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# Mathematical Modeling in Cellular Dynamics: Applications to Cancer Research

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## THÈSE DE DOCTORAT

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**Modélisation et Analyse de Modèles en Dynamique Cellulaire  
avec Applications à des Problèmes Liés aux Cancers**

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# Glossary

<b>angiogenesis</b>	the formation of new blood vessels, a process controlled by chemicals produced in the body that stimulate blood vessels or form new ones. Angiogenesis plays an important role in the growth and spread of cancer. Angiogenesis also occurs in the healthy body for healing of wounds and restoring blood flow to tissues after injury.
<b>antagonistic</b>	referring to any combination of 2 or more drugs, which results in a therapeutic effect that is less than the sum of each drug's effect.
<b>antigenic</b>	having the properties of an antigen.
<b>antigen</b>	any substance capable of inducing a specific immune response and of reacting with the products of that response, i.e., with specific antibody or specifically sensitized T lymphocytes, or both.
<b>apoptosis</b>	a pattern of cell death affecting single cells, marked by shrinkage of the cell, condensation of chromatin, and fragmentation of the cell into membrane-bound bodies that are eliminated by phagocytosis. Often used synonymously with programmed cell death.
<b>cancer</b>	any disorder of cell growth that results in invasion and destruction of surrounding healthy tissue by abnormal cells. Cancer cells arise from normal cells whose nature is permanently changed. They multiply more rapidly than healthy body cells and do not seem subject to normal control by nerves and hormones. They may spread via the bloodstream or lymphatic system to other parts of the body, where they produce further tissue damage (metastases).
<b>carcinogenesis</b>	the origin, production, or development of cancer, including carcinomas and other malignant neoplasms.
<b>CD4<sup>+</sup>T cell</b>	an immunologically important white cell that is responsible for cell-mediated immunity. It is the cell invaded by the human immunodeficiency virus and in which the virus replicates itself.

<b>CD8</b>	a type I transmembrane protein found on suppressor (cytotoxic) T cells, some natural killer cells, and most thymocytes that is involved in T-cell antigen recognition; expressed in some T-cell lymphomas and large granular lymphocyte leukemias.
<b>cell cycle</b>	the periodic biochemical and structural events occurring during proliferation of cells such as in tissue culture; the cycle is divided into phases called G <sub>0</sub> , Gap1 (G <sub>1</sub> ), synthesis (S <sub>1</sub> ), Gap2 (G <sub>2</sub> ), and mitosis (M). The period runs from one division to the next.
<b>chemokines</b>	chemotactic CYTOKINES, a family of about 50 structurally-related heparin-binding proteins that can induce activation and migration of specific types of white cell, attracting them to sites of inflammation by chemotaxis. They have a fundamental role in inflammation and are concerned in the immune system protective responses to infecting organisms. Chemokines are also concerned in ANGIOGENESIS. Chemokines are implicated in allergic rhinitis, rheumatoid arthritis, asthma, atherosclerosis, inflammatory bowel disease, COPD, insulin resistance, obesity-induced diabetes, multiple sclerosis and psoriasis. Chemokine-receptor antagonists are under active investigation.
<b>chemotherapy</b>	treatment of disease by means of chemical substances or drugs; usually used in reference to neoplastic disease.
<b>congenital</b>	existing at, and usually before, birth; referring to conditions that are present at birth, regardless of their causation.
<b>cytotoxic</b>	detrimental or destructive to cells.
<b>cytomegalovirus</b>	any of a group of herpesviruses that attack and enlarge epithelial cells. Such viruses also cause a disease of infants characterized by circulatory dysfunction and microcephaly.
<b>cytokines</b>	a general term for a range of proteins of low molecular weight that exert a stimulating or inhibiting influence on the proliferation, differentiation and function of cells of the immune system. Cytokines include interleukins and interferons.

<b>EBV</b>	abbreviation for Epstein-Barr virus. A herpesvirus of the genus Lymphocryptovirus, one of the etiologic agents of infectious mononucleosis. It has been isolated from cells cultured from Burkitt's lymphoma and has been found in certain cases of nasopharyngeal carcinoma. There may be an association between EBV and chronic fatigue syndrome. High titers of EBV are present in some tumors, but a causative role has not been proven. Called also EB virus.
<b>endotoxin</b>	a toxin contained in the cell walls of some microorganisms, especially gram-negative bacteria, that is released when the bacterium dies and is broken down in the body. Fever, chills, shock, leukopenia, and a variety of other symptoms result, depending on the particular organism and the condition of the infected person.
<b>epigenetic</b>	relating to inheritable changes in the pattern of gene expression caused by factors other than changes in the nucleotide sequence of genes. It is now recognized that cancer is caused both by genetic and epigenetic changes and that these two factors are intimately interrelated in the development of tumours.
<b>erythrocyte</b>	red blood cell; corpuscle; one of the formed elements in peripheral blood. Normally, in humans, the mature form is a non-nucleated, yellowish, biconcave disk, containing hemoglobin and transporting oxygen.
<b>erythropoiesis</b>	red blood cell production that occurs in bone marrow and involves maturation of nucleated precursors into erythrocytes regulated by the hormone erythropoietin produced in the kidneys.
<b>erythropoietin</b>	a glycoprotein hormone synthesized mainly in the kidneys and released into the bloodstream in response to anoxia. The hormone acts to stimulate and to regulate the production of erythrocytes and thus increases the oxygen-carrying capacity of the blood.
<b>growth factor</b>	hematopoietic growth factor (HGF), any of several glycoproteins that regulate the survival, self-renewal, proliferation, and differentiation of hematopoietic progenitor cells. There are two nomenclature groups: interleukins (IL) and colony-stimulating factors (CSF).
<b>helminths species</b>	the word 'helminth' is a general term meaning 'worm', but there are many different types of worms. Prefixes are therefore used to designate types: platy-helminths for flat-worms and nemat-helminths for round-worms.



<b>hematopoiesis</b>	the normal formation and development of blood cells in the bone marrow.
<b>herpesvirus</b>	any of a family of DNA viruses that form characteristic inclusion bodies within the nuclei of host cells and cause diseases such as chickenpox, infectious mononucleosis, herpes simplex, and shingles.
<b>homeostasis</b>	the principle of self-regulating information feedback by which constant conditions are maintained in a biological system such as the human body. Homeostasis is essential to life and applies to thousands of bodily parameters. Some of the more obvious examples are temperature regulation, blood acidity control, blood pressure control, heart rate, blood sugar levels and hormone secretion.
<b>hormesis</b>	the stimulating effect of subinhibitory concentrations of any toxic substance on any organism.
<b>humoral</b>	pertaining to or derived from a body fluid. The humoral part of the immune system includes antibodies and immunoglobulins in blood serum.
<b>IFN-<math>\beta</math></b>	interferon-beta, an interferon produced by fibroblasts in response to viruses or foreign nucleic acids.
<b>immune response</b>	the reaction of the body to foreign or potentially dangerous substances (antigens), particularly disease-producing microorganisms.
<b>immunodeficiency</b>	a condition resulting from a defective immune mechanism; may be primary (due to a defect in the immune mechanism itself) or secondary (dependent on another disease process).
<b>immunosenescence</b>	the age-associated decline of the immune system and host defense mechanisms. Elderly individuals frequently have a decline in cell-mediated immunity and secondary declines in humoral immunity.
<b>immunosuppression</b>	prevention or interference with the development of immunologic response; may reflect natural immunologic unresponsiveness (tolerance), may be artificially induced by chemical, biologic, or physical agents, or may be caused by disease.
<b>immunosuppressive</b>	pertaining to a substance or procedure that lessens or prevents an immune response.
<b>immunosurveillance</b>	theory positing that the immune system eliminates aberrant or tumor cells that arise spontaneously.

<b>immunotherapy</b>	treatment of disease by inducing, enhancing, or suppressing an immune response.
<b>leukopoiesis</b>	the production of white blood cells. Monocytes, neutrophils, basophils, and eosinophils are produced from bone marrow myeloblasts. Lymphocytes develop from lymphoblastic precursors in peripheral lymphoid tissue.
<b>lymphocyte</b>	a family of mononuclear, nonphagocytic white blood cells that circulate in blood, lymph, and peripheral lymphatic tissues. Lymphocytes are categorized as B and T lymphocytes and natural killer cells and are responsible for humoral and cellular immunity and tumor surveillance.
<b>macrophages</b>	white blood cells (activated monocytes) that protect the body against infection and foreign substances by breaking them down into antigenic peptides recognized by circulating T cells.
<b>malignant</b>	(of a tumor) characterized by uncontrolled growth; cancerous, invasive, or metastatic.
<b>MHC</b>	major histocompatibility complex. A small region of the genome that is highly conserved in vertebrate evolution, which encodes three classes of polymorphic molecules known as the immune recognition unit. The MHC is located on the short arm of chromosome 6 in humans, and on chromosome 17 in mice. The products of the MHC gene complex are membrane-bound receptors for antigens and peptides which, when bound, are displayed to T cells; if the bound peptides are recognised by the T cells, an immune response against those peptides is initiated.
<b>multipotent</b>	of stem cells, having the ability to differentiate into several types of specialized cells.
<b>myelogenous</b>	pertaining to the cells produced in bone marrow or the tissue from which such cells originate.
<b>myeloproliferative</b>	relating to excess proliferation of hematopoietic stem cells, chiefly in the bone marrow, as in chronic myelogenous leukemia and polycythemia vera.
<b>natural killer cell</b>	a lymphocyte that is activated by double-stranded RNA or lymphokines and fights off viral infections and tumors without evident antigenic specificity.
<b>neutropenia</b>	abnormal decrease in the neutrophil count associated with acute leukemia, chemotherapy, and idiosyncratic drug reactions, predisposing individuals to infection.

<b>oncogenic</b>	pertaining to the origin and development of tumors or cancer.
<b><math>pO_2</math></b>	the concentration of oxygen in the blood. this commonly measured parameter is an important indicator of the efficiency with which oxygen is transferred from atmosphere to blood. when $pO_2$ drops, respiration is automatically stimulated.
<b>pathogen</b>	any disease-producing agent or microorganism.
<b>phenotype</b>	the observable features of an individual organism that result from an interaction between the genotype and the environment in which development occurs. the interaction is that between nature and nurture. variations due to nature are the inherited aspects of the organism, the genotype, while nurture denotes the (usually not inherited) effects of the environment upon the organism.
<b>platelets</b>	blood platelets or thrombocytes, consisting of non-nucleated cytoplasmic fragments of large bone-marrow cells $3 \mu m$ in diameter called megakaryocytes that have entered the blood circulatory system. platelets play an important part in blood clotting.
<b>pluripotent</b>	relating to or being a cell that is capable of differentiating into cells of any type of tissue except placental tissue.
<b>pre malignant</b>	pertaining to any lesion that is interpreted as precancer.
<b>proliferate</b>	to grow or multiply by rapidly producing new tissue, parts, cells, or offspring.
<b>quiescent</b>	at rest; latent; the $G_0$ stage of the cell cycle.
<b>radiotherapy</b>	the treatment of neoplastic disease by using x-rays or gamma rays to deter the proliferation of malignant cells by decreasing the rate of mitosis or impairing DNA synthesis.
<b>rhinovirus</b>	any of several strains of enterovirus that cause respiratory tract infections, including the common cold.
<b>rotavirus</b>	any of a genus of wheel-shaped reoviruses, including one that causes gastroenteritis, especially in infants and newborn animals.
<b>sporadic</b>	(of a number of events) occurring at scattered, intermittent, and apparently random intervals.
<b>stem cell</b>	a cell that is not differentiated itself but can undergo unlimited division to form other cells, which either remain as stem cells or differentiate to form specialized cells.

<b>T cell</b>	a lymphocyte that participates in cellular immunity, including cell-to-cell communication. The major T cell categories are T-helper and T-suppressor cytotoxic cell.
<b>TGF-<math>\beta</math></b>	transforming growth factor beta; a growth factor synthesized by skeletal cells; found in most species.
<b>Th1</b>	T Helper Cell Type 1.
<b>Th2</b>	T Helper Cell Type 2.
<b>Th17</b>	T helper 17 cells are a subset of T helper cells producing interleukin 17 (IL-17) discovered in 2007. They are considered developmentally distinct from Th1 and Th2 cells and excessive amounts of the cell are thought to play a key role in autoimmune disease such as multiple sclerosis (which was previously thought to be caused by Th1 cells), but also psoriasis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis, and Crohn's disease.
<b>thrombocytopenia</b>	an abnormally low level of platelets in the circulating blood.
<b>transient</b>	pertaining to a condition that is temporary or of short duration, usually not recurring.
<b>Treg</b>	regulatory T cells.
<b>tumor</b>	a new growth of tissue in which cell multiplication is uncontrolled and progressive. Tumors are also called neoplasms, which means that they are composed of new and actively growing tissue. Their growth is faster than that of normal tissue, continuing after cessation of the stimuli that evoked the growth, and serving no useful physiologic purpose.

# Chapter 1

## General Introduction

This thesis deals with several aspects of mathematical modeling and analysis in cellular dynamics. The work fits into the general framework of the study of population dynamics. The population particularly considered in this work is composed of a large amount of cells with both cases of healthy and cancerous cells being investigated. The mathematical framework used in this study relies heavily upon the theory of differential equations. More precisely, the type of differential equations used in order to develop models during this thesis project varies from ordinary differential equations (ODE) to delayed differential equations (DDE) which in turn were actually the result of the method of characteristics being applied on a couple of systems of partial differential equations (PDE).

The first model proposed in this thesis yielded a DDE that featured a distributed delay as well as constant one. A detailed stability analysis of the resulting DDE system was performed with a focus on the analysis of the behavior of the steady states. The trivial steady state, describing cells dying out, was proven to be globally asymptotically stable when it is the only equilibrium of the system using a constructed Lyapunov function. The asymptotic stability of the positive steady state, the most biologically meaningful one, was analyzed using the characteristic equation.

The second model of this thesis resulted in a system of differential equations with a state-dependent delay for which we investigated the existence and stability of the steady states. A sufficient condition for the global asymptotic stability of the trivial steady state was obtained using a Lyapunov-Razumikhin function. The analysis of the positive steady state behavior concluded on the existence of a Hopf bifurcation.

The third and final model proposed in this thesis consists of a system of ODEs that led to highlight the importance of the results yielded by a simple mathematical model in helping to improve our understanding of the complex interactions between the immune system and cancerous cells. The study of the latter model centered on the influence of infections on cancer risk and more precisely the interference of such infections with the immune responses against cancer.

## Motivation

The role of cellular dynamics in cancer prevention and cancer therapies development has become more prominent in the recent decades. Especially the role of Stem Cells dynamics [26, 44].

Stem cells are undifferentiated cells that have the unique capabilities of differentiation into multiple types of specialized cells and unlimited capacities of self-renewal [117]. The earliest and most intensively studied models of lineage-committed stem cells are Hematopoietic Stem Cells (HSCs). In the early 1960s, Till and McCulloch [112] found the first genetic evidence for the existence of HSCs. Ever since, a great deal of models have been proposed either describing normal HSCs dynamics [8, 43], or blood cell diseases like cyclical neutropenia [22, 61], thrombocytopenia [101, 109] or chronic myelogenous leukemia [11, 95] (normal HSCs dynamics are the main focus of the first part of this thesis).

Despite the fact that HSCs dynamics have been intensively studied for several decades, many open questions remain unanswered, due to the difficulty to obtain experimental measurements of some of the mechanisms involved in the hematopoiesis process as well as the complexity of the process itself.

In recent years, there is an increasing amount of evidence suggesting that cancer is originated and sustained by a small subset of the population of cells called Cancer Stem Cells (CSCs) [53]. A cancer stem cell is a cell type within a tumor that possesses the capacity of self-renewal and can give rise to the heterogeneous lineages of cancer cells [38]. CSCs also possess features that enables them to elude the immune system recognition [30] which renders them virtually invisible to the immune response (This particular point is the main focus of the second part of the thesis).

Cancer stem cells have been successfully identified in acute myelogenous leukemia [35, 40], breast cancer [15], brain tumors [63, 74, 107], and pancreas cancer [50].

As the field of stem cell research continues to expand, we do hope to contribute, by the present work, to the understanding of normal stem cell behavior as well as some abnormalities that may sometimes arise in stem cell dynamics.

### 1.1 Hematopoietic Stem Cells

Hematopoietic Stem Cells (HSCs) are the multipotent stem cells, located in the bone marrow, from which originates all differentiated blood cell lineages (red blood cells, white cells and platelets) through the process of hematopoiesis.

Due to the large number of divisions, and the amount of cells and cytokines involved in hematopoiesis, numerous issues may arise at different cellular levels and sometimes lead to disorders affecting blood cells. Among a wide variety of disorders affecting blood cells, myeloproliferative diseases are of great interest. They are characterized by a set of conditions that cause blood cells to grow abnormally. They include chronic

myelogenous leukemia, a cancer of the white blood cells that exhibits, in some cases, periodic oscillations in all blood cell counts (see [96]). Myeloproliferative disorders usually originate from the HSC population: an uncontrolled proliferation of HSCs can upset the entire physiological process and result in a much faster or slower proliferation (i.e., the influence of cell cycle duration which is the main focus of Chapter 3).

A low blood cell counts can be associated with many diseases and disorders that cause the body to have fewer blood cells than usual. It can be associated to a bone marrow failure resulting from a disease affecting another organ (liver or kidney, for instance), or to a side effect of a specific treatment (chemotherapy drugs, for instance).

The process of hematopoiesis comprises of multiple complex mechanisms regulated by a wide range of hormone-like molecules called growth factors that respond to stimuli and enable a balance between differentiation, self-renewal and cell mortality (The main focus of Chapter 2). For instance, in case of a deficiency of oxygen in the blood, mature red blood cells trigger the release of erythropoietin from the kidneys which inhibits apoptosis during hematopoiesis, leading to an increase in red blood cells production [71].

### 1.1.1 HSC dynamics : Mathematical modeling

Mathematical modeling of HSC dynamics has been the focus of a large panel of researchers over the last four decades, with attempts to improve the understanding of the complex mechanisms regulating HSC functions, throughout the course of normal and pathological hematopoiesis. One of the earliest mathematical models that shed some light on this process was proposed by Mackey [76] in 1978 inspired by the work of Lajtha [73], and Burns and Tannock [31]. Mackey's model consists of a system of two delay differential equations describing the evolution of the HSC population divided into proliferating and quiescent cells (also called resting cells). This model has been studied, analyzed and applied to hematological diseases by many authors (see, for instance, [9, 95, 96, 99]). For many years, only systems with discrete delay were proposed to describe HSC dynamics see, for example, [8, 77, 78]. Then, more recently, Adimy and Crauste [3], Adimy, Crauste, and Ruan [9], and Bernard, Bélair, and Mackey [21] proposed and analyzed modified versions of Mackey's model [76] by considering a distribution of cell cycle durations. In 2005, Adimy and Crauste [4] and Adimy, Crauste, and Pujo-Menjouet [12] proposed a model of HSC dynamics in which the cell cycle duration depends upon the cell maturity.

Mathematical models describing the action of growth factors on the hematopoiesis process have been proposed by Bélair et al in 1995 [18], and Mahaffy et al in 1998 [81]. They considered an age-structured model of HSC dynamics, coupled with a differential equation to describe the action of a growth factor on the reintroduction rate from the resting phase to the proliferating one. In 2006, Adimy et al [10] proposed a system of three delay differential equations describing the production of blood cells under the action of growth factors assumed to act on the rate of reintroduction into the proliferating phase. Adimy and Crauste considered and analyzed two models of hematopoiesis dynamics with: the influence of growth factors on HSC apoptosis [5],

and the action of growth factors on the apoptosis rate as well as on the reintroduction rate into the proliferating phase [6].

Many of the aforementioned mathematical models have subsequent implications to cancer prevention, development and treatment.

### 1.1.2 Our contribution to HSC dynamics modeling

The originality of our study regarding the influence of growth factors concentrations on differentiation, proliferation rate and apoptosis lays in the proposed model itself which, to our knowledge, has never been considered in hematopoiesis dynamics beforehand.

Regarding the originality of our study relating to the influence of the total population of quiescent cells on the cell cycle duration, it lays in the refinement of the model proposed by Adimy et al. [13].

## 1.2 Immunosenescence, Cancer and Stem Cells

The immune system is not permanently fully efficient. Indeed, immunosenescence is a process that reflects a gradual decrease of immune system activity with age mainly through a decreased capacity of immunosurveillance [49]. The beginning of immunosenescence is assumed to be associated with the beginning of thymopoiesis decline. Indeed, the thymus play a crucial role in the development of T cells but also in maintaining immune efficiency [102]. Maximal activity is reached at puberty (from 10 to 19 years old according to the World Health Organization) and decrease progressively in adults [108]. The elderly (more than 65 years old (WHO)) usually have i) a depleted population of naive T cells (the set of T lymphocytes that can respond to novel antigens) [92, 93], ii) a shrinking repertoire of T cell clones [55, 83, 93], iii) an increased number of naturally occurring regulatory T cells that down-regulate T cell responses [46, 98], iv) a low grade, pro-inflammatory status [92], and v) increased numbers of myeloid-derived suppressor cells, which are associated with impaired T-cell functioning and produce high amounts of reactive oxygen species [24]. All these immune-associated changes can potentially promote tumor proliferation [55].

### 1.2.1 The Link Between Aging and Cancer : Mathematical modeling

Mathematical models have been used, since 1954, to investigate the link between aging and cancer by correlating increasing incidences of cancer with advancing age to mutation accumulation [16]. More recently, genetic and epigenetic changes in stem cells have been associated with both normal aging processes and cancer risk [23, 36, 106, 111]. Normal aging is linked with lymphocytes immunosenescence leading to increased secretion of cytokines such as  $IL - 6$  and  $TNF - \alpha$  [90]. This state of chronic immune activation has been associated with DNA-modifying events that lead to an increased risk of malignancy [28]. Inflammatory cytokines are also important regulators of stem cell states [70]. Mathematical models have proven useful in the study the effects of stress and hormesis [86] on lifespan and the relationship between accelerated aging



and carcinogenesis [32–34]. Stochastic models have been used to study the balance between damaged and repaired states in stressed worms. Predictions of lifespan using this model matched the experimental observations [33]. Further stochastic models have been used to examine levels of free radicals and cumulative damage to DNA, lipid structures, and proteins, leading to genetic instability and malignant transformation [32]. Predictions from these models matched both experimental data of survival and fertility curves in Mediterranean fruit flies, and cancer incidence in rats exposed to bromode-oxyuridine [33, 34].

### 1.2.2 Our contribution to the modeling of the interactions between aging and cancer

The originality of our study lays in the ability of our model to predict that acute immunosuppressive infections could also impact cancer risk and in a larger extent than persistent infections. Empirical evidences of such situation are obviously harder to identify, but the impact of “common” diseases on immune system and their relation with cancer risk are worthy of investigation. Our results suggest a stronger impact of acute and repeated immune challenges after the beginning of immunosencecence.

## Organization of the thesis

The thesis is structured in two parts besides this introductory chapter. The first part consists of two chapters dedicated to mathematical modeling and analysis of hematopoietic stem cell dynamics.

In chapter 2, we propose and analyze the following age-structured partial differential model for hematopoietic stem cell dynamics, in which proliferation, differentiation and apoptosis are regulated by growth factor concentrations,

$$\begin{aligned} \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= -(\delta + \beta(E_1(t)))n(t, a), \quad a > 0, \\ \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} &= -\gamma(E_2(t))p(t, a), \quad 0 < a < \tau, \\ \frac{\partial m}{\partial t} + \frac{\partial m}{\partial a} &= -\mu m(t, a), \quad a > 0, \end{aligned} \tag{1.2.1}$$

where we denote respectively by  $n(t, a)$ ,  $p(t, a)$  and  $m(t, a)$  the cell population densities of quiescent HSCs, proliferating HSCs and mature cells, with age  $a \geq 0$  at time  $t \geq 0$ . The age represents the time spent by a cell in one of the three compartments. Quiescent cells are assumed to die with a constant rate  $0 \leq \delta \leq 1$ , and they can be introduced into the proliferating phase with a rate  $\beta$  in order to divide. We suppose that  $\beta$  depends upon a growth factor concentration  $E_1$ . We assume that the duration of the proliferating phase is the same for all cells, so  $\tau$  is constant, and describes an average duration of the cell cycle. The population of proliferating cells is controlled by apoptosis  $\gamma \geq 0$ . We assume that the apoptosis rate  $\gamma$  depends upon the concentration of growth factor  $E_2$ . The portion of quiescent cells that differentiate to mature cells is denoted by  $K_N \geq 0$  which, we assume, depends upon a growth factor concentration denoted  $E_3$ , whereas the portion of daughter cells entering the mature phase is denoted

by  $K_P \geq 0$  which, we assume, depends upon a growth factor concentration denoted  $E_4$ .

System (1.2.1) is completed by boundary conditions (for  $a = 0$ ), that describe the flux of cells entering each phase, and by initial conditions (for  $t = 0$ ). The boundary conditions of (1.2.1) are, for  $t > 0$ ,

$$\begin{aligned} n(t, 0) &= 2\alpha p(t, \tau), \\ p(t, 0) &= \beta(E_1(t))N(t), \\ m(t, 0) &= K_N(E_3(t))N(t) + 2K_P(E_4(t))p(t, \tau), \end{aligned} \quad (1.2.2)$$

where

$$N(t) = \int_0^{+\infty} n(t, a) da, \quad P(t) = \int_0^\tau p(t, a) da, \quad M(t) = \int_0^{+\infty} m(t, a) da.$$

Initial conditions of (1.2.1) are given by nonnegative  $L^1$ -functions  $n_0$ ,  $p_0$  and  $m_0$ , such that

$$\begin{aligned} n(0, a) &= n_0(a), \quad m(0, a) = m_0(a), \quad \text{for } a \geq 0, \\ p(0, a) &= p_0(a), \quad \text{for } a \in [0, \tau]. \end{aligned} \quad (1.2.3)$$

The growth factor concentrations  $E_i(t)$ ,  $i = 1, 2, 3, 4$ , follow the evolution equations

$$E_i'(t) = -k_i E_i(t) + f_i(M(t)), \quad (1.2.4)$$

where the coefficients  $k_i > 0$  are the degradation rates of the growth factors  $E_i$ . We assume that the functions  $M \mapsto f_i(M)$  are positive, decreasing and satisfy  $\lim_{M \rightarrow +\infty} f_i(M) = 0$ .

Using the method of characteristics, we reduce the age-structured model (1.2.1)-(1.2.2)-(1.2.3)-(1.2.4) to the following delay differential system

$$\begin{aligned} N'(t) &= -(\delta + \beta(E_1(t)))N(t) \\ &\quad + 2\alpha\beta(E_1(t - \tau))N(t - \tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right), \\ M'(t) &= -\mu M(t) + K_N(E_3(t))N(t) \\ &\quad + 2K_P(E_4(t))\beta(E_1(t - \tau))N(t - \tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right), \\ E_i'(t) &= -k_i E_i(t) + f_i(M(t)). \end{aligned} \quad (1.2.5)$$

We investigate the existence and stability of the steady states of the reduced delay differential system. The trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium of the system using the following constructed Lyapunov functional

$V_\epsilon : (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6 \rightarrow \mathbb{R}_+$ , Defined by

$$\begin{aligned} \Phi &= (\varphi, \psi, \chi_1, \chi_2, \chi_3, \chi_4), \\ V_\epsilon(\Phi) &= \varphi(\bar{t}_\epsilon + \tau) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) \\ &\quad \times \int_{-\tau}^0 \beta(\chi_1(\theta + \bar{t}_\epsilon + \tau))\varphi(\theta + \bar{t}_\epsilon + \tau) d\theta. \end{aligned}$$

The composition with the solution  $X(t) := (N(t), M(t), E_i(t))$  of equation (1.2.5) leads, for  $t \geq \bar{t}_\epsilon + \tau$ , to the function

$$t \mapsto V_\epsilon(X_t) = N(t) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) \int_{t-\tau}^t \beta(E_1(s))N(s)ds.$$

The asymptotic stability of the positive steady state, the most biologically meaningful one, is analyzed using the characteristic equation. This study may be helpful in understanding the uncontrolled proliferation of blood cells in some hematological disorders.

The work presented in Chapter 2 has been published in a peer-reviewed journal and is reproduced in extenso.

In chapter 3, we propose and analyze a mathematical model describing the dynamics of a hematopoietic stem cell population, in which the duration of the cell cycle  $\tau$  depends upon the total population of quiescent cells. The function  $\tau : \mathbb{R}^+ \rightarrow [0, \tau_{max}]$  is supposed to be bounded, positive, continuously differentiable ( $C^2$ ) and increasing. The method of characteristics reduces the age-structured model to a system of differential equations with a state-dependent delay. We perform a detailed stability analysis of the following delay differential equation

$$x'(t) = f(x_t), \quad \text{for } t \geq 0, \quad (1.2.6)$$

where  $x_t$  is defined by  $x_t(\theta) = x(t + \theta)$  for  $\theta \in [-\tau_{max}, 0]$ , and the function  $f : C \rightarrow \mathbb{R}$  is given, for  $\phi \in C$ , the space of continuous functions on  $[-\tau_{max}, 0]$ , by

$$f(\phi) = g(\phi(0), \phi(-\tau(\phi(0)))).$$

The function  $g : (\mathbb{R}^+)^2 \rightarrow \mathbb{R}$  is given by

$$g(x, y) = \frac{-\delta x - \beta(x)x + 2\beta(y)ye^{-\gamma\tau(x)}}{1 + 2\tau'(x)e^{-\gamma\tau(x)}\beta(y)y}, \quad (x, y) \in (\mathbb{R}^+)^2,$$

where  $\delta > 0$  and the function  $\beta$  is assumed to be continuously differentiable, bounded and positive. Furthermore, we assume that  $\beta$  is decreasing with  $\lim_{x \rightarrow +\infty} \beta(x) = 0$ . Afterwards, we consider the following Lyapunov-Razumikhin function

$$V : \mathbb{R}^+ \rightarrow \mathbb{R}^+ \text{ given by } V(x) = x^2/2.$$

Where, for  $x \in \mathbb{R}^+$ ,  $u(x) \leq V(x) \leq v(x)$ , with  $u(x) = x^2/2$  and  $v(x) = x^2$ .

We define  $p : \mathbb{R}^+ \rightarrow \mathbb{R}^+$  by  $p(x) = xe^{2\alpha\tau(\sqrt{2x})}$ ,  $x \in \mathbb{R}^+$  with  $0 < \alpha < \min\{\gamma, \gamma - \ln(2\beta(0)/\delta)/\tau_0\}$ ,

Then, we consider  $x$  to be a solution of (1.2.6) such that, for  $t \geq 0$ ,  $\theta \in [-\tau_{max}, 0]$ ,

$$V(x(t + \theta)) < p(V(x(t))).$$

and we obtain a sufficient condition for the global asymptotic stability of the trivial steady state, describing cell's dying out.

Furthermore, it is shown that a unique non-trivial steady state can appear through a transcritical bifurcation of the trivial steady state. The analysis of the positive steady state's behavior concludes to the existence of a Hopf bifurcation and gives criteria for stability switches. Moreover, we have confirmed the analytical results by numerical simulations.

The work presented in Chapter 3 is soon to be submitted for publication.

The second part of the thesis is comprised of a single chapter where we focus on the interactions between the immune system and cancer cells proliferation. Particularly, in Chapter 4, we consider the compartment of invisible cells in order to deepen our analysis of the aforementioned interactions. We propose the following ODE system

$$\begin{aligned}\frac{dH}{dt} &= \beta_1 H \left(1 - \frac{N}{K}\right) - \mu_1 H, \\ \frac{dP}{dt} &= \beta_1 P \left(1 - \frac{N}{K}\right) + \mu_1 H - (\mu_2 + \omega(t)) P, \\ \frac{dC}{dt} &= \beta_2 C \left(1 - \frac{N}{K}\right) + \mu_2 P - (\mu_3 + \omega(t)) C, \\ \frac{dI}{dt} &= \beta_2 I \left(1 - \frac{N}{K}\right) + \mu_3 C,\end{aligned}$$

where  $H$  represents healthy cells,  $P$  precancerous cells,  $C$  cancerous cells,  $I$  cancerous cells that are invisible to the immune system and  $N$  the total number of cells (i.e.,  $N = H + P + C + I$ ). Precancerous cells become cancerous at rate  $\mu_2$ , and finally invisible at rate  $\mu_3$ . We consider that invisible cancerous cells have acquired the capacity to avoid destruction by immune system whatever the mechanism implied. Healthy and precancerous cells replicate at rate  $\beta_1$  while cancerous and invisible cells replicate at rate  $\beta_2$  (greater than  $\beta_1$ ) with a maximal total number of cells  $K$  (i.e., carrying capacity) in order to induce competition between different kinds of cells. Each precancerous and cancerous cells can be eliminated from the organism through the function  $\omega(t)$ .

Afterwards, we show that the frequency, the duration and the action (positive or negative) of immune challenges may significantly impact tumor proliferation. First, we observe that a long immunosuppressive challenge increases accumulation of cancerous cells. However, short immune challenges result in an even greater accumulation of cancerous cells for the same total duration of immunosuppression. Finally, we show that short challenges of immune activation could lead to a slightly decrease in cancerous cell accumulation compared to a long one.

The work presented in Chapter 4 has been published in a peer-reviewed journal and is reproduced in extenso.

Part I

Hematopoietic Stem Cell  
Dynamics

## Chapter 2

# Age-structured model of hematopoiesis dynamics with growth factor-dependent coefficients \*

### Abstract

We propose and analyze an age-structured partial differential model for hematopoietic stem cell dynamics, in which proliferation, differentiation and apoptosis are regulated by growth factor concentrations. By integrating the age-structured system over the age and using the characteristics method, we reduce it to a delay differential system. We investigate the existence and stability of the steady states of the reduced delay differential system. By constructing a Lyapunov function, the trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium of the system. The asymptotic stability of the positive steady state, the most biologically meaningful one, is analyzed using the characteristic equation. This study may be helpful in understanding the uncontrolled proliferation of blood cells in some hematological disorders.

### 2.1 Introduction

Hematopoiesis is the physiological process that ensures the production and regulation of blood cells. It involves a pool of undifferentiated and self-renewing cells called hematopoietic stem cells (HSCs), located in the bone marrow, from which arises all differentiated blood cell lineages (red blood cells, white cells and platelets).

Proliferation, differentiation and apoptosis are processes occurring during hematopoiesis and are all mediated by a wide range of hormone-like molecules called growth factors. The growth factors play an activator or inhibitor role in this process and they

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act on every cell compartment: primitive stem cells, progenitors and precursors. Their role to maintain homeostasis of blood cells is essential. The production of red blood cells (erythropoiesis) and platelets (megakaryopoiesis) seems to be regulated by specific growth factors whereas white blood cell production (leukopoiesis) is more complicated and less clearly understood. For the red blood cells, the erythropoietin (EPO) helps to regulate erythrocyte production (Adamson [2]). A decrease in mature red blood cell count leads to a decrease in tissue  $pO_2$  levels, which in turn increases the production of EPO by the kidneys and controls erythropoiesis. For the platelets, it seems that their production and regulation are controlled by feedback mechanisms involving specific cytokines such as thrombopoietin (TPO). However, it has been shown that the cytokine TPO affects other cell lines as well (Tanimukai et al [110]), which means that the three lines are probably not fully independent, and there is a feedback control from mature cells to HSCs. Regulation of the multiple fates of HSCs, including quiescence, self-renewal, differentiation and apoptosis, requires the cooperative actions of several growth factors that bind to receptors on these cells. Many of the important players in this regulation have been identified (Tanimukai et al [110]).

Due to the number of divisions, and the quantity of cells and cytokines involved in hematopoiesis, issues may arise at different cellular levels and sometimes result in disorders affecting blood cells. Among a wide variety of disorders affecting blood cells, myeloproliferative diseases are of great interest. They are characterized by a group of conditions that cause blood cells to grow abnormally. They include chronic myelogenous leukemia, a cancer of white blood cells. In some cases, chronic myelogenous leukemia exhibits periodic oscillations in all blood cell counts (see [96]). Myeloproliferative disorders usually originate from the HSC compartment: an uncontrolled proliferation in the HSC compartment can perturb the entire system and leads to a quick or slow proliferation. A low blood counts (white cell count, red cell count, or platelet count) can be associated with many diseases and conditions that cause the body to have too few blood cells. It can be associated to a bone marrow failure, consecutive to disease of another organ (for example, liver or kidney), or secondary to treatment with some drugs (for example, chemotherapy drugs).

Mathematical modeling of hematopoiesis dynamics has been the focus of a large panel of researchers over the last four decades, with attempts to improve the understanding of the complex mechanisms regulating HSC functions, throughout the course of normal and pathological hematopoiesis. One of the earliest mathematical models that shed some light on this process was proposed by Mackey [76] in 1978 inspired by the work of Lajtha [73], and Burns and Tannock [31]. Mackey's model is a system of two delay differential equations describing the evolution of the HSC population divided into proliferating and quiescent cells (also called resting cells). This model has been studied, analyzed and applied to hematological diseases by many authors (see for instance, [9, 77, 78, 95, 96, 99]). We refer the reader interested in this topic, in addition to the previous articles, to the review papers by Adimy and Crauste [7], Haurie et al [59], Mackey et al [79], and the references therein.

Mathematical models describing the action of growth factors on the hematopoiesis

process have been proposed by Bélair et al in 1995 [18], and Mahaffy et al in 1998 [81]. They considered an age-structured model of HSC dynamics, coupled with a differential equation to describe the action of a growth factor on the reintroduction rate from the resting phase to the proliferating one. In 2006, Adimy et al [10] proposed a system of three delay differential equations describing the production of blood cells under the action of growth factors assumed to act on the rate of reintroduction into the proliferating phase. Adimy and Crauste considered and analyzed two models of hematopoiesis dynamics with: the influence of growth factors on HSC apoptosis [5], and the action of growth factors on the apoptosis rate as well as on the reintroduction rate into the proliferating phase [6].

In this paper, we consider the influence of growth factors on the apoptosis rate, on the differentiation rates (of the proliferating and quiescent cells), as well as on the reintroduction rate into the proliferating phase (see Figure 2.1). The resulting system is composed by three age-structured partial differential equations for the different compartments of cell population, coupled with a system of four differential equations to describe the action of growth factors on different parameters of the system. To our knowledge this model has never been considered in hematopoiesis dynamics.

The paper is organized as follows. In section 2.2, we provide some biological background leading to an age-structured partial differential model for HSC dynamics. In section 2.3, we use the method of characteristics to reduce the model to a system of delay differential equations. In section 2.4, we establish some proprieties of the solutions such as positivity and boundedness. In section 2.5, we investigate the existence of steady states. In section 2.6, we prove the global asymptotic stability of the trivial steady state using a Lyapunov function. In section 2.7, we linearize the delay system about each steady state and we deduce the delay-dependent characteristic equation. Then, we obtain the local asymptotic stability of the positive steady state.

## 2.2 Age-structured partial differential model

We consider two cell populations, HSC population (in the bone marrow) and mature blood cell population (in the bloodstream), for instance red blood cells. The HSC population is divided into proliferating and quiescent cells. Proliferating cells are the ones performing the cell division (growth, DNA synthesis and mitosis). Quiescent (or resting) HSCs are actually in a quiescent phase ( $G_0$ -phase). HSCs generate cells that undergo terminal differentiation resulting in mature circulating blood cells. Mature blood cells control the HSC population through growth factors. We denote respectively by  $n(t, a)$ ,  $p(t, a)$  and  $m(t, a)$  the cell population densities of quiescent HSCs, proliferating HSCs and mature cells, with age  $a \geq 0$  at time  $t \geq 0$ . The age represents the time spent by a cell in one of the three compartments. A schematic representation of this model is given in Figure 2.1. Details of the modeling are presented hereafter.

Quiescent cells are assumed to die with a constant rate  $0 \leq \delta \leq 1$ , and they can be introduced into the proliferating phase with a rate  $\beta$  in order to divide. We suppose that  $\beta$  depends upon a growth factor concentration  $E_1$ , that stimulates the proliferative capacity of HSCs: the more growth factor, the more proliferation of HSCs. Hence the feedback induced by the growth factor  $E_1$  is positive, and the function  $\beta$



is supposed to be increasing, with  $\beta(0) = 0$ . As soon as a cell enters the proliferating phase, it is committed to divide a time  $\tau \geq 0$  later. We assume that the duration of the proliferating phase is the same for all cells, so  $\tau$  is constant, and describes an average duration of the cell cycle. The population of proliferating cells is controlled by apoptosis  $\gamma \geq 0$ , which is a programmed cell death that eliminates deficient cells and also maintains the homeostatic state of cell population. We assume that the apoptosis rate  $\gamma$  depends upon the concentration of growth factor  $E_2$  (for example, EPO, see [71]). Since an increase of the growth factor concentration  $E_2$  leads to a decrease of the apoptosis rate, we assume that  $\gamma$  is a decreasing function of  $E_2$  and  $\lim_{E_2 \rightarrow +\infty} \gamma(E_2) = 0$ . The portion of quiescent cells that differentiate to mature cells is denoted by  $K_N \geq 0$  which, we assume, depends upon a growth factor concentration denoted  $E_3$ . Since an increase of growth factor  $E_3$  leads to an increase of the differentiation, we suppose that  $E_3 \mapsto K_N(E_3)$  is an increasing function. Here, we only consider one kind of mature cells, for instance red blood cells. Then, we can consider that  $1 - (\delta + \beta + K_N) \geq 0$ , the remainder of quiescent cells, differentiate to other cell lineages (for instance, white blood cells and platelets). At the end of the proliferating phase, each cell divides into two daughter cells. The daughter cells can either differentiate and enter the mature phase or stay in HSC compartment and enter to the  $G_0$ -phase. We assume that the part of daughter cells  $\alpha \geq 0$  that stay in HSC compartment is constant. This is important because HSCs could maintain their characteristic properties of self-renewal and lack of differentiation could provide an unlimited source of cells to maintain the homeostasis. The portion of daughter cells entering the mature phase is denoted by  $K_P \geq 0$  which, we assume, depends upon a growth factor concentration denoted  $E_4$ . As for quiescent cells, we suppose that  $E_4 \mapsto K_P(E_4)$  is an increasing function and that the portion  $1 - (\alpha + K_P) \geq 0$  of daughter cells differentiate to other cell lineages. We suppose that the mature cells die with a constant rate  $\mu \geq 0$ . All the growth factor concentrations  $E_1, E_2, E_3$  and  $E_4$  are controlled by the mature cells through functions  $f_i, i = 1, 2, 3, 4$  acting as negative feedbacks of the mature blood cells on the production of growth factors (see Figure 2.1).

The densities  $n(t, a), p(t, a)$  and  $m(t, a)$  satisfy, for  $t > 0$ , the system

$$\begin{aligned} \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= -(\delta + \beta(E_1(t)))n(t, a), \quad a > 0, \\ \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} &= -\gamma(E_2(t))p(t, a), \quad 0 < a < \tau, \\ \frac{\partial m}{\partial t} + \frac{\partial m}{\partial a} &= -\mu m(t, a), \quad a > 0. \end{aligned} \tag{2.2.1}$$

System (2.2.1) is completed by boundary conditions (for  $a = 0$ ), that describe the flux of cells entering each phase, and by initial conditions (for  $t = 0$ ). Then the boundary conditions of (2.2.1) are, for  $t > 0$ ,

$$\begin{aligned} n(t, 0) &= 2\alpha p(t, \tau), \\ p(t, 0) &= \beta(E_1(t))N(t), \\ m(t, 0) &= K_N(E_3(t))N(t) + 2K_P(E_4(t))p(t, \tau), \end{aligned} \tag{2.2.2}$$

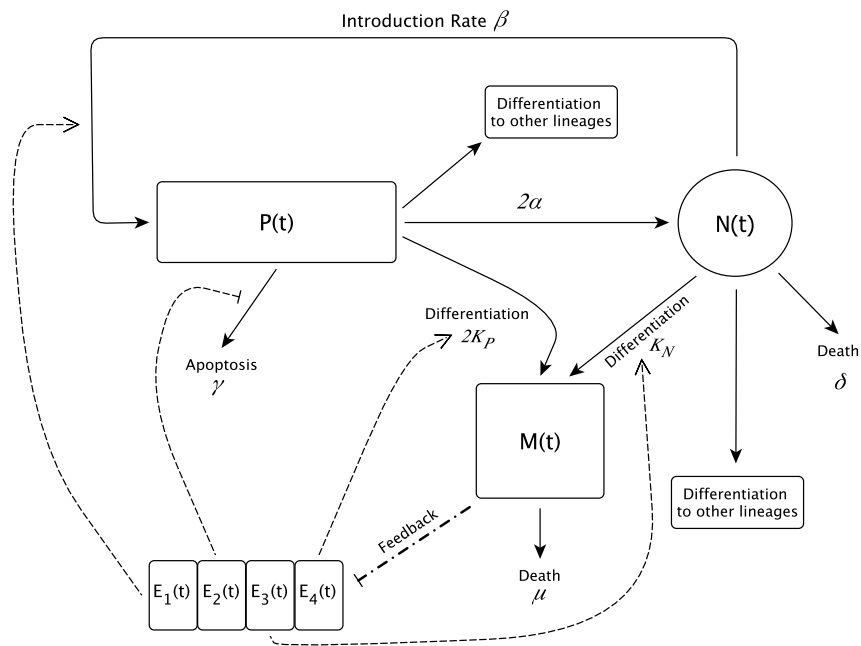


Figure 2.1: Schematic representation of HSC dynamics. Solid arrows represent the mechanisms taken into account: differentiation, cell division, reintroduction into the proliferating phase, apoptosis and natural death. The dependency of the parameters upon growth factors are represented by dashed lines. The dash-dotted line represents the feedback control from mature cells to the growth factors.

where

$$N(t) = \int_0^{+\infty} n(t, a) da, \quad P(t) = \int_0^\tau p(t, a) da, \quad M(t) = \int_0^{+\infty} m(t, a) da,$$

and  $E_i(t)$ ,  $i = 1, 2, 3, 4$ , are growth factor concentrations. Initial conditions of (2.2.1) are given by nonnegative  $L^1$ -functions  $n_0$ ,  $p_0$  and  $m_0$ , such that

$$\begin{aligned} n(0, a) &= n_0(a), & m(0, a) &= m_0(a), & \text{for } a \geq 0, \\ p(0, a) &= p_0(a), & & & \text{for } a \in [0, \tau]. \end{aligned} \quad (2.2.3)$$

In addition, we assume that

$$\lim_{a \rightarrow +\infty} n(t, a) = \lim_{a \rightarrow +\infty} m(t, a) = 0, \quad \text{for } t \geq 0.$$

The growth factor concentrations  $E_i(t)$ , follow the evolution equations

$$E_i'(t) = -k_i E_i(t) + f_i(M(t)), \quad (2.2.4)$$

where the coefficients  $k_i > 0$  are the degradation rates of the growth factors  $E_i$ . We assume that the functions  $M \mapsto f_i(M)$  are positive, decreasing and satisfy  $\lim_{M \rightarrow +\infty} f_i(M) = 0$ .

## 2.3 Reduction to a delay differential system

The age-structured model (2.2.1)-(2.2.2)-(2.2.3)-(2.2.4) can be reduced to a delay differential system. The method of characteristics implies, for  $t > 0$  and  $a \in (0, \tau)$ , that

$$p(t, a) = \begin{cases} p_0(a-t) \exp\left(-\int_0^t \gamma(E_2(s)) ds\right), & \text{if } 0 < t < a, \\ \beta(E_1(t-a)) N(t-a) \exp\left(-\int_{t-a}^t \gamma(E_2(s)) ds\right), & \text{if } 0 < a < t. \end{cases} \quad (2.3.1)$$

Integrating the first equation of (2.2.1) with respect to the age variable, we obtain

$$N'(t) = -\delta N(t) - \beta(E_1(t)) N(t) + n(t, 0).$$

Using the first equation of (2.2.2), we obtain

$$N'(t) = -(\delta + \beta(E_1(t))) N(t) + 2\alpha p(t, \tau).$$

Thanks to (2.3.1), we obtain

$$\begin{aligned} N'(t) &= -(\delta + \beta(E_1(t))) N(t) \\ &+ 2\alpha \begin{cases} p_0(a-t) \exp(-\int_0^t \gamma(E_2(s)) ds), & \text{if } t < \tau, \\ \beta(E_1(t-\tau)) N(t-\tau) \exp(-\int_{t-\tau}^t \gamma(E_2(s)) ds), & \text{if } t > \tau. \end{cases} \end{aligned} \quad (2.3.2)$$

Integrating the last equation of (2.2.1) with respect to the age variable, we obtain

$$M'(t) = -\mu M(t) + m(t, 0). \quad (2.3.3)$$

Then, using the last boundary condition of (2.2.2), we obtain

$$M'(t) = -\mu M(t) + K_N(E_3(t))N(t) + 2K_P(E_4(t))p(t, \tau).$$

We conclude that

$$\begin{aligned} M'(t) &= -\mu M(t) + K_N(E_3(t))N(t) + 2K_P(E_4(t)) \\ &\times \begin{cases} p_0(a-t) \exp(-\int_0^t \gamma(E_2(s)) ds), & \text{if } t < \tau, \\ \beta(E_1(t-\tau))N(t-\tau) \exp(-\int_{t-\tau}^t \gamma(E_2(s)) ds), & \text{if } t > \tau. \end{cases} \end{aligned} \quad (2.3.4)$$

Note that, for  $t > \tau$ , we have

$$P(t) = \int_0^\tau \beta(E_1(t-a))N(t-a) \exp\left(-\int_{t-a}^t \gamma(E_2(s)) ds\right) da.$$

Then, the asymptotic behavior of  $P$  is related to  $E_1$ ,  $E_2$  and  $N$ . On the other hand,  $N$ ,  $M$ , and  $E_i$ , do not depend on  $P$ , then, we can focus on the study of the solutions  $(N, M, E_i)$ . One can notice that, on the interval  $[0, \tau]$  the functions  $(N, M, E_i)$  satisfy a non-autonomous ordinary differential system, and for  $t > \tau$ , they satisfy the delay differential system

$$\begin{aligned} N'(t) &= -(\delta + \beta(E_1(t)))N(t) \\ &\quad + 2\alpha\beta(E_1(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right), \\ M'(t) &= -\mu M(t) + K_N(E_3(t))N(t) \\ &\quad + 2K_P(E_4(t))\beta(E_1(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right), \\ E_i'(t) &= -k_i E_i(t) + f_i(M(t)), \end{aligned} \quad (2.3.5)$$

with initial conditions solutions of the ordinary differential system (2.2.4)-(2.3.2)-(2.3.4) defined on the interval  $[0, \tau]$ . For each continuous initial condition, the system (2.3.5) has a unique solution, defined for  $t > \tau$  (see Hale and Verduyn Lunel [58]). From now on, we make a translation of the initial conditions so as to define them on the interval  $[-\tau, 0]$ , as it can be found in Hale and Verduyn Lunel [58].

## 2.4 Positivity and boundedness of solutions

We focus on the positivity and boundedness properties of the solutions  $(N, M, E_i)$  of system (2.3.5). The following result states that all solutions of system (2.3.5) are nonnegative, provided that initial conditions are nonnegative.

**Proposition 2.4.1.** *The solutions of system (2.3.5) associated with nonnegative initial conditions are nonnegative.*

*Proof.* Let  $(N(t), M(t), E_i(t))$  be a solution of (2.3.5). Firstly, we check that  $N$  is nonnegative. Assume that there exist  $t_0 > 0$  and  $\epsilon \in (0, \tau)$  such that  $N(t) > 0$ , for

$0 < t < t_0$ ,  $N(t_0) = 0$  and  $N(t) < 0$ , for  $t \in (t_0, t_0 + \epsilon)$ . Let  $t \in (t_0, t_0 + \epsilon)$ . It follows from (2.3.5), that

$$N'(t_0) = 2\alpha\beta(E_1(t_0 - \tau))N(t_0 - \tau) \exp\left(-\int_{t_0-\tau}^{t_0} \gamma(E_2(s)) ds\right) > 0.$$

This gives a contradiction. Consequently,  $N(t)$  is nonnegative for  $t \geq 0$ . Using a similar reasoning, we prove that  $M(t)$  is nonnegative. Finally, the positivity of  $E_i(t)$  follows from the fact that  $f_i$  is positive.  $\square$

We now concentrate on the boundedness properties of the solutions of system (2.3.5). We start by proving the following lemma.

**Lemma 2.4.2.** *The solution  $E_i(t)$  of (2.3.5) is strictly decreasing as long as  $E_i(t) > f_i(0)/k_i$ , and either:*

- (i)  $E_i(t) > f_i(0)/k_i$  for all  $t \geq 0$  and then,  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ , or
- (ii) there exists  $\bar{t}_i \geq 0$  such that  $E_i(\bar{t}_i) = f_i(0)/k_i$  and then,  $E_i(t) \leq f_i(0)/k_i$ , for all  $t \geq \bar{t}_i$ .

*Proof.* Using the variation of constant formula, we can write

$$E_i(t) = e^{-k_i t} E_i(0) + e^{-k_i t} \int_0^t e^{k_i s} f_i(M(s)) ds, \quad t \geq 0.$$

Then, we deduce that

$$0 \leq E_i(t) \leq e^{-k_i t} E_i(0) + \frac{f_i(0)}{k_i} (1 - e^{-k_i t}) \leq \max\left\{E_i(0), \frac{f_i(0)}{k_i}\right\}.$$

Therefore,  $E_i$  is bounded. Suppose that  $E_i(t) > f_i(0)/k_i$ . Then

$$E_i'(t) = -k_i E_i(t) + f_i(M(t)) < f_i(0) + f_i(M(t)) \leq 0.$$

Consequently,  $E_i(t)$  is decreasing as long as  $E_i(t) > f_i(0)/k_i$ .

(i) Suppose that  $E_i(t) > f_i(0)/k_i$ , for all  $t \geq 0$ . Then,  $E_i(t)$  is decreasing on  $[0, +\infty)$ , and  $L_i := \lim_{t \rightarrow +\infty} E_i(t)$  exists. Assume by contradiction that  $L_i > f_i(0)/k_i$ . Then

$$E_i'(t) + k_i E_i(t) = f_i(M(t)) \leq f_i(0), \quad t \geq 0.$$

By taking the limit in this last equation, we obtain  $k_i L_i \leq f_i(0)$ . This gives a contradiction. We conclude that  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ .

(ii) Suppose there exists  $\bar{t}_i \geq 0$  such that  $E_i(\bar{t}_i) = f_i(0)/k_i$ . Then

$$E_i'(\bar{t}_i) = -f_i(0) + f_i(M(\bar{t}_i)) \leq 0.$$

Our objective is to prove that  $E_i(t) \leq f_i(0)/k_i$ , for all  $t \geq \bar{t}_i$ . If we suppose the existence of  $\epsilon > 0$  such that  $E_i(\bar{t}_i + \epsilon) > f_i(0)/k_i$ , we obtain a contradiction, because the function  $E_i(t)$  is strictly decreasing as long as  $E_i(t) > f_i(0)/k_i$ .  $\square$

Next, we state and prove a result regarding the boundedness property of the solutions of (2.3.5). In the rest of the paper, we suppose that  $\delta > 0$ . The case  $\delta = 0$  should be treated separately, and so it will not be considered here.

**Proposition 2.4.3.** *Assume that*

$$\left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2}\right)\right) - 1\right)\beta\left(\frac{f_1(0)}{k_1}\right) < \delta. \quad (2.4.1)$$

*Then the solutions of system (2.3.5) are bounded.*

*Proof.* A direct application of Lemma 2.4.2 implies that  $E_i$  are always bounded. Furthermore, it is not difficult to see that the boundedness of  $N$  implies the boundedness of  $M$ . Then, we concentrate on the boundedness of  $N$ .

By (2.4.1) and the continuity of  $\gamma$  and  $\beta$ , we can take  $\epsilon > 0$  small enough such that

$$\left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right)\beta\left(\frac{f_1(0)}{k_1} + \epsilon\right) < \delta. \quad (2.4.2)$$

Lemma 2.4.2 implies that there exists  $\bar{t}_\epsilon \geq 0$  such that  $E_i(t) \leq f_i(0)/k_i + \epsilon$ , for all  $t \geq \bar{t}_\epsilon$ . Consider the function

$$Z_\epsilon(t) = N(t) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right)\left(\int_{t-\tau}^t \beta(E_1(\theta))N(\theta) d\theta\right), \quad t \geq \bar{t}_\epsilon + \tau.$$

It follows that

$$\begin{aligned} Z'_\epsilon(t) &= N'(t) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right)\left(\beta(E_1(t))N(t) \right. \\ &\quad \left. - \beta(E_1(t-\tau))N(t-\tau)\right), \\ &= -(\delta + \beta(E_1(t)))N(t) \\ &\quad + 2\alpha\beta(E_1(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s))ds\right) \\ &\quad + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right)\beta(E_1(t))N(t) \\ &\quad - 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right)\beta(E_1(t-\tau))N(t-\tau). \end{aligned}$$

This implies

$$\begin{aligned} Z'_\epsilon(t) &= -\left[\delta - \left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right)\beta(E_1(t))\right]N(t) \\ &\quad - 2\alpha\left(\exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right)\right)\beta(E_1(t-\tau))N(t-\tau). \end{aligned}$$

As the function  $\gamma$  is decreasing, we have

$$\exp\left(-\int_{t-\tau}^t \gamma(E_2(s))ds\right) \leq \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right), \quad t \geq \bar{t}_\epsilon + \tau.$$

Then

$$Z'_\epsilon(t) \leq -\left(\delta - \left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right)\beta(E_1(t))\right)N(t).$$

We have to consider two cases. Suppose that

$$2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) \leq 1.$$

Then  $Z'_\epsilon(t) \leq 0$ .

Now, suppose that

$$2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) > 1.$$

Since  $\beta$  is increasing, we have

$$\beta(E_1(t)) < \beta\left(\frac{f_1(0)}{k_1} + \epsilon\right).$$

Thanks to (2.4.2), we obtain

$$\delta > \left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right)\beta(E_1(t)).$$

This implies  $Z'_\epsilon(t) \leq 0$  for  $t \geq \bar{t}_\epsilon + \tau$ . We conclude that  $Z_\epsilon$  is bounded. Consequently,  $N$  is also bounded.  $\square$

## 2.5 Existence of steady states

In this section, we study the existence of steady states of (2.3.5). Let  $(\bar{N}, \bar{M}, \bar{E}_i)$  be a steady state of (2.3.5). Then, it satisfies

$$\begin{aligned} (\delta + \beta(\bar{E}_1))\bar{N} &= 2\alpha\beta(\bar{E}_1)\bar{N}e^{-\tau\gamma(\bar{E}_2)}, \\ \mu\bar{M} &= K_N(\bar{E}_3)\bar{N} + 2K_P(\bar{E}_4)\beta(\bar{E}_1)\bar{N}e^{-\tau\gamma(\bar{E}_2)}, \\ k_i\bar{E}_i &= f_i(\bar{M}). \end{aligned} \tag{2.5.1}$$

One can easily see that  $(0, 0, f_i(0)/k_i)$  is always a steady state (the trivial steady state). A nontrivial steady state  $(\bar{N}, \bar{M}, \bar{E}_i) \neq (0, 0, f_i(0)/k_i)$ , satisfies

$$\begin{aligned} \delta &= (2\alpha e^{-\tau\gamma(\bar{E}_2)} - 1)\beta(\bar{E}_1), \\ \bar{N} &= \frac{\mu\bar{M}}{K_N(\bar{E}_3) + 2K_P(\bar{E}_4)\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)}}, \\ \bar{E}_i &= \frac{f_i(\bar{M})}{k_i}. \end{aligned} \tag{2.5.2}$$

It is clear that, the existence and uniqueness of nontrivial steady state is equivalent to finding  $\bar{M} > 0$ , a solution of the equation

$$\delta = \left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(\bar{M})}{k_2}\right)\right) - 1\right)\beta\left(\frac{f_1(\bar{M})}{k_1}\right). \tag{2.5.3}$$

**Proposition 2.5.1.** *Assume that*

$$\delta < \left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2}\right)\right) - 1\right)\beta\left(\frac{f_1(0)}{k_1}\right). \quad (2.5.4)$$

*Then there exists a unique nontrivial steady state  $(\bar{N}, \bar{M}, \bar{E}_i)$  of (2.3.5). If (2.5.4) does not hold, then  $(0, 0, f_i(0)/k_i)$  is the only steady state of (2.3.5).*

*Proof.* We define the function

$$\Psi(x) = \xi(x)\eta(x), \quad x \geq 0,$$

where

$$\xi(x) = 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(x)}{k_2}\right)\right) - 1, \quad \eta(x) = \beta\left(\frac{f_1(x)}{k_1}\right), \quad x \geq 0.$$

Then equation (2.5.3) becomes  $\Psi(x) = \delta$  and inequality (2.5.4) can be written as  $\delta < \Psi(0)$ . Note that  $\lim_{x \rightarrow +\infty} f_i(x) = 0$  and  $\beta(0) = 0$ . Then  $\lim_{x \rightarrow +\infty} \Psi(x) = 0$ . We conclude that (2.5.3) has at least one solution if and only if  $\delta < \Psi(0)$ . To prove the uniqueness, we note that  $\beta$  is increasing,  $f_i$  and  $\gamma$  are decreasing. Then, the functions  $\xi$  and  $\eta$  are decreasing and satisfy  $\lim_{x \rightarrow +\infty} \xi(x) = 2\alpha e^{-\tau\gamma(0)} - 1$  and  $\lim_{x \rightarrow +\infty} \eta(x) = 0$ . Firstly, we suppose that  $2\alpha e^{-\tau\gamma(0)} - 1 \geq 0$ . Then,  $\xi(0) > 0$ . Consequently,  $\Psi$  is positive, decreasing on  $[0, +\infty)$  and satisfies  $\lim_{x \rightarrow +\infty} \Psi(x) = 0$ . We conclude that (2.5.3) has a unique positive solution  $\bar{M}$  if and only if  $\delta < \Psi(0)$ . Secondly, we suppose that  $2\alpha e^{-\tau\gamma(0)} - 1 < 0$  and  $\xi(0) > 0$ . Then, there exists a unique  $\tilde{M} > 0$  such that  $\Psi(\tilde{M}) = 0$ ,  $\Psi(x) > 0$  for  $0 \leq x < \tilde{M}$  and  $\Psi(x) < 0$  for  $x > \tilde{M}$ . Consequently,  $\Psi$  is positive and decreasing on the interval  $[0, \tilde{M}]$  with  $\Psi(\tilde{M}) = 0$ . Then (2.5.3) has a unique solution  $\bar{M} \in (0, \tilde{M})$  if and only if  $\delta < \Psi(0)$ . The existence and uniqueness of  $\bar{E}_i$  and  $\bar{N}$  follow immediately from (2.5.2). This completes the proof.  $\square$

Note that condition (2.5.4) is equivalent to

$$\begin{aligned} 1 \geq \alpha > \alpha_{\min} &:= \frac{\delta + \beta(f_1(0)/k_1)}{2\beta(f_1(0)/k_1)} = \frac{1}{2} + \frac{\delta}{2\beta(f_1(0)/k_1)}, \\ 0 \leq \tau < \tau_{\max} &:= \frac{1}{\gamma(f_2(0)/k_2)} \ln\left(\frac{2\alpha\beta(f_1(0)/k_1)}{\delta + \beta(f_1(0)/k_1)}\right). \end{aligned} \quad (2.5.5)$$

In the next section, we analyze the asymptotic behavior of the solutions of system (2.3.5) by studying the asymptotic stability of its steady states.

## 2.6 Global asymptotic stability of trivial steady state

We assume, throughout this section, that the function  $\beta$  is continuously differentiable on  $[0, +\infty)$ . We begin by establishing the global asymptotic stability of the trivial steady state  $(0, 0, f_i(0)/k_i)$ . First let us recall a useful lemma (see Gopalsamy [51]), that will allow us to establish the next result.

**Lemma 2.6.1.** *Let  $f : (a, +\infty) \rightarrow \mathbb{R}$ ,  $a \in \mathbb{R}$ , be a differentiable function. If  $\lim_{t \rightarrow +\infty} f(t)$  exists and  $f'(t)$  is uniformly continuous on  $(a, +\infty)$ , then*

$$\lim_{t \rightarrow +\infty} f'(t) = 0.$$



**Lemma 2.6.2.** *Let  $(N(t), M(t), E_i(t))$  be a bounded solution of (2.3.5). Then, the following three statements are equivalent*

$$\lim_{t \rightarrow +\infty} N(t) = 0, \quad \lim_{t \rightarrow +\infty} M(t) = 0, \quad \lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i, \quad i = 1, 2, 3, 4.$$

*Proof.* We begin by proving that  $\lim_{t \rightarrow +\infty} N(t) = 0$  if and only if  $\lim_{t \rightarrow +\infty} M(t) = 0$ . We first assume that  $\lim_{t \rightarrow +\infty} N(t) = 0$ . We have  $M'(t) = -\mu M(t) + F(t)$ , with

$$\begin{aligned} F(t) &= K_N(E_3(t))N(t) + 2K_P(E_4(t))\beta(E_1(t - \tau)) \\ &\quad \times N(t - \tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right). \end{aligned}$$

Then  $\lim_{t \rightarrow +\infty} F(t) = 0$ . Using the variation of constant formula, we can write

$$M(t) = e^{-\mu t} M(0) + e^{-\mu t} \int_0^t e^{\mu s} F(s) ds, \quad t \geq 0.$$

Let  $\epsilon > 0$  be fixed. Since  $N(t)$  tends to zero when  $t$  tends to  $+\infty$ , there exists  $t_\epsilon > 0$  such that

$$F(t) < \frac{\mu\epsilon}{2}, \quad e^{-\mu t} \left( M(0) + \int_0^{t_\epsilon} e^{\mu s} F(s) ds \right) < \frac{\epsilon}{2}, \quad \text{for } t \geq t_\epsilon.$$

Then, for  $t \geq t_\epsilon$ , we have

$$M(t) \leq e^{-\mu t} \left( M(0) + \int_0^{t_\epsilon} e^{\mu s} F(s) ds \right) + e^{-\mu t} \left( \int_{t_\epsilon}^t e^{\mu s} F(s) ds \right),$$

with

$$e^{-\mu t} \left( \int_{t_\epsilon}^t e^{\mu s} F(s) ds \right) \leq \frac{\epsilon}{2} (1 - e^{\mu(t_\epsilon - t)}) \leq \frac{\epsilon}{2}.$$

Consequently,  $M(t) < \epsilon$  for  $t \geq t_\epsilon$ . We have proved that  $\lim_{t \rightarrow +\infty} M(t) = 0$ .

Secondly, we assume that  $\lim_{t \rightarrow +\infty} M(t) = 0$ . Then the solution  $(N, M, E_i)$  is bounded, and the derivative  $(N', M', E'_i)$  is also bounded. Furthermore,  $M'(t)$  is differentiable for  $t > \tau$ , and since  $N, M, E_i, N', M', E'_i$  are bounded for  $t > \tau$ ,  $M''$  is bounded. Then  $M'$  is uniformly continuous. Consequently, Lemma 2.6.1 implies that  $\lim_{t \rightarrow +\infty} M'(t) = 0$ . From the equation satisfied by  $M$ , we deduce that  $\lim_{t \rightarrow +\infty} F(t) = 0$ . In particular,  $\lim_{t \rightarrow +\infty} K_N(E_3(t))N(t) = 0$ . Suppose that  $\lim_{t \rightarrow +\infty} K_N(E_3(t)) = 0$ . That means that  $\lim_{t \rightarrow +\infty} E_3(t) = 0$ . Then, from the equation satisfied by  $E_3$ , we deduce that  $\lim_{t \rightarrow +\infty} f_3(M(t)) = 0$ . This gives a contradiction because  $\lim_{t \rightarrow +\infty} M(t) = 0$  and  $f_3(0) > 0$ . Then, we conclude that  $\lim_{t \rightarrow +\infty} N(t) = 0$ . Thirdly, we assume that  $\lim_{t \rightarrow +\infty} M(t) = 0$  and we will prove that  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ . Thanks to Lemma 2.4.2, it suffices to prove the result for the case  $E_i(t) < f_i(0)/k_i$  for all  $t > \bar{t}$ . Without loss of generality, we can choose  $\bar{t} = 0$ . We put  $F_i(t) = f_i(0)/k_i - E_i(t)$  and  $G_i(t) = f_i(0) - f_i(M(t))$ . Then,  $F_i$  satisfies the following differential equation

$$F'_i(t) = -k_i F_i(t) + G_i(t),$$

with  $F_i(t) > 0$  and  $G_i(t) > 0$  for all  $t \geq 0$  and  $\lim_{t \rightarrow +\infty} G_i(t) = 0$ . Then, using the same argument as in the first part of this proof, we obtain  $\lim_{t \rightarrow +\infty} F_i(t) = 0$ . This means that  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ .

Finally, we suppose that  $\lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i$ . Then by Lemma 2.6.1, we have  $\lim_{t \rightarrow +\infty} E_i'(t) = 0$ . We deduce that  $\lim_{t \rightarrow +\infty} f_i(M(t)) = f_i(0)$ . As the function  $f_i$  is continuous and strictly decreasing from  $[0, +\infty)$  into  $(0, f_i(0)]$ , we conclude that  $\lim_{t \rightarrow +\infty} M(t) = 0$ . This completes the proof.  $\square$

Next, we prove a result dealing with the global asymptotic stability of the trivial steady state  $(0, 0, f_i(0)/k_i)$ .

**Theorem 2.6.3.** *Assume that (2.4.1) holds. That is to say that  $(0, 0, f_i(0)/k_i)$  is the only steady state. Then, all solutions  $(N(t), M(t), E_i(t))$  of (2.3.5) converge to  $(0, 0, f_i(0)/k_i)$ ,  $i = 1, 2, 3, 4$ .*

*Proof.* As in the proof of Proposition 2.4.3, we take  $\epsilon > 0$  small enough such that

$$\left(2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right)\beta\left(\frac{f_1(0)}{k_1} + \epsilon\right) < \delta,$$

and  $\bar{t}_\epsilon \geq 0$  such that  $E_i(t) \leq f_i(0)/k_i + \epsilon$ , for all  $t \geq \bar{t}_\epsilon$ . Consider the functional  $V_\epsilon : (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6 \rightarrow \mathbb{R}_+$ , Defined by

$$\begin{aligned} \Phi &= (\varphi, \psi, \chi_1, \chi_2, \chi_3, \chi_4), \\ V_\epsilon(\Phi) &= \varphi(\bar{t}_\epsilon + \tau) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) \\ &\quad \times \int_{-\tau}^0 \beta(\chi_1(\theta + \bar{t}_\epsilon + \tau))\varphi(\theta + \bar{t}_\epsilon + \tau) d\theta. \end{aligned}$$

The composition with the solution  $X(t) := (N(t), M(t), E_i(t))$  of equation (2.3.5) leads, for  $t \geq \bar{t}_\epsilon + \tau$ , to the function

$$t \mapsto V_\epsilon(X_t) = N(t) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) \int_{t-\tau}^t \beta(E_1(s))N(s)ds.$$

Then, the derivative along the solution of system (2.3.5) gives

$$\begin{aligned} &\frac{d}{dt}V_\epsilon(X_t) \\ &= N'(t) + 2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) [\beta(E_1(t))N(t) - \beta(E_1(t-\tau))N(t-\tau)], \\ &= -(\delta + \beta(E_1(t)))N(t) \\ &\quad + 2\alpha\beta(E_1(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E_2(s)) ds\right) \\ &\quad + 2\alpha \exp(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)) [\beta(E_1(t))N(t) - \beta(E_1(t-\tau))N(t-\tau)], \\ &= -\left(\delta - [2\alpha \exp(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)) - 1]\beta(E_1(t))\right)N(t) \\ &\quad - 2\alpha \left[\exp(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)) - \exp\left(-\int_{-\tau}^0 \gamma(E_2(t+s)) ds\right)\right] \\ &\quad \times \beta(E_1(t-\tau))N(t-\tau). \end{aligned}$$

Let  $-\tau \leq s \leq 0$ . Since  $t \geq \bar{t}_\epsilon + \tau$ , then  $E_i(t+s) < \frac{f_i(0)}{k_i} + \epsilon$ . Consequently,  $-\gamma(E_2(s+t)) < -\gamma(\frac{f_2(0)}{k_2} + \epsilon)$  and  $\beta(E_1(t)) < \beta(\frac{f_1(0)}{k_1} + \epsilon)$ . This implies

$$\begin{aligned} \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) &> \exp\left(-\int_{-\tau}^0 \gamma(E_2(s+t)) ds\right), \\ \delta &> \left[2\alpha \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2} + \epsilon\right)\right) - 1\right] \beta(E_1(t)). \end{aligned}$$

Thus,

$$\dot{V}_\epsilon(\Phi) \leq 0, \quad \text{for all } \Phi \in (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6,$$

where  $\dot{V}_\epsilon$  is the derivative of  $V_\epsilon$  along the solutions of (2.3.5). Now, let

$$S := \{\Phi \in (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6 : \dot{V}_\epsilon(\Phi) = 0\}.$$

We deduce that

$$S = \{\Phi \in (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6 : \varphi(\bar{t}_\epsilon + \tau) = \varphi(\bar{t}_\epsilon) = 0\}.$$

We also consider the set  $\Omega$ , defined as the largest set in  $S$  which is invariant with respect to system (2.3.5). Let  $X_t$  be a solution of (2.3.5) associated with an initial condition  $\Phi \in \Omega$ . Then,  $X_t \in \Omega$  for all  $t \geq \bar{t}_\epsilon + \tau$  is equivalent to  $N(t) = 0$  for all  $t \geq \bar{t}_\epsilon + \tau$ . Consequently,

$$\Omega = \{0\} \times (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^5.$$

From Hale and Verduyn Lunel [58, page 143], all bounded solutions  $X_t$  of (2.3.5) converge to  $\Omega$  as  $t$  tends to  $+\infty$ . From Proposition 2.4.1, all solutions of (2.3.5) are bounded provided that (2.4.1) holds. Then, all solutions  $X_t$  converge to  $\Omega$ . We deduce that for all  $\Phi \in (C([\bar{t}_\epsilon, \bar{t}_\epsilon + \tau], \mathbb{R}_+))^6$ ,

$$\lim_{t \rightarrow +\infty} N(t) = 0.$$

Then, from Lemma 2.6.2, we conclude that

$$\lim_{t \rightarrow +\infty} M(t) = 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} E_i(t) = f_i(0)/k_i, \quad i = 1, 2, 3, 4.$$

This completes the proof.  $\square$

Next, we linearize system (2.3.5) about its steady states, and we determine the characteristic equation. Let  $(\bar{N}, \bar{M}, \bar{E}_i)$  be a steady state of (2.3.5). We set

$$X(t) = N(t) - \bar{N}, \quad Y(t) = M(t) - \bar{M}, \quad Z_i(t) = E_i(t) - \bar{E}_i.$$

The linearized system of (2.3.5) around  $(\bar{N}, \bar{M}, \bar{E}_i)$  is

$$\begin{aligned}
X'(t) &= -(\delta + \beta(\bar{E}_1))X(t) - \beta'(\bar{E}_1)\bar{N}Z_1(t) \\
&\quad + 2\alpha\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)}X(t - \tau) + 2\alpha\bar{N}\beta'(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)}Z_1(t - \tau) \\
&\quad - 2\tau\alpha\bar{N}\beta(\bar{E}_1)\gamma'(\bar{E}_2)e^{-\tau\gamma(\bar{E}_2)}\int_{-\tau}^0 Z_2(t + s) ds, \\
Y'(t) &= -\mu Y(t) + K_N(\bar{E}_3)X(t) + K'_N(\bar{E}_3)\bar{N}Z_3(t) \\
&\quad + 2K_P(\bar{E}_4)\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)}X(t - \tau) + 2K'_P(\bar{E}_4)\beta(\bar{E}_1)\bar{N}e^{-\tau\gamma(\bar{E}_2)}Z_4(t) \\
&\quad + 2K_P(\bar{E}_4)\beta'(\bar{E}_1)\bar{N}e^{-\tau\gamma(\bar{E}_2)}Z_1(t - \tau) \\
&\quad - 2\tau K_P(\bar{E}_4)\beta(\bar{E}_1)\bar{N}\gamma'(\bar{E}_2)e^{-\tau\gamma(\bar{E}_2)}\int_{-\tau}^0 Z_2(t + s) ds, \\
Z'_i(t) &= -k_i Z_i(t) + f'_i(\bar{M})Y(t).
\end{aligned} \tag{2.6.1}$$

The above system has the form

$$U'(t) = AU(t) + BU(t - \tau) + C\left(\int_{-\tau}^0 U(t + s) ds\right), \tag{2.6.2}$$

with  $U(t) = (X(t), Y(t), Z_i(t))^T \in \mathbb{R}^6$ , where

$$\begin{aligned}
A &= \begin{pmatrix} -(\delta + \beta(\bar{E}_1)) & 0 & -\beta'(\bar{E}_1)\bar{N} & 0 & 0 & 0 \\ K_N(\bar{E}_3) & -\mu & 0 & 0 & K'_N(\bar{E}_3)\bar{N} & \bar{N}H_4 \\ 0 & f'_1(\bar{M}) & -k_1 & 0 & 0 & 0 \\ 0 & f'_2(\bar{M}) & 0 & -k_2 & 0 & 0 \\ 0 & f'_3(\bar{M}) & 0 & 0 & -k_3 & 0 \\ 0 & f'_4(\bar{M}) & 0 & 0 & 0 & -k_4 \end{pmatrix}, \\
B &= \begin{pmatrix} H_0 & 0 & \bar{N}H_1 & 0 & 0 & 0 \\ \bar{H}_0 & 0 & \bar{N}\bar{H}_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad C = \begin{pmatrix} 0 & 0 & 0 & \bar{N}H_2 & 0 & 0 \\ 0 & 0 & 0 & \bar{N}\bar{H}_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},
\end{aligned}$$

with

$$\begin{aligned}
H_0 &:= 2\alpha\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)} \geq 0, \\
H_1 &:= \frac{dH_0}{d\bar{E}_1} = 2\alpha\beta'(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)} \geq 0, \\
H_2 &:= \frac{dH_0}{d\bar{E}_2} = -2\tau\alpha\beta(\bar{E}_1)\gamma'(\bar{E}_2)e^{-\tau\gamma(\bar{E}_2)} \geq 0,
\end{aligned}$$

and

$$\begin{aligned}\bar{H}_0 &:= 2K_P(\bar{E}_4)\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)} \geq 0, \\ \bar{H}_1 &:= \frac{d\bar{H}_0}{d\bar{E}_1} = 2K_P(\bar{E}_4)\beta'(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)} \geq 0, \\ \bar{H}_2 &:= \frac{d\bar{H}_0}{d\bar{E}_2} = -2\tau K_P(\bar{E}_4)\beta(\bar{E}_1)\gamma'(\bar{E}_2)e^{-\tau\gamma(\bar{E}_2)} \geq 0, \\ \bar{H}_4 &:= \frac{d\bar{H}_0}{d\bar{E}_4} = 2K'_P(\bar{E}_4)\beta(\bar{E}_1)e^{-\tau\gamma(\bar{E}_2)} \geq 0.\end{aligned}$$

The relationship between the expressions  $H_0$  and  $\bar{H}_0$  is given by

$$\alpha\bar{H}_0 = K_P(\bar{E}_4)H_0.$$

The characteristic equation associated to the steady state  $(\bar{N}, \bar{M}, \bar{E}_i)$  is

$$\Delta(\lambda) = \det\left(\lambda I - A - Be^{-\lambda\tau} - C \int_{-\tau}^0 e^{\lambda\theta} ds\right) = 0. \quad (2.6.3)$$

Then, we have the following result.

**Theorem 2.6.4.** *The trivial steady state of (2.3.5) is unstable when (2.5.4) holds.*

*Proof.* When  $(\bar{N}, \bar{M}, \bar{E}_i) = (0, 0, f_i(0)/k_i)$  system (2.6.2) becomes

$$U'(t) = AU(t) + BU(t - \tau), \quad (2.6.4)$$

with  $U(t) = (X(t), Y(t), Z_i(t))^T \in \mathbb{R}^6$ ,

$$A = \begin{pmatrix} -(\delta + \beta(f_1(0)/k_1)) & 0 & 0 & 0 & 0 & 0 \\ K_N(f_3(0)/k_3) & -\mu & 0 & 0 & 0 & 0 \\ 0 & f'_1(0) & -k_1 & 0 & 0 & 0 \\ 0 & f'_2(0) & 0 & -k_2 & 0 & 0 \\ 0 & f'_3(0) & 0 & 0 & -k_3 & 0 \\ 0 & f'_4(0) & 0 & 0 & 0 & -k_4 \end{pmatrix},$$

and

$$B = 2\beta\left(\frac{f_1(0)}{k_1}\right) \exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2}\right)\right) \begin{pmatrix} \alpha & 0 & 0 & 0 & 0 & 0 \\ K_P(f_4(0)/k_4) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

The characteristic equation (2.6.3) becomes

$$\Delta(\lambda) = \det(\lambda I - A - Be^{-\lambda\tau}) = 0.$$

Then

$$\Delta(\lambda) = (\lambda + \mu) \prod_{i=1}^4 (\lambda + k_i) \bar{\Delta}(\lambda),$$

where

$$\bar{\Delta}(\lambda) = \lambda + \delta + \beta\left(\frac{f_1(0)}{k_1}\right) - 2\alpha\beta\left(\frac{f_1(0)}{k_1}\right) \exp\left(-\tau\left(\lambda + \gamma\left(\frac{f_2(0)}{k_2}\right)\right)\right).$$

The eigenvalues of (2.6.4) are  $\lambda = -\mu < 0$ ,  $\lambda = -k_i < 0$ ,  $i \in 1, 2, 3, 4$  and roots of the equation  $\bar{\Delta}(\lambda) = 0$ .

Let  $\lambda \in \mathbb{R}$ . We have

$$\begin{aligned} \bar{\Delta}'(\lambda) &= 1 + 2\alpha\tau\beta\left(\frac{f_1(0)}{k_1}\right) \exp\left(-\tau\left(\lambda + \gamma\left(\frac{f_2(0)}{k_2}\right)\right)\right) > 0, \\ \bar{\Delta}(0) &= \delta - 2\alpha\left(\exp\left(-\tau\gamma\left(\frac{f_2(0)}{k_2}\right)\right) - 1\right)\beta\left(\frac{f_1(0)}{k_1}\right), \\ \lim_{\lambda \rightarrow +\infty} \bar{\Delta}(\lambda) &= +\infty. \end{aligned}$$

Thanks to (2.5.4), we have  $\bar{\Delta}(0) < 0$ . Thus, there exists  $\lambda_0 > 0$  such that  $\bar{\Delta}(\lambda_0) = 0$ . Hence, the instability of the trivial steady state holds.  $\square$

The last theorem completes the global asymptotic stability of the trivial steady state  $(0, 0, f_i(0)/k_i)$  obtained in Theorem 2.6.3, and allows us to entirely determine its dynamics.

## 2.7 Local asymptotic stability of the positive steady state

We assume throughout this section, that condition (2.5.4) is satisfied, or equivalently (2.5.5), to ensure the existence and uniqueness of the positive steady state  $(\bar{N}, \bar{M}, \bar{E}_i)$  of (2.3.5). The nature of the characteristic equation associated to the linearized system around  $(\bar{N}, \bar{M}, \bar{E}_i)$  induces some technical difficulties. To avoid these difficulties, we make the following assumption

$$k_i = k, \quad f_i = f, \quad E_i = E, \quad i = 1, 2, 3, 4.$$

Then system (2.3.5) becomes

$$\begin{aligned} N'(t) &= -(\delta + \beta(E(t)))N(t) \\ &\quad + 2\alpha\beta(E(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E(s)) ds\right), \\ M'(t) &= -\mu M(t) + K_N(E(t))N(t) \\ &\quad + 2K_P(E(t))\beta(E(t-\tau))N(t-\tau) \exp\left(-\int_{t-\tau}^t \gamma(E(s)) ds\right), \\ E'(t) &= -kE(t) + f(M(t)). \end{aligned} \tag{2.7.1}$$

The linearized system of (2.7.1) around the positive steady state  $(\bar{N}, \bar{M}, \bar{E})$  has the form

$$U'(t) = AU(t) + BU(t-\tau) + C\left(\int_{-\tau}^0 U(t+s) ds\right), \tag{2.7.2}$$

with  $U(t) = (X(t), Y(t), Z(t))^T \in \mathbb{R}^3$ ,

$$A = \begin{pmatrix} -(\delta + \beta(\bar{E})) & 0 & -\beta'(\bar{E})\bar{N} \\ K_N(\bar{E}) & -\mu & K'_N(\bar{E})\bar{N} + 2K'_P(\bar{E})\beta(\bar{E})\bar{N}e^{-\tau\gamma(\bar{E})} \\ 0 & f'(\bar{M}) & -k \end{pmatrix},$$

$$B = \begin{pmatrix} 2\alpha\beta(\bar{E})e^{-\tau\gamma(\bar{E})} & 0 & 2\alpha\bar{N}\beta'(\bar{E})e^{-\tau\gamma(\bar{E})} \\ 2K_P(\bar{E})\beta(\bar{E})e^{-\tau\gamma(\bar{E})} & 0 & 2K_P(\bar{E})\beta'(\bar{E})\bar{N}e^{-\tau\gamma(\bar{E})} \\ 0 & 0 & 0 \end{pmatrix},$$

$$C = \begin{pmatrix} 0 & 0 & -2\tau\alpha\bar{N}\beta(\bar{E})\gamma'(\bar{E})e^{-\tau\gamma(\bar{E})} \\ 0 & 0 & -2\tau K_P(\bar{E})\beta(\bar{E})\bar{N}\gamma'(\bar{E})e^{-\tau\gamma(\bar{E})} \\ 0 & 0 & 0 \end{pmatrix}.$$

The associated characteristic equation becomes

$$\Delta(\lambda) = \det \left( \lambda I - A - B e^{-\lambda\tau} - C \int_{-\tau}^0 e^{\lambda\theta} ds \right) = 0. \quad (2.7.3)$$

The condition (2.5.5) becomes

$$1 \geq \alpha > \alpha_{\min} := \frac{1}{2} + \frac{\delta}{2\beta(f(0)/k)}, \quad (2.7.4)$$

$$0 \leq \tau < \tau_{\max} := \frac{1}{\gamma(f(0)/k)} \ln \left( \frac{2\alpha\beta(f(0)/k)}{\delta + \beta(f(0)/k)} \right).$$

First, let us suppose that  $\tau = 0$ . Then (2.7.2) becomes

$$U'(t) = (A + B)U(t), \quad (2.7.5)$$

where

$$A + B = \begin{pmatrix} -(\delta - (2\alpha - 1)\beta(\bar{E})) & 0 & (2\alpha - 1)\beta'(\bar{E})\bar{N} \\ \Lambda(\bar{E}) & -\mu & \Lambda'(\bar{E})\bar{N} \\ 0 & f'(\bar{M}) & -k \end{pmatrix},$$

with  $\Lambda(\bar{E}) = K_N(\bar{E}) + 2K_P(\bar{E})\beta(\bar{E})$ . In fact, under condition (2.7.4), the steady state  $(\bar{N}, \bar{M}, \bar{E})$  satisfies

$$(2\alpha - 1)\beta(\bar{E}) = \delta, \quad \Lambda(\bar{E})\bar{N} = \mu\bar{M}, \quad k\bar{E} = f(\bar{M}).$$

Then the characteristic equation of (2.7.5),

$$\det(\lambda I - A - B) = 0,$$

becomes

$$\lambda \left[ (\lambda + \mu)(\lambda + k) - f'(\bar{M})\Lambda'(\bar{E})\bar{N} \right] - (2\alpha - 1)\Lambda(\bar{E})f'(\bar{M})\beta'(\bar{E})\bar{N} = 0.$$

This is equivalent to

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \quad (2.7.6)$$

where

$$\begin{aligned} a_1 &= \mu + k > 0, & a_2 &= \mu k - f'(\bar{M})\Lambda'(\bar{E})\bar{N} > 0, \\ a_3 &= -(2\alpha - 1)\Lambda(\bar{E})f'(\bar{M})\beta'(\bar{E})\bar{N} > 0. \end{aligned}$$

We have

$$a_1 a_2 - a_3 = \mu k(\mu + k) - \bar{N} f'(\bar{M}) [(\mu + k)\Lambda'(\bar{E}) - (2\alpha - 1)\Lambda(\bar{E})\beta'(\bar{E})].$$

Then, by applying the Ruth-Hurwitz criterion, we obtain the following lemma.

**Lemma 2.7.1.** *All roots of (2.7.6) have negative real parts if and only if*

$$\mu k(\mu + k) - \bar{N} f'(\bar{M}) [(\mu + k)\Lambda'(\bar{E}) - (2\alpha - 1)\Lambda(\bar{E})\beta'(\bar{E})] > 0. \quad (2.7.7)$$

We also have the following lemma.

**Lemma 2.7.2.** *Assume that*

$$\mu + k > \frac{(2\alpha - 1)\Lambda(\beta^{-1}(\delta/2\alpha - 1))\beta'(\beta^{-1}(\delta/2\alpha - 1))}{\Lambda'(\beta^{-1}(\delta/2\alpha - 1))}, \quad (2.7.8)$$

*Then, all roots of (2.7.6) have negative real parts.*

*Proof.* Since  $f'(\bar{M}) < 0$ ,  $\Lambda'(\bar{E}) > 0$  and  $\beta'(\bar{E}) > 0$ , the hypothesis

$$(\mu + k)\Lambda'(\bar{E}) > (2\alpha - 1)\Lambda(\bar{E})\beta'(\bar{E})$$

implies that (2.7.7) is satisfied. Furthermore, we have  $\bar{E} = \beta^{-1}(\delta/2\alpha - 1)$ . Then, (2.7.8) implies (2.7.7). Consequently, if (2.7.8) is satisfied, then all roots of (2.7.6) have negative real parts.  $\square$

**Theorem 2.7.3.** *Assume that (2.5.4) and (2.7.7) hold. Then there exists  $\tau^* \in [0, \tau_{\max})$  such that the positive steady state  $(\bar{N}, \bar{M}, \bar{E})$  is locally asymptotically stable for  $\tau \in [0, \tau^*)$ .*

*Proof.* A direct application of Lemma 2.7.1 implies that  $(\bar{N}, \bar{M}, \bar{E})$  is locally asymptotically stable when  $\tau = 0$ . Furthermore,  $\Delta := \Delta(\lambda, \tau)$  given by (2.7.3) is analytic in  $\lambda$  and  $\tau$ . Then, as  $\tau$  varies the zeros of  $\lambda \mapsto \Delta(\lambda, \tau)$  stay in the open left half-plane for  $\tau$  small enough. If instability occurs for a particular value of  $\tau$ , a characteristic root must intersect the imaginary axis. Then, there exists  $\tau^* \in [0, \tau_{\max})$  such that for  $\tau \in [0, \tau^*)$ , all the roots of (2.7.3) have negative real parts.  $\square$

## 2.8 Numerical illustrations

In this section, we perform some numerical simulations to illustrate the behavior of the steady states. Let us choose the functions  $\beta$ ,  $\gamma$ ,  $K_P$ ,  $K_N$  and the negative feedback  $f$  as follows

$$\begin{aligned} \beta(E) &= \frac{\hat{\beta}E}{1 + E}, & \gamma(E) &= \frac{\gamma_0}{1 + E^a}, & K_P(E) &= \frac{\hat{K}_P E}{1 + E}, \\ K_N(E) &= \frac{\hat{K}_N E}{1 + E}, & f(M) &= \frac{f_0}{1 + M^b}, \end{aligned}$$



with

$$\delta + \hat{\beta} + \hat{K}_N \leq 1 \quad \text{and} \quad \alpha + \hat{K}_P \leq 1.$$

From (2.5.5) the positive steady state  $(\bar{N}, \bar{M}, \bar{E})$  exists if and only if

$$1 \geq \alpha > \alpha_{\min} := \frac{1}{2} + \frac{\delta}{2\beta(f_1(0)/k_1)},$$

$$0 \leq \tau < \tau_{\max} := \frac{1}{\gamma(f_2(0)/k_2)} \ln \left( \frac{2\alpha\beta(f_1(0)/k_1)}{\delta + \beta(f_1(0)/k_1)} \right).$$

We fix all the parameters except the delay  $\tau$ . The values of the fixed parameters are  $\delta = 0.08 \text{ day}^{-1}$ ,  $\mu = 0.05 \text{ day}^{-1}$ ,  $k = 0.6 \text{ day}^{-1}$ ,  $\alpha = 0.8$ ,  $\hat{\beta} = 0.8 \text{ day}^{-1}$ ,  $\gamma_0 = 0.2 \text{ day}^{-1}$ ,  $a = 3$ ,  $\hat{K}_P = 0.18 \text{ day}^{-1}$ ,  $\hat{K}_N = 0.1 \text{ day}^{-1}$ ,  $f_0 = 1$ ,  $b = 7$ . With these values, we have  $\tau_{\max} = 9.052 \text{ days}$  and  $\alpha_{\min} = 0.58$ . Then, the above condition of existence of positive steady state becomes  $0 \leq \tau < 9.052$ .

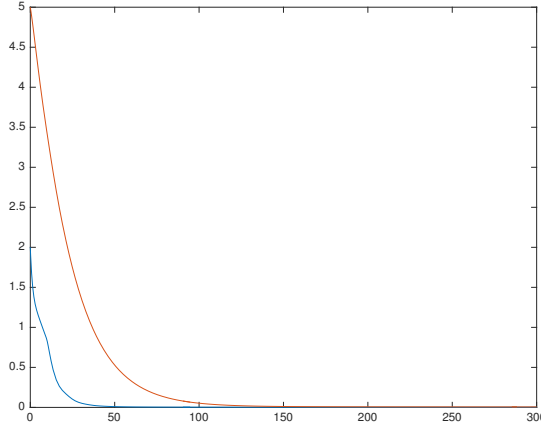


Figure 2.2: Global asymptotic stability of the trivial steady state  $(\bar{N} = 0, \bar{M} = 0)$ . When  $\tau = 9.5 \text{ days} > \tau_{\max} = 9.052 \text{ days}$ , the trivial steady state is the only steady state and it is globally asymptotically stable.

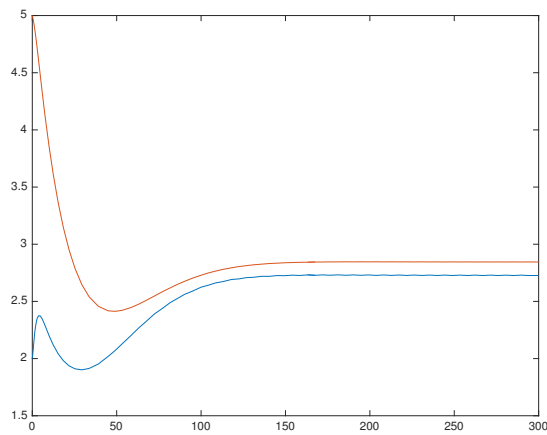


Figure 2.3: Local asymptotic stability of the positive steady state  $(\bar{N}, \bar{M})$ . When  $\tau = 1 \text{ day} < \tau_{\max} = 9.052 \text{ days}$ , the positive steady state is locally asymptotically stable

# Chapter 3

## Hematopoietic Stem Cells dynamics model with state dependent delay\*

### Abstract

We propose and analyze a mathematical model describing the dynamics of a hematopoietic stem cell population, in which the duration of the cell cycle depends upon the total population of quiescent cells. The method of characteristics reduces the age-structured model to a system of differential equations with a state-dependent delay. We perform a detailed stability analysis of the resulting delay differential system. By constructing a Lyapunov-Razumikhin function, we obtain a sufficient condition for the global asymptotic stability of the trivial steady state, describing cell's dying out. It is shown that a unique non-trivial steady state can appear through a transcritical bifurcation of the trivial steady state. The analysis of the positive steady state's behavior concludes to the existence of a Hopf bifurcation and gives criteria for stability switches. We confirmed the analytical results by numerical simulations.

### 3.1 Age-structured partial differential model

We consider two cell population densities in resting and proliferating phase, denoted respectively by  $n(t, a)$  and  $p(t, a)$ , which have spent a time  $a \geq 0$  in their phase at time  $t \geq 0$ .

Resting cells are assumed to die at a constant rate  $\delta > 0$ , which can also take into account cell differentiation. They can be introduced into the proliferating phase with a rate  $\beta$  in order to divide, which is supposed to depend upon the total population of quiescent cells (see Mackey [76])

$$N(t) = \int_0^{\infty} n(t, a) da. \quad (3.1.1)$$

The function  $\beta$  is assumed to be continuously differentiable, bounded and positive. Furthermore, we assume that  $\beta$  is decreasing with  $\lim_{x \rightarrow +\infty} \beta(x) = 0$ . These

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\*M. Adimy, Y. Bourfia, M. L. Hbid, Hematopoietic Stem Cells dynamics model with state dependant delay, soon to be submitted.

assumptions describe the fact that the proliferation rate is a decreasing function of the quiescent population.

It is usually believed that the function  $\beta$  is a monotone decreasing Hill function (see [76]), given by

$$\beta(x) = \frac{\beta_0 \theta^r}{\theta^r + x^r}, \quad x \geq 0, \quad (3.1.2)$$

with  $\beta_0 > 0, \theta \geq 0$  and  $r > 0$ . The parameter  $\beta_0$  is the maximal rate of reentry into proliferation,  $\theta$  is the number of resting cells for which  $\beta$  possesses a maximal exchange rate with the resting phase, and  $r$  describes the sensitivity of the population with regards to the changes it may undergo.

The population of proliferating cells can die by apoptosis at a constant rate  $\gamma \geq 0$ . During mitosis, cells at age  $\tau$  divide into two daughter cells that immediately enter the resting phase, thus completing the cell cycle. We assume that the cell cycle duration  $\tau$  depends upon the total population of quiescent cells given by (3.1.1), i.e.,  $\tau = \tau(N(t))$

The function  $\tau$  is supposed to be bounded, positive, continuously differentiable ( $C^2$ ) and increasing (a deficiency of hematopoietic stem cells is supposed to shorten the cell cycle duration). We define

$$\tau_0 := \inf_{x \geq 0} \tau(x) = \tau(0) \quad \text{and} \quad \tau_{\max} = \sup_{x \geq 0} \tau(x).$$

The densities  $n(t, a)$  and  $p(t, a)$  satisfy, for  $t > 0$ , the system

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -(\delta + \beta(N(t)))n, \quad a > 0, t > 0, \quad (3.1.3)$$

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} = -\gamma p, \quad 0 < a < \tau(N(t)), t > 0, \quad (3.1.4)$$

where  $N(t)$  denotes the total population of resting cells, defined by (3.1.1), with initial conditions given by nonnegative  $L^1$  functions  $n_0$  and  $p_0$  such that

$$n(0, a) = n_0(a), \quad a \geq 0 \quad \text{and} \quad p(0, a) = p_0(a), \quad a \in [0, \tau(N(0))]. \quad (3.1.5)$$

The boundary conditions of (3.1.3)-(3.1.4), describing the flux of cells between the two phases, are given by

$$n(t, 0) = 2 \left(1 - \tau'(N(t))N'(t)\right) p(t, \tau(N(t))), \quad (3.1.6)$$

$$p(t, 0) = \beta(N(t))N(t). \quad (3.1.7)$$

Moreover, in order to give meaning to the total population  $N(t)$ , we suppose that  $\lim_{a \rightarrow +\infty} n(t, a) = 0$ .

Denote by  $P(t)$  the total population of proliferating stem cells at time  $t$ . Then

$$P(t) = \int_0^{\tau(N(t))} p(t, a) da, \quad t \geq 0.$$

Integrating (3.1.3) with respect to the age variable, and using (3.1.6), we obtain

$$N'(t) = -\delta N(t) - \beta(N(t))N(t) + 2 \left(1 - \tau'(N(t))N'(t)\right) p(t, \tau(N(t))), \quad \text{for } t \geq 0. \quad (3.1.8)$$

Using the method of characteristics (see Webb [118]), the solution  $p(t, a)$  of (3.1.4), (3.1.7) and (3.1.5) is given, for  $t > 0$  and  $0 < a < \tau(N(t))$ , by

$$p(t, a) = \begin{cases} p_0(a - t)e^{-\gamma t}, & \text{if } 0 \leq t < a, \\ \beta(N(t - a))N(t - a)e^{-\gamma a}, & \text{if } 0 \leq a \leq t. \end{cases} \quad (3.1.9)$$

Since resting cells are introduced into the proliferating phase with a rate  $\beta$ , then  $p_0(0)$ , the population of cells introduced at time  $t = 0$  into the cell cycle, should satisfy the classical compatibility condition

$$p_0(0) = \beta(N(0))N(0). \quad (3.1.10)$$

This condition ensures the continuity of  $p(t, a)$  on the line  $t = a$ .

Note that

$$P(t) = \begin{cases} e^{-\gamma t} \left( \int_0^t e^{\gamma\theta} \beta(N(\theta))N(\theta)d\theta + \int_0^{\tau(N(t))-t} p_0(\theta)d\theta \right), & t < \tau(N(t)), \\ e^{-\gamma t} \int_{t-\tau(N(t))}^t e^{\gamma\theta} \beta(N(\theta))N(\theta)d\theta, & t \geq \tau(N(t)). \end{cases} \quad (3.1.11)$$

The variable  $P(t)$  is straightforwardly continuous for  $t \geq 0$ , and since  $\tau$  is continuously differentiable it is also continuously differentiable provided that (3.1.10) holds true.

Using (3.1.9), we finally obtain, for  $0 \leq t \leq \tau(N(t))$ ,

$$N'(t) = -(\delta + \beta(N(t)))N(t) + 2 \left( 1 - \tau'(N(t))N'(t) \right) p_0(\tau(N(t)) - t)e^{-\gamma t}, \quad (3.1.12)$$

and, for  $t > \tau(N(t))$ ,

$$N'(t) = -(\delta + \beta(N(t)))N(t) + 2 \left( 1 - \tau'(N(t))N'(t) \right) e^{-\gamma\tau(N(t))} \beta(N(t - \tau(N(t))))N(t - \tau(N(t))). \quad (3.1.13)$$

Equation (3.1.13) becomes, for  $t > \tau(N(t))$ ,

$$N'(t) = \frac{-\delta N(t) - \beta(N(t))N(t) + 2\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))e^{-\gamma\tau(N(t))}}{1 + 2\tau'(N(t))e^{-\gamma\tau(N(t))}\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))} \quad (3.1.14)$$

Moreover,

$$N(0) = \int_0^\infty n_0(a)da.$$

One can notice that problem (3.1.12)–(3.1.14) is a nonlinear nonautonomous ordinary differential equation for  $t < \tau(N(t))$ , whereas, for  $t \geq \tau(N(t))$ , it is a system of differential equations with state-dependent delay. Let us concentrate on system (3.1.12)–(3.1.14) for  $t \in [0, \tau_{\max}]$ .

Consider the differential equation

$$\frac{dx}{dt}(t) = \begin{cases} -\delta x(t) - \beta(x(t))x(t) + 2 \left( 1 - \tau'(x(t))x'(t) \right) p_0(\tau(x(t)) - t)e^{-\gamma t}, & 0 \leq t \leq \tau(x(t)), \\ \frac{-\delta x(t) - \beta(x(t))x(t) + 2\beta(x(t - \tau(x(t))))x(t - \tau(x(t)))e^{-\gamma\tau(x(t))}}{1 + 2\tau'(x(t))e^{-\gamma\tau(x(t))}\beta(x(t - \tau(x(t))))x(t - \tau(x(t)))}, & \tau(x(t)) < t \leq \tau_{\max}, \end{cases}$$

$$x(0) = \int_0^\infty n_0(a)da. \quad (3.1.15)$$

For a smooth enough function  $p_0$  satisfying (3.1.10), (3.1.15) has a unique continuously differentiable solution  $\phi$  defined on  $[0, \tau_{\max}]$  (see Walther [116]). Then the equation (3.1.14) becomes the following delay differential equation, for  $t \geq \tau_{\max}$ ,

$$\begin{cases} \frac{dy}{dt}(t) = \frac{-\delta y(t) - \beta(y(t))y(t) + 2\beta(y(t - \tau(y(t))))y(t - \tau(y(t)))e^{-\gamma\tau(y(t))}}{1 + 2\tau'(y(t))e^{-\gamma\tau(y(t))}\beta(y(t - \tau(y(t))))y(t - \tau(y(t)))}, \\ y(\theta) = \phi(\theta), \quad 0 \leq \theta \leq \tau_{\max}. \end{cases}$$

Thus, by making a change of variable  $N(t) := y(t + \tau_{\max})$ , system (3.1.12)–(3.1.14) can be written as a state-dependent delay differential equation for  $t \geq 0$ ,

$$N'(t) = \frac{-\delta N(t) - \beta(N(t))N(t) + 2\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))e^{-\gamma\tau(N(t))}}{1 + 2\tau'(N(t))e^{-\gamma\tau(N(t))}\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))}, \quad (3.1.16)$$

with, for  $\theta \in [-\tau_{\max}, 0]$ ,  $N(\theta) = \phi(\theta + \tau_{\max})$ .

Existence and uniqueness of solutions of (3.1.16) cannot be easily deduced. Equation (3.1.16) writes

$$x'(t) = g(x(t), x(t - \tau(x(t)))) \quad \text{for } t \geq 0,$$

where the function  $g : (\mathbb{R}^+)^2 \rightarrow \mathbb{R}$  is given by

$$g(x, y) = \frac{-\delta x - \beta(x)x + 2\beta(y)ye^{-\gamma\tau(x)}}{1 + 2\tau'(x)e^{-\gamma\tau(x)}\beta(y)y}, \quad (x, y) \in (\mathbb{R}^+)^2.$$

This equation can also be written in the following general form

$$x'(t) = f(x_t), \quad \text{for } t \geq 0, \quad (3.1.17)$$

where  $x_t$  is defined by  $x_t(\theta) = x(t + \theta)$  for  $\theta \in [-\tau_{\max}, 0]$ , and the function  $f : C \rightarrow \mathbb{R}$  is given, for  $\phi \in C$ , the space of continuous functions on  $[-\tau_{\max}, 0]$ , by

$$f(\phi) = g(\phi(0), \phi(-\tau(\phi(0)))).$$

Since the functions  $\beta(x)$  and  $\tau(x)$  are continuously differentiable on  $[0, +\infty)$ , then  $g$  is also continuously differentiable on  $(\mathbb{R}^+)^2$ . Therefore existence and uniqueness of a solution of (3.1.16) defined on  $[0, +\infty)$  for an initial condition belonging to  $C^1$ , the space of continuously differentiable function on  $[-\tau_{\max}, 0]$ , follow from Mallet-Paret et al. [84]. One may note that it is not reasonable to expect a well-posed state-dependent delay differential problem by searching for solutions in  $C$  (see Walther [116]).

One can notice that equation (3.1.16) does not depend on the proliferating cell population  $P$ , whereas the converse is not true.

## 3.2 Properties of the model and existence of steady states

We focus, in this section, on the positivity and boundedness properties of solutions of (3.1.16).

We suppose, from now on, that existence and uniqueness of solutions of (3.1.16) hold for  $t \in [-\tau_{\max}, +\infty)$ .

Since we're dealing with cell population counts, it is imperative to prove positivity and boundedness of solutions of (3.1.16). Those properties are stated in the following proposition.

**Proposition 3.2.1.** *The solutions of (3.1.16) are nonnegative, and provided that  $\delta > 0$  they are bounded.*

*Proof.* These results are straightforward and can be obtained, for instance, using a method similar to the one presented in Adimy et al. [9].  $\square$

The expression of  $P(t)$  in (3.1.11) gives more detailed information about the influence of the behavior of  $N(t)$  on the stability and periodicity of the solutions  $P(t)$ . The following lemma, which states these results, is immediately obtained by using (3.1.11).

**Lemma 3.2.2.** *Let  $(P(t), N(t))$  be a solution of (3.1.11) and (3.1.16). If  $N_\infty := \lim_{t \rightarrow \infty} N(t)$  exists, then*

$$\lim_{t \rightarrow \infty} P(t) = \begin{cases} N_\infty \beta(N_\infty) \left( \frac{1 - e^{-\gamma \tau(N_\infty)}}{\gamma} \right), & \text{if } \gamma > 0, \\ N_\infty \beta(N_\infty) \tau(N_\infty), & \text{if } \gamma = 0. \end{cases}$$

*If  $N(t)$  is  $T$ -periodic, then  $P(t)$  is also  $T$ -periodic.*

In particular, Lemma 3.2.2 establishes the influence of (3.1.16) on the stability of the entire system. We now focus on the existence of steady states of (3.1.16).

**Proposition 3.2.3.** *Assume  $\delta > 0$  and*

$$\tau_0 < \frac{1}{\gamma} \ln \left( \frac{2\beta(0)}{\beta(0) + \delta} \right). \quad (3.2.1)$$

*Then equation (3.1.16) has two steady states  $N \equiv 0$  and  $N \equiv N^* > 0$ , where*

$$(2e^{-\gamma \tau(N^*)} - 1)\beta(N^*) = \delta. \quad (3.2.2)$$

*If (3.2.1) does not hold, then  $N \equiv 0$  is the only steady state of (3.1.16).*

*Proof.* Define, for  $N \geq 0$ , the function  $\chi(N) := (2e^{-\gamma \tau(N)} - 1)\beta(N)$ . Then

$$\chi(0) = (2e^{-\gamma \tau_0} - 1)\beta(0) > \delta \quad \text{and} \quad \lim_{N \rightarrow +\infty} \chi(N) = 0.$$

Consequently, equation (3.2.2) has at least one positive solution  $N^*$ . Moreover, since  $\tau$  is increasing then  $\chi$  is decreasing, and provided that  $\chi(N) > 0$ ,  $N^*$  is unique.  $\square$

### 3.3 Linearization and Characteristic Equation

We are interested in the asymptotic stability of the two steady states of system (3.1.16),  $N \equiv 0$  and  $N \equiv N^*$ . To reach our objective, we linearize system (3.1.16) about one of its steady states and determine the associated characteristic equation.

Let  $J : C^1 \rightarrow \mathbb{R}$  be the map defined, for  $\phi \in C^1$ , by

$$J(\phi) = \phi(-\tau(\phi(0))).$$

The derivatives of  $J$  have the form

$$\frac{d}{d\phi} J(\phi) \psi = -\tau'(\phi(0)) \phi'(-\tau(\phi(0))) \psi(0) + \psi(-\tau(\phi(0))), \quad \phi, \psi \in C^1.$$

Then, for a steady state  $x^* \in \{0, N^*\}$  of (3.1.16), the linearized function  $f$  of (3.1.17) around  $x^*$  is, for  $\psi \in C^1$ ,

$$\begin{aligned} Df(x^*)\psi &= -\frac{\delta + \beta(x^*) + \beta'(x^*)x^*}{(1 + 2\tau'(x^*)e^{-\gamma\tau(x^*)}\beta(x^*)x^*)^2} \psi(0) \\ &\quad - 2\frac{1 + x^*\tau'(x^*)(\delta + \beta(x^*))}{(1 + 2\tau'(x^*)e^{-\gamma\tau(x^*)}\beta(x^*)x^*)^2} \gamma e^{-\gamma\tau(x^*)} \tau'(x^*) \beta(x^*) x^* \psi(0) \\ &\quad - 2\frac{\delta + \beta(x^*) + \beta'(x^*)x^*}{(1 + 2\tau'(x^*)e^{-\gamma\tau(x^*)}\beta(x^*)x^*)^2} e^{-\gamma\tau(x^*)} \tau'(x^*) \beta(x^*) x^* \psi(0) \\ &\quad + 2\frac{\delta + \beta(x^*) - 2\beta(x^*)e^{-\gamma\tau(x^*)}}{(1 + 2\tau'(x^*)e^{-\gamma\tau(x^*)}\beta(x^*)x^*)^2} e^{-\gamma\tau(x^*)} \tau''(x^*) \beta(x^*) (x^*)^2 \psi(0) \\ &\quad + 2\frac{1 + x^*\tau'(x^*)(\delta + \beta(x^*))}{(1 + 2\tau'(x^*)e^{-\gamma\tau(x^*)}\beta(x^*)x^*)^2} e^{-\gamma\tau(x^*)} [\beta'(x^*)x^* + \beta(x^*)] \psi(-\tau(x^*)). \end{aligned}$$

Using (3.2.2), it follows that the characteristic equation associated with the linearization of (3.1.16) around  $x^*$  is

$$\begin{aligned} \Delta(\lambda) &= \lambda + \delta + \bar{\beta} + \bar{\alpha} \left[ 1 + \bar{\zeta} \tau'(x^*) \right] \tau'(x^*) e^{-\gamma\tau(x^*)} \\ &\quad + \bar{\eta} \left[ \delta + \bar{\beta} \right] \tau'(x^*) e^{-\gamma\tau(x^*)} \\ &\quad - 2\bar{\beta} \left[ 1 + \bar{\zeta} \tau'(x^*) \right] e^{-\gamma\tau(x^*)} e^{-\lambda\tau(x^*)}, \end{aligned} \tag{3.3.1}$$

where

$$\bar{\alpha} = 2\gamma\beta(x^*)x^*, \quad \bar{\beta} = \beta(x^*) + \beta'(x^*)x^*, \quad \bar{\eta} = 2\beta(x^*)x^*,$$

and

$$\bar{\zeta} = x^* (\delta + \beta(x^*)).$$

In the next section we focus on the stability of the trivial steady state of (3.1.16).



### 3.4 Global Asymptotic Stability of the Trivial Steady State

First, we are interested in the local asymptotic stability of the trivial steady state of (3.1.16). The characteristic equation (3.3.1) becomes, when  $x^* = 0$ ,

$$\Delta(\lambda) = \lambda + \delta + \beta(0) - 2\beta(0)e^{-\gamma\tau_0}e^{-\lambda\tau_0}.$$

Let  $\lambda \in \mathbb{R}$ . We have

$$\frac{d\Delta}{d\lambda}(\lambda) = 1 + 2\tau_0e^{-\gamma\tau_0}\beta(0)e^{-\lambda\tau_0} > 0,$$

$$\Delta(0) = \delta + \beta(0) - 2\beta(0)e^{-\gamma\tau_0} = \delta - (2e^{-\gamma\tau_0} - 1)\beta(0),$$

and  $\lim_{\lambda \rightarrow \infty} \Delta(\lambda) = +\infty$ . Then there exists  $\lambda_0 \in \mathbb{R}$ , which is unique, such that  $\Delta(\lambda_0) = 0$ . When (3.2.1) holds, then  $\Delta(0) < 0$ , so  $\lambda_0 > 0$ , which proves the instability of the trivial steady state.

When (3.2.1) does not hold, we show that all roots  $\lambda \neq \lambda_0$  of  $\Delta$  satisfy  $\text{Re}(\lambda) < \lambda_0$ .

Suppose that  $\lambda = \rho + i\sigma$  is a root of  $\Delta$  such that  $\lambda \neq \lambda_0$ .

Considering the real parts of  $\Delta = 0$  we get

$$\rho - \lambda_0 = 2\beta(0)e^{-\gamma\tau_0} \left( e^{-\rho\tau_0} \cos(\sigma\tau_0) - e^{-\lambda_0\tau_0} \right). \quad (3.4.1)$$

By contradiction, we suppose that  $\rho > \lambda_0$  then  $e^{-\rho\tau_0} \cos(\sigma\tau_0) - e^{-\lambda_0\tau_0} < 0$ . We obtain a contradiction, thus  $\rho \leq \lambda_0$ . Now, if  $\rho = \lambda_0$ , (3.4.1) implies

$$\cos(\sigma\tau_0) = 1, \quad \text{for } \tau_0 \geq 0.$$

It follows that  $\sin(\sigma\tau_0) = 0$ , considering the imaginary part of equation  $\Delta = 0$  we get

$$\sigma + 2\beta(0)e^{-\gamma\tau_0}e^{-\rho\tau_0} \sin(\sigma\tau_0) = 0,$$

then  $\sigma = 0$  and  $\lambda = \lambda_0$  which gives a contradiction. Therefore  $\rho < \lambda_0$ .

We can now conclude that the trivial steady state  $N \equiv 0$  of (3.1.16) is locally asymptotically stable when

$$\frac{1}{\gamma} \ln \left( \frac{2\beta(0)}{\beta(0) + \delta} \right) < \tau_0 \leq \frac{1}{\gamma} \ln \left( \frac{2\beta(0)}{\delta} \right),$$

and unstable when

$$\tau_0 < \frac{1}{\gamma} \ln \left( \frac{2\beta(0)}{\beta(0) + \delta} \right).$$

When condition (3.2.1) holds and the trivial steady state  $N \equiv 0$  is the only equilibrium, we can give a necessary and sufficient condition for  $N \equiv 0$  to be globally asymptotically stable using a Lyapunov-Razumikhin function (see [57]).

The following result deals with the global asymptotic stability of the trivial steady state.

**Theorem 3.4.1.** *Assume*

$$\frac{1}{\gamma} \ln \left( \frac{2\beta(0)}{\delta} \right) < \tau_0. \quad (3.4.2)$$

*Then the trivial steady state of (3.1.16) is globally asymptotically stable.*

*Proof.* Consider the Lyapunov function  $V : \mathbb{R}^+ \rightarrow \mathbb{R}^+$  given by  $V(x) = x^2/2$ . We have, for  $x \in \mathbb{R}^+$ ,  $u(x) \leq V(x) \leq v(x)$ , with  $u(x) = x^2/2$  and  $v(x) = x^2$ .

Define  $p : \mathbb{R}^+ \rightarrow \mathbb{R}^+$  by  $p(x) = xe^{2\alpha\tau(\sqrt{2x})}$ ,  $x \in \mathbb{R}^+$ , with  $0 < \alpha < \min\{\gamma, \gamma - \ln(2\beta(0)/\delta)/\tau_0\}$ . Let  $N$  be a solution of (3.1.16) such that, for  $t \geq 0$ ,  $\theta \in [-\tau_{\max}, 0]$ ,

$$V(N(t+\theta)) < p(V(N(t))). \quad (3.4.3)$$

Then, for  $t \geq 0$ ,  $N(t - \tau(N(t))) \leq e^{\alpha\tau(N(t))}N(t)$ . It follows that, for  $t \geq 0$ ,

$$\begin{aligned} \dot{V}(N(t)) &= \frac{-(\delta + \beta(N(t)))N(t)^2}{1 + 2\tau'(N(t))e^{-\gamma\tau(N(t))}\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))} \\ &\quad + \frac{2e^{-\gamma\tau(N(t))}\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))N(t)}{1 + 2\tau'(N(t))e^{-\gamma\tau(N(t))}\beta(N(t - \tau(N(t))))N(t - \tau(N(t)))} \quad (3.4.4) \\ &\leq -\delta N(t)^2 + 2e^{-\gamma\tau(N(t))}\beta(0)e^{\alpha\tau(N(t))}N(t)^2, \\ &= -\left[\delta - 2e^{-(\gamma-\alpha)\tau(N(t))}\beta(0)\right]N(t)^2. \end{aligned}$$

Let  $W : \mathbb{R}^+ \rightarrow \mathbb{R}$  be the map defined, for  $x \in \mathbb{R}^+$ , by  $W(x) = \left[\delta - 2e^{-(\gamma-\alpha)\tau(x)}\beta(0)\right]x^2$ .

From (3.4.2),  $W$  is a positive nondecreasing function.

Moreover, (3.4.4) gives  $\dot{V}(N(t)) \leq -W(N(t))$  whenever (3.4.3) holds true. Since  $u(r) \rightarrow \infty$  as  $r \rightarrow \infty$ , conditions of [56, Theorem 5.2] hold and so the conclusion.  $\square$

In the next section, we focus on the behavior of the positive steady state of (3.1.16).

### 3.5 Transcritical Bifurcation and Hopf Bifurcation

This section is dedicated to the local asymptotic stability analysis of the positive steady state  $N \equiv N^*$  of equation (3.1.16).

Throughout this section, we consider the function  $\tau$  to be given by  $\tau(x) = \mu\tilde{\tau}(x)$ , where  $\mu$  is a positive parameter and  $\tilde{\tau} : \mathbb{R}^+ \rightarrow \mathbb{R}^+$  is a positive, increasing, bounded and differentiable function. Equation (3.1.16) reads

$$N'(t) = \frac{-\delta N(t) - \beta(N(t))N(t) + 2\beta(N(t - \mu\tilde{\tau}(N(t))))N(t - \mu\tilde{\tau}(N(t)))e^{-\gamma\mu\tilde{\tau}(N(t))}}{1 + 2\mu\tilde{\tau}'(N(t))e^{-\gamma\mu\tilde{\tau}(N(t))}\beta(N(t - \mu\tilde{\tau}(N(t))))N(t - \mu\tilde{\tau}(N(t)))}, \quad (3.5.1)$$

Moreover, to ensure the existence of the positive steady state  $N^*$  of (3.5.1), we assume that condition (3.2.1) holds. Condition (3.2.1) is equivalent to

$$\beta(0) > \delta \quad \text{and} \quad 0 \leq \mu < \frac{1}{\tilde{\tau}(0)\gamma} \ln\left(\frac{2\beta(0)}{\delta + \beta(0)}\right) := \bar{\mu}. \quad (3.5.2)$$

Inequalities (3.5.2) describe a situation in which the maximal introduction rate  $\beta(0)$  has to be larger than the mortality rate  $\delta$  and where the cell cycle duration  $\tau$  cannot take too long in order for system (3.5.1) to exhibit a positive steady state other than the trivial one describing the cell's dying out.

The positive steady state  $N^*$  depends upon the parameter  $\mu$  and is given implicitly by

$$\left(2e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} - 1\right) \beta(N^*(\mu)) = \delta, \quad \mu \in [0, \bar{\mu}). \quad (3.5.3)$$

Using the Implicit Functions Theorem, we find that  $N^*$  is a decreasing continuously differentiable function of  $\mu$ . Furthermore, from (3.5.2) and (3.5.3), one obtains

$$N^*(\mu = 0) = \beta^{-1}(\delta) \quad \text{and} \quad \lim_{\mu \rightarrow \bar{\mu}} N^*(\mu) = 0. \quad (3.5.4)$$

From (3.3.1), the characteristic equation associated with  $N^*(\mu)$  is written as

$$\begin{aligned} \Delta(\lambda, \mu) &= \lambda + \delta + \bar{\beta}(\mu) + \bar{\alpha}(\mu) \left[1 + \mu\bar{\zeta}(\mu)\tilde{\tau}'(N^*(\mu))\right] \mu\tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} \\ &\quad + \bar{\eta}(\mu) \left[\delta + \bar{\beta}(\mu)\right] \mu\tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} \\ &\quad - 2\bar{\beta}(\mu) \left[1 + \mu\bar{\zeta}(\mu)\tau'(N^*(\mu))\right] e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} e^{-\lambda\mu\tilde{\tau}(N^*(\mu))}, \end{aligned} \quad (3.5.5)$$

where

$$\bar{\alpha}(\mu) = 2\gamma\beta(N^*(\mu))N^*(\mu), \quad \bar{\beta}(\mu) = \beta(N^*(\mu)) + \beta'(N^*(\mu))N^*(\mu),$$

$$\bar{\eta}(\mu) = 2\beta(N^*(\mu))N^*(\mu) \quad \text{and} \quad \bar{\zeta}(\mu) = N^*(\mu) (\delta + \beta(N^*(\mu))).$$

Now, we investigate local asymptotic stability of  $N^*(\mu)$  in a neighborhood of  $\bar{\mu}$ .

The following result states the existence of a transcritical bifurcation of the positive steady state when  $\mu = \bar{\mu}$ .

**Theorem 3.5.1.** *When  $\mu = \bar{\mu}$ , the positive steady state undergoes a transcritical bifurcation, that is when  $\mu$  increases and remains in the interval  $[0, \bar{\mu})$  close to  $\bar{\mu}$ , the positive steady state is locally asymptotically stable whereas the trivial steady state is unstable, and when  $\mu > \bar{\mu}$  the trivial steady state is locally asymptotically stable and is the only steady state of (3.5.1).*

*Proof.* First, notice that when  $\bar{\beta}(\mu) > 0$  then characteristic roots of (3.5.5) have negative real parts. Indeed, assume  $\bar{\beta}(\mu) > 0$  and consider  $\Delta(\lambda, \mu)$  as a function of real  $\lambda$ . Then  $\lambda \mapsto \Delta(\lambda, \mu)$  is an increasing function such that  $\lim_{\lambda \rightarrow +\infty} \Delta(\lambda, \mu) = +\infty$  and using the definitions of  $\bar{\alpha}(\mu)$ ,  $\bar{\beta}(\mu)$ ,  $\bar{\eta}(\mu)$ ,  $\bar{\zeta}(\mu)$  and the fact that  $N^*(\mu)$  is a steady state of (3.5.1) we get

$$\begin{aligned} \Delta(0, \mu) &= -2\mu\delta\beta'(N^*(\mu))N^*(\mu)\tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} \\ &\quad - (2e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} - 1)N^*(\mu)\beta'(N^*(\mu)) \\ &\quad + \bar{\alpha}(\mu) \left[1 + \mu\bar{\zeta}(\mu)\tilde{\tau}'(N^*(\mu))\right] \mu\tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))}, \end{aligned}$$

we easily see that

$$\Delta(0, \mu) > 0.$$

Thus, there exists a unique  $\lambda^* < 0$  such that  $\Delta(\lambda^*, \mu) = 0$ . Separating real and imaginary parts in (3.5.5), one can easily show that all characteristic roots  $\lambda \neq \lambda^*$  satisfy  $\text{Re}(\lambda) < \lambda^*$ . The local asymptotic stability of the positive steady state when  $\bar{\beta}(\mu) > 0$  immediately follows.

Finally, one has to note that when  $\mu$  is close to  $\bar{\mu}$ ,  $\mu < \bar{\mu}$ , then  $N^*(\mu)$  is close to zero (see (3.5.4)), therefore  $\bar{\beta}(\mu) \approx \beta(0) > 0$ . The conclusion follows.  $\square$

Local asymptotic stability of the positive steady state when  $\mu = 0$  is established in the following lemma.

**Lemma 3.5.2.** *Assume  $\mu = 0$ . Then the steady state  $N^*$  of system (3.5.1) is locally asymptotically stable.*

*Proof.* Let  $\mu = 0$ . From (3.5.5),  $\Delta(\lambda, 0) = \lambda + \delta - \bar{\beta}(0)$ . Then,  $\lambda = \bar{\beta}(0) - \delta$  is the unique eigenvalue associated with the characteristic equation. On the other hand,  $N^*(0) = \beta^{-1}(\delta) > 0$ , so  $\lambda = \beta'(N^*(0))N^*(0) < 0$ . This concludes the proof.  $\square$

Thus,  $N^*(\mu)$  is locally asymptotically stable for  $\mu = 0$  and the stability can be lost as  $\mu$  increases away from 0, with  $\mu < \bar{\mu}$ , only if purely imaginary characteristic roots appear. One may note that  $N^*(\mu)$  is locally asymptotically stable for  $\mu < \bar{\mu}$ ,  $\mu$  close to  $\bar{\mu}$  (see Theorem 3.5.1), so if stability is lost as  $\mu$  increases away from zero a second switch must be observed as  $\mu$  keeps on increasing and reaches  $\bar{\mu}$ .

Define, for  $\mu \in [0, \bar{\mu})$ ,

$$b(\mu) = \delta + \bar{\beta}(\mu) + \left( \bar{\eta}(\mu) \left[ \delta + \bar{\beta}(\mu) \right] + \bar{\alpha}(\mu) \left[ 1 + \mu \bar{\zeta}(\mu) \tilde{\tau}'(N^*(\mu)) \right] \right) \mu \tilde{\tau}'(N^*(\mu)) e^{-\gamma \mu \tilde{\tau}(N^*(\mu))}$$

and

$$c(\mu) = -2\bar{\beta}(\mu) \left[ 1 + \mu \bar{\zeta}(\mu) \tau'(N^*(\mu)) \right] e^{-\gamma \mu \tilde{\tau}(N^*(\mu))}.$$

Then (3.5.5) becomes

$$\Delta(\lambda, \mu) = \lambda + b(\mu) + c(\mu) e^{-\lambda \mu \tilde{\tau}(N^*(\mu))}. \quad (3.5.6)$$

In the following, we investigate the existence of purely imaginary roots of (3.5.6). It is obvious that  $\lambda = 0$  is not a characteristic root of (3.5.6). Indeed,

$$\begin{aligned} b(\mu) + c(\mu) &= -2\mu \delta \beta'(N^*(\mu)) N^*(\mu) \tau'(N^*(\mu)) e^{-\gamma \mu \tilde{\tau}(N^*(\mu))} \\ &\quad - (2e^{-\gamma \mu \tilde{\tau}(N^*(\mu))} - 1) N^*(\mu) \beta'(N^*(\mu)) \\ &\quad + 2\gamma \beta(N^*(\mu)) N^*(\mu) \left[ 1 + \mu \bar{\zeta}(\mu) \tilde{\tau}'(N^*(\mu)) \right] \mu \tau'(N^*(\mu)) e^{-\gamma \mu \tilde{\tau}(N^*(\mu))}, \end{aligned}$$

Since  $\delta - (2e^{-\gamma \mu \tilde{\tau}(N^*(\mu))} - 1) \beta(N^*(\mu)) = 0$ , we obtain  $2e^{-\gamma \mu \tilde{\tau}(N^*(\mu))} - 1 > 0$  and

$$\Delta(0, \mu) = b(\mu) + c(\mu) > 0.$$

It follows that  $\lambda = 0$  is not an eigenvalue.

Let  $\lambda = i\omega$ ,  $\omega > 0$  be a pure imaginary eigenvalue of (3.5.6). Separating real and imaginary parts, we obtain

$$\begin{cases} \omega &= c(\mu) \sin(\omega\mu\tilde{\tau}(N^*(\mu))), \\ b(\mu) &= -c(\mu) \cos(\omega\mu\tilde{\tau}(N^*(\mu))). \end{cases} \quad (3.5.7)$$

One can notice that if  $i\omega$  is a purely imaginary root of (3.5.6) then so is  $-i\omega$ . A necessary condition for equation (3.5.6) to have purely imaginary roots is

$$|c(\mu)| > |b(\mu)|. \quad (3.5.8)$$

If no  $\mu \in [0, \bar{\mu})$  fulfills condition (3.5.8), then the characteristic equation (3.5.6) has no purely imaginary root. Consequently, from Lemma 3.5.2, all eigenvalues of (3.5.6) have negative real parts and the steady state  $N^*(\mu)$  is locally asymptotically stable for all  $\mu \in [0, \bar{\mu})$ .

We have already checked that  $b(\mu) + c(\mu) > 0$ . Then, for (3.5.8) to hold true, it is necessary that  $c(\mu) > 0$ , that is  $\bar{\beta}(\mu) < 0$ . A sufficient condition for (3.5.8) is then  $b(\mu) < 0$ , which is equivalent to

$$\begin{aligned} &\delta + \bar{\beta}(\mu) \\ &+ \left( \bar{\eta}(\mu) \left[ \delta + \bar{\beta}(\mu) \right] + \bar{\alpha}(\mu) \left[ 1 + \mu\bar{\zeta}(\mu)\bar{\tau}'(N^*(\mu)) \right] \right) \mu\bar{\tau}'(N^*(\mu)) e^{-\gamma\mu\bar{\tau}(N^*(\mu))} < 0. \end{aligned} \quad (3.5.9)$$

From now on, we assume there exists  $\mu^* \in (0, \bar{\mu})$  such that (3.5.8) is fulfilled for  $\mu \in [0, \mu^*)$ .

System (3.5.7) is equivalent to

$$\cos(\omega\mu\tau^*(\mu)) = -\frac{b(\mu)}{c(\mu)}, \quad \sin(\omega\mu\tau^*(\mu)) = \frac{\omega}{c(\mu)}, \quad (3.5.10)$$

where  $\tau^*(\mu) = \tilde{\tau}(N^*(\mu))$ . Therefore adding the squares of both sides of (3.5.10), purely imaginary eigenvalues  $i\omega$  of (3.5.6), with  $\omega > 0$ , must satisfy

$$\omega = \left( c^2(\mu) - b^2(\mu) \right)^{\frac{1}{2}}. \quad (3.5.11)$$

Thus, in the following, we will think of  $\omega$  as  $\omega(\mu)$ ,  $\mu \in [0, \mu^*)$ . Substituting expression (3.5.11) for  $\omega$  in (3.5.10), we obtain

$$\begin{cases} \cos \left( \mu\tau^*(\mu) \left( c^2(\mu) - b^2(\mu) \right)^{\frac{1}{2}} \right) &= -\frac{b(\mu)}{c(\mu)}, \\ \sin \left( \mu\tau^*(\mu) \left( c^2(\mu) - b^2(\mu) \right)^{\frac{1}{2}} \right) &= \frac{\left( c^2(\mu) - b^2(\mu) \right)^{\frac{1}{2}}}{c(\mu)}. \end{cases} \quad (3.5.12)$$

From the above reasoning, values of  $\mu \in [0, \mu^*)$  solutions of system (3.5.12) generate positive  $\omega(\mu)$  given by (3.5.11), and hence yield imaginary eigenvalues of (3.5.6). Consequently, we look for positive solutions  $\mu$  of (3.5.12) in the interval  $[0, \mu^*)$ . They satisfy

$$\mu\tau^*(\mu) \left( c^2(\mu) - b^2(\mu) \right)^{\frac{1}{2}} = \arccos \left( -\frac{b(\mu)}{c(\mu)} \right) + 2k\pi, \quad k \in \mathbb{N}_0,$$

where  $\mathbb{N}_0$  denotes the set of all nonnegative integers. We set

$$\mu^k(\mu) := \frac{\arccos\left(-\frac{b(\mu)}{c(\mu)}\right) + 2k\pi}{\tau^*(\mu)(c^2(\mu) - b^2(\mu))^{\frac{1}{2}}}, \quad k \in \mathbb{N}_0, \mu \in [0, \mu^*].$$

Values of  $\mu$  for which  $\omega(\mu) = (c^2(\mu) - b^2(\mu))^{\frac{1}{2}}$  is a solution of (3.5.7) are roots of the functions

$$Z_k(\mu) = \mu - \mu^k(\mu), \quad k \in \mathbb{N}_0, \mu \in [0, \mu^*]. \quad (3.5.13)$$

The roots of  $Z_k$  can be found using popular software, but are hard to determine with analytical tools [19]. The following lemma states some straightforward properties of the  $Z_k$  functions.

**Lemma 3.5.3.** *For  $k \in \mathbb{N}_0$ ,*

$$Z_k(0) < 0 \quad \text{and} \quad \lim_{\mu \rightarrow \mu^*} Z_k(\mu) = -\infty.$$

*Therefore, provided that no root of  $Z_k$  is a local extremum, the number of positive roots of  $Z_k$ ,  $k \in \mathbb{N}_0$ , on the interval  $[0, \mu^*]$  is even. Moreover, if  $Z_k$  has no root on the interval  $[0, \mu^*]$ , then  $Z_j$ , with  $j > k$ , does not have positive roots.*

*Remark 1.* The last statement in Lemma 3.5.3 implies, in particular, that, if  $Z_0$  has no positive root, then (3.5.7) has no positive solution, and equation (3.5.6) does not have pure imaginary roots.

The search for purely imaginary roots ends up finding positive real roots of real functions  $Z_k$ , that can mostly be handled numerically. In the following proposition however, we establish some properties of purely imaginary roots of equation (3.5.6) using a method described in [72].

**Proposition 3.5.4.** *Let  $\pm i\omega(\mu_c)$ , with  $\omega(\mu_c) > 0$  and  $\mu_c \in (0, \mu^*)$ , be a pair of purely imaginary roots of equation (3.5.6) when  $\mu = \mu_c$ . Then  $\pm i\omega(\mu_c)$  are simple roots of (3.5.6) such that*

$$\begin{aligned} & \text{sign} \left\{ \frac{d\text{Re}(\lambda(\mu))}{d\mu} \right\}_{\mu=\mu_c} \\ &= \text{sign} \{ c^3(\mu_c \hat{\tau}'_c + \tau_c^*) + c^2 c' \mu_c \tau^* - c(b^2(\mu_c \hat{\tau}'_c + \tau_c^*) + b' + b b' \mu_c \tau_c^*) + c' b \}, \end{aligned} \quad (3.5.14)$$

with  $\tau_c^* = \tau^*(\mu_c)$ ,  $\hat{\tau}'_c = d\tau^*(\mu_c)/d\mu$ ,  $b = b(\mu_c)$ ,  $c = c(\mu_c)$ ,  $b' = b'(\mu_c)$  and  $c' = c'(\mu_c)$ .

*Proof.* Let  $\lambda(\mu)$  be a family of roots of (3.5.6), so  $\Delta(\lambda(\mu), \mu) = 0$ , such that  $\lambda(\mu_c) = i\omega(\mu_c)$ . Then,

$$\frac{d\lambda}{d\mu}(\mu) \Delta_\lambda(\lambda, \mu) + \Delta_\mu(\lambda, \mu) = 0, \quad (3.5.15)$$

where

$$\Delta_\lambda(\lambda, \mu) := \frac{d\Delta}{d\lambda}(\lambda, \mu) = 1 - c(\mu)\mu\tau^*(\mu)e^{-\lambda\mu\tau^*(\mu)},$$

and

$$\Delta_\mu(\lambda, \mu) := \frac{d\Delta}{d\mu}(\lambda, \mu) = b'(\mu) - [c(\mu)(\mu\hat{\tau}'(\mu) + \tau^*(\mu))\lambda - c'(\mu)]e^{-\lambda\mu\tau^*(\mu)},$$

with  $\hat{\tau}'(\mu) = d\tilde{\tau}(N^*(\mu))/d\mu$ .

Assume, by contradiction, that  $\lambda(\mu_c) = i\omega(\mu_c)$  is not a simple root of (3.5.6). Then

$$\Delta_\lambda(i\omega(\mu_c), \mu_c) = 1 - \mu_c \tau_c^* c(\mu_c) e^{-i\omega(\mu_c) \mu_c \tau_c^*} = 0.$$

Using (3.5.6) for  $\mu = \mu_c$ , we then deduce  $b(\mu_c) + 1/(\mu_c \tau_c^*) + i\omega(\mu_c) = 0$ , and consequently  $\omega(\mu_c) = 0$ , which gives a contradiction. It follows that all purely imaginary roots of (3.5.6) are simple.

In the following, we do not mention the dependence of the coefficients  $\tau^*$ ,  $\hat{\tau}'$ ,  $b$  and  $c$  (and their derivatives) with respect of  $\mu$ .

Since  $\Delta(\lambda, \mu) = 0$ , we deduce  $e^{\lambda \mu \tau^*} = -c/(\lambda + b)$ . Therefore from (3.5.15) we obtain

$$\left(\frac{d\lambda}{d\mu}\right)^{-1} = \frac{c + c\mu\tau^*(\lambda + b)}{[c' - c\lambda(\mu\hat{\tau}' + \tau^*)](\lambda + b) - b'c}.$$

Taking the real part of the above equality for  $\mu = \mu_c$ , we obtain

$$\begin{aligned} & \mathcal{R}e \left( \frac{d\lambda}{d\mu} \right)^{-1} \Big|_{\mu=\mu_c} \\ &= \frac{[c^2(1 + b\mu_c\tau_c^*)(\mu_c\hat{\tau}'_c + \tau_c^*) + \mu_c\tau_c^*c(c' - bc(\mu_c\hat{\tau}'_c + \tau_c^*))]\omega(\mu_c)^2 + c(1 + b\mu_c\tau_c^*)(c'b - b'c)}{(b'c - c'b - c(\mu_c\hat{\tau}'_c + \tau_c^*)\omega(\mu_c)^2)^2 + ((c' - bc(\mu_c\hat{\tau}'_c + \tau_c^*))\omega(\mu_c)^2)}. \end{aligned}$$

Notice that  $\text{sign}\{d\mathcal{R}e(\lambda)/d\mu\} = \text{sign}\{\mathcal{R}e(d\lambda/d\mu)^{-1}\}$ . Since  $i\omega(\mu_c)$  is a purely imaginary root of (3.5.5), then, from (3.5.11),  $\omega(\mu_c)^2 = c^2 - b^2$ , and we obtain

$$\begin{aligned} & \text{sign} \left\{ \frac{d\mathcal{R}e(\lambda)}{d\mu} \Big|_{\mu=\mu_c} \right\} \\ &= \text{sign} \{ c[c^3(\mu_c\hat{\tau}'_c + \tau_c^*) + c^2c'\mu_c\tau_c^* - c(b^2(\mu_c\hat{\tau}'_c + \tau_c^*) + b' + bb'\mu_c\tau_c^*) + c'b] \}. \end{aligned}$$

As we already noticed, if equation (3.5.5) has pure imaginary roots then necessarily  $c > 0$ . We deduce (3.5.14) and the proof is complete.  $\square$

We can now state and prove the following theorem dealing with the asymptotic stability of the positive steady state  $N^*$ .

**Theorem 3.5.5.** *Assume (3.5.2) holds true,  $\beta$  and  $\tau$  are  $C^2$  functions. If no  $\mu \in [0, \bar{\mu})$  satisfies (3.5.8), then the positive steady state  $N^*$  of (3.5.1) is locally asymptotically stable for  $\mu \in [0, \bar{\mu})$ .*

*Assume there exists  $\mu^* \in (0, \bar{\mu})$  such that (3.5.8) is fulfilled for  $\mu \in [0, \mu^*)$ . Then, the following holds true:*

- (i) *If  $Z_0$ , defined in (3.5.13), has no root on the interval  $[0, \mu^*)$ , then the positive steady state  $N^*$  of (3.5.1) is locally asymptotically stable for  $\mu \in [0, \mu^*)$ .*
- (ii) *If  $Z_0$  has at least one positive root  $\mu_c \in (0, \mu^*)$ , then  $N^*$  is locally asymptotically stable for  $\mu \in [0, \mu_c)$ , unstable for  $\mu \geq \mu_c$ ,  $\mu$  in a neighborhood of  $\mu_c$ , and a Hopf bifurcation occurs at  $N^*$  for  $\mu = \mu_c$  if*

$$\begin{aligned} & c^3(\mu_c\hat{\tau}'_c + \tau_c^*) + c^2c'\mu_c\tau_c^* \\ & - c(b^2(\mu_c\hat{\tau}'_c + \tau_c^*) + b' + bb'\mu_c\tau_c^*) + c'b \neq 0. \end{aligned} \tag{3.5.16}$$

When (ii) holds true, several stability switch can potentially occur for every  $\tau = \tau_c$ , roots of  $Z_k$  functions.

*Proof.* From Lemma 3.5.2 we know that  $N^*$  is locally asymptotically stable when  $\mu = 0$ . The first statement is straightforwardly satisfied.

Assume there exists  $\mu^* \in (0, \bar{\mu})$  such that (3.5.8) is fulfilled for  $\mu \in [0, \mu^*)$ . If  $Z_0$  has no positive root on the interval  $(0, \mu^*)$ , then the characteristic equation (3.5.5) has no pure imaginary root (see Remark 1 and Lemma 3.5.3). Consequently, the stability of  $N^*$  cannot be lost when  $\mu$  increases. We obtain the statement in (i).

Now, if  $Z_0$  has at least one positive root, say  $\mu_c \in (0, \mu^*)$ , then equation (3.5.5) has a pair of simple conjugate pure imaginary roots  $\pm i\omega_c$  for  $\mu = \mu_c$ . From (3.5.16) together with Proposition 3.5.4, we have either  $d\mathcal{R}e(\lambda)/d\mu(\mu = \mu_c) > 0$  or  $d\mathcal{R}e(\lambda)/d\mu(\mu = \mu_c) < 0$ . By contradiction, we assume there exists a branch of characteristic roots  $\lambda(\mu)$  such that  $\lambda(\mu_c) = i\omega_c$  and  $d\mathcal{R}e(\lambda(\mu))/d\mu < 0$ , for  $\mu < \mu_c$ ,  $\mu$  close to  $\mu_c$ . Then there exists a characteristic root  $\lambda(\mu)$  such that  $\mathcal{R}e(\lambda(\mu)) > 0$  and  $\mu < \mu_c$ . Since  $N^*$  is locally asymptotically stable when  $\mu = 0$ , applying Rouché's Theorem [41], we obtain that all characteristic roots of (3.5.5) have negative real parts when  $\mu \in [0, \mu_c)$ , and we obtain a contradiction. Thus,

$$\left. \frac{d\mathcal{R}e(\lambda)}{d\mu} \right|_{\mu=\mu_c} > 0. \quad (3.5.17)$$

Now, let  $N$  be a solution of equation (3.1.16). Then the function  $x$  defined, for  $t \geq 0$ , by

$$x(t) := N(\mu t) \quad (3.5.18)$$

satisfies

$$\dot{x}(t) = \zeta(\mu, x_t), \quad (3.5.19)$$

where  $\zeta : \mathbb{R}^+ \times C \rightarrow \mathbb{R}$  is given by

$$\zeta(\mu, \phi) = \frac{-\mu(\delta + \beta(\phi(0)))\phi(0) + 2\mu\beta(\phi(-\tilde{\tau}(\phi(0))))\phi(-\tilde{\tau}(\phi(0)))e^{-\gamma\mu\tilde{\tau}(\phi(0))}}{1 + 2\mu\tilde{\tau}'(\phi(0))e^{-\gamma\mu\tilde{\tau}(\phi(0))}\beta(\phi(-\tilde{\tau}(\phi(0))))\phi(-\tilde{\tau}(\phi(0)))}, \quad (3.5.20)$$

In order to prove the Hopf bifurcation for equation (3.1.16), from the change of variable in (3.5.18), it suffices to prove the Hopf bifurcation for (3.5.19). In [45], Eichmann stated some conditions on the function  $\zeta$  allowing a Hopf bifurcation to occur at the positive steady state of (3.5.19). The function  $\zeta$  defined above satisfies in particular the assumptions in [45], that are not recalled here for the sake of clarity.

The characteristic equation associated with the equilibrium  $N^*$  of (3.5.19) is

$$\begin{aligned} \tilde{\Delta}(\lambda, \mu) &= \lambda + \mu(\delta + \bar{\beta}) + \mu^2\bar{\alpha} \left[ 1 + \mu\bar{\zeta}\tilde{\tau}'(N^*(\mu)) \right] \tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} \\ &\quad + \mu^2\bar{\eta} \left[ \delta + \bar{\beta} \right] \tau'(N^*(\mu))e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} \\ &\quad - 2\mu\bar{\beta} \left[ 1 + \mu\bar{\zeta}\tau'(N^*(\mu)) \right] e^{-\gamma\mu\tilde{\tau}(N^*(\mu))}e^{-\lambda\mu\tilde{\tau}(N^*(\mu))}. \end{aligned} \quad (3.5.21)$$



Let  $\lambda \in \mathbb{C}$ . One can see that  $\tilde{\Delta}(\mu\lambda, \mu) = \mu\Delta(\lambda, \mu)$  for all  $\mu \in [0, \bar{\mu}]$ . Then, for  $\mu \in (0, \bar{\mu})$ ,  $\lambda$  is an eigenvalue associated with (3.5.21) if and only if  $\lambda/\mu$  is an eigenvalue associated with (3.5.5). Thus, it is straightforward that (3.5.21) has a unique pair of simple conjugate purely imaginary eigenvalues for  $\mu = \mu_c$ , that satisfy (3.5.17), since these properties hold for the characteristic equation (3.5.5). Then, from [45], a Hopf bifurcation occurs at  $N^*$  when  $\mu = \mu_c$ . This concludes the proof.  $\square$

## 3.6 Numerical illustrations

We consider  $\beta$  as a Hill function, given by (3.1.2). The following values for the parameters are chosen according to [76, 95, 96],

$$\delta = 0.05 \text{ day}^{-1}, \quad \gamma = 0.2 \text{ day}^{-1}, \quad \beta_0 = 1.77 \text{ day}^{-1} \quad \text{and} \quad r = 3. \quad (3.6.1)$$

The value of  $\theta$  is set to  $\theta = 1 \text{ cell.g}^{-1}$ , which is not relevant for a quantitative analysis, but does not modify the qualitative behavior of solutions of (3.1.16).

The delay function  $\tilde{\tau}$  is chosen as

$$\tilde{\tau}(N) = \tilde{\tau}_0 + (\tilde{\tau}_{\max} - \tilde{\tau}_0) \frac{N}{N + \theta_\tau},$$

with  $\tilde{\tau}_{\max} > \tilde{\tau}_0 > 0$  and  $\theta_\tau > 0$  (otherwise the delay is constant). Hence  $\tilde{\tau}(N)$ , and consequently  $\tau(N)$ , is an increasing bounded positive function. One may note that  $\tau_0 = \mu\tilde{\tau}_0$  and  $\tau_{\max} = \mu\tilde{\tau}_{\max}$ .

We use MATLAB, and the solver DDESD [105] for state-dependent delay differential equations, to numerically compute the solutions of (3.1.16).

We choose, for the remaining parameters, the following values

$$\tilde{\tau}_0 = 0.1 \text{ day}, \quad \tilde{\tau}_{\max} = 1 \text{ day} \quad \text{and} \quad \theta_\tau = 1 \text{ cell.g}^{-1}. \quad (3.6.2)$$

With values in (3.6.1) and (3.6.2), a unique positive steady state  $N^*(\mu)$  of (3.1.16) exists (condition (3.2.1) holds true) for  $\mu < \bar{\mu}$ , where computations give  $\bar{\mu} \approx 33$ . We obtain the functions  $Z_k$  defined in Lemma 3.5.3. The function  $Z_0$  has two roots in  $(0, \mu^*)$ ,  $\mu_1 = 3.72$  and  $\mu_2 = 5.92$ , and the function  $Z_1$  has no roots.

### 3.6.1 Discussion

The main result of this chapter is Theorem 3.5.5 describing the occurrence of periodic solutions, in our model, through a Hopf bifurcation. This is illustrated in Figure 3.1 where we see that the solutions of (3.1.16) periodically oscillate when  $\mu = \mu_1$  with a period of about 20 days. Variations of the delay function  $\tilde{\tau}(N(t))$  are also displayed. The same periodic behavior is observed.

Periodic solutions can be linked to some periodic hematological disorders that are characterized by significant oscillations of circulating blood cells count with periods ranging from weeks (19 to 21 days in case of cyclical neutropenia [59]) to several months (30 to 100 days in case of chronic myelogenous leukemia [59]). Periodic hematological disorders are of great interest and may offer an undisputed opportunity to better understand some yet unknown hematopoiesis mechanisms. Our numerical simulations suggest that our model could be applied to some cases of cyclical neutropenia.

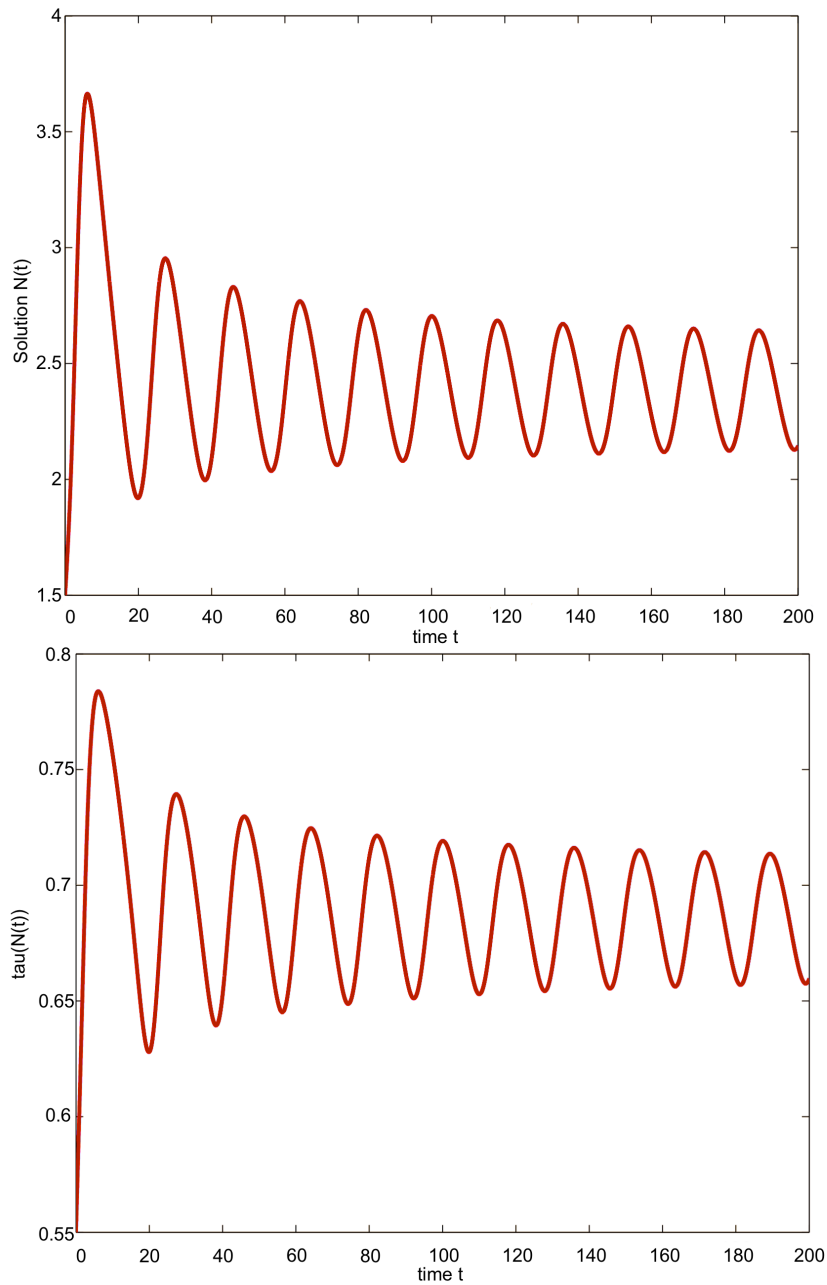


Figure 3.1: Top: Periodic Solution at the Hopf Bifurcation. With parameters given by (3.6.1) and (3.6.2) the solution of (3.1.16) undergoes a Hopf bifurcation when  $\mu = 3.72$ , thus periodic solutions are observed. Bottom: The corresponding delay function  $\tilde{\tau}(N(t))$ .

## Part II

# Cancer cells Proliferation: Immune System Response

## Chapter 4

# Interactions between immune challenges and cancer cells proliferation: timing does matter! \*

### Abstract

The immune system is a key component of malignant cells control and it is also involved in the elimination of pathogens that threaten the host. Despite our body is permanently exposed to a myriad of pathogens, the interference of such infections with the immune responses against cancer has been poorly investigated. Through a mathematical model, we show that the frequency, the duration and the action (positive or negative) of immune challenges may significantly impact tumor proliferation. First, we observe that a long immunosuppressive challenge increases accumulation of cancerous cells only if it occurs 14 years after the beginning of immunosenescence. However, short immune challenges result in an even greater accumulation of cancerous cells for the same total duration of immunosuppression. Finally, we show that short challenges of immune activation could lead to a slightly decrease in cancerous cell accumulation compared to a long one. Our results predict that frequent and acute immune challenges could have a different and in some extent higher impact on cancer risk than persistent ones even they have been much less studied in cancer epidemiology. These results are discussed regarding the existing empirical evidences and we suggest potential novel indirect role of infectious diseases on cancer incidence which should be investigated to improve prevention strategies against cancer.

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## 4.1 Introduction

While cancer remains one of the main causes of death in Western countries [47], its burden is increasing in low-and middle-income countries [80]. Today, the most common approach for removing cancer cells is to treat affected individuals through surgery, cytotoxic drugs, and/or radiotherapy [14]. Nevertheless, immunotherapy [87], aiming to stimulate the immune system to improve the control of cancerous cell proliferation [89], holds promise to be an alternative of current classic therapies.

In fact, the immune system has three major roles in cancer suppression [103, 115]. First, it can eliminate oncogenic pathogens (i.e. infectious organisms recognized to have a contribution to carcinogenesis [121]) and therefore protect the host from developing the associated tumor. Second, it can prevent pro-tumoral inflammatory environment by resolving inflammation right after pathogen elimination [104]. Finally, immunosurveillance bring into play many cells both from innate and adaptive immunity, especially T cells [115], that eliminate tumor cells and produce signaling molecules (cytokines) at both the tumor and peripheral sites [75].

However, it is now well recognized that immune system fails to avoid cancer proliferation and can have a paradoxical role which has been explained by the immunoeediting hypothesis [39]. At some point, immune clearance is switched to escape mechanisms, such as recruitment of immunosuppressive cells, allowing an increase in cancerous cell accumulation in late cancer stage [42]. Immune cells can also promote angiogenesis, produce growth factors and increase chronic inflammation in the tumor microenvironment which are considered as hallmarks of cancer and could result in activation of premalignant lesions[39, 52].

Humans are probably exposed to a high number of immune challenges (through contact, ingestion and inhalation) [17] which could impact the roles of the immune system in carcinogenesis. Especially, our immune system is implicated in control/elimination of intra- and extra-cellular infectious agents through a complex network of interdependent immune pathways that also involves adaptive immunity against cancerous cells control [48]. However, the role of immune challenges following infections, which could divert adaptive immunity against cancerous cells, has been poorly investigated.

First, infections could have a detrimental role for the host by reducing immune responses against cancerous cells. In fact, they can induce immunosuppression, here defined as a decrease in efficiency of innate and adaptive actors (due to depletion of dividing cells for instance). HIV infection is one of the most well-known examples of an immunosuppressive virus as it depletes CD4<sup>+</sup> T cells [25]. These CD4 helper T cells produce high level of IFN- $\gamma$ , as well as chemokines, that enhance the priming and expansion of CD8 cytotoxic cells which eliminate cancerous cells [68]. Helminths species are also able to impair immune efficiency through their immunoregulatory roles [82]. In fact, helminths are known to inhibit T cell proliferation and to promote expansion of Treg cells which are able to impede effective immunity against cancer by secreting

TGF- $\beta$  [68].

Second, infections are known to induce adaptive immune responses that could boost the elimination of cancerous cells. Early after an infection, the quantity of humoral and cellular effectors increases during acute inflammation and could cross react with tumoral antigens [88, 113]. In addition, the well-known trade-off between the Th1/Th17 and Th2 immune pathways suggests that Th1 or Th2 cytokines are able to downregulate each other and the associated humoral and cellular effectors [67]. However, Th1 activation is associated with protection against some cancers [54, 64]. In fact, it results in recruitment of natural killer (NK) cells and type I macrophages to tumor sites, which can act in concert toward tumor control [91]. Thus, all the infections that activate Th1 could reduce cancerous cell accumulation.

The timing of these immune challenges may also be crucial since our immune system is not permanently fully efficient. Indeed, immunosenescence is a process that reflects a gradual decrease of immune system activity with age mainly through a decreased capacity of immunosurveillance [49]. The beginning of immunosenescence is assumed to be associated with the beginning of thymopoiesis decline. Indeed, the thymus plays a crucial role in the development of T cells but also in maintaining immune efficiency [102]. Maximal activity is reached at puberty (from 10 to 19 years old according to the World Health Organization) and decrease progressively in adults [108]. The elderly (> 65 years old; WHO) usually have the following: (i) a depleted population of naive T cells (the set of T lymphocytes that can respond to novel antigens) [92, 93], (ii) a shrinking repertoire of T cell clones [55, 83, 93], (iii) an increased number of naturally occurring regulatory T cells that down-regulate T cell responses [46, 98], (iv) a low grade, pro-inflammatory status [92], and (v) increased numbers of myeloid-derived suppressor cells, which are associated with impaired T-cell functioning and produce high amounts of reactive oxygen species [24]. All these immune-associated changes can potentially promote tumor proliferation [55].

While the role of immunosenescence on cancer development has already been suggested [93], the combination of this long-term irreversible process with sporadic, transient immune challenges has rarely been considered. In this article, we explore theoretically the combined role of immunosenescence with both persistent and repeated acute immune challenges on proliferation of cancerous cells. To this purpose, we consider that challenges could reduce or boost immune responses against cancerous cells. We also discuss the potential consequences of our findings in terms of cancer prevention.

## 4.2 Materials and Methods

We explored the combined influence of immunosenescence with sporadic and partial alteration of immune system functioning on the accumulation of cancerous cells through the following theoretical framework:

$$\begin{aligned}
\frac{dH}{dt} &= \beta_1 H \left(1 - \frac{N}{K}\right) - \mu_1 H, \\
\frac{dP}{dt} &= \beta_1 P \left(1 - \frac{N}{K}\right) + \mu_1 H - (\mu_2 + \omega(t)) P, \\
\frac{dC}{dt} &= \beta_2 C \left(1 - \frac{N}{K}\right) + \mu_2 P - (\mu_3 + \omega(t)) C, \\
\frac{dI}{dt} &= \beta_2 I \left(1 - \frac{N}{K}\right) + \mu_3 C,
\end{aligned}$$

where  $H$  represents healthy cells,  $P$  precancerous cells,  $C$  cancerous cells, and  $I$  cancerous cells that are invisible to the immune system. In a sequential manner, healthy cells become precancerous at rate  $\mu_1$  which represent (precancerous cells meet the following criteria: (i) they increase the risk of cancer; (ii) cancerous cells arise from precancerous cells and (iii) precancerous cells are different from cancerous cells and normal cells but share some of their molecular and phenotypic properties [20]). Then, precancerous cells become cancerous at rate  $\mu_2$ , and finally invisible at rate  $\mu_3$ . We consider that invisible cancerous cells have acquired the capacity to avoid destruction by immune system whatever the mechanism implied (e.g. loss of MHC molecules and secretion of cytokines). Healthy and precancerous cells replicate at rate  $\beta_1$  while cancerous and invisible cells replicate at rate  $\beta_2$  (greater than  $\beta_1$ ) with a maximal total number of cells  $K$  (i.e. carrying capacity) in order to induce competition between different kinds of cells. We assumed that cancerous cells ( $C$  and  $I$ ) are autonomous and do not depend of precancerous cells to survive. Such assumption could have an impact only if precancerous cells disappeared from the population, which is unlikely to occur with our parameters chosen in accordance with the available literature (Figure 4.1).

Each precancerous and cancerous cells can be eliminated from the organism through the function  $\omega(t)$ . This function, temporally forced, aims to mimic the efficiency of the immune system during the lifetime of the organism considered. Five main parameters describe this function:

$$\begin{aligned}
\omega(t) &= a_1, & \text{if } t < b_0, \\
\omega(t) &= a_1 - a_2 t, & \text{if } t > b_0, \\
\omega(t) &= (a_1 - a_2 t)a_3, & \text{if } c_n > t > d_n, \\
&\text{with } \omega(t) < a_1
\end{aligned}$$

where  $a_1$  represents the immune system efficiency before the beginning of immunosenescence (occurring at time  $b_0$ ). When immunosenescence starts, we assume that the immune system's efficiency decreases linearly with time through a coefficient  $a_2$ . As the number of immune challenges encountered in one life is particularly hard

Parameter	Definition	Value	Additional information	Reference
$\beta_1$	Replication rate of healthy cells and precancerous cells	$[0.45-1.2].\text{cell.day}^{-1}$ mean= $0.82.\text{cell.day}^{-1}$	20 to 53H (example for gastric tissues)	[1]
$\beta_2$	Replication rate of non healthy cells	$[0.46-1.8].\text{cell.day}^{-1}$ mean= $1.13.\text{cell.day}^{-1}$	13-52H ( example for gastric tissues)	[1]
K	Carrying capacity of the tissue	$10^{13}$	Assuming the total number of cells in human body is $3.72 \cdot 10^{13}$ .	[2]
$\mu_1$	Mutation rate from healthy to pre-cancerous cell	$2.99 \cdot 10^{-6}.\text{year}^{-1}$	Based on Human mutation rate ( $10^{-8}$ . generation) and 299 cell generation per year.	[3]
$\mu_2$	Mutation rate from pre-cancerous cell to cancerous cell	$2.99 \cdot 10^{-6}.\text{year}^{-1}$	Idem	[3]
$\mu_3$	Mutation rate from cancerous cell to invisible cell	$4.12 \cdot 10^{-6}.\text{year}^{-1}$	Based on human mutation rate ( $10^{-8}$ . generation) and 412 cell generation per year.	[3]
$b_0$	Beginning of immunosenescence	20 years	The thymopoiesis starts to decline in healthy adults after 20 years.	[4]
$a_1$	Immune efficiency before immunosenescence	0.7	Fixed	
$a_2$	Rate at the immune system's efficiency decreases	$0.003.\text{year}^{-1}$	Fixed to have a 70% reduction over 50 years of immunosenescence, as documented for the decrease of B cell stimulation in elderly individuals	[5]
$a_3$	Amplitude of immune alteration	$\pm 0.7$	Fixed	

1. Aziz, F., Yang, X., Wen, Q. & Yan, Q. 2015 A method for establishing human primary gastric epithelial cell culture from fresh surgical gastric tissues. *Mol. Med. Rep.* **12**, 2939–2944.
2. Klein, C. a 2006 Random mutations, selected mutations: A PIN opens the door to new genetic landscapes. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 18033–4. (doi:10.1073/pnas.0609000103)
3. Roach, J. C. et al. 2010 Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science* **328**, 636–9. (doi:10.1126/science.1186802)
4. Steinmann, G. G. 1986 Changes in the human thymus during aging. *Curr Top Pathol* **75**, 43–88.
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Figure 4.1: Parameters values chosen in accordance with the available literature.



to determine, we choose a restrictive number of 30 challenges from ages 20 to 80 years. During an immune challenge  $n$  (starting at time  $c_n$  and ending at time  $d_n$ , thus for a duration  $d_n - c_n$ ), the immune system efficiency is multiplied by a proportion  $a_3$  that characterizes the amplitude and the direction of this immune system alteration (with  $-1 < a_3 < 1$ ; allowing a gradual efficiency from immunosuppression when  $0 < a_3 < 1$  with a positive impact on cancerous cells proliferation to a negative impact through immune system activation when  $-1 < a_3 < 0$ ). We assume that these immune challenges occur evenly between the beginning of immunosenescence and the end of life. In other words, the duration between each challenge will be identical. This flexible function allows us to study different scenarios of temporary and partial alteration of the immune efficiency which few of them are illustrated in Figure 4.2. While our theoretical framework can address a gradient in the duration of immune challenges, we consider that an acute immune challenge lasts for  $< 6$  months whereas persistent ones alter immune system for a longer period of time.

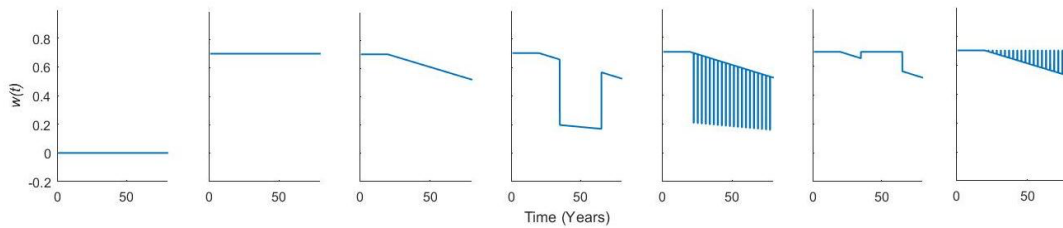


Figure 4.2: Examples of different immune system activity across ages (0 to 80).

We explore the respective contribution of the duration and the frequency of immune challenges on the number of cancerous cells at the age of 80 (assumed to be the end of individual's life), used as an estimation of cancer risk. We start all our simulations by considering that individuals have only healthy cells ( $S = K$ ,  $P = 0$ ;  $C = 0$ ;  $I = 0$ ). Finally, we test for the sensitivity of these impacts through a Latin Hypercube Sampling [62] with 100 iterations that allows exploring the robustness of our conclusion by adding uncertainties around parameters values.

## 4.3 Results

### Influence of timing and duration of a single immunosuppressive challenge

We first aimed to quantify the influence of the duration and timing of a single immunosuppressive challenge on cancerous cell accumulation at the end of individual life. Figure 4.3 shows that a long episode of immunosuppression leads to large accumulations of non-healthy cells by avoiding their elimination by the immune system.

Our theoretical framework also shows that the timing of the challenge through the lifespan is worth of consideration. In fact, Figure 4.3 highlights that a persistent

immunosuppressive challenge occurring before immunosenescence will not significantly impact cancerous cell accumulation even if it persists during 40 years. To have a significant increase of nonhealthy cells at the age of 80 years, the challenge must occur at least 14 years after the beginning of immunosenescence. Since the immune system is weaker at this time than before immunosenescence, numerous cancerous invisible cells may have emerged during the immunosuppressive challenge, yielding a continuous proliferation of these cells, even when the individual recovers. In addition, even if the immunosuppressive challenge occurs 25 years after the beginning of immunosenescence, it will have an impact on cancerous cell accumulation only if it persists 29 years.

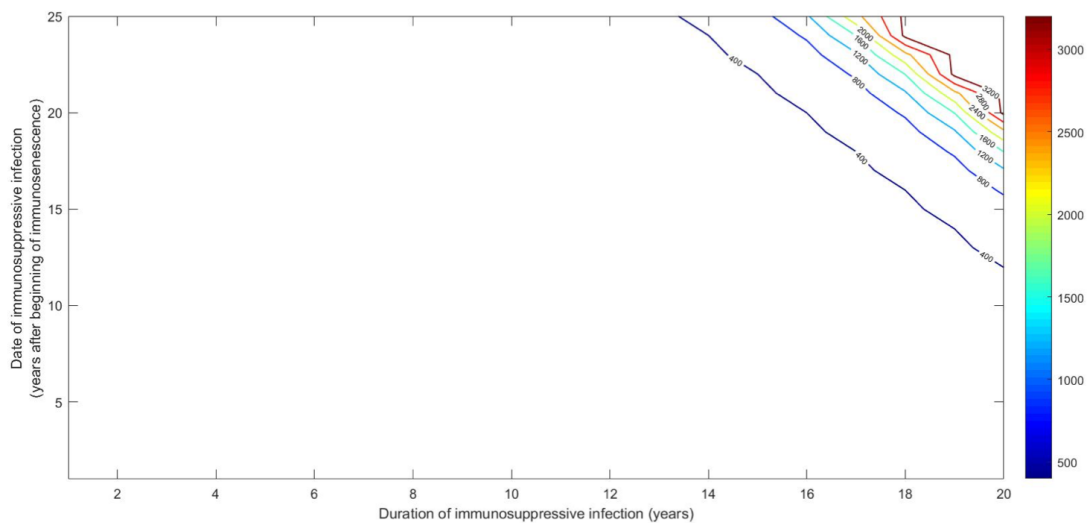


Figure 4.3: Contour plot of the number of cancerous cells at 80 (ranging from dark blue for accumulation of less than 500 cancer cells to dark red for situations with more than 3000 cells) according to the date of an immunosuppressive infection after the beginning of immunosenescence and its duration. The maximal number of cancerous cells accumulates for 20 challenges with a total duration of 40 years (i.e., 3311 cells). Parameters are detailed in Figure 4.1

### Combined effect of duration and the number of immunosuppressive challenges

We then explored the combined influence of the duration and number of immunosuppressive challenges on cancerous cell accumulation. As previously said, we assumed that challenges are evenly distributed after the beginning of immunosenescence.

First, we observe that several short immune challenges could lead to larger accumulation of nonhealthy cells than a long episode lasting for the same total duration of immunosuppression (quantified by the product between number of immunosuppressive challenges and their duration) (Figure 4.4). The positive relation between total

immunosuppression and number of cancerous cells accumulated (Figure 4.4 Inplot) suggests that the role of acute challenges is worthy of consideration.

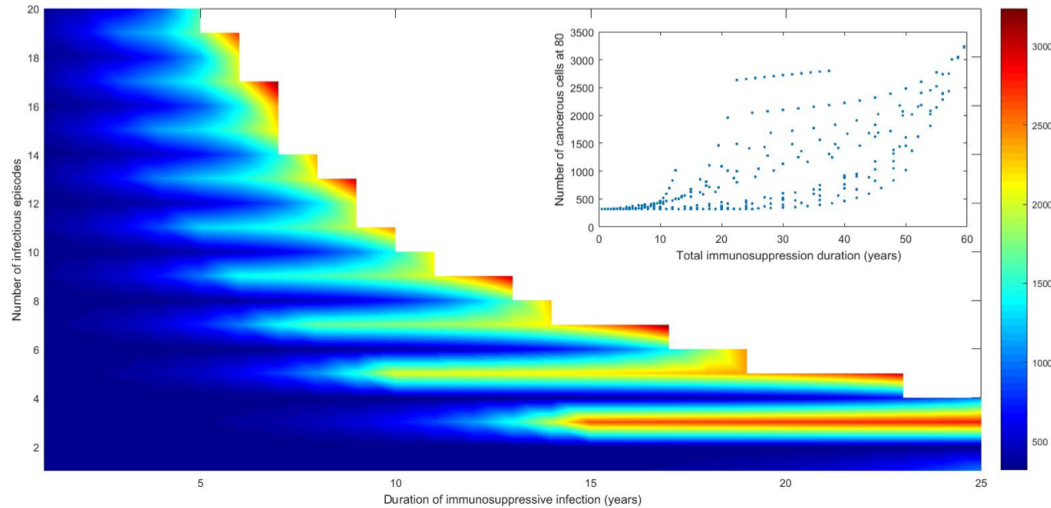


Figure 4.4: Influence of the number of immunosuppressive infections and their duration on the accumulation of cancerous cells (range from dark blue for accumulation of less than 500 cancer cells to dark red of more than 2500 cells) . White area represents parameters sets where total immunosuppression period is greater than 60 years. The maximal number of cancerous cells accumulated at 80 is of 2653 cells. (Inplot) Relationship between total immunosuppression duration and accumulation of cancerous cells. Parameters are detailed in Figure 4.1.  $c_n$  and  $d_n$  are modified along axes.

Then, to confirm this observation, we explored two different scenarios where challenges can be persistent or acute and evenly repeated 30 times. We found that a single long immunosuppression challenge leads to a very small change in cancerous cells accumulation while 30 repeated short challenges covering the same total duration are expected to produce a sharper increase in the proliferation of cancerous cells (Figure 4.5). These conclusions are robust to sensitivity analysis and also hold when partial immunosuppression of weaker amplitude is considered (see Supplementary Fig. S1 in Appendix A).

### Influence of immune activation challenges combined with immunosenescence

Noticing the significant effect of repeated immunosuppressive challenges on accumulation of cancerous cells, we then looked at the influence of immune activation challenges on the same estimation of cancer risk. With our realistic parameters, we found that a long period of immune activation slightly reduce the number of cancerous cells (Supplementary Fig. S2 in Appendix A). In addition, 30 repeated immune stimulations

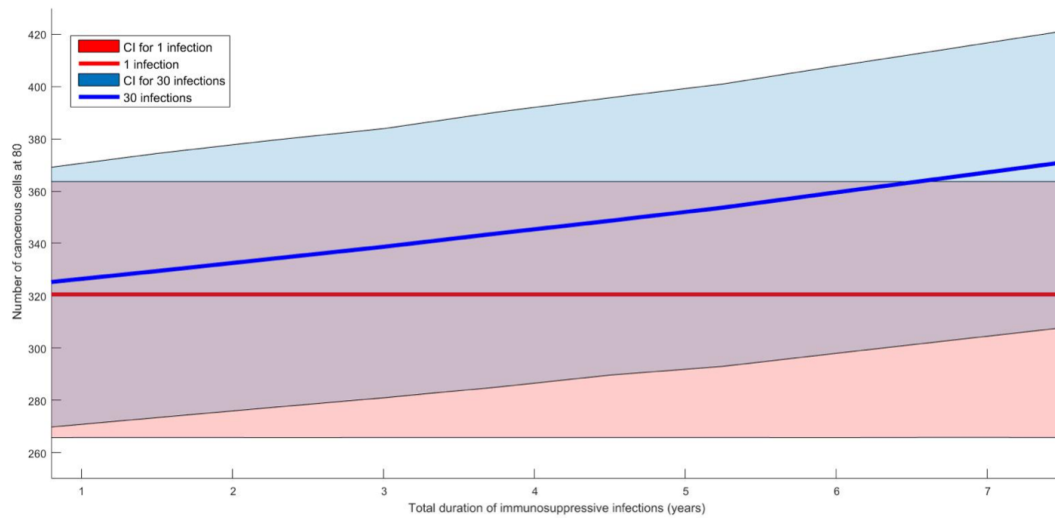


Figure 4.5: Influence of the number of immunosuppressive infections on the accumulation of cancerous cells. For a total immunosuppression duration indicated on x-axis (in years), red area shows that a single immunosuppressive infection has almost no influence of number of cancerous cells at the end of individual life. On the opposite, blue area shows the sharp increase in this abundance of cancerous cells when immunosuppression is distributed over 30 short infections. The maximal accumulation of cancerous cells for 30 challenges and a total duration of 7.5 years is of 370 cells. Parameters are detailed in Figure 4.1. Areas are confidence intervals quantified by a Latin Hypercube Sampling (LHS) with 100 iterations allowing testing sensitivity for a 5% change in all parameter values and solid lines represent the median value obtained from LHS.

lead to a higher decrease of cancerous cells than a single long one for the same total duration (Figure 4.6 and Supplementary Fig. S3 in Appendix A), but with weak amplitude. Since we assume that immune system efficiency cannot be higher than before immunosenescence, the net increase of immune system activation cannot be of the same magnitude than negative effects (e.g. an increase of 70% could result in a "net" increase much lower because the maximal activity is constrained by the immune system efficiency before immunosenescence beginning, as shown in Figure 4.2).

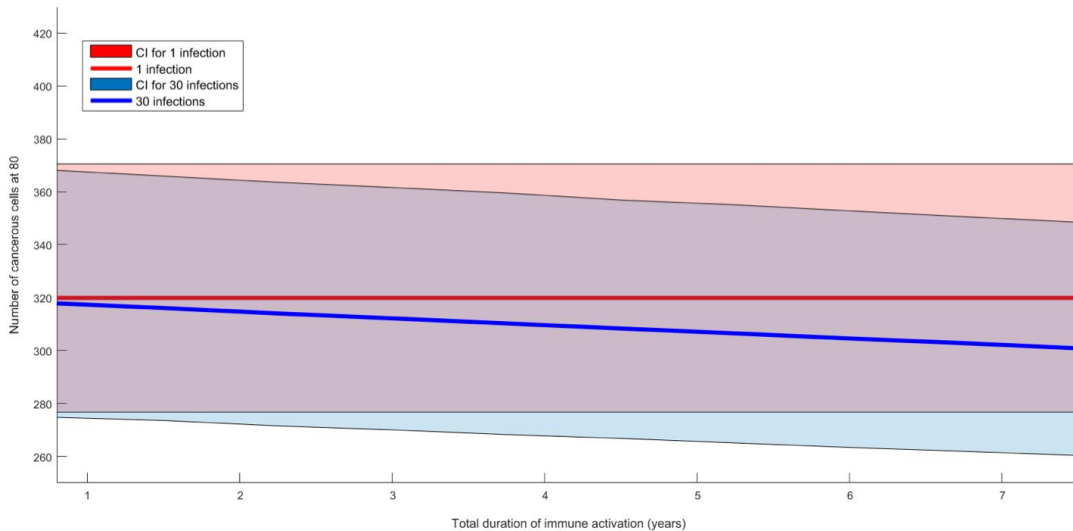


Figure 4.6: Influence of the number of immune activation following infections on the accumulation of cancerous cells. For a total immune activation duration indicated on x-axis (in years), red area shows that a single infection has almost no influence of number of cancerous cells at the end of individual life. Blue area shows the slight decrease in this abundance of cancerous cells when immune activation is distributed over 30 short infections. The minimal accumulation of cancerous cells for 30 challenges and a total duration of 7.5 years is of 305 cells. Parameters are detailed in Figure 4.1. Areas are confidence intervals quantified by a Latin Hypercube Sampling (LHS) with 100 iterations allowing testing sensitivity for a 5% change in all parameter values and solid lines represent the median value obtained from LHS.

## 4.4 Discussion

Our model describes the paradoxical role of immune challenges on cancer risk with a particular emphasis on the neglected role of acute challenges (i.e. alteration of immune efficiency for less than 6 months). These immune challenges can be beneficial for cancerous cell proliferation when they downregulate the adaptive immune response to cancer (called immunosuppressive challenges) or detrimental to cancerous cell proliferation when they upregulate this immune pathway (immune activation challenges). First, our model predicts that repeated acute immunosuppressive challenges may in-

crease cancer proliferation in a greater extent than a persistent one for the same total immunosuppression duration. Frequent immunosuppressive episodes, combined with immunosenescence, may result in the immune system's failure in controlling cancer cells growth and density, due to immunosuppressive episodes occurring prior to the recovery of maximal elimination of cancerous cells. In contrast, repeated short immune activation episodes could slightly reduce the accumulation of cancerous cells compared to a single persistent challenge. Regular activation of the immune system could offset the action of immunosenescence and therefore may offer a protection regarding age-related cancerous cell accumulation.

As for any modeling approach, our model is based on a series of simplifying assumptions that deserved to be discussed. First of all, as dynamics and cross-talk with the immune system could be different for congenital and acquired cancer, further studies need to assess the influence of immune challenges on cancerous cell accumulation for each of them. Then, we assumed that the immune system removes cancerous and precancerous cells in an identical manner, whatever their phenotype. This should be relaxed in future studies regarding the huge diversity of cancerous and precancerous cells [120], which suggests that immune effectors can specifically target only some cancerous clones. Third, we made the hypothesis that immunosenescence follows a purely gradual process, while it is possible that nonlinear relationships exist between age and immune function, especially in the very elderly [119]. To take into account this issue, we tested different immunosenescence curve shapes but they do not significantly change our results (Supplementary Fig. S4 in Appendix A). The parameter values chosen in this study may influence the quantitative outcomes of our theoretical framework, but we would like to point out that our conclusions are robust to changes in the parameter space (as shown in Supplementary Data, see in Appendix A).

While more realistic and complex models can be compared with empirical data, we nevertheless believe that our simple and general model can nevertheless provide a number of testable predictions on how immune challenges may affect the risk of malignancy via the immune system. Indeed, a lot of uncertainties are documented on what could be the impact of each component of the immune system on cancerous cell proliferation [52]. Therefore, a model with a greater complexity will have to deal with a lot of speculation about each of these components, decreasing its relevance to study transient immune challenges over cancer progression. While this should be a natural next step of our research work, it was then important highlighting this possibility through a simple model.

The originality of our study is to predict that acute immunosuppressive infections could also impact cancer risk and in a larger extent than persistent infections. Empirical evidences of such situation are obviously harder to identify, but the impact of "common" diseases on immune system and their relation with cancer risk are worthy of investigation. In fact, a protein secreted by influenza A virus (pandemic flu) inhibits  $IFN\beta$  expression and therefore suppresses both innate and acquired immune responses [60]. In addition, other common viruses as rhinovirus, responsive of common cold and rotavirus, agent of gastroenteritis, have also been associated with a immune deficiency

in infected people [69, 97]. As individuals may experience several episodes of flu, common cold and gastroenteritis during their course of life, these numerous short induced immunosuppression periods will probably not be neutral concerning the accumulation of cancerous cells. However, history of common colds or gastroenteritis prior to cancer diagnostic has been associated with a decreased cancer risk in a cohort study [1]. It may suggest that infections have a complex impact on immune responses to cancer and that further studies need to consider the temporal dynamic of immune challenges following the entry of an infectious organism. Finally, a complete and persistent immunosuppression following infections seems unlikely and latent infections (EBV and Herpesvirus) could rather produce short immunosuppression challenges each time they reactivate.

Conversely, our results suggest that multiple immune activations across life could decrease cancer risk comparing to a single one. The discontinuity theory proposed by Pradeu and colleagues [94] could give an explanation to this result. The theory states that immune responses are induced by the appearance of molecular motifs that are different from those with which the immune system has regularly interacted so far and could be tolerant regarding to motifs that are persistent. As a matter of fact, apparent protection against lung cancer has been observed in humans frequently exposed to cattle in the dairy industry [85]. It is possible that this protection is provided by endotoxins present in the dust which are known to be potent immune stimulating factors [100]. Moreover, evidences of acute infections being antagonistic to cancer has been reviewed by [37].

We do believe that this study could be the first step to envision innovative guidelines for cancer prevention and identification of groups at risk for cancer. Impacts of immune challenges are particularly worth of interest to study the observed disparity of cancer incidences between low and high-income countries. Our results suggest a stronger impact of acute and repeated immune challenges after the beginning of immunosenescence. This situation could be applied to high-income countries where longer lifespan have been shown to induce chronic low-grade inflammation, contributing to immune disorders in older individuals [114]. Even if poor-quality of available data and the comparatively shorter life expectancy may explain lower cancer incidence in low-income countries [27], we suggest that it could also be linked to the frequency and the nature of immune challenges (numerous short periods of immune activation). It may also depend on variability of individuals immune system (see Supplementary Fig. S5). In fact, it has been shown that variation in the human immune system is largely driven by nonheritable influences [29]. Depending on their environment, individuals will: (i) have different quantity of energy available to invest in their immune responses and (ii) meet different infectious burden and thus different levels of selective pressure to develop a fully efficient immune system [66]. In addition, antigenic exposure early in life through common infections is recognized to be essential for establishing an immunological memory [65]. All these sources of variation may impact the frequency and the time of infection but they could also directly impact the probability to develop cancer.

Finally, exploring the consequences of frequent immune challenges could become an interesting alternative way to design more integrative public health strategies, moreover regarding the issue of chemotherapy resistance that puzzles the scientific community since decades and the development of immunotherapy strategies.



# Conclusion and Perspectives

In the first part of this thesis, by proposing and analyzing two mathematical models describing healthy hematopoietic stem cells dynamics, we aimed to reach two distinct but all too important objectives. From a mathematical stand point, we aspired to contribute to the study of age-structured models and the theory of differential equations with distributed delay as well as those with state dependent delay. From a biological stand point, we aspired to emphasize the influence of some factors and/or parameters, related to hematopoietic stem cells dynamics such as growth factors, differentiation, proliferation, cell cycle duration and apoptosis, on blood cells behavior and count in the bloodstream.

The second part of this thesis focused on cancerous cells dynamics and their interactions with immune system responses. Where we argued that frequent and acute immune challenges could have a different and, in some extent, higher impact on cancer risk than persistent ones. These results allowed us to suggest a potential novel indirect role of infectious diseases on cancer incidence which should be subject to future investigations in order to improve prevention strategies against cancer. The fact that these novel, and important, results emerged from a rather simple Ordinary Differential Equations model encourages us to continue down this path by proposing other "more mathematically challenging" models that might help us refine our biological results.

The main reason we have used mathematical models and computer simulations, to describe stem cell dynamics, is their keen ability to predict biological systems and their behavior that would be difficult to conduct experimentally or formulated through statistical data alone. Indeed, lab experiments can be costly, time consuming and subject to biological variation through constantly changing external conditions, whereas mathematical and numerical models are able to give many answers, to possibly not yet known scenarios, since complex biological dynamics are reduced to key mechanisms which enables a more robust analysis of the way the system changes if any of these mechanisms are interrupted.

Moreover, mathematical models and computational approaches have a rather untapped potential in biomedical research, which has not yet reached full acceptance by experimentalists and clinicians in many laboratories. We do hope that this thesis would contribute to convince of the importance to incorporate a dialog between biologists, clinicians and mathematicians in order to use mathematical models as predictive tools in future research. We do also believe that such interdisciplinary effort, if carried

out on a more regular basis, would eventually lead to some invaluable insights that can be translated into the clinic to ultimately benefit patients.

# **Appendix A**

## **Supplementary data to Chapter 4**

## Supplementary materials

### Impact of weaker immunosuppression amplitude

In Chapter 4, we show that repeated short immunosuppressive infections have a larger impact on cancerous cells than a single long one. Nevertheless, we assumed in the main text that immune system activity is decreased by 70% during infections. Figure S1 shows that an infection decreasing immune system activity by only 10% of its capacity leads to similar conclusion, even if the pattern is less striking.

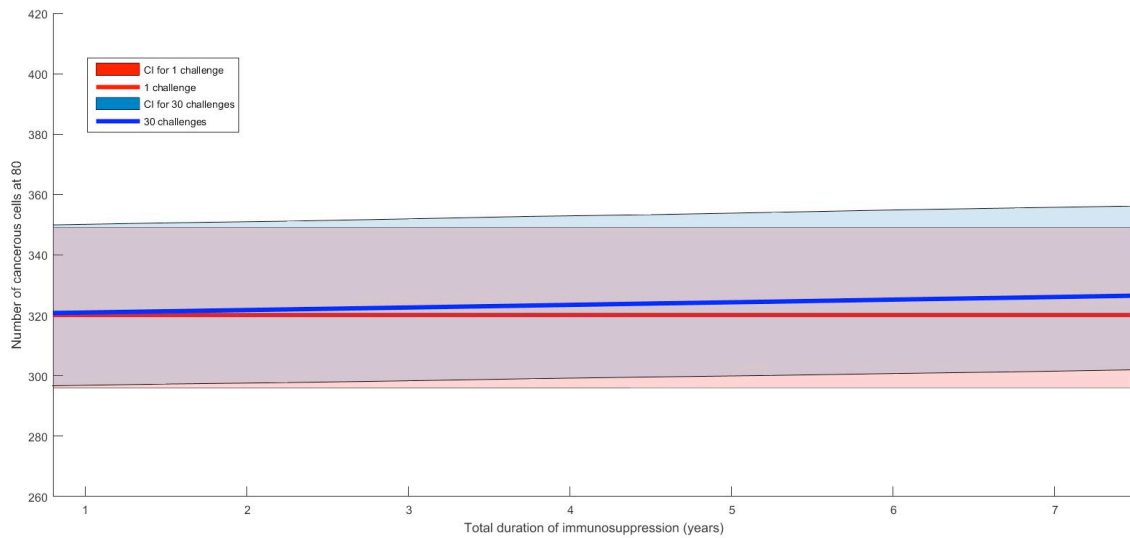


Figure S1: Same figure than Figure 4.5, but with an amplitude of immunosuppression of 10% instead of 70% ( $a_3=0.1$ ).

**Influence of immune activation following infections on the accumulation of cancerous cells.**

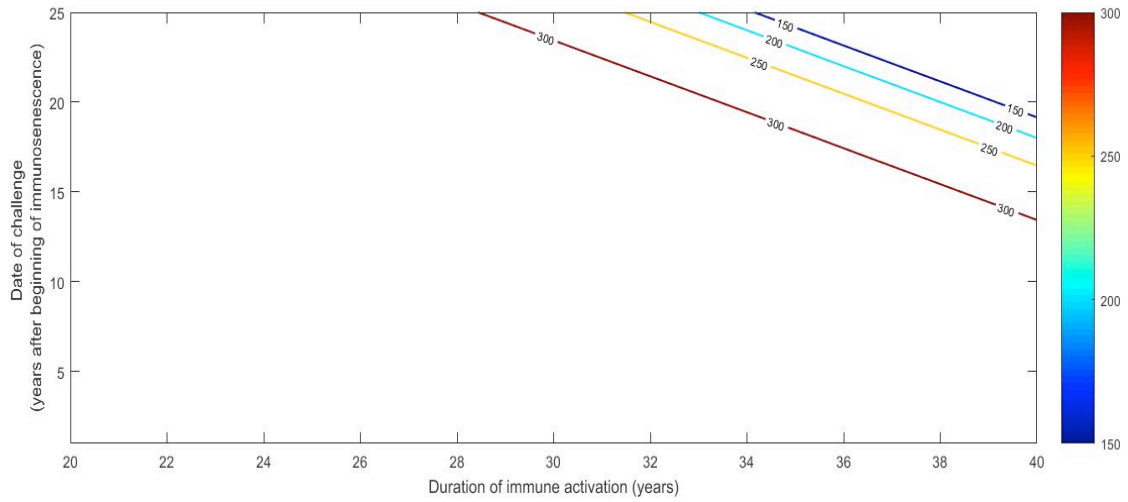


Figure S2: Same figure than Figure 4.3, considering an immune activation following the infection ( $a_3=-0.7$ ).

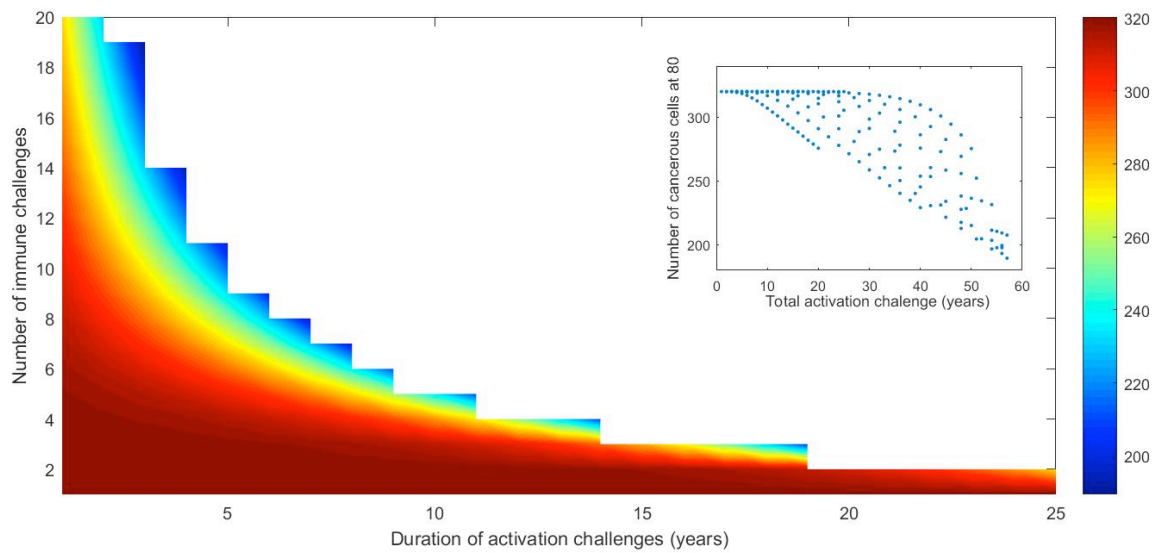


Figure S3: Same figure than Figure 4.4, considering an immune activation following the immune challenge ( $a_3=-0.7$ ).

### Impact of later immunosenescence start

For our principal results, immunosenescence has been started at 20 according to the beginning of thymic output reduction (Figure 4.1). However telomere length of CD4+ T cells decline around 45 years (See Aydar et al.). Figure S4 shows that a later immunosenescence start to similar conclusions for immunosuppressive infection and the greater accumulation of cancerous cells in the case of 30 repeated acute infections is even more striking.

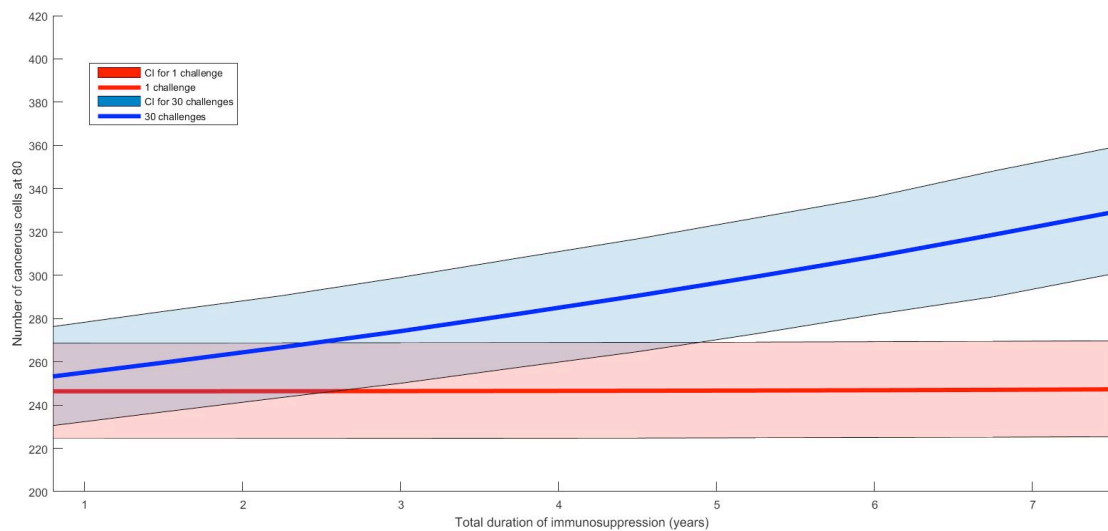


Figure S4: Same figure than Figure 4.5, but here immunosenescence starts at 45 instead of 20 ( $b_0=45$ ).

### Impact of initial strength of immune system

For our principal results, we assumed that immune system efficiency before the beginning of immunosenescence allows the elimination of 70% of cancerous cells ( $a_1$ , Figure 4.1). However, the immune system of individual is extremely variable

depending on available energy and personal history of infection. Figure S5 shows that a weaker basal immune efficiency leads to similar conclusions for immunosuppressive infection.

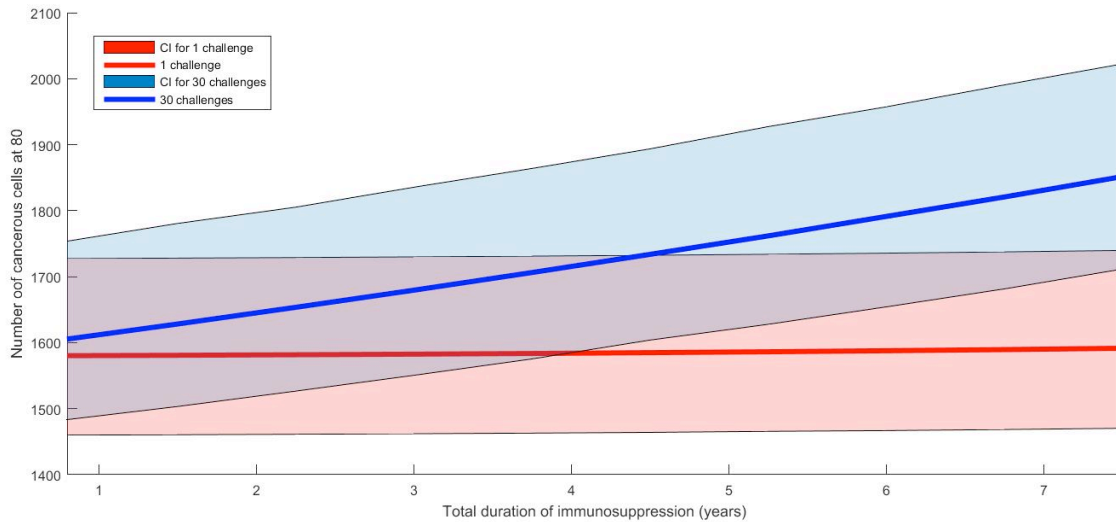


Figure S5: Same figure than Figure 4.5, but here immune efficiency before immunosenescence is of 40% ( $a_1=0.4$ ).

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# Sujet : Modélisation et Analyse de Modèles en Dynamique Cellulaire avec Applications à des Problèmes Liés aux Cancers

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**Résumé :** Cette thèse s'insère dans le cadre général de l'étude de la dynamique des populations. La population prise en compte étant constituée de cellules souches normales et/ou cancéreuses. Nous proposons et analysons trois modèles mathématiques décrivant la dynamique de cellules souches. Le premier modèle proposé est un modèle d'équations aux dérivées partielles structurées en âge que nous transformons, via la méthode des caractéristiques, en un système d'équations différentielles à retard pour lequel on étudie l'existence et la stabilité des points d'équilibres. En construisant une fonction de Lyapunov, on démontre que l'équilibre trivial est globalement asymptotiquement stable lorsqu'il est le seul équilibre du système. En utilisant l'équation caractéristique, nous analysons la stabilité asymptotique de l'équilibre positif. On effectue, après, des simulations numériques permettant d'illustrer le comportement des états d'équilibres. Dans le deuxième modèle, on considère que la durée du cycle cellulaire dépend de la population totale de cellules quiescentes. La méthode des caractéristiques nous permet de réduire notre modèle structuré en âge à un système d'équations différentielles avec un retard dépendant de l'état pour lequel on effectue une analyse détaillée de la stabilité. En construisant une fonction de Lyapunov-Razumikhin, nous obtenons une condition suffisante pour la stabilité globale de l'équilibre trivial. On montre qu'un unique point d'équilibre non-trivial peut apparaître par l'intermédiaire d'une bifurcation transcritique de l'équilibre trivial. Une analyse du comportement de l'état d'équilibre positif nous permet de conclure l'existence d'une bifurcation de Hopf. Nous confirmons, ensuite, les résultats analytiquement obtenus par des simulations numériques. Pour le troisième et dernier modèle de cette thèse, on propose un système d'équations différentielles ordinaires décrivant la dynamique de cellules souches saines et cancéreuses et prenant en compte leurs interactions avec les réponses immunitaires. Ce modèle nous a permis de souligner l'ampleur de l'impact que peuvent avoir différentes infections sur la prolifération tumorale que ce soit par le biais de leurs fréquences, leurs durées ou la façon dont ils agissent sur le système immunitaire.

**Mots clés :** Dynamique cellulaire; immunosénescence; cancer; équation aux dérivées partielles structurées en âge; équation différentielle à retard; retard dépendant de l'état; fonction de Lyapunov; bifurcation de Hopf

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## Subject : Mathematical Modeling in Cellular Dynamics: Applications to Cancer Research

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**Abstract** : This thesis fits into the general framework of the study of population dynamics. The population particularly considered in this work is comprised of stem cells with both cases of healthy and cancerous cells being investigated. We propose and analyze three mathematical models describing stem cells dynamics. The first model is an age-structured partial differential model that we reduce to a delay differential system using the characteristics method. We investigate the existence and stability of the steady states of the reduced delay differential system. By constructing a Lyapunov function, the trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium of the system. The asymptotic stability of the positive steady state, the most biologically meaningful one, is analyzed using the characteristic equation. We, then, conduct some numerical simulations to illustrate the behavior of the steady states. In the second model, the duration of the cell cycle is considered to depend upon the total population of quiescent cells. The method of characteristics reduces the age-structured model to a system of differential equations with a state-dependent delay. We perform a detailed stability analysis of the resulting delay differential system. By constructing a Lyapunov-Razumikhin function, we obtain a sufficient condition for the global asymptotic stability of the trivial steady state. It is shown that a unique non-trivial steady state can appear through a transcritical bifurcation of the trivial steady state. The analysis of the positive steady state's behavior concludes to the existence of a Hopf bifurcation and gives criteria for stability switches. We confirm the analytical results by numerical simulations. The third and final model, proposed in this thesis, is an ordinary differential equations model describing healthy and cancerous stem cells dynamics and their interactions with immune system responses. Through this model, we show that the frequency, the duration of infections and their action (positive or negative) on immune responses may impact significantly tumor proliferation.

**Keywords** : Cell dynamics; immunosenescence; cancer; age-structured partial differential equation; delay differential equation; state-dependent delay; Lyapunov function; Hopf bifurcation