \in U_1^{\kappa, \nu} \times U_2^{\kappa, \nu} \Rightarrow (\mu, c) = (\mu^\varepsilon, c^\varepsilon)(x, y),$ in particular $(\mu^0, c^0)(\kappa, \nu) = (\bar{\mu}, \bar{c}).$

If we take out of a region in which for $\varepsilon = 0$ the number of roots in the right half plane equals $2k, k \geq 0,$ a small open δ -tube around the boundary curves and restrict it to a rectangle we obtain a compact set, in which for $\varepsilon = 0$ the number of roots in the right half plane still equals $2k.$ The set is given by

$$\Omega_{2k}^{K, \delta} := \begin{cases} \{(\mu^*(\nu), c) : \mu^*(\nu), c \leq K, \nu \in J_0, c \in [\xi\mu^*(\nu) + \delta, c^*(\nu) - \delta]\}, & k = 0, \\ \{(\mu, c) : \mu, c \leq K, \exists \nu_1 \in J_k, \nu_2 \in J_{k+1} \text{ s.th. } \mu^*(\nu_1) = \mu^*(\nu_2) = \mu, \\ c \in [c^*(\nu_1) + \delta, c^*(\nu_2) - \delta]\}, & k \geq 1. \end{cases}$$

One of our main conclusions is now, that we can for these sets slightly increase ε and obtain stability results:

THEOREM 5.16. *For all $K > 0, \delta > 0$ there exists some $\bar{\varepsilon} > 0,$ such that for all division rates $\beta_\varepsilon, \varepsilon \in (0, \bar{\varepsilon}],$ the following holds. If either $q \in [0, \bar{q}(r_0)], c > \xi\mu$ and $\mu, c \leq K$ or $q \in (\bar{q}(r_0), 1]$ and $(\mu, c) \in \Omega_0^{K, \delta}$ then the positive equilibrium is stable. If $q \in (\bar{q}(r_0), 1]$ and $(\mu, c) \in \Omega_{2k}^{K, \delta}, k \geq 1$ the positive equilibrium is unstable and the number of roots in the right half plane equals $2k.$*

5.1.3. Constant cell division. In our second submodel we describe division via a constant rate $\beta = \frac{\mu r_0}{2 - r_0}.$ Then, from the characteristic equation (5.2) one can derive the characteristic equation for constant cell division in a straightforward manner as

$$(5.9) \quad 0 = \lambda^2 + p_1(\mu, c)\lambda + p_2(\mu, c), \text{ with}$$

$$(5.10) \quad p_1(\mu, c) := \frac{2(1 - \alpha r_0)}{2 - r_0} \mu - a_2(\mu, c)^T, \quad p_2(\mu, c) := \frac{2(r_0 - 1)}{2 - r_0} \mu (c - \xi\mu).$$

Next, since $l_1(q)r_0 + l_2(q) > 0$ and $-l_2(q) > 0$ for $q \in (\frac{1}{2}, 1]$

$$(5.11) \quad c = \eta\mu, \quad \eta := \xi + \left\{ \frac{2(1 - \alpha r_0)}{2 - r_0} + \frac{(1 - \alpha)r_0}{r_0 - 1} \right\} \left(-\frac{(r_0 - 1)l_2(q)}{l_1(q)r_0 + l_2(q)} \right)^{-1}$$

defines a straight line in the μ - c -parameter plane with a slope greater than the one of the existence boundary. In the appendix we prove

THEOREM 5.17. *The positive equilibrium is stable for $q \in [0, \frac{1}{2}].$ For $q \in (\frac{1}{2}, 1]$ it is stable if $c < \eta\mu$ and unstable if $c > \eta\mu.$*

6. Discussion. In this manuscript we have developed a cell population model in which the cell cycle is incorporated via age dependence in the division and mortality processes (Figure 2.1). After division we have included two possibilities, transition to quiescence or commitment to proliferation. Our quiescent cells are recruited at a rate that is controlled by the population, with a weight $q \leq 1/2$ on the quiescent sub-population. To our knowledge this is the first analysis of a model that combines all of these features.

In [1, 6] all cells alive divide whereas in our model cells may not divide. In [24] the cell size is partitioned upon division among the two daughter cells, whereas in our model the state at birth of the daughter cells is at age zero, so at the boundary of the state space.

As discussed in the introduction, the role of the quiescent phase is relevant in many tissues, healthy (e.g. blood cells) or tumor (cancer stem cell hypothesis). In [1, 6] the decision on quiescence is taken immediately after division and only then. In [33, 5] going quiescent is modeled independently of the division process but depends on the internal state of the cell and the state remains unchanged upon going quiescent. [1, 23] model the cell decay rate and division rate as independent of what we call proliferation age. Moreover, in [1, 6, 20, 23] after division cells necessarily enter the quiescent phase. Also in these models the population controls the length of the cell cycle via the recruitment rate. In [1] additionally the duration of the proliferative phase is controlled by the quiescent population.

An interpretation of the control mechanism is that cells compete for oxygen. It seems established in modeling and experiments that for cancer cells a lack of oxygen favors quiescence, see e.g. [2] and references therein. We thus assume that the recruitment rate is an increasing function of the oxygen concentration. Suppose that the oxygen dynamics are governed by the ODE

$$\frac{d}{dt}E(t) = \lambda - (c_P P(t) + c_Q Q(t)) E(t),$$

where E is the concentration of oxygen, λ is its inflow rate and c_P and c_Q are consumption rates by proliferating and quiescent cells, respectively. Using a quasi steady state approximation we obtain that

$$E(t) \approx \frac{\lambda}{(c_P + c_Q) \{(1 - q) P(t) + q Q(t)\}}, \quad \text{where } q := \frac{c_Q}{c_P + c_Q}$$

is the relative oxygen consumption rate of quiescent cells. In [24] the authors argue that a quiescent cell does not likely enter the proliferating state as a tumor grows and model the recruitment rate non-increasing with (total unweighted) population size. In [33, 34] the recruitment rate is given as a decreasing function of the number of proliferating cells. In [29] the corresponding basis are molecules that deactivate receptors on the surface of cells and thereby inhibit mitosis, also mentioning that the precise signaling pathway is not understood. It is concluded that the recruitment rate decreases with the concentration of molecules. Apparently these molecules are produced by the quiescent cells, as their concentration is assumed to be directly proportional to the concentration of quiescent cells. Hence the recruitment rate decreases with the concentration of quiescent cells. Similar approaches are followed in [1, 6, 20, 23]. With the use of the weights we have captured all of the above mentioned approaches. One may additionally consider dependency of the consumption rates on the phase in the cell cycle [5] or age, which here for simplicity we did not do.

Our necessary condition for the existence of a population equilibrium ($R_0(G(0)) > 1$) means that the population undergoes net growth due to an excess of resources when oxygen consumption is low. Similarly it is necessary that the population undergoes decay due to a lack of resources when oxygen consumption is very big ($R_0(G(\infty)) < 1$). To study parameter dependencies we have defined a plane spanned by two free parameters, cell mortality μ and maximum (i.e. in the limit of zero consumption) recruitment rate c (Figure 5.1). In this plane we have computed an existence boundary ($R_0(G(0)) = 1$) to one side of which the population equilibrium can exist and to the other of which it can not. The boundary curve then consists of those points where proliferation under a maximum recruitment, that corresponds to a zero population, balances total cell death.

Our next task was an analysis of the stability of equilibria, i.e., whether or not in the neighborhood of an equilibrium for large times the population converges towards the equilibrium. Then if the zero equilibrium is stable, the cell population will go extinct, which can be interpreted e.g. as recovery from a tumor. Stability of the positive equilibrium can be related to establishment of the cell population, healthy or tumor, whereas oscillations correspond to disorders of healthy cells or reoccurrence of a tumor.

We have computed a stability boundary that by definition in our model partitions the parameter plane into a region in which the population equilibrium is stable and a region in which it is unstable but there is a stable limit cycle (Hopf-bifurcation). The emergence of oscillations under variation of the free parameters can at first approach be interpreted as follows. A net increase in the population proliferation rate is triggered as a result of the increased recruitment rate. The corresponding increase in population depletes resources and yields a reduction in the recruitment rate, which in turn triggers a net decay of the population, whereby an increase of the recruitment rate ensues. The result of this process is sustained oscillatory behavior. For this oscillatory behavior to be stable, the death rate μ must be small enough, otherwise depletion of the population by apoptosis wipes out the oscillations. A visualization of this phenomenon is obtained by taking a path in the parameter plane (Figure 5.1) from the stability region into the instability region. We have seen however that (in)stability also depends on the fixed parameters (Theorems 5.16 and 5.17): As we have discussed there are several ways in which in the literature the division process is modeled. We have here compared two extreme cases, concentrated division, i.e., a point in the cell cycle outside of which division is impossible, and - the analogy of the ODE model- where division occurs at a constant, i.e. cycle-stage-independent, rate. Additionally the way in which the quiescent phase was modeled proved to be crucial. We have seen that here the speed at which quiescent cells enter the proliferating compartment, the weight that the quiescent population has in triggering the recruitment of quiescent cells and the mortality of quiescent cells are relevant.

For a comparison of the two division submodels, we have found it instructive to distinguish between a quiescent population that is more ($q \in (\bar{q}(r_0), 1/2]$) and one that is less ($q \in [0, \bar{q}(r_0))$) committed to participate in the control of recruitment. If the quiescent population is participating more, then, if division is modeled as constant and undelayed, the feedback mechanism leads to a stable equilibrium, see Theorem 5.17. If the division event occurs with a delay, then the feedback mechanism may lead to oscillations, see Figure 5.1. Hence, in this case, division delay may lead to oscillations or a model with constant division rate seems not suitable to reproduce oscillations and is thus too simplistic.

In our concentrated division model we find a period at the population level exceeding the length of the proliferation phase. (Indeed, by the Hopf-bifurcation theorem, close to the crossing of the stability boundary C_0 there is an oscillating solution with period in the range $(2, \infty)$, as for the curve parameter then $\nu \in (0, \pi)$ and the period equals $2\pi/\nu$, whereas our division delay is normalized to one.) Oscillations of the number of cells with a period that is longer than the cell cycle have been observed in periodic hematological disorders, see [22] and the references therein. This phenomenon was also detected in the models of [6, 17], where an increase in proliferating stem cell mortality can prolong the period of oscillation of the number of cells. As discussed, the scenario described by the model in [6] has several differences compared to the one we have investigated here.

In a follow up project we would like to incorporate more feedback mechanisms into the model, such as a control in the probability to go quiescent. Moreover, one could investigate an alternative division probability with a maximum, by using a rate of the form $\beta(a) = ae^{-\kappa a}$, $\kappa > 0$, instead of a measure. Finally, it may be interesting to reinterpret our model as a rudimentary stem cell model, where the proliferating population corresponds to a self-renewing stem cell population and the “decision point” is related to the pluripotency of stem cells, and to extend or modify the model in this direction.

To our knowledge our work is, after [13], the second proof, that the linearized stability and Hopf-bifurcation results in [14, 15] can be applied to population models and the first elaborated application of infinite delays and to cell population models. We also hope to show that the efforts to create the setting of a population model formulated as renewal equations are compensated by a relatively standard way to verify differentiability conditions.

It then remains the nontrivial task to analyze the type of quasi-polynomials that result as characteristic equations. We have seen how the use of Dirac-measures helps to make models parameter-scarce. As many theories do not allow for the use of Dirac-measures (see below for an exception) we have elaborated a method to show that the analysis of characteristic equations is stable when passing from admissible model-ingredients to the limit of Dirac-measures.

In the limit of the Dirac-measure the characteristic equation has the form

$$(6.1) \quad e^{-\lambda} (a_1 \lambda + a_2) = \lambda + a_3$$

and we have tried to thoroughly analyze this equation. To our knowledge, for this equation there does not exist a complete analysis in any parameter plane in the literature, for related analysis see [10, 28, 38]. We hope that the parameter plane method or even its application to the concrete equation could be of more general use.

We remark that our model can be interpreted as an age-structured population model. Such models are traditionally formulated as transport equations [41]. A corresponding partial differential equation for our model is for $t > 0$

$$(6.2) \quad \begin{aligned} \partial_t p(t, \theta) + \partial_\theta p(t, \theta) &= -(\mu + \beta(\theta))p(t, \theta), \quad \theta > 0, \\ \partial_t q(t, \theta) + \partial_\theta q(t, \theta) &= -(\mu + I(t))q(t, \theta), \quad \theta > 0, \end{aligned}$$

$$(6.3) \quad p(t, 0) = 2\alpha \int_0^\infty \beta(\theta)p(t, \theta)d\theta + I(t) \int_0^\infty q(t, \theta)d\theta,$$

$$(6.4) \quad \begin{aligned} q(t, 0) &= 2(1 - \alpha) \int_0^\infty \beta(\theta)p(t, \theta)d\theta, \\ I(t) &= G((1 - q) \int_0^\infty p(t, \theta)d\theta + q \int_0^\infty q(t, \theta)d\theta), \\ p(0, \theta) &= p_0(\theta), \quad q(0, \theta) = q_0(\theta). \end{aligned}$$

Here p and q are the respective population densities of proliferating and quiescent populations with initial densities p_0 and q_0 . We get a corresponding system for concentrated division (ignoring the p -population with age greater than one) if we set $\beta \equiv 0$ in (6.2) and replace (6.3–6.4) by

$$(6.5) \quad p(t, 0) = \alpha r_0 p(t - 1, 0) + I(t) \int_0^\infty q(t, \theta)d\theta,$$

$$(6.6) \quad q(t, 0) = (1 - \alpha)r_0 p(t - 1, 0).$$

In [39] the authors have established semiflows for Cauchy-problems induced by semi-linear perturbations of Hille-Yosida operators and applied the theory to an age-structured population model, where per capita birth rates are described by cumulative birth measures. The corresponding model (32) in [39] has a boundary condition of the form

$$(6.7) \quad u(t, 0) = f(u(t, \cdot)).$$

Due to the difference between modeling giving birth ($B\delta_1(\omega) = \int_{\omega} \beta(a)da$) and division ($B\delta_1(\omega) = \int_{\omega} \beta(a)e^{-\int_0^a \beta(\alpha)d\alpha}da$) as concentrated we can not write (6.5–6.6) in the form (6.7). It would be interesting to investigate if the theory in [39] can still be applied to our model.

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REFERENCES

- [1] M. ADIMY, F. CRAUSTE, M.L. HBID, AND R. QESMI *Stability and Hopf bifurcation for a cell population model with state- dependent delay*, SIAM J. Appl. Math., 70 (2010), pp. 1611–1633.
- [2] T. ALARCÓN, H. M. BYRNE, AND P. K. MAINI, *A mathematical model of the effects of hypoxia on the cell-cycle of normal and cancer cells*, J. Theoret. Biol., 229 (2004), pp. 395–411.
- [3] T. ALARCÓN AND H. J. JENSEN, *Quiescence: a mechanism for escaping the effects of drug on cell populations*, J. Roy. Soc. Interface, 8 (2011), pp. 99–106.
- [4] S. ARTAVANIS-TSAKONAS, M. D. RAND, AND R. J. LAKE, *Notch signaling: Cell fate control and signal integration in development*, Science, 284 (1999), pp. 770–776.
- [5] F. BEKKAL BRIKCI, J. CLAIRAMBAULT, B. RIBBA, AND B. PERTHAME, *An age-and-cyclin-structured cell population model for healthy and tumoral tissues*, J. Math. Biol. 57 (2008), pp. 91–110.
- [6] S. BERNARD, J. BÉLAIR, AND M. C. MACKAY, *Oscillations in cyclical neutropenia: new evidence based on mathematical modeling*, J. Theoret. Biol., 223 (2003), 283–298.
- [7] R. BORGES, *Mathematical models of physiologically structured cell populations*, Ph. D. thesis, Universitat Autnoma de Barcelona, Barcelona, 2012.
- [8] R. BORGES, Á. CALSINA, AND S. CUADRADO, *Oscillations in a molecular structured cell population model*, Nonlinear Anal. Real World Appl., 12 (2011), pp. 1911 – 1922.
- [9] S. BUCZACKI, R. J. DAVIES, AND D. J. WINTON, *Stem cells, quiescence and rectal carcinoma: an unexplored relationship and potential therapeutic target*, Brit. J. Canc., 105 (2011), pp.1253–1259.
- [10] S. CHENG, AND Y. LIN, *Dual sets of envelopes and characteristic regions of quasi-polynomials*, World Scientific Publishing Co. Pte. Ltd., Hackensack, NJ, 2009.
- [11] H. A. COLLER, *The essence of quiescence*, Science, 334 (2011), pp. 1074–1075.
- [12] M. DEAN, T. FOJO, AND S. BATES, *Tumour stem cells and drug resistance*, Nat. Rev. Canc., 5 (2005), pp. 275–284.
- [13] A.M. DE ROOS, O. DIEKMANN, M. GYLLENBERG, J.A.J. METZ, AND S. NAKAOKA, *Daphnia revisited: local stability and bifurcation theory for physiologically structured population models explained by way of an example*, J. Math. Biol., 61 (2010), pp. 277–318. DOI 10.1007/s00285-009-0299-y
- [14] O. DIEKMANN, PH. GETTO, AND M. GYLLENBERG, *Stability and bifurcation analysis of Volterra functional equations in the light of suns and stars*, SIAM J. Math. Anal., 39 (2007), pp. 1023–1069.

- [15] O. DIEKMANN AND M. GYLLENBERG, *Equations with infinite delay: Blending the abstract and the concrete*, J. Differential Equations 252 (2012), pp. 819–851.
- [16] O. DIEKMANN AND J. A. P. HEESTERBEEK, *Mathematical Epidemiology of Infectious Diseases*, John Wiley and Sons Ltd, 2000.
- [17] O. DIEKMANN AND K. KORVASOVÁ, *A didactical note on the advantage of using two parameters in Hopf bifurcation studies*, Submitted to J. Biol. Dyn..
- [18] O. DIEKMANN, S. VAN GILS, S. M. VERDUYN LUNEL, AND H.-O. WALTHER, *Delay Equations, Functional-, Complex-, and Nonlinear Analysis*, Springer Verlag, New York, 1995.
- [19] M. DOUMIC-JAUFFRET, P. KIM, AND B. PERTHAME, *Stability analysis of a simplified yet complete model for chronic myelogenous leukemia*, Bull. Math. Biol., 72 (2010), pp. 1732–1759.
- [20] I. DROBNJAK, A. C. FOWLER, AND M. C. MACKEY *Oscillations in a maturation model of blood cell production*, SIAM J. Appl. Math., 66 (2006), pp. 2027–2048.
- [21] A. DUCROT, F. LE FOLL, P. MAGAL, H. MURAKAWA, J. PASQUIER, AND G. F. WEBB, *An in vitro cell population dynamics model incorporating cell size, quiescence and contact inhibition*, Math. Models Methods Appl. Sci., 21 (2011), pp. 871–892.
- [22] C. FOLEY AND M. C. MACKEY, *Dynamic hematological disease: a review*, J. Math. Biol., 58 (2009), pp. 285–322.
- [23] A. C. FOWLER, AND M. C. MACKEY *Relaxation oscillations in a class of delay differential equations*, SIAM J. Appl. Math., 63 (2002), pp. 299–323.
- [24] M. GYLLENBERG AND G. WEBB, *A nonlinear structured population model of tumor growth with quiescence*. J. Math. Biol., 28 (1990), pp. 671–694.
- [25] J. K. HALE, *Ordinary Differential Equations*, Dover Publications, Inc. 1969.
- [26] J. K. HALE AND S. M. VERDUYN LUNEL, *Introduction to Functional Differential Equations*, Springer Verlag, New York, 1991.
- [27] H. KIELHÖFER, *Bifurcation Theory: An Introduction with Applications to PDEs*, Springer AMS 165.
- [28] Y. KUANG, *Delay differential equations with applications in population dynamics*, Mathematics in Science and Engineering, 191. Academic Press, Inc., Boston, MA, 1993.
- [29] M.C. MACKEY, *Unified hypothesis for the origin of aplastic anemia and periodic hematopoiesis*, Blood, 51 (1978), pp. 941–956.
- [30] Y. MATSUMOTO, H. IWASAKI, AND T. SUDA, *Maintenance of Adult Stem Cells: Role of the Stem Cell Niche*, in Adult Stem Cells: Biology and Methods of Analysis, D.G. Phinney (ed.), Humana Press, pp. 35–55, 2011.
- [31] J.A.J. METZ AND O. DIEKMANN, *The Dynamics of Physiologically Structured Populations*, LNB 68, Springer, Berlin, 1986.
- [32] T. REYA, S. J. MORRISON, M. F. CLARKE, AND I. L. WEISSMAN, *Stem cells, cancer, and cancer stem cells*, Nature, 414 (2001), pp. 105–111.
- [33] I. ROEDER, M. HERBERG, AND M. HORN, *An “age” structured model of hematopoietic stem cell organization with application to chronic myeloid leukemia*, Bull. Math. Biol., 71 (2009), pp. 602–626.
- [34] I. ROEDER AND M. LOEFFLER, *A novel dynamic model of hematopoietic stem cell organization based on the concept of within-tissue plasticity*, Experim. Hematol., 30 (2002), pp. 853 – 861.
- [35] W.M. RUESS, *Linearized stability and regularity for nonlinear age- dependent population models*, Functional analysis and evolution equations, H. Amann, W. Arendt, M. Hieber, F. Neubrander, S. Nicaise, and J. von Below (Eds.) Birkhauser, Basel, 561-576, 2008.
- [36] H. SMITH, *An Introduction to Delay Differential Equations with Applications to the Life Sciences*, Texts in Applied Mathematics 57, Springer, New York, 2010.
- [37] H. SMITH, *Hopf Bifurcation in a System of Functional Equations Modeling the Spread of an Infectious Disease*, SIAM J. Appl. Math., 43 (1983), pp. 370–385.
- [38] G. STÉPÁN, *Retarded Dynamical Systems: Stability and Characteristic Functions*, vol. 210 of Pitman Research Notes in Mathematics, Longman, Essex, 1989.
- [39] H. THIEME AND H. VOSSLER, *Semilinear perturbations of Hille Yosida operators in Mathematical Modelling of Population Dynamics*, R. Rudnicki (ed.) Banach Center Publ.63, Polish Academy of Sciences, Warsaw, pp. 87–122, 2004.
- [40] J. E. VISVADER AND G. J. LINDEMAN, *Cancer stem cells in solid tumours : accumulating evidence and unresolved questions*, Nat. Rev. Canc., 8 (2008), pp. 755–768.
- [41] G.F. WEBB *Theory of Nonlinear Age-Dependent Population Dynamics*, Marcel Dekker, 1985.

Appendix A.

Proof of Proposition 3.4 We show that S is C^1 , the result for R is similar. We first show that $A : L_{\rho,+}^{1,1} \rightarrow L_{\rho,+}^{\infty,1}$

$$A(\psi)(a) := \int_0^a \tilde{\mathcal{F}}(\alpha - \theta) \psi(-\theta) e^{-\int_\theta^\alpha \psi(-\sigma) d\sigma} \mathcal{F}_\beta(\theta) d\theta$$

is C^1 with derivative given for $\psi, \bar{\psi} \in L_{\rho,+}^{1,1}$ as

$$DA(\bar{\psi})\psi(a) := \int_0^a \tilde{\mathcal{F}}(\alpha - \theta) \mathcal{F}_\beta(\theta) e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} [\psi(-\theta) - \bar{\psi}(-\theta) \int_\theta^\alpha \psi(-\sigma) d\sigma] d\theta.$$

Showing continuous differentiability for the remaining terms of S can be done with the same techniques and it then follows by the sum- and product rules that S is C^1 . We first show that the candidate is well-defined:

$$\begin{aligned} e^{\rho a} |DA(\bar{\psi})\psi(a)| &\leq K e^{-(\kappa-\rho)a} \int_0^a |\psi(-\theta) - \bar{\psi}(-\theta) \int_\theta^\alpha \psi(-\sigma) d\sigma| d\theta \\ &\leq K e^{-(\kappa-\rho)a} \int_0^a |\psi(-\theta)| d\theta (1 + \int_0^a \bar{\psi}(-\theta) d\theta) \\ &\leq K e^{-(\kappa-2\rho)a} \|\psi\|_{1,\rho} (1 + \int_0^a \bar{\psi}(-\theta) d\theta) \\ &\leq K_1 e^{-(\kappa-3\rho)a} \|\psi\|_{1,\rho} (1 + \|\bar{\psi}\|_{1,\rho}) \leq K_2 \|\psi\|_{1,\rho} \end{aligned}$$

for appropriately defined $K_1 \geq 0$ and $K_2 = K_2(\|\bar{\psi}\|_{1,\rho}) \geq 0$. Hence $\|DA(\bar{\psi})\psi\|_{\infty,\rho} \leq K_2 \|\psi\|_{1,\rho}$ and thus the candidate is a well-defined bounded linear operator on $L_{\rho,+}^{1,1}$. Next, for $\psi, \bar{\psi} \in L_{\rho,+}^{1,1}$ one has

$$\begin{aligned} \Delta_a &:= e^{\rho a} | [A(\psi) - A(\bar{\psi}) - DA(\bar{\psi})(\psi - \bar{\psi})](a) | \\ &\leq e^{-(\kappa-\rho)a} K \int_0^a |\psi(-\theta) e^{-\int_\theta^\alpha \psi(-\sigma) d\sigma} - \bar{\psi}(-\theta) e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} \\ &\quad - e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} [\psi(-\theta) - \bar{\psi}(-\theta) - \bar{\psi}(-\theta) \int_\theta^\alpha \psi(-\sigma) - \bar{\psi}(-\sigma) d\sigma]| d\theta \\ &= e^{-(\kappa-\rho)a} K \int_0^a |\psi(-\theta) (e^{-\int_\theta^\alpha \psi(-\sigma) d\sigma} - e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma}) \\ &\quad + e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} \bar{\psi}(-\theta) \int_\theta^\alpha \psi(-\sigma) - \bar{\psi}(-\sigma) d\sigma| d\theta \\ &\leq K e^{-(\kappa-\rho)a} \int_0^a |\psi(-\theta)| [(e^{-\int_\theta^\alpha \psi(-\sigma) d\sigma} - e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma}) \\ &\quad - e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} \int_\theta^\alpha \bar{\psi}(-\sigma) - \psi(-\sigma) d\sigma]| d\theta \\ &\quad + K e^{-(\kappa-\rho)a} \int_0^a e^{-\int_\theta^\alpha \bar{\psi}(-\sigma) d\sigma} |\bar{\psi}(-\theta) - \psi(-\theta)| \int_\theta^\alpha |\bar{\psi}(-\sigma) - \psi(-\sigma)| d\sigma d\theta \\ &=: \Delta_a^1 + \Delta_a^2 \end{aligned}$$

for obviously defined Δ_a^1, Δ_a^2 . By the mean value theorem and the fact that e is Lipschitz on $(-\infty, 0]$ we get that

$$\begin{aligned} & |e^{-\int_\theta^a \psi(-\sigma)d\sigma} - e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma} - e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma} \int_\theta^a \bar{\psi}(-\sigma) - \psi(-\sigma)d\sigma| \\ & \leq |e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma + \xi[-\int_\theta^a \psi(-\sigma)d\sigma + \int_\theta^a \bar{\psi}(-\sigma)d\sigma]} - e^{-\int_\theta^a \bar{\psi}(-\sigma)d\sigma}| \int_\theta^a |\bar{\psi}(-\sigma) - \psi(-\sigma)|d\sigma \\ & \leq K_2 \left(\int_\theta^a |\psi(-\sigma) - \bar{\psi}(-\sigma)|d\sigma \right)^2 \leq K_2 e^{2\rho} \|\psi - \bar{\psi}\|_{1,\rho}^2 \end{aligned}$$

for some $K_2 \geq 0$ and some $\xi \in [0, 1]$. Hence,

$$\begin{aligned} \Delta_a^1 & \leq K_3 e^{-(\kappa-3\rho)a} \int_0^a |\psi(-\theta)|d\theta \|\psi - \bar{\psi}\|_{1,\rho}^2 \\ (A.1) \quad & \leq K_3 e^{-(\kappa-4\rho)a} \|\psi\|_{1,\rho} \|\psi - \bar{\psi}\|_{1,\rho}^2 \end{aligned}$$

for some $K_3 \geq 0$. Next,

$$\begin{aligned} \Delta_a^2 & \leq K e^{-(\kappa-\rho)a} \int_0^a |\bar{\psi}(-\theta) - \psi(-\theta)|d\theta \int_0^a |\psi(-\sigma) - \bar{\psi}(-\sigma)|d\sigma \\ (A.2) \quad & \leq K e^{-(\kappa-3\rho)a} \|\psi - \bar{\psi}\|_{1,\rho}^2. \end{aligned}$$

By (A.1–A.2) one has that $\sup_{a \in [0, \infty)} \text{ess}_a \Delta_a$ is $o(\|\psi - \bar{\psi}\|_{1,\rho})$. This shows differentiability of A . It remains to show that the derivative is continuous. That means that for $\bar{\psi}, \psi \in L_{\rho,+}^{1,1}$ and $\chi \in L_{\rho,+}^{1,1}$ the essential supremum of

$$a \mapsto e^{\rho a} |[DA(\psi)\chi - DA(\bar{\psi})\chi](a)|$$

should be $o(\|\psi - \bar{\psi}\|_{1,\rho})$. The proof involves no other technicalities than the ones used to show differentiability and we omit it. \square

Proof of Proposition 5.1 We apply (4.4) to the terms of the characteristic equation and write G' instead of $G'(G^{-1}(I))$ so that we get

$$\begin{aligned} m_{11} & = 2 \left\{ \alpha + (1-\alpha)I \int_0^\infty e^{-\theta(\lambda+I)} \tilde{\mathcal{F}}(\theta)d\theta \right\} \int_0^\infty e^{-\lambda\theta} \beta(\theta) \mathcal{F}_\beta(\theta)d\theta, \\ m_{12} & = 2b(1-\alpha) \int_0^\infty \tilde{\mathcal{F}}(\theta)e^{-I\theta} \left(1 - I \frac{1-e^{-\lambda\theta}}{\lambda} \right) d\theta \int_0^\infty e^{-\lambda\theta} \beta(\theta) \mathcal{F}_\beta(\theta)d\theta, \\ m_{21} & = G' \left[(1-q) \left\{ \alpha + (1-\alpha)I \int_0^\infty e^{-(\lambda+I)\theta} \tilde{\mathcal{F}}(\theta)d\theta \right\} \int_0^\infty e^{-\lambda a} \mathcal{F}_\beta(a)da \right. \\ & \quad \left. + q(1-\alpha) \int_0^\infty e^{-(\lambda+I)a} \tilde{\mathcal{F}}(a)da \right], \\ m_{22} & = G'b(1-\alpha) \left\{ -q \int_0^\infty \tilde{\mathcal{F}}(a)e^{-Ia} \frac{1-e^{-\lambda a}}{\lambda} da \right. \\ & \quad \left. + (1-q) \int_0^\infty \tilde{\mathcal{F}}(\theta)e^{-I\theta} \left(1 - I \frac{1-e^{-\lambda\theta}}{\lambda} \right) d\theta \int_0^\infty \mathcal{F}_\beta(\theta)e^{-\lambda\theta} d\theta \right\}. \end{aligned}$$

Next, we use

$$\begin{aligned}\widehat{\mathcal{F}}_\beta(\lambda) &= \frac{1}{\lambda + \mu}(1 - \widehat{\beta\mathcal{F}}_\beta(\lambda)), \text{ to get} \\ m_{11} &= \frac{2\widehat{\beta\mathcal{F}}_\beta(\lambda)[\alpha(\mu + \lambda) + I]}{\mu + \lambda + I}, \quad m_{12} = \frac{2b(1 - \alpha)(\mu + \lambda)}{(\mu + I)(\mu + \lambda + I)}\widehat{\beta\mathcal{F}}_\beta(\lambda), \\ m_{21} &= \frac{G'\{(1 - q)[\alpha(\mu + \lambda) + I](1 - \widehat{\beta\mathcal{F}}_\beta(\lambda)) + q(1 - \alpha)(\mu + \lambda)\}}{(\mu + \lambda)(\mu + \lambda + I)}, \\ m_{22} &= \frac{G'b(1 - \alpha)}{(\mu + I)(\mu + \lambda + I)}\{(1 - q)(1 - \widehat{\beta\mathcal{F}}_\beta(\lambda)) - q\}.\end{aligned}$$

It follows that

$$\begin{aligned}m_{11}m_{22} - m_{12}m_{21} - m_{22} &= \frac{G'b(1 - \alpha)}{(\mu + I)(\mu + \lambda + I)}\left\{-\frac{2q\widehat{\beta\mathcal{F}}_\beta(\lambda)[\alpha(\mu + \lambda) + I]}{\mu + \lambda + I}\right. \\ &\quad \left.- \frac{2q\widehat{\beta\mathcal{F}}_\beta(\lambda)(1 - \alpha)(\mu + \lambda)}{\mu + \lambda + I} - (1 - q)(1 - \widehat{\beta\mathcal{F}}_\beta(\lambda)) + q\right\} \\ &= -\frac{G'b(1 - \alpha)}{(\mu + I)(\mu + \lambda + I)}[2\widehat{\beta\mathcal{F}}_\beta(\lambda)l_1 + l_2], \\ 1 - m_{11} &= \frac{(\lambda + \mu)(1 - 2\alpha\widehat{\beta\mathcal{F}}_\beta(\lambda)) + I(1 - 2\widehat{\beta\mathcal{F}}_\beta(\lambda))}{\lambda + I + \mu}, \\ (\lambda + I + \mu)(m_{11}m_{22} - m_{21}m_{12} - m_{22} + 1 - m_{11}) & \\ &= -\frac{G'b(1 - \alpha)}{\mu + I}(2\widehat{\beta\mathcal{F}}_\beta(\lambda)l_1 + l_2) + (\lambda + \mu)(1 - 2\alpha\widehat{\beta\mathcal{F}}_\beta(\lambda)) + I(1 - 2\widehat{\beta\mathcal{F}}_\beta(\lambda)) \\ &= 2\widehat{\beta\mathcal{F}}_\beta(\lambda)[- \alpha\lambda - \frac{G'b(1 - \alpha)}{\mu + I}l_1 - \alpha\mu - I] + \lambda - \frac{G'b(1 - \alpha)}{\mu + I}l_2 + \mu + I.\end{aligned}$$

Hence, the characteristic equation can be written as

$$2\widehat{\beta\mathcal{F}}_\beta(\lambda)[- \alpha\lambda - \frac{G'b(1 - \alpha)}{\mu + I}l_1 - \alpha\mu - I] + \lambda - \frac{G'b(1 - \alpha)}{\mu + I}l_2 + \mu + I = 0.$$

Now, note that $\int_0^\infty \mathcal{F}_\beta(a)da = \frac{1}{\mu}(1 - \frac{1}{2}r_0)$. Then the equation gets the representation that is claimed if we use that $b = \frac{r_0G^{-1}(I)\mu}{r_0l_1 + l_2}$, $\mu + I = \frac{\mu r_0(1 - \alpha)}{r_0 - 1}$ and $\alpha\mu + I = \frac{\mu(1 - \alpha)}{r_0 - 1}$. \square

Proof of Lemma 5.4 (i) is trivial. Suppose now that λ solves (5.2). Then

$$|\lambda - a_2|^2 = |\widehat{m}(\lambda)|^2|\alpha\lambda + a_1|^2.$$

By Lemma 5.3 (i) then

$$(x + r_0a_1)^2 + y^2 = |\widehat{m}(\lambda)|^2[(\alpha x + a_1)^2 + \alpha^2y^2].$$

Then, if $x > 0$ by (i) and since $r_0a_1 > 0$

$$(x + r_0a_1)^2 + y^2 < (\alpha r_0x + a_1r_0)^2 + (\alpha y r_0)^2 < (x + a_1r_0)^2 + y^2,$$

which is a contradiction. If $x = 0$, then

$$(r_0 a_1)^2 + y^2 \leq (r_0 a_1)^2 + (\alpha y r_0)^2,$$

which is $y^2 \leq (\alpha r_0 y)^2$. Hence, if $y \neq 0$ we get $1 \leq (\alpha r_0)^2 < 1$, which is also a contradiction. \square

Proof of Lemma 5.5 For $\lambda = x + iy$ we define $r(x, y) := \operatorname{Re} \widehat{m}_b(\lambda)$, $i(x, y) := \operatorname{Im} \widehat{m}_b(\lambda)$. Then $r(0) = r_0$, $i(0) = 0$, $\partial_x r(0) = \partial_y i(0) = -r_0$ and $\partial_y r(0) = \partial_x i(0) = 0$. Then the realification of (5.2) is $G(\mu, c, x, y) = 0$, where

$$\begin{aligned} G_1(\mu, c, x, y) &= (\alpha x + a_1)r(x, y) - \alpha y i(x, y) - x + a_2, \\ G_2(\mu, c, x, y) &= \alpha y r(x, y) + (\alpha x + a_1)i(x, y) - y. \end{aligned}$$

From the analysis of the complex equation, we know that $(\mu, \xi\mu, 0, 0)$ solves the realification. For this point we compute

$$\partial_x G_1 = \partial_y G_2 = \alpha r_0 - 1 - r_0 a_1 (\mu, \xi\mu)^T < 0, \quad \partial_y G_1 = \partial_x G_2 = 0,$$

such that $\det \partial_{x,y} G \neq 0$. Then by the implicit function theorem there exists some $\delta > 0$ and C^1 -functions $\phi_j(\xi\mu - \delta, \xi\mu + \delta) \rightarrow \mathbb{R}$, $j = 1, 2$ such that $G(\mu, c, \phi_1(c), \phi_2(c)) = 0$ and $\phi'(\xi\mu) = -[\partial_{x,y} G]^{-1} \partial_c G$. Now

$$\begin{aligned} \partial_{(x,y)} G &= -\sqrt{\det \partial_{(x,y)} G} I \Rightarrow (\partial_{(x,y)} G)^{-1} = -\frac{1}{\sqrt{\det \partial_{(x,y)} G}} I, \\ \partial_c G_1 &= r_0 a_{12} + a_{22} = -(r_0 - 1) < 0. \end{aligned}$$

Hence $\phi'_1(\xi\mu) < 0$ and the statement follows. \square

Proof of Lemma 5.6 First note that (5.2) is equivalent to

$$\lambda(1 - \alpha \widehat{m}_b(\lambda)) = a_2 + a_1 \widehat{m}_b(\lambda).$$

Hence, $|\lambda|(1 - \alpha |\widehat{m}_b(\lambda)|) \leq |a_2| + |a_1| |\widehat{m}_b(\lambda)|$. As $x \geq 0$, we have that $1 - \alpha |\widehat{m}(\lambda)| \geq 1 - \alpha r_0 > 0$ and $\widehat{m}(\lambda) \leq r_0$. Thus

$$|\lambda| \leq \frac{|a_2| + |a_1| r_0}{1 - \alpha r_0}.$$

This implies the statement. \square

For the proofs of Propositions 5.9 and 5.12 below we define a function $G = (G_1, G_2)$ with $G_j : \mathbb{R}^4 \rightarrow \mathbb{R}$ for $j \in \{1, 2\}$ via

$$(A.3) \quad G_1(\mu, c, \kappa, \nu) := \operatorname{Re} H(\mu, c, \kappa + i\nu), \quad G_2(\mu, c, \kappa, \nu) := \operatorname{Im} H(\mu, c, \kappa + i\nu).$$

With a straightforward calculation one obtains

LEMMA A.1.

(A.4)

$$G_1(\mu, c, \kappa, \nu) = e^{-\kappa} r_0 \{ \alpha(\kappa \cos \nu + \nu \sin \nu) + a_1(\mu, c)^T \cos \nu \} - \kappa + a_2(\mu, c)^T,$$

(A.5)
$$G_2(\mu, c, \kappa, \nu) = e^{-\kappa} r_0 \{ \alpha(\nu \cos \nu - \kappa \sin \nu) - a_1(\mu, c)^T \sin \nu \} - \nu.$$

G satisfies the Cauchy-Riemann equations, i.e.

(A.6)
$$\partial_\kappa G_1 = \partial_\nu G_2, \quad \partial_\nu G_1 = -\partial_\kappa G_2.$$

Proof of Lemma 5.8 We consider dependency of the sign of $m(\nu)$ on q .

LEMMA A.2. For every k the following statements hold. If $q \in [0, \bar{q}(r_0)]$ then $m(\nu) < 0$ for $\nu \in I_k$. If $q \in (\bar{q}(r_0), 1]$ then

(A.7)
$$m(\nu) \begin{cases} < 0 & \text{for } \nu \in I_k \setminus (J_k \cup \{\nu_k\}), \\ = 0 & \text{for } \nu = \nu_k, \\ > 0 & \text{for } \nu \in J_k. \end{cases}$$

Proof. To consider q -dependency of m we rewrite $m(\nu)$ as $m(q, \nu)$. For $q \in [0, 1]$ and any k one has

(A.8)
$$\lim_{\nu \downarrow 2k\pi} m(q, \nu) = \alpha r_0 - 1 < 0, \quad \lim_{\nu \uparrow (2k+1)\pi} m(q, \nu) = (\alpha r_0 + 1) \frac{l_1(q)r_0 - l_2(q)}{l_1(q)r_0 + l_2(q)},$$

$$\partial_\nu m(q, \nu) = \frac{r_0(l_1(q) - \alpha l_2(q))}{l_1(q)r_0 + l_2(q)} \sin \nu, \quad \text{for } \nu \in I_k.$$

With $q_1 := \frac{2\alpha+1}{4\alpha+3} \in (0, 1)$ for $\nu \in I_k$ with straightforward calculations one gets

(A.9)
$$\text{sign } \partial_\nu m(q, \nu) = \text{sign}(q - q_1) \text{ and } 0 < q_1 < \bar{q}(r_0) < 1.$$

For $q \in [0, \bar{q}(r_0))$ it holds that $\lim_{\nu \uparrow (2k+1)\pi} m(q, \nu) < 0$ by (A.8) and Lemma 5.7. Hence, for both intervals $[0, q_1]$ and $(q_1, \bar{q}(r_0))$ we have negativity on the boundary values of I_k and monotonicity in between. Hence $m(q, \nu) < 0$ for all $(q, \nu) \in [0, \bar{q}(r_0)) \times I_k$. By (A.9) we have that $\frac{\partial}{\partial \nu} m(\bar{q}(r_0), \nu) > 0$ for $\nu \in I_k$. Thus for $q = \bar{q}(r_0)$ and $\nu \in I_k$ by Lemma 5.7 it holds that $m(q, \nu) < \lim_{\nu \uparrow (2k+1)\pi} m(q, \nu) = 0$. Therefore, we obtain the first statement. For $q \in (\bar{q}(r_0), 1]$ we have that $\lim_{\nu \uparrow (2k+1)\pi} m(q, \nu) > 0$ by (A.8) and Lemma 5.7. By (A.9), for $q \in (\bar{q}(r_0), 1]$, $m(q, \nu)$ is monotonously increasing with respect to $\nu \in I_k$. From the definition of ν_k , it follows that, for fixed $q \in (\bar{q}(r_0), 1]$, $\nu = \nu_k$ is the unique solution of $m(q, \nu) = 0$. Hence, we have shown (A.7). \square

LEMMA A.3. For every k the following statements hold. If $q \in [0, \bar{q}(r_0)]$ then $\mu^*(\nu) < 0$ for $\nu \in I_k$. If $q \in (\bar{q}(r_0), 1]$ then $c^*(\nu) > 0$ for $\nu \in J_k \cup \{\nu_k\}$ and

(A.10)
$$\mu^*(\nu) \begin{cases} < 0 & \text{for } \nu \in I_k \setminus (J_k \cup \{\nu_k\}), \\ = 0 & \text{for } \nu = \nu_k, \\ > 0 & \text{for } \nu \in J_k. \end{cases}$$

Proof. As $\frac{\nu}{\sin \nu} > 0$ for $\nu \in I_k$, it follows that $\text{sign } \mu^*(\nu) = \text{sign } m(\nu)$ for $\nu \in I_k$. By Lemma A.2 the first statement and (A.10) in the second statement hold. Since $1 - \cos \nu > 0$ for $\nu \in I_k$, if $m(\nu) \geq 0$ then $c^*(\nu) > 0$ by (5.7). \square

Now, by Lemma A.3, for every k , the curve C_k does not reach the interior of the existence region if $q \in [0, \bar{q}(r_0)]$. Next, we assume that $q \in (\bar{q}(r_0), 1]$ holds. By Lemma A.3 the curve $(\mu^*, c^*)(\nu)$ is located in the third or fourth (closed) quadrant for $\nu \in I_k \setminus J_k$ and in the first (open) quadrant for $\nu \in J_k$. Using (5.6) and (5.7) one can see that $c^*(\nu) > \xi\mu^*(\nu)$ for $\nu \in I_k$ holds. Thus the curve lies above the existence boundary. Hence Lemma 5.8 is proven. \square

Next, note that if ν solves $G(\mu, c, \kappa, \nu) = 0$, then so does $-\nu$

Proof of Proposition 5.9 We suppose that there exists a point (μ, c) inside the existence region where the characteristic equation has a purely imaginary root $\lambda = i\nu$, $\nu \in \mathbb{R}$. Without loss of generality $\nu \geq 0$. Then $G(\mu, c, 0, \nu) = 0$. One has that

$$(A.11) \quad 0 = r_0 a_1(\mu, c)^T \cos \nu + \alpha r_0 \nu \sin \nu + a_2(\mu, c)^T,$$

$$(A.12) \quad 0 = \alpha r_0 \nu \cos \nu - r_0 a_1(\mu, c)^T \sin \nu - \nu.$$

We claim that $\nu \neq k\pi$ for any nonnegative integer k . Suppose that $\nu = 0$. Then, by (A.11) it holds that

$$(A.13) \quad r_0 a_1(\mu, c)^T + a_2(\mu, c)^T = 0.$$

Since $r_0 a_1(\mu, c)^T + a_2(\mu, c)^T = -(r_0 - 1)(c - \xi\mu) < 0$, we get a contradiction to (A.13). Thus $\nu \neq 0$. Next suppose $\nu = k\pi$ for some $k \in \mathbb{N}$. Then $k\pi((-1)^k \alpha r_0 - 1) = 0$ by (A.12), a contradiction. Thus $\nu \neq k\pi$. Hence there exists $k \in \mathbb{N}_0$ such that $\nu \in (k\pi, (k+1)\pi)$. Now, note that (A.11) and (A.12) are equivalent to

$$(A.14) \quad A \begin{pmatrix} \mu \\ c \end{pmatrix} = \frac{\nu}{r_0 \sin \nu} \begin{pmatrix} \alpha r_0 \cos \nu - 1 \\ r_0 \cos \nu - \alpha r_0^2 \end{pmatrix}, \quad A := \begin{pmatrix} a_1 \\ a_2 \end{pmatrix}.$$

Next note that $\det A = -(1 - \alpha) \neq 0$. One then can check that

$$(A.15) \quad \begin{pmatrix} \mu \\ c \end{pmatrix} = \frac{\nu}{\sin \nu} A^{-1} \begin{pmatrix} \alpha r_0 \cos \nu - 1 \\ -r_0(\alpha r_0 - \cos \nu) \end{pmatrix} = \begin{pmatrix} \mu^*(\nu) \\ c^*(\nu) \end{pmatrix}.$$

As (μ, c) lies in the existence region, we can exclude that $\nu \in ((2k+1)\pi, (2k+2)\pi)$ and thus $\nu \in I_k$. If $q \in [0, \bar{q}(r_0)]$, since we assumed that (μ, c) is a point in the existence region, by Lemma 5.8 we get a contradiction. Hence, the characteristic equation does not have purely imaginary roots for any (μ, c) inside the existence region. If $q \in (\bar{q}(r_0), 1]$, Lemma 5.8 implies $\nu \in J_k \subset I_k$. Then one can use the above transformations to easily deduce both implications stated for $q \in (\bar{q}(r_0), 1]$. \square

Proof of Lemma 5.11 First, note that $\frac{\nu}{\sin \nu}(1 - \cos \nu)$ is increasing on I_k . To show that μ^* and c^* are increasing, it is sufficient to show that $\frac{\nu}{\sin \nu} m(\nu)$ is increasing. One can see that

$$\begin{aligned} \frac{\nu}{\sin \nu} m(\nu) &= \frac{l_1(q)r_0 - \alpha r_0 l_2(q)}{l_1(q)r_0 + l_2(q)} n(q, \nu) \quad \text{with} \quad \frac{l_1(q)r_0 - \alpha r_0 l_2(q)}{l_1(q)r_0 + l_2(q)} > 0, \\ n(q, \nu) &:= \frac{\nu}{\sin \nu} (\rho(q) - \cos \nu) \quad \text{for} \quad (q, \nu) \in D_k := (\bar{q}(r_0), 1] \times I_k. \end{aligned}$$

by Lemma 5.7. Let $(q, \nu) \in D_k$. With $h(q, \nu) := \rho(q)(\sin \nu - \nu \cos \nu) - \cos \nu \sin \nu + \nu$ it holds that $\partial_\nu n(q, \nu) = \frac{h(q, \nu)}{\sin^2 \nu}$. Thus $\text{sign}(d_\nu \frac{\nu}{\sin \nu} m(\nu)) = \text{sign} \partial_\nu n(q, \nu) = \text{sign} h(q, \nu)$.

In the following we prove that $h(q, \nu) > 0$. For $q \in (\bar{q}(r_0), 1]$ we get that

$$(A.16) \quad \lim_{\nu \downarrow 2k\pi} h(q, \nu) = (1 - \rho(q)) 2k\pi, \quad k \in \mathbb{N}_0, \quad \text{thus} \quad \lim_{\nu \downarrow 2k\pi} h(q, \nu) > 0, \quad k \in \mathbb{N},$$

$$(A.17) \quad \lim_{\nu \uparrow (2k+1)\pi} h(q, \nu) = (1 + \rho(q)) (2k + 1)\pi > 0 \quad \text{for} \quad k \in \mathbb{N}_0,$$

$$(A.18) \quad \partial_\nu h(q, \nu) = \sin \nu (\rho(q)\nu + 2 \sin \nu) \quad \text{and}$$

$$(A.19) \quad \text{sign } \rho(q) = \text{sign}(q - q_2(r_0)), \quad q_2(r_0) := \frac{\alpha r_0^2 + 2}{3\alpha r_0^2 + 4} > \bar{q}(r_0).$$

Then $\partial_\nu h(q, \nu) > 0$ for $(q, \nu) \in [q_2(r_0), 1] \times I_k$ by (A.18). Since we have (A.16) we get $h(q, \nu) > 0$ for $(q, \nu) \in [q_2(r_0), 1] \times I_k$. We now fix $q \in (\bar{q}(r_0), q_2(r_0))$. By (A.18)

$$(A.20) \quad \text{sign } \partial_\nu h(q, \nu) = \text{sign } h_1(\nu), \quad \text{where } h_1(\nu) := \rho(q)\nu + 2 \sin \nu, \quad \text{moreover}$$

$$(A.21) \quad \lim_{\nu \rightarrow k\pi} h_1(\nu) = \rho(q)k\pi \quad \text{and for } k \in \mathbb{N} \quad \lim_{\nu \rightarrow k\pi} h_1(\nu) < 0.$$

We get $h'_1(\nu) = \rho(q) + 2 \cos \nu$. For a fixed q , $h'_1(\nu)$ decreases with respect to $\nu \in I_k$. Using (A.19), one can compute that $\lim_{\nu \downarrow 2k\pi} h'_1(\nu) = \rho(q) + 2 > 0$ and $\lim_{\nu \uparrow (2k+1)\pi} h'_1(\nu) = \rho(q) - 2 < 0$. Thus there is exactly one root of $h'_1(\nu) = 0$ in every interval I_k . We define $j_k := \arccos(-\frac{1}{2}\rho(q)) + 2k\pi$. Consequently we have

$$(A.22) \quad \text{sign } h'_1(\nu) = \text{sign}(j_k - \nu)$$

Thus h_1 has exactly one local extremum, a maximum at $\nu = j_k$. First, we consider the case $k = 0$. By (A.21) and (A.22) there is exactly one solution s_0 of $h_1(\nu) = 0$ for $\nu \in I_0$. Now $\text{sign } h_1(\nu) = \text{sign}(s_0 - \nu)$. Then, by (A.20) h is strictly monotonically increasing with respect to $\nu \in (0, s_0)$ and strictly monotonically decreasing with respect to $\nu \in (s_0, \pi)$. Hence $h(q, \nu) > \min\{\lim_{\nu \downarrow 0} h(q, \nu), \lim_{\nu \uparrow \pi} h(q, \nu)\} = 0$ by (A.16) and (A.17). Now for $k \in \mathbb{N}$, one has either $h_1(j_k) \leq 0$ or $h_1(j_k) > 0$. If $h_1(j_k) \leq 0$, then $h_1(\nu) \leq 0$ and by (A.20) also $\partial_\nu h(q, \nu) \leq 0$. It follows that $h(q, \nu) > \lim_{\nu \uparrow (2k+1)\pi} h(q, \nu) > 0$ by (A.17). Next we assume that $h_1(j_k) > 0$ holds. By (A.20), (A.21) and (A.22) there exist $s_k, s'_k, s_k < s'_k, s_k \in (2k\pi, j_k)$ and

$$\text{sign } \partial_\nu h(q, \nu) = \text{sign } h_1(\nu) = \begin{cases} -1 & \text{for } \nu \in (2k\pi, s_k) \cup (s'_k, (2k+1)\pi), \\ 0 & \text{for } \nu \in \{s_k, s'_k\}, \\ -1 & \text{for } \nu \in (s_k, s'_k), \end{cases} \quad \text{hence}$$

$$(A.23) \quad h(q, \nu) \geq \min \left\{ h(q, s_k), \lim_{\nu \uparrow (2k+1)\pi} h(q, \nu) \right\}.$$

Since we have (A.17), we prove that $h(q, s_k) > 0$. Next $\sin s_k = -\frac{1}{2}\rho(q)s_k$ by (A.20). Then $h(q, s_k) = s_k(-\frac{1}{2}\rho^2(q) + 1 - \frac{1}{2}\rho(q)\cos s_k)$. One has $\cos j_k = -\frac{1}{2}\rho(q) > 0$ by (A.19). As $s_k \in (2k\pi, j_k)$ also $\cos s_k > 0$, hence we obtain that $h(q, s_k) > 0$. We have shown that $h(q, \nu) > 0$ for $(q, \nu) \in (\bar{q}(r_0), q_2(r_0)) \times I_k$. \square

Proof of Proposition 5.12 Let $\nu \in J_k, k \in \mathbb{N}_0$. By Proposition 5.9 for $(\mu^*, c^*)(\nu)$ there are exactly two imaginary roots. We define a matrix

$$(A.24) \quad M(\nu) := \partial_{(\mu, c)} G(\mu^*(\nu), c^*(\nu), 0, \nu) = \begin{pmatrix} a_{11} \cos \nu + a_{21} & a_{12} \cos \nu + a_{22} \\ -a_{11} \sin \nu & -a_{12} \sin \nu \end{pmatrix}, \quad \text{with}$$

$$\det M(\nu) = \sin \nu \det A = -(1 - \alpha) r_0 \sin \nu < 0$$

(see the proof of Proposition 5.9 for $\det A$). Then the normal vector that points left of C_k at $(\mu^*, c^*)(\nu)$ is

$$-NM^{-1}(\nu)\mathbf{w}(\nu), \text{ where } N := \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} \text{ and } \mathbf{w}(\nu) := \partial_\nu G(\mu^*(\nu), c^*(\nu), 0, \nu).$$

We consider a path that crosses C_k at $(\mu^*, c^*)(\nu)$ transversally from right to left. The path has a tangent vector

$$(A.25) \quad \mathbf{g} \in \mathbb{R}^2, \text{ with } \mathbf{g} \cdot (-NM^{-1}(\nu)\mathbf{w}(\nu)) > 0.$$

We define $W(\nu) := \partial_{(\kappa, \nu)} G(\mu^*(\nu), c^*(\nu), 0, \nu)$. Using (A.6) we compute that

$$\begin{aligned} \det W(\nu) &= \left(1 + r_0 a_1 (\mu^*(\nu), c^*(\nu))^T - \alpha r_0\right)^2 + (\alpha r_0)^2 \nu^2 + 2\alpha r_0 \nu \sin \nu \\ &\quad - 2 \left(r_0 a_1 (\mu^*(\nu), c^*(\nu))^T - \alpha r_0\right) (1 - \cos \nu). \end{aligned}$$

Since it holds that $G_2(\mu^*(\nu), c^*(\nu), 0, \nu) = 0$, we have that $a_1(\mu^*(\nu), c^*(\nu))^T = \frac{\nu}{\sin \nu} (\alpha r_0 \cos \nu - 1) < 0$. Thus $\det W(\nu) > 0$. Hence there exists a neighborhood of $(\mu^*, c^*)(\nu)$ and two functions ϕ_1 and ϕ_2 that for (μ, c) in the neighborhood are partially differentiable and satisfy $G(\mu, c, \phi_1(\mu, c), \phi_2(\mu, c)) = 0$ with $\phi_1(\mu^*(\nu), c^*(\nu)) = 0$ and $\phi_2(\mu^*(\nu), c^*(\nu)) = \nu$. Note that $G(\mu, c, \phi_1(\mu, c), -\phi_2(\mu, c)) = 0$ for (μ, c) in the neighborhood. Next, we consider a path $\gamma(s)$, $s \in \mathbb{R}$ in the parameter plane such that as s increases γ crosses the curve C_k at the point $(\mu^*, c^*)(\nu)$ transversally from right to left with $\gamma(0) = (\mu^*, c^*)(\nu)$. For s such that $\gamma(s)$ is in the domain of ϕ_1 , we define $r(s) := \phi_1(\gamma(s))$. Since $\gamma'(0) = \mathbf{g}$ we obtain that $r'(0) = \mathbf{g} \cdot \partial_{(\mu, c)} \phi_1(\mu^*(\nu), c^*(\nu))$. By the implicit function theorem it holds that

$$\begin{aligned} \partial_{(\mu, c)} \phi_1(\mu^*(\nu), c^*(\nu)) &= -\frac{1}{\det W(\nu)} \begin{pmatrix} -\partial_\mu G_2 & \partial_\mu G_1 \\ -\partial_c G_2 & \partial_c G_1 \end{pmatrix}_{(\mu^*(\nu), c^*(\nu), 0, \nu)} \mathbf{w}(\nu) \\ &= \frac{(\det M(\nu))NM^{-1}(\nu)}{\det W(\nu)} \mathbf{w}(\nu) \quad \text{and thus} \\ r'(0) &= \frac{\det M(\nu)}{\det W(\nu)} \mathbf{g} \cdot (NM^{-1}(\nu)\mathbf{w}(\nu)) > 0 \end{aligned}$$

by (A.24) and (A.25). Hence two roots cross with positive speed when we cross C_k from right to left transversally. \square

Proof of Lemma 5.15

$$(A.26) \quad \begin{aligned} \det \partial_{(\mu, c)} g|_{\varepsilon=0} &= \det \begin{pmatrix} r_0 e^{-\kappa} a_{11} \cos \nu + a_{21} & r_0 e^{-\kappa} a_{12} \cos \nu + a_{22} \\ -r_0 e^{-\kappa} a_{11} \sin \nu & -r_0 e^{-\kappa} a_{12} \sin \nu \end{pmatrix} \\ &= r_0 e^{-\kappa} \sin \nu \det A. \end{aligned}$$

We have seen that $\det A \neq 0$. So if $\det \partial_{(\mu, c)} g|_{\varepsilon=0} = 0$ then $\nu = k\pi$ for some $k \in \mathbb{N}$. But then for the second component of g

$$0 = g_2(0, \kappa, k\pi, \bar{\mu}, \bar{c}) = k\pi(e^{-\kappa} r_0 \alpha (-1)^k - 1).$$

This is a contradiction since $\kappa \geq 0$ and $r_0 \alpha < 1$. As g is C^1 the statement follows from the implicit function theorem. \square

Proof of Theorem 5.16 We apply Lemma 5.15. For the stability assertion we show the case $q \in (\bar{q}(r_0), 1]$, the first case can be shown similarly. Let $(\mu_i, c_i) \in \Omega_0^{K,\delta}$. We first show

$$\exists \delta_i, \varepsilon_i > 0, \text{ s.th. } \forall \varepsilon \in [0, \varepsilon_i] \text{ and } (\mu, c) \in (\mu_i, c_i) + B_{\delta_i}(0)$$

the number of roots with $\kappa \geq 0$ is zero. Suppose, this wasn't true. Then by the compactness of $\Omega_0^{K,\delta}$ and the a priori estimate there exist converging sequences for $n \rightarrow \infty$

$$\varepsilon_n \rightarrow 0, (\mu_n, c_n) \rightarrow (\mu_i, c_i), \kappa_n \geq 0, \nu_n \geq 0, \kappa := \lim \kappa_n \geq 0, \nu := \lim \nu_n \geq 0,$$

such that by the continuity of g

$$0 = g(\varepsilon_n, \kappa_n, \nu_n, \mu_n, c_n) \rightarrow g(0, \kappa, \nu, \mu_i, c_i) \neq 0,$$

which is a contradiction. Now by the compactness of $\Omega_0^{K,\delta}$

$$\begin{aligned} \exists n \in \mathbb{N}, (\mu_i, c_i) \in \Omega_{2k}^{K,\delta}, \delta_i, \varepsilon_i > 0, i = 1 \dots n, \text{ s.th. } \Omega_{2k}^{K,\delta} \subset \bigcup_{i=1}^n (\mu_i, c_i) + B_{\delta_i}(0) \text{ and} \\ \forall \varepsilon \in [0, \bar{\varepsilon}], \bar{\varepsilon} := \min_{i=1 \dots n} \varepsilon_i, \forall (\mu, c) \in \bigcup_{i=1}^n (\mu_i, c_i) + B_{\delta_i}(0) \end{aligned}$$

the number of roots with $\kappa \geq 0$ is zero. Hence for $(\mu, c) \in \Omega_0^{K,\delta}$ and $\varepsilon \in (0, \bar{\varepsilon}]$ we can conclude stability.

Let now $(\mu_i, c_i) \in \Omega_{2k}^{K,\delta}$. Then we can choose $\delta_i, \varepsilon_i > 0$ such that for $\varepsilon \in [0, \varepsilon_i]$, $(\mu, c) \in (\mu_i, c_i) + B_{\delta_i}(0)$ the number of roots in the right half plane equals $2k$. As $\Omega_{2k}^{K,\delta}$ is compact

$$\begin{aligned} \exists n \in \mathbb{N}, (\mu_i, c_i) \in \Omega_{2k}^{K,\delta}, \delta_i, \varepsilon_i > 0, i = 1 \dots n, \text{ s.th. } \Omega_{2k}^{K,\delta} \subset \bigcup_{i=1}^n (\mu_i, c_i) + B_{\delta_i}(0) \text{ and} \\ \forall \varepsilon \in [0, \bar{\varepsilon}], \bar{\varepsilon} := \min_{i=1 \dots n} \varepsilon_i, \forall (\mu, c) \in \bigcup_{i=1}^n (\mu_i, c_i) + B_{\delta_i}(0) \end{aligned}$$

the number of roots with $\kappa \geq 0$ is $2k$. The statement follows. \square

Proof of Theorem 5.17 We can compute that

$$(A.27) \quad p_1(\mu, c) = \left\{ \frac{2(1 - \alpha r_0)}{2 - r_0} + \frac{(1 - \alpha) r_0}{r_0 - 1} \right\} \mu + \frac{(r_0 - 1) l_2}{l_1 r_0 + l_2} (c - \xi \mu).$$

Now, $\text{sign } l_2(q) = \text{sign}(1/2 - q)$. Thus $p_1(\mu, c) > 0$ for $q \in [0, 1/2]$. For $q \in (1/2, 1]$ one has $p_1(\mu, \eta\mu) = 0$ and $\partial_c p_1(\mu, c) < 0$. Thus $\text{sign } p_1(\mu, c) = \text{sign}(\eta\mu - c)$. As $p_2(\mu, c) > 0$ the conclusion of the theorem follows by the Routh-Hurwitz criterion. \square

TABLE A.1

Model ingredients and symbols used in the main text with interpretations and references to sections and equations in which they are introduced or specified.

Symbol	Short description	References
a	age, proliferation age	2.1
a_i, a_{ij}	characteristic equation in μ - c -space	Lemma 5.2
α	probability of going quiescent after birth	2.1
$b(t)$	population birth rate at time t	2.2
B	division probability, concentrated division	5
$\beta(a)$	individual division rate	2.1, 5
$\bar{\beta}$	division rate, constant division	5.1.3
c	maximum recruitment rate	5
$c^*(\nu)$	c -component of bifurcation curve	(5.7)
C_k	bifurcation curve	5.1.1
η	proportionality factor, constant division	(5.11)
$F(\varphi, \psi)$	operator defining renewal equation	3.1
$\hat{f}(\lambda)$	Laplace transform	5
$\mathcal{F}(a)$	survival in proliferation if no division	2.1
$\tilde{\mathcal{F}}(a)$	survival in quiescence if no recruitment	2.1
$\mathcal{F}_\beta(a)$	(unconditioned) survival in proliferation	2.2
$G(N)$	individual recruitment rate	2.1, 5
$H(\mu, c, \lambda)$	characteristic equation, concentrated division	(5.5)
$I(t)$	individual recruitment rate at time t	2.2
I_k	domain of bifurcation curve	5.1.1
J_k	domain of curve in existence region	Lemma 5.7
$l_i(q), i = 1, 2$	representation of bifurcation curves	5
m_{ij}	entries of characteristic matrix	(3.9-3.12)
$m(\nu)$	term in bifurcation curves	5.1.1
$M(\lambda)$	characteristic matrix	(3.8-3.9)
μ	mortality rate	$(0, \infty)$ 4,5
$\mu^*(\nu)$	μ -component of bifurcation curves	(5.6)
$N(t)$	weighted total population at time t	(2.1)
ν	parameter for bifurcation curves	5.1.1
ν_k	ν -value defining J_k	Lemma 5.7
$P(t)$	total proliferating population at time t	2.1, (2.9)
$p_i(\mu, c), i = 1, 2$	characteristic equation, constant division	(5.10)
q	relative weight of quiescent population	2.1
$\bar{q}(r_0)$	q -value defining bifurcation curves	5.1.1
Ω_S, Ω_U	regions of (in)-stability	5.1.1
$Q(t)$	total quiescent population at time t	2.1, (2.10)
$R(\psi)$	operator in b -component of renewal equation	(2.4)
r_0	expected daughter production in proliferation	4
$R_0(I)$	expected reproduction number	(4.1)
$\rho(q)$	auxiliary function to define ν_k	Lemma 5.7
$S(\psi)$	operator in I -component of renewal equation	(2.5)
ξ	proportionality factor in existence boundary	(4.9)