Mathematical models of physiologically structured cell populations

Ricardo Borges Rutz
Tesi Doctoral - 2012

Departament de Matemàtiques
Facultat de Ciències
Universitat Autònoma de Barcelona

Directors: Àngel Calsina Ballesta
Sílvia Cuadrado Gavilán

Contents

Agraïments

Aquí vull donar les gràcies a totes les persones que han fet possible realitzar aquest somni i acabar aquest treball.

Primer de tot, vull agrair als meus pares, Romeu i Reni, i les meves *ties-mares*, la Zezinha, la Ereni i la Ceny. Ells han sigut la base de la meva vida, sempre m'han donat tot l'amor i recolzament que he necessitat. A vosaltres, *muito obrigado do fundo do meu coração!*

Vull agrair al professor Carlos Antonio Campani de la *Universidade Federal de Pelotas* (UFPel) que va ser la persona que em va explicar què era la recerca i és per *culpa* seva que vaig anar estudiar a la *Universidade Federal do Rio Grande do Sul* (UFRGS) la carrera de matemàtiques.

Dels anys de la carrera, a més a més de tots els amics i companys, he d'agrair al meu gran mestre, el professor Eduardo H. M. Brietzke. Em va ensenyar molta anàlisi, però més que això, va ser la seva manera clara i tranquil·la de fer matemàtiques el que em va motivar a continuar en aquest camí. Com a professor, la meva màxima aspiració sempre ha estat ser com ell.

També és responsable de la meva continuïtat a la recerca l'Alexandre Baraviera. Em va fer moltes classes a la carrera, però més que un professor, ha estat un amic. Van ser moltes tardes que vam passar xerrant de matemàtiques, física, llibres, recerca i Europa ... em va ajudar a obrir el meus horitzons.

D'aquesta etapa encara he d'agrair a una última persona, l'Adriano Tort. No ha estat professor meu mai però m'ha ensenyat molt, i durant el màster hem compartit assignatures, i la seva claredat en el raonament, la senzillesa dels seus arguments, les ganes que hi posava sempre m'han seduït. Sempre feia que les matemàtiques semblessin més fàcils, més interessants, més aplicables.

Com a conseqüència d'aquestes experiències, arribo a Catalunya i a la Universitat Autònoma de Barcelona (UAB). Encara que no siguin persones, estic agraït a totes dues. A la UAB sempre he trobat els medis necessaris per poder continuar els meus estudis, un lloc públic i de qualitat per desenvolupar la meva recerca, el suport que un estudiant de doctorat necessita. I de Catalunya, tot el que en digués seria poc. És el país que he triat per viure i per fer-lo meu. Aquí he trobat les roques d'escalada, els amics, la família, el paisatge ... tot el que buscava.

Aquí a Catalunya, a la UAB, he d'agrair especialment al Departament de Matemàtiques i a tots els professors del programa de doctorat. Vaig rebre una molt bona formació i tot el suport que he necessitat. També agraeixo al Leopoldo i al Set, companys de les assignatures de doctorat, molts dies d'estudi que vam compartir junts. També als professors dels cursos de Català de la UAB que sempre han tingut paciència i moltes ganes de transmetre els seus coneixements.

Dues persones especials sense les quals aquest treball no existiria són els meus directors de tesi, l'Àngel i la Sílvia. No tinc paraules per agrair-los l'ajuda i les hores que m'han dedicat, tota la formació matemàtica que m'han donat i també els consells a les hores de dubte, les advertències a les hores que *m'adormia o que em desviava del camí*. Han estat i són exemples. La Sílvia, amb la seva visió pràctica, amb el seu rigor i ganes de fer matemàtiques, m'ha aportat molt en aquests anys. L'Àngel, que com el seu nom ja indica, ha estat el meu àngel de la guarda. En aquests anys m'ha dedicat molt de temps, m'ha ensenyat molt, i no només matemàtiques sinó que també molta biologia, a més d'història, llengua i cultura catalana, anglès. M'ha ensenyat molt amb l'exemple, sempre ple d'entusiasme en aprendre coses noves, en entendre i en donar una interpretació biològica a tot, amb una paciència sense fi. Totes les paraules d'agraïment serien poques. També he d'agrair al professor Odo Diekmann l'ajut i l'orientació que m'ha donat, impresindible per elaborar part d'aquest treball.

A més a més de l'àmbit de les matemàtiques, no puc deixar d'agrair a altres persones que m'han acompanyat en aquest camí. Els meus germans SCREAM, que encara que lluny sempre han estat al meu costat. En particular l'Izaias que en aquests anys ha estat un company de moltes xerrades, *un amigo de verdade*. Al Mano, sempre amb aquells e-mails emotius. A l'Aurora i la Yolanda, amigues que sempre m'han recolzat en tot. El Thomas, amic de tantes aventures (i escalades). Als meus companys de l'escalada, amics amb els quals he compartit tants dies a la muntanya, ... a la Claudia i al Max, al Frank, a la Flavie, a la Laia i l'Olliver, a la Sara, a la Marianne, al Pau, a l'Helena, al Sergi i a la Montse, al Vini i a la Sarah, al Lluís, quants moments increïbles hem passat junts en els últims anys.

Vull acabar donant les gràcies a la meva família, la Montse (Guapeta) i a la (petita) Júlia. Amb la Montse he tingut la sort de trobar tota una família, els seus pares, el Víctor i la Miriam, són més que sogres, són amics de veritat. Gràcies a tota la família Villasante, a la Nuri i al Josep, i al Víctor i a la Cris. La Montse ha estat la meva companya en aquests anys, companya en tot, i sempre ha estat al meu costat, sempre m'ha recolzat, sempre ha tingut paraules d'ànims. Em sento molt estimat i això m'omple de felicitat. I ara amb la petita Jùlia això només pot millorar. Moltes gràcies.

Introduction

It is commonly asserted that the study of population dynamics started at the end of the 18th-century with a model proposed in 1798 by T.R. Malthus, [52]. In his work, Malthus supposed that the growth rate of the population was proportional to the total population size. Malthus was concerned with the evolution of society and his model reflects that the growth of the population opposes to the unlimited progress of society. This model was very criticized for being not realistic. However, if we look at the predictions of the model, maybe it will not seem so unrealistic (see [55], pg.2). In the 19th-century more realistic models were proposed to deal with the effects of limitations of resources or crowding, for instance, the work of Verhulst in 1838, [68], is an example of it.

An important advance in population dynamics was the introduction of structured population models, the first ones being the age structured models. The first work on a population which takes into account the age of individuals can be traced back to L. Euler (1760), see [37]. Much later, and along similar lines, F.R. Sharpe and Lotka in 1911 in [61] (and A.G. McKendrick in 1926, [51]) proposed models were the age structure was considered. These models motivated the development of many mathematical tools, in particular, the study of (Volterra) integral equations. The main result already stated in the work of Sharpe and Lotka was the (continuous version of the) so called fundamental theorem of demography (see [71]). Despite this progress, all the models were linear, which did not allow to include effects of limitations of resources or crowding. It was in 1974 when M.Gurtin and R.C. MacCamy (see [42]) introduced the first model of nonlinear age population dynamics. Since then, a variety of structured population models have been studied where the vital rates considered: fertility, mortality, individual growth rate, the rate of cell differentiation, etc., depend on internal variables (of the individuals). These internal variables are often, the age (in models of demography, [72]), the size (see [44] and [53]), the age of infection (models in epidemiology, [27], [22] and [32]), the degree of cell differentiation (see [33]) and also the content of certain proteins (see [13] and [12]). In all these models, interesting mathematical properties were analyzed, trying to connect the results with biological behaviors.

The use of the theory of structured population dynamics in order to study cell populations began in 1959 with the paper [69] where Von Foerster derived the complete differential equation for the age density function of cells (and later on that of Bell and Anderson [15]). Since then, many researchers have contributed to this field (see for instance [53], [7], [2]). Two of them were M. Gyllenberg and G. F. Webb. They published several works were they divided the cells into two types: proliferating and quiescent cells. In many cases, in cell populations, not all the individuals are growing and proliferating, but some of them are in a rest phase. In particular, it is known that the quiescence is responsible for prolonged periods of apparent tumor inactivity. Bertuzzi et al. in [16] claim that every realistic model of tumor cell population must consider quiescence. Normally, the proliferating cells are growing and some of them become quiescent, that is, in a resting stage and later, they can return to the proliferating phase. The quiescent cells do not lose their reproductive capacity, only that they do not divide while they remain quiescent. Moreover, the reasons why some cells become quiescent and why some quiescent cells come back to the proliferating phase are not exactly known.

L. H. Hartwell, R. T. Hunt and P. M. Nurse have discovered two groups of proteins, namely cyclin and CDK (cyclin dependent kinases), that control the transition phases on the cell cycle. In 2001 these three researchers received the Nobel Prize in Physiology or Medicine for their complete description of the cyclin and CDK mechanisms, which are central to the regulation of the cell cycle. These proteins act as regulators of the transition between the proliferating and the quiescent phase. It has been shown (see [47], [63]) that an overexpression of cyclin reduces this transition rate. In [12] and [13] a nonlinear cell population model for both, tumoral and healthy tissue is introduced in which cells are structured with respect to age and with respect to the content of cyclin and CDK.

In this thesis we will consider a model similar to the one presented in [12] and [13], but here we assume that the parameter functions are age independent, which gives a model where the structure is only with respect to the cyclin content. The resulting system is still a first order nonlinear partial differential equations system with non local terms. To study this system we will use the theory of positive linear semigroups and the semilinear formulation, which are very powerful tools to deal with the analysis of this kind of models, both from the point of view of the initial value problem as well as the existence and stability of steady states. In the last chapter we also present an alternative model (where some hypotheses change a little bit and others are introduced) and use the so called cumulative or delayed formulation of structured population dynamics ([22] and [23]). This last part of the study was suggested by Prof. Odo Diekmann from Utrecht University.

The model proposed

Bekkal Brikci et al. presented in [12] and [13] a nonlinear model of cell population dynamics. In these works, a cell population model for both, tumoral and healthy tissue is introduced in which cells are structured with respect to age and with respect to the content of a group of proteins called cyclin and CDK (Cyclin Dependent Kinases). As Hartwell et al. show in [46], these proteins play a central role in the regulation of the cell cycle (see also [67]).

They propose the following nonlinear system:

$$\begin{cases} \dfrac{\partial}{\partial t}p(t,a,x) + \dfrac{\partial}{\partial a}p(t,a,x) + \dfrac{\partial}{\partial x}\big(\Gamma(a,x)p(t,a,x)\big) = \\ \qquad = -\big[L(a,x)+F(a,x)+d_1\big]p(t,a,x) + G(N(t))q(t,a,x), \\ \dfrac{\partial}{\partial t}q(t,a,x) = L(a,x)p(t,a,x) - \big[G(N(t))+d_2\big]q(t,a,x) \end{cases} \tag{1}$$

where $p(t,a,x)$ and $q(t,a,x)$ are the densities of proliferating and quiescent cells, respectively, at time t with respect to age a and content x of $cyclin$.

To this system it is added the boundary condition (at $a=0$)

$$p(t,0,x) = 2\int_0^{x_m}\int_0^{+\infty}\frac{F(a,y)}{y}\chi_{[0,y]}(x)p(t,a,y)\,da\,dy$$

and the definition

$$N(t) = \int_0^{x_m} \int_0^{+\infty} \big[\phi^*(a,x)p(t,a,x) + \psi^*(a,x)q(t,a,x)\big]\, dadx.$$

This describes the following biological situation: the cells are structured both with respect to age and with respect to the content of a certain group of proteins called cyclin and CDK. The proliferating cells grow and divide, giving birth at the end of the cell cycle to new cells, or else transit to the quiescent compartment, whereas quiescent cells do not age nor divide nor change their cyclin content but either transit back to the proliferating compartment or else stay in the quiescent compartment. Moreover, both proliferating and quiescent cells may experiment apoptosis, i.e. programmed cell death. The only nonlinear term is a recruitment term of quiescent cells going back to the proliferating phase. This term depends on a measure of the total population and tends to zero when the total number of cells goes to infinity in the case of healthy tissue but remains bounded away from zero in the tumoral case. In the first chapter we will explain the main hypotheses and how to derive the dependence of cyclin content with respect to age.

In the major part of this thesis we work out an age independent version of the model considered in [12] and [13], that is, the following first order nonlinear partial differential equations system with nonlocal terms structured only with respect to the cyclin content

$$\left\{\begin{array}{rcl} \dfrac{\partial}{\partial t}p(x,t) + \dfrac{\partial}{\partial x}\big(\Gamma(x)p(x,t)\big) & = & -\big[L(x) + F(x) + d_1\big]p(x,t) \\ & & +G(N(t))q(x,t) + 2\int_x^{x_M} \frac{F(y)}{y}p(y,t)dy, \\ \dfrac{\partial}{\partial t}q(x,t) & = & L(x)p(x,t) - \big[G(N(t)) + d_2\big]q(x,t) \end{array}\right. \tag{2}$$

where $p(x,t)$ and $q(x,t)$ are the density of proliferating and quiescent cells (respectively) at time t with respect to the cyclin content x.

If we think in a compartment description, we could represent it as described in figure 1.

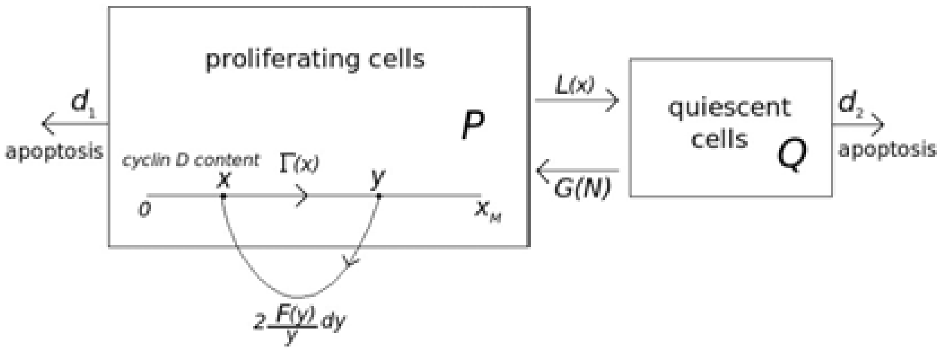

Figure 1: Compartmental description

The functions that appear in the system have the following biological interpretation:

$\Gamma(x)$ denotes the evolution speed of cyclin content with respect to time. In [12] the authors develop an ordinary differential equations model at an intracellular scale for the cyclin synthesis based on the works [3], [11] and [62] which produces a growth speed Γ vanishing at 0 and at the maximum value of cyclin content x_M.

The transition rate $L(x)$ from proliferating to quiescent is assumed to be decreasing to take into account that, as we mentioned before, a larger amount of cyclin content inhibits this transition.

Since high levels of cyclin enhance the progression through the cell cycle until mitosis (see for instance [70], [63]), the cell division rate $F(x)$ is assumed to be increasing (as a function of the cyclin content).

A particular feature of the birth term in (2),

$$2\int_{x}^{x_M} \frac{F(y)}{y} p(y,t)dy \tag{3}$$

is that the distribution of the cellular material between daughter cells is assumed to be unequal. Mathematical models of cell population with unequal cell division can be found in [49], [5] and [6] where distribution of RNA content between daughter cells is studied. In [14], a model for the progression through the cell cycle with unequal distribution of the cyclin content between daughter cells is considered. In system (2), the non local term (3) gives the inflow of newborn cells. It assumes that cells with cyclin content y $(> x)$ divide at a rate $F(y)$ producing two new cells with cyclin content x and $y - x$ where (as in [12], [13], [17] and [18]) x is a uniformly distributed (on $[0, y]$) random variable. In the last Chapter we generalize the probability distribution of the cyclin content of the newborn cells to any absolutely continuous distribution with bounded density.

The transition rate G from quiescent to proliferating stage is assumed to depend on a weighted total population number N (to take into account those cells that are qualified to be recruited again for the proliferating stage, see [12], [13]).

For the age and cyclin cell population model, the authors prove, under suitable hypotheses, the boundedness of the solutions in the case of healthy tissue, as well as the exponential growth of the solutions in the tumoral case. They also give conditions which imply polynomial growth.

Structure of the thesis

In this work we start, at Chapter 1, by understanding the production of cyclin depending on the cell age as a synthesis process enhanced by others molecules that are taken into account as some aggregated variable. Based on this we obtain the shape of a very important ingredient of the model, the function Γ that represents the evolution speed of cyclin with respect to the time/age. The other functions that appear in the system are also introduced. Next, the age and cyclin system (which is studied in [12] and [13]) is derived using the compartmental point of view. Once we have this system, and since the functional dependence on age is not so important (for instance, for Γ, the age dependence is negligible if we assume that some constants are large), we assume that the functions $\Gamma, L, F, \phi^*, \psi^*$ are age independent. With this at hand we derive system (2) which is still a system of first order nonlinear partial differential equations. One important thing in this work is that the system considered is simpler that the one presented in [12] but it retains the biological interest, the properties and the mathematical behavior.

In the first Chapter we also make other assumptions to simplify further the system and derive an ordinary differential equations system. This part does not have biological interest because we have to assume that the parameter functions are cyclin independent, i. e., they are constant. This model is not a particular case of system (2) because the functions do not depend on cyclin, but it helps us to understand the mathematical behavior of system (2). In the ordinary differential equations model we can analyze the complete behavior of the system and show that for certain parameter values we can obtain an unstable non trivial equilibrium point. These results help us to earn insight on the main system. In Chapters 3 and 4 we use these results in order to find parameter values that give rise to unstable non trivial equilibrium solutions. From the known results for the finite dimensional reduced case, we obtain that the steady state remains stable for a large set of values of the parameters, but it becomes unstable through a Hopf bifurcation for others, giving rise to periodic oscillations of the populations.

In Chapter 2 we start by explaining model (2). The hypotheses about every function that appear in the system are made, as well as some biological interpretation. Once we have all the ingredients, first of all we prove global existence, uniqueness and positiveness of the solutions of the initial value problem. In order to do it we rewrite system (2) in an abstract form

$$\frac{d}{dt}u(t) = \mathbf{A}u(t) + f(u(t))$$

and show that the linear operator $\mathbf{A}$ is the infinitesimal generator of a positive C_0 semigroup. For this we work out all the details (see Proposition 2). Even though the proof is based in the characterization of the generator of the translation semigroup (see [9], A-I 2.4), it is much more involved due to the fact that the characteristic lines of the first equation in (2) are neither straight lines nor level curves of the solutions. We also use a C^1-linearization result (Lemma 2.2.1) for the characteristic equation around the extreme points of the interval. On the other hand we use the standard semilinear formulation (see [57]) for the nonlinear (abstract) equation since f is locally Lipschitz in L^1, and obtain a unique global positive solution for any positive initial condition in L^1 (Theorems 2.2.4 and 2.2.5).

In Chapter 3 we prove the existence and uniqueness of a nontrivial steady state of system (2) under suitable hypotheses (see Theorem 3.1.5). As it is often done in similar situations, the problem is related to proving the existence (and uniqueness) of a positive normalized eigenvector. This eigenvector corresponds to the dominant eigenvalue of a certain positive linear operator parameterized by the value of the (one dimensional) feedback variable G. The existence of both dominant eigenvalue and (unique) positive eigenvector is given by a version of the infinite dimensional Perron-Frobenius theorem. In the proof we also show that the existence and uniqueness of a nontrivial steady state also needs that the eigenvalue vanishes at a certain value $\hat{G}$ of the parameter and then the steady state is obtained as a scalar multiple of the eigenvector such that it closes the feedback loop in the sense that the value of the feedback variable for it equals $\hat{G}$. These results are substantially included in [17].

In [12] and [13] there is numerical evidence of stability of the steady state for the healthy tissue in all the cases they analyze. In Chapter 4 we include numerical simulations based on the integration along the characteristic lines (see [1]). With the help of these numerical simulations we find instability of the steady state for parameter values compatible with the ones which give instability in the finite dimensional model of Chapter 1. We also include a computation showing the existence of x-independent solutions for a very particular choice of the parameter values and functions defining the model. These results are substantially included in [18].

In Chapter 5 we use the so-called cumulative or delayed formulation of the structured population dynamics (see [28], [29] and [30]). In particular we have considered a different version of the model studied in the previous chapters, where one assumes that proliferating cells can become quiescent only once opposed to the other approach where these transitions can occur infinitely many times and moreover, we also assume that there is a particular value x_b of the cyclin content that separates cells which still cannot divide from the others which are able to divide. Furthermore, here the state variables are no more densities but the flux of the cells across the point x_b and the feedback variable. Finally, the model equation turns out to be a delay equation relating the current values of these variables with their history (their value in the past). Using this, one can prove existence and uniqueness of solutions of the initial value problem, and the linear stability principle by means of a semi-linear formulation in the framework of dual semigroups, and so different from the one used in Chapter 2.

Preliminaries

In this preliminary chapter we introduce some definitions, notations and theorems that we will use later.

Definitions and notations

Definition 0.1. A linear semigroup on a Banach space X is a one-parameter family $(S(t))_{t\geq 0}$ of bounded linear operators on X such that,

$$S(0) = Id,$$

$$S(t)S(s) = S(t+s),$$

for all $t, s \geq 0$.

Definition 0.2. A one-parameter semigroup $(S(t))_{t\geq 0}$ is called strongly continuous if

$$\lim_{t\to t_0} \|S(t)f - S(t_0)f\| = 0$$

for all $f \in X$ and $t, t_0 \geq 0$.

In this work all the semigroups that we will consider will be strongly continuous one-parameter semigroups of linear operators on a Banach space X. The semigroup property $S(t+s) = S(t)S(s)$, for all $t, s > 0$ implies that in the definition it suffices to take $t_0 = 0$.

On the other hand, for any strongly continuous semigroup $S(t)$ there exist $M \geq 1$ and $w \in R$ such that

$$\|S(t)\| \leq Me^{wt}.$$

Definition 0.3. By the growth bound of the semigroup $(S(t))_{t\geq 0}$ we understand the number

$$\omega := \inf\{w \in \mathbb{R} : \text{ there exists } M \in \mathbb{R} \text{ such that } \|S(t)\| \leq Me^{wt} \text{ for } t \geq 0\}.$$

Definition 0.4. To every semigroup $(S(t))_{t\geq 0}$ there belongs an operator $(A, D(A))$, called the generator and defined on the domain

$$D(A) := \{f \in X : \lim_{h\to 0^+} \frac{S(t)f - f}{h} \text{ exists in } X\}$$

by

$$Af := \lim_{h\to 0^+} \frac{S(t)f - f}{h} \text{ for } f \in D(A).$$

Definition 0.5. We say that a strongly continuous semigroup $(S(t))_{t\geq 0}$ is bounded if there exists $M \in \mathbb{R}$ such that for every $t \geq 0$ we have $\|S(t)\| \leq M$.

We say that this semigroup is compact if $S(t)$ is compact for all $t > 0$ (i.e., $S(t)$ sends bounded sets to sets with compact closure).

Definition 0.6. The resolvent set of a linear operator A on a Banach space X is defined by

$$\rho(A) = \{\lambda \in \mathbb{C} : (\lambda - A)^{-1} \text{ exists with domain } X \text{ and it is a bounded linear operator.}\}$$

i.e., $\lambda - A$ is a bijection from $D(A)$ to X and $(\lambda - A)^{-1}$ is continuous.

Definition 0.7. By spectrum of an operator A we understand the set $\sigma(A) = \mathbb{C}\backslash\rho(A)$.

We denote by $P_\sigma(A)$ the set of eigenvalues of A, i.e., those λ such that $\ker(\lambda - A) \neq \{0\}$.

Definition 0.8. We say that an operator K is A-compact if $K(\lambda_0 - A)^{-1}$ is compact for some $\lambda_0 \in \rho(A)$.

Definition 0.9. We define the spectral radius of a bounded linear operator S by

$$r(S) := \sup\{|\lambda| : \ \lambda \text{ belongs to the spectrum of } S\} = \sup \|S^n\|^{1/n} \leq \|S\|.$$

The spectral bound of the generator A is defined by

$$s(A) := \sup\{Re\lambda : \ \lambda \text{ belongs to } \sigma(A)\}.$$

The growth bound of the generator A is $\omega(A) := \omega = \omega(S(t))$.

Definition 0.10. In the case that λ_0 is an isolated point of the spectrum of A, we define the algebraic multiplicity of λ_0 as the dimension of the spectral subspace corresponding to λ_0 (i.e., the subspace $\bigcup_n \ker(\lambda_0 - A)^n$), while the geometric multiplicity is the dimension of the kernel of the operator $\lambda_0 - A$.

In the case that the algebraic multiplicity of λ_0 is 1 we call λ_0 an algebraically simple pole.

Definition 0.11. We say that a positive linear operator K (i. e., such that $Kv \geq 0$ whenever $v \geq 0$) is irreducible in $L^1(\alpha, \beta)$ if for all $f > 0$ and for all $[a, b] \subset (\alpha, \beta)$, there exists $n \in \mathbb{N}$ such that $\int_a^b K^n f > 0$.

We say that a positive semigroup $S(t)$ is irreducible in $L^1(\alpha, \beta)$ if for all $p_0 > 0$ and for all $[a, b] \subset (\alpha, \beta)$, there exists $t > 0$ such that $\int_a^b S(t)p_0 > 0$.

A characterization of irreducible semigroup is that the resolvent operator of the generator is strictly positive i. e., it maps nonnegative (nonzero) functions to strictly positive functions a. e.

Definition 0.12. Let us consider the following semilinear initial value problem

$$\begin{cases} \frac{d}{dt}u(t) + Au(t) = f(u(t)), \ \ t > 0, \\ \qquad\qquad u(0) = u_0, \end{cases} \tag{4}$$

where A is the infinitesimal generator of a C_0-semigroup $S(t)$, $t > 0$, on a Banach space X, $f : X \to X$ satisfies a Lipschitz condition in u, and $u_0 \in X$.

We define a Mild solution of (4) as a continuous function u which is a solution of the following integral equation

$$u(t) = S(t)u_0 + \int_0^t S(t-s)f(u(s))ds.$$

Theorems on positive semigroups

Theorem 0.13. *Suppose that A is the generator of a positive linear semigroup and K is a positive bounded linear operator.*

If A is K-compact and if $s(A+K) > s(A)$ then $s(A+K)$ is a pole of finite algebraic multiplicity of the resolvent operator of $A+K$ and hence an eigenvalue.

Proof.: See [9], pages 317-319.

Theorem 0.14. *Suppose that B is the generator of an irreducible positive semigroup on a Banach lattice X. If $s(B)$ is a pole of the resolvent, then it has algebraic (and geometric) multiplicity 1.*

The corresponding residue has the form $P =< \cdot, \phi > u$, where $\phi \in X'$ is a positive eigenvector of B', $u \in X$ is a positive eigenvector of B and $< u, \phi >= 1$.

Proof.: See [9], pages 310.

Theorem 0.15. *Suppose that S is an irreducible semigroup on the Banach lattice X and let B be its generator. Assume that $s(B) = 0$ and that there exists a positive linear form $\psi \in D(B')$ (where B' denotes the adjoint of B) with $B'\psi \leq 0$.*

If $P_\sigma(B) \cap i\mathbb{R}$ is non-empty, then the following assertions are true:

(a) 0 is the only eigenvalue of B admitting a positive eigenvector.

(b) If $Bh = i\alpha h$ $(h \neq 0, \alpha \in \mathbb{R})$, then $|h|$ is a quasi-interior point (a strictly positive function a. e. when X is L^1).

Proof.: See [9], page 312.

Theorem 0.16. *Let A be the generator of a positive semigroup and K a positive bounded linear operator. Then the following alternative holds:*

(i) The spectral radius of $K(\lambda - A)^{-1}$ is less than 1, for all $\lambda > s(A)$. Then $s(A+K) = s(A)$.

(ii) There exists $\lambda > s(A)$ such that the spectral radius of $K(\lambda - A)^{-1}$ is larger than or equal to 1. Then $s(A+K) > s(A)$.

Proof.: See Theorem 3.3 in [66], where it is stated in a more general setting, more precisely for the so-called resolvent positive θ operators.

Proposition 0.17. *Let C be the generator of a positive semigroup (in particular a positive bounded linear operator). Then*

$$s(C) \geq \sup\{\lambda \in \mathbb{R} : \; Cf \geq \lambda f \quad \textit{for some} \quad 0 < f \in D(C)\}.$$

Proof.: Let $\lambda > s(C)$ and $0 < f \in D(C)$ such that $Cf \geq \lambda f$. Then $(\lambda - C)f \leq 0$, and hence, since the resolvent operator $(\lambda - C)^{-1}$ of the generator of a positive semigroup is positive (see [9]) we have $f = (\lambda - C)^{-1}(\lambda - C)f \leq 0$, a contradiction.

See Corollary B-II, 1.14 in [9] where the same proposition is stated in spaces of continuous functions.

Theorem 0.18. *Let A be the generator of a strongly continuous semigroup $(S(t))_{t\geq 0}$ and let K be a bounded linear operator. Then $A + K$ with domain $D(A+K) = D(A)$ is the generator of a strongly continuous semigroup $(\tilde{S}(t))_{t\geq 0}$.*

Moreover, $(\tilde{S}(t))$ is the solution of the following integral equation

$$\tilde{S}(t)f = S(t)f + \int_0^t S(t-s)K\tilde{S}(s)f ds \quad \textit{for} \quad t \geq 0, f \in X.$$

Proof.: See [9], page 44 and its references.

Theorem 0.19. *(Rellich-Kondrachov Theorem for bounded domains)*

Let Ω be a bounded C^1 domain. Then the injection $W^{1,1}(\Omega) \subset L^1(\Omega)$ is a compact operator.

Proof.: See [19], page 169.

Theorem 0.20. *Let B_1 and B_2 be two linear operators with strictly positive resolvent and such that*

$$(\lambda - B_1) \geq (\lambda - B_2) \text{ for } \lambda > \max\big(S(B_1), S(B_2)\big)$$

and that $S(B_i)$ is a pole of the resolvent of B_i, $i = 1, 2$.

Then $s(B_1) > s(B_2)$.

Proof.: See [10].

Dual semigroups

Definition 0.21. Given a linear semigroup $S(t)$ on a Banach space X, we define the dual semigroup $S^*(t)$ by taking the adjoint operator $S^*(t)$ for any t, i. e.,

$$< u, S^*(t)\phi >=< S(t)u, \phi > \quad \text{for } u \in X, \phi \in X^*.$$

Definition 0.22. The subspace $X^\odot$ of the dual space X^* with respect to a strongly continuous semigroup $S(t)$ is defined as the (closed) maximal invariant subspace on which $S^*(t)$ is strongly continuous, i. e.,

$$X^\odot = \{\phi \in X^* \ : \ \lim_{t \to 0^+} \|S^*(t)\phi - \phi\| = 0\}.$$

Definition 0.23. We call $S^\odot(t)$ to the restriction of $S^*(t)$ to $X^\odot$.

So, we have that $X^{\odot\odot}$ is the subspace of the dual $X^{\odot *}$ where the (bi)dual semigroup $S^{\odot *}(t)$ is strongly continuous.

Definition 0.24. We define the embedding $j : X \to X^{\odot *}$ by

$$< jx, \phi >=< x, \phi >$$

for $x \in X$ and $\phi \in X^\odot$.

Remark 1. The range of j lies in $X^{\odot\odot}$.

Indeed, given any $x \in X$ we must show that

$$\lim_{t\to 0^+} \|S^{\odot *}(t)jx - jx\| = 0,$$

i.e., that we have $\lim_{t\to 0^+} < S^{\odot *}(t)jx - jx, \phi^{\odot} >= 0$ uniformly for $\phi^{\odot} \in X^{\odot}$ with norm equal 1. But,

$$\left|< S^{\odot *}(t)jx - jx, \phi^{\odot} >\right| = \left|< jx, S^{\odot}(t)\phi^{\odot} - \phi^{\odot} >\right|$$

$$= \left|< x, S^{\odot}(t)\phi^{\odot} - \phi^{\odot} >\right| = \left|< S(t)x - x, \phi^{\odot} >\right| \leq \|S(t)x - x\| \longrightarrow_{t\to 0^+} 0,$$

where the inequality follows from $\|\phi^{\odot}\| = 1$.

Definition 0.25. We say that a Banach space X is sun-reflexive with respect to a semigroup $S(t)$ if the embedding j is such that $j(X) = X^{\odot\odot}$.

Definition 0.26. Let us consider the following semilinear initial value problem

$$\begin{cases} \frac{d}{dt}u(t) + Au(t) = f(u(t)), \;\; t > 0, \\ u(0) = u_0, \end{cases} \tag{5}$$

where A is the infinitesimal generator of a C_0-semigroup $S(t)$, $t > 0$, on a Banach space X, $f : X \to X^{\odot *}$ satisfies a Lipschitz condition in u, and $u_0 \in X$.

We define as Mild solution of (5) a continuous function u which is a solution of the following integral equation

$$u(t) = S(t)u_0 + j^{-1}\left(\int_0^t S^{\odot *}(t-s)f(u(s))ds\right).$$

Remark 2. In order that this variation of constants equation makes a sense we need that the integral takes values in the range of j. What is always true is that it takes values in $X^{\odot\odot}$ provided that $t \to f(u(t))$ is norm continuous (see [24], Theorem 3.2). So, this suffices in the case that X is sun reflexive. Otherwise, it is still possible to prove directly that the integral takes values in $j(X)$ in some very important cases, significantly for our purposes in the case of delay equations (see [29] [30] and Chapter 5).

Chapter 1

The age and cyclin cell population model. An oversimplified version

In the first part of this chapter we present the model studied in [12] and [13] which is a structured cell population model. The structure is based on internal variables (age and the content of a certain protein called Cyclin as we explained before). Here we also introduce the functions that appear on the system and we do some basic assumptions on them. This assumptions will allow us to simplify the model. Assuming that the main functions do not depend on age, it leads us to a first order nonlinear partial differential equations system without boundary condition. More than that, if we simplify further the model assuming that some functions do not depend on the cyclin content, we can show that it is possible to find an unstable nontrivial equilibrium. This will be studied in section 1.2.

To present the model studied in [12] and [13], let us start by considering the variation of the amount of the cyclin with respect to the age.

1.1 The complete model

Let x be the amount of the complex $cyclin$ inside a cell and w an aggregated variable representing the amount of the various molecules involved in the synthesis of $cyclin$. We consider x and w as regulating variables in a simple nonlinear system of ordinary differential equations (ODEs) with respect to the cell age a. The synthesis of x occurs at a rate c_1 and its degradation at a rate c_2; we assume that the synthesis of w is induced by growth factors at a constant rate c_3, its degradation occurring at a rate c_4. The ODE model can thus be written as follows:

$$\begin{cases} \dfrac{dx}{da} = c_1 \dfrac{x}{1+x} w - c_2 x, \quad x(0) = x_0 > 0, \\ \dfrac{dw}{da} = c_3 - c_4 w, \quad w(0) = w_0 > 0. \end{cases} \tag{1.1}$$

The only nonlinearity of this model is located in the term $c_1 \dfrac{x}{1+x}$ representing a positive autoregulation coefficient with saturation for x under the linear influence of the lumped variable w. Substituting the solution of the second equation of (1.1), we can reduce (1.1) to an equation in x:

$$\frac{dx}{da} = c_1 \frac{x}{1+x} \left(\frac{c_3}{c_4} + e^{-c_4 a} \big(w_0 - \frac{c_3}{c_4} \big) \right) - c_2 x, \quad x(0) = x_0. \tag{1.2}$$

A natural quantity arises in the qualitative analysis of (1.2), the x-nullcline:

$$X(a) = \frac{c_1}{c_2} \left(\frac{c_3}{c_4} + e^{-c_4 a} \big(w_0 - \frac{c_3}{c_4} \big) \right) - 1.$$

We assume that $w_0 \leq \dfrac{c_3}{c_4}$ and $c_1 c_3 > c_2 c_4$ which is a way to express that the lumped variable w is increasing from its initial to its asymptotic value. Therefore, a fundamental property of equation (1.2) is that the cyclin concentration x is limited by:

$$x_M = \frac{c_1 c_3}{c_2 c_4} - 1 > 0. \tag{1.3}$$

We keep this simple model for our next purpose which is to describe a population of cells, in a proliferative or quiescent state.

Before introducing the system, we have to define some functions.

The function Γ represents the evolution speed of $cyclin$ with respect to time which is given by equation (1.2), with $w_1 = w_0 - \dfrac{c_3}{c_4} \leq 0$:

$$\frac{dx}{da} = \Gamma(a, x) = c_1 \frac{x}{1+x} \left(\frac{c_3}{c_4} + e^{-c_4 a} w_1 \right) - c_2 x. \tag{1.4}$$

Let $p(t, a, x)$ and $q(t, a, x)$ be the densities of proliferating and quiescent cells, respectively, at time t with respect to age a and content x of $cyclin$.

We also consider a "total weighted population", i.e., an effective population density, N defined by:

$$N(t) = \int_0^{x_M} \int_0^{+\infty} \big[\phi^*(a, x)p(t, a, x) + \psi^*(a, x)q(t, a, x)\big]\, dadx.$$

Here the weights $\phi^*(a, x)$ and $\psi^*(a, x)$ represent environmental factors such as growth and anti-growth factors acting on the populations of proliferating and quiescent cells, respectively.

Exits from the quiescent compartment are due either to apoptosis (physiological cell death) at a rate d_2 or to transition to the proliferative phase according to a "recruitment" or "getting in the cycle" function G, which is assumed to be a smooth strictly decreasing function of the total weighted population N while, in the case of healthy tissue, tends to 0 when N goes to infinity. We also assume that cells may leave the proliferative compartment due either to apoptosis, with rate d_1, or to cell division with rate $F(a, x)$ or finally entering the quiescent one according to a "demobilization" or "leak" function $L(a, x)$. The functions L and G represent the core mechanism of exchange from proliferation to quiescent and vice-versa, respectively. Quiescent cells are assumed to be halted in their individual physiological evolution, in the sense that once a cell becomes quiescent, its age and cyclin content are fixed at their last values as belonging to a proliferative cell. In this way, quiescent cells do not age and do not change their cyclin content.

In [12], [13], the following nonlinear system is proposed to model the biological situation just described:

$$\begin{cases} \dfrac{\partial}{\partial t}p(t, a, x) + \dfrac{\partial}{\partial a}p(t, a, x) + \dfrac{\partial}{\partial x}\big(\Gamma(a, x)p(t, a, x)\big) = \\ \qquad\qquad = -\big[L(a, x) + F(a, x) + d_1\big]p(t, a, x) + G(N(t))q(t, a, x), \\ \dfrac{\partial}{\partial t}q(t, a, x) = L(a, x)p(t, a, x) - \big[G(N(t)) + d_2\big]q(t, a, x) \end{cases} \tag{1.5}$$

with the boundary condition (at $a = 0$)

$$p(t,0,x) = 2\int_0^{x_m}\int_0^{+\infty} \frac{F(a,y)}{y}\chi_{[0,y]}(x)p(t,a,y)dady$$

and the definition

$$N(t) = \int_0^{x_m}\int_0^{+\infty} \big[\phi^*(a,x)p(t,a,x) + \psi^*(a,x)q(t,a,x)\big]dadx.$$

The boundary condition corresponds to the birth rate of cells with a cyclin content x and assumes that a dividing cell with cyclin content $y(>x)$ and any age a divides at a rate $F(a,y)$ producing two cells (of age 0) with cyclin content x and $y-x$ following a uniform probability distribution on the interval $[0,y]$.

Now let us assume that the functions $\Gamma, L, F, \phi^*, \psi^*$ do not depend on a, i. e.

$$\Gamma(a,x) = \Gamma(x),\ L(a,x) = L(x),\ F(a,x) = F(x),$$
$$\phi^*(a,x) = \phi^*(x),\ \psi^*(a,x) = \psi^*(x).$$

In [12] and [13] a somehow particular form of functions L, F and G is assumed. In the forthcoming we assume, apart from the above mentioned hypotheses on G, that L and F are bounded, positive continuous functions of x and that $\frac{F(x)}{x}$ is also bounded.

Let us introduce

$$P(t,x) = \int_0^{+\infty} p(t,a,x)da, \qquad Q(t,x) = \int_0^{+\infty} q(t,a,x)da.$$

Assuming that $\Gamma(a,x) = \Gamma(x)$ corresponds to assuming c_3 and c_4 very large in order to still have $\frac{c_3}{c_4} > w_0$ and $e^{-c_4 a}w_1$ be negligible. Then (1.4) reduces to

$$\Gamma(x) = c_1\frac{x}{1+x}\left(\frac{c_3}{c_4}\right) - c_2 x = c_2\left(\frac{c_1 c_3}{c_2 c_4}\frac{x}{1+x} - x\right) =$$

$$= c_2 x\left(\left(\frac{c_1 c_3}{c_2 c_4} - 1\right)\frac{1}{1+x} - \frac{x}{1+x}\right),$$

i. e.,

$$\Gamma(x) = c_2 \frac{x(x_M - x)}{1 + x}. \tag{1.6}$$

Integrating system (1.5) with respect to a we have

$$\begin{cases} \dfrac{\partial}{\partial t}P(t,x) + p(t,a,x)\Big|_{a=0}^{a=+\infty} + \dfrac{\partial}{\partial x}\big(\Gamma_1(x)P(t,x)\big) = \\ \qquad\qquad = -\big[L(x) + F(x) + d_1\big]P(t,x) + G(N(t))Q(t,x), \\ \dfrac{\partial}{\partial t}Q(t,x) = L(x)P(t,x) - \big[G(N(t)) + d_2\big]Q(t,x), \end{cases}$$

where, moreover,

$$\lim_{a \to +\infty} p(t,a,x) = 0$$

and

$$p(t,0,x) = 2\int_0^{x_M}\int_0^{+\infty} \frac{F(y)}{y}\chi_{[0,y]}(x)p(t,a,y)da dy = $$

$$= 2\int_x^{x_M} \frac{F(y)}{y}P(t,y)dy.$$

Then

$$\begin{cases} \dfrac{\partial}{\partial t}P(t,x) + \dfrac{\partial}{\partial x}\big(\Gamma(x)P(t,x)\big) = \\ \quad = -\big[L(x) + F(x) + d_1\big]P(t,x) + G(N(t))Q(t,x) + 2\int_x^{x_M} \frac{F(y)}{y}P(t,y)dy, \\ \dfrac{\partial}{\partial t}Q(t,x) = L(x)P(t,x) - \big[G(N(t)) + d_2\big]Q(t,x). \end{cases} \tag{1.7}$$

System (1.7) is still a first order nonlinear partial differential equations system. In contrast to (1.5) there is no boundary condition (this is related with the fact that $\Gamma(0) = 0$) and now the inflow term corresponding to newborn cells appears into the (first) equation as a non local (integral) term. In the next chapter we will discuss about the hypotheses on the functions that appear on system (1.7) and their biological interpretation.

On the other hand, in the next section we will analyze a simpler case just to increase intuition. This reduced model cannot be considered a particular case of the structured model because we have to assume that the functions involved are independent of the cyclin content.

1.2 An ordinary differential equations system

Here we will study a simplified case that does not have biological interest. Even though, this mathematical model can help us to understand the behavior of the model (1.7). We will assume that the parameter functions in the model are constant (also cyclin-content independent), which reduces it to a system of two ordinary differential equations. With these assumptions we can analyze the complete asymptotic behavior of the system and show that it is possible to find conditions to have an unstable non trivial equilibrium point. The instability appears through a Hopf bifurcation which leads to the existence of stable self-sustained oscillations of the populations. Unfortunately, this reduced model cannot be considered a particular case of the structured model because we have to assume that the functions involved are independent of the cyclin content.

To consider this simpler case, let us assume that the functions L, F, ϕ^*, ψ^* do not depend on x, i. e. they are constant. We also assume that

$$d_1 < F < d_1 + L. \tag{1.8}$$

Integrating system (1.7) with respect to x and with the notation

$$\overline{P}(t) = \int_0^{x_M} P(t,x)dx, \qquad \overline{Q}(t) = \int_0^{x_M} Q(t,x)dx$$

we have

$$\begin{cases} \dfrac{\partial}{\partial t}\overline{P}(t) + \Gamma(x)P(t,x)\Big|_{x=0}^{x=x_M} = -(L+F+d_1)\overline{P}(t) + \\ \qquad\qquad\qquad + G(N(t))\overline{Q}(t) + 2F\int_0^{x_M}\int_x^{x_M}\frac{P(t,y)}{y}dydx, \\ \dfrac{\partial}{\partial t}\overline{Q}(t) = L\overline{P}(t) - \big[G(N(t)) + d_2\big]\overline{Q}(t). \end{cases}$$

Now using that $\Gamma(0) = \Gamma(x_M) = 0$, we have

$$2F \int_0^{x_M} \int_x^{x_M} \frac{P(t,y)}{y} dydx = 2F \int_0^{x_M} \int_0^{y} \frac{P(t,y)}{y} dxdy =$$

$$= 2F \int_0^{x_M} P(t,y)dy = 2F\overline{P}(t)$$

from where we derive the following system of ordinary differential equations:

$$\begin{cases} \dot{\overline{P}}(t) = -(L - F + d_1)\overline{P}(t) + G(N(t))\overline{Q}(t), \\ \dot{\overline{Q}}(t) = L\overline{P}(t) - \big[G(N(t)) + d_2\big]\overline{Q}(t). \end{cases} \tag{1.9}$$

Next we will analyze this ordinary differential equations system to see that under some hypotheses it is possible to find an unstable non trivial equilibrium and hence oscillations via a Hopf bifurcation.

Let us set

$$(0 <\ )\ \alpha = L - F + d_1, \text{ and } N(t) = \phi^*\overline{P}(t) + \psi^*\overline{Q}(t), \text{ with } \phi^*, \psi^* \in \mathbb{R}^+. \tag{1.10}$$

For system (1.9), the equilibrium points satisfy:

$$0 = -\alpha\overline{P} + G(N)\overline{Q} \quad \text{that implies} \quad \overline{P} = \frac{G(N)\overline{Q}}{\alpha},$$

$$0 = L\overline{P} - \big(G(N) + d_2\big)\overline{Q} \quad \text{that implies} \quad \overline{P} = \frac{\big(d_2 + G(N)\big)\overline{Q}}{L}.$$

Then, the first possibility is $(0,0)$ or, if $\overline{Q} \neq 0$ then

$$\frac{G(N)}{\alpha} = \frac{d_2 + G(N)}{L} \qquad \text{or equivalently} \quad G(N) = \frac{\alpha d_2}{L - \alpha}.$$

Therefore $(0,0)$ is always an equilibrium solution and, since we are assuming that G is strictly decreasing and tends to 0 when N tends to infinity, there exists a non trivial equilibrium $(\hat{P}, \hat{Q})$ if and only if $G(0) > \frac{\alpha d_2}{L-\alpha} (> 0)$ (where $\frac{\alpha d_2}{L-\alpha} > 0$ because $F > d_1$), because then there exists a unique solution $\hat{N}$ of the equation $G(N) = \frac{\alpha d_2}{L-\alpha}$. Now using (1.10), this equilibrium is given by

$$(\hat{P}, \hat{Q}) = \left(\frac{\hat{N} d_2}{(L-\alpha)\psi^* + d_2\phi^*}, \frac{\hat{N}(L-\alpha)}{(L-\alpha)\psi^* + d_2\phi^*} \right).$$

Notice that the condition on existence of nontrivial equilibrium can be written as

$$G(0)(\alpha - L) + \alpha d_2 < 0.$$

Now we will study the stability of the equilibrium points.

The Jacobian matrix of the system is:

$$J(\overline{P}, \overline{Q}) = \begin{pmatrix} -\alpha + \phi^* G'(N)\overline{Q} & \overline{Q}\psi^* G'(N) + G(N) \\ L - \overline{Q}\phi^* G'(N) & -\overline{Q}\psi^* G'(N) - (d_2 + G(N)) \end{pmatrix}.$$

Then, for the point$(0,0)$ we have

$$J(0,0) = \begin{pmatrix} -\alpha & G(0) \\ L & -(d_2 + G(0)) \end{pmatrix}$$

$$|J(0,0) - \lambda I| = \lambda^2 + \big(\alpha + d_2 + G(0)\big)\lambda + \big(\alpha d_2 + (\alpha - L)G(0)\big).$$

So,

$$\lambda = \frac{-\big(\alpha + d_2 + G(0)\big) \pm \sqrt{\big(\alpha + d_2 + G(0)\big)^2 - 4\big(\alpha d_2 + (\alpha - L)G(0)\big)}}{2}.$$

We have two cases: If $G(0)(\alpha - L) + \alpha d_2 \geq 0$, then $(0,0)$ is the unique equilibrium point and it is asymptotically stable because when the strict inequality holds, either $\lambda_{1,2} \in \mathbb{R}$ with $\lambda_1, \lambda_2 < 0$ or $\lambda = a \pm ib,\ \ a < 0$.

In the other case, if $G(0)(L - \alpha) + \alpha d_2 < 0$, then there is another equilibrium point $(\hat{P}, \hat{Q})$, and moreover $\lambda_{1,2} \in \mathbb{R},\ \ \lambda_1 < 0, \lambda_2 > 0$ which implies that $(0,0)$ is a saddle point.

For the equilibrium point $(\hat{P}, \hat{Q})$ we have

$$J(\hat{P}, \hat{Q}) = \begin{pmatrix} -\alpha + \phi^* G'(\hat{N})\hat{Q} & \hat{Q}\psi^* G'(\hat{N}) + G(\hat{N}) \\ L - \hat{Q}\phi^* G'(\hat{N}) & -\hat{Q}\psi^* G'(\hat{N}) - (d_2 + G(\hat{N})) \end{pmatrix}$$

and

$$|J(\hat{P},\hat{Q})-\lambda I| = \lambda^2 - tr(J(\hat{P},\hat{Q}))\lambda + det(J(\hat{P},\hat{Q})),$$

where

$$tr(J(\hat{P},\hat{Q})) = -\alpha + \phi^* G'(\hat{N})\hat{Q} - \hat{Q}\psi^* G'(\hat{N}) - (d_2 + G(\hat{N})) =$$
$$= -\alpha - d_2 - G(\hat{N}) + (\phi^* - \psi^*)G'(\hat{N})\hat{Q}$$

and

$$det(J(\hat{P},\hat{Q})) = \big(\alpha - \phi^* G'(\hat{N})\hat{Q}\big)\big(\hat{Q}\psi^* G'(\hat{N}) + d_2 + G(\hat{N})\big) -$$
$$-\big(L - \hat{Q}\phi^* G'(\hat{N})\big)\big(\hat{Q}\psi^* G'(\hat{N}) + G(\hat{N})\big) =$$

$$= \big[\alpha\psi^*\hat{Q}G'(\hat{N}) + \alpha d_2 + \alpha G(\hat{N}) - \phi^*\psi^*\hat{Q}^2 G'(\hat{N})^2 - \phi^* d_2 \hat{Q}G'(\hat{N}) - \phi^*\hat{Q}G'(\hat{N})G(\hat{N})\big] -$$
$$-L\psi^*\hat{Q}G'(\hat{N}) - LG(\hat{N}) + \phi^*\psi^*\hat{Q}^2 G'(\hat{N})^2 + \phi^*\hat{Q}G'(\hat{N})G(\hat{N}) =$$
$$= \alpha d_2 + (\alpha - L)\frac{\alpha d_2}{L-\alpha} + \hat{Q}G'(\hat{N})\big[\alpha\psi^* - \phi^* d_2 - L\psi^*\big] =$$
$$= \hat{Q}G'(\hat{N})\big[(\alpha - L)\psi^* - \phi^* d_2\big].$$

So,

$$|J(\hat{P},\hat{Q}) - \lambda I| = \lambda^2 + \big[\alpha + d_2 + G(\hat{N}) + (\psi^* - \phi^*)G'(\hat{N})\hat{Q})\big]\lambda + \hat{Q}G'(\hat{N})\big[(\alpha - L)\psi^* - \phi^* d_2\big].$$

Then we have that

$$\lambda = \Bigg[-\Big(\alpha + d_2 + G(\hat{N}) + (\psi^* - \phi^*)G'(\hat{N})\hat{Q}\Big) \pm$$
$$\sqrt{\Big(\alpha + d_2 + G(\hat{N}) + (\psi^* - \phi^*)G'(\hat{N})\hat{Q}\Big)^2 - 4\hat{Q}G'(\hat{N})\big[(\alpha - L)\psi^* - \phi^* d_2\big]}\Bigg] \Big/ 2.$$

To simplify notation, let us define

$$A := \alpha + d_2 + G(\hat{N}) + (\psi^* - \phi^*)G'(\hat{N})\hat{Q}$$

and

$$B := 4\hat{Q}G'(\hat{N})\big[(\alpha - L)\psi^* - \phi^* d_2\big].$$

Then we can write

$$\lambda = \frac{-A \pm \sqrt{A^2 - B}}{2}.$$

By (1.8), we have that

$$(\alpha - L)\psi^* - \phi^* d_2 = (d_1 - F)\psi^* - \phi^* d_2 < 0,$$

and by hypothesis,

$$G(\hat{N}) > 0,$$

$$G'(\hat{N}) < 0$$

and then, we can see that

$$\alpha + d_2 + G(\hat{N}) > 0,$$

and

$$B = 4\hat{Q}G'(\hat{N})\big[(\alpha - L)\psi^* - \phi^* d_2\big] > 0.$$

We have to consider 2 cases:

(i) $0 \leq \psi^* \leq \phi^*$ and $\psi^* + \phi^* > 0$.

Then $A > 0$, $B > 0$ which gives us an asymptotically stable equilibrium point, because either $\lambda_{1,2} < 0$ or $Re\lambda_{1,2} < 0$.

(ii) $0 \leq \phi^* < \psi^*$.

Since $B > 0$, the point $(\hat{P}, \hat{Q})$ is unstable if

$$A = \alpha + d_2 + G(\hat{N}) + (\psi^* - \phi^*)G'(\hat{N})\hat{Q} < 0$$

or equivalently,

$$G'(\hat{N}) < -\frac{\alpha + d_2 + G(\hat{N})}{(\psi^* - \phi^*)\hat{Q}}.$$

Assuming that $G(x) = \dfrac{1}{1 + x^n}$, we have that

$$G'(x) = -\frac{nx^{n-1}}{(1 + x^n)^2}$$

and then the following inequality must hold

$$-\frac{n\hat{N}^{n-1}}{(1 + \hat{N}^n)^2} = G'(\hat{N}) < -\frac{\alpha + d_2 + G(\hat{N})}{(\psi^* - \phi^*)\hat{Q}} = -\frac{\alpha + d_2 + \frac{\alpha d_2}{L-\alpha}}{(\psi^* - \phi^*)\dfrac{\hat{N}(L-\alpha)}{(L-\alpha)\psi^* + d_2\phi^*}} =$$

$$= -\frac{\Big(\alpha(L-\alpha) + d_2(L-\alpha) + \alpha d_2\Big)\Big((L-\alpha)\psi^* + d_2\phi^*\Big)}{\hat{N}(\psi^* - \phi^*)(L-\alpha)^2},$$

which is equivalent to

$$n > \frac{(1 + \hat{N}^n)^2}{\hat{N}^n}\frac{\Big(\alpha(L-\alpha) + d_2 L\Big)\Big((L-\alpha)\psi^* + d_2\phi^*\Big)}{(\psi^* - \phi^*)(L-\alpha)^2}$$

and as $G(\hat{N}) = \dfrac{1}{1 + \hat{N}^n} = \dfrac{\alpha d_2}{L - \alpha}$ we have that the inequality can be written also as

$$n > \frac{1+\hat{N}^n}{\hat{N}^n}(1+\hat{N}^n)\frac{\Big(\alpha(L-\alpha)+d_2L\Big)\Big((L-\alpha)\psi^*+d_2\phi^*\Big)}{(\psi^*-\phi^*)(L-\alpha)^2} =$$

$$= \frac{1+\hat{N}^n}{\hat{N}^n}\frac{L-\alpha}{\alpha d_2}\frac{\Big(\alpha(L-\alpha)+d_2L\Big)\Big((L-\alpha)\psi^*+d_2\phi^*\Big)}{(\psi^*-\phi^*)(L-\alpha)^2} =$$

$$= \frac{1+\hat{N}^n}{\hat{N}^n}\frac{\Big(\alpha(L-\alpha)+d_2L\Big)\Big((L-\alpha)\psi^*+d_2\phi^*\Big)}{\alpha d_2(\psi^*-\phi^*)(L-\alpha)}$$

i.e., n must satisfy the following condition

$$n > \frac{1+\hat{N}^n}{\hat{N}^n}\frac{\Big(\alpha(L-\alpha)+d_2L\Big)\Big((L-\alpha)\psi^*+d_2\phi^*\Big)}{\alpha d_2(\psi^*-\phi^*)(L-\alpha)}. \tag{1.11}$$

In particular, if $\phi^* = 0$, this condition reduces to

$$n > \frac{1+\hat{N}^n}{\hat{N}^n}\left(\frac{L-\alpha}{d_2}+\frac{L}{\alpha}\right). \tag{1.12}$$

To show an example, let us assume

$$d_1 = 2, \;\; d_2 = 1, \;\; \phi^* = \frac{1}{2}, \;\; \psi^* = 3, \;\; F = 4, \;\; L = 3. \tag{1.13}$$

Then $\alpha = 1$ and

$$G(\hat{N}) = \frac{\alpha d_2}{L-\alpha} = \frac{1}{2} = \frac{1}{1+\hat{N}^n} \Leftrightarrow \hat{N} = 1 \Rightarrow \hat{Q} = \frac{2}{6+\frac{1}{2}} = \frac{4}{13}.$$

To have instability, the condition (1.11) must hold:

$$n > \frac{1+1}{1}\frac{\Big(1(3-1)+3\Big)\Big((3-1)3+\frac{1}{2}\Big)}{1(3-\frac{1}{2})(3-1)} = \frac{2*5*\frac{13}{2}}{\frac{5}{2}*2} = 13,$$

i.e., with $n = 14$ we have instability.

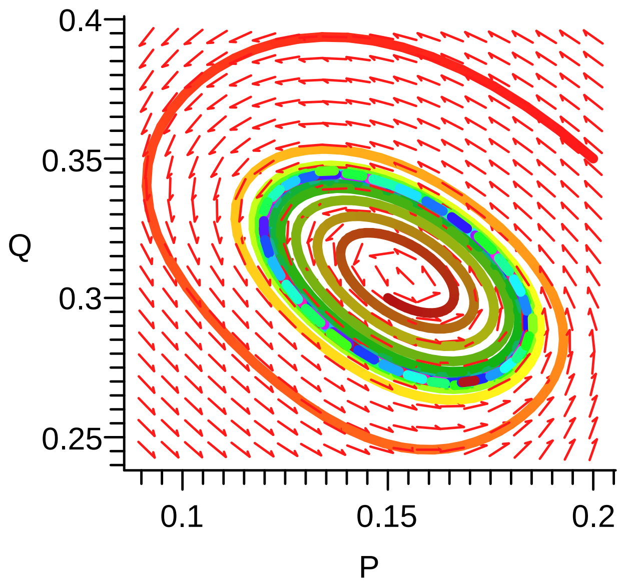

Figure 1.1: Illustration for the problem with assumptions (1.13).

To show that it is possible to have instability with smaller n, let ϵ be small and let us take

$$d_1 = 0, \;\; d_2 = \frac{1}{8}, \;\; \phi^* = 0, \;\; \psi^* = c, \;\; c \text{ constant}, \;\;\; F = \epsilon, \;\;\; L = 5\epsilon.$$

Then $\alpha = 4\epsilon$ and

$$G(\hat{N}) = \frac{\alpha d_2}{L - \alpha} = \frac{1}{2} = \frac{1}{1 + \hat{N}^n} \Leftrightarrow \hat{N} = 1 \Rightarrow \hat{Q} = \frac{\epsilon}{\epsilon c} = \frac{1}{c}.$$

To have instability, the condition (1.12) must hold:

$$n > \frac{1+1}{1}\Big(\frac{5\epsilon - 4\epsilon}{\frac{1}{8}} + \frac{5\epsilon}{4\epsilon}\Big) = 2(8\epsilon + \frac{5}{4}) = 16\epsilon + \frac{5}{2}.$$

i.e., for ϵ sufficiently small, we have instability with $n = 3$.

In the next chapter we will explain the model and the main hypotheses on the functions, as well the biological meaning of each one. We also prove, under suitable hypothesis, the existence, uniqueness and the positivity of the solution for the problem (1.7).

Chapter 2

A cyclin-structured cell population model

2.1 Introduction

In this chapter we present the age independent version of the model considered in [12] and [13]. This model was studied in [17] and in section 1.1 we have given a basic introduction of it. At this point we will explain with more detail this model. We will also change a little bit the notation of system (1.7) to present the following first order nonlinear partial differential equations system with nonlocal terms structured only with respect to the cyclin content

$$\left\{\begin{array}{rcl} \dfrac{\partial}{\partial t}p(x,t)+\dfrac{\partial}{\partial x}\big(\Gamma(x)p(x,t)\big) & = & -\big[L(x)+F(x)+d_1\big]p(x,t) \\ & & +G(N(t))q(x,t)+2\int_x^{x_M}\frac{F(y)}{y}p(y,t)dy, \\ \dfrac{\partial}{\partial t}q(x,t) & = & L(x)p(x,t)-\big[G(N(t))+d_2\big]q(x,t) \end{array}\right. \tag{2.1}$$

where $p(x,t)$ and $q(x,t)$ are the densities of proliferating and quiescent cells (respectively) at time t with respect to the cyclin content x.

$\Gamma(x)$ denotes the evolution speed of cyclin content with respect to time. In [12] the authors develop an ordinary differential equations model at an intracellular scale for the cyclin synthesis based on the works [3], [11] and [62] which produces a growth speed Γ vanishing at 0 and at the maximum value of cyclin content x_M (see also Chapter 1).

The transition rate $L(x)$ from proliferating to quiescent is assumed to be decreasing to take into account that, as we mentioned in the introduction, a larger amount of cyclin content inhibits this transition.

On the other hand, since high levels of cyclin enhance the progression through the cell cycle until mitosis (see for instance [63], [70]), the cell division rate $F(x)$ is assumed to be increasing.

A particular feature of the birth term in (2.1) is that the distribution of the cellular material between daughter cells is assumed to be unequal. Mathematical models of cell population with unequal cell division can be found in [5], [6] and [49], where distribution of RNA content between daughter cells is studied. Also in [14] a model for the progression through the cell cycle with unequal distribution of the cyclin content between daughter cells is considered. In (2.1), the non local term gives the inflow of newborn cells. It assumes that cells with cyclin content y $(> x)$ divide at a rate $F(y)$ producing two new cells with cyclin content x and $y-x$ where (as in [12], [13], [17] and [18]) x is a uniformly distributed (on $[0, y]$) random variable.

The transition rate G from quiescent to proliferating stage is assumed to depend on a weighted total population N (to take into account those cells that are qualified to be recruited again for the proliferating stage, see [12], [13]).

We denote the total weighted population by

$$N(t) = N(p(x,t), q(x,t)) := \int_0^{x_M} \big[\phi(x)p(x,t) + \psi(x)q(x,t)\big]\, dx$$

where $\phi(x)$ and $\psi(x)$ are positive bounded functions. Cells can leave the quiescent stage because of apoptosis, that is assumed to occur at a rate d_2, or because of transition back to the proliferating stage that is assumed to occur according to a “recruitment” function G which is assumed to be a smooth strictly decreasing function of the total weighted population, satisfying $G(0) > 0$ and that tends to 0 when N goes to infinity (case of healthy tissue, see [12]). We also assume that G

satisfies a uniformly Lipschitz condition.

In this chapter we proved, under some assumptions, the existence and uniqueness of a steady state for model (2.1) when the rate of quiescent cells going back to the proliferating stage decreases to zero as the total weighted population grows to infinity (this corresponds to the case of healthy tissue, see [12], [13]).

We assume that L and F are bounded, positive and continuous functions and that $\frac{F(x)}{x}$ has a finite positive limit when x goes to 0 (implying in particular $F(0) = 0$). $\Gamma(x)$, as we said before, represents the evolution speed of cyclin content with respect to time. We assume that $\Gamma \in C^2[0, x_M]$, $\Gamma(0) = \Gamma(x_M) = 0$, $\Gamma(x) > 0$ for all $x \in (0, x_M)$ and the lateral derivatives satisfy $\Gamma'(0) > 0$, $\Gamma'(x_M) < 0$. In particular, there exists $K > 0$ such that $-K < \Gamma'(x) < K$ for all $x \in (0, x_M)$.

Finally, for simplicity in the notation, let us denote $\bar{L} = \sup_x L(x)$, $\bar{F} = \sup_x F(x)$, $\bar{\Gamma} = \sup_x \Gamma(x)$, let $\bar{G}$ be any number larger than $G(0)$ and $M := \max\{d_2 + \bar{G}, \bar{L} + \bar{F} + d_1\}$.

2.2 Existence, uniqueness and positiveness

Let us show the existence and uniqueness of solutions of model (2.1) with initial conditions $(p_0, q_0) \in (L^1(0, x_M))^2 =: X$.

In order to see this, we start by adding and subtracting $\bar{G}q(x,t)$ to the second equation of (2.1) and rewriting the resulting system in an abstract form as

$$\frac{d}{dt}u(t) = \mathbf{A}u(t) + f(u(t)) \tag{2.2}$$

where $u(t)(x) := \begin{pmatrix} p(x,t) \\ q(x,t) \end{pmatrix}$,

$$\mathbf{A}u(t)(x) := \begin{pmatrix} -\frac{\partial}{\partial x}\big(\Gamma(x)p(x,t)\big) - \big[L(x) + F(x) + d_1\big]p(x,t) \\ L(x)p(x,t) - \big[\bar{G} + d_2\big]q(x,t), \end{pmatrix} \tag{2.3}$$

and

$$f(u(t))(x) = \begin{pmatrix} G(N(t))q(x,t) + 2\int_x^{x_M} \frac{F(y)}{y} p(y,t)dy \\ \big[\bar{G} - G(N(t))\big] q(x,t) \end{pmatrix}.$$

We will show that the operator $\mathbf{A}$ is the infinitesimal generator of a positive C_0 semigroup on X. To see this we rewrite $\mathbf{A}$ as the sum of two operators, $\mathbf{A_1}$ and $\mathbf{A_2}$, where

$$\mathbf{A_1}\begin{pmatrix} p(x) \\ q(x) \end{pmatrix} = \begin{pmatrix} -\dfrac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) \\ 0 \end{pmatrix} - M\begin{pmatrix} p(x) \\ q(x) \end{pmatrix},$$

and

$$\mathbf{A_2}\begin{pmatrix} p(x) \\ q(x) \end{pmatrix} = \begin{pmatrix} \big[M - \big(L(x) + F(x) + d_1\big)\big]p(x) \\ L(x)p(x) + \big[M - \big(\bar{G} + d_2\big)\big]q(x) \end{pmatrix}.$$

The operator $\mathbf{A_2}$ is positive and bounded (by the definition of M), and using Theorem 1.3 and Theorem 1.10 from [36], in order to see that $\mathbf{A}$ is the infinitesimal generator of a positive C_0 semigroup, it is enough to see that $\mathbf{A_1}$ is the infinitesimal generator of a positive C_0 semigroup. Moreover, as M is a constant, to see that $\mathbf{A_1}$ is the infinitesimal generator of a positive C_0 semigroup it suffices to show that the operator

$$\bar{\mathbf{A}}\begin{pmatrix} p(x) \\ q(x) \end{pmatrix} := \begin{pmatrix} -\dfrac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) \\ 0 \end{pmatrix} =: \begin{pmatrix} \bar{\mathbf{A}}^{\mathbf{1}}p(x) \\ 0 \end{pmatrix} \tag{2.4}$$

defined on a suitable domain generates a positive strongly continuous semigroup. Furthermore, the domain of $\mathbf{A}$ will coincide with the domain of $\bar{\mathbf{A}}$, which is given in Proposition 2.

We will use the Method of Characteristics to prove that $\bar{\mathbf{A}}$ is the infinitesimal generator of a positive C_0 semigroup. So, at this point we need to consider the solution of

$$\begin{cases} z'(t) &= \Gamma(z(t)), \\ z(0) &= x. \end{cases} \tag{2.5}$$

Let $\phi(t,x)$ be the unique solution of the initial value problem for the characteristic equation (2.5).

It is well known that, setting $\xi = \phi(t,x)$, then the derivative of the solution satisfies

$$\begin{cases} \dfrac{\partial}{\partial t}\dfrac{\partial \xi}{\partial x} &= \Gamma'(\phi(t,x))\dfrac{\partial \xi}{\partial x}, \\ \dfrac{\partial \xi}{\partial x}(0) &= 1, \end{cases}$$

which implies that

$$\frac{\partial \xi}{\partial x} = e^{\int_0^t \Gamma'(\phi(\sigma,x))d\sigma}. \tag{2.6}$$

We will see that the operator $\bar{\mathbf{A}}$ is the infinitesimal generator of the positive semigroup $T(t)$ explicitly given by

$$\begin{aligned} \left(T(t)\begin{pmatrix} p_0 \\ q_0 \end{pmatrix}\right)(x) &= \begin{pmatrix} p_0(\phi(-t,x))e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} \\ q_0(x) \end{pmatrix} \\ &=: \begin{pmatrix} (T^1(t)p_0)(x) \\ q_0(x) \end{pmatrix}. \end{aligned} \tag{2.7}$$

Proposition 1. (2.7) defines a strongly continuous semigroup.

Proof. We first show that (2.7) defines a semigroup. Obviously, $T(0) = Id$. Now, let us show that $T^1(t) : L^1 \to L^1$ and also $T(t) : (L^1)^2 \to (L^1)^2$ have the semigroup property.

For all $p_0 \in L^1$, $x \in (0, x_M)$, denoting by

$$p_t(x) := p_0(\phi(-t,x))e^{-\int_0^t \Gamma'(\phi(\sigma-t,x))d\sigma},$$

we have

$$\Big(T^1(s)\big(T^1(t)p_0\big)\Big)(x) = \Big(T^1(s)p_t\Big)(x) = p_t(\phi(-s,x))e^{-\int_0^s \Gamma'(\phi(\sigma-s,x))d\sigma}$$

$$= p_0(\phi(-t,\phi(-s,x)))e^{-\int_0^t \Gamma'(\phi(\sigma-t,\phi(-s,x)))d\sigma}e^{-\int_0^s \Gamma'(\phi(\sigma-s,x))d\sigma}$$

$$= p_0(\phi(-s-t,x))e^{-\int_0^t \Gamma'(\phi(\sigma-t-s,x))d\sigma}e^{-\int_t^{s+t} \Gamma'(\phi(\tau-t-s,x))d\tau}$$

$$= p_0(\phi(-(s+t),x))e^{-\int_0^{s+t} \Gamma'(\phi(\tau-(s+t),x))d\tau} = \Big(T^1(s+t)p_0\Big)(x),$$

where we have used that ϕ is solution of (2.5) and the change of variables $\tau = \sigma + t$. Using that $T^1(t)$ has the semigroup property it is immediate to see that $T(t)$ has the same property.

Indeed, for all $p_0, q_0 \in L^1$, $x \in (0, x_M)$, we have

$$\left(T(s)\left(T(t)\begin{pmatrix} p_0 \\ q_0 \end{pmatrix}\right)\right)(x) = \left(T(s)\begin{pmatrix} T^1(t)p_0 \\ q_0 \end{pmatrix}\right)(x)$$

$$= \begin{pmatrix} T^1(s+t)p_0 \\ q_0 \end{pmatrix}(x) = \left(T(s+t)\begin{pmatrix} p_0 \\ q_0 \end{pmatrix}\right)(x).$$

To see that the semigroup defined by (2.7) is strongly continuous we have to see that for any initial condition $p_0(x) \in L^1(0, x_M)$,

$$\lim_{t \to 0} \| (T^1(t)p_0)(x) - p_0(x) \|_{L^1} = 0.$$

We have that, for $\epsilon > 0$, there exists $p_1 \in C_0^\infty$ (with the absolute value of the derivative bounded by C) such that $\| p_0 - p_1 \| < \frac{\epsilon}{6}$.

Then let us estimate $\| T^1(t)p_0 - T^1(t)p_1 \|$ and $\| T^1(t)p_1 - p_1 \|$.

Let us first show that $\| T^1(t) \| = 1$. In fact,

$$\| T^1(t)p_0 \| = \int_0^{x_M} | p_0(\phi(-t,x))e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} | \, dx$$

$$= \int_{\phi(-t,0)}^{\phi(-t,x_M)} | \big(p_0(\xi) | \, d\xi \; = \int_0^{x_M} | p_0(\xi) | \, d\xi,$$

which holds for all $p_0 \in L^1(0, x_M)$, which implies that $\| T^1(t) \| = 1$. Here we made $\xi = \phi(-t, x)$ (and then, by (2.6), $\dfrac{d\xi}{dx} = e^{-\int_0^t \Gamma'(\phi(s-t,x))ds}$). It comes directly from here that

$$\| T^1(t)p_0 - T^1(t)p_1 \| \leq \| T^1(t) \| \| p_0 - p_1 \| \leq \frac{\epsilon}{6}.$$

Let t_1 be such that $te^{Kt}C\bar{\Gamma}x_M < \frac{\epsilon}{6}$ for all $t \leq t_1$ (where recall that K is such that $-K < \Gamma'(x) < K$ for all $x \in (0, x_M)$), and t_2 such that $\| p_1 \| | e^{Kt} - 1 | < \frac{\epsilon}{6}$, for all $t \leq t_2$. Then, for all $t \leq \bar{t}$ where $\bar{t} = \min\{t_1, t_2\}$ we have that the last inequalities hold and

$$\begin{aligned}
&\| T^1(t)p_1 - p_1 \| = \\
&= \int_0^{x_M} | p_1(\phi(-t,x))e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - p_1(x) | \, dx \\
&\leq \int_0^{x_M} | \big(p_1(\phi(-t,x)) - p_1(x)\big)e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} | \, dx \\
&\qquad\qquad + \int_0^{x_M} | p_1(x)\big(e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - 1\big) | \, dx \\
&\leq N \int_0^{x_M} | \phi(-t,x) - x | \, e^{Kt}dx + \int_0^{x_M} | p_1(x) || \, e^{Kt} - 1 | \, dx \\
&\leq te^{Kt}C\bar{\Gamma}x_M + \| p_1 \| | e^{Kt} - 1 | < \tfrac{\epsilon}{6} + \tfrac{\epsilon}{6} = \tfrac{\epsilon}{3}.
\end{aligned} \tag{2.8}$$

Then for $t \leq \bar{t}$ we have

$$\begin{aligned}
&\| (T^1(t)p_0)(x) - p_0(x) \| \\
&\leq \| T^1(t)p_0 - T^1(t)p_1 \| + \| T^1(t)p_1 - p_1 \| + \| p_0 - p_1 \| < \epsilon,
\end{aligned}$$

which concludes the proof.

□

The next step is to show that the linear operator $\bar{\mathbf{A}}$ given in (2.3) with a suitable domain generates the semigroup given by (2.7). Let us see some previous results that will help in this proof.

A direct and rigorous characterization of the domain is technically difficult due to the fact that Γ vanishes at both extreme points of the interval $[0, x_M]$. On the other hand, this fact is also responsible for the absence of boundary conditions restricting the domain (see Lemma 2.2.1 below). In particular, to deal with the limit appearing in the definition of infinitesimal generator we will use the following version of the C^1-linearization around an equilibrium of a scalar ordinary differential equation (see for instance [39] where the analytic case is considered).

Lemma 2.2.1. Let $\Gamma(x)$ be a Lipschitzian function such that $\Gamma(0) = 0, \Gamma'(0) = a \neq 0$, and $\int_0^x \dfrac{\Gamma(s) - as}{s^2} ds < \infty$, and let $\phi(t,x)$ be the solution of the initial value problem (2.5).
Then

$$H(x) := xe^{-\int_0^x \dfrac{\Gamma(s) - as}{\Gamma(s)s} ds}$$

is a C^1 function with $H'(0) = 1$,

$$\Gamma(x)H'(x) = aH(x)$$

and such that $H(\phi(t,x)) = e^{at}H(x)$ in a neighborhood of 0.

Proof. First of all, notice that the last hypothesis is equivalent to the integrability of $\dfrac{\Gamma(s)-as}{\Gamma(s)s}$ at 0 which implies that the function H is well defined in a neighborhood of 0.

For $x \neq 0$,

$$H'(x) = e^{-\int_0^x \frac{\Gamma(s)-as}{\Gamma(s)s}ds} - xe^{-\int_0^x \frac{\Gamma(s)-as}{\Gamma(s)s}ds}\Big(\frac{\Gamma(x)-ax}{\Gamma(x)x}\Big)$$

$$= e^{-\int_0^x \frac{\Gamma(s)-as}{\Gamma(s)s}ds}\frac{ax}{\Gamma(x)},$$

i.e., $\Gamma(x)H'(x) = aH(x)$.

For $x = 0$ we have that

$$\lim_{x\to 0}\frac{H(x)}{x} = e^{-\lim_{x\to 0}\int_0^x \frac{\Gamma(s)-as}{\Gamma(s)s}ds} = 1 = H'(0).$$

Moreover, H is C^1 because

$$\lim_{x\to 0} H'(x) = \lim_{x\to 0} e^{-\int_0^x \frac{\Gamma(s)-as}{\Gamma(s)s}ds}\frac{ax}{\Gamma(x)} = a\lim_{x\to 0}\frac{x}{\Gamma(x)} = 1.$$

To see that $H(\phi(t,x)) = e^{at}H(x)$ we set $\phi(t,x) := H^{-1}(e^{at}H(x))$ and show that ϕ satisfies (2.5). Indeed,

$$\frac{\partial\phi}{\partial t} = \frac{1}{H'(H^{-1}(e^{at}H(x)))}ae^{at}H(x)$$

$$= \frac{\Gamma(\phi(t,x))}{aH(H^{-1}(e^{at}H(x)))}ae^{at}H(x) = \Gamma(\phi(t,x)),$$

and $\phi(0,x) = H^{-1}(H(x)) = x$, which ends the proof. $\square$

Remark 3. If $\Gamma(x) \in C^2$ and $\Gamma(0) = 0, \Gamma'(0) = a \neq 0$, then Lemma 2.2.1 holds, since by Taylor's Theorem, we can write

$$\Gamma(x) = \Gamma'(0)x + \Gamma''(\xi_x)\frac{x^2}{2},$$

for some $\xi_x \in (-x, x)$ and

$$\lim_{x\to 0} \frac{\Gamma(x) - ax}{x^2} = \lim_{x\to 0} \frac{\Gamma''(\xi)}{2} = \frac{\Gamma''(0)}{2}.$$

Remark 4. There exist C^1 functions such that $H(x)$ cannot be defined. For instance, let us consider

$$\Gamma(x) = \begin{cases} x + \dfrac{x}{\ln|x|}, & x \neq 0, x \in (-1,1), \\ 0, & x = 0. \end{cases}$$

For $x \neq 0$, we have that

$$\Gamma'(x) = 1 + \frac{\ln|x| - 1}{(\ln|x|)^2}.$$

Then Γ belongs to C^1 since

$$\Gamma'(0) = \lim_{x\to 0} \frac{\Gamma(x)}{x} = 1 + \lim_{x\to 0} \frac{1}{\ln|x|} = 1$$

and

$$\lim_{x\to 0} \Gamma'(x) = \lim_{x\to 0} \left(1 + \frac{\ln|x| - 1}{(\ln|x|)^2}\right) = 1.$$

On the other hand, we cannot define $H(x)$ since

$$\int_0^{1/2} \frac{\Gamma(s) - as}{s^2} ds = \int_0^{1/2} \frac{1}{s\ln|s|} ds = -\infty.$$

Remark 5. There exist functions which are not of class C^2 (e.g., $\Gamma(x) = x + |x|^{3/2}$) and even functions that do not belong to class C^1, such that Lemma 2.2.1 still holds. For instance, consider

$$\Gamma(x) = \begin{cases} x + x^2 \sin(\dfrac{1}{x}) & x \neq 0, \\ 0, & x = 0. \end{cases}$$

For $x \neq 0$, we have that

$$\Gamma'(x) = 1 + 2x\sin(1/x) - \cos(1/x),$$

whereas $\Gamma'(0) = \lim_{x\to 0} \dfrac{\Gamma(x)}{x} = 1$.
So Γ does not belong to C^1 class since

$$\lim_{x\to 0}\Big(1 + 2x\sin(1/x) - \cos(1/x)\Big)$$

does not exist.

Nevertheless, here we can apply the Lemma because Γ satisfies a Lipschitz condition and

$$\int_0^x \frac{\Gamma(s) - as}{s^2} ds = \int_0^x \sin(1/s) ds < \infty.$$

Lemma 2.2.2. Let $\phi(t,x)$ be defined as the solution of the initial value problem (2.5). Then for all $t_0 > 0$, the continuous function $\bar{F}(x,t) := \dfrac{\phi(-t,x) - x}{\Gamma(x)t}$ defined for $(x,t) \in (0, x_M) \times (0, t_0]$ can be extended to a continuous function (also denoted) $\bar{F}$ on $[0, x_M] \times [0, t_0]$ such that $\bar{F}(x, 0) = -1$.

Moreover, denoting by L_H and $L_{H^{-1}}$ the Lipschitz constants of H and H^{-1} respectively, we have that

$$\left|\frac{\phi(-t,x) - x}{\Gamma(x)t}\right| \leq L_H L_{H^{-1}} \frac{e^{-\Gamma'(0)t} - 1}{\Gamma'(0)t}.$$

Proof. It suffices to show the existence of the limit at points of the form $(0,t)$, (x_M, t) and $(x, 0)$, and that it equals -1 in the last case. Let us recall that $\gamma(x) > 0$ on $(0, x_M)$ and so $a := \Gamma'(0) > 0$.

Rewriting the function $\dfrac{\phi(-t,x) - x}{\Gamma(x)t}$ by means of the function H given by Lemma 2.2.1, we have in a neighborhood of $x = 0$,

$$\begin{aligned}
\frac{\phi(-t,x) - x}{\Gamma(x)t} &= \frac{H^{-1}(e^{-at}H(x)) - H^{-1}(H(x))}{H(x)at} H'(x) \\
&= (H^{-1})'(\xi_{x,t}) \frac{e^{-at} - 1}{at} H'(x)
\end{aligned}$$

where $e^{-at}H(x) < \xi_{x,t} < H(x)$.

Using this it is not difficult to see that

$$\bar{F}(0,t) = \lim_{(x,\tau)\to(0,t)} \bar{F}(x,\tau) = \frac{e^{-at}-1}{at}.$$

In the same way, if $\Gamma'(x_M) = b$, an appropriate version of Lemma 2.2.1 gives

$$\bar{F}(x_M,t) = \frac{e^{-bt}-1}{bt}.$$

On the other hand, using that

$$\frac{\partial}{\partial\tau}\phi(\tau,x) = \lim_{t\to\tau}\frac{\phi(t,x)-x}{t} = \Gamma(\phi(\tau,x)),$$

we can also see that $\bar{F}(x,0) = -1$.

We also need a bound for the function $\dfrac{\phi(-t,x)-x}{\Gamma(x)t}$. Using the function H given by Lemma 2.2.1 we have that

$$\left|\frac{\phi(-t,x)-x}{\Gamma(x)t}\right| = \left|\frac{H^{-1}(e^{-\Gamma'(0)t}H(x)) - H^{-1}(H(x))}{\Gamma'(0)H(x)t}H'(x)\right|$$

$$\leq L_H L_{H^{-1}}\left|\frac{e^{-\Gamma'(0)t}H(x)-H(x)}{\Gamma'(0)H(x)t}\right| \leq L_H L_{H^{-1}}\left|\frac{e^{-\Gamma'(0)t_0}-1}{\Gamma'(0)t_0}\right|.$$

□

The next result connects the linear operator $\bar{\mathbf{A}}$ with the semigroup T and plays a very important role in order to establish the existence and uniqueness result.

The proof is a little technical and it is somehow similar to the corresponding one in the case of the translation semigroup (see [9], A-I, 2.4), being the main difficulty the presence of the characteristic system, which can be dealt with thanks to Lemma 2.2.2.

Proposition 2. The infinitesimal generator of the semigroup given explicitly by (2.7) is the linear operator $\bar{\mathbf{A}}$ defined by (2.4) with domain

$$D = \{u(x) = (p_0(x), q_0(x)) \in (L^1(0, x_M))^2 : (\Gamma p_0)'(x) \in L^1(0, x_M)\}. \quad (2.9)$$

Proof. We divide the proof into two parts. In the first one we prove that, for the functions u belonging to the set D, the limit involved in the definition of the generator exists and equals $\bar{\mathbf{A}}u$. In the second one, we prove that a function v in the domain of the generator $\mathbf{A_G}$ belongs to the set D. As a consequence, $\mathbf{A_G}v = \bar{\mathbf{A}}v$.

Part 1:

Let us take $(p_0(x), q_0(x)) \in D$. We want to show that

$$\lim_{t\to 0^+} \left\| \frac{T^1(t)p_0(x) - p_0(x)}{t} - \bar{\mathbf{A}}^{\mathbf{1}} p_0(x) \right\|_{L^1} = 0.$$

That is, let us consider

$$\int_0^{x_M} \left| \frac{(T^1(t)p_0 - p_0)(x)}{t} - \bar{\mathbf{A}}^{\mathbf{1}} p_0(x) \right| dx$$

$$= \int_0^{x_M} \left| \frac{1}{t}\Big(p_0(\phi(-t,x)) e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - p_0(x) \Big) + (\Gamma p_0)'(x) \right| dx$$

$$\leq \int_0^{x_M} |p_0(\phi(-t,x))| \left| \frac{\Gamma(x) e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - \Gamma(\phi(-t,x))}{\Gamma(x)t} \right| dx$$

$$+ \int_0^{x_M} \left| \frac{\Gamma(\phi(-t,x))p_0(\phi(-t,x)) - \Gamma(x)p_0(x)}{\Gamma(x)t} + (\Gamma p_0)'(x) \right| dx =: I_1 + I_2$$

where we will see that both terms go to 0 when t goes to 0. Here we will use Lebesgue dominated convergence theorem (LDCT) several times.

Step 1:

Let us show that the first term of the expression above, I_1, tends to 0 as t goes to 0. Let us observe that making the change of variables $\xi = \phi(-t,x)$ (see (2.6)) and using the semigroup property of ϕ, we have that

$$\int_0^{x_M} |p_0(\phi(-t,x))| \left| \frac{\Gamma(x)e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - \Gamma(\phi(-t,x))}{\Gamma(x)t} \right| dx$$

$$= \int_{\phi(-t,0)}^{\phi(-t,x_M)} |p_0(\xi)| \left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s-t,\phi(t,\xi)))ds}}{\Gamma(\phi(t,\xi))t} \right| d\xi$$

$$= \int_0^{x_M} |p_0(\xi)| \left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma(\phi(t,\xi))t} \right| d\xi.$$

Now, in order to apply the LDCT we show that the integrand converges pointwise to 0 when t goes to 0. In fact, for a fixed $x \in (0, x_M)$, applying the l'Hôpital rule we have

$$\lim_{t\to 0} \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma(\phi(t,\xi))t}$$

$$= \lim_{t\to 0} \frac{\Gamma'(\phi(t,\xi))\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}\Gamma'(\phi(t,\xi))}{\Gamma'(\phi(t,\xi))\Gamma(\phi(t,\xi))t + \Gamma(\phi(t,\xi))}$$

$$= \lim_{t\to 0} \left(\frac{\Gamma'(\phi(t,\xi))}{\Gamma(\phi(t,\xi))} \right) \left(\frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma'(\phi(t,\xi))t + 1} \right) = 0$$

whenever $\xi \in (0, x_M)$.

On the other hand, since p_0 belongs to L^1, to apply the LDCT we only have to show that

$$\left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi)))ds}}{\Gamma(\phi(t,\xi))t} \right|$$

is bounded by a constant on $[0, x_M] \times [0, t_0]$ for some $t_0 > 0$.

Using the mean value theorem, the bound K for the absolute value of the derivative of Γ and Lemma 2.2.2, we have that

$$\left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma(\phi(t,\xi))t} \right|$$

$$= \left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\phi(t,\xi))e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma(\phi(t,\xi))t} \right.$$

$$\left. + \frac{\Gamma(\phi(t,\xi))e^{\int_0^t \Gamma'(\phi(s,\xi))ds} - \Gamma(\xi)e^{\int_0^t \Gamma'(\phi(s,\xi))ds}}{\Gamma(\phi(t,\xi))t} \right|$$

$$\leq \left| \frac{e^{\int_0^t \Gamma'(\phi(s,\xi))}ds - 1}{t} \right| + \left| e^{\int_0^t \Gamma'(\phi(s,\xi))}ds \right| \left| \frac{\Gamma(\phi(t,\xi)) - \Gamma(\xi)}{\Gamma(\phi(t,\xi))t} \right|$$

$$\leq \left| e^{\int_0^{\tau_\xi} \Gamma'(\phi(\tau_\xi,\xi))ds}\Gamma'(\phi(s,\xi)) \right| + e^{Kt}K \left| \frac{\phi(t,\xi) - \xi}{\Gamma(\phi(t,\xi))t} \right|$$

$$\leq Ke^{Kt} + Ke^{Kt} \left| \bar{F}(\phi(t,\xi),t) \right| \leq Ke^{Kt_0}\Big(1 + L_H L_{H^{-1}} \frac{1 - e^{-\Gamma'(0)t_0}}{-\Gamma'(0)t_0}\Big),$$

since $\dfrac{1 - e^{-\Gamma'(0)t}}{-\Gamma'(0)t}$ is increasing.
This implies that

$$\lim_{t\to 0^+} \int_0^{x_M} |p_0(\phi(-t,x))| \left| \frac{\Gamma(x)e^{-\int_0^t \Gamma'(\phi(s-t,x))ds} - \Gamma(\phi(-t,x))}{\Gamma(x)t} \right| dx = 0.$$

Step 2:

To finish the Part 1 of the proof we have to show that, when t goes to 0,

$$\lim_{t\to 0^+} \int_0^{x_M} \left| \frac{\Gamma(\phi(-t,x))p_0(\phi(-t,x)) - \Gamma(x)p_0(x)}{\Gamma(x)t} + (\Gamma p_0)'(x) \right| dx = 0.$$

This step is more technical. We will decompose this integral in two terms and show that each one goes to 0 when t goes to 0. Indeed,

$$\int_0^{x_M} \left| \frac{\Gamma(\phi(-t,x))p_0(\phi(-t,x)) - \Gamma(x)p_0(x)}{\Gamma(x)t} + (\Gamma p_0)'(x) \right| dx$$

$$
\begin{aligned}
&= \int_0^{x_M} \left| \frac{1}{\Gamma(x)t} \int_x^{\phi(-t,x)} (\Gamma p_0)'(s)ds + (\Gamma p_0)'(x) \right| dx \\
&= \int_0^{x_M} \left| \frac{1}{\Gamma(x)t} \int_x^{\phi(-t,x)} \big((\Gamma p_0)'(s) - (\Gamma p_0)'(x)\big)ds \right. \\
&\qquad \left. + \left(1 + \frac{\phi(-t,x) - x}{\Gamma(x)t}\right) (\Gamma p_0)'(x) \right| dx \\
&\leq \int_0^{x_M} \frac{1}{\Gamma(x)t} \int_{\phi(-t,x)}^{x} |(\Gamma p_0)'(s) - (\Gamma p_0)'(x)| ds dx \\
&+ \int_0^{x_M} \left| 1 + \frac{\phi(-t,x) - x}{\Gamma(x)t} \right| |(\Gamma p_0)'(x)| dx =: I_{21} + I_{22}.
\end{aligned}
$$

Let us first see that I_{22} goes to 0 when t goes to 0.

As $(\Gamma p_0(x))' \in L^1$ and moreover by Lemma 2.2.2, $\dfrac{\phi(-t,x) - x}{\Gamma(x)t} \to -1$ pointwise when t goes to 0, the integrant of I_{22} goes to 0 pointwise when t goes to 0. Moreover, also by Lemma 2.2.2,

$$
\begin{aligned}
&\left| 1 + \frac{\phi(-t,x) - x}{\Gamma(x)t} \right| |(\Gamma p_0)'(x)| \\
&\leq \left(1 + L_H L_{H^{-1}} \left| \frac{e^{-\Gamma'(0)t_0} - 1}{\Gamma'(0)t_0} \right| \right) |(\Gamma p_0)'(x)|,
\end{aligned}
$$

for $t < t_0$. Therefore the claim follows from the LDCT.

Finally, we shall show that I_{21} also tends to 0 when t goes to 0. Here we will make a linear change of variables ($s = x + \Gamma(x)tz$) and we will also use that, since $\dfrac{\phi(-t,x) - x}{\Gamma(x)t}$ is continuous, it attains its minimum value. We denote by

$$
m_\phi(t) := \min_{x \in [0,x_m]} \Big(\frac{\phi(-t,x) - x}{\Gamma(x)t} \Big).
$$

Then we have

$$I_{21} = \int_0^{x_M} \frac{1}{\Gamma(x)t} \int_{\phi(-t,x)}^{x} |(\Gamma p_0)'(s) - (\Gamma p_0)'(x)| ds dx$$

$$= \int_0^{x_M} \int_{\frac{\phi(-t,x)-x}{\Gamma(x)t}}^{0} |(\Gamma p_0)'(x + \Gamma(x)tz) - (\Gamma p_0)'(x)| dz dx$$

$$\leq \int_{m_\phi(t)}^{0} \int_0^{x_M} |(\Gamma p_0)'(x + \Gamma(x)tz) - (\Gamma p_0)'(x)| dx dz.$$

Given $\epsilon > 0$ there exists a function g of class C^1 such that

$$\int_0^{x_M} |(\Gamma(x) p_0)'(x) - g(x)| dx < \frac{\epsilon}{6}. \tag{2.10}$$

Since $z \in [\frac{\phi(-t,x)-x}{\Gamma(x)t}, 0]$, by Lemma 2.2.2,

$$|\Gamma'(x)tz| \leq K L_H L_{H^{-1}} \frac{e^{|\Gamma'(0)|t} - 1}{|\Gamma'(0)|},$$

we have that there exists a small enough t_0 such that

$$1 + \Gamma'(x)tz \geq 1 - K L_H L_{H^{-1}} \frac{e^{|\Gamma'(0)|t_0} - 1}{|\Gamma'(0)|} > 1/2.$$

So,

$$\int_0^{x_M} |(\Gamma p_0)'(x + \Gamma(x)tz) - g(x + \Gamma(x)tz)| dx$$

$$\leq \int_0^{x_M} \frac{1}{1 + \Gamma'(x)tz} |(\Gamma p_0)'(s) - g(s)| ds$$

$$\leq 2 \int_0^{x_M} |(\Gamma p_0)'(s) - g(s)| ds < \frac{\epsilon}{3}, \tag{2.11}$$

where we have made the change of variables $s = x + \Gamma(x)tz$ and used the fact that it does not change the integration limits.

On the other hand, as g is a function of class C^1, we can write that

$$\int_0^{x_M} |g(x+\Gamma(x)tz) - g(x)|dx \leq \|g'\|_\infty \int_0^{x_M} |\Gamma(x)tz|dx$$
$$\leq \|g'\|_\infty t \frac{e^{|\Gamma'(0)|t} - 1}{|\Gamma'(0)|} \int_0^{x_M} |\Gamma(x)|dx < \frac{\epsilon}{3}, \tag{2.12}$$

which holds for any $t < t_1$, for some t_1 smaller than t_0.

Finally, using (2.10), (2.11), (2.12) we can write that

$$I_{21} \leq \int_{m_\phi(t)}^0 \int_0^{x_M} |(\Gamma p_0)'(x+\Gamma(x)tz) - (\Gamma p_0)'(x)|dxdz$$
$$\leq \int_{m_\phi(t)}^0 \int_0^{x_M} |(\Gamma p_0)'(x+\Gamma(x)tz) - g(x+\Gamma(x)tz)|dxdz$$
$$+ \int_{m_\phi(t)}^0 \int_0^{x_M} |g(x) - g(x+\Gamma(x)tz)|dxdz$$
$$+ \int_{m_\phi(t)}^0 \int_0^{x_M} |g(x) - (\Gamma p_0)'(x)|dxdz \leq \epsilon|m_\phi(t)|$$

which by Lemma 2.2.2 implies that I_{21} goes to 0 when t goes to 0, and ends this part of the proof.

Part 2:

To conclude the proof we only have to see that all the functions in the domain of the generator belong to the set D.

Let us assume that $(p_0(x), q_0(x))$ belongs to the domain of the generator, i.e., that there exists

$$\lim_{t\to 0^+} \frac{\begin{pmatrix} T^1(t)p_0 \\ q_0 \end{pmatrix}(x) - \begin{pmatrix} p_0(x) \\ q_0(x) \end{pmatrix}}{t} =: A_G \begin{pmatrix} p_0(x) \\ q_0(x) \end{pmatrix}. \tag{2.13}$$

Denoting the first component of A_G by ${A_G}^1$ and the second by ${A_G}^2$, it is obvious that ${A_G}^2 = 0$.

Using the Taylor expansion for ϕ, $\phi(-t,a) = a - \Gamma(a)t + \frac{\Gamma'(c)\Gamma(c)}{2}t^2$, where $c \in (\phi(-t,a), a)$, we can write,

$$\frac{1}{t}\int_{\phi(-t,a)}^{a} p_0(x)dx = \frac{1}{t}\int_{a-\Gamma(a)t+\frac{\Gamma'(c)\Gamma(c)}{2}t^2}^{a} p_0(x)dx$$

$$= \Big(\Gamma(a) - \frac{\Gamma'(c)\Gamma(c)}{2}t\Big)\Big(\frac{1}{\Gamma(a)t - \frac{\Gamma'(c)\Gamma(c)}{2}t^2}\Big)\int_{a-\Gamma(a)t+\frac{\Gamma'(c)\Gamma(c)}{2}t^2}^{a} p_0(x)dx.$$

So, assuming that a is a Lebesgue point of p_0 (see [60]), we have

$$\lim_{t\to 0^+}\frac{1}{t}\int_{\phi(-t,a)}^{a} p_0(x)dx = \Gamma(a)p_0(a). \tag{2.14}$$

On the other hand, for $a, b \in (0, x_M)$, we have

$$\int_a^b \frac{(T^1(t)p_0)(x) - p_0(x)}{t}dx$$

$$= \frac{1}{t}\int_a^b p_0(\phi(-t,x))e^{-\int_0^t \Gamma'(\phi(s-t,x))ds}dx - \frac{1}{t}\int_a^b p_0(x)dx$$

$$= \frac{1}{t}\int_{\phi(-t,a)}^{\phi(-t,b)} p_0(\xi)d\xi - \frac{1}{t}\int_a^b p_0(x)dx = \frac{1}{t}\int_{\phi(-t,a)}^{a} p_0(x)dx - \frac{1}{t}\int_{\phi(-t,b)}^{b} p_0(x)dx,$$

i.e.,

$$\frac{1}{t}\int_{\phi(-t,a)}^{a} p_0(x)dx = \int_a^b \frac{(T^1(t)p_0)(x) - p_0(x)}{t}dx + \frac{1}{t}\int_{\phi(-t,b)}^{b} p_0(x)dx, \tag{2.15}$$

where, in the last but one equality we made the change of variable $\xi = \phi(-t,x)$ and use (2.6).

We fix a Lebesgue point b of p_0. Using (2.15) and (2.14),

$$\lim_{t\to 0^+}\frac{1}{t}\int_{\phi(-t,a)}^{a} p_0(x)dx$$

$$= \lim_{t\to 0^+}\int_a^b \frac{(T^1(t)p_0)(x) - p_0(x)}{t}dx + \lim_{t\to 0^+}\frac{1}{t}\int_{\phi(-t,b)}^{b} p_0(x)dx$$

$$= \int_a^b {A_G}^1 p_0(x)dx + \Gamma(b)p_0(b).$$

Then, for all Lebesgue points $x \in (0, x_M)$, we can write, using (2.14) again ,

$$\Gamma(x)p_0(x) = \lim_{t \to 0^+} \frac{1}{t} \int_{\phi(-t,x)}^{x} p_0(s)ds = \Gamma(b)p_0(b) + \int_x^b {A_G}^1 p_0(s)ds,$$

which holds a.e. since the set of non-Lebesgue points has zero measure (see [60]).

With this we have that the function Γp_0 is absolutely continuous, which implies that $(\Gamma p_0)' \in L^1$ by the Fundamental Theorem of Calculus (for instance, see [60], Theorem 7.20), i.e., we have that $(p_0, q_0) \in D$. □

Corollary 1. The linear operator $\mathbf{A}$ defined by (2.3) with domain given by (2.9) is the infinitesimal generator of a C_0 semigroup on the Banach space $X = (L^1(0, x_M))^2$.

Proof. It follows from the beginning of section 2.2 and Proposition (2.9). □

Now we will prove the local existence and uniqueness result. Even though negative solutions do not have biological meaning, in order to apply a general result in semilinear evolution equations, we extend the definition of the function G to the whole real line, assuming that the extension satisfies the same conditions, i.e., it is smooth, bounded above by $\bar{G}$ and its derivative is bounded by G'. So the theorem below is stated in the whole space X and we leave the proof of positiveness of solutions with positive initial conditions until Theorem 2.2.5.

Theorem 2.2.3. For all initial conditions $u_0 = (p_0, q_0) \in X = L^1 \times L^1$, there exists a unique mild solution $u(t)$ of (2.2) (see definition 0.12) defined on a maximal interval of existence $[0, T_M)$. Moreover, if $T_M < \infty$, then

$$\lim_{t \to T_M} \|u(t)\| = \infty.$$

Proof. We use Theorem 1.4 from ([57], Chapter 6, page 185).

In order to apply the Theorem we need to prove two things:

(i) $\mathbf{A}$ is the infinitesimal generator of a C_0 semigroup on X.

This holds from the Corollary above.

(ii) f satisfies a local Lipschitz condition on the Banach space X.

We have that G is globally Lipschitzian with constant G'. As we want to show that f is locally Lipschitzian, we assume that

$$\int_0^{x_M} |q(x)|dx < Q.$$

With this considerations, let $\begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix}$ and $\begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \in X = (L^1(0, x_M))^2$. Denoting by

$$N_i = \int_0^{x_M} \big[\phi(x)p_i(x) + \psi(x)q_i(x)\big]dx$$

for $i = 1, 2$, and assuming that $\phi(x) \le \phi^*$, $\psi(x) \le \psi^*$, we have

$$\left\| f\begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - f\begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|$$

$$= \left\| \begin{pmatrix} (G(N_1)q_1(x) - G(N_2)q_2(x)) + 2\int_x^{x_M} \dfrac{F(y)}{y}(p_1(y) - p_2(y))dy \\ \big[\bar{G} - G(N_1)\big]q_1(x) - \big[\bar{G} - G(N_2)\big]q_2(x) \end{pmatrix} \right\|.$$

First of all, let us point out that

$$|N_1 - N_2| = \left| \int_0^{x_M} \big[\phi(x)(p_1(x) - p_2(x)) + \psi(x)(q_1(x) - q_2(x))\big]dx \right|$$

$$\le \phi^* \int_0^{x_M} |(p_1(x) - p_2(x))|dx + \psi^* \int_0^{x_M} |(q_1(x) - q_2(x))|dx$$

$$\le \phi^* \left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\| + \psi^* \left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|$$

$$\le (\phi^* + \psi^*) \left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|,$$

which implies

$$\int_0^{x_M} |G(N_1)q_1(x) - G(N_2)q_2(x)|dx$$

$$\le \int_0^{x_M} |G(N_1)(q_1(x)-q_2(x))|dx + \int_0^{x_M} |(G(N_1)-G(N_2))q_2(x)|$$

$$\le \bar{G}\int_0^{x_M} |q_1(x)-q_2(x)|dx + G'\int_0^{x_M} |(N_1-N_2)q_2(x)|$$

$$\le \bar{G}\left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|$$

$$+ G'(\phi^*+\psi^*)\left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\| \int_0^{x_M} |q_2(x)|$$

$$\le \Big(\bar{G} + G'(\phi^*+\psi^*)Q\Big)\left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|. \qquad (2.16)$$

On the other hand,

$$\int_0^{x_M} |2\int_x^{x_M} \frac{F(y)}{y}(p_1(y)-p_2(y))dy|dx$$

$$\le 2\int_0^{x_M}\int_x^{x_M} |\frac{F(y)}{y}(p_1(y)-p_2(y))|dydx$$

$$= 2\int_0^{x_M}\int_0^{y} \frac{F(y)}{y}|p_1(y)-p_2(y)|dxdy = 2\int_0^{x_M} F(y)|p_1(y)-p_2(y)|dy$$

$$\le 2\bar{F}\int_0^{x_M} |p_1(y)-p_2(y)|dy \le 2\bar{F}\left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|. \qquad (2.17)$$

And finally,

$$\int_0^{x_M} |\bar{G}q_1(x) - \bar{G}q_2(x)|dx$$

$$= \bar{G}\int_0^{x_M} |q_1(x)-q_2(x)|dx \le \bar{G}\left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|. \qquad (2.18)$$

Therefore, using (2.16), (2.17) and (2.18),

$$\left\| f\begin{pmatrix} p_1 \\ q_1 \end{pmatrix}(x) - f\begin{pmatrix} p_2 \\ q_2 \end{pmatrix}(x) \right\|$$

$$\int_0^{x_M} \left| (G(N_1)q_1(x) - G(N_2)q_2(x)) + 2\int_x^{x_M} \frac{F(y)}{y}(p_1(y) - p_2(y))dy \right| dx$$

$$\int_0^{x_M} \left| [\bar{G} - G(N_1)]q_1(x) - [\bar{G} - G(N_2)]q_2(x) \right| dx$$

$$\leq 2\int_0^{x_M} |G(N_1)q_1(x) - G(N_2)q_2(x)|dx$$

$$+ \int_0^{x_M} |2\int_x^{x_M} \frac{F(y)}{y}(p_1(y) - p_2(y))dy|dx + \int_0^{x_M} |\bar{G}q_1(x) - \bar{G}q_2(x)|dx$$

$$\leq \left[2\Big(\bar{G} + G'(\phi^* + \psi^*)Q \Big) + 2\bar{F} + \bar{G} \right] \left\| \begin{pmatrix} p_1(x) \\ q_1(x) \end{pmatrix} - \begin{pmatrix} p_2(x) \\ q_2(x) \end{pmatrix} \right\|,$$

which ends the proof.

□

Let us now prove the global existence of the solutions.

Theorem 2.2.4. For all initial conditions $u_0 = (p_0, q_0) \in (L^1(0, x_M))^2$, there exists a unique mild solution $u(t)$ of (2.2) defined on $[0, \infty)$.

Proof. By Theorem 2.2.3, let $u(t)$ be the solution of (2.2) defined on $[0, T_M)$.

First of all, let us point out that if $f : X \to X$ satisfies

$$\|f(u)\| \leq C_1\|u\| + C_2, \tag{2.19}$$

then, as u is the solution of the integral equation

$$u(t) = S(t)u_0 + \int_0^t S(t-s)f(u(s))ds,$$

for $t \in [0, t_M)$, where S is a C_0-semigroup such that $\|S(t)\| \leq Ce^{wt}$, we have that

$$\|u(t)\| \leq Ce^{wt}\|u_0\| + Ce^{wt}\int_0^t e^{-ws}(C_1\|u(s)\| + C_2)ds$$

$$= Ce^{wt}\|u_0\| + CC_2\frac{e^{wt}-1}{w} + CC_1e^{wt}\int_0^t e^{-ws}\|u(s)\|ds.$$

Since w can be assumed to be positive, this implies

$$e^{-wt}\|u(t)\| \leq \Big(C\|u_0\| + \frac{CC_2}{w}\Big) + CC_1\int_0^t e^{-ws}\|u(s)\|ds.$$

Applying the Gronwall inequality (for instance see [43]), we have that

$$e^{-wt}\|u(t)\| \leq C\Big(\|u_0\| + \frac{C_2}{w}\Big)e^{CC_1t},$$

i.e.,

$$\|u(t)\| \leq C\Big(\|u_0\| + \frac{C_2}{w}\Big)e^{(CC_1+w)t},$$

and this inequality holds for all $t \in [0, T_M]$.

Applying Theorem 2.2.3, we have that $T_M = \infty$ provided that f satisfies (2.19).

In fact, for $u(x) = (p(x), q(x)) \in (L^1(0, x_M))^2$,

$$\|f(u(x))\| = \left\|\begin{pmatrix} (G(N)q(x) + 2\int_x^{x_M}\frac{F(y)}{y}p(y)dy \\ \big[\bar{G} - G(N)\big]q(x) \end{pmatrix}\right\|$$

$$\leq \int_0^{x_M}|(G(N)q(x))|dx + 2\int_0^{x_M}\int_x^{x_M}\frac{F(y)}{y}|p(y)|dydx +$$

$$\int_0^{x_M}|(\bar{G} - G(N))q(x)|dx$$

$$\leq \bar{G}\int_0^{x_M}|q(x)|dx + 2\bar{F}\int_0^{x_M}|p(y)|dy + \bar{G}\int_0^{x_M}|q(x)|dx,$$

i.e.,

$$\|f(u)\| \leq 2(\bar{G} + \bar{F})\|u\|$$

which finishes the proof. □

Once we have existence and uniqueness, another natural question is about the positiveness of the solution. It is natural if we want that our problem makes biological sense.

Theorem 2.2.5. For all positive initial conditions $u_0 = (p_0, q_0) \in L^1 \times L^1$, the solution of (2.2) will be positive on $(0, +\infty)$.

Proof. We recall the fixed point argument that provides the mild solution. A solution of (2.2) satisfies the following integral equation

$$u(t) = S(t)u_0 + \int_0^t S(t-s)f(u(s))ds, \tag{2.20}$$

where S is the positive semigroup generated by the operator $\mathbf{A}$.

As we saw before, S is positive and since u_0 is positive and because f maps positive functions on positive functions, we have that

$$u_1(t) = S(t)u_0 + \int_0^t S(t-s)f(u_0)ds$$

will be positive too. By induction we can construct a positive sequence $(u_n)_n$ given by

$$u_{n+1}(t) = S(t)u_n + \int_0^t S(t-s)f(u_n(s))ds.$$

Since the cone of positive functions on L^1 is closed, we have that the limit of the sequence, $u(t)$, is positive. □

Chapter 3

Equilibria of the cyclin-structured model

It this chapter we will show the existence of steady states of system (2.1). The hypotheses on the functions are the same that appear on the section 2.1. As we saw before, this is a simplified version of the model introduced in [12], [13] where we assume that the parameter functions are age-independent, which leads to a system where the structure is only with respect to cyclin content, that is still a first order nonlinear partial differential equations system with non local terms.

The abstract structure of the model allows the reduction of the problem of finding nontrivial equilibria to the problem of existence of a positive eigenvector corresponding to the dominant eigenvalue of a certain linear operator which is the infinitesimal generator of an irreducible positive semigroup. This linear operator is obtained from considering the vital and transition rates given by fixing the values of an interaction variable, which summarizes the competition effect of the population on each individual. In the literature dealing with dominant eigenvalues, positive eigenvectors and asynchronous exponential growth of structured populations, the theory of linear semigroups (the first paper [71] applying this theory to population dynamics considers the age-structured case) and the theory of positive operators (see [53] and [45] where size structured cell populations are considered) have been used extensively.

We use positive linear semigroup theory (see [9], [23]) in order to establish conditions for the existence of the dominant eigenvalue and uniqueness of a (normalized) corresponding positive eigenvector of the linear operator mentioned above. As a consequence we prove in Theorem 3.1.5 existence and uniqueness of a non trivial steady state under additional hypotheses which only amount to say that the population increases in "ideal" conditions with respect to competition (i.e. when the population is very small) and decreases in "starvation" conditions (i.e. when the population is very large).

We will start by reducing the existence of steady states to the eigenproblem. In the next section, following the lines of the book [9] (Chapter III), we decompose the operator as the sum of a generator A of a positive semigroup and a compact perturbation K. As usual the most difficult condition to check is that the spectral bound of the perturbed operator $A + K$ is strictly larger than the spectral bound of the operator A. Theorem 3.3 in [66] states that the previous condition holds whenever the spectral radius of the compact operator $KR(\lambda, A)$ (where $R(\lambda, A)$ is the resolvent operator) is larger than or equal to 1 for some λ larger than the spectral bound of A. In [66] the author applies the theorem to a population structured by age and size for which the spectral radius of this compact operator can be explicitly computed, being the clue that the size distribution at birth is a fixed measure, which in its turn implies that the operator is of rank one.

In our case this explicit computation is no longer possible and we obtain the condition on the spectral radius under some hypotheses by using a pointwise inequality for a test function (Lemma 3.1.2 and Proposition 6). We also give conditions ensuring non existence of an eigenvalue of the operator $A + K$ larger than the spectral bound of A (Theorem 3.1.4).

An alternative approach to the existence of solution to the eigenproblem in a single equation for a size structured cell population is given in [54] by means of proving the convergence of an approximate problem. The paper [31] gives a proof of existence and uniqueness of the steady state of the model proposed in [12] by means of regularization and application of the classical Krein-Rutman theorem in the case that the transition rate from proliferating to quiescent stages is independent of cyclin content.

3.1 Steady states

A steady state of system (2.1) is a solution $(p(x), q(x)) \in (L^1(0, x_M))^2$ of the system of equations

$$\begin{cases} 0 &= -\dfrac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) - \big[L(x)+F(x)+d_1\big]p(x) \\ & \quad +G(N)q(x) + 2\int_x^{x_M} \frac{F(y)}{y}p(y)dy, \\ 0 &= L(x)p(x) - \big[G(N)+d_2\big]q(x), \end{cases} \tag{3.1}$$

with $N = \int_0^{x_M} \big(\phi^*(x)p(x) + \psi^*(x)q(x)\big)dx$. For each (p,q), N is a real number and $G(N)$ too. We will denote $G(N)$ by $\hat{G}$.

System (3.1) can be reduced to a unique equation for p which leads to

$$0 = -\frac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) - \left[L(x)+F(x)+d_1 - \frac{\hat{G}L(x)}{\hat{G}+d_2}\right]p(x) + 2\int_x^{x_M} \frac{F(y)}{y}p(y)dy.$$

For values of $\hat{G}$ in the range of the function G, let us consider the unbounded linear operator in $L^1(0,x_M)$

$$\begin{aligned} \mathrm{B}_{\hat{G}}p(x) &:= -\frac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) - \left[\tfrac{d_2}{\hat{G}+d_2}L(x) + F(x) + d_1\right]p(x) \\ &+ \quad 2\int_x^{x_M} \tfrac{F(y)}{y}p(y)dy. \end{aligned} \tag{3.2}$$

In order to find nontrivial solutions of (3.1) we have to find positive eigenvectors of eigenvalue zero of the operator $\mathrm{B}_{\hat{G}}$. We will show that for any $\hat{G} \in (0, G(0))$, the operator $B_{\hat{G}}$ has, under suitable hypotheses, a simple real eigenvalue $\lambda_{\hat{G}} = s(B_{\hat{G}})$ (the spectral bound of $B_{\hat{G}}$), and that $\lambda_{\hat{G}}$ is the unique eigenvalue with corresponding positive eigenvector. Furthermore we will have that the function $\hat{G} \in (0, G(0)) \to \lambda_{\hat{G}}$ is strictly increasing and continuous. Assuming that $\lambda_0 < 0 < \lambda_{G(0)}$ the function $\lambda_{\hat{G}}$ has a unique zero that we will denote by $\hat{G}_0$. In this case

$$\mathrm{B}_{\hat{G}_0} c p_{\hat{G}_0}(x) = 0, \ \forall c \in \mathbb{R},$$

where $p_{\hat{G}_0}$ is an eigenvector associated with the eigenvalue $\lambda_{\hat{G}_0} = 0$, $p_{\hat{G}_0} > 0$, $\int_0^{x_M} p_{\hat{G}_0}(x)dx = 1$.
In order that $cp_{\hat{G}_0}$ is the first component of a steady state we still have to find the scalar c which is determined as follows (implying uniqueness of the non trivial

steady state). As G is strictly decreasing in N and tends to 0 when N goes to infinity, we have a unique N_0 such that $\hat{G}_0 = G(N_0)$. Since the following must hold

$$N_0 = c\int_0^{x_M} \big(\phi^*(x) + \frac{L(x)\psi^*(x)}{\hat{G}_0 + d_2}\big)p_{\hat{G}_0}(x)dx,$$

there exists a unique $c_0 \in \mathbb{R}^+$, namely

$$c_0 = \frac{N_0}{\int_0^{x_M} \big(\phi^*(x) + \frac{L(x)\psi^*(x)}{\hat{G}_0+d_2}\big)p_{\hat{G}_0}(x)dx}$$

such that the point $\left(c_0 p_{\hat{G}_0}(x), \dfrac{c_0 L(x) p_{\hat{G}_0}(x)}{\hat{G}_0 + d_2}\right)$ satisfies (3.1), that is, it is the unique positive steady state of system (2.1).

3.1.1 The eigenvalue problem

In this section we will prove that under suitable hypotheses the operator $B_{\hat{G}}$ defined in (3.2) has an algebraically simple dominant eigenvalue $\lambda_{\hat{G}}$ for any $\hat{G}$ in $(0, G(0))$ with a corresponding positive eigenvector and moreover that it is the only eigenvalue of $B_{\hat{G}}$ with a positive eigenvector.
Let us denote

$$r_{\hat{G}}(x) = \frac{d_2}{\hat{G} + d_2}L(x) + F(x) + d_1$$

and let us consider the operator $B_{\hat{G}}$ in the following way

$$\mathrm{B}_{\hat{G}}p(x) = A_{\hat{G}}p(x) + Kp(x), \tag{3.3}$$

where

$$\begin{aligned} A_{\hat{G}}p(x) &= -\frac{\partial}{\partial x}\big(\Gamma(x)p(x)\big) - r_{\hat{G}}(x)p(x), \\ Kp(x) &= 2\int_x^{x_M} \tfrac{F(y)}{y}p(y)dy. \end{aligned} \tag{3.4}$$

The existence of a dominant eigenvalue with a corresponding positive eigenvector of $B_{\hat{G}}$ will be proved using the following result.

Theorem 3.1.1. Suppose $A_{\hat{G}}+K$ is the generator of an irreducible positive linear semigroup. If $A_{\hat{G}}$ is K-compact, i.e. if $K(\lambda - A_{\hat{G}})^{-1}$ is compact for some $\lambda > s(A_{\hat{G}})$ (the spectral bound of $A_{\hat{G}}$), and $s(A_{\hat{G}} + K) > s(A_{\hat{G}})$ then $s(A_{\hat{G}} + K)$ is a simple dominant eigenvalue of $A_{\hat{G}} + K$ and its corresponding eigenvector is strictly positive. Moreover $s(A_{\hat{G}}+K)$ is the only eigenvalue of $A_{\hat{G}}+K$ admitting a positive eigenvector.

Proof. The first statement is given by Propositions CIII-3.18 and CIII-3.14 in [9]. The existence of a strictly positive eigenfunction corresponding to the eigenvalue $s(A_{\hat{G}} + K)$ follows from an application of Theorem 8.17 in [23]. This theorem also gives existence of a positive eigenfunction of the adjoint operator of $A_{\hat{G}} + K$ corresponding to $s(A_{\hat{G}} + K)$. Moreover, since 0 is an eigenvalue of the operator $A_{\hat{G}} + K - s(A_{\hat{G}} + K)$, Theorem CIII-3.8 in [9] gives the last assertion of the theorem. □

Let us now show that the operators $A_{\hat{G}}$ and K fulfill the hypotheses required in Theorem 3.1.1.

Proposition 3. K is a compact operator.

Proof. Taking the derivative in the L^1 sense we have that $D(Kp)(x) = -2\dfrac{F(x)}{x}p(x)$. Then, if $\|p\|_{L^1} \leq c''$,

$$\begin{aligned}
\|Kp\|_{L^1} &= \left| \int_0^{x_M} 2 \int_x^{x_M} \frac{F(y)}{y} p(y)dy\, dx \right| \\
&\leq 2 \int_0^{x_M} \int_0^{y} \frac{F(y)}{y} |p(y)|dx\, dy \\
&= 2 \int_0^{x_M} F(y)|p(y)|dy \\
&\leq 2c' x_M \|p\|_{L^1} \\
&\leq 2c'c'' x_M
\end{aligned}$$

and

$$\|D(Kp)\|_{L^1} = \left| \int_0^{x_M} -2\frac{F(x)}{x} p(x)dx \right| \leq 2c'\|p\|_{L^1} \leq 2c'c'',$$

where c' denotes an upper bound on $\dfrac{F(x)}{x}$. Then $\|Kp\|_{W^{1,1}} \leq c$. That is, the operator K maps $L^1(0, x_M)$ into $W^{1,1}(0, x_M)$ as a bounded linear operator, and the operator $K : L^1(0, x_M) \longrightarrow L^1(0, x_M)$ is compact by the Rellich-Kondrachov theorem. $\square$

Proposition 4. Let $A_{\hat{G}}$ and K be the operators defined by (3.4). The operator $B_{\hat{G}} = A_{\hat{G}} + K$ generates an irreducible semigroup $S(t)$.

Proof. $A_{\hat{G}}$ is the generator of a positive linear semigroup $T_0(t)$ given by the solution to the initial value problem for the first order linear partial differential equation

$$\begin{aligned} \tfrac{\partial}{\partial t}p(x,t) + \tfrac{\partial}{\partial x}(\Gamma(x)p(x,t)) + r_{\hat{G}}(x)p(x,t) &= 0, \\ p(x,0) = p_0, & \end{aligned}$$

which can be explicitly solved by the characteristic lines method:

$$\big(T_0(t)p_0\big)(x) = p_0(\varphi(-t,x))e^{-\int_0^t \left(\Gamma'(\varphi(s-t,x))+r_{\hat{G}}(\varphi(s-t,x))\right)ds}. \tag{3.5}$$

where $\varphi(t,x)$ is the (unique) solution to the initial value problem

$$\begin{cases} z'(t) = \Gamma(z(t)), \\ z(0) = x. \end{cases} \tag{3.6}$$

Notice that for any $x \in (0, x_M)$, φ is an increasing function of t and $\lim_{t\to+\infty} \varphi(t,x) = x_M$.
Since K is a positive bounded operator $A_{\hat{G}} + K$ is the generator of a positive semigroup $S(t)$ (see [57]) given by the solution of the integral equation

$$S(t)p_0 = T_0(t)p_0 + \int_0^t T_0(t-s)KS(s)p_0 ds.$$

Iterating once this equation we have

$$\begin{aligned} S(t)p_0 &= T_0(t)p_0 + \textstyle\int_0^t T_0(t-s)K\Big(T_0(s)p_0 + \int_0^s T_0(t-\sigma)KS(\sigma)p_0 d\sigma\Big)ds \\ &= T_0(t)p_0 + \textstyle\int_0^t T_0(t-s)KT_0(s)p_0 ds \\ &\quad + \textstyle\int_0^t\int_0^s T_0(t-s)KT_0(t-\sigma)KS(\sigma)p_0 d\sigma ds \\ &\geq \textstyle\int_0^t T_0(t-s)KT_0(s)p_0 ds =: T_1(t)p_0. \end{aligned}$$

So, in order to show that $S(t)$ is irreducible it suffices to show that for any $p_0 \in L^1(0, x_M)$, $p_0 > 0$ and any $\phi \in L^\infty(0, x_M)$, $\phi > 0$ there exists t_0 such that for $t > t_0$,

$$\int_0^{x_M} \phi(x) T_1(t) p_0(x) dx = \int_0^t \int_0^{x_M} \phi(x) T_0(t-s) K T_0(s) p_0(x) dx ds > 0. \quad (3.7)$$

For any $v \in L^1(0, x_M)$, let us define

$$I_v := \{x \in (0, x_M) \text{ such that } v(y) = 0 \text{ a.e. on } \quad [x, x_M)\}.$$

and

$$\hat{x}_v := \begin{cases} \inf I_v, & \text{if } I_v \neq \emptyset \\ x_M, & \text{if } I_v = \emptyset. \end{cases}$$

Notice that $\hat{x}_{p_0} > 0$.
By (3.5) and the definition of $\varphi(t, x)$ we can see that

$$\hat{x}_{T_0(t)p_0} = \hat{x}_{p_0(\varphi(-t, \cdot))} = \varphi(t, \hat{x}_{p_0}) \in [\hat{x}_{p_0}, x_M].$$

On the other hand, as $\dfrac{F(y)}{y} > 0$ for all y and

$$Kv(x) = 2\int_x^{x_M} \frac{F(y)}{y} v(y) dy = 2\int_x^{\hat{x}_v} \frac{F(y)}{y} v(y) dy$$

then, for any $v > 0$, $Kv(x) > 0$ if and only if $x < \hat{x}_v$.
With this at hand we have that

$$(KT_0(s)p_0)(x) > 0 \text{ if and only if } x < \varphi(s, \hat{x}_{p_0}).$$

Then

$$(T_0(t-s)KT_0(s)p_0)(x) > 0 \text{ if and only if } x < \varphi(t-s, \varphi(s, \hat{x}_{p_0})) = \varphi(t, \hat{x}_{p_0})$$

by the semigroup property of the solutions of the ordinary differential equation (3.6).

Finally, let us consider $\phi \in L^\infty(0, x_M)$, $\phi > 0$. Since $\lim_{s \to +\infty} \varphi(s, \hat{x}_{p_0}) = x_M$, there exists t_0 such that ϕ does not vanish a.e. on $(0, \varphi(t_0, \hat{x}_{p_0}))$. Then for $t > t_0$ (3.7) holds. $\square$

In order to see that the operator $B_{\hat{G}} = A_{\hat{G}} + K$ satisfies the hypotheses of Theorem 3.1.1 it only remains to show that the inequality $s(A_{\hat{G}} + K) > s(A_{\hat{G}})$ holds. Theorem 1.1 in [66] states that $s(A_{\hat{G}} + K) > s(A_{\hat{G}})$ if there exists $\lambda > s(A_{\hat{G}})$ such that the spectral radius of $KR(A_{\hat{G}}, \lambda)$ is larger than or equal to 1. The latter will be proved, under suitable hypotheses, by means of the following two results, the first one of which is a rather abstract lemma whereas the second one is a result about the semigroup $T_0(t)$ and its infinitesimal generator $A_{\hat{G}}$.

Lemma 3.1.2. Let C be a positive bounded linear operator in a Banach lattice. If there exists $f > 0$ such that $Cf \geq f$ then the spectral radius of C is greater than or equal to 1.

Proof. Since $Cf - f \geq 0$ and C is a positive operator, we have

$$0 \leq C(Cf - f) = C^2 f - Cf \leq C^2 f - f,$$

and, iterating, $C^n f \geq f$. Hence, $\|C^n f\| \geq \|f\|$ which implies $\|C^n\|^{1/n} \geq 1$ and the claim follows.

□

Proposition 5. Let T_0 be the positive linear semigroup generated by the operator $A_{\hat{G}}$ and let us denote by $\omega_0(T_0)$ and $s(A_{\hat{G}})$ their growth bound and spectral bound respectively. Then $s(A_{\hat{G}}) = \omega_0(T_0) = -\min\{r_{\hat{G}}(0), r_{\hat{G}}(x_M)\}$.

Proof. The first equality holds for any positive semigroup in L^1 (see [23]). As the differential equation (3.6) is autonomous and $\Gamma(0) = \Gamma(x_M) = 0 < \Gamma(x)$ for $x \in (0, x_M)$, the map $x \in (0, x_M) \to \varphi(t, x) \in (0, x_M)$ is a diffeomorphism for any real t, with inverse $x \in (0, x_M) \to \varphi(-t, x) \in (0, x_M)$. Moreover,

$$\frac{\partial \varphi}{\partial x}(t, x) = e^{\int_0^t \Gamma'(\varphi(s,x))ds}.$$

From (3.5) it follows

$$\begin{aligned} \|T_0(t)p_0\| &= \int_0^{x_M} |p_0(\varphi(-t, x))e^{-\int_0^t \left(\Gamma'(\varphi(s-t,x)) + r_{\hat{G}}(\varphi(s-t,x))\right)ds}|dx \\ &= \int_0^{x_M} |p_0(y)|e^{-\int_0^t r_{\hat{G}}(\varphi(s,y))ds} dy, \end{aligned}$$

where we have made the change of variables $y = \varphi(-t, x)$, i.e., $x = \varphi(t, y)$ and $\dfrac{dx}{dy} = e^{\int_0^t \Gamma'(\varphi(s,y))ds}$. Let us now define $M := \min\{r_{\hat{G}}(0), r_{\hat{G}}(x_M)\}$ and recall that

$M > 0$. We shall prove that $s(A_{\hat{G}}) = -M$. By continuity of Γ and $r_{\hat{G}}$, and the positivity of Γ in $(0, x_M)$, for all sufficiently small $\varepsilon > 0$, there exists an interval $I = (\delta, x_M - \delta) \subset (0, x_M)$ such that

$$\Gamma(x) > \varepsilon \text{ if } x \in I \quad \text{and} \quad r_{\hat{G}}(x) > M - \varepsilon \text{ if } \quad x \in (0, x_M)\backslash I. \tag{3.8}$$

The first inequality in (5.3.1) implies that for any $y \in (0, x_M)$, the length of the interval $\{s : \varphi(s, y) \in I\}$ is smaller than $\frac{x_M}{\varepsilon}$. Then, for $t > \frac{x_M}{\varepsilon}$, by the second inequality in (5.3.1),

$$\int_0^t r_{\hat{G}}(\varphi(s, y))ds > (M - \varepsilon)(t - \frac{x_M}{\varepsilon}).$$

So,

$$\|T_0(t)\| \leq e^{x_M(\frac{M}{\varepsilon}-1)}e^{(-M+\varepsilon)t},$$

and then, $\omega_0(T_0) = \lim_{t\to+\infty} \dfrac{\ln(\|T_0(t)\|)}{t} \leq -M + \varepsilon$ for all sufficiently small $\varepsilon > 0$, i.e., $\omega_0(T_0) \leq -M$.

Moreover, δ can be chosen such that either $r_{\hat{G}}(x) < M + \varepsilon$ if $x > x_M - \delta$ (when $M = r_{\hat{G}}(x_M)$) or $r_{\hat{G}}(x) < M + \varepsilon$ if $x < \delta$ (when $M = r_{\hat{G}}(0)$), or both (if $r_{\hat{G}}(0) = r_{\hat{G}}(x_M)$). In the first case, taking $u_\delta(x) = \frac{1}{\delta}\chi_{(x_M-\delta,x_M)}(x)$, we have (for all sufficiently small $\varepsilon > 0$),

$$\|T_0(t)u_\delta\| = \int_{x_M-\delta}^{x_M} \frac{1}{\delta}e^{-\int_0^t r_{\hat{G}}(\varphi(s,y))ds}dy \geq e^{(-M-\varepsilon)t},$$

and $\omega_0(T_0) = \lim_{t\to+\infty} \dfrac{\ln(\|S(t)\|)}{t} \geq -M - \varepsilon$. Finally, in the second case, i.e., when $M = r_{\hat{G}}(0)$, for all $t > 0$ there exists $\delta_0 < \delta$ such that $\varphi(s, y) < \delta$ (and hence $r_{\hat{G}}(\varphi(s, y)) < M + \varepsilon$) whenever $y < \delta_0$ and $s < t$.

Then, taking $u_{\delta_0}(x) = \frac{1}{\delta_0}\chi_{(0,\delta_0)}(x)$, we have (for all sufficiently small $\varepsilon > 0$),

$$\|T_0(t)u_{\delta_0}\| = \int_0^{\delta_0} \frac{1}{\delta_0}e^{-\int_0^t r_{\hat{G}}(\varphi(s,y))ds}dy \geq e^{(-M-\varepsilon)t},$$

which leads to $\omega_0(T_0) \geq -M$. With this we finish the proof that $\omega_0(T_0) = -M$. □

Before stating the next result of this subsection, we shall introduce some notation. Let us define the constants c_0, c_1, c_2 and c_3 in the following way

$$c_0 = \inf_{y\in[0,x_M]} \left(\frac{F(y)}{y}\right) > 0,$$

$$c_1 = \sup\{c > 0 : \Gamma(x) \geq cx(x_M - x),\ \ \forall x \in (0, x_M)\} = \inf \frac{\Gamma(x)}{x(x_M - x)} > 0,$$

$$c_2 = \inf\{c > 0 : r_{\hat{G}}(x) \leq r_{\hat{G}}(x_M) + c(x_M - x),\ \ \forall x \in (0, x_M)\},$$

$$c_3 = \inf\{c > 0 : r_{\hat{G}}(x) \leq r_{\hat{G}}(0) + cx\ \ \forall x \in (0, x_M)\}.$$

Using the hypotheses on $F(x)$ and $\Gamma(x)$, the constants c_0 and c_1 are well defined, and with this at hand, we can prove the next result.

Proposition 6. Let us assume that c_2 and c_3 are well defined and that either

(i) $r_{\hat{G}}(x_M) \leq r_{\hat{G}}(0)$

or

(ii) $r_{\hat{G}}(0) < r_{\hat{G}}(x_M)$ and

$$\frac{2c_0 x_M}{(\frac{c_3}{c_1})^{\frac{c_3}{c_3 - c_1}} (\max_x r_{\hat{G}}(x) - r_{\hat{G}}(0))} > 1 \quad (\text{if} \quad c_3 \neq c_1)$$

$$\text{or} \quad \frac{2c_0 x_M}{e(\max_x r_{\hat{G}}(x) - r_{\hat{G}}(0))} > 1 \quad (\text{if} \quad c_3 = c_1).$$

Then the spectral radius of the operator $KR(A_{\hat{G}}, \lambda)$ is larger than or equal to 1.

Proof. The resolvent operator $R(A_{\hat{G}}, \lambda)$ can be explicitly computed by the variation of constants formula as the unique L^1 solution to the linear ordinary differential equation

$$(\Gamma(x)p(x))' + (\lambda + r_{\hat{G}}(x))p(x) = f(x), \quad x \in (0, x_M),$$

i.e. $\big(R(A_{\hat{G}}, \lambda)f\big)(x) = \frac{1}{\Gamma(x)} \int_0^x e^{-\int_s^x \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} f(s) ds.$
Let us proceed to prove that hypothesis (i) as well as hypothesis (ii) imply that the hypothesis of Lemma 3.1.2 holds and then the claim follows. For $\delta_0 \in (0, x_M)$ to be chosen later, we define the function $f(x) := \chi_{[0, x_M - \delta_0]}(x)$. We just have to show that for some $\lambda > s(A_{\hat{G}})$, $KR(A_{\hat{G}}, \lambda)f(x) \geq f(x)$, which reduces to see $KR(A_{\hat{G}}, \lambda)f(x) \geq 1$ for all $x \in [0, x_M - \delta_0]$.

We begin by deriving the following bound:

$$\begin{aligned}
KR(A_{\hat{G}},\lambda)f(x) &= 2\int_x^{x_M}\frac{F(y)}{y}\frac{1}{\Gamma(y)}\int_0^y e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}\chi_{[0,x_M-\delta_0]}(s)dsdy \\
&\geq 2\int_{x_M-\delta_0}^{x_M}\frac{F(y)}{y}\frac{1}{\Gamma(y)}\left(\int_0^{x_M-\delta_0} e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}ds\right)dy \\
&= 2\left(\int_0^{x_M-\delta_0} e^{-\int_s^{x_M-\delta_0} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}ds\right) \\
&\quad \left(\int_{x_M-\delta_0}^{x_M}\frac{F(y)}{y}\frac{1}{\Gamma(y)}e^{-\int_{x_M-\delta_0}^{y} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}dy\right) \\
&\geq 2c_0\left(\int_0^{x_M-\delta_0} e^{-\int_s^{x_M-\delta_0} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}ds\right) \\
&\quad \left(\int_{x_M-\delta_0}^{x_M}\frac{1}{\Gamma(y)}e^{-\int_{x_M-\delta_0}^{y} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}dy\right).
\end{aligned}$$

(i) First notice that $c_2 \geq 0$. Let δ_0 be sufficiently small such that $\delta_0 < \dfrac{c_0c_1x_M}{4(c_1+c_2)c_2}$ (no condition if $c_2 = 0$). We shall show that

$$\int_{x_M-\delta_0}^{x_M}\frac{1}{\Gamma(y)}e^{-\int_{x_M-\delta_0}^{y} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}dy \geq \frac{1}{\lambda + r_{\hat{G}}(x_M) + c_2\delta_0} \tag{3.9}$$

and for $\lambda + r_{\hat{G}}(x_M) > 0$ and $\delta_0 > 0$ sufficiently small,

$$\int_0^{x_M-\delta_0} e^{-\int_s^{x_M-\delta_0} \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}ds \geq \frac{c_1x_M}{4(c_1+c_2)}. \tag{3.10}$$

With this, for all $x \in [0, x_M - \delta_0]$,

$$KR(A_{\hat{G}},\lambda)f(x) \geq 2c_0\frac{c_1x_M}{4(c_1+c_2)}\frac{1}{\lambda + r_{\hat{G}}(x_M) + c_2\delta_0}.$$

By the choice of δ_0, taking λ sufficiently close to $s(A_{\hat{G}}) = -r_{\hat{G}}(x_M)$, we have

$$\lambda + r_{\hat{G}}(x_M) + c_2\delta_0 \leq \frac{c_0 c_1 x_M}{2(c_1 + c_2)}$$

and then $KR(A_{\hat{G}}, \lambda)f(x) \geq 1$ for all $x \in [0, x_M - \delta_0]$.
Let us now prove (3.9) and (3.10). To see (3.10) we note that for all σ in $(0, x_M)$,

$$\frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} \leq \frac{\lambda + r_{\hat{G}}(x_M) + c_2(x_M - \sigma)}{c_1\sigma(x_M - \sigma)}$$

and then, for s in $(0, x_M - \delta_0)$, a straightforward integration yields

$$\begin{aligned} -\int_s^{x_M-\delta_0} \tfrac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma &\geq -\tfrac{\lambda + r_{\hat{G}}(x_M) + c_2 x_M}{c_1 x_M} \ln\left(\tfrac{x_M - \delta_0}{s}\right) \\ &\quad + \tfrac{\lambda + r_{\hat{G}}(x_M)}{c_1 x_M} \ln\left(\tfrac{\delta_0}{x_M - s}\right), \end{aligned}$$

which implies

$$e^{-\int_s^{x_M-\delta_0} \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} \geq \left(\frac{\delta_0}{x_M - s}\right)^{\frac{\lambda + r_{\hat{G}}(x_M)}{c_1 x_M}} \left(\frac{s}{x_M - \delta_0}\right)^{\frac{\lambda + r_{\hat{G}}(x_M) + c_2 x_M}{c_1 x_M}}.$$

If $s < x_M - \delta_0$ then $\dfrac{s}{x_M - \delta_0} < 1$ and $\dfrac{\delta_0}{x_M - s} < 1$. So, applying the Monotonous Convergence Theorem

$$\begin{aligned} \int_0^{x_M-\delta_0} e^{-\int_s^{x_M-\delta_0} \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} ds &\geq \int_0^{x_M-\delta_0} \left(\tfrac{\delta_0}{x_M - s}\right)^{\frac{\lambda + r_{\hat{G}}(x_M)}{c_1 x_M}} \\ &\quad \left(\tfrac{s}{x_M - \delta_0}\right)^{\frac{\lambda + r_{\hat{G}}(x_M) + c_2 x_M}{c_1 x_M}} ds \\ &\quad \xrightarrow{\lambda \to -r_{\hat{G}}(x_M)^+} \int_0^{x_M-\delta_0} \left(\tfrac{s}{x_M - \delta_0}\right)^{\frac{c_2}{c_1}} ds \\ &= \tfrac{(x_M - \delta_0)c_1}{c_1 + c_2}, \end{aligned}$$

which for $\lambda + r_{\hat{G}}(x_M)$ and δ_0 sufficiently small, implies (3.10).

On the other hand, note that

$$r_{\hat{G}}(x) \le r_{\hat{G}}(x_M) + c_2\delta_0 \quad \text{for all} \quad x \in (x_M - \delta_0, x_M).$$

Using this we obtain

$$\begin{aligned}
\int_{x_M-\delta_0}^{x_M} \frac{1}{\Gamma(y)} e^{-\int_{x_M-\delta_0}^{y} \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} dy &\ge \int_{x_M-\delta_0}^{x_M} \frac{1}{\Gamma(y)} e^{-(\lambda + r_{\hat{G}}(x_M) + c_2\delta_0) \int_{x_M-\delta_0}^{y} \frac{1}{\Gamma(\sigma)} d\sigma} dy \\
&= \frac{1}{\lambda + r_{\hat{G}}(x_M) + c_2\delta_0},
\end{aligned}$$

which finishes this part of the proof.

(ii) Following exactly the same lines and denoting by $R = \max_{\sigma \in [0, x_M]} r_{\hat{G}}(\sigma)$, we can also bound

$$\int_{x_M-\delta_0}^{x_M} \frac{1}{\Gamma(y)} e^{-\int_{x_M-\delta_0}^{y} \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} dy \ge \frac{1}{R - r_{\hat{G}}(0)}$$

when $\lambda + r_{\hat{G}}(0) > 0$ is sufficiently small.

On the other hand, using the definition of c_3 (which is necessarily positive) we bound $\frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} \le \frac{\lambda + r_{\hat{G}}(0) + c_3\sigma}{c_1\sigma(x_M - \sigma)}$.

In the same way as in the case (i) we obtain (if $c_3 \ne c_1$)

$$\begin{aligned}
\int_0^{x_M-\delta_0} e^{-\int_s^{x_M-\delta_0} \frac{\lambda + r_{\hat{G}}(\sigma)}{\Gamma(\sigma)} d\sigma} ds &\ge \int_0^{x_M-\delta_0} \left(\frac{s}{x_M - \delta_0}\right)^{\frac{\lambda + r_{\hat{G}}(0)}{c_1 x_M}} \left(\frac{\delta_0}{x_M - s}\right)^{\frac{\lambda + r_{\hat{G}}(0) + c_3 x_M}{c_1 x_M}} ds \\
&\xrightarrow{\lambda \to -r_{\hat{G}}(x_0)^+} \int_0^{x_M-\delta_0} \left(\frac{\delta_0}{x_M - s}\right)^{\frac{c_3}{c_1}} ds \\
&= \frac{c_1 x_M}{c_3 - c_1} \left(\frac{\delta_0}{x_M} - \left(\frac{\delta_0}{x_M}\right)^{\frac{c_3}{c_1}}\right).
\end{aligned}$$

Hence, for all $\delta_0 \in (0, x_M)$

$$KR(\lambda, A_{\hat{G}})f(x) \ge 2c_0 \left(\frac{c_1 x_M}{c_3 - c_1}\right) \left[\frac{\delta_0}{x_M} - \left(\frac{\delta_0}{x_M}\right)^{\frac{c_3}{c_1}}\right] \frac{1}{R - r_{\hat{G}}(0)},$$

and

$$\begin{aligned} KR(\lambda, A_{\hat{G}})f(x) &\geq \tfrac{2c_0 x_M}{R - r_{\hat{G}}(0)} \max_{y\in(0,1)} \tfrac{1}{\frac{c_3}{c_1}-1}\left(y - y^{\frac{c_3}{c_1}}\right) \\ &= \tfrac{2c_0 x_M}{R - r_{\hat{G}}(0)} \frac{1}{\left(\frac{c_3}{c_1}\right)^{\frac{c_3}{c_3-c_1}}} > 1 \end{aligned}$$

The case $c_3 = c_1$ is completely analogous. □

Theorem 3.1.3. Under the hypotheses on the model and one of those of Proposition 6, the operator $B_{\hat{G}} = A_{\hat{G}} + K$ has a (dominant) real eigenvalue $s(B_{\hat{G}})$, the corresponding eigenvector is positive and $s(B_{\hat{G}})$ is the unique eigenvalue of $B_{\hat{G}}$ with a positive eigenvector.

Proof. By the paragraph following the proof of Proposition 4, it follows immediately from Theorem 3.1.1 and Propositions 3, 4 and 6. □

What we have proved so far is that under the hypotheses on the model, whenever Proposition 6 holds, there exists a dominant eigenvalue of the operator $B_{\hat{G}}$. When $s(A_{\hat{G}}) = -r_{\hat{G}}(0) > -r_{\hat{G}}(x_M)$ the dominant eigenvalue does not always exist. In Proposition 6 we have given a sufficient condition for existence. The next result gives a sufficient condition for non existence.

Theorem 3.1.4. Under the hypotheses on the model, if $s(A_{\hat{G}}) = -r_{\hat{G}}(0) > -r_{\hat{G}}(x)$ for all $x \in (0, x_M)$ and

$$\sup_{(0,x_M)} \left(\frac{F(y)}{r_{\hat{G}}(y) - r_{\hat{G}}(0)} \right) < \frac{1}{2}, \tag{3.11}$$

then there is not a real eigenvalue larger than $s(A_{\hat{G}})$ with positive eigenvector of the operator $A_{\hat{G}} + K$.

Proof. Let us assume the existence of a real eigenvalue and a positive eigenvector of the operator $A_{\hat{G}} + K$, that is, a positive solution of the equation

$$(\lambda - A_{\hat{G}})u(x) = Ku(x).$$

Let us assume $\lambda > s(A_{\hat{G}}) = -r_{\hat{G}}(0)$. Then defining $w = Ku(x)$ we will have $u = R(A_{\hat{G}}, \lambda)w$ and $w = KR(A_{\hat{G}}, \lambda)w$. Integrating the operator K we first note that for all u,

$$\int_0^{x_M} Ku(x)dx = 2\int_0^{x_M}\int_x^{x_M}\frac{F(y)}{y}u(y)dydx = 2\int_0^{x_M}F(y)u(y)dy.$$

Integrating, interchanging integration order and finally integrating by parts, we obtain

$$\begin{aligned}
\int_0^{x_M} w(x)dx &= \int_0^{x_M} KR(A_{\hat{G}},\lambda)w(x)dx \\
&= 2\int_0^{x_M} F(y)R(A_{\hat{G}},\lambda)w(y)dy \\
&= 2\int_0^{x_M} F(y)\tfrac{1}{\Gamma(y)}\int_0^y e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}w(s)dsdy \\
&= 2\int_0^{x_M}\int_s^{x_M}\frac{F(y)}{r_{\hat{G}}(y)-r_{\hat{G}}(0)}\frac{r_{\hat{G}}(y)-r_{\hat{G}}(0)}{\Gamma(y)}e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}dy\, w(s)ds \\
&\le 2\sup_{(0,x_M)}\left(\frac{F(y)}{r_{\hat{G}}(y)-r_{\hat{G}}(0)}\right)\int_0^{x_M}\int_s^{x_M} -e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(0)}{\Gamma(\sigma)}d\sigma} \\
&\quad \frac{d}{dy}e^{\left(-\int_s^y \frac{r_{\hat{G}}(\sigma)-r_{\hat{G}}(0)}{\Gamma(\sigma)}d\sigma\right)}dy\, w(s)ds \\
&= 2\sup_{(0,x_M)}\left(\frac{F(y)}{r_{\hat{G}}(y)-r_{\hat{G}}(0)}\right) \\
&\quad \int_0^{x_M}\left(1-(\lambda+r_{\hat{G}}(0))\int_s^{x_M}\tfrac{1}{\Gamma(y)}e^{-\int_s^y \frac{\lambda+r_{\hat{G}}(\sigma)}{\Gamma(\sigma)}d\sigma}dy\right)w(s)ds \\
&\le 2\sup_{(0,x_M)}\left(\frac{F(y)}{r_{\hat{G}}(y)-r_{\hat{G}}(0)}\right)\int_0^{x_M} w(s)ds,
\end{aligned}$$

which obviously implies the necessary condition

$$\sup_{(0,x_M)}\left(\frac{F(y)}{r_{\hat{G}}(y)-r_{\hat{G}}(0)}\right)\ge\frac{1}{2}.$$

□

Remark 6. Notice that (3.11) does not hold if $L(x)$ decreases (which is assumed in [12], [13]). Indeed,

$$\frac{F(y)}{r_{\hat{G}}(y) - r_{\hat{G}}(0)} = \frac{F(y)}{F(y) + \frac{d_2}{\hat{G}+d_2}(L(y) - L(0))} > 1 \quad \text{for all} \quad y \in (0, x_M).$$

Remark 7. It is easy to see directly that if the hypotheses of Theorem 3.1.4 hold (nonexistence example), then

$$\frac{2c_0 x_M}{(\frac{c_3}{c_1})^{\frac{c_3}{c_3-c_1}}(\max_x r_{\hat{G}}(x) - r_{\hat{G}}(0))} < 1$$

meaning that we are not under the hypotheses of Proposition 6 (sufficient condition for existence). Indeed, (3.11) implies

$$\frac{2c_0 x_M}{(\frac{c_3}{c_1})^{\frac{c_3}{c_3-c_1}}(\max_x r_{\hat{G}}(x) - r_{\hat{G}}(0))} \leq \frac{2\frac{F(x_M)}{x_M}x_M}{(\frac{c_3}{c_1})^{\frac{c_3}{c_3-c_1}}(r_{\hat{G}}(x_M) - r_{\hat{G}}(0))} < \frac{1}{(\frac{c_3}{c_1})^{\frac{c_3}{c_3-c_1}}} < 1.$$

3.1.2 Properties of the function $\lambda_{\hat{G}}$ and existence and uniqueness of the non trivial steady state

The results proved above and the following proposition give the existence and uniqueness of a steady state of system (2.1).

Proposition 7. The dominant eigenvalue of the operator $B_{\hat{G}}$, $\lambda_{\hat{G}}$ is a strictly increasing and continuous function of $\hat{G}$.

Proof. $s(B_{\hat{G}})$ is a pole of $R(B_{\hat{G}}, \lambda)$ and $R(B_{\hat{G}}, \lambda)$ is strictly positive because $B_{\hat{G}}$ generates an irreducible semigroup (see [9]).
Moreover, since $B_{\hat{G}_1} \geq B_{\hat{G}_2}$ if $\hat{G}_1 > \hat{G}_2$,

$$R(B_{\hat{G}_1}, \lambda) - R(B_{\hat{G}_2}, \lambda) = R(B_{\hat{G}_1}, \lambda)(B_{\hat{G}_1} - B_{\hat{G}_2})R(B_{\hat{G}_2}, \lambda) \geq 0$$

for $\lambda > \max(s(B_{\hat{G}_1}), s(B_{\hat{G}_2}))$ and then Proposition A2 in [10] gives $s(B_{\hat{G}_1}) > s(B_{\hat{G}_2})$.
Continuity follows from standard perturbation results on eigenvalues (see [48]).

□

Theorem 3.1.5. Under the hypotheses of Theorem 3.1.3 let $\lambda_{\hat{G}}$ be the dominant eigenvalue and $p_{\hat{G}}$ the corresponding eigenvector of the operator $B_{\hat{G}}$. Let us assume that λ_0 is negative and that $\lambda_{G(0)}$ is positive. Then, then there exists a unique positive steady state of system (2.1) given by $\left(c_0 p_{\hat{G}_0}(x), \dfrac{c_0 L(x) p_{\hat{G}_0}(x)}{\hat{G}_0 + d_2}\right)$, where $\hat{G}_0$ is the unique zero of $\lambda_{\hat{G}}$ and

$$c_0 = \frac{G^{-1}(\hat{G}_0)}{\int_0^{x_M} \left(\phi^*(x) + \frac{L(x)\psi^*(x)}{\hat{G}_0 + d_2}\right) p_{\hat{G}_0}(x) dx}.$$

Proof. See Theorem 3.1.3, Proposition 7 and the beginning of section 3.1. □

Here we have proved the existence and the uniqueness of a steady state in the age independent case. In the next chapter we will show that for particular values of the parameters, there exist solutions that do not depend on the cyclin content. We will make numerical simulations for the general case obtaining, for some values of the parameters convergence to the steady state but also oscillations of the population for others.

Chapter 4

Oscillations on a cyclin-structured model

In the present chapter we are interested in the asymptotic behavior of the time dependent solutions of (2.1) also in the case of healthy tissue. We start by, in the first section, proving the existence, for some values of the parameters, of solutions of system (2.1) that do not depend on the cyclin content and hence satisfy an ordinary differential equations system. We analyze the complete asymptotic behavior of this ordinary differential equations system showing that the unique nontrivial steady state (when it exists) is asymptotically stable under some conditions and unstable when the reverse conditions hold. The instability appears through a Hopf bifurcation which leads to the existence of stable self-sustained oscillations of the populations. In section 4.2 we use a numerical scheme to illustrate the possible asymptotic behaviors of system (2.1). We obtain, depending on the values of the parameters, existence of stable and unstable equilibria as well as stable limit cycles. The equilibrium instability is linked to the delay caused by the quiescent stage. Moreover it arises when the reverse transition G from quiescent to proliferating depends essentially on the quiescent population. This result is similar to the one obtained in [38] where the authors study therapy strategies for cyclical neutropenia which is an haematological disease characterized by oscillations in the neutrophil population. They build a delayed differential equations model for the regulation of stem cells and neutrophil production in which the transition rate only depends on the quiescent population number and they also obtain oscillations of the population.

The numerical scheme we use is based on a discretization of system (2.1) by means of a time invariant grid, called the natural grid (see [64], [4], [50], [1]) which is obtained by an explicit integration of the characteristic equation.

The approximate solution is computed by means of a predictor-corrector method which numerically integrates the system along the characteristics as in [64] and [4]. It also involves the numerical computations of integrals corresponding to the non local term in the first equation in system (2.1). In contrast to [64] and [4], where at any time time step, integration over the whole interval is performed, we have to approximate the integral value at any point of the grid. To avoid algorithmic complication we use a trapezoidal quadrature rule (of second order accuracy). This explains the use of a second order Runge-Kutta method and not a higher order one. The presence of the non local term in system (2.1), modeling unequal cell division, is also the main difference with respect to the model in [1] from the point of view of numerical requirements.

Finally, in the Appendix we have performed two tests for the numerical scheme, the first one comparing the numerical solution to an exact solution for a simplified version of system (2.1) without non local terms, and the second one comparing the numerical solutions of system (2.1) in the case of x-independent solutions with the solutions of the corresponding ordinary differential system.

4.1 x-independent solutions

In this section we look for solutions of system (2.1) that do not depend on the cyclin content x, that is, solutions of the form $(p(t), q(t))$. From the second equation in (2.1) we obtain that, in order to have solutions that are independent of x we must impose that the leak function is constant, that is, we must assume $L(x) = L_0 > 0$. From the first equation in (2.1) we then have that an x-independent solution $(p(t), q(t))$ of (2.1) must satisfy the equality

$$\dot{p}(t) + \Gamma'(x)p(t) = -(L_0 + F(x) + d_1)p(t) + 2p(t)\int_x^{x_M} \frac{F(y)}{y} dy + G(N(t))q(t),$$

or, equivalently

$$\dot{p}(t) = -(L_0 + F(x) + \Gamma'(x) + d_1 - 2\int_x^{x_M} \frac{F(y)}{y} dy)p(t) + G(N(t))q(t),$$

which implies that

$$L_0 + F(x) + \Gamma'(x) + d_1 - 2\int_x^{x_M} \frac{F(y)}{y} dy \tag{4.1}$$

should be constant. Deriving, we have that the equality

$$F'(x) + \Gamma''(x) + 2\frac{F(x)}{x} = 0 \tag{4.2}$$

must hold. Solving (4.2) and using that $\lim_{x\to 0} \frac{F(x)}{x} =: b < \infty$ we have that

$$F(x) = -\frac{1}{x^2}\int_0^x s^2\Gamma''(s)\mathrm{d}s. \tag{4.3}$$

Substituting (4.3) in (4.1) and evaluating at $x = x_M$ we have that

$$L_0 + F(x) + \Gamma'(x) + d_1 - 2\int_x^{x_M} \frac{F(y)}{y} dy = L_0 + d_1 - A$$

with

$$A = \frac{1}{x_M^2}\int_0^{x_M} s^2\Gamma''(s)\mathrm{d}s - \Gamma'(x_M). \tag{4.4}$$

Notice that, integrating the above equation on the interval $(0, x_M)$ we also get $A = \frac{1}{x_M}\int_0^{x_M} F(x)\mathrm{d}x$.

So, system (2.1) has x-independent solutions $(p(t), q(t))$ if $L(x)$ is a constant L_0 and (4.3) holds. Conversely, if the same conditions hold and $(p(t), q(t))$ satisfies the ordinary differential equations system

$$\begin{cases} \dot{p} = (A - L_0 - d_1)p + G(N(t))q, \\ \dot{q} = L_0 p - (d_2 + G(N(t))q, \end{cases} \tag{4.5}$$

where $N := N(p,q) = p\int_0^{x_M}\phi(x)dx + q\int_0^{x_M}\psi(x)dx =: k_1p + k_2q$ with k_1, k_2 positive real numbers and A given by (4.4), then $(p(t), q(t))$ is an x-independent solution of system (2.1).

4.1.1 Equilibria

Let us now study the existence of equilibria of system (4.5) (which will imply the existence of x-independent equilibria of system (2.1) under the conditions above).

Proposition 8. System (4.5) has a unique non trivial equilibrium solution if and only if the inequalities

$$\frac{A}{d_1 + L_0} < 1 < \frac{A}{d_1 + L_0 \frac{d_2}{d_2 + G(0)}} \tag{4.6}$$

hold.

Proof. A non trivial equilibrium solution $(\hat{p}, \hat{q})$ of system (4.5) satisfies:

$$\begin{aligned} 0 &= (A - L_0 - d_1)\hat{p} + G(\hat{N})\hat{q} \\ 0 &= L_0\hat{p} - \big(G(\hat{N}) + d_2\big)\hat{q} \end{aligned}$$

that is, $\hat{p} = \frac{G(\hat{N})\hat{q}}{L_0 + d_1 - A} = \frac{\left(d_2 + G(\hat{N})\right)\hat{q}}{L_0}$, where $\hat{N} = k_1\hat{p} + k_2\hat{q}$.
Since $\hat{q} \neq 0$ this is equivalent to

$$G(\hat{N}) = \frac{(L_0 + d_1 - A)d_2}{A - d_1} \tag{4.7}$$

Since G is an strictly decreasing function that tends to zero then N tends to infinity, there will be a unique solution, $\hat{N}$ of (4.7) (and therefore a unique nontrivial equilibrium point) if and only if

$$0 < \frac{(L_0 + d_1 - A)d_2}{A - d_1} < G(0).$$

And easy computation shows that the previous inequalities are equivalent to (4.6). □

Remark 8. If we think of system (4.5) as a model for the dynamics of a population with two groups of individuals where A denotes the per capita birth rate of the first group, d_1 and d_2 the mortality rates and L_0 and $G(N)$ the transition rates between the two groups, then the inequalities (4.6) can be interpreted using the concept of the expected number of offspring of an individual in its lifespan R_0 assuming a constant value of the "interaction" variable N. Indeed, let us compute

R_0 for this model.

Let X be a random variable denoting the number of offspring in the lifespan of an individual and Z be a random variable taking the value 0 if an individual taken at random does not go to the quiescent stage, 1 if it goes once to the quiescent stage and returns back to the proliferating one, and so on. Note that $Z=0$ is the event that an exponentially distributed random variable with expected value $\frac{1}{L_0}$ takes a value larger than another independent exponentially distributed random variable with expected value $\frac{1}{d_1}$ and therefore $P(Z=0)=\frac{d_1}{d_1+L_0}$. In the same way we obtain that $P(Z=1)=\frac{L_0}{d_1+L_0}\frac{G(N)}{d_2+G(N)}\frac{d_1}{d_1+L_0}$, $P(Z=2)=\left(\frac{L_0}{d_1+L_0}\frac{G(N)}{d_2+G(N)}\right)^2\frac{d_1}{d_1+L_0}$,..., $P(Z=k)=\left(\frac{P(Z=1)}{P(Z=0)}\right)^k P(Z=0)$.
Then

$$\begin{aligned}
R_0(N) &= E(X)=\textstyle\sum_{k=0}^{\infty}E(X|Z=k)P(Z=k)\\
&= E(X|Z=0)P(Z=0)\textstyle\sum_{k=0}^{\infty}\left(\frac{P(Z=1)}{P(Z=0)}\right)^k\\
&= \tfrac{A}{d_1}\left(\tfrac{d_1}{d_1+L_0}\right)\textstyle\sum_{k=0}^{\infty}\left(\frac{L_0}{d_1+L_0}\frac{G(N)}{d_2+G(N)}\right)^k\\
&= \left(\tfrac{A}{d_1+L_0}\right)\left(\tfrac{1}{1-\frac{L_0G(N)}{(d_1+L_0)(d_2+G(N))}}\right)\\
&= \tfrac{A}{d_1+L_0\frac{d_2}{d_2+G(N)}}
\end{aligned}$$

where we have used that $E(X|Z=k)=E(X|Z=0)=\dfrac{A}{d_1}$ since system (4.5) assumes that the second group of individuals do not reproduce, $\dfrac{1}{d_1}$ is the expected lifetime of a reproducing individual and A the per capita and time unit fertility.

The inequalities (4.6) in Proposition 8 correspond to assuming $R_0(0)>1$ and $R_0(\infty)<1$ (recall that $G(\infty)=0$).

4.1.2 Asymptotic behavior

Proposition 9. Let us assume that $\frac{A}{d_1+L_0\frac{d_2}{d_2+G(0)}}\leq 1$. Then the trivial equilibrium is a global attractor of system (4.5).

Proof. First notice that if $A \leq d_1$ then $(p+q)' \leq 0$ and the claim follows. Now let us assume $A > d_1$ and notice that by hypothesis $L_0 + d_1 - A > 0$.

By the implicit function theorem, the isoclines of system (4.5) define functions $p = F_1(q)$ and $p = F_2(q)$ respectively through the relations

$$p = \frac{G(N(p,q))q}{L_0 + d_1 - A} \quad \text{and} \quad p = \frac{\big(d_2 + G(N(p,q))\big)q}{L_0}. \tag{4.8}$$

We obviously have $F_1(0) = F_2(0) = 0$. Moreover, for all positive q we have that $F_1(q) < F_2(q)$. Indeed, since $\frac{A}{d_1 + L_0 \frac{d_2}{d_2 + G(0)}} \leq 1$ or, equivalently $(L_0 + d_1 - A)d_2 - G(0)(A - d_1) \geq 0$, G is strictly decreasing and $A > d_1$ we have

$$(L_0 + d_1 - A)d_2 - G(N)(A - d_1) > 0$$

for all $N > 0$.
Let us now assume that there exists a positive $\hat{q}$ such that $\hat{p}_2 := F_2(\hat{q}) \leq F_1(\hat{q}) =: \hat{p}_1$. We will have

$$\hat{p}_2 = \frac{\big(d_2 + G(N(\hat{p}_2, \hat{q}))\big)\hat{q}}{L_0} \leq \hat{p}_1 = \frac{G(N(\hat{p}_1, \hat{q}))\hat{q}}{L_0 + d_1 - A}.$$

Hence

$$(L_0 + d_1 - A)d_2 - G(N(\hat{p}_2, \hat{q}))(A - d_1) \leq L_0(G(N(\hat{p}_1, \hat{q})) - G(N(\hat{p}_2, \hat{q}))) \leq 0$$

since $\hat{p}_2 \leq \hat{p}_1$, N is increasing as function of p and G is decreasing; a contradiction. Now notice that for any q_0, the regions $\{(p,q) : q \leq q_0 \quad \text{and} \quad p \leq F_2(q)\}$ are positively invariant and that any trajectory eventually enters some of them since $\lim_{q \to \infty} F_2(q) = \infty$ and $\dot{p}(t) < 0$ if $p(t) > F_2(q(t))$. These bounded regions cannot contain periodic orbits due to the direction of the vector field on the isocline lines. The statement about asymptotic behavior follows from the Bendixson-Poincaré theorem.

□

Proposition 10. Let us assume that $\frac{A}{d_1 + L_0} \geq 1$. Then all the trajectories of system (4.5) are unbounded.

Proof. Under this hypothesis only the isocline of horizontal vector field remains in the open first quadrant. The direction of the vector field in the first quadrant gives the statement. □

Remark 9. As before, the results can be interpreted in terms of R_0. The assumption in Proposition 9 is that $R_0 < 1$ in ideal conditions (zero population number) ensuring extinction. The assumption in Proposition 10 is that $R_0 > 1$ in starvation conditions (infinite population number) giving rise to unbounded population.

The two previous propositions give us the behavior of system (4.5) when there is not nontrivial steady state. Under the hypotheses of Proposition 8, system (4.5) has a unique non trivial steady state that can be written

$$(\hat{p}, \hat{q}) = \Big(\frac{\hat{N} d_2}{(A-d_1)k_2 + d_2 k_1}, \frac{\hat{N}(A-d_1)}{(A-d_1)k_2 + d_2 k_1}\Big)$$

where $\hat{N}$ is the unique solution of $G(\hat{N}) = \frac{(L_0+d_1-A)d_2}{A-d_1}$. Indeed, using (4.8) and (4.7) we have $\hat{p} = \frac{d_2}{A-d_1}\hat{q}$ and so $\hat{N} = k_1\hat{p} + k_2\hat{q} = (k_1\frac{d_2}{A-d_1} + k_2)\hat{q}$ which clearly implies the claim.

Theorem 4.1.1. Under the hypotheses of Proposition 8 the unique non trivial steady state $(\hat{p}, \hat{q})$ of system (4.5) is (locally) asymptotically stable whenever $\big(A - d_1 - L_0 - d_2 - G(\hat{N}) + \hat{q}G'(\hat{N})(k_1 - k_2)\big) < 0$ and it is unstable if the reverse strict inequality holds. In particular it is asymptotically stable if $k_1 \geq k_2$.

Proof. The Jacobian matrix of system (4.5) at the steady state is given by

$$J(\hat{p}, \hat{q}) = \begin{pmatrix} A - d_1 - L_0 + k_1 G'(\hat{N})\hat{q} & \hat{q}k_2 G'(\hat{N}) + G(\hat{N}) \\ L_0 - \hat{q}k_1 G'(\hat{N}) & -\hat{q}k_2 G'(\hat{N}) - (d_2 + G(\hat{N})). \end{pmatrix}$$

Denoting by λ_1 and λ_2 the two eigenvalues of $J(\hat{p}, \hat{q})$ and using (4.7) we have that

$$\lambda_1\lambda_2 = \hat{q}G'(\hat{N})\big(k_2(d_1 - A) - k_1 d_2\big).$$

Under the hypotheses of Proposition 8 which imply $A > d_1$ and since $G'(\hat{N}) < 0$ we then always have that $\lambda_1\lambda_2 > 0$. On the other hand

$$\lambda_1 + \lambda_2 = A - d_1 - L_0 - d_2 - G(\hat{N}) + \hat{q}G'(\hat{N})(k_1 - k_2),$$

giving the first statement. Assuming $k_1 \geq k_2$ we obtain using (4.6), that $\lambda_1 + \lambda_2 < 0$ which gives the second statement.

□

Since the previous theorem reduces the study of the stability of the non trivial steady state to the study of the sign of the trace of the Jacobian matrix, in the following we choose particular forms of the function G and find reasonable values of the parameters that make the trace negative and so give instability.

Let us take $G(N) = G(0)e^{-cN}$ and assume $k_2 > k_1$. Then using that $G(\hat{N}) = \frac{(L_0+d_1-A)d_2}{A-d_1}$, $\hat{q} = \frac{\hat{N}(A-d_1)}{(A-d_1)k_2+d_2k_1}$ and denoting by $A_1 := A - d_1$ we have

$$\begin{aligned}
\lambda_1 + \lambda_2 &= A_1 - L_0 - d_2 - \tfrac{(L_0-A_1)d_2}{A_1} + \tfrac{\hat{N}A_1}{A_1k_2+d_2k_1}\big(- c\tfrac{(L_0-A_1)d_2}{A_1}\big)(k_1 - k_2) \\
&= A_1 - L_0 - d_2 - \tfrac{(L_0-A_1)d_2}{A_1} - \frac{\ln\left(\frac{G(0)}{\frac{(L_0-A_1)d_2}{A_1}}\right)A_1}{A_1k_2+d_2k_1}\big(\tfrac{(L_0-A_1)d_2}{A_1}\big)(k_1 - k_2)
\end{aligned}$$

We can see then that $\lambda_1 + \lambda_2 < 0$ is equivalent to

$$\begin{aligned}
\ln(G(0)) &< \ln\left(\tfrac{(L_0-A_1)d_2}{A_1}\right) + \frac{\frac{A_1}{d_2}+\frac{L_0}{L_0-A_1}}{k-1}(k + \tfrac{d_2}{A_1}) \\
&=: H(k, L_0, A_1, d_2)
\end{aligned} \tag{4.9}$$

where we have denoted by $k = \frac{k_2}{k_1}$ (assuming $k_1 > 0$). Then, a necessary and sufficient condition for the eigenvalues to have negative real part is

$$G(0) < e^{H(k,L_0,A_1,d_2)}. \tag{4.10}$$

Whenever $G(0) = e^{H(k,L_0,A_1,d_2)}$ we will have purely imaginary eigenvalues. Considering H as a function of A_1 and d_2 it can be seen that the infimum value of H is

$$\lim_{A_1 \to 0} H(k, L_0, A_1, A_1) = \ln(L_0) + 2\Big(\frac{k+1}{k-1}\Big). \tag{4.11}$$

Indeed, let us consider, for fixed k and L_0, the function

$$h(u, v) = \ln v + \ln u + (\frac{1}{u} + \frac{L_0}{v})\frac{k+u}{k-1}$$

defined on $\mathbb{R}^{2+}$ and notice $H(k, L_0, A_1, d_2) = h(\frac{d_2}{A_1}, L_0 - A_1)$. Then we will have

$$\begin{aligned}
\inf_{\{(A_1,d_2)\in\mathbb{R}^{2+}:A_1<L_0\}} H(k, L_0, A_1, d_2) &= \inf_{\{(A_1,d_2)\in\mathbb{R}^{2+}:A_1<L_0\}} h(\tfrac{d_2}{A_1}, L_0 - A_1) \\
&= \inf_{\{(u,v)\in\mathbb{R}^{2+}:v<L_0\}} h(u, v) \\
&= h(1, L_0) = \ln L_0 + 2\tfrac{k+1}{k-1},
\end{aligned}$$

where the last but one equality is proven as follows. The function h is of class C^1 on $R := \{(u,v) \in \mathbb{R}^{2+} : v < L_0\}$ with limit equal to infinity at any point of the two coordinate axes as well as when u tends to infinity, with no critical points in R since $\frac{\partial h}{\partial v}(u,v) = \frac{1}{v^2}(v - L_0\frac{k+u}{k-1}) < 0$ for $v < L_0$ and such that has a (unique) minimum point on the remaining part of the boundary of R ($v = L_0$, i.e., $A_1 = 0$) at $u = 1$ ($d_2 = A_1$) since $\frac{\partial h}{\partial u}(u, L_0) = \frac{(u+k)(u-1)}{(k-1)u^2}$.
From (4.10) and (4.11) we have that, in particular, a sufficient condition for stability is

$$G(0) < L_0 e^{2\left(\frac{k+1}{k-1}\right)}.$$

Moreover, if $A_1 = d_2$ and they are small enough, then the reverse inequality gives instability. We use this to find moderate values of the parameters that lead to instability of the steady state giving rise to a limit cycle as can be seen in figure 4.1. The case $k_1 = 0$ can be analyzed in the same way.

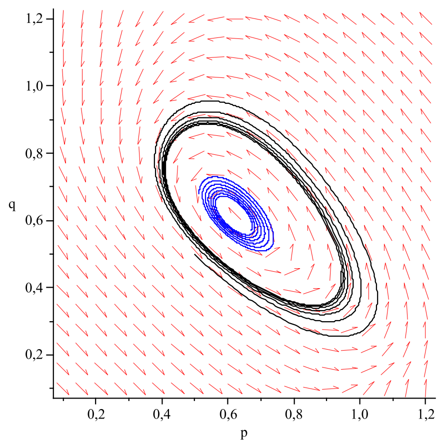

Figure 4.1: Illustration with $k = 6$, $A_1 = d_2 = 0.1$, $L_0 = 0.2, G(0) = 7.5$. Notice $G(0) = 7.5 > e^{H(6,0.2,0.1,0.1)} = 6.67$.

In a similar way, taking $G(N) = \dfrac{G(0)}{1+N^n}$ (which is the nonlinearity considered in [12] and [13]) we can find values of the parameters that also lead to instability of the steady state going to a limit cycle as can be seen in figure 4.2.

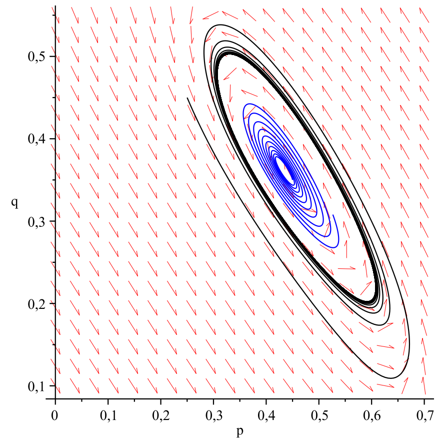

Figure 4.2: Illustration with $k = 4, n = 4$, $A_1 = 0.1, d_2 = 0.12$, $L_0 = 0.5, G(0) = 6.5$.

4.2 Numerical simulation

We now go back to the full problem (2.1) and describe a numerical scheme and the numerical results obtained by using it. In particular we emphasize the asymptotic behavior of x-dependent solutions, showing the existence of stable and unstable equilibria, as well as stable limit cycles, depending on the different values of the parameters. To begin with, following the lines of [64] and [4], we build up the so-called natural grid, i.e. a grid such that, in the case of a single equation, which is the situation in [4], consists of a set of points $\{(x_i, t_j) : -1 \leq i \leq n+1, 0 \leq j \leq m\}$ in such a way that (x_{i-1}, t_{j-1}) and (x_i, t_j) belong to the same characteristic line. Notice that (2.1) is a system of two first order partial differential equations and consequently, it has two families of (base) characteristic lines. This fact in general would complicate the build up of a natural grid, which should be such that the points of the grid are intersection points of characteristics of the two families.

Fortunately, the equations in (2.1) are autonomous and moreover, the characteristics of the second one are straight vertical lines in the plane (x, t). This allows to extend the procedure of [4] to our case, and we shall obtain a rectangular grid (with edges parallel to the coordinate axes) with uniform time step size and nonuniform x step size. On the other hand, since Γ vanishes at both ends of the interval $(0, x_M)$, $x = 0$ and $x = x_M$ will be characteristic lines (for both equations) whereas the other characteristics (of the first equation) will not cross the ends of the interval.

Let us call $\Psi(t;s,x)$ the solution of the initial value problem for the characteristic equation

$$z'(t)=\Gamma(z(t)), \quad z(s)=x,$$

and let us also define $\Phi(t,x)=\Psi(t;0,x)$. Unlike [4] we assume that this equation can be solved explicitly and so we have the exact solution. Indeed, our computations are all based in taking $x_M=1$ and $\Gamma(x)=x(1-x)$. We begin by choosing an arbitrary (small) positive number x_0 and compute T such that $\Phi(T,x_0)=1-x_0$. Then we take $n=[T\max(\Gamma)/x_0]+1$ (here [ ] stands for the integer part), the time step size $h=T/n$, a natural number $m\geq n$ and the grid defined by:

$$G=\{(x_i,t_j): t_j=jh, j=0,...,m, x_i=\Phi(t_i,x_0), i=0,...,n, x_{-1}=0, x_{n+1}=1\}.$$

and notice that

$$x_i=\Phi(t_i,x_0)=\Phi(h,\Phi(t_{i-1},x_0))=\Phi(h,x_{i-1})$$

and so $x_i-x_{i-1}\leq\max(\Gamma)h\leq x_0$. Hence, the size of the x steps is bounded by x_0.
We will use this grid to compute an approximate solution of the initial value problem for (2.1), with initial conditions $p(x,t)=p^0(x)$ and $q(x,t)=q^0(x)$.

Now we explain how to compute the approximate solution at time t_j given an approximate solution till time t_{j-1}. Let us assume that we already have an approximate solution up to time step $j-1$ (for some $j\geq 1$) given by the values (p_i^{j-1},q_i^{j-1}), at the points $(x_i,t_{j-1}), i=-1,...,n+1$, taking into account that $p_i^0=p^0(x_i), \quad q_i^0=q^0(x_i)$, and let us assume that $(p(x,t),q(x,t))$ is an exact solution to (2.1) such that $p(x_i,t_{j-1})=p_i^{j-1}$ and $q(x_i,t_{j-1})=q_i^{j-1}$. Let us also call $S(x,t)=2\int_x^1\frac{F(y)}{y}p(y,t)dy$ and $N(t):=\int_0^1\phi(x)p(x,t)+\psi(x)q(x,t)dx$.

Now we define, for $i=1,...,n$, $P_i(t)=p(\Psi(t;t_{j-1},x_{i-1}),t)$ and, for $i=-1,...,n+1$, $Q_i(t)=q(x_i,t)$. We also define $f(x,p,q,S,N):=-[\Gamma'(x)+L(x)+F(x)+d_1]p+G(N)q+S$ and $g(x,p,q,N):=L(x)p-(G(N)+d_2)q$. We will have, for $i=1,...,n$, the following ordinary differential equations

$$\begin{aligned}
\frac{dP_i}{dt}(t) &= p_t(\Psi(t;t_{j-1},x_{i-1}),t) + p_x(\Psi(t;t_{j-1},x_{i-1}),t)\Psi_t(t;t_{j-1},x_{i-1}) \\
&= p_t(\Psi(t;t_{j-1},x_{i-1}),t) + \Gamma(\Psi(t;t_{j-1},x_{i-1}))p_x(\Psi(t;t_{j-1},x_{i-1}),t) \\
&= f(\Psi(t;t_{j-1},x_{i-1}),P_i(t),q(\Psi(t;t_{j-1},x_{i-1}),t),S(\Psi(t;t_{j-1},x_{i-1}),t),N(t)), \\
P_i(t_{j-1}) &= p(x_{i-1},t_{j-1}) = p_{i-1}^{j-1},
\end{aligned}$$

and, for $i = -1, ..., n+1$,

$$\frac{dQ_i}{dt}(t) = g(x_i, p(x_i,t), q(x_i,t), N(t)),$$

$$Q_i(t_{j-1}) = q(x_i, t_{j-1}) = q_i^{j-1}.$$

Notice that the boundary values of P have to be treated specially, and in fact, the following holds for $P_{-1}(t) = p(0,t)$:

$$\frac{dP_{-1}}{dt}(t) = f(0, P_{-1}(t), q(0,t), S(0,t), N(t)), \quad P_{-1}(t_{j-1}) = p_{-1}^{j-1},$$

and the following for $P_{n+1}(t) = p(1,t)$:

$$\frac{dP_{n+1}}{dt}(t) = f(1, P_{n+1}(t), q(1,t), 0, N(t)), \quad P_{n+1}(t_{j-1}) = p_{n+1}^{j-1}.$$

So the next time step approximate solution, i.e., the values of the pair $(p_i^j, q_i^j) = (p(x_i,t_j), q(x_i,t_j))$, $i = -1, ..., n+1$, except p_0^j, can be approximately computed as the approximate values of $(P_i(t_j), Q_i(t_j))$ by means of a (single step application of an) explicit two stages Runge-Kutta method as the Heun's method or predictor-corrector method. Of course, the computation of the values of f and g involve quadratures (the values of $N(t_{j-1})$ and of $S(x_i, t_{j-1})$) which are simply approximated by the trapezoidal rule. The value of p_0^j is obtained by interpolation using p_{-1}^j and p_1^j since there is no previously computed value of p on the characteristic line through (x_0, t_j).

Going to some details, the numerical scheme works as follows. Let us first use the initial conditions to set $p_i^0 = p^0(x_i)$, $q_i^0 = q^0(x_i)$, $i = -1, ..., n+1$. Then, assuming we know p_i^{j-1} and q_i^{j-1} for $i = -1, ..., n+1$ and some $j \geq 1$, we compute the approximate solution for the next time step j in two steps. For the first one, let us set, using the trapezoidal rule,

$$N^{j-1} = \sum_{i=-1}^{n} (\phi(x_i)p_i^{j-1} + \psi(x_i)q_i^{j-1} + \phi(x_{i+1})p_{i+1}^{j-1} + \psi(x_{i+1})q_{i+1}^{j-1})\frac{x_{i+1} - x_i}{2},$$

$S_{n+1}^{j-1} = 0$, and,

$$S_i^{j-1} = 2\sum_{k=i}^{n} (\frac{F(x_k)p_k^{j-1}}{x_k} + \frac{F(x_{k+1})p_{k+1}^{j-1}}{x_{k+1}})\frac{x_{k+1} - x_k}{2}$$

for $i = -1, ..., n$ (here $\frac{F(x_{-1})}{x_{-1}}$ means $\lim_{x \to 0^+} \frac{F(x)}{x}$). Then we compute

$$k_{p,-1}^j = f(x_{-1}, p_{-1}^{j-1}, q_{-1}^{j-1}, S_{-1}^{j-1}, N^{j-1}),$$

$$k_{p,i}^j = f(x_{i-1}, p_{i-1}^{j-1}, q_{i-1}^{j-1}, S_{i-1}^{j-1}, N^{j-1}) \quad i = 1, ..., n,$$

$$k_{p,n+1}^j = f(x_{n+1}, p_{n+1}^{j-1}, q_{n+1}^{j-1}, S_{n+1}^{j-1}, N^{j-1}),$$

and $k_{q,i}^j = g(x_i, p_i^{j-1}, q_i^{j-1}, N^{j-1})$ for $i = -1, ..., n+1$.
Then we define the "predicted" values for p and q as

$$p_{-1}^{*j} = p_{-1}^{j-1} + hk_{p,-1}^j,$$

$$p_i^{*j} = p_{i-1}^{j-1} + hk_{p,i}^j \quad i = 1, ..., n,$$

$$p_{n+1}^{*j} = p_{n+1}^{j-1} + hk_{p,n+1}^j$$

and $q_i^{*j} = q_i^{j-1} + hk_{q,i}^j \quad i = -1, ..., n+1$.
As we have already said, the value of p_0^{*j} is obtained by interpolation. Namely, $p_0^{*j} = p_{-1}^{*j}(1 - \frac{x_0}{x_1}) + p_1^{*j}\frac{x_0}{x_1}$.
For the second step, almost as above, we set

$$N^{*j} = \sum_{i=-1}^{n} (\phi(x_i)p_i^{*j} + \psi(x_i)q_i^{*j} + \phi(x_{i+1})p_{i+1}^{*j} + \psi(x_{i+1})q_{i+1}^{*j})\frac{x_{i+1} - x_i}{2},$$

$S^{*j}_{n+1} = 0$, and,

$$S^{*j}_i = 2\sum_{k=i}^{n}(\frac{F(x_k)p^{*j}_k}{x_k} + \frac{F(x_{k+1})p^{*j}_{k+1}}{x_{k+1}})\frac{x_{k+1}-x_k}{2}$$

for $i = -1, ..., n$ (with the same meaning as above of $\frac{F(x_{-1})}{x_{-1}}$).
Analogously as above we now compute,

$$k^{*j}_{p,i} = f(x_i, p^{*j}_i, q^{*j}_i, S^{*j}_i, N^{*j})$$

for $i = -1, ..., n+1$ except $i = 0$, and

$$k^{*j}_{q,i} = g(x_i, p^{*j}_i, q^{*j}_i, N^{*j}) \quad i = -1, ..., n+1.$$

Finally we take the following "predicted-corrected" values for p and q,

$$p^j_{-1} = p^{j-1}_{-1} + \frac{h}{2}(k^j_{p,-1} + k^{*j}_{p,-1}),$$

$$p^j_i = p^{j-1}_{i-1} + \frac{h}{2}(k^j_{p,i} + k^{*j}_{p,i}) \quad i = 1, ..., n,$$

$$p^j_{n+1} = p^{j-1}_{n+1} + \frac{h}{2}(k^j_{p,n+1} + k^{*j}_{p,n+1})$$

and $q^j_i = q^{j-1}_i + \frac{h}{2}(k^j_{q,i} + k^{*j}_{q,i}) \quad i = -1, ..., n+1$,
and, again by interpolation, $p^j_0 = p^j_{-1}(1 - \frac{x_0}{x_1}) + p^j_1\frac{x_0}{x_1}$.

We have performed some tests of validity of the numerical scheme which are developed in the appendix. The first one consists in the comparison between the approximate solution given by the method and the exact solution to a local partial differential system with the same main part (i.e., the part containing the partial derivatives) as system (2.1). In the second one we compare the approximate solution given by the method in the case when there are x-independent solutions, i.e., when $L(x) \equiv L_0, F(x) = \frac{2x}{3}$ (since (4.3) with $\Gamma(s) = s(1-s)$), and the initial conditions are x-independent with the "exact" solution of System (4.5).

Applying the numerical scheme to system (2.1) we observe different kind of behavior depending on the parameter values that we show in figures 4.3, 4.4 and 4.5.

Note that in order to attain a particular final time (different and not an integer multiple of T defined at the beginning of the section) we have modified slightly the construction of the natural grid.

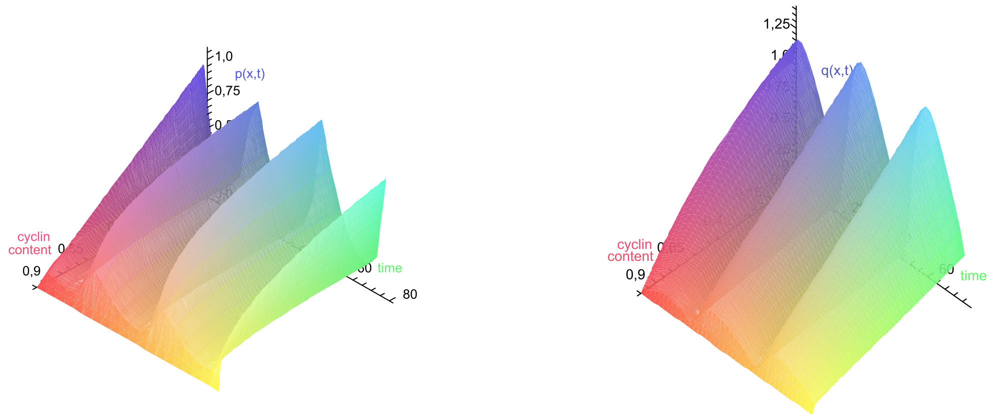

Figure 4.3: Illustration for oscillation behavior with numerical parameters $x_0 = 0.02, T_f = 80, n = 98, m = 980, h = 0.0816$ and with the model parameters $L(x) = 0.4 - \frac{x}{4}, F(x) = 0.9x, d_1 = 0.2333, d_2 = 0.12, G(x) = \frac{8}{1+x^5}, \phi(x) \equiv 1, \psi(x) \equiv 5$ and $p(x,0) = 1 - x, q(x,0) = 1 - x^2$.

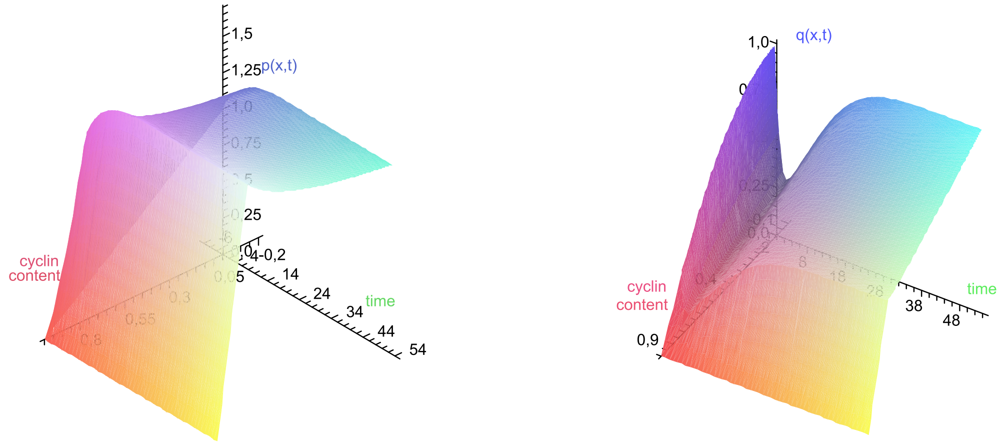

Figure 4.4: Illustration for convergence to equilibria behavior with $x_0 = 0.02, T_f = 55, n = 98, m = 980, h = 0.056$ and with the parameters $L(x) = 0.4 - \frac{x}{4}, F(x) = 0.6x, d_1 = 0.1, d_2 = 0.15, G(x) = \frac{5}{1+x^2}, \phi(x) \equiv 1, \psi(x) \equiv 3$ and $p(x,0) = 1 - x, q(x,0) = 1 - x^2$.

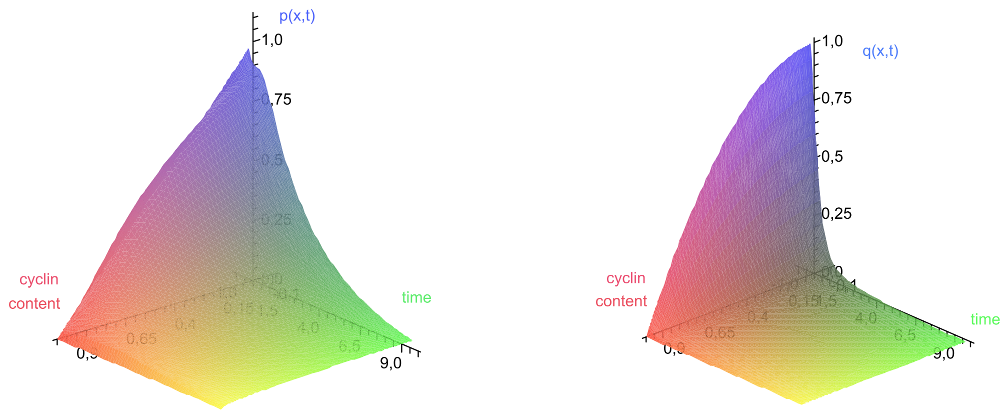

Figure 4.5: Illustration for extinction behavior with $x_0 = 0.02, T_f = 10, n = 100, m = 125, h = 0.08$ and with the parameters $L(x) = 0.4 - \frac{x}{4}, F(x) = x, d_1 = 0.7, d_2 = 1, G(x) = \frac{5}{1+x^2}, \phi(x) \equiv 1, \psi(x) \equiv 5$ and $p(x,0) = 1 - x, q(x,0) = 1 - x^2$.

Chapter 5

Renewal equations

In the following we will consider a variation of the model presented in section 2.1 and studied along Chapters 2, 3 and 4. This model was proposed and worked out in an oral communication by Odo Diekmann and is based on the so-called cumulative or delayed formulation of the structured population dynamics ([28] and [29]).

This is a work in progress. Our aim is to use the theory of delay equations in order to linearize around the equilibrium points and obtain a characteristic equation to study the asymptotic behavior of solutions, which could not be done with traditional techniques of partial differential equations.

5.1 The model

We consider a model based on the one introduced by Bekkal Brikci et al. (see [12] and [13]), but using a different approach and different techniques. Our model is similar to the one studied in the first chapters of this thesis but with some different hypotheses on the biological system. As in the previous chapters, cells are structured by the content of cyclin x which is limited by some constant $x_M > 0$. Here we assume that only cells with a large content of cyclin can divide, i.e., there exists some positive constant $x_b < x_M$ such that if a cell has less cyclin than x_b, then it is not able to divide. We also assume that when a cell divides, both resulting cells from this division have cyclin content bigger than some positive constant x_m and smaller than x_b (notice that this requires that $x_b \geq \frac{x_M}{2}$ and $x_m \leq \frac{x_b}{2}$). When the cyclin content x of a cell is less than x_b, it can be in the proliferating or in the quiescent stage whereas division can only occur in the proliferating stage and when $x > x_b$ and it happens with rate $F(x)$ (we recall from previous chapters that F is a positive bounded function). Cells can also leave the proliferating stage by apoptosis (programmed cell death) which occurs with rate d_1 depending on cyclin content (different from what was assumed in the preceding chapters). The other way to leave the proliferating stage is to go to the quiescent one.

Another difference is that cells in the proliferating stage can only go to the quiescent stage once and only when they have less cyclin content than x_b. This transition occurs according to a "leak" function $L(x)$ (which as before, we assume positive and bounded). In the quiescent stage cells do not change their cyclin content and only can leave this stage by two ways. One way is by apoptosis which is assumed to happen with rate d_2 that depends on cyclin content (also different from what was assumed before) and the other way is going back to the proliferating stage. This transition rate is denoted by I which is a function $G(N)$ where N stands for a weighted population number as in the previous chapters.

Here we will assume that both death rates $d_1(x)$ and $d_2(x)$ are bounded below by a positive constant.

Proliferating cells increase their cyclin content. The function $\Gamma(x)$ represents the growth rate (evolution speed) of the cyclin content of each individual cell. $\Gamma(x)$ is a smooth strictly positive function of $x \in [x_m, x_M)$ vanishing at x_M.

With this we can define the function $A(x, \xi)$ which is the time a cell needs to increase its cyclin content from ξ to x ignoring a possible quiescent phase, i.e.,

$$A(x, \xi) := \int_\xi^x \frac{d\sigma}{\Gamma(\sigma)}.$$

Let us denote by $\mathcal{F}_0(x, \xi)$ the probability that a cell does not die and does not go to the quiescent stage while it increases its cyclin content from ξ to $x < x_b$. This is given by

$$\mathcal{F}_0(x, \xi) := e^{-\int_\xi^x \frac{d_1(\sigma)+L(\sigma)}{\Gamma(\sigma)} d\sigma}.$$

In the same way, for cells that have already been in the quiescent stage and came back to the proliferating stage we define the function $\mathcal{F}_1(x, \xi)$ as the survival probability from ξ to x, i. e., the probability that a cell does not die while it increases its cyclin content from ξ to x , i. e.,

$$\mathcal{F}_1(x,\xi) := e^{-\int_\xi^x \frac{d_1(\sigma)}{\Gamma(\sigma)}d\sigma}$$

for $x_m \le \xi \le x \le x_b$.

Finally, let $\mathcal{F}_2(x,\xi)$ be the survival probability from ξ to x, where $x_b \le \xi < x \le x_M$, that is, the probability that a (proliferating) cell does not die nor divide while it increases its cyclin content from ξ to x. This is given by

$$\mathcal{F}_2(x,\xi) := e^{-\int_\xi^x \frac{d_1(\sigma)+F(\sigma)}{\Gamma(\sigma)}d\sigma}.$$

Defining $u(t)$ as the flux at the point x_b, we can express the density n at time t of cells with cyclin content x as

$$n(t,x) = \frac{1}{\Gamma(x)}u(t - A(x_b,x))\mathcal{F}_2(x_b,x),$$

where $x_b < x < x_M$.

In terms of these quantities we compute the population birth rate at time t with cyclin content η as

$$b(t,\eta) = 2\int_{x_b}^{x_M} \widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)u(t - A(\theta,x_b))d\theta,$$

where $\widehat{\psi}(\theta,\cdot)$ is the probability density of the cyclin content of a daughter cell of a dividing cell with cyclin content $\theta > x_b$. For further use, we assume that $\widehat{\psi}$ is a bounded function, by a constant $\widehat{\psi}_\infty$. This is a slight generalization of the previous chapters where we assumed a uniform distribution of the cyclin content of the newborn cells.

Notice that when $\theta < x_b + x_m$ then $supp\widehat{\psi}(\theta,\cdot) \subset [x_m, \theta - x_m]$ and that when $\theta > x_b + x_m$ (obviously only possible if $x_b + x_m < x_M$) then $supp\widehat{\psi}(\theta,\cdot) \subset [\theta - x_b, x_b]$. Moreover, $\widehat{\psi}(\theta,\theta-\eta) = \widehat{\psi}(\theta,\eta)$ which implies that the expected cyclin content of the daughter is $\int \eta\widehat{\psi}(\theta,\eta)d\eta = \frac{\theta}{2}$.

Let us also define $p_0(t,x)$ as the density of cells at time t and cyclin content $x < x_b$ that are in the proliferating stage but never were in the quiescent stage, which is given by

$$p_0(t,x) = \frac{1}{\Gamma(x)}\int_{x_m}^{x} b(t - A(x,\eta),\eta)\mathcal{F}_0(x,\eta)d\eta.$$

The density of quiescent cells will be denoted by $q(t, \zeta)$. This is given by all the proliferating cells with cyclin content ζ that changed to quiescent in the past and are still alive and remain quiescent. That is

$$q(t,\zeta) = \int_0^{+\infty} L(\zeta) p_0(t-\tau,\zeta) e^{-d_2(\zeta)\tau - \int_{t-\tau}^{t} I(\sigma)d\sigma} d\tau.$$

Finally, the density of proliferating cells at time t and cyclin content $x < x_b$ that have been quiescent is

$$p_1(t,x) = \frac{1}{\Gamma(x)} \int_{x_m}^{x} q(t-A(x,\zeta),\zeta) I(t-A(x,\zeta)) \mathcal{F}_1(x,\zeta) d\zeta.$$

By substitution we can write p_0 and p_1 as follows

$$p_0(t,x) = \frac{2}{\Gamma(x)} \int_{x_m}^{x} \int_{x_b}^{x_M} \widehat{\psi}(\theta,\eta) \frac{F(\theta)}{\Gamma(\theta)} \mathcal{F}_2(\theta,x_b) \mathcal{F}_0(x,\eta) \\ u(t-A(x,\eta)-A(\theta,x_b)) d\theta d\eta, \tag{5.1}$$

$$p_1(t,x) = \frac{1}{\Gamma(x)} \int_{x_m}^{x} \int_0^{+\infty} L(\zeta) p_0(t-\tau-A(x,\zeta),\zeta) e^{-d_2(\zeta)\tau - \int_{t-\tau-A(x,\zeta)}^{t-A(x,\zeta)} I(\sigma)d\sigma} d\tau \\ I(t-A(x,\zeta)) \mathcal{F}_1(x,\zeta) d\zeta. \tag{5.2}$$

5.2 Renewal equation

Let us now introduce parameterized families of linear functionals on the space of histories of u (the space of integrable real valued functions defined on $(-\infty, 0]$).

Let us define $u_t(\tau) := u(t+\tau)$ for $-\infty < \tau \leq 0$.
From (5.1) we write

$$\Gamma(x) p_0(t,x) = \mathcal{L}_0(x) u_t$$

where $\mathcal{L}_0(x)$ is a linear map from $L_1((-\infty, 0]; \mathbb{R})$ into $\mathbb{R}$ given explicitly by

$$\mathcal{L}_0(x)\phi = 2\int_{x_m}^{x}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x,\eta)\phi(-A(x,\eta)-A(\theta,x_b))d\theta d\eta.$$

Similarly from (5.2) we write

$$\Gamma(x)p_1(t,x) = \mathcal{L}_1(x,I_t)u_t$$

where

$$\mathcal{L}_1(x,\psi)\phi := \int_{x_m}^{x}\int_0^{+\infty}\frac{L(\zeta)}{\Gamma(\zeta)}\mathcal{L}_0(\zeta)\phi_{-\tau-A(x,\zeta)}e^{-d_2(\zeta)\tau-\int_{-\tau-A(x,\zeta)}^{-A(x,\zeta)}\psi(\sigma)d\sigma}$$

$$\psi(-A(x,\zeta))\mathcal{F}_1(x,\zeta)d\tau d\zeta.$$

With this we can write a renewal equation

$$u(t) \quad = \quad \Gamma(x_b)p_0(t,x_b) + \Gamma(x_b)p_1(t,x_b),$$

i.e.,

$$u(t) = \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b,I_t)\big)u_t, \tag{5.3}$$

which expresses the fact that the flux crossing the point x_b is given by the sum of the flux of proliferating cells that never were into the quiescent stage plus the flux of proliferating cells that have been quiescent once.

The expression for $\mathcal{L}_0(x_b)$ and $\mathcal{L}_1(x_b,I_t)$ can be simplified somewhat as follows.

Defining for $x_m \le \eta \le \theta \le x_M$,

$$\mathcal{F}(\theta,\eta) := e^{-\int_\eta^\theta \frac{d_1(\sigma)+F(\sigma)}{\Gamma(\sigma)}d\sigma}$$

where we adopt the convention that $F(\sigma) = L(\sigma)$ for $\sigma < x_b$ (we can do this because this functions have disjoint support), we have

$$\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x_b,\eta) = \mathcal{F}(\theta,\eta).$$

Moreover, $A(\theta,x_b) + A(x_b,\eta) = A(\theta,\eta)$ and then we obtain

$$\mathcal{L}_0(x_b)\phi = 2\int_{x_m}^{x_b}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\phi(-A(\theta,\eta))d\theta d\eta.$$

In the case of $\mathcal{L}_1$, we multiply and divide by $e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}$ and use the identities $\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x_b,\zeta)\mathcal{F}_0(\zeta,\eta) = \mathcal{F}(\theta,\eta)$, and $A(\theta,x_b)+A(x_b,\zeta)+A(\zeta,\eta) = A(\theta,\eta)$. We have to use a three step version of these identities and compensate the fact that from ζ to x_b we have survival described by $\mathcal{F}_1$ (and not by $\mathcal{F}_0$).

$$\mathcal{L}_1(x_b,\psi)\phi := 2\int_{x_m}^{x_b}\int_0^{+\infty}\frac{L(\zeta)}{\Gamma(\zeta)}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_m}^{\zeta}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)$$

$$\phi(-\tau-A(\theta,\eta))d\theta d\eta\,\psi(-A(x_b,\zeta))e^{-d_2(\zeta)\tau-\int_{-\tau-A(x_b,\zeta)}^{-A(x_b,\zeta)}\psi(\sigma)d\sigma}d\tau d\zeta.$$

5.2.1 Constant I

When I is independent of time (and positive), the linear renewal equation (5.3) is time-translation invariant, with a positive kernel. Exponential growth or decay is fully determined by the value of $R_0(I)$ relative to 1, where $R_0(I)$ is the integral of the kernel.

Indeed, left us first prove the following

Proposition 11. For any $I \geq 0$, the operator

$$\mathcal{L}_I := \mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)$$

is a positive bounded linear form on the space $L^1_\rho(\mathbb{R}_-,\mathbb{R})$ of the locally integrable functions such that

$$\int_{-\infty}^{0} e^{\rho\theta}|u(\theta)|d\theta < \infty$$

for any $\rho \in (0, d_0)$ where $d_0 := \min(d_1, d_2)$, $d_1 := \inf d_1(z)$ and $d_2 := \inf d_2(z)$.

Proof. This can be directly seen as follows:

$$|\mathcal{L}_0(x_b)\phi| \leq 2\widehat{\psi}_\infty F_\infty \int_{x_m}^{x_b}\int_{x_b}^{x_M}\frac{\mathcal{F}(\theta,\eta)}{\Gamma(\theta)}|\phi(-A(\theta,\eta))|d\theta d\eta$$

$$\leq 2\widehat{\psi}_\infty F_\infty \int_{x_m}^{x_b}\int_{x_b}^{x_M} \frac{e^{-d_1 A(\theta,\eta)}}{\Gamma(\theta)}|\phi(-A(\theta,\eta))|d\theta d\eta$$

$$\leq 2\widehat{\psi}_\infty F_\infty \int_{x_m}^{x_b}\int_0^\infty e^{-d_1 t}|\phi(-t)|dtd\eta = 2\widehat{\psi}_\infty F_\infty \int_0^\infty\int_{x_m}^{x_b} d\eta e^{-d_1 t}|\phi(-t)|dt$$

$$= 2\widehat{\psi}_\infty F_\infty (x_b - x_m)\int_0^\infty e^{-d_1 t}|\phi(-t)|dt = 2\widehat{\psi}_\infty F_\infty (x_b - x_m)\int_{-\infty}^0 e^{d_1 s}|\phi(s)|ds,$$

where we made (for any η) the change of variables $A(\theta,\eta) = t$ in the third inequality and we interchanged the integration limits in the subsequent equality.

So, for $\rho \leq d_1$ and $C = 2\widehat{\psi}_\infty F_\infty (x_b - x_m)$ we have that

$$|\mathcal{L}_0(x_b)\phi| \leq C\|\phi\|_{L^1_\rho}.$$

For $\mathcal{L}_1$ we have to make a similar but more complicated computation. Let us start by noting that, as above,

$$\left|\int_{x_m}^{\zeta}\int_{x_b}^{x_M} \widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\phi(-\tau - A(\theta,\eta))d\theta d\eta\right|$$

$$\leq \int_{x_m}^{x_b}\int_{x_b}^{x_M} \widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)|\phi(-\tau - A(\theta,\eta))|d\theta d\eta$$

$$\leq \widehat{\psi}_\infty F_\infty (x_b - x_m)\int_0^\infty e^{-d_1 t}|\phi(-\tau - t)|dt$$

$$\leq \widehat{\psi}_\infty F_\infty (x_b - x_m)e^{d_1\tau}\int_{-\infty}^{-\tau} e^{d_1 s}|\phi(s)|ds.$$

Let us use this in the computation of a bound for $\mathcal{L}_1$,

$$|\mathcal{L}_1(x_b, I)\phi| \leq 2\int_{x_m}^{x_b}\int_0^{+\infty} \frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\left[\int_{x_m}^{\zeta}\int_{x_b}^{x_M} \widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\right.$$

$$\left.|\phi(-\tau - A(\theta,\eta))|d\theta d\eta\right] I e^{-d_2(\zeta)\tau - I\tau}d\tau d\zeta$$

$$\leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \int_{x_m}^{x_b} \int_0^{+\infty} \frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)} d\sigma} \left[e^{d_1 \tau} \int_{-\infty}^{-\tau} e^{d_1 s} |\phi(s)| ds \right] e^{-d_2(\zeta)\tau} d\tau d\zeta$$

$$\leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \int_0^{A(x_b,x_m)} \int_0^{+\infty} L_\infty e^{L_\infty t} e^{(d_1-d_2)\tau} \int_{-\infty}^{-\tau} e^{d_1 s} |\phi(s)| ds d\tau dt$$

$$= 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \Big(e^{L_\infty A(x_b,x_m)} - 1 \Big) \int_0^{+\infty} \int_{-\infty}^{-\tau} e^{(d_1-d_2)\tau} e^{d_1 s} |\phi(s)| ds d\tau$$

$$= 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \Big(e^{L_\infty A(x_b,x_m)} - 1 \Big) \int_{-\infty}^{0} e^{d_1 s} |\phi(s)| \int_0^{-s} e^{(d_1-d_2)\tau} d\tau ds$$

At this point we consider three cases:
$i)$ $d_1 < d_2$:
We have that, for $s < 0$,

$$\int_0^{-s} e^{(d_1-d_2)\tau} d\tau < \int_0^{+\infty} e^{-(d_2-d_1)\tau} d\tau = \frac{1}{(d_2 - d_1)}$$

which implies that

$$|\mathcal{L}_1(x_b, I)\phi| \leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \Big(e^{L_\infty A(x_b,x_m)} - 1 \Big) \frac{1}{(d_2 - d_1)} \int_{-\infty}^{0} e^{d_1 s} |\phi(s)| ds.$$

Then, for $\rho \leq d_1$ and $C = 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \Big(e^{L_\infty A(x_b,x_m)} - 1 \Big) \frac{1}{(d_2 - d_1)}$, we have the claim.

$ii)$ $d_1 = d_2$:
Using that $xe^{-\alpha x} \leq \frac{1}{\alpha e}$ for any $\alpha > 0$, then for any $\rho < d_1$, we have that

$$|\mathcal{L}_1(x_b, I)\phi| \leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I \Big(e^{L_\infty A(x_b,x_m)} - 1 \Big) \int_{-\infty}^{0} -s e^{d_1 s} |\phi(s)| ds$$

$$= 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big) \int_{-\infty}^{0} -s e^{(d_1-\rho)s} e^{\rho s} |\phi(s)| ds$$

$$\leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big) \frac{1}{(d_1-\rho)e} \int_{-\infty}^{0} e^{\rho s} |\phi(s)| ds = C_\rho \|\phi\|_{L^1_\rho},$$

where $C_\rho = 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big) \dfrac{1}{(d_1-\rho)e}$.

$iii)$ $d_1 > d_2$:

In this case we take $\rho < d_2$ and using the Mean Value Theorem for the function e^z we have that

$$\int_{-\infty}^{0} e^{d_1 s} |\phi(s)| \int_{0}^{-s} e^{(d_1-d_2)\tau} d\tau ds = \int_{-\infty}^{0} \frac{e^{-(d_1-d_2)s} - 1}{d_1 - d_2} e^{d_1 s} |\phi(s)| ds$$

$$= \int_{-\infty}^{0} \frac{e^{d_2 s} - e^{d_1 s}}{d_1 - d_2} |\phi(s)| ds = \int_{-\infty}^{0} (-s) \frac{e^{(d_2-\rho)s} - e^{(d_1-\rho)s}}{(d_2-\rho)s - (d_1-\rho)s} e^{\rho s} |\phi(s)| ds$$

$$= \int_{-\infty}^{0} (-s) e^{z(s)} e^{\rho s} |\phi(s)| ds \leq \int_{-\infty}^{0} (-s) e^{-(d_2-\rho)(-s)} e^{\rho s} |\phi(s)| ds$$

$$\leq \frac{1}{(d_2-\rho)e} \int_{-\infty}^{0} e^{\rho s} |\phi(s)| ds,$$

where $(d_1 - \rho)s < z(s) < (d_2 - \rho)s$ and we used the same inequality as in case ii.

So, taking $C_\rho = 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big) \dfrac{1}{(d_2-\rho)e}$ we have

$$|\mathcal{L}_1(x_b, I)\phi|$$

$$\leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big) \int_{-\infty}^{0} e^{d_1 s} |\phi(s)| \int_{0}^{-s} e^{(d_1-d_2)\tau} d\tau ds$$

$$\leq 2\widehat{\psi}_\infty F_\infty(x_b - x_m) I\Big(e^{L_\infty A(x_b,x_m)} - 1\Big)\frac{1}{(d_2-\rho)e}\int_{-\infty}^0 e^{\rho s}|\phi(s)|ds = C_\rho\|\phi\|_{L^1_\rho}.$$

In the three cases, taking $\rho < d_0$ the claim follows.

□

By the Riesz representation theorem, then there exists a positive kernel $k \in L^\infty_\rho(\mathbb{R}_+, \mathbb{R})$ such that

$$\mathcal{L}_I u = \int_0^\infty k(s)u(-s)ds.$$

In fact it is immediate to show that k belongs to $L^1_\rho(\mathbb{R}_+, \mathbb{R})$, for any $\rho \in (0, d_0)$ (see Corollary 3.2, [30]).

Indeed, let us take $\rho' < \rho$. Then

$$\|k\|_{L^1_{\rho'}} = \int_0^\infty e^{\rho' s}|k(s)|ds = \int_0^\infty e^{(\rho'-\rho)s}e^{\rho s}|k(s)|ds$$

$$\leq \|k\|_{L^\infty_\rho}\int_0^\infty e^{(\rho'-\rho)s}ds = \frac{1}{\rho-\rho'}\|k\|_{L^\infty_\rho}.$$

So, in the case of constant I, equation (5.3) can be written as a linear renewal equation

$$u(t) = \int_0^\infty k(s)u(t-s)ds.$$

It is well known that the behaviour of the solutions of the last equation depend on the roots of the equation $1 - \hat{k}(\lambda) = 0$, where $\hat{k}$ is the Laplace transform of the kernel k, which has an abscissa of convergence not large than d_0 (see [41]).

In particular, all the solutions of (5.3) decay at an exponential rate ρ if there are no roots with real part larger than $-\rho$ (see Theorem 3.12 from [30]), whereas there are solutions exponentially increasing if and only if there is a positive root of $\hat{k}(\lambda) = 1$.

The "only if" claim follows from the fact that $\hat{k}$ is a strictly decreasing function with limit 0 at infinity when restricted to real arguments. Hence, since a complex (non real) root satisfies

$$1 = Re\,\hat{k}(\lambda) < \hat{k}(Re\lambda),$$

this implies the existence of a real root larger than $Re\lambda$.

Finally, the mentioned properties of $\hat{k}$ as a function of real argument also imply that there is a positive root if and only if

$$1 < \hat{k}(0) = \int_0^\infty k(s)ds = \mathcal{L}_I\mathbf{1} =: R_0(I).$$

This allows us to state the following theorem

Theorem 5.2.1. Let us consider a constant positive I in the linear renewal equation

$$u(t) = \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)\big)u_t = \mathcal{L}_I u_t.$$

Then

$a)$ All the solutions of the equation tend exponentially to 0 if $R_0(I) = \mathcal{L}_I\mathbf{1} < 1$.

$b)$ If $R_0(I) > 1$, there are solutions which grow exponentially.

So, let us compute

$$\begin{aligned} R_0(I) &= \Big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)\Big)\mathbf{1} \\ &= 2\int_{x_m}^{x_b}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\tfrac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta \\ &+ 2\int_{x_m}^{x_b}\tfrac{L(\zeta)}{\Gamma(\zeta)}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\tfrac{I}{I+d_2(\zeta)}\int_{x_m}^{\zeta}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\tfrac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta d\zeta \end{aligned}$$

Since $R_0(I)$ is a monotone increasing function, the equation

$$R_0(I) = 1$$

has a unique solution $I = \bar{I}$ in $(0, +\infty)$ if and only if $R_0(0) < 1$ and $R_0(\infty) > 1$. Moreover, note that

$$R_0(0) = 2\int_{x_m}^{x_b}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta$$

while, integrating by parts after computing the limit when I tends to ∞,

$$
\begin{aligned}
R_0(\infty) &= 2\int_{x_m}^{x_b} e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta \\
&= 2\int_{x_m}^{x_b}\mathcal{F}_1(x_b,\zeta)\int_{x_b}^{x_M}\widehat{\psi}(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta.
\end{aligned}
$$

Remark 10. In the case that d_2 does not depend on cyclin content, we can compute a little further using also integration-by-parts for the second integral. This leads to

$$
R_0(I) = 2\frac{d_2}{I+d_2}\int_{x_m}^{x_b}\left(1+\frac{I}{d_2}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\right)\int_{x_b}^{x_M}\widehat{\psi}(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta.
$$

5.2.2 Feedback

Let N be the weighted total population size. Here, to avoid confusion, we will change the name of the weights. We will use $w(x)$ for proliferating and $\hat{w}(x)$ for quiescent cells. Then, we define the weighted total population size by

$$
\begin{aligned}
N(t) &:= \int_{x_m}^{x_b}\left[w(x)\big(p_0(t,x)+p_1(t,x)\big)+\hat{w}(x)q(t,x)\right]dx+\int_{x_b}^{x_M}w(x)n(t,x)dx \\
&= \int_{x_b}^{x_M}\frac{w(x)}{\Gamma(x)}\mathcal{F}(x,x_b)u(t-A(x,x_b))dx \\
&+ \int_{x_m}^{x_b}\left[\frac{w(x)}{\Gamma(x)}\Big(\mathcal{L}_0(x)u_t+\mathcal{L}_1(x,I_t)u_t\Big)+\widehat{w}(x)\mathcal{L}_2(x,I_t)u_t\right]dx
\end{aligned}
$$

where

$$
\begin{aligned}
\mathcal{L}_2(x,\psi)\phi &:= 2\int_0^{+\infty}\frac{L(x)}{\Gamma(x)}\int_{x_m}^{x}\int_{x_b}^{x_M}\widehat{\psi}(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)\mathcal{F}(x,\eta) \\
&\quad \phi(-\tau-A(x,\eta)-A(x_b,\theta))\,d\theta d\eta e^{-d_2(x)\tau-\int_{-\tau}^0\psi(\sigma)d\sigma}d\tau.
\end{aligned}
$$

Now defining

$$
\begin{aligned}
\mathcal{L}_N(\psi)\phi &= \int_{x_b}^{x_M}\frac{w(x)}{\Gamma(x)}\mathcal{F}_2(x,x_b)\phi(-A(x,x_b))dx \\
&+ \int_{x_m}^{x_b}\left[\frac{w(x)}{\Gamma(x)}\Big(\mathcal{L}_0(x)+\mathcal{L}_1(x,\psi)\Big)+\widehat{w}(x)\mathcal{L}_2(x,\psi)\right]\phi dx
\end{aligned}
$$

we can write

$$
N(t) = \mathcal{L}_N(I_t)u_t.
$$

So, if we finally require

$$I(t) = G(N(t)),$$

then the nonlinear system of renewal equations is given by

$$\left\{ \begin{array}{rcl} u(t) & = & \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I_t)\big)u_t \\ I(t) & = & G(\mathcal{L}_N(I_t)u_t). \end{array} \right. \tag{5.4}$$

The first thing that we are interested in showing is the existence and uniqueness of solution for this system.

5.3 Existence and Uniqueness of solution

In order to show the existence and uniqueness of solution for the system (5.4) we use the theory developed by Odo Diekmann and Mats Gyllenberg. As a reference we suggest the works [28], [29] and [30].

Let us write

$$x(t) = \begin{pmatrix} u(t) \\ I(t) \end{pmatrix},$$

and

$$F\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, y_2)\big)y_1 \\ \\ \mathcal{G}(\mathcal{L}_N(y_2)y_1). \end{pmatrix},$$

Then (5.4) is equivalent to the renewal equation

$$x(t) = F(x_t) \tag{5.5}$$

where

$$x_t(\theta) = \begin{pmatrix} u_t(\theta) \\ I_t(\theta) \end{pmatrix} = \begin{pmatrix} u(t+\theta) \\ I(t+\theta) \end{pmatrix}, \forall \theta \leq 0.$$

We will prove existence and uniqueness of solution for (5.5) plus some initial condition

$$x(\theta) = \phi(\theta), \text{for } \theta \in (-\infty, 0]. \tag{5.6}$$

Following the work [29] we will show the existence and uniqueness of solution for an abstract integral equation (AIE) associated to our problem and after, we will show the equivalence between the two formulations.

5.3.1 Abstract Integral Equation (AIE)

Here we consider the history space X as the space $L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ with the norm defined by

$$\|\psi\| = \int_{-\infty}^{0} e^{\rho\theta}|\psi(\theta)|d\theta, \text{ for } \psi \in X.$$

Let be $T_0 := \{T_0(t)\}_{t\geq 0}$ be a strongly continuous semigroup of bounded linear operators on $X = L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ with infinitesimal generator A_0. Strong continuity means that

$$\lim_{t\to 0} \|T_0(t)\phi - \phi\|_{L^1_\rho} = 0, \ \forall \phi \in X.$$

The adjoint of T_0 is $T_0^* := \{T_0^*(t)\}_{t\geq 0}$ where $T_0^*(t) : X^* \to X^*$ is the adjoint operator of $T_0(t)$. T_0^* is a semigroup on the dual space X^*.

Now one defines the sun-subspace of the dual space X^* where the adjoint operator T_0^* is strongly continuous, i.e.,

$$X^{\odot} := \{\phi^* \in X^* | \lim_{t\to 0} \|T_0^*(t)\phi^* - \phi^*\| = 0\}.$$

When T_0 is defined by translation to the left and extension by 0, one can show (see [20], [40], [56] for the case with $\rho = 0$ and [29] for the case with weight) that $L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)^{\odot} = BUC_\rho(\mathbb{R}_+;\mathbb{R}^2)$ where the space of exponentially bounded and uniformly continuous functions is endowed with the norm

$$\|\phi^{\odot}\|^{\infty}_{\rho} = \sup_{\theta\in\mathbb{R}_+} e^{\rho\theta}\|\phi^{\odot}(\theta)\|_{\infty} < \infty.$$

For $x \in X, \phi \in X^{\odot}, \phi^{\odot *} \in X^{\odot *}$ we will use the convention that

$$\phi(x) =< x, \phi > \text{ and } \phi^{\odot *}(\phi) =< \phi^{\odot *}, \phi > .$$

With this we will define the linear duality mapping $j : X \to X^{\odot *}$ by

$$< jx, \phi >=< x, \phi >= \phi(x), \ \ x \in X, \phi \in X^{\odot}.$$

If $x \neq y$, then there exist ϕ in $X^{\odot}$ such that $\phi(x) \neq \phi(y)$, which implies that j is an injection.

Defining $T_0(t)$ as the semigroup of translations to the left and extension by 0 and using the variation of constants formula we can write the following Abstract Integral Equation (AIE):

$$u(t) = T_0(t)\varphi + j^{-1}\int_0^t T_0{}^{\odot *}(t-s)(l \circ F)(u(s))ds \,, \tag{5.7}$$

where $F : X \to \mathbb{R}^2$ is a nonlinear map and $l : \mathbb{R}^2 \to X^{\odot *}$ is a bounded linear injection given by

$$< lx, \phi >= x \cdot \phi(0) \;\text{ for all }\; x \in \mathbb{R}^2, \;\; \phi \in X^{\odot}$$

where $\cdot$ is the scalar product in $\mathbb{R}^2$ and evaluation at 0 is well defined since ϕ is a continuous function.

We need that the integral that appears in (5.7) belongs to the range of j and in order to use Banach fixed point theorem to prove the existence and uniqueness of solution we need an estimate of the integral.

The authors in [29] make the following assumption:

Hypothesis 5.3.1. There exist $M \geq 1$ and $\lambda \in \mathbb{R}$ such that for any continuous function $h : \mathbb{R} \to \mathbb{R}^2$ and all $t > 0$ one has

$$\int_0^t T_0{}^{\odot *}(t-s)lh(s)ds \;\in\; j(X),$$

$$\|j^{-1}\int_0^t T_0{}^{\odot *}(t-s)lh(s)ds\| \leq M\int_0^t e^{\lambda(t-s)}|h(s)|ds.$$

For the case of renewal equations that this hypothesis holds (with $\lambda = -\rho$) is proven in [29], Corollary 2.4 and [30], Corollary 3.5.

The main result that we need at this point is the following:

Theorem 5.3.1. Let Hypothesis 5.3.1 hold and assume that F is (globally) Lipschitz continuous. Then for all $\varphi \in X$, the Abstract Integral Equation has a unique solution $u(t) = \Sigma(t)\phi$ on $[0, +\infty)$. The family $\{\Sigma(t)\}_{t\geq 0}$ of nonlinear operators is a semigroup on X.

Diekmann and Gyllenberg prove this theorem in [29] and [30]. With this at hand, they prove the equivalence between the AIE formulation and the nonlinear renewal equation 5.5 in Theorem 3.7 in [30] (see also [29], Theorem 3.2).

For the sake of completeness we also give this theorem

Theorem 5.3.2. Let $\varphi \in X = L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ be given.

$a)$ Suppose that $x \in L^1_{loc}((-\infty,\infty);\mathbb{R}^2)$ satisfies (5.5) with an initial condition $x(\theta) = \varphi(\theta)$, for $\theta \in (-\infty, 0]$. Then the function $u : [0,\infty) \to X$ defined by $u(t) := x_t$ is continuous and satisfies the abstract integral equation (AIE).

$b)$ If $u : [0,\infty) \to X$ is continuous and satisfies the abstract integral equation, then the function x defined by

$$x(t) := \begin{cases} \varphi(t) & \text{for } -\infty < t < 0, \\ F(u(t)) & \text{for } t \geq 0, \end{cases}$$

specifies an element of $L^1_{loc}((-\infty,\infty);\mathbb{R}^2)$ and satisfies 5.5 with an initial condition $x(\theta) = \varphi(\theta)$, for $\theta \in (-\infty, 0]$.

The hypothesis of global Lipschitzianity of the function F is rather restrictive and, in fact, it is clear that it does not hold for our F (for instance, even if we erase the exponential factor containing one of the arguments, $\mathcal{L}_1$ is still bilinear).

Nevertheless, standard variations of the statements of Theorem 5.3.1 and Theorem 5.3.2 could be proven in the case of local Lipschitz condition (see [25]) substituting global existence by the well known result that a solution is defined on a bounded maximal interval only if it escapes to infinity.

On the other hand, since F leaves invariant the positive cone of X, the solutions with positive initial conditions will remain positive.

5.4 Steady state and linearization

Obviously, $(0, G(0))$ is a trivial stationary solution of (5.4).

To find a nontrivial steady state of (5.4), we first need to be able to solve

$$R_0(I) = 1.$$

Since R_0 is a monotone increasing function, $R_0(0) < 1 < R_0(\infty)$ are necessary and sufficient condition in order that this equation has a (unique) solution I. Then any constant u satisfies the first renewal equation in 5.4 if we put $I(t) \equiv \bar{I}$. We find the right constant $\bar{u}$ from the second equation:

$$\bar{u} = \frac{1}{\mathcal{L}_N(\bar{I})\mathbf{1}} G^{-1}(\bar{I}) \tag{5.8}$$

provided that $\bar{I}$ belongs to the image of $[0, +\infty)$ under G. Since G is monotonously decreasing, this amounts to $G(\infty) < \bar{I} < G(0)$. Summarizing, we can state

Proposition 12. Assuming that G is strictly monotone decreasing, (5.4) has a (unique) non-trivial stationary solution if and only if

$$R_0(G(\infty)) < 1 < R_0(G(0)).$$

Now we are interested in linearizing system (5.4) in order to write a characteristic equation which can help us to find stability criteria for the steady state.

Let us introduce into (5.4) the following "translation to the origin" change of variables

$$\begin{cases} u(t) &= \bar{u} + y(t), \\ I(t) &= \bar{I} + z(t), \end{cases} \tag{5.9}$$

where $\bar{u}$ is given by (5.8) and $\bar{I}$ is the unique solution for $R_0(I) = 1$.

In order to prove a linearized stability principle (see Theorem 3.25, [30]) around $(y, z) = (0, 0)$ we need that the function $F : L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \longrightarrow \mathbb{R}^2$ defined by

$$\begin{pmatrix} u \\ I \end{pmatrix} \mapsto \begin{pmatrix} \mathcal{L}_0 u + \mathcal{L}_1(I)u \\ G(\mathcal{L}_N(I)u). \end{pmatrix}$$

is of class $\mathcal{C}^1$.

We can decompose this function in this way:
Let $B : \mathbb{R}^2 \longrightarrow \mathbb{R}^2$ be defined as

$$B\begin{pmatrix} x \\ y \end{pmatrix} \mapsto \begin{pmatrix} x \\ G(y) \end{pmatrix}.$$

As G is a continuous differentiable function, B is of class $\mathcal{C}^1$.

Let $C : L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \times \left(L^1_\rho(\mathbb{R}_-, \mathbb{R}^2)^*\right)^3 \longrightarrow \mathbb{R}^2$ be defined by

$$\begin{pmatrix} u \\ \phi \\ \psi \\ \gamma \end{pmatrix} \mapsto \begin{pmatrix} < u, \phi > + < u, \psi > \\ < u, \gamma > \end{pmatrix}.$$

Note that C is a smooth function.

If we define the map $D : L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \longrightarrow L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \times \left(L^1_\rho(\mathbb{R}_-, \mathbb{R}^2)^*\right)^3$ by

$$\begin{pmatrix} u \\ I \end{pmatrix} \mapsto \begin{pmatrix} u \\ \mathcal{L}_0 \\ \mathcal{L}_1(I) \\ \mathcal{L}_N(I). \end{pmatrix},$$

then we have that

$$F \begin{pmatrix} u \\ I \end{pmatrix} = B\left(C\left(D\begin{pmatrix} u \\ I \end{pmatrix}\right)\right)$$

and to show that F is continuous differentiable is equivalent to show that D is continuously differentiable.

This is still in progress. Even though proving the differentiability of D, which essentially amounts to proving the differentiability of $\mathcal{L}_1(\cdot)$, seems attainable, the computation of the representation kernel $k \in L^\infty_\rho(\mathbb{R}_+, \mathbb{R}^2)$ and hence, that of the characteristic equation $\det\left(I - \hat{k}(\lambda)\right) = 0$ is clearly much more difficult.

Appendix for the numerical simulations

The first test that we have performed compares the approximate solution given by the method and the exact solution of the following system

$$\begin{cases} \dfrac{\partial}{\partial t}u(x,t) + \dfrac{\partial}{\partial x}\big(x(1-x)u(x,t)\big) = u(x,t) + v(x,t), \\ \dfrac{\partial}{\partial t}v(x,t) = -v(x,t), \end{cases} \tag{1}$$

for $t > 0$ and $x \in [0,1]$, supplemented by initial conditions of the form $u(x,0) = u^0(x)$ and $v(x,0) = v^0(x)$. System (1) can obviously be reduced to a single p.d.e. of the form

$$\frac{\partial}{\partial t}u(x,t) + x(1-x)\frac{\partial}{\partial x}u(x,t) = 2xu(x,t) + v^0(x)e^{-t}, u(x,0) = u^0(x).$$

Assuming that u^0 and v^0 are C^1 functions, the method of characteristics yields an explicit solution of the above problem in the form

$$u(x,t) = [\frac{e^t\Phi(-t,x)}{x}]^2 u_0(\Phi(-t,x)) + \frac{xe^{-t}}{(1-x)^3}[F(x) - F(\Phi(-t,x))], \; s \in (0,1), \; t \in \mathbb{R},$$

where $\Phi(t,x)$ is given, as above, by the solution of the initial value problem

$$z'(t) = \Gamma(z(t)), \quad z(0) = x,$$

and F is a primitive of the function $(\frac{1}{y} - 1)^2 v^0(y)$. This can be checked by means of a straightforward but tedious computation. Obviously, $v(x,t) = v^0(x)e^{-t}$.

The numerical scheme for this system has to be adapted somehow and of course it turns to be simpler. In particular, we simply have $f(x,u,v) = 2xu + v, g(x,u,v) = -v$.

Table 1 shows the comparative results when one chooses $u^0(x) = 1 - x^2$ and $v^0(x) = x^2$. The column "error" (relative error in L^1 norm) is evaluated as

$$\frac{\int_0^1 (|u_a(x,t) - u(x,t)|dx + \int_0^1 |v_a(x,t) - v(x,t)|dx}{\int_0^1 (|u(x,t)| + |v(x,t)|)dx},$$

where the subscript "a" refers to "approximate". Here we consider $T_f = 1$.

Table 1:

x_0	n	h	m	CPU time in seconds	error
0.02	117	0.0666	15	-	$1.5 \cdot 10^{-3}$
0.015	168	0.05	20	0.5	$8.7 \cdot 10^{-4}$
0.01	230	0.04	25	1	$5.5 \cdot 10^{-4}$
0.005	530	0.02	50	4.7	$1.4 \cdot 10^{-4}$
0.002	1612	0.0077	130	42	$2.1 \cdot 10^{-5}$
0.001	3519	0.00392	255	228	$5.6 \cdot 10^{-6}$

The second test that we have performed compares the approximate solution given by the numerical method with the solution of the ordinary differential System (4.5) for values of the parameters that give x-independent solutions and convergence to the steady state. The parameters used are $L(x) = 0.4, F(x) = \frac{2x}{3}, \phi(x) = 1, \psi(x) = 3, d_1 = 0.1333, d_2 = 0.15, G(N) = \frac{5}{1+N^2}$ and the initial conditions $p(x,0) = 1$ and $q(x,0) = 0.7$. The results are shown in Table 2.

In Table 3 the parameters have been chosen like in Figure 4.2 in such a way that we compare approximate solutions given by the method and solutions to System (4.5) in the case of oscillations. The parameters used are $L(x) = 0.5, F(x) = \frac{2x}{3}, \phi(x) = 1, \psi(x) = 4, d_1 = 0.2333, d_2 = 0.12, G(N) = \frac{6.5}{1+N^4}$ and the initial conditions $p(x,0) = 0.25$ and $q(x,0) = 0.45$.

Table 2:

T_f	x_0	n	h	m	CPU time in seconds	error
1	0.1	22	0.2	5	< 0.1	$5 \cdot 10^{-5}$
	0.05	59	0.1	10	< 0.1	$1.3 \cdot 10^{-5}$
	0.01	230	0.04	25	2.5	$2 \cdot 10^{-6}$
	0.002	1612	0.0077	130	99	$5 \cdot 10^{-8}$
10	0.1	12	0.333	30	0.2	$1.7 \cdot 10^{-5}$
	0.05	30	0.2	50	1	$5.8 \cdot 10^{-5}$
	0.01	234	0.0385	260	18	$2.1 \cdot 10^{-6}$
	0.002	1554	0.00772	1295	1000	$1 \cdot 10^{-7}$
50	0.1	11	0.4545	110	1	$8.9 \cdot 10^{-9}$
	0.05	30	0.1666	300	5	$1.3 \cdot 10^{-9}$

Table 3:

T_f	x_0	n	h	m	CPU time in seconds	error
1	0.1	22	0.2	5	< 0.1	$5.6 \cdot 10^{-4}$
	0.01	230	0.04	25	4	$2.4 \cdot 10^{-5}$
	0.002	1612	0.0077	130	122	$1.7 \cdot 10^{-6}$
10	0.1	12	0.333	30	< 1	$2.6 \cdot 10^{-3}$
	0.01	234	0.0385	260	37	$4 \cdot 10^{-5}$
50	0.1	11	0.4545	110	1	0.02
	0.05	30	0.1666	300	7	$3.3 \cdot 10^{-3}$

Bibliography

[1] Abia, L., Angulo, O., López-Marcos, J.C. and López-Marcos, M.A., *Numerical schemes for a size-structured cell population model with equal fission*, Mathematical and Computer Modelling, 50 (2009), 653-664.

[2] Adimy, M. and Pujo-Menjouet, L., *Asymptotic behavior of a singular transport equation modelling cell division*, Discrete Contin. Dyn. Syst. Ser. B, 3(3) (2003), 439-456.

[3] Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. and Watson, J. D., *Molecular Biology of the Cell*, Garland, New York, 1994.

[4] Angulo, O. and López-Marcos, J. C., *Numerical schemes for size-structured population equations*, Math. Biosci. 157(1-2) (1999), 169-188.

[5] Arino, O. and Kimmel, M., *Asymptotic analysis of a cell cycle model based on unequal division*, Siam J. Appl. Math., 47 (1987), 128-145.

[6] Arino, O. and Kimmel, M., *Asymptotic behavior of a nonlinear functional-integral equation of cell kinetics with unequal division*, J. Math. Biol, 27 (1989), 341-354.

[7] Arino, O., *A survey of structured cell population dynamics*, Acta Biotheor., 43 (1995), 3-25.

[8] Arino, O., Sánchez, E. and Webb, G.F., *Necessary and sufficient conditions for asynchronous exponential growth in age structured cell populations with quiescence*, J. Math. Anal. Appl, 215(2) (1997), 499-513.

[9] Arendt, W., Grabosch, A., Greiner, G., Groh, U., Lotz, H.P., Moustakas, U., Nagel, R., Neubrander, F. and Schlotterbeck, U. *One-parameter Semigroups of Positive Operators*. Lecture Notes in Mathematics, 1184. Springer-Verlag, Berlin, 1986.

[10] Arendt, W. and Batty C. J. K., *Principal eigenvalues and perturbation*. Operator theory in function spaces and Banach lattices, 39 - 55, Oper. Theory Adv. Appl., 75. Birkhauser, Basel, 1995.

[11] Bagowski, C. P., Besser, J., Frey, C. R. and Ferrell, J. E., *The JNK cascade as a biochemical switch in mammalian cells: ultrasensitive and all-or-none responses*, Curr. Biol. 13(4) (2003), 315-320.

[12] Bekkal Brikci, F., Clairambault, J., Ribba, B. and Perthame, B., *An age-and-cyclin-structured cell population model with proliferation and quiescence*, J. Math. Biol. 57(1) (2008), 91-110.

[13] Bekkal Brikci, F., Clairambault, J. and Perthame, B., *Analysis of a molecular structured population model with possible polinomial growth for the cell division cycle*, Math. Comput. Model. 47(7-8) (2008), 699-713.

[14] Bekkal-Brikci, F., Chiorino, G. and Boushaba, K., *G1/S transition and cell population dynamics*, Netw. Heterog. Media 4(1) (2009), 67-90.

[15] Bell, G. and Anderson, E., *Cell growth and division. Mathematical model with applications to cell volume distributions in mammalian suspension cultures*, Biophys. J. 7 (1967) 329-351.

[16] Bertuzzi, A., Gandolfi, A. and Giovenco, M.A., *Mathematical models of the cell cycle with a view to tumor studies*, Math. Biosci. 53 (1981), 159-188.

[17] Borges, R., Calsina, À. and Cuadrado, S., *Equilibria of a cyclin structured cell population model*, Discrete Contin. Dyn. Syst. Ser. B, 11 (2009), 613-627.

[18] Borges, R., Calsina, À. and Cuadrado, S., *Oscillations in a molecular structured cell population model*, Nonlinear Anal. Real World Appl. 12(4) (2011), 1911-1922.

[19] Brézis, H., *Analyse fonctionelle : théorie et applications*, Masson, Paris [etc.], 1983.

[20] Butzer P. L. and Berens, H., *Semi-Groups of Operators and Approximation*, Springer-Verlag, Berlin, Heidelberg, New York, 1967.

[21] Calsina, A. and Cuadrado, S., *Small mutation rate and evolutionary stable strategies in infinite dimensional adaptive dynamics*. J. Math Biol., 48 (2004), 135-159.

[22] Calsina, A., Palmada, J. M. and Ripoll, J., *Optimal latent period in a bacteriophage population model structured by infection-age*, Mathematical Models and Methods in Applied Sciences, 21(4) (2011), 693-718.

[23] Clément, Ph., Heijmans, H.J.A.M., Angenent, S., Van Duijn, C.J. and de Pagter, B., *One-parameter Semigroups*, CWI Monographs, 5. North-Holland Publishing Co., Amsterdam, 1987.

[24] Clément Ph., Diekmann, O., Gyllenberg, M., Heijmans, H.J.,A.M. and Thieme H.R., *Perturbation theory for dual semigroups. I. The sun reflexive case*, Math. Ann., 277 (1987), 709-725.

[25] Clément, Ph., Diekmann, O., Gyllenberg, M., Heijmans, H.J.A.M. and Thieme,H.R., *Perturbation theory for dual semigroups III. Nonlinear Lipschitz continuous perturbations in the sun reflexive case.* In Proceedings of the Conference on Volterra integro-differential equations in Banach spaces and applications, Trento 1987, G. Da Prato and M. Iannelli (Eds.), Pitman research Notes in Mathematics Series, 190, 67-89, 1989.

[26] Diekmann, O., Gyllenberg, M., Thieme, H. and Lunel. S. V., *A cell-cycle model revised*, Report AM-R9305, CWI, 1992.

[27] Diekmann, O. and Heesterbeek, J. A. P., *Mathematical Epidemiology of Infective Diseases: Model Building, Analysis and Interpretation*, New York: Wiley, 2000.

[28] Diekmann, O., Getto, P. and Gyllenberg, M., *Stability and bifurcation analysis of Volterra functional equations in the light of suns and stars*, SIAM J. Math Anal. 39(4) (2007/08), 1023-1069.

[29] Diekmann, O. and Gyllenberg, M., *Abstract delay equations inspired by population dynamics*, In Functional analysis and evolution equations, Amann, H., Arendt, W., Hieber, M., Neubrander, F., Nicaise, S. and von Below, J. (Eds.) Birkhauser, Basel, 187-200, 2007.

[30] Diekmann, O. and Gyllenberg, M., *Equations with infinite delay: blending the abstract and the concrete*, J. Differential Equations 252(2) (2012), 819-851.

[31] Doumic, M., *Analysis of a population model structured by the cells molecular content*, Math. Model. Nat. Phenom. 2 (2007), 121-152.

[32] Ducrot A. and Magal, P., *Travelling wave solutions for an infection-age structured epidemic model with external supplies*, Nonlinearity, 24 (2011), 2891-2911.

[33] Dyson, J.,Villella-Bressan, R. and Webb, G. F., *A nonlinear age and maturity structured model of population dynamics. II. Chaos*, J. Math. Anal. Appl. 242(2) (2000), 255-270.

[34] Dyson, J., Villella-Bressan, R. and Webb, G., *Asynchronous exponential growth in an age structured population of proliferating and quiescent cells*, Mathematical biosciences, 177-178 (2002), 73-83.

[35] Dyson, J., Vilella-Bressan, R. and Webb, G., *The steady state of a maturity structured tumor cord cell population*, Mathematical models in cancer (Nashville, TN, 2002). Discrete Contin. Dyn. Syst. Ser. B, 4 (2004), 115-134.

[36] Engel, K-J. and Nagel, R., *One-parameter semigroups for linear evolution equations: an IC design perspective*, Springer-Verlag, New York, Boston, 2000.

[37] Euler, L., *Recherches générales sur la mortalité et la multiplication du genre humain*, Mémoires de l´Académie Royale des Sciences et Belles Lettres de Berlin, 16 (1767), 144-164.

[38] Foley, C., Bernard, S. and Mackey, M. C., *Cost-effective G-CSF therapy strategies for cyclical neutropenia: Mathematical modelling based hypotheses*, J. Theor. Biol. 238(4) (2006), 754-763.

[39] Garijo, A., Gasull, A. and Jarque, X., *Normal forms for singularities of one dimensional holomorphic vector fields*, Eletronic Jounal of Differential Equations, 122 (2004), 1-7.

[40] Greiner, G. and van Neerven, J.M.A.M., *Adjoints of semigroups acting on vector valued function spaces*, Israel Journal of Mathematics, 77 (1992), 305-333.

[41] Gripenberg, G., *Volterra integral and functional equations*, Cambridge University Press, 1990.

[42] Gurtin, M. E. and MacCamy, R. C., *Non-linear age-dependent population dynamics*, Archive for Rational Mechanics and Analysis, 54(3) (1974), 281-300.

[43] Guzman, M. de, *Ecuaciones diferenciales ordinarias: teoria de estabilidad y control*, Alhambra, Madrid, 1980.

[44] Gyllenberg, M. and Webb, G., *Age-size structure in populations with quiescence*, Math. Biosci. 86(1) (1987), 67-95.

[45] Gyllenberg, M. and Webb, G., *A nonlinear structured population model of tumor growth with quiescence*, Journal of Mathematical Biology, 28 (1990), 671-694.

[46] Hartwell, L.H. and Kastan, M.B., *Cell cycle control and cancer*, Science, 266 (1994), 1821-1828.

[47] Hitomi, M. and Stacey, D. W., *Cellular ras and cyclin D1 are required during different cell cycle phases in cycling NIH 3T3 cells*, Mol. Cell. Biol. 19(7) (1999), 4623-4632.

[48] Kato, T., *Perturbation theory for linear operators*. Die Grundlehren der mathematischen Wissenschaften, Band 132. Springer-Verlag, New York, 1966.

[49] Kimmel, M., Darzynkiewicz, Z., Arino, O. and Traganos, F., *Analysis of a cell cycle model based on unequal division of metabolic constituents to daughter cells during cytokinesis*, J. Theor. Biol. 110(4) (1984), 637-664.

[50] Kostova, T., *An explicit third-order numerical method for size-structured population equations*, Numer. Methods Partial Differential Equations 19(1) (2003), 1-21.

[51] McKendrick, A. G., *Applications of mathematics to medical problems*, Proceedings of the Edinburgh. Mathematics Society, 44 (1926), 98-130.

[52] Malthus, T. R., *An essay on the principle of population*, Printed for J. Johnson, in St. Paul´s Church-Yard, London, 1798.

[53] Metz J.A.J., and Diekmann, O., *The dynamics of physiologically structured populations* (Amsterdam, 1983). Lecture Notes in Biomath, 68. Springer, Berlin, 1986.

[54] Michel, P., *Existence of a solution to the cell division eigenproblem*, Math. Models Methods Appl. Sci. 16 (2006), 1125-1153.

[55] Murray, J. D., *Mathematical biology*. Springer, Berlin, 3rd ed., 2002-2003.

[56] van Neerven, J., *The adjoint of a semigroup of linear operators*, Lecture Notes in Mathematics, 1529. Springer-Verlag, Berlin, 1992.

[57] Pazy, A., *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Applied Mathematical Sciences, 44, Springer-Verlag, New York, 1983.

[58] Rossa, B., *Asynchronous exponential growth in a size structured cell population with quiescent compartment*, in: O. Arino, D. Axelrod, M. Kimmel (Eds.), Mathematical Population Dynamics, vol. 2, Wuerz, Canada, 1995.

[59] Rudin, W., *Principles of mathematical analysis*, McGraw-Hill, Auckland (3th ed.), 1976.

[60] Rudin, W., *Real and complex analysis*, McGraw-Hill, New York (3th ed.), 1987.

[61] Sharpe, F.R. and Lotka, A.J., *A problem in age-distribution*, Philosophical Magazine, 21 (1911), 435-438.

[62] Sherr, C. J., *D-type cyclins*, Trends Biochem. Sci. 20(5) (1995), 187-190.

[63] Stacey, D. W., *Cyclin D1 serves as a cell cycle regulatory switch in actively proliferating cells*, Curr. Option. Cell Biol, 15(2) (2003), 158-163.

[64] Sulsky, D., *Numerical solution of structured population models. II. Mass structure*, J. Math. Biol. 32(5) (1994), 491-514.

[65] Thieme, H. R., *Remarks on resolvent positive operators and their perturbation*, Discrete Contin. Dyn. Syst. Ser. A, 4(1998), 73-90.

[66] Thieme, H. R., *Positive perturbation of operator semigroups: Growth bounds, essential compactness, and assynchronous exponential growth*, Discrete Contin. Dyn. Syst. Ser. A, 4 (1998), 735-764.

[67] Umeda, M., Shimotohno, A. and Yamaguchi, M., *Control of Cell Division and Transcription by Cyclin-dependent Kinase-activating Kinases in Plants*, Plant Cell Physiol. 46(9) (2005), 1437-1442.

[68] Verhulst, P.F., *Notice sur la loi que la population pursuit dans son accroissement*, Correspondance Mathématique et Physique 10 (1838), 113-121.

[69] Von Foerster, H., *Some remarks on changing populations*, The Kinetics of Cellular Proliferation (Frederick Stohlman, ed.), Grune and Stratton, New York, 382-407, 1959.

[70] Yang, K., Hitomi, M. and Stacey, D. W., *Variations in cyclin D1 levels through the cell cycle determine the proliferative fate of a cell*, Cell Division 1 (2006), 32.

[71] Webb, G. F., *A semigroup proof of the Sharpe-Lotka theorem*, Infinite-dimensional Systems (Retzhof, 1983), 254-268, Lecture Notes in Math., 1076, Springer, Berlin, 1984.

[72] Webb, G., *Theory of Nonlinear Age-Dependent Population Dynamics*, Dekker, New York, 1985.