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INFLUENCE OF THE AGE STRUCTURE ON THE STABILITY IN A TUMOR-IMMUNE MODEL FOR CHRONIC MYELOID LEUKEMIA

Kyriaki Dariva[1] and Thomas Lepoutre[2,*]

Abstract. In this paper a model of tumor-immune response for chronic myeloid leukemia (CML) is proposed and analyzed. It is based on the ordinary differential equations' models (ODE) studied in A. Besse, et al., Bull. Math. Biol. (2017) 1–27, G.D. Clapp, et al., Cancer Res. 75 (2015) 4053–4062. The proliferation of cells, their differentiation in the bone marrow and the interactions of leukemic and immune cells are described. The model is based on a non-monotonic immune response. At low levels immune response increases with the tumor load, whereas at high levels tumor is suppressing the effect of the immune system (immunosuppression). We consider that the age of cells is described by a continuous variable which we use to structure the system and obtain a partial differential equations' model (PDEs). We analyze the stability of the equilibrium points of the model and compare it to the case of A. Besse, et al., Bull. Math. Biol. (2017) 1–27 where age was described as a discrete state. In particular, an equilibrium point describing remission, induced by a control of the immune system, is shown to be unstable in certain situations for the PDE model, whereas in A. Besse, et al., Bull. Math. Biol. (2017) 1–27 it was systematically stable.

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1. Introduction

Chronic myeloid leukemia is a myeloproliferative disorder that is characterized by an elevated number of circulating undifferentiated white blood cells. When untreated, CML inevitably progresses to an acute phase that is lethal. The only curative therapy for CML is bone marrow transplantation but it is not always an option. It is based on the phase of the disease and the patient's reaction to drugs. Transplantation is not advised for patients in blast crisis [11] while due to the superiority of the drug treatments it is generally chosen for patients resistant to multiple drugs [7, 10, 13]. Pharmacological treatment can induce long-lasting remission with cure being rare, though not impossible. There is clinical evidence that remission is mediated by the immune system although its action on the leukemic cells is yet to be thoroughly understood [12, 17, 21]. Recent trials have shown that remission can be maintained up to 7 years after treatment cessation [14]. This involvement of the immune system is supported by many mathematical models of tumor-immune interaction [2], [3], [6], [8], [9].

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[1] Univ Lyon, Université Jean Monnet Saint-Étienne, CNRS UMR 5208, Inria, Institut Camille Jordan, 42023 Saint-Etienne, France.
[2] Univ Lyon, Inria, Université Claude Bernard Lyon 1, CNRS UMR5208, Institut Camille Jordan, 69603 Villeurbanne, France.

* Corresponding author: thomas.lepoutre@inria.fr

The model in [3] is simplified and analyzed in [2]. The ODE system proposed in [2] is the following

$$\begin{cases} \frac{\mathrm{d}c}{\mathrm{d}t} = rc(1-\frac{c}{K}) - \mu cz, \\ \frac{\mathrm{d}y_2}{\mathrm{d}t} = a_1 c - d_2 y_2 - \mu y_2 z, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = s - S(y_2)z, \end{cases} \tag{1.1}$$

where y_2 is the population of mature leukemic cells, c the leukemic stem cells and z the immune cells. The function S describes the immune response which is a combination of repression and activation of the immune population by the leukemic cells. In the absence of leukemia it is the natural death of immune cells ($S(0) \geq 0$). The response S is positive when repression is stronger than activation and negative in the reverse case. It is assumed that S has two regions of monotony: it is non-increasing for small values of y_2 and non-decreasing for large values of y_2. This implies that at low leukemic loads the immune system gets activated whereas at larger leukemic loads repression is observed.

CML is characterized by a single mutation resulting from the translocation between chromosomes 9 and 22. The gene ABL1 of chromosome 9 is juxtaposed onto the gene BCR of chromosome 22 to give the fusion gene BCR-ABL1 which is contained in the chromosome of Philadelphia (Ph). Ph entails the synthesis of a tyrosine kinase protein which makes the stem cells divide uncontrollably [5]. Leukemic cells' proliferation process begins in the bone marrow by the activation of quiescent cancer stem cells. Once activated, these non-differentiated cells divide, and then differentiate into blood cells. The small number and the low basal activity of stem cells make any direct characterization of these cells difficult. Once committed to differentiation, leukemic cells will divide over twenty times before being released in the blood. They are then generically called mature cells (actually, in certain phases, immature cells can be released in the blood). Circulating leukemic cells are not dividing anymore, and are cleared from the blood within a few days, so the BCR-ABL/ABL rate represents evolution of the disease in bone marrow, with a delay of few weeks.

The Tyrosine kinase inhibitor (TKI) Imatinib is the first treatment to have specifically targeted the BCR-ABL gene in leukemic cells. In the case of treatment with standard doses, Imatinib limits the leukemic cells' proliferation and promotes apoptosis (cell death) of leukemic cells with acceptable effects. After the important trial StopImatinib [14] and others that followed (see [19] for a review), it has been established that a small subset of patients who achieve deep response can safely stop the treatment. This is called treatment-free remission (TFR). There is increasing evidence that these patients might still harbor leukemic cells, suggesting control of the disease rather than its eradication. One of the main contributions of [2] is that with (1.1) the TFR is generically interpreted as a remission equilibrium (a terminology that was first introduced in [6]). With their model the disease is controlled by the immune system without complete eradication of the stem cells. This approach has been also considered in [8] and it appears to be very consistent with recent methods of slower treatment cessation [4]. In contrast to that, previous models [15, 18] describing CML under TKI treatment, although very successful in explaining the biphasic decline of CML cells, were interpreting TFR as eradication of leukemic cells. That fact is not the case for all patients.

In this paper it is proposed a model of PDE, structured in age, that describes the interactions of immune and leukemic cells. In terms of modeling this is justified by the fact that age increases continuously from stem cells to fully differentiated cells. The system is a generalization of (1.1) where only two compartments of the leukemic cells are considered: stem cells and fully differentiated (mature) cells. The question that we address is how an age structure can change the stability chart of the model.

Let $x \in \mathbb{R}^+$ be a variable that describes the age of a cell. The value $x = 0$ stands for stem cells while x describes time once the cell is committed to differentiation and has left the stem cell compartment. Our PDE model is the structured analogue of (1.1)

$$\begin{cases} \frac{\mathrm{d}c}{\mathrm{d}t} = rc(1-\frac{c}{K}) - \mu_c cz, \\ \frac{\partial u}{\partial t}(t,x) + \frac{\partial u}{\partial x}(t,x) = h(x)u(t,x) - \mu_u u(t,x)z, \\ u(t,0) = ac(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} = s - S(I)z, \end{cases} \tag{1.2}$$

with $I = \int_0^\infty w(x)u(t,x)\mathrm{d}x$ the weighted population of leukemic differentiated cells. Here $w \in L^\infty(\mathbb{R}^+)$ is a nonnegative bounded weight that describes a different stimulation based on different ages. The initial conditions are $(c^0, u^0, z^0) \in \mathbb{R}_+ \times L^1_+(\mathbb{R}_+) \times \mathbb{R}_+$ and the variables of the model

- $c(t)$: the concentration of leukemic stem cells at time t.
- $u(t,x)$: the density of committed leukemic cells of age x at time t.
- $z(t)$: the concentration of immune cells at time t.

As in [2] the leukemic stem cells are under logistic growth with rate r, carrying capacity K and μ_c the efficacy of the immune system over the leukemic stem cells.

For the leukemic cells committed to differentiation we suppose that the velocity of differentiation is constant and equal to 1. The function $h(x) = p(x) - d(x)$ is the balance between the proliferation and natural death rates respectively, two positive real valued functions of the age. The parameter μ_u is the efficacy of the immune cells over the leukemic differentiated cells. For biological reasons we expect proliferation p to vanish for large values of x, in contrast to d. This corresponds to a negative h after a certain age and translates into a death rate which exceeds the proliferation rate for large values of x. When h and w are constant the system has a closed ODE form with variables c, I, z and reduces to the ODE [2].

The equation for the immune population is the same as in [2]. Here s is the natural source of immune cells while the function S describes the immune response and has the same properties as in the ODE case. An example of S that is used as a response function was first introduced in [3]

$$S(I) = S(0) - \alpha \frac{2YI}{Y^2 + I^2},$$

The constant Y is a positive threshold such that S is decreasing for $I \leq Y$ and increasing for $I \geq Y$. To be as general as possible, only the monotony structure is kept, leading to the following assumptions on S

$$S \in C^2(\mathbb{R}^+), \exists Y > 0,\ S' < 0 \ \text{ on } (0,Y) \text{ and } S' > 0, \text{ on } (Y,\infty). \tag{1.3}$$

Note that if we integrate u in (1.2) along characteristics we obtain a reformulation of the system as a delay differential equation (DDE). Indeed,

$$u(t,x) = ac(t-x)\mathrm{e}^{\int_0^x h(s)\mathrm{d}s - \mu_u \int_0^x z(t-x+s)\mathrm{d}s}, \quad t > x.$$

We compute I:

$$\begin{aligned} I(t) &= \int_0^\infty w(x)u(t,x)\mathrm{d}x \\ &= \int_0^\infty ac(t-x)w(x)\mathrm{e}^{\int_0^x h(s)\mathrm{d}s - \mu_u \int_0^x z(t-x+s)\mathrm{d}s}\mathrm{d}x \\ &= \int_0^\infty c(t-x)\mathrm{e}^{-\mu_u \int_0^x z(t-x+s)\mathrm{d}s} q(x)\mathrm{d}x, \end{aligned}$$

with $q(x) = a\mathrm{e}^{\int_0^x h(y)\mathrm{d}y} w(x)\mathrm{d}x$. In that way we have the following distributed delay differential model on (c,z).

$$\begin{cases} \frac{\mathrm{d}c}{\mathrm{d}t} = rc(1 - \frac{c}{K}) - \mu_c cz, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = s - S\left(\int_0^\infty c(t-x)\mathrm{e}^{-\mu_u \int_0^x z(t-x+s)\mathrm{d}s} q(x)\mathrm{d}x\right) z. \end{cases} \tag{1.4}$$

The model has three possible types of equilibrium points: the disease free ($I = 0$) equilibrium, the low ($S'(I) < 0$) and the high ($S'(I) > 0$) equilibrium points. We will show that as in the ODE case studied in [2] there cannot be more than one positive equilibrium in the region where S is decreasing. We call the equilibrium point located in that region remission equilibrium.

For the disease free equilibrium and the high equilibrium points the structure is shown to be qualitatively similar to [2]. For the remission equilibrium (if it exists), the situation can be very different compared to [2].

The stability of the remission equilibrium is fully characterized by the roots $\lambda \in \mathbb{C}$ of the characteristic equation,

$$P(\lambda) - Q(\lambda) \int_0^\infty \mathrm{e}^{-\lambda x} \bar{p}(x) \mathrm{d}x = 0.$$

where $\bar{p}$ is a probability density on $\mathbb{R}^+$ corresponding to the normalized distribution of the differentiated cells. P and Q are polynomials with $degP = 3$ and $degQ = 1$ unless $\mu_c = \mu_u$ when Q reduces to a constant. Their definition can be found in (3.6). In the ODE model the remission equilibrium cannot lose its stability. We show here that the shape of the distribution $\bar{p}$ affects the stability of the remission equilibrium. This result is proven in the case of a Dirac distribution which shows that the PDE is not a trivial extension of the ODE.

The paper is organized as follows. Firstly, the well-posedness of the system is established under reasonable hypotheses. Secondly, the equilibrium points of the system are characterized and their stability is studied. It is shown that the stability of the remission equilibrium can be affected by the distribution of the leukemic differentiated cells. Conditions allowing this instability are analyzed and finally the consequence of changing the distribution of age on the potential destabilization of the equilibrium points of (1.1) using biologically relevant parameters is investigated.

2. Analysis of the model

2.1. Definitions

2.1.1. Immune window

We recall the assumptions on S. $S \in C^2(\mathbb{R}^+)$ and a $Y \geq 0$ exists such that $S' < 0$ in $(0, Y)$ and $S' > 0$ in $(Y, +\infty)$.

Definition 2.1. We call immune window the set of values of I where $S(I)$ is negative.

If the immune window is not empty, then it is an interval $(y_{\min}, y_{\max})$. In that case it is characterized as the region where the tumor load makes the activation exceed the repression leading to expansion of the immune population. If the immune window exists, it is then interpreted as the region where the tumor load is neither too high (immunossupression inhibits the growth) nor too low (in which case the immune population may not be stimulated at all).

Remark 2.2. If the immune window is not empty, no relevant (*i.e.* nonnegative) equilibrium point can satisfy $I \in (y_{\min}, y_{\max})$. Equilibrium points are located in the zone of I where $S(I) \geq 0$. Consequently, we are looking for equilibrium points either in $\mathbb{R}^+$ or in an interval of the form $(0, y_{min}) \cup (y_{max}, +\infty)$.

2.1.2. Solution of the system

Definition 2.3. Let $u_0 \in L^\infty(\mathbb{R}^+) \cap L^1(\mathbb{R}^+)$ and $(c^0, z^0) \in \mathbb{R}^2_+$. Assume $w, h \in L^\infty(\mathbb{R}^+)$ and $\limsup_{+\infty} h < 0$. A mild solution of the system (1.2) is a triplet $(c(t), u(t, x), z(t))$ in the space $C([0, \infty), \mathbb{R}^+) \times C([0, \infty), L^1_+(\mathbb{R}^+)) \times$

$C([0,\infty),\mathbb{R}^+)$ which satisfies equations (1.2) and has the integral form:

$$\begin{cases} c(t) = c^0 + \int_0^t rc(s)(1-\frac{c(s)}{K}) - \mu_c c(s)z(s)\mathrm{d}s, \\ u(t,x) = \begin{cases} u^0(x-t)\mathrm{e}^{\int_{x-t}^x (h(s)-\mu_u z(s+t-x))\mathrm{d}s}, & x-t \geq 0 \\ ac(t-x)\mathrm{e}^{\int_0^x (h(s)-\mu_u z(s+t-x))\mathrm{d}s}, & x-t<0 \end{cases} \\ z(t) = z^0 + \int_0^t (s - S(I(t'))z(t'))\mathrm{d}t'. \end{cases} \tag{2.1}$$

The existence and the uniqueness of the solution is a consequence of the Picard iteration argument. As proven below, the components of the solution are globally bounded.

Lemma 2.4. *Assume $u^0 \in L^1(\mathbb{R}^+)$, $w \in L^\infty(\mathbb{R}^+)$ and $\limsup_{+\infty} h < 0$. There are constants $c^\infty, z^\infty, I^\infty$, depending only on the initial conditions and the parameters, such that for all $t \in \mathbb{R}^+$*

$$\begin{aligned} 0 \leq c(t) \leq c^\infty, \\ 0 \leq I(t) \leq I^\infty, \\ 0 \leq z(t) \leq z^\infty. \end{aligned}$$

Proof. The bound of c results from the logistic growth since $c \leq max\{c^0, K\}$. As

$$\limsup_{+\infty} h < 0,$$

$\mathrm{e}^{\int_0^x h(s)\mathrm{d}s}$ is integrable and $\sup_{0\leq t\leq x} \mathrm{e}^{\int_{x-t}^x h(s)\mathrm{d}s} = C_h < +\infty$. Then from (2.1)

$$I(t) = \int_0^{+\infty} w(x)u(t,x)\mathrm{d}x = \int_0^t w(x)u(t,x)\mathrm{d}x + \int_t^{+\infty} w(x)u(t,x)\mathrm{d}x,$$

we get

$$\int_0^t w(x)u(t,x)\mathrm{d}x \leq ac^\infty ||w||_\infty \int_0^{+\infty} \mathrm{e}^{\int_0^x h(s)\mathrm{d}s}\mathrm{d}x$$

$$\int_t^{+\infty} w(x)u(t,x)\mathrm{d}x \leq C_h \|w\|_\infty \|u^0\|_1$$

In total, there is a constant I^∞ such that

$$I(t) \leq I^\infty.$$

Finally, for the global bound of z we proceed as follows. Set $J(t) = \|w\|_\infty \int_0^\infty u(t,x)\mathrm{d}x$ and consider a positive number $\eta > 0$ such that $\eta > \frac{\|S'\|_{L^\infty((0,I^\infty))}}{\mu_u}$. Define the function

$$r(\eta) = \inf_{[0,I^\infty]} \left(S(I) + \eta\mu_u I\right).$$

With the η chosen $r(\eta)$ is positive and increasing so $r(\eta) = S(0)$. The computations for the bound I^∞ ensure that

$$0 \leq I(t) \leq J(t) \leq I^\infty.$$

Consequently,

$$\begin{aligned}\dot{J} &\leq (ac^\infty \|w\|_\infty + \sup h \|w\|_\infty J) - \mu_u z J \\ &\leq ac^\infty \|w\|_\infty + \sup h \|w\|_\infty I^\infty - \mu_u z J\end{aligned}$$

Set $C_{I^\infty} = ac^\infty \|w\|_\infty + \sup h \|w\|_\infty I^\infty$ and combine the following

$$\begin{cases} \dot{J} \leq C_{I^\infty} - \mu_u z J \\ \dot{z} = s - S(I) z \end{cases}$$

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}(z + \eta J) &\leq (s + \eta C_{I^\infty}) - z(\mu_u \eta J + S(I)), \\ &= (s + \eta C_{I^\infty} + \eta J(\mu_u \eta J + S(I))) - (z + \eta J)(\mu_u \eta J + S(I)), \\ &\leq \underbrace{(s + \eta C_{I^\infty} + \eta I^\infty (\mu_u \eta I^\infty + \|S\|_\infty))}_{C_\eta} - (z + \eta J)(\mu_u \eta J + S(I)), \\ &\leq C_\eta - (z + \eta J)(\mu_u \eta I + S(I)), \\ &\leq C_\eta - (z + \eta J) r(\eta),\end{aligned}$$

with C_η a positive constant depending on η. Hence

$$z(t) \leq z(t) + \eta J(t) \leq \max\left(z^0 + \eta J(0), \frac{C_\eta}{r(\eta)}\right).$$

Set z^∞ for the global bound of z and this concludes the proof. □

2.2. Existence of equilibrium points

The equilibrium points are triplets of the form $(\bar{c}, \bar{u}(x), \bar{z}) \in \mathbb{R}^+ \times L^1(\mathbb{R}^+) \times \mathbb{R}^+$ obtained as solutions of $\frac{\mathrm{d}c}{\mathrm{d}t} = 0$, $\frac{\partial u}{\partial t} = 0$, $\frac{\mathrm{d}z}{\mathrm{d}t} = 0$. In what follows, we will distinguish two sorts of equilibrium points:

- The disease free equilibrium (DFE) $(0, 0, \frac{s}{S(0)})$ which always exists,
- The equilibrium points with positive leukemic load which we call positive equilibria. They are characterized in the following way

Those that belong in the nondecreasing area of S which are called high equilibria, and those in the nonincreasing area of S that are called remission equilibria.

Proposition 2.5. *The system has always a disease free equilibrium* $(0, 0, \frac{s}{S(0)})$. *The positive equilibrium points, if they exist, they are implicitly described by the value of* $\bar{I} = \int_0^\infty w(x)\bar{u}(x)\mathrm{d}x$ *in the following way*

$$\begin{cases} \bar{c} = \frac{K}{r}\left(r - \mu_c \frac{s}{S(\bar{I})}\right), \\ \bar{u}(x) = \frac{aK}{r}\left(r - \mu_c \frac{s}{S(\bar{I})}\right) \mathrm{e}^{H(x) - \mu_u \frac{s}{S(\bar{I})} x}, \\ \bar{z} = \frac{s}{S(\bar{I})}, \end{cases} \tag{2.2}$$

where we have set $H(x) = \int_0^x h(s)\mathrm{d}s$. *Consequently, a positive value of* $\bar{I}$ *leads by* (2.2) *to a non negative equilibrium if*

- $S(\bar{I}) > \frac{\mu_c s}{r}$,
- $\bar{I}$ *is a solution of the fixed point equation*

$$F(I) = I,$$

where F *is defined by*

$$F(I) = \int_0^\infty \frac{aK}{r}\left(r - \mu_c \frac{s}{S(I)}\right) w(x) \mathrm{e}^{H(x) - \mu_u \frac{s}{S(I)} x} \mathrm{d}x.$$

Proof. We are looking for equilibrium points which are the solutions of the following system

$$\begin{cases} 0 = r\bar{c}(1 - \frac{\bar{c}}{K}) - \mu_c \bar{c}\bar{z}, \\ \frac{\mathrm{d}\bar{u}}{\mathrm{d}x}(x) = h(x)\bar{u}(x) - \mu_u \bar{u}(x) z, \\ \bar{u}(0) = a\bar{c}, \\ 0 = s - S(\bar{I})\bar{z}. \end{cases}$$

We solve the system and we obtain

$$\begin{cases} 0 = \bar{c}((r - \frac{r\bar{c}}{K}) - \mu_c \bar{z}), \\ \bar{u}(x) = \bar{u}(0)\mathrm{e}^{\int_0^x h(s)\mathrm{d}s - \mu_u \bar{z} x}, \\ \bar{u}(0) = a\bar{c}, \\ \bar{z} = \frac{s}{S(\bar{I})}. \end{cases}$$

We deduce that either $\bar{c} = 0$ and consequently $\bar{u}(0) = 0$. Hence $\bar{u}(x) = 0$ and $\bar{z} = \frac{s}{S(0)}$. In this case we have the disease free equilibrium point

$$(\bar{c}, \bar{u}, \bar{z}) = (0, 0, \frac{s}{S(0)}).$$

If $\bar{c} \neq 0$ then $\bar{c} = K\left(1 - \frac{\mu_c \bar{z}}{r}\right)$ and $\bar{z} = \frac{s}{S(\bar{I})}$. This imposes $S(\bar{I}) > 0$ and $S(\bar{I}) > \frac{\mu_c s}{r}$ so that $\bar{z} > 0$ and $\bar{c} > 0$ respectively. The formulation on $\bar{u}$ is obtained after integration along characteristics and the fixed point formulation is immediately derived. □

Proposition 2.6. *Let* Y *be the positive threshold where* S *changes monotony.*

- *If*

$$rS(0) - \mu_c s > 0 \tag{2.3}$$

  there exists at least one positive equilibrium. If $S(Y) \leq 0$ *there exists exactly one in the region* $(0, Y)$*, the remission equilibrium.*
- *If* $rS(0) - \mu_c s \leq 0$*, no remission equilibrium exists. High equilibrium points may still exist in* $(Y, +\infty)$.

Proof. The positive equilibrium points are determined by the values of $\bar{I}$ that solve the equation

$$F(I) - I = 0, \quad S(\bar{I}) > \frac{\mu_c s}{r}.$$

Let Y_* be

$$Y_* = min\left\{Y, inf\left(x \leq Y \text{ such that } S(x) \leq \frac{\mu_c s}{r}\right)\right\},$$

with the infimum of the empty set being 0. The fixed point equation $F(I) - I = 0$ is rewritten as

$$F(I) - I = \int_0^\infty \frac{aK}{r}\left(r - \mu_c \frac{s}{S(I)}\right) w(x) \mathrm{e}^{H(x) - \mu_u \frac{s}{S(I)} x} \mathrm{d}x - I = 0.$$

At the equilibrium

$$\begin{aligned} F'(\bar{I}) - 1 &= \int_0^\infty \frac{aK}{r}\left(\mu_c s \frac{S'(\bar{I})}{S^2(\bar{I})} + (r - \mu_c \frac{s}{S(\bar{I})})\mu_u s \frac{S'(\bar{I})}{S^2(\bar{I})} x\right) w(x) \mathrm{e}^{H(x) - \mu_u \frac{s}{S(\bar{I})} x} \mathrm{d}x - 1, \\ &= S'(\bar{I}) \int_0^\infty \frac{aK}{r}\left(\frac{s}{S^2(\bar{I})}\left(\mu_c + \mu_u (r - \mu_c \frac{s}{S(\bar{I})}) x\right)\right) w(x) \mathrm{e}^{H(x) - \mu_u \frac{s}{S(\bar{I})} x} \mathrm{d}x - 1. \end{aligned}$$

Note that S is decreasing in $(0, Y)$.

- If $S(0) > \frac{\mu_c s}{r}$ and $S(Y) < 0$, $Y_* < Y$ and no solution exists in (Y_*, Y). In $(0, Y_*]$, S is monotonic and $S > \frac{\mu_c s}{r}$, so $F'(\bar{I}) - 1 \leq 0$. The function $F(I) - I$ decreases from $F(0) > 0$ to $-Y_*$ and a unique solution of the fixed point equation exists.
- If $S(0) > \frac{\mu_c s}{r}$ and $S(Y) \geq 0$ the immune window does not exist. In that case F may not vanish (when $S(Y) > \frac{\mu_c s}{r}$) but a solution to the fixed point equation will always exist in $\mathbb{R}$. That is because $F - I$ is defined on $\mathbb{R}$, $F(0) > 0$ and $\lim_{I \to +\infty} F(I) - I = -\infty$. If the equilibrium satisfies $0 < \bar{I} < Y$ we still call remission equilibrium but the existence of such an equilibrium is not guaranteed.
- If $S(0) \leq \frac{\mu_c s}{r}$, $Y_* = 0$ and no solution exists in $(0, Y)$. If any, it is in the region $(I_0, +\infty)$, with $I_0 = inf\{x > Y \text{ such that } S(x) > \frac{\mu_c s}{r}\}$, and is associated to high equilibrium points.

□

3. Stability analysis

We are now ready to study the stability of the identified equilibrium points. The stability of the DFE and the high equilibrium points is similar to the ODE case studied in [2]. The remission steady state behaves in a different manner. Whereas it was unconditionally stable in [2], stability can be lost in the PDE depending on the distribution of the differentiated cells. For that reason the essential result of this section concerns the stability of the remission point.

Stability analysis is reduced to the study of the characteristic equation associated to the linear system. To prove that the solutions of the characteristic equation determine stability we have to proceed as follows:

1. Firstly we show that linear stability entails stability of the non linear system in a sense to be precised.
2. Then we express the solution of the linear system as the image of a linear semi-group and prove that the stability of the equilibrium points is determined by the eigenvalues of the semi-group's generator.
3. Finally we derive a characteristic equation and study the behavior of its roots.

Remark 3.1. Points 1 and 2 are proved in Appendix B and A respectively. The study of the characteristic equation is the essential part of this paper and is detailed below.

Theorem 3.2. *If a stationary point $(\bar{c}, \bar{u}, \bar{z})$ is linearly exponentially stable, then it is also non linearly stable in the sense that if initial conditions (c_0, u_0, z_0) take values close to the equilibrium:*

$$\|(c_0 - \bar{c}, u_0 - \bar{u}, z_0 - \bar{z})\|_X \leq C_1,$$

then the solution (c, u, z) of the non linear system at time t satisfies:

$$\|(c-\bar{c}, u-\bar{u}, z-\bar{z})(t)\|_X < C_2 \mathrm{e}^{-C_3 t},$$

with C_1, C_2, C_3 positive constants.

Proof. See Appendix B for the proof. □

The linear system around $(\bar{c}, \bar{u}(x), \bar{z})$ is written as

$$\begin{cases} \frac{\mathrm{d}c}{\mathrm{d}t} = (r - \frac{2r\bar{c}}{K} - \mu_c \bar{z})c - \mu_c \bar{c} z, \\ \frac{\partial u}{\partial t}(t,x) + \frac{\partial u}{\partial x}(t,x) = h(x)u(t,x) - \mu_u \bar{u} z - \mu_u u \bar{z}, \\ u(t,0) = ac(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} = -S(\bar{I})z - \bar{z}S'(\bar{I})I. \end{cases} \tag{3.1}$$

We consider the semi-group $T(t)$ defined on $X = \mathbb{R} \times L^1(\mathbb{R}^+) \times \mathbb{R}$ by

$$\begin{cases} T(t) : X \to X, \\ (c_0, u_0(x), z_0) \mapsto (c(t), u(t,x), z(t)), \end{cases} \tag{3.2}$$

which to an initial condition associates a solution of (3.1). Denote by A the infinitesimal generator of the semi-group

$$\begin{cases} A : D(A) \subset X \to X, \\ D(A) = \{(c, u, z) \in \mathbb{R} \times W^{1,1}(\mathbb{R}^+) \times \mathbb{R}, \quad u(0) = ac.\} \end{cases}$$

Proposition 3.3. *Consider a steady state $(\bar{c}, \bar{u}, \bar{z})$ and a complex number λ satisfying $Re(\lambda) > -\mu_u \bar{z}$. We introduce the notation*

$$E_\lambda(x) = a\mathrm{e}^{\int_0^x h(s)\mathrm{d}s - \mu_u \bar{z} x} \mathrm{e}^{-\lambda x} = \bar{u}(x)\mathrm{e}^{-\lambda x},$$

and the matrix $M(\lambda)$

$$M(\lambda) = \begin{bmatrix} \lambda + 2\frac{r\bar{c}}{K} - r + \mu_c \bar{z} & \mu_c \bar{c} \\ S'(\bar{I})\bar{z} \int_0^\infty w(x) E_\lambda(x) \mathrm{d}x & \lambda + S(\bar{I}) - \bar{z}\mu_u S'(\bar{I}) \int_0^\infty w(x)\bar{u}(x) \int_0^x \mathrm{e}^{-\lambda(x-y)} dy dx \end{bmatrix}.$$

Then λ satisfies necessarily one of these two properties

- $\det(M) \neq 0$ *and* $(A - \lambda)$ *is invertible (λ is in the resolvent set of A),*
- $\det M = 0$ *and λ is an eigenvalue of A.*

Proof. We solve the resolvent operator $A - \lambda$ for a given λ, that is we look for a nontrivial solution (C, U, Z) of the problem with a source $(c_1, u_1, z_1), u_1 \in L^1(\mathbb{R})$

$$\begin{cases} (\lambda + 2\frac{r\bar{c}}{K} - r + \mu_c)C + \mu_c \bar{c} Z = c_1, \\ \lambda U(x) + \frac{dU(x)}{\mathrm{d}x} - h(x)U(x) + \mu_u \bar{z} U + \mu_u \bar{u} Z = u_1(x), \\ U(0) = aC, \\ \lambda Z + S(\bar{I})Z + \bar{z}S'(\bar{I}) \int_0^\infty w(x)U(x)\mathrm{d}x = z_1. \end{cases}$$

With our notations,

$$U(x) = CE_\lambda(x) - \mu_u Z \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} \bar{u}(y)\mathrm{d}y + \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y)\mathrm{d}y,$$

and

$$\int_0^{+\infty} w(x)U(x)\mathrm{d}x = C\int_0^{+\infty} w(x)E_\lambda(x)\mathrm{d}x - \mu_u Z \int_0^{+\infty} w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)}\bar{u}(y)\mathrm{d}y\mathrm{d}x + \int_0^{+\infty} w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y)\mathrm{d}y\mathrm{d}x. \quad (3.3)$$

We set:

- $J_C(\lambda) = \int_0^{+\infty} w(x)E_\lambda(x)\mathrm{d}x$,
- $J_Z(\lambda) = \int_0^{+\infty} w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)}\bar{u}(y)\mathrm{d}y\mathrm{d}x$,
- $J_1(\lambda) = \int_0^{+\infty} w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y)\mathrm{d}y\mathrm{d}x$.

So that

$$\int_0^{+\infty} w(x)U(x)\mathrm{d}x = CJ_C(\lambda) - \mu_u Z J_Z(\lambda) + J_1(\lambda).$$

By assumption $\Re(\lambda) > -\mu_u\bar{z}$ so $u_1 \in L^1$ and we have no integrability issues. Indeed, $\int_y^x h$ is bounded from above if $y < x$, so $\frac{E_\lambda(x)}{E_\lambda(y)}$ is controlled by $K\mathrm{e}^{-(Re(\lambda)+\mu_u\bar{z})(x-y)} = K\mathrm{e}^{-\epsilon(x-y)}$ with $\epsilon > 0$. Moreover

$$\frac{E_\lambda(x)}{E_\lambda(y)}\bar{u}(y) = \bar{u}(x)\mathrm{e}^{-\lambda(x-y)}.$$

In particular,

$$\|w(x)E_\lambda(x)\|_1 \le K_1,\ \left\|w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)}\bar{u}(y)\mathrm{d}y\right\|_1 \le \frac{K_2}{\epsilon}\|\bar{u}\|_1,\ \left\|w(x)\int_0^x \frac{E_\lambda(x)}{E_\lambda(y)}u_1(y)\mathrm{d}y\right\|_1 \le \frac{K_2}{\epsilon}\|u_1\|_1.$$

So the problem has a solution if and only if we can solve the linear problem in C, Z

$$\begin{cases} (\lambda + 2\frac{r\bar{c}}{K} - r + \mu_c)C + \mu_c\bar{c}Z = c_1, \\ \bar{z}S'(\bar{I})J^C(\lambda)C + (\lambda + S(\bar{I}) - \mu_u\bar{z}S'(\bar{I})J^Z(\lambda))Z = z_1 - \bar{z}S'(\bar{I})J_1(\lambda). \end{cases}$$

The problem can be written in a matrix form

$$M(\lambda)\begin{pmatrix} C \\ Z \end{pmatrix} = \begin{pmatrix} c_1 \\ z_1 - \bar{z}S'(\bar{I})J_1(\lambda) \end{pmatrix}.$$

Then we have the possibilities:

- $detM = 0$. The matrix M is not invertible and a nontrivial solution associated to a right-hand side 0 exists. This leads to the construction of eigenvectors.
- $detM \neq 0$. The matrix M is invertible and a unique solution exists, showing that the operator $A - \lambda$ is invertible.

□

The characteristic equation of the linear system around an equilibrium is given by:

$$\det(M(\lambda)) = 0.$$

The solutions of this equation are the eigenvalues of the operator A and correspond to the solutions of the system with exponential form $(C\mathrm{e}^{\lambda t}, U(x)\mathrm{e}^{\lambda t}, Z\mathrm{e}^{\lambda t})$. If all roots have $\Re(\lambda) < 0$ the equilibrium is stable. If there is a root with $\Re(\lambda) > 0$ the equilibrium is unstable. These solutions correspond to the eigenvectors of the operator A.

Note that if the age x was bounded $0 < x < x_{max}$, then the fact that the study of stability would reduce to the study of the eigevalues of A is a well known result [20]. When age is not bounded $x \in \mathbb{R}^+$ a proof is needed because problems of compactness may appear. For our operator, the eigenvalues of A still determine stability and a detailed proof is provided in Appendix A.

3.1. Stability of the DFE and the high equilibrium points

The stability conditions for the DFE are given in the following proposition.

Proposition 3.4. *The DFE is linearly unstable if* $r - \mu_c s/S(0) > 0$ *and linearly stable if* $r - \mu_c s/S(0) < 0$.

Proof. With the equilibrium $\bar{c} = 0, \bar{u} = 0, \bar{z} = s/S(0)$ the matrix $M(\lambda)$ is upper triangular and $\det(M(\lambda)) = (\lambda - r + \mu_c s/S(0))(\lambda + S(0))$. There is a positive eigenvalue if and only if $r - \mu_c s/S(0) > 0$. □

Proposition 3.5. *The stability of the high equilibrium is determined by the sign of* $\det(M(0))$. *More precisely,*

- *if* $\det(M(0) > 0$ *the equilibrium is stable.*
- *if* $\det M(0) < 0$ *the equilibrium is unstable.*

Proof. The positive $\bar{c}$ satisfies $\mu_c \bar{z} = r - \frac{r\bar{c}}{K}$ so the first diagonal coefficient of M can be re-expressed as $\lambda + \frac{r\bar{c}}{K}$. The determinant becomes

$$\begin{aligned}\det M(\lambda) = \left(\lambda + \frac{r\bar{c}}{K}\right)\left(\lambda + S(\bar{I}) - \bar{z}\mu_u S'(\bar{I})\int_0^\infty w(x)\bar{u}(x)\int_0^x \mathrm{e}^{-\lambda y}\mathrm{d}y\mathrm{d}x\right)\\ - \mu_c \bar{c} S'(\bar{I})\bar{z}\int_0^\infty w(x)E_\lambda(x)\mathrm{d}x. \end{aligned} \tag{3.4}$$

For $\Re(\lambda) > -min(\frac{r\bar{c}}{K}, \mu_u \bar{z})$ and $S'(\bar{I}) > 0$ using the following results:

$$\Re(E_\lambda(x)) \le |E_\lambda(x)| \le E_{\Re(\lambda)}(x),$$

and

$$\frac{1}{|\lambda + a|} \le \frac{1}{\Re(\lambda) + a}, \quad \textit{for} \quad \Re(\lambda) + a > 0.$$

We have

$$\begin{aligned}\frac{\det M(\lambda)}{(\lambda + \frac{r\bar{c}}{K})(\lambda + S(\bar{I}))} =& 1 - \bar{z}\mu_u S'(\bar{I})\int_0^\infty w(x)\bar{u}(x)\int_0^x \frac{\mathrm{e}^{-\lambda y}}{\lambda + S(\bar{I})}\mathrm{d}y\mathrm{d}x\\ &- \mu_c \bar{c} S'(\bar{I})\bar{z}\int_0^\infty w(x)\frac{E_\lambda(x)}{(\lambda + \frac{r\bar{c}}{K})(\lambda + S(\bar{I}))}\mathrm{d}x\end{aligned}$$

so

$$\begin{aligned}\left|\frac{\det M(\lambda)}{(\lambda+\frac{r\bar{c}}{K})(\lambda+S(\bar{I}))}\right| \geq & 1-\bar{z}\mu_u S'(\bar{I})\int_0^\infty w(x)\bar{u}(x)\int_0^x \frac{\mathrm{e}^{-\Re(\lambda)y}}{\Re(\lambda)+S(\bar{I})}\mathrm{d}y\mathrm{d}x \\ & -\mu_c\bar{c}S'(\bar{I})\bar{z}\int_0^\infty w(x)\frac{E_{\Re(\lambda)}(x)}{(\Re(\lambda)+\frac{r\bar{c}}{K})(\Re(\lambda)+S(\bar{I}))}\mathrm{d}x \\ = & \frac{\det M(\Re(\lambda))}{(\Re(\lambda)+\frac{r\bar{c}}{K})(\Re(\lambda)+S(\bar{I}))}.\end{aligned}$$

The inequality is strict for λ complex. In particular $det(M(\lambda))=0$ implies then $det(M(\Re(\lambda))<0$. Since the function

$$\lambda \mapsto \frac{\det M(\lambda)}{(\lambda+\frac{r\bar{c}}{K})(\lambda+S(\bar{I}))},$$

(seen as function over $\mathbb{R}$) is increasing on $]-\min(\frac{r\bar{c}}{K},\mu_u\bar{z},S(\bar{I})),+\infty[$, with limit 1 as $\lambda\to+\infty$, and becomes 0 for any real eigenvalue, the stability is determined by a real eigenvalue. In particular, this function changes sign at most once. If it remains positive on the whole interval, $\det(M)$ cannot vanish for any λ satisfying $Re(\lambda)\geq-\min(\frac{r\bar{c}}{K},\mu_u\bar{z},S(\bar{I}))$ and consequently $\det(M)>0$. Otherwise, there is a unique real root λ_0 of the function and since the function is increasing, we have $\det(M(0))>0$ if $\lambda_0<0$ and vice versa. □

The following result establishes the alternation of stability in the high equilibrium points. It is equivalent to theorem 2 of [2].

Proposition 3.6. *The stability of the high equilibrium points is alternated. The set of values of I associated to high equilibria has a minimum and the equilibrium associated to this minimum is unstable. More precisely, we can order the values of I*

$$I_1\leq I_2\leq ...\leq I_N, \textit{with}\quad N\equiv 0 \mod 2$$

with multiple roots of $F(I)-I=0$ being considered separately. A simple root with even (respectively odd) index corresponds to a stable (respectively unstable) equilibrium.

Proof. With the same computations as above

$$\begin{aligned}\frac{\det(M(0))}{\frac{r\bar{c}}{K}S(\bar{I})} =& 1-\bar{z}\mu_u S'(\bar{I})\int_0^\infty w(x)\bar{u}(x)\frac{x}{S(\bar{I})}\mathrm{d}y\mathrm{d}x \\ & -\mu_c\bar{c}S'(\bar{I})\bar{z}\int_0^\infty w(x)\frac{E_0(x)}{\frac{r\bar{c}}{K}S(\bar{I})}\mathrm{d}x \\ =& 1-F'(\bar{I}).\end{aligned}$$

Since the equilibrium points are characterized as fixed points of F and in the considered region F is increasing, at the lowest (high) equilibrium $F'(\bar{I})>1$, then at the next one $F'(\bar{I})<1$ etc. The last one (which exists because F is bounded and hence we have a maximum number for solutions) is generically stable (see Figure 1 for an example). Double roots of $F(I)-I$ are treated in the same way, they correspond to two roots with alternating stability. The situation is qualitatively the same as in [2]. □

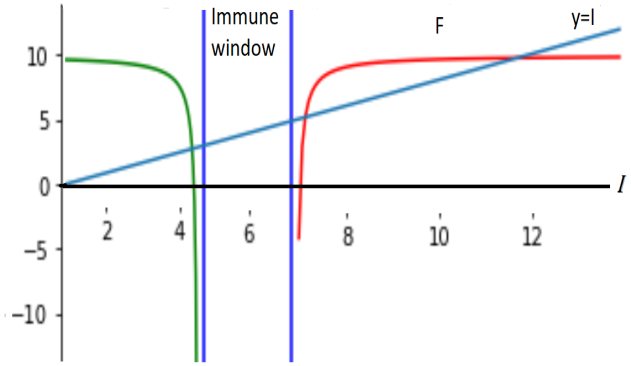

FIGURE 1. Example of the graph of a function F (green and red curve). Intersections with the identity I confirm stability changes with respect to the sign of $1 - F'(\bar{I})$. Since $F(I)$ is bounded, the last intersection occurs necessarily for $F'(I) < 1$, implying that the largest equilibrium is stable.

3.1.1. Stability of the remission equilibrium

Here we show that the age structure affects the stability of the remission equilibrium. To emphasize the role of aging, we fix the values of $\bar{c}, \bar{I}, \bar{z}$ and consider the shape of the weighted committed cell distribution

$$\bar{p}(x) = \frac{w(x)\bar{u}(x)}{\int_0^\infty w(y)\bar{u}(y)\mathrm{d}y} = \frac{w(x)\bar{u}(x)}{\bar{I}}. \tag{3.5}$$

The first result concerns the localization of the real eigenvalues.

Proposition 3.7. *For a remission equilibrium, there cannot be a real eigenvalue λ such that*

$$\lambda > -\min(\frac{r\bar{c}}{K}, \mu_u\bar{z}, S(\bar{I})).$$

Proof. The computation is the same as for high equilibrium points but now $S'(I) < 0$, so we have

$$\lambda > -\min(\frac{r\bar{c}}{K}, \mu_u\bar{z}, S(\bar{I})) \quad \text{consequently} \quad \frac{\det(M(\lambda))}{(\lambda + \frac{r\bar{c}}{K})(\lambda + S(\bar{I}))} > 0,$$

which leads to the conclusion. □

Proposition 3.8. *Every eigenvalue λ associated to the remission equilibrium with*

$$\Re(\lambda) > -\min(\frac{r\bar{c}}{K}, \mu_u\bar{z}, S(\bar{I})),$$

is a solution of the characteristic equation $det(M(\lambda)) = 0$. Because 0 is not a root, we can also consider the roots of $\lambda det(M(\lambda)) = 0$ for $\lambda \neq 0$. This leads to the simplified version

$$P(\lambda) + Q(\lambda)\int_0^\infty \frac{w(x)\bar{u}(x)}{\bar{I}}\mathrm{e}^{-\lambda x}\mathrm{d}x = 0, \quad \textit{for} \quad \lambda \neq 0 \tag{3.6}$$

where P, Q are the following polynomials

$$P(\lambda) = \lambda^3 + (R+S)\lambda^2 + (RS+D)\lambda + DR,$$
$$Q(\lambda) = \left(\frac{\mu_c}{\mu_u} - 1\right) D\lambda - DR.$$

We have introduced notations for the positive quantities

$$R = \frac{r\bar{c}}{K},\ S = S(\bar{I}),\ D = -\mu_u s \frac{S'(\bar{I})\bar{I}}{S(\bar{I})}.$$

Proof. Since 0 is not a root of (3.6), we simply write from (3.4) the equation satisfied by $\lambda \det(M)$ when $\lambda \neq 0$. In particular, in this case

$$\lambda \int_0^x \mathrm{e}^{-\lambda y} \mathrm{d}y = (1 - \mathrm{e}^{-\lambda x}).$$

With simple computations we derive:

$$\lambda \det(M(\lambda)) = \lambda(\lambda+R)(\lambda+S) - \bar{z}\mu_u S'(\bar{I})\bar{I}(\lambda+R) +$$
$$\bar{z}\mu_u S'(\bar{I})(\lambda+R)\left(\int_0^\infty w(x)u(\bar{x})\mathrm{e}^{-\lambda x}\mathrm{d}x\right) - \lambda\mu_u \bar{c} S'(\bar{I})\bar{c}\int_0^\infty \frac{1}{\bar{c}} w(x)u(\bar{x})\mathrm{e}^{-\lambda x}\mathrm{d}x. \tag{3.7}$$

Replacing $D = -\mu_u s \frac{S'(\bar{I})}{S(\bar{I})}\bar{I}$ and extending the polynomials, we obtain the result. □

Now that we have established this expression of the characteristic equation we can discuss the influence of the shape of the probability distribution $\bar{p}$ on the stability. There are two model parameters that can be modified without affecting the values of $\bar{c}, \bar{I}, \bar{z}$. That is the shape of $\bar{p}$ and the slope of the derivative $S'(\bar{I})$ which is encoded in the parameter D.

3.1.2. Stability for the exponential distribution

The case of exponential distribution $\bar{p}(x) = \gamma_0 \mathrm{e}^{-\gamma_0 x}$ corresponds to the model presented in [2]. In this case, the eigenvalues whose real part is above $-\mu_u \bar{z}$ are the (nonzero) solutions of the equation

$$\lambda(\lambda+R)(\lambda+S) + D(\lambda+R) + D\left(\left(\frac{\mu_c}{\mu_u} - 1\right)\lambda - R\right)\frac{\gamma_0}{\gamma_0+\lambda} = 0.$$

This equation reduces to the third degree polynomial

$$\chi(\lambda) = (\lambda+\gamma_0)(\lambda+R)(\lambda+S) + D(\lambda + R + \frac{\mu_c}{\mu_u}) = 0.$$

And then, we can check that any solution satisfies

$$\Re(\lambda) \leq -\min(R, S, \gamma_0) < 0.$$

The following result is proven in [2] for $\mu_u = \mu_c$. We extend it for $\mu_c \leq \mu_u$.

Proposition 3.9. *Assume $\mu_c \leq \mu_u$, then there exists no root of the polynomial χ with nonnegative real part.*

Proof. Under the assumption $\mu_c \leq \mu_u$ we can easily check that

$$\chi(-R - S - \gamma_0) < 0.$$

Moreover $\chi(-R) > 0$, hence there exists a negative root λ_1 of χ such that $-R - S - \gamma_0 < \lambda_1 < -R$. We have already established the absence of positive real roots in [2], therefore we only need to investigate complex roots that appear in conjugate pairs, say $z, \bar{z}$. If $z, \bar{z}$ are roots of χ, then

$$2\Re(z) + \lambda_1 = -R - S - \gamma_0.$$

And therefore $\Re(z) < 0$. □

3.1.3. Stability for the Dirac distribution

We are now investigating the limiting case of the Dirac distribution $\bar{p}(x) = \delta(x - \tau)$, $\tau > 0$, for which computations can be done explicitly. The Dirac can be obtained from (3.5) by taking degenerate weights w and keeping $\bar{I} =$ fixed, if we pose

$$w(x) = \frac{\bar{I}}{\bar{u}(x)}\delta(x - \tau).$$

To proceed we make some changes on the characteristic equation. Rewrite the characteristic equation as follows

$$\lambda(\lambda^2 + (R + S)\lambda + RS + D) + DR\int_0^{+\infty}(1 - \mathrm{e}^{-\lambda x})\frac{w(x)\bar{u}(x)}{\bar{I}}\mathrm{d}x = 0.$$

Divide by R^2 and set $\bar{\lambda} = \frac{\lambda}{R}$, $\bar{S} = \frac{S}{R}$ and $\bar{D} = \frac{D}{R^2}$. With simple calculations we end up with

$$\bar{\lambda}(\bar{\lambda}^2 + (1 + \bar{S})\bar{\lambda} + \bar{S} + \bar{D}) + \bar{D}\int_0^{+\infty}(1 - \mathrm{e}^{-y\bar{\lambda}})\frac{w(\frac{y}{R})u(\bar{\frac{y}{R}})}{\bar{I}}d(\frac{y}{R}) = 0.$$

If X is distributed with probability function $\bar{p}(x)\mathrm{d}x$, then $Y = RX$ has probability function $\bar{p}(\frac{y}{R})\frac{\mathrm{d}y}{R}$. For the Dirac this means changing τ to $R\tau$. In that, if Y is destabilized with $1, \bar{S}, \bar{D}$ (the characteristic equation has solutions with positive real parts), then X is destabilized with R, S, D and inversely. We will omit using the tilda symbol to simplify the notations. The equation that we will be studying is

$$\lambda((\lambda + 1)(\lambda + S) + D) + D\mathbb{E}[1 - \mathrm{e}^{-\lambda Y}] = 0,$$

where the expected value is taken with respect to a Dirac δ_τ distribution.

We are looking for purely imaginary roots $\pm i\omega$, $\omega > 0$ of the equations. This leads for $\omega > 0$ to the equation

$$-i\omega^3 - \omega^2(1 + S) + i\omega(S + D) + D = D\mathrm{e}^{-i\omega\tau}. \tag{3.8}$$

Taking modules on both sides

$$(\omega^3 - (S + D)\omega)^2 + (\omega^2(1 + S) - D)^2 = D^2. \tag{3.9}$$

Which can be simplified to a quadratic polynomial by writing $y = \omega^2$

$$y^2 + y(S^2 + 1 - 2D) + S^2 + D^2 - 2D = 0,$$

since 0 is not a solution of (3.6). We can also rewrite it as a quadratic polynomial of D

$$D^2 - 2D(y + 1) + y^2 + y(1 + S^2) + S^2 = 0. \tag{3.10}$$

In that we have two different approaches. We can either solve D as a function of ω^2 or ω^2 as a function of D.

Lemma 3.10. *($D(\omega)$) Let ω be a positive real number. The roots of the polynomial (3.10) are*

$$D_\pm = \omega^2 + 1 \pm \sqrt{(1 - S^2)(\omega^2 + 1)}.$$

If $S \leq 1$ the solutions are real and positive and satisfy $D > 1 - \sqrt{1 - S^2}$. If $S > 1$ no real solution exists.

If a set of parameters is given, then D, S should satisfy

$$S \leq 1, \tag{3.11}$$

and

$$D \geq 1 - \sqrt{1 - S^2}. \tag{3.12}$$

for solutions of (3.9) to exist.

Lemma 3.11. *Assume $S \leq 1$, then equation (3.9) has a positive root*

$$\omega_+^2 = \frac{1}{2}\left(2D - 1 - S^2 + (1 - S^2)\sqrt{1 + \frac{4D}{1 - S^2}}\right). \tag{3.13}$$

If additionally $D \geq \left(1 + \sqrt{1 - S^2}\right)$, then there is a second positive root

$$\omega_-^2 = \frac{1}{2}\left(2D - 1 - S^2 - (1 - S^2)\sqrt{1 + \frac{4D}{1 - S^2}}\right). \tag{3.14}$$

We also have the identities

$$\begin{cases} \text{for all} & D \geq \left(1 + \sqrt{1 - S^2}\right),\ D_-(\omega_+(D)) = D, \\ \text{for all} & D \geq \left(1 + \sqrt{1 - S^2}\right), D_+(\omega_-(D)) = D, \\ \text{for all} & \omega > 0,\ \omega = \omega_+(D_-(\omega)) = \omega_-(D_+(\omega)). \end{cases} \tag{3.15}$$

Corollary 3.12. *For a given distribution, if we have a solution of the form $i\omega$ to (3.6), then necessarily conditions (3.11), (3.12) hold and ω satisfies the inequalities:*

$$\begin{cases} 0 < \omega \leq \omega_+(D), & if \quad D < \left(1 + \sqrt{1 - S^2}\right), \\ \omega_-(D) \leq \omega \leq \omega_+(D), & if \quad D \geq \left(1 + \sqrt{1 - S^2}\right). \end{cases} \tag{3.16}$$

For a general distribution the inequalities are strict whereas for the Dirac equality holds. Consequently, if no Dirac loses stability, then no other distribution does.

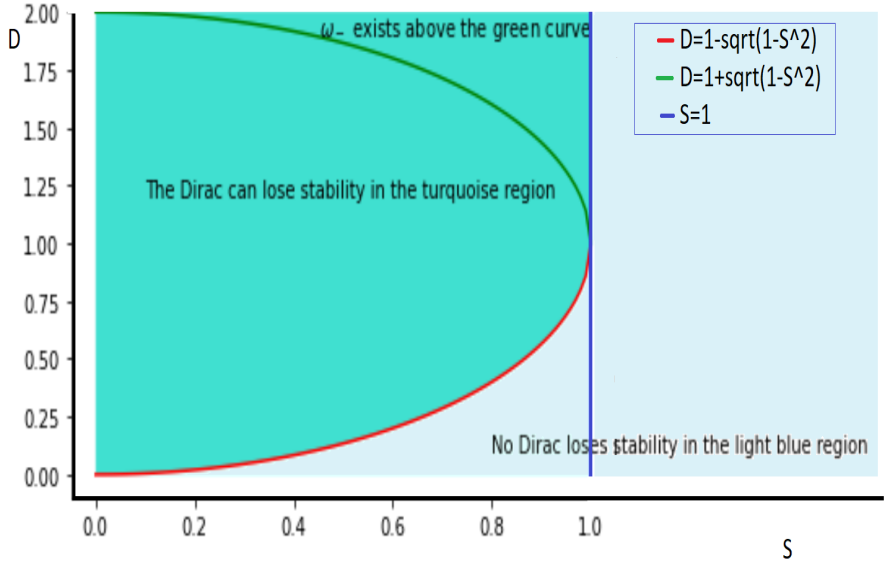

FIGURE 2. Stability chart for the Dirac distribution. For $S \geq 1$ no destabilization is possible. Otherwise, if $D \geq 1 - \sqrt{1-S^2}$ Dirac can lose stability because ω_+ exists. In the region $D \geq 1 + \sqrt{1-S^2}$, ω_- exists as well.

Proof. The characteristic equation for a distribution $\bar{p}$ at $i\omega$ becomes

$$\begin{aligned} i\omega^3 - \omega^2(1+S) + i\omega(S+D) + D = D\int_0^{+\infty} cos(\omega y)\bar{p}(y)\mathrm{d}y - iD\int_0^{+\infty} sin(\omega y)\bar{p}(y)\mathrm{d}y \\ \text{or} \quad i\omega^3 - \omega^2(1+S) + i\omega(S+D) + D = D\mathbb{E}[cos(\omega Y)] - iD\mathbb{E}[sin(\omega Y)]. \end{aligned} \tag{3.17}$$

If $\bar{p}(x) = \delta(x-\tau)$ we have the equation (3.9) and the solutions $\omega_\pm$ as explained above. Otherwise, comparing modules

$$(\omega^3 - (S+D)\omega)^2 + (\omega^2(1+S) - D)^2 < D^2.$$

As above, since 0 is not a solution, this reduces to $y = \omega^2$ satisfies

$$y^2 + y(S^2 + 1 - 2D) + S^2 + D^2 - 2D < 0.$$

The quadratic polynomial is negative in the regions of ω^2 defined above. See Figure 2 □

Lemma 3.13. *The stability boundary for the Dirac distribution is given by the graph*

$$\tau(D) = \tau(\omega_+(D)) = \frac{1}{\omega_+(D)}\left(\frac{3\pi}{2} + \arctan\left(\frac{D - \omega_+^2(D)}{\omega_+(D)S}\right) - \arctan(\omega_+(D))\right). \tag{3.18}$$

Proof. For $\tau = 0$ the equilibrium is stable. Indeed from the characteristic equation

$$\lambda\left((\lambda+1)(\lambda+S) + D\right) = 0$$

Since $\lambda \neq 0$ we obtain the quadratic polynomial

$$\lambda^2 + (1+S)\lambda + (S+D) = 0$$

which has two roots

$$\lambda_{1,2} = \frac{-(1+S) \pm \sqrt{(1+S)^2 - 4(S+D)}}{2}$$

with negative real parts. For $\tau > 0$, from (3.8) we have

$$\begin{cases} -\omega^3 + \omega(S+D) = D\sin(-\omega\tau), \\ -\omega^2(1+S) + D = D\cos(-\omega\tau). \end{cases}$$

So

$$\frac{P_2(i\omega)}{D} = E[\mathrm{e}^{i\omega Y}],$$

with respect to δ_τ. Where $P_2(\lambda) = -\lambda^3 + (1+S)\lambda^2 - (S+D)\lambda + D$. The complex number $\frac{P_2(i\omega)}{D}$ has modulus 1.

Hence

$$\begin{pmatrix} \cos(\omega\tau) \\ \sin(\omega\tau) \end{pmatrix} = \begin{pmatrix} \frac{-\omega^2(1+S)+D}{D} \\ \frac{\omega^3-(S+D)\omega}{D} \end{pmatrix}.$$

Using the matrix equality

$$\sqrt{\omega^2+1}\begin{pmatrix} \sin(\arctan(\omega)) & \cos(\arctan(\omega)) \end{pmatrix} = \begin{pmatrix} \omega & 1 \end{pmatrix},$$

and multiplying each side with this equation we obtain

$$\begin{aligned} D\sqrt{\omega^2+1}\sin(\omega\tau + \arctan(\omega)) &= -\omega S(\omega^2+1), \\ D\sqrt{\omega^2+1}\cos(\omega\tau + \arctan(\omega)) &= (1+\omega^2)(D-\omega^2). \end{aligned}$$

Since $-\omega S(\omega^2+1) < 0$, we have

$$\omega\tau + \arctan(\omega) \in [\pi, 2\pi],$$

or equivalently

$$-\frac{\pi}{2} < \omega\tau + \arctan(\omega) - \frac{3\pi}{2} < \frac{\pi}{2}.$$

So

$$\tan(\omega\tau + \arctan(\omega) - \frac{3\pi}{2}) = \frac{\cos(\omega\tau + \arctan(\omega))}{-\sin(\omega\tau + \arctan(\omega))} = \frac{(1+\omega^2)(D-\omega^2)}{\omega S(\omega^2+1)}.$$

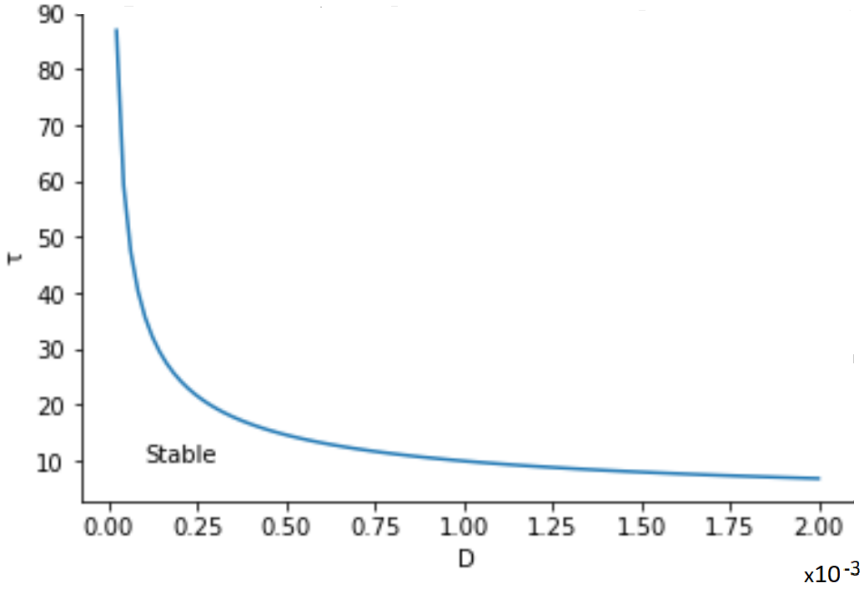

FIGURE 3. Stability boundary given by a single Dirac distribution.

Finally

$$\tau = \frac{1}{\omega}\left(\frac{3\pi}{2} + \arctan\left(\frac{D-\omega^2}{\omega S}\right) - \arctan(\omega)\right).$$

Clearly τ is a decreasing function of ω. So the boundary is given by ω_+ and not ω_-, Figure 3. □

3.1.4. Stability boundary for two Dirac masses: Suboptimality of the Dirac solutions

The characteristic equation for $\mu_u = \mu_c$ becomes

$$\frac{P(\lambda)}{D} = \mathbb{E}(\mathrm{e}^{-\lambda X}), \tag{3.19}$$

where $\mathbb{E}$ denotes the mean value with respect to the distribution $\bar{p}(x)$.

In the case of $P(\lambda) = \lambda + a$, a first degree polynomial, it has been established in [1] that the Dirac is the less stable distribution among all distributions with the same mean. This means that if an unstable distribution with mean $\bar{X}$ exists, then the Dirac $\delta_{\bar{X}}$ is also unstable. In what follows we prove that this is not the case for our model where $\deg P = 3$. In particular, we prove that for certain parameters we can find an unstable distribution, which is not a Dirac, with mean $\bar{X} < \tau_+$.

We will give an answer to the following question

Question 3.14. Given S and D and $\tau(\omega_+(D))$ defined in (3.18), is a distribution whose mean value satisfies

$$E(x) = \int_0^{+\infty} x\bar{p}(x)\mathrm{d}x < \tau(\omega_+(D)),$$

necessarily stable?

Theorem 3.15. *There exists a value of S, say S^*, such that for all $S \in (0, S^*)$ there exists a value of D and a distribution X such that $E(X) < \tau(D)$ and equation (3.19) is satisfied for some $i\omega$.*

Proof. Let us write

$$\begin{cases} x(\omega) = 1 - \frac{\omega^2(S+1)}{D}, \\ y(\omega) = \frac{\omega^3 - \omega(S+D)}{D}. \end{cases}$$

The point (x, y) is inside the unit disk, so we can write

$$x + iy = \sqrt{x^2 + y^2} \mathrm{e}^{i\beta(\omega)},$$

with $\beta \in [0, 2\pi[$ and $\sqrt{x^2 + y^2} < 1$.

Lemma 3.16. *Let $\omega \in (\omega_-, \omega_+)$ and consider the argument*

$$\theta'(\omega) = \pi - 2 \arctan(\frac{y}{1-x}),$$

the number

$$q(\omega) = \frac{y^2 + (1-x)^2}{2(1-x)} \in [0, 1],$$

and the distribution :

$$\bar{p}_\omega = q(\omega)\delta_{\frac{\theta'}{\omega}} + (1 - q(\omega))\delta_0.$$

For every $\omega \in]\omega_-, \omega_+[$ (or in $]0, \omega_+[$ if ω_- is not defined), we have

$$\frac{P(i\omega)}{D} = \int_0^\infty \mathrm{e}^{-i\omega x} \bar{p}_\omega(\mathrm{d}x).$$

That is (3.19) is satisfied with $\lambda = i\omega$ for the distribution $\bar{p_\omega}$.

Proof. For $\omega \in (\omega_-, \omega_+)$, $x^2 + y^2 \leq 1$ by construction. Then we easily check

$$\begin{cases} \cos(\theta') = \frac{y^2 - (1-x)^2}{(y^2 + (1-x)^2)^2}, \\ \sin(\theta') = \frac{2y(1-x)}{(y^2 + (1-x)^2)^2}. \end{cases}$$

If we denote by $\mathbb{E}_{\bar{p}_\omega}$ the mean with respect to the distribution $\bar{p}_\omega$, we obtain

$$\begin{cases} \mathbb{E}_{\bar{p}_\omega}(\cos(\omega X)) = x(\omega), \\ \mathbb{E}_{\bar{p}_\omega}(\sin(\omega X)) = y(\omega), \end{cases}$$

which is a necessary and sufficient condition for (3.19) to be satisfied for $\lambda = i\omega$, $\omega \neq 0$. □

Note that $q(\omega_+) = 1, \theta'(\omega_+) = \beta(\omega_+)$ and $\frac{q(\omega_+)\theta'(\omega_+)}{\omega_+} = \tau(\omega_+)$ for the Dirac.

Lemma 3.17. *Let us denote $\tau_{\bar{p}}(\omega) = \int_0^\infty x\bar{p}_\omega(\mathrm{d}x)$. A value S^* exists such that for every $S \in (0, S^*)$ there exists a value of D such that*

$$\frac{d\tau_{\bar{p}}(\omega)}{d\omega} \mid_{\omega=\omega_+} > 0.$$

In the above case $\mathbb{E}_{\bar{p}_\omega}(X) < \tau(\omega_+(D))$ for $\omega < \omega_+$ close enough to ω_+.

Proof. Let us differentiate $\tau_{\bar{p}}(\omega)$.

$$\frac{d}{d\omega}\tau_{\bar{p}}(\omega) = \theta' \frac{d}{d\omega}\frac{q}{\omega} + \frac{q}{\omega}\frac{d\theta'}{d\omega}(\omega).$$

We compute the terms separately

$$\theta'(\omega) = \pi - 2\arctan\left(\frac{y}{1-x}\right) = \pi - 2\arctan\left(\frac{\omega^2 - (S+D)}{\omega(S+1)}\right).$$

So,

$$\begin{aligned}\frac{d\theta'}{d\omega}(\omega) &= -2\frac{1}{1+\frac{(\omega^2-(S+D))^2}{\omega^2(S+1)^2}}\left(\frac{1}{S+1} + \frac{S+D}{\omega^2(S+1)}\right) \\ &= -2\frac{(S+1)(\omega^2+S+D)}{\omega^2(S+1)^2 + (\omega^2-(S+D))^2}.\end{aligned}$$

For the second term

$$\frac{q}{\omega} = \frac{(\omega^3 - \omega(S+D))^2 + \omega^4(S+1)^2}{2\omega^2(S+1)D\omega} = \frac{(\omega^2-(S+D))^2 + \omega^2(S+1)^2}{2(S+1)D\omega}.$$

Therefore

$$\begin{aligned}\frac{d}{d\omega}\frac{q}{\omega} &= \frac{1}{2D(S+1)\omega^2}\left(2\omega^2\left(2(\omega^2-(S+D)) + (S+1)^2\right)\right) - ((\omega^2-(S+D))^2 + \omega^2(S+1)^2) \\ &= \frac{1}{2D(S+1)\omega^2}\left(3\omega^4 + \omega^2((S+1)^2 - 2S - 2D) - (S+D)^2\right).\end{aligned}$$

We end up with the following

$$\begin{aligned}\frac{d}{d\omega}\tau_{\bar{p}}(\omega) \mid_{\omega_+} =& \theta'\left(\frac{1}{2D(S+1)\omega^2}\left(3\omega^4 + \omega^2((S+1)^2 - 2S - 2D) - (S+D)^2\right)\right) \\ &- \frac{q}{\omega}2\frac{(S+1)(\omega^2+S+D)}{\omega^2(S+1)^2 + (\omega^2-(S+D))^2}.\end{aligned}$$

At $\omega = \omega_+$, $q(\omega_+) = 1$ by construction so

$$\begin{aligned}\frac{d}{d\omega}\tau_{\bar{p}}(\omega) \mid_{\omega_+} =& \theta'\left(\frac{1}{2D(S+1)\omega^2}\left(3\omega^4 + \omega^2((S+1)^2 - 2S - 2D) - (S+D)^2\right)\right) \\ &- \frac{2}{\omega}\frac{(S+1)(\omega^2+S+D)}{\omega^2(S+1)^2 + (\omega^2-(S+D))^2}.\end{aligned}$$

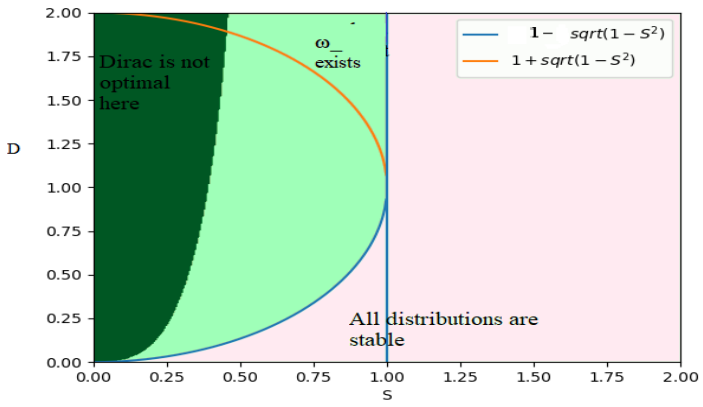

FIGURE 4. in the dark green region of non optimality of the Dirac, the distribution that is used is the sum of two Dirac masses. The boundary is obtained by the relation $\frac{d\tau_{\bar{p}}(\omega)}{d\omega} > 0$. Note that this region may be larger than what we see in the graph since there are probably other distributions that are less stable than the Dirac.

By the definition of ω_+, if $D = \frac{S(1+S)}{1-S}$ then $\omega_+^2 = S + D$. Therefore $y(\omega_+) = 0$, so that $\beta(\omega_+) = \theta'(\omega_+) = \pi$. In this case

$$\begin{aligned}\frac{d}{d\omega}\tau_{\bar{p}}(\omega)\mid_{\omega_+} =& \pi\left(\frac{1}{2D(S+1)(S+D)}\left(3(S+D)^2+(S+D)((S+1)^2-2S-2D)-(S+D)^2\right)\right)\\ &-\frac{2}{\sqrt{(S+D)}}\frac{(S+1)((S+D)+S+D)}{(S+D)(S+1)^2}\\ &=\pi\frac{(S+1)}{2D}-\frac{4}{(S+1)\sqrt{S+D}}.\end{aligned}$$

Therefore the derivative has the sign of

$$\pi - \frac{8D}{(S+1)^2\sqrt{S+D}} = \pi - \frac{4\sqrt{2S}}{\sqrt{1-S}(S+1)}.$$

which is positive if and only if $\frac{4\sqrt{2S}}{\sqrt{1-S}(S+1)} < \pi$, if and only if $32\frac{S}{1-S} < \pi^2(S^2+2S+1)$, if and only if $(S^2+2S+1)(1-S) > \frac{32}{\pi^2}S$.

As $g(S) = \frac{\pi^2}{32}(-S^3-S^2+S+1)$ is decreasing on $(0,1)$, there is unique solution S^* of $g(S) = S$. On $(0,S^*)$, $g(S) > S$, so S^* defines the interval we are looking for. □

This ends the proof of Theorem 3.15. □

The graphe Figure 4 summarizes our results:

4. APPLICATION USING BIOLOGICALLY RELEVANT PARAMETERS

To test the theoretical results of the previous section, we work with the ODE system 1.1 which can be obtained from the PDE 1.2 by setting

$$\mu_c = \mu_u = \mu,\ a = a_1,\ h(x) = -d_2.$$

TABLE 1. Universal parameters for the constant coefficient case.

K	41.667
d_2	0.0375
r	0.00777
a_1 (without treatment)	1.350e+05

TABLE 2. Patient dependent parameters as estimated in Table 3 of [2].

Patient	d	μ	y_{min}	y_{max}
1	0.051	3.647e-6	6.610e4	3.624e5
2	0.026	2.405e-8	3.831e4	3.055e5
3	0.054	4.224e-7	1.617e4	3.133e5
4	0.181	8.499e-6	1.206e3	1.090e4
5	0.038	5.723e-9	1.841e3	3.401e4
6	0.058	1.358e-9	7.143e3	7.576e4

We remind that when the coefficients of the PDE are constant this leads to an exponential distribution for the equilibrium point, a case that has already been estimated on patients in [2]. Hence, we have access to realistic parameters that are estimated under treatment. For the non-treated case one should simply modify a_1 (in a way that is precised later). We choose the following S:

$$S(y) = d\frac{(y - y_{min})(y - y_{max})}{y^2 + y_{min}y_{max}},$$

where d stands for the natural death rate of immune cells since $d = S(0)$. The universal parameters are given in the table 1 and are the same as in [2] and the patient dependent parameters are given in Table 2.

With these choices, there is always a positive equilibrium of the ODE 1.1 satisfying $\bar{y}_2 < y_{min}$. In the presence of a high equilibrium point (which will satisfy $\bar{y}_2 > y_{max}$) this corresponds to a remission equilibrium.

Since we are interested in the effect of the distribution in the stability of the remission equilibrium we set $\bar{I} = \bar{y}_2$ and $\mu_u = \mu_c$. The critical $\tau = \tau(D, S)$ of destabilization depends on the parameters D, S and exists under the constraint (3.12) and (3.11). Without the normalization of the parameters, the value of the critical delay depends on S, D, R and is given by $\frac{1}{R}\tau\left(1, \frac{S}{R}, \frac{D}{R^2}\right)$ which exists under the constraints

$$D \geq R^2(1 - \sqrt{1 - \frac{S^2}{R^2}}). \tag{4.1}$$

and

$$R^2 \geq S^2, \tag{4.2}$$

respectively. Without treatment the remission equilibrium does not lose stability for any patient since the condition (4.2) is never satisfied. This is summarized in the Table 3

On the other hand we observe destabilization under treatment for some patients. To account for treatment, we divide α_1 by a factor k_{inh} indicating the inhibitory effects. In the Table 4 we see the values of S, D and the critical τ for the patients under treatment. Whenever $\tau = +\infty$ the equilibrium is stable. In the case of destabilization

TABLE 3. Parameters for patients without treatment: condition (4.2) is never satisfied.

Patient	$\bar{I}$	$\frac{R^2}{S^2}$
1	6.0928e+04	1.7578e-06
2	3.8292e+04	0.0615
3	1.6053e+04	8.1206e-06
4	1.0176e+03	7.1767e-12
5	1.8408e+03	0.0012
6	7.1428e+03	0.1349

TABLE 4. Parameters for patients under treatment.

Patient	a_1 (under treatment)	S	D	τ (in days)
1	5.4e02	3.26e-03	2.4054e-04	No destabilization
2	1.2e02	1.44e-05	1.0526e-04	158.8137
3	3.2e02	3.723e-04	3.5612e-04	142.9637
4	0.2e02	2.489e-02	9.9090e-04	No destabilization
5	0.3e02	3.6e-06	2.4709e-04	100.8270
6	0.5e02	1.447e-06	3.1349e-04	89.6290

under treatment, we have not specified the meaning of this destabilization. We make the conjecture that it corresponds to the appearance of oscillations and the existence of a Hopf bifurcation but simulations need to be done to verify this assumption. The bifurcation analysis is left to a future work.

5. Discussion and conclusion

In this work it is proven that the age structure of the leukemic cells affects the stability status of the equilibrium points of the tumor-immune model of CML introduced in [2, 3]. In particular, the remission equilibrium is not systematically stable and the stability loss is proven in the degenerate case of a Dirac distribution for the leukemic committed cells, which shows that the PDE is not a trivial extension of the ODE. To prove the result, an explicit counter example is created giving a threshold of the delay. Although this is not a universal bound (in contrast to scalar models), it gives an order of magnitude of the mean age of the distribution that can destabilize the equilibrium. A further analysis of this destabilization is the scope of a futur work. We conjecture that it corresponds to a Hopf bifurcation and consequently the instability does not necessarily imply a systematic relapse (it could be a limit cycle instead).

Appendix A. Elements of spectral theory

We start this section with some elements of spectral theory that we use for our stability analysis. Their proofs can be found in [16], while next to each result we give the page where one can find it. We keep the same notations as in [16]. In particular in what follows $rg(A)$ stands for the range of A, namely the image space of the operator.

Definition A.1. (p. 36)
A familly $(T(t))_{t\geq 0}$ of bounded linear operators on a Banach space X is called strongly continuous (one parameter) semi-group (or C_0 semi-group) if the functional equation holds:

$$\begin{cases} T(t+s) = T(t)T(s) \quad for \quad all \quad t,s \geq 0, \\ T(0) = I \end{cases}$$

and the orbit maps

$$\xi_x : t \to \xi_x(t) := T(t)x,$$

are continuous from $\mathbb{R}^+$ into X for every $x \in X$.

Remark A.2. The second property can also be expressed by saying that the map

$$t \to T(t),$$

is continuous from $\mathbb{R}^+$ into the space of all bounded operators on X endowed with the strong operator topology.

Definition A.3. The generator $A : D(A) \subset X \to X$ of a strongly continuous semi-group $(T(t))_{t\geq 0}$ on a Banach space X is the operator:

$$Ax := \dot{\xi}_x(0) = lim_{h\to 0}\frac{T(h)x - x}{h},$$

defined for every x in the domain:

$$D(A) := \{x \in X : \xi_x \quad is \quad differentiable\}.$$

Definition A.4. For a closed operator $A : D(A) \subseteq X \to X$ we define:

a) The point spectrum: (p.241)

$$P_\sigma(A) = \{\lambda \in \mathbb{C} : \lambda - A \text{ is not injective}\}$$

All $\lambda \in P_\sigma(A)$ are called the eigenvalues of A and every $x \neq 0 \in D(A)$ that satisfies $(\lambda - A)x = 0$ is an eigenvector of A associated to the eigenvalue λ.

b) The approximate point spectrum of A: (p.242)

$$A_\sigma(A) = \{\lambda \in \mathbb{C} : \lambda - A \text{ is not injective or } rg(\lambda - A) \text{ is not closed in X}\}$$

All $\lambda \in A_\sigma(A)$ are called approximate eigenvalues of A.

c) The residual spectrum of A: (p.243)

$$R_\sigma(A) = \{\lambda \in \mathbb{C} : rg(\lambda - A) \text{ is not dense in X}\}$$

Lemma A.5. *(p.242)*
For a closed operator $A : D(A) \subset X \to X$ and a complex number $\lambda \in \mathbb{C}$ we have that: $\lambda \in A_\sigma(A)$ if and only if there is a sequence $(x_n)_{n\in\mathbb{N}} \subset D(A)$, called approximate eigenvector, such that $\|x_n\| = 1$ and $lim_{n\to\infty}\|Ax_n - \lambda x_n\| = 0$.

Theorem A.6. ***Spectral theorem for point and residual spectrum*** *(p.277)*
For the generator $(A, D(A))$ of a strongly continuous semi group $(T(t))_{t\geq 0}$ defined on a Banach space, we have the following identities:

$$P_\sigma(T(t))\backslash\{0\} = \mathrm{e}^{tP_\sigma(A)},$$

$$R_\sigma(T(t))\backslash\{0\} = \mathrm{e}^{tR_\sigma(A)}$$

for every $t \geq 0$.

Definition A.7. (p.250) Let $A : D(A) \subset X \to X$ be a closed operator. Then,

$$s(A) = sup\{\Re(\lambda) : \lambda \in \sigma(A)\}$$

is the spectral bound of A.

Moreover,

$$\omega_0 = inf\{\omega \in \mathbb{R}, \text{ such that there exists, } M_\omega \geq 1 : \|T(t)\| \leq M_\omega e^{\omega t} \text{ for every } t \geq 0\}$$

is the growth bound of A.

Proposition A.8. *(p.251) For the growth and the spectral bound of an operator A that is the infinitesimal generator of a semi group* $(T(t))_{t\geq 0}$ *we have:*

$$-\infty \leq s(A) \leq \omega_0 = inf_{t>0}\frac{1}{t}log\|T(t)\| = lim_{t\to\infty}\frac{1}{t}log\|T(t)\|$$

$$= \frac{1}{t_0}logr(T(t_0)) < \infty,$$

for every $t_0 > 0$. *In particular, the spectral radius of* $T(t)$ *is given by*

$$r(T(t)) = e^{\omega_0 t},$$

for every $t \geq 0$.

Proposition A.9. *(p.39)*
For a strongly continuous semi group $(T(t))_{t\geq 0}$ *there are constants* $\omega \in \mathbb{R}$ *and* $M \geq 1$ *such that*

$$\|T(t)\| \leq Me^{\omega t}$$

for every $t \geq 0$.

A.1 Eigenvalues determine stability for the semigroup (3.2).

Proposition A.10. *The growth bound* ω_0 *of the linear semi group defined in* (3.2) *satisfies* $\omega_0 \leq \max(-\mu_u\bar{z}, s(A))$ *where we have classically denoted* $s(A) = \sup_{\lambda\in\sigma(A)} Re(\lambda)$. *In particular if* $s(A) < 0$ *the steady state is linearly exponentially (and also non-linearly) stable.*

Proof. Firstly, observe that the difficulty derives from lack of compactness (if age lied in a bounded interval, we would be able to derive the result immediately from eventual compactness). For the proof we will need some properties and definitions from spectral analysis given in the beginning of this section. First notice that all elements of $\sigma(T(t))$ have exponential form. For the point and the residual spectrum it is a result of spectral theorem. For the approximate spectrum it is immediate from its limit property. Indeed if μ is an approximate eigenvalue of $T(t)$ and x_0^n an approximate eigenvector then taking the limit

$$lim_{n\to+\infty}\|T(t)x_n^0 - \mu x_0^n\| = 0,$$

we get after some easy calculation that the limit of the approximate eigenvector x_0 is a proper vector hence μ has exponential form lets say $e^{\lambda t}$. Then the eigenvector and the eigenvalue define a solution with exponential profile

of the linear problem, let's say: $c_n^0 \mathrm{e}^{\lambda t}, u_n^0(x)\mathrm{e}^{\lambda t}, z_n^0 \mathrm{e}^{\lambda t}$. Back to our proof, it suffices to prove that the approximate spectrum of $T(t)$ does not contain any element $\mathrm{e}^{\lambda t}$ with $Re(\lambda) > -\mu_u \bar{z}$. Therefore, we consider a sequence x_n^0 such that $\|T(t)x_n^0 - \mathrm{e}^{\lambda t}x_0^n\| \to 0$. Let c_n^0, u_n^0, z_n^0 be the components of x^0 and define $c_n(s), u_n(s), z_n(s)$ as the solution of the linear problem with initial data c_n^0, u_n^0, z_n^0. It is straightforward to derive a bound on

$$\sup_{[0,t]}|c_n(s)| + \int_0^\infty |u_n(s,x)|\mathrm{d}x + |z_n(s)| \leq M \max(1, \mathrm{e}^{\omega_0 t}).$$

From the Arzela-Ascoli theorem in the components associated to c, z we have the convergence (up to subsequence)

$$\sup_{[0,t]}|c_n(s) - c^\infty(s)| + |z_n(s) - z^\infty(s)| \to 0.$$

Then, keeping the previous notations, we can solve the equations on u_n leading to

$$u_n(t,x) = \begin{cases} u_n^0(x-t)\frac{E_0(x)}{E_0(x-t)} - \mu_u \bar{u}(x)\int_0^t z_n(s)\mathrm{d}s \text{ if } x - t \geq 0, \\ c_n(t-x)E_0(x) - \mu_u \bar{u}(x)\int_0^x z_n(t-x+s), x - t < 0. \end{cases}$$

Hence we infer the (pointwise) convergence of u_n^0 on $[0,t]$ (simply using the second line) towards

$$\begin{aligned} u_n^0(x) \to \quad & \mathrm{e}^{-\lambda t}\left(c^\infty(t-x)E_0(x) - \mu_u \bar{u}(x)\int_{t-x}^t z^\infty(s)\,\mathrm{d}s\right) \\ & = \mathrm{e}^{-\lambda(t-x)}c^\infty(t-x)E_\lambda(x) - \mathrm{e}^{-\lambda t}\mu_u \bar{u}(x)\int_{t-x}^t z^\infty(s)\,\mathrm{d}s. \end{aligned}$$

Noting

$$\frac{E_0(x)}{E_0(x-t)}\mathrm{e}^{-\lambda t} = \frac{E_\lambda(x)}{E_\lambda(x-t)}, \qquad \frac{E_0(x+t)}{E_0(x)}\bar{u}(x) = \bar{u}(x+t),$$

Since we have by construction, $c^\infty(t) = c^\infty(0)\mathrm{e}^{\lambda t}$, we can naturally extend $s \mapsto c^\infty(s)\mathrm{e}^{-\lambda s}$ into a (continuous) t periodic function $c_p^\infty(.)$ on $\mathbb{R}$. Similarly, we define $z_p^\infty(.)$. This writing is then quite convenient since it allows a condensed formula for the pointwise limit

$$u^\infty(x) = c_p^\infty(t-x)E_\lambda(x) - \mu_u \bar{u}(x)\int_{t-x}^t \mathrm{e}^{\lambda(s-t)}z_p^\infty(s)\,\mathrm{d}s.$$

If the above limits are nonzero, we have just built an eigenvector of $T(t)$ with eigenvalue $\mathrm{e}^{\lambda t}$ (and we are dealing with the point spectrum instead of the approximate point spectrum). In this case, we have $\lambda \leq s(A)$. On the other hand, if the pointwise limit is 0, it means that the sequence presents compactness problem. By construction $u_0^n \to u^\infty$ in L^1 on compact intervals. Since the total mass is preserved, it means that we have mass going to ∞. In this case, the c, z components go to zero and hence so does u_0^n on any compact interval. So for any fixed $R > 0$ we have

$$\|T(t)x^n\| = \int_R^\infty |u^n(t,x)|\mathrm{d}x + o(1) \leq \|u_0^n\| \sup_{R,\infty}\frac{E_0(x+t)}{E_0(x)} + o(1).$$

So

$$e^{\lambda t} \leq \limsup_{x\to+\infty} \frac{E_0(x+t)}{E_0(x)} = \limsup_{x\to+\infty} e^{\int_x^{x+t} h-\mu_u \bar{z}} \leq e^{-\mu_u \bar{z} t}.$$

In this case, the hypothesis $e^{\lambda t} \leq e^{-\mu_u \bar{z} t}$ entails that $\lambda \leq -\mu_u \bar{z}$. □

Corollary A.11. *Let $(T(t))_{t\geq 0}$ denote the linear semi-group defined in (3.2) and A its infinitesimal generator. If all the eigenvalues of A have negative real part then T is exponentially stable. That is, there are $M > 0, \lambda_0 > 0$ strictly positive constants such that*

$$||T(t)|| \leq M e^{-\lambda_0 t}.$$

Proof. As already shown, the growth bound of T satisfies

$$\omega_0 \leq max(-\mu_u \bar{z}, s(A)).$$

By assumption $s(A) \leq 0$. We have to show that $s(A) \neq 0$. Since all eigenvalues of A have negative real part it suffices to prove that the eigenvalues do not accumulate around 0. The eigenvalues λ with $\Re(\lambda) > -\mu_u \bar{z}$ are roots of the characteristic equation

$$det(M(\lambda)) = 0.$$

The function $det(M(\lambda))$ is analytic on $D = \{z \in \mathbb{C} \text{ such that } \Re(z) > -\mu_u \bar{z}\}$. We will show that there is a constant K such that all eigenvalues have bounded modulus $|\lambda| \leq K$. Hence, in the compact set $B = \{z \in \mathbb{C}, |z| \leq K\}$, $detM(\lambda)$ has finitely many zeros so no accumulation is possible. Indeed $det(M(\lambda))$ is of the form

$$(\lambda + K_1)(\lambda + K_2) = (\lambda + K_1)K_3 I_1(\lambda) + K_4 I_2(\lambda),$$

with K_1, K_2, K_3, K_4 constants and $I_1 = \int_0^{+\infty} w(x)\bar{u}(x) \int_0^x e^{-\lambda(x-y)} dy dx$, $I_2 = \int_0^{+\infty} w(x)\bar{u}(x) e^{-\lambda x} dx$. On D both integrals are uniformly bounded, so there are K_5, K_6 such that eigenvalues satisfy an inequality of the form

$$|\lambda + K_1||\lambda + K_2| - K_3 K_5 |\lambda + K_1| \leq K_4 K_6$$

Since the modulus of the left hand side goes to $+\infty$ when $|\lambda| \to +\infty$, there is a K such that $|\lambda| < K$. □

Appendix B. Proof of Theorem 3.2

If a stationary point $(\bar{c}, \bar{u}, \bar{z})$ is linearly exponentially stable, then it is also non linearly stable in the sense that if initial conditions (c_0, u_0, z_0) take values close to the equilibrium:

$$\|(c_0 - \bar{c}, u_0 - \bar{u}, z_0 - \bar{z})\|_X \leq C_1,$$

then the solution (c, u, z) of the non linear system at time t satisfies:

$$\|(c - \bar{c}, u - \bar{u}, z - \bar{z})(t)\|_X < C_2 e^{-C_3 t},$$

with C_1, C_2, C_3 positive constants.

Proof. We write the perturbed system around a steady state $(\bar{c}, \bar{u}, \bar{z})$. If $(c(t), u(x,t), z(t))$ is a solution, then the perturbation $(\delta c, \delta u, \delta z) = (c - \bar{c}, u - \bar{u}, z - \bar{z})$ satisfies:

$$\begin{cases} \frac{\mathrm{d}\delta c}{\mathrm{d}t} = (r - \frac{2r\bar{c}}{K} - \mu_c \bar{z})\delta c - \mu_c \bar{c}\delta z - \mu_c \delta c \delta z - \frac{r}{K}\delta_c^2, \\ \frac{\partial \delta u}{\partial t}(t,x) + \frac{\partial \delta u}{\partial x}(t,x) = h(x)\delta u(t,x) - \mu_u \bar{z}\delta u(t,x) - \mu_u \bar{u}(x)\delta z(t) - \mu_u \delta u \delta z, \\ \delta u(t,0) = a\delta c(t), \\ \frac{\mathrm{d}\delta z}{\mathrm{d}t} = -S(\bar{I})\delta z - \bar{z}S'(\bar{I})\delta I \\ (-S(\bar{I} + \delta I) + S(\bar{I}) + S'(\bar{I})\delta I)\bar{z} + (-S(\bar{I} + \delta I) + S(\bar{I}))\delta z. \end{cases}$$

Therefore, if L is the linear part of the system, we can write the equation in the form:

$$\dot{Y} = LY + \omega(t),$$

where we have written

$$Y(t) = \begin{pmatrix} c(t) \\ u(t,.) \\ z(t) \end{pmatrix},$$

$$\omega(t,x) = \begin{pmatrix} -\mu_c \delta c(t)\delta z(t) - \frac{r}{K}\delta_c^2 \\ -\mu_u \delta u(t,x)\delta z(t) \\ (-S(\bar{I} + \delta I(t)) + S(\bar{I}) + S'(\bar{I})\delta I(t))\bar{z} + (-S(\bar{I} + \delta I(t)) + S(\bar{I}))\delta z(t) \end{pmatrix}.$$

We restrict ourselves to admissible perturbations (we impose initially that $(\bar{c} + \delta c(0), \bar{u} + \delta u(0,.), \bar{z} + \delta z(0)) \geq 0$ and defined in the appropriate space),
$\bar{I} + \delta I$ is uniformly bounded since I has a global bound. So in a neighborhood of the remission equilibrium we can assume that there exists a constant, independent of the perturbation, such that

$$\bar{I} + \delta I(t) \leq B,$$

This ensures, by Taylor expansion, the existence of a constant K, independent of the perturbation, such that if we start in the latter neighborhood of the equilibrium point then

$$|(S(\bar{I} + \delta I(t)) - S(\bar{I}) - S'(\bar{I})\delta I(t))\bar{z} - (S(\bar{I} + \delta I(t)) - S(\bar{I}))\delta z(t)| \leq K(|\delta I|^2 + |\delta z|^2).$$

From all these remarks, we infer the existence of a constant still denoted by K, such that

$$\|\omega(t)\|_X \leq K\|(\delta c, \delta u, \delta z)\|_X^2.$$

Finally, if we denote by T the semi-group associated to the linear operator above, we can derive from Duhamel's formula

$$\left(\delta c, \delta u, \delta z\right)(t) = T(t)\left(\delta c, \delta u, \delta z\right)(0) + \int_0^t T(t-s)\omega(s)\mathrm{d}s.$$

In terms of norms, this can be written as:

$$\left\|\left(\delta c, \delta u, \delta z\right)(t)\right\| \leq \|T(t)\| \left\|\left(\delta c, \delta u, \delta z\right)(0)\right\| + K\int_0^t \|T(t-s)\| \left\|\left(\delta c, \delta u, \delta z\right)(s)\right\|^2 \mathrm{d}s.$$

If the linear system is exponentially stable then two positive constants exist M, λ_0 such that $\|T(t)\| \leq M\mathrm{e}^{-\lambda_0 t}$. Now set $y = \left\|\left(\delta c, \delta u, \delta z\right)(t)\right\|$,

$$y(t) \leq M\mathrm{e}^{-\lambda_0 t} y_0 + KM \int_0^t \mathrm{e}^{-\lambda_0 (t-s)} y^2(s) \mathrm{d}s,$$

which leads to

$$y(t)\mathrm{e}^{\lambda_0 t} \leq My_0 + KM \int_0^t \mathrm{e}^{-\lambda_0 s} (y(s)\mathrm{e}^{\lambda_0 s})^2 \mathrm{d}s,$$

For $y_0 \leq \frac{\lambda_0}{4M^2K}$, we conclude by bootstrap argument that:

$$y(t)\mathrm{e}^{\lambda_0 t} \leq \frac{1}{2}\left(\frac{\lambda_0}{MK} + \sqrt{(\frac{\lambda_0}{MK})^2 - 4\frac{\lambda_0 y_0}{K}}\right),$$

which leads to the conclusion. □

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