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Local asymptotic stability of a system of integro-differential equations describing clonal evolution of a self-renewing cell population under mutation

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Abstract In this paper we consider a system of non-linear integro-differential equations (IDEs) describing evolution of a clonally heterogeneous population of malignant white blood cells (leukemic cells) undergoing mutation and clonal selection. We prove existence and uniqueness of non-trivial steady states and study their asymptotic stability. The results are compared to those of the system without mutation. Existence of equilibria is proved by formulating the steady state problem as an eigenvalue problem and applying a version of the Krein-Rutmann theorem for Banach lattices. The stability at equilibrium is analysed using linearisation and the Weinstein-Aronszajn determinant which allows to conclude local asymptotic stability.

Keywords Selection mutation process · integro-differential equations · cell differentiation model · stationary solutions · asymptotic stability

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1 Introduction

The paper is devoted to the analysis of a system of integro-differential equations (IDEs) describing clonal evolution of a self-renewing cell population. The

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population is heterogeneous with respect to the self-renewal ability of dividing cells, a property that may change due to cancerous mutations. The model is applied to describe dynamics of acute leukemias, an important type of malignant proliferative disorders of the blood forming system.

Acute leukemias show a considerable inter-individual genetic heterogeneity and a complex genetic relationship among different clones, i.e. subpopulations consisting of genetically identical cells [32]. Similarly to the healthy hematopoietic system, the leukemic cell bulk is maintained by cells with stem-like properties that can divide and give rise to progeny cells which either adopt the same cell route as the parent cell (undergo self-renewal) or differentiate to a more specialised cell type [32]. There exists theoretical [39] and experimental [34, 47] evidence suggesting that the self-renewal ability of leukemic stem cells has a significant impact on disease dynamics and patient prognosis [43]. Increased self-renewal confers a competitive advantage on cancer cell clones by leading to aggressive expansion of both stem and non-stem cancer cells and can be responsible for the clonal selection observed in experimental and clinical data [46]. The latter has been investigated using mathematical models of evolution of an arbitrary number of leukaemic clones coupled to a healthy cell lineage [8, 40]. A mathematical proof of clonal selection has been shown in Ref. [8] exploiting the analytical tractability of the model with a continuum of heterogeneous clones differing with respect to the stem cell self-renewal ability. A similar result has been recently obtained in Ref. [30] for an extended model with two-parameter heterogeneity with respect to cancer stem cell self-renewal fraction and proliferation rate. It was shown that while increased proliferation rates may lead to a rapid growth of respective clones, the long-term selection process is governed by increased self-renewal of the most primitive subpopulation of leukemic cells [40, 30]. Mathematical analysis of the model provided an understanding of the link between the observed selection phenomenon and the nonlocal mode of growth control in the model, resulting from description of different plausible feedback mechanisms. Moreover, comparison of patient data and numerical simulations of the model allowing emergence of new clones suggested that self-renewal of leukemic clones increases with the emergence of clonal heterogeneity [42]. An open question is whether a mutation process with phenotypic heterogeneity in the course of disease may change the observed selection effect. To address this question, we propose an extension of the basic clonal selection model from Ref. [8] to account for the process of mutations.

The model from Ref. [8] takes the form

$$\begin{cases} \frac{\partial}{\partial t} v(t, x) = 2 \left(1 - \frac{a(x)}{1+k\rho(t)} \right) pu(t, x) - dv(t, x), \\ \frac{\partial}{\partial t} u(t, x) = \left(\frac{2a(x)}{1+k\rho(t)} - 1 \right) pu(t, x), \\ v(0, x) = v_0(x), \\ u(0, x) = u_0(x), \end{cases} \quad (1)$$

where $x \in \Omega \subset \mathbb{R}$, $a \in C(\overline{\Omega})$, $p, k, d \in \mathbb{R}_+$ and $\rho(t) = \int_{\Omega} v(t, x) dx$.

The model describes evolution of one healthy cell lineage and an arbitrary number of leukemic clones, where the structural variable $x \in \Omega$ represents a continuum of possible cell clones (e.g. characterised by different gene expression levels) differing with respect to the self-renewal ability of dividing cells. We follow the convention that $x = x_0 \in \Omega$ corresponds to healthy cells whereas different leukemic clones are characterised by different values of $x \in \Omega \setminus \{x_0\}$. The description of cell differentiation within each cell line is given by a two-compartment version of the multi-compartment system established in [33], mathematically studied in [26] and applied to patient data in [39]. The model focuses on self-renewal of primitive cells $u(t, x)$ and their differentiation to mature healthy cells $v(t, x_0)$ or leukemic blasts $v(t, x)$, $x \in \Omega \setminus \{x_0\}$, which do not divide and for which the death rate has been denoted by d . The two-compartment architecture is based on a simplified description of the multi-stages differentiation process. A dividing cell gives rise to two progeny cells. A progeny cell is either more specialised than the mother cell, i.e., it is differentiated, or it is a copy of the mother cell (the case of self-renewal). The proliferation rate is denoted by the constant p . The function $a(x)$ describes the fraction (probability) of self-renewal of cells of clone x , where dependence on x reflects the clonal heterogeneity. The feedback signal that promotes the self-renewal of dividing cells is modelled using a Hill function $\frac{1}{1+k\rho(t)}$, where the parameter $k > 0$ is related to the degradation rate of the feedback signal [33]. This formula has been derived from a simple model of cytokine dynamics using a quasi-stationary approximation [21], motivated by biological findings presented in [27, 28]. Implementing other plausible regulation mechanisms led to a similar model dynamics that can reproduce the clinical observation [41, 44].

In [8] it has been shown that the solution (u, v) of system (1) converges in the space of positive Radon measures $\mathcal{M}^+(\Omega)$ to a measure with support contained in the set of maximal values of the self-renewal fraction function a . In particular, if the set of maximal values of a consists solely of discrete points, the solution (u, v) converges to a sum of Dirac measures. In [30], it has been shown that a similar result holds for a model with multiple compartments under an additional assumption preventing Hopf bifurcation that may occur in the model with at least three-stages maturation structure [26].

The purpose of this paper is to extend the clonal selection model (1) to include a process causing phenotypic heterogeneity with respect to x . The process is called “mutation”, although mechanistically, it amounts to a continuously distributed change of the phenotype in each round of division. Biologically, there exist at least two ways such process can be accomplished: (1) A continuous variable (“quantitative trait” in population genetics vocabulary [22]) can be a result of a superposition of discrete effects of mutations in a number of genes. Otherwise, it may be an effect of a discrete mutation in one gene, modulated by controlled or random gene expression varying from cell to cell, and hence “random” or “diffuse” [3]. Mathematically, this distinction

does not seem to matter much. As the aim of the model is to provide insights into multi-clonal cell dynamics under evolution of the stem cell self-renewal ability, we do not account for mechanistic details of the mutation process but focus on its mapping into the self-renewal parameter.

There are essentially two ways to model mutations in a continuous setting. First, it can be done by adding a diffusive term, which may be introduced using a Laplacian, as in Ref. [35,37,29,2]. Such models are based on the assumption that mutations can occur at all times within a cell's life cycle and are not limited to division, as it is the case in epigenetic modifications. Consequently, such mutations do not change the overall number of individuals and only affect their distribution with respect to the structure variable. From a mathematical point of view the diffusive ansatz provides good properties of the obtained solution and allows using the library of methods for semi-linear parabolic equations. Nevertheless, as the references above indicate, there exists a difficulty with characterisation of the long-term behaviour. Alternatively, mutations can be modelled with an integral operator, see for instance [7,9,10,23,31]. This approach includes mutations that occur during proliferation, which seems biologically realistic in case of genetic mutations [1]. In contrast to the diffusive ansatz, the mutation kernel approach can be used to model discontinuous changes in genotype or phenotype. For example, if for a given x , $\kappa(x, y) = a_1 \mathbb{1}_{\{(x-\delta_1, x+\delta_2)\}} + a_2 \mathbb{1}_{\{(1-\delta_2, 1)\}}(y)$, then this is equivalent to modelling expected (mean) values of the effects of a change which avoids the interval $(x + \delta_1, 1 - \delta_2)$. This can be called a jump, while strictly speaking, the definition might require δ_1 or δ_2 being infinitesimally small. Mathematical disadvantage of the integral operators is the non-local structure which makes the analysis more complicated.

Selection processes under mutation have been studied using both classes of mutation models, however using different methods to show convergence of the solutions, in the limit of small or rare mutations, to weighted Dirac measures. In case of a reaction-diffusion equation (RDE), the most common ansatz is to transform the RDE into a Hamilton-Jacobi equation, for which the viscosity solution provides the desired convergence result [35,37]. For scalar equations, this transformation can be performed by setting $\varphi_\varepsilon(t, x) = \varepsilon \ln(u_\varepsilon(t, x))$ where $u_\varepsilon(t, x)$ is the unknown of the RDE [18]. In case of a system of equations, the latter ansatz strongly depends on the structure of the model, since it is necessary to transform a system into a scalar Hamilton-Jacobi equation. In contrast, if mutation is modelled by an integral term, appropriate mathematical tools are provided by theory of positive semigroups and the infinite dimensional version of the Perron-Frobenius theorem.

In this paper, we focus on the effect of rare mutations taking place during proliferation [1], and propose a model based on integro-differential equations where we assume that, during proliferation, a mutation occurs with probability ε . We prove, under suitable hypotheses, existence of locally asymptotically

stable steady states of the model, which converge, for $\varepsilon \rightarrow 0$, to a weighted Dirac measure located at the point of maximum fitness of the corresponding pure selection model (1). The mathematical tools applied to analysis of the selection-mutation model are based on the ones used in [14,15] and extended here to a system of two phenotype-structured populations in a non-compact domain. Similar results can be shown for small mutations that occur independently of the proliferation process [10].

The paper is structured as follows. In Section 2 we introduce the model with mutations and justify its well-posedness. Section 3 is devoted to existence and uniqueness of stationary solutions. Convergence of the steady states for the zero limit of mutation rate is studied in Section 4. In Section 5, we show local asymptotic stability of the stationary solution of the model. The paper is completed with two appendices providing technical proofs needed for the results in Section 5 and Section 3 respectively.

2 Selection-mutation model and its assumptions

We extend system (1) to account for mutations described by an integral kernel operator and consider the following system of integro-differential equations,

$$\begin{cases} \frac{\partial}{\partial t} v_\varepsilon(t, x) = 2 \left(1 - \frac{a(x)}{1+k\rho_\varepsilon(t)} \right) p u_\varepsilon(t, x) - d v_\varepsilon(t, x), \\ \frac{\partial}{\partial t} u_\varepsilon(t, x) = \left(\frac{2a(x)}{1+k\rho_\varepsilon(t)} - (1 + \varepsilon) \right) p u_\varepsilon(t, x) + \varepsilon p \int_\Omega \kappa(x, y) u_\varepsilon(t, y) dy, \\ v_\varepsilon(0, x) = v^0(x), \\ u_\varepsilon(0, x) = u^0(x), \end{cases} \quad (2)$$

where $\rho_\varepsilon(t) = \int_\Omega v_\varepsilon(t, x) dx$.

As previously, $u_\varepsilon(t, x)$ denotes the density of dividing cells structured with respect to the trait x that represents the expression level of genes influencing self-renewal ability of the cells, while $v_\varepsilon(t, x)$ denotes the resulting mature cells for $x = x_0 \in \Omega$ or leukemic blasts of clone x for $x \in \Omega \setminus \{x_0\}$. The growth terms describing self-renewal and differentiation of dividing cells, regulated by a nonlocal nonlinear feedback from all non-dividing cells are taken from model (1) in Ref. [8]. Additionally, the model accounts for mutations that take place during proliferation at a rate $\varepsilon \in (0, 1]$. If a mutation occurs, then the probability density that an individual with trait y mutates into one with trait x is denoted by $\kappa(x, y)$.

After scaling (multiplying ρ_ε , v_ε and u_ε by k) one can assume that $k = 1$ and after scaling time, one can assume that the proliferation rate is $p = 1$ with d being replaced by $\theta = \frac{d}{p}$. Without loss of generality we consider then the

following system of integro-differential equations:

$$\begin{cases} \frac{\partial}{\partial t} v_\varepsilon(t, x) = 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon(t)}\right) u_\varepsilon(t, x) - \theta v_\varepsilon(t, x), \\ \frac{\partial}{\partial t} u_\varepsilon(t, x) = \left(\frac{2a(x)}{1+\rho_\varepsilon(t)} - (1 + \varepsilon)\right) u_\varepsilon(t, x) + \varepsilon \int_{\Omega} \kappa(x, y) u_\varepsilon(t, y) dy, \\ v_\varepsilon(0, x) = v^0(x), \\ u_\varepsilon(0, x) = u^0(x), \end{cases} \quad (3)$$

where $\rho_\varepsilon(t) = \int_{\Omega} v_\varepsilon(t, x) dx$.

In the remainder of this paper, we make the following assumptions:

Assumption 1

1. $\Omega \subset \mathbb{R}$ is open and bounded.
2. $a \in C^1(\overline{\Omega})$ with $0 < a(x) < 1$ for all $x \in \Omega$ and there exists $x_* \in \Omega$ such that $a(x_*) > \frac{1}{2}$ (otherwise, as shown in [8], the population dies out). Moreover, there exists a single point $\bar{x} \in \Omega$ where the maximal value of the self-renewal function is attained, i.e. $\bar{x} = \operatorname{argmax}_{x \in \Omega} a(x)$, $\bar{a} = a(\bar{x})$.
3. $u^0, v^0 \in L^1(\Omega)$ with $u^0, v^0 > 0$.
4. $\kappa \in C(\overline{\Omega} \times \overline{\Omega})$ is nonnegative and such that $\int_{\Omega} \kappa(x, y) dx = 1$. Moreover, we assume that there exists $\delta > 0$ such that the support of $\kappa(\cdot, y)$ contains the interval $(y - \delta, y + \delta)$ for each $y \in \Omega$. In particular, for small $\delta > 0$ the model describes small mutations (small values of the distance between the traits) that occur with positive probability.

System (3) can be written as

$$\begin{pmatrix} v_\varepsilon \\ u_\varepsilon \end{pmatrix}_t = A \begin{pmatrix} v_\varepsilon \\ u_\varepsilon \end{pmatrix} + f(u(t), v(t)),$$

where

$$A = \begin{pmatrix} -\theta & 0 \\ 0 & -\varepsilon + \varepsilon \int_{\Omega} \kappa(x, y) \cdot dy \end{pmatrix}$$

and

$$\begin{aligned} f : L^1(\Omega) \times L^1(\Omega) &\longrightarrow L^1(\Omega) \times L^1(\Omega) \\ (v_\varepsilon(t), u_\varepsilon(t)) &\longmapsto \left(2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon(t)}\right) u_\varepsilon(t), \left(\frac{2a(x)}{1+\rho_\varepsilon(t)} - 1\right) u_\varepsilon(t)\right). \end{aligned}$$

Since the operator A is the infinitesimal generator of a C^0 positive semigroup and f is locally Lipschitz, existence and uniqueness of local mild solutions of the initial value problem for (3) follow from application of the theory of semilinear evolution equations [36]. Notice that, since the right hand-side of (3) is a bounded and (locally) Lipschitz function in $L^1(\Omega) \times L^1(\Omega)$, the same result follows from an application of the Picard-Lindelöf theorem in Banach spaces [5]. Boundedness of total mass (see Appendix A) implies that solutions are global.

Numerical observation. Numerical simulations of the model suggest a selection effect, similar to that in the pure selection model (1). The difference is that, depending on the size of mutation frequency ε , we observe a distribution of the different cell clones around the one with the highest self-renewal fraction, see Figure 1. Convergence of the system to a solution concentrated around the most aggressive phenotype is a fast process and does not depend on initial data. The remainder of this paper is devoted to a rigorous proof of this observation.

3 Existence and uniqueness of non-trivial steady states

In general, the stationary problem for selection-mutation equations can be reduced (see [9]) to a fixed point problem for a real function whose definition depends on the existence and uniqueness of a dominant eigenvalue and a corresponding positive eigenvector of a certain linear operator (obtained by fixing the nonlinearity in the model). To solve the problem for system (3), we follow an approach proposed in Ref. [14] for the stationary problem of a predator-prey model consisting of an IDE coupled with an ordinary differential equation (ODE). The structure of the ODE considered in [14] is a logistic type equation for which the steady state is given by a constant. Consequently, the steady state of the IDE depends on this constant that can be interpreted as a parameter. All together, the steady state problem can be reformulated as an eigenvalue problem, associated to the eigenvalue 0, for which a positive eigenfunction is sought. The latter still depends on the parameter given by the steady state of the ODE (which in [14] was the prey population at equilibrium). To solve the coupled problem, it is necessary to choose the parameter in such a way that the eigenvalue problem and the steady state problem for the ODE are solved simultaneously. It results in solving a fixed point problem. In the remainder of this section, we adapt this approach to the cell population model (3) which consists of a system of two IDE's.

3.1 Eigenvalue problem

To find steady states of model (3), we consider the model obtained by integrating over the structure variable x the first equation in (3)

$$\begin{cases} \frac{d}{dt}\rho_\varepsilon(t) &= \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon(t)}\right) u_\varepsilon(t, x) dx - \theta\rho_\varepsilon(t), \\ \frac{\partial}{\partial t}u_\varepsilon(t, x) &= \left(\frac{2a(x)}{1+\rho_\varepsilon(t)} - (1 + \varepsilon)\right) u_\varepsilon(t, x) + \varepsilon \int_{\Omega} \kappa(x, y)u_\varepsilon(t, y) dy, \\ u_\varepsilon(0, x) &= u^0(x), \\ \rho_\varepsilon(0) &= \int_{\Omega} v^0(x) dx. \end{cases} \quad (4)$$

Since the nonlinearity depends only on the total population of mature cells (the integral of the second variable), the integrated equation becomes an ordinary differential equation for $\rho_\varepsilon(t)$. Consequently, the first component of a

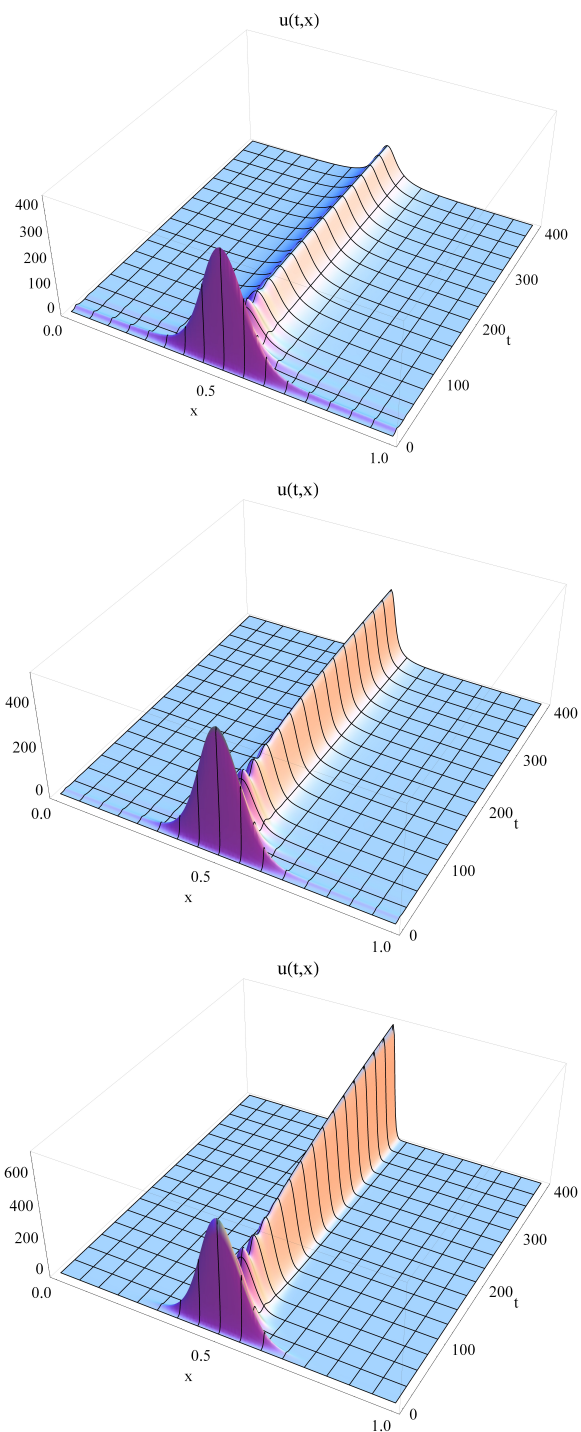


Fig. 1: The simulations depict the solution $u_\varepsilon(t, x)$ of model (2), for different values of ε . Going from top to bottom, the values of ε are $\frac{3}{4}$, $\frac{1}{3}$ and $\frac{1}{100}$. The presented simulations were done for parameters $k = 0.01$, $p = 0.9$ and $d = 0.2$ and a mutation operator with a scaled Gaussian kernel.

steady state $(\rho_\varepsilon, u_\varepsilon(x))$ of system (4) is a constant. Furthermore, the first component of the (corresponding) steady state of system (3) can be computed by inserting the steady state of system (4) $(\rho_\varepsilon, u_\varepsilon(x))$ into the first equilibrium equation of (3) and solving it for v_ε .

The (nontrivial) equilibria of system (4) are given by the solutions of

$$\begin{cases} 0 = \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon}\right) u_\varepsilon(x) dx - \theta \rho_\varepsilon, \\ 0 = \left(\frac{2a(x)}{1+\rho_\varepsilon} - (1+\varepsilon)\right) u_\varepsilon(x) + \varepsilon \int_{\Omega} \kappa(x, y) u_\varepsilon(y) dy. \end{cases} \quad (5)$$

Let us define for $\rho_\varepsilon > 0$,

$$\begin{aligned} B_{\varepsilon, \rho_\varepsilon} : L^1(\Omega) &\rightarrow L^1(\Omega), & B_{\varepsilon, \rho_\varepsilon} u_\varepsilon(x) &:= \left(\frac{2a(x)}{1+\rho_\varepsilon} - (1+\varepsilon)\right) u_\varepsilon(x), \\ K_\varepsilon : L^1(\Omega) &\rightarrow L^1(\Omega), & K_\varepsilon u_\varepsilon(x) &:= \varepsilon \int_{\Omega} \kappa(x, y) u_\varepsilon(y) dy, \\ C_{\varepsilon, \rho_\varepsilon} : L^1(\Omega) &\rightarrow L^1(\Omega), & C_{\varepsilon, \rho_\varepsilon} u_\varepsilon &:= B_{\varepsilon, \rho_\varepsilon} u_\varepsilon + K_\varepsilon u_\varepsilon. \end{aligned} \quad (6)$$

If a non-trivial steady state of system (4) exists, the first equation of system (5) provides a constant solution $\rho \in (0, \infty)$. The second equation of system (5) can be then interpreted as an eigenvalue problem for $C_{\varepsilon, \rho}$, which depends on the parameter ρ . Thus, we are looking for a function $\varphi_{\varepsilon, \rho}$ and a constant $\lambda_\varepsilon(\rho)$ such that

$$C_{\varepsilon, \rho} \varphi_{\varepsilon, \rho} = \lambda_\varepsilon(\rho) \varphi_{\varepsilon, \rho}. \quad (7)$$

The first component of the steady state of system (4) is then given by the solution ρ_ε of the equation $\lambda_\varepsilon(\rho) = 0$. Denoting by $\varphi_{\varepsilon, \rho_\varepsilon}$ the corresponding normalised eigenfunction, the second component of the steady state of (4) has the form $u_\varepsilon = c_\varepsilon \varphi_{\varepsilon, \rho_\varepsilon}$ where $c_\varepsilon \in (0, \infty)$ satisfies

$$c_\varepsilon = \frac{\theta \rho_\varepsilon}{\int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon}\right) \varphi_{\varepsilon, \rho_\varepsilon}(x) dx}.$$

Let us observe that 0 is an eigenvalue with corresponding eigenfunction $\varphi_{\varepsilon, \rho}$ of $C_{\varepsilon, \rho}$ if and only if

$$\begin{aligned} B_{\varepsilon, \rho} \varphi_{\varepsilon, \rho} + K_\varepsilon \varphi_{\varepsilon, \rho} &= 0, \\ \Leftrightarrow K_\varepsilon \varphi_{\varepsilon, \rho} &= -B_{\varepsilon, \rho} \varphi_{\varepsilon, \rho}, \\ \Leftrightarrow K_\varepsilon (-B_{\varepsilon, \rho}^{-1} \psi_{\varepsilon, \rho}) &= \psi_{\varepsilon, \rho} \end{aligned}$$

with $\psi_{\varepsilon,\rho} := -B_{\varepsilon,\rho}\varphi_{\varepsilon,\rho}$. This means that $\psi_{\varepsilon,\rho}$ is an eigenfunction corresponding to eigenvalue 1 of the operator $T_{\varepsilon,\rho} : L^1(\Omega) \rightarrow L^1(\Omega)$ given by

$$\begin{aligned} T_{\varepsilon,\rho}u &:= K_\varepsilon \circ (-B_{\varepsilon,\rho}^{-1}u) \\ &= \varepsilon \int_{\Omega} \kappa(x,y) \frac{1+\rho}{(1+\rho)(1+\varepsilon) - 2a(y)} u(y) dy. \end{aligned} \quad (8)$$

Remark 1 The equivalence of the eigenvalues 1 of the operator $T_{\varepsilon,\rho}(= K_\varepsilon \circ (-B_{\varepsilon,\rho}^{-1}))$ and 0 of the operator $C_{\varepsilon,\rho}(= B_{\varepsilon,\rho} + K_\varepsilon)$ is exploited in [14], but the idea goes back to [6, Proposition 2.1]. We choose to study the eigenvalue problem for the operator $T_{\varepsilon,\rho}$, because it allows a direct application of the version for Banach lattices of the well-known Krein-Rutmann theorem [16]. Alternatively, one can directly study the eigenvalue problem for the operator $C_{\varepsilon,\rho}$ that would require more work. Existence of a strictly dominant eigenvalue of $C_{\varepsilon,\rho}$ can be obtained from an application of a result of Greiner (Corollary 1.8 in Ref. [24]) that provides existence of an algebraically simple, strictly dominant eigenvalue of a perturbation $B + K$ of the generator of a positive semigroup by a positive bounded irreducible operator K satisfying that there exists an integer n such that $(KR(\lambda, B))^n$ is compact for all λ with $\operatorname{Re}\lambda > s(B)$ and that $s(B + K) > s(B)$.

Remark 2 While analysis of the spectral bound of the operator $C_{\varepsilon,\rho}$ corresponds to study the Malthusian parameter (exponential growth rate) of the population, the approach chosen in this paper to analyse of the spectral radius of the so-called next-generation operator $T_{\varepsilon,\rho}(= K_\varepsilon \circ (-B_{\varepsilon,\rho}^{-1}))$ leads to the basic reproduction number of the population [17], [45].

We proceed then to investigate the eigenvalue problem for the operator $T_{\varepsilon,\rho}$. We define

$$\hat{\rho}_\varepsilon := \frac{2\bar{a}}{1+\varepsilon} - 1 \quad (9)$$

where $\bar{a} = \max_x a(x) = a(\bar{x})$. Notice that $T_{\varepsilon,\rho}$ is a positive operator for $\rho \in (\hat{\rho}_\varepsilon, +\infty)$.

Proposition 1 *Let $T_{\varepsilon,\rho}$ be the linear operator defined in (8) for $\rho \in (\hat{\rho}_\varepsilon, +\infty)$. Its spectral radius $r(T_{\varepsilon,\rho})$ is an algebraically simple eigenvalue of $T_{\varepsilon,\rho}$ with a corresponding strictly positive eigenfunction. Moreover, $r(T_{\varepsilon,\rho})$ is the only eigenvalue of $T_{\varepsilon,\rho}$ having a positive eigenfunction.*

Proof By the Krein-Rutman theorem for Banach lattices, see [16, Theorem 12.3], the problem reduces to proving that $T_{\varepsilon,\rho}$ is a compact positive irreducible operator.

$T_{\varepsilon,\rho}$ is a positive operator by definition and the choice of ρ . It is also evident that $T_{\varepsilon,\rho}$ is a bounded operator.

Let us start by proving that $T_{\varepsilon, \rho}$ is irreducible. Indeed, the assumption on the support of $\kappa(\cdot, y)$ implies that

$$\int_{S^c} \int_S \kappa(x, y) dx dy > 0$$

for each measurable set S such that both S and S^c have positive measure (see [10] for more details), which is a characterisation for the irreducibility of the kernel operator $Tf(x) := \int_0^\infty \kappa(x, y)f(y)dy$ (see [38], V.6). Since, for $\rho \in \hat{\rho}_\varepsilon, +\infty)$ the function $\frac{1+\rho}{(1+\rho)(1+\varepsilon)-2a(y)}$ is strictly positive, the operator $T_{\varepsilon, \rho}$ is irreducible.

Applying [20, Corollary 5.1] with

$$\tilde{\kappa}(x, y) := \kappa(x, y) \frac{1 + \rho}{(1 + \rho)(1 + \varepsilon) - 2a(y)},$$

and

$$\bar{\kappa}(x, y) := \begin{cases} \tilde{\kappa}(x, y), & y \in \Omega \\ 0, & y \notin \Omega \end{cases},$$

we obtain that $T_{\varepsilon, \rho} : L^1(\Omega) \rightarrow L^1(\Omega)$ is compact if and only if for all $\iota > 0$, there exist $\delta > 0, R > 0$ such that for almost all $x \in \Omega$ and for every $h \in \mathbb{R}$ with $|h| < \delta$

$$\int_{\mathbb{R} \setminus B_R(0)} |\bar{\kappa}(x, y)| dy < \iota, \quad \int_{\mathbb{R}} |\bar{\kappa}(x, y+h) - \bar{\kappa}(x, y)| dy < \iota.$$

Let $\iota > 0$ be arbitrary but fixed.

As Ω is bounded, let us choose $R > 0$ such that

$$|\Omega \setminus B_R(0)| < \frac{\iota}{\max_{(x, y) \in \overline{\Omega}^2} \tilde{\kappa}(x, y)}.$$

Then,

$$\int_{\mathbb{R} \setminus B_R(0)} |\bar{\kappa}(x, y)| dy = \int_{\Omega \setminus B_R(0)} |\tilde{\kappa}(x, y)| dy \leq \max_{(x, y) \in \overline{\Omega}^2} \tilde{\kappa}(x, y) |\Omega \setminus B_R(0)| < \iota.$$

Due to the dominated convergence theorem and the continuity of $\tilde{\kappa}$, it holds

$$\int_{\mathbb{R}} |\bar{\kappa}(x, y+h) - \bar{\kappa}(x, y)| dy = \int_{\Omega} |\tilde{\kappa}(x, y+h) - \tilde{\kappa}(x, y)| dy < \iota,$$

for $|h|$ small enough, which completes the proof.

From the previous proposition we have that the operator $T_{\varepsilon,\rho}$ admits a strictly positive eigenfunction corresponding to the eigenvalue $r(T_{\varepsilon,\rho})$. What is left to show, in order to obtain equilibria, is that it is possible to choose ρ such that $r(T_{\varepsilon,\rho}) = 1$ and that this choice of ρ is unique (remember that showing $r(T_{\varepsilon,\rho}) = 1$ is equivalent to showing $\lambda_\varepsilon(\rho) = 0$).

The idea is to prove that $r(T_{\varepsilon,\rho})$ is continuous with respect to ρ and strictly monotone. The idea of using continuous dependence goes back to the late 1980s (see [6], [12]).

Lemma 1 *Let $T_{\varepsilon,\rho}$ be the linear operator defined in (8) for $\rho \in (\hat{\rho}_\varepsilon, +\infty)$. Its spectral radius, $r(T_{\varepsilon,\rho})$ is a continuous function of ρ . Moreover, there exists ε_0 such that for $\varepsilon < \varepsilon_0$, $r(T_{\varepsilon,\rho})$ is strictly decreasing.*

Proof (Proof of Lemma 1) Continuity of $r(T_{\varepsilon,\rho})$ with respect to ρ follows from the continuity of a finite system of eigenvalues of a closed operator [25, Chapter IV, §3.5].

For the monotonicity, we use Gelfand's formula for the spectral radius of a bounded linear operator A on a Banach space

$$r(A) = \lim_{n \rightarrow \infty} \|A^n\|_\infty^{\frac{1}{n}},$$

where $\|\cdot\|_\infty$ is the operator norm. We have to show that

$$\|T_{\varepsilon,\rho_1}^n\|_\infty^{\frac{1}{n}} > \|T_{\varepsilon,\rho_2}^n\|_\infty^{\frac{1}{n}} \text{ for } \rho_1 < \rho_2.$$

A straightforward proof by induction provides the formula

$$T_{\varepsilon,\rho}^n u(x) = \int_{\Omega^n} \kappa(x, y_n) \prod_{i=1}^{n-1} \kappa(y_i, y_{i+1}) \frac{(1+\rho)^n}{\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))} u(y_n) dy_1 \cdots dy_n.$$

In order to obtain monotonicity, we compute the derivative of $T_{\varepsilon,\rho}^n$ with respect to ρ . Another straightforward proof by induction (see Appendix C) shows that $\frac{d}{d\rho} T_{\varepsilon,\rho}^n < 0$ for ε small enough. Thus $T_{\varepsilon,\rho_1}^n u > T_{\varepsilon,\rho_2}^n u$ for all $u \in L^1(\Omega)$, $u \geq 0$ and $\rho_1 < \rho_2$. Then, taking the operator norm on both sides and using that the function $x \mapsto x^{\frac{1}{n}}$ is strictly monotone, we obtain

$$\|T_{\varepsilon,\rho_1}^n\|_\infty^{\frac{1}{n}} \geq \|T_{\varepsilon,\rho_2}^n\|_\infty^{\frac{1}{n}} \text{ for all } n \in \mathbb{N} \Rightarrow r(T_{\varepsilon,\rho_1}) \geq r(T_{\varepsilon,\rho_2}) \text{ for } \rho_1 < \rho_2.$$

The argument for strict monotonicity is the same as in Ref. [14].

Up to this point we have showed that the spectral radius $r(T_{\varepsilon,\rho})$ is a continuous and strictly decreasing function of ρ . Hence it is necessary to prove that there exists some $\rho \in (\hat{\rho}_\varepsilon, \infty)$ such that $r(T_{\varepsilon,\rho}) = 1$. This is provided by

Lemma 2 *For all $\varepsilon < \varepsilon_0$, there exists a unique $\rho \in (\hat{\rho}_\varepsilon, \infty)$ such that*

$$r(T_{\varepsilon,\rho}) = 1.$$

Proof We observe that

$$\lim_{\rho \rightarrow \infty} T_{\varepsilon, \rho} = \frac{\varepsilon}{1 + \varepsilon} \int_{\Omega} \kappa(x, y) u_{\varepsilon}(y) dy := T_{\varepsilon}.$$

T_{ε} is a bounded operator, hence the spectrum is bounded. Since $r(T_{\varepsilon}) \leq \|T_{\varepsilon}\|_{\infty}$ we obtain $r(T_{\varepsilon}) < 1$. As $r(T_{\varepsilon, \rho})$ is continuous with respect to ρ , we can find $\rho_1 \in (\hat{\rho}_{\varepsilon}, \infty)$ such that $r(T_{\varepsilon, \rho_1}) < 1$. On the other hand, since

$$\|T_{\varepsilon, \rho}\|_{\infty} = \sup_{\substack{u \in L^1(\Omega) \\ \|u\|_{L^1(\Omega)}=1}} \left| \varepsilon \int_{\Omega} \kappa(x, y) \frac{1 + \rho}{((1 + \rho)(1 + \varepsilon) - 2a(y))} u(y) dy dx \right|$$

and $r(T_{\varepsilon, \rho}) = \lim_{n \rightarrow \infty} \|T_{\varepsilon, \rho}^n\|^{\frac{1}{n}}$ we have that $\lim_{\rho \rightarrow \hat{\rho}_{\varepsilon}} r(T_{\varepsilon, \rho}) = +\infty$. Lemma 1 and the intermediate value theorem imply the statement.

We can now formulate the theorem giving existence and uniqueness of steady states of system (3).

Theorem 1 *There exists some $\varepsilon_0 > 0$ such that for all $\varepsilon < \varepsilon_0$ there exists a unique, non-trivial steady state $(v_{\varepsilon}, u_{\varepsilon})$ of system (3).*

Proof Combination of Proposition 1 and Lemma 2 yields the existence of a unique, non-trivial steady state $(\rho_{\varepsilon}, u_{\varepsilon})$ of system (4). Substituting it in the first equilibrium equation in system (3), we obtain the first component of its unique, non-trivial steady state $(v_{\varepsilon}, u_{\varepsilon})$.

4 Convergence of the steady states

Once we have proved, for ε small enough, existence of a stationary solution $(v_{\varepsilon}, u_{\varepsilon})$ of system (3), we are interested in the behavior of this steady state when the mutation rate goes to zero.

In order to study it, we recall the equivalence between the eigenvalue problem for the operators $C_{\varepsilon, \rho} = B_{\varepsilon, \rho} + K_{\varepsilon}$ and $T_{\varepsilon, \rho} = K_{\varepsilon}(B_{\varepsilon, \rho})^{-1}$ which is

$$\begin{aligned} B_{\varepsilon, \rho} \varphi_{\varepsilon, \rho} + K_{\varepsilon} \varphi_{\varepsilon, \rho} &= \lambda_{\varepsilon}(\rho) \varphi_{\varepsilon, \rho} \\ \Leftrightarrow K_{\varepsilon} (\lambda_{\varepsilon}(\rho) - B_{\varepsilon, \rho})^{-1} \psi_{\varepsilon, \rho} &= \psi_{\varepsilon, \rho}, \end{aligned}$$

for $\psi_{\varepsilon, \rho} = (\lambda_{\varepsilon}(\rho) - B_{\varepsilon, \rho}) \varphi_{\varepsilon, \rho}$. That is, $\varphi_{\varepsilon, \rho}$ is an eigenfunction of $C_{\varepsilon, \rho}$ corresponding to eigenvalue $\lambda_{\varepsilon}(\rho)$ if and only if 1 is an eigenvalue of $K_{\varepsilon}(\lambda_{\varepsilon}(\rho) - B_{\varepsilon, \rho})^{-1}$ with eigenfunction $\psi_{\varepsilon, \rho}$.

The proof of convergence of the steady state consists of the following steps: We begin by showing that $\lambda_{\varepsilon}(\rho)$ is a strictly dominant eigenvalue of $C_{\varepsilon, \rho}$ with a corresponding strictly positive eigenfunction. Then we show that for

$\varepsilon \rightarrow 0$, $\lambda_\varepsilon(\rho) \rightarrow \max_{x \in \bar{\Omega}} \left(\frac{2a(x)}{1+\rho} - 1 \right)$ pointwise, from which we conclude convergence of the corresponding eigenfunctions $\varphi_{\varepsilon,\rho}$. Additionally, convergence of the eigenvalues $\lambda_\varepsilon(\rho)$ allows deducing convergence of ρ_ε (first component of the steady state of system (4)), and ultimately convergence of the steady state.

4.1 Existence of eigenvalues

Following [6, Theorem 2.2], in order to show that $\lambda_\varepsilon(\rho)$ is a strictly dominant eigenvalue of $C_{\varepsilon,\rho}$ with a corresponding strictly positive eigenfunction, it is sufficient to find some

$$\lambda_1 > s(B_{\varepsilon,\rho}) = \max_{x \in \bar{\Omega}} \left(\frac{2a(x)}{1+\rho} - (1+\varepsilon) \right)$$

such that $r(K_\varepsilon(\lambda_1 Id - B_{\varepsilon,\rho})^{-1}) > 1$, (where $s(A)$ and $r(A)$ denote respectively the spectral bound and the spectral radius of a linear operator A).

We use the following characterisation of the spectral bound of the generator A of a strongly continuous positive semigroup

$$s(A) \geq \sup\{\mu \in \mathbb{R} \quad : \quad Af \geq \mu f \quad \text{for some } 0 < f \in D(A)\}. \quad (10)$$

This property of the spectral bound is stated in Ref. [4] in $C(K)$, the space of all real-valued continuous functions on a compact space K , but the proof also holds for any generator of a positive semigroup in a Banach lattice such that the spectral bound and the growth bound coincide, which is the case in L^p -space, $1 \leq p < \infty$, [49].

Proposition 2 *There exists $\lambda_1 > s(B_{\varepsilon,\rho})$ such that $r(K_\varepsilon(\lambda_1 Id - B_{\varepsilon,\rho})^{-1}) > 1$.*

Proof Let us define function $q : \mathbb{R} \times \Omega \rightarrow \mathbb{R}$ by

$$q(\lambda, y) := \lambda - \left(\frac{2a(y)}{1+\rho} - (1+\varepsilon) \right).$$

Then, we need to prove that

$$\exists \lambda_1 > s(B_{\varepsilon,\rho}) \exists g \in L^1(\Omega), g > 0 \forall x \in \Omega : \quad \varepsilon \int_{\Omega} \kappa(x, y) q(\lambda_1, y)^{-1} g(y) dy > g(x).$$

Observe that $\operatorname{argmin}_{x \in \Omega} q(s(B_{\varepsilon,\rho}), x) = \operatorname{argmax}_{x \in \Omega} \left(\frac{2a(x)}{1+\rho} - (1+\varepsilon) \right) = \bar{x}$.

Using the definition of q , we obtain

$$\begin{cases} q(s(B_{\varepsilon,\rho}), \bar{x}) & = 0, \\ \frac{\partial}{\partial y} q(s(B_{\varepsilon,\rho}), y)|_{y=\bar{x}} & = 0. \end{cases} \quad (11)$$

Choosing $g = \chi_{B_\delta(\bar{x})}$, for a small $\delta > 0$, we estimate

$$\begin{aligned} \varepsilon \int_{\Omega} \kappa(x, y) q(\lambda_1, y)^{-1} g(y) \, dy &= \varepsilon \int_{B_\delta(\bar{x})} \kappa(x, y) q(\lambda_1, y)^{-1} \, dy \\ &\geq \varepsilon \min_{x, y \in [\bar{x}-\delta, \bar{x}+\delta]^2} \kappa(x, y) \int_{B_\delta(\bar{x})} q(\lambda_1, y)^{-1} \, dy \end{aligned} \quad (12)$$

Expanding the function q using the Taylor formula up to the 0th order around \bar{x} yields

$$q(\lambda_1, y) = q(\lambda_1, \bar{x}) + o(\|y - \bar{x}\|). \quad (13)$$

Inserting equation (13) into inequality (12) leads to

$$\begin{aligned} \varepsilon \int_{\Omega} \kappa(x, y) q(\lambda_1, y)^{-1} g(y) \, dy &\geq \\ \varepsilon \min_{x, y \in [\bar{x}-\delta, \bar{x}+\delta]^2} \kappa(x, y) \int_{B_\delta(\bar{x})} \frac{1}{q(\lambda_1, \bar{x}) + o(\|y - \bar{x}\|)} \, dy &> 1, \end{aligned}$$

by using the first equation of (11), choosing δ small enough and λ_1 close enough to $s(B_{\varepsilon, \rho})$.

4.2 Convergence of the eigenvalues and the eigenfunctions

Now that we have proved existence of a strictly dominant eigenvalue $\lambda_\varepsilon(\rho)$ of the operator $C_{\varepsilon, \rho}$ we can formulate a result about its limiting behavior.

Lemma 3 *Let $\lambda_\varepsilon(\rho)$ be the strictly dominant eigenvalue of the operator $C_{\varepsilon, \rho}$ defined in (6), then*

$$\lambda_\varepsilon(\rho) \xrightarrow{\varepsilon \rightarrow 0} \max_{x \in \bar{\Omega}} \left(\frac{2a(x)}{1 + \rho} - 1 \right).$$

Proof For notational simplicity, we denote $\mu(x) := \left(\frac{2a(x)}{1 + \rho} - 1 \right)$,

$\mu_\varepsilon(x) := \left(\frac{2a(x)}{1 + \rho} - (1 + \varepsilon) \right)$. We want to show that for all $\delta > 0$ there exists ε_0 such that for all $\varepsilon < \varepsilon_0$ it holds

$$\lambda_\varepsilon(\rho) \in B_\delta(\mu(\bar{x})),$$

where recall that \bar{x} denotes the point where the maximal value of the self-renewal function is attained.

We begin by proving that $\lambda_\varepsilon(\rho) \leq \mu(\bar{x})$.

The assumptions on κ imply that

$$\forall u \in L^1(\Omega), u \geq 0 \exists \Omega' \subset \Omega \forall x \in \Omega' : \int_{\Omega} \kappa(x, y) u(y) \, dy \leq u(x) \quad (14)$$

where Ω' is not a Lebesgue null set.

Assuming otherwise,

$$\int_{\Omega} \kappa(x, y)u(y) \, dy - u(x) > 0,$$

for almost all x , and integrating the left hand side with respect to x , using $\int_{\Omega} \kappa(x, y)dx = 1$, we obtain $\int_{\Omega} \int_{\Omega} \kappa(x, y)u(y)dy - u(x)dx = 0$, which is a contradiction.

Taking $f_1(x) := \chi_{\Omega'}\varphi_{\varepsilon, \rho}(x)$ where $\varphi_{\varepsilon, \rho}$ is the positive eigenfunction corresponding to the eigenvalue $\lambda_{\varepsilon}(\rho)$ and Ω' being a set of positive measure such that (14) holds for $\varphi_{\varepsilon, \rho}$,

$$\begin{aligned} \lambda_{\varepsilon}(\rho)f_1(x) &= \left(\frac{2a(x)}{1+\rho} - 1\right) f_1(x) - \varepsilon f_1(x) + \varepsilon \int_{\Omega'} \kappa(x, y)f_1(y)dy \\ &\leq \left(\frac{2a(x)}{1+\rho} - 1\right) f_1(x). \end{aligned}$$

Hence, by (10) we conclude that $\lambda_{\varepsilon}(\rho) \leq \mu(x) \leq \mu(\bar{x})$.

We show now that for all $\delta > 0$, there exists ε_0 such that it holds

$$\lambda_{\varepsilon}(\rho) \geq \mu(\bar{x}) - \delta$$

for any $\varepsilon < \varepsilon_0$.

Let δ be such that $\mu_{\varepsilon}(x) \geq \mu_{\varepsilon}(\bar{x}) - \delta$ for $x \in \Omega'$, where $\Omega' \subset \Omega$ is a suitably chosen set. Let us consider a smooth function u with $\text{supp } u \subset \Omega'$. Then, due to the positivity of K_{ε} , it holds

$$C_{\varepsilon, \rho}u = B_{\varepsilon, \rho}u + K_{\varepsilon}u \geq \mu_{\varepsilon}(x)u \geq (\mu_{\varepsilon}(\bar{x}) - \delta)u.$$

By inequality (10), we obtain $\lambda_{\varepsilon}(\rho) \geq \mu_{\varepsilon}(\bar{x}) - \delta$. Furthermore, we know

$$|\mu(x) - \mu_{\varepsilon}(x)| \leq \varepsilon \leq \delta.$$

Thus, we conclude

$$\forall \delta > 0 \exists \varepsilon_0 > 0 \forall \varepsilon < \varepsilon_0 : \lambda_{\varepsilon}(\rho) \in B_{2\delta}(\mu(\bar{x})).$$

Proposition 3 *Let $\varphi_{\varepsilon, \rho}$ be the unique positive eigenfunction corresponding to the eigenvalue $\lambda_{\varepsilon}(\rho)$ of the operator $C_{\varepsilon, \rho}$ defined in (6). Then*

$$\varphi_{\varepsilon, \rho} \rightarrow \delta_{\bar{x}} \quad \text{in } \mathcal{M}^+(\Omega), \quad \text{as } \varepsilon \rightarrow 0,$$

where \rightarrow denotes narrow convergence and \bar{x} is the unique value where the maximum of the self-renewal function $a(x)$ is attained.

Remark 3 We use the notion of the narrow convergence. A sequence $(\mu_n)_{n \in \mathbb{N}} \subset \mathcal{M}(S)$, where S is a metric space, converges narrowly to a measure $\mu \in \mathcal{M}(S)$ iff

$$\lim_{n \rightarrow \infty} \int_S \psi(x) d\mu_n(x) = \int_S \psi(x) d\mu(x) \quad \forall \psi \in C_b(S).$$

In probability theory, the latter convergence is also known as the weak convergence of measures. Narrow convergence is metrizable with the flat norm (bounded Lipschitz distance), i.e., the convergence result can be understood in a suitable metric in the space of positive Radon measures. We refer to [19] for different notions of convergence in measures.

Proof To prove convergence of the steady state, we make an ansatz that the eigenfunctions form a Dirac sequence.

By Proposition 2 and [6, Theorem 2.2], the eigenfunction $\varphi_{\varepsilon, \rho}$ of $C_{\varepsilon, \rho}$ is strictly positive, $\varphi_{\varepsilon, \rho} > 0$ for all $\varepsilon > 0$. As an eigenfunction in $L^1(\Omega)$, it can be normalised to $\|\varphi_{\varepsilon, \rho}\|_{L^1(\Omega)} = 1$. It remains to show that

$$\int_{\Omega^c} \varphi_{\varepsilon, \rho}(x) dx \xrightarrow{\varepsilon \rightarrow 0} 0$$

for $\Omega^c \subset \Omega$ with $\bar{x} \notin \Omega^c$ and $\text{dist}(\bar{x}, \Omega^c) > 0$.

According to Lemma 3, it holds $\lambda_\varepsilon(\rho) \rightarrow \max_{x \in \Omega} \left(\frac{2a(x)}{1+\rho} - 1 \right)$ for $\varepsilon \rightarrow 0$. Hence, for any Ω^c as defined above, it is possible to choose $\varepsilon < \varepsilon_0$ such that

$$\forall x \in \Omega^c : \quad \lambda_\varepsilon(\rho) > \left(\frac{2a(x)}{1+\rho} - 1 \right). \quad (15)$$

Integrating the eigenvalue problem for $C_{\varepsilon, \rho}$, we obtain

$$\begin{aligned} 0 &= \int_{\Omega^c} \left(\frac{2a(x)}{1+\rho} - (1+\varepsilon) \right) \varphi_{\varepsilon, \rho}(x) - \lambda_\varepsilon(\rho) \varphi_{\varepsilon, \rho}(x) dx \\ &\quad + \varepsilon \int_{\Omega^c} \int_{\Omega} \kappa(x, y) \varphi_{\varepsilon, \rho}(y) dy dx \\ &\leq \left(\max_{x \in \Omega^c} \left(\frac{2a(x)}{1+\rho} - 1 \right) - \lambda_\varepsilon(\rho) \right) \int_{\Omega^c} \varphi_{\varepsilon, \rho}(x) dx + \\ &\quad \varepsilon \int_{\Omega^c} \int_{\Omega} \kappa(x, y) \varphi_{\varepsilon, \rho}(y) dy dx. \end{aligned}$$

By inequality (15), the first term is negative and bounded, hence by rearranging the inequality we obtain, for a constant $C > 0$,

$$C \int_{\Omega^c} \varphi_{\varepsilon, \rho}(x) dx \leq \varepsilon \int_{\Omega^c} \int_{\Omega} \kappa(x, y) \varphi_{\varepsilon, \rho}(y) dy dx \leq \varepsilon.$$

Consequently, $\varphi_{\varepsilon, \rho}$ is a Dirac sequence and converges subsequently to a Dirac measure concentrated in \bar{x} .

4.3 Convergence of the steady states

Now we prove convergence of the steady states $(\rho_\varepsilon, u_\varepsilon)$ for $\varepsilon \rightarrow 0$. As a first step, we show

Proposition 4 *Let ρ_ε be the unique zero of $\lambda_\varepsilon(\rho)$, hence the first component of the steady state of system (4) and let $\bar{\rho}_0 := 2\bar{a} - 1$. Then*

$$\rho_\varepsilon \xrightarrow{\varepsilon \rightarrow 0} \bar{\rho}_0.$$

Proof Notice that $\bar{\rho}_0$ is the unique zero of the decreasing function $\lambda_0(\rho) := \max_{x \in \Omega} \left(\frac{2a(x)}{1+\rho} - 1 \right)$. Lemma 3 and the fact that $\lambda_0(\rho)$ changes sign (recall that, by Assumption 1 there exists $x_* \in \Omega$ such that $a(x_*) > \frac{1}{2}$) prove the statement.

The next result provides convergence of the family of steady states of system (4).

Theorem 2 *Let $(\rho_\varepsilon, u_\varepsilon)$ be the family of stationary solutions of System (4). Then*

$$u_\varepsilon \rightharpoonup \bar{\rho}_1 \delta_{\bar{x}} \quad \text{in } \mathcal{M}^+(\Omega), \quad \rho_\varepsilon \rightarrow \bar{\rho}_0 \quad \text{in } \mathbb{R},$$

where \rightharpoonup denotes narrow convergence in measures (see Remark 3), $\bar{\rho}_0 = 2\bar{a} - 1$, $\bar{\rho}_1 = \theta(2\bar{a} - 1)$ and \bar{x} is the isolated point where the maximum of the self-renewal function $a(x)$ is attained $\bar{x} = \arg \max_{x \in \Omega} a(x)$.

Proof Convergence of ρ_ε has already been proven in Proposition 4.

Convergence of u_ε is done in two steps. By construction $u_\varepsilon = c_\varepsilon \varphi_{\varepsilon, \rho_\varepsilon}$, where $\varphi_{\varepsilon, \rho_\varepsilon}$ is the unique (normalised) eigenfunction corresponding to the zero eigenvalue of the operator $C_{\varepsilon, \rho_\varepsilon}$ defined in (6) and $c_\varepsilon = \frac{\theta \rho_\varepsilon}{\int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon} \right) \varphi_{\varepsilon, \rho_\varepsilon}(x) dx}$.

Thus, we want to prove that both, the constants c_ε and the eigenfunctions $\varphi_{\varepsilon, \rho_\varepsilon}$, converge.

The same argument as in Proposition 3 yields convergence of $\varphi_{\varepsilon, \rho_\varepsilon}$ to the Dirac delta located at \bar{x} . Because of this property of $\varphi_{\varepsilon, \rho_\varepsilon}$ and convergence of ρ_ε , it follows

$$c_\varepsilon = \frac{\theta \rho_\varepsilon}{\int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon} \right) \varphi_{\varepsilon, \rho_\varepsilon} dx} \xrightarrow{\varepsilon \rightarrow 0} \frac{\theta \bar{\rho}_0}{2 \left(1 - \frac{\bar{a}}{1+\bar{\rho}_0} \right)} = \bar{\rho}_1.$$

This concludes the proof.

We can finally formulate the result giving the behavior for small mutation rate of the equilibria of System (3).

Theorem 3 *Let $(v_\varepsilon, u_\varepsilon)$ be the family of stationary solutions of System (3). Then, for $\varepsilon \rightarrow 0$,*

$$(v_\varepsilon, u_\varepsilon) \rightharpoonup (\bar{\rho}_0 \delta_{\bar{x}}, \bar{\rho}_1 \delta_{\bar{x}}) \quad \text{in } \mathcal{M}^+(\Omega),$$

where \rightharpoonup denotes narrow convergence in measures (see Remark 3), $\bar{\rho}_0 = 2\bar{a} - 1$, $\bar{\rho}_1 = \theta(2\bar{a} - 1)$ and \bar{x} is the unique value where the maximum of the self-renewal function $a(x)$ is attained.

Proof Theorem 2 provides convergence of the second component of the steady state. The first component can be written as

$$v_\varepsilon(x) = \frac{2}{\theta} \left(1 - \frac{a(x)}{1 + \rho_\varepsilon} \right) u_\varepsilon(x) =: g_\varepsilon(x) u_\varepsilon(x).$$

Proposition 4 implies that for any $f \in C_c$

$$g_\varepsilon(x) f(x) \xrightarrow{\varepsilon \rightarrow 0} \frac{2}{\theta} \left(1 - \frac{a(x)}{1 + \bar{\rho}_0} \right) f(x) =: g_0(x) f(x) \quad \text{strongly,}$$

which, by Proposition 3.13 in [5], implies that

$$\langle g_\varepsilon(x) f(x), u_\varepsilon(x) \rangle \xrightarrow{\varepsilon \rightarrow 0} \langle g_0(x) f(x), \bar{\rho}_1 \delta_{\bar{x}} \rangle,$$

that is,

$$v_\varepsilon \rightharpoonup g_0(\bar{x}) \bar{\rho}_1 \delta_{\bar{x}} = (2\bar{a} - 1) \delta_{\bar{x}}$$

which concludes the proof.

5 Stability of the steady states

Selection-mutation equations can be written, in a general way, in the form

$$\frac{\partial}{\partial t} z(t, x) = A_\varepsilon(F(z))z, \quad (16)$$

with F being a linear function from the state space to an m -dimensional space and such that $A_\varepsilon(E)$ is a linear operator for a fixed $E = F(z)$.

Assuming that equation (16) has a semilinear structure and the spectral mapping property holds (i.e., the growth bound of a semigroup is equal to the spectral bound of its generator, which is the case in L^1), the principle of linearised stability [48] yields local asymptotic stability of a steady state if the spectrum of the corresponding linearisation is located entirely in the open left half plane. A stability result for equation (16) is provided in Ref. [11]. It is shown using the principle of linearised stability and the fact that, in case of finite dimensional nonlinearity, the linearised operator at the steady state is a degenerated perturbation of a known operator with spectral bound equal to 0. This reduces the computation of the spectrum of the linearisation to the

computation of zeroes of the so-called Weinstein-Aronszajn determinant [25].

System (4) can be written in form (16) with

$$F : \mathbb{R} \times L^1(\Omega) \rightarrow \mathbb{R}, (\rho, u) \mapsto \rho, \quad (17)$$

and

$$A_\varepsilon \left(F \begin{pmatrix} \rho \\ u \end{pmatrix} \right) = A_\varepsilon(\rho) = \begin{pmatrix} -\theta & \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho} \right) \cdot dx \\ 0 & \left(\frac{2a(x)}{1+\rho} - (1+\varepsilon) \right) + \varepsilon \int_{\Omega} \kappa(x, y) \cdot dy \end{pmatrix}.$$

Note that operator $A_\varepsilon(\rho)$ generates a C^0 positive semigroup. Indeed, $A_\varepsilon(\rho)$ can be written in the following way

$$A_\varepsilon(\rho) = \begin{pmatrix} -\theta & 0 \\ 0 & \left(\frac{2a(x)}{1+\rho} - (1+\varepsilon) \right) \end{pmatrix} + \begin{pmatrix} 0 & \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho} \right) \cdot dx \\ 0 & \varepsilon \int_{\Omega} \kappa(x, y) \cdot dy \end{pmatrix},$$

where the first term is the generator of a C^0 positive semigroup and the second term is a linear positive operator, thus the sum generates a C^0 positive semigroup.

Linearising system (4) at the steady state $z_\varepsilon := (\rho_\varepsilon, u_\varepsilon)$, i.e., taking a perturbation $z = z_\varepsilon + \bar{z}$, applying the stationary equation $\frac{\partial}{\partial t} z_\varepsilon = 0$ and Taylor's formula, we obtain

$$\begin{pmatrix} \bar{\rho}' \\ \frac{\partial \bar{u}}{\partial t} \end{pmatrix} = (\tilde{A}_\varepsilon + S_\varepsilon) \begin{pmatrix} \bar{\rho} \\ \bar{u} \end{pmatrix},$$

where

$$\begin{aligned} \tilde{A}_\varepsilon = A_\varepsilon(\rho_\varepsilon) &= \begin{pmatrix} -\theta & \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon} \right) \cdot dx \\ 0 & \left(\frac{2a(x)}{1+\rho_\varepsilon} - (1+\varepsilon) \right) + \varepsilon \int_{\Omega} \kappa(x, y) \cdot dy \end{pmatrix}, \\ S_\varepsilon &= \begin{pmatrix} \int_{\Omega} \frac{2a(x)u_\varepsilon}{(1+\rho_\varepsilon)^2} & 0 \\ -\frac{2a(x)u_\varepsilon}{(1+\rho_\varepsilon)^2} & 0 \end{pmatrix}. \end{aligned} \quad (18)$$

with $\tilde{A}_\varepsilon, S_\varepsilon$ defined in $\mathbb{R} \times L^1(\Omega)$.

We also define the following ‘‘limit’’ operators in $\mathbb{R} \times \mathcal{M}^+(\Omega)$

$$\begin{aligned} \tilde{A}_0 = A_0(\bar{\rho}_0) &= \begin{pmatrix} -\theta & \int_{\Omega} 2 \left(1 - \frac{a(x)}{1+\bar{\rho}_0} \right) \cdot dx \\ 0 & \left(\frac{2a(x)}{1+\bar{\rho}_0} - 1 \right) \end{pmatrix}, \\ S_0 &= \begin{pmatrix} \frac{2\bar{a}\bar{\rho}_1}{(1+\bar{\rho}_0)^2} & 0 \\ -\frac{2\bar{a}\bar{\rho}_1}{(1+\bar{\rho}_0)^2} \delta_{\bar{x}} & 0 \end{pmatrix}. \end{aligned} \quad (19)$$

where $\bar{\rho}_0$ and $\bar{\rho}_1$ are given by Theorem 2.

As mentioned before, our aim is to apply the stability result given in Ref. [11] to system (4). For the sake of completeness, we summarize the two relevant theorems [11, Theorem 1 and 2] into the following theorem (for $m = 1$ which is the case for our model):

Theorem 4 *Let z_ε be a non-trivial positive steady state of equation (16), where F is a linear function from the state space to an m -dimensional space and, for a fixed $E = F(z)$, $A_\varepsilon(E)$ is a generator of a C^0 positive semigroup on the state space. Let $\tilde{A}_\varepsilon + S_\varepsilon$ be the linearisation of A_ε at the equilibrium z_ε . Let $\omega_\varepsilon(\lambda)$, $\omega_0(\lambda)$ be the Weinstein-Aronszajn determinants for $\tilde{A}_\varepsilon + S_\varepsilon$ and $\tilde{A}_0 + S_0$, respectively and $D := \{\lambda \in \mathbb{C} \mid \Re(\lambda) \geq 0, \lambda \neq 0\}$. Let $\omega_\varepsilon(\lambda), \omega_0(\lambda)$ be holomorphic functions in D such that $\omega_0(\lambda)$ does not vanish in D and*

$$\omega_\varepsilon(\lambda) \xrightarrow{\varepsilon \rightarrow 0} \omega_0(\lambda) \quad (20)$$

uniformly in λ on compact sets in D . Additionally, assume that

$$\exists L > 0 \forall |\lambda| > L : \quad \left\| S_\varepsilon R(\lambda, \tilde{A}_\varepsilon) \right\|_\infty < \frac{1}{2}. \quad (21)$$

If 0 is a strictly dominant eigenvalue of \tilde{A}_ε with algebraic multiplicity 1, P_ε is the projection onto the eigenspace of the eigenvalue 0 and

$$F(P_\varepsilon S_\varepsilon z_\varepsilon) \neq 0 \quad \text{and} \quad \liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \lambda F\left((\tilde{A}_\varepsilon - \lambda)^{-1} S_\varepsilon z_\varepsilon\right) \neq 0, \quad (22)$$

then for ε small enough the steady state z_ε is locally asymptotically stable.

Theorem 5 *Let Assumption 1 hold and additionally, let κ be separable in its variables, i.e.,*

$$\exists \kappa_1, \kappa_2 \in C(\bar{\Omega}) : \kappa(x, y) = \kappa_1(x)\kappa_2(y).$$

Then, for ε small enough, the steady state $(\rho_\varepsilon, u_\varepsilon)$ of system (4) is locally asymptotically stable.

The proof of this theorem is a direct application of Theorem 4. Since it is technical, it is deferred to Appendix B.

Theorem 6 *Let Assumption 1 hold and additionally, let κ be separable in its variables, i.e.*

$$\exists \kappa_1, \kappa_2 \in C(\bar{\Omega}) : \kappa(x, y) = \kappa_1(x)\kappa_2(y).$$

Then, for ε small enough, the steady state $(v_\varepsilon, u_\varepsilon)$ of system (3) is locally asymptotically stable.

Proof By Theorem 5, it only remains to prove the result for the first component of the steady state $v_\varepsilon(x)$. It holds

$$\frac{\partial}{\partial t} v_\varepsilon(t, x) = F(u_\varepsilon(t, x), \rho_\varepsilon(t)) - \theta v_\varepsilon(t, x)$$

with $F(u_\varepsilon(t, x), \rho_\varepsilon(t)) := 2 \left(1 - \frac{a(x)}{1 + \rho_\varepsilon(t)}\right) u_\varepsilon(t, x)$ and

$$v_\varepsilon(t, x) = v_0(x) e^{-\theta t} + \int_0^t F(u_\varepsilon(\tau, x), \rho_\varepsilon(\tau)) e^{-\theta(t-\tau)} d\tau.$$

Then, since $(v_\varepsilon(x), u_\varepsilon(x))$ is an equilibrium of system (3), it follows

$$\begin{aligned} \|v_\varepsilon(t, x) - v_\varepsilon(x)\|_{L^1(\Omega)} &= \int_\Omega |v_0(x) e^{-\theta t} + \int_0^t F(u_\varepsilon(\tau, x), \rho_\varepsilon(\tau)) e^{-\theta(t-\tau)} d\tau \\ &\quad - \frac{F(u_\varepsilon(x), \rho_\varepsilon)}{\theta}| dx \\ &\leq \int_\Omega |v_0(x) e^{-\theta t}| dx + \int_0^t e^{-\theta(t-\tau)} \int_\Omega |F(u_\varepsilon(\tau, x), \rho_\varepsilon(\tau)) \\ &\quad - F(u_\varepsilon(x), \rho_\varepsilon)| dx d\tau + \int_\Omega |F(u_\varepsilon(x), \rho_\varepsilon)| dx \\ &\quad \left(\int_0^t e^{-\theta(t-\tau)} d\tau - \frac{1}{\theta} \right) \end{aligned}$$

which tends to zero as $t \rightarrow \infty$ due to Theorem 5 (for more details on the second term see the proof of Lemma 7 in [8]).

6 Discussion

Acute myeloid leukemia is an aggressive cancer of the blood forming system. The malignant cell population is composed of multiple clones that evolve over time. Clonal data reflect the mechanisms linked to clonal properties such as self-renewal ability and proliferation of leukemic stem cells, which govern treatment response and relapse. In particular, recent insights from experimental and theoretical models suggest that self-renewal not only influences the stem cell population but has a crucial impact on dynamics of non-stem cells. Increased self-renewal confers competitive advantage on cancer cell clones by leading to aggressive expansion of both stem and non-stem cancer cells. Recent models suggest that self-renewal is the key parameter to understand clonal competition, selection and emergence of resistance in cancer cell populations.

In this paper, in order to study the impact of self-renewal on evolution of intra-patient cancer heterogeneity, we propose a mathematical model that accounts for dynamics of healthy and cancerous white blood cell populations governed by self-renewal and differentiation processes that exhibit clonal heterogeneity. The model describes evolution of a continuum of cell clones structured by the self-renewal potential. It is an extension of the model introduced

in [8], where it was shown that experimentally observed clonal selection can be explained by heterogeneity of self-renewal capacity of leukemic stem cells. Clones with the highest stem cell self-renewal are selected due to a nonlocal competition for regulatory factors such cytokines. Our aim is to check if the clonal selection acts also in the system perturbed by mutations. The latter increase clonal heterogeneity in the course of disease by introducing new clones with perturbed stem cell self-renewal capacity. The model we consider is a system of integro-differential equations for the populations of primitive and mature cells, both structured by their mutation stage x . Clonal heterogeneity is modelled by assuming the self-renewal fraction to be a function of the structure variable x . Heterogeneity emergence is described by an integral operator with mutation probability ε . Applying a version of the Krein-Rutmann theorem, we show in Section 3 existence of steady states of our selection-mutation model, which are proved, in Section 4, to converge as $\varepsilon \rightarrow 0$ to a weighted Dirac mass at the point of maximum fitness of the pure selection model studied in [8]. Finally, we show local asymptotic stability of the steady states.

The convergence holds in the sense of narrow convergence in Radon measures. In general, we cannot expect the strong (norm- total variation) convergence of the solution to a stationary solution. For initial data in $L^1(\Omega)$, the model solutions for any finite time point are uniformly continuous with respect to the Lebesgue measure. As $u_\varepsilon \rightharpoonup \bar{\rho}_1 \delta_{\bar{x}}$ narrowly, the distance between the two solutions $TV(u_\varepsilon, \bar{\rho}_1 \delta_{\bar{x}}) \geq 2\bar{\rho}_1$. Alternatively, the problem can be treated by considering convergence with respect to an appropriate metric, for example flat metric (bounded Lipschitz distance), for details see [8, 19] and references therein.

Our results demonstrate that mutations do not prevent the clonal selection and dominance of clones with the highest stem cell self-renewal potential. The persistent clones exhibit some heterogeneity with respect to the self-renewal values located near its maximum. This range of heterogeneity becomes smaller as the mutation rate decreases, which means that, for small mutation rates, model dynamics coincides with dynamics observed in [8] with initially assumed clonal heterogeneity. Certainly, new mutations leading to an increased stem cells self-renewal in the course of disease will lead to different clonal composition of cancer relapse comparing to the primary manifestation. However, as discussed in [8, 40] our models do not allow distinguishing between new mutations after the first therapy and persistence of preleukemic cells (small populations) that cannot be detected at the diagnosis but may dominate in relapses. In summary, the selection-mutation model proposed in this paper provides a mathematically rigorous proof that mutations do not change the selection process. Hence, our model analysis confirms the “mechanistic” explanation for the clonal selection phenomena observed in acute leukemias, which is based on a non-local cytokine-based regulation of stem cell self-renewal. Importance of this observation in the context of leukemia evolution, emergence of resistance in response to cytotoxic chemotherapy and dynamics of the disease relapses has been discussed in [8, 40] and in a broader context in the review paper [43]. In particular, model-based analysis of acute myeloid leukemia pa-

tients data suggested that the increased self-renewal is correlated with a poor patient prognosis [39].

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7 Appendix A

Lemma 4 *Let $\nu(t) = \int_{\Omega} u(t, x) dx$. Under the Assumptions 1, the function $U(t) = \frac{\nu(t)}{\rho(t)}$ is uniformly bounded on $\mathbb{R}^+ \times \Omega$.*

Proof The equation for $U(t)$ reads, for $t > 0$

$$\begin{aligned} \frac{\partial}{\partial t} U(t) &= \frac{1}{\rho(t)} \left(\int_{\Omega} \left(\frac{2a(x)}{1 + \rho(t)} - 1 \right) u(t, x) dx - 2 \frac{\nu(t)}{\rho^2(t)} \int_{\Omega} \left(1 - \frac{a(x)}{1 + \rho(t)} \right) u(t, x) dx \right) + \theta \frac{\nu(t)}{\rho(t)} \\ &\leq U(t) \left(2\bar{a} + \theta - 2(1 - \bar{a}) U(t) \right), \end{aligned} \quad (23)$$

where the latter estimate holds because

$$\left(\frac{2a(x)}{1 + \rho(t)} - 1 \right) + \theta \leq 2\bar{a} + \theta$$

and

$$1 - \frac{a(x)}{1 + \rho(t)} > 1 - \bar{a}.$$

Since the right-hand side of equation (23) is a logistic type nonlinearity, we conclude that

$$U(t) \leq \max \left\{ U(0), \frac{2\bar{a} + \theta}{2(1 - \bar{a})} \right\} =: M_1 \quad \forall (t, x) \in \mathbb{R}^+ \times \Omega.$$

By definition of U we can infer that

$$\nu(t) \leq M_1 \rho(t) \quad \forall (t, x) \in \mathbb{R}^+ \times \Omega.$$

Lemma 5 *Under the Assumptions 1, the total masses $\nu(t)$ and $\rho(t)$ are uniformly bounded.*

Proof Integrating the second equation in (4) and applying Lemma 4 we obtain

$$\frac{d}{dt} \nu(t) \leq \left(\frac{2\bar{a}}{1 + \frac{\nu(t)}{M_1}} - 1 \right) \nu(t)$$

from which we can conclude that

$$\nu(t) \leq \max \{ \nu(0), (2\bar{a} - 1)M_1 \} =: M_2.$$

From the first equation in (4) and using the previous inequality, we obtain

$$\frac{d}{dt}\rho(t) \leq 2\nu(t) - \theta\rho(t) \leq 2M_2 - \theta\rho(t)$$

and thus

$$\rho(t) \leq \max \left\{ \rho(0), \frac{2M_2}{\theta} \right\}.$$

8 Appendix B

Here we provide the proof of Theorem 5. The proof is divided into several parts, each dealing with a different assumption of the stability theorem 4.

8.1 Convergence of the Weinstein-Aronszajn determinants

The operators S_ε and S_0 defined in (18) and (19) are one-dimensional range operators with basis

$$\left(\int_{\Omega} \frac{2a(x)u_\varepsilon}{(1+\rho_\varepsilon)^2} dx \right) \quad \text{and} \quad \left(\frac{2\bar{a}\bar{\rho}_1}{(1+\bar{\rho}_0)^2} \delta_{\bar{x}}, \right) \quad (24)$$

respectively. Therefore the Weinstein-Aronszajn determinants

$$\begin{aligned} \omega_\varepsilon(\lambda) &:= \det \left(Id + S_\varepsilon R(\tilde{A}_\varepsilon, \lambda) |_{rg(S_\varepsilon)} \right) \\ \omega_0(\lambda) &:= \det \left(Id + S_0 R(\tilde{A}_0, \lambda) |_{rg(S_0)} \right) \end{aligned} \quad (25)$$

are well defined. In the next lemma we prove convergence result (20).

Lemma 6 *Let $\omega_\varepsilon(\lambda), \omega_0(\lambda)$ be the Weinstein- Aronszajn determinants defined in (25). Then,*

$$\omega_\varepsilon(\lambda) \xrightarrow{\varepsilon \rightarrow 0} \omega_0(\lambda)$$

uniformly in $\lambda \in D = \{ \lambda \in \mathbb{C} \mid \Re(\lambda) \geq 0, \lambda \neq 0 \}$. Both $\omega_\varepsilon(\lambda)$ and $\omega_0(\lambda)$ are holomorphic in D .

Proof In order to prove convergence, we estimate

$$|\omega_\varepsilon(\lambda) - \omega_0(\lambda)| \leq \left| \det \left(Id + S_\varepsilon R(\tilde{A}_\varepsilon, \lambda) \Big|_{rg(S_\varepsilon)} \right) - \det \left(Id + S_\varepsilon R(\tilde{A}_0, \lambda) \Big|_{rg(S_\varepsilon)} \right) \right| \\ + \left| \det \left(Id + S_\varepsilon R(\tilde{A}_0, \lambda) \Big|_{rg(S_\varepsilon)} \right) - \det \left(Id + S_0 R(\tilde{A}_0, \lambda) \Big|_{rg(S_0)} \right) \right|.$$

For the first term on the right-hand side it can be shown, in the same way as in [15, proof of Proposition 1] that

$$\left\| S_\varepsilon(\tilde{A}_\varepsilon - \lambda) \Big|_{R(S_\varepsilon)}^{-1} - S_\varepsilon(\tilde{A}_0 - \lambda) \Big|_{R(S_\varepsilon)}^{-1} \right\|_\infty \xrightarrow{\varepsilon \rightarrow 0} 0.$$

It remains to prove that

$$\left| \det \left(Id + S_\varepsilon R(\tilde{A}_0, \lambda) \Big|_{R(S_\varepsilon)} \right) - \det \left(Id + S_0 R(\tilde{A}_0, \lambda) \Big|_{R(S_0)} \right) \right| \xrightarrow{\varepsilon \rightarrow 0} 0.$$

For this purpose we compute the determinant explicitly. The basis of $rg(S_\varepsilon)$ is given by (24). Then, a direct computation yields

$$S_\varepsilon R(\tilde{A}_0, \lambda) \Big|_{R(S_\varepsilon)} = -\frac{1}{\theta + \lambda} \int_\Omega \frac{2a(x)u_\varepsilon(x)}{(1 + \rho_\varepsilon)^2} dx \\ + \frac{1}{\theta + \lambda} \int_\Omega 2 \left(1 - \frac{a(x)}{1 + \bar{\rho}_0} \right) \frac{1}{\left(\frac{2a(x)}{1 + \bar{\rho}_0} - 1 \right) - \lambda} \frac{2a(x)u_\varepsilon(x)}{(1 + \rho_\varepsilon)^2} dx.$$

According to Theorem 2, we know that ρ_ε converges strongly to $\bar{\rho}_0$ in \mathbb{R} and u_ε converges narrowly to $\bar{\rho}_1 \delta_{\bar{x}}$ in $\mathcal{M}^+(\Omega)$. Hence,

$$S_\varepsilon R(\tilde{A}_0, \lambda) \Big|_{R(S_\varepsilon)} \xrightarrow{\varepsilon \rightarrow 0} -\frac{1}{\theta + \lambda} \frac{2\bar{a}\bar{\rho}_1}{(1 + \bar{\rho}_0)^2} - \frac{1}{\lambda(\theta + \lambda)} 2 \left(1 - \frac{\bar{a}}{1 + \bar{\rho}_0} \right) \frac{2\bar{a}\bar{\rho}_1}{(1 + \bar{\rho}_0)^2} \\ = S_0 R(\tilde{A}_0, \lambda) \Big|_{R(S_0)}.$$

By definition of the Weinstein-Aronszajn determinant, $\omega_\varepsilon(\lambda)$ and $\omega_0(\lambda)$ are holomorphic in D , see [25, p. 245].

8.2 Boundedness of $S_\varepsilon R(\lambda, \tilde{A}_\varepsilon)$

Lemma 7 *There exists a constant $L > 0$ such that for all $|\lambda| > L$*

$$\left\| S_\varepsilon R(\lambda, \tilde{A}_\varepsilon) \right\|_\infty < \frac{1}{2}.$$

Proof Since $\sup_{\varepsilon < \varepsilon_0} \left\| \tilde{A}_\varepsilon \right\|_\infty$ and $\sup_{\varepsilon < \varepsilon_0} \|S_\varepsilon\|_\infty$ are bounded, we obtain for $|\lambda| > 2 \left\| \tilde{A}_\varepsilon \right\|_\infty$

$$\left\| S_\varepsilon R(\lambda, \tilde{A}_\varepsilon) \right\|_\infty = \left\| S_\varepsilon \lambda^{-1} \sum_{n=0}^{\infty} \left(\lambda^{-1} \tilde{A}_\varepsilon \right)^n \right\|_\infty \leq \frac{\|S_\varepsilon\|_\infty}{\lambda - \left\| \tilde{A}_\varepsilon \right\|_\infty} \leq \frac{2 \|S_\varepsilon\|_\infty}{|\lambda|}.$$

Choosing $L > \max \left\{ 2 \left\| \tilde{A}_\varepsilon \right\|_\infty, 4 \|S_\varepsilon\|_\infty \right\}$ leads to the assertion.

8.3 Proof of hypotheses (22) (excluding 0 and values with small positive real part from the spectrum)

Lemma 8 *For the steady state $z_\varepsilon := (\rho_\varepsilon, u_\varepsilon(x))$ of system (4), it holds*

$$F(P_\varepsilon S_\varepsilon z_\varepsilon) \neq 0. \quad (26)$$

Proof From the definition of F given in formula (17), it is sufficient to show that $P_\varepsilon S_\varepsilon z_\varepsilon \neq 0$. Since 0 is a simple strictly dominant eigenvalue of operator \tilde{A}_ε , we can decompose the space $L^1(\Omega) = \langle z_\varepsilon \rangle \oplus \text{Range}(\tilde{A}_\varepsilon)$ (see Theorem A.3.1 in [13]). Hence, we have to prove that $S_\varepsilon z_\varepsilon \notin \text{Range}(\tilde{A}_\varepsilon)$ what is equivalent to showing that

$$\left\langle \begin{pmatrix} \rho_\varepsilon^* \\ u_\varepsilon^* \end{pmatrix}, S_\varepsilon \begin{pmatrix} \rho_\varepsilon \\ u_\varepsilon \end{pmatrix} \right\rangle \neq 0, \quad (27)$$

where $(\rho_\varepsilon^*, u_\varepsilon^*)$ is the eigenfunction corresponding to the eigenvalue 0 of the adjoint operator \tilde{A}_ε^* . The adjoint operator reads

$$\tilde{A}_\varepsilon = \begin{pmatrix} -\theta & 0 \\ 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon}\right) \left(\frac{2a(x)}{1+\rho_\varepsilon} - (1+\varepsilon)\right) + \varepsilon \int_\Omega \kappa(y, x) \cdot dy & \end{pmatrix}$$

and we obtain that $\rho_\varepsilon^* = 0$. This implies that u_ε^* is an eigenfunction corresponding to the zero eigenvalue of the operator $\left(\frac{2a(x)}{1+\rho_\varepsilon} - (1+\varepsilon)\right) \cdot + \varepsilon \int_\Omega \kappa(y, x) \cdot$ which is the adjoint operator of $B_{\varepsilon, \rho} + K_\varepsilon$ defined by formulas (6). This operator is a generator of an irreducible positive semigroup in the Banach lattice $L^1(\Omega)$, as it is the perturbation by an irreducible operator of the generator of a positive semigroup. By Proposition 3.5 in [4] we obtain that u_ε^* is strictly positive, which, together with the fact that $\rho_\varepsilon^* = 0$, implies that

$$\left\langle \begin{pmatrix} \rho_\varepsilon^* \\ u_\varepsilon^* \end{pmatrix}, S_\varepsilon \begin{pmatrix} \rho_\varepsilon \\ u_\varepsilon \end{pmatrix} \right\rangle = - \int_\Omega \frac{2a(x)u_\varepsilon(x)\rho_\varepsilon u_\varepsilon^*(x)}{(1+\rho_\varepsilon)^2} \neq 0$$

The last step is to show

Lemma 9 *For the steady state z_ε , it holds*

$$\liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \lambda F \left((\tilde{A}_\varepsilon - \lambda)^{-1} S_\varepsilon z_\varepsilon \right) \neq 0. \quad (28)$$

Proof We start by computing the resolvent operator $R(\lambda, \tilde{A}_\varepsilon)$,

$$(\tilde{A}_\varepsilon - \lambda)^{-1} = \begin{pmatrix} \frac{-1}{\theta + \lambda} & \frac{1}{\theta + \lambda} \int_\Omega 2 \left(1 - \frac{a(x)}{1+\rho_\varepsilon}\right) R(\lambda, C_{\varepsilon, \rho_\varepsilon}) \cdot dx \\ 0 & R(\lambda, C_{\varepsilon, \rho_\varepsilon}) \end{pmatrix},$$

where recall that $C_{\varepsilon, \rho_\varepsilon}$ is defined in (6). Condition (28) reads

$$\begin{aligned} & \liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \lambda F \left((\tilde{A}_\varepsilon - \lambda)^{-1} S_\varepsilon \begin{pmatrix} \rho_\varepsilon \\ u_\varepsilon \end{pmatrix} \right) \\ &= \liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \frac{-\lambda}{\theta + \lambda} \left(\int_\Omega 2 \left(1 - \frac{a(x)}{1 + \rho_\varepsilon} \right) R(\lambda, C_{\varepsilon, \rho_\varepsilon}) \frac{2a(x)u_\varepsilon \rho_\varepsilon}{(1 + \rho_\varepsilon)^2} dx \right. \\ & \quad \left. + \int_\Omega \frac{2a(x)u_\varepsilon \rho_\varepsilon}{(1 + \rho_\varepsilon)^2} dx \right) \neq 0. \end{aligned}$$

Since the limit of the second term is zero, condition (28) becomes

$$\liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \frac{-1}{\theta + \lambda} \int_\Omega 2 \left(1 - \frac{a(x)}{1 + \rho_\varepsilon} \right) \lambda R(\lambda, C_{\varepsilon, \rho_\varepsilon}) \frac{2a(x)u_\varepsilon \rho_\varepsilon}{(1 + \rho_\varepsilon)^2} dx \neq 0$$

Determination of the limit is difficult. Since 0 is an eigenvalue of $C_{\varepsilon, \rho_\varepsilon}$, the limiting behaviour of $\lambda R(\lambda, C_{\varepsilon, \rho_\varepsilon})$ for λ tending to zero is not obvious, because the resolvent tends to infinity ($C_{\varepsilon, \rho_\varepsilon}$ tends to a multiplication operator), while λ tends to zero.

However, separation of variables of the kernel κ allows an explicit derivation of the resolvent $R(\lambda, C_{\varepsilon, \rho_\varepsilon})$ which facilitates the computation of the previous limit. Under this assumption, we write

$$C_{\varepsilon, \rho_\varepsilon} u = \left(\frac{2a(x)}{1 + \rho_\varepsilon} - (1 + \varepsilon) \right) u + \varepsilon \kappa_1(x) \int_\Omega \kappa_2(y) u(y) dy = -\alpha_\varepsilon(x) u + \varepsilon \kappa_1(x) Lu,$$

where $\alpha_\varepsilon(x) := \left(1 + \varepsilon - \frac{2a(x)}{1 + \rho_\varepsilon} \right) > 0$, since ρ_ε is the first component of the steady state of system (4), and $Lu = \int_\Omega \kappa_2(y) u(y) dy$. Following the scheme proposed in [11, Section 4.2] for the explicit computation of the resolvent operator $R(\lambda, C_{\varepsilon, \rho_\varepsilon})$, we obtain

$$R(\lambda, C_{\varepsilon, \rho_\varepsilon}) g = \frac{1}{\varepsilon \lambda} L \left(\frac{\kappa_1(x)}{\alpha_\varepsilon(x)(\alpha_\varepsilon(x) + \lambda)} \right)^{-1} \left[-(\alpha_\varepsilon(x) + \lambda)^{-1} g \right. \quad (29)$$

$$\left. + \varepsilon (\alpha_\varepsilon(x) + \lambda)^{-1} g L ((\alpha_\varepsilon(x) + \lambda)^{-1} \kappa_1(x)) \right. \quad (30)$$

$$\left. - \varepsilon (\alpha_\varepsilon(x) + \lambda)^{-1} \kappa_1(x) L ((\alpha_\varepsilon(x) + \lambda)^{-1} g) \right]. \quad (31)$$

Let us define

$$\beta_\varepsilon(x) := \frac{2a(x)\rho_\varepsilon}{(1 + \rho_\varepsilon)^2}, \quad H_\varepsilon(x) := 2 \left(1 - \frac{a(x)}{1 + \rho_\varepsilon} \right),$$

in order to shorten the notational effort. Note that

$$\lim_{\varepsilon \rightarrow 0} H_\varepsilon(x) = 2 \left(1 - \frac{a(x)}{1 + \bar{\rho}_0} \right) =: H(x), \quad \lim_{\varepsilon \rightarrow 0} \beta_\varepsilon(x) = \frac{2a(x)\bar{\rho}_0}{(1 + \bar{\rho}_0)^2} =: \beta(x).$$

We need to determine the following limiting process

$$\liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \int_{\Omega} H_{\varepsilon}(x) \lambda R(\lambda, C_{\varepsilon, \rho_{\varepsilon}}) \beta_{\varepsilon}(x) u_{\varepsilon}(x) \, dx =: \liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \Xi(\varepsilon, \lambda).$$

Substituting the expression of the resolvent operator derived in (29), we obtain

$$\begin{aligned} \Xi(\varepsilon, \lambda) &= \int_{\Omega} H_{\varepsilon}(x) \frac{1}{\varepsilon} L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} \\ &\quad \left[-(\alpha_{\varepsilon}(x) + \lambda)^{-1} \beta_{\varepsilon}(x) u_{\varepsilon}(x) + \varepsilon (\alpha_{\varepsilon}(x) + \lambda)^{-1} \beta_{\varepsilon}(x) u_{\varepsilon}(x) L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y) + \lambda} \right) \right. \\ &\quad \left. - \varepsilon (\alpha_{\varepsilon}(x) + \lambda)^{-1} \kappa_1(x) L \left(\frac{\beta_{\varepsilon}(y) u_{\varepsilon}(y)}{\alpha_{\varepsilon}(y) + \lambda} \right) \right] dx. \end{aligned}$$

For a better distinction between the terms, let us define

$$I := - \int_{\Omega} \frac{1}{\varepsilon} H_{\varepsilon}(x) L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} (\alpha_{\varepsilon}(x) + \lambda)^{-1} \beta_{\varepsilon}(x) u_{\varepsilon}(x) \, dx,$$

$$II := \int_{\Omega} H_{\varepsilon}(x) (\alpha_{\varepsilon}(x) + \lambda)^{-1} \beta_{\varepsilon}(x) u_{\varepsilon}(x) L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y) + \lambda} \right) \, dx,$$

$$III := - \int_{\Omega} H_{\varepsilon}(x) (\alpha_{\varepsilon}(x) + \lambda)^{-1} \kappa_1(x) L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} L \left(\frac{\beta_{\varepsilon}(y) u_{\varepsilon}(y)}{\alpha_{\varepsilon}(y) + \lambda} \right) \, dx,$$

$$\Xi(\varepsilon, \lambda) = I + II + III.$$

Using the steady state equation

$$u_{\varepsilon} = \varepsilon \frac{\kappa_1(x)}{\alpha_{\varepsilon}(x)} L u_{\varepsilon}, \quad (32)$$

we obtain

$$\begin{aligned} I &= - \int_{\Omega} H_{\varepsilon}(x) \frac{\beta_{\varepsilon}(x) \kappa_1(x) L u_{\varepsilon}}{\alpha_{\varepsilon}(x)(\alpha_{\varepsilon}(x) + \lambda)} L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} \, dx \\ &= - L u_{\varepsilon} \int_{\Omega} H_{\varepsilon}(x) \frac{\beta_{\varepsilon}(x)}{\kappa_2(x)} \frac{\kappa_1(x) \kappa_2(x)}{\alpha_{\varepsilon}(x)(\alpha_{\varepsilon}(x) + \lambda)} L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1} \, dx. \end{aligned}$$

The sequence g_{ε} denoted by

$$g_{\varepsilon}(x) := \frac{\kappa_1(x) \kappa_2(x)}{\alpha_{\varepsilon}(x)(\alpha_{\varepsilon}(x) + \lambda)} L \left(\frac{\kappa_1(y)}{\alpha_{\varepsilon}(y)(\alpha_{\varepsilon}(y) + \lambda)} \right)^{-1},$$

defines a Dirac sequence. The definition also guarantees that

$$\forall \varepsilon > 0 : \quad g_\varepsilon(x) > 0 \text{ and } \int_{\Omega} g_\varepsilon(x) \, dx = 1.$$

Let $\bar{x} = \operatorname{argmax}_{x \in \bar{\Omega}} a(x)$ and take $\Omega^c \subset \Omega$ such that $\bar{x} \notin \Omega^c$ and $\operatorname{dist}(\bar{x}, \Omega^c) > 0$.

It follows from Theorem 2 that

$$\alpha_\varepsilon(x) = \left(1 + \varepsilon - \frac{2a(x)}{1 + \rho_\varepsilon} \right) \xrightarrow{\varepsilon \rightarrow 0} \left(1 - \frac{2a(x)}{1 + \bar{\rho}_0} \right).$$

We conclude that $\frac{\kappa_1(x)\kappa_2(x)}{\alpha_\varepsilon(x)(\alpha_\varepsilon(x)+\lambda)}$ converges and is subsequently bounded on Ω^c .

Then, using $1 = \varepsilon L\left(\frac{\kappa_1(x)}{\alpha_\varepsilon(x)}\right)$, we estimate

$$\begin{aligned} \int_{\Omega} \frac{\kappa_1(x)\kappa_2(x)}{\alpha_\varepsilon(x)(\alpha_\varepsilon(x)+\lambda)} \, dx &\geq \frac{1}{\max_{x \in \Omega^c}(\alpha_\varepsilon(x)+\lambda)} \int_{\Omega} \frac{\kappa_1(x)\kappa_2(x)}{\alpha_\varepsilon(x)} \, dx = \frac{1}{\max_{x \in \Omega^c}(\alpha_\varepsilon(x)+\lambda)} L\left(\frac{\kappa_1}{\alpha_\varepsilon}\right) \\ &= \frac{1}{\varepsilon \max_{x \in \Omega^c}(\alpha_\varepsilon(x)+\lambda)} \xrightarrow{\varepsilon \rightarrow 0} \infty. \end{aligned}$$

This implies that

$$\forall \Omega^c \subset \Omega, \bar{x} \notin \Omega^c, \operatorname{dist}(\bar{x}, \Omega^c) > 0 : \quad \int_{\Omega^c} g_\varepsilon(x) \, dx \rightarrow 0 \quad \text{for } \varepsilon \rightarrow 0.$$

Since we additionally know by Theorem 2 that u_ε converges narrowly, we infer

$$Lu_\varepsilon = \int_{\Omega} \kappa_2(y)u_\varepsilon(y) \, dy \rightarrow \bar{\rho}_1 \kappa_2(\bar{x}) \quad \text{for } \varepsilon \rightarrow 0.$$

Thus, we obtain

$$I \xrightarrow{\varepsilon \rightarrow 0} -\bar{\rho}_1 H(\bar{x})\beta(\bar{x}) < 0.$$

Computing the limit for II and III and using equality (32), we obtain

$$\begin{aligned} \liminf(II + III) &= \liminf_{(\varepsilon, \lambda) \rightarrow (0^+, 0)} \varepsilon \left[\int_{\Omega} H_\varepsilon(x) \frac{Lu_\varepsilon \beta_\varepsilon(x)}{\kappa_2(x)} \frac{\kappa_1(x)\kappa_2(x)}{\alpha_\varepsilon(x)(\alpha_\varepsilon(x)+\lambda)} \right. \\ &\quad \left. L\left(\frac{\kappa_1(y)}{\alpha_\varepsilon(y)(\alpha_\varepsilon(y)+\lambda)}\right)^{-1} \cdot \left(L\left(\frac{\kappa_1(y)}{\alpha_\varepsilon(y)+\lambda}\right) - \frac{\alpha_\varepsilon(x)}{\beta_\varepsilon(x)} L\left(\frac{\beta_\varepsilon(y)\kappa_1(y)}{\alpha_\varepsilon(y)(\alpha_\varepsilon(y)+\lambda)}\right) \right) \, dx \right] \\ &= 0 \end{aligned}$$

which concludes the proof.

Remark 4 Note that the separation of variables of κ is needed only, because of the explicit computation of the resolvent $R(\lambda, C_{\varepsilon, \rho_\varepsilon})$. All results up to this point do not need this assumption and work for Assumption 1 alone.

9 Appendix C

In this appendix we prove that the operators

$$T_{\varepsilon, \rho}^n u(x) = \int_{\Omega^n} \kappa(x, y_n) \prod_{i=1}^{n-1} \kappa(y_i, y_{i+1}) \frac{(1+\rho)^n}{\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))} u(y_n) dy_1 \cdots dy_n.$$

defined in the proof of Lemma 1 satisfy $\frac{d}{d\rho} T_{\varepsilon, \rho}^n < 0$ for ε small enough. The differential operator and the integral can be interchanged, because of Leibniz' integral rule. This implies denoting by $d\mathbf{y} = dy_1 \cdots dy_n$

$$\begin{aligned} \frac{d}{d\rho} (T_{\varepsilon, \rho}^n u)(x) &= \\ \frac{d}{d\rho} \int_{\Omega^n} \kappa(x, y_n) \prod_{i=1}^{n-1} \kappa(y_i, y_{i+1}) \frac{(1+\rho)^n}{\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))} u(y_n) d\mathbf{y} &= \\ \int_{\Omega^n} \kappa(x, y_n) \prod_{i=1}^{n-1} \kappa(y_i, y_{i+1}) \frac{d}{d\rho} \frac{(1+\rho)^n}{\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))} u(y_n) d\mathbf{y}. \end{aligned}$$

Both κ and u are positive functions, so the sign of the derivative is solely determined by the derivative of the fraction. Performing the derivative yields

$$\begin{aligned} \frac{d}{d\rho} \frac{(1+\rho)^n}{\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))} &= \\ \frac{n(1+\rho)^{n-1} \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))}{\left(\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right)^2} &= \\ \frac{(1+\rho)^n \frac{d}{d\rho} \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i))}{\left(\prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right)^2}. \end{aligned}$$

Again we see that it is sufficient to look only at a small part of this derivative to determine the sign, namely the numerator. The claim is

$$n \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) - (1+\rho) \frac{d}{d\rho} \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) < 0$$

and can be shown by induction over $n \in \mathbb{N}$.

Let $n = 1$, then

$$((1+\rho)(1+\varepsilon) - 2a(y_1)) - (1+\rho)(1+\varepsilon) = -2a(y_1) < 0,$$

by Assumption 1.

Let the statement be true for $n \in \mathbb{N}$. Then have a look at the derivative for $n + 1$

$$\begin{aligned}
& (n+1) \prod_{i=1}^{n+1} ((1+\rho)(1+\varepsilon) - 2a(y_i)) \\
& - (1+\rho) \frac{d}{d\rho} \prod_{i=1}^{n+1} ((1+\rho)(1+\varepsilon) - 2a(y_i)) \\
= & n \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \cdot ((1+\rho)(1+\varepsilon) - 2a(y_{n+1})) \\
& + \prod_{i=1}^{n+1} ((1+\rho)(1+\varepsilon) - 2a(y_i)) \\
& - (1+\rho) \left[\frac{d}{d\rho} \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \cdot ((1+\rho)(1+\varepsilon) - 2a(y_{n+1})) \right. \\
& \left. + \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right] \\
= & ((1+\rho)(1+\varepsilon) - 2a(y_{n+1})) \left[n \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right. \\
& \left. - (1+\rho) \frac{d}{d\rho} \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right] \\
& + \left[\prod_{i=1}^{n+1} ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right. \\
& \left. - (1+\rho) \prod_{i=1}^n ((1+\rho)(1+\varepsilon) - 2a(y_i)) \right] < 0,
\end{aligned}$$

because the first term is negative due to the induction assumption and the second term is negative because $1 + \rho > (1 + \rho)(1 + \varepsilon) - 2a(y_{n+1})$ for ε small enough.

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