Ecuaciones diferenciales no lineales con retardo y aplicaciones a la biología

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2017

UNIVERSIDAD DE BUENOS AIRES

Facultad de Ciencias Exactas y Naturales

Departamento de Matemática

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Tesis presentada para optar por el título de Doctor de la Universidad de Buenos Aires en el área Ciencias Matemáticas

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Buenos Aires, .

Fecha de defensa: 22 de febrero de 2017.

Ecuaciones diferenciales no lineales con retardo y aplicaciones a la biología.

En esta tesis estudiamos ecuaciones diferenciales resonantes no lineales con retardo motivadas por diferentes aplicaciones biológicas. Más específicamente, los modelos que estudiamos surgen como generalizaciones del modelo de Wheldon para la Leucemia Mieloide Crónica (CML) y de los formulados por Mackey-Glass para el estudio de la regulación de la hematopoyesis. Los modelos planteados en esta tesis tienen no linealidades que involucran varios retardos dependientes del tiempo y, el operador lineal de diferenciación asociado al problema tiene núcleo no trivial. En los casos para los cuales hallamos condiciones para la existencia y multiplicidad de soluciones positivas periódicas, este fenómeno de resonancia nos lleva a implementar la teoría de grado topológico de Leray-Schauder. Sin embargo, estos métodos topológicos generalmente no se extienden al espacio de las funciones casi periódicas debido a la falta de compacidad del operador solución involucrado y, en consecuencia, es preciso utilizar otros métodos. Si lo analizamos desde el punto de vista biológico, los problemas casi periódicos son más realistas y por eso interesantes de estudiar, aunque desde el punto de vista matemático el análisis se torna más complicado. Para el análisis de existencia de soluciones positivas casi periódicas, en esta tesis se desarrollaron teoremas de punto fijo en conos adecuados.

Además de la existencia, otro problema relevante concierne a la estabilidad de las soluciones. En particular, es especialmente importante la estabilidad exponencial, ya que, por un lado, se cuantifica la tasa de convergencia y, por otro lado, es robusta a perturbaciones. Usando una desigualdad de tipo Halanay planteamos un teorema para la estabilidad global explonencial en el caso de parámetros dependientes del tiempo. Más aun, damos cotas explícitas para el rango de convergencia. Luego, empleando este resultado, obtenemos condiciones suficientes para la estabilidad de la solución casi periódica del modelo estudiado.

Palabras clave: Ecuaciones diferenciales no lineales con retardo; Soluciones periódicas positivas; Teoremas de punto fijo; Multiplicidad; Atractor global; Teoría de grado; Soluciones casi periódicas positivas; Unicidad; Estabilidad exponencial global; Leucemia Mieloide Crónica; Hematopoyesis.

Clasificación AMS: 34K20,34A34, 92D25, 34K45, 34K12, 34K13, 34K25

Nonlinear delay differential equations and applications in Biology.

In this thesis we study nonlinear differential equations with delay that arise on different biological applications. More specifically, the models under consideration emerge as a generalization motivated by the Wheldon model for chronic myeloid leukemia (CML) and by Mackey-Glass models for studying the regulation of hematopoiesis. The models proposed in this thesis have nonlinearities that involve several time-dependent delays, and the linear differentiation operator associated to the problem has a non-trivial kernel. In cases for which we find conditions for the existence and multiplicity of positive periodic solutions, this resonance effect leads us to implement the theory of topological degree of Leray-Schauder. However, in general, the above mentioned topological methods cannot be extended to the more general space of almost periodic functions. This impediment is due to the lack of compactness of the involved solution operators. Thus, other methods must be employed. For the existence of almost periodic solutions we develop fixed point theorems in appropriate cones. From the biological point of view, an important feature of the almost periodic problems consists in the fact that they are more realistic and, consequently, more interesting to study.

Besides existence, another relevant matter is to determine whether or not the obtained solutions are stable. In particular, exponential stability is especially important for two reasons: on the one hand, the rate of convergence is quantified and, on the other hand, it is robust to perturbations. We prove a global exponential stability lemma by means of a Halanay-type inequality in the time-dependent parameters. Moreover, we give explicit bounds for the convergence rate. Our results allow to deduce sufficient conditions to ensure global exponential stability of almost periodic solutions of the model under consideration.

Keywords: Nonlinear delay differential equations; Positive periodic solutions; Fixed point theorems; Multiplicity; Global attractor; Degree theory; Positive almost periodic solutions; Uniqueness; Global exponential stability; Chronic Mieloid Leukemia; Hematopoiesis.

Classification AMS: 34K20,34A34, 92D25, 34K45, 34K12, 34K13, 34K25

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Introducción

Las ecuaciones diferenciales parciales y ordinarias como objeto de modelado de sistemas biológicos data de largo tiempo, por ejemplo Malthus y Verhulst las emplearon para modelar el crecimiento poblacional o Lotka y Volterra para el modelo predador-presa.

Mientras en muchas situaciones se asume que el sistema en consideración está gobernado por un principio de "causalidad", es decir, el estado futuro del sistema es independiente del pasado, un modelo más realista debe incluír algo de la historia pasada del sistema.

También uno podría preguntarse por qué estudiar este tipo de ecuaciones cuando las ecuaciones sin retardo son mucho más conocidas y están vastamente estudiadas. La respuesta resulta bastante intuitiva si pensamos en situaciones reales, en procesos poblacionales tanto biológicos, como físicos, económicos, etc. Estos procesos, en general, involucran tiempo de retardo. Los tiempos de retardo ocurren muy a menudo, en casi toda situación, por lo tanto, ignorar esto es ignorar la realidad. Esta es nuestra motivación para estudiar este tipo de ecuaciones en la presente tesis.

Desde el punto de vista teórico, la complejidad observada en las ecuaciones con retardo en muchos casos es mayor a la observada en las ecuaciones sin él. Por ejemplo, podríamos mencionar el siguiente ejemplo, que aunque simple, muestra la complejidad de este tipo de ecuaciones: si consideramos una ecuación diferencial (no lineal) como, por ejemplo, el modelo de crecimiento poblacional sin retardo, esto es, una ecuacíon de la forma $\frac{dx}{dt} = f(x)$ donde x representa la cantidad de habitantes y t el tiempo transcurrido, no puede exhibir un ciclo límite. Sin embargo, una ecuación de este estilo que incluya un parámetro y un retardo puede exhibir movimiento periódico, cuasi-periódico así como también caótico.

Siguiendo con el mismo ejemplo, si además para un tiempo inicial t_0 se fija el punto $x_0 = x(t_0)$ en el espacio Euclídeo, entonces el problema a valores inciales resulta tener una única solución. Por otro lado, si consideramos la ecuación diferencial con retardo

$$\frac{dx}{dt} = f(x(t-\tau)),$$

para plantear un análogo al problema a valores iniciales surge una pregunta obvia: qué condiciones iniciales son necesarias?, primero observemos que para calcular la tasa de cambio en t_0 es necesario tener el valor de $x(t_0-\tau)$ y en $t_0+\epsilon$, el valor de $x(t_0+\epsilon-\tau)$. De esta manera, se deduce que para plantear un problema a valores iniciales uno necesita dar una función inicial, el valor de $x(t)$ en todo $[-\tau, 0]$. De esta manera, cada función inicial determina una única solución a la ecuación diferencial con retardo (este resultado lo formalizaremos en el capítulo siguiente). El punto importante a resaltar es que, a diferencia de las ecuaciones ordinarias, si a la función inicial le pedimos que sea continua, entonces el espacio de soluciones tiene la misma dimensionalidad que $C([t_0-\tau, t_0], \mathbb{R})$. O sea, el problema se convierte en uno de dimensión infinita.

Más específicamente, en lo que respecta a esta tesis, los problemas biológicos que dieron origen y la motivaron son el modelo planteado por Wheldon (1975) para la leucemia mieloide crónica (CML):

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)}, \end{aligned} \tag{1}$$

donde $M(t)$ es el número de células en la médula; $B(t)$ es el número de células blancas y τ representa el tiempo medio de maduracion de las células madre.

En 1979 Mackey y Glass llamaron a esta clase enfermedades fisiológicas periódicas, como es el caso de la leucemia mieloide crónica, con el nombre de *enfermedades dinámicas* y plantearon un estudio de varios ejemplos de este tipo de enfermedades. Unos de los más estudiados son los planteados para modelar regulación de la hematopoyesis:

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n P^m(t-\tau)}{\theta^n + P^n(t-\tau)} - \gamma P(t) \tag{2}$$

y

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n}{\theta^n + P^n(t-\tau)} - \gamma P(t), \tag{3}$$

aquí $P(t)$ denota la densidad de las células maduras en el torrente sanguíneo y τ es el tiempo de retardo entre la producción de células maduras en la médula ósea y su maduración hasta que son liberadas en el torrente sanguíneo. En su trabajo original [35], Mackey y Glass consideraron el exponente $m = 1$ en (2).

Tales modelos de regulación de la producción de células sanguíneas incorporan un tiempo de retardo impuesto por el tiempo de desarrollo celular y son propensos a desarrollar oscilaciones.

Los modelos de Wheldon y Mackey-Glass serán nuestra motivación principal en el desarrollo de esta tesis.

Esta tesis está organizada de la siguiente manera. En el Capítulo que sigue damos los conceptos y resultados teóricos necesarios para una comprensión total los capítulos siguientes. En la primera Sección damos las definiciones y propiedades básicas que refieren a las ecuaciones diferenciales con retardo. En la Sección siguiente se presentan preliminares topológicos donde hacemos un repaso de la teoría de grado topológico para luego llegar a la teoría de continuación, la cual será empleada en los Capítulos 4 y 5. En la Sección siguiente, presentamos el espacio de las funciones casi periódicas así como también las definiciones y propiedades mas relevantes que luego usaremos para deducir nuevos resultados en los dos últimmos Capítulos. Finalmente, para cerrar el Capítulo hacemos un repaso por las propiedades principales de los resultados y definiciones del análisis no lineal en conos abstractos.

En el Capítulo 3 damos una introducción a los problemas biológicos planteados por Wheldon, Mackey y Glass

En el Capítulo 4, tomando como base el modelo de Wheldon (1975) lo enriquecemos introduciendo un microambiente dependiente del tiempo y funciones dependientes del tiempo para modelar la eficacia de las drogas. El modelo resultante es una clase especial de sistema noautónomo, no lineal de ecuaciones diferenciales con retardo. Vía métodos topológicos,

probamos la existencia de soluciones periódicas positivas. Finalmente, formulamos algunos problemas y conjeturas abiertas relevantes.
Los resultados de este capítulo se encuentran publicados en: Electronic Journal of Differential Equations. Ver [3]. `http://ejde.math.tstate.edu/Volumes/2013/272/amster.pdf`

En el Capítulo 5 estudiamos una ecuación de primer orden noautónoma no lineal con varios retardos dependientes del tiempo cuya motivación surge de la ecuación de Mackey-Glass para la regulación de la hematopoyesis. Usando teoría de grado topológico probamos, bajo condiciones apropiadas, la existencia de múltiples soluciones periódicas. Más aun, mostramos que las condiciones son necesarias, en el sentido que si se asumen ciertas condiciones complementarias entonces el equilibrio trivial es un atractor global para las soluciones positivas y por lo tanto no existen soluciones periódicas positivas.
Los resultados de este capítulo se encuentran publicados en: Journal of Applied Mathematics and Computing. Ver : [2]. `http://link.springer.com/article/10.1007/s12190-016-1051-6`

Nuestro resultado principal en el Capítulo 6 refiere a la formulación de un teorema de punto fijo en conos abstractos. En la segunda parte del Capiítulo deducimos diversos teoremas que aseguran la existencia de soluciones casi periódicas para distintos problemas abstractos. Finalmente, para cerrar el Capítulo damos ejemplos que ilustran la aplicabilidad de nuestros resultados. Los resultados de este Capítulo cumplen múltiples roles: sirven para ampliar resultados ya conocidos así como también para simplificar demostraciones ya existentes.

En el Capítulo 7 retomamos el modelo generalizado formulado en el Capítulo 5 y lo analizamos en el espacio de Banach de las funciones casi periódicas. Obtenemos resultados de existencia y unicidad de soluciones positivas casi periódicas por medio de la implementación de los resultados obtenidos en el Capítulo anterior. Más aun, damos ciertos criterios que garantizan que la solución obtenida es globalmente exponencialmente estable. Finalmente, usando teoremas de punto fijo, obtenemos condiciones suficientes de existencia y no existencia de soluciones de (2) para el caso $m > 1$. De esta manera, damos una respuesta al problema abierto de existencia planteado por diversos autores para el caso $m > 1$ [13, 14, 32].
Los resultados de este capítulo correspondientes al modelo más general fueron enviados para su publicación.

Chapter 1

Introduction

The use of differential equations to model biological systems has a long history, for example, Malthus and Verhulst employed them in models of population and Lotka and Volterra in the prey-predator model.

Since several situations are assumed governed by a instantaneous effect that is, the future state of the system in consideration is independent of the past and it is determined only by the information bringing by the present time. A more realistic model must include some of the past history of the system.

However, why study such equations when differential equations without delay are sufficiently studied? The answer is quite intuitive, in many biological, physical, chemical, etc., population processes involve a time delay. Delayed times occur very often, in almost any situation. This is our motivation to study this type of equations in the present thesis

Delay differential equations have several features which make its analysis more complicated than its analogous model without delay. For example, the following very simple model shows the complexity of this type of equations: consider the differential nonlinear equation without delay $\frac{dx}{dt} = f(x)$ where x represents the number of inhabitants and t the elapsed time, this equation has no limit cycle. However, including a parameter and a delay, the solution x can exhibit periodic, quasi-periodic as well as, chaotic behavior.

With the same model without delay in mind, if together with the initial time t_0 the point $x_0 = x(t_0)$ in the Euclidean space is fixed, the initial value problem has a unique solution. On the other hand, if we consider the delay differential equation:

$$\frac{dx}{dt} = f(x(t-\tau)),$$

an obvious question arises: what initial conditions are necessary? Clearly, to know the rate of change at t_0 one needs the values $x(t_0)$ and $x(t_0-\tau)$. Thus, initial value problem requires more information than the initial value problem without delay. One needs to give an initial function, that is, information of $x(t)$ on the entire interval $[-\tau, 0]$. Thus, each initial function determines a unique solution to the delay differential equation (this result shall be studied in the next chapter). It is worth noticing that, if we require that initial functions be continuous, then the space of solutions has the same dimensionality as $C([t_0-\tau, t_0], \mathbb{R})$. That is, the problem becomes infinite dimensional.

In this context, one of the biological problems which give rise and motivation to this thesis are the Wheldon model (1975) for the chronic mieloid leukimia (CML):

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)}, \end{aligned} \tag{1.1}$$

where $M(t)$ is the number of cells in the marrow; $B(t)$ is the number of white blood cells and τ represents mean time for stem cell maturity.

Physiological periodic diseases, such as chronic mieloid leukimia, have been termed *dynamical diseases* by Glass and Mackey (1979) who have made a study of several models for different diseases. For example, for the control of hematopoiesis, they proposed the following models:

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n P^m(t-\tau)}{\theta^n + P^n(t-\tau)} - \gamma P(t). \tag{1.2}$$

and

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n}{\theta^n + P^n(t-\tau)} - \gamma P(t). \tag{1.3}$$

where $P(t)$ is the density of mature circulating cells, τ is the delay between the initiation of cellular production in the bone marrow and the release of mature cells into the blood. In their original work [35], Mackey and Glass consider $m = 1$ in equation (1.2).

Such models of regulation of blood cell production incorporate a time delay imposed by the time for cellular development and are prone to develop oscillations.

Wheldon and Mackey-Glass models are the cornerstones of this present work.

This thesis is organized as follows:

In the next Chapter, we give concepts and theoretical results needed to fully understand the following chapters. It is divided in four sections. First, basic properties and definitions concerning delay differential equations are given. Then, the degree theory and continuation theory are described; in the third Section we introduce the Banach space of almost periodic functions, the main results and concepts are exposed. In the last section, classical concepts of nonlinear analysis in abstract cones are described and fixed point theorems and definitions are enumerated.

Chapter 3 is a brief but thorough history of the biological problems considered by Wheldon, Mackey and Glass.

In Chapter 4, the Wheldon model (1975) of a chronic myelogenous leukemia dynamics is modified and enriched by the introduction of a time-varying micro-environment and time-dependent drug efficacies. The resulting model is a special class of nonautonomous nonlinear system of differential equations with delays. Via topological methods, the existence of positive periodic solutions is proven. Finally, we introduce our main insight and formulate some relevant open problems and conjectures. *The results from this chapter were published in: Electronic Journal of Differential Equations. See [3].* `http://ejde.math.txstate.edu/Volumes/2013/272/amster.pdf`

In Chapter 5 an nonautonomous nonlinear first order delay differential equation with several time-dependent delays is studied. The motivation arises from the Mackey-Glass model for the

regularization of the hematopoiesis process. Using topological degree methods we prove, under appropriate conditions, the existence of multiple positive periodic solutions. Moreover, we show that the conditions are necessary, in the sense that if some sort of complementary conditions are assumed then the trivial equilibrium is a global attractor for the positive solutions and hence periodic solutions do not exist.
The results from this chapter were published in: Journal of Applied Mathematics and Computing. See : [2]. `http://link.springer.com/article/10.1007/s12190-016-1051-6`

Our main result in Chapter 6 is the formulation of a fixed point theorem in abstract cones. In addition, from this abstract Theorem, we deduce results for the existence of almost periodic solutions for abstract models, thus unifying the analysis of a broad class of biological scalar models in a single setting. Finally, we provide some examples which illustrate the applicability of our results. Our technique fulfills multiple roles: it can be used to expand on well-known results as well as to shorten existing proofs.

Finally, Chapter 7 deals with the hematopoiesis problem in the space of almost periodic functions. We consider the model in Chapter 5 in the Banach space of the almost periodic functions. Both existence and uniqueness of almost periodic functions are studied. Moreover, we give criteria to ensure that the obtained solution is globally exponentially stable. The end of this Chapter deals with the existence and nonexistece of almost periodic solution of (2) for the case $m > 1$. Thus, we give answers to the open problem proposed by several authors, see for example [13, 14, 32].
The results from the more general model were submitted for publication.

Resumen del capítulo 2

En este Capítulo presentamos conceptos y resultados teóricos necesarios para la comprensión total de los capítulos siguientes.
Está dividido en cuatro secciones:

En la Sección 2.1 nos focalizamos en la teoría básica de las ecuaciones diferenciales con retardo. Comenzamos con un ejemplo que nos permitirá visualizar de manera simple las diferencias que pueden presentarse entre las ecuaciones diferenciales con y sin retardo. En la Subsección 2.1.1 damos teoremas de unicidad, existencia local y global de solución. En la Subsección 2.1.2 damos una extensión del operador de Poincaré adaptada al caso de ecuaciones con retardo. Luego de plantear distintos resultados concluímos que este tipo de operadores no suelen ser útiles para este tipo de ecuaciones.

En la Sección 2.2, damos una introducción a la teoría de grado y teoremas de continuación. Comenzamos con una aproximación intuitiva de la definición de grado en $\mathbb{R}^n$, en particular para el caso $n = 2$. Luego extendemos esta definición a funciones continuas en un espacio arbitrario de dimensión finita. Esto nos llevará a la definición del grado de Brouwer. En la Subsección 2.2.3 extendemos el grado de Brouwer a espacios de Banach E generales, es decir, ahora E puede tener dimensión infinita. La Subsección 2.2.4 es acerca de teoremas de continuación, planteamos distintos resultados de existencia por medio del grado topológico para resolver problemas del tipo $Lu = Nu$, donde $L : D \subset E \to F$ es un operador lineal y $N : E \to F$ es continuo. Finalmente, en la Subsección 2.2.5 presentamos un teorema de continuación planteado en [4], que asegura la existencia de soluciones T-periódicas en una ecuación funcional del tipo

$$x'(t) = \Phi(x)(t),$$

donde C_T es el conjunto de funciones continuas T-periódicas y $\Phi : C_T \to C_T$. Este teorema será clave para la obtención de condiciones suficientes de existencia y multiplicidad en el Capítulo 5.

En la Sección 2.3 introducimos el espacio de Banach de las funciones casi periódicas y damos los conceptos y resultados más importantes de este espacio. En la Subsección 2.3.1 damos la caracterización de funciones casi periódicas $f : \mathbb{R} \to \mathbb{C}$ dada por Bochner en términos de convergencia de suceciones de familias de traslaciones y la dada por Bohr basada en cuasi-períodos. Luego planteamos propiedades básicas de estas funciones y resultados de estabilidad. En la subsección 2.3.2 presentamos la clase de funciones uniformemente casi periódicas (u.a.p.) y un resultado que asegura que si una función $f(t, x)$ está en la clase u.a.p y $\varphi(t)$ es una función casi periódica, entonces $f(t, \varphi(t))$ es casi periódica. Este resultado será importante en los últimos dos Capítulos . En la última Subsección damos una introducción a las funciones casi periódicas $f : \mathbb{R} \to X$ donde ahora X es un espacio de Banach. El objetivo principal de esta Subsección es dar un criterio de compacidad que permita entender por qué los métodos clásicos del análisis no lineal tales como teoría de grado, teoremas de punto fijo de Leggett-Williams y Schauder entre otros, no pueden ser extendidos de manera natural al espacio de Banach de funciones casi periódicas.

En la Sección 2.4, está focalizada en el análisis no lineal en conos abstractos. Damos definiciones y propiedades básicas y luego hacemos una breve introducción a la teoría de punto fijo de operadores monótonos.

Chapter 2

Preliminaries

2.1 Basic properties of delay differential equations

This Section concerns definitions and theorems of delay differential equations theory which we shall employ along this thesis. We refer to the books of Driver [15], Hale [26] or Murray [39] for a more detailed analysis of this subject.

Let us begin this section with an example, the well known logistic model which helps us to introduce and get a best understanding of delayed models.

Example 2.1.1 ***Logistic equation***
Let $N(t)$ be the population of the species at time t, then the rate of change results

$$\frac{dN}{dt} = \text{ births - deaths + migration.} \tag{2.1}$$

Consider birth and death terms proportional to N and without migration, then the simplest delay differential equation modeling this situation is given by :

$$\frac{dN}{dt} = bN(t) - dN(t) \tag{2.2}$$

with b and d beingpositive constants. If we consider $N(0) = N_0$, the initial population, then

$$N(t) = N_0 e^{(b-d)t} \tag{2.3}$$

is the solution of equation (2.2). Thus if $b < d$ then the population is extinguished while if $b > d$, then populations that obey this type of equations are said to be undergoing exponential growth. This constitutes the simplest minimal model of bacterial growth, moreover, this represents the growth of any reproducing population. This approach first applied by Malthus in 1798, is fairly unrealistic.

In the long time there must be some adjustment to such exponential growth. Verhulst (1838, 1845) proposed that a self-limiting process should operate when a population becomes too large. Verhulst suggested a somewhat more realistic model admitting that the growth rate coefficient will not be constant but will diminish as N(t) grows, because of overcrowding and shortage of food. This leads to the differential equation:

$$\frac{dN}{dt} = rN(t)\left(1 - \frac{N(t)}{K}\right), \tag{2.4}$$

where r and K are positive constants. In this model the per capita survival rate is r (1 - N /K); that is, it is dependent on N . The constant K is the carrying capacity of the environment, which is usually determined by the available sustaining resources.

The carrying capacity K determines the size of the stable steady state population while r is a measure of the rate at which it is reached.

Equation (2.4) *with* $N(0) = N_0$ *can be solved by separation of variables and the solution obtained is:*

$$N(t) = \frac{N_0 e^{rt}}{1 + \frac{N_0}{K}\left(e^{rt} - 1\right)}. \tag{2.5}$$

From (2.5)*, as* t *becomes large enough, regardless of the value of* $N_0 > 0$*, the size of population* N *tends to the equilibrium value, the carrying capacity K. Indeed, from* (2.4)*, if* $N_0 < K$*,* $N(t)$ *increases monotonically to* K *and, if* $N_0 > K$ *it decreases monotonically to* K*.*

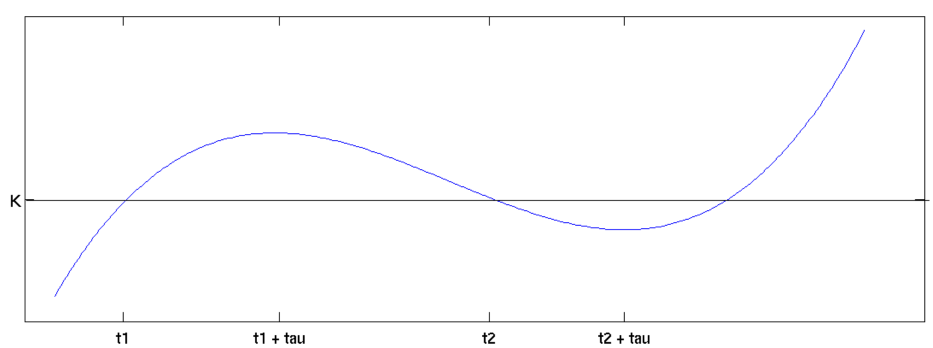
However, one of the deficiencies of model (2.4) *is that the birth rate is considered to act instantaneously whereas there may be a time delay involved (gestation period, time to reach maturity, etc.)*

In order to overcome this deficiency, it is possible to consider the following simple generalization of 2.4 proposed by Hutchinson (1948) [30], namely, the differential delay equation

$$\frac{dN}{dt} = rN(t)\left(1 - \frac{N(t-\tau)}{K}\right). \tag{2.6}$$

The inclusion of the delay τ *implies that the regulatory effect depends on the population at an earlier time,* $t - \tau$*, rather than that at* t*.*

We can get some qualitative properties of solutions of (2.4) *by means of the following heuristic reasoning.*



Suppose there exists a time t_1 *such that*

$$N(t-\tau) < K \textit{ for all } t < t_1 \textit{ and } N(t_1) = K.$$

From (2.6)*, we have* $1 - \frac{N(t-\tau)}{K} > 0$ *and then* $N(t)$ *is increasing at* t_1 *since* $\frac{dN}{dt} > 0$*. At time* $t = t_1 + \tau$*,*

$$N(t-\tau) = N(t_1) = K \text{ which implies } \frac{dN}{dt} = 0.$$

For times $t_1 + \tau < t < t_2$, $N(t-\tau) > K$ *and so* $\frac{dN}{dt} < 0$ *then* $N(t)$ *decreases until* $t = t_2 + \tau$ *since at this time*

$$N(t_2 + \tau - \tau) = N(t_2) = K \text{ which implies } \frac{dN}{dt} = 0.$$

Therefore, (2.6) *has the possibility of oscillatory behavior.*

Before leaving this example, it should be mentioned that, contrary to the delayed model, a differential equation model for population growth without delay, namely like

$$\frac{dN}{dt} = f(N), \tag{2.7}$$

cannot have limit cycle behavior. Indeed, suppose that equation (2.7) *has a periodic solution with period* T *; that is,* $N(t+T) = N(t)$*. Multiplying the equation by* $\frac{dN}{dt}$ *we have*

$$\left(\frac{dN}{dt}\right)^2 = f(N)\frac{dN}{dt},$$

integrating from t *to* $t+T$ *we obtain*

$$\begin{aligned}\int_t^{t+T} \left(\frac{dN}{dt}\right)^2 dt &= \int_t^{t+T} f(N)\frac{dN}{dt}\, dt \\ &= \int_{N(t)}^{N(t+T)} f(N)\, dN \\ &= 0.\end{aligned}$$

since $N(t) = N(t+T)$*. However, we can observe that the left-hand integral is positive since* $(\frac{dN}{dt})^2$ *cannot be identically zero, so we have a contradiction. We conclude that, the differential equation* $\frac{dN}{dt} = f(N)$ *cannot have periodic solutions.*

Next theorems and properties of delay differential equations in this Section will be aimed at showing how similar they are to ordinary differential equations. However, similar does not mean equivalent, so one should be careful about the details in the proofs. After each theorem, we will refer to the books where a more detailed analysis of the subject can be found.

Notation 2.1.1 *The set* $C([-\tau, 0], \mathbb{R}^n)$ *of all continuous functions mapping* $[-\tau, 0]$ *to* $\mathbb{R}^n$ *shall be denoted by* $\mathcal{C}$*. And for any set* A *in* $\mathbb{R}^n$ *we shall denote* $\mathcal{C}_A = C([-\tau, 0], A)$*. An interval in* $\mathbb{R}$ *shall be denoted by* J*.*

For a function $\psi \in \mathcal{C}_A$ we define the sup-norm,

$$||\psi||_\tau = \sup_{-\tau \le \sigma \le 0} ||\psi(\sigma)||, \tag{2.8}$$

where $||\cdot||$ denotes the Euclidean norm.

Remark 2.1.1 *In the case when $A = \mathbb{R}^n$, $\mathcal{C}_A = \mathcal{C}$ is a linear Banach space with the norm $||\cdot||_\tau$. On the other hand, if $A \neq \mathbb{R}^n$, $||\cdot||_\tau$ is not a norm in $\mathcal{C}_A$. However, $||\cdot||_\tau$ may always be considered a norm in the space $\mathcal{C}$.*

Definition 2.1.1 *Let $F : J \times \mathcal{C}_A \to \mathbb{R}^n$ and $\mathcal{B} \subset J \times \mathcal{C}_A$. We say F is Lipschitz on $\mathcal{B}$ with constant K if*

$$||F(t,\psi) - F(t,\psi')|| \leq K||\psi - \psi'||_\tau$$

for some $K \geq 0$ and any $(t,\psi), (t,\psi') \in \mathcal{B}$.

In the next existence and uniqueness theorems the following weaker condition shall be assumed:

Definition 2.1.2 *The functional $F : J \times \mathcal{C}_A \to \mathbb{R}^n$ is said to be locally Lipchitz if for every (t,ψ) in $J \times \mathcal{C}_A$ there exists a neighborhood U of (t,ψ) such that f restricted to U is Lipschitz.*

Here the Lipschitz constant for F depends on the set U.

Let $x_t \in C([-\tau, 0], \mathbb{R}^n)$ be the function defined by

$$x_t(\theta) = x(t+\theta), \text{ for } \theta \in [-\tau, 0].$$

Observe that x_t is obtained by considering $x(s)$ for $t - \tau \leq s \leq t$ and then translating this segment of x to $[-\tau, 0]$ as we can see in Figure 2.1. If x is a continuous function, then x_t is a continuous function on $[-\tau, 0]$.

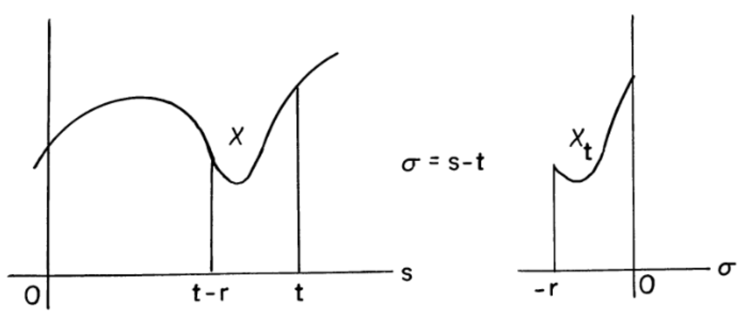


Figure 2.1: Translated segment of x.

Let $F : J \times \mathcal{C}_\mathcal{A} \to \mathbb{R}^n$. We say that the equation

$$x'(t) = F(t, x_t). \tag{2.9}$$

is a *delay functional differential equation.*

Equation (2.9) is a very general type of equation and includes, for example, ordinary differential equations when $\tau = 0$

$$x'(t) = F(x(t));$$

the integro-differential equation

$$x'(t) = \int_{-\tau}^{0} g(t, \theta, x(t+\theta))d\theta,$$

as well as, if we consider the operator $F(\psi) = f(\psi(0), \psi(-\tau))$ where $f : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$ is a nonlinear function, the nonlinear delay differential equation

$$x'(t) = f(x(t), x(t-\tau)).$$

Throughout this thesis we shall focus on this last type of equations and we shall consider both constant and bounded time-dependent delays.

In addition, ones requires an initial function. Indeed, an appropriate initial condition for equation (2.9) is

$$x_{t_0} = \varphi, \qquad \varphi \in \mathcal{C}_A. \tag{2.10}$$

Let β be a constant, $t_0 < \beta \leq \infty$ and let be $F : [t_0, \beta) \times \mathcal{C}_A \subset \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$. We shall refer to the system

$$\begin{cases} x'(t) &= F(t, x_\tau), \qquad t \in [t_0, \beta) \\ x_{t_0} &= \varphi, \qquad \varphi \in \mathcal{C}_A. \end{cases} \tag{2.11}$$

as the *initial value problem* of (2.9).

Definition 2.1.3 *A function $x : [\tau - t_0, \beta] \to \mathbb{R}^n$ is a solution of the initial value problem* (2.11) *if there exists $\beta_1 \in (t_0, \beta)$ such that the following conditions are fulfilled:*

1. $x \in C([\tau - t_0, \beta], \mathbb{R}^n)$
2. $x_{t_0} = \varphi, \qquad \varphi \in \mathcal{C}_A$
3. $(t, x_t) \in Dom(F)$ *and x satisfies equation* (2.9) *for all $t \in [t_0, \beta_1)$*

Definition 2.1.4 *A functional $F : [t_0, \beta) \times \mathcal{C}_A \to \mathbb{R}^n$ is said to be quasi-bounded if for each D closed bounded subset of A and β_1, $t < \beta_1 < \beta$, F is bounded in $[t_0, \beta_1] \times \mathcal{C}_D$.*

Definition 2.1.5 *Let x on $[t_0 - r, \beta_1)$ and on $[t_0 - r, \beta_2)$ be solutions of the problem* (2.11). *Suppose that $\beta_1 < \beta_2$, we say is a continuation of x, or x can be continued to $[t_0 - r, \beta_2)$. We will say that a solutions is non-continuable if it has no continuation.*

2.1.1 Existence and uniqueness of solutions

The following condition shall be useful to ensure uniqueness of solution. Observe that condition (C) is weaker than continuity:

Condition (C): We say that $F(t, x_t)$ satisfies condition (C) if it is continuous with respect to t in $[t_0, \beta)$ for each given continuous function $x : [t_0 - r, \beta) \to A$.

Theorem 2.1.1 *(Uniqueness) Let $F : [t_0, \beta) \times \mathcal{C}_A \to \mathbb{R}^n$ be locally Lipschitz and let it satisfy Condition (C). Then, given any $\varphi \in \mathcal{C}_A$, (2.9)-(2.10) has at most one solution on $[t_0 - r, \beta_1)$ for any $\beta_1 \in (t_0 - r, \beta]$.*

Proof: Page 296 [15]. ∎

It is interesting to mention that in the literature on delay differential equations, it is usually assumed, instead of condition (C), that F is continuous on $J \times \mathcal{C}_A$. The fact is that continuity of F implies condition (C), confirming the aforementioned statement.

Theorem 2.1.2 *(Local existence) Let $F : [t_0, \beta) \times \mathcal{C}_A \to \mathbb{R}^n$ be locally Lipschitzian and satisfying Condition (C). Then, for each $\varphi \in \mathcal{C}_A$, problem (2.11) has a unique solution $x(t)$ defined on $[t_0, t_0 + \delta]$ for some positive δ.*

Proof: Page 301 [15]. ∎

Theorem 2.1.3 *(Maximal solution) Let $F : [t_0, \beta) \times \mathcal{C}_A \to \mathbb{R}^n$ be locally Lipschitzian and quasi-bounded satisfying Condition (C). Then, for each $\varphi \in \mathcal{C}_A$ problem (2.11) has a unique noncontinuable solution x defined on $[t_0 - \tau, \beta_1)$; and if $\beta_1 < \beta$, then, for every compact set $D \subset A$*

$$x(t) \notin D \qquad \text{for some } t \in (t_0, \beta_1).$$

Proof: Page 306 [15] ∎

Corollary 2.1.1 *(Global existence) Let $A = \mathbb{R}^n$ and $F : [t_0, \beta) \times \mathcal{C}_A \to \mathbb{R}^n$ be locally Lipschitzian and satisfy condition (C). Assume further that*

$$||F(t, \psi)|| < M(t) + N(t)||\psi||_\tau \text{ on } [t_0, \beta) \times \mathcal{C},$$

where M and N are continuous positive functions on $[t_0, \beta)$. Then there exists an unique noncontinuable solution of problem (2.11) on $[t_0 - \tau, \beta)$.

2.1.2 A periodicity theorem: the Poincaré operator

In this section we shall give an extension of the Poincaré operator adapted to delay differential equations.

Definition 2.1.6 *Suppose $(X, |\cdot|)$ is a Banach space, $U \subset X$, and $x \in U$. Given a map $A : U \setminus \{x\} \to X$, the point $x \in U$ is said to be an **ejective point** of A if there is an open neighborhood $G \subset X$ of x such that for every $y \in G \cap U$, $y \neq x$, there is an integer $m = m(y)$ such that $A^m y \notin G \cap U$.*

Let M be a positive constant. Define the sets $S_M := \{x \in X : |x| = M\}$ and $B_M := \{x \in X : |x| < M\}$. Then $S_M = \partial B_M$.

Theorem 2.1.4 *Let $K \subset X$ be a closed, bounded, convex and infinite-dimensional set, $A : K \diagdown \{x_0\} \to K$ completely continuous, and $x_0 \in K$ an ejective point of A. Then, there exists a fixed point of A in $K \diagdown \{x_0\}$. If K is finite dimensional and x_0 is an extreme point of K, then the same conclusion holds.*

Theorem 2.1.5 *Let $K \subset X$ be a closed and convex set in X, $A : K \diagdown \{x_0\} \to K$ completely continuous, $0 \in K$ an ejective point of A, and there is an $M > 0$ such that $Ax = \lambda x$, $x \in K \cap S_M$ implies $\lambda < 1$. Then, there exists a fixed point of A in $K \cap B_M \diagdown \{0\}$, if either K is infinite dimensional or 0 is an extreme point of K.*

Proof:(Theorems 2.1.4-2.1.5). Page 249 [26]. ■

Remark 2.1.2 *In the application of Theorems 2.1.4-2.1.5 to delay functional differential equations, the mapping A is usually similar to the map of Poincaré in ordinary differential equations. Indeed, suppose that there exists a set $K \subset C$ and suppose that for each $\varphi \in K$ the solution $x(t, \varphi; t_0 = 0)$ of (2.11) returns to K in some time $\tau := \tau(\varphi) > 0$; that is $x_\tau(\varphi) \in K$ if $\varphi \in K$. The mapping A is defined by:*

$$A : K \to K, \qquad A\varphi := x_{\tau(\varphi)}(t, \varphi; t_0 = 0).$$

By Theorems 2.1.4-2.1.5, the operator A is compact, then there would be a $\phi \in K$ such that $A\varphi = \phi$ and, thus, a $\tau(\phi)$-solution of (2.11) with initial function $x_0 = \phi$.

We wish to obtain nonconstant periodic solutions, and if there is a constant $a \in \mathbb{R}^n$ such that the constant function $a \in C$, $a(\theta) = a$ for all $\theta \in [-r, 0]$, satisfies $a \in K$, $f(a) = 0$, then the only fixed point of A is a. On the other hand, if K does not contain such constant functions, then there is a nonconstant periodic solution. However, in the applications, the construction of such K is very difficult and often other methods must be employed.

2.2 The degree theory

We begin this section with an intuitive approach to the degree. This approach shall allow us introduce the basic aspects of the topological degree in a more general context.

2.2.1 Intuitive approach of degree

Let us start with a well known situation, let us define the degree for the case $n = 2$. In this case, the degree can be regarded as an "algebraic count" of the zeros of a continuous function. Indeed, identify $\mathbb{C}$ with $\mathbb{R}^2$ and let us start assuming that $f : \overline{\Omega} \to \mathbb{C}$ is analytic and $\gamma : [0, 1] \to \overline{\Omega}$ is a simple continuous closed curve oriented counterclockwise and such that $\partial\Omega$ can be parametrized by the curve γ. If f does not vanish over $\partial\Omega$ then we have the so called "zeros and poles theorem"

$$\#\{z \in \Omega : f(z) = 0\} = \frac{1}{2\pi i} \int_\gamma \frac{f'(z)}{f(z)} dz. \tag{2.12}$$

This theorem provides the exact number from zeros of f in Ω counted with their multiplicities.

This number will be called the degree of f at 0 over Ω, namely:

$$deg(f,\Omega,0)=\frac{1}{2\pi i}\int_\gamma \frac{f'(z)}{f(z)}dz. \tag{2.13}$$

More generally, we can consider a point $p \notin \partial f(\Omega)$ and, similarly to the case $p=0$, we compute the degree of f at p over Ω:

$$deg(f,\Omega,p)=\frac{1}{2\pi i}\int_\gamma \frac{f'(z)}{f(z)-p}dz. \tag{2.14}$$

This number computes the number of zeros of the equation $f(z)=p$ for $z\in\Omega$.

Some properties can be deduced from the definition:

1. $deg(Id,\Omega,p)=\begin{cases}1 & \text{if } p\in\Omega\\ 0 & \text{if } p\notin\Omega\end{cases}$ where Id is the identity operator.
2. $deg(f,\Omega,p)=deg(f-p,\Omega,0)$ (translation).
3. If $\Omega_1,\Omega_2\subset\Omega$ with $\Omega_1\cap\Omega_2=\emptyset$ and $f\neq p$ over $\overline{\Omega}-(\Omega_1\cup\Omega_2)$, then
$$deg(f,\Omega,p)=deg(f,\Omega_1,p)+deg(f,\Omega_2,p).$$

The next property needs the following definition: Let $f,g:\Omega\to\mathbb{C}$ continuous such that $p\notin f(\partial\Omega)$ and $p\notin g(\partial\Omega)$. We say that $f\sim g$ (f and g are *homotopic*) if there exists a continuous function $h:\overline{\Omega}\times[0,1]\to\mathbb{C}$ such that

$$h(z,0)=f(z) \;\; and h(z,1)=g(z), \quad \text{for all } z\in\Omega$$

and

$$h(z,\lambda)\neq p, \quad \text{for all } z\in\partial\Omega \text{ and } \lambda\in[0,1].$$

4. If $f\sim g$, then $deg(f,\Omega,p)=deg(g,\Omega,p)$.

In particular, this last property implies that the degree depends only on the value of f over his boundary. Indeed, if $f=g$ on $\partial\Omega$, then we can define the following homotopy between f and g: $h(z,\lambda)=\lambda g(z)+(1-\lambda)f(z)$.

5. If $deg(f,\Omega,p)\neq 0$, then f takes the value p at least once in Ω.
6. If $f=g$ over γ, then $deg(f,\Omega,p)=deg(g,\Omega,p)$.

Actually, these results become trivial if we recall the analytic continuation principle: let f,g be analytic and $f=g$ on $\partial\Omega$, then $f=g$.

Property 3 implies the next two properties:

7. If $\Omega=\emptyset$ then $deg(f,\Omega,p)=0$,

and the solution property is obtained:

8. If f does not vanish in Ω, then $deg(f,\Omega,p)=0$,

which is deduced taking $\Omega_1=\Omega_2=\emptyset$.

In what follows, we shall see that the preceding definition may be extended for arbitrary n and continuous functions. Furthermore, the degree shall be defined as a mapping that satisfies properties $(1)-(4)$. Indeed, this extension can be done in a unique way.

2.2.2 The Brouwer degree

Now we are in a position to provide an extended the definition of degree for arbitrary continuous functions f in an arbitrary finite dimensional space.

Let the set of admissible functions be given by

$$\mathcal{A}(y) := \{f \in C(\overline{\Omega}, \mathbb{R}^n) : f \neq y \text{ in } \partial\Omega\}.$$

Lemma 2.2.1 *If $f \in \mathcal{A}(y)$ and $g \in C(\overline{\Omega}, \mathbb{R}^n)$ satisfies the inequality $||g-f||_{L^\infty} < d(y, f(\partial\Omega))$ where $d(\cdot,\cdot)$ is the distance, then $g \in \mathcal{A}(y)$. That is, $\mathcal{A}(y)$ is an open set.*

Let us define the concepts of Critical and Regular values.

Definition 2.2.1 *Let $U \subset \mathbb{R}^n$ be open and $f : U \to \mathbb{R}^m$ be of class C^1. Assume that $m \leq n$. A vector $p \in \mathbb{R}^m$ is called a regular value of f if $Df(x) : \mathbb{R}^n \to \mathbb{R}^m$ is surjective for all $x \in f^{-1}(p)$. The set of **regular values** of f is defined as follows:*

$$RV(f) = \{y \in \mathbb{R}^m : \forall x \in f^{-1}(y), Df(x) : \mathbb{R}^n \to \mathbb{R}^m \textit{ is onto } \}$$

*and the set of **critical values** is defined as:*

$$CV(f) = \mathbb{R}^m \setminus RV(f).$$

From this definition is tautologically verified that all values $p \notin f(U)$ are regular.

Let us firstly observe that if $f : \overline{\Omega} \to \mathbb{R}^n$ is a C^1 function such that $f \neq p$ on $\partial\Omega$ and p is a regular value of f, then the set $f^{-1}(p)$ is finite. This allows the following definition of Degree on regular values.

Definition 2.2.2 *Let $y \in RV(f)$, then the Brouwer Degree is defined as:*

$$deg(f, \Omega, y) = \sum_{x \in f^{-1}(y)} sgn(J_f(x)),$$

where $J_f(x) = det(Df(x))$.

We now give the tools to extend the previous definition for arbitrary continuous f in such a way that properties $(1)-(4)$ are satisfied. The first step is to state a version of Sard's Theorem:

Theorem 2.2.1 *Let $m \leq n$ and $f : U \subset \mathbb{R}^n \to \mathbb{R}^m$ be a C^1 function. Then the set of critical values $CV(f)$ has measure 0. In particular, the set of regular values $RV(f)$ is dense in $\mathbb{R}^m$.*

Let $C^1_{reg}(\overline{\Omega}, \mathbb{R}^m)$ be the set of functions in $C^1(\overline{\Omega}, \mathbb{R}^m)$ for wich $0 \in RV(f)$. The following Lemma is a consequence of Sard's Theorem.

Lemma 2.2.2 *$C^1_{reg}(\overline{\Omega}, \mathbb{R}^m)$ is dense in $C(\overline{\Omega}, \mathbb{R}^m)$.*

In next Lemma we consider the point $p = 0$ without loss of generality.

Lemma 2.2.3 *Let $f \in C^1(\overline{\Omega}, \mathbb{R}^m)$ be such that $0 \in RV(f)$ and $f \neq 0$ in $\partial\Omega$. Then, there exists a neighborhood V of 0 such that if $y \in V$. Then, $y \in RV(f)$ and $f \neq y$ in $\partial\Omega$. Moreover,*

$$deg(f, \Omega, y) = deg(f, \Omega, 0).$$

This Lemma says that the Brouwer degree is constant in a ball small enough around 0 for a given function f and a set Ω.

Lemma 2.2.4 *Let $f \in C^1_{reg}(\overline{\Omega}, \mathbb{R}^n)$. There exists $\epsilon > 0$ such that if $g \in C^1(\overline{\Omega}, \mathbb{R}^n)$ verifies $||g - f||_{L^\infty} < \epsilon$ then, $0 \in RV(g), g \neq 0$ in $\partial\Omega$ and $deg(g, \Omega, 0) = deg(f, \Omega, 0)$.*

Proposition 2.2.1 *Let $\Omega \subset \mathbb{R}^n$ be an open and bounded set, and let $y \in \mathbb{R}^n$. Then there exists a unique continuous function*

$$deg(\,\cdot\,, \Omega, y) : \mathcal{A}(y) \to \mathbb{Z}$$

with the following properties:

1. *Normalization: If $y \in \Omega$, then $deg(Id, \Omega, y) = 1$;*
2. *Translation invariance: $deg(f, \Omega, y) = deg(f - y, \Omega, 0)$;*
3. *Additivity: If Ω_1, Ω_2 are two open disjoint subsets of Ω, then the following holds: If $y \notin f(\overline{\Omega} - (\Omega_1 \cup \Omega_2))$ then:*
$$deg(f, \Omega, y) = deg(f|_{\overline{\Omega_1}}, \Omega_1, y) + deg(f|_{\overline{\Omega_2}}, \Omega_2, y);$$
4. *Homotopy invariance: If $h : \overline{\Omega} \times [0,1] \to \mathbb{R}^n$ is continuous and $h(x, \lambda) \neq y$ for all $x \in \partial\Omega$, $\lambda \in [0,1]$, then $deg(h(\cdot, \lambda), \Omega, y)$ does not depend on $\lambda \in [0,1]$. Moreover, y can be replaced by a continuous function $y : [0,1] \to \mathbb{R}^n$ such that the previous condition is valid.*

Definition 2.2.3 *The function*

$$deg(\,\cdot\,, \Omega, y) : \mathcal{A}(y) \to \mathbb{Z}$$

*is called the **Brouwer's degree**.*

Proposition 2.2.2 *The Brouwer's degree satisfies:*

1. *Solution: If $deg(f, \Omega, y) \neq 0$, then $y \in f(\Omega)$, moreover, $f(\Omega)$ is a neighborhood of y;*
2. *Excision: If Ω_1 is an open subset of Ω, $y \neq f(\overline{\Omega} - \Omega_1)$, then*
$$deg(f, \Omega, y) = deg(f, \Omega_1, y).$$

We remark that the Brouwer degree can be generalized to finite n-dimensional Banach spaces E. Indeed, it is possible by identifying E with $\mathbb{R}^n$. Moreover, if we consider $\Omega \subset \mathbb{R}^n$ and functions $f \in C(\Omega, \mathbb{R}^m)$ with $m \leq n$, then the degree can also be defined:

Lemma 2.2.5 *Let $\Omega \subset \mathbb{R}^n$ be open and bounded, let $f \in C(\overline{\Omega}, \mathbb{R}^m)$ and let $m < n$. Identify $\mathbb{R}^m$ with $\mathbb{R}^m \times \{0\} \subset \mathbb{R}^n$. Let also be $g : \overline{\Omega} \to \mathbb{R}^n$ given by $g(x) = x - f(x)$. Then for every $y \in \mathbb{R}^m - g(\partial\Omega)$ we have:*

$$deg(g, \Omega, y) = deg(g\big|_{\overline{\Omega} \cap \mathbb{R}^m}, \Omega \cap \mathbb{R}^m, y)$$

We refer to the books of Amster [1] or Lloyd [34], for a more detailed analysis of this subject.

2.2.3 The Leray-Schauder degree

Now we will extend the Brouwer degree to general Banach spaces E. It is not possible for arbitrary continuous functions.

For infinite dimensional spaces, Leray and Schauder showed that the theory of topological degree can be extended for compact perturbations of the identity. We will consider operators $\mathcal{F}$ of the form $\mathcal{F} = Id - \mathcal{K}$, where $\mathcal{K} : \overline{\Omega} \to E$ is a compact operator and Id is the identity operator. This kind of operators can be approximated by finite range operators:

Lemma 2.2.6 *Given $\epsilon > 0$ there is an operator $F_\epsilon : \overline{\Omega} \to E$ continuous such that $Rg(F_\epsilon) \subset V_\epsilon$, with $dim(V_\epsilon) < \infty$ and such that $||\mathcal{F}(x) - F_\epsilon(x)|| < \epsilon$, for all $x \in \overline{\Omega}$.*

The following lemma is deduced from compactness:

Lemma 2.2.7 *Let $\Omega \subset E$ be open and bounded, and let $K : \overline{\Omega} \to E$ be compact. If $\mathcal{K}x \neq x$, for all $x \in \partial\Omega$, then*

$$\inf_{x \in \partial\Omega} ||x - \mathcal{K}x|| > 0.$$

Proof: Page 132 [1]. ■

Now, we are able to define the Leray-Schauder degree:

Definition 2.2.4 *Let E be a Banach space. Let $\Omega \subset E$ be a bounded domain and $\mathcal{K} : \overline{\Omega} \to E$ a compact operator such that $(I - \mathcal{K})x \neq 0$, for all $x \in \partial\Omega$ and let*

$$\epsilon < \frac{1}{2} \inf_{x \in \partial\Omega} ||x - \mathcal{K}x||.$$

We define the Leray-Schauder's degree as

$$deg_{LS}(I - \mathcal{K}, \Omega, 0) := deg(I - \mathcal{K}_\epsilon\big|_{V_\epsilon}, \Omega \cap V_\epsilon, 0)$$

where $\mathcal{K}_\epsilon$ is such that $Rg(\mathcal{K}_\epsilon) \subset V_\epsilon$ and that $||\mathcal{K}(x) - \mathcal{K}_\epsilon(x)|| < \epsilon$, for all $x \in \overline{\Omega}$.

To see that the Leray-Schauder degree is well defined, let K_ϵ and $\tilde{K}_\epsilon$ be ϵ-approximations of K with ranges in the finite dimensional subspaces V_ϵ and $\tilde{V}_\epsilon$, respectively. By Lemma 2.2.5, if $V := V_\epsilon + \tilde{V}_\epsilon$, then defining the isomorphisms with the corresponding Euclidean spaces yields

$$deg((I - K_\epsilon)\big|_{V_\epsilon}, \Omega \cap V_\epsilon, 0) = deg((I - K_\epsilon)\big|_{V}, \Omega \cap V, 0),$$

$$deg((I - \tilde{K}_\epsilon)\big|_{\tilde{V}_\epsilon}, \Omega \cap \tilde{V}_\epsilon, 0) = deg((I - \tilde{K}_\epsilon)\big|_{V}, \Omega \cap V, 0).$$

Moreover, the homotopy

$$h(x, \lambda) := \lambda(I - K_\epsilon) + (1 - \lambda)(I - \tilde{K}_\epsilon) \neq 0, \quad \text{on } \partial(\Omega \cap V) \subset \partial\Omega \cap V.$$

We remark that the properties of Leray-Schauder and Brouwer degrees are analogous. Here, the most important properties that shall be used in this thesis:

1. *Normalization:* $deg(Id, \Omega, p) = \begin{cases} 1 & \text{if } p \in \Omega \\ 0 & \text{if } p \notin \Omega \end{cases}$
2. *Solution:* If $deg_{LS}(\mathcal{F}, \Omega, 0) \neq 0$, then $\mathcal{F}$ has at least one zero in Ω;
3. *Excision:* If $\Omega_1 \subset \Omega$ is open and F does not vanish in $\overline{\Omega} \setminus \Omega_1$, then $deg(F, \Omega, p) = deg(F, \Omega_1, p)$.
4. *Homotopy invariance:* If $\mathcal{F}_\lambda = Id - \mathcal{K}_\lambda$ with $\mathcal{K}_\lambda : \overline{\Omega} \to E$ compact such that $\mathcal{K}_\lambda u \neq u$ for all $u \in \partial\Omega$, $\lambda \in [0,1]$ and $\mathcal{K} : \overline{\Omega} \times [0,1] \to E$ given by $\mathcal{K}(u, \lambda) := \mathcal{K}_\lambda(u)$ is continuous, then $deg_{LS}(\mathcal{F}_\lambda, \Omega, 0)$ does not depend on λ.
5. If $\mathcal{K}(\overline{\Omega}) \subset V$, with $V \subset E$ a finite dimensional subespace, then

$$deg(\mathcal{F}, \Omega, 0)_{LS} = deg_B(\mathcal{F}\big|_{\overline{\Omega} \cap V}, \Omega \cap V, 0),$$

   where deg_B denotes Brouwer's degree.

It is interesting to note that *homotopy invariance* requires the additional hypothesis: h is of the form $h(\cdot, \lambda) := \mathcal{F}_\lambda = I - \mathcal{K}_\lambda$ with $\mathcal{K}_\lambda$ compact.

2.2.4 Continuation theorems

Now, the objective is to obtain existence results by using topological degree for solving the following problem:

Let E and F be Banach spaces. A wide range of problems in nonlinear analysis may be presented in the form of an abstract equation

$$Lu = Nu, \tag{2.15}$$

where $L : D \subset E \to F$ is a linear operator and $N : E \to F$ is continuous.

Let us consider the nonresonant case, in which L is invertible. Assume that L has a compact inverse and N maps bounded sets into bounded sets; then problem (2.15) may be written as $u = Ku$, where $K = L^{-1}N : E \to E$ is compact. Let h be the homotopy $h(u, \lambda) = u - \lambda K u$; by the properties of the Leray-Schauder degree it is immediate the existence of at least one solution of (2.15), provided that we are able to find a open bounded $\Omega \subset E$ such that $0 \in \Omega$ and $u \neq Ku$ for $u \in \partial\Omega$ and $\lambda \in (0,1)$. Indeed, we may assume that $u \neq Ku$ for $u \in \partial\Omega$, since, otherwise K has already a fixed point. Moreover, $deg(h(u, 0)) \neq 0$ since $0 \in \Omega$, and hence

$$deg(I - K, \Omega, 0) = deg(I, \Omega, 0) = 1.$$

More concretely,

Theorem 2.2.2 *Let E and F be Banach spaces, and let $L : D \subset E \to F$ be linear, $N : E \to F$ continuous. Assume that L is one-to-one and $K := L^{-1}N$ is compact. Furthermore, assume there exists a bounded and open subset $\Omega \subset E$ with $0 \in \Omega$ such that the equation $Lu = \lambda Nu$ has no solutions in $\partial\Omega \cap D$ for any $\lambda \in (0,1)$. Then the problem $Lu = Nu$ has at least one solution in Ω.*

However, a wide range of different results can be obtained in more general contexts. For example, the following problem is about the existence of T-periodic solutions of the first-order delay differential system:

$$x' = f(t, x(t), x(t-\tau)) \tag{2.16}$$

with $\tau > 0$ and $f : \mathbb{R} \times \mathbb{R}^{2n} \to \mathbb{R}^n$ continuous and T-periodic in t, that is $f(t+T, u, v) = f(t, u, v)$ for all $(t, u, v) \in \mathbb{R} \times \mathbb{R}^{2n}$. An appropriate Banach space is:

$$C_T := \{u(t) \in C(\mathbb{R}, \mathbb{R}) : u(t+T) = u(t) \text{ for all } t\} \tag{2.17}$$

equipped with the usual uniform norm. Note that $L : D = C_T \cap C^1(\mathbb{R}, \mathbb{R}^n) \to C_T$ is not invertible since its kernel is the set of constant functions, identified with $\mathbb{R}^n$. Moreover, if $u \in D$ and $u' = \varphi$, then

$$\overline{\varphi} := \frac{1}{T}\int_0^T \varphi(s)ds = 0. \tag{2.18}$$

On the other hand, for any $\varphi \in C_T$ such that $\overline{\varphi} = 0$ all its primitives $c + \int_0^T \varphi(s)ds$ belong to D, so $\varphi \in Im(L)$. That is, the range of L is the set of zero-average functions. Thus, define

$$\overline{C}_T := \{\varphi \in C_T : \overline{\varphi} = 0\}$$

and $K : \overline{C}_T \to D$, such that $LK\varphi = \varphi$ for all $\varphi \in \overline{C}_T$, that is, K is a right inverse of φ, for convenience we choose K a compact operator such that:

$$K\varphi(t) := -\frac{1}{T}\int_0^T \int_0^s \varphi(r)dr\, ds + \int_0^t \varphi(s)ds.$$

It is readily seen that $(K\varphi)' = \varphi$ and $K\varphi(t+T) - K\varphi(t) = \int_t^{t+T} \varphi(s)ds = 0$; moreover $\int_0^T K\varphi(t)dt = 0$.

Next, we define the operator $N : C_T \to C_T$, $Nu(t) := f(t, u(t), u(t-\tau)$. It is clear that our original problem is equivalent to the system of equations:

$$\overline{Nu} = 0 \text{ and } \qquad u = \overline{u} + KNu.$$

It is worth noticing that if $\overline{Nu} \neq 0$ then Nu would not belong to the domain of K and then second equality could not be well defined. Since we want to bring out the problem to a fixed point equation we should restrict ourselves to $\{u \in C_T : \overline{Nu} = 0\}$. To overcome this problem we consider the equivalent system:

$$\overline{Nu} = 0 \text{ and } \qquad u = \overline{u} + K(Nu - \overline{Nu}).$$

We obtain the one-parameter family of problems $h(u, \lambda) = 0$, where the homotopy $h : C_T \times [0, 1] \to C_T$ is defined by:

$$h(u, \lambda) = u - (\overline{u} + \overline{Nu} + \lambda K(Nu - \overline{Nu})). \tag{2.19}$$

When $\lambda > 0$, it is readily seen that $h(u, \lambda) = 0$ if and only if

$$u'(t) = \lambda f(t, u(t), u(t-\tau)). \tag{2.20}$$

The operator $h(u, 0) - u = -(\overline{u} + \overline{Nu}) \in R^n$ for all u. According to properties of the Leray-Schauder degree, if there exists an open bounded set $\Omega \subset C_T$ such that $h(\cdot, 0)$ does not vanish when $u \in \partial\Omega$ for some $\Omega \subset C_T$ open and bounded, then

$$deg(h(\cdot, 0), \Omega, 0) = (-1)^n deg(\phi, \Omega \cap \mathbb{R}^n, 0),$$

where $\phi : \mathbb{R}^n \to \mathbb{R}^n$ is given by $\phi(u) := -\overline{Nu} = -\frac{1}{T}\int_0^T f(t, u, u)dt$.

More concretely, we have proved the following continuation theorem:

Theorem 2.2.3 *Assume there exists an open bounded $\Omega \subset C_T$ such that the following conditions are fulfilled:*

1. *Problem* (2.20) *has no solutions on $\partial\Omega$ for $0 < \lambda < 1$;*
2. *$\phi(u) \neq 0$ for $u \in \partial\Omega \cap \mathbb{R}^n$, with $\phi(u) := -\frac{1}{T}\int_0^T f(t, u, u)dt$;*
3. *$deg(\phi, \Omega \cap \mathbb{R}^n, 0) \neq 0$.*

Then (2.16) *has at least one solution $u \in \overline{\Omega}$.*

2.2.5 Continuation theorem for a functional equation

In [4], authors establish a continuation theorem for an abstract functional differential equation, that will be the key for our periodic existence results in chapter 5.

More concretely, they consider the functional equation:

$$x'(t) = \Phi(x)(t), \tag{2.21}$$

where the functional $\Phi : C_T \to C_T$ is continuous and maps bounded sets in bounded sets and C_T is defined as in (2.17), denoting the space of continuous T-periodic functions.

We define, for $r < s$, the set

$$X_r^s := \{u(t) \in C_T : r < u(t) < s \text{ for all } t\}.$$

The closure of X_r^s shall be denoted by $cl(X_r^s)$. The maximum value and the minimum value of an arbitrary function $\varphi \in C_T$ shall be denoted respectively by φ_{max} and φ_{min}, namely

$$\varphi_{max} = \max_{[0,T]} \varphi(t), \qquad \varphi_{min} = \min_{[0,T]} \varphi(t),$$

and $\overline{\varphi}$ defined as in (2.18).

We consider the natural inclusion $\mathbb{R} \subset C_T$ and define a mapping $\phi : \mathbb{R} \to \mathbb{R}$ as follows,

$$\phi(\gamma) = \overline{\Phi(\gamma)} = \frac{1}{T}\int_0^T \Phi(\gamma)(t)dt. \tag{2.22}$$

Actually, for simplicity we are using the same symbol to denote both a real number γ and the constant function $x(t) \equiv \gamma$, ignoring the isomorphism between $\mathbb{R}$ and the set of constant functions in $\mathbb{R}$. However, it is important to notice that if $x \in C_T$ is the constant function given by $x(t) = \gamma$ for all t. Thus, $\Phi(x)$ is an element of C_T and ϕ is well defined.

Theorem 2.2.4 *Assume there exist constants $r < s$ such that*

- *If $x'(t) = \lambda\Phi(x)(t)$ for some $x \in cl\,(X_s^r)$ and $0 < \lambda < 1$, then $x \in X_s^r$.*
- *$\phi(r)\phi(s) < 0$.*

Then (2.21) *has at least one solution $x \in cl\,(X_s^r)$.*

Proof: [4] The proof follows from similar arguments to those employed in Theorem 2.2.3. ■

2.3 Almost periodic functions

Here we enumerate the main results in the classical theory of almost periodic functions, we will deal with this space in Chapter 7. For a more detailed analysis of this subject, see the books of Fink [18] and Corduneanu [12].

2.3.1 Definitions and general properties

Almost periodic functions are intended to be generalizations of periodic functions in some sense. We shall introduce this generalization in a natural way to understand better the importance of this space.

Let be the Banach space

$$BC = \{\text{bounded and continuous functions } p : \mathbb{R} \to \mathbb{C}\}$$

be equipped with the norm

$$||p||_\infty = \sup_{t \in \mathbb{R}} |p(t)|.$$

For each $T > 0$

$$Per_T = \{\text{continuous and } T\text{-periodic functions}\}$$

is a linear subspace. The class of periodic functions

$$Per = \bigcup_{T>0} Per_T f,$$

has not linear structure and it is not closed under uniform limits. The space AP($\mathbb{C}$) is the algebraic and topological closure of Per in BC, that is,

$$Per \subset AP(\mathbb{C}) \subset BC.$$

AP is the smallest Banach space that satisfies this chain of inclusions. Thus AP($\mathbb{C}$) is a complete normed space of functions that contains all periodic functions. In particular, it is closed under sums and uniform limits.

There are several known equivalent definitions of almost periodic functions, the choice depends on the property to be proven.

Together with the properties and definitions we shall give examples for periodic functions. These examples will permit us to more easily understand the parallelism between periodic and almost periodic functions.

Among these different definitions we shall focus on both Bochner's characterization in terms of sequential convergence of families translates and Bohr's definition based on the quasi-periods.

Definition 2.3.1 *(Bochner) A $f : \mathbb{R} \to \mathbb{C}$ is almost periodic if from every sequence $\{\alpha'_n\}$ one can extract a subsequence $\{\alpha_n\}$ such that*

$$\lim_{n\to\infty} f(t+\alpha_n)$$

exists uniformly on the real line.

This definition appeared for the first time in *Bochner, Beitrage zur Theorie der fastperiodiche Funktionen. I: Functionen einer Variablen, Math. Ann. 96 (1927), 119-147.*

It is easy to prove that periodic functions satisfy Definition 2.3.1. Indeed, let f be a T-periodic function and $\{\alpha'_n\}$ an arbitrary sequence. From the given sequence $\{\alpha'_n\}$ we define the bounded sequence $\{\alpha'_n (\mathrm{mod\,T})\}$, we may select a subsequence $\{\alpha_n (\mathrm{mod\,T})\}$ such that converges to α_0. Then, if $\{\alpha_n\}$ is the associated subsequence, we have

$$\lim_{n\to+\infty} f(t+\alpha_n) = f(t+\alpha_0).$$

Now, we shall introduce the Bohr's definition. First, some previous definitions and notation are needed.

Definition 2.3.2 *A subset S of $\mathbb{R}$ is called* ***relatively dense*** *if there exists a positive number L such that*

$$[a, a+L] \cap S \neq \emptyset \textit{ for all } a \in \mathbb{R}.$$

The number L is called the inclusion length.

Roughly speaking, the complement of S should not contain arbitrarily long intervals.

For example, if we consider $S = \mathbb{Z}$, then $[a, a+1] \cap \mathbb{Z} \neq \emptyset$ for all $a \in \mathbb{R}$. In this case, the inclusion lenght number is $L = 1$ and $\mathbb{Z}$ is relatively dense. In the other hand, if we consider $S = \mathbb{N}$, there no exists a number L such that $[a, a+1] \cap \mathbb{N} \neq \emptyset$ for all $a \in \mathbb{R}$. Thus, $\mathbb{N}$ is not a relatively dense set.

Definition 2.3.3 *For any bounded complex function f and $c > 0$, we define*

$$T(f,\epsilon) = \{\tau : |f(t+\tau) - f(t)| < \epsilon \textit{ for all } t\}. \tag{2.23}$$

$T(f,\epsilon)$ is called the ϵ-translation set of f.

Definition 2.3.4 *(Bohr) A function $f : \mathbb{R} \to \mathbb{C}$ is called* ***almost periodic*** *if for every $\epsilon > 0$, $T(f,\epsilon)$ is relatively dense.*

For T-periodic functions it is clear that $T(f,\epsilon)$ is relatively dense since the functions satisfy $f(t+nT) = f(t)$ for all $n \in \mathbb{N}$, that is, $nT \in T(f,\epsilon)$ for all ϵ. Thus, given $\epsilon > 0$ taking $L(\epsilon) = T$ such that $[a, a+T] \cap T(f,\epsilon) \neq \emptyset$.

The geometric significance of $T(f,\epsilon)$ for almost periodic functions is a generalization of the idea of periodic functions, where the translated graph differs from the graph of f at least within ϵ if $\tau \in T(f,\epsilon)$.

Lemma 2.3.1 *Let $f : \mathbb{R} \to \mathbb{C}$. f has the property given by Definition 2.3.1 if and only if f has the property given by Definition 2.3.4.*

Proof: Page 16 [11] ■

Lemma 2.3.2 *Let $f, g \in AP(\mathbb{C})$ and $\lambda \in \mathbb{C}$. Then the following properties are fulfilled:*

(a) *$f+g, f\cdot g$ and $\lambda f \in AP(\mathbb{C})$.*

(b) *If $\inf_{t\in\mathbb{R}} |f(t)| > 0$, then $\frac{1}{f(t)} \in AP(\mathbb{C})$.*

(c) *f is bounded.*

(d) *f is uniformly continuous.*

(e) *If F is uniformly continuous on the range of f, then $F \circ f \in AP(\mathbb{C})$.*

(f) *Let $\mathcal{F}$ be a finite family of almost periodic solutions. Then, for every $\epsilon > 0$*

$$\bigcap_{f\in\mathcal{F}} T(f,\epsilon) \text{ is relatively dense.}$$

(g) *If $f, g \in AP(\mathbb{C})$, then $h(t) = f(t-g(t)) \in AP(\mathbb{C})$.*

(h) *Let $\inf_{t\in\mathbb{R}} g(t) > 0$. Then $F \in AP(\mathbb{R})$, where*

$$F(t) = \int_{-\infty}^{t} e^{-\int_s^t g(u)du} f(s)ds, \qquad t \in \mathbb{R}.$$

Proof: For proofs of (a)-(e) and (f) see Chapter 1 [18] and Chapter 2 page 19 respectively.

Let us prove property (g). Let $\epsilon > 0$, from the uniform continuity of f there exists $\delta(\epsilon) > 0$ such that

$$|f(x) - f(y)| < \frac{\epsilon}{2} \text{ for all } x, y \text{ such that } |x-y| < \delta.$$

Moreover, δ may by chosen in such a way that $\delta \in (0, \frac{\epsilon}{2})$.

Let $\tau \in T(f, \frac{\delta}{2}) \cap T(g, \frac{\delta}{2})$, in view of the uniform continuity of f and the almost periodicity of f and g we obtain:

$$\begin{aligned}
\big|h(t+\tau) - h(t)\big| &= \big|f(t+\tau-g(t+\tau)) - f(t-g(t))\big| \\
&\le \big|f(t+\tau-g(t+\tau)) - f(t+\tau-g(t))\big| + \big|f(t+\tau-g(t)) - f(t-g(t))\big| \\
&\le \frac{\epsilon}{2} + \frac{\delta}{2} < \epsilon.
\end{aligned}$$

Since, by property (f), $T(f, \frac{\delta}{2}) \cap T(g, \frac{\delta}{2})$ is relatively dense we conclude that $h(t) \in AP(\mathbb{C})$. ■

As an example, $h(t) = \cos(t) + \cos(\sqrt{2}t)$ is almost periodic by property (a). However, the equation $\cos(t) + \cos(\sqrt{2}t) = 0$ has only one solution, thus $h(t)$ is not a periodic function.

Another interesting difference between periodic and almost periodic function is given by the following example:

Example 2.3.1 *Let $f_n : \mathbb{R} \to \mathbb{R}$ be the $2\pi 5^n$-periodic functions defined by $f_n(x) := \sin\,(\frac{x}{5^n})$, for each $n \in \mathbb{N}$. It is readily seen that the series $\sum_{n=1}^{\infty} \frac{\sin\,(\frac{x}{5^n})}{5^n}$ converges uniformly and absolutely on n, then the function $f(x) := \sum_{n=1}^{\infty} \frac{\sin\,(\frac{x}{5^n})}{5^n}$ is well defined and*

$$|f(x)| < \sum_{n=0}^{\infty} \frac{1}{5^n} := S. \tag{2.24}$$

Moreover, $f(x)$ is a positive almost periodic function.

Consider the subsequence $\{x_n\}_{n\in\mathbb{N}}$, where $x_n := \frac{5^n\pi}{2}$. Observe that x_n is the first positive value where $f_n(x) = 1$. Moreover, $f_k(x_n) = 1$ for all $0 < k \leq n$.

Thus,

$$f(x_n) \to S \text{ as } n \to \infty \text{ and } f(x) \neq S \text{ for any } x \in \mathbb{R}. \tag{2.25}$$

Let us define the positive almost periodic function $g(x) := S - f(x)$. In view of (2.24) and (2.25) we have

$$\inf_x g(x) = 0 \text{ and } g(x) > 0 \text{ for all } x \in \mathbb{R}.$$

The study of existence of almost periodic solutions plays a central role in differential equations and their applications. In addition, other interesting property to be analyzed is the stability of such solutions. More precisely, we shall focus on the stability of almost periodic solutions of (2.9).

For simplicity, a solution of the initial value problem (2.11) shall be denoted by $x(t; t_0, \varphi)$.

Lema 2.3.1 *Let $f, g \in AP(\mathbb{C})$. Suppose that $\lim_{t\to\infty} f(t) = 0$, then $f \equiv 0$.*

Proof: Consider the sequence $\alpha_n' = n \in \mathbb{N}$, by Bochner' s definition, there exists an increasing subsequence $\{\alpha_n\}$ such that $f(t + \alpha_n)$ converges uniformly on the real line. Moreover, $f(t + \alpha_n)$ converges uniformly to 0, the limit is given by the pointwise convergence.

Thus, defining $f_{\alpha_n}(t) := f(t + \alpha_n)$, we get

$$||f||_{\infty,\mathbb{R}} = ||f_{\alpha_n}||_{\infty,\mathbb{R}} = 0.$$

We conclude that $f \equiv 0$. ■

The following corollary is a direct consequence of Lemma 2.3.1. It shall be useful in Chapter 7 to conclude uniqueness of solutions.

Corollary 2.3.1 *Let $f, g \in AP(\mathbb{C})$. Let $\epsilon > 0$, if there exists $t_0(\epsilon) > 0$ such that $|f(t) - g(t)| < \epsilon$ for all $t \geq t_0$, then $f \equiv g$ for all $t \in \mathbb{R}$.*

Definition 2.3.5 *Let be $\epsilon > 0$. An almost periodic solution $\tilde{x}(t)$ of (2.9) is **globally asymptotically stable** if there exists $t_{\epsilon,\varphi} := t(\epsilon, \varphi) > 0$ and such that for every $x(t; t_0, \varphi)$ solution of (2.11)*

$$|\tilde{x}(t) - x(t; t_0, \varphi)| < \epsilon \text{ for all } t > t_{\epsilon,\varphi}.$$

In view of Corollary 2.1.1 we have the following result:

Theorem 2.3.1 *(Uniqueness) Let $x(t)$ be an almost periodic solution of* (2.9)*. Assume that $x(t)$ is globally asymptotically stable. Then $x(t)$ is the unique solution of* (2.9) *in $AP(\mathbb{C})$.*

Definition 2.3.6 *An almost positive periodic solution $\tilde{x}(t)$ of* (2.9) *is **globally exponentially stable** if there exist constants $t_{\varphi,\tilde{x}}$, $K_{\varphi,\tilde{x}}$ and $\rho > 0$ such that every solution $x(t; t_0, \varphi)$ of (7.1) and (7.4) satisfies,*

$$|x(t; t_0, \varphi) - \tilde{x}(t)| < K_{\varphi,\tilde{x}} e^{-\rho t} \qquad \text{for all } t > t_{\varphi,\tilde{x}}.$$

It is clear that global exponential stability implies asymptotic stability. Thus, if an almost periodic solution is globally asymptotically stable, then it is unique.

2.3.2 Uniformly almost periodic families. The class u.a.p

Consider the differential equation

$$x' = f(t, x), \tag{2.26}$$

where f is an almost periodic solution as a function of t and x is considered a parameter. In order to search almost periodic solutions $\varphi(t)$, it is necessary to consider the composition $f(t, \varphi(t))$. Is this an almost periodic function? The answer is, in general, negative. For example, the function $f(t, x) = \sin\,(xt)$ with $x \in \mathbb{R}$ is periodic in t for each x. However, if we consider $\varphi(t) = \sin\,(t)$ the composition $f(t, \varphi(t)) = \sin\,(t \sin\,(t))$ is not uniformly continuous, thus it is not almost periodic.

Let Ω be a subset of E^n, the n-dimensional space $\mathbb{R}^n$ (or $\mathbb{C}^n$) with the usual Euclidean norm. We shall consider functions of the form $f(t, x)$ defined on the set $\mathbb{R} \times \Omega$ and with values in E^n. We shall assume that any function appearing in next Theorem and definition is continuous on $\mathbb{R} \times \Omega$.

Definition 2.3.7 *A function $f(t, x)$ is called **almost periodic in t, uniformly with respect to** $x \in \Omega$, if to any $\epsilon > 0$ corresponds a number $l(\epsilon)$ such that any interval of the real line of length $l(\epsilon)$ contains at least one number τ for which*

$$|f(t + \tau, x) - f(t, x)| < \epsilon, \;\; x \in \Omega, \;\; t \in \mathbb{R}. \tag{2.27}$$

Again, the number τ is called an ϵ-translation number of $f(t, x)$. The uniform dependence on x follows from the fact that τ and $l(\epsilon)$ are independent of x.

This definition is just one of the possible ways to introduce the notion of uniform almost periodicity and we refer to [18] for alternative formulations.

We shall say that $f(t, x)$ is in **the class u.a.p** (uniformly almost periodic) if

$$f(t, x) \in \{f : \mathbb{R} \times \Omega \to \mathbb{R} \text{ such that } f \text{ is almost periodic in } t \text{ uniformly with respect to } x\}. \tag{2.28}$$

The following Lemma shall be useful in Chapters 6 and 7.

Lemma 2.3.3 *If $f, r : \mathbb{R} \to \mathbb{R}$ are functions in $AP(\mathbb{R})$, then $r(t)f(x)$ is in the class u.a.p.*

Lemma 2.3.4 *Let Ω be a closed bounded set and $f(t,x)$ a function in the class u.a.p. Then $f(t,x)$ is bounded and uniformly continuous on $\mathbb{R}\times\Omega$.*

Proof: Page 52 [12]. ■

Lemma 2.3.5 *Let Ω be a closed bounded set $f(t,x)$ and $g(t,x)$ be functions in the class u.a.p. Then the following conditions are fulfilled:*

1. *$f(t,x)+g(t,x)$ and $f(t,x).g(t,x)$ are in the class u.a.p.;*
2. *If $|g(t,x)|\geq m>0$, then $f(t,x)/g(t,x)$ is in the class u.a.p.*

Proof: Page 56 [12]. ■

The following Theorem shall be especially useful in Chapter 6, where we shall give existence results of almost periodic solutions of differential equations.

Theorem 2.3.2 *If $\varphi\in AP(E^n)$ and $f(\cdot,x)\in AP(E^n)$ uniformly for x in compact subsets of E^n, then $f(t,\varphi(t))\in AP(E^n)$.*

Proof: Page 27 [18] or page 57 [12]. ■

2.3.3 Almost periodic functions in Banach spaces

In this section we shall denote by X complex Banach space with the norm topology $||\cdot||$ and consider functions $f:\mathbb{R}\to X$ with values in the Banach space X. For a more detailed analysis we refer to the Chapter 6 of [12].

Definition 2.3.8 *A continuous function $f:\mathbb{R}\to X$ is called* ***almost periodic****, if for any $\epsilon>0$ there exists a number $l(\epsilon)>0$ such that any interval on the real line of length $l(\epsilon)$ contains at least one point τ such that*

$$||f(t+\tau)-f(t)||<\epsilon,\ \textit{for all}\ t\in\mathbb{R}.$$

The main goal in this section is to establish a compactness criterion for families of almost periodic functions in the topology of AP(X). This criterion shall be very helpful to understand and clarify why classical methods such as degree theory, super and sub solutions method, Leggett-Williams and Schauder fixed point theorems among others cannot be extended naturally to the space of almost periodic functions.

Theorem 2.3.3 *Let $\mathcal{R}=\{f_1(t),\cdots,f_m(t)\}$ be a finite family of almost periodic functions, $f_i:\mathbb{R}\to X$. Let $\epsilon>0$. Then, there exist common ϵ-translation numbers for these functions.*

Proof: Consider the almost periodic function $f:\mathbb{R}\to X^m$, $f(t)=(f_1(t),\cdots,f_m(t))$ associated with the set $\mathcal{R}$. Let the norm in X^m be defined by

$$||x||=\sum_{i=1}^{m}||x_i||,$$

where $x = (x_1, \cdots, x_m) \in X^m$. It is clear that every sequence $\{f(t+\alpha'_n)\}$ of translations of f has a subsequence that converges uniformly on the real line.

From the almost periodicity of f(t) it follows that for every $\epsilon > 0$, there exists $l(\epsilon)$, such that any interval of length l includes on $\mathbb{R}$ contains at least one number τ, such that

$$||f(t+\tau) - f(t)|| < \epsilon, \qquad t \in \mathbb{R}. \tag{2.29}$$

In view of the definition of the norm in X^m and (2.29)

$$||f_i(t+\tau) - f_i(t)|| < \epsilon, \;\; t \in \mathbb{R}, i = 1, \cdots, m,$$

which proves the theorem. ■

From Theorem 2.3.3 it is clear that a finite family of almost periodic functions is equi-almost periodic, more concretely:

Definition 2.3.9 *We say that the functions belonging to a family $\mathcal{F}$ are **equi-almost periodic** if given $\epsilon > 0$, then $\bigcap_{f\in\mathcal{F}}\{\tau : ||f(t-\tau) - f(t)|| < \epsilon\}$ is relatively dense.*

Theorem 2.3.4 *A family $\mathcal{F}$ of function from AP(X) is relatively compact if and only if the following conditions are fulfilled:*

1. *$\mathcal{F}$ is equi-continuous;*
2. *for any $t \in \mathbb{R}$, the set of values of functions from $\mathcal{F}$ is relatively compact in X.*
3. *$\mathcal{F}$ is equi-almost periodic;*

Proof: Page 143 [12]. ■

It is worth noticing that, this theorem is slightly different of Arzela-Ascoli' s Theorem, now it is needed an additional statement to ensure the relatively compactness of the family $\mathcal{F} \subset AP(X)$. However, this additional condition is one of the main problem for the aforementioned methods. All these methods usually fail in the almost periodic case because of a lack of compactness of the nonlinear operators associated with the equation in the space of almost periodic functions.

Example 2.3.2 *Let $\mathcal{F} = \left\{\sin\left(\frac{t}{n}\right)\right\}_{n\in\mathbb{N}} \subset AP(\mathbb{R})$. It is clear that family $\mathcal{F}$ satisfies conditions (1) and (2) of Theorem 2.3.4 on $\mathbb{R}$. However, $\mathcal{F}$ is not precompact in $AP(\mathbb{R})$ since from $\left\{\sin\left(\frac{t}{n}\right)\right\}_{n\in\mathbb{N}}$ it is not possible to extract a uniform convergent subsequence on $\mathbb{R}$. Indeed, on the one hand, the pointwise limit is equal to 0. On the other hand, if we consider $t_n = \frac{2n}{\pi}$ then $\sin\left(\frac{t_n}{n}\right) = 1$ for all $n \in \mathbb{N}$. Thus, there is no subsequence of $\left\{\sin\left(\frac{t}{n}\right)\right\}_{n\in\mathbb{N}}$ that converges to 0.*

2.4 Nonlinear analysis in abstract cones

In this Section we shall introduce definitions and properties of cones. We shall follow the presentation by Guo and Lakshmikanthan in [23], for the proofs of all the results stated in this section refer to these books, where they give a more detailed analysis of this subject.

2.4.1 Basic properties and definitions

Definition 2.4.1 *Let X be a real Banach space. A nonempty closed set $C \subset X$ is called a* ***cone*** *if the following conditions are fulfilled:*

$$(a)\ C + C \subset C \qquad (b)\ C \cap -C = \{0\} \qquad (c)\ C \text{ is convex,}$$

where 0 denotes the zero element of X.

Every cone C induces a partial order $\leq$ in X given by

$$x \leq y \text{ if and only if } y - x \in C.$$

If $x \leq y$ and $x \neq y$, we write $x < y$. A set $\{z \in X / x \leq z \leq y\}$ is called an ***order interval*** *and shall be denoted as $[x, y]$. The interior of C shall be denoted by C°. A cone C satisfying $C^\circ \neq \emptyset$ is called a* ***solid cone***. *A cone C is called* ***normal*** *if there exists a constant $N > 0$ such that*

$$0 \leq x \leq y \text{ implies that } ||x|| \leq N||y||.$$

The smaller constant N satisfying the inequality is called the normal constant of C.

If X is a normed space, then we shall also require compatibility with the topology, that is:

$$\text{if } x_n \to x,\ y_n \to y, \text{ and } x_n \leq y_n, \text{ then } x \leq y,$$

this property is equivalent to:

$$\text{if } z_n \geq 0 \text{ and } z_n \to z, \text{ then } z \geq 0.$$

Thus, the order induced by C is compatible with the norm if and only if C is closed.

An elementary example of a compatible cone includes

$$C = \{x \in C([0,1]) : x(t) \geq 0, \text{ for all } t \in [0,1]\},$$

this cone induces the pointwise order in $C([0,1])$. Let $x(t) \equiv 2$, $y(t) = \cos\,(t) + 4$ be functions in C, an example of an order interval in this cone is

$$[x, y] = \{u \in C([0,1]) : 2 \leq u(t) \leq \cos\,(t) + 4, \text{ for all } t \in [0,1]\}.$$

Theorem 2.4.1 *Let C be a cone in X. Then the following assertion are equivalent:*

1. *C is normal;*
2. *there exists a positive constant δ such that $||x + y|| \geq \delta$, $\forall x, y \in C$, $||x|| = ||y|| = 1$;*
3. *$x_n \leq z_n \leq y_n$, $n = 1, 2, \ldots$ and $||x_n - x|| \to 0$, $||y_n - x|| \to 0$ imply $||z_n - x|| \to 0$;*
4. *every order interval $[x, y] = \{z \in X : x \leq z \leq y\}$ is bounded.*

Geometrically, from equivalence 1. and 2. we can understand *normality* as a condition over the angle between any two unitary vectors $x, y \in C$, it has to be bounded away from π. Roughly speaking, a normal cone cannot be too large.

Example 2.4.1 *Let $AP(\mathbb{R})$ be the Banach space of almost periodic real functions equipped with the usual uniform norm, and*

$$P := \{x \in AP(\mathbb{R}) : x(t) \geq 0, \forall t \in \mathbb{R}\}. \tag{2.30}$$

It is easy to see that the cone P is normal and solid. Indeed, P induces a pointwise order in $AP(\mathbb{R})$. Let $x, y \in P$, then $0 \leq x \leq y$ is equivalent to $0 \leq x(t) \leq y(t)$ for all $t \in \mathbb{R}$, thus $||x||_\infty \leq ||y||_\infty$ and P is normal with constant $N = 1$. In addition, it is readily verified that

$$P^\circ = \{x \in P : \exists \epsilon > 0 \text{ such that } x(t) \geq \epsilon, \text{ for all } t \in \mathbb{R}\} \tag{2.31}$$

and that $x \equiv a \in \mathbb{R}_{>0}$ is an element of P. Hence P is a solid cone.

2.4.2 Fixed points of monotone operators

Definition 2.4.2 *Let $(X, \leq)$ be an ordered Banach space and let $E \subset X$. An operator $\Phi : E \times E \to X$ is called a* ***mixed monotone operator*** *if $\Phi(x, y)$ is nondecreasing in x and nonincreasing in y. An element $\tilde{x} \in E$ is called a* ***fixed point*** *of Φ if $\Phi(\tilde{x}, \tilde{x}) = \tilde{x}$.*

In Section 7 we shall deal with fixed points of increasing and mixed monotone operators. Theorems of this type are useful for nonlinear differential and integral equations.

Example 2.4.2 *Let $X = AP(\mathbb{R})$ and P° be defined as in* (2.31).

Let us consider the following nonlinear nonautonomous delay differential equation, namely, the production destruction-model with two delays:

$$x'(t) = f(t, x(t - \tau(t)), x(t - \mu(t))) - b(t)x(t), \tag{2.32}$$

where $\tau(t), \mu(t)$ and $b(t)$ are positive almost periodic functions and $f : \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ is increasing in the second variable and nonincreasing in the third variable.

Let $\Phi : P^\circ \times P^\circ \to P^\circ$ be the operator defined by:

$$\Phi(x, y)(t) = \int_{-\infty}^{t} e^{\int_s^t b(u)du} f(s, x(s - \tau(s)), y(s - \mu(s)))ds.$$

Due to the monotonicity of the function $f(t, x, y)$ in the variables x and y the nonlinear operator Φ is mixed monotone in P°.

Moreover, if $x \in P^\circ$ is a fixed point of the mixed monotone operator Φ then x is a positive almost periodic solution of (2.32) *(see Lemma 6.2.1 in Chapter 6). In Section 7 we shall give criteria to ensure the existence of such fixed points.*

Resumen del capítulo 3

Este Capítulo contiene una breve explicación de los dos problemas biológicos que motivaron esta tesis. Estos son:

El modelo de Wheldon para la leucemia mieloide crónica

$$\begin{aligned}\frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)},\\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)},\end{aligned} \tag{2.33}$$

y los planteados por Mackey y Glass para la regulación de la hematopoiesis

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n P^m(t-\tau)}{\theta^n + P^n(t-\tau)} - \gamma P(t). \tag{2.34}$$

donde $m = 0, 1$.

También damos un repaso de los resultados obtenidos por diferentes autores y las generalizaciones consideradas por ellos. Además, proponemos los siguientes modelos más generales:

Para el modelo de Wheldon (2.33):

$$\begin{aligned}\frac{dM}{dt} &= \frac{\alpha(t)M(t)}{1+\beta(t)M^n(t-\tau_1)} - \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t)M(t),\\ \frac{dB}{dt} &= -\omega(t)B(t) + \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t),\end{aligned} \tag{2.35}$$

y para el modelo de Mackey-Glass (2.34):

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - b(t)x(t) \tag{2.36}$$

Estas generalizaciones serán estudiadas en los Capítulos siguientes.

Chapter 3

Introduction to the biological models

3.1 Modified Wheldon Model of CML

3.1.1 Background

Chronic myelogenous leukemia (CML) is the cancer of the blood in which too many granulocytes, a type of white blood cell, are produced in the marrow, and it makes up about 10 to 15 percent of all leukemias (see, for example, [20, 28, 38, 45, 46]). In 1974 T.E. Wheldon in the paper [60] (see also [58]) introduced the following model of granulopoiesis (granulocyte production)

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)}, \end{aligned} \tag{3.1}$$

where all parameters are positive constants. In model (3.1), $M(t)$ is the number of cells in the marrow; $B(t)$ is the number of white blood cells; β is the coupling constant for the cell production loop; α is the maximum rate of cell production; λ is the maximum rate of release of mature cells from marrow; μ is the coupling constant for the release loop; ω is the constant rate for the loss of granulocytes from blood to tissue; τ represents the mean time for stem cell maturity; n controls gain of cell production loop and m controls gain of release loop.

However, model (3.1) has a major drawback, i.e., it describes a wrong mechanism. At the (unique) nontrivial equilibrium point (M_*, B_*) of system (3.1), we have:

$$\omega B_* = \frac{\alpha}{1+\beta M_*^n}. \tag{3.2}$$

Thus, the B-population in the Wheldon model is inversely proportional to the M-population; the latter does not have any biological explanation.

To reanimate the Wheldon model, we used Wheldon's remarks in his later work [59] to introduce a new mechanism:

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha M(t)}{1+\beta M^n(t-\tau_1)} - \frac{\lambda M(t)}{1+\mu B^m(t-\tau_2)}, \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t-\tau_2)}. \end{aligned} \tag{3.3}$$

This model creates a time-delay loop triggering stem cell production and a fast loop regulating release of mature cells in the blood. Studies of the model imply that the oscillatory pattern in leukemia may be brought forth in two principal ways, either by an increased cell production rate or by an increased maturation time. Note also that model (3.3) assumes that there is a direct negative feedback from mature to the precursors of those cells. Time delay τ_1 (τ in model (3.1)) represents a mean time for $M-$ cell maturity. A stimulator/inhibitor mechanism is presented by the second term in both equations, where a time delay τ_2 is a lag between when $B-$cells are initiated and when an apparent tumor progressed (the latency time) since each cell cycle phase is dependent on the completion of the previous ones.

Remark 3.1.1 *Note that the first term in* (3.1) *is a decreasing function of M*

$$\frac{\alpha}{1+\beta M^n},$$

whereas in model (3.3)

$$\frac{\alpha M}{1+\beta M^n}$$

is a one-hump function, resulting in a relationship between stem cells and white blood cells more realistic than in (3.2)*:*

$$\omega B_* = \frac{\alpha M_*}{1+\beta M_*^n}. \tag{3.4}$$

Exposure to chemoradiation therapy will kill not only cancer cells, but other rapidly dividing cells in the body as well (e.g. the cells in the bone marrow that go on to become white blood cells), and will therefore suppress immune system [7]– [9] [20,36,45,50,57]. Note that for a new model the complete recovery is possible for sufficiently high drug dosage (see Figure below).

It is well recognized that tumor microenvironment changes with time and in response to treatment. These fluctuations can modulate tumor progression and acquired treatment resistance. Latest clinical studies on periodic hematological diseases suggest oscillations of some blood elements e.g., leukocytes, platelets, reticulocytes (see, for example, [17,36,38,50]). Henceforth, to model changes that develop in the tumor microenvironment over time, we assume model parameters are time-varying functions.
Thus, to enrich the model we incorporate time-dependent parameters

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha(t) M(t)}{1+\beta(t) M^n(t-\tau_1)} - \frac{\lambda(t) M(t)}{1+\mu(t) B^m(t-\tau_2)} - \delta p(t) M(t), \\ \frac{dB}{dt} &= -\omega(t) B(t) + \frac{\lambda(t) M(t)}{1+\mu(t) B^m(t-\tau_2)} - \delta q(t) B(t), \end{aligned} \tag{3.5}$$

where $p(t) = p(c)$ and $q(t) = q(c)$ are the varying effectiveness of the drug, and $c = c(t)$ is the drug concentration at time t. Traditionally, this pharmacokinetic is modeled by linear functions, namely $p(c) = \alpha c(t)$ and $g(c) = \beta c(t)$ where α and β are the appropriate drug sensitivity

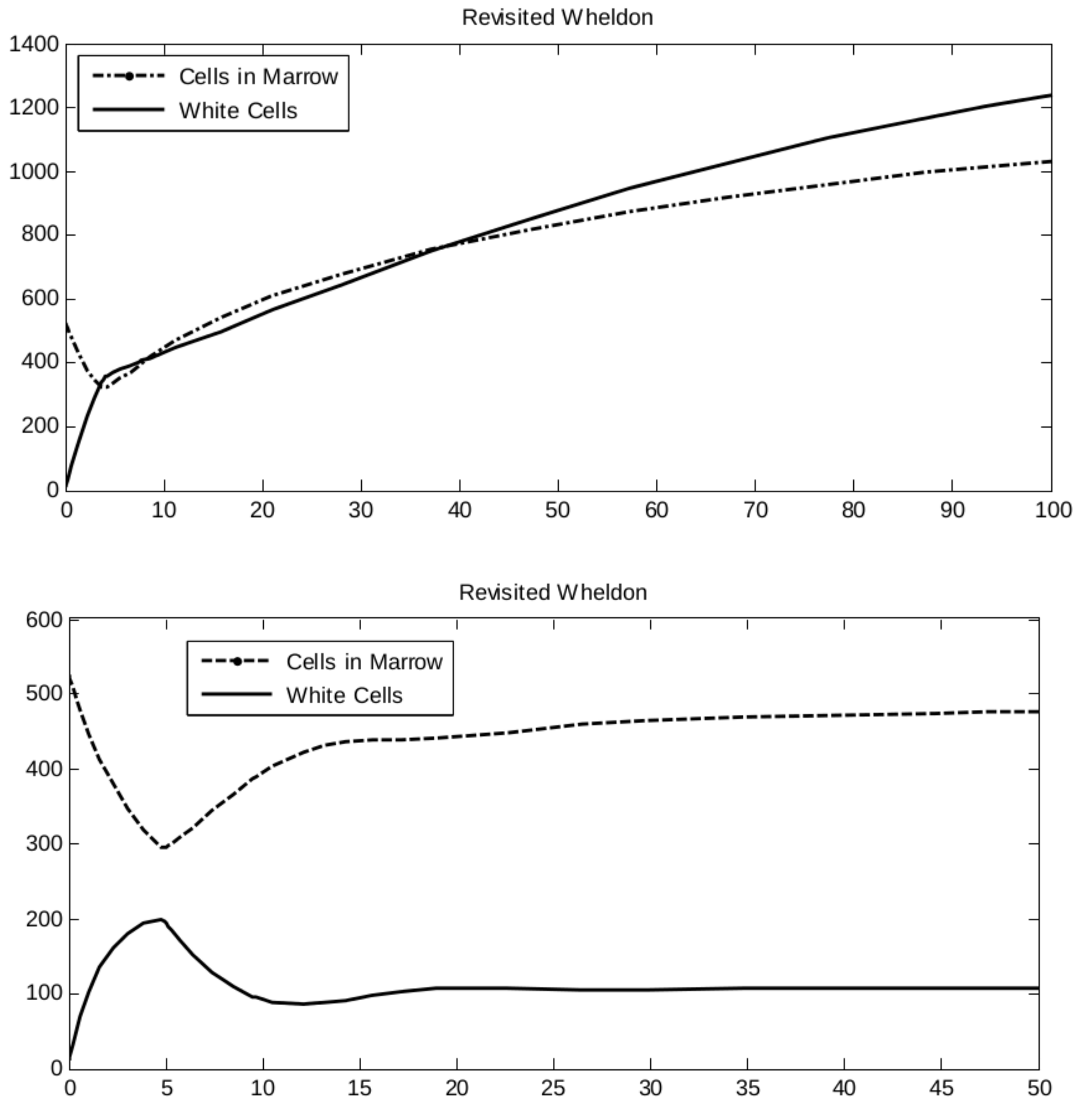


Figure 3.1: *Dynamics before therapy and after therapy.*

parameters. Clearly, $\alpha = \beta$ if the drugs are cycle-non-specific, i.e., they will be equally toxic to all types of cells. Some types of chemotherapy can be modeled based on a non-monotone one-humped functions- $p(c) = \alpha c(t)e^{-ac(t)}$ and $q(c) = \beta c(t)e^{-bc(t)}$. It will be assumed that $\alpha(t), \beta(t), \omega(t), \lambda(t), \mu(t), p(t)$ and $q(t)$ are continuous, positive and T-periodic functions and $\tau_{1,2} > 0$ are fixed delays. The parameter δ is assumed to be 1 or 0 according the presence or absence of pharmacokinetics. Different and interesting models of CML were recently examined in [6, 16, 28, 49].

3.2 Mackey-Glass model

The following nonlinear autonomous delay differential equation was proposed by Mackey and Glass [35] to study the regulation of hematopoiesis:

$$\frac{dP(t)}{dt} = \frac{\lambda\theta^n P(t-\tau)}{\theta^n + P^n(t-\tau)} - \gamma P(t). \tag{3.6}$$

Here $\lambda, \theta, n, \gamma, \tau$ are positive constants, $P(t)$ is the concentration of cells in the circulating blood and the flux function $f(v) = \frac{\lambda\theta^n v}{\theta^n + v^n}$ of cells into the blood stream depends on the cell concentration at an earlier time. The delay τ describes the time between the start of cellular production in the bone marrow and the release of mature cells into the blood. It is assumed that the cells are lost at a rate proportional to their concentration, namely $\gamma P(t)$, where γ is the decay rate. This equation constitutes a model of a 'dynamic disease'. This type of equation for population dynamics has attracted the interest of many researchers. Different aspects and properties of (3.6) have been studied by various authors, see for example [19, 22, 39].

Most often, the environment varies with time; thus, it is intuitive to assume that this fact influences many biological dynamical systems and suggests the need of considering time-dependent parameters. Moreover, as remarked in [10, 31, 47], more realistic models are those in which periodicity of the environment and time delay play a role (for more details, see e.g. [40]). In view of this, the following model was proposed in [47]:

$$x'(t) = \frac{q(t)x(t)}{r + x^n(t-mT)} - p(t)x(t) \tag{3.7}$$

where m and n are positive integers, p and q are positive T-periodic functions and the delay $\tau := mT$ is a multiple of the period determined by the environment.

In order to establish a more realistic model, it is convenient to introduce a more general delay that extends the two above-referred cases. Instead of assuming that the delay is constant or a multiple of the period of the environment, more general models are obtained by assuming that the time delay τ is an arbitrary continuous nonnegative T-periodic function depending on t. The more general equation

$$x'(t) = \frac{a(t)x(t-\tau(t))}{1 + x^n(t-\tau(t))} - b(t)x(t) \tag{3.8}$$

where a, b and τ are continuous positive T-periodic functions was studied for example in [51–53, 61, 64]. Different aspects of equation (3.8) have been considered; in particular, existence of positive T-periodic solutions was proven, in most cases, using appropriate fixed point theorems. In [61], coincidence degree theory was employed to prove the existence of a positive T-periodic solution under a condition that can be regarded as a particular application of Theorem 5.2.2, case (2) below. Moreover, when $a(t) = \gamma b(t)$ for some $\gamma > 0$ and when τ, a and b are constant, the conditions $\gamma > 1$ and $a > b$ respectively are both necessary and sufficient for the existence of positive T-periodic solutions.

The following more general model was studied in [8] and [33]:

$$x'(t) = \sum_{k=1}^{M} \frac{r_k(t)x^\delta(t-g_k(t))}{1 + x^\gamma(t-g_k(t))} - b(t)x(t). \tag{3.9}$$

Here, γ is a positive constant and r_k, b are positive T-periodic continuous functions. For $\delta = 1$, existence and uniqueness of positive T-periodic solutions was studied in [8] for the particular case of constant proportional delays $g_k \equiv l_k T$; moreover, for general continuous, positive T-periodic g_k, attractiveness of some specific positive periodic solutions was studied. For the case $\delta = 0$ and g_k continuous positive and T-periodic, existence and uniqueness of positive T-periodic solutions of (3.9) was proven in [33] by fixed point methods, provided that one of the following conditions is satisfied:

$$(1)\ \gamma \leq 1 \quad \text{or} \quad (2)\ \gamma > 1 \text{ and } \left(\frac{e^{\int_0^T b(u)du}}{e^{\int_0^T b(u)du} - 1} \int_0^T \sum_{k=1}^{M} r_k(t)dt\right)^{\gamma} \leq \frac{1}{\gamma - 1}.$$

Motivated by the previous discussion, we shall consider the following more general nonlinear nonautonomous model with several delays

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t - \tau_k(t))}{1 + x^{n_k}(t - \mu_k(t))} - b(t)x(t) \tag{3.10}$$

where $r_k(t), b(t), \tau_k(t)$ and $\mu_k(t)$ are positive and T-periodic functions and λ_k, m_k, n_k are positive constants.

Existence of solutions of (3.10) under appropriate conditions follows from several abstract results, although multiplicity results are more scarce. For example, in [27] and [64] a Krasnoselskii type fixed point theorem in cones were employed in order to obtain conditions for the existence of at least two T-periodic solutions of the general equation

$$x'(t) = -a(t)x(t) + f(t, x(t - \tau_1(t)), \ldots, x(t - \tau_n(t))). \tag{3.11}$$

It is observed, however, that these results can be applied only to few particular sub-cases of (3.10). In such cases, the conclusions are comparable to our results below. Moreover, the existence of three nonnegative periodic solutions of (3.11) was studied by using Leggett-Williams fixed point theorem in [5, 42–44]. However, the conditions obtained in [42], as pointed out by the authors, are very difficult to apply to (3.10) with $M = 1, m = 1, \tau = \mu$. Thus, they established a complementary result with more straightforward conditions that can be applied to this model. Unfortunately, in [43], the authors observed that this latter result was incorrect. In section [43, Applications], the hematopoiesis model (3.10) for $M = 1, \tau = \mu$ was studied. The conditions obtained by the authors are similar to the ones proposed in Theorem 4.2 (1) below, although only two of the three T-periodic solutions are positive and the third one is positive if $f(t, 0)$ is not identically zero. This assumption is very restrictive and clearly not fulfilled in (5.1). We may also mention the work [66], in which the existence of at least $2n$ solutions of (3.11) is proven, although the conditions are not applicable to our model. Moreover, all the mentioned works do not contemplate the *superlinear* case of (3.10) (that is, $m_k > n_k + 1$ for some k). From the biological point of view, this makes sense since the nonlinearity is a measure of the cellular production in the bone marrow, and therefore it should be bounded; however, the superlinear case is also of mathematical interest in order to obtain a complete picture of the different cases in (3.10).

A more realistic way to avoid the periodicity conditions consists in considering almost periodic effects. This is interesting for several reasons: on the one hand, these more general effects include periodicity and allow more realistic assumptions: for example,time-dependent parameters with different periods. On the other hand, since almost periodicity is more general, a central mathematical issue relies on the fact that the involved operators are no longer compact. Due to this fact, the aforementioned methods cannot be extended in a direct way for the almost periodic problem (see [41], [48]) and other methods must be employed.

For the almost periodic case we shall consider the model (3.10) with a slight modification, namely:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - b(t)x(t) \tag{3.12}$$

where $r_k, b : \mathbb{R} \to (0,+\infty)$ and $\tau_k : \mathbb{R} \to [0,+\infty)$ are almost periodic functions, in addition $b(t)$ has positive infimum, λ_k, n_k, m_k are constants such that $\lambda_k, n_k \in (0,+\infty)$ and $m_k \in [0,1]$.

In [11,62,63,65] sufficient criteria were established for the existence of positive almost periodic solutions of (3.12) with $m = 0$ (monotone decreasing nonlinearity). In [63], a fixed point theorem was employed to prove the existence and uniqueness of almost periodic solutions under conditions that can be regarded as particular applications of Theorem 7.1.1 and Theorem 7.1.4 case (a) below. In [65], using the contraction mapping principle, the authors obtained sufficient criteria for the existence in a bounded region under the assumption $n > 0$. However, as pointed out in [63], Theorem 3.1 in [65] has a mistake, which invalidates the case $n \leq 1$. In [55], the authors proved a fixed point theorem that allows to deduce the existence and uniqueness of positive almost periodic solutions of (3.12) with $M, m = 1$ and $n > m$ (single-humped nonlinearity) in a bounded region.

More recently, using similar methods to those in [11], criteria for existence and uniqueness were established in [32] when $n \geq m$ for $0 \leq m \leq 1$ (sum of single-humped functions when $n > m$, or monotone increasing and bounded nonlinearity when $n = m$).This case was also considered in [13] by employing a fixed point theorem in a cone. The results obtained for the several cases treated in [14] by a fixed point theorem can be regarded as particular applications of Theorems 7.1.1-7.1.2 and Theorem 7.1.4 below.

Besides existence, another relevant matter is to determine whether or not the obtained solutions are stable. In particular, exponential stability is especially important for two reasons: on the one hand, the rate of convergence is quantified and, on the other hand, it is robust to perturbations.

For example, in [62] sufficient conditions for the global attractiveness of positive almost periodic solutions of (3.12) with $m = 0$ were established as an answer to a question raised by Gyori and Ladas [24, p.322], although global exponential stability was not discussed. In [63], Gronwall's inequality was employed to establish global exponential stability for the case $M = 1$ and $m = 0$ under restrictions on the delay. In [11, 65] the case $m = 0$ and in [32] without the restriction $m = 0, 1$ was analysed. However, to the best of our knowledge, the global exponential stability has not been sufficiently studied when $m \neq 0, 1$.

It is important to notice that aforementioned authors obtained sufficient conditions for the existence and uniqueness of almost periodic solutions with positive infimum of (3.12), but only for the case $0 \leq m_k \leq 1$. In addition, in [13, 14, 32], authors proposed the Open Problem of extending existence results to the case $m_k > 1$. With that end in mind, our aim is to establish sufficient existence and nonexistence conditions for a simplified model, namely:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^m(t-\tau_k(t))}{1+x^n(t-\tau_k(t)} - b(t)x(t), \text{ with } m > 1. \tag{3.13}$$

Resumen del capítulo 4

Uno de nuestros objetivos en este Capítulo es modificar y enriquecer el modelo formulado por Wheldon (1975) para modelar la dinámica de la leucemia mieloide crónica (LMC). Para ello incorporamos al modelo el microambiente dependiente del tiempo y la eficacia del fármaco dependiente del tiempo. El modelo resultante es el siguiente sistema de ecuaciones diferenciales no lineales no autónomas con retardo:

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha(t)M(t)}{1+\beta(t)M^n(t-\tau_1)} - \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t)M(t), \\ \frac{dB}{dt} &= -\omega(t)B(t) + \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t), \end{aligned} \tag{3.14}$$

donde $\alpha(t), \beta(t), \lambda(t), \mu(t)$ y $\omega(t)$ son continuas, positivas y T-periódicas.

Este capítulo está organizado de la siguiente manera:

La primera parte del capítulo, Sección 4.1, está dedicada a estudiar la existencia de soluciones. Vía métodos topológicos mostramos bajo qué condiciones el modelo propuesto admite soluciones positivas y T-periódicas. En la Subsección 4.1.1 damos condiciones suficientes para la existencia de soluciones positivas y T-periódicas en el caso $\delta = 0$ en (3.14), es decir, sin presencia de farmacocinética y en la Subsección 4.1.2 para el caso $\delta = 1$, es decir, en presencia de farmacocinética.

En la segunda parte, Sección 4.2, estudiamos la unicidad o multiplicidad de puntos de equilibrio positivos para el caso autónomo y analizamos las posibles propiedades oscilatorias de dichas soluciones.

Finalmente, en la Sección 4.3 formulamos ciertos problemas abiertos y conjeturas.

Chapter 4

Wheldon model

Our goal in this chapter is to modify and enrich the Wheldon model (1975) of a chronic myelogenous leukemia (CML) dynamics by introduction of a time-varying microenvironment and time-dependent drug efficacies. The resulting model is the following nonautonomous nonlinear system of differential equations with delays:

$$\begin{aligned}\frac{dM}{dt} &= \frac{\alpha(t)M(t)}{1+\beta(t)M^n(t-\tau_1)} - \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t)M(t),\\ \frac{dB}{dt} &= -\omega(t)B(t) + \frac{\lambda(t)M(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t),\end{aligned} \tag{4.1}$$

Throughout the Chapter, it will be assumed that $\alpha(t), \beta(t), \omega(t), \lambda(t), \mu(t), p(t)$ and $q(t)$ are continuous, positive and T-periodic functions and $\tau_{1,2} > 0$ are fixed delays. The parameter δ is assumed to be 1 or 0 according the presence or absence of pharmacokinetics.

Via topological methods, the existence of positive periodic solutions is proven. We introduce our main insight and formulate some relevant open problems and conjectures.

It is worth noticing that, for the set of nonnegative initial conditions, the solution of problem (4.1) is globally defined and positive over $[0, +\infty)$. Indeed,

Theorem 4.0.1 *Let $\varphi_i : [-\tau_i, 0] \to [0, +\infty)$ be continuous functions such that $\varphi_i > 0$. Then there exists a unique positive solution of problem (4.1) defined on $(0, +\infty)$ under initial conditions*

$$\begin{aligned} M(t) &= \varphi_1(t) \qquad -\tau_1 \le t \le 0,\\ B(t) &= \varphi_2(t) \qquad -\tau_2 \le t \le 0.\end{aligned}$$

Proof: Set $R(t) := \ln M(t)$, then the system becomes

$$\begin{aligned} R'(t) &= \frac{\alpha(t)}{1+\beta(t)e^{nR(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t),\\ B'(t) &= -\omega(t)B(t) + \frac{\lambda(t)e^{R(t)}}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t).\end{aligned} \tag{4.2}$$

Suppose that $M(t)$ and $B(t)$ are defined and positive for $t < t_0$, then from the inequalities $-\lambda(t) - \delta p(t) < R'(t) < \alpha(t)$ it is clear that $R(t)$ is defined up to t_0. Moreover, $B'(t) < \lambda e^{R(t)}$ and hence $B(t)$ is defined in t_0. Finally, if $B(t_0) = 0$ then $B'(t_0) > 0$, a contradiction.

■

In the next section we shall prove, under appropriate conditions, the existence of at least one positive T-periodic solution: namely, a pair (M, B) of C^1 functions satisfying

$$M(t+T) = M(t) > 0, \qquad B(t+T) = B(t) > 0$$

for all $t \in \mathbb{R}$. In view of the preceding result, one might attempt to define a Poincaré-like operator in order to apply some fixed point theorem. However, as we remark in Section 2.2 the conditions for such a procedure seem to be very restrictive; thus we apply, instead, the Leray-Schauder degree theory [34,37] over an appropriate open subset of $C_T \times C_T$, where C_T is defined as in (2.17).

4.1 Existence of periodic solutions

4.1.1 Case 1: No pharmacokinetic

Theorem 4.1.1 *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t)$ and $\omega(t)$ are continuous, positive and T-periodic. Furthermore, assume that:*

1. $n > \frac{m}{m+1}$.
2. $\alpha(t) > \lambda(t) > \omega(t)$ *for all* t.

Then system (4.1) *with* $\delta = 0$ *admits at least one positive T-periodic solution.*

Proof: Set $u(t) = \ln M(t)$ and $v(t) = \ln B(t)$, then (4.1) with $\delta = 0$ reads

$$u'(t) = \frac{\alpha(t)}{1+\beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)e^{mv(t-\tau_2)}} := \psi_1(u,v)(t),$$

$$v'(t) = -\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1+\mu(t)e^{mv(t-\tau_2)}} := \psi_2(u,v)(t).$$

In order to prove the existence of T-periodic solutions of this system, we shall apply the continuation method [37]. Adapted to this case, the method guarantees the existence of solutions, provided there exists an open bounded set $\Omega \subset C_T \times C_T$ such that

1. For $\sigma \in (0,1]$, the system
$$u'(t) = \sigma\psi_1(u,v)(t),$$
$$v'(t) = \sigma\psi_2(u,v)(t)$$
has no T-periodic solutions on $\partial\Omega$.

2. $deg(F, \Omega \cap \mathbb{R}^2, 0)$ is well defined and different from 0, where the function $F : \mathbb{R}^2 \to \mathbb{R}^2$ is defined by
$$F(u,v) := \frac{1}{T}\int_0^T \left(\frac{\alpha(t)}{1+\beta(t)e^{nu}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}, \frac{\lambda(t)e^{u-v}}{1+\mu(t)e^{mv}} - \omega(t)\right) dt.$$

For simplicity, we divide the proof in two steps.

First step: Let $\Omega_0 := (-R, R) \times (-R, cR) \subset \mathbb{R}^2$, where c is a fixed constant such that $\frac{1}{m+1} < c < \frac{n}{m}$. We claim that $deg(F, \Omega_0, 0) = 1$ for $R > 0$ large enough.

Indeed, let us firstly assume that $-R \leq v \leq cR$, then

$$F_1(R, v) = \frac{1}{Te^{nR}} \int_0^T \frac{\alpha(t)e^{nR}}{1 + \beta(t)e^{nR}} - \frac{\lambda(t)e^{nR}}{1 + \mu(t)e^{mv}}\, dt.$$

As $nR > mcR$, it follows that $F_1(R, v) \leq F_1(R, cR) < 0$ for $R \gg 0$. On the other hand,

$$F_1(-R, v) = \frac{1}{T} \int_0^T \frac{\alpha(t)}{1 + \beta(t)e^{-nR}} - \frac{\lambda(t)}{1 + \mu(t)e^{mv}}\, dt \geq \frac{1}{T} \int_0^T \frac{\alpha(t)}{1 + \beta(t)e^{-nR}}\, dt - \overline{\lambda}.$$

The right-hand side term tends to $\overline{\alpha} - \overline{\lambda}$ as $R \to +\infty$; thus, as $\alpha(t) > \lambda(t)$ for all t, we deduce that $F_1(-R, v) > 0$ for $R \gg 0$.

Next, assume that $|u| \leq R$ and compute

$$F_2(u, cR) = -\overline{\omega} + \frac{1}{T} \int_0^T \frac{\lambda(t)e^{u-cR}}{1 + \mu(t)e^{mcR}}\, dt \leq -\overline{\omega} + \frac{1}{T} \int_0^T \frac{\lambda(t)e^{(1-c)R}}{1 + \mu(t)e^{mcR}}\, dt \to -\overline{\omega}$$

as $R \to +\infty$ since $c(m + 1) > 1$, and

$$F_2(u, -R) = -\overline{\omega} + \frac{1}{T} \int_0^T \frac{\lambda(t)e^{u+R}}{1 + \mu(t)e^{-mR}}\, dt \geq -\overline{\omega} + \frac{1}{T} \int_0^T \frac{\lambda(t)}{1 + \mu(t)e^{-mR}}\, dt.$$

Here, the right-hand side term tends to $\overline{\lambda} - \overline{\omega}$ as $R \to +\infty$. This quantity is positive since $\lambda(t) > \omega(t)$ for all t, so we conclude that $F_2(u, cR) < 0 < F_2(u, -R)$ for $R \gg 0$. Thus, we may define the homotopy

$$H(u, v, \sigma) := \sigma F(u, v) - (1 - \sigma)(u, v),$$

which does not vanish on $\partial\Omega_0$. It follows that $deg(F, \Omega_0, 0) = deg(-Id, \Omega_0, 0) = (-1)^2 = 1$.

Remark 4.1.1 *As a consequence, it is deduced that F vanishes in Ω_0. In particular, when α, β, λ and μ are positive constants we deduce that the system has a positive equilibrium, as it shall be proven in section 4.2 by direct computation.*

Second step: Let

$$\Omega := \{(u, v) \in C_T \times C_T : \|u\|_\infty < R, -R < v(t) < cR \text{ for all } t\}.$$

We claim that if R is large enough then the T-periodic solutions of the system

$$u'(t) = \sigma\psi_1(u, v)(t),$$

$$v'(t) = \sigma\psi_2(u, v)(t)$$

with $0 < \sigma \leq 1$ do not belong to $\partial\Omega$.

Indeed, suppose firstly that $u_{\max} = R > \frac{v_{\max}}{c}$ and take $\xi \in [0, T]$ is such that $u_{\max} = u(\xi)$. From the first equation of the system we obtain

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} = \frac{\lambda(\xi)}{1+\mu(\xi)e^{mv(\xi-\tau_2)}} > \frac{\lambda(\xi)}{1+\mu(\xi)e^{mcR}}.$$

Moreover, observe that $u'(t) > -\lambda(t)$ for all t, so by periodicity we deduce that

$$u(\xi-\tau_1) - R \geq -\int_{\xi}^{kT+\xi-\tau_1} \lambda(t)\,dt \geq -\int_0^T \lambda(t)\,dt := -C_1$$

where k is the first natural number such that $kT > \tau_1$. It follows that

$$\alpha(\xi) > \lambda(\xi)\frac{1+\beta(\xi)e^{nu(\xi-\tau_1)}}{1+\mu(\xi)e^{mcR}} > \lambda(\xi)\frac{1+\beta(\xi)e^{n(R-C_1)}}{1+\mu(\xi)e^{mcR}}.$$

The right-hand side of this inequality tends uniformly to $+\infty$ as $R \to +\infty$. Now assume that $v_{\max} = cR \geq cu_{\max}$, then take $\eta \in [0, T]$ such that $v(\eta) = v_{\max}$ and deduce, from the second equation of the system:

$$\omega(\eta) = \frac{\lambda(\eta)e^{u(\eta)-v(\eta)}}{1+\mu(\eta)e^{mv(\eta-\tau_2)}} \leq \frac{\lambda(\eta)e^{(1-c)R}}{1+\mu(\eta)e^{mv(\eta-\tau_2)}}.$$

As before, from the inequality $v'(t) \geq -\omega(t)$ it is seen that

$$v(\eta-\tau_2) - cR \geq -\int_{\eta}^{lT+\eta-\tau_2} \omega(t)\,dt \geq -\int_0^T \omega(t)\,dt := -C_2,$$

where l is the first natural number such that $lT > \tau_2$. This implies

$$\omega(\eta) \leq \frac{\lambda(\eta)e^{(1-c)R}}{1+\mu(\eta)e^{m(cR-C_2)}} \to 0$$

uniformly as $R \to +\infty$. We conclude that $u_{\max}$ and $v_{\max}$ cannot be arbitrarily large.

Next, suppose that $u_{\min} = -R < v_{\min}$ and $\xi \in [0, T]$ be such that $u_{\min} = u(\xi)$. As before,

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} = \frac{\lambda(\xi)}{1+\mu(\xi)e^{mv(\xi-\tau_2)}} < \frac{\lambda(\xi)}{1+\mu(\xi)e^{-mR}}$$

and hence

$$\alpha(\xi) < \lambda(\xi)\frac{1+\beta(\xi)e^{nu(\xi-\tau_1)}}{1+\mu(\xi)e^{-mR}}.$$

As $u(\xi-\tau_1) \leq -R + \int_{\xi-\tau_1}^{\xi} \lambda(t)\,dt$, the right-hand side of the last inequality tends uniformly to $\lambda(\xi)$ as $R \to +\infty$. In the same way, if $v(\eta) = v_{\min} = -R \leq u_{\min}$, then it is seen that

$$\omega(\eta) \geq \frac{\lambda(\eta)}{1+\mu(\eta)e^{mv(\eta-\tau_2)}} \to \lambda(\eta)$$

uniformly as $R \to +\infty$. As $\alpha(t) > \lambda(t) > \omega(t)$ for all t, we deduce that R cannot be arbitrarily large and the claim is proven.

■

4.1.2 Case 2: With pharmacokinetic

Theorem 4.1.2 *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t), \omega(t), p(t)$ and $q(t)$ are positive and T-periodic. Furthermore, assume that:*

$$\alpha(t) - p(t) > \lambda(t) > \omega(t) + q(t)$$

for all t. Then system (4.1) with $\delta = 1$ admits at least one positive T-periodic solution.

Proof: We shall follow the general outline of the previous proof. As before, set $u(t) = \ln M(t)$ and $v(t) = \ln B(t)$, then the model with $\delta = 1$ reads

$$u'(t) = \frac{\alpha(t)}{1 + \beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1 + \mu(t)e^{mv(t-\tau_2)}} - p(t) := \psi_1^{p,q}(u,v)(t),$$

$$v'(t) = -\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1 + \mu(t)e^{mv(t-\tau_2)}} - q(t) := \psi_2^{p,q}(u,v)(t).$$

For the first step, let us consider now $F^{p,q} : \mathbb{R}^2 \to \mathbb{R}^2$ given by

$$F^{p,q}(u,v) := F(u,v) - (\overline{p}, \overline{q})$$

with F as in the previous proof. First, assume that $|v| \leq R$. Then

$$F_1^{p,q}(R,v) = \frac{1}{T}\int_0^T \frac{\alpha(t)}{1 + \beta(t)e^{nR}} - \frac{\lambda(t)}{1 + \mu(t)e^{mv}}\, dt - \overline{p} < 0$$

for $R \gg 0$. On the other hand,

$$F_1^{p,q}(-R,v) = \frac{1}{T}\int_0^T \frac{\alpha(t)}{1 + \beta(t)e^{-nR}} - \frac{\lambda(t)}{1 + \mu(t)e^{mv}}\, dt - \overline{p}$$

$$\geq \frac{1}{T}\int_0^T \frac{\alpha(t)}{1 + \beta(t)e^{-nR}}\, dt - \overline{\lambda} - \overline{p}.$$

The last term tends to $\overline{\alpha} - \overline{\lambda} - \overline{p}$ as $R \to +\infty$; thus, as $\alpha(t) > \lambda(t) + p(t)$ for all t, we deduce that $F_1^{p,q}(-R,v) > 0$ for $R \gg 0$.

Next, assume that $|u| \leq R$ and compute

$$F_2^{p,q}(u,R) \leq \int_0^T \frac{\lambda(t)}{1 + \mu(t)e^{mR}}\, dt - \overline{\omega} - \overline{q} < 0$$

for $R \gg 0$ and

$$F_2^{p,q}(u,-R) \geq \frac{1}{T}\int_0^T \frac{\lambda(t)}{1 + \mu(t)e^{-mR}}\, dt - \overline{\omega} - \overline{q}.$$

Here, the right-hand side term tends to $\overline{\lambda} - \overline{\omega} - \overline{q}$ as $R \to +\infty$. This quantity is positive since $\lambda(t) > \omega(t) + q(t)$ for all t, so we conclude that $F_2^{p,q}(u,R) < 0 < F_2^{p,q}(u,-R)$ for $R \gg 0$. As in the previous proof, we conclude that $deg(F^{p,q}, (-R,R)^2, 0) = 1$.

For the second step, set

$$\Omega := \{(u(t), v(t)) \in C_T \times C_T : \|u\|_\infty < R, \|v\|_\infty < R\}.$$

As before, we claim that if R is large enough then the T-periodic solutions of the system

$$u'(t) = \sigma\psi_1^{p,q}(u,v)(t),$$
$$v'(t) = \sigma\psi_2^{p,q}(u,v)(t)$$

with $0 < \sigma \leq 1$ do not belong to $\partial\Omega$. Indeed, suppose firstly that $u_{max} = R > v_{max}$, then take $\xi \in [0,T]$ is such that $u_{max} = u(\xi)$ and from the first equation we obtain

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} > \frac{\lambda(\xi)}{1+\mu(\xi)e^{mR}} + p(\xi).$$

As before, using now the fact that $u'(t) > -\lambda(t) - p(t)$ for all t we deduce that

$$u(\xi-\tau_1) - R \geq -\int_0^T [\lambda(t) + p(t)]\,dt := -C_1^{p,q}.$$

It follows that

$$\frac{\alpha(\xi)}{p(\xi)} > 1 + \beta(\xi)e^{nu(\xi-\tau_1)} \geq 1 + \beta(\xi)e^{n(R-C_1^{p,q})}$$

and hence R cannot be arbitrarily large. On the other hand, assume that $u_{max} \leq v_{max} = R$, then take $\eta \in [0,T]$ such that $v(\eta) = v_{max}$ and deduce, from the second equation of the system, that

$$\omega(\eta) + q(\eta) \leq \frac{\lambda(\eta)}{1+\mu(\eta)e^{mv(\eta-\tau_2)}}$$

and, from the inequality $v'(t) \geq -\omega(t) - q(t)$, that

$$v(\eta-\tau_2) - R \geq -\int_0^T [\omega(t) + q(t)]\,dt := -C_2^{p,q}.$$

This implies

$$\omega(\eta) + q(\eta) \leq \frac{\lambda(\eta)}{1+\mu(\eta)e^{m(R-C_2^{p,q})}} \to 0$$

uniformly as $R \to +\infty$. We conclude that u_{max} and v_{max} cannot be arbitrarily large.

Next, suppose that $u_{\min} = -R < v_{\min}$ and $\xi \in [0,T]$ be such that $u_{\min} = u(\xi)$. As before, it follows that

$$\frac{\alpha(\xi)}{1+\beta(\xi)e^{nu(\xi-\tau_1)}} < \frac{\lambda(\xi)}{1+\mu(\xi)e^{-mR}} + p(\xi)$$

and hence

$$\alpha(\xi) < \left(\frac{\lambda(\xi)}{1+\mu(\xi)e^{-mR}} + p(\xi)\right)\left(1+\beta(\xi)e^{nu(\xi-\tau_1)}\right).$$

Thus, the right-hand side of the last inequality tends uniformly to $\lambda(\xi) + p(\xi)$ as $R \to +\infty$. In the same way, if $v(\eta) = v_{\min} = -R \leq u_{\min}$, then

$$\omega(\eta) + q(\eta) \geq \frac{\lambda(\eta)}{1+\mu(\eta)e^{mv(\eta-\tau_2)}} \to \lambda(\eta)$$

uniformly as $R \to +\infty$. As $\alpha(t) - p(t) > \lambda(t) > \omega(t) + q(t)$ for all t, we deduce that R cannot be arbitrarily large and the proof is complete. ■

4.2 Some remarks about equilibrium points

In this section, we briefly discuss the uniqueness or multiplicity of positive equilibrium points for the autonomous case and make some comments on possible oscillation properties of the solutions.

With this aim, assume that all the parameters of (4.1) are constant, then the existence of at least one positive equilibrium (M_*, B_*) is easily shown, provided that

$$n > (1-\delta)\frac{m}{m+1}, \qquad \alpha > \lambda - \delta p.$$

Indeed, consider the system

$$\begin{aligned} \tfrac{\alpha}{1+\beta M^n} &= \tfrac{\lambda}{1+\mu B^m} + \delta p, \\ (\omega + \delta q)B &= \tfrac{\lambda M}{1+\mu B^m} \end{aligned} \tag{4.3}$$

and let

$$c(B) := \frac{B(1+\mu B^m)(\omega+\delta q)}{\lambda}.$$

Then (4.3) has at least a positive solution if and only if the function $\varphi : [0, +\infty) \to \mathbb{R}$ given by

$$\varphi(B) := \frac{\alpha}{1+\beta c(B)^n} - \frac{\lambda}{1+\mu B^m} - \delta p$$

has at least a positive root. This is easily verified, since

$$\varphi(0) = \alpha - \lambda - \delta p > 0$$

and

$$\lim_{B\to+\infty} \varphi(B) = -\delta p.$$

Thus, the result follows for $\delta = 1$. When $\delta = 0$, condition $n > \frac{m}{m+1}$ implies $\varphi(B) < 0$ for $B \gg 0$ and so completes the proof.

It is worth noticing that the number of equilibria depends on the parameters of the system. Although more precise computations are possible, we shall not pursue a detailed analysis here and restrict ourselves to some elementary comments. Consider, for instance, the case $\delta = 0$, then

$$B_* = \frac{\alpha M}{\omega(1+\beta M^n)}.$$

Calling $z = 1 + \beta M^n$, we obtain the following equation for z:

$$z = \frac{\alpha}{\lambda} + r\left[\frac{\sqrt[n]{z-1}}{z}\right]^m := \psi(z),$$

where $r = \frac{\alpha^{m+1}\mu}{\omega^m \beta^{m/n}\lambda}$. The function $z - \psi(z)$ is negative for $z = 1$ and, as $n > \frac{m}{m+1}$, tends to $+\infty$ as $z \to +\infty$. Next, we compute

$$\psi'(z) = \frac{rm(z-1)^{\frac{m-n}{n}}}{nz^{m+1}}[n-(n-1)z],$$

$$\psi''(z) = \frac{rm(z-1)^{\frac{m-2n}{n}}}{nz^{m+2}}[az^2 + bz + c],$$

where

$$a = \frac{n-1}{n}[n + m(n-1)], \qquad b = -2[n + m(n-1)], \qquad c = (m+1)n.$$

In particular, ψ vanishes at most twice in $(1, +\infty)$, which implies that the system cannot have more than 3 positive equilibrium points.

When $n \neq 1$, the quadratic $az^2 + bz + c$ has two different real roots, namely

$$R_{\pm} = \frac{n}{n-1}\left(1 \pm \frac{1}{\sqrt{n + m(n-1)}}\right).$$

Let us prove, in the first place, that the positive equilibrium is unique when $m \leq n$. This is immediate for $m < n$, since the function $z - \psi(z)$ is strictly decreasing near 1, and ψ'' vanish at most once in $(1, +\infty)$. When $m = n$, there are two different cases:

- If $n \leq 1$, then ψ'' does not vanish in $(1, +\infty)$.
- If $n > 1$, then direct computation shows that the equation $\psi'(z) = 1$ has at most one solution in $(1, +\infty)$.

In both cases, the function $z - \psi(z)$ has at most one critical point in $(1, +\infty)$ and the claim follows.

The situation is different when $m > n$: for instance, if r is large enough then there are 3 positive equilibria, provided that $\frac{\alpha}{\lambda}$ is sufficiently close to 1. Indeed, we may set, for example, $R > 1$ as the largest root of the quadratic function $az^2 + bz + c$, namely

$$R = \begin{cases} \frac{m+1}{2} & \text{if } n = 1, \\ R_- & \text{if } n < 1, \\ R_+ & \text{if } n > 1, \end{cases}$$

with $R_{\pm}$ as before. Next, consider the function $g(z) = z - \psi(z) + \frac{\alpha}{\lambda} - 1$ and fix r such that $r > \frac{R^m}{(R-1)^{\frac{m-n}{n}}}$. Then $g(R) < 0$ and, as $g(1) = 0$ and $g'(1) = 1$, it is seen that g has exactly one zero in $(1, R)$ and another one in $(R, +\infty)$. Now let

$$\varepsilon = \max_{1 \leq z \leq R} g(z),$$

then the function $z - \psi(z)$ has 3 zeros when $\frac{\alpha}{\lambda} < 1 + \varepsilon$.

In view of the previous example, a natural question arises: is it possible to find a sharp set of sufficient conditions for the uniqueness of the positive equilibrium when $m > n$? For example, a sufficient condition when $n \leq 1$ is

$$\frac{\alpha}{\lambda} \geq R$$

with R as before: indeed, in this case $\psi'(z) > 0$ in $(1, +\infty)$, so $\psi(z) > z$ in $[1, R]$ and ψ'' does not vanish after R, so the equation $\psi'(z) = 1$ has at most one solution in $(R, +\infty)$.

When $n > 1$, a sufficient condition for uniqueness of the positive equilibrium is:

$$\frac{\alpha}{\lambda} \geq \frac{n}{n-1}.$$

Indeed, in this case ψ strictly increases up to $z = \frac{n}{n-1}$ and strictly decreases after that point. As $\psi(z) > z$ on $\left(1, \frac{n}{n-1}\right)$ it follows that the equation $\psi(z) = z$ has exactly one solution. Observe that $R > \frac{n}{n-1}$, so the previous condition is sharper than the condition $\frac{\alpha}{\lambda} \geq R$.

Also, it is worth noticing that, in all cases, if r is small then the equilibrium is unique. More precisely, for $n \leq 1$ the function ψ' is positive and achieves its absolute maximum at $z = R$; thus, a sufficient condition for uniqueness is:

$$\psi'(R) < 1. \tag{4.4}$$

For $n > 1$, the function ψ' achieves its absolute maximum at $z = R_- > 1$. This yields the sufficient condition

$$\psi'(R_-) < 1. \tag{4.5}$$

Conditions (4.4) and (4.5) are obviously satisfied when a is small.

The presence of delays yields also an interesting matter about the oscillation properties of the autonomous model. This is an interesting field of research that can be the object of a future work; here, we shall only prove some behavior that might indicate the presence of oscillation.

In more precise terms, we set a positive equilibrium (M_*, B_*) as the center of coordinates and denote by Q_j the j-th quadrant, namely

$$Q_1 := \{(M, B) : M > M_*, B > B_*\},$$

$$Q_2 := \{(M, B) : M < M_*, B > B_*\},$$

$$Q_3 := \{(M, B) : M < M_*, B < B_*\},$$

$$Q_4 := \{(M, B) : M > M_*, B < B_*\}.$$

We shall prove that, under appropriate conditions, if a non-constant positive solution starts in $\overline{Q}_2$ or $\overline{Q}_4$ then it cannot remain there for all t.

Proposition 4.2.1 *Let $\tau_1 > \frac{(1+\beta M_*^n)^2}{n\alpha\beta M_*^n}$ and assume that there are no equilibrium points in Q_4. Then there exists a sequence $t_n \to +\infty$ such that, for all n, $M(t_n) < M_*$ or $B(t_n) > B_*$.*

Proposition 4.2.2 *Let $\tau_1 > \frac{(1+\beta M_*^n)^2}{n\alpha\beta M_*^n}$ and assume that there are no equilibrium points in Q_2. Then there exists a sequence $t_n \to +\infty$ such that, for all n, $M(t_n) > M_*$ or $B(t_n) < B_*$.*

In other words, a non-constant positive solution starting at $\overline{Q}_2$ or $\overline{Q}_4$ might abandon the respective quadrant and never return, or it might eventually come back but then it leaves the quadrant again and so on.

Lemma 4.2.1 *Assume that $R(t_1 - \tau_1) \geq R(t_2 - \tau_1)$ and $B(t_1 - \tau_2) \leq B(t_2 - \tau_2)$, at least one of the inequalities being strict. If $R(t_1) \geq R(t_2)$ and $B(t_1) \leq B(t_2)$, at least one of the inequalities being strict, then $R'(t_1) < R'(t_2)$ and $B'(t_1) > B'(t_2)$.*

Proof: It suffices to observe that the right hand side of the first equation of (4.2) is strictly decreasing in the variables $R(t-\tau_1)$ and strictly increasing in the variable $B(t-\tau_2)$, and the right hand side of the second equation of (4.2) is strictly increasing in the variable $R(t)$ and strictly decreasing in the variables $B(t)$ and $B(t-\tau_2)$. Then $R'(t_1) < R'(t_2)$ and $B'(t_1) > B'(t_2)$. ■

Remark 4.2.1 *As in the previous Lemma 4.2.1, it is easily seen that if $R(t) > R_* := ln(M_*)$ for $t \in [t_0-\tau_1, t_1)$ and $B(t) < B_*$ for all $t \in [t_0-\tau_2, t_1)$ then $R'(t) < 0 < B'(t)$ for all $t \in [t_0, t_1]$. If $R(t_1) = R_*$ or $B(t_1) = B_*$, then there exists $\eta > 0$ such that $(R(t), B(t)) \notin \overline{Q}_4$ for $t \in (t_1, t_1+\eta)$. On the other hand, if $R(t) > R_*$ for all $t \geq t_0 - \tau_1$ and $B(t) < B_*$ for all $t \geq t_0 - \tau_2$ then $R'(t) < 0 < B'(t)$ for all $t \geq t_0$ and, if there are no equilibrium points in Q_4, then $R(t) \to R_*$ and $B(t) \to B_*$.*

Proof of Proposition 4.2.1: Suppose that $M(t) > M_*$ for all $t \geq t_0 - \tau_1$ and $B(t) < B_*$ for all $t \geq t_0 - \tau_2$. A simple computation shows that

$$R'(t) = -A(R(t-\tau_1) - R_*) - C(B_* - B(t-\tau_2)),$$

with

$$A = A(R(t), R(t-\tau_1)) := \frac{\alpha\beta(e^{nR_*} - e^{nR(t-\tau_1)})}{(1+\beta e^{nR(t-\tau_1)})(1+\beta e^{nR_*})(R_* - R(t-\tau_1))} > 0,$$

$$C = C(B(t), B(t-\tau_2)) := \frac{\lambda\mu(B_*^m - B^m(t-\tau_2))}{(1+\mu B_*^m)(1+\mu B^m(t-\tau_2))(B_* - B(t-\tau_2))} > 0,$$

$$A(R(t), R(t-\tau_1)) \to \frac{n\alpha\beta e^{nR_*}}{(1+\beta e^{nR_*})^2} \qquad \text{as } t \to +\infty$$

and

$$C(B(t), B(t-\tau_2)) \to \frac{\lambda\mu m B_*^{m-1}}{(1+\mu B_*^m)^2} \qquad \text{as } t \to +\infty.$$

Moreover,

$$R(t-\tau_1) - R_* = R(t-\tau_1) - R(t) + R(t) - R_* = -\tau_1 R'(\theta) + R(t) - R_*$$

for some mean value $\theta \in (t-\tau_1, t)$. From Lemma 4.2.1 with $t_1 = \theta$ and $t_2 = t$, it follows that $R'(\theta) < R'(t)$.

Thus,

$$R'(t) < -A(R(t) - R_*) - C(B_* - B(t-\tau_2)) + \tau_1 A R'(t).$$

Observe that the hypothesis says that $\tau_1 > \frac{(1+\beta e^{nR_*})^2}{n\alpha\beta e^{nR_*}}$. Without loss of generality, we may assume that t_0 is large enough so that $\tau_1 A(R(t), R(t-\tau_1)) > 1$, then

$$(\tau_1 A - 1)R'(t) > A(R(t) - R_*) + C(B_* - B(t-\tau_2)) > 0,$$

a contradiction.

4.3 Open Problems

We outline some problems that might be of interest for scientists who plan to start future research in this field.

1. Use Lyapunov-like functionals to find sufficient conditions for the global stability of a non-trivial equilibrium of the autonomous model.

2. Prove or disprove that for a new model the complete recovery is possible for sufficiently high drug dosage; examine permanence, persistence and extinction of the solutions.

3. Define the required type, frequency and intensity of the cancer treatment that switch unfavorable oscillatory dynamics of a system to a non-oscillatory state.

Resumen del capítulo 5

En este Capítulo nuestro objetivo principal es establecer criterios suficientes para garantizar, por un lado, la existencia de soluciones positivas T-periódicas de

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\mu_k(t))} - b(t)x(t) \tag{4.6}$$

donde $r_k(t), b(t), \tau_k(t)$ y $\mu_k(t)$ son funciones postivas y T-periódicas y λ_k, m_k, n_k son constantes positivas y, por otro lado, obtener condiciones suficientes para la multiplicidad de soluciones. Usando teoría de grado, obtenemos un conjunto de condiciones naturales y simples de verificar para la existencia de una o más soluciones. Más aun, en algunos casos también obtenemos condiciones necesarias para la existencia de soluciones positivas y T-periódicas.

Para simplificar algunos cálculos, consideramos $y(t) := \ln(x(t))$ y transformamos (5.1) en la siguiente ecuación equivalente

$$y'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{m_k y(t-\tau_k(t))-y(t)}}{1+e^{n_k y(t-\mu_k(t))}} - b(t). \tag{4.7}$$

Este cambio de variables no solo simplifica ciertos cálculos si no que también asegura que toda solución $y(t)$ de (4.7) es una solución positiva de (4.6).

Este Capítulo está organizado de la siguiente manera:

En la Sección 5.1 introducimos resultados preliminares y notación que serán usados durante todo el Capítulo.

En la Sección 5.2 por medio del Teorema 5.1.1 probamos la existencia de soluciones T-periódicas positivas para los diferentes casos de nolinealidades del modelo.

En la Sección 5.3, damos condiciones suficientes para la existencia de 2, 3 o 4 soluciones T-periódicas positivas.

En la Sección 5.4 presentamos un ejemplo de (4.6) con al menos 6 soluciones T-periódicas positivas.

En la Sección 5.5 establecemos condiciones necesarias para la existencia de soluciones T-periódicas positivas. Más precisamente, establecemos condiciones que son incompatibles con aquellas obtenidas en los resultados de existencia y tales que implican que todas las soluciones positivas tienden a 0 cuando $t \to +\infty$ y, en consecuencia, no pueden ser periódicas.

Finalmente, en la Sección 5.6 damos nuestras conclusiones y conjeturas.

Chapter 5

Mackey-Glass model: Periodic case

Our goal in this Chapter is to establish sufficient criteria to guarantee, on the one hand, the existence of positive T-periodic solutions of

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t - \tau_k(t))}{1 + x^{n_k}(t - \mu_k(t))} - b(t)x(t) \tag{5.1}$$

where $r_k(t), b(t), \tau_k(t)$ and $\mu_k(t)$ are positive and T-periodic functions and λ_k, m_k, n_k are positive constants and, on the other hand, obtain sufficient conditions for the multiplicity of such solutions. Using the degree theory, we shall obtain a set of natural and easy-to-verify conditions for the existence of one or more solutions. Moreover, in some cases we shall also find necessary conditions for the existence of positive periodic solutions. More precisely, we shall establish conditions that are incompatible with the ones obtained for the existence results and which imply that all positive solutions tend to 0 as $t \to +\infty$.

5.1 Preliminaries.

Throughout this Chapter we shall follow the notation given in Chapter 2 Section 2.2.5.

In order to simplify some computations, we set $y(t) := \ln(x(t))$ and transform (5.1) into the equivalent equation

$$y'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{m_k y(t - \tau_k(t)) - y(t)}}{1 + e^{n_k y(t - \mu_k(t))}} - b(t). \tag{5.2}$$

Finally we define, for convenience, the function $\phi : \mathbb{R} \to \mathbb{R}$ by

$$\phi(\gamma) := \sum_{k=1}^{M} \lambda_k \overline{r}_k \frac{e^{(m_k - 1)\gamma}}{1 + e^{n_k \gamma}} - \overline{b}. \tag{5.3}$$

The proof of our results shall be based on the continuation method. Specifically, we shall apply the following existence theorem, which can be directly deduced from Theorem 2.2.4 in Chapter 2.

Theorem 5.1.1 *Assume there exist constants $\gamma_1 < \gamma_2$ such that*

1. *If $y \in cl(X_{\gamma_1}^{\gamma_2})$ satisfies*

$$y'(t) = \sigma \left(\sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{m_k y(t-\tau_k(t)) - y(t)}}{1 + e^{n_k y(t-\mu_k(t))}} - b(t) \right) \tag{5.4}$$

   for some $\sigma \in (0,1)$, then $y \in X_{\gamma_1}^{\gamma_2}$.

2. *$\phi(\gamma_1)\phi(\gamma_2) < 0$.*

Then (5.2) has at least one solution in $X_{\gamma_1}^{\gamma_2}$.

Roughly speaking, if ϕ has different signs at both ends of some interval $[\gamma_1, \gamma_2] \subset \mathbb{R}$ then the continuation theorem guarantees the existence of a T-periodic solution y of (5.2) such that $y(t) \in (\gamma_1, \gamma_2)$ for all t. However, the first condition of Theorem 5.1.1 requires, in some sense, that the sign of ϕ does not change too fast.

The main part of our analysis shall be based on a study of the behavior of ϕ. For a proof of the existence of at least one solution it suffices, in most cases, to consider its behavior at $\pm\infty$; for the multiplicity results, a more careful study is needed, in order to find intervals of positivity and negativity of ϕ that are sufficiently large, so the conditions of the continuation theorem can be fulfilled. With this end in mind, we shall consider the sets

$$M_1 := \{k : 0 < m_k < 1\},\ M_2 := \{k : m_k = 1\},\ M_3 := \{k : 1 < m_k < n_k + 1\}$$

$$M_4 := \{k : m_k = n_k + 1\},\ M_5 := \{k : m_k > n_k + 1\}$$

and the mappings

$$\phi_i(\gamma) := \sum_{k \in M_i} \lambda_k \overline{r}_k \frac{e^{(m_k - 1)\gamma}}{1 + e^{n_k \gamma}}, \tag{5.5}$$

so we may write $\phi(\gamma) = \sum_{i=1}^{5} \phi_i(\gamma) - \overline{b}$. For notation convenience, we also define $B := T\overline{b} = \int_0^T b(t)\, dt$.

This setting proves to be useful, since the limits $\lim_{\gamma \to \pm\infty} \phi_i(\gamma)$ are easy to compute and, moreover, $\phi_i(\gamma)$ is strictly monotone for $i \neq 3$ and a sum of one-hump functions for $i = 3$. Thus, the behavior of ϕ can be understood by studying the interaction of these different terms.

5.2 Existence of positive T-periodic solutions.

In order to present our existence results in a more comprehensive way, we shall consider three different cases: the *superlinear* case ($m_k > n_k + 1$ for some k), the *sublinear* case ($m_k < n_k + 1$ for all k) and the *asymptotically linear* case ($m_k \leq n_k + 1$ for all k and $m_j = n_j + 1$ for some j). We give a detailed proof only of the first result, since the other two follow similarly.

Theorem 5.2.1 *Assume $m_j > n_j + 1$ for some j. Furthermore, assume that one of the following conditions is fulfilled:*

1. *$m_k > 1$ for all k.*

2. $m_k \geq 1$ *for all* k, $m_i = 1$ *for some* i *and* $\sum_{k \in M_2} \lambda_k r_k(t) e^B < b(t)$ *for all* t.

3. $m_i < 1$ *for some* i *and* $\sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma_1} e^{m_k B}}{1+e^{n_k \gamma_1}} < b(t)$ *for all* t *and some constant* γ_1.

Then (5.1) admits at least one positive T*-periodic solution.*

Theorem 5.2.2 *Assume* $m_k < n_k + 1$ *for all* k. *Furthermore, assume that one of the following conditions is fulfilled:*

1. $m_i < 1$ *for some* i.

2. $m_k \geq 1$ *for all* k, $m_i = 1$ *for some* i *and* $\sum_{k \in M_2} \lambda_k r_k(t) > b(t)$ *for all* t.

3. $m_k > 1$ *for all* k *and*
$$\sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma_1}}{1+e^{n_k(\gamma_1+B)}} > b(t)$$
for all t *and some arbitrary constant* γ_1.

Then (5.1) admits at least one positive T*-periodic solution.*

Theorem 5.2.3 *Assume* $m_k \leq n_k + 1$ *for all* k *and* $m_j = n_j + 1$ *for some* j. *Furthermore, assume that one of the following conditions is fulfilled:*

1. $m_k > 1$ *for all* k *and* $\sum_{k \in M_4} \lambda_k r_k(t) e^{-Bm_k} > b(t)$ *for all* t.

2. $m_k \geq 1$ *for all* k, $m_i = 1$ *for some* i, $\sum_{k \in M_4} \lambda_k r_k(t) e^{-Bm_k} > b(t)$ *and* $\sum_{k \in M_2} \lambda_k r_k(t) e^B < b(t)$ *for all* t.

3. $0 < m_i < 1$ *for some* i *and* $\sum_{m_k \in M_4} \lambda_k r_k(t) e^{Bn_k} < b(t)$ *for all* t.

Then (5.1) admits at least one positive T*-periodic solution.*

Proof of Theorem 5.2.1: Let y be a T-periodic solution of (5.4) with $0 < \sigma < 1$, then $y'(t) \geq -b(t)$ and hence $y(t_1) - y(t_2) \leq \int_0^T b(t)dt$ for any $t_1 \leq t_2 \leq t_1 + T$. This implies, since $y(t)$ is T-periodic, that $y_{max} - y_{min} \leq \int_0^T b(t)dt = B$. Moreover, since $m_k > n_k + 1$ for some k it follows that $\phi(\gamma) > 0$ when γ is large enough. Assume that y_{max} is achieved at some value t^*, that is $y(t^*) = y_{max}$, then $y'(t^*) = 0$. Hence from (5.4) we deduce, since $\sigma > 0$,
$$\begin{aligned} b(t^*)e^{y_{max}} &= \sum_{k=1}^{M} \lambda_k r_k(t^*) \frac{e^{m_k y(t^*-\tau_k(t^*))}}{1+e^{n_k y(t^*-\mu_k(t^*))}} \\ &\geq \sum_{k=1}^{M} \lambda_k r_k(t^*) \frac{e^{m_k(y_{max}-B)}}{1+e^{n_k y_{max}}} \end{aligned}$$
and consequently
$$b(t^*) \geq \sum_{k=1}^{M} \lambda_k r_k(t^*) \frac{e^{(m_k-1)y_{max}} e^{-Bm_k}}{1+e^{n_k y_{max}}}.$$
Again, since $m_k > n_k + 1$ for some k we deduce that y_{max} cannot be too large. Thus, we may fix $\gamma_2 \gg 0$ such that $y_{max} < \gamma_2$ for every $y \in C_T$ satisfying (5.4) and $\phi(\gamma_2) > 0$. In a similar fashion, we look for $\gamma_1 < \gamma_2$ such that $\phi(\gamma_1) < 0$ and $y_{min} > \gamma_1$.

Case 1: $m_k > 1$ *for all* k. Here

$$\phi(\gamma) \to -\overline{b} \qquad \text{as } \gamma \to -\infty.$$

Let $y \in C_T$ be a solution of (5.4) and fix t_* such that $y(t_*) = y_{min}$, then

$$b(t_*) \le \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{(m_k-1)y_{min}} e^{Bm_k}}{1 + e^{n_k y_{min}}}$$

Suppose that $y_{min} = \gamma_1$, then

$$b(t_*) \le \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma_1 + Bm_k}}{1 + e^{n_k \gamma_1}}.$$

The right-hand side of the latter inequality tends to zero as $\gamma_1 \to -\infty$. We deduce that y_{min} cannot take arbitrarily large negative values; hence, it suffices to take $\gamma_1 \ll 0$.

Case 2. $m_k \ge 1$ *for all* k *and* $m_j = 1$ *for some* j. In this case,

$$\phi(\gamma) \to \sum_{k \in M_2} \lambda_k \overline{r_k} - \overline{b} < \sum_{k \in M_2} \lambda_k \overline{r_k} e^{B} - \overline{b} < 0$$

as $\gamma \to -\infty$. On the other hand, if $y \in C_T$ satisfies (5.4) then

$$\begin{aligned} b(t_*) &\le \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{(m_k-1)y_{min} + Bm_k}}{1 + e^{n_k y_{min}}} \\ &= \sum_{k \in M_3} \lambda_k r_k(t_*) e^{Bm_k} \frac{e^{(m_k-1)y_{min}}}{1 + e^{n_k y_{min}}} + \sum_{k \in M_2} \lambda_k r_k(t_*) \frac{e^{B}}{1 + e^{n_k y_{min}}} \end{aligned}$$

and, again, we deduce that y_{min} cannot take too large negative values. Thus, it suffices to take $\gamma_1 \ll 0$.

Case 3. $m_k < 1$ *for some* k. From the hypothesis,

$$\phi(\gamma_1) = \sum_{k=1}^{M} \lambda_k \overline{r_k} \frac{e^{(m_k-1)\gamma_1}}{1 + e^{n_k \gamma_1}} - \overline{b} \le \sum_{k=1}^{M} \lambda_k \overline{r_k} \frac{e^{(m_k-1)\gamma_1} e^{Bm_k}}{1 + e^{n_k \gamma_1}} - \overline{b} < 0.$$

Moreover, if y_{min} is achieved at some value t_*, then

$$b(t_*) \le \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{(m_k-1)y_{min}} e^{Bm_k}}{1 + e^{n_k y_{min}}}.$$

We conclude that $y_{min} > \gamma_1$.

■

Remark 5.2.1 *It is easy to verify that the second condition in Theorem 5.2.3 can be replaced by*

2′. $m_k \ge 1$ *for all* $k, m_i = 1$ *for some* $i, \sum_{k \in M_4} \lambda_k r_k(t) e^{Bn_k} < b(t)$ *and* $\sum_{k \in M_2} \lambda_k r_k(t) > b(t)$ *for all* t.

5.3 Multiplicity

In this section, we shall employ Theorem 5.1.1 in order to prove the existence of multiple solutions. It is worth noticing that, when ϕ is monotone, it changes sign at most once and the method cannot be applied. On the other hand, when ϕ is non-monotone, it is not enough to obtain intervals of positivity and negativity: as mentioned, it is required that ϕ does not change sign too fast. For a more detailed analysis, the following functions shall be helpful:

$$\alpha(\gamma,t) := \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma} e^{-Bm_k}}{1+e^{n_k(\gamma+B)}} - b(t)$$

$$\beta(\gamma,t) := \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma} e^{Bm_k}}{1+e^{n_k(\gamma-B)}} - b(t)$$

As before, our results shall be presented in three different theorems, for the superlinear, sublinear and asymptotically linear cases.

Theorem 5.3.1 *Assume that $m_j > n_j + 1$ for some j.*

1. *Let $m_k > 1$ for all k and $1 < m_i < n_i + 1$ for some i. Assume there exist constants $\gamma_1 < \gamma_2$ such that*
$$\alpha(\gamma_1,t) > 0 > \beta(\gamma_2,t) \text{ for all } t.$$
Then (5.1) admits at least 3 positive T-periodic solutions.

2. *Let $m_k \geq 1$ for all k, $m_i = 1$ for some i, $m_k \notin (1, n_k+1)$ for all k. Assume that*
$$\sum_{k\in M_2} \lambda_k r_k(t) > b(t) \text{ for all } t$$
and there exists γ_1 such that
$$\beta(\gamma_1,t) < 0 \text{ for all } t.$$
Then (5.1) admits at least 2 positive T-periodic solutions.

3. *Let $m_k \geq 1$ for all k, $m_i = 1$ for some i and $1 < m_s < n_s + 1$ for some s. Assume that*
$$\sum_{k\in M_2} \lambda_k r_k(t) e^{B} < b(t) \text{ for all } t$$
and there exist constants $\gamma_1 < \gamma_2$ such that
$$\alpha(\gamma_1,t) > 0 > \beta(\gamma_2,t) \text{ for all } t.$$
Then (5.1) admits at least 3 positive T-periodic solutions.

4. *Let $m_i < 1$ for some i, $m_k \notin (1, n_k+1)$ for all k. Assume*
$$\beta(\gamma_1,t) < 0 \text{ for all } t \text{ and some constant } \gamma_1.$$
Then (5.1) admits at least 2 positive T-periodic solutions.

5. *Let $m_i < 1$ for some i, $1 < m_s < n_s + 1$ for some s. Assume there exist some constants $\gamma_1 < \gamma_2 < \gamma_3$ such that*

$$\alpha(\gamma_2, t) > 0 > \beta(\gamma_i, t) \text{ for all } t,$$

for $i = 1, 3$. Then (5.1) admits at least 4 positive T-periodic solutions.

Theorem 5.3.2 *Assume that $m_k < n_k + 1$ for all k.*

1. *Let $m_k > 1$ for all k and assume there exists a constant γ_1 such that*

$$\alpha(\gamma_1, t) > 0 \text{ for all } t.$$

Then (5.1) admits at least 2 positive T-periodic solutions.

2. *Let $m_k \geq 1$ for all k, $m_i = 1$, $m_j > 1$ for some i, j. Assume that*

$$\sum_{k \in M_2} \lambda_k r_k(t) e^B < b(t) \text{ for all } t$$

and there exists a constant γ_1 such that

$$\alpha(\gamma_1, t) > 0 \text{ for all } t.$$

Then (5.1) admits at least 2 positive T-periodic solutions.

3. *Let $0 < m_i < 1$, $m_j > 1$ for some i, j. Assume there exist some constants $\gamma_1 < \gamma_2$ such that*

$$\alpha(\gamma_2, t) > 0 > \beta(\gamma_1, t) \text{ for all } t.$$

Then (5.1) admits at least 3 solutions.

Theorem 5.3.3 *Assume that $m_k \leq n_k + 1$ for all k and $m_j = n_j + 1$ for some j.*

1. *Let $m_k > 1$ for all k and $1 < m_i < n_i + 1$ for some i. Assume that*

$$\sum_{k \in M_4} \lambda_k r_k(t) e^{B n_k} < b(t) \text{ for all } t$$

and there exists a constant γ_1 such that

$$\alpha(\gamma_1, t) > 0 \text{ for all } t.$$

Then (5.1) admits at least 2 positive T-periodic solutions.

2. *Let $0 < m_i < 1$ for some i, $m_k \notin (1, n_k + 1)$ for all k. Assume that*

$$\sum_{k \in M_4} \lambda_k r_k(t) e^{-B m_k} > b(t) \text{ for all } t$$

and there exists γ_1 such that

$$\beta(\gamma_1, t) < 0 \text{ for all } t.$$

Then (5.1) admits at least 2 positive T-periodic solutions.

3. Let $0 < m_i < 1$ *and* $1 < m_s < n_s + 1$ *for some* i, s. *Assume that*

$$\sum_{k \in M_4} \lambda_k r_k(t) e^{Bn_k} < b(t)$$

and there exist constants $\gamma_1 < \gamma_2$ *such that*

$$\alpha(\gamma_2, t) > 0 > \beta(\gamma_1, t) \text{ for all } t.$$

Then (5.1) has at least 3 *positive* T*-periodic solutions.*

As before, we shall only prove the first case of Theorem 5.3.1, since all the remaining cases follow in an analogous way.

Proof of Theorem 5.3.1, case 1: We shall apply Theorem 5.1.1 on open bounded sets $X_{\gamma_0}^{\gamma_1}$, $X_{\gamma_1}^{\gamma_2}$ and $X_{\gamma_2}^{\gamma_3}$, with $\gamma_0 < \gamma_1$ and $\gamma_3 > \gamma_2$ to be determined. To begin, observe that

$$\phi(\gamma) \to -\bar{b} \qquad \text{as } \gamma \to -\infty$$

and

$$\phi(\gamma) \to +\infty \qquad \text{as } \gamma \to +\infty.$$

In the same way of Theorem 5.2.1 it is proven that, if $\gamma_0 \ll 0$ then there exists $y \in X_{\gamma_0}^{\gamma_1}$ solution of (5.2).

On the other hand, for all t it is seen that

$$\phi(\gamma_1) > \alpha(\gamma_1, t) > 0.$$

Moreover, if $y \in cl(X_{\gamma_1}^{\gamma_2})$ is a solution of (5.4) with $0 < \sigma < 1$ and $y_{min} = y(t_*)$, then

$$b(t_*) e^{y_{min}} = \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{m_k y(t_* - \tau_k(t_*))}}{1 + e^{n_k y(t_* - \mu_k(t_*))}}$$

$$> \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{m_k y_{min}}}{1 + e^{n_k (y_{min} + B)}} > \sum_{k=1}^{M} \lambda_k r_k(t_*) \frac{e^{m_k y_{min}} e^{-Bm_k}}{1 + e^{n_k (y_{min} + B)}}.$$

It follows that $y_{min} \neq \gamma_1$.

Furthermore,

$$\phi(\gamma_2) < \beta(\gamma_2, t) < 0$$

for all t and we deduce as before that $y_{max} \neq \gamma_2$.

Finally, the existence of $\gamma_3 \gg 0$ such that the problem has a solution $y \in X_{\gamma_2}^{\gamma_3}$ follows as in Theorem 5.2.1. ■

The following lemma shows, in the context of Theorem 5.3.1 (case 1), that if r_k, m_k and n_k are given, then it is possible to find parameters λ_k such that assumptions are fulfilled. Analogous arguments are valid for the remaining cases.

Lemma 5.3.1 *Let $r_k, b : \mathbb{R} \to \mathbb{R}_{>0}$ be continuous and T-periodic functions and $m_k, n_k \in \mathbb{R}_{>0}$ such that $m_k > 1$ for all k, $1 < m_j < n_j + 1$ for some j, $m_i > n_i + 1$ for some i. Then there exist λ_k and $\gamma_1 < \gamma_2$ such that*

$$\alpha(\gamma_1, t) > 0 > \beta(\gamma_2, t) \text{ for all } t.$$

Proof: Using the sets M_i as before, we may write α and β as

$$\alpha(\gamma, t) = \sum_{i=1}^{5} \alpha_i(\gamma, t) - b(t), \qquad \beta(\gamma, t) = \sum_{i=1}^{5} \beta_i(\gamma, t) - b(t),$$

where

$$\alpha_i(\gamma, t) := \sum_{k \in M_i} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma} e^{-Bm_k}}{1 + e^{n_k(\gamma+B)}}, \quad \beta_i(\gamma, t) := \sum_{k \in M_i} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma} e^{Bm_k}}{1 + e^{n_k(\gamma-B)}}.$$

Observe that, for each $t \in [0, T]$ and $i = 1, \ldots, 5$, the functions $\alpha_i(\cdot, t)$ and $\beta_i(\cdot, t)$ have the same qualitative behavior as the mappings ϕ_i given by (5.5).

We begin by setting the parameters $\lambda_k \in M_3$. For arbitrary γ_1, take $\lambda_k \in M_3$ large enough such that

$$\alpha(\gamma_1, t) \geq \sum_{k \in M_3} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma_1} e^{-Bm_k}}{1 + e^{n_k(\gamma_1+B)}} - b(t) > 0.$$

For $\epsilon \in (0, b_{min})$, there exists $R > \gamma_1$ such that

$$\beta_3(\gamma, t) = \sum_{k \in M_3} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma} e^{Bm_k}}{1 + e^{n_k(\gamma-B)}} < \sum_{k \in M_3} \lambda_k r_k^{max} \frac{e^{(m_k-1)\gamma} e^{Bm_k}}{1 + e^{n_k(\gamma-B)}} < \epsilon$$

for $\gamma > R$ and all t. Thus, we may fix $\gamma_2 > R$ and proceed with the remaining parameters.

Next, for $k \in M_4 \cup M_5$ we set λ_k small enough so that

$$\sum_{k \in M_4 \cup M_5} \lambda_k (r_k)_{max} \frac{e^{(m_k-1)\gamma_2} e^{Bm_k}}{1 + e^{n_k(\gamma_2-B)}} < b_{min} - 2\epsilon$$

and hence

$$(\beta_4 + \beta_5)(\gamma_2, t) = \sum_{k \in M_4 \cup M_5} \lambda_k r_k(t) \frac{e^{(m_k-1)\gamma_2} e^{Bm_k}}{1 + e^{n_k(\gamma_2-B)}} < b_{min} - 2\epsilon < b(t) - 2\epsilon.$$

Thus the conclusion follows since

$$\beta(\gamma_2, t) = (\beta_3 + \beta_4 + \beta_5)(\gamma_2, t) - b(t) < \epsilon - 2\epsilon < 0$$

and

$$\alpha(\gamma_1, t) = (\alpha_3 + \alpha_4 + \alpha_5)(\gamma_1, t) - b(t)$$

$$> \alpha_3(\gamma_1, t) - b(t) > 0$$

∎

5.4 Example

As shown in Theorem 5.3.1, case 5, equation (5.1) has at least 4 positive T-periodic solutions. The following example shows that, in fact, the problem may have more solutions. Consider:

- $k = 4$,
- $b(t) = 1.1 + 0.02\cos\left(\frac{2\pi t}{T}\right)$,
- $T = 0.005$, $m_1 = 0.95$, $n_1 = 2$,
- $\lambda_1 r_1(t) = 0.04 + 0.002\cos\left(\frac{2\pi t}{T}\right)$,
- $m_2 = 4.73$, $n_2 = 3.74$,
- $\lambda_2 r_2(t) = 1.3 + 0.002\cos\left(\frac{2\pi t}{T}\right)$,
- $m_3 = 1.0001$, $n_3 = 10.2$,
- $\lambda_3 r_3(t) = 0.9 + 0.002\cos\left(\frac{2\pi t}{T}\right)$,
- $m_4 = 1.12$, $n_4 = 0.11$,
- $\lambda_4 r_4(t) = 0.06 + 0.002\cos\left(\frac{2\pi t}{T}\right)$.

Set $\gamma_1 = -5$, $\gamma_2 = -0.3$ $\gamma_3 = 0.2$, $\gamma_4 = 5$, $\gamma_5 = 34$. It is verified (see Figure 1) that

$$\alpha(\gamma_2, t) > 0.09, \alpha(\gamma_4, t) > 0.1 \text{ for all } t$$

and

$$\beta(\gamma_1, t) < -0.08, \beta(\gamma_3, t) < -0.01, \beta(\gamma_5, t) < -0.01 \text{ for all } t.$$

Moreover, since $0 < m_1 = 0.95 < 1$ and $m_4 = 1.12 > n_4 + 1 = 1.11$, it follows that

$$\lim_{\gamma\to-\infty} \phi(\gamma) = \lim_{\gamma\to+\infty} \phi(\gamma) = +\infty.$$

Thus, as in the previous proofs, we may set $\gamma_0 \ll 0$ and $\gamma_6 \gg 0$ in such a way that the problem has a solution in $X_{\gamma_k}^{\gamma_{k+1}}$ for $k = 0, \ldots, 5$. We conclude that (5.1) has at least six positive 0.005-periodic solutions for arbitrary nonnegative 0.005-periodic delays τ_k, μ_k.

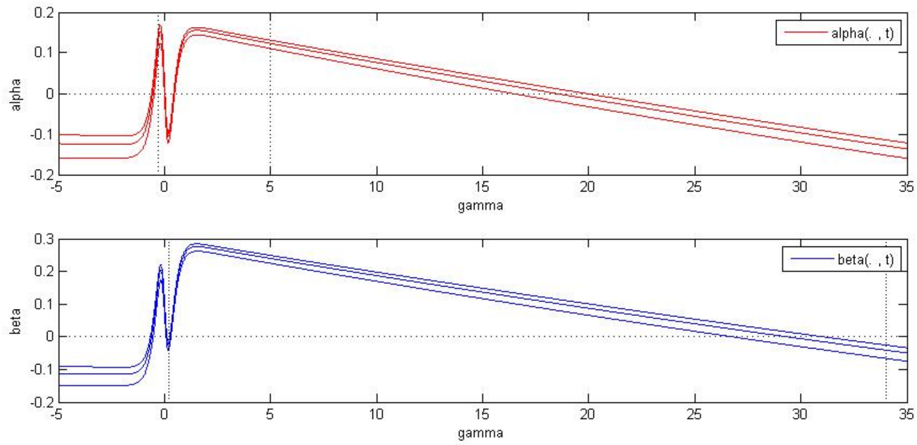


Figure 5.1: $\alpha(\cdot, t)$ and $\beta(\cdot, t)$ for each $t \in [0 : 0.01 : T]$.

5.5 Necessary conditions

In this section we shall prove that, under certain assumptions, the trivial equilibrium is a global attractor for the positive solutions of (5.1). This proves, in particular, that positive T-periodic solutions cannot exist. As we shall see at the end of the section, both in the case that $m_j < 1$ for some j and the superlinear case, the autonomous problem admits positive equilibrium points and hence 0 cannot be a global attractor for the positive solutions. Hence, we shall consider only the case $1 \leq m_k \leq n_k + 1$ for all k and, thus, our non-existence result can be regarded, in some sense, as complementary to Theorem 5.2.2 (cases 2 and 3) and Theorem 5.2.3 (cases 1 and 2).

Throughout this section we shall assume that $\mu_k(t) \leq \tau_k(t)$. For convenience, we define $\upsilon := \max_{1 \leq k \leq M, t \in \mathbb{R}} \{\tau_k(t)\}$

Remark 5.5.1 *Let be $y(t)$ a solution of (5.2). Then*

$$y'(t) \geq -b(t)$$

and hence $y(t_1) \leq y(t_2) + \int_{t_1}^{t_2} b(t)dt$ for any $t_1 \leq t_2$. In particular, this implies that

$$y(t - \tau_k(t)), y(t - \mu_k(t)) \leq L + y(t), \tag{5.6}$$

where $L = \max_{t \in [0,T]} \int_{t-\upsilon}^{t} b(s)ds$ and

$$y(t - \tau_k(t)) \leq y(t - \mu_k(t)) + B_k, \tag{5.7}$$

where $B_k = \max_{t \in [0,T]} \int_{t-\tau_k(t)}^{t-\mu_k(t)} b(s)ds$.

Theorem 5.5.1 *Let $1 \leq m_k \leq n_k + 1$ for all k. Assume that*

$$\sum_{k=1}^{M} \lambda_k r_k(t) e^{m_k B_k} \leq b(t). \tag{5.8}$$

Then every positive solution of (5.1) *tends to* 0 *as $t \to +\infty$. In particular (5.1) has no positive T-periodic solutions.*

Proof: We shall prove that every solution of (5.2) tends to $-\infty$ as $t \to +\infty$. To this end, let y be a solution of (5.2) and suppose firstly that there exists a sequence $\{t_j\}_{j\in\mathbb{N}}$ such that $t_j \nearrow +\infty$, $y'(t_j) \geq 0$, and $y(t) < y(t_j)$ for all $t_1 - \upsilon \leq t < t_j$. It follows from (5.7)-(5.8) that

$$0 \leq y'(t_j) \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} \frac{e^{m_k y(t_j-\mu_k(t_j))-y(t_j)}}{1+e^{n_k y(t_j-\mu_k(t_j))}} - b(t_j)$$

and hence

$$\begin{aligned} 0 &\leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{y(t_j-\mu_k(t_j))-y(t_j)} - b(t_j) \\ &< \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} - b(t_j) \leq 0, \end{aligned}$$

a contradiction. We conclude that, on the one hand y' cannot be nonnegative on $(t_0, +\infty)$ and, on the other hand, for any t_0 and $\limsup_{t\to+\infty} y(t) := \omega_1 \neq +\infty$. Thus, we may consider the two possible cases:

Case I: There exists $t_0 > 0$ large enough such that $y'(t) \leq 0$ for all $t \geq t_0$. It follows that $y(t) \to \alpha \in [-\infty, +\infty)$ as $t \to +\infty$ and we claim that $\alpha = -\infty$. Indeed, otherwise we may define

$$V := \min_{t\in[0,T]} \left\{ \sum_{k=1}^{M} \lambda_k r_k(t) \left(1 - \frac{e^{(m_k-1)\alpha}}{1+e^{n_k\alpha}}\right) \right\} > 0,$$

and choose an arbitrary $\epsilon > 0$ small enough such that $\sum_{k=1}^{M} \lambda_k r_k(t)\epsilon < \frac{V}{2}$ for all t. Fix $t_1 \geq t_0$ such that $\frac{e^{m_k y(t-\tau_k(t))-y(t)}}{1+e^{n_k y(t-\mu_k(t))}} < \frac{e^{(m_k-1)\alpha}}{1+e^{n_k\alpha}} + \epsilon$ for all $t \geq t_1$, then from (5.8) we deduce:

$$\begin{aligned} y'(t) &= \sum_{k=1}^{M} \lambda_k r_k(t) \frac{e^{m_k y(t-\tau_k(t))-y(t)}}{1+e^{n_k y(t-\mu_k(t))}} - b(t) \\ &\leq \sum_{k=1}^{M} \lambda_k r_k(t) \left(\frac{e^{(m_k-1)\alpha}}{1+e^{n_k\alpha}} + \epsilon\right) - b(t) \\ &< \sum_{k=1}^{M} \lambda_k r_k(t) e^{m_k B_k} \left(\frac{e^{(m_k-1)\alpha}}{1+e^{n_k\alpha}} - 1\right) + \frac{V}{2} \\ &< -\frac{V}{2} \end{aligned}$$

a contradiction.

Case II. $y(t)$ is oscillatory. Suppose that $\limsup_{t\to+\infty} y(t) > -\infty$, then we may set $\{t_j\}_{j\in\mathbb{N}}$ such that $t_j \nearrow +\infty$, $y'(t_j) = 0$, $\lim_{j\to+\infty} y(t_j) = \limsup_{t\to+\infty} y(t) = \omega_1 \in \mathbb{R}$. Define $\limsup_{j\to+\infty} y(t_j - \mu_k(t_j)) := \omega_2 \leq \omega_1$.

If $\omega_2 = -\infty$, then

$$0 = y'(t_j) \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) \frac{e^{m_k(B_k+y(t_j-\mu_k(t_j)))-y(t_j)}}{1+e^{n_k y(t_j-\mu_k(t_j))}} - b(t_j)$$

thus,

$$b(t_j)e^{y(t_j)} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{y(t_j-\mu_k(t_j))}.$$

Next, take a large enough constant $S > 0$. For $j \gg 0$, we obtain:

$$b(t_j)e^{y(t_j)} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{-S}$$

and hence

$$b_{min} e^{\omega_1 - \epsilon} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{-S}.$$

This contradicts the fact that $\omega_1 \in \mathbb{R}$. Now suppose $\omega_2 \in \mathbb{R}$, then

$$b(t_j)e^{y(t_j)} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{y(t_j-\mu_k(t_j))}.$$

Let $\epsilon > 0$, for j large enough,

$$b(t_j)e^{y(t_j)} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{\omega_2+\epsilon}$$

then

$$b(t_j)e^{\omega_1-\epsilon} \leq \sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} e^{\omega_2+\epsilon}$$

$$e^{\omega_1-\epsilon} \leq e^{\omega_2+\epsilon}$$

Since ϵ is arbitrary we deduce that $\omega_1 = \omega_2$. Finally, define $V > 0$ as in the previous case, with $\alpha = \omega_1 = \omega_2$ and fix $\epsilon > 0$ such that $\sum_{k=1}^{M} \lambda_k r_k(t_j) e^{m_k B_k} \epsilon < \frac{V}{2}$. As before, we deduce that $y'(t_j) < -\frac{V}{2}$, a contradiction.

■

As a final remark, let us show that both in the case $m_j < 1$ for some j and the superlinear case, the autonomous problem admits positive equilibrium points. Indeed, assume that b and r_k are constant and $\sum_{k=1}^{M} \lambda_k r_k \leq b$. Let $f : \mathbb{R} \to \mathbb{R}$ be given by $f(u) = \sum_{k=1}^{M} \lambda_k r_k \frac{e^{(m_k-1)y}}{1+e^{n_k y}} - b$; then it suffices to prove that f has at least one zero. For the superlinear case (namely, $m_j > n_j + 1$ for some j), it is seen that

$$f(0) = \sum_{k=1}^{M} \lambda_k r_k \frac{1}{2} - b < \sum_{k=1}^{M} \lambda_k r_k - b \leq 0$$

and

$$\lim_{u\to+\infty} f(u) = +\infty$$

so f vanishes in $(0, +\infty)$. If $m_i \leq n_i + 1$ for all i and $m_j < 1$ for some j, then we deduce as before that $f(0) < 0$ and

$$\lim_{u\to-\infty} f(u) = +\infty.$$

Thus, f vanishes in $(-\infty, 0)$ and the conclusion follows.

5.6 Conclusions

By applying a theorem based on the continuation method, the results given in this Chapter provide sufficient conditions for existence and multiplicity of positive periodic solutions for a generalized hematopoiesis model.

It is observed that, in some particular cases, our methods guarantee the existence but not multiplicity of solutions. However, this fact does not automatically imply uniqueness; thus, it is an interesting problem to analyze, for such cases, whether or not uniqueness of positive periodic solutions can be proved.

We shall resume this topic in the next chapter.

Resumen del capítulo 6

La primera parte de este Capítulo está dedicada a la formulación de teoremas de punto fijo, primero en conos abstractos y luego en el cono de las funciones casi periódicas no negativas. Luego planteamos distintos modelos abstractos y de los resultados de punto fijo deducimos teoremas de existencia en el espacio de funciones casi periódicas.

El Capítulo está organizado de la siguiente manera:

En la Sección 6.1 damos un Teorema de punto fijo para operadores monótonos mixtos en conos abstractos. Luego hacemos una modificación de este teorema considerando el cono de funciones casi periódicas no negativas.

En la Sección 6.2 estudiamos ecuaciones abstractas del tipo

$$x'(t) = \sum_{k=1}^{M} F_k(t, x(t-\tau_k(t))) + \sum_{k=1}^{N} G_k(t, x(t-\mu_k(t))) - b(t)x(t). \tag{5.9}$$

Consideramos τ_k, μ_k y $b \in AP(\mathbb{R})$, b es una función con ínfimo positivo, τ_k y μ_k son no negativas, F_k, G_k pertenecen a la clase u.a.p y $F_k(t,\cdot), G_k(t,\cdot), \big|_{\mathbb{R}>0} \subset \mathbb{R}_{>0}$ para todo $t \in \mathbb{R}$. Además suponemos que F_k son funcions crecientes y G_k decrecientes.

Para estas ecuaciones adaptamos los teoremas obtenidos en la Sección previa y obtenemos criterios simples de verificar para la existencia de soluciones positivas casi periódicas.

En la Sección 6.3 damos Ejemplos de modelos biológicos que ilustran la aplicabilidad de nuestros resultados. Específicamente, empleamos los teoremas de la Sección previa para probar la existencia de soluciones casi periódicas con ínfimo positivo para el modelo de Nicholson:

$$x'(t) = \sum_{k=1}^{M} p_k(t)x(t-\tau_k(t))e^{x(t-\tau_k(t))} - b(t)x(t), \quad \delta = 0, 1, \tag{5.10}$$

y para un modelo de tipo Lasota-Wasewska

$$x'(t) = \sum_{k=1}^{M} c_k(t)e^{-\beta_k(t)x(t-\tau_k(t))} - b(t)x(t). \tag{5.11}$$

Chapter 6

Fixed point theorems in abstract cones

In this Chapter we shall formulate fixed point theorems in cones. Then, we shall deduce existence theorems in the space of almost periodic functions.

Motivated by the biological applications we shall provide some examples which, in addition, shall illustrate the applicability of our results.

The following notation shall be used throughout this Chapter. The supremum value and the infimum value of a bounded continuous function $f : \mathbb{R} \to \mathbb{R}$ shall be denoted respectively by f^* and f_*, namely

$$f^* := \sup_{t \in \mathbb{R}} f(t), \qquad f_* := \inf_{t \in \mathbb{R}} f(t). \tag{6.1}$$

6.1 Fixed point theorems

The following fixed point theorems shall play an important role in Chapter 7.

Theorem 6.1.1 *Let P be a normal cone in a real Banach space X, and $\Phi : P^\circ \times P^\circ \to P^\circ$. Assume that*

(I) there exist $u_0, v_0 \in P^\circ$, $u_0 \le v_0$, $u_0 \le \Phi(u_0, v_0)$ and $v_0 \ge \Phi(v_0, u_0)$;

(II) Φ is a mixed monotone operator on $[u_0, v_0]$;

(III) there exists a function $\phi : (0,1) \to (0, +\infty)$ such that $\phi(\gamma) > \gamma$ for all $\gamma \in (0,1)$, and for any $x, y \in [u_0, v_0]$

$$\Phi(\gamma x, \gamma^{-1} y) \ge \phi(\gamma)\Phi(x, y), \quad \text{for all } \gamma \in (0,1).$$

Then Φ has exactly one fixed point $\tilde{x}$ in $[u_0, v_0]$.

Moreover, for any initial $x_0, y_0 \in [u_0, v_0]$, the iterative sequences

$$x_n = \Phi(x_{n-1}, y_{n-1}), \quad y_n = \Phi(y_{n-1}, x_{n-1}), \;\; n \in \mathbb{N}, \tag{6.2}$$

satisfy

$$||x_n - \tilde{x}||, ||y_n - \tilde{x}|| \to 0 \;\; (n \to +\infty).$$

Proof: For $n \in \mathbb{N}$, define $u_n := \Phi(u_{n-1}, v_{n-1})$ and $v_n := \Phi(v_{n-1}, u_{n-1})$. Since Φ is a mixed monotone operator, by (I) we deduce

$$u_0 \leq u_1 = \Phi(u_0, v_0) \leq \Phi(v_0, u_0) = v_1 \leq v_0,$$

and inductively we obtain

$$u_0 \leq u_1 \leq \ldots \leq u_n \leq \ldots \leq v_n \leq \ldots \leq v_1 \leq v_0. \tag{6.3}$$

Since P° is a open set and $u_n \in P^\circ$, there exists a constant $\delta > 0$ such that $u_n - \lambda v_n \in P^\circ$ for any $\lambda \in (0, \delta)$. Thus, the constant $\lambda_n := \sup\{\lambda : u_n \geq \lambda v_n\}$ is well defined and positive. It is clear that

$$u_n \geq \lambda_n v_n \tag{6.4}$$

and the inequality $u_n \leq v_n$ implies $\lambda_n \leq 1$. Moreover, since $u_{n+1} \geq u_n \geq \lambda_n v_n \geq \lambda_n v_{n+1}$, it is seen that $\lambda_{n+1} \geq \lambda_n$. We claim that $\overline{\lambda} := \lim_{n\to+\infty} \lambda_n = 1$. Indeed, if this is not true then $\overline{\lambda} \in (0, 1)$ and there are two cases:

Case 1. There exists $\overline{n}$ such that $\lambda_{\overline{n}} = \overline{\lambda}$. Then $\lambda_n = \overline{\lambda}$, $u_n \geq \overline{\lambda} v_n$ for all $n > \overline{n}$ which, together with $(II), (III)$ and (6.3), yields

$$u_{n+1} = \Phi(u_n, v_n) \geq \Phi(\overline{\lambda} v_n, \overline{\lambda}^{-1} u_n) \geq \phi(\overline{\lambda})\Phi(v_n, u_n) = \phi(\overline{\lambda}) v_{n+1}.$$

Thus $\lambda_{n+1} \geq \phi(\overline{\lambda}) > \overline{\lambda}$, which contradicts the fact that $\lambda_{n+1} = \overline{\lambda}$.

Case 2. $\lambda_n < \overline{\lambda}$, for all n. Then

$$u_{n+1} = \Phi(u_n, v_n) \geq \Phi\left(\lambda_n v_n, \lambda_n^{-1} u_n\right) = \Phi\left(\frac{\lambda_n}{\overline{\lambda}} \overline{\lambda} v_n, \frac{\overline{\lambda}}{\lambda_n} \overline{\lambda}^{-1} u_n\right)$$

$$\geq \phi\left(\frac{\lambda_n}{\overline{\lambda}}\right) \Phi\left(\overline{\lambda} v_n, \overline{\lambda}^{-1} u_n\right) > \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right) \Phi(v_n, u_n) \geq \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right) v_{n+1}.$$

Thus $\lambda_{n+1} \geq \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right)$. Letting $n \to \infty$, we deduce that $\overline{\lambda} \geq \phi\left(\overline{\lambda}\right) > \overline{\lambda}$, a contradiction.

Hence $\overline{\lambda} = 1$ and from (6.3)-(6.4) it follows that, for any k,

$$0 \leq u_{n+k} - u_n \leq v_n - u_n \leq v_n - \lambda_n v_n = (1 - \lambda_n) v_n \leq (1 - \lambda_n) v_0. \tag{6.5}$$

By the normality of P and (6.5),

$$||u_{n+k} - u_n|| \leq N(1 - \lambda_n)||v_0|| \to 0 \quad \text{as } n \to \infty.$$

Thus, $\{u_n\}_{n\in\mathbb{N}}$ is a Cauchy sequence. This implies that there exists $\overline{u} \in [u_0, v_0]$ such that $u_n \to \overline{u}$. Similarly,

$$0 \leq v_n - u_n \leq v_n - \lambda_n v_n = (1 - \lambda_n) v_n \leq (1 - \lambda_n) v_0.$$

Again, by the normality of P

$$||v_n - u_n|| \leq N(1 - \lambda_n)||v_0|| \to 0 \quad \text{as } n \to \infty,$$

and consequently $v_n \to \overline{u}$. Hence, since Φ is a mixed monotone operator on $[u_0, v_0]$, it follows that

$$u_{n+1} = \Phi(u_n, v_n) \le \Phi(\overline{u}, \overline{u}) \le \Phi(v_n, u_n) = v_{n+1.}$$

We conclude that $\overline{u} = \Phi(\overline{u}, \overline{u})$.

Suppose now that $\overline{w} \in [u_0, v_0]$ is another fixed point of Φ. Define $\alpha := \sup\{\tilde{\alpha} \in (0,1) : \tilde{\alpha}\overline{w} \le \overline{u} \le \frac{1}{\tilde{\alpha}}\overline{w}\}$. Thus, $\alpha\overline{w} \le \overline{u} \le \alpha^{-1}\overline{w}$ and $\alpha \in (0,1]$. Suppose that $\alpha \in (0,1)$, then $\phi(\alpha) > \alpha$,

$$\overline{u} = \Phi(\overline{u}, \overline{u}) \le \Phi(\frac{1}{\alpha}\overline{w}, \alpha\overline{w}) \le \phi(\alpha)^{-1}\Phi(\overline{w}, \overline{w}) = \phi(\alpha)^{-1}\overline{w},$$

and

$$\overline{u} = \Phi(\overline{u}, \overline{u}) \ge \Phi(\alpha\overline{w}, \frac{1}{\alpha}\overline{w}) \ge \phi(\alpha)\Phi(\overline{w}, \overline{w}) = \phi(\alpha)\overline{w}.$$

Thus, by the definition of α we have $\phi(\alpha) \le \alpha$, which is a contradiction. We conclude that $\alpha = 1$ and therefore $\overline{w} = \overline{u}$.

Finally, let be (x_0, y_0) any initial condition in $[u_0, v_0] \times [u_0, v_0]$ and (x_n, y_n) the iterative sequences given by (6.2). Since Φ is a mixed monotone operator, we have

$$u_1 = \Phi(u_0, v_0) \le x_1 = \Phi(x_0, y_0) \le \Phi(v_0, u_0) = v_1$$

and

$$u_1 = \Phi(u_0, v_0) \le y_1 = \Phi(y_0, x_0) \le \Phi(v_0, u_0) = v_1,$$

and inductively we obtain $x_n, y_n \in [u_n, v_n]$. Thus, it is clear that

$$||x_n - \tilde{x}||, ||y_n - \tilde{x}|| \to 0 \text{ as } n \to +\infty.$$

The proof is complete. ■

Corollary 6.1.1 *Let P be a normal cone in a real Banach space X, and $\Phi : P^\circ \to P^\circ$. Assume that*

(I) there exist $u_0, v_0 \in P^\circ$, $u_0 \le v_0$, $u_0 \le \Phi(u_0)$ and $v_0 \ge \Phi(v_0)$;

(II) Φ is a nondecreasing operator on $[u_0, v_0]$;

(III) there exists a function $\phi : (0,1) \to (0, +\infty)$ such that $\phi(\gamma) > \gamma$ for all $\gamma \in (0,1)$, and for any $x \in [u_0, v_0]$

$$\Phi(\gamma x) \ge \phi(\gamma)\Phi(x), \quad \textit{for all } \gamma \in (0,1).$$

Then Φ has exactly one fixed point $\tilde{x}$ in $[u_0, v_0]$.

Moreover, for any initial $x_0 \in [u_0, v_0]$, the iterative sequence

$$x_n = \Phi(x_{n-1}), \;\; n \in \mathbb{N}, \tag{6.6}$$

satisfies

$$||x_n - \tilde{x}|| \to 0 \;\; (n \to +\infty).$$

Corollary 6.1.2 *Let P be a normal cone in a real Banach space X, and $\Phi : P^\circ \to P^\circ$. Assume that*

(I) *there exist $u_0, v_0 \in P^\circ$, $u_0 \le v_0$, $u_0 \le \Phi(v_0)$ and $v_0 \ge \Phi(u_0)$;*

(II) *Φ is a nonincreasing operator on $[u_0, v_0]$;*

(III) *there exists a function $\phi : (0,1) \to (0, +\infty)$ such that $\phi(\gamma) > \gamma$ for all $\gamma \in (0,1)$, and for any $x \in [u_0, v_0]$*

$$\Phi(\gamma^{-1}x) \ge \phi(\gamma)\Phi(x), \quad \textit{for all } \gamma \in (0,1).$$

Then Φ has exactly one fixed point $\tilde{x}$ in $[u_0, v_0]$.

Moreover, for any initial $x_0 \in [u_0, v_0]$, the iterative sequence

$$x_n = \Phi(x_{n-1}), \;\; n \in \mathbb{N}, \tag{6.7}$$

satisfies

$$||x_n - \tilde{x}|| \to 0 \;\; (n \to +\infty).$$

Remark 6.1.1 *It is worth noticing that Corollaries 6.1.1 and 6.1.2 are the same result as those fixed point theorems established by Wang et al. in [55] and [54] respectively. Hence, Theorem 6.1.1 generalizes both results.*

We establish the following abstract fixed point Lemma as a consequence of Theorem 6.1.1. This Lemma shall be the key for the study of the simplified model of hematopoiesis in Chapter 7. We include a proof for the sake of completeness.

Let us now consider the cone

$$P = \{x \in AP(\mathbb{R}) : x(t) \ge 0 \quad \text{for all } t \in \mathbb{R}\}$$

and

$$P^\circ = \{x \in AP(\mathbb{R}) : x \text{ has positive infimum } \}$$

its interior.

Lemma 6.1.1 *Assume that the following conditions are fulfilled*

(I) there exist $u_0, v_0 \in P^\circ$, $u_0 < v_0$ and

$$\Phi : \left[\frac{(u_0)_*}{v_0^*}u_0, v_0\right] \times \left[u_0, \frac{v_0^*}{(u_0)_*}v_0\right] \subset P^\circ \times P^\circ \to P^\circ;$$

(II) $u_0 \le \Phi(u_0, v_0)$ and $v_0 \ge \Phi(v_0, u_0)$;

(III) Φ is a mixed monotone operator on $[u_0, v_0]$;

(IV) there exists a function $\phi : \left[\frac{(u_0)_*}{v_0^*}, 1\right) \to (0, +\infty)$ *such that* $\phi(\gamma) > \gamma$*, for any* $x, y \in [u_0, v_0]$

$$\Phi(\gamma x, \gamma^{-1} y) \geq \phi(\gamma)\Phi(x, y), \quad \textit{for all } \gamma \in \left[\frac{(u_0)_*}{v_0^*}, 1\right).$$

Then Φ *has exactly one fixed point* $\tilde{x}$ *in* $[u_0, v_0]$.

Moreover, for any initial $x_0, y_0 \in [u_0, v_0]$*, the iterative sequences*

$$x_n = \Phi(x_{n-1}, y_{n-1}), \;\; y_n = \Phi(y_{n-1}, x_{n-1}), \;\; n \in \mathbb{N},$$

satisfy

$$||x_n - \tilde{x}||, ||y_n - \tilde{x}|| \to 0 \;\; (n \to +\infty). \tag{6.8}$$

Proof: For $n \in \mathbb{N}$, define $u_n := \Phi(u_{n-1}, v_{n-1})$ and $v_n := \Phi(v_{n-1}, u_{n-1})$. Since Φ is a mixed monotone operator, by (I) we deduce

$$u_0 \leq u_1 = \Phi(u_0, v_0) \leq \Phi(v_0, u_0) = v_1 \leq v_0,$$

and inductively we obtain

$$u_0 \leq u_1 \leq \ldots \leq u_n \leq \ldots \leq v_n \leq \ldots \leq v_1 \leq v_0. \tag{6.9}$$

Since P° is a open set and $u_n \in P^\circ$, there exists a constant $\delta > 0$ such that $u_n - \lambda v_n \in P^\circ$ for any $\lambda \in (0, \delta)$. Thus, the constant $\lambda_n := \sup\{\lambda : u_n \geq \lambda v_n\}$ is well defined and

$$u_n \geq \lambda_n v_n. \tag{6.10}$$

Moreover, since $u_{n+1} \geq u_n \geq \lambda_n v_n \geq \lambda_n v_{n+1}$, it is seen that $\lambda_{n+1} \geq \lambda_n$ and inductively we obtain

$$\lambda_0 \leq \lambda_1 \leq \cdots \leq \lambda_n \leq \cdots \leq 1.$$

Thus, in view of the inequality $\lambda_0 \geq \frac{(u_0)_*}{v_0^*}$ we deduce that $\frac{(u_0)_*}{v_0^*} \leq \lambda_n \leq 1$.

Let us define $\overline{\lambda} := \lim_{n \to +\infty} \lambda_n$. Firstly, it is important to notice that,

$$\frac{(u_0)_*}{v_0^*} u_0 \leq \overline{\lambda} u_0 \leq \overline{\lambda} v_n \leq v_0 \leq \frac{v_0^*}{(u_0)_*} v_0$$

and

$$\frac{(u_0)_*}{v_0^*} u_0 \leq u_0 \leq \overline{\lambda}^{-1} u_0 \leq \overline{\lambda}^{-1} u_n \leq \frac{v_0^*}{(u_0)_*} v_0.$$

Now, we claim that $\overline{\lambda} = 1$. Indeed, if this is not true then $\overline{\lambda} < 1$ and there are two cases:

Case 1. There exists $\overline{n}$ such that $\lambda_{\overline{n}} = \overline{\lambda}$. Then $\lambda_n = \overline{\lambda}$, $u_n \geq \overline{\lambda} v_n$ for all $n > \overline{n}$ which, together with $(II), (III)$ and (6.9), yields

$$u_{n+1} = \Phi(u_n, v_n) \geq \Phi(\overline{\lambda} v_n, \overline{\lambda}^{-1} u_n) \geq \phi(\overline{\lambda})\Phi(v_n, u_n) = \phi(\overline{\lambda}) v_{n+1}.$$

Thus $\lambda_{n+1} \geq \phi(\overline{\lambda}) > \overline{\lambda}$, which contradicts the fact that $\lambda_{n+1} = \overline{\lambda}$.

Case 2. $\lambda_n < \overline{\lambda}$, for all n. Then

$$u_{n+1} = \Phi(u_n, v_n) \geq \Phi\left(\lambda_n v_n, \lambda_n^{-1} u_n\right) = \Phi\left(\frac{\lambda_n}{\overline{\lambda}} \overline{\lambda} v_n, \frac{\overline{\lambda}}{\lambda_n} \overline{\lambda}^{-1} u_n\right)$$

$$\geq \phi\left(\frac{\lambda_n}{\overline{\lambda}}\right) \Phi\left(\overline{\lambda} v_n, \overline{\lambda}^{-1} u_n\right) > \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right) \Phi(v_n, u_n) \geq \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right) v_{n+1}.$$

Thus $\lambda_{n+1} \geq \frac{\lambda_n}{\overline{\lambda}} \phi\left(\overline{\lambda}\right)$. Letting $n \to \infty$, we deduce that $\overline{\lambda} \geq \phi\left(\overline{\lambda}\right) > \overline{\lambda}$, a contradiction.

Hence $\overline{\lambda} = 1$ and from (6.9)-(6.10) it follows that, for any k,

$$0 \leq u_{n+k} - u_n \leq v_n - u_n \leq v_n - \lambda_n v_n = (1 - \lambda_n) v_n \leq (1 - \lambda_n) v_0. \tag{6.11}$$

By the normality of P and (6.5), there exists $\overline{u} \in [u_0, v_0]$ such that $u_n \to \overline{u}$. In addition,

$$0 \leq v_n - u_n \leq v_n - \lambda_n v_n = (1 - \lambda_n) v_n \leq (1 - \lambda_n) v_0,$$

and again, by the normality of P

$$||v_n - u_n|| \leq N(1 - \lambda_n)||v_0||.$$

Thus, we have $v_n \to \overline{u}$ as $n \to \infty$.

Since Φ is a mixed monotone operator on $[u_0, v_0]$, we conclude that $\overline{u} = \Phi(\overline{u}, \overline{u})$.

Suppose now that $\overline{w} \in [u_0, v_0]$ is another fixed point of Φ. Define $\alpha := \sup\{\tilde{\alpha} \in (0,1) : \tilde{\alpha}\overline{w} \leq \overline{u} \leq \tilde{\alpha}^{-1}\overline{w}\}$. Since $\overline{u}, \overline{w}$ have positive infimum, α is well defined. Thus, $\alpha\overline{w} \leq \overline{u} \leq \alpha^{-1}\overline{w}$ and $\alpha \in \left[\frac{(u_0)_*}{v_0^*}, 1\right]$. Suppose that $\alpha \in \left[\frac{(u_0)_*}{v_0^*}, 1\right)$, then $\phi(\alpha) > \alpha$,

$$\overline{u} = \Phi(\overline{u}, \overline{u}) \leq \Phi(\frac{1}{\alpha}\overline{w}, \alpha\overline{w}) \leq \phi(\alpha)^{-1}\Phi(\overline{w}, \overline{w}) = \phi(\alpha)^{-1}\overline{w},$$

and

$$\overline{u} = \Phi(\overline{u}, \overline{u}) \geq \Phi(\alpha\overline{w}, \frac{1}{\alpha}\overline{w}) \geq \phi(\alpha)\Phi(\overline{w}, \overline{w}) = \phi(\alpha)\overline{w}.$$

Thus, by the definition of α we have $\phi(\alpha) \leq \alpha$, which is a contradiction. We conclude that $\alpha = 1$ and therefore $\overline{w} = \overline{u}$.

Finally, (6.8) follows from the same arguments to those employed in Theorem 6.1.1. The proof is complete. ■

As before, we have the following Corollaries.

Corollary 6.1.3 *Assume that the following conditions are fulfilled*

(I) there exist $u_0, v_0 \in P^\circ$, $u_0 < v_0$ *and* $\Phi : \left[\frac{(u_0)_*}{v_0^*} u_0, v_0\right] \subset P^\circ \to P^\circ$*;*

(II) $u_0 \leq \Phi(u_0)$ *and* $v_0 \geq \Phi(v_0)$*;*

(III) Φ *is a nondecreasing operator on* $[u_0, v_0]$*;*

(IV) there exists a function $\phi : \left[\frac{(u_0)_*}{v_0^*}, 1\right) \to (0, +\infty)$ *such that* $\phi(\gamma) > \gamma$, *and for any* $x \in [u_0, v_0]$

$$\Phi(\gamma x) \geq \phi(\gamma)\Phi(x), \quad \textit{for all } \gamma \in \left[\frac{(u_0)_*}{v_0^*}, 1\right).$$

Then Φ *has exactly one fixed point* $\tilde{x}$ *in* $[u_0, v_0]$.

Moreover, for any initial $x_0 \in [u_0, v_0]$, *the iterative sequence*

$$x_n = \Phi(x_{n-1}), \ \ n \in \mathbb{N}, \tag{6.12}$$

satisfies

$$||x_n - \tilde{x}|| \to 0 \ \ (n \to +\infty).$$

Corollary 6.1.4 *Assume that the following conditions are fulfilled*

(I) there exist $u_0, v_0 \in P^\circ$, $u_0 < v_0$ *and* $\Phi : \left[u_0, \frac{v_0^*}{(u_0)_*} v_0\right] \subset P^\circ \to P^\circ$;

(II) $u_0 \leq \Phi(v_0)$ *and* $v_0 \geq \Phi(u_0)$;

(III) Φ *is a nonincreasing operator on* $[u_0, v_0]$;

(IV) there exists a function $\phi : \left[\frac{(u_0)_*}{v_0^*}, 1\right) \to (0, +\infty)$ *such that* $\phi(\gamma) > \gamma$, *and for any* $x \in [u_0, v_0]$

$$\Phi(\gamma^{-1} x) \geq \phi(\gamma)\Phi(x), \quad \textit{for all } \gamma \in \left[\frac{(u_0)_*}{v_0^*}, 1\right).$$

Then Φ *has exactly one fixed point* $\tilde{x}$ *in* $[u_0, v_0]$.

Moreover, for any initial $x_0 \in [u_0, v_0]$, *the iterative sequence*

$$x_n = \Phi(x_{n-1}), \ \ n \in \mathbb{N}, \tag{6.13}$$

satisfies

$$||x_n - \tilde{x}|| \to 0 \ \ (n \to +\infty).$$

Remark 6.1.2 *It is worth noticing that, both in Theorem 6.1.1 and Lemma 6.1.1, function* ϕ *need not be continuous.*

6.2 Almost periodic solutions of general equations

It is important here to recall the different Definitions and properties we studied in Chapter 2 Subsection 2.3.2 as we are going to refer to them often in this Section.

Let us consider the following abstract problems:

$$x'(t) = \sum_{k=1}^{M} F_k(t, x(t - \tau_k(t))) + \sum_{k=1}^{N} G_k(t, x(t - \mu_k(t))) - b(t)x(t), \tag{6.14}$$

$$x'(t) = \sum_{k=1}^{M} F_k(t, x(t - \tau_k(t))) - b(t)x(t) \tag{6.15}$$

and

$$x'(t) = \sum_{k=1}^{N} G_k(t, x(t - \mu_k(t))) - b(t)x(t). \tag{6.16}$$

We assume that τ_k, μ_k and $b \in AP(\mathbb{R})$, b has positive infimum, τ_k and μ_k are nonnegative, F_k, G_k are in the class u.a.p and $F_k(t,\cdot), G_k(t,\cdot)\big|_{\mathbb{R}_{>0}} \subset \mathbb{R}_{>0}$ for all $t \in \mathbb{R}$. In addition, F_k are nondecreasing and G_k are nonincreasing functions.

Let us first of all prove the following Lemma, which give us a integral formula for the almost periodic solutions of (6.14).

Lemma 6.2.1 *Let $x(t)$ be a bounded solution of*

$$x'(t) = \sum_{k=1}^{R} p_k(t, x(t - \tau_k(t))) - b(t)x(t) \tag{6.17}$$

$$x(t) = \varphi(t), \ \ if \ \ t \in [t_0 - \nu, t_0) \tag{6.18}$$

with $\nu = \sup_{t \in \mathbb{R}}\{\tau_k(t) : k = 1, \cdots, R\}$. Then for $t_1 \geq t_0$

$$x(t) = x(t_1)e^{-\int_{t_1}^{t} b(u)du} + \int_{t_1}^{t} e^{-\int_{s}^{t} b(u)du} \sum_{k=1}^{R} p_k(s, x(s - \tau_k(s)))ds.$$

Moreover, if $x(t)$ is globally defined, then

$$x(t) = \int_{-\infty}^{t} e^{-\int_{s}^{t} b(u)du} \sum_{k=1}^{R} p_k(s, x(s - \tau_k(s)))ds.$$

<u>*Proof*</u>: From (6.17) we have:

$$\begin{aligned}\left(x(t)e^{\int_{t_0}^{t} b(u)du}\right)' &= x'(t)e^{\int_{t_0}^{t} b(u)du} + x(t)e^{\int_{t_0}^{t} b(u)du}b(t) \\ &= e^{\int_{t_0}^{t} b(u)du} \sum_{k=1}^{R} p_k(t, x(t - \tau_k(t)))\end{aligned}$$

and integrating from t_1 to t we obtain

$$x(t)e^{\int_{t_0}^{t} b(u)du} = x(t_1)e^{\int_{t_0}^{t_1} b(u)du} + \int_{t_1}^{t} e^{\int_{t_0}^{s} b(u)du} \sum_{k=1}^{R} p_k(s, x(s - \tau_k(s)))ds$$

and then,

$$x(t) = x(t_1)e^{-\int_{t_1}^{t} b(u)du} + \int_{t_1}^{t} e^{-\int_{s}^{t} b(u)du} \sum_{k=1}^{R} p_k(s, x(s - \tau_k(s)))ds.$$

In addition, if $x(t)$ is defined on the whole real line and, taking the limit on the right-hand side of the equality we deduce that

$$x(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{R} p_k(s, x(s-\tau_k(s)))ds.$$

The proof is complete. ■

Let F_k, G_k, τ_k, μ_k and b defined as before. Define the operators Φ, $\tilde{\Phi}$ and $\bar{\Phi}$ given by

$$\Phi(x,y)(t) := \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{M} F_k(s, x(s-\tau_k(s))) + \sum_{k=1}^{N} G_k(s, y(s-\mu_k(s))) \right] ds, \tag{6.19}$$

$$\Phi(x)(t) := \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{M} F_k(s, x(s-\tau_k(s))) \right] ds \tag{6.20}$$

and

$$\Phi(y)(t) := \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{N} G_k(s, y(s-\mu_k(s))) \right] ds. \tag{6.21}$$

We consider the natural inclusion $\mathbb{R} \subset AP(\mathbb{R})$ and define the mapping $A : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ as follows. Let $x_a \in AP(\mathbb{R})$ be the constant function defined by $x_a(t) = a$ for all t. Thus we may set the following functions which shall be useful in Section 6.3 and Chapter 7, namely

$$A(u,v) := \Phi(x_u, y_v) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{M} F_k(s,u) + \sum_{k=1}^{N} G_k(s,v) \right] ds, \tag{6.22}$$

$$B(u) := \Phi(x_u, y_v) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{M} F_k(s,u) \right] ds. \tag{6.23}$$

and

$$C(v) := \Phi(x_u, y_v) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{k=1}^{N} G_k(s,v) \right] ds. \tag{6.24}$$

We establish the following existence theorem:

Theorem 6.2.1 *Assume there exists constants $0 < u_0 < v_0$ such that*

(I) $A(u_0, v_0) \geq u_0$ and $A(v_0, u_0) \leq v_0$;

(II) $F_k(t, \cdot)$ is nondecreasing in $\left[\frac{u_0^2}{v_0}, v_0\right]$ and strictly concave in $[0, v_0]$ for all $k = 1, \dots, M$;

(III) $\frac{1}{G_k(t,\cdot)}$ is nondecreasing in $\left[u_0, \frac{v_0^2}{u_0}\right]$ and concave in $[0, \frac{v_0^2}{u_0}]$ for all $k = 1, \dots, N$;

(IV) $\inf_{t\in\mathbb{R}} F_k(\cdot, x) > 0$ and $\inf_{t\in\mathbb{R}} G_k(\cdot, x) > 0$, for all $x \in \left[\frac{u_0^2}{v_0}, \frac{v_0^2}{u_0}\right]$.

Then (6.14) has a unique almost periodic solution $u_0 \leq x(t) \leq v_0$.

Proof: First observe that by continuity of $F_k(t,\cdot)$ and $G_k(t,\cdot)$ we may assume that $F_k(t,0) \geq 0$ for $k = 1,\cdots,M$ and $G_k(t,0) > 0$ for $k = 1,\cdots,N$.

In the setting of Lemma 6.1.1 we have that

$$\Phi(u_0,v_0) = A(u_0,v_0) \geq u_0 \text{ and } \Phi(v_0,u_0) = A(u_0,v_0) \leq v_0.$$

Due to the monotonicity of the functions $F_k(t,\cdot)$ and $G_k(t,\cdot)$, the nonlinear operator Φ is monotone mixed in $[u_0,v_0]$. For simplicity denote $I \times J = \left[\frac{u_0^2}{v_0}, v_0\right] \times \left[u_0, \frac{v_0^2}{u_0}\right]$. Let us prove that $\Phi(I \times J) \subset P^\circ$. For $(x,y) \in I \times J$ we have

$$\Phi(x,y)(t) \geq \int_{-\infty}^{t} e^{-b^*(t-s)} \left[\sum_{k=1}^{M} \inf_{t\in\mathbb{R}} F_k\left(t, \frac{u_0^2}{v_0}\right) + \sum_{k=1}^{N} \inf_{t\in\mathbb{R}} G_k\left(t, \frac{v_0^2}{u_0}\right)\right] ds$$

which, in view of assumption (IV), shows that

$$\Phi(x,y)(t) \geq \sum_{k=1}^{M} \frac{\inf_{t\in\mathbb{R}} F_k\left(t, \frac{u_0^2}{v_0}\right)}{b^*} + \sum_{k=1}^{N} \frac{\inf_{t\in\mathbb{R}} G_k\left(t, \frac{v_0^2}{u_0}\right)}{b^*} = \tilde{\epsilon} > 0.$$

In addition, by Lemma 2.3.2 and Theorem 2.3.2 it follows that $\Phi(x,y) \in AP(\mathbb{R})$. Thus, the inclusion $\Phi(I \times J) \subset P^\circ$ is satisfied. Moreover, for all $x,y \in [u_0,v_0]$ and $\gamma \in \left[\frac{u_0}{v_0}, 1\right)$, in view of assumption (IV) we have

$$\begin{aligned}
\Phi(\gamma x, \gamma^{-1} y)(t) &= \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k=1}^{M} F_k(s, \gamma x(s-\tau_k(s))) + \sum_{k=1}^{N} G_k(s, \gamma^{-1} y(s-\mu_k(s)))\right) ds \\
&= \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k=1}^{M} F_k(s, x(s-\tau_k(s))) \frac{F_k(s, \gamma x(s-\tau_k(s)))}{F_k(s, x(s-\tau_k(s)))}\right. \\
&+ \left.\sum_{k=1}^{N} G_k(s, x(s-\mu_k(s))) \frac{G_k(s, \gamma^{-1} x(s-\mu_k(s)))}{G_k(s, x(s-\mu_k(s)))}\right) ds \\
&\geq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k=1}^{M} F_k(s, x(s-\tau_k(s))) \inf_{\substack{u\in[u_0,v_0] \\ t\in R}} \frac{F_k(t,\gamma u)}{F_k(t,u)}\right. \\
&+ \left.\sum_{k=1}^{N} G_k(s, x(s-\tau_k(s))) \inf_{\substack{u\in[u_0,v_0] \\ t\in R}} \frac{G_k(t,\gamma^{-1} u)}{G_k(t,u)}\right) ds \\
&\geq \Phi(x,y)(t) \min\left\{\inf_{\substack{u\in[u_0,v_0] \\ t\in\mathbb{R} \\ k=1,\cdots,M}} \frac{F_k(t,\gamma u)}{F_k(t,u)}, \inf_{\substack{u\in[u_0,v_0] \\ t\in\mathbb{R} \\ k=1,\cdots,N}} \frac{G_k(t,\gamma^{-1} u)}{G_k(t,u)}\right\}.
\end{aligned}$$

Consider the mapping $\phi : \left[\frac{u_0}{v_0}, 1\right) \to (0, +\infty)$ defined by

$$\phi(\gamma) := \min \left\{ \inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}\\ k=1,\cdots,M}} \frac{F_k(t,\gamma u)}{F_k(t,u)}, \inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}\\ k=1,\cdots,N}} \frac{G_k(t,\gamma^{-1}u)}{G_k(t,u)} \right\}. \tag{6.25}$$

Then the following inequality is satisfied

$$\Phi(\gamma x, \gamma^{-1} y)(t) \geq \Phi(x,y)(t)\phi(t),$$

for all $\gamma \in \left[\frac{u_0}{v_0}, 1\right)$ and $x, y \in [u_0, v_0]$.

In addition, $\phi(\gamma)$ needs to satisfy the condition $\phi(\gamma) > \gamma$. In order to prove that , we fix arbitrary $\gamma \in \left[\frac{u_0}{v_0}, 1\right)$ and, for each $k \in \{1, \cdots, M\}$ consider the function $h_k : \mathbb{R} \times [u_0, v_0] \to \mathbb{R}$ defined by

$$h_k(t,u) = F_k(t,\gamma u) - \gamma F_k(t,u).$$

Due to the concavity of $F_k(t,\cdot)$ on $[0, v_0]$ we have

$$\begin{aligned} h_k(t,u) &= F_k(t,\gamma u) - \gamma F_k(t,u) \\ &> \gamma F_k(t,u) + (1-\gamma)F_k(t,0) - \gamma F_k(t,u) \geq 0, \quad \text{for all } u \in [u_0, v_0]. \end{aligned}$$

This implies $\frac{F_k(t,\gamma u)}{F_k(t,u)} > \gamma$ for all $u \in [u_0, v_0]$. Moreover, since $F_k(t,0) \geq 0$ for all $t \in \mathbb{R}$, due to the continuity and monotonicity of $F_k(t,\cdot)$, we have

$$\inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}}} \frac{F_k(t,\gamma u)}{F_k(t,u)} > \gamma.$$

Thus,

$$\inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}\\ k=1,\cdots,M}} \frac{F_k(t,\gamma u)}{F_k(t,u)} > \gamma, \text{ for each } \gamma \in \left[\frac{u_0}{v_0}, 1\right). \tag{6.26}$$

Now we fix arbitrary $\gamma \in \left[\frac{u_0}{v_0}, 1\right)$ and $k \in \{1, \cdots, N\}$. We need to verify that

$$\frac{G_k(t,\gamma^{-1}u)}{G_k(t,u)} > \gamma, \quad \text{for all } u \in [u_0, v_0],$$

this inequality is equivalent to

$$\frac{1}{G_k(t,u)} - \gamma \frac{1}{G_k(t,\gamma^{-1}u)} > 0, \quad \text{for all } u \in [u_0, v_0]. \tag{6.27}$$

In order to simplify some computations, we set $v := \gamma^{-1}u$ and transform (6.27) into the equivalent equation

$$\frac{1}{G_k(t,\gamma v)} - \gamma\frac{1}{G_k(t,v)} > 0, \quad \text{for all } v \in \left[\frac{u_0}{\gamma}, \frac{v_0}{\gamma}\right].$$

Consider the function $\overline{h_k} : \left[\frac{u_0}{\gamma}, \frac{v_0}{\gamma}\right] \times \mathbb{R} \subset \left[u_0, \frac{v_0^2}{u_0}\right] \times \mathbb{R} \to \mathbb{R}$ defined by

$$\overline{h_k}(t,v) = L_k(t,\gamma v) - \gamma L_k(t,v),$$

with $L_k(t,v) := \frac{1}{G_k(t,v)}$. In view of the concavity of $L_k(t,\cdot)$ on $\left[0, \frac{v_0^2}{u_0}\right]$ we have

$$\begin{aligned}\overline{h_k}(t,v) &= L_k(t,\gamma v) - \gamma L_k(t,v)\\ &\geq (1-\gamma)L_k(t,0) + \gamma L_k(t,v) - \gamma L_k(t,v)\\ &(1-\gamma)L_k(t,0) > 0,\end{aligned}$$

which implies

$$\frac{L_k(t,\gamma v)}{L_k(t,v)} > \gamma, \quad \text{for all } v \in \left[\frac{u_0}{\gamma}, \frac{v_0}{\gamma}\right] \subset \left[u_0, \frac{v_0^2}{u_0}\right].$$

Hence, $\frac{G_k(t,\gamma^{-1}u)}{G_k(t,u)} > \gamma$ for all $u \in [u_0, v_0]$. Moreover, because $G_k(t,0) > 0$ for all $t \in \mathbb{R}$ and due to the continuity and monotonicity of $G_k(t,\cdot)$, we have

$$\inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}}} \frac{G_k(t,\gamma^{-1}u)}{G_k(t,u)} > \gamma.$$

Thus, we deduce

$$\inf_{\substack{u\in[u_0,v_0]\\ t\in\mathbb{R}\\ k=1,\cdots,N}} \frac{G_k(t,\gamma^{-1}u)}{G_k(t,u)} > \gamma, \text{ for each } \gamma \in \left[\frac{u_0}{v_0}, 1\right). \tag{6.28}$$

Hence, (6.25), (6.26) and (6.28) yield

$$\phi(\gamma) > \gamma \text{ for all } \gamma \in \left[\frac{u_0}{v_0}, 1\right),$$

and applying Lemma 6.1.1 we conclude that $\Phi(x,y)$ has a unique fixed point in $[u_0, v_0]$. Due to Lemma 6.2.1, we are just saying that this fixed point is the unique almost periodic solution $x(t)$ of (6.14) which satisfies $u_0 \leq x(t) \leq v_0$. The proof is complete.

■

Let $B(x)$ and $C(y)$ the functions defined in (6.23)-(6.24). For the existence of almost periodic solutions with positive infimum of equations 6.15 and 6.16, we have the next two Corollaries :

Corollary 6.2.1 *Assume there exists constants $0 < u_0 < v_0$ such that*

1. $B(u_0) \geq u_0$ *and* $B(v_0) \leq v_0$
2. $F_k(t,\cdot)$ *is nondecreasing in* $\left[\frac{u_0^2}{v_0}, v_0\right]$ *and strictly concave in* $[0, v_0]$ *for all* $k = 1, \ldots, M$*;*
3. $\inf_{t\in\mathbb{R}} F_k(\cdot, x) > 0$, *for all* $x \in \left[\frac{u_0^2}{v_0}, v_0\right]$.

Then (6.15) *has a unique almost periodic solution* $u_0 \leq x(t) \leq v_0$.

Corollary 6.2.2 *Assume there exists constants* $0 < u_0 < v_0$ *such that*

1. $C(v_0) \geq u_0$ *and* $C(u_0) \leq v_0$
2. $\frac{1}{G_k(t,\cdot)}$ *is nondecreasing in* $\left[u_0, \frac{v_0^2}{u_0}\right]$ *and concave in* $\left[0, \frac{v_0^2}{u_0}\right]$ *for all* $k = 1, \ldots, N$*;*
3. $\inf_{t\in\mathbb{R}} G_k(\cdot, x) > 0$, *for all* $x \in \left[u_0, \frac{v_0^2}{u_0}\right]$.

Then (6.16) *has a unique almost periodic solution* $u_0 \leq x(t) \leq v_0$.

The following Remarks are consequence of above results and shall be useful in Section 6.3 and Chapter 7.

Remark 6.2.1 *On the one hand, if there exist* $r_k, f_k : \mathbb{R} \to (0, +\infty)$ *and* $\overline{r}_k, g_k : \mathbb{R} \to (0, +\infty)$ *positive almost periodic functions such that*

$$F_k(t,x) = r_k(t) f_k(x), \ \forall k = 1, \cdots, M \ \text{ and } \ G_k(t,x) = \overline{r}_k(t) g_k(x), \ \forall k = 1, \cdots, N. \qquad (6.29)$$

Then conditions (IV) *in Theorem 6.2.1 and* (3) *Corollaries 6.2.1-6.2.2 can be replaced by:*

(a) $(r_j)_* > 0$ *or* $(\overline{r}_j)_* > 0$ *for some* j.

On the other hand, conditions (IV) *and* (3) *can be replaced by*

(b) $\inf_{t\in\mathbb{R}} F_j(t,x) > 0$ *and* $\inf_{t\in\mathbb{R}} G_s(t,x) > 0$,

for all $F_j(t,x)$ *and* $G_s(t,x)$ *that cannot be written as in* (6.29).

Remark 6.2.2 *In Theorem 6.2.1 and Corollary 6.2.1, condition*

- $F_k(t,\cdot)$ *is nondecreasing in* $\left[\frac{u_0^2}{v_0}, v_0\right]$ *and strictly concave in* $[0, v_0]$ *for all* $k = 1, \ldots, M$;

can be replaced by

- *For each* $k = 1, \ldots, M$; $F_k(t,\cdot)$ *satisfies one of the following conditions:*
  1. $F_k(t,\cdot)$ *is nondecreasing in* $\left[\frac{u_0^2}{v_0}, v_0\right]$ *and strictly concave in* $[0, v_0]$*;*
  2. $F_k(t,\cdot)$ *is nondecreasing in* $\left[\frac{u_0^2}{v_0}, v_0\right]$ *and, there exists a constant* $\delta \geq 0$ *such that* $F_K(t,\cdot)$ *is strictly concave in* $[0, \delta]$ *and*

$$F_k(t,x) = F_k(t,\delta) \text{ for all } x \in [\delta, v_0].$$

6.3 Applications to biological models

In this section we provide some examples which illustrate the applicability of our results.

6.3.1 Nicholson's blowflies model

The first model we consider is the following generalized Nicholson model:

$$x'(t) = \sum_{k=1}^{M} p_k(t) f(x(t - \tau_k(t))) - b(t)x(t), \tag{6.30}$$

where p_k, τ_k and $b \in AP(\mathbb{R})$ and $f : \mathbb{R} \to \mathbb{R}$ is given by $f(x) = xe^{-x}$. We assume that, $b_* > 0$, $(p_j)_* > 0$ for some j and τ_k are nonnegative.

Observe that from Lemma 2.3.3, $p_k(t)f(x(t-\tau_k(t)))$ is in the class u.a.p. for all $k = 1, \cdots, M$.

Theorem 6.3.1 *Assume that*

$$1 < \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} p_k(s) \leq e, \text{ for all } t \in \mathbb{R} \tag{6.31}$$

Then (6.30) *has a unique almost periodic solution with positive infimum. Moreover, this solution satisfies* $x(t) \leq 1$ *for all* $t \in \mathbb{R}$

Proof: Let us verify that assumptions of Corollary 6.2.1 are satisfied.

Under assumption (6.31), we may choose a positive constant ϵ small enough such that

$$\int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} p_k(s)ds \geq e^{\epsilon}, \tag{6.32}$$

next, we define $u_0 = \epsilon$ and set $v_0 = 1$. Then clearly, the function $f(x) = xe^{-x}$ is increasing in $(0, v_0)$, in particular, it is in (u_0, v_0). In addition, f is concave in $(0, v_0)$ and $f\big|_{\mathbb{R}_{>0}} > 0$.

Moreover, in view of inequality (6.32), it is easily verified that $B(u_0) \geq u_0$ and, from condition (6.31) we get

$$B(v_0) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} p_k(s)e^{-1} \leq 1 = v_0.$$

Thus, by Corollary 6.2.1, equation (6.30) has a unique solution in $[\epsilon, 1]$ and, as ϵ was chosen arbitrarily close to 0, there is a unique almost periodic solution with positive infimum in $[0, 1]$.

Finally, uniqueness of the solution can be proven in a direct way using Lemma 6.2.1. Indeed, all almost periodic solutions satisfy

$$x(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) x(s - \tau_k(s)) e^{-x(s-\tau_k(s))} ds \tag{6.33}$$

$$\leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} p_k(s)e^{-1} ds \leq 1, \tag{6.34}$$

Hence, equation (6.30) has a unique solution in $AP(\mathbb{R})$. The proof is complete.

■

6.3.2 Lasota-Wazewska model

The following model we consider is a Lasota-Wazewska-type model with a nonincreasing nonlinearity.

In [21] authors studied the existence of an almost periodic solution of the model:

$$x'(t) = c(t)e^{-\beta x(t-\tau)} - b(t)x(t) \tag{6.35}$$

assuming that β and τ are positive constants and, $c, b : \mathbb{R} \to (0, +\infty)$ are almost periodic functions. This type of equation was used by Wazewska-Czyzewska and Lasota [56] as a model for the survival of red blood cells in an animal.

The following more general model was studied in [29]:

$$x'(t) = \sum_{k=1}^{M} c_k(t)e^{-\beta_k(t)x(t-\tau_k(t))} - b(t)x(t). \tag{6.36}$$

Here, $c_k, \beta_k, \tau_k, b : \mathbb{R} \to (0, +\infty)$ are almost periodic functions, and $b_* > 0$, $(c_k)_* > 0$ for all k. The authors established sufficient criteria to guarantee the existence of a unique positive almost periodic solution in the region

$$\mathcal{B} = \{x \in AP(\mathbb{R}) : M_2 \leq x(t) \leq M_1\} \tag{6.37}$$

where $M_1 := \frac{\sum_{k=1}^{M}(c_k)^*}{b_*}$ and $M_2 := \frac{\sum_{k=1}^{M}(c_k)_* e^{M_1\beta_k^*}}{b^*}$.

We shall employ Corollary 6.2.2 to establish sufficient uniqueness conditions for the generalized model (6.36).

Theorem 6.3.2 *Assume that $\beta_k, b, c_k, \tau_k \in AP(\mathbb{R})$, $b_* > 0$, $(c_j)_* > 0$ for some j, β_k are positive and τ_k are nonnegative functions. Then* (6.36) *has a unique almost periodic solution $x(t)$ with a positive infimum.*

Moreover, this solution satisfies $x(t) \leq \frac{\sum_{k=1}^{M}(c_k)^*}{b_*}$.

<u>Proof</u>: Define $G_k(t, x) := \sum_{k=1}^{M} c_k(t)e^{-\beta_k(t)x}$. Let $\varphi(t)$ be a positive almost periodic function. By Lemma 2.3.2, it is seen that the composition $G_k(\cdot, \varphi(\cdot - \tau_k(\cdot))) \in AP(\mathbb{R})$. In addition, it is clear that

$$\frac{1}{G_k(t,x)} = \frac{e^{\beta_k(t)x}}{\sum_{k=1}^{M} c_k(t)}$$

is nondecreasing and convex in its second variable.

We may choose positive constants u_0, v_0 such that

$$u_0 < \frac{\sum_{k=1}^{M}(c_k)_*}{b^*}e^{v_0} \leq \frac{\sum_{k=1}^{M}(c_k)^*}{b_*} < v_0. \tag{6.38}$$

It is clear that (6.38) is satisfied when u_0, v_0 are positive constants small and large enough respectively.

$$C(u_0) = \Phi(u_0) = \int_{-\infty}^{t} e^{-\int_s^t b(r)dr} \sum_{k=1}^{M} c_k(s) e^{-\beta_k(s)u_0} ds \leq \frac{\sum_{k=1}^{M} (c_k)^*}{b_*} < v_0$$

and

$$C(v_0) = \Phi(v_0) = \int_{-\infty}^{t} e^{-\int_s^t b(r)dr} \sum_{k=1}^{M} c_k(s) e^{-\beta_k(s)v_0} ds \geq \frac{\sum_{k=1}^{M} (c_k)_*}{b^*} e^{-\beta_k^* v_0} > u_0.$$

Thus, we conclude from Corollary 6.2.2 that (6.36) has a unique almost periodic solution $x \in [u_0, v_0]$. Moreover, since $u_0 > 0$ can be chosen arbitrarily small, as well as v_0 can be chosen arbitrarily large, if $\tilde{x}(t) \in P^\circ$ is another solution of (6.36), then $u_0 \leq \tilde{x}(t)$. Hence, $\tilde{x} = x$.

Finally, in view of Lemma 6.2.1, the solution x satisfies

$$x(t) \leq \frac{\sum_{k=1}^{M} (c_k)^*}{b_*}.$$

■

Remark 6.3.1 *It is interesting to note that assumptions in Corollary 6.2.2 are easier to verify than those in [29] where authors employ the contraction mapping Theorem. Moreover, our result ensures that the solution found in the bounded set $\mathcal{B}$, actually is the unique almost periodic solutions with positive infimum of* (6.36) *in P°.*

Resumen del capítulo 7

En la primera parte de este Capítulo consideramos el modelo generalizado de Mackey-Glass estudiado en el Capítulo 5:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - b(t)x(t), \tag{6.39}$$

donde $r_k(t), b(t), \tau_k(t) \in AP(\mathbb{R})$, λ_k y n_k son constantes positivas y $0 \leq m_k \leq 1$. Asumimos que $\tau_k(t)$ son no negativas para todo k, $b_* > 0$ y que para algún j, $(r_j)_* > 0$.

Para este modelo damos condiciones suficientes que garantizan la existencia y en ciertos casos también la unicidad de soluciones casi periódicas positivas de (6.39) y la estabilidad exponencial global de tales soluciones. Es importante hacer hincapié en que nuestros criterios no requieren restricciones para las funciones retardo. Para obtener los criterios para la existencia y unicidad de soluciones positivas casi periódicas utilizamos los resultados formulados en el Capítulo previo y luego, por medio de desigualdades de tipo Halanay (ver [25]) formulamos un Lemma que asegura la estabilidad global exponencial de dichas soluciones bajo condiciones simples de aplicar.

En la segunda parte del Capítulo consideramos una versión simplificada del modelo (6.39):

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m}(t-\tau_k(t))}{1+x^{n}(t-\tau_k(t))} - b(t)x(t). \tag{6.40}$$

Consideramos el caso sublineal y asumiremos que $m > 1$, más específicamente: asumimos que $1 < m < n+1$. Para este modelo simplificado damos condiciones para la existencia de soluciones positivas casi periódicas, respondiendo de esta manera el problema abierto formulado entre otros por los autores en [15] y [32]. Finalmente, obtenemos condiciones para la no existencia de soluciones casi periódicas de (6.40).

Finalmente, formulamos algunos problemas abiertos

Chapter 7

Mackey-Glass model: Almost periodic case

In this Chapter we shall consider two models with several delays, in the first part of this Chapter we shall consider the more general model

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - b(t)x(t), \quad 0 \leq m_k \leq 1 \tag{7.1}$$

where $r_k(t), b(t)$ and $\tau_k(t) \in AP(\mathbb{R})$, $\tau_k(t)$ are nonnegative and λ_k, n_k are positive constants.

For (7.1) we shall introduce sufficient conditions to guarantee the existence and uniqueness of positive almost periodic solutions of (7.1) and the global exponential stability of such solutions. It is worth noticing that our criteria do not require restrictions for the delay. To this end, we shall employ results formulated in Chapter 6 and, by means of a Halanay-type inequality [25, Chapter 4], we shall establish a simple global exponential stability lemma. Then, we shall focus on a simplified version of (7.1), namely:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^{m}(t-\tau_k(t))}{1+x^{n}(t-\tau_k(t))} - b(t)x(t). \tag{7.2}$$

Our goal in the last part of this Chapter shall be give answers to the proposed existence open problems when $m > 1$. Lemma 6.1.1 shall be the key point in our criteria for the existence of positive almost periodic solutions. Finally, we shall formulate a theorem for the nonexistence of solutions when $m > 1$.

Througouth this Chapter, we shall assume that

$$b_* > 0 \qquad \text{and} \qquad (r_j)_* > 0 \text{ for some } j \in \{1, \cdots, M\}. \tag{7.3}$$

7.1 Main results for the general model: Case $0 \leq m_k \leq 1$

In this Section, we state our results on existence, uniqueness and global exponential stability of positive almost periodic solutions of (7.1).

Throughout this Chapter we shall follow the notation given in (6.1), Chapter 6.

In addition, we shall denote

$$\upsilon := \max_{1\le k\le M}\left\{\sup_{t\in\mathbb{R}}\tau_k(t)\right\}.$$

Due to the biological interpretation of the model, we shall consider as an admissible initial condition for equation (7.1) only continuous positive functions, namely

$$x(t_0 - t) = \varphi(t), \qquad \varphi \in C([0,\upsilon],(0,+\infty)). \tag{7.4}$$

A solution of the initial value problem (7.1)-(7.4) shall be denoted by $x(t;t_0,\varphi)$.

7.1.1 Existence and uniqueness

The main part of our existence and uniqueness analysis shall be based on the study of the behavior of the term production. It is worthy to notice there are four possible behaviors for $N_k(x) = \frac{x^{m_k}}{1+x^{n_k}}$, namely: strictly increasing and unbounded ($m_k > n_k > 0$), strictly increasing and bounded ($0 < m_k = n_k$), a single-humped function ($0 < m_k < n_k$) and strictly decreasing ($m_k = 0$).

In order to present our existence-uniqueness proofs in a more comprehensive way, let us firstly introduce the cases where $n_k \le 1$ when $m_k = 0$. The analogous cases, allowing also that $n_k > 1$ when $m_k = 0$, shall be treated later.

For simplicity of notation, let us define the constants:

$$V := \min_{k:0<m_k<n_k}\left\{\left(\frac{m_k}{n_k - m_k}\right)^{\frac{1}{n_k}}\right\}, \tag{7.5}$$

$$S := \min_{\{n_k>1:m_k=0\}}\left\{\left(\frac{1}{n_k - 1}\right)^{\frac{1}{n_k}}\right\} \tag{7.6}$$

and

$$T := \min\{V, S\}. \tag{7.7}$$

Theorem 7.1.1 *Assume that $n_k \le m_k$ for all k such that $m_k > 0$ and $n_k \le 1$ for all k such that $m_k = 0$. Furthermore, assume that one of the following conditions is fulfilled:*

(a) $0 \le m_j < 1$ *and* $(r_j)_* > 0$ *for some* j .

(b) $m_k = 1$ *for all* k *and* $(H_1) : \sum_{k=1}^{M} \lambda_k (r_k)_* > b^*$.

Then (7.1) *has exactly one almost periodic solution with positive infimum.*

Theorem 7.1.2 *Assume that $n_k \ge m_k$ for all k such that $m_k > 0$ and $n_k \le 1$ for all k such that $m_k = 0$. Moreover, suppose there exists i such that $n_i > m_i > 0$. Let*

$$\int_{-\infty}^{t} e^{-\int_s^t b(u)du}\sum_{k=1}^{M}\lambda_k r_k(s)ds \le V. \tag{7.8}$$

Furthermore, assume that one of the following conditions is fulfilled:

(a) $0 \leq m_j < 1$ *and* $(r_j)_* > 0$ *for some* j.

(b) $m_k = 1$ *for all* k *and* $\sum_{k=1}^{M} \lambda_k (r_k)_* > b^*$.

Then (7.1) *has exactly one almost periodic solution with positive infimum.*

Theorem 7.1.3 *Assume that* $n_i > m_i > 0$ *and* $n_s < m_s$ *for some* i, s *and let* $n_k \leq 1$ *for all* k *such that* $m_k = 0$. *Furthermore, assume that*

$$\sum_{k:n_k<m_k} \lambda_k r_k^* \frac{V^{m_k-1}}{1+V^{n_k}} + \sum_{\{k:m_k=0\}\cup\{k:n_k\geq m_k>0\}} \lambda_k r_k^* \frac{1}{V} \leq b_*. \tag{7.9}$$

and that one of the following conditions is fulfilled:

(a) $0 \leq m_j < 1$ *and* $(r_j)_* > 0$ *for some* j .

(b) $m_k = 1$ *for all* k *and* $(H_2) : \sum_{\{k:m_k=1\}} \lambda_k (r_k)_* > b^*$.

Then (7.1) *has at least one almost periodic solution with positive infimum.*

Theorem 7.1.4 *Assume that* $n_k \geq m_k$ *for all* k *such that* $m_k > 0$ *and*

$$\int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) ds \leq T. \tag{7.10}$$

Furthermore, assume that $(r_s)_* > 0$ *and* $n_s > 1$ *for some* s *such that* $m_s = 0$.
Then (7.1) *has exactly one almost periodic solution with positive infimum.*

Theorem 7.1.5 *Assume there exist* i *such that* $n_i < m_i$ *and*

$$\sum_{k:n_k<m_k} \lambda_k r_k^* \frac{T^{m_k-1}}{1+T^{n_k}} + \sum_{\{k:m_k=0\}\cup\{k:n_k\geq m_k>0\}} \lambda_k r_k^* \frac{1}{T} \leq b_*. \tag{7.11}$$

Furthermore, assume that $(r_s)_* > 0$ *and* $n_s > 1$ *for some* s *such that* $m_s = 0$.
Then (7.1) *has at least one positive almost periodic solution with positive infimum.*

Remark 7.1.1 *Since we clearly have*

$$\int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) ds \leq \sum_{k=1}^{M} \frac{\lambda_k r_k^*}{b_*} < +\infty,$$

it follows that assumption (7.8) in Theorem 7.1.2 can be replaced by following condition, which is easier to verify:

$$\sum_{k=1}^{M} \frac{\lambda_k r_k^*}{b_*} \leq V.$$

Similarly, condition (7.10) *in Theorem 7.1.4 can be replaced by* $\sum_{k=1}^{M} \frac{\lambda_k r_k^*}{b_*} \leq T$.

Remark 7.1.2 ***(Uniqueness of periodic solution)*** *Sufficient criteria for the existence of positive T-periodic solutions of (7.1) were established in the above chapter by using topological degree methods. It is worth mentioning that the referred work deals only with existence and multiplicity, and conditions for uniqueness of solutions are not given.*

As remarked above, some properties of T-periodic functions do not hold for the more general case of almost periodic functions and, consequently, the results on existence of positive T-periodic solutions in above chapter cannot be directly applied to (7.1). Despite of that, it is still possible to compare Theorem 5.2.2 in Chapter 5 with Theorems 7.1.1, 7.1.2 and 7.1.3 assuming that b, r_k and τ_k are positive T-periodic functions and $m_k > 0$ for all k. The methods used in the present paper provide also uniqueness of solutions, although more restrictive conditions are needed. For example, the results for the periodic case do not impose conditions on the (positive) constants m_k, but the uniqueness result requires that $m_k \leq 1$ for all k. Moreover, if $m_k = 1$ for all k, then the existence result in Theorem 5.2.2 assumes that $\sum_{k=1}^{M} \lambda_k r_k(t) > b(t)$, while the existence and uniqueness result provided by this paper employs the stronger condition $\sum_{k=1}^{M} \lambda_k (r_k)_* > b^*$.

7.1.2 Global exponential stability

Let $x(t; t_0, \varphi)$ be a solution of the initial value problem (7.1)-(7.4), and $\tilde{x}(t)$ an almost periodic solution with positive infimum of (7.1), and define the set

$$A := \{k : n_k > m_k(3 + 2\sqrt{2})\}.$$

We have the following results

Theorem 7.1.6 *Let η, R and $t_{\varphi,\tilde{x}}$ be positive constants such that $\eta < \tilde{x}(t), x(t; t_0, \varphi) < R$, for all $t \geq t_{\varphi,\tilde{x}}$. Assume $m_k \geq 0$ and $n_k > 0$ for all $k = 1, \ldots, M$.*

Set

$$p(t) = \sum_{k \in A} \lambda_k r_k(t) \frac{(n_k - m_k)^2}{4 n_k} + \sum_{k \notin A} \lambda_k r_k(t) m_k,$$

and assume that

$$\inf_{t \geq t_{\varphi,\tilde{x}}} \{b(t) - p(t)\} > 0.$$

Then $\tilde{x}(t)$ is ***globally exponentially stable****. i.e., there exist positive constants ρ, $K_{\varphi,\tilde{x}}$ and $t_{\varphi,\tilde{x}}$ such that*

$$|x(t; t_0, \varphi) - \tilde{x}(t)| < K_{\varphi,\tilde{x}} e^{-\rho t} \text{ for all } t \geq t_{\varphi,\tilde{x}}.$$

Remark 7.1.3 *As we shall see in next section, it is always possible to find constants η, R and $t_{\varphi,\tilde{x}}$ such that assumptions of Theorem 7.1.6 are fulfilled.*

Remark 7.1.4 ***(Uniqueness)*** *Theorem 7.1.3 and Theorem 7.1.5 only ensure the existence of at least one positive almost periodic solutions of* (7.1)*. However, under extra assumptions, the global exponential stability of such solutions is ensured. Thus, under this extra assumptions, from Corollary 2.3.1 we can conclude the existence of an unique almost periodic solution of* (7.1) *with positive infimum.*

With the same techniques applied in Theorem 7.1.6 we obtain the following global exponential stability result for the more general model:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) f_k(x(t-\tau_k(t))) - b(t)x(t) \tag{7.12}$$

where the functions f_k are Lipschitz with constant L_k.

Theorem 7.1.7 *Suppose that $\tilde{x}(t)$ is an almost periodic solution of* (7.12)*. Set*

$$p(t) = \sum_{k=1}^{M} \lambda_k r_k(t) L_k$$

and assume that

$$\inf_{t \geq t_{\varphi,\tilde{x}}} \{b(t) - p(t)\} > 0.$$

Then $\tilde{x}(t)$ is globally exponentially stable.

7.2 Preliminaries

In this section, we provide preliminary results which will be used in the proofs of our main results.

Our stability result, that is Theorems 7.1.6 and 7.1.7, shall be based on the following result, which is a generalization of [67, Lemma 3] for the case with time-dependent parameters. Moreover, we shall give explicit bounds for the convergence rate.

Firstly, let us recall the definition of the upper Dini derivative of a continuous function f:

$$D^+ f(t) = \limsup_{h \to 0^+} \frac{f(t+h) - f(t)}{h}.$$

Lema 7.2.1 *Let $x(t)$ be a continuous nonnegative function on $t \geq t_0 - \upsilon$ satisfying the following inequality*

$$D^+ x(t) \leq -k_1(t)x(t) + k_2(t)\overline{x}(t) \text{ for } t \geq t_0 \tag{7.13}$$

where $k_1(t)$ and $k_2(t)$ are nonnegative, continuous and bounded functions and $\overline{x}(t) = \sup_{t-\upsilon \leq s \leq t} x(s)$. Suppose

$$\alpha = \inf_{t \geq t_0} \{k_1(t) - k_2(t)\} > 0.$$

Then there exists a positive constant $\tilde{\rho} > 0$ such that

$$x(t) \leq \overline{x}(t_0) e^{-\tilde{\rho}(t-t_0)} \tag{7.14}$$

holds for all $t \geq t_0$. Moreover, the decay rate $\tilde{\rho}$ is such that

$$0 < \inf_{t \in \mathbb{R}} \left\{ \frac{(k_1(t) - k_2(t))k_1(t)}{k_1(t) - k_2(t) + k_2(t)e^{\upsilon k_1(t)}} \right\} < \tilde{\rho} < k_1^*.$$

Proof: Define the function f by

$$f(t,\rho) := -k_1(t) + k_2(t)e^{\rho\upsilon} + \rho. \tag{7.15}$$

For each fixed t, f is a strictly increasing continuous function; in addition, $f(t,0) = -k_1(t) + k_2(t) < 0$ and $f(t,k_1(t)) = k_2(t)e^{k_1(t)\upsilon} > 0$. Thus, for each t there exists a unique $\rho_t \in (0, k_1^*)$ which satisfies $f(t,\rho_t) = 0$. Moreover, because $f(t,\cdot)$ is a convex function we deduce that

$$\rho_t > \frac{(k_1(t) - k_2(t))k_1(t)}{k_1(t) - k_2(t) + k_2(t)e^{\upsilon k_1(t)}}, \tag{7.16}$$

where the right side of the inequality is the intersection between the x-axis and the segment connecting points $f(t,0)$ and $f(t,k_1(t))$.

Now let

$$\tilde{\rho} := \inf\{\rho_t : t \in \mathbb{R}\} \tag{7.17}$$

and

$$y(t) := \overline{x}(t_0)e^{-\tilde{\rho}(t-t_0)}, \;\; t \geq t_0 - \upsilon. \tag{7.18}$$

Let $c > 1$ be an arbitrary constant, then in view of (7.18)

$$x(t) < cy(t), \;\; t_0 - \upsilon \leq t \leq t_0.$$

We claim that

$$x(t) < cy(t) \text{ for } t > t_0. \tag{7.19}$$

Indeed, suppose that (7.19) does not hold, then there exist $t_1 > t_0$ and $\delta > 0$ for which

$$x(t) \leq cy(t) \text{ for } \;\; t_0 - \upsilon \leq t \leq t_1 \;\;\text{ and }\;\; x(t_1 + \tilde{\delta}) > cy(t_1) \text{ for all } \tilde{\delta} \in (0,\delta). \tag{7.20}$$

According to (7.13) and (7.20), it follows that

$$\begin{aligned}
D^+x(t_1) &\leq -k_1(t_1)x(t_1) + k_2(t_1)\overline{x}(t_1) \\
&= -k_1(t_1)cy(t_1) + k_2(t_1)\overline{x}(t_1) \\
&\leq -k_1(t_1)cy(t_1) + k_2(t_1) \sup_{t_1-\upsilon\leq s\leq t_1} \{cy(s)\} \\
&= -k_1(t_1)cy(t_1) + k_2(t_1) \sup_{t_1-\upsilon\leq s\leq t_1} \{c\overline{x}(t_0)e^{-\tilde{\upsilon}(s-t_0)}\} \\
&= -k_1(t_1)cy(t_1) + k_2(t_1)c\overline{x}(t_0)e^{-\tilde{\upsilon}(t_1-\upsilon-t_0)} \\
&\leq -k_1(t_1)cy(t_1) + k_2(t_1)cy(t_1-\upsilon)
\end{aligned}$$

and in view of (7.18) we have

$$= c[-k_1(t_1) + k_2(t_1)e^{\tilde{\rho}\upsilon}]\overline{x}(t_0)e^{-\tilde{\rho}(t_1-t_0)}$$

using the definition of $f(t,\rho)$ (7.15) we have $f(t_1,\rho_{t_1}) = 0$, and by convexity we deduce that

$$< c\left(-\tilde{\rho}\overline{x}(t_0)e^{-\tilde{\rho}(t_1-t_0)}\right)$$

$$= cy'(t_1), \tag{7.21}$$

On the other hand, (7.20) yields

$$\begin{aligned} D^+x(t_1) &= \limsup_{h\to 0^+} \frac{x(t_1+h)-x(t_1)}{h} \\ &\geq \limsup_{h\to 0^+} \frac{x(t_1+h)-cy(t_1)}{h} \\ &> \limsup_{h\to 0^+} \frac{cy(t_1+h)-cy(t_1)}{h} \\ &= cy'(t_1) \end{aligned}$$

then (7.20) contradicts (7.21). Hence (7.19) holds for any $t > t_0$. By letting $c \to 1$ we obtain

$$x(t) \leq \overline{x}(t_0)e^{-\tilde{\rho}(t-t_0)}.$$

Finally, (7.16)-(7.17) yield

$$0 < \inf_{t\in\mathbb{R}} \left\{ \frac{(k_1(t)-k_2(t))k_1(t)}{k_1(t)-k_2(t)+k_2(t)e^{vk_1(t)}} \right\} < \tilde{\rho} < k_1^*,$$

and the proof is complete.

■

Observe that Theorem 7.1.6 requires the existence of constants η, R and $t_{\varphi,\tilde{x}}$ such that $\eta < \tilde{x}(t), x(t;t_0,\varphi) < R$. This fact shall be guaranteed by the following assumption, that will be assumed throughout the rest of the section:

$$\sum_{k=1}^{M} \lambda_k (r_k)_* > b^*. \tag{7.22}$$

Remark 7.2.1 *If (7.22) holds, then we may fix a positive constant $\eta > 0$ such that*

$$\frac{\eta^{m_j-1}}{1+\eta^{n_j}} > \frac{b^*}{\sum_{k=1}^{M} \lambda_k (r_k)_*} \tag{7.23}$$

for all $j = 1, \ldots, M$. Furthermore, if $n_k > m_k > 0$ for some k, then we can observe that the constant η previously defined can be chosen in such a way that $0 < \eta < V$ with V defined in (7.5) and, consequently, we may also fix $\tilde{\eta} > \eta$ such that

$$\sum_{k:n_k>m_k>0} \frac{\eta^{m_k}}{1+\eta^{n_k}} = \sum_{k:n_k>m_k>0} \frac{\tilde{\eta}^{m_k}}{1+\tilde{\eta}^{n_k}}, \text{ if } n_j > m_j \text{ for some } j, \tag{7.24}$$

and $\tilde{\eta} = +\infty$ otherwise.

On the other hand, a simple computation shows that

$$\sup_{u>0} \left\{ \frac{u^{m_k}}{1+u^{n_k}} \right\} \leq 1, \text{ for } n_k \geq m_k \geq 0. \tag{7.25}$$

Remark 7.2.2 *Let $x(t)$ be a positive solution of (7.1). Then*

$$x'(t) \geq -b(t)x(t),$$

and hence $\frac{x(t_1)}{x(t_2)} \leq e^{\int_{t_1}^{t_2} b(t)dt}$ for any $t_1 \leq t_2$. In particular, this implies that

$$x(t-\tau_k(t)) \leq Lx(t), \tag{7.26}$$

where $L := \max_{t\in\mathbb{R}} e^{\int_{t-\upsilon}^{t} b(s)ds}$.

Lema 7.2.2 *If $x(t) := x(t;t_0,\varphi)$ is a solution of (7.1)-(7.4), then it is positive and bounded.*

Proof: Suppose firstly there exists $\tilde{t}$ such that $x(\tilde{t}) = 0$ and $x(t) > 0$ for all $t \in [t_0, \tilde{t})$, then

$$\lim_{t\to\tilde{t}^-} x'(\tilde{t}) = \sum_{k=1}^{M} \frac{x^{m_k}(\tilde{t}-\tau_k(\tilde{t}))}{1+x^{n_k}(\tilde{t}-\tau_k(\tilde{t}))} > 0,$$

a contradiction. Next, suppose that $x(t)$ is unbounded, then there exists a sequence $t_j \to +\infty$ such that $\lim_{t_j\to+\infty} x(t_j-\upsilon) = +\infty$. From Remark 7.2.2, it follows that $x(t_j-\upsilon) \leq Lx(t_j)$ and $x(t_j-\upsilon) \leq Lx(t_j-\tau_k(t_j))$ for $k = 1,\ldots,k$, which implies

$$x(t_j), x(t_j-\tau_k(t_j)) \to +\infty \text{ as } t_j \to +\infty. \tag{7.27}$$

Due to (7.1) and (7.26) we get

$$\begin{aligned}
x'(t_j) &= \left[\sum_{k=1}^{M} \lambda_k r_k(t_j) \frac{x^{m_k}(t_j-\tau_k(t_j))}{x(t_j)\left(1+x^{n_k}(t_j-\tau_k(t_j))\right)} - b(t_j)\right] x(t_j) \\
&\leq \left[\sum_{k=1}^{M} \lambda_k r_k(t_j) L \frac{x^{m_k-1}(t_j-\tau_k(t_j))}{1+x^{n_k}(t_j-\tau_k(t_j))} - b(t_j)\right] x(t_j).
\end{aligned}$$

Thus, from (7.27) we deduce the existence of a positive constant J such that $x'(t_j) < -J < 0$ for all j large enough. In addition,

$$x(t_j) = x(t_0) + \int_{t_0}^{t_j} x'(s)ds \leq x(t_0) - J(t_j - t_0), \text{ for } j \text{ large enough.}$$

This yields

$$x(t_j) \to -\infty \text{ as } j \to +\infty,$$

a contradiction.

■

Corollary 7.2.1 *Let $x(t)$ be a solution of* (7.1). *Then $x(t)$ is globally defined.*

Proof: Proof follows from Theorem 2.1.3. ■

In next lemmas lower bounds shall require, instead, assumptions (7.23) and (7.24). Proof of these latter bounds shall be omitted because they are analogous those given in [32, 63] (see [32, Lemma 2.2] and [63, Lemma 5]).

Lemma 7.2.1 *Assume that* $n_k \geq m_k$ *for all* k *and* $\eta < \frac{1}{b_*}\sup_{t\geq t_0}\left\{\sum_{k=1}^{M}\lambda_k r_k(t)\right\} < \tilde{\eta}$, *where* η *and* $\tilde{\eta}$ *are defined as in Remark 7.2.1 and choose* $\epsilon > 0$ *such that* $\eta < R < \tilde{\eta}$ *with*

$$R := \epsilon + \frac{1}{b_*}\sup_{t\geq t_0}\left\{\sum_{k=1}^{M}\lambda_k r_k(t)\right\}.$$

Then there exists $t_\varphi > t_0$ *such that*

$$\eta < x(t;t_0,\varphi) < R \text{ for all } t \geq t_\varphi.$$

Proof: Integrate (7.1) to obtain

$$\begin{aligned} x(t) &= e^{-\int_{t_0}^{t} b(u)du}x(t_0) + \int_{t_0}^{t} e^{-\int_{s}^{t} b(u)du}\sum_{k=1}^{M}\lambda_k r_k(s)\frac{x^{m_k}(s-\tau_k(s))}{1+x^{n_k}(s-\tau_k(s))}ds \\ &\leq e^{b_*(t_0-t)}x(t_0) + \frac{1-e^{b_*(t_0-t)}}{b_*}\sup_{t\geq t_0}\left\{\sum_{k=1}^{M}\lambda_k r_k(t)\right\}. \end{aligned}$$

Thus, for $t > t_0$ large enough

$$x(t) < \epsilon + \frac{1}{b_*}\sup_{t\geq t_0}\left\{\sum_{k=1}^{M}\lambda_k r_k(t)\right\}.$$

■

Lemma 7.2.2 *Let* $n_j < m_j$ *for some* j *and let* η *and* $\tilde{\eta}$ *be defined as in Remark 7.2.1. Suppose there exists a positive constant* $W \in (\eta, \tilde{\eta})$ *such that*

$$\sup_{t\geq t_0}\left\{\sum_{k:m_k\leq n_k}\lambda_k r_k(t)\right\} + \sup_{t\geq t_0}\left\{\sum_{k:m_k>n_k}\lambda_k r_k(t)\frac{(LW)^{m_k-n_k}}{W} - b(t)\right\}W < 0. \tag{7.28}$$

Then there exists $t_\varphi > t_0$ *such that*

$$\eta < x(t;t_0,\varphi) < W \text{ for all } t \geq t_\varphi.$$

Proof: In the first place, suppose that $x(t_1) < W$ for some $t_1 > t_0$. We claim that $x(t) < W$ for all $t > t_1$. Indeed, otherwise there exists $\bar{t} \in (t_1, +\infty)$ such that

$$x(\bar{t}) = W \text{ and } x(t) < W \text{ for all } t \in [t_1, \bar{t}),$$

which together with (7.25)-(7.26) and (7.28) yields

$$\begin{aligned}
0 < x'(\bar{t}) &= \sum_{k=1}^{M} \lambda_k r_k(\bar{t}) \frac{x^{m_k}(t-\tau_k(\bar{t}))}{1+x^{n_k}(\bar{t}-\tau_k(\bar{t}))} - b(\bar{t})x(\bar{t}) \\
&\leq \sum_{k:m_k\leq n_k} \lambda_k r_k(\bar{t}) + \sum_{k:m_k>n_k} \lambda_k r_k(\bar{t}) x^{m_k-n_k}(\bar{t}-\tau_k(\bar{t})) - b(\bar{t})x(\bar{t}) \\
&= \sum_{k:m_k\leq n_k} \lambda_k r_k(\bar{t}) + \left(\sum_{k:m_k>n_k} \lambda_k r_k(\bar{t}) L^{m_k-n_k} W^{m_k-n_k-1} - b(\bar{t}) \right) W \\
&\leq \sup_{t>t_0} \left\{ \sum_{k:m_k\leq n_k} \lambda_k r_k(t) \right\} + \sup_{t>t_0} \left\{ \sum_{k:m_k>n_k} \lambda_k r_k(t) L^{m_k-n_k} W^{m_k-n_k-1} - b(t) \right\} W = \zeta < 0,
\end{aligned}$$

a contradiction.

Suppose that $x(t_0) \geq W$, again in view of (7.25)-(7.26) and (7.28) we have

$$\begin{aligned}
x'(t_0) &\leq \sum_{k:m_k\leq n_k} \lambda_k r_k(t_0) + \left(\sum_{k:m_k>n_k} \lambda_k r_k(t_0) L^{m_k-n_k} x^{m_k-n_k-1}(t_0) - b(t_0) \right) x(t_0) \\
&\leq \sum_{k:m_k\leq n_k} \lambda_k r_k(t_0) + \left(\sum_{k:m_k>n_k} \lambda_k r_k(t_0) L^{m_k-n_k} W^{m_k-n_k-1} - b(t_0) \right) x(t_0) \\
&\leq \sup_{t\geq t_0} \left\{ \sum_{k:m_k\leq n_k} \lambda_k r_k(t) \right\} + \sup_{t\geq t_0} \left\{ \sum_{k:m_k>n_k} \lambda_k r_k(t) L^{m_k-n_k} W^{m_k-n_k-1} - b(t) \right\} W \\
&:= \zeta < 0.
\end{aligned}$$

Furthermore, by continuity, there exists $\beta \geq t_0$ such that

$$x'(t) \leq \zeta < 0 \qquad \text{for all } t \in [t_0, \beta]. \tag{7.29}$$

Thus, β can be chosen in such a way that $x(\beta) = W$, so there exists $t_1 > \beta$ such that $x(t_1) < W$ and the proof follows.

■

Remark 7.2.3 *In Lemma 7.2.1, if $m_k = 0$ for all k then the following explicit formula for the lower bound is obtained:* $\eta = \frac{\sum_{k=0}^{M} \lambda_k (r_k)_*}{b^*(1+W^{n_k})}$.

7.3 Proofs of the main results

In this section we shall give a detailed proof for some of our main results given in Section 7.1, the other ones follow analogously and are consequently omitted.

We shall use the following notation $f_k(x) = \frac{x^{m_k}}{1+x^{n_k}}$ and $g_k(x) = \frac{1}{1+x^{n_k}}$ to denote the nonlinearities of (7.1). In addition, the functions $A(u,v)$ and $B(u)$ shall be defined as in (6.22) and (6.23) respectively.

It is worth mentioning that by Lemma 2.3.3, the functions $F_k(t,x) := \lambda_k r_k(t) f_k(x)$ and $G_k(t,x) := \lambda_k r_k(t) g_k(x)$ are in the class u.a.p.

Proof of Theorem 7.1.1: Let us verify that assumptions of Theorem 6.2.1 are satisfied. With that end in mind, let us observe that the functions $f_k(x)$ and $\frac{1}{g_k(x)}$ are increasing and concave on $(0, +\infty)$. In addition, it is seen that for K large enough we have

$$\sum_{k:m_k>0} \frac{\lambda_k r_k^*}{b_*} \frac{K^{m_k-1}}{1+K^{n_k}} + \sum_{k:m_k=0} \frac{\lambda_k}{b_*} r_k^* \frac{1}{K} \le 1. \tag{7.30}$$

Let us fix the constant function $v_0 := K > 1$, where K satisfies (7.30). Under assumption $0 \le m_j < 1$ for some j, we may choose a constant $\epsilon \in (0, K)$ such that

$$\frac{\lambda_j (r_j)_*}{b^*} \frac{\epsilon^{m_j-1}}{1+\epsilon^{n_j}} \ge 1, \qquad \text{if } m_j < 1 \tag{7.31}$$

or such that

$$\frac{\lambda_j (r_j)_*}{b^*} \frac{1}{(1+K^{n_j})\epsilon} \ge 1, \qquad \text{if } m_j = 0. \tag{7.32}$$

Let $A(u,v)$ be the function defined in (6.22). Set $u_0 := \epsilon$ and, by virtue of (7.30) we obtain

$$\begin{aligned} A(v_0, u_0) &= \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{\{k:m_k>0\}} \lambda_k r_k(s) \frac{v_0^{m_k}}{1+v_0^{n_k}} + \sum_{\{k:m_k=0\}} \lambda_k r_k(s) \frac{1}{1+u_0^{n_k}} \right] ds \\ &\le \sum_{k:m_k>0} \frac{\lambda_k r_k^*}{b_*} \frac{K^{m_k}}{1+K^{n_k}} + \sum_{k:m_k=0} \frac{\lambda_k r_k^*}{b_*} \frac{1}{1+\epsilon^{n_k}} \le K := v_0, \end{aligned}$$

and from (7.31)-(7.32) it follows that

$$A(u_0, v_0) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left[\sum_{\{k:m_k\neq 0\}} \lambda_k r_k(s) \frac{u_0^{m_k}}{1+u_0^{n_k}} + \sum_{\{k:m_k=0\}} \lambda_k r_k(s) \frac{1}{1+v_0^{n_k}} \right] ds$$

$$\ge \frac{\lambda_j (r_j)_*}{b^*} \frac{u_0^{m_j}}{1+u_0^{n_j}} \ge u_0, \qquad \text{if } m_j < 1 \tag{7.33}$$

or,

$$A(u_0, v_0) \ge \frac{\lambda_j (r_j)_*}{b^*} \frac{1}{(1+v_0^{n_j})} \ge u_0, \qquad \text{if } m_j = 0, \tag{7.34}$$

that is, we conclude that $A(u_0, v_0) \ge u_0$.

Thus, in view of Theorem 6.2.1 and Remark 6.2.1 we conclude that (7.1) has a unique almost periodic solution $\tilde{x}$ such that $\epsilon \le \tilde{x}(t) \le K$.

It remains to analyze the case $m_k = 1$ for all k. As before, we choose $v_0 = K$ large enough satisfying (7.30). By virtue of assumption (H_1), there is a positive constant $\epsilon \in (0, K)$ small enough such that

$$\sum_{k:m_k=1} \frac{\lambda_k (r_k)_*}{b^*} \frac{\epsilon}{1+\epsilon^{n_k}} \geq \epsilon. \tag{7.35}$$

Define $u_0 = \epsilon$, where ϵ satisfies (7.35). The remaining conditions, $B(u_0) \geq u_0$ and $B(v_0) \leq v_0$ are proved analogously to the previous case. By Corollary 6.2.1 it is seen that there exists a unique almost periodic solution $\tilde{x} \in [u_0, v_0]$. To conclude, observe that, in both cases, the function $v_0 := K$ can be chosen arbitrarily large, as well as $u_0 = \epsilon$ can be chosen arbitrarily small. Thus, if $\tilde{y}(t)$ is another positive almost periodic solution, then we may assume that $\epsilon \leq \tilde{y}(t) \leq K$. Hence, $\tilde{x} = \tilde{y}$ and the proof is complete.

■

Next we shall prove Theorem 7.1.2. Observe that the assumptions allow not only bounded monotone nonlinear terms ($n_k = m_k > 0$ or $m_k = 0$) but also nonlinear single-humped terms ($n_k > m_k > 0$), which are neither monotone increasing nor decreasing. Thus, Theorem 6.2.1 cannot be applied for an arbitrary large interval as in the aforementioned case. To overcome this difficulty, we define appropriate truncation functions. We shall consider Remark 6.2.2 in order to define these functions.

Proof of Theorem 7.1.2: Let us define the following truncation functions p_k for $x > 0$. If k is such that $n_k = m_k > 0$, then let

$$p_k(x) := \frac{x^{m_k}}{1+x^{n_k}}, \tag{7.36}$$

and, if k is such that $n_k > m_k > 0$, then we set

$$p_k(x) := \begin{cases} \frac{x^{m_k}}{1+x^{n_k}} & \text{if} \quad x \leq V \\ \frac{V^{m_k}}{1+V^{n_k}} := C_k & \text{if} \quad x > V \end{cases}, \tag{7.37}$$

with V defined in (7.5). Let us consider the following associated equation

$$x'(t) = \sum_{k:m_k>0} \lambda_k r_k(t) p_k(x(t-\tau_k(t))) + \sum_{k:m_k=0} \lambda_k r_k(t) \frac{1}{1+x^{n_k}(t-\mu_k(t))} - b(t)x(t). \tag{7.38}$$

Next we turn our attention to give sufficient conditions in order to guarantee the existence of a unique almost periodic solution of the equation (7.38).

First, we consider the case $0 \leq m_j < 1$ for some j. Let $u_0 = \epsilon$ be chosen as in (7.31)-(7.32) and let $v_0 = K$, with K large enough such that

$$\sum_{k:m_k>0} \frac{\lambda_k r_k^*}{b_*} f_k(K) \frac{1}{K} + \sum_{k:m_k=0} \frac{\lambda_k r_k^*}{b_*} \frac{1}{K} \leq 1,$$

by a simple computation we obtain that $A(u_0, v_0) \geq u_0$ and $A(v_0, u_0) \leq v_0$. In addition, the functions $p_k(x)$ and $\frac{1}{g_k(x)}$ are increasing and concave on $(0, +\infty)$ and $(r_j)_* > 0$ for some j.

Again, in view of Theorem 6.2.1 and Remark 6.2.1 we conclude that (7.38) has a unique almost periodic solution such that $\epsilon \leq \tilde{x}(t) \leq K$. Moreover, the function $v_0 := K$ can be chosen arbitrarily large, as well as $u_0 = \epsilon$ can be chosen arbitrarily small. Thus, if $\tilde{y}(t)$ is another positive almost periodic solution of (7.38), then we may assume that $\epsilon \leq \tilde{y}(t) \leq K$. Hence, $\tilde{x} = \tilde{y}$, that is, equation (7.38) has a unique almost periodic solution with positive infimum.

Finally, it only remains to show that under assumptions of Theorem 7.1.2 this solution $\tilde{x}(t)$ is the unique positive almost periodic solution with positive infimum of (7.1). That is, (7.38) and (7.1) have the same almost periodic solutions. Indeed, in view of Lemma 6.2.1, the unique almost periodic solution with positive infimum of (7.38) satisfies

$$\tilde{x}(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k:m_k>0} \lambda_k r_k(s) f_k(\tilde{x}(s-\tau_k(s))) + \sum_{k:m_k=0} \lambda_k r_k(s) \frac{1}{1+\tilde{x}^{n_k}(s-\tau_k(s))} \right) ds. \tag{7.39}$$

According to (7.8) and (7.25), it follows that

$$\tilde{x}(t) \leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) ds \leq V.$$

Thus, we get

$$f_k(\tilde{x}(s-\tau_k(s))) = \frac{\tilde{x}^{m_k}(s-\tau_k(s))}{1+\tilde{x}^{n_k}(s-\tau_k(s))}$$

for all k such that $n_k \geq m_k$. We conclude that

$$\tilde{x}(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{\tilde{x}^{m_k}(s-\tau_k(s))}{1+\tilde{x}^{n_k}(s-\tau_k(s))} ds$$

and hence $\tilde{x}$ is a solution of (7.1). Moreover, suppose that z is another positive almost periodic solution of (7.1), then

$$z(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{z^{m_k}(s-\tau_k(s))}{1+z^{n_k}(s-\tau_k(s))} ds$$

and from (7.8) and (7.25)

$$z(t) \leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) ds \leq V. \tag{7.40}$$

Hence, z is a solution of (7.38) and we conclude that $z = \tilde{x}$.

The case $m_k = 1$ for all k follows analogously and we omit the proof.

■

In the previous proof, we chose appropriate truncation functions $p_k(x)$ that allowed us to obtain the unique almost periodic solution with positive infimum of problem (7.1) in the presence of nonlinear single-humped terms ($n_k > m_k > 0$). Observe that the assumptions in Theorem 7.1.3 admit also unbounded ($n_k < m_k$) terms. Thus, the preceding argument cannot be applied because a uniform bound as in (7.40) does not hold.

Proof of Theorem 7.1.3: First observe that as mentioned in previous proofs, functions $\frac{1}{g_k(y)}$ are increasing and concave in $(0, +\infty)$.

In the setting of Theorem 6.2.1, let $v_0 = V$, with V the constant defined in (7.5).

Under assumption $0 \leq m_j < 1$ for some j, we define $u_0 = \epsilon < V$ defined as in (7.31)-(7.32). Then clearly the functions $f_k(x)$ are nondecreasing and concave on $[0, v_0]$. In addition, the function $A(u, v)$ defined as in (6.22) satisfies

$$A(u_0, v_0) \geq \sum_{k:m_k>0} \frac{\lambda_k (r_k)_*}{b^*} \frac{u_0^{m_k}}{(1 + u_0^{n_k})} + \sum_{k:m_k=0} \frac{\lambda_k (r_k)_*}{b^*} \frac{1}{(1 + v_0^{n_k})} \geq \frac{\lambda_j (r_j)_*}{b^*} \frac{u_0^{m_j}}{(1 + u_0^{n_j})} \geq u_0,$$

and, in view of (7.9) and (7.25) we obtain

$$A(v_0, u_0)(t) \leq \sum_{k:m_k>0} \frac{\lambda_k r_k^*}{b_*} \frac{v_0^{m_k}}{1 + v_0^{n_k}} + \sum_{k:m_k=0} \frac{\lambda_k r_k^*}{b_*} \frac{1}{1 + u_0^{n_k}}$$

$$\leq \left(\sum_{k:n_k<m_k} \frac{\lambda_k r_k^*}{b_*} \frac{v_0^{m_k-1}}{1 + v_0^{n_k}} + \sum_{\{k:n_k \geq m_k>0\} \cup \{k:m_k=0\}} \frac{\lambda_k r_k^*}{b_*} \frac{1}{v_0} \right) v_0 \leq v_0.$$

Thus, we conclude from Theorem 6.2.1 and Remark 6.2.1 that (7.1) has a unique almost periodic solution $\tilde{x}(t) \in [u_0, v_0]$.

Now, it remains to analyze the case $m_k = 1$ for all k, by virtue of (H_2) there is a constant $\epsilon \in (0, v_0)$ such that

$$\sum_{k:m_k=1} \frac{\lambda_k (r_k)_*}{b^*} \frac{\epsilon}{1 + \epsilon^{n_k}} \geq \epsilon. \tag{7.41}$$

Again, let us define $u_0 = \epsilon$, so it is readily seen that the functions $f_k(x)$ are nondecreasing and concave on $[0, v_0]$. The remaining conditions, $B(u_0) \geq u_0$ and $B(v_0) \leq v_0$ are proved similarly to the first case. The conclusion follows by applying Corollary 6.2.1.

■

Next we shall prove Theorem 7.1.4. Observe that, the more restrictive condition, $n_s > 1$ for some s such that $m_s = 0$, yields that functions $\frac{1}{g_k(x)}$ are increasing, but, unlike the previous cases, these functions are not concave in $(0, +\infty)$. Thus, assumptions of Theorem 6.2.1 are not satisfied. However, the more general fixed point theorems, that is Theorem 6.1.1 or Lemma 6.1.1, may be employed.

Proof of Theorem 7.1.4: Let us define the functions h_k as follows. If k is such that $n_k \leq 1$ and $m_k = 0$ then

$$h_k(y) = \frac{1}{1 + y^{n_k}},$$

and if k is such that $n_k > 1$ and $m_k = 0$, then we set

$$h_k(y) = \begin{cases} \frac{1}{1+y^{n_k}} & \text{if} \quad y \leq S \\ \frac{1}{1+S^{n_k}} & \text{if} \quad y > S \end{cases},$$

where S is the constant defined in (7.6) and set the functions $p_k(x)$ defined as in (7.36)-(7.37).

Let us consider the following associated equation

$$x'(t) = \sum_{k:m_k>0} \lambda_k r_k(t) f_k(x(t-\tau_k(t))) + \sum_{k:m_k=0} \lambda_k r_k(t) h_k(y(s-\tau_k(s))) - b(t)x(t). \tag{7.42}$$

Define the operator Φ by

$$\Phi(x,y)(t) := \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k:m_k>0} \lambda_k r_k(s) p_k(x(s-\tau_k(s))) + \sum_{k:m_k=0} \lambda_k r_k(s) h_k(y(s-\tau_k(s))) \right) ds \tag{7.43}$$

for all $t \in \mathbb{R}$.

Due to the monotonicity of the functions $h_k(y)$ and $p_k(x)$, the nonlinear operator Φ is monotone mixed in $P^\circ \times P^\circ$. Let us firstly prove that $\Phi(P^\circ \times P^\circ) \subset P^\circ$. For $(x,y) \in P^\circ \times P^\circ$, there exist $\kappa_1, \kappa_2 > 0$ such that $\kappa_1 \leq x(t), y(t) \leq \kappa_2$ for all $t \in \mathbb{R}$. Then

$$\Phi(x,y)(t) \geq \int_{-\infty}^{t} e^{-b^*(t-s)} \left(\sum_{k:m_k>0} \lambda_k (r_k)_* p_k(\kappa_1) + \sum_{k:m_k=0} \lambda_k (r_k)_* h_k(\kappa_2) \right) ds$$

which shows that

$$\Phi(x,y)(t) \geq \sum_{k:m_k>0} \frac{\lambda_k}{b^*} (r_k)_* p_k(\kappa_1) + \sum_{k:m_k=0} \frac{\lambda_k}{b^*} (r_k)_* h_k(\kappa_2) = \tilde{\epsilon} > 0.$$

In addition, by Lemma 2.3.2 it follows that $\Phi(x,y) \in AP(\mathbb{R})$. Thus, the inclusion $\Phi(P^\circ \times P^\circ) \subset P^\circ$ is satisfied.

It is seen that for K large enough we have

$$\sum_{k:m_k>0} \frac{\lambda_k (r_k)^*}{b_*} f_k(K) \frac{1}{K} + \sum_{k:m_k=0} \frac{\lambda_k (r_k)^*}{b_*} \frac{1}{K} \leq 1.$$

Let us fix $v_0 := K > S$ and let $u_0 = \epsilon < T$ be chosen as in (7.31)-(7.32), with T the constant defined in (7.7). Thus, $\Phi(u_0, v_0) \geq u_0$ and $\Phi(v_0, u_0) \leq v_0$.

Let the function $\phi : (0,1) \to (0, +\infty)$ be given by

$$\phi(\gamma) = \min \{\theta(\gamma), \vartheta(\gamma), \psi(\gamma)\}, \tag{7.44}$$

where

$$\theta(\gamma) = \min \left\{ \min_{k:n_k=m_k} \left\{ \frac{\gamma^{m_k}(1+\epsilon^{n_k})}{1+\gamma^{n_k}\epsilon^{n_k}} \right\}, \min_{\{n_k \leq 1 : m_k=0\}} \left\{ \frac{1+K^{n_k}}{1+\gamma^{-n_k}K^{n_k}} \right\} \right\}, \tag{7.45}$$

$$\vartheta(\gamma) := \min_{k:n_k>m_k>0} \left\{ 1, \gamma^{m_k} \frac{1+V^{n_k}}{1+\gamma^{n_k}V^{n_k}}, \gamma^{m_k} \frac{1+\epsilon^{n_k}}{1+\gamma^{n_k}\epsilon^{n_k}} \right\} \tag{7.46}$$

and

$$\psi(\gamma) := \min_{\{n_k>1 : m_k=0\}} \left\{ 1, \ \frac{1+(\gamma S)^{n_k}}{1+S^{n_k}} \right\}. \tag{7.47}$$

It is easy to see that $\phi(\gamma) > \gamma$ for all $\gamma \in (0,1)$.

Since for each k such that $0 < m_k < n_k$, $\gamma \in (0,1)$ and $x > 0$ we have

$$\frac{p_k(\gamma x)}{p_k(x)} \geq \begin{cases} \gamma^{m_k} \frac{1+\epsilon^{n_k}}{1+\gamma^{n_k}\epsilon^{n_k}} & \text{if} \quad x \leq V \\ \gamma^{m_k} \frac{1+V^{n_k}}{1+\gamma^{n_k}V^{n_k}} & \text{if} \quad V < x \leq \frac{1}{\gamma}V \\ 1 & \text{if} \quad x > \frac{1}{\gamma}V, \end{cases}$$

and, for each k such that $n_k > 1$ and $m_k = 0$, $\gamma \in (0,1)$ and $y > 0$ we have

$$\frac{h_k(\gamma^{-1}y)}{h_k(y)} \geq \begin{cases} \frac{1+(\gamma S)^{n_k}}{1+S^{n_k}} & \text{if} \quad y \leq S \\ 1 & \text{if} \quad y > S, \end{cases}$$

then, by a direct computation we obtain

$$\Phi(\gamma x, \gamma^{-1}y) \geq \phi(\gamma)\Phi(x,y) \text{ for all } \gamma \in (0,1) \text{ and } x,y \in [u_0,v_0].$$

Thus, by Theorem 6.1.1 Φ has a unique fixed point $\tilde{x} \in [u_0, v_0]$. Hence, by Lemma 6.2.1, we conclude that $\tilde{x}$ is the unique solution of (7.42) such that $\epsilon \leq \tilde{x}(t) \leq K$. Moreover, since $u_0 = \epsilon$ can be chosen arbitrarily small as well as $v_0 = K$ can be chosen large enough, then $\tilde{x}(t)$ is the unique almost periodic solution with a positive infimum of equation (7.42).

It only remains to show that under the assumptions of Theorem 7.1.4, both equations (7.1) and (7.42) have the same almost periodic solutions. Indeed, in view of Lemma 6.2.1, the unique almost periodic solution with positive a infimum of (7.42) satisfies

$$\tilde{x}(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \left(\sum_{k:m_k>0} \lambda_k r_k(s) p_k(\tilde{x}(s-\tau_k(s))) + \sum_{k:m_k=0} \lambda_k r_k(s) h_k(\tilde{x}(s-\tau_k(s))) \right) ds. \tag{7.48}$$

According to (7.8) and (7.25), it follows that

$$\tilde{x}(t) \leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) ds \leq T.$$

Thus, we get

$$p_k(\tilde{x}(s-\tau_k(s))) = \frac{\tilde{x}^{m_k}(s-\tau_k(s))}{1+\tilde{x}^{n_k}(s-\tau_k(s))}$$

for all k such that $n_k \geq m_k$ and,

$$h_k(\tilde{x}(s-\tau_k(s))) = \frac{1}{1+\tilde{x}^{n_k}(s-\tau_k(s))}$$

for all k such that $n_k \geq m_k$. We conclude that

$$\begin{aligned}\tilde{x}(t) &= \int_{-\infty}^{t} e^{-\int_s^t b(u)du}\left(\sum_{k:m_k>0}\lambda_k r_k(s)\frac{\tilde{x}^{m_k}(s-\tau_k(s))}{1+\tilde{x}^{n_k}(s-\tau_k(s))} + \sum_{k:m_k=0}\lambda_k r_k(s)\frac{1}{1+\tilde{x}^{n_k}(s-\tau_k(s))}\right)ds \\ &= \int_{-\infty}^{t} e^{-\int_s^t b(u)du}\sum_{k=1}^{M}\lambda_k r_k(s)\frac{\tilde{x}^{m_k}(s-\tau_k(s))}{1+\tilde{x}^{n_k}(s-\tau_k(s))}ds\end{aligned}$$

and hence $\tilde{x}$ is a solution of (7.1). Moreover, suppose that z is another positive almost periodic solution of (7.1), then

$$z(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du}\sum_{k=1}^{M}\lambda_k r_k(s)\frac{z^{m_k}(s-\tau_k(s))}{1+z^{n_k}(s-\tau_k(s))}ds$$

and from (7.10) and (7.25)

$$z(t) \leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du}\sum_{k=1}^{M}\lambda_k r_k(s)ds \leq V. \tag{7.49}$$

Hence, z is a solution of (7.38) and we conclude that $z = \tilde{x}$.

The proof is complete.

■

In order to prove Theorem 7.1.6 we shall employ Lemma 7.2.1. Moreover, we shall assume that there exist constants $0 < \eta < R$ and $t_{\varphi,\tilde{x}}$ such that $\eta < \tilde{x}(t), x(t;t_0,\varphi) < R$ for all $t \geq t_{\varphi,\tilde{x}}$. Such bounds can be obtained under conditions of Lemmas 7.2.1 and 7.2.2.

Before jumping into the proof, let us give a simple Lemma.

Lemma 7.3.1 *Let $m \geq 0$, $n > 0$ be constants. The function $g_{m,n}(u) = \frac{m+(m-n)u}{(1+u)^2}$ satisfies:*

$$\left|g_{m,n}(u)\right| \leq \begin{cases} \frac{(n-m)^2}{4n} & \text{if } n > m(3+\sqrt{2}) \\ m & \text{otherwise,} \end{cases} \tag{7.50}$$

for all $u \geq 0$.

Proof: If $m \geq n$, then $g_{m,n}$ is nonincreasing and $g_{m,n}(0) = m$. When $m < n$, it is easy to verify that $g_{m,n}$ is nonincreasing on $\left[0, \frac{n+m}{n-m}\right)$ and increasing on $\left(\frac{n+m}{n-m}, +\infty\right)$. Moreover, $g_{m,n}(0) = m$, $g_{m,n}(\frac{n+m}{n-m}) = -\frac{(n-m)^2}{4n}$ and $\lim_{u\to+\infty} g(u) = 0$. Finally, is easy to see that $\frac{(n-m)^2}{4n} > m$ if and only if $n > m(3+2\sqrt{2})$. This analysis completes the proof. ■

Proof of Theorem 7.1.6: Let $\tilde{x}(t)$ be a positive almost periodic solution of (7.1) and $x(t) = x(t;t_0,\varphi)$ the solution of the initial value problem (7.1)-(7.4). Define $y(t) := \tilde{x}(t) - x(t)$ with $t \in [t_0 - \upsilon, +\infty)$, then we have

$$y'(t) = \sum_{k=1}^{M}\lambda_k r_k(t)\left[\frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - \frac{\tilde{x}^{m_k}(t-\tau_k(t))}{1+\tilde{x}^{n_k}(t-\tau_k(t))}\right] - b(t)y(t). \tag{7.51}$$

Computing the upper right Dini derivative of $|y(t)|$ and from the mean-value theorem we have

$$D^+|y(t)| \leq \sum_{k=1}^{M} \lambda_k r_k(t) \left| \frac{x^{m_k}(t-\tau_k(t))}{1+x^{n_k}(t-\tau_k(t))} - \frac{\tilde{x}^{m_k}(t-\tau_k(t))}{1+\tilde{x}^{n_k}(t-\tau_k(t))} \right| - b(t)|y(t)|$$

$$= \sum_{k=1}^{M} \lambda_k r_k(t) \left| \frac{\theta^{m_k-1}(t-\tau_k(t))\left[m_k + (m_k - n_k)\theta^{n_k}(t-\tau_k(t))\right]}{(1+\theta^{n_k}(t-\tau_k(t)))^2} \right| \left|x(t-\tau_k(t)) - \tilde{x}(t-\tau_k(t))\right| - b(t)|y(t)|$$

$$< \sum_{k=1}^{M} \lambda_k r_k(t) \eta^{m_k-1} \left|g_{m_k,n_k}\left(\theta^{n_k}(t-\tau_k(t))\right)\right| \left|x(t-\tau_k(t)) - \tilde{x}(t-\tau_k(t))\right| - b(t)|y(t)|,$$

where $\theta(t)$ lies between $x(t)$ and $\tilde{x}(t)$. In view of Lemma 7.3.1 we obtain

$$\leq p(t)\overline{|y(t)|} - b(t)|y(t)|, \text{ for all } t \geq t_{\varphi,\tilde{x}}$$

where $\overline{|y(t)|} := \sup_{t-v \leq s \leq t}\{|y(s)|\}$.

Thus, by Lemma 7.2.1 there exists $\rho > 0$ such that

$$|\tilde{x}(t) - x(t)| = |y(t)| \leq \overline{|y(t_{\varphi,\tilde{x}})|} e^{-\rho(t-t_{\varphi,\tilde{x}})} = K_{\varphi,\tilde{x}} e^{-\rho t} \text{ for all } t \geq t_{\varphi,\tilde{x}}$$

and the proof is complete. ■

7.4 A simplified model: Case $(m > 1)$.

In this Section we consider the existence and nonexistence of positive almost periodic solutions of the following simpler Mackey-Glass equation:

$$x'(t) = \sum_{k=1}^{M} \lambda_k r_k(t) \frac{x^m(t-\tau_k(t))}{1+x^n(t-\tau_k(t))} - b(t)x(t), \quad \text{with } m > 1 \tag{7.52}$$

where $r_k(t), b(t)$ and $\tau_k(t) \in AP(\mathbb{R})$, $r_k(t)$ are positive, $\tau_k(t)$ is nonnegative and λ_k, n are positive constants.

Observe that the condition on m yields that function $f(x) = \frac{x^m}{1+x^n}$ is increasing on $(0, +\infty)$ when $m \geq n$ and on $(0, V)$ when $m < n$, but, unlike the cases in previous Section, this function has a change of concavity on these intervals. Indeed, when $m \geq n$, there is a constant $0 < \nu < V$ such that the function $f(x)$ is convex on $(0, \nu)$ and then becomes concave on (ν, V). A similar condition is obtained when $m \geq n$. Thus, the assumptions in Corollary 6.2.1 are not satisfied. Moreover, the more general fixed point theorem, that is Theorem 6.1.1, also fails. In this last case, the reason is interesting to explain. Classical fixed point theorems such as Theorem 6.1.1 usually involve functions such as $\phi : (0,1) \to (0, +\infty)$ or $\phi : (0,1) \times P^\circ \times P^\circ \to (0, +\infty)$ satisfying $\phi(\gamma) > \gamma$ or $\phi(\gamma, x, y) > \gamma$ for all $x, y \in P^\circ$ and $\gamma \in (0,1)$ respectively. The main problem for the case $m > 1$ is that condition, $\phi(\gamma) > \gamma$ is not fulfilled when $\gamma \approx 0$. To overcome this problem we shall employ Lemma 6.1.1. Observe that this Lemma is a slight modification of Theorem 6.1.1, the main change is the assumption of the existence of a function $\phi : \left[\frac{(u_0)_*}{v_0^*}, 1\right) \subset (0,1) \to (0, +\infty)$ where $\frac{(u_0)_*}{v_0^*}$ is a positive constant.

Remark 7.4.1 *In order to simplify some notation, we define the constant*

$$B := A\left[\frac{nA^n}{(m-1)(1+A^n)}\right]^{\frac{1}{n-m+1}}, \tag{7.53}$$

where A is a positive constant.

Observe that, $A > \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}$ if and only if $\left[\frac{nA^n}{(m-1)(1+A^n)}\right]^{\frac{1}{n-m+1}} > 1$ or, equivalently

$$B > A \text{ if and only if } A > \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}. \tag{7.54}$$

7.4.1 Existence and nonexistence of positive almost periodic solutions.

Theorem 7.4.1 *Assume that $n > m-1 > 0$ and $n \leq m$. Let A be a constant such that $A > \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}$ and B defined in (7.53). Furthermore, assume that*

$$\frac{1+A^n}{A^{m-1}} \leq \sum_{k=1}^{M} \lambda_k \frac{(r_k)_*}{b^*} \leq \sum_{k=1}^{M} \lambda_k \frac{(r_k)^*}{b_*} \leq \frac{1+B^n}{B^{m-1}}. \tag{7.55}$$

Then (7.52) has a unique almost periodic solution $x \in [A, B] \subset P^\circ$.

Proof: Let us verify that assumptions of Corollary 6.1.3 are fulfilled. Consider the positive constant functions $u_0 = A$ and $v_0 = B$.

Set the operator

$$\Phi(x)(t) := \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{x^m(s-\tau_k(s))}{1+x^n(s-\tau_k(s))} ds \quad \text{for all } t \in \mathbb{R}. \tag{7.56}$$

Clearly the function $f(u) = \frac{u^m}{1+u^n}$ is nondecreasing on $(0, +\infty)$, in particular on $[A, B]$. Thus, we deduce that Φ is a nondecreasing operator on $[u_0, v_0]$. Moreover, Φ satisfies $\Phi(P^\circ) \subset P^\circ$. Indeed, let $x \in P^\circ$, then there exists $\epsilon > 0$ such that $x(t) \geq \epsilon$ for all $t \in \mathbb{R}$. Thus, by the monotonicity of f we have

$$\Phi(x)(t) \geq \int_{-\infty}^{t} e^{-b^*(t-s)} \sum_{k=1}^{M} \lambda_k (r_k)_* \frac{\epsilon^m}{1+\epsilon^n} ds$$

which shows that

$$\Phi(x)(t) \geq \sum_{k=1}^{M} \frac{\lambda_k}{b^*} (r_k)_* \frac{\epsilon^m}{1+\epsilon^n} := \tilde{\epsilon} > 0.$$

In addition, by Lemma 2.3.2 it follows that $\Phi(x) \in AP(\mathbb{R})$.

Now, by virtue of (7.55) we find

$$\Phi(u_0) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{u_0^m}{1+u_0^n} ds \geq \sum_{k=1}^{M} \frac{\lambda_k (r_k)_*}{b^*} \frac{u_0^m}{(1+u_0^n)} \geq u_0,$$

and

$$\Phi(v_0)(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{v_0^m}{1+v_0^n} ds \leq \sum_{k=1}^{M} \frac{\lambda_k r_k^*}{b_*} \frac{v_0^m}{1+v_0^n} \leq v_0.$$

Finally, it only remains to show that condition (IV) of Corollary 6.1.3 is satisfied. Let $x \in [u_0, v_0]$ and $\gamma \in \left[\frac{A}{B}, 1\right)$

$$\begin{aligned}\Phi(\gamma x)(t) &= \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{x^m(s-\tau_k(s))}{1+x^n(s-\tau_k(s))} \gamma^m \frac{1+x^n(s-\tau_k(s))}{1+\gamma^n x^n(s-\tau_k(s))} ds \\ &\geq \Phi(x)(t) \gamma^m \frac{1+A^n}{1+\gamma^n A^n}.\end{aligned}$$

Let $\phi : \left[\frac{A}{B}, 1\right) \to (0, +\infty)$ be the mapping defined by

$$\phi(\gamma) = \gamma^m \frac{1+A^n}{1+\gamma^n A^n}.$$

Thus,

$$\Phi(\gamma x)(t) \geq \phi(\gamma)\Phi(x)(t), \text{ for each } \gamma \in \left[\frac{A}{B}, 1\right) \text{ and } x \in [u_0, v_0].$$

In order to prove that $\phi(\gamma) > \gamma$ for convenience, we define the function

$$M(\gamma) := \gamma^{m-1}(1+A^n) - (1+\gamma^n A^n),$$

by a direct computation we can see that $M(\gamma)$ achieves the maximum in $\gamma_{\max} = \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n-m+1}} = \frac{A}{B}$, $M(1) = 0$ and M is strictly decreasing in $\left(\frac{A}{B}, 1\right)$, which implies that $M(\gamma) > 0$ for all $\gamma \in \left[\frac{A}{B}, 1\right)$. Thus,

$$\begin{aligned} M(\gamma) = \gamma^{m-1}(1+A^n) - (1+\gamma^n A^n) > 0, &\quad \text{for all } \gamma \in \left[\frac{A}{B}, 1\right) \\ \iff \frac{\gamma^{m-1}(1+A^n) - (1+\gamma^n A^n)}{1+\gamma^n A^n} > 0, &\quad \text{for all } \gamma \in \left[\frac{A}{B}, 1\right) \\ \iff \frac{\phi(\gamma)}{\gamma} - 1 > 0, &\quad \text{for all } \gamma \in \left[\frac{A}{B}, 1\right). \end{aligned}$$

Therefore, ϕ satisfies $\phi(\gamma) > \gamma$ for $\gamma \in \left[\frac{A}{B}, 1\right)$.

We conclude that (7.52) has a unique almost periodic solution $x \in [u_0, v_0]$. ■

Theorem 7.4.2 *Assume that $n > m-1 > 0$ and $n > m$. Set $B = \left(\frac{m}{n-m}\right)^{\frac{1}{n}}$ and let A be the constant as in* (7.53)*. Furthermore, assume that*

$$\frac{1+A^n}{A^{m-1}} \le \sum_{k=1}^{M} \lambda_k \frac{(r_k)_*}{b^*} \le \sum_{k=1}^{M} \lambda_k \frac{r_k^*}{b_*} \le \frac{1+B^n}{B^{m-1}}. \tag{7.57}$$

Then (7.52) *has a unique almost periodic solution $x \in [A, B] \subset P^\circ$.*

Proof: We claim that $A > \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}$; indeed, otherwise the constant A would satisfy $A \le \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}$, so from (7.53) we have

$$\begin{aligned}\left(\frac{m}{n-m}\right)^{\frac{1}{n}} &= A\left(\frac{n}{m-1}\frac{A^n}{1+A^n}\right)^{\frac{1}{n-m+1}} \\ &\le \left(\frac{m-1}{n-m+1}\right)^{\frac{1}{n}}\left(\frac{n}{m-1}\frac{\frac{m-1}{n-m+1}}{1+\frac{m-1}{n-m+1}}\right)^{\frac{1}{n-m+1}}.\end{aligned}$$

After some simplifications we obtain

$$\frac{m}{n-m} \le \frac{m-1}{n-m+1}$$

and so

$$\frac{1}{n-m} \le -\frac{1}{m}.$$

This is a contradiction, thus our claim is true. Moreover, this implies that $A < B$.

Let $u_0 = A$, $v_0 = B = \left(\frac{m}{n-m}\right)^{\frac{1}{n}}$, Φ the operator defined in (7.56) and $\phi : [\frac{A}{B}, 1) \to (0, +\infty)$ the function defined in (7.4.1).

It is readily seen that the function $f(u) = \frac{u^m}{1+u^n}$ is nondecreasing on $[0, B]$. Thus, we deduce that Φ is a nondecreasing operator on $[0, v_0]$. Moreover, Φ satisfies $\Phi\left(\left[\frac{u_0^2}{v_0}, v_0\right]\right) \subset P^\circ$. Let $x \in \left[\frac{u_0^2}{v_0}, v_0\right]$, then $x(t) \ge \frac{u_0^2}{v_0}$ for all $t \in \mathbb{R}$ and, by the monotonicity of f we have

$$\Phi(x)(t) \ge \int_{-\infty}^{t} e^{-b^*(t-s)} \sum_{k=1}^{M} \lambda_k (r_k)_* \frac{\left(\frac{u_0^2}{v_0}\right)^m}{1+\left(\frac{u_0^2}{v_0}\right)^n} ds$$

which shows that

$$\Phi(x)(t) \ge \sum_{k=1}^{M} \frac{\lambda_k}{b^*}(r_k)_* \frac{\left(\frac{u_0^2}{v_0}\right)^m}{1+\left(\frac{u_0^2}{v_0}\right)^n} := \tilde{\epsilon} > 0.$$

In addition, by Lemma 2.3.2 it follows that $\Phi(x) \in AP(\mathbb{R})$.

The remaining conditions of Lemma 6.1.1 can be easily proven, indeed the proof is an analogue of those given above and we omit it. ∎

Remark 7.4.2 *Theorems 7.4.1 and 7.4.2 answer the Open Problem formulated in [13, 14], that is, the existence of almost periodic solutions with positive infimum of* (7.52).

The following Lemma shall be used in our next nonexistence theorem.

Lemma 7.4.1 *Let $m, n > 0$ and $x \geq 0$. Then the function $g(x) = \frac{m+(m-n)x}{1+x}$ satisfies*

$$|g(x)| \leq \max\{m, |m-n|\} := g_{\max}. \tag{7.58}$$

Proof: The conclusion follows by checking that $g(0) = m$, $\lim_{x \to +\infty} g(x) = m - n$ and $g(x)$ is nonincreasing. ■

Lemma 7.4.2 *Assume that $n \geq m - 1 \geq 0$ and*

$$\sum_{k=1}^{M} \lambda_k \frac{r_k^*}{b_*} < \frac{1}{g_{\max}},$$

where $g_{\max}$ is defined as in (7.58). *Then* (7.52) *has no positive almost periodic solutions.*

Proof: Consider the operator $\Phi : P \to P$,

$$\Phi(x)(t) = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{x^m(s - \tau_k(s))}{1 + x^n(s - \tau_k(s))} ds.$$

Let $x, y \in P$, we shall show that Φ is a contraction operator

$$|\Phi(x)(t) - \Phi(y)(t)| = \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \left| \frac{x^m(s - \tau_k(s))}{1 + x^n(s - \tau_k(s))} - \frac{y^m(s - \tau_k(s))}{1 + y^n(s - \tau_k(s))} \right| ds$$

$$\leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{\xi^{m-1}(s - \tau_k(s))}{1 + \xi^n(s - \tau_k(s))} \left| \frac{m + (m-n)\xi^n(s - \tau_k(s))}{1 + \xi^n(s - \tau_k(s))} \right| ds||x - y||$$

where ξ lies between x and y in view of (7.25) and Lemma 7.4.1 we have

$$\leq \int_{-\infty}^{t} e^{-\int_s^t b(u)du} m \sum_{k=1}^{M} \lambda_k r_k(s) ds||x - y||$$

$$\leq \sum_{k=1}^{M} \lambda_k \frac{r_k^*}{b_*} g_{\max}||x - y||.$$

Thus, Φ is a contraction which implies that Φ has a unique fixed point $x \in P$, $\Phi(x) = x$. Thus the conclusion follows since $0 \in P$ is a fixed point of Φ, equivalently, from Lemma 6.2.1 $x(t) \equiv 0$ is the unique solution of (7.52). ■

Lemma 7.4.3 *Let $n \geq m \geq 0$. Then* (7.52) *has no almost periodic solutions $x(t)$ such that $x(t) \in \left(\sum_{k=1}^{M} \lambda_k \frac{r_k^*}{b_*}, +\infty\right)$.*

Proof: It is a direct consequence of Lemma 6.2.1 and (7.25). Indeed, let $x(t)$ be an almost periodic solution of (7.52), then

$$x(t) = \int_{-\infty}^{t} e^{\int_s^t b(u)du} \sum_{k=1}^{M} \lambda_k r_k(s) \frac{x^m(s - \tau_k(s))}{1 + x^n(s - \tau_k(s))} ds \leq \sum_{k=1}^{M} \lambda_k \frac{r_k^*}{b_*}.$$

The proof is complete. ■

7.5 Open problems

We outline some open problems:

1. Prove or disprove the existence of positive almost periodic solutions for the asymptotic linear ($n = m - 1$) and/or superlinear ($n < m - 1$) cases of (7.52) and its generalization (7.1).

2. Give conditions to ensure the stability of the positive almost periodic solutions of (7.52).

Chapter 8

Work in progress & Future work

8.1 Work in progress

We are working on the following problems:

1. To obtain results of existence related to the concavity and/or convexity of the nonlinearity involved, in a similay way as we did in Theorem 6.2.1, for the following abstract problem:

$$x'(t) = \sum_{k=1}^{M} F_k(t, x(t - \tau_k(t))) - \sum_{k=1}^{N} H_k(t, x(t - \mu_k(t))) - b(t)x(t), \tag{8.1}$$

   where τ_k, μ_k and $b \in AP(\mathbb{R})$, b has positive infimum, τ_k and μ_k are nonnegative, F_k, H_k are in the class u.a.p and $F_k(t,\cdot), H_k(t,\cdot)\big|_{\mathbb{R}_{>0}} \subset \mathbb{R}_{>0}$ for all $t \in \mathbb{R}$. In addition, F_k, H_k are nondecreasing functions.

2. As we mentioned before, the classical topological methods of super and sub solutions is an important tool for the study of periodic second order differential equations. However, these methods fail when we try to extend them in a direct way to the almost periodic case [41,48]. One of the principal reason is the lack of compactness of the involved operators.

   We are working on an extention of super and sub solutions method to the almost periodic case. In particular, for the second order equation

$$u'' + cu' = f(t, u) \tag{8.2}$$

   where $f : \mathbb{R}\times\mathbb{R} \to \mathbb{R}$ is almost periodic in t uniformly in x and the constant c is in $[0, +\infty)$. By the assumption of the existence of almost periodic super and sub solutions of (8.2) we study the existence of almost periodic solutions $x(t)$ for (8.2).

   Our work aims to extend existence results, where the existence of periodic sub and super-solutions imply the existence of periodic solutions.

   In [48] the authors analize the almost periodic equation (8.2) with $c = 1$. They obtain existence results employing the method of super and subsolutions. However, we think that their work has a mistake in the proof of one lemma. We are looking for a counterexample.

8.2 Future work

We outline some problems in the field of periodic and almost periodic functions.

With respect to the Wheldon model we present the following open problems:

1. Use Lyapunov-like functionals to find sufficient conditions for the global stability of a non-trivial equilibrium of the autonomous model.

2. Prove or disprove that for a new model the complete recovery is possible for sufficiently high drug dosage; examine permanence, persistence and extinction of the solutions.

3. Define the required type, frequency and intensity of the cancer treatment that switch unfavorable oscillatory dynamics of a system to a non-oscillatory state.

In addition, we present some open questions and future line of investigation related to the Mackey-Glass model:

4. Prove or disprove the existence of positive almost periodic solutions for the asymptotic linear ($n = m - 1$) and/or superlinear ($n < m - 1$) cases of (7.52) and its generalization (7.1).

5. Give conditions to ensure the stability of the positive almost periodic solutions of (7.52).

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Agradecimientos

A Pablo por su paciencia y por confiar en mí. Especialmente por darme independencia en el final de este doctorado.

A los jurados por el trabajo que se tomó cada uno en leer esta tesis y por las sugerencias que me hicieron.

Al grupo "pamster", por tantas cenas y charlas compartidas. Gracias miles. A Manu por el dibujo que no entró en la tesis y en especial a Carlos A. con quien he compartido tantas charlas biomatemáticas.

A mis primeras compañeras de oficina, las chicas de la 2034, con quienes compartí los primeros cuatro años de mi doctorado. Gracias por estar cuando las necesité, por los consejos, por las charlas y por todo. Coti, Mari P., Ani S., Manu, Maggie y Patricia. La oficina más bella.

A mis actuales compañeros, los de la 2046 (autoproclamada "la mejor"). Ustedes bancaron este último tramo de mi tesis, uno de los más movidos. Gracias y gracias. Román, Andre, Anto, Fran, Nico F., Nico S., Caro M. y también sumo a Euge.

A todos los chicos y chicas con los que compartí algún deporte o almuerzo en este último tiempo. Pegarle a una pelota cuando te trabás en una cuenta es una buena terapia.

A las dos profesoras que admiro. A ustedes tuve el privilegio de tenerlas como docentes durante la licenciatura y el doctorado. Constanza y Alicia, dos personas que contagian su entusiasmo por enseñar.

A los que están desde el día uno. Javi y Mariii, son lo mejor de lo mejor. También a Sol, que siempre me desea lo mejor y Flefli que le pone mucha onda a la vida. Sólo puedo sentir amor por ustedes. Gracias por estar ahí siempre presentes.

A los que se fueron sumando a lo largo del camino, personas muy valiosas que aportan cosas buenas a mi vida. Lore, Andrés M. y Alexis.

A Martín, mi "cornerstone". Gracias por todo lo que ya te dije en persona.

A Perrrla, quien me ayudó en los inicios y se mantuvo presente a lo largo del camino.

A mis hermanos. Diego y David son los mejores. Siempre presentes, siempre dispuestos a todo. Son un pilar importante en mi vida. Son tan buenos que eligieron (respectivamente) como esposas a mis cuñadas Nati y Carla que son lo más y las quiero mucho. Más aún, me dieron unos sobrinos divinos que me hacen bien y me alegraban el día cuando una cuenta no salía y mi ánimo no era el mejor.

A Mich Donovan, mi fiel compañera de estudio desde hace 9 años.

Para el final, quería agradecer y dedicar esta tesis a mis papás. Dos personas que hicieron todo lo que estuvo a su alcance para que yo esté aca. Siento un agradecimiento y amor infinito por ustedes y nunca me voy a cansar de decirles gracias. GRACIAS.