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Kyriaki Dariva. Contributions to the stability analysis of cell population models.. Mathematics [math]. Université Claude Bernard Lyon 1, 2022. English. NNT: . tel-03956608v1

HAL Id: tel-03956608

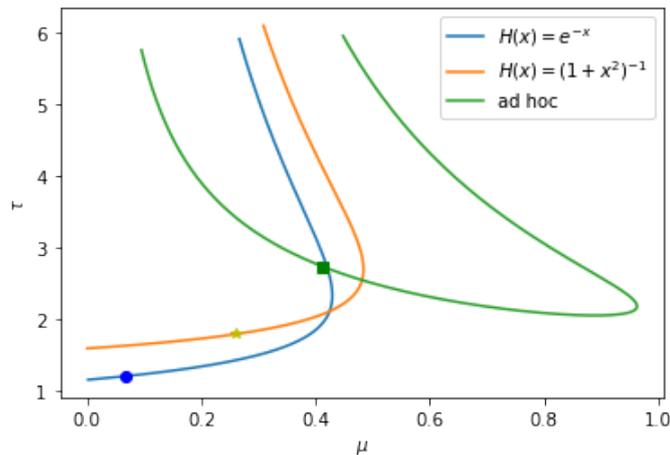
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Submitted on 25 Jan 2023 (v1), last revised 20 Jul 2023 (v2)

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Contributions à l'étude de la stabilité dans des modèles de populations de cellules.



Kyriaki DARIVA

Thèse de doctorat

Université Claude Bernard Lyon 1
École doctorale **InfoMath**, ED 512
Spécialité : **Mathématiques**
N. d'ordre 2022LYSE1097

Contributions à l'étude de la stabilité dans des modèles de populations de cellules.

Thèse de doctorat

Soutenue publiquement le 17 juin 2022 par

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Résumé

L'objectif de cette thèse est d'étudier avec des modèles mathématiques structurés la leucémie myéloïde chronique (LMC), la leucémie lymphoïde chronique (LLC) et l'hématopoïèse. L'hématopoïèse est le processus de production des cellules sanguines qui peut être associée à des maladies hématologiques comme la leucémie. La LMC touche les cellules myéloïdes matures et la LLC les lymphoïdes matures.

Dans un premier temps nous modélisons la LMC avec un système d'EDP qui généralise le modèle EDO d'interaction entre leucémie et système immunitaire introduit par Besse et al. en 2018. Nous étudions l'impact de la distribution des cellules leucémiques différenciées sur la stabilité des équilibres. Nous montrons qu'il y a des distributions qui peuvent déstabiliser l'équilibre de rémission, un point qui était toujours stable avec l'EDO. L'étude de la stabilité se ramène à l'étude du signe de $\Re(\lambda)$ des racines d'une équation du type: $P(\lambda) + Q(\lambda) \int_0^{+\infty} \bar{p}(x)e^{-\lambda x} dx = 0$, où P, Q sont des polynômes de degré 3 et 1 respectivement. Nous caractérisons complètement la stabilité quand \bar{p} est un Dirac. Puis nous montrons que le Dirac n'est pas optimal au sens où il y a des distributions instables dont la moyenne $\bar{\tau}$ est plus petite que la moyenne du stable Dirac $\delta_{\bar{\tau}}$.

Ensuite nous proposons et nous analysons quatre modèles d'EDP pour la LLC. L'objectif est de choisir le modèle le plus pertinent pour décrire sa dynamique sous traitement. Nous concluons qu'un modèle de compétition serait le meilleur choix pour expliquer certains phénomènes cliniques mais en même temps un modèle continu n'apporte pas plus d'information qu'un modèle discret d'EDO. Par conséquent, les EDO sont préférables par rapport aux EDP pour la LLC.

Dans le dernier chapitre nous modélisons l'hématopoïèse avec un modèle à retard. L'intérêt est que les points d'équilibre, donc leur stabilité aussi, dépendent du retard. Plus précisément, la stabilité est caractérisée par le signe de la partie réelle $\Re(\lambda)$ des racines de l'équation: $P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0$ où P, Q sont des polynômes de degré 2 et 1 qui dépendent du retard. Un point d'équilibre perd sa stabilité quand l'équation a des racines purement imaginaires $i\omega$ avec $\omega \neq 0$. Un critère standard pour une bifurcation de Hopf et l'apparition des solutions périodiques est l'existence des solutions (conjuguées) purement imaginaires qui traversent l'axe imaginaire (sans que ω soit nul) quand un paramètre du modèle bouge. Les oscillations des solutions du système de départ sont liées à des maladies hématologiques. Nous avons trouvé un critère qui permet de caractériser la stabilité de tout point d'équilibre étant donné les paramètres du modèle.

Mots-clés: LMC, LLC, hématopoïèse, EDP, EDR, EDO, stabilité, bifurcation de Hopf, oscillations.

Contributions to the stability analysis of cell population models.

Summary

The objective of this PhD is the study of Chronic Myeloid leukemia (CML), Chronic Lymphoid Leukemia (CLL) and hematopoiesis with structured mathematical models. The hematopoiesis is the process of blood cell production that can be associated to hematological diseases such as leukemia.

Firstly, we model CML with a system of PDE that generalizes the ODE model of interaction between leukemia and immune system introduced by Besse et al. in 2018. We study the impact of the distribution of leukemic differentiated cells on the stability of the steady states. We show that there are distributions that can destabilize the remission equilibrium which was constantly stable for the ODE. The stability analysis reduces to the study of the sign of $\Re(\lambda)$ of the roots of an equation of the form $P(\lambda) + Q(\lambda) \int_0^{+\infty} \bar{p}(x)e^{-\lambda x} dx = 0$, with P and Q polynomials of degree 3 and 1 respectively. We completely characterize stability for \bar{p} a Dirac. Then we show that the Dirac is not optimal in the sense that there are unstable distributions whose mean $\bar{\tau}$ is smaller than the mean of the stable $\delta_{\bar{\tau}}$.

Secondly, we propose and analyze four PDE models for CLL. The objective is to choose the most pertinent one to describe the dynamics under treatment. We conclude that a model of competition could better explain certain clinical phenomena but at the same time a continuous model does not give more information than a discrete model of ODE. Consequently, the ODE are preferable than PDE for CLL.

Lastly, we model the hematopoiesis with a delay differential system. The interest is that its equilibrium points, hence their stability, depend on the delay. More precisely, stability is characterized by the sign of the real part $\Re(\lambda)$ of the roots of the equation $P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0$ where P, Q are polynomials of degree 2 and 1 respectively that depend on the delay. An equilibrium loses stability when this equation has purely imaginary solutions $i\omega$ with $\omega \neq 0$. A standard criterion for a Hopf bifurcation and existence of periodic solutions, is that a pair of purely imaginary (conjugate) roots cross the imaginary axis (with $\omega \neq 0$) as a parameter varies. Oscillations of the solutions of the initial system are related to hematological diseases. We found a criterion that permits to characterize the stability of any point given the parameters of the model.

Keywords: CML, CLL, hematopoiesis, PDE, ODE, DDE, stability, Hopf bifurcation, oscillations.

Résumé substantiel

L'objectif de cette thèse est d'étudier, avec des modèles mathématiques structurés, la leucémie myéloïde chronique (LMC), la leucémie lymphoïde chronique (LLC) ainsi que l'hématopoïèse.

Contexte biologique

L'hématopoïèse est la production des cellules sanguines, un processus contrôlé par un mécanisme de retro control de cellules matures vers les cellules souches. Plus précisément, des facteurs de prolifération (comme certaines molécules qui jouent le rôle des hormones d'activation et/ou d'inhibition) agissent pour réguler la procédure. Les anomalies dans le mécanisme de retro control sont associées à des maladies sanguines, comme par exemple la LMC.

La LMC est un cancer du sang dû à une mutation dans les globules blancs ou dans les cellules souches. Une prolifération incontrôlable des cellules augmente la population des globules blancs dont le nombre reste au-dessus d'un seuil normal. Ceci active le système immunitaire pour agir contre la leucémie mais en présence d'une charge tumorale très élevée, le système immunitaire est inhibé, un phénomène qu'on appelle immunosuppression. Pour gérer la LMC efficacement, les patients ont besoin du traitement qui est, dans la plupart des cas aujourd'hui, un traitement ciblé par les inhibiteurs de tyrosine kinase (ITK). Les ITK ont eu beaucoup de succès, surtout l'Imatinib vu que le taux de survie sous ce traitement est comparable à celui d'un individu sain.

La LLC est un cancer du sang où un grand nombre de lymphocytes B ne meurt pas et s'accumule dans le sang. Les cellules prolifèrent dans les ganglions, la rate et la moelle osseuse. Cliniquement, les mutations liées à la LLC ne sont pas encore parfaitement comprises avec une difficulté supplémentaire due au fait que beaucoup de mutations se développent au fur et à mesure. Le microenvironnement de la LLC joue un rôle important parce que les interactions entre molécules et récepteurs cellulaires affectent les migrations des cellules cancéreuses. Plus précisément, les B-LLC cellules sont attirées par des molécules appelées chemokines (ex. SDF1) et passent aux ganglions où elles se fixent aux sites de multiplication pour se diviser. Une fois divisées elles fuient les ganglions et retournent dans le sang pour maturer progressivement.

La leucémie myéloïde chronique

Dans un premier temps, nous construisons un modèle d'interaction entre LMC et système immunitaire qui généralise le modèle d'EDO étudié par Besse et al. en 2018. Nous structurons la population des cellules leucémiques en maturité $x \in \mathbb{R}^+$ et nous étudions

la stabilité des points d'équilibre du modèle :

$$\begin{cases} \frac{dc}{dt} = rc(1 - \frac{c}{K}) - \mu_c cz, \\ \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) = h(x)u(t, x) - \mu_u u(t, x)z, \\ gu(t, 0) = ac(t), \\ \frac{dz}{dt} = s - S(I)z, \end{cases} \quad (1)$$

avec des conditions initiales $(c^0, u^0, z^0) \in \mathbb{R}_+ \times L_+^1(\mathbb{R}_+) \times \mathbb{R}_+$. Les variables du modèle sont:

- $c(t)$: la concentration des cellules leucémiques souches au temps t .
- $u(t, x)$: la densité des cellules leucémiques différenciées de maturité x au temps t et $I = \int_0^\infty w(x)u(t, x)dx$ est la population totale pondérée des cellules. Ici w est un poids non négatif, borné qui décrit une stimulation qui change selon la maturité.
- $z(t)$: la concentration des cellules immunitaires au temps t .

S est une fonction qui décrit la stimulation du système immunitaire en présence de la maladie. Si S change sa monotonie, supposons qu'il existe un I_{ref} tel que S est décroissante avant I_{ref} et croissante après. A priori, S peut prendre des valeurs négatives. Nous appelons fenêtre immunitaire la zone où $S < 0$. C'est une région où la population immunitaire augmente donc elle n'est pas inhibée par la leucémie. Nous pouvons classer les équilibres non triviaux selon qu'ils soient dans la region de décroissance ou croissance de S . Les derniers sont appelés équilibres hauts, leurs stabilités sont alternées (comme dans le cas du modèle d'EDO) et l'équilibre avec la plus grande valeur de \bar{I} est stable. Dans la zone où $\bar{I} < I_{ref}$ il ne peut y avoir plus qu'un équilibre qu'on appelle équilibre de rémission. Dans le cas d'EDO avec $\mu_u = \mu_c$ il est toujours stable. Ce n'est pas le cas dans le modèle d'EDP parce qu'ici sa stabilité peut être perdue. Le but de notre analyse était de caractériser les distributions, notées \bar{p} , qui permettent la perte de stabilité. L'équation caractéristique est donnée par:

$$P(\lambda) + Q(\lambda) \int_0^{+\infty} \bar{p}(x)e^{-\lambda x} dx = 0,$$

où P est un polynôme de degré 3 et Q de degré 1. On dit qu'un point d'équilibre est stable si toutes les racines $\lambda \in \mathbb{C}$ ont $\Re(\lambda) < 0$. Sinon, s'il existe λ avec $\Re(\lambda) > 0$ il est instable.

Nous avons déterminé la valeur minimale τ^* telle que l'équilibre perd la stabilité pour $\bar{p} = \delta_{\tau^*}$ et soit stable pour $\bar{p} = \delta_\tau, \tau < \tau^*$. Nous voudrions voir si toute distribution de moyenne plus petite que τ^* serait stable comme Fabien Crauste et Samuel Bernard ont prouvé dans leur papier de 2015 pour un polynôme P de degré 1 et Q constant. Leur résultat est le suivant:

Résultat: Si une distribution de Dirac de moyenne τ est stable alors toute autre distribution de moyenne inférieure ou égale à τ est aussi stable.

Avec ce résultat Fabien Crauste et Samuel Bernard ont pu trouvé la plus petite moyenne qui déstabilise le point d'équilibre.

Dans notre cas ou P est un polynôme de degré 3, le Dirac n'a pas la propriété d'optimalité. Nous construisons comme contre-exemple une distribution dont la moyenne est plus petite que celle d'un Dirac stable mais qui est instable. Il s'agit d'une somme de deux masses de Dirac. Nous pouvons construire une somme de trois, quatre Dirac etc qui déstabilisent.

La leucémie lymphoïde chronique

Ensuite, nous étudions la LLC avec des modèles continus structurés en âge. Nous voulons découvrir comment la maladie se progresse et choisir le modèle qui décrit mieux sa dynamique. Le paradoxe en LLC est le phénomène de PRL (*prolonged lymphocytosis* en anglais). C'est un terme qui décrit la situation clinique d'un patient avec une maladie résiduelle élevée sous traitement, mais qui se comporte bien avec un bon pronostic.

Nous construisons 4 modèles mathématiques et nous les analysons. Pour décrire la PRL nous avons supposé que les cellules B-LLC forment deux sous-populations qui sont en compétition pour se fixer aux sites de multiplication : les résistantes au traitement et les sensibles. Les résistantes ont acquis des mutations donc le traitement n'a pas d'effet sur eux alors que les sensibles peuvent être éliminées par le traitement. Le modèle que nous trouvons le plus pertinent est le suivant :

$$\left\{ \begin{array}{l} \frac{d\psi_s^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_s^* - \mu_{nd}^*\psi_s^* + \int_0^\infty \phi_s(t, x)\alpha_s(x)dx, \\ \frac{d\psi_r^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}^*\psi_r^* + \int_0^\infty \phi_r(t, x)\alpha_r(x)dx, \\ \frac{d\psi_s}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}\psi_s - \zeta_0^s\psi_s, \\ \frac{d\psi_r}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}\psi_r - \zeta_0^r\psi_r, \\ \frac{\partial\phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_s(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\ \frac{\partial\phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_r(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\ \phi_s(t, 0) = \zeta_0^s\psi_s(t), \\ \phi_r(t, 0) = \zeta_0^r\psi_r(t), \end{array} \right. \quad (2)$$

avec des conditions initiales positives.

Les indices s, r décrivent les cellules sensibles et résistantes respectivement pour les variables suivantes:

- $\phi(t, x)$: densité des cellules B-LLC dans le sang, de maturité x au temps t .
- $\psi^*(t)$: concentration des cellules B-LLC dans les ganglions, susceptibles de maturation et d'attachement aux sites de multiplication.
- $\psi(t)$: cellules après multiplication dans les ganglions au temps t .

Enfin β est une fonction décroissante qui représente le taux d'attachement aux sites de multiplication et dépend de la population totale $\bar{\psi}_s^* + \bar{\psi}_r^*$.

Nous identifions trois types d'équilibre :

1. L'équilibre sain : $\mathcal{E}_0 = (0, 0, 0, 0, 0, 0)$.
2. L'équilibre d'un espèce : $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$ et $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$.
3. L'équilibre à deux espèces : $\mathcal{E}_p = p\mathcal{E}_s + (1 - p)\mathcal{E}_r, p \in (0, 1)$.

Concernant la stabilité des points d'équilibre on a le théorème suivant :

Theorem 1. *a) Si l'équilibre sain \mathcal{E}_0 est le seul point d'équilibre du système alors il est stable. Sinon il est instable.*

b) Nous considérons les points d'équilibre d'un seul espèce : $\mathcal{E}_s = (\bar{\psi}_s^, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$ et $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$.*

(a) Si $\beta(\bar{\psi}_s^) < \beta(\bar{\psi}_r^*)$ alors \mathcal{E}_s est localement stable et \mathcal{E}_r est instable.*

(b) Si $\beta(\bar{\psi}_r^) < \beta(\bar{\psi}_s^*)$ alors \mathcal{E}_r est localement stable et \mathcal{E}_s est instable.*

(c) Si $\beta(\bar{\psi}_r^) = \beta(\bar{\psi}_s^*)$ il existe un nombre infini des points d'équilibre de la forme:*

$$p\mathcal{E}_s + (1 - p)\mathcal{E}_r, \quad p \in (0, 1)$$

où tous sont asymptotiquement instables.

D'après ce théorème la stabilité locale ne dépend que de β . Comme β est décroissant, si le nombre des cellules sensibles est plus petit que le nombre des résistantes à l'équilibre, alors \mathcal{E}_s est instable et \mathcal{E}_r est stable. Ceci implique que si des cellules sensibles arrivent et perturbent l'équilibre \mathcal{E}_r alors finalement elles seront éliminées. Il s'agit d'une leucémie agressive ou le traitement n'a pas d'effet. Nous observons la situation inverse quand il a plus des résistantes à l'équilibre.

Enfin, il existe une dose unique qui permet aux deux sous populations de coexister. Si on augmente la dose, le traitement tue plus des sensibles et si on la diminue il tue moins de sensibles, donc nous attendons à ce que plus de places sont occupées par les sensibles dans les sites de multiplication. Dans ce cas, la population des résistantes n'augmente pas trop, une situation favorable pour gérer la maladie.

La conclusion que nous obtenons est qu'avec un modèle d'EDP nous n'arrivons pas à avoir meilleurs résultats qu'avec un modèle à compartiments d'EDO, donc il n'y a pas besoin de passer aux modèles continus pour la LLC.

Hématopoïèse

Enfin, nous modélisons l'hématopoïèse avec un modèle d'équations à retards. Nous supposons que la différenciation des cellules est une procédure discrète qui se fait dans

des compartiments différents, commence aux cellules souches et se termine au niveau mature. Nous aboutissons au système suivant :

$$\begin{cases} U_0'(t) &= rU_0(t) \left(1 - \frac{U_0(t)}{K(U_n(t))} \right) - \delta U_0(t), \\ U_n'(t) &= -\mu_n U_n(t) + h e^{-\mu\tau} H(U_n(t-\tau)) U_0(t-\tau). \end{cases} \quad (3)$$

avec les conditions initiales:

$$(U_0(t), U_n(t)) = (\phi(t), \psi(t)), \quad t \in [-\tau, 0], \quad \text{avec } (\phi, \psi) \in C([-\tau, 0], \mathbb{R}^2).$$

Ici U_0 décrit les cellules souches et U_n les matures. Nous nous intéressons à la stabilité des points d'équilibre parce que dans le cas de l'hématopoïèse, la perte de stabilité et l'existence des solutions périodiques (donc apparition des oscillations) est liées à des maladies hématologiques. Mathématiquement, il s'agit d'une solution purement imaginaire $\lambda = i\omega$ de l'équation du type :

$$P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0$$

avec P, Q des polynômes de degrés 2 et 1 en λ .

La difficulté de caractériser la stabilité en prenant le retard comme paramètre de bifurcation, est liée au fait que les équilibres dépendent du retard, donc à chaque fois que τ change, l'équilibre qu'on regarde change. Nous donnons un critère qui permet de caractériser la stabilité de tout point d'équilibre étant donnés les paramètres du système.

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Chapter 1

Introduction

1.1 Structured population and delay models

Differential equations are widely used in biology as they are a helpful tool to study many biological problems. Most often Ordinary Differential Equations (ODE) are used, which means that the models are constructed by keeping only the time variable. ODE models are exploitable and helpful to make predictions while they can be chosen based on the available data. Nevertheless, it is also important to consider models where more variables intervene and reveal characteristics among individuals that can vary from one to the other. Such variables can give a conceptual insight into certain phenomena even if they are not directly measurable. Taking such characteristics into account leads us to *structured population models*. Examples of such models can be found in [76, 86] where it is thoroughly explained how one can pass from differential equations to structured population dynamics and the utility of such a structure to represent a physical, physiological, epidemiological or ecological variable. Examples of variables that can be used for this purpose are the age, the immunity level, affinity with a tissue, defense ability of a cell, fitness, maternity to name but a few.

Structuring populations can result in models where other variables, apart from time, appear. Variables that describe certain traits can be included in an ordinary differential equation, whereas when the variable evolves all along the life of the species, this leads to a linear, semi-linear or non linear Partial Differential Equation (PDE). Moreover, the existence of a stage structure results in the need of incorporation of time delays since the through-stage survival rate is often a function of time delays. Those models may involve delay dependent parameters and are called Delay Differential Equation (DDE) models [3].

In the next chapters we build and study models of structured population dynamics for chronic myeloid leukemia (CML) and chronic lymphoid leukemia (CLL) where the structure leads to a PDE. We are interested in investigating how the behavior of the system changes in the presence of a structure variable compared to an ODE version of the system. Moreover, we study the process of hematopoiesis with a Delay Differential Equation (DDE) which results from structuring the system with respect to the age of

each cell population (age being the time spent at each compartment of differentiation). The presence of delays complicates the task of an analytic study as steady states depend on the delay making stability hard to determine. Before detailing more we give a biological context.

1.2 Hematopoiesis

1.2.1 Normal and abnormal hematopoiesis

Hematopoiesis is the process by which the body produces blood cells to maintain homeostasis. Briefly explained homeostasis is the state of steady internal physical and chemical conditions of optimal functioning including body temperature, fluid balance and other variables (wikipedia). The tissue that participates in hematopoiesis is the bone marrow and from the same hematopoietic stem cell (HSC) all blood elements can arise through the process of differentiation. HSC either proliferate (self renewal capacity) giving cells of the same maturity or divide in one of the two progenitors of the lymphoid or the myeloid lineage [71] depending on a complex mixture of cytokines.

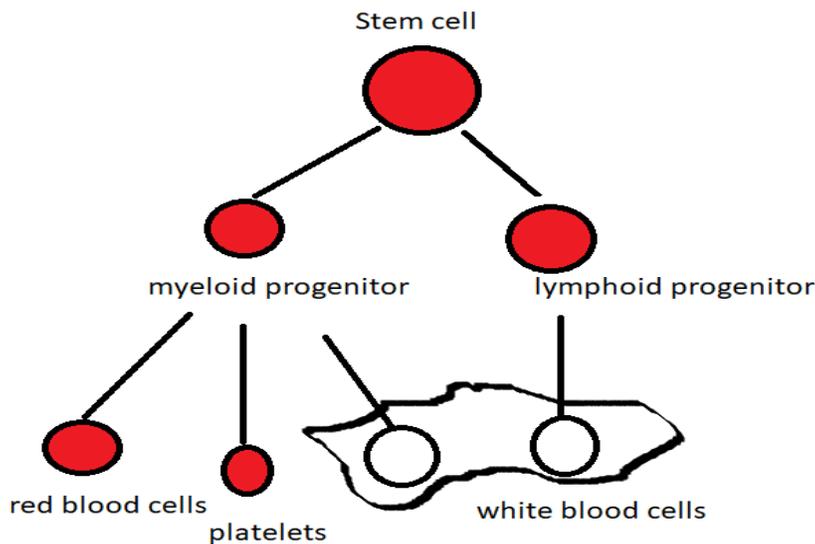


Figure 1.1: hematopoietic lineages.

The myeloid lineage produces red and white blood cells and platelets whereas the lymphoid lineage gives lymphocytes (B or T cells). The number of blood cells in the body is maintained at the desirable levels by HSC that form only a small population.

The white blood cells, either from the lymphoid or the myeloid lineage, include neutrophils, eosinophils, basophils, mast cells, monocytes, macrophages, dendritic cells, natural killer cells, B and T cells and are all cells of the immune system that help fight against infections and other diseases. Platelets protect the body from bleeding and red blood cells contain haemoglobin, a molecule that carries oxygen from the air and gives to blood its characteristic red color. All the above and more details for hematopoiesis can be found in [53]. A detailed schematic representation of hematopoiesis is given at the figure below 1.2 ¹.

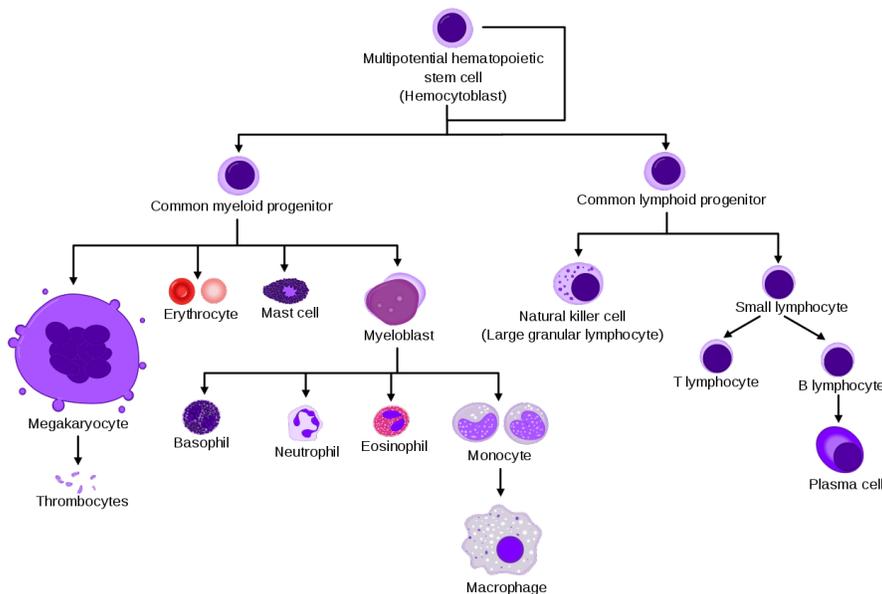


Figure 1.2: a more detailed presentation of HSC products through differentiation.

In healthy individuals the normal lymphocyte count is about 10 billions or more precisely up to 5×10^9 cells per liter of blood. Moreover there are produced 200 billion red cells per day and 400 billion platelets per day. Though, depending on the gender and age, healthy people have certain ranges of different types of cells in their peripheral blood and bone marrow. After the maturation stage in the bone marrow, the vast majority of cells move into the blood stream covering the need of cells in the human body in a daily basis.

Hematopoiesis is a hierarchical system that begins with primitive cells and ends with mature cells. It is a complex biological process that is regulated by specific growth factors (molecules acting like hormones playing an activator/inhibitor role). Such factors are for instance erythropoietin, thrombopoietin, granulocyte stimulating factor, monocyte colony stimulating factor and granulocyte-monocyte stimulating factor [40].

¹source: wikipedia page for Haematopoiesis

This means that there is a feedback control from mature cells to HSCs. Abnormalities in the feedback loop are the major suspects of periodic hematological diseases, such as auto-immune hemolytic anemia ([2], [71]), cyclical neutropenia ([40]), chronic myelogenous leukemia ([34],[89]) to name but a few. In some of these diseases, oscillations occur in all mature blood cells with the same period. The existence of oscillations in more than one cell line seems to be due to their appearance in HSC levels. That is why the dynamics of HSC have attracted attention of modelers for more than thirty years now (see the review of Foley and Mackey [33]). Blood test and bone marrow biopsies are used for diagnosis. In the case of abnormal levels of cells compared to healthy individuals, extra tests and exams are needed because this is a sign of a hematological disease. For instance, Chronic Myelogenous Leukemia and Chronic Lymphoid Leukemia studied in the following chapters are diagnosed when abnormal ranges of blood cells are detected and this is usually related to gene mutations.

1.2.2 Modeling of hematopoiesis

The mathematical study of hematopoiesis dates from 1970 [12]. Since the process is regulated by feedback signals and feedback systems have tendency to oscillate, many mathematicians tried to explain these oscillations with mathematical models. One approach is oriented towards the identification of the origin of oscillations. A second group of modelers departed from the assumption that oscillations start at the stem cell level and lead to stability loss of the control system and a third group of people combined both [32, 40]. Examples of mathematical models of hematopoiesis that incorporate the negative feedback loop to explain oscillations giving rise to hematological diseases are [28] a model of thrombopoiesis, [106] a model of granulopoiesis and the very first attempts to explain CML with modeling [69].

In addition to the above, among the first models we also find that of M.C.Mackey in 1978 [68]. M.C. Mackey was interested in studying the evolution of HSC population without distinguishing between cells according to their level of development. Hematopoietic stem cells compartment is separated in two sub-compartments: proliferating and non-proliferating (quiescent), with quiescent cells representing the main part of the HSC population (90% of HSC are in a non-proliferating compartment, also called G₀-phase [109]). Taking this into account M.C.Mackey considered a system of two non-linear delay differential equations. The delay τ represents the cell cycle duration and the variables of the model P , and N represent the density of the proliferating stem cells and the resting-phase G_0 stem cell population density respectively. The equations are as follows:

$$\begin{cases} \frac{dP}{dt} = -\gamma P + \beta(N)N - \beta(N_\tau)N_\tau e^{-\gamma\tau}, & \tau < t, \\ \frac{dN}{dt} = -\delta N - \beta(N)N + 2\beta(N_\tau)N_\tau e^{-\gamma\tau}, & \tau < t. \end{cases}$$

The parameters of the system describe γ the rate of loss of the proliferating cells and δ the rate of differentiation. $N_\tau = N(t - \tau)$, the factor 2 accounts for mitosis and the function β represents the flux of cells from the proliferating to the non proliferating

compartment. A specific choice was made for β :

$$\beta(N) = \beta_0 \frac{\theta^n}{\theta^n + N^n},$$

with β_0 , θ and n being parameters. β_0 is the maximal rate from cellular movement from G_0 into proliferation and θ is the G_0 stem cell population at which the rate takes half of its maximum value.

This model demonstrates the control for the stem cells production. Their results confirm that the irreversible cell loss from the proliferating phase of the cell cycle leads to hematological diseases such as aplastic anemia and cyclic neutropenia (CN). What is more, it is this irreversible loss that originates the diseases and no involvement of the feedback mechanisms is observed. More information about the origins of CN and the nature of the disease as well as of other hematological disorders can be found in [40].

Another typical example of a negative feedback is the erythroid control system. Such a mechanism can be modeled using DDEs or PDEs [2, 71]. The formalism is quite general so these models could be used to describe other hematopoietic lines apart from erythropoiesis. The paper [71] is an extended version of [2] that was developed because of the incapacity of the latter to explain normal blood loss in a healthy patient (such as blood donation).

Inspired by the modeling of hematopoiesis using DDEs, we studied the dynamics of a system describing the hematopoiesis as a discreet process that is regulated by a feedback mechanism. The appearance of time delays induced by the feedback control from mature to stem cells makes the study of stability a difficult procedure since the equilibrium points depend on the delays. We are interested in the onset of Hopf bifurcations that are interpreted as oscillations in the process. As described above, oscillations in hematopoiesis are related to hematological diseases.

1.3 Chronic Myeloid Leukemia (CML)

1.3.1 CML biological background

The Chronic Myeloid Leukemia (CML) is a cancer of the blood and the bone marrow which affects mostly people of median age, about 30 to 50 years old. It is characterized by the presence of the oncogene BCR-ABL1 which is the product of the translocation between chromosomes 9 and 22 (genetic mutation characterized by the reciprocal exchange of chromosomal material between the two non homologous chromosomes). In particular, the gene ABL1 of chromosome 9 is juxtaposed to the gene BCR of chromosome 22 resulting in the formation of the fusion gene BCR-ABL1 which is present in the chromosome of Philadelphia (Ph), see figure 1.3 ². The protein produced has a tyrosine kinase activity more intense than in normal ABL gene. This information can be found in several sources, see for instance [22]. As this protein controls the process

²source: wikipedia page for Philadelphia chromosome

of differentiation and division of cells, leukemic cells have tendency to proliferate more rapidly and to have better survival capacities than healthy cells while we also observe changes in growth factor dependence and cell adhesion [22, 43].

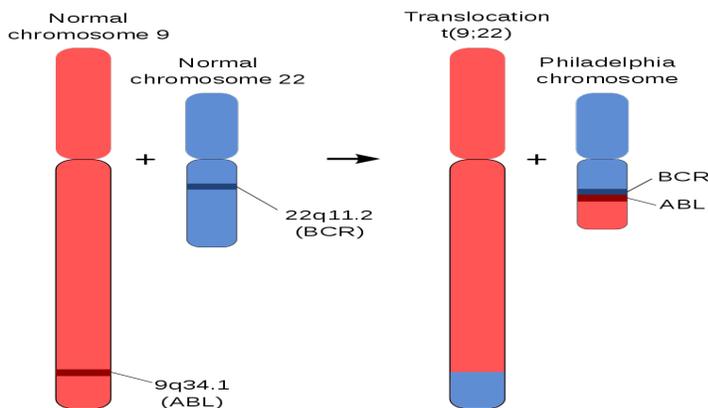


Figure 1.3: formation of the Philadelphia chromosome formation.

The uncontrollable division of cells results in saturation of the bone marrow. Moreover, the cells are mature but incompetent and unable to function properly. The chromosome of Philadelphia can be present in other forms of leukemia (Acute Lymphoid leukemia, Acute Myelogenous leukemia and mixed phenotype acute leukemia) but in CML it has a good prognosis. In CML the BCR-ABL1 protein gives rise to activation of cell signaling pathways and a shift to a cellular environment that supports leukemia.

In the bone marrow, the role of the stem cells is to differentiate and produce blood cells with the process of hematopoiesis. If they do not do so, they have the ability to enter quiescence, a state in which they become insensitive to any stimulation. Similarly to healthy cells, leukemic stem cells can also enter in quiescence where their proliferation is deactivated. As explained in [92], the micro-environment of the bone marrow plays a role in the regulation of hematopoiesis and hosts mature immune cells that occupy similar niches as the leukemic stem cells (LSC). LSCs depend on signals from the micro-environment and can be controlled by activated T-cells. Even though it was hoped that these cells would help to eliminate the therapy resistant LSCs, in reality what actually happens is not thoroughly understood. Finally, in leukemia when the leukemic load highly increases, the immune system is inhibited meaning that the immune cells are not activated to fight against leukemia.

1.3.2 Diagnosis, evolution and prognosis

CML is usually diagnosed in chronic phase (CP) with main symptoms being fatigue, anemia, splenomegaly, abdominal discomfort and episodes of infection [90]. The exact causes are not fully known but high dose of ionizing radiation is a proven risk factor.

When the blood count is abnormally high, PCR method is used to detect the BCR-ABL1 gene. Identification of the Ph chromosome is also necessary. Without treatment the disease quickly progresses from (CP) to blast crisis (BC), sometimes via accelerated phase (AP). In (AP) the blast count in the peripheral blood is 10 – 20% and more than 20% in (BC). Once in (BC) the patient's health deteriorates rapidly and leads to mortality within a year. Symptoms at that stage are infections, bleeding, night sweats, weight loss, fever, anemia or thrombosis due to bone marrow failure. The above information can be found in [42].

Clinically the evolution of the disease is quantified by measuring the ratio of leukemic cells with respect to healthy cells. It is the expression of the genes BCR-ABL1 and ABL gene that is counted with biochemical methods [8]. Moreover, the BCR-ABL1 transcript can be detected with sensitive PCR methods even in healthy individuals but in that case the translocation takes place in an environment that does not support leukemia.

Types of molecular responses: PCR techniques are used to measure the molecular response of patients. The following definitions can be found in [72]. A therapy target is achievement of major molecular response (MMR) that is defined as more than 3-log reduction of BCR-ABL product on International scale (IS). Equivalently this is a $\text{BCR-ABL} \leq 0.1\%$. A current goal in medicine is to go beyond MMR and achieve deep molecular response (DMR) that is subdivided in three possible responses: MR^4 that is more than 4 log reduction of BCR-ABL1 product on IS (equivalently $\text{BCR-ABL} \leq 0.01\%$), $MR^{4.5}$ that is more than 4.5 log reduction of BCR-ABL on IS (or $\text{BCR-ABL} \leq 0.0032\%$) and MR^5 that is a more than 5 log reduction of BCR-ABL on IS (or $\text{BCR-ABL} \leq 0.001\%$).

1.3.3 Treatment

As for most of the cancers, CML was initially treated with chemotherapy which, apart from not being very effective, it also induced many secondary effects. Introduction of interferon- α and stem cell transplantation noticeably improved survival and quality of life [90]. Interferon- α is a molecule that is naturally produced by the immune system in response to viral infections. With IFN- α therapy, the goal is to imitate the immune system and stimulate it to function more effectively [26]. This happens by stimulating T cells and other immune cells and by making cancer cells send out chemicals that attract immune cells to them (see Cancer research UK page for Interferon Alfa). Previously, cytotoxic agents were also used to treat symptoms of CML but they did not manage to alter the development of the disease. The new treatment regimen that is called targeted therapy, focuses on the development of tyrosine kinase inhibitors (TKIs) and has greatly improved patients' outcome (figure 1.4). TKIs selectively target the mutated part and inhibit the BCR-ABL1 kinase activity, hence reducing the frequency of patients progressing to (BC). Overall survival rate has greatly increased after introduction of TKIs, a fact that verifies the importance of BCR-ABL1 signaling. Life expectancy under TKI treatment is comparable to the life expectancy of health individuals [43, 44].

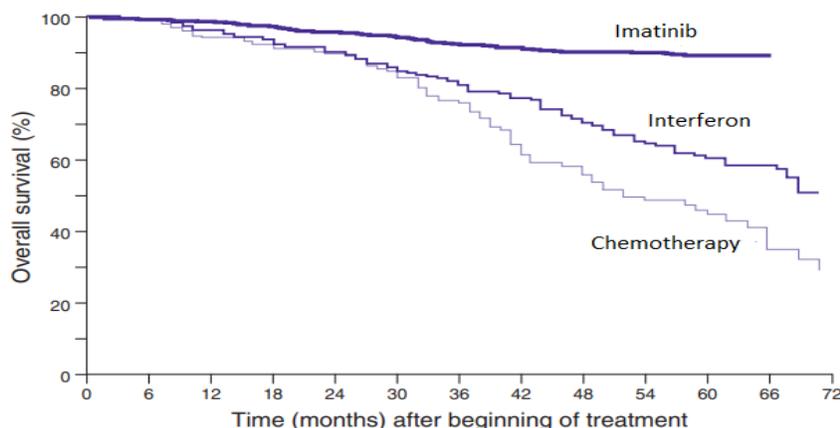


Figure 1.4: overall survival of patients under imatinib, interferon and chemotherapy, figure taken from [27].

The first developed TKI is imatinib, which is generally used as a first line treatment and is proved to be effective in all stages of CML [50, 44, 21]. Imatinib can lead to normal life expectancy for most of the patients diagnosed at chronic phase [44]. Deep molecular response (DMR) is achieved to more than 80% of the patients allowing attempts of treatment cessation, aiming at treatment free remission (TFR) alleviating side effects [101, 73]. Despite advances in treatment, some patients still present resistance to imatinib because of mutations in the BCR-ABL1 protein. In case of resistance to imatinib, second generation TKIs (2G-TKI) are used, such as dasatinib, nilotinib and bosutinib. 2G-TKIs result in more rapid responses and relief of symptoms, but their positive effects are counterbalanced by the drug-induced side effects. Third line treatment (3G-TKI) such as ponatinib, is also used for tyrosine kinase domain mutations. In case of resistance to multiple TKIs or personal preferences of patients, hematopoietic stem cell transplantation is also used to treat patients in CP [100]. Transplant mortality at CP is low but in BC is not recommended [100]. Attention should be drawn when considering patients eligible for transplantation. Those resistant to 2G-TKIs as a first line treatment have low chance of achieving durable response, while those who failed ponatinib are at high risk of progression and hence a transplant should be searched urgently [37].

Treatment and pregnancy-fertility

Even though we are not tackling questions concerning pregnancy or fertility under CML, we briefly mention here what is currently known for those patients, for completeness of the presentation of the CML biological background.

Women under treatment who want to give birth to children should be very careful. Most of the TKIs can lead to teratogenic formations hence treatment should be stopped during pregnancy [85], while TKIs are also excreted to the milk [14]. Concerning

imatinib especially, the risk of abortion and congenital malformations is increased. CML patients often show sperm alternations at diagnosis but sperm quality seems to be unchanged during TKI therapy [83]. Proceeding to fertility preservation prior to cancer therapy is a good approach. Women should be advised avoid becoming pregnant whilst on TKI therapy. Women who want to interrupt treatment in order to become pregnant should be aware that relapse can occur even if they have achieved DMR [85]. In general, advice should be given based on the patient's status and on whether they are on CP, AP or BC. Patients who present with CP disease during pregnancy can safely continue their pregnancy which can be managed with leukapheresis if necessary during the first and subsequent trimesters or with IFN $-\alpha$ being during the second quarter [85].

Treatment free remission (TFR)

Despite the great success of TKIs, in practice we can see CML becoming active again. This may be attributed to the quiescent cells through a mechanism that is not fully understood. The fact that a residual disease remains in the blood, does not necessarily imply relapse. If the tumor load is not high enough it is still manageable and in many cases patients remain in remission after having stopped treatment. As already mentioned, a certain percentage of patients manage to achieve DMR with TKIs. If DMR has been achieved for a long time, treatment discontinuation can be considered. According to many different studies of treatment discontinuation, some of which are listed in the table below, duration of MR⁴ was determined as the most important predictor of TFR. It should be mentioned that treatment discontinuation is only feasible for patients in CP whereas BC remains a challenging situation [44]. According to DESTINY study [17] progressive dose reduction before treatment cessation does not prevent TFR. Consequently, smooth dose reduction could be an attainable regimen to avoid unnecessary over treatment of patients favorable for TFR. An interesting fact is that CML is more aggressive to teenagers than to older people hence TFR for them does not work as well as for elderly [80]. Lastly, according to STop IMatinib (STIM) study [73], patients who relapse do it within the first year, most often after 6 months of treatment discontinuation, whereas a TFR duration of 7 years is feasible for a significant percentage of patients. Lastly, change from first line TKI to 2G-TKI to achieve DMR more quickly is not recommended because of side effects attributed to 2G-TKIs [44].

Name of the study	Year	TKI
STIM	2010	IM
TWISTER	2013	IM
ASTIM	2014	IM
DADI	2015	Dasatinib (2nd line)
ISAV	2015	IM
The role of NK cells in imatinib discontinuation	2016	IM
STIM1	2016	IM
Stopping dasatinib or nilotinib in CML	2016	Dasatinib and nilotinib (2nd line)
D-STOP	2016	IM and Dasatinib
TRAD	2016	IM and Dasatinib
KID	2016	IM
ENESTop	2016	IM to Nilotinib
DESTINY	2017	IM or Dasatinib or Nilotinib
ENESTfreedom	2017	Nilotinib
IMMUNOSTIM	2017	IM
EUROSKI	2018	any TKI
ISAV	2018	IM
STIM2	2018	IM

Table 1.1: table of treatment discontinuation studies. The sources can be found in [17, 29, 46, 47, 49, 52, 56, 63, 64, 65, 73, 79, 80, 84, 91, 98, 99, 101, 104, 108, 112].

It should be clearly mentioned that the mechanisms leading to TFR are not completely understood. A prelude to successful TFR in CML treatment is considered the achievement of deep molecular response as DMR is associated with restoration of immune recovery on TKI. When initiating TKI treatment, immune system reactivation is observed as well as recovery of NK-cells and T cells [48].

In general, patients who relapse after discontinuation regain good response after restarting treatment.

In the following section we give a short presentation of the mathematical modeling for CML. The presentation is mostly organized by groups of people who studied certain phenomena. Moreover there is a link with the treatment cessation trials. According to the first studies concerning TFR, any possibility of success was related to eradication of the cancer before treatment cessation. This type of conclusion was not coherent though with what we observe in clinics. There are patients whose leukemic load is controlled at low levels and who manage TFR without complete eradication of leukemia. Interestingly, according to the DESTINY study [17] there are patients who relapse after abrupt treatment discontinuation whereas when they pass to half dose regimen before cessation they manage TFR. Such observations motivated the mathematical modeling necessitating the construction of models that interpret low leukemia load as a remission steady state under treatment and that the basin of attraction of this steady state can

explain the success of progressive treatment discontinuation.

1.3.4 CML modeling

The modeling approach for CML changed after the introduction of imatinib. At a first place, a general approach was the construction of systems with different compartments that describe a different stage of maturation each. These systems reveal the process of hematopoiesis as this is the process of production of blood cells under differentiation. The levels of differentiation, starting from stem cells to mature blood cells, is described mathematically by different compartments of maturation. Such models can be discrete (ODEs) or continuous (PDEs). Once TKIs were introduced, the modeling was oriented towards the construction of systems that describe the effect of imatinib on the disease progression. For the first era, references can be found in the section of hematopoiesis (ex. Adimy, Mackey). In the sequel we mention some mathematical models that study the interaction between leukemia and imatinib.

Firstly, we mention the Agent Based Models (ABM), for instance [96], in which the destiny of a cell is determined based on its specific characteristics. Despite their utility, such models can be computationally heavy making the need of other types of models more urgent. For that purpose models of Ordinary Differential Equations (ODEs), Partial Differential Equations (PDEs) or Delay Differential Equations (DDEs) have been developed [16, 25, 45, 57, 59, 60, 62, 78, 95] to name but a few.

One of the first who revolutionized the study of CML was Michor who conducted many different studies [1, 24, 77, 78]. The model developed in [78] is at the origin of our modeling. In that study Michor and colleagues considered the four stages of maturation, stem cells, progenitors, differentiated and mature cells, for leukemic and healthy cells. Imatinib reduces the rate at which leukemic cells pass from one stage of differentiation to the other but they conclude that leukemia inevitable persists because they hypothesize that treatment has no effect on stem cells. Consequently, relapses always occur independently of the development of resistant mutations.

In [58] Kim and colleagues incorporate to the model of Michor[78] immune response against leukemia in Imatinib treated patients. With a DDE model they suggest that the immune system can play an important role in the dynamics of CML under treatment.

A different approach of modeling is given in [96] by Roeder et al. who constructed an agent based model (ABM) of CML by separating leukemia cells in two populations, proliferating and quiescent. Whereas cells in the proliferating compartment are sensitive to imatinib, quiescent stem cells are not affected by treatment, they have big potential of reactivation and so relapse upon cessation can be attributed to them. Moreover relapse also occurs in the presence of mutations of the BCR-ABL1 gene that generate resistance to imatinib. Under treatment though, leukemia is well controlled. This result has to be seen in comparison to Michor et al [78] where under treatment relapses always occur independently of the resistance because they supposed that no stem cell is sensitive to imatinib. In [59] Kim et al. developed an analogous PDE model including all complexity of the ABM since they considered a detailed representation of the cell

cycle. In [25] Doumic et al. constructed a less detailed PDE version of the ABM than the PDE given by Kim et al, which coincides with the simulation results of Roeder et al.

In [36] Glauche et al. also inspired by the ABM model, they studied the efficacy of a combination of therapies. They concluded that a constant dose of TKI and Interferon- α is the most appropriate treatment regimen with the best outcome reducing secondary effects. Another study of CML under imatinib with a PDE model derived from the ABM was the one conducted by Besse et al. in [6]. Their results concern dosage in long time scales. They found that the dose needed initially for tumor reduction is largest than the unique dose that maximizes the rate of cancer reduction in long term. Their results could be used to improve conclusions concerning long term responses.

In [62] Komarova and Wodarz developed a model to study drug resistance. Their basic assumption is that imatinib can potentially affect all leukemic cells, even stem cells, and that relapse is a result of acquired mutations. They also use a stochastic approach where they consider the probability of mutation induced resistance to multiple drugs. With only one drug, resistance is independent of the quiescence. When the rate of entrance to quiescence increases (or the rate of exit decreases) the mutant colony grows more slowly but there is more time to grow. Hence time compensates changes in the mutant growth rate. In contrast to that, with multiple drugs, treatment failure is dependent on the quiescent parameters. The higher the rate of entrance in the quiescent state and the lower the rate of exit from it, the higher the probability of 2 drug treatment failure. For an explanation of that phenomenon see [62].

Another work was done by Clapp et al. [16] who developed a system of ODEs inspired by the model of Kim and colleagues [58]. They study the interactions of immune and leukemic population without considering mutants. We give the equations here because a simplification of this model led to model of Besse et al. [5] that we generalize and study with PDEs. A brief description of the equations follows:

$$\begin{cases} y_0' = b_1 y_1 - a_0 y_0 - \mu \frac{y_0 z}{1 + \epsilon y_3^2}, \\ y_1' = a_0 y_0 - b_1 y_1 + r y_1 \left(1 - \frac{y_1}{K}\right) - d_1 y_1 - \mu \frac{y_1 z}{1 + \epsilon y_3^2}, \\ y_2' = \frac{a_1}{inh_1} y_1 - d_2 y_2 - \mu \frac{y_2 z}{1 + \epsilon y_3^2}, \\ y_3' = \frac{a_2}{inh_2} y_2 - d_3 y_3 - \mu \frac{y_3 z}{1 + \epsilon y_3^2}, \\ z' = s - dz + \frac{\alpha y_3 z}{1 + \epsilon y_3^2}, \end{cases}$$

where y_0 and y_1 are the leukemic stem cells population, quiescent and proliferating respectively. Proliferating cells are under logistic growth with rate r and capacity K . Moreover, y_2 are the leukemic progenitors, y_3 the leukemic mature cells and z the immune cells. The transfer rates from one compartment to the other are described by the parameters: b_1, a_0, a_1, a_2 and the natural death rates d_1, d_2, d_3, d . The parameter μ is the efficacy of the immune cells on the leukemic cells and ϵ is the immunosuppression. With inh_1, inh_2 they denote the inhibition of the proliferation induced by treatment and finally αy_3 is the expansion rate of the immune population. Finally, s is the natural source of immune cells.

They studied the biological parameters of the system trying to define which ones are more crucial and better reveal the dynamics of the system.

In [5] to analyze the behavior of the system they reduced the version of Clapp et al. by only considering the leukemic stem cell population y_1 , the mature cells y_2 and the immune cells z . Keeping the population y_1 assures that leukemia has the self renewal properties and that leukemic population continues to proliferate. They also made the assumption that the inhibition effect is only on the rate of expansion of the immune population and not on the capacity of immune cells to eliminate cancer cells. For that reason they ignored the inhibition term $1 + \epsilon y_3^2$ from the competition between y_3, y_1 .

They used a more general function for the stimulation of the immune system denoted by f . Compared to the model of Clapp et al.

$$f(y_2) = d - \frac{\alpha y_2}{1 + \epsilon y_2^2}.$$

More possible choices for f and the expected behavior for each one can be found in [31]. Still the following biological assumptions are satisfied:

- The immune system is activated in the presence of leukemia.
- Leukemia inhibits the production of immune cells (immunosuppression).

The system is as follows:

$$\begin{cases} y_1' = r y_1 \left(1 - \frac{y_1}{K}\right) - d_1 y_1 - \mu y_1 z, \\ y_2' = a_1 y_1 - d_2 y_2 - \mu y_2 z, \\ z' = s - f(y_2) z \end{cases} \quad (1.1)$$

As previously, the stem cells are under logistic growth with rate r and carrying capacity K . f is taken C^2 , decreasing until a certain value and increasing afterwards, see [5]. They characterized completely the asymptotic behavior of the model, its steady states and their stability. They found that the system has always a disease free equilibrium, but whether any treatment or combination of treatments can completely eradicate CML is an open question [15, 97]. They also found a low or remission equilibrium (terminology firstly introduced in [31]) that corresponds to an asymptotic solution in the case where the treatment is not sufficient to eradicate the disease but still manages to keep it at low and controllable levels by the immune system. There are high equilibrium points with alternate stability corresponding to an aggressive disease in the absence of treatment or with no treatment effect. Attraction towards a high equilibrium point could be interpreted as relapse whereas attraction to the low equilibrium as remission. With their model a stable healthy equilibrium cannot coexist with a stable remission equilibrium. A case where there is a stable high equilibrium and a stable remission equilibrium, success of the treatment cessation depends on the basin of attraction of the remission equilibrium. Existence of a high stable equilibrium and a healthy stable

equilibrium means that treatment cessation can potentially lead to eradication of the tumor.

In our work we study the continuous analogue of the ODE (1.1) whose detailed presentation is given in next sections.

Analyzing the equilibrium points and their stability can give us insight into the behavior of the solutions in long term. In the case of treatment dependent parameters, a solution that converges to a disease free steady state would be interpreted as treatment of the disease and convergence to a remission equilibrium would mean that we keep the disease at low levels with a treatment that has control over the disease. Finally convergence towards a high equilibrium means that treatment has no effect on the disease.

1.4 Chronic Lymphoid Leukemia (CLL)

1.4.1 CLL biological background

The Chronic Lymphoid Leukemia (CLL) is a blood cancer of the bone marrow which affects older adults of mean age 70 years old. CLL affects the B-lymphocytes which are cells that play an important role in the immune response to defend exterior agents (bacteria, viruses etc). As all cells, B-Lymphocytes have a limited lifetime which varies from a few days to some months. After this period, they die and they are replaced by new cells. In CLL there is a significant amount of B-cells that do not die because their cell cycle is blocked once they reach maturity. As B-cell production continues, B-lymphocytes accumulate in the blood, lymph nodes, spleen and bone marrow, a phenomenon that explains the increase of volume of the lymph nodes and the spleen. The accumulation of neoplastic cells in the blood explains the rise of absolute lymphocyte count at above 5×10^9 cells per liter compared to normal lymphocyte counts, that is 1 to 4×10^9 per liter [23].

Many studies describing the dynamics of CLL before, during and after treatment cessation have permitted to better understand CLL.

The major difficulty in understanding and managing CLL is that the exact cause of most cases of CLL is not known. CLL usually occurs during a person's lifetime and is not related to inherited DNA mutations. Most often a change can be found at least at one chromosome. The loss of part of chromosome 13 is the most common deletion, but other chromosomes such as 11 and 17 can also be affected, this is written as *del(13q)*, *del(11q)*, or *del(17p)*. Other, less common abnormalities may also be found. These chromosome changes are important in CLL, but it's not yet clear which genes they involve or how exactly they lead to leukemia. Chromosome abnormalities are secondary oncogenic events that accumulate late in the natural history of CLL, while other events occur at the hematopoietic stem cell (HSC) level [7]. Mutations in HSC will produce high numbers of differentiated B-cells. Further stress caused mostly by chemotherapy might give rise to subclonal mutations deteriorating the expressed symptoms [54, 88].

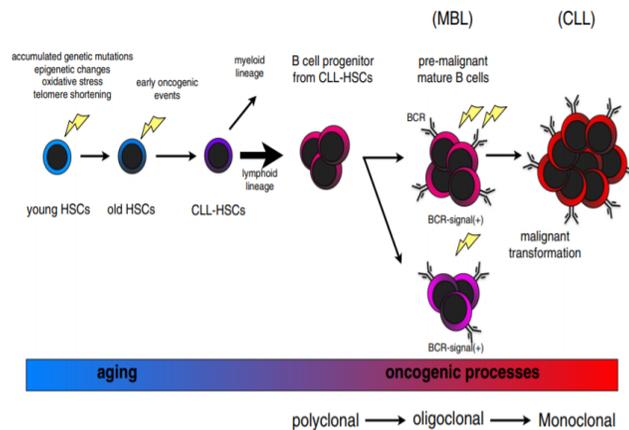


Figure 1.5: progression of the disease from HSC to CLL, taken from [55].

Importance of the microenvironment in CLL.

When we are talking about microenvironment we refer to the cells, the molecules and the structures (such as vessels) that surround and support other cells and tissues. Abnormal cells, such as cancer cells, can change their microenvironment and such changes affect the way cells grow and spread. Studying the microenvironment can give an insight into how cancer cells form and how they can be treated.

The CLL microenvironment consists of stromal cells, follicular dendritic cells, and CD4 T cells in the bone marrow, the lymph nodes and the spleen [10]. It is very important as interactions between chemokines and cell receptors affect migration of cancerous cells [18], figure 1.6. The disease proliferation centers are bone marrow, lymph nodes and spleen, while the CLL cells mature only in peripheral blood. The accumulation and spread of cancerous mature B-cell clones with lower apoptosis in the bone marrow, peripheral blood, lymph nodes and spleen is slow and cause lymphocytosis, lymphadenopathy, splenomegaly and bone marrow failure. Based on the symptoms expression, CLL is classified into Binet or Rai systems:

Stage	Description	Median survival (months)	Risk status
0	Lymphocytosis: lymphocytes in blood $> 15000/mcL$ and $> 40\%$ lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged nodes	100	Intermediate
II	Stage 0-I with enlarged node(s)	70	Intermediate
III	Stage 0-II with hemoglobin less than $11.0g/dL$ or hematocrit $< 33\%$	20	High
IV	Stage 0-III with platelets less than $100000/mcL$	20	High

Table 1.2: Rai classification system.

Stage	Criteria	Median survival (years)
A	No anemia, no thrombocytopenia, fewer than 3 lymphoid areas enlarged	14
B	No anemia, no thrombocytopenia, three or more areas enlarged	5
C	Anemia ($Hb < 10g/dl$) and/or platelets $< 10^11/L$	2.5

Table 1.3: Binet classification system.

Nevertheless, the precise way CLL interacts with its microenvironment is still unknown. Many in vivo and in vitro experiments study these interactions and the progression of the disease in different parts of the body. In particular, in vitro studies have been done to better understand the interactions between chemokines and cell receptors that affect migration [67, 9, 11].

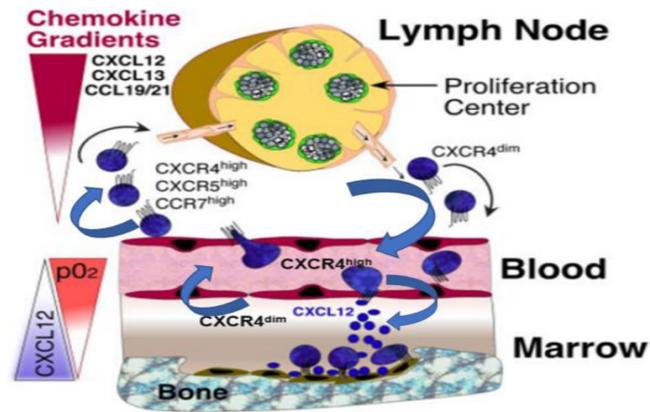


Figure 1.6: CLL trafficking and interactions with the microenvironment. Picture taken from [11].

One of the most important *in vivo* experiments was done by Messmer et al [75] where they estimated the growth, birth and death rate of B-CLL cells in peripheral blood. The experimental protocol and all the details are given in [75] but we briefly present the procedure here as well. Messmer and colleagues used a nonradioactive labeling method to measure B-CLL kinetics. Nineteen patients (16 of whom had never received treatment and 3 had received treatment more than 6 months ago) drank an aliquot of deuterated water 2H_2O daily for 84 days. 2H incorporation into DNA of newly divided cells was measured and birth rates were calculated. The difference between the birth and growth rates was defined as the death rate. They fitted their data using an one and a two compartment model. The model with two compartments fits the data better since B-CLL cells proliferate in the tissues and then enter the blood circulation inducing time delays. The conclusion of the study was that CLL is not a static disease that results from accumulation of B-cells than do not die properly. Rather, it is a dynamic process as cells die and proliferate at high levels.

Patient	Single-compartment model, death, %/day ^A	Two-compartment model, death, %/day ^A	Single- compartment model, b ^B %/day ^A	Two- compartment model, b ^B %/day ^A
CLL107	0.21	0.22	0.22	0.23
CLL109	<i>0.25</i>	<i>0.24</i>	<i>0.12</i>	<i>0.11</i>
CLL165	0.20	0.21	0.13	0.14
CLL169	0.49	0.49	0.49	0.49
CLL189	0.14	0.15	0.80	0.81
CLL280	<i>0.13</i>	<i>0.13</i>	<i>0.22</i>	<i>0.22</i>
CLL282	<i>-0.10</i>	<i>-0.26</i>	<i>0.55</i>	<i>0.39</i>
CLL321	0.27	0.26	0.30	0.29
CLL331	0.21	0.21	0.24	0.24
CLL332	<i>-0.39</i>	<i>-0.33</i>	0.18	0.24
CLL336	0.69	0.70	0.40	0.41
CLL355	<i>-0.06</i>	0.15	0.24	0.45
CLL360	0.97	0.79	0.66	0.48
CLL394	0.13	0.14	0.17	0.18
CLL400	1.02	1.05	1.73	1.76
CLL403	<i>-0.07</i>	0.15	0.17	0.39
CLL408	2.13	2.14	1.08	1.09
CLL418	<i>0.42</i>	–	<i>0.28</i>	–
CLL472	0.58	0.59	0.53	0.54

^AItalicized values indicate poor model fits.

Figure 1.7: death and birth rates as measured by Messmer et al with a single and two compartment model adapted from [75].

It should be noted that the data Messmer et al present are the number of B-CLL cells within each patient over a certain period of time (approximately 200-250 days) that are marked with heavy water. This cell count corresponds only to a fraction of the entire B-CLL cell population. For some patients the fit was poor. This is not surprising since the model only tracks birth and death of cells, and does not account for any other cell dynamics, such as immune system interference. In some cancer cases, immune system can explain the disease progression that could not be interpreted as birth and death cycles or treatment.

1.4.2 Treatment

The way CLL is treated has evolved over the years. At first place, doctors observed the progression of the disease and prescribed drugs (alkylating agents) whose major action was to prevent DNA synthesis [93]. With this method remission and overall response was low. Later another method was adopted. Doctors prescribed purine analogs, which mimic the metabolic purines and prevent DNA replication [107]. In recent years, a combination of both (with slightly increased remission and overall response), or chemoimmunotherapy is preferred. Immune drugs (such as Rituximab, Ofatumumab) doubled remission and overall response and chemoimmunotherapy is an effective treatment strategy in CLL. In most patients chemosensitivity is observed initially but relapses always occur until a refractory stage. Novel therapeutic agents are used nowadays that target CLL signaling pathways and disrupt tumor microenvironment interactions. The most common regimen is ibrutinib- a targeted therapy against

BTK protein, figure 1.8. The inhibition of BTK activity by ibrutinib is associated with several anti-leukemic effects on the lymphocytes including inhibition of proliferation, egress from lymph nodes (tumoral niches), inhibition of CXCR4 dependent homing to niches, and death in blood and niches [20, 87]. Attention should be drawn though on adverse events during the first year of treatment because of high plasma exposure to ibrutinib [35]. Ibrutinib is either metabolized into dihydrodiol-ibrutinib or excreted through other elimination routes. In [35] they explored the link between treatment discontinuation after one year and ibrutinib in CLL. Patients who stopped because of toxicity had significantly higher ibrutinib area under the curve (the curve describes the variation of the drug concentration in blood as a function of time). No association was found between cessation of therapy due to disease progression and ibrutinib. As they mentioned, the relationship between ibrutinib exposure at first month and discontinuation after 12 months is an important endpoint because it reveals that stopping ibrutinib during the first year of therapy has a negative impact on overall survival (OS) and progression free survival (PFS).

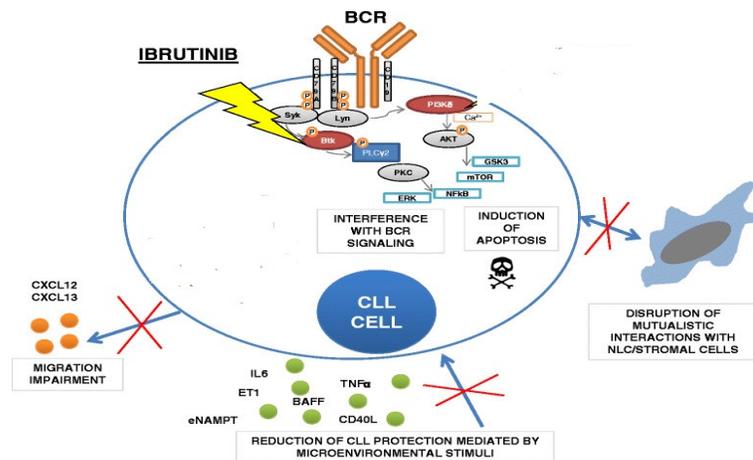


Figure 1.8: ibrutinib action in CLL, source [70].

For CLL cells that transit to the lymph nodes, the migration rates were estimated in [110]. Wodarz et al studied with an ODE model the kinetics of CLL cells after the administration of ibrutinib. They found that under ibrutinib cells in the blood die 3 times more and in the tissues 5 times more than without treatment. B-CLL cells redistribute into the blood with a total nodal decline (due to death and redistribution) indicating that reduction of tissue disease burden is largely caused by CLL cell death. The redistribution rate was $0.8\% \pm 0.5\%$ of cells redistribute per day.

In [13] Byrd and colleagues compared ibrutinib and ofatumumab with a biological study done in previously treated patients of Chronic Lymphoid Leukemia. Ibrutinib significantly improved progression-free survival (PFS), overall survival (OS) and response rate (RR) of patients. More specifically, PFS was prolonged with ibrutinib (median not reached at 9.4 months whereas median duration of PFS with ofatumumab

was 8.1 months). In patients with 17p13.1 deletion, in ibrutinib group PFS was not reached while in ofatumumab group it was 5.8 months. Ibrutinib also increased overall survival: in 12 months the OS rate was 90% in the ibrutinib group and 81% in the ofatumumab group. 43% of the patients in the ibrutinib group had a partial response (PR), as compared with 4% in the ofatumumab group. Treatment exposure was longer (median duration 8.6 months with ibrutinib and 5.3 months with ofatumumab). Finally after discontinuation of treatment, fatal events occurred at 4% of ibrutinib patients and 5% of ofatumumab patients.

The efficacy of the treatment of CLL depends on several factors like the age of the patient, the physical condition, the chromosomal mutations, the mutational status of the heavy chain of immunoglobulin (IgVh). In [51] the prognostic factors used as clinical markers are listed. Poor prognosis is related, for instance, to high CD38 expression, high Zap-70 expression and unmutated heavy chain of immunoglobulin (IgVh-UM). As shown in [19] mutated IGHV is correlated with improvement in both progression free survival and overall survival. However, IGHV status is not typically a major factor in the decision of when to initiate therapy. It can influence choice of therapy, with mutated IGHV patients being better candidates for chemoimmunotherapy, while unmutated IGHV patients are more likely to benefit from a novel agent based approach.

Abbreviations	Meaning
Overall survival (OS)	Time until death (from any cause)
Progression free survival (PFS)	Time until progression or death
Partial response (PR)	Decrease in the size of a tumor or in the amount of cancer
Complete response (CR)	Disappearance of all signs of cancer in the body
Overall response (OR)	Proportion of patients with partial or complete response
Objective response rate (RR)	Proportion of patients with reduction on tumor burden

Table 1.4: endpoints used in studies.

1.4.3 CLL modeling

There are some mathematical models that capture the dynamics of B-CLL cells [61, 82, 94, 102, 110], but the selection of the appropriate model could be challenging as many factors should be taken into account beforehand. Some of these factors are the measurements or the available data which are gathered with costly procedures or painful exams.

As far as the data is concerned, typically there is access to blood measurements and sometimes to tomography (CT) scans that help clinicians count the volume of the lymph nodes and the spleen. We present here briefly the nature of the data available in clinics but we do not use these data to make our analysis.

Concerning blood measurements, the number of lymphocytes per micro-liter of blood is measured directly by serial complete blood counts. This number is multiplied by the blood volume of each patient, estimated from the body weight, and yields the total number of lymphocytes in the blood. For the total number of cells in tissues we consider that in enlarged nodes the majority of the volume is determined by CLL-cells. This is not the case for the spleen whose average size is not negligible in healthy individuals.

Studying the available data can help mathematicians derive the equations that will guide their modeling. In practice, the partial CT scans and the tissue volumetric data that are available are much less than blood measurements. Usually several hospital visits are planned for patients, where pharmacokinetic blood sampling is performed in a time period of at least a year. In [74] with real time imaging of CLL directional migration, they showed that migration of CLL cells depends on protein CIP4 which is a key regulator of chemotaxis in CLL. CIP4 is expressed at abnormal levels in CLL suggesting that CIP4 removal impairs directional migration.

Apart from all the above, biological markers that are not often used, such as the CXCR4 adhesion marker, should also be taken into account.

The data collected by Messmer and colleagues were used in many future studies one of which is by Nanda et al [82]. They constructed a mathematical model for CLL including immune response. They considered the development of B-CLL (denoted by B) cells along with three components of the cellular immune response to B-CLL: natural killer cells (NK) (denoted by N), helper T-cells (denoted by T_H) and cytotoxic T cells (denoted by T). The model is as follows:

$$\begin{cases} \frac{dB}{dt} = b_B + (r - d_B)B - d_{BN}BN - d_{BT}BT, \\ \frac{dN}{dt} = b_N - d_NN - d_{NB}NB, \\ \frac{dT}{dt} = b_T - d_TT - d_{TB}TB + ka_{T_H} \frac{B^L}{s+B^L} T_H, \\ \frac{dT_H}{dt} = b_{T_H} - d_{T_H}T_H + a_{T_H} \frac{B^L}{s+B^L} T_H. \end{cases}$$

In this system b_B, b_N, b_T, b_{T_H} represent the natural sources of these cells from another compartment, d_B, d_N, d_T, d_{T_H} are the natural death rates, $d_{BN}, d_{BT}, d_{NB}, d_{TB}$ are the interaction rates and r is the division rate. The T cell recruitment term $ka_{T_H} \frac{B^L}{s+B^L} T_H$, is a fraction k of the newly activated $CD4^+$ helper T cells. Finally stimulation and recruitment are represented by the saturation-limited term $a_{T_H} \frac{B^L}{s+B^L} T_H$.

Nanda and colleagues used Messmer et al. measurements to assign value ranges to the model parameters representing growth and natural death rate of B-CLL cells. With their model they determined factors that affect the disease progression, for example the parameters describing the ability of T cells to kill B-CLL cells d_{BT} , the recruitment rate of new T-cells a_{T_H} and the natural source of B-CLL cells b_B from another compartment (not the blood) such as the bone marrow. Their results indicate a reduced effect of the immune system over time, hence cell lysis assays may be good prognostic indicator. Moreover the parameter measuring the strength of the adaptive immune response, was

found to have the greatest effect on both the short and long term development of the disease. Any therapy that targets these parameters is worth a careful study.

Another important study, that has already been mentioned in the previous section, was conducted by Wodarz and Komarova [110] where they measured the kinetics of CLL with an ODE model. Their model has two ODE compartments:

$$\begin{cases} \frac{dx}{dt} = -mx - d_1(x - c), \\ \frac{dy}{dt} = mx - d_2y, \end{cases}$$

with positive initial conditions. CLL lymphocytes in the tissues and blood are denoted by x and y respectively. The natural death rates are denoted by the parameters d_1, d_2 and m is the transfer rate from the one compartment to the other. The parameter c is a constant that is used to describe the decline of the B lymphocytes towards a steady state. It is used as an input and not as an output of the model because in that way the results are more consistent with the available data. As already mentioned, their basic result is the estimation of the migration rates of the cells and the rate of redistribution. They found a significant positive correlation between the rate of nodal decline and the death rate of tissue cells but no correlation was found between the rate of nodal decline and the rate of CLL cell redistribution. This result indicates that reduction of the tumor load is mostly attributed to death in the tissues and not to the redistribution of cells from tissues to the blood. More recent data though seem to contradict this result and suggest that ibrutinib empties the lymph nodes by a combination of increasing the transfer rate from tissues to blood.

Komarova and Wodarz also created a stochastic model [61] that was estimated by using data both from Messmer et al. and the previous work of Wodarz et al. They estimated the time required for resistance to grow at detectable levels. This time is highly variable from one patient to the other and is predicted with a high level of accuracy. Resistant mutants have a small fitness advantage in the absence of treatment compared to sensitive cells. Moreover the model can predict the time that ibrutinib can suppress disease and whether chemo-immunotherapy can reduce tumor load prior to ibrutinib therapy with satisfactory results concerning progression free survival.

The major concern which drives our analysis in the following chapters is the phenomenon of prolonged lymphocytosis (PRL). One year after initiation of ibrutinib, around 20 per cent of the patients present lymphocytosis higher than fifty per cent of baseline, but surprisingly this residual disease does not affect prognosis [111]. The pathophysiology of PRL remains obscure. Preliminary studies have suggested that PRL is prevalent in IgHV mutated CLL. Intriguingly, despite the persistence of high tumour burden, the prognosis of patients with PRL seems to be at least as good as for patients with complete response. In [111] Woyach et al. confirmed that in most patients with PRL, BTK remains kinase inactive with ibrutinib but BCR signaling pathway is not inhibited. Although cells are unable to be stimulated by BTK-dependent pathways, they remain responsive because the BCR signaling proteins AKT and ERK can be activated by CD40L. The fact that they are not dependent on BCR signaling for survival makes

them resistant to ibrutinib-induced apoptosis. In the same study they also confirmed that no transcriptional consequences because of BTK downstream are apparent, hence there is no gene expression changes. Moreover epigenetic alternation of Zap-70 is not altered in PRL and persistent lymphocytes are not actively proliferating. The phenotype of persistent lymphocytes shows that most probably PRL represents a subgroup of quiescent anergic cells.

1.5 Detailed plan

1.5.1 Mathematical analysis of a continuous model of interaction of CML with the immune system

In chapter 2 we study the continuous analogue of the system of ODEs analyzed in [5] which we structure in maturity. Let $x \in \mathbb{R}^+$ be the variable describing maturity with $x = 0$ corresponding to stem cells. Our system is as follows:

$$\begin{cases} \frac{dc}{dt} = rc\left(1 - \frac{c}{K}\right) - \mu_c cz \\ \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) = h(x)u(t, x) - \mu_u u(t, x)z \\ gu(t, 0) = ac(t) \\ \frac{dz}{dt} = s - S(I)z \end{cases} \quad (1.2)$$

with initial conditions $(c^0, u^0, z^0) \in \mathbb{R}_+ \times L^1_+(\mathbb{R}_+) \times \mathbb{R}_+$ where the variables of the model are :

- $c(t)$: the concentration of leukemic stem cells at time t .
- $u(t, x)$: the density of leukemic differentiated cells of maturity x at time t and $I = \int_0^\infty w(x)u(t, x)dx$ with w a bounded weight.
- $z(t)$: the concentration of immune cells at time t .

The parameters μ_u, μ_c describe the efficacy of the immune cells over the leukemic differentiated cells and stem cells respectively. S is the inhibition function and w is a weight taking into account the different stimulation based on different levels of maturity. An important fact here is that S is not monotonic. In particular we suppose that there is a value I_0 such that:

$$S \text{ decreasing in } (0, I_0) \quad \text{and} \quad S \text{ increasing in } (I_0, +\infty).$$

The function h is the balance between proliferation and death of leukemic cells of maturity x : $h(x) = p(x) - d(x)$. When h is constant the system reduces to the ODE model studied in [5] but when h depends on x the system is a PDE model richer than the simple ODE.

Typically, the steady states are the points towards which the solutions of the system could converge in long term. Consequently, if we want to make predictions concerning asymptotic behavior of the model, identifying the equilibrium points and their stability is necessary and informative. For this model we have three types of steady states:

- Disease free equilibrium $(0, 0, 0)$.
- Remission (or low in [5]) equilibrium $(\bar{c}, \bar{u}(x), \bar{z})$ with $\bar{I} = \int_0^{+\infty} w(x)\bar{u}(x)dx < I_0$.
- Disease (or high in [5]) steady states $(\bar{c}, \bar{u}(x), \bar{z})$ with $\bar{I} > I_0$.

We are interested in the effect that the complex structure can have on the stability of the equilibrium points and particularly on the remission equilibrium which was always stable with the ODE model when $\mu_c = \mu_u$. For this purpose we will investigate the effect of a and h on the stability of the remission steady state, keeping the values of \bar{c} , $\bar{I} = \int_0^{+\infty} w(x)\bar{u}(x)dx$ and \bar{z} constant (so that instability is driven by the shape of $\bar{p}(x) = \frac{w(x)\bar{u}(x)}{\int_0^{+\infty} w(x)\bar{u}(x)dx}$ and nothing else).

The stability of the remission is fully characterized by the roots of the following equation:

$$P(\lambda) + Q(\lambda) \int_0^{+\infty} e^{-\lambda x} \bar{p}(x) dx = 0, \quad (1.3)$$

where

$$\bar{p}(x) = \frac{w(x)\bar{u}(x)}{\int_0^{+\infty} w(x)\bar{u}(x)dx},$$

and

$$P(\lambda) = \lambda^3 + (R + S)\lambda^2 + (RS + D)\lambda + DR,$$

$$Q(\lambda) = \left(\frac{\mu_c}{\mu_u} - 1 \right) D\lambda - DR,$$

with $R = \frac{r\bar{c}}{K}$, $S = S(\bar{I})$ and $D = -\mu_u s \frac{S'(\bar{I})\bar{I}}{S(\bar{I})}$ (recall that $S(\bar{I}) > 0$ outside of the immune window).

Analysis of degenerate cases, for example when \bar{p} is a Dirac distribution, allows us to show that the steady state can lose stability based on the shape of \bar{p} , while we can also determine the mean age of the distribution that can destabilize the equilibrium.

We set $\mu_c = \mu_u$.

We chose to study the Dirac distribution first because the computations can be done easily. Consequently, apart from numerical results, we can also obtain analytic results. Then, we tried to make conclusions for more general distributions. A similar approach is presented in [4], where Bernard and Crauste studied a characteristic equation of the same type, with P a linear function and Q constant. In particular, they treated the function: $F : \mathbb{C} \rightarrow \mathbb{C}$

$$F(\lambda) = \lambda + a + b \int_0^{+\infty} e^{-\lambda \tau} d\eta(\tau),$$

which is the characteristic function of the linear equation:

$$\frac{dx}{dt} = -ax - b \int_0^{+\infty} x(t - \tau) d\eta(\tau),$$

where $a, b \in \mathbb{R}$ and η is a cumulative probability distribution:

$$\eta : [0, +\infty) \rightarrow [0, 1],$$

monotone, non decreasing, right continuous with corresponding probability density function $f(\tau)$ given by:

$$d\eta(\tau) = f(\tau)d\tau.$$

With the following definition of stability:

Definition 1. *The delay distribution η (or the density f) is called stable if all roots of the characteristic equation have $\Re(\lambda) < 0$. If at least one characteristic root has positive real part, then the distribution (or the density f) is called unstable.*

They gave conditions over the parameters that make the Dirac stable and they also determined the minimum mean value of the distribution (namely the value of the delay τ) for stability loss. Then they showed that a distribution with n discrete delays and mean E is more stable than the distribution with a single discrete delay E . Finally, stability of discrete delays implies the stability of general distributions. In total, they prove that the Dirac is the less stable distribution among all distributions with the same mean. Meaning that, whenever the Dirac of a certain mean E is stable, then all other distributions with mean E are stable as well.

This is a strong result, since they manage to compare all distributions with the Dirac of a single delay. This result motivated our analysis. Starting from the Dirac destabilization we wanted to determine a minimal mean age of stability loss for general distributions. However we prove that in the case of P a polynomial of third degree and Q constant, Dirac does not have this optimal property. We construct a concrete counter example of a distribution that is less stable than the Dirac, in the sense that it is not a Dirac, it has the same mean as a stable Dirac but it is unstable.

The counter example

Consider the characteristic equation (1.3) as described above. The coefficients of P, Q depend on three parameters R, S, D . With a scaling procedure we are led to the study of a characteristic equation where $R = 1$, hence finally only two parameters S, D intervene. Solutions of the form $\bar{p} = \delta_\tau$ and $\lambda = i\omega$ can exist only for ω that satisfies $|P(i\omega)| = |Q(i\omega)|$. There are either zero, one or two positive solutions ω and they do not depend on τ .

Let $\omega_+ > \omega_-$ be the positive values that give purely imaginary solutions of (1.3) for the Dirac distribution δ_τ , of the form $\lambda = i\omega_\pm$ (note that ω_- may not exist).

We prove that the critical delay for stability loss has the specific expression:

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

Note that for a given equilibrium, S is fixed but D can change if we change the derivative of S without changing its value at \bar{I} . That is why we consider everything as a function only of D and not S .

We show that for all S lying in a certain interval $(0, S^*)$, S^* is defined in the CML chapter, we can always find a D and a distribution X , whose mean value is smaller than the critical τ corresponding to S and D and is such that the equation (1.3) is satisfied for some $i\omega$. That is

$$\begin{cases} E(X) < \tau(S, D), \\ \text{and} \\ P_{D,S}(i\omega) + Q_{D,S}(i\omega) \int_0^{+\infty} e^{-i\omega x} X(x) dx = 0. \end{cases}$$

An example of such a distribution is a sum of two Dirac masses and it is described below. Let $0 < S \leq 1$ and $D \geq 1 - \sqrt{1 - S^2}$. Then for any $\omega \in (\omega_-, \omega_+)$ (or in $(0, \omega_+)$ if ω_- does not exist) set:

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

and consider the argument:

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

and the number:

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

Take the distribution:

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

Then for every $\omega \in (\omega_-, \omega_+)$ (or in $(0, \omega_+)$ if ω_- does not exist) equation (1.3) is satisfied for $\lambda = i\omega$ and $\bar{p}(x) = p_\omega$.

We conclude the chapter 2 with a study of the behavior of the system using realistic parameters. In the case of constant coefficients in our system, the PDE becomes an ODE and the parameters have already been estimated in [5]. Using these parameter values we do our numerical simulations to find the time τ (in days) needed for stability loss with and without treatment. A table with the results is provided in the end of chapter 2.

1.5.2 Mathematical analysis of continuous models of CLL

In chapter 3 we propose and analyze four continuous models of CLL. The objective is to choose the most appropriate one based on the available data and the mechanism that we want to investigate. We start with two models that describe the total B-CLL population with a single variable. They differ in the way they model the B-CLL behavior in the lymph nodes. Then, in each model we separate the B-CLL population

in two sub populations: the cells that are resistant to Ibrutinib and the sensitive to Ibrutinib. We get then two new models that generalize the first ones by describing better the cell populations that are in competition for a place to the multiplication sites. Since the goal is to give an interpretation of the prolonged lymphocytosis (PRL) it seems more accurate to allege that the two sub-populations are in competition for a place to the nurse. That is why we should consider that resistant and sensitive cells have a different contribution to the dynamics.

All four models are explained and analyzed in chapter 3. We explain now the two models of competition.

We call nurse cell sites the tissues maturation loci. In that context, attachment to the nurse means the attachment of cells to the multiplication sites.

1. First model:

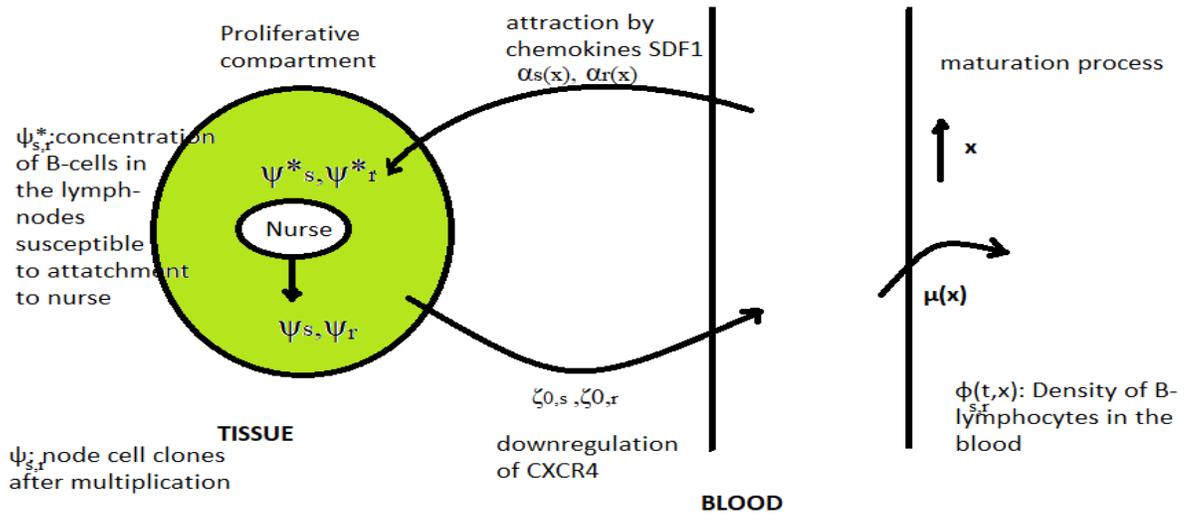


Figure 1.9: schematic representation of model 1.

Let $x \in \mathbb{R}^+$ denote the maturity of a cell in the blood. $x = 0$ corresponds to a

newly formed cell that we call stem cell.

$$\left\{ \begin{array}{l} \frac{d\psi_s^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_s^* - \mu_{nd}^*\psi_s^* + \int_0^\infty \phi_s(t, x)\alpha_s(x)dx, \\ \frac{d\psi_r^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}^*\psi_r^* + \int_0^\infty \phi_r(t, x)\alpha_r(x)dx, \\ \frac{d\psi_s}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}\psi_s - \zeta_0^s\psi_s, \\ \frac{d\psi_r}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_s^* - \mu_{nd}\psi_r - \zeta_0^r\psi_r, \\ \frac{\partial\phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_s(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\ \frac{\partial\phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_r(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\ \phi_s(t, 0) = \zeta_0^s\psi_s(t), \\ \phi_r(t, 0) = \zeta_0^r\psi_r(t). \end{array} \right. \quad (1.4)$$

Take positive initial conditions. B-CLL cells are either resistant, with subscript r, or sensitive, with subscript s. Hence:

- ϕ : stands for the density of B-CLL cells in the blood.
- ψ^* : stands for the concentration of B-lymphocytes in the lymph nodes, susceptible to maturation and to attachment to nurse.
- ψ : stands for the node cell clones after multiplication.

α is the affinity with the nodes and is an increasing function of maturity, β is a decreasing function describing the rate of attachment to the nurse and the rest of the parameters are either the transition or the death rates. γ is the multiplication rate.

We identified the equilibrium points of the system and conducted the stability analysis of the linearized model. There are four types of equilibria:

- The trivial equilibrium $\mathcal{E}_0 = (0, 0, 0, 0, 0, 0)$.
- The single species equilibrium without sensitive components:
 $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$.
- The single species equilibrium without resistant components:
 $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$.
- The equilibrium where all the components are non zero which have the form $\mathcal{E} = p\mathcal{E}_s + (1 - p)\mathcal{E}_r$ with $p \in (0, 1)$.

We prove that stability depends solely on the rate of attachment to the nurse β . If $\beta(\bar{\psi}_s^*) < \beta(\bar{\psi}_r^*)$ then \mathcal{E}_s is stable and \mathcal{E}_r is unstable. Inversely, if $\beta(\bar{\psi}_r^*) < \beta(\bar{\psi}_s^*)$ then \mathcal{E}_r is stable and \mathcal{E}_s is unstable. Equilibrium points of the fourth type \mathcal{E} are asymptotically unstable.

As β is decreasing we interpret this result as follows: when sensitive are less in number in the steady state, hence more rapidly fixed to the nurse, then when resistant cells arrive (corresponding to a perturbation of the equilibrium) they

manage to eliminate sensitive cells (since \mathcal{E}_r is stable). The inverse situation is observed when more resistant cells exist in the steady state.

From our analysis we know that there is a unique dose that guarantees coexistence of resistant and sensitive cells. Our stability results are local, which is not fully satisfactory. Global stability analysis should be conducted to make sure that the stability results are interpreted as invasion of one of the two populations over the other. More specifically, the parameters' choice will determine whether $\beta(\bar{\psi}_s) > \beta(\bar{\psi}_r)$ or not and if stability is global, resistant or sensitive cells will win even if initially the leukemic values were not close to the steady state values. Note that as ibrutinib can affect only sensitive cells, the critical dose should be adjusted (in particular decreased) so that sensitive cells are kept at some level that does not make resistant win and govern dynamics. If this is the case, stability of sensitive equilibrium is a favorable situation for PRL and a leukemia with good prognosis.

2. Second model:

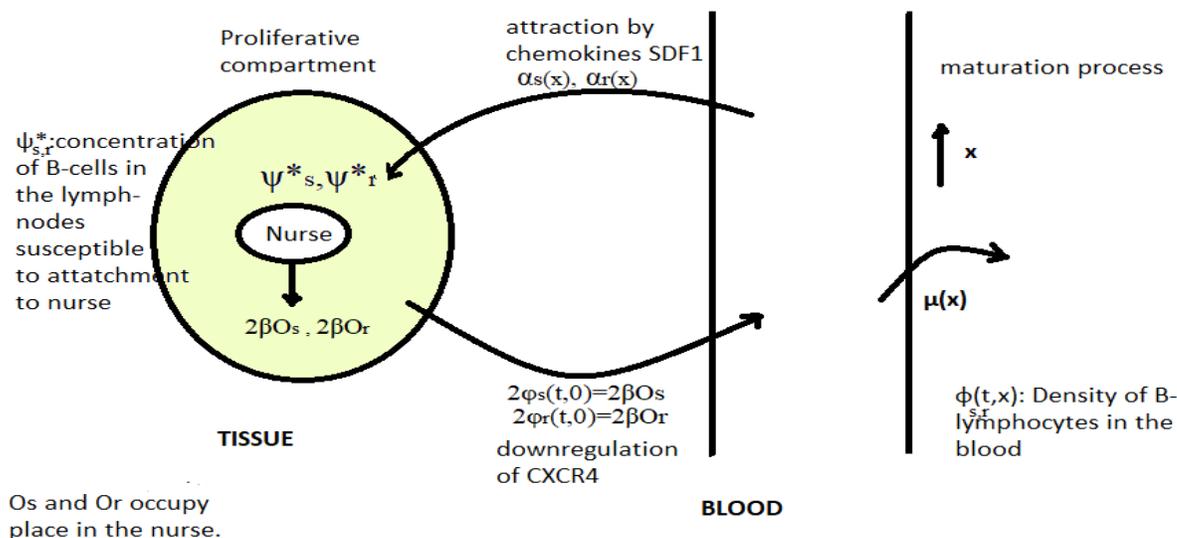


Figure 1.10: schematic representation of model 2.

Here the variables $\psi^*(t)$ and $\phi(t, x)$ have the same meaning as in the previous model. $O_{s,r}$ stands for occupied and is used to describe the cells in the tissues (sensitive or resistant) that have already been fixed to a multiplication site. The total number of the multiplication sites is finite N_g so the cells that are in competition with ψ^* for a place in the nurse are $N_g - O_s - O_r$. β is the division rate.

$$\begin{cases}
\frac{d\psi_s^*}{dt} = (N_g - O_s(t) - O_r(t))(\int_0^\infty \phi_s(t, x)\alpha_s(x)dx - a_s\psi_s^*) - \mu^*\psi_s^*, \\
\frac{d\psi_r^*}{dt} = (N_g - O_s(t) - O_r(t))(\int_0^\infty \phi_r(t, x)\alpha_r(x)dx - a_r\psi_r^*) - \mu^*\psi_r^*, \\
\frac{dO_s}{dt} = -\beta O_s + a_s(N_g - O_s(t) - O_r(t))\psi_s^*, \\
\frac{dO_r}{dt} = -\beta O_r + a_r(N_g - O_s(t) - O_r(t))\psi_r^*, \\
\frac{\partial \phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_s(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\
\phi_s(t, 0) = 2\beta O_s(t), \\
\frac{\partial \phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_r(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\
\phi_r(t, 0) = 2\beta O_r(t),
\end{cases} \quad (1.5)$$

with positive initial conditions. Suppose that initially:

$$O_s^0 + O_r^0 < N_g,$$

and that the rate of attachment to the nurse is higher for sensitive than resistant cells:

$$a_s > a_r.$$

after division each cell gives 2 daughter cells. The system has four types of equilibrium points:

- The trivial equilibrium $(0, 0, 0, 0, 0, 0)$.
- The single species equilibrium without sensitive components:
 $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{O}_r, \bar{\phi}_r(x))$.
- The single species equilibrium without resistant components:
 $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s(x), 0, 0, 0)$.
- The equilibrium with all of the components non zero $\mathcal{E} = p\mathcal{E}_s + (1 - p)\mathcal{E}_r$, with $p \in (0, 1)$.

The conclusions that we make are the same as for the previous model. At the steady state, if the sensitive cells occupy more multiplication sites than the resistant cells (meaning that $\bar{O}_s > \bar{O}_r$), then the equilibrium \mathcal{E}_s is stable and \mathcal{E}_r is unstable. Otherwise the resistant equilibrium is stable and \mathcal{E}_s unstable. A detailed analysis and an explanation of why the other model is more appropriate is provided in chapter 3.

1.5.3 Mathematical analysis of a delay model of hematopoiesis

In chapter 4 we propose a system of equations consisting of an ODE and N transport equations that describe the hematopoiesis as a discrete process that takes place in the bone marrow. We make sure that the self renewal properties of hematopoietic stem

cells are taken into consideration by imposing a logistic growth of this population. The carrying capacity is a function of the total mature population of blood cells, inducing a negative feedback control for this process. The system is structured in age (corresponding to the time spent at each compartment of differentiation). By integrating the PDE over the age variable we end up with a system of delay differential equations that we use to make our analysis. The delay τ that appears describes the total age, or equivalently the total time spent at the hematopoietic compartments. The equations are the following:

$$\begin{cases} U_0'(t) &= rU_0(t) \left(1 - \frac{U_0(t)}{K(U_n(t))}\right) - \delta U_0(t), \\ U_n'(t) &= -\mu_n U_n(t) + h e^{-\mu\tau} H(U_n(t-\tau)) U_0(t-\tau), \end{cases} \quad (1.6)$$

with U_0 representing the stem cells and U_n the mature population of all ages.

We conduct the stability analysis of the model which turns to be a complicated issue because the equilibrium points depend on the delay. Stability is reduced to the study of the roots of the characteristic equation:

$$\lambda^2 + p\lambda + \alpha + (q(\tau)\lambda + c(\tau))e^{-\lambda\tau} = 0,$$

where the coefficients q, c depend on the delay.

Oscillations appear when a Hopf bifurcation happens, that is when a pair of purely imaginary conjugate solutions of the equation exist and cross the imaginary axis of \mathbb{C} , with non zero imaginary part, as a parameter of the system varies [105].

In the paper of Kuang and Beretta [3] we can find the general analysis for transcendental equations with delay dependent coefficients. The results can be used in our particular case to determine whether destabilization is possible or not. In the region of possible destabilization we have to find whether stability switch actually happens. If this is the case, we want to determine the parameters that entail stability loss and appearance of oscillations. We found a criterion that help us give a global answer so that for any choice of the parameters we can know whether the equilibrium is stable or not. In particular, the equilibrium points are solutions of the following equations:

$$\mu_n \bar{U}_n = h e^{-\mu\tau} \left(1 - \frac{\delta}{r}\right) H(\bar{U}_n) K(\bar{U}_n) \quad \text{and} \quad \bar{U}_0 = \left(1 - \frac{\delta}{r}\right) K(\bar{U}_n). \quad (1.7)$$

With simple calculations that can be found in chapter 4, the coefficients q and c are written as:

$$\begin{cases} q = -\mu_n \frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)}, \\ c = -(r - \delta) \mu_n \frac{\bar{U}_n K'(\bar{U}_n)}{K(\bar{U}_n)}. \end{cases}$$

We noticed that \bar{U}_n depends on the delay only through the product $\mu\tau$. We dissociate \bar{U}_n and τ in the following way. We let μ, τ be free parameters and we are placed on the curves $\mu\tau = c_0$, c_0 constant. On each such curve q and c are constant as well so the

Hayes theorem is applied [41] and gives a critical τ^* for destabilization. Then, for any μ and τ given, a $c_0 = \mu\tau$ corresponds to a particular curve and by comparing τ with the $\tau_{c_0}^*$ we manage to give an answer concerning stability of the equilibrium.

Firstly, we started with the analysis of the particular case K constant and independent of \bar{U}_n which corresponds to $c = 0$. The characteristic equation becomes a transcendental equation whose polynomial part is of the first degree and bifurcation analysis is conducted. Stability charts are provided. Then we analyze the case $K = K(\bar{U}_n)$ dependent on the equilibrium component hence dependent on the delay. The same criterion as in the case K constant holds and is extended to the general case. Again, for any parameter choice we can give an answer of whether the equilibrium is stable or not.

Chapter 2

A model of interaction of CML and immune system

Summary

We propose and analyze a system of partial differential equations (PDEs) for chronic myeloid leukemia (CML), generalizing the ordinary differential equations' system (ODE) proposed in [5, 16]. This model describes the proliferation and differentiation of leukemic cells in the bone marrow and the interactions of leukemic and immune cells. We consider that the differentiation of cells can be described by a continuous variable which we use to structure our system. The model is based on a non-monotonic immune response. At low levels, immune response increases with the tumor load whereas for high levels, tumor is suppressing the effect of immune system (immunosuppression). We analyze the stability of the steady states of the model and compare it to the case of [5] where maturity was described as a discrete state. In particular, a steady state describing remission induced by a control due to the immune system is shown to be unstable in certain situations for the PDE model, whereas in [5] it was systematically stable.

2.1 Introduction

Many mathematical models describing the dynamics of CML during treatment and after treatment cessation have permitted to better understand the mechanism of remission and relapse. A tumor-immune interaction model focusing on the mechanism of immunosuppression was introduced in [16]. This system was simplified and analyzed in [5]. With this approach, treatment free remission (TFR) is generically interpreted as a remission steady state (terminology introduced in [31]) where the disease is controlled by the immune system without complete eradication of stem cells. This approach has been also considered in [31] and [38]). We notice that this appears to be very consistent with recent methods of progressive treatment cessation [17].

2.2 The model

We propose a model of PDEs that describes the interactions of immune and leukemic cells. Although we have a theoretical approach in this work, one should consider that parameters describing proliferation and death rates of leukemic cells are treatment-dependent (effect of treatment on other parameters is possible but that would correspond to less understood mechanisms). Our model is a generalization of a model of ODEs proposed in [5] where two levels of maturation of leukemic cells are considered: stem cells and fully differentiated (mature).

Such a generalization is coherent and informative, because we know that a structure of maturity exists and the time spent at differentiation affects the dynamics of the cells. In [5] where they consider that cells differentiate directly from stem to mature cells, they lose information concerning intermediate stages. Indeed, the time spent at these stages can induce delays that affect the stability of stationary points. Our goal is to investigate whether maturity can affect stability and lead to qualitatively different conclusions or not. With our generalization we consider the total effect of differentiation and not the contribution of separate compartments.

The ODE system is the following:

$$\begin{cases} \frac{dc}{dt} = rc(1 - \frac{c}{K}) - \mu cz, \\ \frac{dy_2}{dt} = a_1 c - d_2 y_2 - \mu y_2 z, \\ \frac{dz}{dt} = s - S(y_2)z, \end{cases} \quad (2.1)$$

where z is the immune cells, y_2 is the population of mature leukemic cells and c the leukemic stem cells. Our PDE model is the continuous analogue of (2.1):

$$\begin{cases} \frac{dc}{dt} = rc(1 - \frac{c}{K}) - \mu_c cz, \\ \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) = h(x)u(t, x) - \mu_u u(t, x)z, \\ gu(t, 0) = ac(t), \\ \frac{dz}{dt} = s - S(I)z, \end{cases} \quad (2.2)$$

with initial conditions $(c^0, u^0, z^0) \in \mathbb{R}_+ \times L^1_+(\mathbb{R}_+) \times \mathbb{R}_+$ where the variables of the model are :

- $c(t)$: the concentration of leukemic stem cells at time t .
- $u(t, x)$: the density of leukemic differentiated cells of maturity x at time t and $I = \int_0^\infty w(x)u(t, x)dx$ is the weighted population of cells. Here w is a nonnegative bounded weight that describes a different stimulation based on different maturities.
- $z(t)$: the concentration of immune cells at time t .

For the leukemic stem cells we consider logistic growth of rate r and carrying capacity K , because this population has self renewal capacities. Let μ_c be a parameter representing the efficacy of the immune system over the leukemic stem cells.

For the leukemic differentiated cells we suppose that the velocity of differentiation is constant and equal to g . 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 maturity. The parameter μ_u is the efficacy of the immune cells over the leukemic differentiated cells.

For the immune cells, we consider s their natural source. The presence of leukemic cells in the blood on the one hand stimulates the immune system but on the other hand it inhibits the production of immune cells. For this reason we consider a function S depending on the total leukemic population which describes the stimulation of the immune system. We make the biological assumption that h is negative after a certain level of maturity. This translates into a death rate which exceeds the proliferation rate when maturity is big enough, simply because in practice there is no cell with infinite maturity. When h and w are constant, this system corresponds to the ODE of [5], but dependence on maturity can make the PDE model richer.

In what follows we suppose that the function S satisfies the following conditions: $S \in C^2(\mathbb{R}^+)$ and that a Y exists such that $S' < 0$ in $(0, Y)$ and $S' > 0$ in $(Y, +\infty)$. As already mentioned, the function S represents the inhibition of the immune system by the leukemic differentiated cells. S can take negative values. We interpret a negative value of this function as the capacity of the immune system to counterbalance the inhibition of the production of immune cells because of leukemic cells.

Definition 2. *We call immune window the set of I where the function $S(I)$ is negative. If it exists, it has the form of an interval (y_{\min}, y_{\max}) .*

Remark 1: depending on the choice of S an immune window may or may not exist. If it does, as it is already mentioned, it has the form of an interval (y_{\min}, y_{\max}) and it corresponds to the region where $S(I) < 0$. The immune window is characterized as the region where the tumor load is such that the stimulation exceeds the natural loss, leading to expansion of the immune population. The tumor load is neither too high (immunosuppression inhibits the growth) nor too low (in which case the immune population may not be stimulated at all). Therefore we are looking for equilibrium points in the zone of I where $S(I) \geq 0$.

Remark 2: we choose to write a negative sign in front of S in our equation (2.2). With this convention a steady state corresponds to $S(\bar{I}) > 0$ and hence we obtain positive equilibrium points as $\bar{z} = +\frac{s}{S(\bar{I})}$. Consequently, when an immune window exists, no relevant (i.e nonnegative) steady state can satisfy $I \in (y_{\min}, y_{\max})$.

In the general case (existence or not of an immune window), we are looking for equilibrium points either in \mathbb{R}^+ or in an interval of the form $(0, y_{\min}) \cup (y_{\max}, +\infty)$.

2.2.1 Well-posedness

Theorem 2. *Let $u_0 \in L^\infty((0, \infty)) \cap L^1((0, \infty))$ and $(c^0, z^0) \in \mathbb{R}_+^2$. Assume $w, h \in L^\infty(\mathbb{R}^+)$ and $\limsup_{+\infty} h < 0$. Then, there is a unique weak solution $(c(t), u(t, x), z(t))$ of the system in the space $C([0, \infty), \mathbb{R}^+) \times C([0, \infty), L_+^1(\mathbb{R}^+)) \times C([0, \infty), \mathbb{R}^+)$.*

The existence and uniqueness of the solution results from the Banach fixed point theorem. We consider the space

$$X = C([0, T], L_+^1(\mathbb{R}^+))$$

with the distance

$$d(u, v) = \sup_{t \in [0, T]} \|u - v\|_{L^1}$$

that makes the space complete. T will be appropriately chosen to apply the fixed point theorem. We construct the following operator.

$$\begin{aligned} \Phi : X &\rightarrow X \\ \bar{u} &\mapsto u \end{aligned} \tag{2.3}$$

where u is a solution of the system:

$$\begin{cases} \bar{I}(t) = \int_0^\infty w(x) \bar{u}(t, x) dx, \\ \frac{dc}{dt} = rc \left(1 - \frac{c}{K}\right) - \mu_c c z, \\ \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) = h(x) u(t, x) - \mu_u u(t, x) z, \\ gu(t, 0) = ac(t), \\ \frac{dz}{dt} = s - S(\bar{I})z, \\ u = u_0(x), \\ c(0) = c_0, \\ z(0) = z_0. \end{cases}$$

For the proof of the theorem we need the following lemma which proves that the operator Φ is well defined for all $t \in (0, T)$.

Lemma 1. *Let T be a fixed time. For $0 \leq t \leq T$ the components of the solution are well defined with bounds that satisfy:*

$$(i) \quad 0 \leq c \leq B_c, \text{ where } B_c = \max\{K, c_0\},$$

$$(ii) \quad u(t, x) \leq \begin{cases} u^0(x - gt) e^{\frac{H(x) - H(x - gt)}{g}}, & x - gt > 0, \\ a B_c e^{\frac{H(x)}{g}}, & x - gt \leq 0 \end{cases},$$

$$\text{where } H(x) = \int_0^x h(y) dy.$$

Integrating we obtain a uniform bound for $\int_0^\infty u(t, x) dx$:

$$\int_0^\infty u(t, x) dx \leq B_u < \infty,$$

with $B_u = B_u(I_0, T)$ a constant depending on $I_0 = \int_0^\infty u_0(x) dx$.

- (iii) $0 \leq z \leq B_z(z_0, T)$,
 with $B_z(z_0, T) = \left(z^0 + \frac{s}{S^\infty}\right) e^{S^\infty T} - \frac{s}{S^\infty}$, $S^\infty = \max(0, \sup(-S))$.

Proof. For bounds (i) and (iii), we firstly notice that the non negativity is obtained directly from the structure of the system. The upper bounds for (i) and (iii) are respectively consequence of the logistic growth and Gronwall lemma after noticing that z satisfies the equation:

$$\dot{z} \leq s + mz, m = \sup_I S(I).$$

(ii) Non negativity of u is a consequence of the non negativity of ac . For the upper bound bound on I , we can simply notice that u satisfies

$$\begin{cases} \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) \leq h(x)u(t, x), \\ gu(t, 0) \leq aB_c. \end{cases}$$

Therefore, using the characteristics of the transport equation, we have:

$$u(t, x) \leq \begin{cases} u^0(x - gt) e^{\frac{H(x) - H(x - gt)}{g}}, & x - gt > 0, \\ aB_c e^{\frac{H(x)}{g}}, & x - gt \leq 0 \end{cases}$$

Therefore, we have the bound:

$$\int_0^\infty u \leq I_0 \sup_{x, x > 0} e^{\frac{H(x) - H(x - gT)}{g}} + aB_c \int_0^{gT} e^{\frac{H(x)}{g}} dx.$$

Remark: we have an upper bound, since the hypothesis on h ensures that

$$\sup_{0 \leq x < y} e^{\frac{H(y) - H(x)}{g}} = K_h < +\infty$$

From the previous lemma and the Cauchy-Lipschitz theorem we get the existence and uniqueness of z and c for $t \in (0, T)$. As z and c are Lipschitz, they are uniformly continuous and they can be defined on the closed interval $[0, T]$. Once z and c are defined, the boundary conditions are independent of u so we have a solution of the transport equation. The operator Φ is well defined. We show now that the operator has a unique fixed point. To establish the contraction property, we consider two functions \bar{u}_1, \bar{u}_2 and let c_i, u_i, z_i , $i = 1, 2$ be their images through Φ . In the following estimation we use the Gronwall inequality.

Lemma 2. *Given two sources \bar{u}_1, \bar{u}_2 the following inequality holds on $[0, T]$, where we have denoted $\delta c = c_1 - c_2, \delta u = u_1 - u_2, \delta z = z_1 - z_2$,*

$$\frac{d}{dt} (\|\delta c\| + \|\delta z\| + \|\delta u(t)\|_1) \leq C(T) (\|\delta c\| + \|\delta z\| + \|\delta u(t)\|_1) + \bar{C}(T) \|\delta \bar{u}(t)\|_1.$$

Since the degradation terms have a negative contribution, we have immediately

$$\frac{d}{dt}|\delta c| \leq r|\delta c| + \mu B_c|\delta z|.$$

Similarly, by the mean value theorem

$$\begin{aligned} \frac{d}{dt}|\delta z| &\leq \max(-S)|\delta z| + z(t)|S(\bar{I}_1) - S(\bar{I}_2)|, \\ &\leq \max(-S)|\delta z| + B_z(z^0, t)\|S'\|_\infty\|w\|_\infty\|\bar{u}_1 - \bar{u}_2\|_1. \end{aligned}$$

Finally, multiplying the PDE on δu by $\text{sign}(\delta u)$, we get

$$\begin{cases} \partial_t|\delta u| + g\partial_x|\delta u| \leq h(x)\delta u - \mu_u z(t)|\delta u| - \mu_u|u_1||\delta z|, \\ |g|\delta u(t, 0)| \leq a|\delta c(t)|. \end{cases}$$

And integrating, we obtain:

$$\frac{d}{dt} \int_0^\infty |\delta u| dx \leq a|\delta c| + (\sup h) \int_0^\infty |\delta u| dx + \mu_u B_u|\delta z|.$$

Putting everything together, we obtain the lemma with:

$$\begin{aligned} C(T) &= \max(a + r, \mu_c B_c + \max(-S) + \mu_u B_u, \sup h), \\ \bar{C}(T) &= B_z(z^0, T)\|w\|_\infty\|S'\|_\infty. \end{aligned}$$

And as a immediate corollary, we have:

Corollary 1. *Given, c^0, z^0, u^0 for any $T \geq 0$, there exists n such that Φ^n is a contraction. As a consequence the problem admits a unique solution.*

From the Gronwall lemma estimate, we have immediately (using that $\delta u(0) = 0$),

$$\|\delta u\|_1(t) \leq \bar{C}(T) \int_0^t e^{C(T)(t-s)} \|\delta \bar{u}\|_1(s) ds.$$

Then, we recall the classical iteration argument, denoting Φ^n the n times composition of Φ , and $\delta u^n = \Phi^n(\bar{u}_1) - \Phi^n(u_2)$ we have

$$\|\delta u^n\|_1(t) \leq \frac{(\bar{C}(T)e^{C(T)T}t)^n}{n!} \sup_{[0, T]} \|\delta \bar{u}(t)\|.$$

And finally, we have

$$d(\Phi^n(\bar{u})\Phi^n(\bar{v})) \leq \underbrace{\frac{(\bar{C}(T)e^{C(T)T}T)^n}{n!}}_{< 1 \text{ for } n \text{ large enough}} d(\bar{u}, \bar{v}).$$

As a corollary of the Banach fixed-point theorem we deduce that Φ has a unique fixed point.

As z and c are defined for all t in $[0, T]$, u is also defined for all t in $[0, T]$. Since T can be chosen arbitrarily, this procedure defines a solution on every interval of time, and consequently, we have a global solution. \square

2.2.2 Steady states of the system

In what follows, we will distinguish two sorts of steady states:

- 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 are called high equilibrium points and those in the nonincreasing area will be called remission equilibria.

Proposition 1. *The system has always a disease free equilibrium $(0, 0, \frac{s}{S(0)})$. The positive equilibrium points, if they exist, are fully described by the value of $\bar{I} = \int_0^\infty w(x)\bar{u}(x)dx$ in the following way :*

$$\begin{cases} \bar{c} = \frac{K}{r} \left(r - \mu_c \frac{s}{S(\bar{I})} \right), \\ \bar{u}(x) = \frac{aK}{g} \frac{K}{r} \left(r - \mu_c \frac{s}{S(\bar{I})} \right) e^{\frac{H(x)}{g} - \mu_u \frac{s}{S(\bar{I})} \frac{x}{g}}, \\ \bar{z} = \frac{s}{S(\bar{I})}. \end{cases} \quad (2.4)$$

As a consequence, a positive value of I leads by (2.4) to a non negative steady state if:

- $S(\bar{I}) > \frac{\mu_c s}{r}$,
- \bar{I} is a solution of the equation $F(I) = I$ where F is defined by

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

Proof. We are looking for stationary points of the system. These are the solutions of the following system:

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

We solve the system and we obtain:

$$\begin{cases} 0 = \bar{c} \left(r - \frac{r\bar{c}}{K} \right) - \mu_c \bar{c} \bar{z}, \\ \bar{u}(x) = \bar{u}(0) e^{\frac{1}{g} \int_0^x h(s) ds - \frac{1}{g} \mu_u \bar{z} x}, \\ g\bar{u}(0) = a\bar{c}, \\ \bar{z} = \frac{s}{S(\bar{I})} \end{cases} .$$

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 we have $\bar{c} \neq 0$ then immediately $\bar{c} = K - \frac{\mu_c \bar{z}}{r}$, $\bar{z} = \frac{s}{S(\bar{I})}$ which leads to the condition $S(\bar{I}) > 0$ to make sure that $\bar{z} > 0$ and to the condition $S(\bar{I}) > \frac{\mu_c s}{r}$ to have $\bar{c} > 0$. The formulation for \bar{u} is obtained after integration along characteristics and the fixed point formulation is then just a compatibility condition. \square

Proposition 2. • *If $rS(0) - \mu_c s > 0$ there exists at least one positive equilibrium.*

Moreover, if the function $rS(I) - \mu_c s$ has two zeros, I_{min}, I_{max} , then there exists a unique positive equilibrium parametrized by a value of I in the zone $(0, I_{min})$, that we call remission equilibrium. All other equilibria, if they exist, are parametrized by value of I in (I_{max}, ∞) and we call them high equilibrium points.

- *If $rS(0) - \mu_c s \leq 0$ then no remission equilibrium can exist (high equilibria may exist in $(y_{max}, +\infty)$).*

Proof. We reformulate the fixed point :

We introduce the function

$$f(I) = \frac{\mu_u}{\mu_c} \frac{1}{g} \left(r - \mu_c \frac{s}{S(I)} \right),$$

and the function ψ

$$\psi(x) = a \frac{\mu_c K}{r \mu_u} w(x) e^{\frac{1}{g} \int_0^x h(s) ds - \frac{r \mu_u}{\mu_c g} x},$$

so that F is written in the condensed form:

$$F(I) = f(I) \int_0^\infty \psi(x) e^{f(I)x} dx.$$

- (a) We observe that f starts by being positive: $f(0) = \frac{\mu_u}{\mu_c} \frac{1}{g} \left(r - \frac{\mu_c s}{S(0)} \right) = \frac{\mu_u}{\mu_c g} \frac{S(0)r - \mu_c s}{S(0)} > 0$.

We compute the derivative of f :

$$f'(I) = \frac{s \mu_u}{g} \frac{S'(I)}{S(I)^2}$$

and the derivative of F :

$$F'(I) = f'(I) \int_0^\infty \psi(x) e^{f(I)x} dx + f(I) f'(I) \int_0^\infty x \psi(x) e^{f(I)x} dx.$$

The function f has the same monotony as S . We have two situations:

- f is nonnegative on \mathbb{R}_+ . The existence of an equilibrium is simply due to the fact that the continuous function $F(I) - I$ (defined then on \mathbb{R}_+) changes sign between 0 and $+\infty$ ($F(\infty)$ is finite).
- f vanishes. We note I_{min} its first zero. By construction, f is decreasing on $(0, Y)$. If it does not vanish before Y , it does not vanish at all. If it does, the first zero I_{min} is located in $[0, Y]$. In that case $F(I) - I$ changes sign between 0 and I_{min} and it is also decreasing, making the fixed point unique in $[0, I_{min}]$. Due to its shape, f vanishes at most twice. We call I_{max} the second zero (if it exists). By a symmetric argument, we have $Y \leq I_{max}$ and $S'(I) \geq 0$ on $[I_{max}, +\infty[$. Since there cannot be any fixed points of F in $[I_{min}, I_{max}]$ all the remaining equilibria can only correspond to values of I located in $]I_{max}, +\infty[$ and are therefore high equilibria. If $I_{max} > F(0)$ there is no intersection with the bisector after y_{max} . Otherwise, the number of intersection points depends on the variations of F .

(b) In that case f starts by being non positive: $f(0) = \frac{\mu_u}{g\mu_c} \frac{S(0)r - \mu_c s}{S(0)} \leq 0$. As f is decreasing until Y and increasing afterwards, we see that: If f has no zeros then f is always negative and there is no intersection with the bisector. If f has a zero in $(y_{max}, +\infty)$ then the intersections with the bisector, if any, correspond to equilibrium points with high tumor concentration. \square

Remark: if there is no immune window ($S(I)$ positive on \mathbb{R}^+) there is always an equilibrium but we do not call it remission equilibrium point anymore.

2.2.3 Stability analysis

2.2.4 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 [81]. Next to each result we give the page where one can find it in [81].

Definition 3. (p.36)

A family $(T(t))_{t \geq 0}$ of bounded linear operators on a Banach space X is called strongly continuous (one parameter) semigroup (or C_0 semigroup) if the functional equation holds:

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

and the orbit maps

$$\xi_x : t \rightarrow \xi_x(t) := T(t)x$$

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

Remark: the second property can also be expressed by saying that the map

$$t \rightarrow T(t)$$

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

Definition 4. *The generator $A : D(A) \subset X \rightarrow X$ of a strongly continuous semigroup $(T(t))_{t \geq 0}$ on a Banach space X is the operator:*

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

defined for every x in the domain:

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

Definition 5. *For a closed operator $A : D(A) \subseteq X \rightarrow X$ 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)*

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

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

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

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

Lemma 3. *(p.242)*

For a closed operator $A : D(A) \subset X \rightarrow X$ 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 $\lim_{n \rightarrow \infty} \|Ax_n - \lambda x_n\| = 0$.

Theorem 3. 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:

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

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

for every $t \geq 0$.

Definition 6. (p.250) Let $A : D(A) \subset X \rightarrow X$ be a closed operator. Then,

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

is the spectral bound of A .

Moreover,

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

is the growth bound of A .

Proposition 3. (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:

$$\begin{aligned} -\infty \leq s(A) \leq \omega_0 &= \inf_{t>0} \frac{1}{t} \log \|T(t)\| = \lim_{t \rightarrow \infty} \frac{1}{t} \log \|T(t)\| \\ &= \frac{1}{t_0} \log r(T(t_0)) < \infty \end{aligned}$$

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 4. (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

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

for every $t \geq 0$.

2.2.5 From linear to nonlinear stability

We are now ready to study the stability of the identified equilibrium points.

Theorem 4. If a stationary point is linearly exponentially stable, then it is also non linearly stable.

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

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

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

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

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

A few important remarks:

- We restrict ourselves to admissible perturbations (namely we impose initially $(\bar{c} + \delta c(0), \bar{u} + \delta u(0, \cdot), \bar{z} + \delta z(0)) \geq 0$ and in the appropriate space),
- we have already established (in the existence proof) the uniform bound of I (and thereby of $\bar{I} + \delta I$) so that in a neighborhood of the steady state we can assume 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 steady state, we have

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

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 T_L the semigroup associated to the linear operator above, we can derive from Duhamel's formula

$$(\delta c, \delta u, \delta z)(t) = T_L(t) (\delta c, \delta u, \delta z)(0) + \int_0^t T_L(t-s) \omega(s) ds.$$

In terms of norms, this can be written as:

$$\|(\delta c, \delta u, \delta z)(t)\| \leq \|T_L(t)\| \|(\delta c, \delta u, \delta z)(0)\| + K \int_0^t \|T_L(t-s)\| \|(\delta c, \delta u, \delta z)(s)\|^2 ds.$$

Since the linear exponential stability of the steady state is characterized by the existence of two positive constants M, λ_0 such that $\|T_L(t)\| \leq M e^{-\lambda_0 t}$, we have, denoting $y = \|(\delta c, \delta u, \delta z)(t)\|$,

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

which leads to

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

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

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

which leads to the conclusion. \square

The linear system around an equilibrium is written as:

$$\begin{cases} \frac{dc}{dt} = \left(r - \frac{2r\bar{c}}{K} - \mu_c \bar{z}\right)c - \mu_c \bar{c}z, \\ \frac{\partial u}{\partial t}(t, x) + g \frac{\partial u}{\partial x}(t, x) = h(x)u(t, x) - \mu_u \bar{u}z - \mu_u u\bar{z}, \\ u(t, 0) = \frac{ac(t)}{g}, \\ \frac{dz}{dt} = -S(\bar{I})z - \bar{z}S'(\bar{I})I, \end{cases} \quad (2.5)$$

where $I = \int_0^{+\infty} w(x)u(t, x)dt$.

We have proved that the nonlinear stability stems from the behavior of (2.5).

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

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

which to an initial condition associates a solution of (L).

Let A be its infinitesimal generator defined on $\mathbb{R} \times W^{1,1}(\mathbb{R}^+) \times \mathbb{R}$ under the boundary condition.

Then the linear system can be written like:

$$\begin{pmatrix} \frac{dc}{dt} \\ \frac{\partial u}{\partial t} \\ \frac{dz}{dt} \end{pmatrix} = A \begin{pmatrix} c \\ u \\ z \end{pmatrix}$$

Proposition 5. 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

$$E_\lambda(x) = \frac{a}{g} e^{\frac{1}{g}(\int_0^x h(s)ds - \mu_u \bar{z}x)} e^{-\frac{\lambda x}{g}}$$

and the matrix $M(\lambda)$

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

Then M is well defined and λ satisfies necessarily one of these two properties

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

Proof. We try to solve the resolvent operator for a given λ , that is we look for a nontrivial solution (C, U, Z) of the problem with a source

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

With our notations,

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

and

$$\begin{aligned} & \int_0^{+\infty} w(x)U(x)dx = \\ C \int_0^{+\infty} w(x)E_\lambda(x)dx - \frac{\mu_u Z}{g} \int_0^{+\infty} w(x) \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} \bar{u}(y) dy dx + \int_0^{+\infty} w(x) \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y) dy dx. \end{aligned} \quad (2.6)$$

We set:

- $J^C(\lambda) = \int_0^{+\infty} w(x)E_\lambda(x)dx,$
- $J^Z(\lambda) = \frac{1}{g} \int_0^{+\infty} w(x) \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} \bar{u}(y) dy dx,$
- $J_1(\lambda) = \int_0^{+\infty} w(x) \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y) dy dx.$

So that the above equations become:

$$\int_0^{+\infty} w(x)U(x)dx = CJ^C(\lambda) - \mu_u Z J^Z(\lambda) + J_1(\lambda).$$

As $\Re(\lambda) > -\mu_u\bar{z}$, $u_1 \in L^1$ we have no integrability issues. Indeed, $\int_y^x h$ is bounded from above if $y < x$, so $E_\lambda(x)/E_\lambda(y)$ is controlled by $Ke^{-(\Re(\lambda) + \mu_u\bar{z})(x-y)} = Ke^{-\epsilon(x-y)}$ with $\epsilon > 0$. In particular, it is straightforward to see that:

$$\|E_\lambda\|_1 \leq \frac{K}{\epsilon}, \quad \left\| \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} \bar{u}(y) dy \right\|_1 \leq \frac{K}{\epsilon} \|\bar{u}\|_1, \quad \left\| \int_0^x \frac{E_\lambda(x)}{E_\lambda(y)} u_1(y) dy \right\|_1 \leq \frac{K}{\epsilon} \|u_1\|_1.$$

So the problem has a solution iff 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 terms of matrices if we notice that:

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

The system can be written as

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

Then we have the following alternative:

- if the matrix is not invertible, there exists a nontrivial solution associated to a source 0 which leads to the construction of an eigenvector,
- in the opposite case, the problem is uniquely solvable which makes $(A - \lambda)$ invertible.

This ends the proof of the proposition. □

Proposition 6. *The growth bound of the linear semi group 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 (and also non-linearly) stable.*

Proof. Firstly, observe that the difficulty derives from some lack of compactness (if maturity lied in a bounded interval, we would be able to derive the result immediately from an eventual compactness). For the proof we 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:

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

we finally 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 us say: $c_n^0 e^{\lambda t}, u_n^0(x) e^{\lambda t}, z_n^0 e^{\lambda t}$. Back to our proof, it suffices to prove that the approximate spectrum of $T_L(t)$ does not contain any element $e^{\lambda t}$ with $\Re(\lambda) > -\mu_u\bar{z}$. Therefore,

we consider a sequence x_n^0 such that $\|T_L(t)x_n^0 - e^{\lambda t}x_0^n\| \rightarrow 0$. Let c_n^0, u_n^0, z_n^0 be the components of x_n^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

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

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

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

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

$$u_n(t, x) = \begin{cases} u_n^0(x - gt) \frac{E_0(x)}{E_0(x-gt)} - \mu_u \bar{u}(x) \int_0^t z_n(s) ds, & \text{if } x - gt > 0, \\ \frac{c_n(t-x/g)}{g} E_0(x) - \mu_u \bar{u}(x) \int_0^{x/g} z_n(t - x/g + s) ds, & \text{if } x - gt < 0 \end{cases}$$

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

$$\begin{aligned} u_n^0(x) &\rightarrow e^{-\lambda t} \left(\frac{c^\infty\left(t - \frac{x}{g}\right)}{g} E_0(x) - \mu_u \bar{u}(x) \int_{t-x/g}^t z^\infty(s) ds \right) \\ &= \frac{e^{-\lambda(t-x/g)} c^\infty\left(t - \frac{x}{g}\right)}{g} E_\lambda(x) - e^{-\lambda t} \mu_u \bar{u}(x) \int_{t-x/g}^t z^\infty(s) ds. \end{aligned}$$

Noting

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

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

$$u^\infty(x) = \frac{c_p^\infty\left(t - \frac{x}{g}\right)}{g} E_\lambda(x) - \mu_u \bar{u}(x) \int_{t-x/g}^t e^{\lambda(s-t)} z_p^\infty(s) ds.$$

If the above limits are nonzero, we have just built an eigenvector of $T(t)$ with eigenvalue $e^{\lambda t}$ (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 $u_0^n \rightarrow u^\infty$ 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:

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

So

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

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

2.2.6 Disease free equilibrium and high steady states

First consequence of the former section concerns the disease free equilibrium.

Proposition 7. *For the disease free steady state, the growth bound of the linearized semigroup satisfies $\omega_0 \leq \max(-\mu_u \bar{z}, r - \mu_c s/S(0), -S(0))$. In particular, 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. In this case we have $\bar{c} = 0, \bar{u} = 0, \bar{z} = s/S(0)$, so the matrix $M(\lambda)$ is upper triangular and $\det(M(\lambda)) = (\lambda - r + \mu_c s/S(0))(\lambda + S(0))$. If $\max(-\mu_u \bar{z}, r - \mu_c s/S(0), -S(0)) > 0$ then $s(A) \geq \omega_0$, hence $s(A) = \omega_0$. \square

We turn now to the high steady states for which S is increasing.

Proposition 8. *Stability of high equilibrium points is given by real eigenvalues.*

The main reason is that in this case the induced linear semigroup applied to $(c, u, -z)$ (one has to change the sign for the variable z) is a positive semigroup. In any case, we can establish it directly from the equation on $\det M(\lambda)$ from proposition 5 to have immediately a link with the alternated stability shown in [5].

For the positive steady states, it is more convenient to use $2\frac{r\bar{c}}{K} + \mu_c \bar{z} - r = \frac{r\bar{c}}{K}$ so the determinant can be written as

$$\begin{aligned} \det M(\lambda) &= \left(\lambda + \frac{r\bar{c}}{K} \right) \left(\lambda + S(\bar{I}) - \bar{z}\mu_u S'(\bar{I}) \int_0^\infty w(x)\bar{u}(x) \int_0^{x/g} e^{-\lambda y} dy dx \right) \\ &\quad - \mu_c \bar{c} S'(\bar{I}) \bar{z} \int_0^\infty w(x) E_\lambda(x) dx. \end{aligned} \quad (2.7)$$

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

$$\Re(E_\lambda(x)) \leq |E_\lambda(x)| \leq E_{\Re(\lambda)}(x), \quad \left| \frac{1}{(\lambda + a)} \right| \leq \frac{1}{\Re(\lambda) + a}, \quad \Re(\lambda) + a > 0.$$

that

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

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 $] - \min(\frac{r\bar{c}}{K}, \mu_u \bar{z}, S(\bar{I})), +\infty[$ 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 $\omega_0 < 0$ and $\det(M) > 0$. Otherwise, ω_0 is precisely the unique zero of the function and therefore since the function is increasing, we have $\det(M(0)) > 0$ if $\omega_0 < 0$ and vice versa.

We finish this section with an equivalent result as in theorem 2, Chapter 2 of [5].

Proposition 9. *The stability of high equilibrium points is alternated. The set of I associated to high equilibria has a minimum and the equilibrium associated to this minimum is unstable.*

Proof. With the same computations as above, we have that $\det(M(0))$ is equal to:

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

In particular, ω_0 has the sign of $F'(\bar{I}) - 1$. Since the steady states are characterized as fixed points of F and in the considered region F is increasing, at the lowest (high) fixed point $F'(\bar{I}) > 1$, then at the next one $F'(\bar{I}) < 1$, etc (except for double roots where stability is not given by ω_0). The last one (which exists because F is bounded and hence we have a maximum number for solutions) is generically stable (see figure 2.1 for an example). The situation is qualitatively the same as in [5] (the number of high steady states might depend on the structure but this point is not as crucial as the potential destabilization of the remission steady state). \square

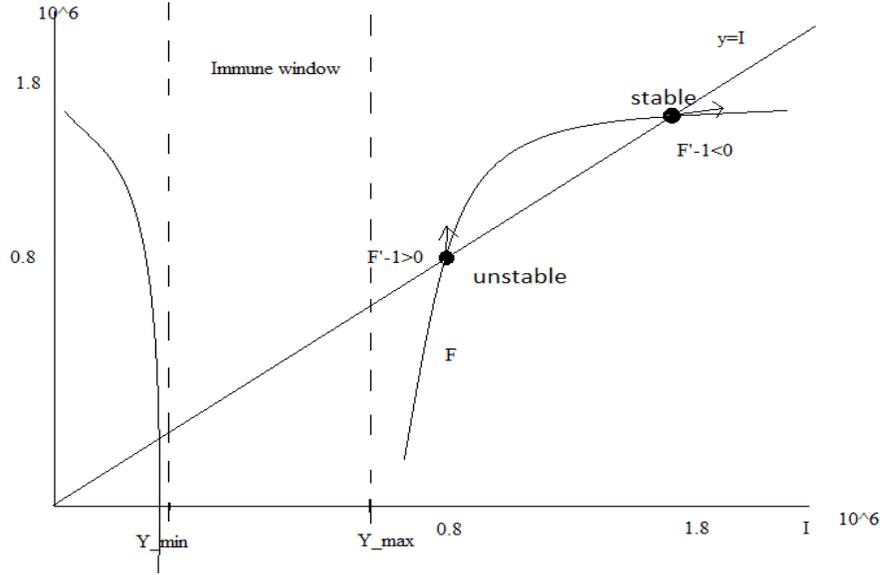


Figure 2.1: example of a function F that is concave after y_{max} . Intersections with the bisector confirm that stability changes based on the sign of $1 - F'(\bar{I})$. When $F'(\bar{I}) < 1$ the equilibrium corresponding to \bar{I} is stable, which is the case of the last point.

2.2.7 Stability of the remission equilibrium

Since our goal is to investigate the effect of the maturity on the structure of our system, we will work with fixed values of \bar{c} , \bar{I} , \bar{z} in order to see how the shape of

$$\bar{p}(x) = \frac{w(x)\bar{u}(x)}{\int_0^\infty w(y)\bar{u}(y)dy} = \frac{w(x)\bar{u}(x)}{\bar{I}}, \quad (2.8)$$

can affect the result.

Proposition 10. *For a remission steady state, there cannot be a real eigenvalue such that*

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

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

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

which leads to the conclusion. \square

As a direct consequence, we can now simplify the problem.

Proposition 11. *Every eigenvalue associated to the remission steady state, such that*

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

is a nonzero root of the equation

$$P(\lambda) + Q(\lambda) \int_0^\infty \frac{w(x)\bar{u}(x)}{\bar{I}} e^{-\lambda \frac{x}{g}} dx = 0, \quad (2.9)$$

Moreover P, Q are the following polynomials:

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

where we have introduced notations for the positive quantities

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

Proof. Since 0 is not a root, we simply write from (2.7) the equation satisfied by $\lambda \det(M)$ when $\lambda \neq 0$. In particular, in this case

$$\lambda \int_0^{x/g} e^{-\lambda y} dy = (1 - e^{-\lambda x/g}).$$

With simple computations we derive:

$$\lambda \det(M(\lambda)) = \lambda(\lambda + R)(\lambda + S) - \bar{z}\mu_u S'(\bar{I})\bar{I}(\lambda + R) + \quad (2.10)$$

$$\bar{z}\mu_u S'(\bar{I})(\lambda + R) \left(\int_0^\infty w(x)u(\bar{x})e^{-\lambda x/g} dx \right) - \lambda\mu_u \bar{c} S'(\bar{I})\bar{c} \int_0^\infty \frac{1}{\bar{c}} w(x)u(\bar{x})e^{-\lambda x/g} dx. \quad (2.11)$$

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

Once 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. We can have a glimpse on the stability boundary in specific cases. In our equation there are two parameters that can be modified without changing the values of $\bar{c}, \bar{I}, \bar{z}$: that is the shape of the distribution \bar{p} and the slope of the derivative $S'(\bar{I})$ which is encoded in the positive parameter D .

2.2.8 The case of exponential distribution [5]

The case of an exponential distribution, $\bar{p} = \gamma_0 e^{-\gamma_0 x}$ corresponds to the study done in [5]. In this case, the eigenvalues above $-\mu_u \bar{z}$ are the (nonzero) solutions of the equation:

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

This can be reduced (since 0 is not an acceptable root) to the third degree polynomial:

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

And then, we can check that any solution satisfies:

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

We extend a bit the result in [5].

Proposition 12. *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

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

Moreover $\chi(-R) > 0$, hence there exists a negative root λ_1 of χ such that $-R - S - \gamma_0 g < \lambda_1 < -R$. We have already established the absence of positive real roots in [5], 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

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

And therefore $\Re(z) < 0$. □

2.2.9 Stability boundary for a Dirac distribution in τ , when $\mu_c = \mu_u$ and $g = 1$

We are now investigating the extreme case of a Dirac distribution, for which explicit computations can be done. In this part we limit ourselves to the case $\mu_c = \mu_u$.

To proceed it is useful to make the following changes on the characteristic equation:

Rewrite the characteristic equation as follows:

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

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:

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

If X is distributed with probability function $\bar{p}(x)dx$, then $Y = RX$ has probability function $\bar{p}(\frac{y}{R})\frac{dy}{R}$. For the Dirac it corresponds to 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.

To simplify the notations, we will omit using tilda notations. The equation that we will be studying is:

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

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

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

$$-i\omega^3 - \omega^2(1 + S) + i\omega(S + D) + D = De^{-i\omega\tau}. \quad (2.12)$$

It is very useful to notice that this equation implies in particular (comparing modulus of both sides)

$$(\omega^3 - (S + D)\omega)^2 + (\omega^2(1 + S) - D)^2 = D^2. \quad (2.13)$$

Which can be simplified by writing $y = \omega^2$

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

since 0 is not a solution. which is a quadratic polynomial of y . We can also rewrite it as a quadratic polynomial of D :

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

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 4 (Solving $D(\omega)$). *Given a frequency $\omega > 0$, there exist (up to multiplicity)*

- *Either two positive solutions to the equation (2.13) if*

$$(1 - S^2)(\omega^2 + 1) \geq 0 \quad (2.14)$$

which is a double root if this quantity is zero.

They are given by:

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

- *or no nonnegative solutions otherwise.*

When we start with S and D given, then a necessary condition for solutions to (2.13) to exist is:

$$S \leq 1, \quad (2.15)$$

and

$$D \geq 1 - \sqrt{1 - S^2}. \quad (2.16)$$

Proof. If we consider D as the unknown, we are looking for positive roots of the quadratic polynomial:

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

Noticing that this is decreasing on \mathbb{R}_- , and $P_{\omega^2}(0) > 0$, we see immediately that real roots are necessarily positive, so that the discriminant is non negative.

$$\Delta = 4(\omega^2 + 1)^2 - 4(\omega^4 + S^2 + \omega^2(1 + S^2)) = 4(1 - S^2)(\omega^2 + 1),$$

leading to condition (2.14). Calculation of the roots is then straightforward and we obtain the last condition by minimizing D_- . \square

Lemma 5. *Assume (2.15) is satisfied, then a solution to (2.13) is given by*

$$\omega_+^2 = \frac{1}{2} \left(2D - 1 - S^2 + (1 - S^2) \sqrt{1 + \frac{4D}{1 - S^2}} \right). \quad (2.17)$$

If additionally $D \geq (1 + \sqrt{1 - S^2})$, then we have a second solution that makes sense,

$$\omega_-^2 = \frac{1}{2} \left(2D - 1 - S^2 - (1 - S^2) \sqrt{1 + \frac{4D}{1 - S^2}} \right). \quad (2.18)$$

We also have the identities

$$\begin{cases} \forall D \geq (1 + \sqrt{1 - S^2}), & D_-(\omega_+(D)) = D, \\ \forall D \geq (1 + \sqrt{1 - S^2}) & D_+(\omega_-(D)) = D, \\ \forall \omega > 0, & \omega = \omega_+(D_-(\omega)) = \omega_-(D_+(\omega)). \end{cases} \quad (2.19)$$

Corollary 2. *For a general distribution (not a Dirac), if we have a solution of the form $i\omega$ to (2.9), then necessarily conditions (2.15), (2.16) hold and ω^2 satisfies the inequalities:*

$$\begin{cases} 0 < \omega^2 \leq \omega_+(D), & \text{if } D < (1 + \sqrt{1 - S^2}), \\ \omega_-^2(D) \leq \omega^2 \leq \omega_+^2(D), & \text{if } D \geq (1 + \sqrt{1 - S^2}). \end{cases} \quad (2.20)$$

So, if no Dirac loses stability, then no other distribution does.

Proof. We simply solve the quadratic polynomial. If $D < (1 + \sqrt{1 - S^2})$ there is only one root. Otherwise there are two. The quadratic polynomial is negative in the regions of ω^2 defined above. \square

Lemma 6. *The boundary is given by the graph:*

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

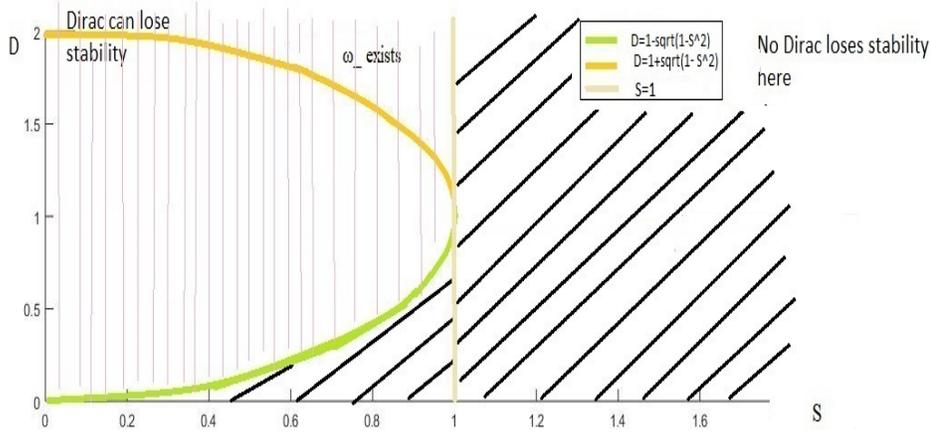


Figure 2.2: stability chart for the Dirac distribution. For $S \geq 1$ no destabilization is possible. Otherwise, if $D \geq 1 - \sqrt{1 - S^2}$ Dirac can lose stability because ω_+ exists. In the region $D \geq 1 + \sqrt{1 - S^2}$, ω_- exists as well.

Proof. From (2.12) 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

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

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

Hence

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

Multiplying by the matrix

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

we obtain

$$D\sqrt{\omega^2 + 1} \sin(\omega\tau + \arctan(\omega)) = -\omega S(\omega^2 + 1) < 0$$

With similar computations, we have :

$$D\sqrt{\omega^2 + 1} \cos(\omega\tau + \arctan(\omega)) = (1 + \omega^2)(D - \omega^2).$$

Consequently

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

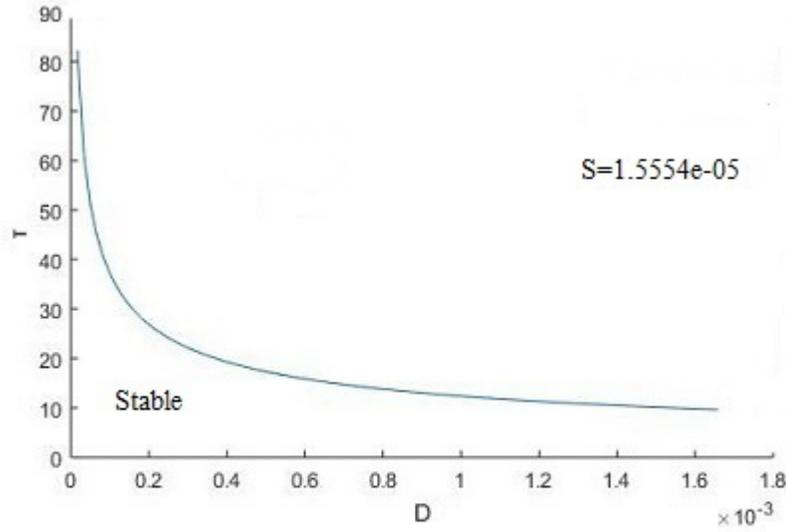


Figure 2.3: stability boundary given by a single Dirac distribution

or equivalently

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

So

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

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_- , graph 2.3. \square

We will be always looking for the minimal positive τ .

2.2.10 Stability boundary for two Dirac masses: Suboptimality of the Dirac solutions

The characteristic equation for $\mu_u = \mu_c$ is the following:

$$\frac{P(\lambda)}{D} = E(e^{-\lambda X}) \quad (2.21)$$

where E denotes the mean value with respect to the distribution $\bar{p}(x)$. In the case of a first degree polynomial $P(\lambda) = \lambda + a$ it has been established in [4] that the Dirac is the

less stable distribution among all distributions with the same mean. This means that if a distribution exists with mean \bar{X} and for which we have instability, then the Dirac $\delta_{\bar{X}}$ is also unstable.

In what follows we prove that this is not the case for our model. In particular, we prove that for certain parameters we can find an unstable distribution, which is not a Dirac, with mean $\bar{X} < \tau_+$.

The question that we answer is the following:

Question 1. *Given S and D , does a distribution whose mean value satisfies:*

$$E(x) = \int_0^{+\infty} x\bar{p}(x)dx < \tau_+(S, D)$$

is necessarily stable? Recall that τ_+ is defined by lemma 6.

Theorem 5. *There exists a value of S , say S^* , such that for all $S \in (0, S^*)$ there exists a D and a distribution X such that $E(X) < \tau(S, D)$ and equation (2.21) is satisfied for some $i\omega$.*

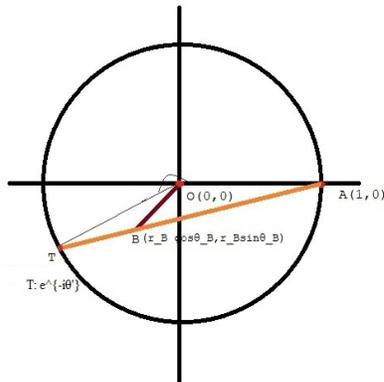
Remark: ideally we would like to determine:

$$\bar{\tau}(\omega) = \inf\left\{\tau_{\bar{p}} = \int_0^{+\infty} x\bar{p}(x)dx, \text{ such that } \int_0^{+\infty} e^{-i\omega x}\bar{p}(x)dx = \frac{P(i\omega)}{D}\right\},$$

but this is left to some future work.

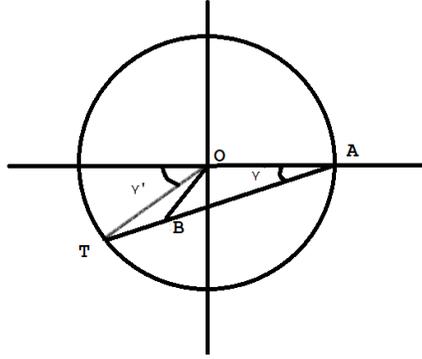
Proof. • Step 1: Combination of two Dirac masses:

For a general distribution, not a single Dirac, $\frac{P(i\omega)}{D}$ is a point in the unit disk, say $B = r_B e^{i\theta_B}$.



If we extend the line that passes through $A(1,0)$ and $B : (r_B e^{i\theta_B})$, we meet the circle at a point $T : e^{-i\theta'}$ whose coordinates are:

$$T = (\cos \theta', -\sin \theta')$$



Set $\theta_T = 2\pi - \theta'$.

Now observe that:

$$-\gamma = \arg\left(\frac{z_0 - z_A}{z_B - z_A}\right)$$

where z_0, z_A, z_B are the complex numbers corresponding to A, B, O . Then, $e^{-i\gamma}$ is on the same line as the complex number $\frac{z_0 - z_A}{z_B - z_A}$.

$$\text{As } \frac{z_0 - z_A}{z_B - z_A} = \frac{-1}{r_B e^{i\theta_B} - 1} = \frac{(1 - r_B \cos \theta_B) + i r_B \sin \theta_B}{(1 - r_B \cos \theta_B)^2 + (r_B \sin \theta_B)^2}$$

we obtain

$$\begin{cases} \cos(-\gamma) = \frac{1 - r_B \cos \theta_B}{(1 - r_B \cos \theta_B)^2 + (r_B \sin \theta_B)^2} \\ \sin(-\gamma) = \frac{r_B \sin \theta_B}{(1 - r_B \cos \theta_B)^2 + (r_B \sin \theta_B)^2} \end{cases}$$

As $\gamma \in (-\frac{\pi}{2}, \frac{\pi}{2})$ we can take the tangent,

$$\tan(-\gamma) = \frac{r_B \sin \theta_B}{1 - r_B \cos \theta_B}.$$

So

$$-\gamma = \arctan\left(\frac{r_B \sin \theta_B}{1 - r_B \cos \theta_B}\right).$$

Moreover,

$$\theta_T = \pi + \gamma'$$

As γ' and γ have the arc on the circle, $\gamma' = 2(-\gamma)$.

Finally:

$$\theta_T = \pi + 2 \arctan\left(\frac{r_B \sin \theta_B}{1 - r_B \cos \theta_B}\right).$$

As $\theta' = 2\pi - \theta_T$ we induce that:

$$\theta' = \pi - 2 \arctan\left(\frac{r_B \sin \theta_B}{1 - r_B \cos \theta_B}\right)$$

B is the barycenter of segment AT so B can be written as a convex combination of the two points A and T .

Let's say

$$r_B e^{i\theta_B} = qT + (1 - q)A.$$

So

$$q = \frac{r_B \sin \theta_B}{\sin \theta_T}.$$

As $\frac{P(i\omega)}{D} = r_B e^{i\theta_B} = (1 - q)1 + qe^{-i\theta'}$ we conclude that if \bar{p} is a sum of two Dirac masses, then

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

- Step 2: Proof of the theorem

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 it as

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

with $\beta \in [0, 2\pi[$.

Lemma 7. *Let $\omega \in (\omega_-, \omega_+)$ and consider the argument*

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

the number

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

and the distribution :

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

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

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

That is (2.21) is satisfied with $\lambda = i\omega$ for the distribution \bar{p}_ω .

Proof of the lemma

We notice that for $\omega \in (\omega_-, \omega_+)$ we have $x^2 + y^2 \leq 1$ by construction. We easily check

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

Finally, if we denote $E_{\bar{p}_\omega}$ the mean with respect to the distribution \bar{p}_ω , we obtain then

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

which is necessary and sufficient condition for (2.21) to be satisfied for $\lambda = i\omega$, $\omega \neq 0$. \square

Obviously we have $q(\omega_+) = 1$, $\theta'(\omega_+) = \beta(\omega_+)$ and $\frac{q(\omega_+)\theta'(\omega_+)}{\omega_+} = \tau(\omega_+)$ corresponding to the Dirac.

The core of the proof lies in the following remark:

Lemma 8. *Let us denote $\tau_{\bar{p}}(\omega) = \int_0^\infty x \bar{p}_\omega(dx)$. Then, there exists an S^* such that for every $S \in (0, S^*)$ there exists a D such that the following holds:*

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

Indeed, in this situation, $E_{\bar{p}_\omega}(X) < \tau_+$ for $\omega < \omega_+$ close enough to ω_+ , and Question 1 has an affirmative answer.

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 that,

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

For the second term, we notice

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

Therefore

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

We end up with the following:

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

Since we simply want an evaluation at $\omega = \omega_+$ and $q(\omega_+) = 1$ by construction, the formula is then a (little) simplified.

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

Finally, by definition of ω_+ , we notice that for $D = \frac{S(1+S)}{1-S}$, we have the equality $\omega_+^2 = S+D$ and thereby $y(\omega_+) = 0$, so that $\beta(\omega_+) = \theta'(\omega_+) = \pi$. If we are in this situation, the computation is simplified a lot more:

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

Therefore the derivative has the sign of

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

This quantity 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 point of intersection S^* with the bisector. On $(0, S^*)$, g is above the bisector, so S^* defines the interval we are looking for. \square

Numerically we can see from the graph below 2.4, that there are some values of ω for which $\bar{p}(x)$ is unstable, having a smaller mean than the mean of the Dirac.

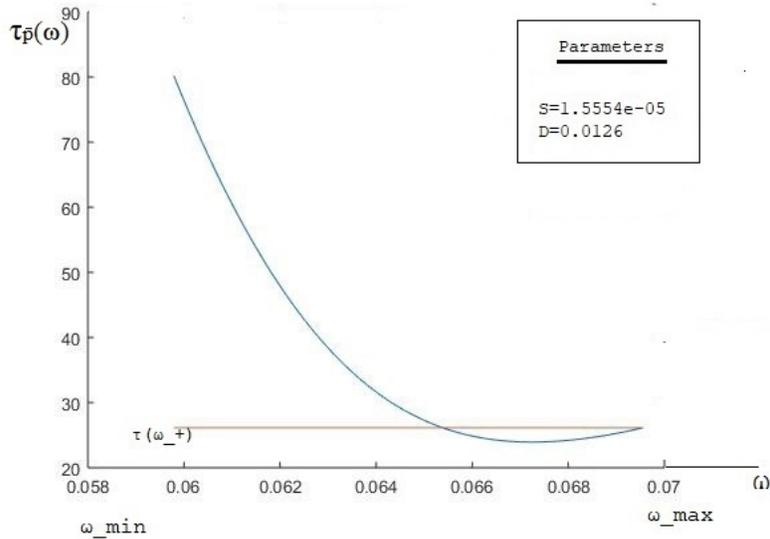


Figure 2.4: graph of the mean value of the distribution with two Dirac masses and the mean value of the single Dirac $\tau(\omega_+)$.

The graph below summarizes our results:

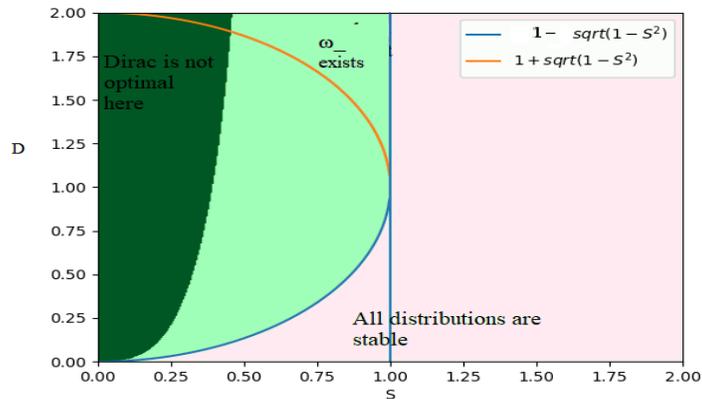


Figure 2.5: in the green region of non optimality of the Dirac, the distribution that is less stable is the sum of two Dirac masses. Its boundary is obtained by the relation $\frac{d\tau_{\bar{p}}(\omega)}{d\omega} > 0$. Note that this region may be larger than what we see in the graph as there are probably other distributions, apart from the sum of two Diracs, that are less stable as well.

2.3 Behavior of the system using realistic parameters

To test the theoretical results found in the previous section, we recall that the case of constant coefficients, leading to an exponential distribution for the steady state, has been estimated on patients. We refer to [5]. This gives us access to realistic parameters. Those parameters were estimated under treatment but we can modify (one of) them to have access to the non treated case. From the PDE system 2.2 we can obtain the ODE system (2.1) by setting:

$$\mu_c = \mu_u = \mu, a = a_1, g = 1, h(x) = -d_2.$$

We choose the following S :

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

and we take the same universal parameters as in [5]:

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

Table 2.1: universal parameters for the constant coefficient case.

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

Table 2.2: patient dependent parameters as estimated in table 3 of [5]

With these parameters, there is always a positive steady state for (2.1) satisfying $\bar{y}_2 < y_{min}$. In the presence of a high steady state (which will satisfy $\bar{y}_2 > y_{max}$) this corresponds to a remission steady state.

Therefore, to apply our results, we work with a value $\bar{I} = \bar{y}_2$, with $g = 1$ and $\mu_u = \mu_c$ to have insight into the effect of the distribution. We give here the relevant values for the patient dependent parameters.

Returning to what we had before normalisation, we obtain the following value for the critical τ in the case of a Dirac distribution:

$$\tau_+(R, S, D) = \frac{1}{R} \tau_+ \left(1, \frac{S}{R}, \frac{D}{R^2} \right). \quad (2.22)$$

under the constraint (corresponding to (2.15) before normalisation):

$$R^2 \geq S^2, \quad (2.23)$$

and (corresponding to (2.16))

$$D \geq R^2 \left(1 - \sqrt{1 - \frac{S^2}{R^2}} \right). \quad (2.24)$$

Without treatment the remission equilibrium does not lose stability for any patient. We can see from the table 2.3 that condition (2.23) is never satisfied in the non treated case.

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 2.3: parameters for patients without treatment: condition (2.23) is never satisfied.

On the other hand, under treatment we observe destabilization for some patients. To account for treatment, we have to divide α_1 by a factor k_{inh} indicating the inhibitory effects. In table 2.4 we see the values of S, D and critical τ for the patients under treatment. Whenever $\tau = +\infty$ we have a stable equilibrium. In the case of treatment we

Patient	a_1 (under treatment)	S	D	τ (in days)
1	5.4e02	3.26e-03	2.4054e-04	$+\infty$
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	$+\infty$
5	0.3e02	3.6e-06	2.4709e-04	100.8270
6	0.5e02	1.447e-06	3.1349e-04	89.6290

Table 2.4: parameters for patients under treatment (fitted in [5]).

do not know whether this destabilization corresponds to relapse or to another behavior (formation of a limit cycle for example). This is to be considered in some future work.

2.4 Discussion and conclusion

In this chapter we have presented and studied a model that is the structured analogue of the simple ODE model analyzed in [5].

Such generalization permits to investigate the effect of a complex maturity structure on the stability of equilibrium points and particularly of the remission steady state. The remission equilibrium that was systematically stable with the ODE model, can lose stability with the PDE structure based on the choice of the distribution of the leukemic cells in the bone marrow. The distribution can change when the balance function h changes. Actually h is the net difference between the proliferation and the natural death of differentiated cells.

With this structure we take into consideration the effect of the maturation process since the time spent at differentiation induces time delays that can make an equilibrium unstable. In practice cells never pass immediately from stem to mature level, consequently using only ordinary equations for stem and mature population can never be accurate enough in the conclusions concerning stability of equilibria.

Stability reduces to the study of roots of the characteristic equation:

$$P(\lambda) + Q(\lambda) \int_0^{+\infty} \bar{p}(x)e^{-\lambda x} dx = 0$$

where P and Q are polynomials of the third and first degree respectively. We fix an equilibrium. Then we can study the effect of the distribution \bar{p} on the stability.

Such equations naturally arise in the study of stability in delay differential systems. We wanted to see what happens to stability when there is a single delay, that is a distribution function $\bar{p} = \delta_\tau$. We provided the stability charts and concluded that there is a region, defined by $S > 1$ and D , where if no Dirac distribution is unstable, then no other distribution can lose stability. As $S = S(\bar{I})$, the parameter D can change without changing $S(\bar{I})$ if we consider a function S that at \bar{I} takes the same value but with a different inclination, namely a different derivative at the point \bar{I} .

For a fixed S , the curve of τ as a function of D , so actually as a function of $S'(\bar{I})$, gives a boundary that specifies the delays for which stability is not lost. Equivalently, this boundary gives the minimum mean value of the Dirac distribution for stability loss.

We prove that there is a whole interval J of possible values of S , $J \subset (0, 1)$, for which there is always a D and an unstable distribution whose mean value is smaller than the Dirac corresponding to S and D . Consequently the Dirac is not optimal in that case. This means that in that region stability of the Dirac cannot be used to make conclusions about more general distributions.

The counter example that we provide to prove that Dirac is not optimal is a sum of two Dirac distributions. We can still use three or either four Dirac sums to provide examples of distributions that are less stable than the critical Dirac for a certain choice of S and D . No conclusions can be made for continuous counter examples. We suspect that we can always choose a finite $n \in \mathbb{N}$ and construct sums of n Diracs as counter example but no continuous distribution would work. This is still to be verified.

Finally, we used realistic parameters of CML patients estimated in [5] to numerically find the value of τ needed for stability loss. As τ corresponds to the time spent at differentiation, it should have normal orders of magnitude to account for loss of remission at real patients. Indeed, it was found to have the order of 2, that is around 10^2 days under treatment. Without treatment, no patient in our set lost stability. That makes us pose the question of interpretation of this stability loss in mathematical and biological terms. Whether it corresponds to relapse or some other behavior it is not known and has to be considered in a future work.

Chapter 3

Modeling of Chronic Lymphoid Leukemia (CLL)

Summary

This work has been done following discussions with David Coulette, Emmanuel Grenier (UMPA, ENS Lyon) and Pierre Sujobert (Hospices Civils de Lyon) in order to extend their unpublished work on modeling chronic lymphoid leukemia (CLL) with ODEs. We study the CLL and we model the CLL-kinetics under ibrutinib. The scientific work that led to the current knowledge and provided us with the necessary information to construct our models is presented in the introduction. We investigate the paradox of prolonged lymphocytosis (PRL) in patients with good prognosis. We proceed with the mathematical modeling trying to get an insight into the mechanisms that are not thoroughly understood and to give answers to clinical questions. We propose two generic models to describe CLL dynamics and we study their limitations. To overcome these limitations we separate the cell populations into sensitive and resistant to ibrutinib. Mathematical analysis leads to conclusions that could explain the clinical paradox of PRL.

3.1 First type of model with and without competition

We study the counter intuitive phenomenon of PRL with good prognosis. For this purpose we construct the models based on our knowledge of CLL dynamics. That is, the disease proliferation centers are the tissues (lymph nodes and spleen) and the cells mature in the blood. For a division to happen, the cell must be linked to specific places in the tissues, that we call multiplication sites. After competition with other cells, a cell that manages to be fixed to a site proliferates and then reenters the blood circulation.

Definition 7. *Let $x \in \mathbb{R}^+$ be a continuous variable representing maturity. We say that a cell is differentiated if its maturity is $x > 0$. Cells with maturity $x = 0$ are called*

stem cells.

3.1.1 Model without competition

Our first model is a system of PDEs:

$$\begin{cases} \frac{d\psi^*}{dt} = -\beta(\psi^*)\psi^* - \mu_{nd}^*\psi^* + \int_0^\infty \phi(t, x)\alpha(x)dx, \\ \frac{d\psi}{dt} = \gamma\beta(\psi^*)\psi^* - \mu_{nd}\psi - \zeta_0\psi, \\ \frac{\partial\phi}{\partial t}(t, x) + g\frac{\partial\phi}{\partial x}(t, x) = -\mu(x)\phi(t, x) - \alpha(x)\phi(t, x), \\ g\phi(t, 0) = \zeta_0\psi(t), \end{cases} \quad (3.1)$$

with initial conditions:

$$\psi(0) = \psi_0 \geq 0, \quad \phi(0, x) = \phi_0(x) \geq 0, \quad \psi^*(0) = \psi_0^* \geq 0.$$

The variables represent the following quantities:

- $\phi(t, x)$: density of B-CLL cells in the blood of maturity x at time t .
- $\psi^*(t)$: concentration of B-lymphocytes in the lymph nodes, susceptible to maturation and to attachment to nurse.
- $\psi(t)$: node cell clones after multiplication at time t .

In our system $\alpha(x)$ is the homing affinity at maturity x . Natural death rates are described by: $\mu(x)$ the natural death rate of B-cells in the blood with maturity x , and μ_{nd}, μ_{nd}^* the apoptosis rate in the tissues. The velocity of differentiation of B-cells in the blood is constant g . Division of cells happens in the tissues with attachment to multiplication sites at a rate $\beta(\psi^*)$. We suppose that the number of multiplication sites is finite.

Remark in this context we will call nurse cells sites the tissues maturation loci so when we refer to attachment to the nurse we will mean the attachment of cells to the multiplication sites.

Then the function β is decreasing as the more cells in the tissues the smaller the rate of attachment to the nurse. The assumptions that we make for β are:

$$\begin{cases} \beta' < 0 & \text{in } \mathbb{R}^+, \\ x \mapsto x\beta(x) & \text{increasing.} \end{cases} \quad (3.2)$$

Biologically, this assumption makes sense since the number of multiplication sites is finite, hence the more cells enter the lymph nodes and the spleen, the less place is free for new cells to be linked to multiplication sites so the rate of attachment decreases. The assumption on $x\beta(x)$ is done to simplify stability analysis. After attachment to the nurse, multiplication happens at a rate γ . Finally, cells return to the blood circulation with a node to blood transfer rate ζ_0 .

The following picture shows schematically the route of B-CLL cells from blood to the nodes and reversely:

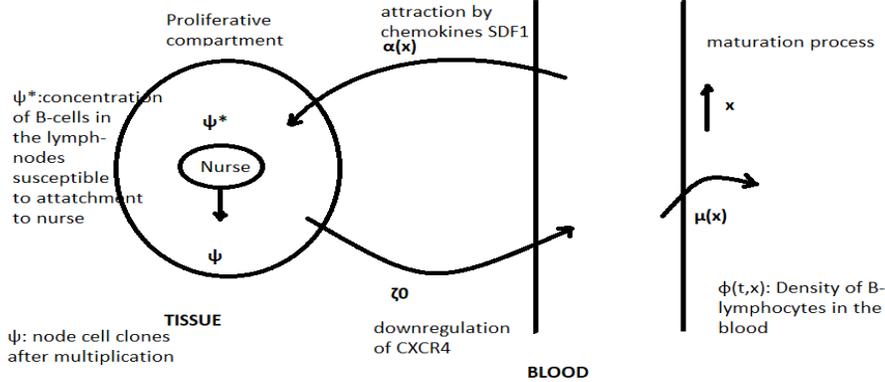


Figure 3.1: schematic presentation of the model.

We are studying the dynamics under ibrutinib treatment, which affects affinity with nodes, transition and apoptotic rates in the tissues of B-lymphocytes. This means that in our system the parameters that depend on treatment are $\alpha(x)$, ζ_0 and μ_{nd}, μ_{nd}^* . In particular, apoptotic rates and transition from tissues to blood increase while affinity with nodes decreases under ibrutinib.

3.1.2 Well-posedness

Theorem 6. *Suppose $\alpha(x) + \mu(x) \in L^\infty(\mathbb{R}^+)$, $\beta \in C^1(\mathbb{R}^+)$. Consider initial conditions $\phi_0 \in L^\infty(\mathbb{R}^+) \cap L^1(\mathbb{R}^+)$ and $(\psi_0, \psi_0^*) \in \mathbb{R}_+^2$. Then, there exists a solution $(\psi^*(t), \psi(t), \phi(t, x))$ in the weak sense in $C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+))$. This solution is unique.*

Proof. We will prove the existence and uniqueness of solution using the fixed point theorem. Let $T > 0$ be a fixed time point and consider the Banach space:

$$X = C([0, T], L^1(\mathbb{R}^+)),$$

endowed with the norm $\|f\|_X = \sup_{[0, T]} \|f\|_{L^1}$.

We construct the following operator:

$$\Phi : X \rightarrow X,$$

which sends $\phi_1 \in X$ to the solution of the system:

$$\begin{cases} \frac{d\psi^*}{dt} = -\beta(\psi^*)\psi^* - \mu_{nd}^*\psi^* + \int_0^\infty \phi_1(t, x)\alpha(x)dx, \\ \frac{d\psi}{dt} = \gamma\beta(\psi^*)\psi^* - \mu_{nd}\psi - \zeta_0\psi, \\ \frac{\partial\phi}{\partial t}(t, x) + g\frac{\partial\phi}{\partial x}(t, x) = -\mu(x)\phi(t, x) - \alpha(x)\phi(t, x), \\ g\phi(t, 0) = \zeta_0\psi(t). \end{cases} \quad (3.3)$$

As the equations are not coupled, the existence of a solution of such a system in the appropriate spaces is an immediate consequence of the Cauchy-Lipschitz theorem and the characteristics method for the transport term.

We will prove that there is a $q \in \mathbb{N}$ such that the operator Φ has a q -order term that is a contraction and so Φ has a unique fixed point in X . This fixed point will be the solution of our system in $[0, T]$.

For $t < T$ we have the following estimation on ψ^* .

$$\frac{d\psi^*}{dt} = -\beta(\psi^*)\psi^* - \mu_{nd}^*\psi^* + \int_0^\infty \phi_1(t, x)\alpha(x)dx \leq -\mu_{nd}^*\psi^* + \|\alpha\|_{L^\infty}\|\phi_1(t)\|_{L^1}.$$

Set

$$M_{\phi_1} = \|\alpha\|_{L^\infty}\|\phi_1\|_X.$$

So:

$$\psi^*(t) \leq \psi^*(0) + \frac{M_{\phi_1}}{\mu_{nd}^*}.$$

Moreover:

$$\begin{aligned} \frac{d(\psi_1 - \psi_2)}{dt} &= \gamma\beta(\psi_1^*)\psi_1^* - \gamma\beta(\psi_2^*)\psi_2^* - \mu_{nd}(\psi_1 - \psi_2) - \zeta_0(\psi_1 - \psi_2) \\ &= -(\mu_{nd} + \zeta_0)(\psi_1 - \psi_2) + \gamma\beta(\psi_1^*)(\psi_1^* - \psi_2^*) + \gamma(\beta(\psi_1^*) - \beta(\psi_2^*))\psi_2^* \end{aligned}$$

So

$$\frac{d|\psi_1 - \psi_2|}{dt} \leq -(\mu_{nd} + \zeta_0)|\psi_1 - \psi_2| + \gamma\beta_T|\psi_1^* - \psi_2^*| + \gamma\|\beta'\|_{L^\infty}\left(\frac{M_{\phi_2}}{\mu_{nd}^*} + \psi_2^*(0)\right)|\psi_1^* - \psi_2^*|.$$

Which gives

$$\|\psi_1 - \psi_2\|_{L^\infty} \leq K(T)\|\psi_1^* - \psi_2^*\|_{L^\infty},$$

where $K(T) = T(\gamma\beta_T + \gamma\|\beta'\|_{L^\infty}(\frac{M_{\phi_2}}{\mu_{nd}^*} + \psi_2^*(0)))$.

Similarly

$$\|\psi_1^* - \psi_2^*\|_{L^\infty} \leq \frac{\|\alpha\|_\infty}{\mu_{nd}^*}\|\phi_1 - \phi_2\|_X.$$

From the transport equation we get:

$$\|\bar{\phi}_1 - \bar{\phi}_2\|_X \leq Tg\zeta_0\|\psi_1 - \psi_2\|_\infty.$$

Combining all three inequalities we get:

$$\|\bar{\phi}_1 - \bar{\phi}_2\|_X + \|\psi_1^* - \psi_2^*\|_{L^\infty} + \|\psi_1 - \psi_2\|_{L^\infty} \leq \frac{\|\alpha\|_\infty}{\mu_{nd}^*}(1 + K(T)(Tg\zeta_0 + 1))\|\phi_1 - \phi_2\|_X,$$

$$\|\Phi(\phi_1) - \Phi(\phi_2)\| \leq B_T\|(\phi_1) - (\phi_2)\|.$$

with $B_T = \|\alpha\|_\infty(1 + K(T)(Tg\zeta_0 + 1))$.

By iteration:

$$\|\Phi^q(\phi_1) - \Phi^q(\phi_2)\| \leq \frac{B_T^q}{q!}\|(\phi_1) - (\phi_2)\|_X.$$

As general term of a converging series, this term $\frac{B_T^q}{q!}$ tends to 0, so there is a q^* -power that makes it less than 1.

Φ^{q^*} is a contraction, so Φ has a unique fixed point. The fixed point is defined for all $[0, T]$ and as $\frac{B_T^q}{q!}$ tends to zero for any $T > 0$, we can define a solution for all positive T , so there exist as solution for all $t \in \mathbb{R}^+$. \square

3.1.3 Steady States

In what follows we will distinguish two sorts of steady states:

- The trivial steady state $(0, 0, 0)$ which corresponds to absence of leukemia.
- The disease steady state $(\bar{\psi}^*, \bar{\psi}, \bar{\phi}(x))$ where all the components are positive.

Set

$$I = \int_0^\infty \frac{\alpha(x)}{g} e^{-\int_0^x \frac{\mu(s)+\alpha(s)}{g} ds} dx,$$

and suppose

$$I > \frac{\zeta_0 + \mu_{nd}}{\zeta_0 \gamma}, \quad (3.4)$$

in what follows.

Theorem 7. *The equilibrium points of the system $(\bar{\psi}^*, \bar{\psi}, \bar{\phi}(x))$ are given by:*

$$\begin{cases} \bar{\psi} = \frac{\gamma \beta(\bar{\psi}^*) \bar{\psi}^*}{\zeta_0 + \mu_{nd}}, \\ \bar{\phi}(x) = \frac{\zeta_0 \bar{\psi}}{g} e^{-\int_0^x \frac{\mu(x_1) + \alpha(x_1)}{g} dx_1}, \end{cases}$$

with ψ^* a solution of the following equation:

$$\psi^* \beta(\psi^*) = \frac{\mu_{nd}^* \psi^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1}, \quad (3.5)$$

0 is always solution to this equation, so the trivial equilibrium $(0, 0, 0)$ always exists. If

$$\beta(0) \leq \frac{\mu_{nd}^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1}, \quad (3.6)$$

this is the only equilibrium point.

Otherwise, for β decreasing there is a unique nontrivial equilibrium point $(\bar{\psi}^*, \bar{\psi}, \bar{\phi}(x))$.

Proof. The equilibrium points are solutions of the following system:

$$\begin{cases} 0 = -\mu_{nd}^* \bar{\psi}^* - \beta(\bar{\psi}^*) \bar{\psi}^* + \int_0^\infty \alpha(x) \bar{\phi}(x) dx, \\ 0 = -\mu_{nd} \bar{\psi} + \gamma \beta(\bar{\psi}^*) \bar{\psi}^* - \zeta_0 \bar{\psi}, \\ \frac{d\bar{\phi}(x)}{dx} = -\mu(x) \bar{\phi}(x) - \alpha(x) \bar{\phi}(x). \end{cases}$$

Leading to:

$$\begin{cases} \bar{\psi} = \frac{\gamma \beta(\bar{\psi}^*) \bar{\psi}^*}{\zeta_0 + \mu_{nd}}, \\ \bar{\phi}(x) = \frac{\zeta_0 \bar{\psi}}{g} e^{-\int_0^x \frac{\mu(x_1) + \alpha(x_1)}{g} dx_1}, \\ \bar{\psi}^* = \frac{\int_0^\infty \alpha(x) \bar{\phi}(x) dx}{\mu_{nd}^* + \beta(\bar{\psi}^*)}. \end{cases}$$

Moreover:

$$\bar{\psi}^* = \frac{1}{\mu_{nd}^* + \beta(\bar{\psi}^*)} \zeta_0 \bar{\psi}^* I.$$

This equivalent to solve:

$$\bar{\psi}^* = \zeta_0 \frac{1}{\mu_{nd}^* + \beta(\bar{\psi}^*)} \frac{\gamma \beta(\bar{\psi}^*)}{\zeta_0 + \mu_{nd}} \bar{\psi}^* I.$$

Set

$$G(\bar{\psi}^*) = \bar{\psi}^* \left(\mu_{nd}^* + \beta(\bar{\psi}^*) \left(1 - \frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I \right) \right).$$

In that, the equation that we have to solve is:

$$G(\bar{\psi}^*) = 0.$$

If $\bar{\psi}^* = 0$ we find the trivial equilibrium $(0, 0, 0)$. If $\bar{\psi}^* \neq 0$ we end up with:

$$\beta(\bar{\psi}^*) = \frac{\mu_{nd}^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1}.$$

If

$$\|\beta\|_\infty \leq \frac{\mu_{nd}^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1},$$

then there is only the trivial equilibrium point. As β is decreasing this is equivalent to $\beta(0) \leq \frac{\mu_{nd}^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1}$. Otherwise, there is a unique non trivial equilibrium. □

As already mentioned, β is such that the function h defined below is increasing:

$$h(\psi^*) = \psi^* \beta(\psi^*).$$

We should note that the monotony of β entails either one or two equilibrium points whereas the monotony of h is necessary only for the stability analysis.

An example of such a function is the saturation model. That is β satisfying:

$$\psi^* \beta(\psi^*) = V_{max} \frac{\psi^*}{v + \psi^*}.$$

where V_{max}, v are positive constants representing (respectively) the maximum value of the function $\psi^* \beta(\psi^*)$ and the value at which this function becomes half of its maximum.

In what follows we will consider h with $h' > 0$ and suppose that it exists a $\lambda_0 < 0$:

$$\int_0^\infty \frac{\alpha(x)}{g} e^{-\int_0^x \frac{\mu(s) + a(s) + \lambda_0}{g} ds} dx < +\infty. \quad (3.7)$$

We also choose β such that (3.6) does not hold, hence:

$$\beta(0) > \frac{\mu_{nd}^*}{\frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I - 1}.$$

3.1.4 Stability analysis

We are now ready to study the stability of the identified equilibrium points. As mentioned above, an equilibrium of the form $(0, 0, 0)$ where all the components are zero, is interpreted as absence of leukemia. We wish to describe prolonged lymphocytosis, a situation which corresponds to a remaining tumor load in long term under treatment. Hence, we are interested in the existence and stability of the non trivial equilibrium.

In this section we give local stability results for both the trivial and the non trivial equilibrium. Local stability of the linear system around an equilibrium entails local stability of the initial system. The idea of the proof of such a statement and the appropriate notion of stability are given in the first chapter of CML. For this reason we will not present here a detailed proof of the equivalence between linear and non linear stability.

Fix an equilibrium point $(\bar{\psi}^*, \bar{\psi}, \bar{\phi})$. The linear system around it is given by:

$$\begin{cases} \frac{d\psi^*}{dt} = -h'(\bar{\psi}^*)\psi^* - \mu_{nd}^*\psi^* + \int_0^\infty \phi(t, x)\alpha(x)dx, \\ \frac{d\psi}{dt} = \gamma h'(\bar{\psi}^*)\psi^* - \mu_{nd}\psi - \zeta_0\psi, \\ \frac{\partial \phi}{\partial t}(t, x) + g \frac{\partial \phi}{\partial x}(t, x) = -\mu(x)\phi(t, x) - \alpha(x)\phi(t, x), \\ g\phi(t, 0) = \zeta_0\psi(t). \end{cases}$$

The system preserves the positivity, so real eigenvalues govern stability. See [81] Chapter VI. We also give a detailed proof here without using the result of [81]. For that, we need the following lemma.

Lemma 9. *Let $a, b \in \mathbb{R}^+$ and $0 \leq f \in L^1(\mathbb{R}_+)$. Assume that it exists a $\lambda_0 > 0$ such that:*

$$\int_0^\infty e^{\lambda_0 x} f(x) dx < \infty.$$

On $[-\lambda_0, +\infty[$ define the function F :

$$F(\lambda) = (\lambda + a)(\lambda + b) - \int_0^\infty f(x)e^{-\lambda x} dx.$$

If there is $\lambda \in \mathbb{C}$, such that

$$\Re(\lambda) > -\min(a, b, \lambda_0) \text{ and } F(\lambda) = 0,$$

then F also admits a real root λ^* with $\lambda^* > -\min(a, b, \lambda_0)$. Moreover:

$$F(\lambda) = 0 \Rightarrow \Re(\lambda) \leq \lambda^*.$$

and λ^* has the sign of $-F(0)$.

Proof. Consider the equation

$$F(\lambda) = 0 \tag{3.8}$$

Set $m = \min\{\lambda_0, a, b\}$. We prove that for

$\Re(\lambda) > -m$ a real eigenvalue, denoted by λ^* , determines the stability. Define the function

$$Q(\lambda) = \frac{\int_0^\infty f(x)e^{-\lambda x} dx}{(\lambda + a)(\lambda + b)}.$$

Assume there is an eigenvalue λ with $\Re(\lambda) > -m$. Then λ satisfies:

$$Q(\lambda) = 1.$$

Trivially we have that:

$$|Q(\lambda)| \leq Q(\Re(\lambda)).$$

Equality holds if and only if $\lambda \in \mathbb{R}$. Otherwise, the inequality is strict for complex eigenvalues:

$$1 < Q(\Re(\lambda)).$$

The function Q is decreasing over the reals in $(-m, +\infty)$ hence from intermediate values theorem for Q , there should be a $\lambda^* \in \mathbb{R}$ where:

$$Q(\lambda^*) = 1.$$

This proves that a real eigenvalue exists. Moreover

$$1 = |Q(\lambda)| \leq Q(\Re(\lambda)).$$

so

$$Q(\lambda^*) \leq Q(\Re(\lambda)).$$

Since Q is decreasing in $(-m, +\infty)$, $\Re(\lambda) \leq \lambda^*$.

If $\Re(\lambda) \in (-\infty, -m]$ any spectral value has negative real part so stability is not affected. As stability is governed by reals, it suffices to see how the graphs of $(\lambda + a)(\lambda + b)$ and $\int_0^\infty f(x)e^{-\lambda x} dx$ behave. Their values at zero show whether their point of intersection is located on the right or the left half plane. If $F(0) > 0$ then $\lambda^* < 0$ and if $F(0) < 0$ then $\lambda^* > 0$. \square

Theorem 8. *If (3.6) is satisfied, then the trivial equilibrium is the unique equilibrium of the system and it is locally stable.*

If another equilibrium exists then it is locally stable and $(0, 0, 0)$ is unstable.

Proof. Let us consider solutions of the linear system with exponential profile:

$$(\Psi^* e^{\lambda t}, \Psi e^{\lambda t}, \Phi(x) e^{\lambda t}).$$

Solutions of that form determine asymptotic behavior. If we replace these solutions to the system we end up with a system of four unknown quantities: Ψ^* , Ψ , Φ and λ .

$$\begin{cases} \lambda \Psi^* = -h'(\bar{\psi}^*)\Psi^* - \mu_{nd}^*\Psi^* + \int_0^\infty \Phi(x)\alpha(x)dx, \\ \lambda \Psi = \gamma h'(\bar{\psi}^*)\Psi^* - \mu_{nd}\Psi - \zeta_0\Psi, \\ \lambda \Phi(x) + g\frac{\partial \Phi(x)}{\partial x} = -\mu(x)\Phi(x) - a(x)\Phi(x), \\ g\Phi(0) = \zeta_0\Psi. \end{cases}$$

These four equations define the associated eigenvalue problem. If all solutions in λ have negative real part, then the equilibrium is stable, whereas if at least one solution has λ with positive real part, then the equilibrium is unstable.

The eigenvalue problem reduces to one single equation, the so called characteristic equation of the system:

$$(\lambda + h'(\bar{\psi}^*) + \mu_{nd}^*)(\lambda + \mu_{nd} + \zeta_0) = \int_0^\infty \frac{\zeta_0 \gamma h'(\bar{\psi}^*)}{g} \alpha(x) e^{-\int_0^x \frac{\mu(s)+a(s)}{g} ds} e^{-\lambda \int_0^x \frac{1}{g} ds} dx.$$

Set:

$$I(\lambda) = \int_0^\infty \frac{\alpha(x)}{g} e^{-\int_0^x \frac{\mu(s)+a(s)}{g} ds} e^{-\lambda \int_0^x \frac{1}{g} ds} dx.$$

Finally

$$(\lambda + h'(\bar{\psi}^*) + \mu_{nd}^*)(\lambda + \mu_{nd} + \zeta_0) = \zeta_0 \gamma h'(\bar{\psi}^*) I(\lambda). \quad (3.9)$$

We use lemma 9 with

$$F(\lambda) = (\lambda - a)(\lambda - b) - \zeta_0 \gamma h'(\bar{\psi}^*) I(\lambda), \quad (3.10)$$

$$a = h'(\bar{\psi}^*) + \mu_{nd}^*, \quad (3.11)$$

$$b = \mu_{nd} + \zeta_0. \quad (3.12)$$

Note that $F = F_{\bar{\psi}^*}$ and that:

$$\frac{1}{\mu_{nd} + \zeta_0} F_{\bar{\psi}^*}(0) = G'(\bar{\psi}^*).$$

From lemma (9) we know that a real eigenvalue determines stability of (3.9) and that the equilibrium is stable if $F_{\bar{\psi}^*}(0) > 0$ and unstable if $F_{\bar{\psi}^*}(0) < 0$.

Find

$$G'(x) = \mu_{nd}^* + (x\beta(x))' \left(1 - \frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I\right).$$

At the trivial equilibrium $(0, 0, 0)$, $G'(0) = \mu_{nd}^* + \beta(0) \left(1 - \frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I\right)$ which is negative.

At the non trivial equilibrium $\bar{\psi}^* \neq 0$ and from the equation over G we have:

$$\mu_{nd}^* + \beta(\bar{\psi}^*) \left(1 - \frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I\right) = 0.$$

So

$$G'(\bar{\psi}^*) = \bar{\psi}^* \beta'(\bar{\psi}^*) \left(1 - \frac{\zeta_0 \gamma}{\zeta_0 + \mu_{nd}} I\right) > 0,$$

which is positive. □

It is not clear whether the disease equilibrium corresponds to prolonged lymphocytosis or to some other high tumor load without good prognosis. This is a hint that the B-CLL population should be studied in more details. In particular, the phenomenon of prolonged lymphocytosis with good prognosis shows that there should be a subset of B-CLL lymphocytes that remains in the blood. These cells are not aggressive, most probably because treatment can have control over them. To investigate this assumption, we separate B-CLL cells into resistant and sensitive to ibrutinib that are in competition to be fixed to multiplication sites. Resistant to ibrutinib are the cells that have gained mutations in BTK and treatment has no effect on them. Treatment controls only sensitive cells.

3.1.5 Model with competition

Our second model is a more detailed version of the first model. The equations that govern dynamics are of the same type but the B-CLL cells are either resistant, with subscript r, or sensitive, with subscript s.

Until recently there was no way to distinguish between the two populations as clustering of their gene expression profiles showed transcriptional similarity. Nevertheless, in a recent work presented in [66] they used single-cell multi-omics and they managed to show that these populations differ in their response to therapeutic challenge. Mutated cells escape from BTK inhibition, whereas sensitive cells had a signature of hypoxia, cellular stress and quiescence. This result, in combination with [111] where they phenotypically classified PRL cells as quiescent anergic, could be a good sign that sensitive population could describe PRL.

$$\left\{ \begin{array}{l} \frac{d\psi_s^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_s^* - \mu_{nd}^*\psi_s^* + \int_0^\infty \phi_s(t, x)\alpha_s(x)dx, \\ \frac{d\psi_r^*}{dt} = -\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}^*\psi_r^* + \int_0^\infty \phi_r(t, x)\alpha_r(x)dx, \\ \frac{d\psi_s}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}\psi_s - \zeta_0^s\psi_s, \\ \frac{d\psi_r}{dt} = \gamma\beta(\psi_s^* + \psi_r^*)\psi_r^* - \mu_{nd}\psi_r - \zeta_0^r\psi_r, \\ \frac{\partial\phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_s(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\ \frac{\partial\phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_r(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\ \phi_s(t, 0) = \zeta_0^s\psi_s(t), \\ \phi_r(t, 0) = \zeta_0^r\psi_r(t), \end{array} \right. \quad (3.13)$$

with initial conditions:

$$\begin{aligned} \psi_s(0) = \psi_s^0 \geq 0, \quad \phi_s(0, x) = \phi_s^0(x) \geq 0, \quad \psi_s^*(0) = \psi_s^{*,0} \geq 0, \\ \psi_r(0) = \psi_r^0 \geq 0, \quad \phi_r(0, x) = \phi_r^0(x) \geq 0, \quad \psi_r^*(0) = \psi_r^{*,0} \geq 0. \end{aligned}$$

The parameters describe the same quantities as in the first model and there is no coupling of the equations apart from the rate of attachment to the nurse β that depends on the total population of B lymphocytes. As we can see from the equations, β is a function of $\psi_s^* + \psi_r^*$.

Theorem 9. Suppose $\alpha_r(x) + \mu(x) \in L^{+\infty}(\mathbb{R}^+)$, $\alpha_s(x) + \mu(x) \in L^{+\infty}(\mathbb{R}^+)$ and $\beta \in L^{+\infty}(\mathbb{R}^+) \cap C^1(\mathbb{R}^+)$.

Consider initial conditions $\phi_r^0, \phi_s^0 \in L^\infty(\mathbb{R}^+) \cap L^1(\mathbb{R}^+)$ and $(\psi_s^0, \psi_r^0, \psi_s^{*,0}, \psi_r^{*,0}) \in \mathbb{R}_+^4$. Then, there exists a solution $(\psi_s^*(t), \psi_s(t), \phi_s(t, x), \psi_r^*(t), \psi_r(t), \phi_r(t, x))$ in the weak sense in $C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+)) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+))$. This solution is unique.

Proof. Well-posedness of the above system can be proven exactly in the same way as for the first model. It is an application of the Banach fixed point theorem and the estimations are done similarly. \square

3.1.6 Steady states

We distinguish 3 sorts of steady states:

1. The disease free steady state where all the components are 0: $(0, 0, 0, 0, 0, 0)$.
2. The single species steady states where either the resistant or the sensitive are non zero: $(\bar{\psi}_s^*, \bar{\psi}_s, \phi_s(x), 0, 0, 0)$ or $(0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \phi_r(x))$.
3. The disease steady states where all components are non zero: $(\bar{\psi}_s^*, \bar{\psi}_s, \phi_s(x), \bar{\psi}_r^*, \bar{\psi}_r, \phi_r(x))$.

In what follows we will set:

$$\begin{cases} I_r(\lambda) = \int_0^\infty \alpha_r(x) e^{-\int_0^x \lambda + \alpha_r(s) + \mu(s) ds}, \\ I_s(\lambda) = \int_0^\infty \alpha_s(x) e^{-\int_0^x \lambda + \alpha_s(s) + \mu(s) ds} \end{cases} .$$

We suppose that:

$$I_s(0) > \frac{\zeta_0^s + \mu_{nd}}{\zeta_0^s \gamma},$$

$$I_r(0) > \frac{\zeta_0^r + \mu_{nd}}{\zeta_0^r \gamma},$$

and β is such that:

$$\begin{cases} \beta : \text{decreasing}, \\ x \mapsto x\beta(x) \text{ increasing}. \end{cases}$$

The assumption on the monotony of $x\beta(x)$ is only useful for the stability analysis.

Theorem 10. *Equilibrium points*

- a) **Disease free steady state:** The system has always a trivial equilibrium point $(0, 0, 0, 0, 0, 0)$.
- b) **Single species steady state:**

- If

$$\beta(0) > \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^r}{\mu_{nd}+\zeta_0^r}I_r(0) - 1},$$

there is an equilibrium point $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$. The components are given by,

$$\begin{cases} \bar{\psi}_r = \frac{\gamma\beta(\bar{\psi}_r^*)\bar{\psi}_r^*}{\mu_{nd}+\zeta_0^r}, \\ \bar{\phi}_r(x) = \zeta_0^r \bar{\psi}_r e^{-\int_0^x \mu(s)+\alpha_r(s)ds}. \end{cases}$$

with $\bar{\psi}_r^*$ solution of

$$\beta(\bar{\psi}_r^*) = \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^r}{\mu_{nd}+\zeta_0^r}I_r(0) - 1}.$$

- If

$$\beta(0) > \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^s}{\mu_{nd}+\zeta_0^s}I_s(0) - 1},$$

there is an equilibrium point $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$, with components given by:

$$\begin{cases} \bar{\psi}_s = \frac{\gamma\beta(\bar{\psi}_s^*)\bar{\psi}_s^*}{\mu_{nd}+\zeta_0^s}, \\ \bar{\phi}_s(x) = \zeta_0^s \bar{\psi}_s e^{-\int_0^x \mu(s)+\alpha_s(s)ds}, \end{cases}$$

and $\bar{\psi}_s^*$ solution of:

$$\beta(\bar{\psi}_s^*) = \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^s}{\mu_{nd}+\zeta_0^s}I_s(0) - 1}.$$

- c) **Positive steady state:** Keep the same notations as above for the single species equilibrium points $\mathcal{E}_r, \mathcal{E}_s$. If

$$\beta(\bar{\psi}_s^*) = \beta(\bar{\psi}_r^*), \quad (3.14)$$

there are infinitely many positive equilibrium points. They are convex combinations of the aforementioned steady states. That is, there is a parameter $p \in (0, 1)$ such that the equilibrium points have the form:

$$p\mathcal{E}_s + (1-p)\mathcal{E}_r.$$

More precisely:

$$\begin{cases} \bar{\psi}_s^{*p} = pb, \\ \bar{\psi}_r^{*p} = (1-p)b, \\ \bar{\psi}_s^p = p \frac{\gamma\beta(b)b}{\mu_{nd}+\zeta_0^s}, \\ \bar{\psi}_r^p = (1-p) \frac{\gamma\beta(b)b}{\mu_{nd}+\zeta_0^r}, \\ \bar{\phi}_s^p(x) = p\zeta_0^s \frac{\gamma\beta(b)b}{\mu_{nd}+\zeta_0^s} e^{-\int_0^x \mu(s)+\alpha_s(s)ds}, \\ \bar{\phi}_r^p(x) = (1-p)\zeta_0^r \frac{\gamma\beta(b)b}{\mu_{nd}+\zeta_0^r} e^{-\int_0^x \mu(s)+\alpha_r(s)ds}. \end{cases}$$

Proof. Equilibrium points are solutions of the following system:

$$\begin{cases} \beta(\bar{\psi}_s^* + \bar{\psi}_r^*)\bar{\psi}_s^* + \mu_{nd}^*\bar{\psi}_s^* = \int_0^\infty \bar{\phi}_s(x)\alpha_s(x)dx, \\ \beta(\bar{\psi}_s^* + \bar{\psi}_r^*)\bar{\psi}_r^* + \mu_{nd}^*\bar{\psi}_r^* = \int_0^\infty \bar{\phi}_r(x)\alpha_r(x)dx, \\ \gamma\beta(\bar{\psi}_s^* + \bar{\psi}_r^*)\bar{\psi}_s^* = \mu_{nd}\bar{\psi}_s + \zeta_0^s\bar{\psi}_s, \\ \gamma\beta(\bar{\psi}_s^* + \bar{\psi}_r^*)\bar{\psi}_r^* = \mu_{nd}\bar{\psi}_r + \zeta_0^r\bar{\psi}_r, \\ \frac{d\bar{\phi}_s}{dx} = -\mu(x)\bar{\phi}_s(x) - \alpha_s(x)\bar{\phi}_s(x), \\ \bar{\phi}_s(0) = \zeta_0^s\bar{\psi}_s, \\ \frac{d\bar{\phi}_r}{dx} = -\mu(x)\bar{\phi}_r(x) - \alpha_r(x)\bar{\phi}_r(x), \\ \bar{\phi}_r(0) = \zeta_0^r\bar{\psi}_r. \end{cases}$$

Observe that $(0, 0, 0, 0, 0, 0)$ is always a solution to this system. Otherwise we get

$$\bar{\phi}_s(x) = \zeta_0^s\bar{\psi}_s e^{-\int_0^x \mu(s) + \alpha_s(s) ds},$$

and

$$\bar{\phi}_r(x) = \zeta_0^r\bar{\psi}_r e^{-\int_0^x \mu(s) + \alpha_r(s) ds}.$$

Set

$$\begin{cases} G_s(x) = \mu_{nd}^* + \beta(x) \left(1 - \frac{\zeta_0^s \gamma}{\mu_{nd} + \zeta_0^s} I_s(0) \right), \\ G_r(x) = \mu_{nd}^* + \beta(x) \left(1 - \frac{\zeta_0^r \gamma}{\mu_{nd} + \zeta_0^r} I_r(0) \right). \end{cases}$$

Hence we have to solve

$$\bar{\psi}_s^* G_s(\bar{\psi}_s^* + \bar{\psi}_r^*) = 0,$$

and

$$\bar{\psi}_r^* G_r(\bar{\psi}_s^* + \bar{\psi}_r^*) = 0.$$

- If $\bar{\psi}_s^* = 0$ and $\bar{\psi}_r^* \neq 0$ then,
 $\bar{\psi}_s = 0$ and $\bar{\phi}_s(x) = 0$, and the system reduces to

$$G_r(\bar{\psi}_r^*) = 0.$$

This case has already been treated previously in theorem 7.

- Similarly, if $\bar{\psi}_r^* = 0$ and $\bar{\psi}_s^* \neq 0$ the system reduces to:

$$G_s(\bar{\psi}_s^*) = 0.$$

It is also treated in theorem 7.

- If $\bar{\psi}_s^* \neq 0$ and $\bar{\psi}_r^* \neq 0$ we will use superscripts p for the positive steady states to avoid any ambiguity with the single species components.

The two equations give:
$$\begin{cases} \beta(\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p}) = \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^s}{\mu_{nd} + \zeta_0^s} I_s(0) - 1}, \\ \beta(\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p}) = \frac{\mu_{nd}^*}{\frac{\gamma\zeta_0^r}{\mu_{nd} + \zeta_0^r} I_r(0) - 1}. \end{cases}$$

This is possible if and only if:

$$\frac{\gamma\zeta_0^s}{\mu_{nd} + \zeta_0^s} I_s(0) = \frac{\gamma\zeta_0^r}{\mu_{nd} + \zeta_0^r} I_r(0).$$

This entails:

$$\beta(\bar{\psi}_s^*) = \beta(\bar{\psi}_r^*) = \beta(\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p}),$$

and as β is decreasing this gives:

$$\bar{\psi}_s^* = \bar{\psi}_r^*.$$

Again from the monotony of β , there is a unique solution for $\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p}$, say b , which is equal to $b = \bar{\psi}_s^* = \bar{\psi}_r^*$, so infinitely many possible choices of $\bar{\psi}_s^{*p}$ and $\bar{\psi}_r^{*p}$, all in the line $\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p} = b$. All other components are determined by $\bar{\psi}_s^{*p}$ and $\bar{\psi}_r^{*p}$ by the relations:

$$\begin{cases} \bar{\psi}_s^p = \frac{\gamma\beta(b)\bar{\psi}_s^{*p}}{\mu_{nd} + \zeta_0^s}, \\ \bar{\psi}_r^p = \frac{\gamma\beta(b)\bar{\psi}_r^{*p}}{\mu_{nd} + \zeta_0^r}, \end{cases}$$

and the relations for $\bar{\phi}_s^p$ and $\bar{\phi}_r^p$ given above. The fact that:

$$\bar{\psi}_s^{*p} + \bar{\psi}_r^{*p} = b,$$

is equivalent to the existence of a parameter $p \in (0, 1)$ such that:

$\bar{\psi}_s^{*p} = pb$ and $\bar{\psi}_r^{*p} = (1-p)b$, hence the expression of the equilibrium components has the general form:

$$p\mathcal{E}_s + (1-p)\mathcal{E}_r, \quad p \in (0, 1).$$

□

Equation (3.14) describes a degenerate case where it makes no sense to talk about resistant and sensitive cells separately. That is: our model predicts that coexistence of resistant and sensitive cells is not possible unless a rare case where the parameters satisfy:

$$\frac{\zeta_0^s}{\mu_{nd} + \zeta_0^s} \int_0^\infty \alpha_s(x) e^{-\int_0^x \mu(s) + \alpha_s(s)} dx = \frac{\zeta_0^r}{\mu_{nd} + \zeta_0^r} \int_0^\infty \alpha_r(x) e^{-\int_0^x \mu(s) + \alpha_r(s)} dx.$$

As parameters depend on treatment, relation (3.14) can be seen as the equation describing the unique dose that should be administered so that resistant and sensitive cells coexist in long term. Stability analysis will give an insight into CLL dynamics when the dose given is either increased or diminished with respect to the critical dose.

3.1.7 Stability analysis

As usually, stability analysis reduces to stability analysis of the linear system. Let us consider an equilibrium point:

$$((\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))),$$

and the linear system around it:

$$\left\{ \begin{array}{l} \frac{d\psi_s^*}{dt} = (-\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^* - \mu_{nd}^*\psi_s^* - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*\bar{\psi}_s^*)\psi_r^* + \int_0^\infty \phi_s(t, x)\alpha_s(x)dx, \\ \frac{d\psi_r^*}{dt} = (-\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^* - \mu_{nd}^*\psi_r^* - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*\bar{\psi}_r^*)\psi_s^* + \int_0^\infty \phi_r(t, x)\alpha_r(x)dx, \\ \frac{d\psi_s}{dt} = (\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*)\psi_s^* + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*\psi_r^* - \mu_{nd}\psi_s - \zeta_0^s\psi_s, \\ \frac{d\psi_r}{dt} = (\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*)\psi_r^* + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*\psi_s^* - \mu_{nd}\psi_r - \zeta_0^r\psi_r, \\ \frac{\partial\phi_s}{\partial t}(t, x) + \frac{\partial\phi_s}{\partial x}(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\ \frac{\partial\phi_r}{\partial t}(t, x) + \frac{\partial\phi_r}{\partial x}(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\ \phi_s(t, 0) = \zeta_0^s\psi_s, \\ \phi_r(t, 0) = \zeta_0^r\psi_r. \end{array} \right. \quad (3.15)$$

Theorem 11. a) *If the trivial equilibrium is the only equilibrium of the system then it is stable otherwise it is unstable.*

b) *Consider the equilibrium points $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$ and $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$ describing the single species steady states.*

(a) *If $\beta(\bar{\psi}_s^*) < \beta(\bar{\psi}_r^*)$ then \mathcal{E}_s is locally stable and \mathcal{E}_r is unstable.*

(b) *If $\beta(\bar{\psi}_r^*) < \beta(\bar{\psi}_s^*)$ then \mathcal{E}_r is locally stable and \mathcal{E}_s is unstable.*

(c) *If $\beta(\bar{\psi}_r^*) = \beta(\bar{\psi}_s^*)$ there are infinitely many equilibrium points of the form:*

$$p\mathcal{E}_s + (1-p)\mathcal{E}_r, \quad p \in (0, 1)$$

where all of them are asymptotically unstable.

Proof. For stability we study the associated eigenvalue problem. To get it we replace solutions of exponential form to the system (3.15):

$$\psi_s^* e^{\lambda t}, \psi_r^* e^{\lambda t}, \psi_s e^{\lambda t}, \psi_r e^{\lambda t}, \phi_s(x) e^{\lambda t}, \phi_r(x) e^{\lambda t}.$$

We obtain:

$$\left\{ \begin{array}{l} \lambda\psi_s^* = (-\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^* - \mu_{nd}^*\psi_s^* + (-\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*)\psi_r^* + \int_0^\infty \phi_s(x)\alpha_s(x)dx, \\ \lambda\psi_r^* = (-\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) - \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^* - \mu_{nd}^*\psi_r^* + (-\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*)\psi_s^* + \int_0^\infty \phi_r(x)\alpha_r(x)dx, \\ \lambda\psi_s = (\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*)\psi_s^* + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*\psi_r^* - \mu_{nd}\psi_s - \zeta_0^s\psi_s, \\ \lambda\psi_r = (\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*)\psi_r^* + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*\psi_s^* - \mu_{nd}\psi_r - \zeta_0^r\psi_r, \\ \phi_s(x) = \zeta_0^s\psi_s e^{-\int_0^x (\mu(s) + \alpha_s(s) + \lambda) ds}, \\ \phi_r(x) = \zeta_0^r\psi_r e^{-\int_0^x (\mu(s) + \alpha_r(s) + \lambda) ds}. \end{array} \right. \quad (3.16)$$

By recalling the definition of $I_s(\lambda)$ and $I_r(\lambda)$ the above system takes the matrix form:

$$A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*} \begin{pmatrix} \psi_s^* \\ \psi_r^* \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad (3.17)$$

where $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}$ is a 2×2 matrix whose elements are:

- $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 1) = \lambda + \beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^* + \mu_{nd}^* - \zeta_0^s I_s(\lambda) \left(\frac{\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*}{\lambda + \mu_{nd} + \zeta_0^s} \right),$
- $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 2) = \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^* - \zeta_0^s I_s(\lambda) \left(\frac{\gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_s^*}{\lambda + \mu_{nd} + \zeta_0^s} \right),$
- $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 1) = \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^* - \zeta_0^r I_r(\lambda) \left(\frac{\gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*}{\lambda + \mu_{nd} + \zeta_0^r} \right),$
- $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 2) = \lambda + \beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^* + \mu_{nd}^* - \zeta_0^r I_r(\lambda) \left(\frac{\gamma\beta(\bar{\psi}_r^* + \bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*)\bar{\psi}_r^*}{\lambda + \mu_{nd} + \zeta_0^r} \right).$

Write $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}$ in a block form:

$$\begin{pmatrix} \lambda + \mu_{nd}^* + \beta(\bar{\psi}_r^* + \bar{\psi}_s^*)(1 - \zeta_0^s I_s(\lambda) \frac{\gamma}{\lambda + \mu_{nd} + \zeta_0^s}) & 0 \\ 0 & \lambda + \mu_{nd}^* + \beta(\bar{\psi}_r^* + \bar{\psi}_s^*)(1 - \zeta_0^r I_r(\lambda) \frac{\gamma}{\lambda + \mu_{nd} + \zeta_0^r}) \end{pmatrix} + \quad (3.18)$$

$$\beta'(\bar{\psi}_r^* + \bar{\psi}_s^*) \begin{pmatrix} \bar{\psi}_s^* \left(1 - \frac{\gamma\zeta_0^s I_s(\lambda)}{\lambda + \mu_{nd} + \zeta_0^s} \right) & \bar{\psi}_s^* \left(1 - \frac{\gamma\zeta_0^s I_s(\lambda)}{\lambda + \mu_{nd} + \zeta_0^s} \right) \\ \bar{\psi}_r^* \left(1 - \frac{\gamma\zeta_0^r I_r(\lambda)}{\lambda + \mu_{nd} + \zeta_0^r} \right) & \bar{\psi}_r^* \left(1 - \frac{\gamma\zeta_0^r I_r(\lambda)}{\lambda + \mu_{nd} + \zeta_0^r} \right) \end{pmatrix}. \quad (3.19)$$

We can immediately make the following remarks:

- For the trivial equilibrium point this matrix is diagonal.
- For the single species steady states the matrix becomes triangular (upper if $\bar{\psi}_r^* = 0$ and lower if $\bar{\psi}_s^* = 0$).
- For the positive steady state the matrix is full.

The system (3.17) has a non trivial solution if and only if:

$$\det(A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}) = 0.$$

We are looking for which λ this is possible.

- For $(0, 0, 0, 0, 0, 0)$ the matrix is diagonal. Consequently the equations are not coupled and the eigenvalue problem can be treated as two independent blocks by studying the sub systems with resistant and sensitive components separately. This analysis has already be done in the previous section for the stability of the model without competition. See theorem 8.

Indeed:

$$\det(A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}) = A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 1)A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 2),$$

which reduces to:

$$\begin{cases} \lambda + \beta(0) + \mu_{nd}^* - \zeta_0^s \frac{\gamma\beta(0)}{\lambda + \mu_{nd} + \zeta_0^s} I_s(\lambda) = 0, \\ or \\ \lambda + \beta(0) + \mu_{nd}^* - \zeta_0^r \frac{\gamma\beta(0)}{\lambda + \mu_{nd} + \zeta_0^r} I_r(\lambda) = 0. \end{cases} \quad (3.20)$$

If this is the only equilibrium, from theorem 10 we know that

$$\beta(0) \leq \frac{\mu_{nd}^*}{\zeta_0^r \frac{\gamma I_r(0)}{\mu_{nd} + \zeta_0^r} - 1} \quad and \quad \beta(0) \leq \frac{\mu_{nd}^*}{\zeta_0^s \frac{\gamma I_s(0)}{\mu_{nd} + \zeta_0^s} - 1}.$$

So

$$\begin{cases} (\mu_{nd}^* + \beta(0))(\mu_{nd} + \zeta_0^r) \geq \zeta_0^r \gamma I_r(0) \beta(0), \\ (\mu_{nd}^* + \beta(0))(\mu_{nd} + \zeta_0^s) \geq \zeta_0^s \gamma I_s(0) \beta(0), \end{cases}$$

and $(0, 0, 0, 0, 0, 0)$ is stable. On the other hand, if at least one non trivial equilibrium exists, at least one of the reverse inequalities holds. In that case we can always find solutions with $\Re(\lambda) > 0$. Let's say for example that

$$\beta(0) > \frac{\mu_{nd}^*}{\zeta_0^r \frac{\gamma I_r(0)}{\mu_{nd} + \zeta_0^r} - 1} \quad and \quad \beta(0) \leq \frac{\mu_{nd}^*}{\zeta_0^s \frac{\gamma I_s(0)}{\mu_{nd} + \zeta_0^s} - 1}.$$

Then

$$\begin{cases} (\mu_{nd}^* + \beta(0))(\mu_{nd} + \zeta_0^r) < \zeta_0^r \gamma I_r(0) \beta(0), \\ (\mu_{nd}^* + \beta(0))(\mu_{nd} + \zeta_0^s) \geq \zeta_0^s \gamma I_s(0) \beta(0). \end{cases}$$

For $\psi_r^* \neq 0$ from the second equation of (3.20) we deduce that $\lambda > 0$. The same λ is a solution of the second equation as well so $\psi_s^* = 0$. This is a possible solution which indicates instability.

b) Single species steady states.

- For \mathcal{E}_s the matrix is upper triangular so again:

$$\det(A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}) = A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 1)A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 2).$$

Either

$$A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 1) = 0,$$

or

$$A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 2) = 0.$$

Consider the second term:

$$(\lambda + \beta(\bar{\psi}_s^*) + \beta'(\bar{\psi}_s^*)\bar{\psi}_s^* + \mu_{nd}^*)(\lambda + \mu_{nd} + \zeta_0^s) = I_s(\lambda)(\gamma\beta(\bar{\psi}_s^*) + \gamma\beta'(\bar{\psi}_s^*)\bar{\psi}_s^*).$$

This leads to a stable equilibrium and the proof of stability in that case can be found in theorem 8. From the first term:

$$(\lambda + \beta(\bar{\psi}_s^*) + \mu_{nd}^*)(\lambda + \mu_{nd} + \zeta_0^r) = \gamma \zeta_0^r \beta(\bar{\psi}_s^*) I_r(\lambda). \quad (3.21)$$

In that case we can work only with the resistant subsystem as it is independent of the sensible part and solve for λ . Real eigenvalues with $\Re(\lambda) > 0$ can be found as solutions of equation (3.21).

From lemma 9 we know that real eigenvalues of this equation determine stability. The equilibrium is stable if we have:

$$(\beta(\bar{\psi}_s^*) + \mu_{nd}^*)(\mu_{nd} + \zeta_0^r) > \gamma \zeta_0^r \beta(\bar{\psi}_s^*) I_r(0),$$

if and only if:

$$1 + \frac{\mu_{nd}^*}{\beta(\bar{\psi}_s^*)} > \frac{\gamma \zeta_0^r I_r(0)}{\mu_{nd} + \zeta_0^r}.$$

From the expression of the components of the equilibrium $(0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$ we deduce that:

$$1 + \frac{\mu_{nd}^*}{\beta(\bar{\psi}_s^*)} > 1 + \frac{\mu_{nd}^*}{\beta(\bar{\psi}_r^*)}.$$

Which holds if and only if:

$$\beta(\bar{\psi}_r^*) > \beta(\bar{\psi}_s^*).$$

- Similarly for \mathcal{E}_r the matrix is lower triangular with:

$$\det(A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}) = A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(1, 1) A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}(2, 2),$$

leading to either a stable perturbation of $(0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$,

or:

$$(\lambda + \beta(\bar{\psi}_r^*) + \mu_{nd}^*)(\lambda + \mu_{nd} + \zeta_0^s) = \gamma \zeta_0^s \beta(\bar{\psi}_r^*) I_s(\lambda). \quad (3.22)$$

By replacing the components of $(\bar{\psi}_s^*, \bar{\psi}_s, \bar{\phi}_s(x), 0, 0, 0)$ as in the previous case we get that $(0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$ is stable if $\beta(\bar{\psi}_r^*) < \beta(\bar{\psi}_s^*)$ and unstable otherwise.

- If $\bar{\psi}_r^* \neq 0$ and $\bar{\psi}_s^* \neq 0$ the matrix $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}$ is full. $\lambda = 0$ is an eigenvalue with corresponding eigenvector $v = \begin{pmatrix} 1 \\ -1 \end{pmatrix}$. Indeed for $\lambda = 0$ the first diagonal block of $A_{\lambda, \bar{\psi}_s^*, \bar{\psi}_r^*}$ reduces to the zero matrix since its elements are exactly the equation of the steady states. The other part entails:

$$\begin{pmatrix} \bar{\psi}_s^* \left(1 - \frac{\gamma \zeta_0^s I_s(\lambda)}{\lambda + \mu_{nd} + \zeta_0^s}\right) & \bar{\psi}_s^* \left(1 - \frac{\gamma \zeta_0^s I_s(\lambda)}{\lambda + \mu_{nd} + \zeta_0^s}\right) \\ \bar{\psi}_r^* \left(1 - \frac{\gamma \zeta_0^r I_r(\lambda)}{\lambda + \mu_{nd} + \zeta_0^r}\right) & \bar{\psi}_r^* \left(1 - \frac{\gamma \zeta_0^r I_r(\lambda)}{\lambda + \mu_{nd} + \zeta_0^r}\right) \end{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

For $\lambda = 0$ we cannot conclude for the local stability. We have an equilibrium point \mathcal{E}_p for all $p \in (0, 1)$ of the form:

$$\mathcal{E}_p = p\mathcal{E}_s + (1 - p)\mathcal{E}_r.$$

Fix a $p = p^*$ and start from \mathcal{E}_{p^*} . Any small perturbation of the equilibrium, say $\epsilon > 0$, leads to the equilibrium $\mathcal{E}_{p^*+\epsilon}$ so there is no possibility to converge back to \mathcal{E}_{p^*} as time goes to $+\infty$. Consequently, none of these equilibrium points is asymptotically stable.

□

The theorem concerning stability has a biological interpretation. As stability depends solely on the rate of attachment to the multiplication sites β , it seems that the rate of attachment to the nurse determines dynamics in long term. Since β is decreasing, if sensitive cells are linked to multiplication sites with a higher rate than resistant ones, they should be less in number at the steady state. In that case, the equilibrium with only sensitive components is unstable and the equilibrium with only resistant components is locally stable. This means that if sensitive cells arrive (which corresponds to a perturbation of the equilibrium $(0, 0, 0, \bar{\psi}_r^*, \bar{\psi}_r, \bar{\phi}_r(x))$) they are finally eliminated. This is a situation of an aggressive leukemia that cannot be managed by ibrutinib treatment.

On the contrary, if resistant cells are more likely to be linked to multiplication sites because their rate of attachment is higher, then sensitive are more in number and eliminate resistant cells in long term.

It is already mentioned that resistant and sensitive cells are in competition for a place in the multiplication sites. Moreover, there is a critical dose, described by (3.14), which guaranties coexistence of the two populations in long term. Stability analysis shows that resistant and sensitive equilibrium cannot be stable simultaneously. As a result, if we change the critical dose, one of the two populations will disappear asymptotically.

More specifically, if the critical dose is increased, ibrutinib will kill more sensitive cells. Consequently, at the steady state more place will be available in the multiplication sites for resistant cells. In that case, the population that goes extinct is the sensitive B-CLL cells. When resistance governs dynamics prognosis cannot be good since ibrutinib has no effect on resistant clones.

On the other hand, if the critical dose is decreased, ibrutinib will kill less sensitive cells. Hence, at the steady state they will occupy more places in the multiplication sites.

We believe that if treatment keeps sensitive cells up to a certain threshold so that more sites are occupied by them and not by resistant cells, then the growth of resistant population will be slowed down and at some cases it will be stopped.

For the moment we only have results concerning local stability, namely population at the steady state. The study of global stability would give us a deeper insight into the dynamics and the importance of the residual disease since the above results would hold even if the population numbers are not close to their equilibrium values. What we

believe that happens is that one of the two sub populations invades the other. If invasion happens then one population goes extinct in long term. For instance, if sensitive cells invade resistant cells, then the latter disappear and there are only sensitive cells left under treatment. This is a favorable situation because treatment can only manage sensitive and not resistant cells. From a clinical viewpoint these results could explain how residual disease can have a positive effect on the outcome of a patient and they indicate that residual disease should not be reduced by other treatment.

3.2 Second type of model with and without competition

We present now another type of models for CLL dynamics. We consider the B-CLL cells in the tissues that are already linked to multiplication sites as a distinct population denoted by O (O stands for occupied cells). As already mentioned, the number of multiplication sites is finite, say N_g . The cells that are not occupied, are in competition with the B-CLL cells that enter the tissues from the blood. Division happens at a rate β and gives 2 daughter cells that enter blood circulation.

3.2.1 Model without competition

$$\begin{cases} \frac{d\psi^*}{dt} = (N_g - O(t)) \int_0^\infty \phi(t, x) \alpha(x) dx - \mu_{nd}^* \psi^* - a \psi^* (N_g - O(t)), \\ \frac{dO}{dt} = -\beta O + a(N_g - O(t)) \psi^*, \\ \frac{\partial \phi}{\partial t}(t, x) + \frac{\partial}{\partial x} \phi(t, x) = -\mu(x) \phi(t, x) - \alpha(x) \phi(t, x), \\ \phi(t, 0) = 2\beta O(t). \end{cases} \quad (3.23)$$

Free cells in the tissues, are linked to the available multiplication sites at a rate a . As previously, $\alpha(x)$ denotes affinity with the nodes and $\mu(x), \mu_{nd}^*$ the natural death rate in the blood and the tissues respectively. Trivially O is uniformly bounded:

$$O(t) < N_g, \forall t \in \mathbb{R}^+,$$

with initial conditions:

$$O(0) = O_0 \geq 0, \quad \phi(0, x) = \phi_0(x) \geq 0, \quad \psi^*(0) = \psi_0^* \geq 0.$$

Theorem 12. *Suppose $\alpha(x) \in L^{+\infty}(\mathbb{R}^+)$. Consider initial conditions $\phi_0 \in L^{+\infty}(\mathbb{R}^+) \cap L^1(\mathbb{R}^+)$ and $(O_0, \psi_0^*) \in \mathbb{R}_+^2$. Then, there exists a solution $(\psi^*(t), O(t), \phi(t, x))$ in the weak sense in $C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+))$. This solution is unique.*

Proof. Existence and uniqueness of a solution is a consequence of the Banach fixed point. The procedure of the proof is the same as for the well-posedness of the first model. \square

3.2.2 Steady states

In what follows we will distinguish two sorts of steady states as always:

- The trivial equilibrium $(0, 0, 0)$ which is the disease free steady state.
- The positive equilibrium $(\bar{\psi}^*, \bar{O}, \bar{\phi}(x))$

Set

$$I = \int_0^\infty \alpha(x) e^{-\int_0^x \mu(s) + \alpha(s) ds} dx.$$

Theorem 13. *The system has always a trivial equilibrium point. If*

$$I > \frac{aN_g + \mu_{nd}^*}{2aN_g^2}, \quad (3.24)$$

a second equilibrium exists $(\bar{\psi}^, \bar{O}, \bar{\phi}(x))$, whose components are given by:*

$$\begin{cases} \bar{O} = N_g - \frac{a + \sqrt{a^2 + 8\mu_{nd}^* a I}}{4aI}, \\ \bar{\psi}^* = \frac{\beta \bar{O}}{a(N_g - \bar{O})}, \\ \bar{\phi}(x) = 2\beta \bar{O} e^{-\int_0^x \mu(s) + \alpha(s) ds}. \end{cases}$$

Proof. An equilibrium point is a solution of the following system:

$$\begin{cases} (N_g - \bar{O}) \int_0^\infty \bar{\phi}(x) \alpha(x) dx = a\bar{\psi}^*(N_g - \bar{O}) + \mu_{nd}^* \bar{\psi}^*, \\ \beta \bar{O} = a\bar{\psi}^*(N_g - \bar{O}), \\ \frac{d\bar{\phi}(x)}{dx} = -\mu(x)\bar{\phi}(x) - \alpha(x)\bar{\phi}(x). \end{cases}$$

Then

$$a\bar{\psi}^* = \frac{\beta \bar{O}}{N_g - \bar{O}}, \quad \bar{\phi}(x) = 2\beta \bar{O} e^{-\int_0^x \mu(s) + \alpha(s) ds}.$$

We replace in the system:

$$\beta \bar{O} (2aI(N_g - \bar{O})^2 - a(N_g - \bar{O}) - \mu_{nd}^*) = 0.$$

If $\bar{O} = 0$ we get the trivial equilibrium. Otherwise, from the first equation:

$$2aI(N_g - \bar{O})^2 - a(N_g - \bar{O}) - \mu_{nd}^* = 0. \quad (3.25)$$

The quadratic polynomial $P(x) = 2aIx^2 - ax - \mu_{nd}^*$ has positive leading coefficient and $P(0) = -\mu_{nd}^* < 0$. So P has a negative and a positive real root, say x_-, x_+ . Since we need the condition

$$0 \leq N_g - \bar{O} \leq N_g,$$

to have pertinent (that is positive) solutions, there is a root of the polynomial with $N_g - \bar{O}$ as unknown if $x_+ < N_g$. This is possible if and only if:

$$P(N_g) > 0,$$

or equivalently,

$$2aIN_g^2 - aN_g - \mu_{nd}^* > 0,$$

which is exactly condition (3.24).

A positive solution in $N_g - \bar{O}$ is then given by the formula:

$$N_g - \bar{O} = \frac{a + \sqrt{a^2 + 8\mu_{nd}^*aI}}{4aI},$$

and this concludes the proof. \square

3.2.3 Stability analysis

We are now ready to study the stability of the identified equilibrium points. We linearize the system around an equilibrium $(\bar{\psi}^*, \bar{O}, \bar{\phi}(x))$ and study linear stability. The linear system is written as:

$$\begin{cases} \frac{d\psi^*}{dt} = (N_g - \bar{O}) \int_0^\infty \phi(t, x) \alpha(x) dx - (a(N_g - \bar{O}) + \mu_{nd}^*)\psi^* + (a\bar{\psi}^* - \int_0^\infty \bar{\phi}(x) \alpha(x) dx)O, \\ \frac{dO}{dt} = -(\beta + a\bar{\psi}^*)O + a(N_g - \bar{O})\psi^*, \\ \frac{\partial \phi(t, x)}{\partial t} + \frac{\partial \phi(t, x)}{\partial x} = -\mu(x)\phi(t, x) - \alpha(x)\phi(t, x), \\ \phi(t, 0) = 2\beta O, \end{cases}$$

with initial conditions:

$$O(0) = O_0 \geq 0, \quad \phi(0, x) = \phi_0(x) \geq 0, \quad \psi^*(0) = \psi_0^* \geq 0$$

Set

$$I(\lambda) = \int_0^\infty \alpha(x) e^{-\int_0^x (\mu(s) + \alpha(s) + \lambda) ds} dx,$$

and note that $I(0) = I$.

Theorem 14. *The trivial equilibrium is stable if and only if it is the only equilibrium of the system. If the positive equilibrium $(\bar{\psi}^*, \bar{O}, \bar{\phi})$ exists then it is stable and the trivial equilibrium is unstable.*

Proof. For stability we study the eigenvalue problem by replacing the exponential profile of solutions:

$$\psi^* e^{\lambda t}, O e^{\lambda t}, \phi(x) e^{\lambda t},$$

we get

$$\begin{cases} \lambda\psi^* = (N_g - \bar{O}) \int_0^\infty \phi(x)\alpha(x)dx - (a(N_g - \bar{O}) + \mu_{nd}^*)\psi^* + (a\bar{\psi}^* - \int_0^\infty \bar{\phi}(x)\alpha(x)dx)O, \\ \lambda O = -(\beta + a\bar{\psi}^*)O + a(N_g - \bar{O})\psi^*, \\ \phi(x) = \phi(0)e^{-\int_0^x (\mu(s) + \alpha(s) + \lambda)ds}, \\ \phi(0) = 2\beta O. \end{cases}$$

For $\lambda \geq \lambda_0$ so that $I(\lambda)$ is well defined, we see the system as:

$$\begin{bmatrix} \lambda + a(N_g - \bar{O}) + \mu_{nd}^* & -2\beta(N_g - \bar{O})I(\lambda) + 2\beta\bar{O}I(0) - a\bar{\psi}^* \\ -a(N_g - \bar{O}) & \lambda + \beta + a\bar{\psi}^* \end{bmatrix} \begin{pmatrix} \psi^* \\ O \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

a) For the trivial equilibrium $(0, 0, 0)$:

$$(\lambda + aN_g + \mu_{nd}^*)(\lambda + \beta) = 2a\beta N_g^2 I(\lambda).$$

Using lemma 9, stability is determined by a real eigenvalue which dominates complex eigenvalues for $\Re(\lambda) \in (-\min\{aN_g + \mu_{nd}^*, \beta, \lambda_0\}, +\infty)$.

Set $a = -(aN_g + \mu_{nd}^*)$, $b = -\beta$ and $F(\lambda) = (\lambda - a)(\lambda - b) - 2a\beta N_g^2 I(\lambda)$ to apply lemma 9. The equilibrium is stable if and only if:

$$F(0) > 0,$$

which gives

$$(aN_g + \mu_{nd}^*)\beta > 2a\beta N_g^2 I,$$

which is exactly the reverse of condition (3.24).

b) For the positive equilibrium characteristic equation is:

$$(\lambda + a(N_g - \bar{O}) + \mu_{nd}^*)(\lambda + \beta + a\bar{\psi}^*) = 2\beta a(N_g - \bar{O})^2 I(\lambda) + a(N_g - \bar{O})(a\bar{\psi}^* - \int_0^{+\infty} \bar{\phi}(x)\alpha(x)dx).$$

Using the expression of the equilibrium this is rewritten as:

$$(\lambda + a(N_g - \bar{O}) + \mu_{nd}^*)(\lambda + \beta + a\bar{\psi}^*) = 2\beta a(N_g - \bar{O})^2 I(\lambda) - a\mu_{nd}^* \bar{\psi}^*.$$

From (3.25) we know that:

$$2a(N_g - \bar{O})^2 = \frac{a(N_g - \bar{O}) + \mu_{nd}^*}{I(0)},$$

hence:

$$(\lambda + a(N_g - \bar{O}) + \mu_{nd}^*)(\lambda + \beta + a\bar{\psi}^*) = \beta(a(N_g - \bar{O}) + \mu_{nd}^*) \frac{I(\lambda)}{I(0)} - a\mu_{nd}^* \bar{\psi}^*.$$

Set

$$n = a(N_g - \bar{O}), \gamma = a\bar{\psi}^*, \text{ and } \frac{I(\lambda)}{I(0)} = E(e^{-\lambda X}).$$

We chose E as a notation because when we divide by $I(0)$ we obtain the integral of $e^{-\lambda x}$ with respect to a probability distribution. Indeed, we have a function whose integral is 1 so we see the quotient $\frac{I(\lambda)}{I(0)}$ as the mean value of the exponential with respect to this distribution.

The characteristic equation is:

$$F(\lambda) = 0,$$

with

$$F(\lambda) = (\lambda + \mu_{nd}^* + n)(\lambda + \beta + \gamma) + \mu_{nd}^* \gamma - \beta(n + \mu_{nd}^*)E(e^{-\lambda X}).$$

This equation cannot have a solution. Indeed, a solution would satisfy:

$$(\lambda + \mu_{nd}^* + n)(\lambda + \beta + \gamma) = -\mu_{nd}^* \gamma + \beta(n + \mu_{nd}^*)E(e^{-\lambda X}).$$

By taking modules of the left and the right hand side we get:

$$\begin{aligned} |(\lambda + \mu_{nd}^* + n)(\lambda + \beta + \gamma)|^2 &> (\beta + \gamma)^2 (\mu_{nd}^* + n)^2 \\ &> (\beta(\mu_{nd}^* + n))^2 \geq |\beta(n + \mu_{nd}^*)E(e^{-\lambda X})|^2. \end{aligned}$$

So

$$|(\lambda + \mu_{nd}^* + n)(\lambda + \beta + \gamma)| > |\beta(n + \mu_{nd}^*)E(e^{-\lambda X})|.$$

Equality is not possible, so there is no $\lambda \in \mathbb{C}$ satisfying $F(\lambda) = 0$.

□

3.2.4 Model with competition

Same as for the second model, we will split B-CLL cells into resistant and sensitive to ibrutinib (with subscripts r and s respectively) to get a more detailed insight into CLL dynamics. We wish to investigate how different behavior with respect to treatment can affect long term behavior and explain PRL. The model is then written:

$$\left\{ \begin{array}{l} \frac{d\psi_s^*}{dt} = (N_g - O_s(t) - O_r(t))(\int_0^\infty \phi_s(t, x)\alpha_s(x)dx - a_s\psi_s^*) - \mu^*\psi_s^*, \\ \frac{d\psi_r^*}{dt} = (N_g - O_s(t) - O_r(t))(\int_0^\infty \phi_r(t, x)\alpha_r(x)dx - a_r\psi_r^*) - \mu^*\psi_r^*, \\ \frac{dO_s}{dt} = -\beta O_s + a_s(N_g - O_s(t) - O_r(t))\psi_s^*, \\ \frac{dO_r}{dt} = -\beta O_r + a_r(N_g - O_s(t) - O_r(t))\psi_r^*, \\ \frac{\partial \phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_s(t, x) = -\mu(x)\phi_s(t, x) - \alpha_s(x)\phi_s(t, x), \\ \phi_s(t, 0) = 2\beta O_s(t), \\ \frac{\partial \phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x}\phi_r(t, x) = -\mu(x)\phi_r(t, x) - \alpha_r(x)\phi_r(t, x), \\ \phi_r(t, 0) = 2\beta O_r(t), \end{array} \right. \quad (3.26)$$

with initial conditions:

$$\begin{aligned} O_s(0) = O_s^0 \geq 0, \quad \phi_s(0, x) = \phi_s^0(x) \geq 0, \quad \psi_s^*(0) = \psi_s^{*,0} \geq 0, \\ O_r(0) = O_r^0 \geq 0, \quad \phi_r(0, x) = \phi_r^0(x) \geq 0, \quad \psi_r^*(0) = \psi_r^{*,0} \geq 0. \end{aligned}$$

Suppose that initially:

$$O_s^0 + O_r^0 < N_g,$$

Then, the occupied cells are uniformly bounded:

$$\sup_{t \in \mathbb{R}^+} \{O_s(t) + O_r(t)\} < N_g.$$

We assume that the rate of attachment to the nurse is higher for sensitive than resistant cells:

$$a_s > a_r.$$

Theorem 15. *Suppose $\alpha_r(x) + \mu(x) \in L^{+\infty}(\mathbb{R}^+)$, $\alpha_s(x) + \mu(x) \in L^{+\infty}(\mathbb{R}^+)$. Consider initial conditions $\phi_r^0, \phi_s^0 \in L^\infty(\mathbb{R}^+) \cap L^1(\mathbb{R}^+)$ and $(O_s^0, O_r^0, \psi_s^{*,0}, \psi_r^{*,0}) \in \mathbb{R}_+^4$. Then, there exists a solution $(\psi_s^*(t), O_s(t), \phi_s(t, x), \psi_r^*(t), O_r(t), \phi_r(t, x))$ in the weak sense in $C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+)) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+) \times C(\mathbb{R}^+, L^1(\mathbb{R}^+))$. This solution is unique.*

Proof. Well-posedness of the above system can be proven exactly in the same way as for the previous models. It is an application of the Banach fixed point theorem and the estimations are done similarly. \square

3.2.5 Steady states

Set

$$I_s = \int_0^\infty \alpha_s(x) e^{-\int_0^x \mu(y) + \alpha_s(y) dy} dx,$$

and

$$I_r = \int_0^\infty \alpha_r(x) e^{-\int_0^x \mu(y) + \alpha_r(y) dy} dx.$$

Theorem 16. 1) $(0, 0, 0, 0, 0, 0)$ is always an equilibrium point.

2) If

$$I_s > \frac{a_s N_g + \mu_{nd}^*}{2a_s N_g^2}, \quad (3.27)$$

$\mathcal{E}_s = (\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s(x), 0, 0, 0)$ is an equilibrium point, where

$$\begin{cases} \bar{O}_s = N_g - \frac{a_s + \sqrt{a_s^2 + 8a_s \mu_{nd}^* I_s}}{4a_s I_s}, \\ \bar{\psi}_s^* = \frac{\beta \bar{O}_s}{a_s (N_g - \bar{O}_s)}, \\ \bar{\phi}_s(x) = 2\beta \bar{O}_s e^{-\int_0^x \mu(s) + \alpha_s(s) ds}. \end{cases}$$

3) If

$$I_r > \frac{a_r N_g + \mu_{nd}^*}{2a_r N_g^2}, \quad (3.28)$$

$\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{O}_r, \bar{\phi}_r(x))$ is an equilibrium point, where

$$\begin{cases} \bar{O}_r = N_g - \frac{a_r + \sqrt{a_r^2 + 8a_r \mu_{nd}^* I_r}}{4a_r I_r}, \\ \bar{\psi}_r^* = \frac{\beta \bar{O}_r}{a_r (N_g - \bar{O}_r)}, \\ \bar{\phi}_r(x) = 2\beta \bar{O}_r e^{-\int_0^x \mu(s) + \alpha_r(s) ds}. \end{cases}$$

4) If \mathcal{E}_s and \mathcal{E}_r are the equilibrium points mentioned above, and moreover

$$\bar{O}_s = \bar{O}_r = \bar{O}, \quad (3.29)$$

then all points of the form:

$$\theta \mathcal{E}_s + (1 - \theta) \mathcal{E}_r, \quad \theta \in (0, 1)$$

are equilibrium points of the system. They have the form $(\bar{\psi}_s^{\theta}, \bar{O}_s^{\theta}, \bar{\phi}_s^{\theta}(x), \bar{\psi}_r^{\theta}, \bar{O}_r^{\theta}, \bar{\phi}_r^{\theta}(x))$, where none of the components is zero. More precisely:

$$\begin{cases} \bar{O}_s^{\theta} = \theta \bar{O}, \\ \bar{O}_r^{\theta} = (1 - \theta) \bar{O}, \\ \bar{\phi}_s^{\theta}(x) = 2\beta \theta \bar{O} e^{-\int_0^x \mu(y) + \alpha_s(y) dy}, \\ \bar{\phi}_r^{\theta}(x) = 2\beta (1 - \theta) \bar{O} e^{-\int_0^x \mu(y) + \alpha_r(y) dy}, \\ \bar{\psi}_s^{\theta} = \frac{\beta \theta \bar{O}}{a_s (N_g - \bar{O})}, \\ \bar{\psi}_r^{\theta} = \frac{\beta (1 - \theta) \bar{O}}{a_r (N_g - \bar{O})}. \end{cases}$$

Proof. Equilibrium points are solutions of:

$$\begin{cases} 0 = (N_g - \bar{O}_s - \bar{O}_r) \left(\int_0^{\infty} \bar{\phi}_s(x) \alpha_s(x) dx - a_s \bar{\psi}_s^* \right) - \mu^* \bar{\psi}_s^*, \\ 0 = (N_g - \bar{O}_s - \bar{O}_r) \left(\int_0^{\infty} \bar{\phi}_r(x) \alpha_r(x) dx - a_r \bar{\psi}_r^* \right) - \mu^* \bar{\psi}_r^*, \\ 0 = -\beta \bar{O}_s + a_s (N_g - \bar{O}_s - \bar{O}_r) \bar{\psi}_s^*, \\ 0 = -\beta \bar{O}_r + a_r (N_g - \bar{O}_s - \bar{O}_r) \bar{\psi}_r^*, \\ \bar{\phi}_s(x) = 2\beta \bar{O}_s e^{-\int_0^x \mu(y) + \alpha_s(y) dy}, \\ \bar{\phi}_r(x) = 2\beta \bar{O}_r e^{-\int_0^x \mu(y) + \alpha_r(y) dy}. \end{cases}$$

Note that $N_g - \bar{O}_s - \bar{O}_r \neq 0$. Indeed if it was 0, then from the above equations we would get $\bar{O}_s = 0$ and $\bar{O}_r = 0$ which entails finally $N_g - \bar{O}_s - \bar{O}_r = N_g$. Hence:

$$\bar{\psi}_s^* = \frac{\beta \bar{O}_s}{a_s (N_g - \bar{O}_s - \bar{O}_r)},$$

$$\bar{\psi}_r^* = \frac{\beta \bar{O}_r}{a_r(N_g - \bar{O}_s - \bar{O}_r)},$$

injecting into the first two equations:

$$\begin{cases} 0 = \beta \bar{O}_s (2a_s(N_g - \bar{O}_s - \bar{O}_r)^2 I_s - a_s(N_g - \bar{O}_s - \bar{O}_r) - \mu_{nd}^*), \\ 0 = \beta \bar{O}_r (2a_r(N_g - \bar{O}_s - \bar{O}_r)^2 I_r - a_r(N_g - \bar{O}_s - \bar{O}_r) - \mu_{nd}^*). \end{cases}$$

- For \mathcal{E}_s the previous equation reduces to:

$$2a_s I_s (N_g - \bar{O}_s)^2 - a_s (N_g - \bar{O}_s) - \mu_{nd}^* = 0. \quad (3.30)$$

This is a second degree polynomial of $N_g - \bar{O}_s$. A positive solution is:

$$\bar{O}_s = N_g - \frac{a_s + \sqrt{a_s^2 + 8a_s \mu_{nd}^* I_s}}{4a_s I_s},$$

and is acceptable if

$$I_s > \frac{a_s N_g + \mu_{nd}^*}{2a_s N_g^2}.$$

- For \mathcal{E}_r the procedure is the same as for the previous case. The equation reduces to:

$$2a_r I_r (N_g - \bar{O}_r)^2 - a_r (N_g - \bar{O}_r) - \mu_{nd}^* = 0, \quad (3.31)$$

and the solution

$$\bar{O}_r = N_g - \frac{a_r + \sqrt{a_r^2 + 8a_r \mu_{nd}^* I_r}}{4a_r I_r},$$

is acceptable if

$$I_r > \frac{a_r N_g + \mu_{nd}^*}{2a_r N_g^2}.$$

- $\bar{O}_r \neq 0$ and $\bar{O}_s \neq 0$. To avoid any ambiguity, we will use superscripts for the components of the double species equilibrium points. In that case we have simultaneously:

$$\begin{cases} 0 = 2a_s(N_g - \bar{O}_s^\theta - \bar{O}_r^\theta)^2 I_s - a_s(N_g - \bar{O}_s^\theta - \bar{O}_r^\theta) - \mu_{nd}^*, \\ 0 = 2a_r(N_g - \bar{O}_s^\theta - \bar{O}_r^\theta)^2 I_r - a_r(N_g - \bar{O}_s^\theta - \bar{O}_r^\theta) - \mu_{nd}^*. \end{cases}$$

For these equations to make sense and to give a solution of $N_g - \bar{O}_s^\theta - \bar{O}_r^\theta$ it comes that:

$$\frac{a_s + \sqrt{a_s^2 + 8a_s \mu_{nd}^* I_s}}{4a_s I_s} = \frac{a_r + \sqrt{a_r^2 + 8a_r \mu_{nd}^* I_r}}{4a_r I_r}.$$

Using the expression of the equilibrium points, this is equivalent to equating the \bar{O}_s and \bar{O}_r components of the single species equilibrium points $\mathcal{E}_s, \mathcal{E}_r$ since:

$$N_g - \bar{O}_r = N_g - \bar{O}_s.$$

All points on the segment:

$$\begin{cases} \bar{O}_s^\theta + \bar{O}_r^\theta = N_g - \frac{a_s + \sqrt{a_s^2 + 8a_s\mu_{nd}^* I_s}}{4a_s I_s}, \\ \bar{O}_s^\theta \geq 0, \\ \bar{O}_r^\theta \geq 0, \end{cases}$$

are solutions and give infinitely many equilibrium points. Their components can be parameterized using a parameter $\theta \in (0, 1)$ as follows:

Set $\bar{O} = N_g - \frac{a_s + \sqrt{a_s^2 + 8a_s\mu_{nd}^* I_s}}{4a_s I_s}$, so $\bar{O} = \bar{O}_r = \bar{O}_s$. Then $\bar{O}_s^\theta + \bar{O}_r^\theta = \bar{O}$ if and only if there is a $\theta \in (0, 1)$ such that:

$$\begin{cases} \bar{O}_s^\theta = \theta \bar{O}, \\ \bar{O}_r^\theta = (1 - \theta) \bar{O}. \end{cases}$$

The rest of the components are found by solving the system in \bar{O}_s^θ and \bar{O}_r^θ . □

Equation (3.29) describes a degenerate case where it makes no real sense to talk about resistant and sensitive cells separately. Again, this model does not predict coexistence of the two populations unless a rare case where the parameters satisfy:

$$\frac{a_s + \sqrt{a_s^2 + 8a_s\mu_{nd}^* I_s}}{4a_s I_s} = \frac{a_r + \sqrt{a_r^2 + 8a_r\mu_{nd}^* I_r}}{4a_r I_r}.$$

Parameters depend on treatment, so this equation describes the unique dose that makes resistant and sensitive coexist. Stability of the equilibrium points will show how solutions behave when treatment is increased or decreased with respect to this dose.

3.2.6 Stability analysis

Stability of the system is studied using the linear system. Let us consider the equilibrium point:

$$(\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s, \bar{\psi}_r^*, \bar{O}_r, \bar{\phi}_r).$$

Set $N = N_g - \bar{O}_s - \bar{O}_r$.

The linear system around the equilibrium is:

$$\begin{cases} \frac{d\psi_s^*}{dt} = N \int_0^\infty \phi_s(t, x) \alpha_s(x) dx + (a_s \bar{\psi}_s^* - 2\beta \bar{O}_s I_s) O_s + (a_s \bar{\psi}_s^* - 2\beta \bar{O}_s I_s) O_r - (a_s N + \mu_{nd}^*) \psi_s^*, \\ \frac{d\psi_r^*}{dt} = N \int_0^\infty \phi_r(t, x) \alpha_r(x) dx + (a_r \bar{\psi}_r^* - 2\beta \bar{O}_r I_r) O_s + (a_r \bar{\psi}_r^* - 2\beta \bar{O}_r I_r) O_r - (a_r N + \mu_{nd}^*) \psi_r^*, \\ \frac{dO_s}{dt} = -(\beta + a_s \bar{\psi}_s^*) O_s + N a_s \psi_s^* - a_s \bar{\psi}_s^* O_r, \\ \frac{dO_r}{dt} = -(\beta + a_r \bar{\psi}_r^*) O_r + N a_r \psi_r^* - a_r \bar{\psi}_r^* O_s, \\ \frac{\partial \phi_s}{\partial t}(t, x) + \frac{\partial}{\partial x} \phi_s(t, x) = -\mu(x) \phi_s(t, x) - \alpha_s(x) \phi_s(t, x), \\ \phi_s(t, 0) = 2\beta O_s(t), \\ \frac{\partial \phi_r}{\partial t}(t, x) + \frac{\partial}{\partial x} \phi_r(t, x) = -\mu(x) \phi_r(t, x) - \alpha_r(x) \phi_r(t, x), \\ \phi_r(t, 0) = 2\beta O_r(t), \end{cases}$$

with typical positive initial conditions. Set

$$I_s(\lambda) = \int_0^\infty \alpha_s(x) e^{-\int_0^x \mu(y) + \alpha_s(y) + \lambda dy} dx,$$

and

$$I_r(\lambda) = \int_0^\infty \alpha_r(x) e^{-\int_0^x \mu(y) + \alpha_r(y) + \lambda dy} dx.$$

Theorem 17. *If the trivial equilibrium is the only equilibrium of the system it is locally stable. If there is at least one other equilibrium it is unstable. Consider now the equilibrium points $\mathcal{E}_r = (0, 0, 0, \bar{\psi}_r^*, \bar{O}_r, \bar{\phi}_r(x))$ and $\mathcal{E}_s = (\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s(x), 0, 0, 0)$. Then if:*

$$\bar{O}_r > \bar{O}_s,$$

the equilibrium \mathcal{E}_r is locally stable and \mathcal{E}_s is unstable. If:

$$\bar{O}_s > \bar{O}_r,$$

\mathcal{E}_s is stable and \mathcal{E}_r is unstable. Finally if

$$\bar{O}_s = \bar{O}_r,$$

there are infinitely many equilibrium points of the form:

$$\theta \mathcal{E}_s + (1 - \theta) \mathcal{E}_r \quad \theta \in (0, 1),$$

and all of them are asymptotically unstable.

Proof. The associated eigenvalue problem is obtained by replacing solutions of the system with exponential form:

$$\psi_s^* e^{\lambda t}, \psi_r^* e^{\lambda t}, O_s e^{\lambda t}, O_r e^{\lambda t}, \phi_s(x) e^{\lambda t}, \phi_r(x) e^{\lambda t},$$

The transport equations give:

$$\begin{cases} \lambda\phi_s(x) + \frac{\partial\phi_s(x)}{\partial x} = -\mu(x)\phi_s(x) - \alpha_s(x)\phi_s(x), \\ \lambda\phi_r(x) + \frac{\partial\phi_r(x)}{\partial x} = -\mu(x)\phi_r(x) - \alpha_r(x)\phi_r(x). \end{cases}$$

Using the definition of $I_s(\lambda)$, $I_r(\lambda)$ and as

$$a_s\bar{\psi}_s^* = \frac{\beta\bar{O}_s}{N},$$

we have:

$$\begin{cases} \psi_s^*(\lambda + a_s N + \mu_{nd}^*) = 2N\beta O_s I_s(\lambda) + \left(\frac{\beta\bar{O}_s}{N} - 2\beta\bar{O}_s I_s\right)O_s + \left(\frac{\beta\bar{O}_s}{N} - 2\beta\bar{O}_s I_s\right)O_r, \\ \psi_r^*(\lambda + a_r N + \mu_{nd}^*) = 2N\beta O_r I_r(\lambda) + \left(\frac{\beta\bar{O}_r}{N} - 2\beta\bar{O}_r I_r\right)O_s + \left(\frac{\beta\bar{O}_r}{N} - 2\beta\bar{O}_r I_r\right)O_r, \\ \left(\lambda + \beta + \frac{\beta\bar{O}_s}{N}\right)O_s = a_s N\psi_s^* - \frac{\beta\bar{O}_s}{N}O_r, \\ \left(\lambda + \beta + \frac{\beta\bar{O}_r}{N}\right)O_r = a_r N\psi_r^* - \frac{\beta\bar{O}_r}{N}O_s. \end{cases} \quad (3.32)$$

We put the system in matrix form:

$$A_{\lambda, \bar{O}_s, \bar{O}_r} \begin{pmatrix} O_s \\ O_r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

where $A_{\lambda, \bar{O}_s, \bar{O}_r}$ is a 2×2 matrix, whose elements are:

- $A_{\lambda, \bar{O}_s, \bar{O}_r}(1, 1) = 2N\beta I_s(\lambda) + \left(\frac{\beta\bar{O}_s}{N} - 2\beta\bar{O}_s I_s\right) - \frac{(\lambda + Na_s + \mu_{nd}^*)(\lambda + \beta + \frac{\beta\bar{O}_s}{N})}{a_s N},$
- $A_{\lambda, \bar{O}_s, \bar{O}_r}(1, 2) = \beta\bar{O}_s \left(\frac{1}{N} - 2I_s - \frac{\frac{1}{N}(\lambda + Na_s + \mu_{nd}^*)}{a_s N}\right),$
- $A_{\lambda, \bar{O}_s, \bar{O}_r}(2, 1) = \beta\bar{O}_r \left(\frac{1}{N} - 2I_r - \frac{\frac{1}{N}(\lambda + Na_r + \mu_{nd}^*)}{a_r N}\right),$
- $A_{\lambda, \bar{O}_s, \bar{O}_r}(2, 2) = 2N\beta I_r(\lambda) + \left(\frac{\beta\bar{O}_r}{N} - 2\beta\bar{O}_r I_r\right) - \frac{(\lambda + Na_r + \mu_{nd}^*)(\lambda + \beta + \frac{\beta\bar{O}_r}{N})}{a_r N}.$

We can immediately make the following remarks:

- For the trivial equilibrium the matrix is diagonal.
- For the single species steady states the matrix is upper ($\bar{O}_r = 0$) or lower triangular ($\bar{O}_s = 0$).
- For the positive steady states the matrix is full.

The system has a non trivial solution if and only if:

$$\det A_{\lambda, \bar{O}_r, \bar{O}_s} = 0.$$

- For equilibrium $(0, 0, 0, 0, 0, 0)$

$$\det A_{\lambda, \bar{O}_r, \bar{O}_s} = A_{\lambda, \bar{O}_r, \bar{O}_s}(1, 1)A_{\lambda, \bar{O}_r, \bar{O}_s}(2, 2),$$

so (3.32) reduces to two uncoupled equations:

$$\begin{cases} (\lambda + a_s N_g + \mu_{nd}^*)(\lambda + \beta) = 2\beta N_g a_s N_g I_s(\lambda), \\ or \\ (\lambda + a_r N_g + \mu_{nd}^*)(\lambda + \beta) = 2\beta N_g a_r N_g I_r(\lambda). \end{cases}$$

If $(0, 0, 0, 0, 0, 0)$ is the only equilibrium of the system, then none of (3.28), (3.27) is satisfied. As ψ_s^* and ψ_r^* cannot be zero simultaneously, say for example that $\psi_s^* \neq 0$ (the other case is treated similarly). Real eigenvalues determine stability. In particular, for

$$(\lambda + a_s N_g + \mu_{nd}^*)(\lambda + \beta) = 2\beta N_g^2 a_s I_s(\lambda),$$

the value at zero determines stability. An equilibrium is stable if and only if:

$$\beta(a_s N_g + \mu_{nd}^*) > 2\beta N_g^2 a_s I_s.$$

If at least one non zero equilibrium exists, then the trivial equilibrium is unstable as we can always find solutions of the above equations with $\lambda > 0$.

- For the single species case \mathcal{E}_r :

$$\det A_{\lambda, \bar{O}_r, \bar{O}_s} = A_{\lambda, \bar{O}_r, \bar{O}_s}(1, 1)A_{\lambda, \bar{O}_r, \bar{O}_s}(2, 2).$$

So either $A_{\lambda, \bar{O}_r, \bar{O}_s}(1, 1) = 0$ or $A_{\lambda, \bar{O}_r, \bar{O}_s}(2, 2) = 0$.

The second possibility gives:

$$(\lambda + a_r N + \mu_{nd}^*)(\lambda + \beta + \frac{\beta \bar{O}_r}{N}) = a_r N(2N\beta I_r(\lambda) + \frac{\beta \bar{O}_r}{N} - 2\beta \bar{O}_r I_r).$$

As in that case $N = N_g - \bar{O}_r$ and $\beta \bar{O}_r = a_r \bar{\psi}_r^*(N_g - \bar{O}_r)$, we can use equation (3.31):

$$(\lambda + a_r(N_g - \bar{O}_r) + \mu_{nd}^*)(\lambda + \beta + \frac{\beta \bar{O}_r}{N_g - \bar{O}_r}) = \beta(a_r(N_g - \bar{O}_r) + \mu_{nd}^*)\frac{I_r(\lambda)}{I_r(0)} - a_r \mu_{nd}^* \bar{\psi}_r^*.$$

In that case the equilibrium is stable. The proof is the same as for the stability of the model without competition since the equation is of the same type.

The other possibility entails:

$$(\lambda + a_s(N_g - \bar{O}_r) + \mu_{nd}^*)(\lambda + \beta) = 2a_s \beta(N_g - \bar{O}_r)^2 I_s(\lambda).$$

The value at zero determines stability. The equilibrium is stable if:

$$a_s(N_g - \bar{O}_r) + \mu_{nd}^* > 2a_s(N_g - \bar{O}_r)^2 I_s.$$

From (3.30) for the $(\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s(x), 0, 0, 0)$ equilibrium we replace I_s , hence this holds if and only if:

$$2a_s(N_g - \bar{O}_s)^2(a_s(N_g - \bar{O}_r) + \mu_{nd}^*) > 2a_s(N_g - \bar{O}_r)^2(a_s(N_g - \bar{O}_s) + \mu_{nd}^*),$$

if and only if:

$$a_s(N_g - \bar{O}_s)(N_g - \bar{O}_r)(\bar{O}_r - \bar{O}_s) > \mu_{nd}^*((N_g - \bar{O}_r)^2 - (N_g - \bar{O}_s)^2),$$

if and only if:

$$a_s \frac{(N_g - \bar{O}_r)(N_g - \bar{O}_s)}{N_g - \bar{O}_s + N_g - \bar{O}_r} (\bar{O}_r - \bar{O}_s) > \mu_{nd}^*(\bar{O}_s - \bar{O}_r),$$

if and only if:

$$\left(a_s \frac{(N_g - \bar{O}_r)(N_g - \bar{O}_s)}{N_g - \bar{O}_s + N_g - \bar{O}_r} + \mu_{nd}^* \right) (\bar{O}_r - \bar{O}_s) > 0.$$

Which is possible if and only if:

$$\bar{O}_r > \bar{O}_s.$$

- For \mathcal{E}_s the same proof holds for stability. As all equations are symmetric with respect to a_s and a_r , we have that, $(\bar{\psi}_s^*, \bar{O}_s, \bar{\phi}_s(x), 0, 0, 0)$ is stable if:

$$a_r(N_g - \bar{O}_s) + \mu_{nd}^* > 2a_r(N_g - \bar{O}_s)^2 I_r,$$

which is equivalent to:

$$\bar{O}_s > \bar{O}_r.$$

- Lastly, if $\bar{O}_r = \bar{O}_s$ the matrix is full and $\lambda = 0$ is an eigenvalue for the eigenvector $v = \begin{pmatrix} 1 \\ -1 \end{pmatrix}$. Indeed, if we replace in the matrix $A_{\lambda, \bar{O}_s, \bar{O}_r}$ the $\lambda = 0$ and from the expression of the steady states:

$$\begin{cases} 2\beta(N_g - \bar{O}_s - \bar{O}_r)I_s - \beta - \frac{\mu_{nd}^*}{a_s(N_g - \bar{O}_s - \bar{O}_r)} = 0, \\ 2\beta(N_g - \bar{O}_s - \bar{O}_r)I_r - \beta - \frac{\mu_{nd}^*}{a_r(N_g - \bar{O}_s - \bar{O}_r)} = 0. \end{cases}$$

we end up with a matrix:

$$\begin{pmatrix} -\frac{\mu_{nd}^*}{a_s(N_g - \bar{O}_s - \bar{O}_r)} \frac{\beta \bar{O}_s}{N_g - \bar{O}_s - \bar{O}_r} - 2\beta \bar{O}_s I_s & -\frac{\mu_{nd}^*}{a_s(N_g - \bar{O}_s - \bar{O}_r)} \frac{\beta \bar{O}_s}{N_g - \bar{O}_s - \bar{O}_r} - 2\beta \bar{O}_s I_s \\ -\frac{\mu_{nd}^*}{a_r(N_g - \bar{O}_s - \bar{O}_r)} \frac{\beta \bar{O}_r}{N_g - \bar{O}_s - \bar{O}_r} - 2\beta \bar{O}_r I_r & -\frac{\mu_{nd}^*}{a_r(N_g - \bar{O}_s - \bar{O}_r)} \frac{\beta \bar{O}_r}{N_g - \bar{O}_s - \bar{O}_r} - 2\beta \bar{O}_r I_r \end{pmatrix}$$

whose eigenvector for $\lambda = 0$ is v .

There are infinitely many equilibrium points as we have already proven. They are of the form:

$$\theta \mathcal{E}_s + (1 - \theta) \mathcal{E}_r, \quad \theta \in (0, 1).$$

Starting from an equilibrium corresponding to θ^* , say $\mathcal{E}^* = \theta^* \mathcal{E}_s + (1 - \theta^*) \mathcal{E}_r$, any small perturbation for $\epsilon > 0$ would lead to the equilibrium $(\theta^* + \epsilon) \mathcal{E}_s + (1 - (\theta^* + \epsilon)) \mathcal{E}_r$. Hence, asymptotically no solution would converge back to \mathcal{E}^* . This does not inhibit though the equilibrium to be locally stable in the strict sense. We have no results concerning local stability. □

We conclude with the following remark: Starting at the steady state, if the sensitive equilibrium occupies a larger part of the multiplication sites than the resistant state \mathcal{E}_r , then \mathcal{E}_s is stable. In the reverse case, the resistant \mathcal{E}_r steady state is stable.

Our last two models reveal the same dynamics of CLL as the first two. As they are qualitatively similar, the choice between them will be based on the available data. Biologically, there is no way to count occupied cells, making the quantities O_s and O_r unobservable. As there is no biological marker that can differentiate occupied from competing for multiplication cells, and because there is no further insight into the dynamics of CLL when we consider the occupied population, we choose the second model as more pertinent for our analysis.

3.3 Discussion

We have proposed and analyzed 4 models of CLL, where the dynamics were described by a continuous variable representing maturity. The existence of such a structure entails the study of PDE systems instead of systems of ODE. Whether such a structure can give a better knowledge of CLL dynamics is still to be answered.

For that we should determine to which extent PDE models lead to essentially different conclusions than ODE models. As we select the second model as more pertinent, we would like to know if it gives essentially different results than an ODE model.

An ODE system that models the same dynamics would describe the process of maturation as a discrete procedure that takes place in the blood. It is expressed with a simple ordinary equation for each level of maturation. An example of such a model can be found in the work of Coulette, Grenier, Sujobert (work in progress).

$$\begin{cases} \frac{d\psi_s^*}{dt} = \sum_n a_{s_n} \phi_{s_n} - \beta(\psi_s^* + \psi_r^*) \psi_s^* - \mu_{nd}^* \psi_s^*, \\ \frac{d\psi_r^*}{dt} = \sum_n a_{r_n} \phi_{r_n} - \beta(\psi_s^* + \psi_r^*) \psi_r^* - \mu_{nd}^* \psi_r^*, \\ \frac{d\psi_s}{dt} = \beta(\psi_s^* + \psi_r^*) \psi_s^* - \zeta_0^s \psi_s - \mu_{nd} \psi_s, \\ \frac{d\psi_r}{dt} = \beta(\psi_s^* + \psi_r^*) \psi_r^* - \zeta_0^r \psi_r - \mu_{nd} \psi_r, \\ \frac{d\phi_{s_n}}{dt} = \zeta_n^s \psi_s + y_{n-1}^s \phi_{s_{n-1}} - y_n^s \phi_n - a_{s_n} \phi_{s_n} - \mu_n \phi_{s_n}, \\ \frac{d\phi_{r_n}}{dt} = \zeta_n^r \psi_r + y_{n-1}^r \phi_{r_{n-1}} - y_n^r \phi_n - a_{r_n} \phi_{r_n} - \mu_n \phi_{r_n}, \end{cases} \quad (3.33)$$

where ψ_s^*, ψ_r^* are the sensitive and resistant home cells, ψ_s, ψ_r are the sensitive and resistant node cells after multiplication and ϕ_{s_n}, ϕ_{r_n} are the blood cells at maturation stage $n \in [0, N]$.

The parameters have the same meaning as in the PDE model. a_{s_n}, a_{r_n} is the homing affinity rate at maturation stage n and ζ_n^s, ζ_n^r the node to blood transfer rate with $\zeta_n^s = 0, \zeta_n^r = 0$ for $n \geq 1$. Moreover y_n^s, y_n^r is the maturation transfer rate from stage n to stage $n + 1$ with $y_{-1} = 0$.

Clinically, the observed quantity that we have is the total blood count,

$$\phi_b = \sum_n (\phi_{s_n} + \phi_{r_n}),$$

so we are led to the study of the following equations for blood, instead of n separate equations:

$$\frac{d(\sum_n \phi_{s_n})}{dt} = \zeta_0^s \psi_s - \sum_n a_{s_n} \phi_{s_n} - \sum_n \mu_n \phi_{s_n},$$

and

$$\frac{d(\sum_n \phi_{r_n})}{dt} = \zeta_0^r \psi_r - \sum_n a_{r_n} \phi_{r_n} - \sum_n \mu_n \phi_{r_n}.$$

With a Michaelis-Menten saturation model for β we are led to the same conclusions as in the PDE model. We conclude that the results are essentially the same as in the case of discrete maturity. Hence, as calculations are simpler there is no need to use partial differential equations if the dynamics revealed are not richer.

Chapter 4

Modeling of hematopoiesis

Summary

We study the hematopoiesis, a process used by the organism to regulate and generate blood cells (red cells, white cells and platelets) and to maintain homeostasis (metabolic equilibrium). Stem cells (HSC) comprise only a small part of the blood population, it is them though that maintain the process. Hematopoiesis is regulated by specific growth factors (molecules acting like hormones playing an activator/inhibitor role). This means that there is a feedback control from mature cells to HSCs. Abnormalities in the feedback loops can lead to hematological diseases. In this work we consider the feedback control from mature blood cells to HSC population using a maturity structured model with the discrete compartments representing the evolution of HSC to mature cells. We identify the equilibrium points and study their stability. The feedback control induces delays making the equilibrium points depend on the sum of these delays. Stability depends on the total duration of hematopoiesis. If the time is very short or very long, stability is maintained since natural cell death governs the dynamics. In intermediate times stability can be lost with switches depending on the total delay. Switches lead to oscillations and oscillations in circulating numbers from normal to low values are related to blood diseases.

4.1 Modeling of hematopoiesis with delay differential equations

4.1.1 Model and well-posedness

In this section, we consider a discrete maturity structured model with $n + 1$ compartments to represent the evolution from HSC to mature blood cell populations through differentiation. We denote by $U_0(t)$ and $U_n(t)$ the total population of primitive HSCs and mature blood cells, respectively. We suppose that the primitive HSCs satisfy the following logistic equation:

$$U_0'(t) = rU_0(t) \left(1 - \frac{U_0(t)}{K(U_n(t))} \right) - \delta U_0(t), \quad (4.1)$$

with r the intrinsic growth rate, δ the maturation rate which contains also the differentiation, and K a decreasing function describing the capacity of the system as a function of the mature population. We denote by τ_i the time spent by the cells in each compartment $i \in I_n := \{1, \dots, n\}$ and by $u_i(t, a)$, for $0 < a < \tau_i$, the cell population densities of the i generation. We also suppose that for the last generation $\tau_n = +\infty$. The age-structured equation satisfied by u_i , $i \in I_n$, is

$$\frac{\partial u_i}{\partial t}(t, a) + \frac{\partial u_i}{\partial a}(t, a) = -\mu_i u_i(t, a), \quad t \geq 0, a \in (0, \tau_i), \quad (4.2)$$

with μ_i the mortality rate. Hence

$$U_i(t) = \int_0^{\tau_i} u_i(t, a) da \quad (4.3)$$

is the total population of cells in the compartment $i \in I_n$. The boundary conditions are

$$u_1(t, 0) = H(U_n(t))U_0(t), \quad u_i(t, 0) = h_{i-1}u_{i-1}(t, \tau_{i-1}), \quad i = 2, \dots, n. \quad (4.4)$$

We suppose that H is a decreasing function with

$$\lim_{U_n \rightarrow \infty} H(U_n) = 0 \quad \text{and} \quad H(0) \leq \delta < 1.$$

In fact $(\delta - H(U_n(t)))U_0(t)$ and $(1 - h_{i-1})u_{i-1}(t, \tau_{i-1})$ are the differentiation to other lineages.

By integrating the equation (4.2) over the age variable for $i = 2, \dots, n-1$ along characteristics, we obtain

$$u_i(t, \tau_i) = e^{-\mu_i \tau_i} u_i(t - \tau_i, 0), \quad \text{for } t > \tau_i.$$

Using the boundary condition (4.4), we get

$$u_i(t, \tau_i) = h_{i-1} e^{-\mu_i \tau_i} u_{i-1}(t - \tau_i, \tau_{i-1}). \quad (4.5)$$

Now, we integrate the equation (4.2), for $i = n$, over the age variable and we take into account the boundary condition (4.4) to obtain

$$U'_n(t) = -\mu_n U_n(t) + h_{n-1} u_{n-1}(t, \tau_{n-1}).$$

We use the expression (4.5), to have the equation

$$U'_n(t) = -\mu_n U_n(t) + \prod_{i=1}^{n-1} h_i e^{-\mu_i \tau_i} H(U_n(t - \tau)) U_0(t - \tau), \quad t > \tau := \sum_{i=1}^{n-1} \tau_i.$$

We suppose that $\mu_1 = \dots = \mu_{n-1} = \mu$ and we set $h := h_1 h_2 \dots h_{n-1}$. Then, we end up with the following system of delay differential equations, for $t > \tau$,

$$\begin{cases} U'_0(t) &= rU_0(t) \left(1 - \frac{U_0(t)}{K(U_n(t))}\right) - \delta U_0(t), \\ U'_n(t) &= -\mu_n U_n(t) + h e^{-\mu\tau} H(U_n(t-\tau)) U_0(t-\tau). \end{cases} \quad (4.6)$$

Studying (U_0, U_n) is enough to have a complete analysis of the initial system since it is totally characterized by these two equations.

The initial condition is given for $t \in [0, \tau]$, by the continuous function $(U_0(t), U_n(t)) = (\phi(t), \psi(t))$. We can make the translation of time $t - \tau$ to define the system for $t > 0$ with an initial condition defined on the interval $[-\tau, 0]$. Then, the system (4.6) will be considered for $t > 0$, with initial conditions given by

$$(U_0(t), U_n(t)) = (\phi(t), \psi(t)), \quad t \in [-\tau, 0], \quad \text{with } (\phi, \psi) \in C([-\tau, 0], \mathbb{R}^2).$$

Theorem 18. *Let τ be a positive delay and $(\phi, \psi) \in C([-\tau, 0], \mathbb{R}^2)$ be initial conditions for $(U_0(t), U_n(t))$ with $t \in [-\tau, 0]$. Let H be a positive, decreasing function with $\lim_{u \rightarrow +\infty} H(u) = 0$ and*

$$\sup_{x \geq 0} (H(x)) \leq \delta < 1.$$

Let K be a positive decreasing function with $\lim_{u \rightarrow +\infty} K(u) = 0$. Under these assumptions the delay differential system has a unique positive solution $(U_0, U_n) \in L^\infty(\mathbb{R}^+) \cap C([0, \infty), \mathbb{R}^+) \times C([0, \infty), \mathbb{R}^+)$.

Proof. It is a well known result. For the proof see J.K Hale Theory of functional differential equations [39]. □

4.1.2 Existence of steady states and properties

In this section we distinguish two sorts of steady states:

- The trivial equilibrium $(\bar{U}_0, \bar{U}_n) = (0, 0)$.
- The positive equilibrium where none of the components \bar{U}_0, \bar{U}_n is 0.

We want to study the existence of steady states of the system (4.6). Let us suppose that the functions K and H are continuously differentiable on \mathbb{R}^+ . Using the variations of H and K we can state the following proposition.

Proposition 13. *The trivial equilibrium $(0, 0)$ always exists. A unique positive equilibrium (\bar{U}_0, \bar{U}_n) exists if and only if*

$$r > \delta. \quad (4.7)$$

In particular if (4.7) is satisfied, the positive equilibrium (\bar{U}_0, \bar{U}_n) is a solution of the system:

$$\mu_n \bar{U}_n = h e^{-\mu\tau} \left(1 - \frac{\delta}{r}\right) H(\bar{U}_n) K(\bar{U}_n) \quad \text{and} \quad \bar{U}_0 = \left(1 - \frac{\delta}{r}\right) K(\bar{U}_n). \quad (4.8)$$

The components (\bar{U}_0, \bar{U}_n) are functions of the delay, they are positive and uniformly upper bounded for all $\tau > 0$.

Proof. The steady states are constant solutions and can be found by solving the system:

$$\begin{cases} r\bar{U}_0 \left(1 - \frac{\bar{U}_0}{K(\bar{U}_n)}\right) - \delta\bar{U}_0 = 0, \\ -\mu_n \bar{U}_n + h e^{-\mu\tau} H(\bar{U}_n) \bar{U}_0 = 0. \end{cases}$$

The trivial solution $(\bar{U}_0, \bar{U}_n) = (0, 0)$ always exists. For $\bar{U}_0 \neq 0$, we find the equations (4.8). Observe that the function E , defined by

$$E(U_n) = h e^{-\mu\tau} \left(1 - \frac{\delta}{r}\right) H(U_n) K(U_n) - \mu_n U_n,$$

is decreasing and satisfies $E(0) > 0$ and $E(+\infty) = -\infty$. So there is a unique \bar{U}_n zero of E . Consequently \bar{U}_0 is unique as well. A remark that will be useful later concerns the dependence on the parameters μ and τ . For all the other parameters kept fixed, the equilibrium components \bar{U}_n, \bar{U}_0 depend on the product

$$\bar{\tau} := \mu\tau.$$

We denote $\bar{U}_0(\bar{\tau})$ and $\bar{U}_n(\bar{\tau})$ to indicate the dependence on $\bar{\tau} = \mu\tau$. From the equations of the equilibrium we have the upper bounds

$$\begin{cases} \bar{U}_0(\bar{\tau}) \leq \left(1 - \frac{\delta}{r}\right) K(0), \\ \bar{U}_n(\bar{\tau}) \leq \frac{h}{\mu_n} e^{-\bar{\tau}} H(0) K(0). \end{cases}$$

By implicit differentiation with respect to $\bar{\tau}$, we see that $\bar{\tau} \mapsto \bar{U}_n(\bar{\tau})$ is decreasing and $\bar{\tau} \mapsto \bar{U}_0(\bar{\tau})$ is increasing. Indeed,

$$\mu_n \frac{\partial \bar{U}_n}{\partial \bar{\tau}} = h e^{-\bar{\tau}} \left(1 - \frac{\delta}{r}\right) \left[-(HK)(\bar{U}_n(\bar{\tau})) + (HK)'(\bar{U}_n(\bar{\tau})) \frac{\partial \bar{U}_n}{\partial \bar{\tau}} \right].$$

Then, we obtain

$$\frac{\partial \bar{U}_n}{\partial \bar{\tau}} = - \frac{h e^{-\bar{\tau}} \left(1 - \frac{\delta}{r}\right) (HK)(\bar{U}_n(\bar{\tau}))}{\mu_n - h e^{-\bar{\tau}} \left(1 - \frac{\delta}{r}\right) (HK)'(\bar{U}_n(\bar{\tau}))}.$$

As both functions K and H are positive and decreasing, $\bar{\tau} \mapsto \bar{U}_n(\bar{\tau})$ is a decreasing function of $\bar{\tau} = \mu\tau$ with $\lim_{\bar{\tau} \rightarrow \infty} \bar{U}_n(\bar{\tau}) = 0$. Furthermore, for $\bar{U}_0 := \bar{U}_0(\bar{\tau})$, we have

$$\frac{\partial \bar{U}_0}{\partial \bar{\tau}} = \left(1 - \frac{\delta}{r}\right) K'(\bar{U}_n(\bar{\tau})) \frac{\partial \bar{U}_n}{\partial \bar{\tau}}.$$

So $\bar{\tau} \mapsto \bar{U}_0(\bar{\tau})$ is increasing with respect to $\bar{\tau}$ and $\lim_{\bar{\tau} \rightarrow \infty} \bar{U}_0(\bar{\tau}) = (1 - \frac{\delta}{r}) K(0)$. As a consequence, we have for all $\bar{\tau} = \mu\tau \geq 0$ the uniform bounds

$$0 < \bar{U}_0(\bar{\tau}) < \left(1 - \frac{\delta}{r}\right) K_0 \quad \text{and} \quad 0 < \bar{U}_n(\bar{\tau}) < \Lambda := \frac{h}{\mu_n} \left(1 - \frac{\delta}{r}\right) H_0 K_0,$$

with $K_0 := K(0)$ and $H_0 := H(0)$. Note that more subtle bounds can be given by

$$\bar{U}_n(\bar{\tau}) \leq \frac{he^{-\bar{\tau}}}{\mu_n} \left(1 - \frac{\delta}{r}\right) H_0 K_0,$$

and

$$0 < \left(1 - \frac{\delta}{r}\right) K \left(\frac{he^{-\bar{\tau}}}{\mu_n} \left(1 - \frac{\delta}{r}\right) H_0 K_0\right) \leq \bar{U}_0(\bar{\tau}) < \left(1 - \frac{\delta}{r}\right) K_0.$$

□

4.1.3 Stability of the steady states

Now we are ready to study the stability of the identified equilibrium points. The objective of this section is to determine under which conditions (if any) stability can be lost and the possibility of existence of Hopf bifurcations for the positive equilibrium.

We will give results concerning local stability, hence we are restrained in studying the stability of the linear system around a steady state.

The linearized system around an equilibrium $(\bar{U}_0, \bar{U}_n) = (\bar{U}_0(\bar{\tau}), \bar{U}_n(\bar{\tau}))$ is given by

$$\begin{cases} x'_0(t) &= \left[r - \delta - 2r \frac{\bar{U}_0}{K(\bar{U}_n)} \right] x_0(t) + r \bar{U}_0^2 \frac{K'(\bar{U}_n)}{K^2(\bar{U}_n)} x_n(t), \\ x'_n(t) &= -\mu_n x_n(t) + he^{-\bar{\tau}} H(\bar{U}_n) x_0(t - \tau) + he^{-\mu\tau} \bar{U}_0 H'(\bar{U}_n) x_n(t - \tau). \end{cases}$$

This delay system has the form

$$X'(t) = A_{\bar{\tau}} X(t) + B_{\bar{\tau}} X(t - \tau),$$

with

$$A_{\bar{\tau}} := \begin{pmatrix} r - \delta - 2r \frac{\bar{U}_0}{K(\bar{U}_n)} & r \bar{U}_0^2 \frac{K'(\bar{U}_n)}{K^2(\bar{U}_n)} \\ 0 & -\mu_n \end{pmatrix}$$

and

$$B_{\bar{\tau}} := he^{-\bar{\tau}} \begin{pmatrix} 0 & 0 \\ H(\bar{U}_n) & \bar{U}_0 H'(\bar{U}_n) \end{pmatrix}.$$

We have the following result concerning asymptotic stability of the trivial equilibrium. This result is independent of the parameters μ and τ .

Proposition 14. *If $\delta > r$ the trivial equilibrium is locally asymptotically stable and when $\delta < r$ it is unstable. Moreover, if*

$$\delta \geq r$$

the trivial equilibrium is globally attractive, in the sense that the solutions of the non-linear system (4.6) converge to 0 when $t \rightarrow +\infty$ independently of the initial conditions.

Proof. The characteristic equation is given by

$$\Delta_\tau(\lambda) := \det(\lambda I - A_{\bar{\tau}} - e^{-\tau\lambda} B_{\bar{\tau}}) = 0.$$

For the trivial equilibrium $(\bar{U}_0, \bar{U}_n) = (0, 0)$, we have

$$A_{\bar{\tau}} := \begin{pmatrix} r - \delta & 0 \\ 0 & -\mu_n \end{pmatrix} \quad \text{and} \quad B_{\bar{\tau}} := h e^{-\bar{\tau}} \begin{pmatrix} 0 & 0 \\ H_0 & 0 \end{pmatrix}.$$

The eigenvalues are $\lambda = -(\delta - r)$ and $\lambda = -\mu_n < 0$. For $\delta > r$, the trivial steady state is locally asymptotically stable and for $\delta < r$ the eigenvalue is positive, hence the equilibrium is unstable. In fact, we can see from (4.6) that for $\delta > r$, the trivial equilibrium is globally attractive. Indeed, if (U_0, U_n) is any solution of (4.6), then the first equation of (4.6) implies

$$U_0(t) \leq U_0(0) e^{-(\delta-r)t} \rightarrow 0,$$

and from the second equation, we obtain

$$U_n(t) \leq e^{-\mu_n t} U_n(0) + h e^{-(\mu+r-\delta)\tau} H_0 U_0(0) \frac{e^{-\mu_n t} - e^{-(\delta-r)t}}{\delta - r - \mu_n} \rightarrow 0.$$

We conclude that for $\delta > r$, the trivial equilibrium is globally attractive.

When $\delta = r$, for nonnegative initial data, $U_0 \geq 0$ and $U_0'(t) \leq -r \frac{U_0(t)^2}{K_0}$. Therefore (excluding the case $r = 0$), $\lim_{t \rightarrow +\infty} U_0 = 0$. As a consequence, the source term for U_n vanishes and we also have $\lim_{t \rightarrow +\infty} U_n = 0$. Note that in the case $r > 0$, $r - \delta > 0$ and $U_0(0) > 0$, we can establish the following bound

$$\limsup_{t \rightarrow +\infty} U_0(t) \leq K_0 \left(1 - \frac{\delta}{r} \right).$$

Indeed, from the ODE over U_0 we get that

$$\frac{dU_0}{dt} \leq r \left(1 - \frac{\delta}{r} - \frac{U_0}{K_0} \right) U_0.$$

For $U_0 \geq K_0(1 - \frac{\delta}{r})$, the function U_0 is decreasing. So, the inequality holds. It is then easy to establish (sequentially) the following bounds

$$\limsup_{t \rightarrow +\infty} U_n(t) \leq R := \frac{h}{\mu_n} H_0 K_0 \left(1 - \frac{\delta}{r} \right) e^{-\bar{\tau}},$$

$$\liminf_{t \rightarrow +\infty} U_0(t) \geq K \left(\limsup_{t \rightarrow +\infty} U_n(t) \right) \left(1 - \frac{\delta}{r} \right) \geq K(R) \left(1 - \frac{\delta}{r} \right) > 0,$$

and

$$\liminf_{t \rightarrow +\infty} U_n(t) \geq \frac{h}{\mu_n} H(R) K(R) \left(1 - \frac{\delta}{r} \right) e^{-\bar{\tau}} > 0.$$

This establishes persistence in the case $r > \delta$. \square

4.1.4 Positive equilibrium

Let (\bar{U}_0, \bar{U}_n) be the positive equilibrium given, for $r > \delta$, by Proposition 13. The matrix $A_{\bar{\tau}}$ becomes

$$A_{\bar{\tau}} := \begin{pmatrix} -(r - \delta) & r(1 - \delta/r)^2 K'(\bar{U}_n) \\ 0 & -\mu_n \end{pmatrix},$$

with $\bar{\tau} = \mu\tau$. Then, the characteristic equation becomes

$$\Delta_{\tau}(\lambda) := \begin{vmatrix} \lambda + r - \delta & -r(1 - \delta/r)^2 K'(\bar{U}_n) \\ -he^{-\bar{\tau}} H(\bar{U}_n) e^{-\lambda\tau} & \lambda + \mu_n - he^{-\bar{\tau}} \bar{U}_0(\tau) H'(\bar{U}_n) e^{-\lambda\tau} \end{vmatrix} = 0. \quad (4.9)$$

This is a transcendental equation whose coefficients depend on the delay. The general case of such type of equations is studied in [3] whereas an equation of the same form as (4.9) is studied in [30]. To determine the local asymptotic stability of (\bar{U}_0, \bar{U}_n) , we are interested in the sign of the real part of the roots of $\Delta_{\tau}(\lambda) = 0$. Following the remark above which concerns the dependence on $\bar{\tau} := \mu\tau$, the characteristic equation is written like

$$(\lambda + r - \delta)(\lambda + \mu_n + q_{\bar{\tau}} e^{-\lambda\tau}) + C_{\bar{\tau}} e^{-\lambda\tau} = 0. \quad (4.10)$$

with

$$q_{\bar{\tau}} = -he^{-\bar{\tau}} \bar{U}_0(\bar{\tau}) H'(\bar{U}_n(\bar{\tau})) = -\mu_n \frac{\bar{U}_n(\bar{\tau}) H'(\bar{U}_n(\bar{\tau}))}{H(\bar{U}_n(\bar{\tau}))} \geq 0 \quad (4.11)$$

and

$$C_{\bar{\tau}} = -he^{-\bar{\tau}} r \left(1 - \frac{r}{\delta} \right)^2 H(\bar{U}_n(\bar{\tau})) K'(\bar{U}_n(\bar{\tau})) = -(r - \delta) \mu_n \frac{\bar{U}_n(\bar{\tau}) K'(\bar{U}_n(\bar{\tau}))}{K(\bar{U}_n(\bar{\tau}))} \geq 0. \quad (4.12)$$

Observe that since $q_{\bar{\tau}} \geq 0$, $C_{\bar{\tau}} \geq 0$, $\mu_n > 0$ and $r - \delta > 0$, $\lambda = 0$ is not a solution of (4.10). In the case of the functions H and K are both constant, $H'(U_n) = K'(U_n) = 0$, the stability analysis is straightforward (the only eigenvalues are $\delta - r$ and $-\mu_n$ and they are negative).

A crucial point is that from the expressions (4.11) and (4.12), we can see the parameters $q_{\bar{\tau}} \geq 0$ and $C_{\bar{\tau}} \geq 0$ directly as functions of \bar{U}_n . In addition, $\bar{\tau} \mapsto \bar{U}_n(\bar{\tau})$ is monotone and bijective function (see the expression of the equilibrium). So we can express $q := q_{\bar{\tau}} = q(\bar{U}_n)$ and $C := C_{\bar{\tau}} = C(\bar{U}_n)$ as functions of \bar{U}_n .

We will perform the stability analysis for μ and τ varying parameters. Keeping τ fixed, the monotone bijection between $\mu\tau$ and \bar{U}_n becomes a monotone bijection between

μ and \bar{U}_n . So we can determine the stability chart in the space (μ, τ) or in $(\frac{1}{\bar{U}_n}, \tau)$. Note that we could have also considered the coordinate space (\bar{U}_n, τ) instead of $(\frac{1}{\bar{U}_n}, \tau)$ but since \bar{U}_n decreases when μ increases, we prefer $\frac{1}{\bar{U}_n}$ so that the horizontal axis changes in the same way in both spaces and points of intersection are equally ordered. In what follows, we distinguish two cases:

- The case where K is independent of U_n , so $C = 0$, and the equation that we have to study has the form:

$$\lambda + \mu_n + q(\bar{U}_n)e^{-\lambda\tau} = 0.$$

- The case where K depends on \bar{U}_n and $K' < 0$.

In both cases the characteristic equation can be written:

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0. \quad (4.13)$$

where P, Q are polynomials of the second and first degree respectively whose coefficients are real, nonnegative and depend on \bar{U}_n (so on $\bar{\tau} = \mu\tau$ as well).

This guides our analysis to study the stability on the curves where the value of $\bar{\tau} := \mu\tau$ is constant but τ varies. Stability changes are fully described by the purely imaginary solutions of the characteristic equation (4.10) [41]. In what follows, the reader should keep in mind that when we differentiate with respect to τ , we will in general mean a partial derivative where r, δ, μ_n, h and $\bar{\tau}$ (so \bar{U}_n as well) are kept constant.

4.1.5 Case of constant carrying capacity K

In this section, we study the case $K(\bar{U}_n) = K_0$ constant with the positive equilibrium (\bar{U}_0, \bar{U}_n) given by

$$\mu_n \bar{U}_n = K_0 h e^{-\mu\tau} \left(1 - \frac{\delta}{r}\right) H(\bar{U}_n) \quad \text{and} \quad \bar{U}_0 = \left(1 - \frac{\delta}{r}\right) K_0.$$

With the previous notations $C = 0$ in that case and the characteristic equation becomes

$$\Delta_\tau(\lambda) := (\lambda + r - \delta)(\lambda + \mu_n + q(\bar{U}_n)e^{-\lambda\tau}) = 0.$$

Then, $\lambda = -(r - \delta) < 0$ is an eigenvalue. The other eigenvalues are roots of

$$\lambda + \mu_n + q(\bar{U}_n)e^{-\lambda\tau} = 0. \quad (4.14)$$

We remark that if $r > \delta$, we always have

$$\lim_{t \rightarrow +\infty} U_0(t) = \bar{U}_0 := \left(1 - \frac{\delta}{r}\right) K_0.$$

Nevertheless, the component U_n can oscillate periodically around \bar{U}_n . Indeed, in (4.14) we have

$$\mu_n > 0 \quad \text{and} \quad q(\bar{U}_n) = -\mu_n \frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)} \geq 0,$$

because H is decreasing and $r > \delta$.

We fix the parameter $\bar{\tau} \geq 0$ and we choose the parameter μ such that $\tau\mu = \bar{\tau}$. On the curve $\mu\tau = \bar{\tau}$, $\bar{U}_n = \bar{U}_n(\bar{\tau})$ is constant and the characteristic equation can be seen as

$$\lambda + \mu_n + q(\bar{U}_n)e^{-\lambda\tau} = 0. \quad (4.15)$$

Note that for fixed \bar{U}_n , if $\tau = 0$, the equation (4.15) has only one root $\lambda = -(\mu_n + q(\bar{U}_n))$ which is negative. For $\bar{\tau}$ fixed, the standard Hayes theorem allows us to define the stability boundary depending on \bar{U}_n . We prove the following lemma that can be found as Theorem 2.5 in [4]. It is also adapted from the general Hayes theorem [41].

Lemma 10. *Suppose that*

$$\frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)} \geq -1$$

(which is equivalent to $\mu_n \geq q(\bar{U}_n)$), or if

$$\frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)} < -1, \quad \text{and} \quad \tau < \tau^*(\bar{U}_n) = \frac{\arccos\left(\frac{H(\bar{U}_n)}{\bar{U}_n H'(\bar{U}_n)}\right)}{\sqrt{\mu_n^2 \left(\left(\frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)}\right)^2 - 1 \right)}},$$

then (4.14) has no roots with positive real part. If $\mu_n < q(\bar{U}_n)$ and $\tau > \tau^*(\bar{U}_n)$, then there exist roots with positive real part.

Consequently, on any curve $\mu\tau = \bar{\tau}$ we fully describe the stability.

Corollary 3. *Let μ, τ be given. Then $\mu\tau = \bar{\tau}$ for some $\bar{\tau}$. The steady state corresponding to this specific μ and τ is stable if $\mu_n \geq q(\bar{U}_n(\bar{\tau}))$ or if $\mu_n < q(\bar{U}_n(\bar{\tau}))$ and $\tau < \tau^*(\bar{U}_n(\bar{\tau}))$. It is linearly unstable if $\mu_n < q(\bar{U}_n(\bar{\tau}))$ and $\tau > \tau^*(\bar{U}_n(\bar{\tau}))$.*

We remark that for stability to be lost, q has to take the value μ_n .

In general $\bar{\tau} \mapsto q(\bar{\tau})$ is not explicit but as soon as H is C^1 on $[0, +\infty)$ we can claim that $\lim_{\infty} q = 0$. Indeed $\bar{U}_n(\bar{\tau}) \rightarrow 0$ as $\bar{\tau} \rightarrow +\infty$. Therefore, there exists an interval $[\bar{\tau}^*, +\infty[$ where $q(\bar{\tau}) \leq \mu_n$ and stability is guaranteed for $\tau \geq \bar{\tau}^*/\mu$. In particular, if $\bar{\tau}^* = 0$, then, the steady state is stable everywhere. Also, in the case $\bar{\tau}^* > 0$ and for a fixed μ , this gives a lower bound for the stability region.

Some simple choices for H . We give now a few examples that will help us categorize the functions. Note that if we assume H to be differentiable at 0, then a sufficiently small steady state (that is a \bar{U}_n under a certain threshold) is always stable since $xH'(x)/H(x) \rightarrow 0$ at 0.

Function	$H(x)$	$1 + \frac{xH'(x)}{H(x)}$	Possible instability
Exponential	$e^{-\lambda x}$	$1 - \lambda x$	$x \geq 1/\lambda$
Hill type	$\frac{\theta^n}{\theta^n + x^n}$	$\frac{\theta^n + (1-n)x^n}{\theta^n + x^n}$	none if $n = 1$, $x \geq \theta(n-1)^{-\frac{1}{n}}$ otherwise
adhoc	(4.16)	$\frac{(x-1)(x-3)}{1+2(x-1)^2}$	$x \in]1, 3[$

Concerning the adhoc function we built a function based on the formula:

$$\frac{H'(x)}{H(x)} = -\frac{x}{1 + 2(x-1)^2}.$$

whose possible domain of instability is a bounded interval in contrast to both the exponential and the Hill type. In particular:

$$1 + \frac{xH'(x)}{H(x)} = \frac{1 + 2(x-1)^2 - x^2}{1 + 2(x-1)^2} = \frac{(x-1)(x-3)}{1 + 2(x-1)^2}.$$

Note that this leads to the formula:

$$H(x) = C_0 \frac{e^{-\frac{\arctan(\sqrt{2}(x-1))}{\sqrt{2}}}}{(1 + 2(x-1)^2)^{1/4}} \quad (4.16)$$

where C_0 is some constant that we propose to fix at 1, so that $H(1) = 1$.

The graphs giving the stability regions of these functions are given in figures 4.1 and 4.2.

Stability boundary

The major difficulty when we want to determine the stability status in terms of the parameters is that it demands a preliminary computation of \bar{U}_n . This means that we have to solve the fixed point equation to find \bar{U}_n .

We can though use an approach where computation of \bar{U}_n can be avoided. Indeed we consider the parameters h, μ_n, r, δ fixed and we determine the stability regions in the coordinates τ, μ . The procedure is the following:

- Find the region(s) where $1 + \frac{xH'(x)}{H(x)} < 0$ (demands reasonable calculations in general). Suppose that it is an interval I .
- Draw the curve $\bar{U}_n \mapsto (\mu^*(\bar{U}_n), \tau^*(\bar{U}_n))$ on I . The first component is defined above. The second can be found using the fixed point equation and solving for μ , so that

$$\mu^*(U) = \frac{1}{\tau^*(U)} \log \left(\frac{h(1 - \frac{\delta}{r}) KH(U)}{\mu_n U} \right).$$

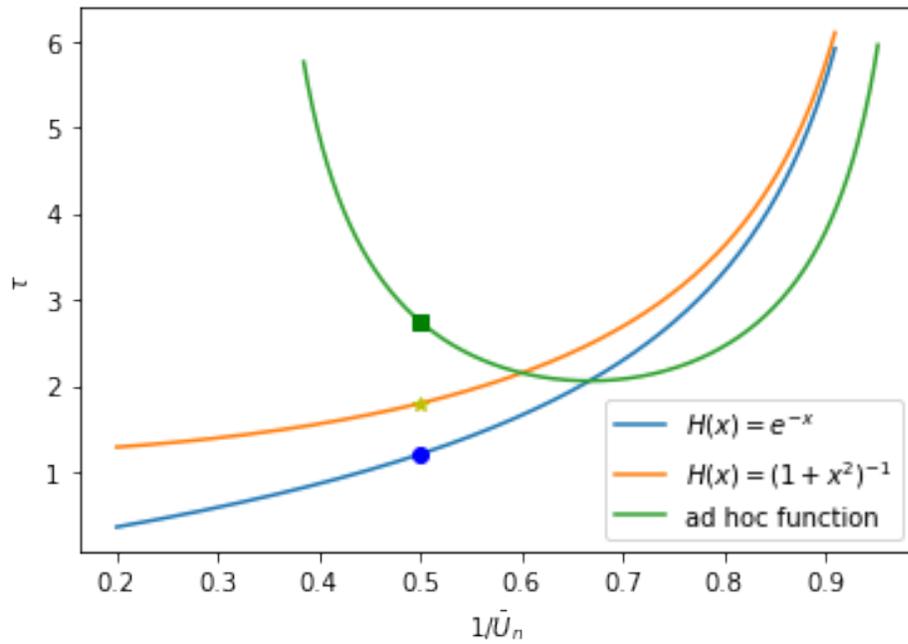


Figure 4.1: stability boundary for 3 functions (stable region below the curve), represented in the coordinates $(\frac{1}{U_n}, \tau)$.

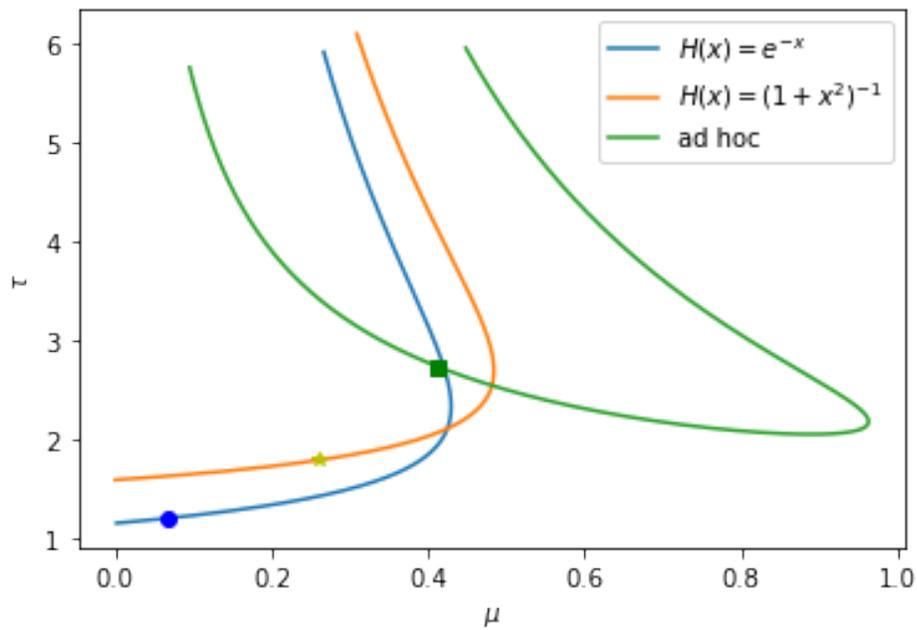


Figure 4.2: stability boundary for 3 functions (stable region on the right), represented in the coordinates (μ, τ) .

Remark In the graphs above we also exhibit three points on the curves corresponding to the same \bar{U}_n . We observe that for the same \bar{U}_n the values of μ are different because the function H in the expression of μ changes.

4.1.6 Varying K

We suppose that the functions K and H are continuously differentiable and decreasing. We consider again the characteristic equation which can be written as

$$0 = \lambda^2 + (r - \delta + \mu_n)\lambda + (r - \delta)\mu_n + \mu_n \bar{U}_n e^{-\lambda\tau} \left(\lambda \left(-\frac{H'(\bar{U}_n)}{H(\bar{U}_n)} \right) + (r - \delta) \left(-\frac{H'(\bar{U}_n)}{H(\bar{U}_n)} - \frac{K'(\bar{U}_n)}{K(\bar{U}_n)} \right) \right). \quad (4.17)$$

For the sake of simplicity we use notations:

$$(h', k') = \left(-\frac{\bar{U}_n H'(\bar{U}_n)}{H(\bar{U}_n)}, -\frac{\bar{U}_n K'(\bar{U}_n)}{K(\bar{U}_n)} \right),$$

and $\tilde{r} = r - \delta$.

Note that for $k' = 0$, we find again that the solutions of (4.17) are both $-\tilde{r}$ and the solutions of (4.14). Let us first look for roots of (4.17) by considering h' and k' fixed. In that way we dissociate the value of \bar{U}_n from that of τ as we did in the case $K' = 0$.

$$\lambda^2 + (\tilde{r} + \mu_n)\lambda + \tilde{r}\mu_n + \mu_n e^{-\lambda\tau}(\lambda h' + \tilde{r}(h' + k')) = 0. \quad (4.18)$$

We investigate the possibility of (4.18) to have purely imaginary solutions $i\omega$. By replacing $\lambda = i\omega$ and taking modules, we find that a necessary condition is to have a root of the polynomial:

$$(\tilde{r}\mu_n - \omega^2)^2 + \omega^2(\tilde{r} + \mu_n)^2 - \mu_n^2(\omega^2 h'^2 + \tilde{r}^2(h' + k')^2) = 0.$$

We see that expression as the value of R at ω^2 :

$$\begin{aligned} R(X) &= X^2 - (2\tilde{r}\mu_n - (\tilde{r} + \mu_n)^2 + \mu_n^2 h'^2) X + \mu_n^2 \tilde{r}^2 (1 - (h' + k')^2), \\ &= X^2 - ((\mu_n^2(h'^2 - 1) - \tilde{r}^2) X + \mu_n^2 \tilde{r}^2 (1 - (h' + k')^2)). \end{aligned}$$

We are only interested in the nonnegative roots of R .

Lemma 11. *Assume $h', k' \geq 0$, Consider the polynomial R .*

- *If $(h' + k') > 1$ R admits exactly one positive root $x_1 = \omega_1^2$, with*

$$\omega_1 = \sqrt{\frac{1}{2} \left[\mu_n^2(h'^2 - 1) - \tilde{r}^2 + \sqrt{(\mu_n^2(h'^2 - 1) - \tilde{r}^2)^2 + 4\mu_n^2 \tilde{r}^2((k' + h')^2) - 1} \right]}. \quad (4.19)$$

- otherwise there is no positive root of R .

Moreover, going back to (4.18), we can claim:

- If $h' + k' \leq 1$, then (4.18) has no solutions with nonnegative real part (for any τ),
- If $h' + k' > 1$, then (4.18) admits solutions with positive real part if and only if $\tau > \tau^*$, where

$$\tau^* = \frac{\arccos\left(\frac{\mu_n \tilde{r} k' (\omega_1^2 - \mu_n \tilde{r}) - \mu_n^2 h' (\omega_1^2 + \tilde{r}^2)}{\mu_n^2 \tilde{r}^2 (k' + h')^2 + \mu_n^2 h'^2 \omega_1^2}\right)}{\omega_1}, \quad (4.20)$$

and ω_1 is given by (4.19).

Proof. Step 1: roots of R .

Assume $h' + k' > 1$, then the constant term $R(0)$ is negative so the product of the roots is negative leading to only one possible configuration: one positive and one negative root of R . Since we are looking for solutions in ω^2 only the positive one is accepted.

As far as the expression of the solution is concerned, we have to solve $R(X) = 0$ and the solution, say X_1 , will be equal to $\omega_1^2 = X_1$.

$R(\omega^2) = 0$ with the above notations gives:

$$\omega^4 - (\mu_n^2 (h'^2 - 1) - \tilde{r}^2) \omega^2 + \mu_n^2 \tilde{r}^2 (1 - (k' + h')^2) = 0.$$

The acceptable solution satisfies :

$$\omega_1^2 = \frac{1}{2} \left(\mu_n^2 (h'^2 - 1) - \tilde{r}^2 + \sqrt{(\mu_n^2 (h'^2 - 1) - \tilde{r}^2)^2 + 4\mu_n^2 \tilde{r}^2 ((k' + h')^2 - 1)} \right), \quad (4.21)$$

and we obtain (4.19) by taking the square root. For the second case $h' + k' \leq 1$, if $i\omega$ is a solution, then by taking modules in the characteristic equation, R can be written as:

$$\begin{aligned} R(X) &= (X + \tilde{r}^2)(X + \mu_n^2) - \mu_n^2 (X h'^2 + \tilde{r}^2 (h' + k')^2) \\ &= (X + \tilde{r}^2)(X + \mu_n^2 (1 - (h' + k')^2)) + \mu_n^2 ((h' + k')^2 - h'^2) X, \end{aligned}$$

Such a factorization immediately shows that in the case $h' + k' \leq 1$ R is nonnegative on \mathbb{R}_+ . This ends step 1.

Step 2: computing τ^* .

Now to determine τ^* the critical delay where stability is lost, we have to go back to the equation (4.18), replace $\lambda = i\omega$, keeping in mind that $\omega = \omega_1(\bar{U}_n)$, and separate real and imaginary parts to get:

$$\begin{cases} \mu_n \tilde{r} (k' + h') \cos(\omega\tau) + \mu_n h' \omega \sin(\tau\omega) &= \omega^2 - \mu_n \tilde{r}, \\ -\mu_n h' \omega \cos(\omega\tau) + \mu_n \tilde{r} (k' + h') \sin(\tau\omega) &= (\mu_n + \tilde{r}) \omega. \end{cases}$$

Then, we obtain

$$\begin{cases} \sin(\omega\tau) = \frac{1}{(\mu_n^2 \tilde{r}^2 (k'+h')^2 + (\mu_n h')^2 \omega^2)} (\mu_n \tilde{r} (k'+h') (\mu_n + \tilde{r}) \omega + \mu_n h' \omega (\omega^2 - \mu_n \tilde{r})) = h_1(\omega), \\ \cos(\omega\tau) = \frac{1}{(\mu_n^2 \tilde{r}^2 (k'+h')^2 + (\mu_n h')^2 \omega^2)} (\mu_n \tilde{r} (k'+h') (\omega^2 - \mu_n \tilde{r}) - (\mu_n + \tilde{r}) \mu_n h' \omega^2) = h_2(\omega). \end{cases} \quad (4.22)$$

As $\omega = \omega_1(\bar{U}_n) \geq 0$

$$h_1 = \frac{\omega \mu_n}{(\mu_n^2 \tilde{r}^2 (k'+h')^2 + (\mu_n h')^2 \omega^2)} (\tilde{r} k' (\mu_n + \tilde{r}) + h' (\omega^2 + \tilde{r}^2)) \geq 0.$$

So $\sin(\omega\tau) > 0$ entails $\omega\tau \in (0, \pi) + 2\pi\mathbb{N}$.

Solve for h_2

$$h_2 = \frac{1}{(\mu_n^2 \tilde{r}^2 (k'+h')^2 + (\mu_n h')^2 \omega^2)} (\mu_n \tilde{r} k' (\omega^2 - \mu_n \tilde{r}) - h' \mu_n^2 (\omega^2 + \tilde{r}^2)),$$

Note that for $k' = 0$ we obtain $h_2 = -\frac{1}{h'}$. Therefore, the solutions are given by

$$\omega_1 \tau_k = \arccos(h_2(\omega_1)) + 2k\pi, k \in \mathbb{N},$$

The first time of destabilization τ^* corresponds to $k = 0$.

Step 3: The fact that there is a unique solution ω_1 permits us to give a stability criterion for all cases. We will show that the sign of

$$\left. \frac{d\Re(\lambda)}{d\tau} \right|_{\tau_k}$$

is the same for all positive $\tau_k, k \in \mathbb{N}$. To initiate our reasoning, we notice that for $\tau = 0$, (4.18) has two solutions both with negative real part (since the sum of the roots is negative and the product positive). Secondly, (4.18) can be written in the form

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0,$$

with P is a polynomial of degree 2 and Q of degree $\leq 1 < \deg(P)$. We have already established that purely imaginary solutions exist only for $\tau = \tau_k$ so we know that the number of solutions of (4.18) with nonnegative real parts does not change in the intervals $]\tau_k, \tau_{k+1}[$. The sign of $\Re(\lambda')$ allows us to establish that it increases at every crossing, preventing the loss of roots with nonnegative real part. Let us prove this sign property. Consider a curve $\tau \mapsto \lambda(\tau)$ that crosses the imaginary axis. We already know that this happens at $\tau = \tau_k$ for some k and $\lambda(\tau_k) = i\omega_1$.

Take the derivative of the characteristic equation at τ_k . Since we have

$$P(\lambda(\tau)) + Q(\lambda(\tau))e^{-\lambda(\tau)\tau} = 0,$$

then:

$$\lambda'(\tau) (P'(\lambda) + Q'(\lambda)e^{-\lambda\tau} - Q(\lambda)\tau e^{-\lambda\tau}) - \lambda Q(\lambda)e^{-\lambda\tau} = 0.$$

At $\tau = \tau_k$, $\lambda Q(\lambda) = i\omega_1 Q(i\omega_1) \neq 0$. In particular this ensures that $\lambda'(\tau_k) \neq 0$. Multiplying by $\bar{Q}(i\omega_1)e^{+i\omega_1\tau_k} = -\bar{P}(i\omega_1)$ leads to

$$\lambda'(\tau_k)(-P'(i\omega_1)\bar{P}(i\omega_1) + Q'(i\omega_1)\bar{Q}(i\omega_1) - \tau_k|Q(i\omega_1)|^2) = i\omega_1|Q(i\omega_1)|^2.$$

Now, since the polynomials have real coefficients, it is worth noticing that

$$\begin{aligned} \frac{d}{d\omega}|P(i\omega)|^2 &= \frac{d}{d\omega}P(i\omega)P(-i\omega) \\ &= i(P'(i\omega)P(-i\omega) - P(i\omega)P'(-i\omega)) \\ &= -2\text{Im}(P'(i\omega)P(-i\omega)) \\ &= -2\text{Im}(P'(i\omega)P(\bar{i}\omega)) \end{aligned}$$

Therefore, we have

$$\text{Im}(-P'(i\omega_1)\bar{P}(i\omega_1) + Q'(i\omega_1)\bar{Q}(i\omega_1)) = \frac{1}{2} \frac{d}{d\omega}(|P(i\omega)|^2 - |Q(i\omega)|^2).$$

Since by construction we have $|P(i\omega)|^2 - |Q(i\omega)|^2 = R(\omega^2)$, we can claim

$$\frac{d}{d\omega}(|P(i\omega)|^2 - |Q(i\omega)|^2) = 2\omega R'(\omega^2).$$

Finally, since in the case $h' + k' > 1$ and ω_1 is the largest root of the second degree polynomial R , we have $R'(\omega_1^2) > 0$. Altogether, this ensures that $D(i\omega_1) = (-P'(i\omega_1)\bar{P}(i\omega_1) + Q'(i\omega_1)\bar{Q}(i\omega_1) - \tau_k|Q(i\omega_1)|^2) \neq 0$. We divide and get:

$$\lambda'(\tau_k) = i \frac{\omega_1|Q(i\omega_1)|^2}{|D(i\omega_1)|^2} \bar{D}(i\omega_1).$$

So that $\text{Re}(\lambda'(\tau_k))$ has the sign of $+\text{Im}(D(i\omega_1))$. Since

$$\begin{aligned} \text{Im}(D(i\omega_1)) &= \text{Im}(-P'(i\omega_1)\bar{P}(i\omega_1) + Q'(i\omega_1)\bar{Q}(i\omega_1) - \tau_k|Q(i\omega_1)|^2) \\ &= \text{Im}(-P'(i\omega_1)\bar{P}(i\omega_1) + Q'(i\omega_1)\bar{Q}(i\omega_1)) \\ &= \frac{1}{2} \frac{d}{d\omega}(|P(i\omega)|^2 - |Q(i\omega)|^2)|_{\omega_1} > 0, \end{aligned}$$

we can conclude

$$\forall k \in \mathbb{N}, \quad \lambda'(\tau_k) > 0. \quad (4.23)$$

This ends the last step and the proof of the lemma. \square

Some choices for H, K For the general case $K' \neq 0$ we choose H, K such that:

$$HK = F.$$

A possible choice is $H(x) = F^\alpha(x)$ and $K(x) = F^{1-\alpha}(x)$ for $\alpha \in [0, 1]$. If we note $f' = -\bar{U}_n \frac{F'(\bar{U}_n)}{F(\bar{U}_n)}$ this implies:

$$\begin{cases} h' = \alpha f', \\ k' = (1 - \alpha) f'. \end{cases}$$

Then we study the following cases:

1. $F(x) = e^{-\lambda x}$,
2. $F(x) = \frac{\theta^n}{\theta^n + x^n}$,
3. $F(x) = C_0 \frac{e^{-\frac{1}{\sqrt{2}} \arctan(\sqrt{2}(x-1))}}{(1+2(x-1)^2)^{1/4}}$. Again we take $C_0 = 1$ so that $F(1) = 1$.

- The $\alpha = 1$ is already treated in the previous section.
- $\alpha = 0.5$ In the following table we give the stability regions:

Function	$H(x)$	$K(x)$	$1 - h' - k'$	Possible instability
Exponential	$e^{-\lambda/2x}$	$e^{-\lambda/2x}$	$1 - \lambda x$	$x \geq 1/\lambda$
Hill type	$\sqrt{\frac{\theta^n}{\theta^n + x^n}}$	$\sqrt{\frac{\theta^n}{\theta^n + x^n}}$	$\frac{\theta^n + (1-n)x^n}{\theta^n + x^n}$	none if $n = 1$, $x \geq \theta(n-1)^{-\frac{1}{n}}$ otherwise
adhoc	(4.24)	(4.24)	$\frac{(x-1)(x-3)}{1+2(x-1)^2}$	$x \in (1, 3)$

The adhoc function mentioned above is given by the formula:

$$H(x) = K(x) = \frac{e^{-\frac{1}{2\sqrt{2}} \arctan(\sqrt{2}(x-1))}}{(1 + 2(x-1)^2)^{1/8}}. \quad (4.24)$$

- $\alpha = 0$. Corresponds to a constant H .

Function	$K(x)$	$1 + \frac{xK'(x)}{K(x)}$	Possible instability
Exponential	$e^{-\lambda x}$	$1 - \lambda x$	$x \geq 1/\lambda$
Hill type	$\frac{\theta^n}{\theta^n + x^n}$	$\frac{\theta^n + (1-n)x^n}{\theta^n + x^n}$	none if $n = 1$, $x \geq \theta(n-1)^{-\frac{1}{n}}$ otherwise
	(4.16)	$\frac{(x-1)(x-3)}{1+2(x-1)^2}$	$x \in]1, 3[$

Values of \bar{U}_n that can lead to instability depend only on F (not on α). This means that only the value of the boundary $\tau^*(\bar{U}_n)$ is affected by α .

Stability boundary

To plot the stability boundary we follow the same procedure as previously:

- Find the region(s) where $1 - h' - k' < 0$. Suppose that it is an interval I .
- Draw the curve $\bar{U}_n \mapsto (\mu^*(\bar{U}_n), \tau^*(\bar{U}_n))$ on I . The first component is defined above. The second can be found using the fixed point equation and solving for μ , so that

$$\mu^*(U) = \frac{1}{\tau^*(U)} \log \left(\frac{h(1 - \frac{\delta}{r}) K(U) H(U)}{\mu_n U} \right).$$

Hopf bifurcation

Note that for any $\bar{U}_n \in I$ there is a $\tau^*(\bar{U}_n)$ where stability is lost. In the coordinate space (μ, τ) if we also plot the curve $(\mu(s), \tau(s))$ with $\mu(s)\tau(s) = \text{constant} = \mu^*(\bar{U}_n)\tau^*(\bar{U}_n)$. Then the curve that is defined as:

$$s \in \mathbb{R}^+ \mapsto \left(\frac{\mu^*(\bar{U}_n)\tau^*(\bar{U}_n)}{s}, s \right).$$

crosses the critical curve since the real part of λ is positive as we proved above. Consequently a Hopf bifurcation occurs when $s = \tau^*(\bar{U}_n)$, see theorem 6.1 in [105].

Now we compare the graph of each function for the four values of $\alpha = 0, 0.2, 0.5, 1$, see figures 4.3, 4.4, 4.5. In the coordinate space $(\frac{1}{\bar{U}_n}, \tau(\bar{U}_n))$ the stable region is below the curve and in the coordinate space $(\mu(\bar{U}_n), \tau(\bar{U}_n))$ the stable region is on the right hand side of the curve.

- **Exponential** $F(x) = e^{-x}$

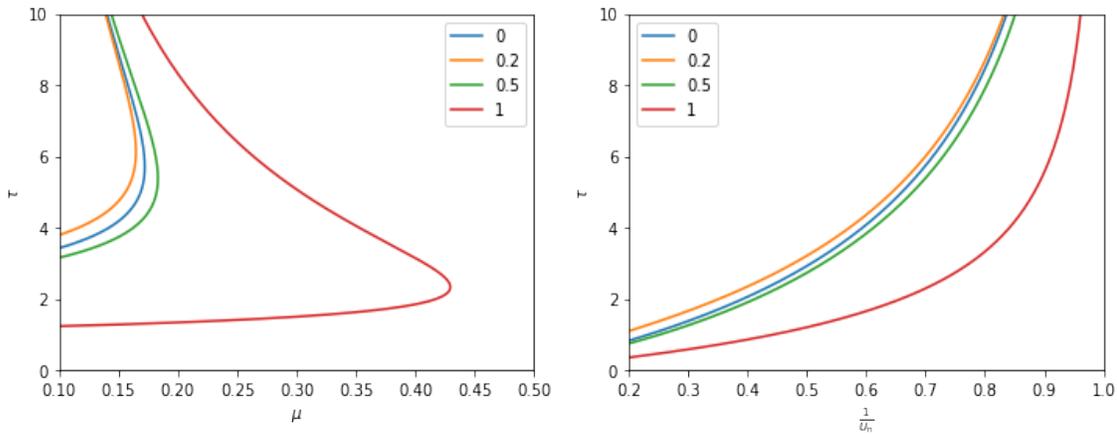


Figure 4.3: stability boundary for different values of α in the coordinates $(\mu(\bar{U}_n), \tau(\bar{U}_n))$ (stability on the right) and $(\frac{1}{\bar{U}_n}, \tau(\bar{U}_n))$ (stability below).

- **Hill type** $F(x) = \frac{1}{1+x^2}$

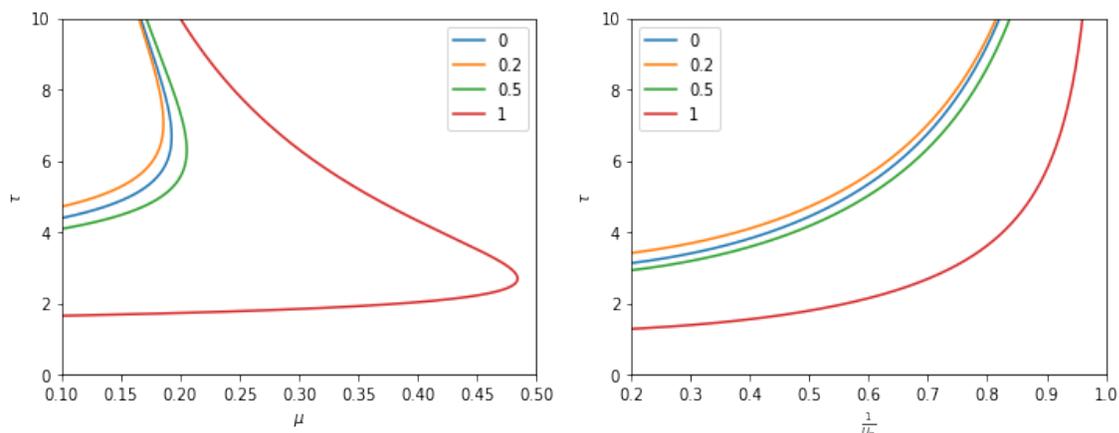


Figure 4.4: stability boundary for different values of α in the coordinates $(\mu(\bar{U}_n), \tau(\bar{U}_n))$ (stability on the right) and $(\frac{1}{\bar{U}_n}, \tau(\bar{U}_n))$ (stability below).

- **Functions:** $H(x)$ and $K(x)$ given by (4.24)

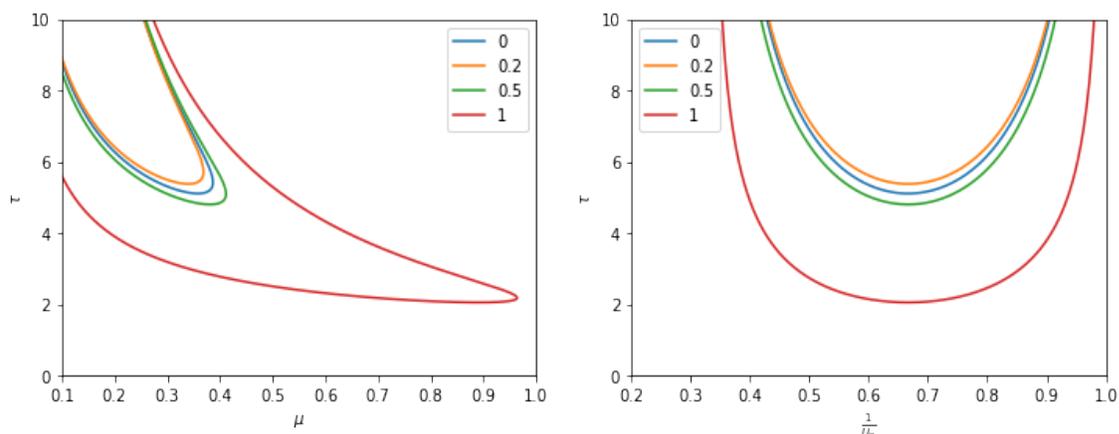


Figure 4.5: stability boundary for different values of α in the coordinates $(\mu(\bar{U}_n), \tau(\bar{U}_n))$ (stability below) and $(\frac{1}{\bar{U}_n}, \tau(\bar{U}_n))$ (stability below).

Concluding remarks If we plot only the values $\alpha = 0, \alpha = 0.5, \alpha = 1$ the curves seem to be in decreasing order with respect to α . But the value $\alpha = 0.2$ confirms that they are not ordered. This observation naturally raises the question of the best control.

4.2 Discussion

We have constructed and studied a system of delay differential equations that describe the process of hematopoiesis in the bone marrow. We consider that this process hap-

pens in discrete compartments, one for each differentiation level, and is regulated by a feedback control that induces time delays, τ_i for the i compartment, with a total delay $\tau = \sum_{i=1}^n \tau_i$. The dynamics depend on the delay which can make the system lose stability. When stability loss is associated to a Hopf bifurcation, then it could be related to the appearance of oscillations. Biologically they are interpreted as oscillations in the blood counts between low and high values, a situation leading to hematological diseases. We did the stability analysis of the steady states that depend on the delay τ . We provide a criterion to characterize any equilibrium point given the parameters of the system.

We prove that a Hopf bifurcation can appear and give the graphs of the stability boundary where the non trivial equilibrium loses stability. We also compare the behavior of this boundary for different choices of K, H when the two functions are related by:

$$HK = F.$$

We chose F either exponential, or Hill or an adhoc function that we constructed so as to have a bounded interval as a region of destabilization. From the above constraint we choose $H = F^\alpha$ and $K = F^{1-\alpha}$. By comparing the graphs for α increasing, we find that $\tau^*(\alpha)$ is not monotonic with respect to α and that the best control (in the sense most stabilizing) seems generally to be a combination of both feedback controls. For the moment we have no analytic results concerning the optimal combination (i.e. the optimal α). We have explored graphically some examples but the optimal control is to be determined at a future work.

Chapter 5

Conclusion-Perspectives

In this manuscript we have modeled three different biological phenomena, the process of hematopoiesis, the dynamics of chronic myeloid leukemia and of chronic lymphoid leukemia under treatment. The objective of our work was to study the stability of different population models described by partial differential equations and/or delay differential equations.

5.1 Summary of the chapters

5.1.1 Chapter 2: Summary and perspectives

In the CML chapter we have generalized a model of interaction between leukemia and immune system that has already been studied in [5]. The model variables in [5] were the leukemic stem cells, the leukemic mature cells and the immune cells. We have used a transport equation to describe maturation as a continuous process and we wanted to see how the dynamics change when maturation is taken into consideration. We have identified three types of equilibrium points, the disease free equilibrium (DFE), the remission equilibrium and the high steady states (high tumor load). Then we conducted the stability analysis of the steady states and we proved that the behavior is qualitatively the same as in [5] for the DFE and the high equilibria (a small difference is that with the ODE there exist only 2 high states whereas with the PDE any even number is possible). For the remission equilibrium that was always stable with the ODE model, the situation is different. The stability is given by the roots of the characteristic equation:

$$P(\lambda) + Q(\lambda) \int_0^{+\infty} e^{-\lambda x/g} \bar{p}(x) dx = 0,$$

with P a polynomial of degree 3 and Q a linear polynomial (which becomes a constant when $\mu_c = \mu_u$). Based on the distribution \bar{p} of the leukemic differentiated cells stability can be lost. When \bar{p} is a Dirac we have determined the boundary of stability loss. Then we investigated the possibility of using the Dirac to make conclusions for more

general distributions. In particular in [4] they have proved that when P is linear and Q a constant, the Dirac is the less stable distribution among all distributions with same mean. This means that whenever the Dirac is stable the other distributions are stable as well. This gives a minimum mean of the distribution for stability loss. In our case the Dirac does not have this optimal property. We construct as a counter example an unstable distribution whose mean is smaller than the mean of a stable Dirac. It is the sum of two Dirac masses. We can always find three, four or more (a countable number) of Dirac sums that destabilize. Finally we used parameters that have already been estimated in literature to find the possible time of destabilization and to estimate its orders of magnitude. Interestingly, without treatment no destabilization happened with our parameters, but under treatment destabilization happens at about 100 days more or less. This raises the question of interpretation of such a destabilization.

Perspectives The main questions that still need to be answered are the following:

- How many high equilibrium points can exist? What functions S can help us study the variations of F and the intersections with the bisector?
- Can we estimate the minimal mean age τ^* such that every distribution \bar{p} that satisfies $\int_0^{+\infty} x\bar{p}(x)dx < \tau^*$ would correspond to a stable steady state? (Note that we can have $\tau^* < \tau(\omega_+)$ where the right hand side corresponds to the best result given by the Dirac distribution).
- Can we characterize a distribution for which this age is reached? Is it continuous?
- What kind of destabilization do we observe? Is it convergence towards another equilibrium or is it a limit cycle or any other behavior that needs to be explained biologically?

That kind of questions remain unanswered and have to be investigated in some future work.

5.1.2 Chapter 3: Summary and concluding remarks

In the CLL chapter we have proposed and analyzed 4 PDE models of chronic lymphoid leukemia that describe the dynamics under treatment (ibrutinib) in particular the homing from blood to the lymph nodes and the proliferation of leukemic cells. The motivation was to understand how prolonged lymphocytocis works and to choose the model that is better adapted. We started with two models that consider the leukemic population as a whole and then we separated CLL-cells in two sub populations, resistant and sensitive to ibrutinib, in both cases. We find that the models of competition are more appropriate to describe dynamics and we give a biological interpretation of the stability results. The general conclusion is negative in the sense that a PDE model cannot give deeper insight into the dynamics than an ODE model (a possible model that gives the same conclusions is proposed by David Coulette, Emamanuel Grenier and Pierre Sujobert-work in progress). In general, with the ODE models of CLL we

need to determine whether in presence of a residual disease the volume of nodes decays or whether lymphadenopathy is also persistent. We also want to know whether the steady states describe the residual disease or whether they indicate a high tumor load and a unmanageable situation. Lastly, treatment cessation and combination of ibrutinib and chemotherapy may work but the class of patients that can stand it is still to be determined.

5.1.3 Chapter 4: Summary and perspectives

In the final chapter we have constructed and analyzed a system of delay differential equations to describe hematopoiesis which is modeled as a biological process that takes place in discrete compartments. These compartments describe the levels of differentiation whereas a feedback control is indicated by the dependence of the carrying capacity of the HSC on the total number of mature cells. The time spent at each compartment of differentiation i is described mathematically by a delay τ_i while the total delay is the sum of all τ_i 's, $\tau = \sum_i \tau_i$. We were interested in the stability of the equilibrium points of the system since stability loss is related to oscillations and oscillations are interpreted biologically as hematological diseases.

With some standard calculations we are led to the study of a delay differential system of two variables U_0, U_n denoting the hematopoietic stem cells and the mature cells respectively. The system is the following and fully describes the process of hematopoiesis. For $t > \tau$,

$$\begin{cases} U_0'(t) &= rU_0(t) \left(1 - \frac{U_0(t)}{K(U_n(t))}\right) - \delta U_0(t), \\ U_n'(t) &= -\mu_n U_n(t) + h e^{-\mu\tau} H(U_n(t-\tau)) U_0(t-\tau). \end{cases} \quad (5.1)$$

with initial conditions given by

$$(U_0(t), U_n(t)) = (\phi(t), \psi(t)), \quad t \in [-\tau, 0], \quad \text{with } (\phi, \psi) \in C([-\tau, 0], \mathbb{R}^2).$$

r stands for the growth rate of HSC and δ is the maturation rate which also contains the differentiation. The detailed definition of the system's parameters and the functions H and K is given in chapter 4.

We have shown that a trivial equilibrium $(0, 0)$ always exists whereas a unique positive equilibrium exists if and only if $r > \delta$. Its components are solutions of the fixed point equations:

$$\mu_n \bar{U}_n = h e^{-\mu\tau} \left(1 - \frac{\delta}{r}\right) H(\bar{U}_n) K(\bar{U}_n) \quad \text{and} \quad \bar{U}_0 = \left(1 - \frac{\delta}{r}\right) K(\bar{U}_n). \quad (5.2)$$

Concerning stability we have shown that if $\delta \geq r$ the trivial equilibrium is globally attractive in the sense that solutions converge to 0 when $t \rightarrow +\infty$ independently of the initial conditions. If $\delta < r$ (same inequality as the sufficient and necessary condition

for the existence of a non trivial equilibrium) $(0, 0)$ is unstable, in particular if $\delta > r$ the trivial steady state is locally asymptotically stable.

The study of the stability of the non trivial equilibrium is reduced to the study of the sign of the real part of the roots of the transcendental equation:

$$(\lambda + r - \delta)(\lambda + \mu_n + q_{\mu\tau}e^{-\lambda\tau}) + C_{\mu\tau}e^{-\lambda\tau} = 0.$$

We have used the transcripts $\mu\tau$ to emphasize the dependence on $\mu\tau$ as a product.

We note that the coefficients of the equation depend on the delay, so τ cannot be used as a bifurcation parameter to do the stability analysis of a certain equilibrium point. To overcome this constraint we follow the steps:

- We do the stability analysis when $K' = 0$ (implying that $C_{\mu\tau} = 0$ see chapter 4) and separately when $K' \neq 0$.
- We observe that the component \bar{U}_n depends on τ only through the product $\mu\tau$ and that there is a bijection between the equilibrium and the $\mu\tau$. We denote $\bar{\tau} = \mu\tau$.
- Then we let μ, τ vary as free parameters but we keep their product fixed $\bar{\tau}$. That is $\tau = \frac{\bar{\tau}}{\mu}$ and the parameters lie on a curve. With this parameterization we can still cover the whole parameter space.
- When $K' = 0$ and $q_{\bar{\tau}}$ is constant the characteristic equation is a transcendental equation that has already been studied by Hayes. Hayes theorem gives the conditions of destabilization and the critical τ^* where this happens. Hence, given μ, τ for a specific equilibrium, we are on a certain curve $\mu\tau = \bar{\tau}$ to whom a τ^* of destabilization is associated. If our delay satisfies $\tau < \tau^*$ the equilibrium is stable, otherwise it is unstable.
- We give the graphs of stable and unstable regions for certain choices of H : exponential, Hill (whose region of possible destabilization is unbounded) and an adhoc function that we constructed so that the domain of destabilization is a bounded interval.
- When $K' \neq 0$ and $q_{\bar{\tau}}$ is fixed the characteristic equation is more complicated. A destabilization happens when purely imaginary roots $\lambda = i\omega$ exist. For our case only one possible ω exists (and not more), a favorable situation to completely characterize the stability regions.
- We determine the critical τ and the regions where stability is maintained and where destabilization happens.
- At the point of destabilization we show the appearance of a Hopf bifurcation. Oscillatory solutions appear, a situation related to oscillating blood counts and hematologic diseases.

- We provide the graphs of stability regions for $HK = F$ an exponential, a Hill and the adhoc function.
- From the equation

$$HK = F,$$

a possible choice for the functions is $H = F^a$ and $K = F^{1-a}$. We also provide the charts for different choices of a , $a = 0, 0.2, 0.5, 1$. Note that when $a = 0$ we have a control given only by K whereas for $a = 1$ the control is given only by H (case $K' = 0$).

- From the graphs we see that the most destabilizing control (corresponding to the largest τ) is given by the combination of both H , K .

Perspectives For the moment we have proven only numerically that the optimal control is associated to a combination of both H and K . No analytic result is given. To determine the optimal control we have to study the variations of τ^* with respect to a , that is the sign of the derivative $\frac{d\tau^*}{da}$ of τ^* with respect to a , or more specifically the

$$\max\{\tau^* | a \in [0, 1]\}.$$

Numerical simulations give us a hint that the monotony of τ^* changes at most once. What we know for the moment is that the maximum is never obtained at $a = 0$. A brief explanation of that fact follows (for the notations of h' , k' , and the expression of the characteristic equation when $K' \neq 0$ see chapter 4). In correspondence to h' and k' we set $f' = -\bar{U}_n \frac{F'(\bar{U}_n)}{F(\bar{U}_n)}$ which implies $h' = af'$ and $k' = (1 - a)f'$.

At $\lambda = i\omega$ the characteristic equation becomes:

$$(i\omega + \bar{r})(i\omega + \mu_n) + \mu_n e^{-i\omega\tau}(i\omega af' + \bar{r}f') = 0. \quad (5.3)$$

We take the derivative with respect to a :

$$i\omega'(a)(i\omega + \mu_n) + i\omega'(a)(i\omega + \bar{r}) + \mu_n e^{-i\omega\tau} i\omega(a)f' + i\mu_n e^{-i\omega\tau} \omega'(a)af' \quad (5.4)$$

$$- \mu_n i e^{-i\omega\tau} (\omega'(a)\tau + \omega(a)\tau'(a))(i\omega af' + \bar{r}f') = 0. \quad (5.5)$$

Then we divide this equation by $(i\omega + \bar{r})(i\omega + \mu_n)$ and also use (5.3) to obtain:

$$\omega'(a) \left[\frac{i}{i\omega + \bar{r}} + \frac{i}{i\omega + \mu_n} + i\tau - i \frac{a}{i\omega a + \bar{r}} \right] + i\omega(a)\tau'(a) - i \frac{i\omega(a)}{i\omega(a)a + \bar{r}} = 0. \quad (5.6)$$

Then since:

$$\omega^2(a) = \frac{1}{2} [(\mu_n af')^2 - \mu_n^2 - f'^2 + \sqrt{(\mu_n af')^2 - \mu_n^2 - \bar{r}^2 + 4\mu_n^2 \bar{r}^2 (f'^2 - 1)}].$$

Differentiate with respect to a

$$2\omega(a)\omega'(a) = \frac{1}{2} \left[2a(\mu_n f')^2 + \frac{\mu_n^2 a f'^2}{\sqrt{(\mu_n af')^2 - \mu_n^2 - \bar{r}^2 + 4\mu_n^2 \bar{r}^2 (f'^2 - 1)}} \right].$$

Then at $a = 0$ since $\omega(a)|_{a=0} \neq 0$ this entails:

$$\omega'(a)|_{a=0} = 0,$$

and (5.6):

$$i\omega(a)\tau'(a) - i\frac{\omega(a)}{\bar{r}} = 0,$$

so

$$\tau'(a)|_{a=0} = \frac{1}{r} > 0.$$

We conclude that the maximum is not obtained at $a = 0$ but more work needs to be done for the variations of τ^* .

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Contributions à l'étude de la stabilité dans des modèles de populations de cellules.

Résumé : L'objectif de cette thèse est d'étudier avec des modèles mathématiques structurés la leucémie myéloïde chronique (LMC), la leucémie lymphoïde chronique (LLC) et l'hématopoïèse. Dans un premier temps nous modélisons la LMC avec un système d'EDP et nous identifions trois types de points d'équilibre : l'équilibre de guérison, de rémission et les équilibres hauts. Nous étudions l'impact de la distribution des cellules leucémiques différenciées sur la stabilité des équilibres et nous montrons qu'il y a des distributions qui peuvent déstabiliser l'équilibre de rémission. Ensuite nous proposons et nous analysons quatre modèles d'EDP pour la LLC. L'objectif est de choisir le modèle le plus pertinent pour décrire sa dynamique sous traitement. Nous concluons qu'un modèle de compétition serait le meilleur choix pour expliquer certains phénomènes cliniques mais en même temps un modèle continu n'apporte pas plus d'information qu'un modèle discret d'EDO. Enfin nous modélisons l'hématopoïèse avec un modèle à retard. Nous cherchons l'apparition d'une bifurcation de Hopf et l'existence des solutions périodiques. Les oscillations des solutions du système de départ sont liées à des maladies hématologiques.

Mots clés : LMC, LLC, hématopoïèse, EDP, EDR, EDO, stabilité, bifurcation de Hopf, oscillations.

Contributions to the stability analysis of cell population models.

Abstract : The objective of this PhD is the study of chronic myeloid leukemia (CML), chronic lymphoid leukemia (CLL) and hematopoiesis with structured mathematical models. Firstly, we model CML with a system of PDEs and we identify three types of equilibrium points : the disease free, the remission and the high equilibrium points. We study the impact of the distribution of leukemic differentiated cells on the stability of the steady states and we show that there are distributions that can destabilize the remission equilibrium. Secondly, we propose and analyze four PDE models for CLL. The objective is to choose the most pertinent one to describe the dynamics under treatment. We conclude that a model of competition could better explain certain clinical phenomena but at the same time a continuous model does not give more information than a discrete model of ODE. Finally, we model the hematopoiesis with a delay differential system and we conduct the stability analysis. We investigate the appearance of a Hopf bifurcation and the existence of periodic solutions, a situation that is related to hematological diseases.

Keywords : CML, CLL, hematopoiesis, PDE, ODE, DDE, stability, Hopf bifurcation, oscillations.

