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Adaptive dynamics of hematopoietic stem cells and their supporting stroma: A model and mathematical analysis

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Abstract

We propose a mathematical model to describe the evolution of hematopoietic stem cells (HSCs) and stromal cells in considering the bi-directional interaction between them. Cancerous cells are also taken into account in our model. HSCs are structured by a continuous phenotype characterising the population heterogeneity in a way relevant to the question at stake while stromal cells are structured by another continuous phenotype representing their capacity of support to HSCs.

We then analyse the model in the framework of adaptive dynamics. More precisely, we study single Dirac mass steady states, their linear stability and we investigate the role of parameters in the model on the nature of the evolutionary stationary distributions (ESDs) such as monomorphism, dimorphism and the uniqueness properties. We also study the dominant phenotypes by an asymptotic approach and we obtain the equation for dominant phenotypes. Numerical simulations are employed to illustrate our analytical results. In particular, we represent the case of the invasion of malignant cells as well as the case of co-existence of cancerous cells and healthy HSCs.

MSC (2010). 35B40, 35Q92, 45J05, 45M10, 92C37, 92D15, 92D25.

Keywords. Adaptive cell population dynamics, hematopoietic stem cells, stromal cells, leukemic stem cells, Dirac concentrations, asymptotic methods.

1 Introduction

Hematopoietic stem cells (HSCs), developing in the bone marrow, are immature cells that are (the earliest in development) precursors of all lineages of blood cells: red blood cells, white blood cells and megacaryocytes (whose fragmentation gives rise to platelets). Blood cell formation, also called hematopoiesis, is a complex phenomenon basing on the self-renewal, differentiation and maturation of HSCs. It produces about $10^{11}$ blood cells per day in humans and is one of the most stable biological processes in vertebrate organisms. A dysfunction in the hematopoietic process...
may induce blood cancer diseases (usually named malignant hemopathies) such as leukaemia where blockade of maturation and of differentiation occurs in the hematopoietic tree. As a consequence, malignant cells, resulting from an accumulation of irregular genetic events, appear and proliferate abnormally.

Many mathematical models have been proposed to understand blood cell development and blood diseases. Mackey [17], inspired by Burns and Tannock [5] and Lajtha [13], have introduced a first mathematical model of the form of a system of delay differential equations for the dynamics of HSCs where the populations are divided into two groups (proliferating cells and quiescent cells) and the time delay corresponds to the proliferating phase duration. Further improvements both in modelling and mathematical analysis are investigated by many authors; see, for example, [2, 3, 18, 26] — models in the form of ODEs or age-structured transport equations with applications to chronic myelogenous leukaemia, [10] — a diffusion model including spatial competition between cells —, reviews [1, 6, 25] and the references therein.

Despite extensive studies on the dynamics of HSCs and diseases of the hematopoietic system, none of the above-mentioned models takes into account the interactions between HSCs and the hematopoietic niche which is a specific microenvironment ensuring the maintenance and regulation of HCSs locally. It is worth noting that the interactions between HSCs and their niche, of which mesenchymal stem cells (MSCs) are the most important component, play a crucial role in the formation of mature blood cells. Also, alterations in the bidirectional exchanges between HSCs and MSCs may give rise among HSCs to blood cancer stem cells, i.e., leukemic stem cells, LSCs.

Note that healthy HSCs need the close presence of stromal cells for their development but stromal cells can proliferate without HSCs. Similar to HSCs, cancer cells in the early stages need stromal cells for their development whereas in the later stages they can proliferate without support cells. In other words, the more malignant a cell is, the more independent of stromal cells it is. Here, cancer cells in earlier stages are cells with few mutation events and cancer cells in later stages stand for the ones with more mutation events. We refer to, for example, [4] for a review of the interaction between HSCs and stromal cells, [11] for acute myeloid leukemic cells.

In the present paper, we introduce a mathematical model for the interaction between HSCs and stromal cells with the aim to better understand the nature of the dialogue between them as well as their dynamics. We also perform a mathematical analysis for the long-time behaviour of the hematopoietic and stromal cells in the framework of adaptive dynamics, see Section 1.2 for a short overview of this theory.

The paper is organised as follows. In the remaining part of this section, we introduce our model and recall some notions in the framework of adaptive dynamics, in particular, evolutionary state distributions (ESDs). In Section 2, we present first mathematical results to verify biological properties concerning the interaction between HSCs and stromal cells. A uniform bound in time and a well-posedness result are given in Section 3. Section 4 is concerned with single steady states and their linear stability. Sufficient conditions for the existence of monomorphic, dimorphic ESDs and the uniqueness of ESDs are presented in Section 5. In Section 6, we study the dominant traits by an asymptotic approach, derive the equation for dominant traits and provide numerical simulations to illustrate our results. Finally, some discussions will be given in Section 7.

1.1 A mathematical model

Let $n_h(t, x)$ be the population density of hematopoietic stem cells (HSCs) and cancer cells at time $t$ with phenotype $x$, continuous structure variable assumed to characterise the population
heterogeneity in a way relevant to the question at stake. Here \( x \) will represent a malignancy potential of HSCs, from its minimal (representing a totally healthy state) to its maximal value (representing maximum malignancy), considered independently of their stromal support. From a biological point of view, \( x \) might represent a pathological combination of both high plasticity (i.e., ability to change phenotype; stem cells are plastic, but physiologically, they not proliferate much) and fecundity (i.e., ability to proliferate; differentiated cells are able to proliferate, but physiologically, they show little plasticity).

Let \( n_s(t, y) \) be their corresponding stromal cell population density - that we will sometimes call support cells - at time \( t \).

Assume for simplicity that \( x \) (here the continuous phenotype variable \( n \)) and \( y \) (here the continuous phenotype variable \( s \)) are real variables with \( x \in (a, b), y \in (c, d) \), where \( 0 < a < b \) and \( 0 < c < d \). Totally healthy HSCs will thus have a phenotype \( x \) close to \( a \), while aggressive leukemic HSCs (i.e., LSCs) will have a phenotype \( x \) close to \( b \). We consider a mathematical model of the form

\[
\begin{cases}
\frac{\partial n_h(t, x)}{\partial t} = \left[r_h(x) - \rho_h(t) - \rho_s(t) + \alpha(x) \Sigma_s(t)\right]n_h, & x \in (a, b), t > 0, \\
\frac{\partial n_s(t, y)}{\partial t} = \left[r_s(y) - \rho_h(t) - \rho_s(t) + \beta(y) \Sigma_h(t)\right]n_s, & y \in (c, d), t > 0.
\end{cases}
\]

This system is completed with initial data

\[
n_h(0, x) = n_{h0}(x) \geq 0, \quad n_s(0, y) = n_{s0}(y) \geq 0.
\]

Here our assumptions and notations are

- The terms \( \Sigma_h(t) := \int_a^b \psi_h(x)n_h(t, x) \, dx, \Sigma_s(t) := \int_c^d \psi_s(y)n_s(t, y) \, dy \) denote an assumed chemical signal (\( \Sigma_h \)) from the hematopoietic immature stem cells (HSCs) to their supporting stroma (MSCs), i.e., “call for support” and conversely, a trophic message (\( \Sigma_s \)) from MSCs to HSCs. The nonnegative functions \( \psi_h, \psi_s \) defined on \((a, b)\) and \((c, d)\) measure the contribution of each phenotype in the interactive messages. Assume that \( \psi'_h \geq 0 \) (the higher the support phenotype in MSCs, the stronger the trophic message to HSCs); in the same way, unless otherwise specified, we shall assume that \( \psi'_s \geq 0 \).

- The term \( r_h \geq 0 \) represents the intrinsic (i.e., without contribution from trophic messages from MSCs, nor limitation by the non local logistic terms \( \rho_h \) and \( \rho_s \), that represent competition for space and nutrients within the whole population of cells) proliferation rate of HSCs. Assume that \( r_h \) is non-decreasing (the more malignant, the more proliferative), \( r_h(a) = 0 \) and \( r_h(b) > 0 \).

- The term \( \alpha \geq 0 \), satisfying \( \alpha' \leq 0 \) and \( \alpha(b) = 0 \), is the sensitivity of HSCs to the trophic messages from support cells.

- For the term \( r_s \geq 0 \), we assume that \( r'_s(y) \leq 0 \) (there is a cost in proliferation for support cells to increase their support capacity). The term \( \beta(y) \geq 0 \) with \( \beta'(y) \geq 0 \) represents the sensitivity of the stromal cells to the (call for support) message coming from HSCs.

As a simple case, the parameters \( r_h, \alpha, r_h, r_h, \psi_h, \psi_s \) can be chosen as linear or quadratic functions. For example, \( r_h, \alpha \) are given by \( r_h = r^*_h(x - a) \) or \( r_h = r^*_h(x - a)^2, \alpha(x) = \alpha^*(b - x) \) with positive constants \( r^*_h, \alpha^* \), \( \psi_h(x) = x, \psi_s(y) = y \).
Let us briefly sum up the meaning of our assumptions. From a biological point of view, the healthy HSCs cannot proliferate without support cells while cancer cells persist even without support cells. In our model \( n_h(t,a) \) corresponds to healthy HSCs and \( n_h(t,b) \) are leukemic cells since the intrinsic proliferation rate \( r_h \) satisfies \( r_h(a) = 0, r_h(b) > 0 \). The monotonicity of \( r_h \) implies that the higher \( x \) is, the more aggressive is a HSC (in fact, a LSC, since it is then cancerous). Also the monotonicity of \( \alpha \) (this function stands for the sensitivity of HSCs to the trophic messages coming from MSCs) indicates that the more aggressive \( x \) is, the less sensitivity has a HSC to the trophic message sent by MSCs (i.e., the more independent it is from the surrounding stroma). Moreover, the condition \( \alpha(b) = 0 \) shows that \( n(t,b) \) (i.e., cancer cells in the latter stages) proliferate independently of the supporting stroma. Furthermore, the monotonicity of \( r_s, \beta \) shows that the more supporting stromal capacity MSCs have, the less they proliferate and the more sensitive to messages from HSCs they are.

A more general model which includes the possibility of mutations has the form:

\[
\begin{aligned}
\partial_t n_h(t,x) &= \mu_h(n_h)_x + \left[ r_h(x) - c_{11}(x)\rho_s(t) - c_{12}(x)\rho_s(t) + \alpha(x)\Sigma_s(t) \right] n_h \\
\partial_t n_s(t,y) &= \mu_s(n_s)_{yy} + \left[ r_s(y) - c_{21}(y)\rho_h(t) - c_{22}(y)\rho_h(t) + \beta(y)\Sigma_h(t) \right] n_s.
\end{aligned}
\tag{1.3}
\]

Here the diffusion terms represent mutation with rates \( \mu_h, \mu_s \) and \( c_{11}, c_{12}, c_{22} \) measure the strength of competition between cells. Problem (1.3) reduces to (1.1) by setting \( \mu_h = \mu_s = 0 \) and \( c_{11}(x) = c_{12}(x) = 1, c_{21}(y) = c_{22}(y) = 1 \). Thus (1.1) can be considered as a good approximation of (1.3) in the regime \( \mu_h, \mu_s << 1 \) which is realistic since mutations occur rarely in physiology (to fix ideas, let us say between once every \( 10^4 \) and \( 10^7 \) cell divisions; of course, in evolved cancers, such low rates may increase).

Since the sign of the terms \( -\rho_t(t) + \alpha(x)\Sigma_t(t) \) and \( -\rho_h(t) + \beta(y)\Sigma_h(t) \) varies in time (also depends on \( x \)), the nature of (1.1) is unknown. It could be competitive or cooperative, or even can vary during evolution. This makes the problem difficult to study. The long-time behaviour for related problems has been studied by several authors. For the case without interaction terms (i.e., \( \Sigma_h = \Sigma_s = 0 \)), we refer to [12, 14, 23]; see also [24] for the case \( \psi_h = \psi_s = 1 \).

### 1.2 Some notions in the theory of adaptive dynamics

Hereafter, we will use the notation \( \int \) to denote the integrals over \( [a,b] \) and \( [c,d] \), as long as there is no risk of confusion. Let \( \hat{n}_h, \hat{n}_s \) be measures defined on \( [a,b], [c,d] \), respectively. We set

\[
\begin{aligned}
\text{supp } \hat{n}_h &= I \subset [a,b], & \text{supp } \hat{n}_s &= J \subset [c,d], \\
\hat{\rho}_h &= \int \hat{n}_h, & \hat{\rho}_s &= \int \hat{n}_s, & \hat{\Sigma}_h &= \int \psi_h(x)\hat{n}_h, & \hat{\Sigma}_s &= \int \psi_s(y)\hat{n}_s, \\
G_h(x) := r_h(x) - \hat{\rho}_h - \hat{\rho}_s + \alpha(x)\hat{\Sigma}_s, & G_s(y) := r_s(y) - \hat{\rho}_h - \hat{\rho}_s + \beta(y)\hat{\Sigma}_h.
\end{aligned}
\tag{1.4}
\]

**Definition 1.1.** The pair \((\hat{n}_h, \hat{n}_s)\) is a steady state of (1.1) if

\[
G_h(x) = 0, \quad G_s(y) = 0 \quad \text{for all } x \in I, y \in J.
\tag{1.5}
\]

**Definition 1.2.** We say that \((\hat{n}_h, \hat{n}_s)\) is an evolutionary state distribution (ESD) of problem (1.1) if it is a steady state (i.e. (1.5) holds) and the condition below is fulfilled

\[
G_h(x) \leq 0 \text{ for all } x \in [a,b] \setminus I, \quad G_s(y) \leq 0 \text{ for all } y \in [c,d] \setminus J.
\tag{1.6}
\]
Remark 1.3. It follows from Definition 1.2 that any $x \in I$ (resp. $y \in J$) is a maximum point of $G_h$ (resp. $G_s$).

As our equation arises from biological cell population dynamics, we only consider non-negative steady states and ESDs in this paper.

In the context of adaptive dynamics, when (1.5) holds, we say that the phenotypes $x \in I, y \in J$ are living in the stationary environment given by $(\hat{\rho}_h, \hat{\rho}_s, \hat{\Sigma}_h, \hat{\Sigma}_s)$. The functions $G_h, G_s$ are fitness functions associated with this environment. The quantities $G_h(x), G_s(y)$ are growth rates of phenotypes $x, y$ and they tell us whether $(x, y)$ can invade this environment: If $G_h(x) > 0, G_s(y) > 0$, $(x, y)$ can grow and the system will reach a new equilibrium. We refer to [7, 19] for more details about the framework of adaptive dynamics.

2 Hematopoietic stem cells or stromal cells without mutual interaction

In the absence of stromal cells, the system (1.1) reduces to the equation

$$\partial_t n_h(t, x) = \left[ r_h(x) - \rho_h(t) \right] n_h, \quad x \in (a, b), t > 0.$$  \hspace{1cm} (2.1)

Similarly, the behaviour of stromal cells without HSCs is given by

$$\partial_t n_s(t, y) = \left[ r_s(y) - \rho_s(t) \right] n_s, \quad y \in (c, d), t > 0.$$  \hspace{1cm} (2.2)

In view of [21, Theorem 2.1, Page 29], we have the following selection principle:

**Lemma 2.1.** Suppose that $r_h$ is bounded and strictly increasing. Suppose furthermore that $r_s$ is bounded and strictly decreasing. Assume that $n_h(0), n_s(0) \in L^1$ are positive on $[a, b]$ and $[c, d]$, respectively.

(i) For (2.1), we have $n_h(t, x) \to r_h(b)\delta_{\{x=b\}}$ weakly in the sense of measures as $t \to \infty$.

(ii) For (2.2), we have $n_h(t, y) \to r_s(c)\delta_{\{y=c\}}$ weakly in the sense of measures as $t \to \infty$.

These results confirm biological properties mentioned in Section 1 about the bi-directional interaction between HSCs and stromal cells. More precisely, in the absence of stromal cells for HSCs or of HSCs for stromal cells, the phenotypes of $n_h$ and $n_s$, respectively, behave as monomorphic. Moreover, Lemma 2.1 (i) implies that healthy hematopoietic cells eventually go extinct while cancer cells (with the phenotype $y = b$) are selected and persist. Furthermore, stromal cells persist without HSCs and stromal cells with the lowest capacity of support will be selected (cf. Lemma 2.1 (ii)).

3 Preliminary estimates and a well-posedness result

For a function $f$ defined on an interval $I$, we set

$$\underline{f} := \min_{x \in I} f(x), \quad \overline{f} := \max_{x \in I} f(x).$$

In the results below, we only need the boundedness of $r_h, r_s, \alpha, \beta, \psi_h, \psi_s$. We do not need the monotonicity assumption of these functions.
**Proposition 3.1.** Assume that \( r_h, r_s, \alpha, \beta, \psi_h, \psi_s \) are non-negative and bounded. Suppose furthermore that
\[
\alpha \psi_s + \beta \psi_h < 4.
\] (3.1)

Set
\[
\rho^M := \max \left( \rho_{h0} + \rho_{s0}, \frac{4 \max(\bar{r}_h, \bar{r}_s)}{4 - (\alpha \psi_s + \beta \psi_h)} \right).
\]

Then the solution of (1.1) is non-negative and satisfies
\[
0 \leq \rho_h(t) + \rho_s(t) \leq \rho^M \text{ for all } t \geq 0.
\] (3.2)

**Proof.** First note that the solution of (1.1) can be written in the form
\[
n_h(t, x) = n_{h0}(x) \exp \left( \int_0^t A(\sigma, x) \, d\sigma \right), \quad n_s(t, y) = n_{s0}(y) \exp \left( \int_0^t B(\sigma, y) \, d\sigma \right),
\]
where
\[
A(\sigma, x) = r_h(x) - \rho_h(\sigma) - \rho_s(\sigma) + \alpha(x) \Sigma_h(\sigma), \quad B(\sigma, y) = r_s(y) - \rho_h(\sigma) - \rho_s(\sigma) + \beta(y) \Sigma_h(\sigma).
\]

Thus \( n_h(t, x) \geq 0, n_s(t, y) \geq 0 \) since \( n_{h0}(x) \geq 0, n_{s0}(y) \geq 0 \). This yields the first inequality of (3.2).

Integrating the two equations in (1.1) yields
\[
\frac{d}{dt}(\rho_h + \rho_s) = -(\rho_h + \rho_s)^2 + \int r_h(x) n_h + \Sigma_h(t) \int \alpha(x) n_h,
\]
\[
\frac{d}{dt}(\rho_h + \rho_s) = -(\rho_h + \rho_s)^2 + \int r_s(y) n_s + \Sigma_h(t) \int \beta(y) n_s.
\]

Summing up these two identities and using the non-negativity of \( n_h, n_s \), we obtain
\[
\frac{d}{dt}(\rho_h + \rho_s) \leq -(\rho_h + \rho_s)^2 + \max(\bar{r}_h, \bar{r}_s)(\rho_h + \rho_s) + \alpha \psi_s \rho_h \rho_s + \beta \psi_h \rho_h \rho_s
\]
\[
\leq -(\rho_h + \rho_s)^2 + \max(\bar{r}_h, \bar{r}_s)(\rho_h + \rho_s) + \frac{\alpha \psi_s + \beta \psi_h}{4} (\rho_h + \rho_s)^2
\]
\[
= \left[ \max(\bar{r}_h, \bar{r}_s) - \frac{\alpha \psi_s + \beta \psi_h}{4} \right] (\rho_h + \rho_s).
\]

Hence the second inequality of (3.2) follows. \( \square \)

**Theorem 3.2.** Let \( n_{h0}, n_{s0} \in L^1(a, b) \times L^1(c, d) \) be non-negative. Then (1.1) possesses a unique solution \((n_h, n_s) \in C^1([0, \infty); L^1(a, b) \times L^1(c, d)) \).
4 Steady states and linear stability

Hereafter, for simplicity, we assume that \( \psi_h(x) = x, \psi_s(y) = y \). Then Problem (1.1) becomes

\[
\begin{align*}
\partial_t n_h(t,x) &= [r_h(x) - \rho_h(t) - \rho_s(x) + \alpha(x) \int g_{n_s}(t,y)dy]n_h, \quad x \in (a, b), t > 0, \\
\partial_t n_s(t,y) &= [r_s(y) - \rho_h(t) - \rho_s(t) + \beta(y) \int x_n_h(t,x)dx]n_s, \quad y \in (c, d), t > 0.
\end{align*}
\] (4.1)

4.1 Single Dirac mass steady states

Let \( \hat{x} \in [a, b], \hat{y} \in [c, d] \). Consider a particular case where hematopoietic and support cells evolve as single Dirac masses concentrated at \( \hat{x}, \hat{y} \). In other words, we focus on the behaviour of the size of the populations. In this case, \( n_h, n_s \) have the form

\[ n_h(t,x) = \rho_h(t)\delta_{(x=\hat{x})}, \quad n_s(t,y) = \rho_s(t)\delta_{(y=\hat{y})}, \]

where \( \rho_h(t), \rho_s(t) \) satisfy

\[
\begin{align*}
\frac{d}{dt}\rho_h &= (r_h(\hat{x}) - \rho_h - (1 - \alpha(\hat{x})\hat{y})\rho_s)\rho_h, \\
\frac{d}{dt}\rho_s &= (r_s(\hat{y}) - (1 - \beta(\hat{y})\hat{x})\rho_h - \rho_s)\rho_s.
\end{align*}
\] (4.2)

We can obtain an explicit form of single Dirac mass steady states.

Lemma 4.1. Let \( \hat{x} \in [a, b], \hat{y} \in [c, d] \) and assume that \( 1 - (1 - \alpha(\hat{x})\hat{y})(1 - \beta(\hat{y})\hat{x}) \neq 0 \). Set

\[
\begin{align*}
\hat{\rho}_h := \frac{r_h(\hat{x}) - r_s(\hat{y})(1 - \alpha(\hat{x})\hat{y})}{1 - (1 - \alpha(\hat{x})\hat{y})(1 - \beta(\hat{y})\hat{x})}, \\
\hat{\rho}_s := \frac{r_s(\hat{y}) - r_h(\hat{x})(1 - \beta(\hat{y})\hat{x})}{1 - (1 - \alpha(\hat{x})\hat{y})(1 - \beta(\hat{y})\hat{x})}.
\end{align*}
\] (4.3)

Then \((\hat{n}_h = \hat{\rho}_h\delta_{(x=\hat{x})}, \hat{n}_s = \hat{\rho}_s\delta_{(y=\hat{y})})\) is a steady state of problem (4.1).

If the three conditions below hold

\[
\begin{align*}
1 - (1 - \alpha(\hat{x})\hat{y})(1 - \beta(\hat{y})\hat{x}) > 0, \\
r_h(\hat{x}) - r_s(\hat{y})(1 - \alpha(\hat{x})\hat{y}) > 0, \\
r_s(\hat{y}) - r_h(\hat{x})(1 - \beta(\hat{y})\hat{x}) > 0,
\end{align*}
\] (4.4)

then \( \hat{\rho}_h > 0, \hat{\rho}_s > 0 \) and \((\hat{n}_h, \hat{n}_s)\) is a linearly stable steady state of (4.2).

Proof. Single Dirac mass steady state solution yields

\[
\begin{align*}
r_h(\hat{x}) - \hat{\rho}_h - \hat{\rho}_s + \alpha(\hat{x})\hat{y}\hat{\rho}_s = 0, \\
r_s(\hat{y}) - \hat{\rho}_h - \hat{\rho}_s + \beta(\hat{y})\hat{x}\hat{\rho}_h = 0.
\end{align*}
\] (4.5)

An elementary calculation shows that \((\hat{\rho}_h, \hat{\rho}_s)\) is a steady state of (4.2) and the corresponding Jacobian matrix is given by

\[
\mathcal{J} = \begin{pmatrix}
-\hat{\rho}_h & -(1 - \alpha(\hat{x})\hat{y})\hat{\rho}_h \\
-\alpha(\hat{x})\hat{y}\hat{\rho}_s & -\hat{\rho}_s
\end{pmatrix}.
\] (4.6)

In view of (4.4), \( \text{tr}(\mathcal{J}) < 0, \det(\mathcal{J}) > 0 \) so that the two eigenvalues of \( \mathcal{J} \) are negative. Thus the linear stability of \((\hat{\rho}_h, \hat{\rho}_s)\) follows. \(\square\)
4.2 Linear stability of single Dirac mass steady states

The results below are concerned with the linear stability of single Dirac mass steady states among perturbations of particular forms.

**Theorem 4.2.** Let \( \hat{n}_h = \hat{\rho}_h \delta_{\{x = \hat{x}\}}, \hat{n}_s = \hat{\rho}_s \delta_{\{y = \hat{y}\}} \) be a steady state of (4.1) as in Lemma 4.1. Assume that (4.4) holds. Let \( x^*, y^* \) satisfy \( x^* \neq \hat{x}, y^* \neq \hat{y} \) and

\[
G_h(x^*) < 0, \quad G_s(y^*) < 0. \tag{4.7}
\]

Then \( (\hat{n}_h, \hat{n}_s) \) is linearly stable among perturbations starting by

\[
n_{h0} := \varepsilon_1 \delta_{\{x = x^*\}} + (\hat{\rho}_h + \varepsilon_2) \delta_{\{x = \hat{x}\}}, n_{s0} := \varepsilon_3 \delta_{\{y = y^*\}} + (\hat{\rho}_s + \varepsilon_4) \delta_{\{y = \hat{y}\}}.
\]

**Proof.** We linearize the system at \((\hat{n}_h, \hat{n}_s)\). For \( g_h(t, x) := n_h(t, x) - \hat{n}_h(x), g_s(t, y) := n_s(t, y) - \hat{n}_s(y) \) we obtain

\[
\begin{align*}
\partial_t g_h &= \begin{bmatrix} r_h(x) - \hat{\rho}_h - \hat{\rho}_s + \alpha(x) \int y \hat{n}_s \end{bmatrix} g_h - \hat{n}_h \int g_h + \hat{n}_s \int g_s - \hat{n}_s \int g_h, \\
\partial_t g_s &= -\int g_h + \beta(y) \int x g_h \hat{n}_s + \int r_s(y) - \hat{\rho}_h - \hat{\rho}_s + \beta(y) \int x \hat{n}_s g_s - \hat{n}_s \int g_s.
\end{align*}
\]

Note that \( g_h, g_s \) have the form

\[
g_h(t, x) = g_h^1(t) \delta_{\{x = x^*\}} + g_h^2(t) \delta_{\{x = \hat{x}\}}, \quad g_s(t, y) = g_s^1(t) \delta_{\{y = y^*\}} + g_s^2(t) \delta_{\{y = \hat{y}\}}.
\]

Therefore, we obtain

\[
\begin{align*}
\partial_t g_h^1 &= \begin{bmatrix} r_h(x^*) - \hat{\rho}_h - \hat{\rho}_s + \alpha(x^*) \hat{\rho}_s \end{bmatrix} g_h^1 - \hat{\rho}_h \int g_h^1 + \hat{\rho}_s \int g_h^2, \\
\partial_t g_h^2 &= \begin{bmatrix} r_s(y^*) - \hat{\rho}_h - \hat{\rho}_s + \beta(y^*) \hat{\rho}_s \end{bmatrix} g_h^2 - \hat{\rho}_h \int g_h^2 + \hat{\rho}_s \int g_h^1, \\
\partial_t g_s^1 &= -\hat{\rho}_h \int g_h^1 + \hat{\rho}_h \alpha(\hat{x}) y^* - 1 \int g_s^1 - \hat{\rho}_h \int g_h^2 + \hat{\rho}_h \alpha(\hat{\rho}_s(\hat{y}) x^* - 1) \int g_h^2 - \hat{\rho}_s g_s^1 + \hat{\rho}_s \beta(\hat{y}) \hat{x} - 1 \int g_h^2, \\
\partial_t g_s^2 &= \hat{\rho}_s \beta(\hat{y}) x^* - 1 \int g_h^1 - \hat{\rho}_s g_s^1 + \hat{\rho}_s \beta(\hat{y}) \hat{x} - 1 \int g_h^2 - \hat{\rho}_s g_s^2.
\end{align*}
\]

The corresponding matrix is given by

\[
\begin{pmatrix}
\begin{array}{cccc}
1 & 0 & 0 & 0 \\
0 & r_h(x^*) - \hat{\rho}_h - \hat{\rho}_s + \alpha(x^*) \hat{\rho}_s & 0 & 0 \\
-\hat{\rho}_h & r_s(y^*) - \hat{\rho}_h - \hat{\rho}_s + \beta(y^*) \hat{\rho}_s & -\hat{\rho}_h & \hat{\rho}_h (\alpha(\hat{x}) y^* - 1) \\
\hat{\rho}_s (\beta(\hat{y}) x^* - 1) & -\hat{\rho}_s & \hat{\rho}_s (\beta(\hat{y}) \hat{x} - 1) & -\hat{\rho}_s
\end{array}
\end{pmatrix}
\]

The eigenvalues of the above matrix are

\[
r_h(x^*) - \hat{\rho}_h - \hat{\rho}_s + \alpha(x^*) \hat{\rho}_s, \quad r_s(y^*) - \hat{\rho}_h - \hat{\rho}_s + \beta(y^*) \hat{\rho}_s
\]

and the two eigenvalues of the matrix \( J \) in (4.6). All are negative due to (4.7) and Lemma 4.1. Thus the stability of \((\hat{n}_h, \hat{n}_s)\) follows. \(\square\)

**Interpretations of Theorem 4.2:** With the notation (1.4), in view of (4.5), we have \( G_h(\hat{x}) = 0, G_s(\hat{y}) = 0 \). Also the conditions \( G_h(x^*) < 0, G_s(y^*) < 0 \) show that the phenotypes \( x^*, y^* \) cannot invade the stable equilibrium \((\hat{n}_h, \hat{n}_s)\). As a consequence, no new equilibrium can be reached but a mutant invading the resident population \((\hat{x}, \hat{y})\).
5 Evolutionary stable distributions (ESDs)

5.1 Sufficient conditions for monomorphic and dimorphic ESDs

Recall that from the definition 1.2, an ESD \((\hat{n}_h, \hat{n}_s)\) is characterised by the conditions (1.5)–(1.6). Graphically, we plot the curve \(x \in [a, b] \mapsto (Z = \alpha(x), W = r_h(x))\) by the blue curve and the red straight line \(Z \hat{\Sigma}_s + W = \hat{\rho}_h + \hat{\rho}_s\); see Figure 1. Then the conditions (1.5)–(1.6) for \(\hat{n}_h\) mean that the blue curve must be below the red line and that the pair \((\alpha(x), r_h(x))\) for all \(x \in I := \text{supp} \hat{n}_h\) are the coordinates of the intersection points between the blue curve and the red line. Similarly, we have the same illustration for \(\hat{n}_s\).

If \(\alpha\) (resp. \(r_h\)) is strictly monotone and if \(r_h(\alpha^{-1}(z))\) (resp. \(\alpha(r_h^{-1})\)) is concave on \([0, \alpha(a)]\) (resp. \([0, r_h(b)]\)). Then there is at most one intersection point satisfying the conditions (1.5)–(1.6) for \(\hat{n}_h\). Thus, the strict monotonicity of \(\alpha\) implies that \(I\) is a singleton, hence \(\hat{n}_h\) is monomorphic. In the case where \(r_h(\alpha^{-1}(z))\) (resp. \(\alpha(r_h^{-1})\)) is convex, \(I\) contains at most two points, thus \(\hat{n}_h\) is at most dimorphic. We state these results in the following theorem.

**Theorem 5.1.** (i) Assume that either \(\alpha\) is strictly monotone and \(r_h(\alpha^{-1})\) is concave on \([0, \alpha(a)]\) or \(r_h\) is strictly monotone and \(\alpha(r_h^{-1})\) is concave on \([0, r_h(b)]\). Then \(\hat{n}_h\) is monomorphic for any ESD \((\hat{n}_h, \hat{n}_s)\) (if it exists).

(ii) Assume that either \(\alpha\) is strictly monotone and \(r_h(\alpha^{-1})\) is convex on \([0, \alpha(a)]\) or \(r_h\) is strictly monotone and \(\alpha(r_h^{-1})\) is convex on \([0, r_h(b)]\). Then \(\hat{n}_h\) is at most dimorphic for any ESD \((\hat{n}_h, \hat{n}_s)\) (if it exists).

(iii) The same conclusions as in items (i), (ii) hold for \(\hat{n}_s\) provided that similar assumptions on \(r_s, \beta\) are supposed.

By Remark 1.3, we can also check if an ESD is monomorphic or dimorphic by studying the set of maximum points of the corresponding fitness functions.

**Theorem 5.2.** The following conclusions hold for any (non-negative) ESD \((\hat{n}_h, \hat{n}_s)\) (if it exists).

(i) If \(r_h, \alpha\) are strictly convex, then \(\hat{n}_h\) is at most dimorphic.
(ii) If \( r_h, \alpha \) are strictly concave, then \( \hat{n}_h \) is monomorphic or vanishes.

(iii) The same conclusions as in items (i), (ii) hold for \( \hat{n}_s \) provided that similar assumptions on \( r_s \) and \( \beta \) are supposed.

Proof. The theorem follows from basic properties of the maximum points of a convex, or concave functions.

The next result is concerned with the existence and uniqueness of ESDs. We also show that the unique ESD is monomorphic and that the concentration points are endpoints of the intervals \((a,b), (c,d)\). For simplicity, set \((a,b) := (1,2), (c,d) := (3,4)\). We will suppose two of the following assumptions:

\( (H_1) \) \( r'_h(x) + 3\alpha'(x) \hat{r}_s < 0 \) for all \( x \in (1,2) \) and \( \beta(y) \geq 1 \) for all \( y \in (3,4) \).

\( (H_2) \) \( r'_h(x) + 4\alpha'(x) \hat{r}_s > 0 \) for all \( x \in (1,2) \) and \( \beta(y) \leq 1/2 \) for all \( y \in (3,4) \).

\( (H_3) \) \( \beta = \beta^* > 0 \) is constant and \( r_s \) is strictly decreasing.

\( (H_4) \) \( \beta \) is strictly increasing and \( r_s = r_s^* > 0 \) is constant.

**Theorem 5.3** (Existence and uniqueness of ESDs). Set \((a,b) := (1,2), (c,d) := (3,4)\). Suppose that \( r_h, \alpha \in C([1,2]) \cap C^1([1,2]), r_s, \beta \in C([3,4]) \cap C^1([3,4])\). Suppose furthermore that the pair \((\hat{n}_h, \hat{n}_s)\) below is non-negative and that the assumptions (depending on situations) mentioned below hold. Then there exists a unique (non-negative) ESD and it is monomorphic or vanishes.

(i) Under the assumptions \((H_1)\) and \((H_3)\), the unique ESD is given by

\[
\hat{n}_h = \frac{r_s(3)(3\alpha(1) - 1)}{1 + (3\alpha(1) - 1)(1 - \beta^*)} \delta_{\{x=1\}}, \quad \hat{n}_s = \frac{r_s(3)}{1 + (3\alpha(1) - 1)(1 - \beta^*)} \delta_{\{y=3\}}.
\]

(ii) Under the assumptions \((H_2)\) and \((H_3)\), the unique ESD is given by

\[
\hat{n}_h = \frac{r_h(2) - r_s(3)}{2\beta^*} \delta_{\{x=2\}}, \quad \hat{n}_s = \frac{r_s(3) - r_h(2)(1 - 2\beta^*)}{2\beta^*} \delta_{\{y=3\}}.
\]

(iii) Under the assumptions \((H_1)\) and \((H_4)\), the unique ESD is given by

\[
\hat{n}_h = \frac{r^*(4\alpha(1) - 1)}{1 + (4\alpha(1) - 1)(1 - \beta(4))} \delta_{\{x=1\}}, \quad \hat{n}_s = \frac{r^*_s}{1 + (4\alpha(1) - 1)(1 - \beta(4))} \delta_{\{y=4\}}.
\]

(iv) Under the assumptions \((H_2)\) and \((H_4)\), the unique ESD is given by

\[
\hat{n}_h = \frac{r_h(2) - r^*_s}{2\beta(4)} \delta_{\{x=2\}}, \quad \hat{n}_s = \frac{r^*_s - r_h(2)(1 - 2\beta(4))}{2\beta(4)} \delta_{\{y=4\}}.
\]

Proof. We only prove (i). The other cases can be proved in the same way. First note that under the assumptions \((H_1)\) and \((H_3)\), \( \beta = \beta^* \geq 1 \). We have \( G_s(y) = r_s(y) - \hat{\rho}_h - \hat{\rho}_s + \beta^* \Sigma_h \) is strictly decreasing (by \((H_3)\)) so that it attains its global maximum only at \( y = 3 \). This, in view of Remark 1.3, yields that \( \text{supp} \hat{n}_s = \{3\} \). As a consequence, \( G_s(3) = 0 \) so that

\[
r_s(3) - \hat{\rho}_s = \hat{\rho}_h - \beta^* \int_1^2 x\hat{n}_h \leq \hat{\rho}_h - \beta^* \int_1^2 \hat{n}_h = \hat{\rho}_h - \beta^* \hat{\rho}_h \leq 0.
\]
Therefore,
\[ 3r_s(3) \leq 3\hat{\rho}_s \leq \int_0^4 y\hat{\gamma}_s = \hat{\Sigma}_s. \]

This together with the property that \( \alpha' \leq 0 \) implies that
\[ G'_h(x) = r'_h(x) + \alpha'(x)\hat{\Sigma}_s \leq r'_h(x) + 3\alpha'(x)r_s(3) < 0 \text{ for all } x \in (1, 2), \]
where we used the hypothesis \((H_1)\) in the last inequality. Consequently, \( G_h \) is strictly decreasing on \([1, 2]\) so that it has only one maximum point \( x = 1 \). Hence \( \hat{n}_h = \{1\} \). The expression of \((\hat{n}_h, \hat{n}_s)\) follows from \((4.3)\) with \((x, y) := (1, 3)\).

In next theorem, we compute all ESDs explicitly. We also see that the dimorphic situation may occur. For simplicity, we only consider the dimorphic distribution for hematopoietic stem cells.

**Theorem 5.4** (Explicit formulas of all ESDs). Set \((a, b) := (1, 2), (c, d) := (3, 4)\). Assume that \( r_h \) is strictly convex and that \( \alpha \) is convex. Suppose furthermore that \((H_3)\) is satisfied (i.e. \( \beta = \beta^* \) is a positive constant and \( r_s \) is strictly decreasing). Then all ESDs are given by

1. \((\hat{n}_h = \hat{\rho}_h\delta_{(x=1)}, \hat{n}_s = \hat{\rho}_s\delta_{(y=3)}\) with
   \[ \hat{\rho}_h = \frac{r_s(3)(3\alpha(1) - 1)}{1 + (3\alpha(1) - 1)(1 - \beta^*)}, \quad \hat{\rho}_s = \frac{r_s(3)}{1 + (3\alpha(1) - 1)(1 - \beta^*)}, \]
   provided that \( \hat{\rho}_h \geq 0, \hat{\rho}_s \geq 0 \) and
   \[ r_h(2) \leq \frac{3\alpha(1)r_s(3)}{1 + (3\alpha(1) - 1)(1 - \beta^*)}. \] (5.1)

2. \((\hat{n}_h = \hat{\rho}_h\delta_{(x=2)}, \hat{n}_s = \hat{\rho}_s\delta_{(y=3)}\) with
   \[ \hat{\rho}_h = \frac{r_s(2) - r_s(3)}{2\beta^*}, \quad \hat{\rho}_s = \frac{r_s(3) - r_h(2)(1 - 2\beta^*)}{2\beta^*}, \]
   provided that \( \hat{\rho}_h \geq 0, \hat{\rho}_s \geq 0 \) and
   \[ r_h(2) \geq 3\alpha(1)\frac{r_s(3) - r_h(2)(1 - 2\beta^*)}{2\beta^*}. \]

3. \((\hat{n}_h = \hat{\rho}_{h1}\delta_{(x=1)} + \hat{\rho}_{h2}\delta_{(x=2)}, \hat{n}_s = \hat{\rho}_s\delta_{(y=3)}\) with
   \[ \hat{\rho}_{h1} = 2r_h(2)\frac{3\alpha(1) - 1}{3\alpha(1)} - \frac{r_h(2) - r_s(3)}{\beta^*}, \]
   \[ \hat{\rho}_{h2} = \frac{r_h(2) - r_s(3)}{\beta^*} - r_h(2)\frac{3\alpha(1) - 1}{3\alpha(1)} \quad \hat{\rho}_s = \frac{r_h(2)}{3\alpha(1)}, \]
   provided that \( \hat{\rho}_{h1} \geq 0, \hat{\rho}_{h2} \geq 0, \hat{\rho}_s \geq 0. \)

**Remark 5.5.** We can also prove similar results as in Theorem 5.4 when we suppose the hypothesis \((H_4)\) instead of \((H_3)\).
Proof. First note that $G_h(x)$ is strictly convex. Thus $G_h$ attains its global maximum only at endpoints of the interval $[1, 2]$. Note also that $G_s(y) = r_s(y) - \rho_h - \rho_s + \beta^* \Sigma_s$ is strictly decreasing so that $y = 3$ is its unique maximum point. The above observations and Remark 1.3 imply that $\text{supp } \hat{n}_s = 3$ and either $\text{supp } \hat{n}_h = \{1\}$ or $\text{supp } \hat{n}_h = \{2\}$ or $\text{supp } \hat{n}_h = \{1, 2\}$.

(i) The case $\text{supp } \hat{n}_h = \{1\}, \text{supp } \hat{n}_s = \{3\}$. The expressions of $\hat{n}_h, \hat{n}_s$ follows from (4.3) with $\hat{x} = 1, \hat{y} = 3$. Because of the convexity of $G_h$ and the decreasing monotonicity of $G_s$, the condition (1.6) is equivalent to $G_h(1) \geq G_h(2)$ which implies (5.1). Similarly, Item (ii) — the case $\text{supp } \hat{n}_h = \{2\}, \text{supp } \hat{n}_s = \{3\}$ — can be treated in the same way.

(ii) The case $\text{supp } \hat{n}_h = \{1, 2\}, \text{supp } \hat{n}_s = \{3\}$. The pair $(\hat{n}_h, \hat{n}_s)$ have the form $\hat{n}_h = \hat{\rho}_h \delta_{\{x=1\}} + \hat{\rho}_h \delta_{\{x=2\}}, \quad \hat{n}_s = \hat{\rho}_s \delta_{\{y=3\}}$.

Thus we have

$$
\hat{n}_h = \hat{\rho}_h \delta_{\{x=1\}} + \hat{\rho}_h \delta_{\{x=2\}}, \quad \hat{n}_s = \hat{\rho}_s \delta_{\{y=3\}}.
$$

The conditions in the definition 1.2 are equivalent to

$$
G_h(1) = G_h(2) = 0, \quad G_s(3) = 0,
$$

that is

$$
\begin{cases}
-\hat{\rho}_h - \hat{\rho}_h - \hat{\rho}_s + 3\alpha(1)\hat{\rho}_s = 0, \\
\hat{r}_h(2) = \hat{\rho}_h - \hat{\rho}_h - \hat{\rho}_s = 0, \\
\hat{r}_s(3) = \hat{\rho}_h - \hat{\rho}_h - \hat{\rho}_s + \beta^*(\hat{\rho}_h + 2\hat{\rho}_h) = 0.
\end{cases}
$$

Solving this system yields the expressions of $\hat{\rho}_h, \hat{\rho}_h, \hat{\rho}_s$.

\[ \square \]

Example: Let us consider a concrete example for $r_h, \alpha, r_s, \beta$:

$$
\hat{r}_h(x) = (x - 1)^2, \quad \alpha(x) = 2 - x, \quad r_s(y) = \frac{1}{2} + \frac{1}{4}(3 - y), \quad \beta = 0.5.
$$

According to Theorem 5.4, there are only two positive ESDs of (4.1) which are

- Monomorphic distribution:

$$
\hat{n}_h(x) = \frac{1}{2} \delta_{\{x=1\}}, \quad \hat{n}_s(y) = \frac{1}{2} \delta_{\{y=3\}}.
$$

- Dimorphic distribution:

$$
\hat{n}_h(x) = \frac{1}{3} \delta_{\{x=1\}} + \frac{1}{3} \delta_{\{x=2\}}, \quad \hat{n}_s(y) = \frac{1}{3} \delta_{\{y=3\}}.
$$

5.2 An entropy functional and the partial uniqueness of ESDs under homogeneity assumptions on stromal cells

In this section, we suppose that all stromal cells have some similar properties. More precisely, we consider the case where the contribution of each phenotype $y$ in the message from stromal cells to HSCs and the sensitivity of stromal cells to the message from HSCs are the same. Mathematically, assume that the weight function $\psi_s(y) = 1$, and that $\beta > 0$ is constant. Suppose furthermore that $\alpha(x) = b - x, \psi_h(x) = x$. Problem (1.1) becomes

$$
\begin{cases}
\partial_t n_h(t, x) = \left[ r_h(x) - \rho_h(t) - \rho_s(t) + (b - x) \int n_s(t, y)dy \right] n_h, \quad x \in (a, b), t > 0, \\
\partial_t n_s(t, y) = \left[ r_s(y) - \rho_h(t) - \rho_s(t) + \beta \int x n_h(t, x)dx \right] n_s \quad y \in (c, d), t > 0.
\end{cases}
$$
Below we state a result about the partially uniqueness of ESD.

**Theorem 5.6** (Partial uniqueness results of ESDs). Assume that \((\hat{n}_h, \hat{n}_s)\) and \((\tilde{n}_h, \tilde{n}_s)\) are two (non-negative) ESDs of the system (5.2). Assume further that \(\beta\) is a positive constant satisfying

\[(\beta(1-b)+1)^2 < 4\beta.\]  \(5.3\)

Then

\[
\hat{\rho}_h = \tilde{\rho}_h =: H, \quad \hat{\rho}_s = \tilde{\rho}_s =: S, \quad \hat{\rho}_h - \tilde{\rho}_h =: \rho\]

\[
\int r_h(x)\hat{n}_h - S \int \hat{n}_h = \int r_h(x)\tilde{n}_h - S \int \tilde{n}_h, \quad \int r_s(y)\hat{n}_s - \beta S \int \hat{n}_h = \int r_s(y)\tilde{n}_s - \beta S \int \tilde{n}_h. \quad \int (b-x)\hat{n}_h = \int (b-x)\tilde{n}_h. \] \(5.4\) \(5.5\) \(5.6\)

Moreover,

(i) If \(r_s\) is strictly decreasing, then \(\hat{n}_s = \tilde{n}_s\) either is monomorphic concentrated at \(y = c\) or vanishes. Also we have

\[
\int r_h(x)\hat{n}_h = \int r_h(x)\tilde{n}_h. \quad \int x\hat{n}_h = \int x\tilde{n}_h. \] \(5.7\) \(5.8\)

(ii) In addition to (i), if \(\hat{n}_s\) does not vanish, then

\[
\int x\hat{n}_h = \int x\tilde{n}_h. \] \(5.9\)

**Proof.** The definition of ESD and the non-negativity of \(\hat{n}_h\) yield that

\[
0 \geq \int \left[ r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b-x) \int \hat{n}_s \right] \hat{n}_h \]

\[
= \int \left\{ \left[ r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b-x) \int \hat{n}_s \right] - \left[ r_h(x) - \tilde{\rho}_h - \tilde{\rho}_s + (b-x) \int \tilde{n}_s \right] \right\} \hat{n}_h = \int \left[ (\hat{\rho}_h - \tilde{\rho}_h) + (\hat{\rho}_s - \tilde{\rho}_s) \right] \hat{n}_h. \]

\(5.9\)

Similarly, it follows from the inequality

\[
\int \left[ r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b-x) \int \hat{n}_s \right] \tilde{n}_h \leq 0, \]

that

\[
[(\hat{\rho}_h - \tilde{\rho}_h) + (\hat{\rho}_s - \tilde{\rho}_s)] \hat{n}_h + (\hat{\rho}_s - \tilde{\rho}_s) \int (b-x)\hat{n}_h \leq 0. \]

\(5.10\)

Summing up (5.9) and (5.10), we obtain

\[
(\hat{\rho}_h - \tilde{\rho}_h)^2 + (\hat{\rho}_s - \tilde{\rho}_s)(\hat{\rho}_h - \tilde{\rho}_h) + (\hat{\rho}_s - \tilde{\rho}_s) \int (b-x)(\hat{n}_h - \tilde{n}_h) \leq 0. \]

\(5.11\)

Similarly, we deduce from the inequality

\[
\int \left[ r_s(y) - \hat{\rho}_h - \hat{\rho}_s + \beta \int x\tilde{n}_h \right] \hat{n}_s + \int \left[ r_s(y) - \tilde{\rho}_h - \tilde{\rho}_s + \beta \int x\hat{n}_h \right] \tilde{n}_s \leq 0, \]

\(5.12\)
that
\[(\hat{\rho}_s - \tilde{\rho}_s)^2 + (\hat{\rho}_s - \tilde{\rho}_s)(\hat{\rho}_h - \tilde{\rho}_h) + \beta \int x(\hat{n}_h - \tilde{n}_h)(\hat{\rho}_s - \tilde{\rho}_s) \leq 0.\]

This together with (5.11) yields
\[\beta(\hat{\rho}_h - \tilde{\rho}_h)^2 + \beta(1 - b)(\hat{\rho}_h - \tilde{\rho}_h)(\hat{\rho}_s - \tilde{\rho}_s) + (\hat{\rho}_s - \tilde{\rho}_s)^2 \leq 0.\]

Equivalently,
\[\left(\sqrt{\beta}(\hat{\rho}_h - \tilde{\rho}_h) + \beta(1 - b) + 1\right)(\hat{\rho}_h - \tilde{\rho}_h)(\hat{\rho}_s - \tilde{\rho}_s) + (\hat{\rho}_s - \tilde{\rho}_s)^2 \leq 0. \quad (5.13)\]

Therefore, the hypothesis (5.3) yields that the equality in (5.13) (also in all above inequalities) holds. Thus each term in (5.13) vanishes so that (5.4) follows. The identities (5.5), (5.6) follow from the fact that
\[
\int \left[r_h(x) - \tilde{\rho}_h - \hat{\rho}_s + (b - x) \int \tilde{n}_h\right] \tilde{n}_h = \int \left[r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b - x) \int \hat{n}_h\right] \hat{n}_h,
\]
\[
\int \left[r_s(y) - \hat{\rho}_h - \hat{\rho}_s + \beta \int x\hat{n}_h\right] \hat{n}_s = \int \left[r_s(y) - \tilde{\rho}_h - \hat{\rho}_s + \beta \int x\tilde{n}_h\right] \tilde{n}_s, \quad (5.14)
\]
respectively.

(i) If \(r_s\) is strictly decreasing on \([c, d]\), the fitness function \(G_s\) attains its global maximum at \(y = c\). Thus \(\hat{n}_s\) and \(\hat{n}_s\) either vanish or are the Dirac mass concentrated at \(y = c\). As a consequence we have \(\hat{n}_s = \tilde{n}_s = S\delta\{y = c\}\) with \(S \geq 0\). Using the formula for \(\hat{n}_s\), (5.5) and (5.6), we obtain (5.7)

(ii) The case \(\hat{n}_s = \tilde{n}_s = S\delta\{y = c\}\) with \(S > 0\). Identity (5.8) follows from (5.6).

**Theorem 5.7** (Entropy functional). Let \((\hat{n}_h, \hat{n}_s)\) be an (non-negative) ESD of problem (5.2). Set
\[E(t) := \beta \int n_h - \beta \int \hat{n}_h \ln(n_h) + \int n_s - \int \hat{n}_s \ln(n_s).\]

Then \(E\) is an entropy functional for (5.2), i.e., \(\frac{d}{dt}E(t) \leq 0\) provide that \(\beta\) is a positive constant satisfying
\[(\beta(1 - b) + 1)^2 \leq 4\beta.\]

Proof. Set
\[E_1 := \int n_h - \int \hat{n}_h \ln(n_h).\]
We have
\[
\frac{d}{dt}E_1(t) = \int \frac{(n_h)_1(n_h - \hat{n}_h)}{n_h} \\
= \int \left[ r_h(x) - \rho_h - \rho_s + (b - x) \int n_s \right] (n_h - \hat{n}_h) \\
= \int \left[ (r_h(x) - \rho_h - \rho_s + (b - x) \int n_s) - (r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b - x) \int \hat{n}_s) \right] (n_h - \hat{n}_h) \\
+ \int \left[ r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b - x) \int \hat{n}_s \right] (n_h - \hat{n}_h) \\
= -(\rho_h - \hat{\rho}_h)^2 - (\rho_h - \hat{\rho}_h)(\rho_s - \hat{\rho}_s) + \int (b - x)(n_h - \hat{n}_h) \int (n_s - \hat{n}_s) \\
+ \int \left[ r_h(x) - \hat{\rho}_h - \hat{\rho}_s + (b - x) \int \hat{n}_s \right] n_h \\
\leq -(\rho_h - \hat{\rho}_h)^2 - (\rho_h - \hat{\rho}_h)(\rho_s - \hat{\rho}_s) + \int (b - x)(n_h - \hat{n}_h) \int (n_s - \hat{n}_s).
\]

In the above inequality, we have used the definition of ESDs and the non-negativity of \( n_h \) (cf. Proposition 3.1). Similarly, for \( E_2 := \int n_s - \int \hat{n}_s \ln(n_s) \), we have
\[
\frac{d}{dt}E_2(t) \leq - (\rho_h - \hat{\rho}_h)^2 - (\rho_h - \hat{\rho}_h)(\rho_s - \hat{\rho}_s) + \beta \int x(n_h - \hat{n}_h) \int (n_s - \hat{n}_s).
\]

Therefore, as \( E = \beta E_1 + E_2 \), we have
\[
\frac{dE}{dt} \leq -\beta(\rho_h - \hat{\rho}_h)^2 - [\beta(1 - b) + 1](\rho_h - \hat{\rho}_h)(\rho_s - \hat{\rho}_s) - (\rho_s - \hat{\rho}_s)^2 \leq 0,
\]
where the last inequality follows from the negativity of the discriminant of this polynomial:
\[
(\beta(1 - b) + 1)^2 - 4\beta \leq 0.
\]

\[\square\]

6 Dynamics of the fittest traits: an asymptotic point of view

We are interested in the dynamics of HSCs and stromal cells with initial data close to a monomorphic state and, in particular, in tracking the movements of concentration point towards an ESD. We follow the analysis in [15] and perform the time change variable \( \tau = t\varepsilon \) to accelerate time and observe the dynamics. The parameter \( \varepsilon \) is also used to measure how close is the distribution from the Dirac distribution.

The change of variable \( t \mapsto \tau \) converts the system (4.1) to:
\[
\begin{align*}
\partial_\tau n_h^x(\tau, x) &= \frac{1}{\varepsilon} \left[ r_h(x) - \rho_h^x(\tau) - \rho_s^x(\tau) + \alpha(x) \Sigma_s(\tau) \right] n_h^x, \quad x \in (a, b), \tau > 0, \\
\partial_\tau n_s^x(\tau, y) &= \frac{1}{\varepsilon} \left[ r_s(y) - \rho_h^x(\tau) - \rho_s^x(\tau) + \beta(y) \Sigma_h(\tau) \right] n_s^x, \quad y \in (c, d), \tau > 0.
\end{align*}
\]
This system is completed with the initial data

\[ n_h^\varepsilon(0, x) = n_{h0}(x) > 0, \quad n_s^\varepsilon(0, y) = n_{s0}(y) > 0. \]

Rather than working on \( n_h^\varepsilon, n_s^\varepsilon \) directly, we define as usual [8, 15, 22] the functions \( u^\varepsilon, v^\varepsilon \) given by

\[ u^\varepsilon(\tau, x) = \varepsilon \ln(n_h^\varepsilon(\tau, x)), \quad u_0^\varepsilon(x) = \varepsilon \ln(n_{h0}(x)), \]
\[ v^\varepsilon(\tau, y) = \varepsilon \ln(n_s^\varepsilon(\tau, y)), \quad v_0^\varepsilon(y) = \varepsilon \ln(n_{s0}(y)). \]

The functions \( u^\varepsilon, v^\varepsilon \) satisfy

\[
\begin{align*}
\partial_\tau u^\varepsilon(\tau, x) & = r_h(x) - \rho_h^\varepsilon(\tau) - \rho_s^\varepsilon(\tau) + \alpha(x) \int y n_s^\varepsilon(\tau, y), & \quad x \in (a, b), \tau > 0, \\
\partial_\tau v^\varepsilon(\tau, y) & = r_s(y) - \rho_h^\varepsilon(\tau) - \rho_s^\varepsilon(\tau) + \beta(y) \int x n_h^\varepsilon(\tau, x), & \quad y \in (c, d), \tau > 0.
\end{align*}
\tag{6.1}
\]

Our purpose is to study the behaviour of \( u^\varepsilon, v^\varepsilon \) as \( \varepsilon \to 0 \) (at least with subsequences). In order to guarantee the existence of a global solution, suppose that (3.1) is fulfilled. Thus, under the assumption that \( \rho_h^0 + \rho_s^0 \) is uniformly bounded, Proposition 3.1 yields that there exists \( (\hat{n}_h, \hat{n}_s) \) such that as \( \varepsilon \to 0 \) (after extracting subsequences),

\[
\begin{align*}
n_h^\varepsilon & \overset{\ast}{\to} \hat{n}_h \text{ in } L^\infty(0, \infty; \mathcal{M}([a, b])), \\
n_s^\varepsilon & \overset{\ast}{\to} \hat{n}_s \text{ in } L^\infty(0, \infty; \mathcal{M}([c, d])).
\end{align*}
\tag{6.2}
\]

**Theorem 6.1.** Assume that \( r_h, \alpha \in C^1([a, b]), r_s, \beta \in C^1([c, d]) \) and that

\[
\rho_h^0 + \rho_s^0 + \|u_0^\varepsilon\|_{C^1([a, b])} + \|v_0^\varepsilon\|_{C^1([c, d])} \leq K_0. \tag{6.4}
\]

Then

(i) The function \( u^\varepsilon \) (resp. \( v^\varepsilon \)) is uniformly Lipschitz continuous on \([0, T] \times [a, b] \) (resp. \([0, T] \times [c, d]) for all \( T > 0 \).

(ii) As \( \varepsilon \to 0 \) (after extractions of subsequences), the functions \( u^\varepsilon \) and \( v^\varepsilon \) converge locally uniformly to Lipschitz continuous functions \( u \) and \( v \). Moreover, \( u, v \) satisfy

\[
\begin{align*}
\begin{cases}
u(\tau, x) = u_0(x) + r_h(x) \tau - \int_0^\tau \int \hat{n}_h - \int_0^\tau \int \hat{n}_s + \alpha(x) \int_0^\tau \int y \hat{n}_s, \\
v(\tau, y) = v_0(y) + r_s(y) \tau - \int_0^\tau \int \hat{n}_h - \int_0^\tau \int \hat{n}_s + \beta(y) \int_0^\tau \int x \hat{n}_h,
\end{cases}
\tag{6.5}
\end{align*}
\]

Furthermore we have for a.e. \( \tau, \)

\[
\text{supp } \hat{n}_h(\tau, \cdot) \subset \{u(\tau, \cdot) = 0\}, \quad \text{supp } \hat{n}_s(\tau, \cdot) \subset \{v(\tau, \cdot) = 0\}.
\]

**Proof.** (i) First note that by Proposition 3.1, there is a constant \( K_1 > 0 \) such that

\[
\|n_h^\varepsilon\|_{L^\infty(0, \infty; L^1([a, b]))} + \|n_s^\varepsilon\|_{L^\infty(0, \infty; L^1([c, d]))} \leq K_1. \tag{6.6}
\]
Differentiating the equation for $u^\varepsilon$ with respect to $x$ yields
\[ \partial_\tau u^\varepsilon_x(\tau, x) = r'_h(x) + \alpha'(x) \int y n^\varepsilon_x(\tau, y) dy. \] (6.7)

Thus, using (6.6), we obtain $|\partial_\tau u^\varepsilon_x(\tau, x)| \leq |r'_h| + |\alpha'| dK_1$ so that
\[ |u^\varepsilon_x(\tau, x)| \leq K_0 + (|r'_h| + |\alpha'| dK_1) \tau. \]

On the other hand, in view of (6.1), we have
\[ |\partial_\tau u^\varepsilon_x(\tau, x)| \leq \bar{r}_h + 2K_1 + \alpha dK_1. \]

Hence $u^\varepsilon$ is uniformly Lipschitz continuous on $[0, \tau] \times [a, b]$. Similarly, the same property holds for $v^\varepsilon$.

(ii) Using the point (i) and the Arzelà–Ascoli Theorem, we may extract subsequences $(u^\varepsilon, v^\varepsilon)$ which converge as indicated in the statement. The equations for $u$ and $v$ are obtained by passing to the limit in (6.1). Moreover, $u, v$ cannot take positive values. Otherwise $(\rho_h^\varepsilon, \rho_s^\varepsilon)$ blows up in the limit as $\varepsilon$ vanishes and this is in contradiction with (6.6). \qed

6.1 Monomorphic states

We provide sufficient conditions so that $(\hat{n}_h, \hat{n}_s)$ defined in (6.2), (6.3) is a monomorphic state.

**Theorem 6.2.** Let all hypotheses as in Theorem 6.1 hold. Suppose furthermore that
\[ \begin{aligned}
& u^\varepsilon_{xx} \leq -K^*, \quad v^\varepsilon_{yy} \leq -K^*, \\
& r''_h(x) \leq 0, \quad \alpha''(x) \leq 0, \quad r''_s(y) \leq 0, \quad \beta''(y) \leq 0.
\end{aligned} \] (6.8)

Then, in the distributional sense
\[ u_{xx} \leq -K^*, \quad v_{yy} \leq -K^*. \]

Thus for all $\tau$, the functions $u(\tau, \cdot), v(\tau, \cdot)$ are concave so that they have a unique maximum point. As a consequence, $\hat{n}_h, \hat{n}_s$ have the form
\[ \hat{n}_h(\tau, x) = \hat{\rho}_h(\tau) \delta_{\{x = \hat{x}(\tau)\}}, \quad \hat{n}_s(\tau, y) = \hat{\rho}_s(\tau) \delta_{\{y = \hat{y}(\tau)\}}. \]

Moreover,
\[ \begin{aligned}
& \text{If } \hat{\rho}_h(\tau) > 0, \text{ then } \max_x u(\tau, x) = u(\tau, \hat{x}(\tau)) = 0, \\
& \text{If } \hat{\rho}_s(\tau) > 0, \text{ then } \max_y v(\tau, y) = v(\tau, \hat{y}(\tau)) = 0.
\end{aligned} \]

**Proof.** Differentiating twice the equation of $u^\varepsilon$, we obtain
\[ \partial_\tau u^\varepsilon_{xx}(\tau, x) = r''_h(x) + \alpha''(x) \int y n^\varepsilon_x(\tau, y) dy \leq 0. \]

Thus $u^\varepsilon_{xx}(\tau, x) \leq u^\varepsilon_{xx}(\tau = 0, x) \leq -K^*$. Therefore $u_{xx} \leq -K^*$. Similarly, $v_{yy} \leq -K^*$. Hence the theorem follows. \qed

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6.2 Equations for concentration points

In this section we derive the equations for the concentration point $\hat{x}(\tau), \hat{y}(\tau)$. Our equations are valid until the time $T^*$ where $\hat{\rho}_h(\tau) > 0, \hat{\rho}_s(\tau) > 0$ and that $\dot{x}(\tau), \dot{y}(\tau)$ do not touch the boundary and that $\dot{x}, \dot{y}$ are smooth enough (see Remark 6.3 below for the regularity of $\dot{x}, \dot{y}$). For all $\tau \in (0, T^*)$ we have $\hat{x}(\tau) \in (a, b)$ is the maximum point of $u(\tau, \cdot)$ on $[a, b]$. It follows that $u_x(\tau, \hat{x}(\tau)) = 0$ so that

$$u_x(\tau, \hat{x}(\tau)) + u_{xx}(\tau, \hat{x}(\tau))\dot{x} = 0 \quad \text{with} \quad \dot{x} := d\hat{x}/d\tau.$$ 

This implies

$$\dot{x}(\tau) = -\frac{1}{u_{xx}(\tau, \hat{x}(\tau))} \left[r'_h(\hat{x}(\tau)) + \alpha'(\dot{x}(\tau)) \int y \hat{\mu}_s \right],$$

$$\dot{y}(\tau) = -\frac{1}{u_{yy}(\tau, \hat{y}(\tau))} \left[r'_s(\hat{y}(\tau)) + \alpha'(\dot{x}(\tau))\beta(\dot{y}(\tau)) \hat{\rho}_s(\tau) \right].$$  

(6.9)

Similarly, we have

$$\dot{x}(\tau) = -\frac{1}{u_{xx}(\tau, \hat{x}(\tau))} \left[r'_h(\hat{x}(\tau)) + \alpha'(\dot{x}(\tau))\beta(\dot{y}(\tau)) \hat{\rho}_h(\tau) \right],$$

$$\dot{y}(\tau) = -\frac{1}{u_{yy}(\tau, \hat{y}(\tau))} \left[r'_s(\hat{y}(\tau)) + \beta'(\dot{y}(\tau))\hat{x}(\tau) \hat{\rho}_s(\tau) \right].$$  

(6.10)

The equations (6.9) and (6.10) describe the dynamics of $\dot{x}(\tau), \dot{y}(\tau)$. We also can obtain a more explicit form of (6.9) and (6.10) by representing $\hat{\rho}_h, \hat{\rho}_s$ in terms of $\dot{x}, \dot{y}$. To that purpose, we first notice that $u(\tau, \hat{x}(\tau)) = 0$ for $\tau \in [0, T^*)$ so that

$$0 = \frac{du(\tau, \hat{x}(\tau))}{d\tau} = u_x(\tau, \hat{x}(\tau)) = r_h(\hat{x}(\tau)) - \hat{\rho}_h(\tau) - \hat{\rho}_s(\tau) + \alpha(\dot{x}(\tau))\dot{y}(\tau)\hat{\rho}_s(\tau).$$

Similarly,

$$r_s(\dot{y}(\tau)) - \hat{\rho}_h(\tau) - \hat{\rho}_s(\tau) + \beta(\dot{y}(\tau))\dot{x}(\tau)\hat{\rho}_h(\tau) = 0.$$ 

Therefore, under the assumption that $1 - (1 - \alpha(\dot{x}(\tau))\dot{y}(\tau))(1 - \beta(\dot{y}(\tau))\dot{x}(\tau)) \neq 0$, we have

$$\hat{\rho}_h(\tau) = \frac{r_h(\hat{x}(\tau)) - r_s(\dot{y}(\tau))(1 - \beta(\dot{y}(\tau))\dot{x}(\tau))}{1 - (1 - \alpha(\dot{x}(\tau))\dot{y}(\tau))(1 - \beta(\dot{y}(\tau))\dot{x}(\tau))},$$

$$\hat{\rho}_s(\tau) = \frac{r_s(\dot{y}(\tau)) - r_s(\dot{x}(\tau))(1 - \beta(\dot{y}(\tau))\dot{x}(\tau))}{1 - (1 - \alpha(\dot{x}(\tau))\dot{y}(\tau))(1 - \beta(\dot{y}(\tau))\dot{x}(\tau))}.$$ 

Substituting these expressions of $\hat{\rho}_h(\tau), \hat{\rho}_s(\tau)$ in (6.9) and (6.10) we obtain

Canonical equations

$$\begin{cases}
\dot{x} = -\frac{1}{u_{xx}(\tau, \hat{x})} \left[r'_h(\hat{x}) + \alpha'(\dot{x})\frac{r_s(\dot{y}) - r_h(\dot{x})(1 - \beta(\dot{y})\dot{x})}{1 - (1 - \alpha(\dot{x})\dot{y})(1 - \beta(\dot{y})\dot{x})} \right], \\
\dot{y} = -\frac{1}{u_{yy}(\tau, \hat{y})} \left[r'_s(\hat{y}) + \beta'(\dot{y})\frac{r_h(\dot{x}) - r_s(\dot{y})(1 - \alpha(\dot{x})\dot{y})}{1 - (1 - \alpha(\dot{x})\dot{y})(1 - \beta(\dot{y})\dot{x})} \right].
\end{cases}$$  

(6.11)

Remark 6.3. In view of the two first equations in (6.5), if $u_0, v_0, r_h, r_s, \alpha, \beta$ are smooth enough (e.g., $C^2$ functions), then $u_{xx}$ is continuous. Thus the right-hand-sides of (6.11) are continuous as functions of $\dot{x}, \dot{y}, \tau$. Therefore, the standard ordinary differential equation theory implies that the solution of (6.11) $(\dot{x}, \dot{y})$ is a $C^1$ function of time. We refer to [20], for a results about the regularity of $u, v$ in the case of Hamilton–Jacobi equations.

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6.3 Numerical illustrations

Let us illustrate numerically some situations for the evolution of HSCs and its support cells with $(a, b) := (1, 2)$, $(c, d) := (3, 4)$.

Figure 2: Behaviour of HSCs (first row) and stromal cells (second row) in time. Stromal cells with best support capacity are selected and healthy HSCs persist (no LSCs).
Figure 3: Evolution of the dominant trait (horizontal axis for the distribution of traits) with time (vertical axis). Left: phenotype $x$ of HSCs. Right: Phenotype $y$ of stromal cells. Monomorphic states for HSCs and stromal cells.

In Figure 2, the population densities for HSCs and their support cells $n_h, n_s$ are monomorphic and behave as Dirac masses. The concentration point of $n_h$ moves towards $x = 1$ and the one of $n_s$ moves towards the point $y = 4$. In this situation, the phenotype $(x, y) = (1, 4)$ is selected. This represents a good scenario: healthy HSCs and stromal cells with the best support capacity are selected. The evolution of the corresponding dominant phenotypes are given in Figure 3.

Figures 4 and 5 below show another monomorphic situation where stromal cells with lowest support capacity are selected. Healthy HSCs cannot survive and cancer cells are selected.
Figure 4: Behaviour of HSCs (first row) and stromal cells (second row) in time. Stromal cells with lowest support capacity are selected. Healthy HSCs go extinct and LSCs persist.

Figure 5: Left: phenotype $x$ of HSCs. Right: Phenotype $y$ of stromal cells (phenotype space in abscissae, time in ordinates). The support is not sufficient and healthy HSCs cannot persist; only LSCs survive. One can notice an apparent fracture between the two populations around the middle of the phenotype space.
Figure 6: Behaviour of HSCs (first row) and stromal cells (second row) in time. Stromal cells with lowest support capacity are selected. HSCs and LSCs coexist (carefully note the concentration around both $x = 1$ and $x = 2$ in the first row).

Figure 7: Left: The dominant phenotypes for HSCs move towards the left and right. The phenotypes $x = 1$ and $x = 2$ are selected, i.e. both healthy and malignant HSCs persist. Right: Evolution of dominant phenotypes for stromal cells. Stromal cells with the lowest capacity of the support are selected. As in the previous case of Figure 5, there is a fracture in phenotype space between the two populations, but in this case, both populations survive.

Figures 6 and 7 represent the dimorphic situation for HSCs. Starting from an initial distri-
bution with one peak at $x = 1.2$. The first dominant phenotype of HSCs moves to the left (only healthy cells selected until $t = 400$). At the time $t = 400$ a second dominant phenotype that is located near $x = 2$ appears and moves towards $x = 2$. In other words, cancerous cells invade the population of HSCs, however without occupying it in totality: healthy HSCs and cancerous cells (LSCs) coexist.

7 Conclusion and perspectives

In this paper, we have introduced a mathematical model for the interaction between hematopoietic stem cells and their support cells. Leukemic stem cells are also taken into account in the model and the phenotype $x$, characterising the population heterogeneity in a way relevant to the question at stake, represents for both the intrinsic proliferation rate of HSCs and the malignancy potential of cancer cells (i.e., as mentioned in the introduction, a proposed pathological combination of both plasticity and fecundity, likely related to how many mutations are involved in cancer cells). Note also that the monotonicity assumption on $r_h$ means that we assumed that the malignant cells proliferate more than healthy HSCs.

We performed a study concerning the adaptive dynamics of HSCs and support cells, in particular, investigating Dirac masses (or sums of Dirac masses) that arose in the solutions of particular cases of the system. Linear stability results for single Dirac mass steady states, suggesting that another phenotype will invade the stationary environment corresponding to the steady state if the corresponding fitness function computed at that phenotype is positive. We suggest that another phenotype will invade the stationary environment corresponding to the question at stake, represents for both the intrinsic proliferation rate of HSCs and the malignancy potential of cancer cells (i.e., as mentioned in the introduction, a proposed pathological combination of both plasticity and fecundity, likely related to how many mutations are involved in cancer cells). Note also that the monotonicity assumption on $r_h$ means that we assumed that the malignant cells proliferate more than healthy HSCs.

Applying an asymptotic approach, we showed that without extinction, the population density of HSCs and of their support cells behave as Dirac masses:

$$n_h^x(\tau, x) \approx \hat{\rho}_h(\tau) \delta_{x=\hat{x}(\tau)}$$ with $\hat{\rho}_h(\tau) > 0 \Leftrightarrow \max_x u(\tau, x) = 0 = u(\tau, \hat{x}(\tau))$

$$n_s^y(\tau, y) \approx \hat{\rho}_s(\tau) \delta_{y=\hat{y}(\tau)}$$ with $\hat{\rho}_s(\tau) > 0 \Leftrightarrow \max_y v(\tau, x) = 0 = v(\tau, \hat{y}(\tau))$.

Here the points of concentration $\hat{x}(\tau), \hat{y}(\tau)$ represent well adapted phenotypes at the time $\tau$. Also these points are maximum points of the phase functions $u(\cdot, \tau)$ and $v(\cdot, \tau)$. The system (6.11) gives us the dynamics of $\hat{x}(\tau), \hat{y}(\tau)$, in other words, the adaptive process for HSCs and its support cells during their evolution. Our numerical illustrations provide the case of the existence of HSCs, or LCSs (only). Also, we illustrate the case of invasion of LCSs as well as the coexistence of HSCs and LSCs. This latter situation does not seem to be usually seen in the clinic of acute leukemias, which may be due to the fact that in reality, the competition for space and nutrients turns to the advantage of leukemic cells (The biological fact is that stromal cells change to adapt to healthy cells or malignant cells. Thus LCSs and HSCs have different hematopoietic niches so that the competitive strength of HSCs and LCSs for space and nutrients will be different). In our model, the advantage of leukemic cells in competition could be represented by a diversified non local logistic term in the equation for HSCs such as $-k_1 \int (b - x)n_h(t, x)dx - k_2 \int (x - a)n_h(t, x)dx$, with $k_2 > k_1$, instead of the neutral term $-\rho_h$, thus attributing more importance in the competition to cells close to the malignant phenotype $x = b$. Or else, could it be that actual biological coexistence between HSCs and LCSs could come from the fact that leukemic cells may have been reduced to a state of dormancy? Note that this perspective of dormancy has recently been investigated in a rather different modelling setting (no adaptive dynamics, no interaction with stromal cells) in [9].
Our analytic results, except in Section 5.2, hold for more general choices of the weight functions $\psi_h, \psi_s$. However, we present our results here mainly for the case $\psi_h = x, \psi_s = y$ to clarify the ideas and avoid complex computations. The mathematical question related to the convergence of the solution of (1.1) to its limit (which is an ESD) remains open. The BV-method (see, for example, [21, 16]) seems not amenable be applied due to the complexity of function parameters. However, we could find an entropy functional for a simplified system (5.2). This functional decreases to $-\infty$, however it could be an essential ingredient to solve this issue.

The present model and its mathematical analysis represent to the best of our knowledge a first attempt to study the interactions between HSCs and their supporting stromal cells in the framework of adaptive dynamics. One could certainly complicate it to introduce multidimensional phenotypes related to refined cell functionalities such as fecundity, viability, plasticity, in the two cell populations, but even simple as it is, it relies on many unknown functions that should first be experimentally evaluated to go further in this modelling work, which we actually plan to do in the future.

References


