Contributions aux équations et inclusions différentielles et applications à des problèmes issus de la biologie cellulaire

Mohamed Helal

N° d'ordre :

REPUBLIQUE ALGERIENNE DEMOCRATIQUE & POPULAIRE
MINISTERE DE L'ENSEIGNEMENT SUPERIEUR & DE LA RECHERCHE SCIENTIFIQUE

UNIVERSITE DJILLALI LIABES
FACULTE DES SCIENCES EXACTES
SIDI BEL ABBÈS

THESE DE DOCTORAT

Présentée par

Mohamed HELAL.

Spécialité : Mathématiques
Option : Mathématiques appliquées

Intitulée

Contributions aux équations et inclusions différentielles et applications à des problèmes issus de la biologie cellulaire

Soutenue le............................

Devant le jury composé de :

Président : (Abdelkader LAKMECHE, Professeur, Université de SBA)
Examinateurs : Mekki TERBECHE, Professeur, Université d'Oran
Mostafa ADIMY, Directeur de recherche, INRIA de Lyon
Abdelghanie OUAHAB, Maître de Conférences « Rang A », Université de SBA
Directeur de thèse :MILOUDI Mostéfa, Maître de Conférences « Rang A », Université de SBA
Co-Directeur de thèse : Laurent PUJO-MENJOUET, Maitre de Conférences, Université de Lyon1

dédicaces

A ma très chère mère,

A la mémoire de mon Père,

A tous les membres de ma famille, petits et grands,

A tous les membres du laboratoire de biomathématique,

Aux enseignants et personnels de la faculté des sciences exactes de l'université de Sidi Bel Abbes.

Acknowledgement

A Part of the work of this thesis was done in Algeria under the supervision of Professors MILOUDI, LAKMECHE and OUAHAB and the other part was realized during my stay in Lyon under the supervision of professor PUJO-MENJOUET.

I express, here, my deepest gratitude to all the professors for suggestions and simulating discussions along the preparation of this work.

Remerciements

Cette thèse est le résultat de la collaboration scientifique avec Laurent PUJO-MENJOUET, Matre de Conférences à l'Université Claude Bernard, Lyon 1 (France), Erwan HINGANT, Post-doctorant à l'université de Concepcion(CHILI), Mostéfa MILOUDI, Matre de Conférences à l'Université Djillali Liabès de Sidi Bel Abbes (Algérie), Abdelakder LAKMECHE, Professeur à l'Université Djillali Liabès de Sidi Bel Abbes (Algérie) et Abdelgnani OUAHAB, matre de Conférences à l'Université Djillali Liabès de Sidi Bel Abbes (Algérie). Je voudrais donc remercier tous, sans vos aides, vos conseils et vos encouragements ce travail n'aurait jamais vu le jour.

Je souhaite exprimer ma profonde gratitude à mes deux directeurs de thèse pour le sujet de thèse qu'ils m'ont proposé et leur encadrement. Le travail sous leur direction m'a permis d'étudier un grand spectre de modèles et de méthodes modernes en mathématiques appliquées. Je remercie mon directeur principal Monsieur **Mostéfa MILOUDI** *pour la confiance qu'il m'a accordée et de m'avoir conseillé durant ces quatre années pour mener à bien ce travail. Je remercie également Monsieur* **Laurent PUJO-MENJOUET** *de m'avoir permis de séjourner au sein de léquipe dracula à L'INRIA et également pour sa disponibilité et ses précieux conseils, la collaboration avec lui m'a appris beaucoup de choses sur d'autres disciplines que les mathématiques, en particulier sur la biologie et la médecine.*

Ensuite je voudrais exprimer ma profonde reconnaissance au président du jury, Monsieur **Abdelkader LAKMECHE**. *Veuillez trouvez ici l'expression de notre grand respect et nos vifs remerciements.*

Je tiens à remercier également les trois examinateurs, Monsieur **Mostafa ADIMY**, *Monsieur* **Mekki TERBECHE** *et Monsieur* **Abdelghani OUAHAB**. *Je suis très honoré qu'ils aient accepté de faire partie de Jury.*

Mes remerciements vont aussi à tous mes collègues de Lyon et de Sidi bel Abbes, qui m'ont permis de passer des années agréables et enrichissantes en leur compagnie.

J'ajoute un grand merci à toutes les personnes qui, par un sourire ou une parole bienveillante, m'ont permis de garder le moral tout au long de ces années d'études.

Enfin, je remercie ma famille, qui a constamment veillé avec patience, à ce que ce travail se déroule dans les meilleures conditions.

Résumé

Ce travail propose différents modèles de mathématiques issus à des phénomènes naturels. L'outil indispensable à cette étude sont les inclusions différentielles, les équations (ou les systèmes d'équations) différentielles ou aux dérivées partielles et la théorie des bifurcations. La nature des ces équations dépend du problème traité : il peut s'agir d'équations de transport, de réaction-diffusion, d'équations non-locales, etc. Nous souhaitons apporter ici quelques informations et explications sur les différents modèles que nous souhaitons étudier,

Dans la première partie, il s'agit d'étudier l'existence des solutions, critère de compacité pour l'ensemble de solutions ainsi que la continuité de l'opérateur solution pour certaines classes d'inclusions différentielles impulsives de type neutre, un exemple d'application est traité à la fin de cet première partie, c'est une extension des résultats obtenus dans l'étude théorique.

La seconde partie s'attache à l'analyse d'un autre modèle mathématique d'écrivant l'évolution de la maladie du cancer, il s'agit d'un système d'équations différentielles avec impulsions, les équations différentielles représentent l'évolution des cellules normales, cancéreuses sensibles et cancéreuses résistantes. Les impulsions représentent la chimiothérapie. On considère le cas de l'absence des cellules de la tumeur et on utilise un traitement préventif pour éradiquer la maladie, on étudie tout d'abord les conditions de stabilité des solutions triviales qui représentent l'éradication de la maladie, puis on traite le cas des bifurcations de solutions non triviales qui représentent le retour de maladie.

On s'intéresse dans la dernière partie à la modélisation de la maladie d'Alzheimer. On construit un modèle qui décrit d'une part la formation de plaque amyloide *in vivo*, et d'autre part les interactions entre les oligomères Aβ et la protéine prion qui induiraient la perte de mémoire. On mène l'analyse mathématique de ce modèle dans un cas particulier puis dans un cas plus général où le taux de polymérisation est une loi de puissance.

Abstract

This thesis deals with a different mathematical models deriving from natural phenomena. The essential tools in this study are differential inclusions, differential or partial differential equations (or systems of equations) and bifurcation theory. The nature of these equations depends on the problem being addressed: it may be transport equations, reaction-diffusion, non-local equations, etc.. We want to provide a several details and explanations of the various models that we want to study.

In the first part we present some existence results of solutions and study the topological structure of solution sets for the impulsive functional differential inclusions with multiple delay. Our existence result relies on a nonlinear alternative for compact u.s.c. maps. Then, we present some existence results and investigate the compactness of solution sets, some regularity of operator solutions and absolute retract (AR). The continuous dependence of solutions on parameters in the convex case is also examined. Applications to a problem from control theory are provided.

The second part is dedicated to the analysis of a new model describing the evolution of populations constituted by normal cells, sensitive and resistant tumor cells, under periodic chemotherapeutic treatment. We study the stability of the trivial periodic solutions and bifurcation of nontrivial periodic solutions by the mean of Lyapunov- Schmidt reduction. The conditions of stability and bifurcation are expressed in terms of the parameters of the system. Our results are applied to models given by Panetta.

In the last part, we are interested in modelling Alzheimer's disease. We introduce a model that describes the formation of amyloids plaques in the brain and the interactions between Aβ-oligomers and Prion proteins which might be responsible of the memory impairment. We carry out the mathematical analysis of the model. Namely, for a constant polymerization rate, we provide existence and uniqueness together with stability of the equilibrium. Finally we study the existence in a more general and biological relevant case, that is when the polymerization depends on the size of the amyloid.

Publications

Existence and solution sets of impulsive functional differential inclusions with multiple delay, *Opuscula Mathematica, 32/2 (2012), 249-283.*

Periodically pulsed chemotherapy with resistant tumor cells, *Acta Universitatis Apulensis, submitted April 2012.*

Alzheimer's disease, analysis of a mathematical model including the role of the prion protein, *Journal of Mathematical Biology, submitted February 2013.*

Contents

Introduction and motivations

0.1 Introduction

Differential equations with impulses were considered for the first time in the 1960's by Milman and Myshkis [136, 137]. After a period of active research, primarily in Eastern Europe during 1960-1970, early studies culminated with the monograph by Halanay and Wexler [96].

The dynamics of many evolving processes are subject to abrupt changes, such as shocks, harvesting, and natural disasters. These phenomena involve short-term perturbations from continuous and smooth dynamics, whose duration is negligible in comparison with the duration of an entire evolution. In models involving such perturbations, it is natural to assume that these perturbations act instantaneously or in the form of "impulses". As a consequence, impulsive differential equations have been developed in modeling impulsive problems in physics, population dynamics, ecology, biotechnology, industrial robotics, pharmacokinetics, optimal control, and so forth. Again, associated with this development, a theory of impulsive differential equations has been given extensive attention. Works recognized as landmark contributions include the books [19, 20, 28, 124, 153] and the papers [2, 45, 46, 80, 81, 75, 129, 149, 163]. There are also many different studies in biology and medicine for which impulsive differential equations provide good models; see, for instance, [3, 117, 118] and the references therein.

In recent years, many examples of differential equations with impulses with fixed moments have flourished in several contexts. In the periodic treatment of some diseases, impulses correspond to administration of a drug treatment or a missing product. In environmental sciences, impulses model seasonal changes of the water level of artificial reservoirs. The theory and applications addressing such problems have greatly involved functional differential equations as well as impulsive functional differential equations. Recently, extensions to functional differential equations with impulsive effects with fixed moments have been studied by Benchohra *et al.* [27, 29, 30] and Ouahab [141], with the use of the nonlinear alternative and Schauder's theorem, as well as by Yujun and Erxin [172] and Yujun [171] by using coincidence degree theory. For other results concerning functional differential equations, we refer the reader to the monographs of Azbelez *et al.* [14], Erbe, Qingai and Zhang [70], Hale and Lunel [97], and Henderson [102].

There is a large variety of motivations that led mathematicians, studying dynamical systems having velocities uniquely determined by the state of the system, but loosely upon it, to replace differential equations

$$y' = f(y)$$

by differential inclusions

$$y' \in F(y).$$

A system of differential inequalities

$$y_i' \le f^i(y_1, \ldots, y_n),\ \ i = 1, \ldots, n,$$

can also be considered as a differential inclusion. If an implicit differential equation

$$f(y, y') = 0$$

is given, then we can put $F(y) = \{v : f(y, v) = 0\}$ to reduce it to a differential inclusion. Differential inclusions are used to study ordinary differential equations with an inaccurately known right-hand side.

As an example, consider the differential equation with discontinuous right-hand side,

$$y' = 1 - 2\text{sgn}y,$$

$$y(0) = 0,$$

where

$$\text{sgn}y = \begin{cases} +1, & \text{if } \ y > 0, \\ 0, & \text{if } \ y = 0, \\ -1, & \text{if } \ y < 0. \end{cases}$$

The classical solution of above problem is defined by

$$y(t) = \begin{cases} 3t + c_1, & \text{if } \ y < 0, \\ \\ -t + c_2, & \text{if } \ y > 0, \end{cases}$$

where c_1 and c_2 are constants. As t increases, the classical solution tends to the line $y = 0$, but it cannot be continued along this line, since the map $y(t) = 0$ so obtained does not satisfy the equation in the usual sense (namely, $y'(t) = 0$, while the right-hand side has the value $1 - 2\text{sgn}0 = 1$). Hence, there are no classical solutions of initial value problems starting with $y(0) = 0$. Therefore, a generalization of the concept of solutions is required.

To formulate the notion of a solution to an initial value problem with a discontinuous right-hand side, we restated the problem as a differential inclusion,

$$y'(t) \in F(y(t)), \quad \text{ a.e. } \ t \in [0, \infty), \ \ y(0) = y_0,$$

where $F : \mathbb{R}^n \to \mathcal{P}(\mathbb{R}^n)$ is a vector set-valued map into the set of all subsets of $\mathbb{R}^n$ that can be defined in several ways. The simplest convex definition of F is obtained by the so-called Filippov regularization [74],

$$F(y) = \bigcap_{\epsilon>0} \overline{conv(f(\{y \in \mathbb{R}^n : \|y\| \leq \epsilon\} \backslash M))},$$

where $F(y)$ is the convex hull of f, $conv$ is the convex hull, M is a null set (*i.e.*, $\mu(M) = 0$, where μ denotes the Lebesgue measure in $\mathbb{R}^n$) and ϵ is the radius of the ball centered at y.

One of the most important examples of differential inclusions comes from control theory. Consider a control system

$$y'(t) = f(y, u), \; u \in U,$$

where u is a control parameter. It appears that the control system and the differential inclusions

$$y' \in f(y, U) = \bigcup_{u \in U} f(y, u)$$

have the same trajectories. If the set of controls depends on y, that is, $U = U(y)$, then we obtain the differential inclusion

$$y' \in F(y, U(y)).$$

The equivalence between a control system and the corresponding differential inclusion is the central idea used to prove existence theorems in optimal control theory.

Since the dynamics of economics, sociology, and biology in macrosystems is multivalued, differential inclusions serve as natural models in macrosystems with hysteresis.

A differential inclusion is a generalization of the notion of an ordinary differential equation. Therefore, all problems considered for differential equations, that is, existence of solutions, continuity of solutions, dependence on initial conditions and parameters, are present in the theory of differential inclusions. Since a differential inclusion usually has many solutions starting at a given point, new issues appear, such as investigation of topological properties of the set of solutions, selection of solutions with given properties, evaluation of the reachability sets, etc.

As a consequence, differential inclusions have been the subject of an intensive study of many researchers in the recent decades; see, for example, the monographs [10, 11, 43, 91, 106, 112, 156, 159] and the papers of Bressan and Colombo [37, 38], Colombo *et al.* [52, 53], Fryszkowsy and Górniewicz [82], Kyritsi *et al.* [119], *etc.*

As for more specialized problems, during the last ten years, impulsive ordinary differential inclusions and functional differential inclusions with different conditions have attracted the attention of many mathematicians. And nowadays, the foundations of the general theory of such kinds of problems are already set up and many of them have been investigated in detail; see [24, 26, 31, 48, 71, 84, 85, 86, 104] and the references therein.

Some of our work is devoted to the existence and stability of solutions for different classes of initial values problems for impulsive differential equation and inclusions with fixed and variable moments.

We now give an overview of the thesis topical arrangement. The first part of this thesis contains three chapters,

In first chapter, we introduce notations, definitions, lemmas, and fixed point theorems that are used in the next sections.

In chapter 2, we present some existence results of solutions and study the topological structure of solution sets for the following first-order impulsive neutral functional differential inclusions with initial condition:

$$\begin{cases} \frac{d}{dt}[y(t)-g(t,y_t)] \in F(t,y_t)+\displaystyle\sum_{i=1}^{n_*} y(t-T_i), & \text{a.e. } t\in J\backslash\{t_1,\ldots,t_m\}, \\ y(t_k^+)-y(t_k^-)=I_k(y(t_k^-)), & k=1,\ldots,m, \\ y(t)=\phi(t), & t\in[-r,0], \end{cases}$$

where $J := [0,b]$ and $0 = t_0 < t_1 < \ldots < t_m < t_{m+1} = b$ $(m \in \mathbb{N}^*)$, F is a set-valued map and g is single map. The functions I_k characterize the jump of the solutions at impulse points t_k $(k = 1,\ldots,m)$. Our existence result relies on a nonlinear alternative for compact u.s.c. maps. Then, we give some existence results and investigate the compactness of solution set, some regularity of operator solutions and absolute retract(AR).The continuous dependence of solutions on parameter in the convex case is also examined.

Applications to a problem from control theory are provided in chapter 3.
The second part of this thesis contains three chapters.

In chapter 4, we give some classical theorems on steady state bifurcations. including the Lyapunov-Schmidt procedure and bifurcation theorems from eigenvalues of odd multiplicity.

The version of the Lyapunov-Schmidt procedure presented here differs slightly from the one given in [132]. The latter is done by decomposing the space into the direct sum of the generalized eigenspace and its complement. While the Lyapunov-Schmidt procedure given here is based on the decomposition of the space into the direct sum of the eigenspace and its complement. This Lyapunov-Schmidt procedure is more natural, and much more convenient to study steady state bifurcations. In fact, it is this difference, together with other ingredients, including in particular the spectral theorem (see Chapter 3 [132]), that made many problems more accessible.

In chapter 5, we consider a nonlinear mathematical model describing the evolution of population constituted by normal cells, sensitive and resistant tumor cells, under periodic chemotherapeutic treatment. We study the stability of the trivial periodic solutions and bifurcation of nontrivial periodic solutions by the mean of Lyapunov-Schmidt reduction. The conditions of stability and bifurcation are expressed in terms of the parameters of the system. Our results are applied to models given by Panetta.

In chapter 6, we give an appendix that contains a details computation of chapter 5.

The final part, Part III contains also three Chapters.

In chapter 7, we introduce some results for L^p, distributions and Sobolev spaces

In chapter 8, We introduce a mathematical model of the *in vivo* progression of Alzheimer's disease with focus on the role of prions in memory impairment. Our model consists of differential equations that describe the dynamic formation of β-amyloid plaques based on the concentrations of Aβ oligomers, PRP^C proteins, and the Aβ-$\times$-PRP^C complex, which are hypothesized to be responsible for synaptic toxicity. We prove the well-posedness of the model and provided stability results for its unique equilibrium, when the polymerization rate of β-amyloid is constant and also when it is described by a power law.

The final chapter, chapter 9, we give Characteristic polynomials of the linearized ODE system and lyapunov function for local and global stability respectively.

economic threshold (ET). The complete expression of an orbitally

Part I

Contribution to theoretical studies of impulsive functional differential inclusions

Chapter 1

Preliminaries

Before giving the main results in the next two chapters, let us recall some notations, definitions, and auxiliary results that will be used throughout this part.

1.1 Spaces used

Let $J := [a, b]$ be an interval of $\mathbb{R}$ and let $(E, |\cdot|)$ be a real Banach space. We denote $C(J, E)$ the Banach space of all continuous functions from J into E with the norm

$$\|y\|_\infty = \sup\{|y(t)| : t \in J\},$$

and let $L^1(J, E)$ be the Banach space of measurable functions that are Bochner integrable and normed by

$$\|y\|_{L^1} = \int_a^b |y(t)|dt.$$

A function $y : J \longrightarrow E$ is Bochner integrable if and only if $|y|$ is Lebesgue integrable. For properties of the Bochner integral, see for instance, Yosida [170].
We also let $AC^i([a, b], E)$ denote the space of i-times differentiable functions $y : (a, b) \to E$, whose i^{th} derivative, $y^{(i)}$, is absolutely continuous.

1.2 Some Properties of Set-Valued Maps

Let (X, d) be a metric space and Y be a subset of X. We denote:

- $\mathcal{P}(X) = \{Y \subset X : Y \neq \emptyset\}$ and
- $\mathcal{P}_p(X) = \{Y \in \mathcal{P}(X) : Y$ has the property "p"$\}$, where p could be: $cl =$ closed, $b =$ bounded, $cp =$ compact, $cv =$ convex, etc.

Thus:

- $\mathcal{P}_{cl}(X) = \{Y \in \mathcal{P}(X) : Y \text{ closed}\}$,
- $\mathcal{P}_{b}(X) = \{Y \in \mathcal{P}(X) : Y \text{ bounded}\}$,
- $\mathcal{P}_{cp}(X) = \{Y \in \mathcal{P}(X) : Y \text{ compact}\}$,
- $\mathcal{P}_{cv}(X) = \{Y \in \mathcal{P}(X) : Y \text{ convex}\}$, where X is normed space,
- $\mathcal{P}_{cv,cp}(X) = \mathcal{P}_{cv}(X) \cap \mathcal{P}_{cp}(X)$ where X is normed space, etc.

Definition 1.1. *A multivalued function (or a multivalued operator, multivalued map, or multimap) from X into Y is a correspondence that associates to each element $x \in X$ a subset $F(x)$ of Y. We denote this correspondence by the symbol: $F : X \to \mathcal{P}(Y)$. We define:*

- *the effective domain $DomF = \{x \in X : F(x) \neq \emptyset\}$.*
- *the graph: $GraF = \{(x, y) \in X \times Y : y \in F(x)\}$.*
- *the range $F(X) = \bigcup_{x \in X} F(x)$.*
- *the image of the set $A \in \mathcal{P}(X)$: $F(A) = \bigcup_{x \in A} F(x)$.*
- *the inverse image of the set $B \in \mathcal{P}(Y)$: $F^{-}(B) = \{x \in X : F(x) \cap B \neq \emptyset\}$.*
- *the strict inverse image of the set $B \in \mathcal{P}(Y)$:*
$$F^{+}(B) = \{x \in DomF : F(x) \subset B\}.$$
- *the inverse multivalued operator, denoted by $F^{-1} : Y \to \mathcal{P}(X)$, is defined by*
$$F^{-1}(y) = \{x \in X : \ y \in F(x)\}.$$
The set $F^{-1}(y)$ is called the fiber of F at the point y.
- *Let $F, G : X \to \mathcal{P}(Y)$ be multifunctions. Then*
$$(F \cup G)(x) = F(x) \cup G(x), \ \text{and} \ (F \cap G)(x) = F(x) \cap G(x).$$

Also, if $F : X \to \mathcal{P}(Y)$ and $G : Y \to \mathcal{P}(Z)$, then the composition $(G \circ F)(\cdot)$ is defined by $(G \circ F)(x) = \cup_{y \in F(x)} G(y)$. Finally, if $F, G : X \to \mathcal{P}(Y)$, then the product $(F \times G)(\cdot)$ is defined by $(F \times G)(x) = F(x) \times G(x)$.

Let us give some properties of a multivalued function.

Proposition 1.2. *([107]) The following properties hold.*

- *If* F, $G : X \to \mathcal{P}(Y)$ *and* $A \subseteq Y$, *then*

$$(F \cup G)^{-}(A) = F^{-}(A) \cup G^{-}(A),\ (F \cup G)^{+}(A) = F^{+}(A) \cup G^{+}(A),$$

and

$$(F \cap G)^{-}(A) \subseteq F^{-}(A) \cap G^{-}(A),\ F^{+}(A) \cap G^{+}(A) \subseteq (F \cap G)^{+}(A).$$

- *If* $F : X \to \mathcal{P}(Y)$, $G : Y \to \mathcal{P}(Z)$, *and* $A \subseteq Z$, *then*

$$(G \circ F)^{-}(A) = F^{-}(G^{-}(A)),\ \text{and } (G \circ F)^{+}(A) = F^{+}(G(A)).$$

- *If* $F : X \to \mathcal{P}(Y)$ *and* $A_i, A \subseteq Y,\ i \in I$, *then*

$$X \backslash F^{-}(A) = F^{+}(Y \backslash A),\ X \backslash F^{+}(A) = F^{-}(Y \backslash A),$$

$$F^{-}(\bigcup_{i \in I} A_i) = \bigcup_{i \in I} F^{-}(A_i),\ F^{-}(\bigcap_{i \in I} A_i) \subseteq \bigcap_{i \in I} F^{-}(A_i),$$

and

$$\bigcup_{i \in I} F^{+}(A_i) \subseteq F(\bigcup_{i \in I} A_i),\ \bigcap_{i \in I} F^{+}(A_i) \subseteq F(\bigcap_{i \in I} A_i).$$

- *If* $F : X \to \mathcal{P}(Y)$ *and* $G : Y \to\ P(Z)$, $A \subseteq Y$, *and* $B \subseteq Z$, *then*

$$(F \times G)^{+}(A \times B) = F^{+}(A) \cap G^{+}(B),$$

$$(F \times G)^{-}(A \times B) = F^{-}(A) \cap G^{-}(B).$$

This is also true for arbitrary products.

Definition 1.3. *A multimap* $F : X \to \mathcal{P}(Y)$ *is convex (closed) valued if* $F(x)$ *is convex (closed) for all* $x \in X$. *We say that* F *is bounded on bounded sets if* $F(B) = \cup_{x \in B} F(x)$ *is bounded in* Y *for all* $B \in \mathcal{P}_b(X)$

$$(i.e.,\ \sup_{x \in B}\{\sup\{|y| : y \in F(x)\}\} < \infty).$$

The set $\Gamma_F \subset X \times Y$, *defined by*

$$\Gamma_F = \{(x, y) : x \in X, y \in F(x)\}$$

is called the graph of F. *We say that* F *is has a closed graph, if* Γ_F *is closed in* $X \times Y$.

Next, we define the Haudorff metric on a metric space, it is used to quantify the distance between subsets of the given metric space.

1.2.1 Hausdorff Metric Topology

Let (X, d) be a metric space. In the following, for given $x \in X$ and $A \in \mathcal{P}(X)$, the distance from x to A is defined by

$$d(x, A) = \inf\{d(x, a) : a \in A\}.$$

Similarly, for $y \in X$ and $B \in \mathcal{P}(X)$

$$d(B, y) = \inf\{d(b, y) : b \in B\}.$$

As usual, $d(x, \emptyset) = d(\emptyset, y) = +\infty$.

Definition 1.4. *Let $A, B \in \mathcal{P}(X)$, we define*

- $H^*(A, B) = \sup\{d(a, B) : a \in A\}$,
- $H^*(B, A) = \sup\{d(A, b) : b \in B\}$.

Then, $H(A, B) = \max(H^*(A, B), H^*(B, A))$ is the Hausdorff distance between A and B.

Remark 1.5. *Given $\epsilon > 0$, let*

$$A_\epsilon = \{x \in X : d(x, A) < \epsilon\}$$

and

$$B_\epsilon = \{x \in X : d(B, x) < \epsilon\}.$$

Then from the above definitions we have

$$H^*(A, B) = \inf\{\epsilon > 0 : A \subset B_\epsilon\},\ H^*(B, A) = \inf\{\epsilon > 0 : B \subset A_\epsilon\}$$

and

$$H(B, A) = \inf\{\epsilon > 0 : B \subset A_\epsilon,\ A \subset B_\epsilon\}.$$

From the definition we can easily prove the following properties:

- $H(A, A) = 0$, for all $A \in \mathcal{P}(X)$,
- $H(A, B) = H(B, A)$, for all $A, B \in \mathcal{P}(X)$,
- $H(A, B) \leq H(A, C) + H(C, B)$, for all $A, B, C \in \mathcal{P}(X)$.

Hence $H(\cdot, \cdot)$ is an extended pseudo-metric on $P(X)$ (i.e., is a pseudo-metric that can also take the value $+\infty$). Moreover, we can prove that (see [115])

$$H(A, B) = 0, \text{ if and only if } \overline{A} = \overline{B}.$$

So $\mathcal{P}_{cl}(X)$ given with the Hausdorff distance (H-distance), $H(\cdot, \cdot)$, becomes a metric space.

Lemma 1.6. *([107]) If $\{A_n,\ A\} \in \mathcal{P}_{cl}(X)$ and $A_n \to A$, then*

$$A = \bigcap_{n\geq 1} \overline{\bigcup_{m\geq n} A_m} = \bigcap_{\epsilon\geq 0} \bigcup_{n\geq 1} \bigcap_{m\geq n} (A_m)_\epsilon.$$

Now let us check the completeness of the metric space $(\mathcal{P}_{cl}(X), H)$.

Theorem 1.7. *([107]) If (X, d) is a complete metric space, then so is the space $(\mathcal{P}_{cl}(X), H)$.*

Lemma 1.8. *([107]) If (X, d) is a complete metric space, then $\mathcal{P}_{cp}(X)$ is a closed subset of $(\mathcal{P}(X), H)$; hence $(\mathcal{P}(X), H)$ is a complete metric space.*

The next lemma is obvious.

Lemma 1.9. *([107]) $\mathcal{P}_{cl,b}(X)$ is a closed subset of $(\mathcal{P}_{cl}(X), H)$. If (X, d) is complete metric space, then so is $\mathcal{P}_{cl,b}(X) = \mathcal{P}_{cl}(X) \cap \mathcal{P}_b(X)$.*

Let us that the metric space is a normed space.

Lemma 1.10. *([107]) If X is a normed space, then $\mathcal{P}_{cl,cv}(X) = \mathcal{P}_{cl}(X) \cap \mathcal{P}_{cv}(X)$ is a closed subset of $(\mathcal{P}_{cl}(X), H)$.*

Combining the previous three Lemmas, leads to the following result:

Proposition 1.11. *([107]) If X is a normed space, then $\mathcal{P}_{cp,cv}(X) \subset \mathcal{P}_{cl,b,cv}(X) \subset \mathcal{P}_{cl,cv}(X)$ and $\mathcal{P}_{cp}(X) \subset \mathcal{P}_{cl,b}(X)$ are closed subspaces of $(\mathcal{P}_{cl}(X), H)$.*

Remark 1.12. *If X is a Banach space, then all the above subsets are complete subspaces of the metric space $(\mathcal{P}_{cl}, H)$.*

Next, let us derive two formulas for the Hausdorff distance. The first formula, known as "Härmondar's formula," concerns sets in $\mathcal{P}_{cl,b,cv}(X)$ and introduces the supremum of the support functions of these sets.

Definition 1.13. *Let $(X, \|\cdot\|)$ be a normed space, X^* its topological dual, and $A \in \mathcal{P}(X)$. The support function $\sigma(\cdot, A)$ of A is a function from X^* into $\overline{\mathbb{R}} = \mathbb{R} \cup \{+\infty\}$ defined by*

$$\sigma(x^*, A) = \sup\{\langle x^*, a\rangle : a \in A\},$$

where the duality bracket $\langle\cdot,\cdot\rangle : X^* \times X \to R$ is defined by $\langle \phi, x\rangle = \phi(x)$.

Lemma 1.14. ([106]) *If X is normed space and $A, B \in \mathcal{P}_{cl,b,cv}(X)$, then*

$$H(A, B) = \sup\{|\langle x^*, A\rangle - \langle x^*, B\rangle : \|x\| \leq 1\}.$$

The second formula for the Hausdorff distance, concerns nonempty subsets of an arbitrary metric space and involves the distance functions from the sets.

Lemma 1.15. ([106]) *If (X, d) is a metric space and $A, B \in P(X)$, then*

$$H(A, B) = \sup\{|d(x, A) - d(x, B)| : x \in X\}.$$

1.2.2 Vietoris Topology

Throughout this section, (X, τ) is a Hausdorff topological space (that is, τ denotes the Haudorff topology on X). Given $A \in \mathcal{P}(X)$, we define

$$A^- = \{B \in \mathcal{P}(X) : A \cap B \neq \emptyset\} \text{ (those sets in } X \text{ that hit } A)$$

and

$$A^+ = \{B \in \mathcal{P}(X) : B \subseteq A\} \text{ (those sets in } X \text{ that "miss" } A^c).$$

Definition 1.16. *The "upper Vietoris topology" (denoted by $\widehat{\tau}_{UV}$) is generated by the base*

$$\mathcal{L}_{UV} = \{U^+ : U \in \tau\}.$$

• *The "lower Vietoris topology" (denoted by $\widehat{\tau}_{LV}$) is generated by the subbase*

$$\mathcal{L}_{LV} = \{U^- : U \in \tau\}.$$

• *The "Vietoris topology" (denoted by $\widehat{\tau}_V$) is generated by the subbase $\mathcal{L}_{UV} \cup \mathcal{L}_{LV}$.*

Remark 1.17. *It follows from the above definition, that a basic element for the Vietoris topology $\widehat{\tau}_V$ is given by*

$$B(U, V_1, \ldots, V_n) = \{A \in \mathcal{P}(X) : A \subseteq U, A \cap V_k \neq \emptyset, k = 1, \ldots, n\},$$

where $U, V_1, \ldots, V_n \in \tau$.

The Vietoris topology is "natural" in the following sense.

Lemma 1.18. *([107]) If $I : X \to \mathcal{P}(X)$ is the injection map defined by $I(x) = \{x\}$, then $I(\cdot)$ is continuous when $\mathcal{P}(X)$ is equipped with the $\widehat{\tau}_V$-topology.*

Example 1.19. The Vietoris topology $\widehat{\tau}_V$ is not the finest topology on $\mathcal{P}(X)$ for which $I(\cdot)$ is continuous.

To see this, let X be an infinite set equipped with the cofinite topology τ_c defined by

$$\tau_c = \{U : U \backslash X, \text{is a finite set}\} \cup \{\emptyset, X\}.$$

Then the closed subsets of X are $\emptyset, X$, and finite subsets of X. Let $\mathcal{F}$ denote the family of nonempty, finite subsets of X. Then $I^{-1}(\mathcal{F})$ is an open set in $(P(X), \widehat{\tau}_V)$ and contains some infinite sets. So $\mathcal{F} \notin \widehat{\tau}_V$ and thus $I(\cdot)$ remains continuous if on $P(X)$, we consider a stronger topology obtained by $\mathcal{F}$ to the original subset $\mathcal{L}_{UV} \cup \mathcal{L}_{LV}$.

As in the above example, let $\mathcal{F}$ denote the family of nonempty and finite subsets of X.

Proposition 1.20. *([107]) The family $\mathcal{F}$ is dense in $(\mathcal{P}(X), \widehat{\tau}_V)$.*

An immediate interesting consequence of the above proposition is the following lemma.

Lemma 1.21. ([106]) *If (X, τ) is a separable Haudorff space, then the space $(\mathcal{P}(X), \widehat{\tau}_V)$ is a separable topological space.*

The next lemmas tells us that under some additional, reasonable conditions on X, the topological space $(\mathcal{P}_{cl}(X), \widehat{\tau}_V)$ has separation properties (that is, Hausdorff properties).

Lemma 1.22. *([107]) If (X, τ) is a regular topological, then $(\mathcal{P}_{cl}(X), \widehat{\tau}_V)$ is a Hausdorff topological space.*

Lemma 1.23. *([107]) If (X, τ) is a Hausdorff topological space, then (X, τ) is compact if and only if $(\mathcal{P}_{cl}(X), \widehat{\tau}_V)$ is compact.*

In general, there is no simple relationship between the Hausdorff pseudo-metric (respectively, metric) topology $\widehat{\tau}_H$ and the Vietoris topology $\widehat{\tau}_V$, defined on $\mathcal{P}(X)$ (respectively, on $\mathcal{P}_{cl}(X)$). However, if we restrict ourselves to $\mathcal{P}_{cp}(X)$, then we have the following result.

Lemma 1.24. ([106]) *If (X, d) is a metric space, then on $\mathcal{P}_{cp}(X)$, the Haudorff metric topology $\widehat{\tau}_H$ and the Vietoris topology $\widehat{\tau}_V$ coincide.*

Next, let us give the continuity concepts for multifunctions.

1.2.3 Continuity Concepts and Their Relations

The three Vietoris topologies introduced in Section 1.2.2 lead to corresponding continuity concepts for multifunctions.

Definition 1.25. *Let $F : X \to \mathcal{P}(Y)$ be a multifunction (set-valued map).*

- *If $F : X \to (\mathcal{P}(Y), \tau_{UV})$ is continuous, then $F(\cdot)$ is said to be upper semicontinuous (u.s.c.)*
- *If $F : X \to (\mathcal{P}(Y), \tau_{LV})$ is continuous, then $F(\cdot)$ is said to be lower semicontinuous (l.s.c.)*
- *If $F : X \to (\mathcal{P}(Y), \tau_V)$ is continuous, then $F(\cdot)$ is said to be continuous (or Vietoris continuous).*

We present a local version of the above definition.

Definition 1.26. *Let $F : X \to \mathcal{P}(Y)$ be a multifunction (set-valued map).*

- *F is said to be u.s.c at $x_0 \in X$ if and only if for each open subset U of Y with $F(x_0) \subseteq U$, there exists an open V of x_0 such that for all $x \in V$, we have $F(x) \subseteq U$.*
- *F is said to be l.s.c at $x_0 \in X$ if the set $\{x \in X : F(x) \cap U \neq \emptyset\}$ is open, for any open set U in Y.*

Then, using the definition of the three Vietoris topologies, we immediately deduce the following results. Let us recall that a set $\mathcal{M}$ with a preorder $\succeq$ is *directed*, if every finite subset has an upper bound. A generalized sequence is a map

$$\mu \in \mathcal{M} \mapsto x_\mu \in X,$$

where (X, τ) is an topological space. An element $x \in X$ is the *limit* of $(x_\mu)_{\mu \in \mathcal{M}}$ if, for every neighborhood $\mathcal{V}$ of x, there exists $\mu_0 \in \mathcal{M}$ such that x_μ belong to $\mathcal{V}$, for all $\mu \succeq \mu_0$.

Proposition 1.27. *([107]) For a multifunction $F : X \to \mathcal{P}(Y)$, the following are equivalent:*

a) F u.s.c.,

b) $F^+(V)$ is open in X for every $V \subseteq Y$ open,

c) For every closed $C \subseteq Y$, $F^-(C)$ is closed in X,

d) $\overline{F^-(D)} \subseteq F^-(\overline{D})$,

*e) For any $x \in X$, if $\{x_\alpha\}_{\alpha \in J}$ is a generalized sequence, $x_\alpha \to x$, and V is an open subset of Y such that $F(x) \subseteq V$,
then there exists $\alpha_0 \in J$ such that, for all $\alpha \in J$ with $\alpha \geq \alpha_0$, we have $F(x_\alpha) \subseteq V$.*

The corresponding result for lower semicontinuity reads as follows.

Proposition 1.28. *([107]) For a multifunction $F : X \to \mathcal{P}(Y)$, the following are equivalent:*

a) F l.s.c,

b) For every $V \subseteq Y$ open, $F^-(V)$ is open in X,

c) For every closed $C \subseteq Y$, $F^+(C)$ is closed in X,

d) $\overline{F^+(D)} \subseteq F^+(\overline{D})$,

e) $F(\overline{A}) \subseteq \overline{F(A)}$, for every set $A \subseteq X$,

*g) For any $x \in X$, if $\{x_\alpha\}_{\alpha \in J}$ is a generalized sequence, $x_\alpha \to x$,
then for every $y \in F(x)$ there exists a generalized sequence $\{y_\alpha\}_{\alpha \in J} \subset Y$, $y_\alpha \in F(x_\alpha)$, $y_\alpha \to y$.*

Remark 1.29. *In the case where X and Y are topological spaces with countable bases, we may take usual sequences instead of generalized ones in conditions e) and g) of Propositions 8 and 1.28, respectively.*

Example 1.30. The following set-valued mappings are u.s.c:

1) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} 1, & x > 0, \\ \{-1, 1\} & x = 0, \\ \{-1\} & x < 0. \end{cases}$$

2) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} x + 1, & x > 0, \\ [-1, 1] & x = 0, \\ x - 1 & x < 0. \end{cases}$$

3) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by $F(x) = [f(x), g(x)]$, where $f, g : \mathbb{R} \to \mathbb{R}$ are l.s.c and u.s.c. functions, respectively.

Example 1.31. The following set-valued mappings are lower semicontinuous:

1) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} [a, b], & x \neq 0, \\ \{\alpha\}, & \alpha \in [a, b]. \end{cases}$$

2) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} [0, |x| + 1], & x \neq 0, \\ \{1\}, & x = 0. \end{cases}$$

3) $F : \mathbb{R} \to \mathcal{P}(\mathbb{R})$ defined by $F(x) = [f(x), g(x)]$, where $f, g : \mathbb{R} \to \mathbb{R}$ are u.s.c and l.s.c. functions, respectively.

4) Let $X = Y = [0, 1]$. Define

$$F(x) = \begin{cases} [0, 1], & x \neq \frac{1}{2}, \\ [0, \frac{1}{2}], & x = \frac{1}{2}. \end{cases}$$

In general, the concepts of upper semicontinuity and lower semicontinuity are distinct. The following standard example illustrates this.

Example 1.32. Let $X = Y = \mathbb{R}$. Define

$$F_1(x) = \begin{cases} \{1\}, & x \neq 0, \\ [0,1], & x = 0, \end{cases} \quad \text{and } F_2(x) = \begin{cases} \{0\}, & x = 0, \\ [0,1], & x \neq 0. \end{cases}$$

We can easily show that F_1 is u.s.c. but not l.s.c., while F_2 is l.s.c. but not u.s.c.

Another useful continuity notion related to the previous ones, can be defined using the graph of a multifunction.

Definition 1.33. *A multifunction is said to be closed if its graph $GraF$ is a closed subset of the space $X \times Y$.*

Here are some equivalent formulations.

Theorem 1.34. *[112] The following conditions are equivalent:*

a) The multifunction F is closed,

b) For every $(x,y) \in X \times Y$ such that $y \notin F(x)$, there exist neighborhoods $V(x)$ of x and $W(y)$ of y such that $F(V(x)) \cap W(y) = \emptyset$,

c) For generalized sequences $\{x_\alpha\}_{\alpha \in J} \subset X$ and $\{y_\alpha\}_{\alpha \in J} \subset Y$, if $x_\alpha \to x$, and $y_\alpha \in F(x_\alpha)$ with $y_\alpha \to y$, then $y \in F(x)$.

Example 1.35. Let $f : Y \to X$ be a continuous onto map between topological spaces. Then the inverse multifunction $F : X \to \mathcal{P}(Y)$ given by $F(x) = f^{-1}(x)$ is closed.

Next, let us give a relationship between u.s.c. and closed multifunctions.

Theorem 1.36. *[107] Let X be a topological space, Y a regular topological space, and $F : X \to \mathcal{P}_{cl}(Y)$ an u.s.c. multifunction. Then F is closed.*

In the next result, we determine sufficient conditions for a closed multifunction to be u.s.c. But before we need to give the following definition.

Definition 1.37. *A multifunction $F : X \to \mathcal{P}(Y)$ is said to be:*

a) compact, if its range $F(X)$ is relatively compact in Y, i.e., $\overline{F(X)}$ is compact in Y;

b) locally compact, if every point $x \in X$ has a neighborhood $V(x)$ such that the restriction of F to $V(x)$ is compact.

c) quasicompact, if its restriction to every compact subset

It is clear that $a) \Longrightarrow b) \Longrightarrow c)$.

Theorem 1.38. *[112] Let $F : X \to \mathcal{P}_{cp}(Y)$ be a closed locally compact multifunction. Then F is u.s.c.*

Example 1.39. The condition of local compactness is essential. The multifunction $F : [-1, 1] \to \mathcal{P}_{cp}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} \{\frac{1}{x}\}, & x \neq 0, \\ \{0\}, & x = 0, \end{cases}$$

is closed but loses its upper semicontinuity at $x = 0$.

Lemma 1.40. ([106]) *If $F : X \to \mathcal{P}(Y)$ has a closed graph and is locally compact (i.e., for every $x \in X$, there exists a $U \in \mathcal{N}(x)$ such that $\overline{F(U)} \in \mathcal{P}_{cp}(Y)$), then $F(\cdot)$ is u.s.c.*

Definition 1.41. *A multifunction $F : X \to \mathcal{P}(Y)$ is said be quasicompact if its restriction to any compact subset $A \subset X$ is compact.*

Lemma 1.42. *[112] If $G : X \to \mathcal{P}_{cp}(Y)$ is quasicompact and has a closed graph, then G is u.s.c.*

Let us give concept of selection,

1.2.4 Selection Functions and Selection Theorems

The basic connection between "multivalued analysis" and "single-valued analysis" is given by the concept of selection.

Definition 1.43. *Let X, Y be nonempty sets and $F : X \to \mathcal{P}(Y)$. The single-valued operator $f : X \to Y$ is called a selection of F if and only if $f(x) \in F(x)$, for each $x \in X$. The set of all selection functions for F is denoted by S_F.*

A famous result is the so-called "Michael selection theorem," auxiliary results proven with the use of the following lemmas.

Lemma 1.44. *[107] Let (X, d) be a metric space, Y be a Banach space, $F_1 : X \to \mathcal{P}(Y)$ be l.s.c., and $F_2 : X \to \mathcal{P}(Y)$ have an open graph such that $F_1(x) \cap F_2(x) \neq \emptyset$, for each $x \in X$. Then the multivalued operator $F_1 \cap F_2$ is l.s.c.*

Lemma 1.45. *[107] Let (X, d) be a metric space, Y be a Banach space, and $F : X \to \mathcal{P}_{cv}(Y)$ be l.s.c. on X. Then, for each $\epsilon > 0$ there exists a continuous function $f_\epsilon : X \to Y$ such that, for all $x \in X$, we have $f_\epsilon(x) \in V(F(x), \epsilon)$.*

Theorem 1.46. *[107]* (Michael's selection theorem) *Let (X, d) be a metric space, Y be a Banach space, and $F : X \to \mathcal{P}_{cl,cv}(Y)$ be l.s.c. on X. Then there exists $f : X \to Y$ that is a continuous selection of F.*

For u.s.c. multifunctions, we have the following approximate selection theorem given by Aubin and Cellina [10].

Theorem 1.47. ([148]) *Let (X, d) be a metric space, Y be a Banach space and $F : X \to \mathcal{P}_{cv}(Y)$ be u.s.c. on X. Then for every $\epsilon > 0$ there exists $f_\epsilon : X \to Y$ that is locally Lipschitzian and satisfies:*

i) $f_\epsilon(X) \in ConvF(X)$,

ii) $Graf_\epsilon \subset V(GraF, \epsilon)$,

where $ConvF$ *is the convex hull of* F.

Let us consider now the selection theorem of Browder [42].

Theorem 1.48. *[107] Let* X *and* Y *be Hausdorff topological vector spaces and* $K \in \mathcal{P}_{cp}(X)$. *Let* $F : K \to \mathcal{P}_{cv}(Y)$ *be a multivalued operator such that* $F^{-1}(y)$ *is open, for each* $y \in Y$. *Then there exists a continuous selection* f *of* F.

Lut us give a new Hausdorff continuity concept.

1.2.5 Hausdorff Continuity

When Y is a metric space, by using the Hausdorff pseudometric, we can define three new continuity concepts that, in general, are distinct from the ones considered in the previous sections. Throughout this section, X is a Hausdorff topological space and Y is a metric space.

Definition 1.49. *A multifunction* $F : X \to \mathcal{P}(Y)$ *is said to be:*

a) H*-u.s.c at* $x_0 \in X$, *if* $H^*(F(x), F(x_0))$ *is continuous at* x_0*; i.e.,*

$$\forall \epsilon > 0, \exists U_\epsilon \in \mathcal{N}(x_0) : \forall x \in U_\epsilon \Longrightarrow H^*(F(x), F(x_0)) < \epsilon,$$

where $\mathcal{N}(x)$ *is a neighborhood filter of of* x.

b) H*-l.s.c at* $x_0 \in X$, *if* $H^*(F(x_0), F(x))$ *is continuous at* x_0*; i.e.,*

$$\forall \epsilon > 0, \exists U_\epsilon \in \mathcal{N}(x_0) : \forall x \in U_\epsilon \Longrightarrow H^*(F(x_0), F(x)) < \epsilon.$$

c) H*-continuous at* x_0, *if it is both* H*-u.s.c and* H*-l.s.c at* x_0.

We start by comparing these continuity concepts with the Vietoris ones studied earlier.

Proposition 1.50. *[107] If* $F : X \to \mathcal{P}(Y)$ *is u.s.c., then* $F(\cdot)$ *is* H*-u.s.c.*

Example 1.51. A single valued mapping $f : \mathbb{R} \to \mathbb{R}$ is H-u.s.c. (H-l.s.c.) if the set valued mapping F defined by $F(t) = [0, f(t)]$ is upper (lower) semicontinuous.

Example 1.52. The converse of Proposition 1.50 is not true in general. We consider the counterexample $F : [0, 1] \to \mathcal{P}(\mathbb{R})$ defined by

$$F(x) = \begin{cases} [0,1], & x \in [0,1), \\ [0,1), & x = 1. \end{cases}$$

It easy to check that $F(\cdot)$ is $H-$u.s.c but not u.s.c at $x = 1$. Indeed note that $F^+((-1, 1)) = \{1\}$ is not an open set.

The second example involves a closed-valued multifunction.

Example 1.53. In the following counterexample, let $F : \mathbb{R} \to \mathcal{P}_{cl}(\mathbb{R}^2)$ be defined by

$$F(x) = \begin{cases} \{[0, z] : z \geq 0\}, & x = 0, \\ \{[x, z] : 0 \leq z \leq \frac{1}{z}\}, & x \neq 0. \end{cases}$$

Then $F(\cdot)$ is H-u.s.c but not u.s.c, since for $C = \{[\frac{1}{n}, n] : n \geq 1\} \subset \mathbb{R}^2$ is closed, but $F^{-}(C)$ is not closed in $\mathbb{R}$.

Proposition 1.54. ([106]) *If $F : X \to \mathcal{P}_{cl}(Y)$ is H-u.s.c., then $F(\cdot)$ is closed.*

For relations between H-u.s.c. multifunctions and single l.s.c, we state the following results.

Proposition 1.55. ([106]) *If $F : X \to \mathcal{P}_{cl}(Y)$ is H-u.s.c., then for every $v \in Y$, $x \to \phi_v(x) = d(v, F(x))$ is l.s.c.*

Proposition 1.56. ([106]) *If $F : X \to \mathcal{P}_{cl}(Y)$ is H-u.s.c., then $F(\cdot)$ is l.s.c.*

Theorem 1.57. ([106]) *Let $F : X \to \mathcal{P}_{cp}(Y)$. The following conditions are equivalent:*

a) F u.s.c. (resp. F l.s.c.),

b) H-u.s.c (resp. H-l.s.c.),

Definition 1.58. *A multivalued operator $N : X \to \mathcal{P}_{cl}(X)$ is called*

a) γ-Lipschitz continuous if and only if there exists $\gamma > 0$ such that

$$H(N(x), N(y)) \leq \gamma d(x, y), \quad \textit{for each } x,\ y \in X,$$

b) a contraction if and only if it is γ-Lipschitz continuous with $\gamma < 1$.

Remark 1.59. *It clear that, if N is Lipschitz continuous, then N is $H-$continuous.*

The following results are easily deduced from the limit properties.

Lemma 1.60. *(see e.g. [11], Theorem 1.4.13) If $G : X \longrightarrow \mathcal{P}_{cp}(X)$ is u.s.c., then for any $x_0 \in X$,*

$$\limsup_{x \to x_0} G(x) = G(x_0).$$

Lemma 1.61. (see e.g. [11, Lemma 1.1.9]) *Let $(K_n)_{n\in\mathbb{N}} \subset K \subset X$ be a sequence of subsets where K is compact in the separable Banach space X. Then*

$$\overline{co}\,(\limsup_{n\to\infty} K_n) = \bigcap_{N>0} \overline{co}\,(\bigcup_{n\geq N} K_n),$$

where $\overline{co}\,A$ refers to the closure of the convex hull of A.

Lemma 1.62. ([125]) *Let X be a Banach space. Let $F : [a,b]\times X \longrightarrow P_{cp,c}(X)$ be an L^1-Carathéodory multivalued map with $S_{F,y} \neq \emptyset$ and let Γ be a linear continuous mapping from $L^1([a,b],X)$ into $C([a,b],X)$. Then the operator*

$$\begin{aligned} \Gamma \circ S_F : C([a,b],X) &\longrightarrow \mathcal{P}_{cp,c}(C([a,b],X)), \\ y &\longmapsto (\Gamma \circ S_F)(y) := \Gamma(S_{F,y}) \end{aligned}$$

is a closed graph operator in $C([a,b],X)\times C([a,b],X)$.

Lemma 1.63. (Mazur's Lemma [139, Theorem 21.4]) *Let E be a normed space and $\{x_k\}_{k\in\mathbb{N}} \subset E$ be a sequence weakly converging to a limit $x \in E$. Then there exists a sequence of convex combinations $y_m = \sum_{k=1}^{m} \alpha_{mk}x_k$ with $\alpha_{mk} > 0$ for $k = 1,2,\dots,m$ and $\sum_{k=1}^{m} \alpha_{mk} = 1$, that converges strongly to x.*

G is said to be *completely continuous* if it is *u.s.c.* and, for every bounded subset $A \subseteq X$, $G(A)$ is relatively compact, i.e. there exists a relatively compact set $K = K(A) \subset X$ such that $G(A) = \bigcup\{G(x),\ x \in A\} \subset K$. G is compact if $G(X)$ is relatively compact. It is called locally compact if, for each $x \in X$, there exists an open neighborhood U of x such that $G(U)$ is relatively compact. G is quasicompact if, for each subset $A \subset X$, $G(A)$ is relatively compact.

Next, let us give several concepts of measurability for a multifunction.

1.2.6 Measurable Multifunctions

Throughout this section, (Ω,Σ) is a measurable space and (X,d) a separable metric space. We define several concepts of measurability for a multifunction $F : \Omega \to \mathcal{P}(X)$.

Definition 1.64. *A multifunction $F : \Omega \to \mathcal{P}(X)$, is said to be:*

a) Strongly measurable, if for every closed $C \subseteq X$, we have

$$F^-(C) = \{\omega \in \Omega : F(\omega) \cap C \neq \emptyset\} \in \Sigma;$$

b) Measurable, if for every open $U \subseteq X$, we have

$$F^-(U) = \{\omega \in \Omega : F(\omega) \cap U \neq \emptyset\} \in \Sigma;$$

c) $F(\cdot)$ is said to b "K-measurable", if for every compact $K \subseteq X$, we have

$$F^-(K) = \{\omega \in \Omega : F(\omega) \cap K \neq \emptyset\} \in \Sigma;$$

d) Graph measurable, if

$$GraF = \{(\omega,x) \in \Omega \times X : x \in F(\omega)\} \in \Sigma \times B(X),$$

where $B(X)$ is the σ-algebra generated by the family of all open sets from X.

Proposition 1.65. *[107] If $F:\Omega\to\mathcal{P}(X)$ is strongly measurable, then $F(\cdot)$ is measurable.*

We next state a few popular notions of measurability of multifunctions.

Proposition 1.66. *[107] $F:\Omega\to\mathcal{P}(X)$ is measurable if and only if, for every $x\in X$, $\omega\to d(x,F(\omega))=\inf\{d(x,x'):x'\in F(\omega)\}$ is a measurable $\overline{\mathbb{R}}_+=\mathbb{R}\cup\{\infty\}-$valued function.*

Proposition 1.67. *[107] If $F:\Omega\to\mathcal{P}(X)$ is measurable, $F(\cdot)$ is graph measurable.*

Recalling that for $U\subseteq X$ open, we have $A\cap U\neq\emptyset$ if and only if $\overline{A}\cap U\neq\emptyset$, we immediately have the following proposition.

Proposition 1.68. *[107] $F:\Omega\to\mathcal{P}(X)$ is measurable if and only if $\overline{F}(\cdot)$ is measurable.*

As it was the case in our topological study of multifunctions, the situation simplifies considerably with compact valued multifunctions.

Proposition 1.69. *[107] If $F:\Omega\to\mathcal{P}_{cp}(X)$, then F is strongly measurable if and only if it is measurable.*

Definition 1.70. *A multi-valued map $F:J\to\mathcal{P}_{cl}(Y)$ is said measurable provided for every open that $U\subset Y$, the set $F^{+1}(U)$ is Lebesgue measurable.*

Lemma 1.71. ([47, 91]) *The mapping F is measurable if and only if for each $x\in Y$, the function $\zeta:J\to[0,+\infty)$ defined by*

$$\zeta(t)=\operatorname{dist}(x,F(t))=\inf\{|x-y|\,:\,y\in F(t)\},\quad t\in J,$$

is Lebesgue measurable.

The following two lemmas are needed in Chapter 2. The first one is the celebrated Kuratowski-Ryll-Nardzewski selection theorem.

Lemma 1.72. ([91, Theorem 19.7]) *Let Y be a separable metric space and $F:[a,b]\to\mathcal{P}_{cl}(Y)$ a measurable multi-valued. Then F has a measurable selection.*

Definition 1.73. *A multi-valued map $G:\Omega\to\mathcal{P}_{\mathcal{P}}(X)$ has a Castaing representation if there exists a family measurable single-valued maps $g_n:\Omega\to X$ such that*

$$G(\omega)=\overline{\{g_n(\omega)\mid n\in\mathbb{N}\}}.$$

The following result is due to Castaing (see [47]).

Theorem 1.74. *[107] Let X be a separable metric space. Then the multivalued map $G:\Omega\to\mathcal{P}(X)$ is measurable if and only if G has a Castaing representation.*

Lemma 1.75. ([173, Lemma 3.2]) *Let $F : [0, b] \to \mathcal{P}(Y)$ be a measurable multi-valued map and $u : [a, b] \to Y$ a measurable function. Then for any measurable $v : [a, b] \to (0, +\infty)$, there exists a measurable selection f_v of F such that for a.e. $t \in [a, b]$,*

$$|u(t) - f_v(t)| \le d(u(t), F(t)) + v(t).$$

Corollary 1.76. *[64] Let $F : [0, b] \to \mathcal{P}_{cp}(Y)$ be a measurable multi-valued map and $u : [0, b] \to E$ a measurable function. Then there exists a measurable selection f of F such that for a.e. $t \in [0, b]$,*

$$|u(t) - f(t)| \le d(u(t), F(t)).$$

By the Mazur Lemma and the above corollary we can easily prove the following corollary.

Corollary 1.77. *[64] Let $G : [0, b] \to \mathcal{P}_{wcp,cv}(E)$ be a measurable multifunction and $g : [0, b] \to E$ a measurable function. Then there exists a measurable selection u of G such that*

$$|u(t) - g(t)| \le d(g(t), G(t)).$$

Corollary 1.78. *[64] Let E be a reflexive Banach space, $G : [0, b] \to \mathcal{P}_{cl,cv}(E)$ be a measurable multifunction, $g : [0, b] \to E$ be a measurable function, and let there exist $k \in L^1([0, b], E)$ such that*

$$G(t) \subseteq k(t)B(0, 1), \ t \in [0, b],$$

where $B(0, 1)$ denotes the closed ball in E. Then there exists a measurable selection u of G such that

$$|u(t) - g(t)| \le d(g(t), G(t)).$$

Definition 1.79. *Let $(E, |\cdot|)$ be a Banach space. A multivalued map $F : [a, b] \times E \to \mathcal{P}(E)$ is said to be Carathéodory if*

(i) $t \longmapsto F(t, y)$ *is measurable for all* $y \in E$,

(ii) $y \longmapsto F(t, y)$ *is u.s.c for almost each* $t \in [a, b]$.
If, in addition,

(iii) for each $q > 0$, there exists $\varphi_q \in L^1([a, b], \mathbb{R}_+)$ such that

$$\begin{aligned} \|F(t, y)\|_{\mathcal{P}} &= \sup\{|v| : v \in F(t, y)\} \le \varphi_q(t), \ \text{for all } |y| \le q \\ &\quad \text{and a.e. } t \in [a, b], \end{aligned}$$

then F is said to be L^1-Carathéodory.

Next, we give some properties of decomposable selection.

1.2.7 Decomposable Selection

Consider a measure space $(T, \mathcal{F}, \mu)$, where $\mathcal{F}$ is a $\sigma-$algebra of subsets of T and μ is a nonatomic probability measurable on $\mathcal{F}$. If E is a Banach space, let $L^1(J, E)$ be the Banach space of all functions $u : T \to E$ which are Bochner $\mu-$integrable.

In what follows, we let χ_S denote the characteristic function

$$\chi_S(s) = \begin{cases} 1, & \text{if } \; s \in S, \\ 0, & \text{if } \; s \notin S. \end{cases}$$

Definition 1.80. *A set $K \subset L^1(J, E)$ is decomposable if, for all, $u, v \in K$, $u\chi_A + v\chi_{T-A} \in K$, whenever $A \in \mathcal{F}$. The collection of all nonempty decomposable subsets of $L^1(T, E)$ is denoted by $D(L^1(T, E))$. For any set $H \subset L^1(T, E)$, the decomposable hull of H is*

$$dec[H] = \cap\{K \in D(L^1(T, E)) : H \subset K\}.$$

Definition 1.81. *Let Y be a separable metric space and let $N : Y \to \mathcal{P}(L^1([a, b], E))$ be a multivalued operator. We say N has property (BC) if*

1) N is l.s.c.,

2) N has nonempty closed and decomposable values.

Let $F : [a, b] \times E \to \mathcal{P}(E)$ be a multivalued map with nonempty compact values. Assign to F the multivalued operator

$$\mathcal{F} : C([a, b], E) \to \mathcal{P}(L^1([a, b], E))$$

by letting

$$\mathcal{F}(y) = \{w \in L^1([a, b], E) : w(t) \in F(t, y(t)) \;\; a.e. \; t \in [a, b]\}.$$

The operator $\mathcal{F}$ is called the Niemytzki operator associated with F.

Definition 1.82. *Let $F : [a, b] \times E \to \mathcal{P}_{cp}(E)$ be a multivalued function. We say F is of l.s.c type if its associated Niemytzki operator $\mathcal{F}$ is l.s.c and has nonempty closed and decomposable values.*

We need the following lemma in nonconvex case.

Lemma 1.83. *[64]* ([79]) *Let $F : J \times E \to \mathcal{P}_{cp}(E)$ be a multivalued map and E be a separable Banach space. Assume that*

(i) $F : J \times E \longrightarrow \mathcal{P}(E)$ is a nonempty compact valued multivalued map such that
a) $(t, y) \mapsto F(t, y)$ is $\mathcal{L} \otimes \mathcal{B}$ measurable;
b) $y \mapsto F(t, u)$ is lower semi-continuous for a.e. $t \in J$;

(ii) for each $r > 0$, there exists a function $h_r \in L^1(J, \mathbb{R}^+)$ such that

$$\|F(t,u)\|_{\mathcal{P}} \leq h_r(t), \text{ for a.e. } t \in J \quad \text{and for } u \in X \text{ with } \|u\| \leq r.$$

Then F is of l.s.c. type.

Next we state a selection theorem due to Bressan and Colombo.

Theorem 1.84. ([36]) *Let Y be separable metric space and let $N : Y \to \mathcal{P}(L^1(J, E))$ be a multi-valued operator that has property (BC). Then N has a continuous selection, i.e., there exists a continuous function (single-valued) $g : Y \to L^1(J, E)$ such that $g(u) \in N(u)$ for every $u \in Y$.*

Given a separable Banach space $(E, |\cdot|)$, for a multi-valued map $F : J \times E \to \mathcal{P}(E)$, denote

$$\|F(t,x)\|_{\mathcal{P}} := \sup\{|v| : v \in F(t,x)\}.$$

Definition 1.85. *F is said*

(a) *integrable if it has a summable selection $f \in L^1(J, E)$,*

(b) *integrably bounded, if there exists $q \in L^1(J, \mathbb{R}^+)$ such that*

$$\|F(t,z)\|_{\mathcal{P}} \leq q(t), \quad \text{for a.e. } t \in J \text{ and every } z \in E.$$

Definition 1.86. *A multi-valued map F is called a Carathéodory function if*

(a) *the function $t \mapsto F(t,x)$ is measurable for each $x \in E$;*

(b) *for a.e. $t \in J$, the map $x \mapsto F(t,x)$ is u.s.c.*

Furthermore, F is L^1-Carathéodory if it is locally integrably bounded, i.e., for each positive r, there exists $h_r \in L^1(J, \mathbb{R}^+)$ such that

$$\|F(t,x)\|_{\mathcal{P}} \leq h_r(t), \quad \text{for a.e. } t \in J \text{ and all } |x| \leq r.$$

Lemma 1.87. *[125]. Given a Banach space E, let $F : [a,b] \times E \longrightarrow \mathcal{P}_{cp,cv}(E)$ be a L^1-Carathédory multi-valued map such that for each $y \in C([a,b], E)$, $S_{F,y} \neq \emptyset$ and let Γ be a linear continuous mapping from $L^1([a,b], E)$ into $C([a,b], E)$. Then the operator*

$$\begin{aligned} \Gamma \circ S_F : C([a,b],E) &\longrightarrow \mathcal{P}_{cp,cv}(C([a,b],E)), \\ y &\longmapsto (\Gamma \circ S_F)(y) := \Gamma(S_{F,y}) \end{aligned}$$

has a closed graph in $C([a,b], E) \times C([a,b], E)$.

For each $x \in C(J, E)$, the set

$$S_{F,x} = \left\{ f \in L^1(J,E) : f(t) \in F(t,x(t)) \text{ for a.e. } t \in [0,b] \right\}$$

is known as the set of selection functions.

Closed graphs

We denote the graph of G to be the set $\mathcal{G}r(G) = \{(x, y) \in X \times Y,\ y \in G(x)\}$.

Definition 1.88. *G is closed if $\mathcal{G}r(G)$ is a closed subset of $X \times Y$, i.e. for every sequences $(x_n)_{n\in\mathbb{N}} \subset X$ and $(y_n)_{n\in\mathbb{N}} \subset Y$, if $x_n \to x_*$, $y_n \to y_*$ as $n \to \infty$ with $y_n \in F(x_n)$, then $y_* \in G(x_*)$.*

We recall the following two results; the first one is classical.

Lemma 1.89. *([59], Proposition 1.2) If $G : X \to \mathcal{P}_{cl}(Y)$ is u.s.c., then $\mathcal{G}r(G)$ is a closed subset of $X \times Y$. Conversely, if G is locally compact and has nonempty compact values and a closed graph, then it is u.s.c.*

Lemma 1.90. *If $G : X \to \mathcal{P}_{cp}(Y)$ is quasicompact and has a closed graph, then G is u.s.c.*

Remark 1.91.

(a) For each $x \in C(J, E)$, the set $S_{F,x}$ is closed whenever F has closed values. It is convex if and only if $F(t, x(t))$ is convex for a.e. $t \in J$.

(b) From [164], Theorem 5.10 (see also [125] when E is finite-dimensional), we know that $S_{F,x}$ is nonempty if and only if the mapping $t \mapsto \inf\{|v| : v \in F(t, x(t))\}$ belongs to $L^1(J)$. It is bounded if and only if the mapping $t \mapsto \|F(t, x(t))\|_{\mathcal{P}} = \sup\{|v| : v \in F(t, x(t))\}$ belongs to $L^1(J)$; this particularly holds true when F is L^1-Carathéodory. For the sake of completeness, we refer also to Theorem 1.3.5 in [112] which states that $S_{F,x}$ contains a measurable selection whenever x is measurable and F is a Carathéodory function.

For additional details on multivalued maps, the books of Aubin and Cellina [10], Aubin and Frankowska [11], Brown *et al.* [43], Deimling [59], Górniewicz [91, 92], Hu and Papageorgiou [106], Petruşel [148], Smirnov [156], and Tolstonogov [159] are excellent sources.

1.3 Fixed Point Theorems

First, we state a result known as the Nonlinear Alternative. By $\overline{U}$ and ∂U we denote the closure of U and the boundary of U, respectively.

Lemma 1.92. (Nonlinear Alternative [89]) *Let X be a Banach space with C a closed and convex subset of X. Assume U is a relatively open subset of C, with $0 \in U$, and $G : \overline{U} \longrightarrow C$ is a compact map. Then either,*

(i) G has a fixed point in $\overline{U}$, or

(ii) there is a point $u \in \partial U$ and $\lambda \in (0, 1)$, with $u = \lambda G(u)$.

There is also a multivalued version of the Nonlinear Alternative.

Lemma 1.93. ([89]) *Let X be a Banach space with $C \subset X$ convex. Assume U is a relatively open subset of C, with $0 \in U$, and let $G : X \to \mathcal{P}_{cp,c}(X)$ be an u.s.c. and compact map. Then either,*

(a) G has a fixed point in $\overline{U}$, or

(b) there is a point $u \in \partial U$ and $\lambda \in (0,1)$, with $u \in \lambda G(u)$.

Lemma 1.94. ([55, 91]) *Let (X,d) be a complete metric space. If $N : X \to \mathcal{P}_{cl}(X)$ is a contraction, then $FixN \neq \emptyset$. Moreover, if N has compact values, then the set $Fix(N)$ is compact.*

Definition 1.95. *A multivalued map $F : X \to \mathcal{P}(E)$ is called an admissible contraction with constant $\{k_\alpha\}_{\alpha\in\Lambda}$ if, for each $\alpha \in \Lambda$, there exists $k_\alpha \in (0,1)$ such that*

i) $d_\alpha(F(x), F(y)) \leq k_\alpha d_\alpha(x,y)$ for all $x, y \in X$.

ii) For every $x \in X$ and every $\varepsilon \in (0,\infty)^\Lambda$, there exists $y \in F(x)$ such that

$$d_\alpha(x,y) \leq d_\alpha(x, F(x)) + \varepsilon_\alpha \ for\ every\, \alpha \in \Lambda.$$

The following nonlinear alternative is due to Frigon.

Lemma 1.96. (Nonlinear Alternative, [78]) *Let E be a Fréchet space and U an open neighborhood of the origin in E, and let $N : \overline{U} \to \mathcal{P}(E)$ be an admissible multivalued contraction. Assume that N is bounded. Then one of the following statements holds:*

(C1) N has at least one fixed point;

(C2) there exists $\lambda \in [0,1)$ and $x \in \partial U$ such that $x \in \lambda N(x)$.

1.4 Conclusion

In this chapter, we have introduce some notations, definitions, lemmas, and fixed point theorems that are used throughout the Chapter 2. These include some topological and analytical properties of set-valued mappings, followed by some fixed point results and measure of noncompactness results in those contexts. The second chapter is devoted to existence results of solutions for the first order impulsive functional differential inclusions problem.

Chapter 2

Existence and solution sets of impulsive functional differential inclusions with multiple delay

In this chapter, we present some existence results of solutions and study the topological structure of solution sets for the following first-order impulsive neutral functional differential inclusions with initial condition:

$$\begin{cases} \frac{d}{dt}[y(t) - g(t, y_t)] \in F(t, y_t) + \sum_{i=1}^{n_*} y(t - T_i), & \text{a.e. } t \in J \backslash \{t_1, \ldots, t_m\}, \\ y(t_k^+) - y(t_k^-) = I_k(y(t_k^-)), & k = 1, \ldots, m, \\ y(t) = \phi(t), & t \in [-r, 0], \end{cases}$$

where $J := [0, b]$ and $0 = t_0 < t_1 < \ldots < t_m < t_{m+1} = b$ ($m \in \mathbb{N}^*$), F is a set-valued map and g is single map. The functions I_k characterize the jump of the solutions at impulse points t_k ($k = 1, \ldots, m$). Our existence result relies on a nonlinear alternative for compact u.s.c. maps. Then, we present some existence results and investigate the compactness of solution set, some regularity of operator solutions and absolute retract(in short AR).The continuous dependence of solutions on parameter in the convex case is also examined. Applications to a problem from control theory are provided.

2.1 Introduction

The dynamics of many processes in physics, population dynamics, biology, medicine may be subject to abrupt changes such as shocks, perturbations (see for instance [3, 117] and the references therein). These perturbations may be seen as impulses. For instance, in the periodic treatment of some diseases, impulses may correspond to the administration of a drug treatment or a missing product. In environmental sciences, impulses can correspond to seasonal changes of the water level of artificial reservoirs. Their models may be described by impulsive differential equations. The mathematical study of boundary value problems for differential equations with impulses were first considered in 1960 by Milman and Myshkis [136] and then followed by a period of active research that culminated in 1968 with the monograph by Halanay and Wexler [96].

Moreover, it is well known that time delay is an important factor of mathematical models in ecology. Usually, time delays in those models are given in two ways: discrete delay and distributed time delay (continuous delay)[147].

For the impulsive model with distributed time delay, papers [94, 157, 133, 111] have investigated some ecological models with distributed time delay and impulsive control strategy. Impulsive functional differential equations with multiple delay arise in the study of pulse vaccination strategies.

Important contributions to the study of the mathematical aspects of such equations have been undertaken in [19, 124, 144, 153] among others. Functional differential equations and inclusions with impulsive effects with fixed moments have been recently addressed by Djebali *et al* [62], Yujun [171] and Yujun and Erxin [172]. Some existence results on impulsive functional differential equations with finite or infinite delay may be found in [142, 143] as well. During the last couple of years, impulsive ordinary differential inclusions and functional differential inclusions with different conditions have been intensely studied (see the book by Aubin [8], as well as the paper [103] and the references therein).

In this chapter, we consider first order impulsive functional differential inclusions with multiple delays of the form:

$$\begin{cases} \frac{d}{dt}[y(t)-g(t,y_t)] \in F(t,y_t) + \sum_{i=1}^{n_*} y(t-T_i), & \text{a.e } t \in J\backslash\{t_1,\ldots,t_m\} \\ y(t_k^+) - y(t_k^-) = I_k(y(t_k^-)), & k=1,\ldots,m \\ y(t) = \phi(t), & t \in [-r,0], \end{cases} \tag{2.1}$$

where $n_* \in \{1,2,\ldots\}$, $r = \max_{1\le i\le n_*} T_i$, $J := [0,b]$, $F : J \times D \to \mathbb{R}^n$ is given function, $D = (C[-r,0],\mathbb{R}^n)$, $0 = t_0 < t_1 < \ldots < t_m < t_{m+1} = b$ and $I_k \in C(\mathbb{R}^n,\mathbb{R}^n), k = 1,2,\ldots,m$, are given functions satisfying some assumptions that will be specified later.

For any function y defined on $[-r,b]$ and any $t \in J\backslash\{t_1,\ldots,t_m\}$ we denote by y_t the element of D defined by $y_t(\theta) = y(t+\theta)$, $\theta \in [-r,0]$.

For single case, some existence results of solutions for Problem (2.1) have been obtained in [142, 143]. Our goal in this chapter is to extend some of these results to the case of differential inclusions; moreover the right-hand side multivalued nonlinearity may be either convex or nonconvex.

In the second part of this chapter, we prove some existence results based on the nonlinear alternative of Leary Schauder type (in the convex case), on the Bressan-Colombo selection theorem and on the Covitz and Nadler fixed point theorem for contraction multi-valued maps in a generalized metric space (in the nonconvex case). The compactness of the solution set and some geometric properties are also provided. This is the content of Section 3. We will also discuss the question of dependance on parameters in Section 4.

2.2 Existence results

Let $J_0 = [0, t_1]$, $J_k = (t_k, t_{k+1}]$, $k = 1, \ldots, m$ and let y_k be the restriction of a function y to J_k. In order to define solutions for Problem (2.1), consider the space of piece-wise continuous functions

$$PC = \{y\colon [0,b] \to \mathbb{R}^n,\ y_k \in C(J_k, \mathbb{R}^n),\ k = 0, \ldots, m, \text{ such that } y(t_k^-) \text{ and } y(t_k^+) \text{ exist and satisfy } y(t_k) = y(t_k^-) \text{ for } k = 1, \ldots, m\}.$$

Endowed with the norm

$$\|y\|_{PC} = \max\{\|y_k\|_\infty,\ k = 0, \ldots, m\},\ \|y_k\|_\infty = \sup_{t \in [t_k, t_{k+1}]} |y(t)|$$

it is a Banach space. Moreover if

$$\Omega = \{y : [-r, b] \to \mathbb{R}^n : y \in PC([0,b], \mathbb{R}^n) \cap D\}$$

then Ω is a Banach space with the norm

$$\|y\|_\Omega = \sup\{|y(t)| :\ t \in [-r, b]\}.$$

Definition 2.1. *A function $y \in \Omega \cap \cup_{k=1}^{k=m} AC(J_k, \mathbb{R})$, is said to be a solution of (2.1) if y satisfies the equation $\frac{d}{dt}(y(t) - g(t, y_t)) = v(t) + \sum_{i=1}^{n_*} y(t - T_i)$ a.e. on J, $t \neq t_k$, $k = 1, \ldots, m$ and the conditions $y(t_k^+) - y(t_k^-) = I_k(y(t_k^-))$, $k = 1, \ldots, m$, $v \in S_{F,y}$ and $y(t) = \phi(t)$ on $[-r, 0]$.*

Lemma 2.2. *Let $f : D \to \mathbb{R}^n$ be a continuous function and assume that the function $t \to g(t, y_t)$ belongs to PC. Then y is the unique solution of the initial value problem*

$$\begin{cases} \frac{d}{dt}(y(t) - g(t, y_t)) = f(y_t) + \sum_{i=1}^{n_*} y(t - T_i) & a.e\ t \in J \backslash \{t_1, \ldots, t_m\} \\ y(t_k^+) - y(t_k) = I_k(y(t_k^-)), & k = 1, \ldots, m \\ y(t) = \phi(t), & t \in [-r, 0], \end{cases} \tag{2.2}$$

where $r = \max_{1\le i\le n_*} T_i$ *if and only if* y *is a solution of impulsive integral functional differential equation*

$$y(t) = \begin{cases} \phi(t), & t\in[-r,0],\\ \phi(0)+g(t,y_t)-g(0,\phi)-\sum_{0<t_k<t}\Delta_k(g(t_k^-,y_{t_k^-})) & \\ +\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds+\int_0^t f(y_s)ds & \\ +\sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds+\sum_{0<t_k<t} I_k(y(t_k^-)), & t\in[0,b], \end{cases} \tag{2.3}$$

where $\Delta_k(g(t_k^-,y_{t_k^-})) = g(t_k^+,y_{t_k^+}) - g(t_k,y_{t_k})$.

Proof. Denote $R_0 = \sum_{i=1}^{n_*}\int_0^{t_1} y(s-T_i)ds$ and $R_k = \sum_{i=1}^{n_*}\int_{t_k}^{t_{k+1}} y(s-T_i)ds$, $k=\{1,\ldots,m\}$. Let y be a possible solution of the problem (2.2). Then $y|_{[-r,t_1]}$ is a solution to $\frac{d}{dt}(y(t)-g(t,y_t)) = f(y_t)+\sum_{i=1}^{n_*} y(t-T_i)\ for\ t\in[0,b]$. Assume that $t_k<t\le t_{k+1}$, $k=1,\ldots,m$. By integration of above inequality yields

$$y(t_1^-)-y(0)-(g(t_1^-,y_{t_1^-})-g(0,\phi)) = \int_0^{t_1} f(y_s)ds+R_0,$$
$$y(t_1^-)-y(0)-(g(t_1^-,y_{t_1^-})-g(0,\phi)) = \int_0^{t_1} f(y_s)ds+R_0,$$
$$y(t_2^-)-y(t_1^+)-(g(t_2^-,y_{t_2^-})-g(t_1^+,y_{t_1^+})) = \int_{t_1}^{t_2} f(y_s)ds+R_1,$$
$$y(t_2^-)-y(t_1^-)-(g(t_2^-,y_{t_2^-})-g(t_1^+,y_{t_1^+})) = I_1(y(t_1^-))+\int_{t_1}^{t_2} f(y_s)ds+R_1,$$
$$\vdots$$
$$\vdots$$
$$\vdots$$
$$y(t_k^-)-y(t_{k-1}^+)-(g(t_k^-,y_{t_k^-})-g(t_{k-1}^+,y_{t_{k-1}^+})) = \int_{t_{k-1}}^{t_k} f(y_s)ds+R_{k-1},$$
$$y(t_k^-)-y(t_{k-1}^-)-(g(t_k^-,y_{t_k^-})-g(t_{k-1}^+,y_{t_{k-1}^+})) = I_k(y(t_k^-))+\int_{t_{k-1}}^{t_k} f(y_s)ds+R_{k-1},$$
$$y(t)-y(t_k^-)-(g(t,y_t)-g(t_k^+,y_{t_k^+})) = I_k(y(t_k^-))+\int_{t_k}^{t} f(y_s)ds+R_k.$$

Then

$$
\begin{aligned}
&y(t_1) - y(0) - (g(t_1, y_{t_1}) - g(0,\phi)) = \int_0^{t_1} f(y_s)ds + R_0,\\
&y(t_2) - y(t_1^-) - (g(t_2, y_{t_2}) - g(t_1^+, y_{t_1^+})) = I_1(y(t_1^-)) + \int_{t_1}^{t_2} f(y_s)ds + R_1,\\
&\vdots\\
&y(t_k^-) - y(t_{k-1}) - (g(t_k, y_{t_k}) - g(t_{k-1}^+, y_{t_{k-1}^+})) = I_k(y(t_k^-)) + \int_{t_{k-1}}^{t_k} f(y_s)ds + R_{k-1},\\
&y(t) - y(t_k^-) - (g(t, y_t) - g(t_k^+, y_{t_k^+})) = I_k(y(t_k^-)) + \int_{t_k}^{t} f(y_s)ds + \sum_{i=1}^{n_*}\int_{t_k-T_i}^{t-T_i} y(s)ds,
\end{aligned}
$$

Adding these together, we get

$$
\begin{aligned}
y(t) &= y(0) + g(t,y_t) - g(0,\phi) + \sum_{0<t_k<t}(g(t_k, y_{t_k}) - g(t_k^+, y_{t_k^+})) + \sum_{0<t_k<t} I_k(y(t_k^-))\\
&+ \int_0^t f(y_s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^{t-T_i} y(s)ds,\\
y(t) &= \phi(0) + g(t,y_t) - g(0,\phi) - \sum_{0<t_k<t}\Delta_k(g(t_k^-, y_{t_k^-})) + \sum_{0<t_k<t} I_k(y(t_k^-))\\
&+ \int_0^t f(y_s)ds + \sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds.
\end{aligned}
$$

□

Remark 2.3. *If g continuous function then the solution of the problem (2.2) is of the form*

$$
\begin{aligned}
y(t) &= \phi(0) + g(t,y_t) - g(0,\phi) + \sum_{0<t_k<t} I_k(y(t_k^-)) + \int_0^t f(y_s)ds\\
&+ \sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds, \quad t\in[0,b].
\end{aligned}
$$

2.2.1 Convex case

Let us introduce the following hypotheses:

($\mathcal{H}_1$) The function $F : J\times D \to \mathcal{P}_{cp,cv}(\mathbb{R}^n)$ is Carathéodory map;

($\mathcal{H}_2$) There exists a function $p \in L^1(J,\mathbb{R}_+)$ and a continuous nondecreasing function $\psi : [0,\infty) \to [0,\infty)$ such that

$$\|F(t,x)\|_{\mathcal{P}} \le p(t)\psi(\|x\|_D) \text{ for a.e. } t\in J \text{ and each } x\in D$$

with

$$\int_c^{\infty}\frac{ds}{s+\psi(s)} = \infty,$$

where

$$c = \frac{1}{1-d_1}[\|\phi\|_D + d_2 + \|g(0,\phi)\|_D + \sum_{i=1}^{n_*} T_i\|\phi\|_D],$$

($\mathcal{H}_3$) For every bounded set $B \in \Omega$, the set $\{t : t \mapsto g(t, y_t),\ y \in B\}$ is equicontinuous in Ω, g is continuous and there exist constants $d_1 \in [0,1)$ and $d_2 > 0$ such that

$$\|g(t,x)\|_D \leq d_1\|x\|_D + d_2 \text{ for all } x \in D.$$

Theorem 2.4. *Assume that the hypotheses* ($\mathcal{H}_1$) − ($\mathcal{H}_3$) *hold. Then the IVP (2.1) has at least one solution.*

Proof. Transform the problem (2.1) into a fixed point problem. Consider the operator $N : \Omega \to \mathcal{P}(\Omega)$ defined by:

$$N(y) = \left\{ h \in \Omega : h(t) = \left\{ \begin{array}{ll} \phi(t), & if\ t \in [-r,0]; \\ \phi(0) + g(t,y_t) - g(0,\phi) + & \\ \displaystyle\sum_{0<t_k<t} I_k(y(t_k^-)) + \int_0^t f(s)ds + & \\ \displaystyle\sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^0 \phi(s)ds, & if\ t \in J, \end{array} \right. \right\}$$

where $f \in S_{F,y}$. Clearly, the fixed points of the operator N are solution of the problem (2.1). We shall show that N satisfies the assumptions of the nonlinear alternative of Leray-Schauder type [89]. The proof is given in several steps.

Step 1: $N(y)$ is convex for each $y \in \Omega$.
Indeed, if h_1, h_2 belong to $N(y)$ then there exist $f_1,\ f_2 \in S_{F,y}$ such that, for each $t \in J$, we have

$$\begin{array}{rcl} h_i(t) & = & \phi(0) + g(t,y_t) - g(0,\phi) + \displaystyle\sum_{0<t_k<t} I_k(y(t_k^-)) + \int_0^t f_i(s)ds \\ & + & \displaystyle\sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^0 y(s)ds, \quad i = 1,\ 2. \end{array}$$

Let $0 \leq d \leq 1$. Then for each $t \in J$, we have

$$\begin{array}{rcl} (dh_1 + (1-d)h_2)(t) & = & \phi(0) + g(t,y_t) - g(0,\phi) + \displaystyle\sum_{0<t_k<t} I_k(y(t_k^-)) \\ & + & \displaystyle\int_0^t [df_1(s) + (1-d)f_2(s)]ds \\ & + & \displaystyle\sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^0 \phi(s)ds. \end{array}$$

Since $S_{F,y}$ is convex (because F has convex value) then

$$dh_1 + (1-d)h_2 \in N(y).$$

Step 2: N maps bounded sets into bounded sets in Ω.
Indeed, it is enough to show that there exists a positive constant l such that for each $y \in \mathcal{B}_q = \{y \in \Omega : \|y\|_\Omega \leq q\}$ one has $\|N(y)\|_{\mathcal{P}(\Omega)} \leq l$. Let $y \in \mathcal{B}_q$ and $h \in N(y)$. Then there exist $f \in S_{F,y}$ such that, for each $t \in J$, we have

$$\begin{aligned} h(t) &= \phi(0) + g(t, y_t) - g(0, \phi) + \sum_{0<t_k<t} I_k(y(t_k^-)) + \int_0^t f(s)ds \\ &+ \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds. \end{aligned}$$

By $(\mathcal{H}_1)$-$(\mathcal{H}_2)$ we have, for each $t \in J$,

$$\begin{aligned} |h(t)| &\leq |\phi(0)| + \|g(t, y_t)\|_D + \|g(0, \phi)\|_D + \sum_{0<t_k<t} |I_k(y(t_k^-))| \\ &+ \int_0^t |f(s)|ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} |y(s)|ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 |\phi(s)|ds. \\ &\leq \|\phi\|_D + d_1 q + d_2 + \|g(0, \phi)\|_D + \sum_{k=1}^m \sup_{u \in B(0,q)} |I_k(u)| \\ &+ \int_0^t p(s)\psi(\|y_s\|_D)ds + bqn_* + r||\phi||n_*. \\ &\leq \|\phi\| + d_1 q + d_2 + \|g(0, \phi)\|_D + m \sup_{u \in B(0,q)} |I_k(u)| \\ &+ b\|p\|_{L^1}\psi(q) + bqn_* + r\|\phi\|n_* := l. \end{aligned}$$

Step 3: N maps bounded sets into equicontinuous sets of Ω.

Using $(\mathcal{H}_3)$ it suffices to show that the operator $N_* : \Omega \to \mathcal{P}(\Omega)$ defined by

$$N_*(y) = \left\{ h \in \Omega : h(t) = \left\{ \begin{array}{ll} \phi(t), & if\ t \in [-r, 0]; \\ \phi(0) + \displaystyle\int_0^t f(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds & \\ + \displaystyle\sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds + \sum_{0<t_k<t} I_k(y(t_k^-)), & if\ t \in J, \end{array} \right. \right\}$$

where $f \in S_{F,y}$.

As in [32] (Th 3.2) we can prove that $N_*(\mathcal{B}_q)$ is equicontinuous.

Step 4: N has closed graph.

Let $y^n \to y^*$, $h_n \in N(y^n)$ and $h_n \to h^*$. We shall prove that $h^* \in N(y^*)$. $h_n \in N(y^n)$ means that there exists $f_n \in S_{F,y^n}$ such that, for each $t \in J$,

$$\begin{aligned} h_n(t) &= \phi(0) + g(t, y_t^n) + g(0, \phi) + \sum_{0<t_k<t} I_k(y^n(t_k^-)) \\ &+ \int_0^t f_n(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y^n(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds. \end{aligned}$$

We have to prove that there exists $v^* \in S_{F,y^*}$ such that, for each $t \in J$,

$$\begin{aligned} h^*(t) &= \phi(0) + g(t, y^*_t) - g(0,\phi) + \sum_{0<t_k<t} I_k(y^*(t_k^-)) \\ &+ \int_0^t f^*(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y^*(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds. \end{aligned}$$

Clearly since I_k, $k = 1, \ldots, m$, are continuous, we obtain that

$$\Bigg\| \Bigg(h_n(t) - \phi(0) - g(t, y^n_t) - g(0,\phi) - \sum_{0<t_k<t} I_k(y^n(t_k^-)) - \sum_{i=1}^{n_*} \int_0^{t-T_i} y^n(s)ds - \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds \Bigg) - \Bigg(h^*(t) - \phi(0) - g(t, y^*_t) - g(0,\phi) - \sum_{0<t_k<t} I_k(y^*(t_k^-)) - \sum_{i=1}^{n_*} \int_0^{t-T_i} y^*(s)ds - \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds \Bigg) \Bigg\|_\Omega$$

tends to 0 as $n \to \infty$.
Consider the operator

$$\Gamma : L^1 \to \Omega,$$
$$f \mapsto \Gamma(f)(t) = \int_0^t f(s)ds.$$

We can see that the operator Γ is linear and continuous. Indeed, one has

$$\|\Gamma\|_\Omega \leq \|p\|_{L^1} \psi(q).$$

From Lemma 1.87, It follows that $\Gamma \circ S_F$ is a closed graph operator. Since

$$\begin{aligned} &h_n(t) - \phi(0) - g(t, y^n_t) - g(0, y_0) - \sum_{0<t_k<t} I_k(y^n(t_k^-)) \\ &- \sum_{i=1}^{n_*} \int_0^{t-T_i} y^n(s)ds - \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds \in \Gamma(S_{F,y_n}), \end{aligned}$$

it follows from Lemma 1.87 that for some $f^* \in S_{F,y^*}$, that

$$h^*(t) = \begin{cases} \phi(t), & t \in [-r, 0] \\ \phi(0) + g(t, y^*_t) - g(0,\phi) + \sum_{0<t_k<t} I_k(y^*(t_k^-)) & \\ + \int_0^t f^*(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y^*(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds, & t \in J. \end{cases}$$

Step 5: A priori bounds on solutions.

Let y be a possible solution of the problem (2.1). Let y be a possible solution of the equation $y \in \lambda N(y)$, for some $\lambda \in (0,1)$. Then there exists $f \in S_{F,y}$ such that

$$y(t) = \begin{cases} \phi(t), & if\ t \in [-r,0]; \\ \phi(0) + g(t,y_t) - g(0,\phi) + \sum_{0<t_k<t} I_k(y(t_k^-)) & \\ + \int_0^t f(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds, & if\ t \in J. \end{cases}$$

Thus

$$y(t) = \lambda \left[\phi(0) + g(t,y_t) - g(0,\phi) + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds + \int_0^t f(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds \right],$$

for all $t \in [0,t_1]$. Hence

$$\begin{aligned} |y(t)| \quad &\leq \quad |\phi(0)| + \|g(t,y_t)\|_D + \|g(0,\phi)\|_D \\ &+ \quad \sum_{i=1}^{n_*} \int_{-T_i}^0 |\phi(s)|ds + \int_0^t |f(s)|ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} |y(s)|ds \\ &\leq \quad \|\phi\|_D + d_1\|y_t\|_D + d_2 + \|g(0,\phi)\|_D \\ &+ \quad \sum_{i=1}^{n_*} T_i\|\phi\|_\infty + n_* \int_0^t |y(s)|ds + \int_0^t p(s)\psi(\|y_s\|_D)ds. \end{aligned} \tag{2.4}$$

We consider the function

$$\mu(t) = \sup\{|y(s)| : -r \leq s \leq t\},\ t \in [0,t_1]. \tag{2.5}$$

Therefore

$$\mu(t) \leq \frac{1}{1-d_1} \left[L_* + \int_0^t p_*(s)(\mu(s) + \psi(\mu(s)))ds \right], \tag{2.6}$$

where

$$L_* = \|\phi\|_D + d_2 + \|g(0,\phi)\|_D + \sum_{i=1}^{n_*} T_i\|\phi\|_D$$

and

$$p_*(t) = n_* + p(t), \quad t \in [0,t_1].$$

Denoting by $\beta(t)$ the right hand side of the last inequality we have

$$\mu(t) \leq \beta(t), \quad t \in [0,t_1],$$

and

$$\beta(0) = \frac{1}{1-d_1}[\|\phi\|_D + d_2 + \|g(0,\phi)\|_D + \sum_{i=1}^{n_*} T_i\|\phi\|_D],$$

and

$$\begin{aligned}\beta'(t) &= \frac{1}{1-d_1}p_*(t)[\psi(\mu(t))+\mu(t)]\\ &\leq \frac{1}{1-d_1}p_*(t)[\psi(\beta(t))+\beta(t)].\end{aligned}$$

This implies that for each $t\in[0,t_1]$

$$\int_{\beta(0)}^{\beta(t)}\frac{ds}{\psi(s)+s}\leq\frac{1}{1-d_1}\int_0^{t_1}p_*(s)ds<\frac{1}{1-d_1}\int_c^{\infty}\frac{ds}{\psi(s)+s}.$$

Thus from $(\mathcal{H}_2)$ there exists a constant K_1 such that $\beta(t)\leq K_1,\ t\in[-r,t_1]$, and hence

$$\sup\{|y(t)|:\ t\in[-r,t_1]\}\leq K_1.$$

- Let $t\in(t_1,t_2]$, then

$$y(t)=\lambda\left[y(t_1^+)+g(t,y_t)-g(t_1,y_{t_1})+\int_{t_1}^{t}f(s)ds+\sum_{i=1}^{n_*}\int_{t_1-T_i}^{t-T_i}y(s)ds\right]$$

and

$$y(t_1^+)=y(t_1)+I_1(y(t_1)).$$

Thus

$$\begin{aligned}|y(t_1^+)| &\leq |y(t_1)|+|I_1(y(t_1))|\\ &\leq K_1+\sup\{|I_1(u)|:|u|\leq K_1\}.\end{aligned}$$

By analogies of above proof we can show that there exists $K_2>0$ such that

$$\sup\{|y(t)|:t\in[t_1,t_2]\}\leq K_2.$$

- We continue this process and also take into account that

$$y(t)=\lambda\left[y(t_m^+)+g(t,y_t)-g(t_m,y_{t_m})+\int_{t_m}^{t}f(s)ds+\sum_{i=1}^{n_*}\int_{t_m-T_i}^{t-T_i}y(s)ds\right],$$

$t\in(t_m,b]$, and

$$y(t_m^+)=y(t_m)+I_1(y(t_m)).$$

We obtain that there exists a constant K_m such that

$$\sup\{|y(t)|:t\in[t_m,b]\}\leq K_m.$$

Consequently, for each possible solution y to $z=\lambda P(z)$ for some $\lambda\in(0,1)$we have

$$\|y\|_\Omega\leq\max\{K_i:i=1,\dots,m\}:=\overline{K}.$$

Set

$$U=\{y\in\Omega:\|y\|_\Omega<\overline{K}+1\}.$$

and consider the operator $N:\overline{U}\to\mathcal{P}_{cv,cp}(\Omega)$. From the choice of U, there is no $y\in\partial U$ such that $y\in\gamma N(y)$ for some $\gamma\in(0,1)$. As a consequence of the Leray-Schauder nonlinear alternative [89], we deduce that N has a fixed point y in U which is a solution of Problem (2.1). □

2.2.2 The nonconvex case

In this section we present a result for a problem (2.1) in the spirit of the linear alternative of Laray-Schauder type [89] for single-valued maps, combined with a selection theorem due to Bressan and Colombo [36] for lower semi-continuous multivalued maps with decomposable values.
Let $\mathcal{A}$ be a subset of $J\times\mathcal{D}$. $\mathcal{A}$ is $\mathcal{L}\otimes\mathcal{B}$ measurable if $\mathcal{A}$ belongs to the σ-algebra generated by all sets of the form $\mathcal{J}\times\mathcal{D}$ where $\mathcal{J}$ is Lebesgue measurable in J and $\mathcal{D}$ is Borel measurable in $\mathcal{D}$. A subset $\mathcal{A}$ of $L^1(J,E)$ is decomposable if for all $w, v\in\mathcal{A}$ and $\mathcal{J}\subset J$ measurable, $w\mathcal{X}_{\mathcal{J}}+v\mathcal{X}_{J-\mathcal{J}}\in A$, where $\mathcal{X}$ stands for the characteristic function.
Let $F:\mathbb{R}^n\to\mathcal{P}(\mathbb{R}^n)$ be a multivalued operator with nonempty closed values. G is lower semi-continuous (l.s.c) if the set $\{x\in X: F(x)\cap B\neq\emptyset\}$ is open for any open set $B\in\mathbb{R}^n$.

Definition 2.5. *Let Y be a separable metric space and let $N:Y\to P(L^1(J,\mathbb{R}^n))$ be a multivalued operator. We say that N has property (BC) if*

1. *N is lower semi-continuous (l.s.c.);*
2. *N has nonempty closed and decomposable values.*

Let $F:J\times D\to\mathcal{P}(\mathbb{R}^n)$ be a multivalued map with nonempty compact values. Assign to F the multivalued operator

$$F:\Omega\to\mathcal{P}(L^1(J,\mathbb{R}^n))$$

by letting

$$\mathcal{F}(y)=\{g\in L^1(J,\mathbb{R}^n): v(t)\in F(t,y_t)\ for\ a.e.\ t\in J\}.$$

The operator F is called the Niemytzki operator associated to F.

Definition 2.6. *Let $F:J\times\mathbb{R}^n\to\mathcal{P}(\mathbb{R}^n)$ be a multivalued function with nonempty compact values. We say F is of lower semi continuous type (l.s.c. type)if its associated Niemytzky operator $\mathcal{F}$ is lower semi-continuous and has nonempty closed and decomposable values.*

Next we state a selection theorem due to Bressan and Colombo [36].

Theorem 2.7. *Let Y be a separable metric space and let $N:Y\to\mathcal{P}(L^1(J,\mathbb{R}^n))$ be a multivalued operator which has property (BC). Then N has a continuous selection. i.e. there exists a continuous function (single-valued) $\tilde{g}:Y\to L^1(J,\mathbb{R}^n)$ such that $\tilde{g}(y)\in N(y)$ for every $y\in Y$.*

Let us introduce the following hypotheses which are used in the sequel:

($\mathcal{A}_1$) $F:J\times D\to\mathcal{P}(\mathbb{R}^n)$ is nonempty compact valued multivalued map such that

a) $(t,x) \mapsto F(t,x)$ is $\mathcal{L}\otimes\mathcal{B}$ mesurable;

b) $x \mapsto F(t,x)$ is lower semi-continuous for a.e. $t \in J$.

$(\mathcal{A}_2)$ For each $q > 0$, there exists a function $h_q \in L^1(J,\mathbb{R}^+)$ such that

$$\|F(t,x)\|_{\mathcal{P}} \leq h_q(t) \ for\ a.e.\ t\in J \ and \ for\ x \in D \ with\ \|x\|_D \leq q.$$

The following lemma is crucial in the proof of our main theorem.

Lemma 2.8. *[79] Let $F : J\times D \to \mathcal{P}(\mathbb{R}^n)$ be a multivalued map with noneempty, compact values. Assume that $(\mathcal{A}_1) - (\mathcal{A}_2)$ hold. Then f is of l.s.c. type.*

Theorem 2.9. *Suppose that $(\mathcal{H}_2) - (\mathcal{H}_3)$ and $(\mathcal{A}_1) - (\mathcal{A}_2)$ hold. Then the problem (2.1) has at least one solution.*

Proof. $(\mathcal{A}_1)$ and $(\mathcal{A}_2)$ imply by Lemma 2.8 that F is of lower semi-continuous type. Then from Theorem 2.7 there exists a continuous function $f : \Omega \to L^1(J,\mathbb{R}^n)$ such that $f(y) \in \mathcal{F}(y)$ for all $y \in \Omega$. Consider the following problem

$$\begin{array}{ll} \frac{d}{dt}[y(t) - g(t,y_t)] = f(y_t) + \sum_{i=1}^{n_*} y(t-T_i), & \text{a.e } t \in J\backslash\{t_1,\ldots,t_m\} \\ y(t_k^+) - y(t_k^-) = I_k(y(t_k^-)), & k = 1,\ldots,m, \\ y(t) = \phi(t), & t \in [-r,0] \end{array} \quad (2.7)$$

Remark 2.10. *If $y \in \Omega$ is a solution of the problem (2.7), then y is solution to the problem (2.1).*

Consider the operator $N_1 : \Omega \to \Omega$ defined by

$$N_1(y) = \begin{cases} \phi(t), & if\ t\in[-r,0]; \\ \phi(0) + g(t,y_t) - g(0,\phi) + \displaystyle\sum_{0<t_k<t} I_k(y(t_k^-)) & \\ + \displaystyle\int_0^t f(s)ds + \sum_{i=1}^{n_*}\int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*}\int_{-T_i}^0 \phi(s)ds, & if\ t \in J. \end{cases}$$

As in Theorem 2.4, we can prove that the single-valued operator G is compact and there exists $M_* > 0$ such that for all possible solutions y, we have $\|y\|_\Omega < M_*$. Now, we only check that N_1 is continuous. Let $\{y^n : n \in \mathbb{N}\}$ converges to some limit y_* in Ω. Then

$$\begin{aligned} \|N_1(y^n) - N_1(y)\|_\Omega &\leq \|g(.,y^n_.) - g(.,y_.)\|_D + \int_0^b |f(y_s^n) - f(y_s)|ds \\ &+ \sum_{k=1}^m |I_k(y^n(t_k^-)) - I_k(y(t_k^-))|. \end{aligned}$$

Since the functions f and $I_k,\ k = 1,\ldots,m$ are continuous, we have

$$\begin{aligned} \|N_1(y_n) - N_1(y)\|_\Omega &\leq \|g(.,y^n_.) - g(.,y_.)\|_D + \int_0^b |f(y_s^n) - f(y_s)|ds \\ &+ \sum_{k=1}^m |I_k(y_n(t_k^-)) - I_k(y(t_k^-))| \end{aligned}$$

which, by continuity of f and I_k $(k = 1, \dots, m)$, tends to 0, as $n \to \infty$. Let

$$U = \{y \in \Omega : \|y\|_\Omega < M_*\}.$$

From the choice of U, there is no $y \in \partial U$ such that $y = \lambda N_1 y$ for in $\lambda \in (0, 1)$. As a consequence of the nonlinear alternative of the Leray-Schauder type [89], we deduce that N_1 has a fixed point $y \in U$ which is a solution of Problem (2.7), hence a solution to the problem (2.1). $\square$

In this part, we present a second existence result to Problem (2.1) with a nonconvex valued right-hand side. First, consider the Hausdorff pseudo-metric distance

$$H_d\colon\ \mathcal{P}(E) \times \mathcal{P}(E) \longrightarrow \mathbb{R}^+ \cup \{\infty\}$$

defined by

$$H_d(A, B) = \max\left\{\sup_{a\in A} d(a, B),\ \sup_{b\in B} d(A, b)\right\}$$

where $d(A, b) = \inf_{a\in A} d(a, b)$ and $d(a, B) = \inf_{b\in B} d(a, b)$. Then $(\mathcal{P}_{b,cl}(E), H_d)$ is a metric space and $(\mathcal{P}_{cl}(X), H_d)$ is a generalized metric space (see [115]). In particular, H_d satisfies the triangle inequality.

Definition 2.11. *A multi-valued operator $N\colon\ E \to \mathcal{P}_{cl}(E)$ is called*

(a) γ-Lipschitz if there exists $\gamma > 0$ such that

$$H_d(N(x), N(y)) \le \gamma d(x, y), \quad \textit{for each}\ \ x,\ y \in E,$$

(b) a contraction if it is γ-Lipschitz with $\gamma < 1$.

Notice that if N is $\gamma-$Lipschitz, then for every $\gamma' > \gamma$,

$$N(x) \subset N(y) + \gamma' d(x, y)B(0, 1),\ \forall\, x, y \in E.$$

Our proofs are based on the following classical fixed point theorem for contraction multi-valued operators proved by Covitz and Nadler in 1970 [55] (see also Deimling, [59] Theorem 11.1).

Lemma 2.12. *Let (X, d) be a complete metric space. If $G : X \to \mathcal{P}_{cl}(X)$ is a contraction, then $FixN \neq \emptyset$.*

Let us introduce the following hypotheses:

$(\overline{\mathcal{A}}_1)$ $F : J \times D \longrightarrow \mathcal{P}_{cp}(\mathbb{R}^n)$; $t \longmapsto F(t, x)$ is measurable for each $x \in D$.

$(\overline{\mathcal{A}}_2)$ There exists constants c_k, such that

$$|I_k(x) - I_k(y)| \le c_k|x - y|,\ \text{for each}\ k = 1, \dots, m,\ \text{and for all}\ \ x, y \in \mathbb{R}^n.$$

$(\overline{\mathcal{A}}_3)$ There exists a function $l \in L^1(J, \mathbb{R}^+)$ such that

$$H_d(F(t,x), F(t,y)) \leq l(t)|x-y|, \text{ for a.e. } t \in J \text{ and all } x, y \in D,$$

with

$$H_d(0, F(t,0)) \leq l(t), \text{ for a.e. } t \in J,$$

$(\overline{\mathcal{A}}_4)$ There exist $c_* > 0$ such that

$$\|g(t,u) - g(t,u_*)\|_D \leq c_* \|u - u_*\|_D \quad \text{for all } u, u_* \in D, \ t \in J.$$

Theorem 2.13. *Let Assumptions $(\overline{\mathcal{A}}_1) - (\overline{\mathcal{A}}_4)$ be satisfied. If $c_* + \sum_{k=1}^{k=m} c_k < 1$, then Problem (2.1) has at least one solution.*

Proof. In order to transform the problem (2.1) into a fixed point problem, let the multi-valued operator $N : \Omega \to \mathcal{P}(\Omega)$ be as defined in Theorem 2.4. We shall show that N satisfies the assumptions of Lemma 2.12.

(a) $N(y) \in \mathcal{P}_{cl}(\Omega)$ for each $y \in \Omega$. Indeed, let $\{h_n : n \in \mathbb{N}\} \subset N(y)$ be a sequence converge to h. Then there exists a sequence $f_n \in S_{F,y}$ such that

$$h_n(t) = \begin{cases} \phi(t), & if \ t \in [-r, 0]; \\ \phi(0) + g(t, y_t) - g(0, \phi) + \sum_{0<t_k<t} I_k(y(t_k^-)) & \\ + \int_0^t f_n(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds, & if \ t \in J. \end{cases}$$

Since $F(\cdot,\cdot)$ has compact values, let $w(\cdot) \in F(\cdot, 0)$ be a measurable function such that

$$|f(t) - w(t)| = d(g(t), F(t,0)).$$

From $(\overline{\mathcal{A}}_1)$ and $(\overline{\mathcal{A}}_2)$, we infer that for a.e. $t \in [0,b]$

$$\begin{array}{rcl} |f_n(t)| & \leq & |f_n(t) - w(t)| + |w(t)| \\ & \leq & l(t)\|y\|_\Omega + l(t) := \widehat{M}(t), \ \forall n \in \mathbb{N}. \end{array}$$

Then the Lebesgue dominated convergence theorem implies that, as $n \to \infty$,

$$\|f_n - f\|_{L^1} \to 0 \text{ and thus } h_n(t) \to h(t)$$

with

$$h(t) = \begin{cases} \phi(t), & if \ t \in [-r, 0]; \\ \phi(0) + g(t, y_t) - g(0, \phi) + \sum_{0<t_k<t} I_k(y(t_k^-)) & \\ + \int_0^t f(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds, & if \ t \in J, \end{cases}$$

proving that $h \in N(y)$.

(b) There exists $\gamma < 1$, such that

$$H_d(N(y), N(\overline{y})) \leq \gamma \|y - \overline{y}\|_\Omega, \text{ for all } y, \overline{y} \in \Omega.$$

Let $y, \overline{y} \in \Omega$ and $h \in N(y)$. Then there exists $v(t) \in F(t, y_t)$, so that

$$\begin{aligned} h(t) &= \phi(0) + g(t, y_t) - g(0, \phi) + \sum_{i=1}^{n_*} \int_{-T_i}^{0} \phi(s) ds + \int_0^t v(s)\, ds \\ &\quad + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s) ds + \sum_{0<t_k<t} I_k(y(t_k^-)). \end{aligned}$$

From $(\overline{\mathcal{A}}_3)$, it follows that

$$H_d(F(t, y_t), F(t, \overline{y}_t)) \leq l(t) \|y_t - \overline{y}_t\|_{\mathcal{D}}.$$

Hence, there is $w \in F(t, \overline{y}_t)$ such that

$$|v(t) - w| \leq l(t) \|y_t - \overline{y}_t\|_D, \quad t \in J.$$

Consider $U : J \to \mathcal{P}(\mathbb{R}^n)$, given by

$$U(t) = \{w \in \mathbb{R}^n : |v(t) - w| \leq l(t) \|y_t - \overline{y}_t\|_D\}.$$

Since the multivalued operator $V(t) = U(t) \cap F(t, \overline{y}_t)$ is measurable (see [11, 47, 91]), by Lemma 1.72, there exists a function $\overline{v}(t)$, which is a measurable selection for V. Thus $\overline{v}(t) \in F(t, \overline{y}_t)$ and

$$|v(t) - \overline{v}(t)| \leq l(t) \|y_t - \overline{y}_t\|_D, \text{ for a.e. } t \in J.$$

Let us define for a.e. $t \in J$

$$\begin{aligned} \overline{h}(t) &= \phi(0) + g(t, \overline{y}_t) - g(0, \phi) + \sum_{i=1}^{n_*} \int_{-T_i}^{0} \phi(s) ds \\ &+ \int_0^t \overline{v}(s)\, ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} \overline{y}(s) ds + \sum_{0<t_k<t} I_k(\overline{y}(t_k^-)). \end{aligned}$$

Then we have

$$\begin{aligned}
|h(t)-\overline{h}(t)| &\le \int_0^t |v(s)-\overline{v}(s)|\,ds + \sum_{k=1}^{n_*}\int_0^{t-T_i} |y(s)-\overline{y}(s)|ds \\
&+ \sum_{0<t_k<t} |I_k(y(t_k^-)) - I_k(\overline{y}(t_k^-))| + \|g(t,y_t)-g(t,\overline{y}_t)\|_D \\
&\le \int_0^t l(s)\|y_s-\overline{y}_s\|_{\mathcal{D}} ds + n_*\int_0^t |y(s)-\overline{y}(s)|ds \\
&+ \sum_{0<t_k<t} c_k|y(t_k)-\overline{y}(t_k)| + c_*\|y_t-\overline{y}_t\|_D \\
&\le \int_0^t l(s)e^{\tau L(s)}ds\|y-\overline{y}\|_* + \int_0^t n_* e^{\tau L(s)}ds\|y-\overline{y}\|_* \\
&+ \sum_{0<t_k<t} c_k e^{\tau L(t)}\|y-\overline{y}\|_* + e^{\tau L(t)}c_*\|y-\overline{y}\|_* \\
&\le \int_0^t \frac{1}{\tau}(e^{\tau L(s)})' ds\|y-\overline{y}\|_* + \left(c_* + \sum_{k=1}^m c_k\right) e^{\tau L(t)}\|y-\overline{y}\|_* \\
&\le e^{\tau L(t)}\left(c_* + \frac{1}{\tau} + \sum_{k=1}^m c_k\right)\|y-\overline{y}\|_*.
\end{aligned}$$

Thus

$$e^{-\tau L(t)}|h(t)-\overline{h}(t)| \le \left(c_* + \frac{1}{\tau} + \sum_{k=1}^m c_k\right)\|y-\overline{y}\|_*,$$

where $L(t) = \int_0^t l^*(s)ds$ and

$$l^*(t) = \begin{cases} 0, & t\in[-r,0], \\ l(t)+n_*, & t\in[0,b], \end{cases}$$

and τ is sufficiently large and $\|\cdot\|_*$ is the Bielecki-type norm on Ω defined by

$$\|y\|_* = \sup\{e^{-\tau L(t)}|y(t)| : -r\le t\le b\}.$$

By an analogous relation, obtained by interchanging the roles of y and $\overline{y}$, it follows that

$$H_d(N(y),N(\overline{y})) \le \left(c_* + \frac{1}{\tau} + \sum_{k=1}^m c_k\right)\|y-\overline{y}\|_* \text{ for all } y,\overline{y}\in\Omega.$$

So, N is a contraction. and thus, by Lemma 2.12, N has a fixed point y, which is a solution to (2.1). □

2.3 Topological structure of solutions set

In this section we prove that the solutions set of Problem (2.1) is compact and the operator solution is u.s.c.

Theorem 2.14. *Under assumptions of Theorem 2.4, the solution set for problem (2.1) is compact, and the operator solution $S(.) : D \to \mathcal{P}(\Omega)$ defined by*

$$S(\phi) = \{y \in \Omega |\ y \ solution\ of\ (2.1)\}$$

is u.s.c.

Proof. Compactness of the solution set. Let $\phi \in D$, then

$$S(\phi) = \{y \in \Omega : y \text{ is a solution of problem } (2.1)\}.$$

From Step 5 of Theorem 2.4, there exists $\widetilde{M}$ such that for every $y \in S(\phi)$, $\|y\|_\Omega \leq \widetilde{M}$. Since N is completely continuous, $N(S(\phi))$ is relatively compact in Ω. Let $y \in S(\phi)$; then $y \in N(y)$ hence $S(\phi) \subset \overline{N(S(\phi))}$ where N is defined in the proof of Theorem 2.4. It remains to prove that $S_F(a)$ is a closed subset in Ω. Let $\{y_n : n \in \mathbb{N}\} \subset S(\phi)$ be such that $(y^n)_{n\in\mathbb{N}}$ converges to y. For every $n \in \mathbb{N}$, there exists v_n such that $v_n(t) \in F(t, y^n_t)$, a.e. $t \in J$ and

$$y^n(t) = \begin{cases} \phi(t), & if\ t \in [-r, 0], \\ \phi(0) + g(t, y^n_t) - g(0, \phi) + \displaystyle\sum_{i=1}^{n_*} \int_{-T_i}^{0} \phi(s)ds & \\ + \displaystyle\int_0^t v^n(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y^n(s)ds + \sum_{0<t_k<t} I_k(y^n(t_k^-)), & if\ t \in J. \end{cases}$$

As in Theorem 2.4 Step 3, we can prove that there exists v such that $v(t) \in F(t, y_t)$ and

$$y(t) = \begin{cases} \phi(t), & if\ t \in [-r, 0], \\ \phi(0) + g(t, y_t) - g(0, \phi) + \displaystyle\sum_{i=1}^{n_*} \int_{-T_i}^{0} \phi(s)ds & \\ + \displaystyle\int_0^t v(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{0<t_k<t} I_k(y(t_k^-)), & if\ t \in J. \end{cases}$$

Therefore $y \in S(\phi)$ which yields that $S(\phi)$ is closed, hence compact subset in Ω.

We will show that $S(.)$ is u.s.c. by proving that the graph

$$\Gamma(\varphi) := \{(y, \varphi) \in \Omega \times D |\ y \in S(\varphi)\}$$

of $S(\varphi)$ is closed. Let$(y^n, \varphi^n) \in \Gamma(\varphi)$, i.e., $y^n \in S(\varphi^n)$, and let $(y^n, \varphi^n) \to (y, \varphi)$

as $n \to \infty$. Since $y^n \in S(\varphi^n)$, there exists $v^n \in L^1(J, \mathbb{R}^n)$ such that

$$y^n(t) = \begin{cases} \phi(t), & if\ t \in [-r, 0], \\ \phi(0) + g(t, y^n_t) - g(0, \phi) + \displaystyle\sum_{i=1}^{n_*} \int_{-T_i}^{0} \phi(s) ds & \\ + \displaystyle\int_0^t v^n(s) ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y^n(s) ds + \sum_{0<t_k<t} I_k(y^n(t_k^-)), & if\ t \in J. \end{cases}$$

Using the fact that (y^n, φ^n) converge to (y, φ), there exists $M > 0$ such that

$$\|\varphi^n\|_D \leq M\ for\ all\ n \in \mathbb{N}.$$

As in Theorem 2.1, we can prove that there exist $\overline{M} > 0$ such that

$$\|y^n\|_\Omega \leq \overline{M}\ for\ all\ n \in \mathbb{N}.$$

By $(\mathcal{H}_2)$, we have,

$$|v^n(t)| \leq p(t)\psi(M),\ t \in J$$

Thus, $v^n(t) \in p(t)\psi(M)\bar{B}(0,1) := \chi(t)$ a.e. $t \in J$. It is clear that $\chi : J \to \mathcal{P}_{cp,cv}(\mathbb{R}^n)$ is a multivalued map that is integrable bounded. Since $\{v^n(.) : n \geq 1\} \in \chi(.)$, we may pass to a subsequence if necessary to obtain that v^n converges to v in $L^1(J, \mathbb{R}^n)$.

It remains to prove that $v \in F(t, y_t)$, for a.e. $t \in J$. Lemma **??** yields the existence of $\alpha_i^n \geq 0,\ i = n, \ldots, k(n)$ such that $\sum_{i=1}^{k(n)} \alpha_i^n = 1$ and the sequence of convex combinations $g_n(\cdot) = \sum_{i=1}^{k(n)} \alpha_i^n v_i(\cdot)$ converges strongly to v in L^1. Since F takes convex values, using Lemma 1.61, we obtain that

$$\begin{array}{rcl} v(t) & \in & \bigcap_{n\geq 1} \overline{\{g_n(t)\}}, \quad \text{a.e. } t \in J \\ & \subset & \bigcap_{n\geq 1} \overline{co}\{v_k(t),\ k \geq n\} \\ & \subset & \bigcap_{n\geq 1} \overline{co}\{\bigcup_{k\geq n} F(t, y_t^k)\} \\ & = & \overline{co}(\limsup_{k\to\infty} F(t, y_t^k)). \end{array} \tag{2.8}$$

Since F is u.s.c. with compact values, then by Lemma 1.60, we have

$$\limsup_{n\to\infty} F(t, y_t^n) = F(t, y_t), \quad \text{for a.e. } t \in J.$$

This with (2.8) imply that $v(t) \in \overline{co}\, F(t, y_t)$. Since $F(.,.)$ has closed, convex values, we deduce that $v(t) \in F(t, y_t)$, for a.e. $t \in J$.

Let

$$z(t)=\begin{cases}\phi(t), & if\ t\in[-r,0],\\ \phi(0)+g(t,y_t)-g(0,\phi)+\displaystyle\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds & \\ +\displaystyle\int_0^t v(s)ds+\sum_{i=1}^{n_*}\int_0^{t-T_i}y(s)ds+\sum_{0<t_k<t}I_k(y(t_k^-)), & if\ t\in J.\end{cases}$$

Since the functions I_k, $k=1,\dots,m$ are continuous, we obtain the estimates

$$\|y^n-z\|_\Omega\leq\|g(t,y_t^n)-g(t,y_t)\|_D+\int_0^b|\bar{v}^n(s)-v(s)|ds$$

$$+\sum_{k=1}^{m}|I_k(y^n(t_k))-I_k(y(t_k))|+\sum_{i=1}^{n_*}\int_0^{t-T_i}|y^n(s)-y(s)|ds.$$

The right-hand side of the above expression tends to 0 as $n\to+\infty$. Hence,

$$y(t)=\begin{cases}\phi(t), & if\ t\in[-r,0],\\ \phi(0)+g(t,y_t)-g(0,\phi)+\displaystyle\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds & \\ +\displaystyle\int_0^t v(s)ds+\sum_{i=1}^{n_*}\int_0^{t-T_i}y(s)ds+\sum_{0<t_k<t}I_k(y(t_k^-)), & if\ t\in J.\end{cases}$$

Thus, $y\in S(\varphi)$, Now show that $S(\varphi)$ maps bounded sets into relatively compact sets of Ω. Let B be a compact set in $\mathbb{R}^n$ and let $\{y^n\}\subset S(B)$. Then there exist $\{\varphi^n\}\subset B$ such that $y^n\in S(\varphi^n)$. Since $\{\varphi^n\}$ is a compact sequence, there exists a subsequence of $\{\varphi^n\}$ converging to φ, so from $(\mathcal{H}_2)$, there exists $M_*>0$ such that

$$\|y^n\|_\Omega\leq M_*,\ n\in\mathbb{N}.$$

We can show that $\{y^n : n\in\mathbb{N}\}$ is equicontinous in Ω. As a consequence of the Arzelá-Ascoli Theorem, we conclude that there exists a subsequence of $\{y^n\}$ converging to y in Ω. By a similar argument to the one above, we can prove that

$$y(t)=\begin{cases}\phi(t), & if\ t\in[-r,0],\\ \phi(0)+g(t,y_t)-g(0,\phi)+\displaystyle\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds & \\ +\displaystyle\int_0^t v(s)ds+\sum_{i=1}^{n_*}\int_0^{t-T_i}y(s)ds+\sum_{0<t_k<t}I_k(y(t_k^-)), & if\ t\in J,\end{cases}$$

where $v\in S_{F,y}$. Thus $y\in S(\varphi)$. This implies that $S(\varphi)$ is u.s.c. □

In this part, we show that the solution set of Problem (2.1) is AR.

Definition 2.15. *A space X is called an absolute retract (in short $X \in AR$) provided that for every space Y, every closed subset $B \subseteq Y$ and any continuous map $f : B \to X$, there exists a continuous extension $\widetilde{f} : Y \to X$ of f over Y, i.e. $\widetilde{f}(x) = f(x)$ for every $x \in B$. In other words, for every space Y and for any embedding $f : X \longrightarrow Y$, the set $f(X)$ is a retract of Y.*

Proposition 2.16. *[151] Let C be a closed, convex subset of a Banach space E and let $N : C \to \mathcal{P}_{cp,cv}(C)$ be a contraction multivalued map. Then $Fix(N)$ is a nonempty, compact AR-space.*

Our contribution is the following:

Theorem 2.17. *Let $F\colon J \times D \to \mathcal{P}_{cp,cv}(\mathbb{R}^n)$ be multivalued. Assume that all conditions of Theorem 2.13 are satisfied. Then the solution set $S_{[-r,b]}(\phi) \in AR$.*

Proof. Let the multi-valued operator $N : \Omega \to \mathcal{P}(\Omega)$ be as defined in Theorem 2.4. Using the fact that $F(.,.)$ has a convex and compact values and by $(\overline{\mathcal{A}}_1) - (\overline{\mathcal{A}}_2)$, then for every $y \in \Omega$ we have $N(y) \in \mathcal{P}_{cv,cp}(\Omega)$. By some Bielecki-type norm on Ω we can prove that N is contraction. Hence, from proposition 2.16, the solution set $S_{[-r,b]}(\phi) = Fix(N)$ is a nonempty, compact AR-space. □

2.4 The parameter-dependant case

In this section, we consider the following parameter impulsive problem:

$$\begin{cases} \dfrac{d}{dt}[y(t) - g(t, y_t)] \in F(t, y_t, \lambda) + \displaystyle\sum_{i=1}^{n_*} y(t - T_i) & \text{a.e } t \in J\backslash\{t_1, \dots, t_m\} \\ y(t_k^+) - y(t_k^-) = I_k(y(t_k^-), \lambda), & k = 1, \dots, m, \\ y(t) = \phi(t), & t \in [-r, 0], \end{cases} \tag{2.9}$$

where $n_* \in \{1, 2, \dots\}$, $r = \max_{1\le i\le n_*} T_i$, $F : J \times D \times \Lambda \to \mathcal{P}_{cp}(\mathbb{R}^n)$ is a multi-valued map with compact values, $I_k(.,.) : \mathbb{R}^n \times \Lambda \to \mathbb{R}^n$, $k = 1, 2, \dots, m$, are continuous functions, (Λ, d_Λ) is a complete metric space.

In the case with no impulses, some existence results and properties of solutions for semilinear and evolutions differential inclusions with parameters were studied by Hu *et al* [109], Papageorgiou and Yannakakis [146] and Tolstonogov [160, 161]; see also [12] for a parameter-dependant first-order Cauchy problem. Very recently the parameter problems of impulsive differential inclusions was studies by Djebali *et al* [62], Graef and Ouahab [93].

2.4.1 The convex case

We will assume the following assumptions.

$(\widetilde{\mathcal{B}}_1)$ The multi-valued map $F(., x, \lambda) : [0, b] \to \mathcal{P}_{cp,cv}(\mathbb{R}^n)$ is measurable for all $x \in \mathbb{R}^n$ and $\lambda \in \Lambda$.

($\widetilde{\mathcal{B}}_2$) The multi-valued map $F(t,.,.): D \times \Lambda \to \mathcal{P}_{cp,cv}(\mathrm{I\!R}^n)$ is u.s.c. for a.e. $t \in [0,b]$.

($\widetilde{\mathcal{B}}_3$) There exists$\alpha \in [0,1)$ and $p, q \in L^1(J, \mathrm{I\!R}_+)$ such that

$$\|F(t,x,\lambda)\|_{\mathcal{P}} \leq p(t)\psi(\|x\|_D), \text{ for a.e. } t \in J \text{ and for all } x \in E, \ \lambda \in \Lambda.$$

Theorem 2.18. *Assume that F satisfies ($\widetilde{\mathcal{B}}_1$) − ($\widetilde{\mathcal{B}}_3$). Then for every fixed $\lambda \in \Lambda$, there exists $y(.,\lambda) \in \Omega$ solution of Problem (2.9).*

Proof. For fixed $\lambda \in \Lambda$, let $F_\lambda(t, y_t) = F(t, y_t, \lambda)$, $(t, y_t) \in [0,b] \times \mathrm{I\!R}^n$ and let $I_k^\lambda(y) = I_k(y,\lambda)$, $k = 1,\dots,m$. It is clear that $F_\lambda(.,u)$ is a measurable multi-valued map for all $u \in \mathrm{I\!R}^n$, $F_\lambda(t,.)$ is u.s.c and

$$\|F_\lambda(t,x)\|_{\mathcal{P}} \leq p(t)\psi(\|x\|_D) \text{ for a.e. } t \in J \text{ and each } x \in D,$$

where $p \in L^1(J, \mathrm{I\!R}^+)$ are as defined in ($\widetilde{\mathcal{B}}_3$). To transform Problem (2.9) into a fixed point problem, consider the operator $N : \Omega \to \mathcal{P}(\Omega)$ defined by:

$$N(y) = \left\{ h \in \Omega : h(t) = \left\{ \begin{array}{ll} \phi(t), & if\ t \in [-r,0]; \\ \phi(0) + g(t,y_t) - g(0,\phi) + \sum_{0<t_k<t} I_k(y(t_k^-),\lambda) + \int_0^t v(s)ds & \\ + \sum_{i=1}^{n_*} \int_0^{t-T_i} y(s)ds + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds, & if\ t \in J, \end{array} \right. \right\}$$

where $v \in S_{F,y}$. Clearly, the fixed points of the operator N are solution of the problem (2.9).
Define the mapping

$$S : \Lambda \to \mathcal{P}_{cp}(\mathrm{I\!R}^n),$$

by

$$S(\lambda) = \{y \in \Omega : y \text{ is a solution of Problem } (2.9)\}.$$

From Theorem 2.4, $S(\lambda) \neq \emptyset$ so that S is well defined. Next, we prove the upper semi-continuity of solutions in respect of the parameter λ. □

Proposition 2.19. *If hypotheses ($\widetilde{\mathcal{B}}_1$) − ($\widetilde{\mathcal{B}}_3$) hold, then S is u.s.c.*

Proof.

Step 1. $S(.) \in \mathcal{P}_{cp}(\mathrm{I\!R}^n)$. Let $\lambda \in \Lambda$ and $y_n \in S(\lambda)$, $n \in \mathrm{I\!N}$. Then there exists $v_n \in S_{F_\lambda, y_n}$ such that

$$y_n(t) = \left\{ \begin{array}{ll} \phi(t), & if\ t \in [-r,0], \\ \phi(0) + g(t,(y_n)_t) - g(0,\phi) + \sum_{i=1}^{n_*} \int_{-T_i}^0 \phi(s)ds & \\ + \int_0^t v_n(s)ds + \sum_{i=1}^{n_*} \int_0^{t-T_i} y_n(s)ds + \sum_{0<t_k<t} I_k(y_n(t_k^-),\lambda), & if\ t \in J. \end{array} \right.$$

From $(\widetilde{\mathcal{B}}_3)$ and the continuity of $I_k,\ k=1,\dots,m$, we can prove that there exists $M>0$ such that $\|y_n\|_\Omega \le M,\ n\in\mathbb{N}$. As in the proof of Theorem 2.4, Steps 2 to 3, we can easily prove that the set $\{y_n : n\ge 1\}$ is compact in Ω; hence there exists a subsequence of $\{y_n\}$ which converges to y in Ω. Since $\{v_n\}(t)$ is integrably bounded, then arguing as in the proof of Theorem 2.14, there exists a subsequence which converges weakly to v and then we obtain at the limit:

$$y(t)=\begin{cases}\phi(t), & if\ t\in[-r,0],\\ \phi(0)+g(t,y_t)-g(0,\phi)+\displaystyle\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds & \\ +\displaystyle\int_0^t v(s)ds+\sum_{i=1}^{n_*}\int_0^{t-T_i}y(s)ds+\sum_{0<t_k<t}I_k(y(t_k^-),\lambda), & if\ t\in J.\end{cases}$$

Hence $S(.)\in\mathcal{P}_{cp}(\mathbb{R}^n)$.

Step 2. $S(.)$ is quasicompact. Let K be a compact set in Λ. To show that $\overline{S(K)}$ is compact, let $y_n\in S(\lambda_n),\ \lambda_n\in K$. Then there exists $v_n\in S_{F(.,.,\lambda_n,y_n)},\ n\in\mathbb{N}$, such that

$$y_n(t)=\begin{cases}\phi(t), & if\ t\in[-r,0],\\ \phi(0)+g(t,(y_n)_t)-g(0,\phi)+\displaystyle\sum_{i=1}^{n_*}\int_{-T_i}^{0}\phi(s)ds & \\ +\displaystyle\int_0^t v_n(s)ds+\sum_{i=1}^{n_*}\int_0^{t-T_i}y_n(s)ds+\sum_{0<t_k<t}I_k(y(t_k^-),\lambda_n), & if\ t\in J.\end{cases}$$

As mentioned in Step 1, $\{y_n : n\ge 1\}$, is compact in Ω then there exists a subsequence of $\{y_n\}$ which converges to y in Ω. Since K is compact, there exists a subsequence $\{\lambda_n : n\ge 1\}$ in K such that λ_n converges to $\lambda\in\Lambda$. As we did above, we can easily prove that there exists $v(\cdot)\in F(\cdot,y_\cdot),\lambda)$ such that y satisfies (2.10).

Step 3. $S(.)$ is closed. For this, let $\lambda_n\in\Lambda$ be such that λ_n converge to λ and let $y_n\in S(\lambda_n),\ n\in\mathbb{N}$ be a sequence which converges to some limit y in Ω. Then y_n satisfies (2.10) and as we did above, we can use $(\widetilde{\mathcal{B}}_3)$ to show that the set $\{y_n : n\ge 1\}$ is equicontinuous in Ω. Hence, by the Arzelá-Ascoli Theorem, we conclude that there exists a subsequence of $\{y_n\}$ converging to some limit y in Ω and there exists a subsequence of $\{v_n\}$ which converges to $v(.)\in F(.,y_.),\lambda)$ such that y satisfies (2.10). Therefore $S(.)$ has a closed graph, hence u.s.c. by Lemma 1.89. □

2.5 Conclusion

In this Chapter we have extended some existence results of solutions for Problem (2.1) obtained in [142, 143] to the case of differential inclusions; moreover the right-hand side multi-valued nonlinearity may be either convex or nonconvex.

this complement is based on the nonlinear alternative of Leary Schauder type (in the convex case), on the Bressan-Colombo selection theorem and on the Covitz and Nadler fixed point theorem for contraction multi-valued maps in a generalized metric space (in the nonconvex case). Compactness of the solution set and some geometric properties are also provided. We have also discusses the question of dependance on parameters. The next chapter is devoted to give an application of the obtained results, to a problem from control theory.

Chapter 3

Application to Control Theory

Many problems in applied mathematics, such as those in control theory, mathematical biologic, economics, and mechanics, lead to the study of differential inclusions. In a differential inclusion the tangent at each state is prescribed by a multifunction instead of the usual single-value function in differential equations. For single-valued functions the controllability may be described by nonlinear differential equations of the form

$$\left\{\begin{array}{rcl} y'(t) &=& f(t, y(t), u(t)), \quad t \in \mathbb{R}_+, \\ y(0) &=& a, \\ u &\in& U, \end{array}\right. \tag{3.1}$$

with constrained control u. Here $f : \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ is a single-valued function measurable in t and continuous in y, u. The time-varying set of constraints function $U : [0, 1] \to \mathcal{P}_{cp}(\mathbb{R})$ is a measurable multi-valued function. By $u \in U$, we mean $u(t) \in U(t)$, for a.e. $t \in J$. Problem (3.1) is solved if there is a control function u for which the problem admits a solution. If we define the multifunction

$$F(t, x) = \{f(t, x, u), \ u \in U\}, \tag{3.2}$$

then Filippov [73] and Ważewski [167] have shown that under some assumptions the control problem (3.1) coincides with the set of Carathéodory solution of the following problem

$$\left\{\begin{array}{rcl} y'(t) &\in& F(t, y(t)), \quad t \in \mathbb{R}_+, \\ y(0) &=& a, \\ u &\in& U, \end{array}\right. \tag{3.3}$$

with right-hand side given by (3.2).

The controllability of ordinary differential equations and inclusions were investigated by many authors (see [13, 22, 76, 32, 115] for instance and the references therein).

And impulsive differential equations and inclusions dealing with control theory were investigated by [4, 25, 95]. Indeed, the first motivation of the study of the concept of differential inclusions comes from the development of some studies in control theory. For more information about the relation between the differential inclusions and control theory, see for instance [11, 77, 116, 156, 159] and the references therein.

Hereafter, we apply the existence results and structure topology and geometry obtained in Sections 3 and 4 to study the impulsive neutral problem, that is Problem (2.1):

$$\begin{cases} \dfrac{d}{dt}[y(t)-g(t,y_t)] \in F(t,y_t) + \displaystyle\sum_{i=1}^{n_*} y(t-T_i), & t\in J\backslash\{t_1,\dots,t_m\} \\ y(t_k^+)-y(t_k^-) = I_k(y(t_k)), & k=1,\dots,m \\ y(t)=\phi(t) & t\in[-r,0] \end{cases} \tag{3.4}$$

with F given by (3.2), $I_k:\mathbb{R}\to\mathbb{R},\ x\to I_k(x)=b_kx,\ \ b_k\in\mathbb{R},\ k=1,\dots,m,$ $J=:[0,1]$ and $g: J\times D\to\mathbb{R}$ is a continuous function $0<t_1<t_2\ldots<t_m<1,\ T_i\in\mathbb{R}_+,\ i=1,\dots,n_*,\ r=\max\limits_{1\le i\le n_*} T_i$.

We need the following auxiliary result in order to prove our main controllability theorem.

Theorem 3.1. *[11] Let $(\Omega,\mathcal{A},\mu)$ be a complete $\sigma-$finite measurable space, X a complete separable metric space and $F:\Omega\to\mathcal{P}(X)$ a measurable set value map with closed images. Consider a Carathéodory set-valued map G from $\Omega\times X$ to a complete separable metric space Y. Then, the map*

$$\Omega\ni\omega\to\overline{G(\omega,F(\omega))}\in\mathcal{P}(Y)$$

is measurable.

Next, we state our main existence result

Theorem 3.2. *Assume that U and f satisfy the following hypotheses:*

($\overline{\mathcal{H}}1$) *$U: J\to\mathcal{P}_{cv,cp}(\mathbb{R}_+)$ is a measurable multi-function and has compact image.*

($\overline{\mathcal{H}}2$) *The function f is linear in the third argument, i.e. there exist Carathéodory functions $f_i: J\times D\to\mathbb{R}$ $(i=1,2)$ such that for a.e. $t\in J$,*

$$f(t,x,u)=f_1(t,x)u+f_2(t,x),\ \forall\,(x,u)\in D\times U.$$

($\overline{\mathcal{H}}3$) *There exist $k \in L^1(J,(0,+\infty))$ and a continuous nondecreasing function ψ such that*

$$|f(t,x,u)| \le k(t)\psi(\|x\|_D),\ \textit{for a.e.}\ \ t \in J, \forall\, x \in D \ \textit{and}\ \forall\, u \in U$$

with

$$\int_0^b k(s)ds < \int_0^\infty \frac{ds}{s+\psi(s)}.$$

($\overline{\mathcal{H}}4$) *For every $M > 0$, there exists $\epsilon > 0$ and a function $R:\ [0,\epsilon] \to \mathrm{I\!R}_+$ with $\lim_{h\to 0} R(h) = 0$, such that for every $y \in \Omega$ satisfying $\|y\|_\Omega \le M$, we have*

$$|g(t,y_t) - g(s,y_s)| \le R(|t-s|)\ \textit{with}\ |t-s| < \epsilon.$$

and there exists $c_* > 0$ such that

$$|g(t,u)| \le c(\|u\|_D + 1), \textit{for every}\ u \in D.$$

Then the control boundary value problem (3.1) has at least one solution.

Proof. • **Claim 1.** Since $U(.)$ is measurable, we can find $u_n : [0,1] \to \mathrm{I\!R},\ n \ge 1$ Lebesgue measurable functions such that

$$U(t) = \overline{\{u_n(t):\ n \ge 1\}} \text{for all } t \in [0,1].$$

From ($\overline{\mathcal{H}}2$) and ($\overline{\mathcal{H}}3$) we have

$$F(t,y_t) = \overline{\{f_1(t,y_t)u_n(t) + f_2(t,y_t):\ n \ge 1\}} \text{for all } t \in [0,b].$$

This implies that the map $t \to F(t,.)$ is a measurable multifunction. By ($\overline{\mathcal{H}}3$) and ($\overline{\mathcal{H}}4$), we have that $F(.,.) \in \mathcal{P}_{cv}(\mathrm{I\!R})$. Using the compactness of U and the continuity of f, we can easily show that $F(.,.) \in \mathcal{P}_{cp}(\mathrm{I\!R})$; then $F(.,.) \in \mathcal{P}_{cp,\,cv}(\mathrm{I\!R})$.

• **Claim 2.** The selection set of F is not empty. Since U is measurable multifunction and has compact image then $\overline{F(t,x)} = F(t,x)$. Let $x \in \mathrm{I\!R}$ then from ($\overline{\mathcal{H}}1$) – ($\overline{\mathcal{H}}3$) the map $(t,u) \to f(t,x,u)$ is L^1-Carathéodory. Hence from Theorem 3.1 $F(.,x)$ is measurable.

• **Claim 3.** Using the fact that U has a compact image and f is an L^1-Carathéodory function, hence we can easily show that $F(t,.)$ is u.s.c. (see [63] Thm 6.3(claim 3)).

• **Claim 4.** Let B be bounded set in Ω, then there exists $M_* > 0$ such that

$$\|u\|_D \le M_*, \quad \text{for every } u \in B.$$

Then

$$|g(t,u)| \le c(M_* + 1),\ \text{for every } u \in B.$$

The first part of the condition $(\overline{\mathcal{H}}4)$, implies that

$$\{t \to g(t, y_t) : \|y\|_\Omega \leq c(M_* + 1)\}$$

is equicontinouous. Therefore all conditions of Theorems 2.4, 2.14 are fulfilled and then Problem (3.4) has at least one solution and solution set is compact. □

The following auxiliary lemma is concerned with measurability for two-variable multi-function:

Lemma 3.3. *[107] Let (Ω, A) be a measurable space, X, Y two separable metric spaces and let $F : \Omega \times X \to \mathcal{P}_{cl}(Y)$ be a multi-function such that*

- *(i) for every $x \in X$, $\omega \to F(\omega, x)$ is measurable,*
- *(ii) for a.e. $\omega \in \Omega$, $x \to F(\omega, x)$ is continuous or H_d-continuous.*

Then the mapping $(\omega, x) \to F(\omega, x)$ is measurable.

Our contribution is the following

Theorem 3.4. *Assume that U and f satisfy the following hypotheses:*

$(\overline{\mathcal{H}}5)$ *$U : J \to \mathcal{P}_{cp}(\mathrm{I\!R})$ is a measurable multi-function.*

$(\overline{\mathcal{H}}6)$ *There exists $k \in L^1(J, (0, +\infty))$ such that*

$$|f(t, x, u) - f(t, y, u)| \leq k(t)\|x - y\|_D, \text{ for a.e. } t \in J, \forall\, x \in D \text{ and } \forall\, u \in U.$$

$(\overline{\mathcal{H}}7)$ *There exists $p \in L^1(J, (0, +\infty))$ such that*

$$|f(t, x, u)| \leq p(t), \text{ for a.e. } t \in J, \forall\, x \in \mathrm{I\!R} \text{ and } \forall\, u \in U.$$

$(\overline{\mathcal{H}}8)$ *there exists $c_* \in (0, 1)$ such that*

$$|g(t, x) - g(t, z)| \leq c_*\|x - z\|_D \text{ for all } x, z \in D.$$

If $c_* + \sum_{i=1}^{m} |b_k| < 1$. Then the solution set of Problem (3.1) is not empty.

Proof. Clearly, $F(., x)$ is measurable multi-function for any fixed x and $F(., .) \in \mathcal{P}_{cp}(\mathrm{I\!R})$. To prove that $F(t, .)$ is a k-Lipschitz, let $x, y \in D$ and $h \in F(t, x)$. Then there exists $u \in U$ such that $h(t) = f(t, x, u)$. From $(\overline{\mathcal{H}}7)$, we get successively the estimates

$$\begin{aligned} d(h, F(t, y)) &= \inf_{z \in F(t,y)} |h - z| \\ &= \inf_{v \in U} |f(t, x, u) - f(t, y, v)| \\ &\leq |f(t, x, u) - f(t, y, u)| \\ &\leq k(t)\|x - y\|_D. \end{aligned}$$

By an analogous relation obtained by interchanging the roles of x and y, we find that for each $l \in F(t,y)$, it holds that

$$d(F(t,x),l) \leq k(t)\|x-y\|_D$$

and hence

$$H_d(F(t,x),F(t,y)) \leq k(t)\|x-y\|_D, \text{ for each } x,y \in \mathbb{R}.$$

So, $F(t,.)$ is a k-Lipschitz. Therefore $F(t,.)$ is H_d-continuous and from Lemma 3.3, the two-variable multi-function $(t,x) \mapsto F(t,x)$ is $\mathcal{L} \otimes \mathcal{B}$ measurable. Then Aumann's selection theorem (see Wagner [164] Theorem 5.10), implies the existence of a measurable selection, hence $S_{F,y}$ has nonempty.

Then $F(t,.)$ is in fact *u.s.c.* (see [59], Proposition 1.1). Finally, notice that $F(t,0)$ is integrably bounded by $(\overline{\mathcal{H}}7)$. Consequently, all the conditions of Theorem 2.13 are met and the solution set of Problem 3.4 is not empty. □

Remark 3.5. *If $F(.,.) \in \mathcal{P}_{cv}(\mathbb{R})$, then under the condition of Theorem 3.4 the solution set of Problem 3.4 is AR-space (see Theorem 2.17).*

Conclusion

In this Chapter we have extended some existence results of solutions for Problem (2.1) obtained in [142, 143] to the case of differential inclusions; moreover the right-hand side multi-valued nonlinearity may be either convex or nonconvex.
this complement is based on the nonlinear alternative of Leary Schauder type (in the convex case), on the Bressan-Colombo selection theorem and on the Covitz and Nadler fixed point theorem for contraction multi-valued maps in a generalized metric space (in the nonconvex case). Compactness of the solution set and some geometric properties are also provided. We have also discusses the question of dependance on parameters. An applications to a problem from control theory are provided.

Next part is dedicated to the analysis of a new model describing the evolution of populations constituted by normal cells, sensitive and resistant tumor cells, under periodic chemotherapeutic treatment.

Part II

Contribution to the study of an impulsive differential equations from cancer treatment problem by chemotherapy: cellular scale

Chapter 4

Local Theory

In this chapter, we recall some classical theorems on steady state bifurcations, including the Lyapunov-Schmidt procedure and bifurcation theorems from eigenvalues of odd multiplicity.

The version of the Lyapunov-Schmidt procedure presented here differs slightly from the one given in [132]. The latter is done by decomposing the space into the direct sum of the generalized eigenspace and its complement. While the Lyapunov-Schmidt procedure given here is based on the decomposition of the space into the direct sum of the eigenspace and its complement. This Lyapunov-Schmidt procedure is more natural, and much more convenient to study steady state bifurcations. In fact, it is this difference, together with other ingredients, including in particular the spectral theorem (see Chapter 3 [132]), that made many problems more accessible.

4.1 The Implicit Function Theorem

One of the most important analytic tools for the solution of a nonlinear problem

$$F(x, y) = 0, \tag{4.1}$$

where F is a mapping $F : U \times V \to Z$ with open sets $U \subset X$, $V \subset Y$, and where X, Y, Z are (real) Banach spaces, is the following Implicit Function Theorem:

Theorem 4.1. *([114]) Let (4.1) have a solution $(x_0, y_0) \in U \times V$ such that the Fréchet derivative of F with respect to x at (x_0, y_0) is bijective:*

$$\begin{aligned} &F(x_0, y_0) = 0, \\ &D_x F(x_0, y_0) : X \to Z \quad \text{is bounded (continuous)} \\ &\text{with a bounded inverse (Banach's Theorem).} \end{aligned} \tag{4.2}$$

Assume also that F and $D_x F$ are continuous:

$$\begin{aligned} &F \in \mathcal{C}(U \times V, Z), \\ &D_x F \in \mathcal{C}(U \times V, L(X, Z)), \end{aligned} \tag{4.3}$$

where $L(X, Z)$ denotes the Banach space of bounded linear operators from X into Z endowed with the operator norm.
Then there exists a neighborhood $U_1 \times V_1$ in $U \times V$ of (x_0, y_0) and a mapping $f : V_1 \to U_1 \subset X$ such that

$$\begin{aligned} &f(y_0) = x_0, \\ &F(f(y), y) = 0 \quad \text{for all } y \in V_1. \end{aligned} \tag{4.4}$$

Furthermore, f is continuous on V_1:

$$f \in \mathcal{C}(V_1, X). \tag{4.5}$$

Finally, every solution of (4.1) in $U_1 \times V_1$ is of the form $(f(y), y)$.

For a proof we refer to [65]. For the prerequisites to this book we recommend also [49], [6], which present sections on analysis in Banach spaces.

Let us consider Y as a space of parameters and X as a space of configurations (a phase space, for example). Then the Implicit Function Theorem allows the following interpretation: the configuration described by problem 4.1 persists for perturbed parameters if it exists for some particular parameter, and it depends smoothly and in a unique way on the parameters. In other words, this theorem describes what one expects: a small change of parameters entails a unique small change of configuration (without any "surprise"). Thus "dramatic" changes in configurations for specific parameters can happen only if the assumptions of Theorem 4.1 are violated, in particular, if

$$D_x F(x_0, y_0) : X \to Z \quad \text{is not bijective.} \tag{4.6}$$

Bifurcation Theory can be briefly described by the investigation of problem (4.1) in a neighborhood of (x_0, y_0) where (4.6) holds. For later use we need the following addition to Theorem 4.1:

> If the mapping F in (4.1) is k-times continuously differentiable on $U \times V$, i.e., $F \in \mathcal{C}^k(U \times V, Z)$, then the mapping f in (4.4) is also k-times continuously differentiable on V_1; i.e., $f \in \mathcal{C}^k(V_1, X)$, $k \geq 1$. If the mapping F is analytic, then the mapping f is also analytic. (4.7)

For a proof we refer again to [65].

4.2 The Method of Lyapunov Schmidt

The method of Lyapunov and Schmidt describes the reduction of problem (4.1) (which is high- or infinite-dimensional) to a problem having only as many dimensions as the defect (4.6). To be more precise, we need the following definition:

Definition 4.2. *A continuous mapping $F : U \to Z$, where $U \subset X$ is open and where X, Z are Banach spaces, is a nonlinear Fredholm operator if it is Fréchet differentiable on U and if $DF(x)$ fulfills the following:*

(i) $\dim N(DF(x)) < \infty$ *(N = null space or kernel),*

(ii) $co \dim R(DF(x)) < \infty$ *(R = range),*

(ii) *$R(DF(x))$ is closed in Z.*

The integer $\dim N(DF(x)) - co \dim R(DF(x))$ *is called the Fredholm index of $DF(x)$.*

Remark 4.3. *As remarked in [113], p.230, assumption (iii) is redundant. If DF depends continuously on x and possibly on a parameter y, in the sense of (4.3), and if U or $U \times V$ is connected in X or also in $X \times Y$, respectively, then it can be shown that the Fredholm index of $DF(x)$ is independent of x; cf.[113], IV. 5.*

We consider now $F : U \times V \to Z$, $U \subset X$, $V \subset Y$, where

$$\begin{aligned} &F(x_0, y_0) = 0 \quad \text{for some} \quad (x_0, y_0) \in U \times V, \\ &F \in \mathcal{C}(U \times V, Z), \\ &DxF \in \mathcal{C}(U \times V, L(X, Z)) \quad (\text{see } (4.3)). \end{aligned} \tag{4.8}$$

We assume that for $y = y_0$ the mapping F is a nonlinear Fredholm operator with respect to x; i.e., $F(., y_0) : U \to Z$ satisfies Definition 4.2. In particular, observe that the spaces N and Z_0 defined below are finite dimensional.

Thus there exist closed complements in the Banach spaces X and Z such that

$$\begin{aligned} X &= N(D_x F(x_0, y_0)) + X_0, \\ Z &= R(D_x F(x_0, y_0)) + Z_0 \end{aligned} \tag{4.9}$$

(see [69], p.553). These decompositions, in turn, define projections

$$\begin{aligned} &P : X \to N \quad \text{along} \quad X_0 \quad (N = N(DxF(x_0, y_0)), \\ &Q : Z \to Z_0 \quad \text{along} \quad R \quad (R = R(DxF(x_0, y_0)), \end{aligned} \tag{4.10}$$

in a natural way. By the Closed Graph Theorem (see [170]) these projections are continuous.

Then the following Reduction Method of Lyapunov.Schmidt holds:

Theorem 4.4. *([114]) There is a neighborhood $U_2 \times V_2$ of (x_0, y_0) in $U \times V \subset X \times Y$ such that the problem*

$$F(x, y) = 0 \quad \text{for} \quad (x, y) \in U_2 \times V_2 \tag{4.11}$$

is equivalent to a finite-dimensional problem

$$\begin{aligned} &\Phi(v, y) = 0 \quad \text{for} \quad (v, y) \in \tilde{U}_2 \times V_2 \subset N \times Y, \text{where} \\ &\Phi : \tilde{U}_2 \times V_2 \to Z_0 \quad \text{is continuous} \\ &\text{and} \quad \Phi(v_0, y_0) = 0, (v_0, y_0) \in \tilde{U}_2 \times V_2. \end{aligned} \tag{4.12}$$

The function Φ, called a bifurcation function, is given by

$$\Phi(v, y) \equiv QF(v + \Psi(v, y), y) = 0,$$

where $\Psi : \tilde{U}_2 \times V_2 \to W_2 \subset X_0$.

(If the parameter space Y is finite-dimensional, then (4.12) is indeed a purely finite-dimensional problem.)

Corollary 4.5. *([114]) In the notation of Theorem 4.4, if $F \in C^1(U \times V, Z)$, we also obtain $\Psi \in C^1(\tilde{U}_2 \times V_2, X_0)$, $\Phi \in C^1(\tilde{U}_2 \times V_2, Z_0)$, and*

$$\begin{aligned} &\Psi(v_0, y_0) = w_0, \\ &D_v\Psi(v_0, y_0) = 0 \in L(N, X_0), \\ &D_v\Phi(v_0, y_0) = 0 \in L(N, Z_0). \end{aligned} \tag{4.13}$$

4.3 An Implicit Function Theorem for One Dimensional Kernels: Turning Points

In this section we consider mappings $F : U \times V \to Z$ with open sets $U \subset X$, $V \subset Y$, where X and Z are Banach spaces, but where this time $Y = \mathbb{R}$.

Following a long tradition, we change the notation and denote parameters in $\mathbb{R}$ by λ. We assume

$$\begin{aligned} &F(x_0, \lambda_0) = 0 \text{ for some } (x_0, \lambda_0) \in U \times V, \\ &\dim N(D_xF(x_0, \lambda_0)) = 1. \end{aligned} \tag{4.14}$$

Obviously, the Implicit Function Theorem, Theorem 4.1, is not directly applicable. We assume now the hypotheses of the Lyapunov-Schmidt reduction (Theorem 4.4) for F with the additional assumption that

$$\begin{aligned} &\text{the Fredholm index of } D_xF(x_0, \lambda_0) \text{ is zero;} \\ &\text{i.e., by (4.14), } co\dim R(D_xF(x_0, \lambda_0)) = 1. \end{aligned} \tag{4.15}$$

Since $Y = \mathbb{R}$, we can identify the Fréchet derivative $D_\lambda F(x, \lambda)$ with an element of Z, namely, by

$$D_\lambda F(x, \lambda)1 = D_\lambda F(x, \lambda) \in Z, 1 \in \mathbb{R}. \tag{4.16}$$

Theorem 4.6. *([114]) Assume that $F : U \times V \to Z$ is continuously differentiable on $U \times V \subset X \times \mathbb{R}$, i.e.,*

$$F \in C^1(U \times V, Z), \tag{4.17}$$

and (4.14), (4.15), (4.16), and that

$$D_\lambda F(x_0, \lambda_0) \notin R(D_xF(x_0, \lambda_0)). \tag{4.18}$$

Then there is a continuously differentiable curve through (x_0, λ_0); that is, there exists

$$\{(x(s), \lambda(s)) | s \in (-\delta, \delta), (x(0), \lambda(0)) = (x_0, \lambda_0)\} \tag{4.19}$$

such that

$$F(x(s), \lambda(s)) = 0 \textit{ for } s \in (-\delta, \delta), \tag{4.20}$$

and all solutions of $F(x, \lambda) = 0$ in a neighborhood of (x_0, λ_0) belong to the curve (4.19).

Corollary 4.7. *([114]) The tangent vector of the solution curve (4.19) at* (x_0, λ_0) *is given by*

$$(\tilde{v}_0, 0) \in X \times \mathbb{R}; \tag{4.21}$$

i.e., (4.19) is tangent at (x_0, λ_0) *to the one-dimensional kernel of* $D_x F(x_0, \lambda_0)$*.*

Let us assume more differentiability on F, namely, $F \in C^2(U \times V, Z)$. Then differentiation of (4.20) with respect to s gives, in view of (**??**),

$$\begin{aligned} \tfrac{d}{ds} F(x(s), \lambda(s))|_{s=0} &= D_x F(x_0, \lambda_0)\dot{x}(0) + D_\lambda F(x_0, \lambda_0)\dot{\lambda}(0) \\ &= D_x F(x_0, \lambda_0)\tilde{v}_0 = 0, \\ \tfrac{d^2}{ds^2} F(x(s), \lambda(s))|_{s=0} &= D^2_{xx} F(x_0, \lambda_0)[\tilde{v}_0, \tilde{v}_0] + D_x F(x_0, \lambda_0)\ddot{x}(0) \\ &+ D_\lambda F(x_0, \lambda_0)\ddot{\lambda}(0) = 0 \end{aligned} \tag{4.22}$$

(observe that $\dot{\lambda}(0) = 0$).
Application of the projection Q (see (4.10)) yields

$$Q D^2_{xx} F(x_0, \lambda_0)[\tilde{v}_0, \tilde{v}_0] + Q D_\lambda F(x_0, \lambda_0)\ddot{\lambda}(0) = 0. \tag{4.23}$$

Since $Q D_\lambda F(x_0, \lambda_0) \neq 0$ by virtue of (4.18), the additional assumption

$$D^2_{xx} F(x_0, \lambda_0)[\tilde{v}_0, \tilde{v}_0] \notin R(D_x F(x_0, \lambda_0)) \tag{4.24}$$

guarantees (according to (4.23), which is an equation in the one-dimensional space Z_0)

$$\ddot{\lambda}(0) > 0 \text{ or } \ddot{\lambda}(0) < 0. \tag{4.25}$$

In the literature, the curve (4.19) through $(x_0, \lambda_0) \in X \times \mathbb{R}$ is commonly called a saddle-node bifurcation, a nomenclature that makes sense only if the vector fields $F(., \lambda) : X \to Z$ generate a flow, which, in turn, requires $X \subset Z$. Since that is not always true in our general setting, we prefer the terminology turning point or fold.

In order to replace the nonzero quantities in (4.23) by real numbers, we introduce the following explicit representation of the projection Q in (4.10). Recall that the complement Z_0 of $R(D_x F(x_0, \lambda_0))$ is one-dimensional:

$$Z_0 = span[\tilde{v}_0^*], \ \tilde{v}_0^* \in Z, \ ||\tilde{v}_0^*|| = 1. \tag{4.26}$$

By the Hahn Banach Theorem (see [170]), there exists a vector

$$\begin{aligned} &\tilde{v}_0' \in Z' \text{ (the dual space) such that } \langle \tilde{v}_0^*, \tilde{v}_0' \rangle = 1 \\ &\text{and} \langle \tilde{z}, \tilde{v}_0' \rangle = 0 \text{ for all} z \in R(D_x F(x_0, \lambda_0)). \end{aligned} \tag{4.27}$$

Here $\langle ., . \rangle$ denotes the duality between Z and Z'. Then the projection Q in (4.10) is given by

$$Qz = \langle \tilde{z}, \tilde{v}_0' \rangle \tilde{v}_0^* \text{ for all } z \in Z, \tag{4.28}$$

and (4.23), (4.24) imply

$$\ddot{\lambda}(0) = -\frac{\langle D^2_{xx} F(x_0, \lambda_0)[\tilde{v}_0, \tilde{v}_0], \tilde{v}_0' \rangle}{\langle D_\lambda F(x_0, \lambda_0), \tilde{v}_0' \rangle}, \tag{4.29}$$

and the sign of $\ddot{\lambda}(0)$ determines the appropriate diagram. If $\ddot{\lambda}(0) = 0$, however, the shape of the curve (4.19) is determined by higher derivatives of $\ddot{\lambda}(0)$ at $s = 0$.

Remark 4.8. *There is also an Implicit Function Theorem for higher-dimensional kernels if the parameter space Y is higher-dimensional, too. To be more precise, if $\dim N(D_xF(x_0, \lambda_0)) = n$ for some $(x_0, \lambda_0) \in U \times V \subset X \times \mathbb{R}^n$ and if a complement of $R(D_xF(x_0, \lambda_0))$ is spanned by $D_{\lambda_i}F(x_0, \lambda_0)$, $i = 1, \ldots, n$, then the analogous proof yields an n-dimensional manifold of the form $\{(x(s), \lambda(s))|s \in \tilde{U}_3 \subset \mathbb{R}^n\} \subset X \times \mathbb{R}^n$ through $(x(0), \lambda(0)) = (x_0, \lambda_0)$ such that $F(x(s), \lambda(s)) = 0$ for all $s \in \tilde{U}_3$ (which is a neighborhood of $0 \in \mathbb{R}^n$). Moreover, the manifold is tangent to $N(D_xF(x_0, \lambda_0)) \times \{0\}$ in $X \times \mathbb{R}^n$.*

4.4 Bifurcation with a One-Dimensional Kernel

We assume the existence of a solution curve of $F(x, \lambda) = 0$ through (x_0, λ_0) and prove the intersection of a second solution curve at (x_0, λ_0), a situation that is rightly called bifurcation. A necessary condition for this is again (4.6), which excludes the application of the Implicit Function Theorem near (x_0, λ_0).

As in Section 4.3, we assume again that the parameter space Y is one-dimensional, *i.e.*, $Y = \mathbb{R}$, and we normalize the first curve of solutions to the so-called trivial solution line $\{(0, \lambda)|\lambda \in \mathbb{R}\}$. This is done as follows: if $F(x(s), \lambda(s)) = 0$, then we set $\tilde{F}(x, s) = F(x(s) + x, \lambda(s))$, and obviously, $\tilde{F}(0, s) = 0$ for all parameters s. Returning to our original notation, this leads to the following assumptions:

$$\begin{aligned} &F(0, \lambda) = 0 \text{ for all} \lambda \in \mathbb{R}, \\ &\dim N(D_xF(0, \lambda_0)) = co\dim R(D_xF(0, \lambda_0)) = 1, \\ &i.e., F(E, \lambda_0) \text{ is a Fredholm operator of index zero.} \end{aligned} \tag{4.30}$$

The assumed regularity of F is as follows:

$$\begin{aligned} &F \in C^2(U \times V, Z), \\ &\text{where } 0 \in U \subset X, \lambda_0 \in V \subset \mathbb{R}, \\ &\text{are open neighborhoods,} \end{aligned} \tag{4.31}$$

where we identify again the derivative $D^2_{x\lambda}F(x, \lambda)$ with an element in $L(X, Z)$; cf.(4.16). By assumption (4.30) we have $D^2_{x\lambda} = D^2_{\lambda x}$ (see [65], [6]).

The Crandall.Rabinowitz Theorem then reads as follows:

Theorem 4.9. *([114]) Assume (4.30), (4.31), and that*

$$\begin{aligned} N(D_xF(0, \lambda_0)) = span[\tilde{v}_0],\ \tilde{v}_0 \in X,\ ||\tilde{v}_0|| = 1, \\ D^2_{x\lambda}F(0, \lambda_0)\tilde{v}_0 \notin R(D_xF(0, \lambda_0)). \end{aligned} \tag{4.32}$$

Then there is a nontrivial continuously differentiable curve through $(0, \lambda_0)$,

$$\{(x(s), \lambda(s))|s \in (-\delta, \delta), (x(0), \lambda(0)) = (0, \lambda_0)\}, \tag{4.33}$$

such that

$$F(x(s), \lambda(s)) = 0 \text{ } \textit{fors} \in (-\delta, \delta), \tag{4.34}$$

and all solutions of $F(x, \lambda)$ *in a neighborhood of* $(0, \lambda_0)$ *are on the trivial solution line or on the nontrivial curve (4.33). The intersection* $(0, \lambda_0)$ *is called a bifurcation point.*

Corollary 4.10. *([114]) The tangent vector of the nontrivial solution curve (4.33) at the bifurcation point* $(0, \lambda_0)$ *is given by*

$$(\tilde{v}_0, \dot{\lambda}(0)) \in X \times \mathbb{R}. \tag{4.35}$$

Under the general assumptions of this section, it is not clear whether the component $\dot{\lambda}(0)$ of the tangent vector (4.35) vanishes. Therefore, for now, we cannot decide on sub-, super-, or transcritical bifurcation. These notions will be specified in the next section.

Remark 4.11. *The generalization of Theorem 4.9 to higher-dimensional kernels is given by Theorem I.19.2 [114], provided that the parameter space is higher-dimensional, too. To be more precise, we need as many parameters as the codimension of the range amounts to.*

Chapter 5

Periodically pulsed chemotherapy with resistant tumor cells

In this chapter we consider a nonlinear mathematical model describing the evolution of population constituted by normal cells, sensitive and resistant tumor cells, under periodic chemotherapeutic treatment. We study the stability of the trivial periodic solutions and bifurcation of nontrivial periodic solutions by the mean of Lyapunov-Schmidt reduction. The conditions of stability and bifurcation are expressed in terms of the parameters of the system. Our results are applied to models given by Panetta [145].

5.1 Introduction

In this work a model for cancer chemotherapy is studied by considering normal-tumor cells interactions. Chemotherapy of tumor models have recently attracted the attention of several authors ([87], [121], [122], [127], [145] and [168]). Our work is inspired from papers [122] and [145], where the authors consider interactions between normal and tumor cells. The interactions taken into account include competition for nutrients, growth factors or the effects of immune system ([23], [44], [54]-[87], [120], [128] and [134]). We note in the above cited papers that these interactions activate tumor evolution in certain cases while it stops it in other cases, depending on the kind and the stage of the tumor. The model we study here is derived from Panetta [145] where the author considers that normal and cancerous cells are in interaction, and the treatment considered there acts instantaneously on all kinds of cells. Note that this treatment is described by impulse effects. The mathematical model obtained is a system of an impulsive differential equations. Numerical analysis of the Panetta model [145] is considered in [168] by Wei *et al.* In this paper, the authors have studied the role of the initial tumor biomass on the evolution of the tumor. In our paper we consider a more general model described by impulsive differential equations. For more details about impulsive differential equations and applications see [15]-[18], [99], [121], [138] and [166]. More specifically, we consider the following system

$$\begin{aligned}
\dot{x}_1(t) &= F_1(x_1(t), x_2(t), x_3(t)), && (5.1)\\
\dot{x}_2(t) &= F_2(x_1(t), x_2(t), x_3(t)), && (5.2)\\
\dot{x}_3(t) &= F_3(x_1(t), x_2(t), x_3(t)), && (5.3)\\
x_1(t_i^+) &= \Theta_1(x_1(t_i), x_2(t_i), x_3(t_i)), && (5.4)\\
x_2(t_i^+) &= \Theta_2(x_1(t_i), x_2(t_i), x_3(t_i)), && (5.5)\\
x_3(t_i^+) &= \Theta_3(x_1(t_i), x_2(t_i), x_3(t_i)), && (5.6)
\end{aligned}$$

where $t_{i+1} - t_i = cste = \tau > 0\ \forall i \in \mathbb{N}$, $x_j \in \mathbb{R}$ and Θ_j is positive smooth function, for $j = \overline{1,3}$.
Variables and functions are the following:
τ : period between two successive drug treatment,
x_j : normal (resp. sensitive tumor and resistant tumor) cell biomass, for $j = 1$ (resp. 2, 3),
$\Theta_j(x_1(t_i), x_2(t_i), x_3(t_i))$: fraction of normal (resp. sensitive tumor, resistant tumor) cells, surviving the i^{th} drug treatment, for $j = 1$ (resp. 2, 3),
$F_j(x_1, x_2, x_3)$: biomass growth of normal (resp. sensitive tumor, resistant tumor) cells for $j = 1$ (resp. 2, 3),
In our study, we first consider the unperturbed problem $\dot{x_1} = F_1(x_1, 0, 0)$, with periodic impulses $x_1(n\tau^+) = \Theta_1(x_1(n\tau), 0, 0)$. We assume that the one dimensional equation (5.1) with impulse equations (5.4)-(5.6) has a periodic stable solution (see [122],[145]). It is called a trivial solution, and could correspond to a preventive treatment. However, from clinical point of view such a treatment is not a warranty that no tumor can develop.
We consider the onset of a tumor in a patient who is under preventive treatment and the displacement of the equilibrium from a situation without cancer cells to one with a significant fraction of them, this corresponds to a bifurcation from a stable equilibrium. We study the dependence of the equilibrium on the time period τ between two drug injections. We show different effects on both normal and tumor cells, that is if τ exceeds a certain value the tumor cells can be reconstituted. In section 5.2, we transform (5.1)-(5.6) into a fixed point problem. In section 5.3, sufficient conditions for stability of the trivial solution are found. Bifurcation is analyzed in section 5.4. In section 5.5, we give a new heterogeneous model containing the two Panetta's models, we apply the results obtained in previous sections to the general model. Concluding remarks are given in section 5.6.

5.2 Hypotheses and definitions

A solution $\xi = (x_1, x_2, x_3)$ of the problem (5.1)-(5.6) is a function defined in $\mathbb{R}_+$, with nonnegative components, continuously differentiable in $\mathbb{R}_+ - \{t_i\}_{i\geq 0}$,

with $t_0 = 0$, and satisfying all of the relations (5.1) through (5.6).
ξ is called a trivial solution of problem (5.1)-(5.6) if its second and third components are zeros, otherwise it is a nontrivial solution. Also, ξ is called trivial (resp. nontrivial) τ-periodic solution if it is a trivial (resp. nontrivial) solution with $\xi(n\tau) = \xi((n+1)\tau)$, for all $n \geq 0$.
In our study, we consider that $\Theta = (\Theta_1, \Theta_2, \Theta_3)$ is positive and that the positive octant is invariant with respect to the flow associated to (5.1)-(5.3). $F = (F_1, F_2, F_3)$ and Θ are assumed smooth enough. Finally, we suppose that $F_2(x_1, 0, x_3) \equiv \Theta_2(x_1, 0, x_3) \equiv 0$, $F_3(x_1, 0, 0) \equiv \Theta_3(x_1, 0, 0) \equiv 0$ and $\Theta_i(X) \neq 0$ $(X \in \mathbb{R}^3_+)$ for $x_i \neq 0$, $i = 1, 2, 3$. Our main objective is to study the stability of the trivial periodic solution, the loss of stability for some values of the parameters, and the onset of nontrivial periodic solutions as a consequence of this lost.
Let Φ be the flow associated to (5.1)-(5.6), we have

$$\xi(t) = \Phi(t, X_0), 0 < t \leq \tau, \tag{5.7}$$

where $\xi(0) = X_0$. We assume that the flow Φ applies up to time τ. So, $\xi(\tau) = \Phi(\tau, X_0)$. Then, within a very small time interval starting at time τ, we assume that the treatment is administered and kills instantaneously a fraction of the population. The term $\xi(\tau^+)$ denote the state of the population after the treatment, $\xi(\tau^+)$ is determined in terms of $\xi(\tau)$ according to equations (5.4)-(5.6). We have $\xi(\tau^+) = \Theta(\xi(\tau)) = \Theta(\Phi(\tau, X_0))$.
Let Ψ be the operator defined by

$$\Psi(\tau, X_0) = \Theta(\Phi(\tau, X_0)), \tag{5.8}$$

and denote by $D_X\Psi$ the derivative of Ψ with respect to X. Then $\xi = \Phi(., X_0)$ is a τ-periodic solution of (5.1)-(5.6) if and only if

$$\Psi(\tau, X_0) = X_0, \tag{5.9}$$

i.e. X_0 is a fixed point of $\Psi(\tau, .)$, and it is exponentially stable if and only if the spectral radius $\rho(D_X\Psi(\tau, .))$ is strictly less than 1 ([110]). A fixed point X_0 of $\Psi(\tau, .)$ is the initial state of (5.1)-(5.6) which gives a τ-periodic solution ξ verifying $\xi(0) = X_0$. Consequently, for each fixed point X_0 of $\Psi(\tau, .)$ there is an associated τ-periodic solution ξ and vice versa.

Remark 5.1. *We say that a fixed point is trivial if it is associated to a trivial periodic solution. The fixed point of $\Psi(\tau, .)$ can be determined using a fixed point method and assuming additional condition on F and Θ ([110]), assumed smooth enough.*
If $x_2 = x_3 = 0$ the problem (5.1), (5.4), has a stable τ_0-periodic solution denoted x_s.
The function $\zeta = (x_s, 0, 0)$ is a τ_0-periodic solution of $(5.1) - (5.6)$ in the three dimensional space.

5.3 Stability of ζ

Denote $x_0 = x_s(0)$, then $(x_0, 0, 0)$ is the initial condition for ζ and $\zeta(0) = (x_0, 0, 0)$. From stability of x_s we obtain

$$\left|\frac{\partial \Theta_1}{\partial x_1}(\Phi(\tau_0, (x_0, 0, 0)))\frac{\partial \Phi_1}{\partial x_1}(\tau_0, (x_0, 0, 0))\right| < 1. \tag{5.10}$$

We have $D_X\Psi(\tau_0, X) = D_X\Theta(\Phi(\tau_0, X))\dfrac{\partial \Phi}{\partial X}(\tau_0, X)$, then for $X_0 = (x_0, 0, 0)$ we obtain

$$\begin{aligned} D_X\Psi(\tau_0, X_0) &= D_X\Theta(\Phi(\tau_0, X_0))\tfrac{\partial \Phi}{\partial X}(\tau_0, X_0) \\ &= \begin{pmatrix} \frac{\partial \Theta_1}{\partial x_1} & \frac{\partial \Theta_1}{\partial x_2} & \frac{\partial \Theta_1}{\partial x_3} \\ 0 & \frac{\partial \Theta_2}{\partial x_2} & 0 \\ 0 & \frac{\partial \Theta_3}{\partial x_2} & \frac{\partial \Theta_3}{\partial x_3} \end{pmatrix} \begin{pmatrix} \frac{\partial \Phi_1}{\partial x_1} & \frac{\partial \Phi_1}{\partial x_2} & \frac{\partial \Phi_1}{\partial x_3} \\ 0 & \frac{\partial \Phi_2}{\partial x_2} & 0 \\ 0 & \frac{\partial \Phi_3}{\partial x_2} & \frac{\partial \Phi_3}{\partial x_3} \end{pmatrix}. \end{aligned}$$

The solution ζ is exponentially stable if and only if the spectral radius is less than one, that is

$$\left|\frac{\partial \Theta_j}{\partial x_j}(\Phi(\tau_0, X_0))\frac{\partial \Phi_j}{\partial x_j}(\tau_0, X_0)\right| < 1, \text{ for } j = 1, 2, 3.$$

Consider the variational equation associated to the system (5.1)-(5.3)

$$\frac{d}{dt}(D_X\Phi(t, X_0)) = D_XF(\Phi(t, X_0))(D_X\Phi(t, X_0)), \tag{5.11}$$

with the initial condition is $D_X\Phi(0, X_0) = Id_{\mathbb{R}^3}$. We obtain

$$\frac{\partial \Phi_1(t, X_0)}{\partial x_1} = e^{\int_0^t \frac{\partial F_1(\zeta(r))}{\partial x_1}dr},$$

$$\frac{\partial \Phi_2(t, X_0)}{\partial x_2} = e^{\int_0^t \frac{\partial F_2(\zeta(r))}{\partial x_2}dr}$$

and

$$\frac{\partial \Phi_3(t, X_0)}{\partial x_3} = e^{\int_0^t \frac{\partial F_3(\zeta(r))}{\partial x_3}dr}$$

for $0 \leq t < \tau_0$ (see Appendix A, subsection 6.1).
We have the following result

Theorem 5.2. *If conditions* $\left|\dfrac{\partial \Theta_j}{\partial x_j}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_j}{\partial x_j}(\zeta(r))dr} < 1$ *for* $j = 1, 2, 3$ *are satisfied, then the trivial solution* $\zeta = (x_s, 0, 0)$ *is exponentially stable.*

Next, we analyze the bifurcation of non trivial periodic solutions of system (5.1) – (5.6) near ζ.

5.4 Critical cases

Let $\bar{\tau}$ and $\bar{X}$ such that $\tau = \tau_0 + \bar{\tau}$ and $X = X_0 + \bar{X}$. The equation (5.9) is equivalent to

$$M(\bar{\tau}, \bar{X}) = 0, \tag{5.12}$$

where $M(\bar{\tau}, \bar{X}) = \big(M_1(\bar{\tau}, \bar{X}), M_2(\bar{\tau}, \bar{X}), M_3(\bar{\tau}, \bar{X})\big) = X_0 + \bar{X} - \Psi(\tau_0 + \bar{\tau}, X_0 + \bar{X})$.
If $(\bar{\tau}, \bar{X})$ is a zero of M, then $(X_0 + \bar{X})$ is a fixed point of $\Psi(\tau_0 + \bar{\tau}, .)$. Since ζ is a trivial τ_0-periodic solution (5.1)-(5.6), then it is associated to the trivial fixed point X_0 of $\Psi(\tau_0, .)$. From the stability of the solution x_s in the one dimensional space, we have

$$1 - \left|\frac{\partial \Theta_1}{\partial x_1}(\zeta(\tau_0))\right| \left|\frac{\partial \Phi_1}{\partial x_1}(\tau_0, (x_0, 0, 0))\right| \neq 0. \tag{5.13}$$

From (5.13) and the implicit function theorem, we have a branch of trivial τ_0- periodic solutions of (5.1)-(5.6). Let

$$D_X M(\bar{\tau}, \bar{X}) = \begin{pmatrix} \acute{a} & \acute{b} & \acute{c} \\ \acute{d} & \acute{e} & \acute{f} \\ \acute{g} & \acute{h} & \acute{i} \end{pmatrix}, \tag{5.14}$$

with $\acute{a} = \acute{a}_0$, $\acute{b} = \acute{b}_0$, $\acute{c} = \acute{c}_0$, $\acute{d} = \acute{d}_0$, $\acute{e} = \acute{e}_0$, $\acute{f} = \acute{f}_0$, $\acute{g} = \acute{g}_0$, $\acute{h} = \acute{h}_0$ and $\acute{i} = \acute{i}_0$, for $(\bar{\tau}, \bar{X}) = (0, 0, 0, 0)$. We have $\acute{d}_0 = 0$, $\acute{f}_0 = 0$, $\acute{g}_0 = 0$ and $\acute{a}_0 > 0$ (see Appendix A, subsection 6.1).
A necessary condition for the bifurcation of non trivial zeros of the function M is that the determinant of the Jacobian matrix $D_X M(0, 0)$ be equal to zero. That is $\acute{e}_0.\acute{i}_0 = 0$.
There are three critical cases: **(C1)** $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$, **(C2)** $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$, and **(C3)** $\acute{e}_0 = 0$ and $\acute{i}_0 = 0$.
Now, we analyze the possible bifurcation in all cases.
(C1): For $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$, we have $M(0, 0) = 0$. Let $D_X M(0, 0) = E$, then $\dim\ker(E) = \operatorname{co}\dim \mathrm{R(E)} = 1$. Denote by P and Q the projectors onto $\ker(E)$ and $R(E)$ respectively, such that $P + Q = Id_{\mathbb{R}^3}$,
$P\mathbb{R}^3 = \mathrm{span}\{\mathrm{Y}_0\} = \mathrm{ker(E)}$, with $\mathrm{Y}_0 = \left(\frac{\acute{c}_0 \acute{h}_0}{\acute{a}_0 \acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}, 1, -\frac{\acute{h}_0}{\acute{i}_0}\right)$ and $Q\mathbb{R}^3 = \mathrm{span}\{(1, 0, 0), (0, 0, 1)\} = R(E)$.
Then $(I - P)\mathbb{R}^3 = \mathrm{span}\{(1, 0, 0), (0, 0, 1)\}$ and $(I - Q)\mathbb{R}^3 = \mathrm{span}\{(0, 1, 0)\}$.
Equation (5.12) is equivalent to

$$\begin{cases} M_1(\bar{\tau}, \alpha Y_0 + Z) &= 0, \\ M_2(\bar{\tau}, \alpha Y_0 + Z) &= 0, \\ M_3(\bar{\tau}, \alpha Y_0 + Z) &= 0, \end{cases} \tag{5.15}$$

where $Z = (z_1, 0, z_3)$, $(\bar{\tau}, \bar{X}) = (\bar{\tau}, \alpha Y_0 + Z)$ and $(\alpha, z_1, z_3) \in \mathbb{R}^3$.
From the first and last equations of (5.15), we have

$$\det \begin{pmatrix} \frac{\partial M_1(0,0)}{\partial z_1} & \frac{\partial M_1(0,0)}{\partial z_3} \\ \frac{\partial M_3(0,0)}{\partial z_1} & \frac{\partial M_3(0,0)}{\partial z_3} \end{pmatrix} = \det \begin{pmatrix} \acute{a}_0 & \acute{c}_0 \\ 0 & \acute{i}_0 \end{pmatrix} = \acute{a}_0.\acute{i}_0 \neq 0.$$

From the implicit function theorem, there exist $\delta > 0$ sufficiently small and a unique continuous function Z^*, such that $Z^*(\bar{\tau}, \alpha) = (z_1^*(\bar{\tau}, \alpha), 0, z_3^*(\bar{\tau}, \alpha))$, $Z^*(0,0) = (0,0,0)$,

$$M_1\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau},\alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau},\alpha)\right)\right) = 0 \qquad (5.16)$$

and

$$M_3\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau},\alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau},\alpha)\right)\right) = 0, \qquad (5.17)$$

for every $(\bar{\tau}, \alpha)$ such that $|\alpha| < \delta$ and $|\bar{\tau}| < \delta$.
Moreover, we have $\dfrac{\partial Z^*}{\partial \alpha}(0,0) = (0,0,0)$ (see Appendix A, subsection 6.3).
Then $M(\bar{\tau}, \bar{X}) = 0$ if and only if

$$f(\bar{\tau},\alpha) = M_2\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau},\alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau},\alpha)\right)\right) = 0. \qquad (5.18)$$

Equation (5.18) is called determining equation and the number of its solutions is equal to the number of periodic solutions of (5.1)-(5.6) (see [49]).
From the Taylor development of f we obtain $f(\bar{\tau},\alpha) = \dfrac{\alpha}{2}(2B\bar{\tau}+C\alpha)+o\left((|\alpha|+|\bar{\tau}|)^2\right)$, (see Appendix A, subsections 6.3 and 6.4). Let $f(\bar{\tau},\alpha) = \dfrac{\alpha}{2}\tilde{f}(\bar{\tau},\alpha)$, where $\tilde{f}(\bar{\tau},\alpha) = 2B\bar{\tau} + C\alpha + \frac{1}{\alpha}o\left((|\alpha|+|\bar{\tau}|)^2\right)$.
So, for $B \neq 0$ (resp. $C \neq 0$) we can use the implicit function theorem which gives us $\bar{\tau} = \sigma(\alpha)$ (resp. $\alpha = \gamma(\bar{\tau})$). Hence $\forall\alpha$ (resp. $\bar{\tau}$) near 0, $\exists\sigma(\alpha)$ (resp. $\gamma(\bar{\tau})$) such that $\tilde{f}(\sigma(\alpha),\alpha) = 0$ (resp. $\tilde{f}(\bar{\tau},\gamma(\bar{\tau})) = 0$) and $\sigma(0) = 0$ (resp. $\gamma(0) = 0$). Then if $BC \neq 0$ we have $\dfrac{\bar{\tau}}{\alpha} \simeq -\dfrac{C}{2B}$.
In conclusion we have the following theorem.

Theorem 5.3. *Let* $\left|\dfrac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0}\frac{\partial F_j}{\partial x_j}(\zeta(r))dr} < 1$ *for* $j = 1,3$ *and* $\left|\dfrac{\partial\Theta_2}{\partial x_2}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0}\frac{\partial F_2}{\partial x_2}(\zeta(r))dr} = 1$, *we have the following results:*

- **a)** *If* $BC \neq 0$ *we have a bifurcation, moreover* $\dfrac{\bar{\tau}}{\alpha} \simeq -\dfrac{C}{2B}$. *Consequently, we have a bifurcation of a nontrivial periodic solutions of (5.1)-(5.6) if* $BC < 0$ *and a subcritical cases if* $BC > 0$.
- **b)** *If* $BC = 0$ *we have an undetermined case.*

(C2): For $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$, we have $M(0,0) = 0$. Let $D_X M(0,0) = E$, then, $\dim\ker(E) = \operatorname{co}\dim \mathrm{R(E)} = 1$. For this case we take $Y_0 = \left(\dfrac{-\acute{c}_0}{\acute{a}_0}, 0, 1\right)$, then

$Q\mathbb{R}^3 = \text{span}\left\{(1,0,0), \left(0,1,\frac{\acute{h}_0}{\acute{e}_0}\right)\right\} = R(E)$, $(I-P)\mathbb{R}^3 = \text{span}\{(1,0,0),(0,1,0)\}$ and $(I-Q)\mathbb{R}^3 = \text{span}\{(0,0,1)\}$.
Let $Z = (z_1, z_2, 0)$, $(\bar{\tau}, \bar{X}) = (\bar{\tau}, \alpha Y_0 + Z)$ and $(\alpha, z_1, z_2) \in \mathbb{R}^3$.
From the first and second equations of (5.15), we have

$$\det \begin{pmatrix} \frac{\partial M_1(0,0)}{\partial z_1} & \frac{\partial M_1(0,0)}{\partial z_2} \\ \frac{\partial M_2(0,0)}{\partial z_1} & \frac{\partial M_2(0,0)}{\partial z_2} \end{pmatrix} = \det \begin{pmatrix} \acute{a}_0 & \acute{b}_0 \\ 0 & \acute{e}_0 \end{pmatrix} = \acute{a}_0.\acute{e}_0 \neq 0.$$

By the implicit function theorem, there exist $\delta > 0$ sufficiently small and a unique continuous function Z^*, such that $Z^*(\bar{\tau}, \alpha) = (z_1^*(\bar{\tau}, \alpha), z_2^*(\bar{\tau}, \alpha), 0)$, $Z^*(0,0) = (0,0,0)$,

$$M_1\left(\bar{\tau}, \left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha + z_1^*(\bar{\tau}, \alpha), z_2^*(\bar{\tau}, \alpha), \alpha\right)\right) = 0 \tag{5.19}$$

and

$$M_2\left(\bar{\tau}, \left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha + z_1^*(\bar{\tau}, \alpha), z_2^*(\bar{\tau}, \alpha), \alpha\right)\right) = 0, \tag{5.20}$$

for every $(\bar{\tau}, \alpha)$ such that $|\alpha| < \delta$ and $|\bar{\tau}| < \delta$.
Moreover $\dfrac{\partial Z^*}{\partial \alpha}(0,0) = (0,0,0)$ (see Appendix A, subsection 6.3).
Then $M(\bar{\tau}, \bar{X}) = 0$ if and only if

$$f(\bar{\tau}, \alpha) = M_3\left(\bar{\tau}, \left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha + z_1^*(\bar{\tau}, \alpha), z_2^*(\bar{\tau}, \alpha), \alpha\right)\right) = 0.$$

We obtain $\tilde{f}(\bar{\tau}, \alpha) = 2B\bar{\tau} + C\alpha + \frac{1}{\alpha} o\left((|\alpha| + |\bar{\tau}|)^2\right)$. We have the following results.

Theorem 5.4. *If* $\left|\dfrac{\partial \Theta_j}{\partial x_j}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_j}{\partial x_j}(\zeta(r))dr} < 1$ *for* $j = 1, 2$ *and* $\left|\dfrac{\partial \Theta_3}{\partial x_3}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_3}{\partial x_3}(\zeta(r))dr} = 1$ *are satisfied, then we have the results of Theorem 5.3.*

Remark 5.5. *In the case* **(C3)** *we obtain* $B = C = 0$. *So in this case, we need to calculate a higher derivatives of* f.

5.5 Applications to cancer model with resistant tumor cells

In Panetta [145], two cancer models with resistant tumor cells are discussed, the first one with acquired resistance and the second one with reduced resistance. In this section we study the more general model including both the acquired resistance an reduced resistance defined by

$$\dot{x}_1(t) = r_1x_1\left(1 - \frac{x_1}{K_1} - \lambda_1(x_2 + x_3)\right), \quad (5.21)$$

$$\dot{x}_2(t) = r_2x_2\left(1 - \frac{x_2 + x_3}{K_2} - \lambda_2(x_1 + x_3)\right) - mx_2, \quad (5.22)$$

$$\dot{x}_3(t) = r_3x_3\left(1 - \frac{x_2 + x_3}{K_3} - \lambda_3(x_1 + x_2)\right) + mx_2, \quad (5.23)$$

$$x_1(t_i^+) = T_1x_1(t_i), \quad (5.24)$$

$$x_2(t_i^+) = (T_2 - R)x_2(t_i), \quad (5.25)$$

$$x_3(t_i^+) = T_3x_3(t_i) + Rx_2(t_i), \quad (5.26)$$

where $t_{i+1} - t_i = \tau > 0$, $\forall i \in \mathbb{N}$, and for $j = \overline{1,3}$, T_j, R are positive constants. The variables and the parameters are
m: acquired resistance parameter, usually it is very small (see [135]),
r_1, r_2, r_3: growth rates of the normal, sensitive tumor and resistant tumor cells, respectively,
K_1, K_2, K_3 : carrying capacities of the normal, sensitive tumor and resistant tumor cells, respectively,
λ_1, λ_2, λ_3: competitive parameters of the normal, sensitive tumor and resistant tumor cells, respectively,
τ: Period of drug dose administration,
T_1, T_2, T_3: survival fractions of normal, sensitive tumor and resistant tumor cells, respectively,
R: fraction of cells mutating due to the drug dose which is less than T_2.
In Figure 5.5 we give a schematic representation of the cancer model.

Remark 5.6.
The problem (5.21), (5.24), obtained by taking $x_2 = 0$ and $x_3 = 0$, has a τ_0-periodic solution
$x_1(t, (x_0, 0, 0)) = x_s(t)$, $0 < t \le \tau_0$, *where*

$$x_s(t) = \frac{K_1(T_1 - e^{-r_1\tau_0})}{(T_1 - e^{-r_1\tau_0}) + (1 - T_1)e^{-r_1 t}}, \quad (5.27)$$

with $x_0 = \dfrac{K_1(T_1 - e^{-r_1\tau_0})}{1 - e^{-r_1\tau_0}}$.
The solution x_s is defined and stable in the one dimensional space if and only if $T_1 > e^{-r_1\tau_0}$, that is

$$\tau_0 > \frac{1}{r_1}\ln\left(\frac{1}{T_1}\right). \quad (5.28)$$

To determine the stability of the trivial solution $\zeta = (x_s, 0, 0)$ in the three dimensional space, we must calculate $\acute{e_0}$ and $\acute{i_0}$. We have $\acute{e_0} = 1 - (T_2 - R)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2 - r_2\lambda_2K_1 - m)\tau_0}$ and $\acute{i_0} = 1 - T_3T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3 - r_3\lambda_3K_1)\tau_0}$.

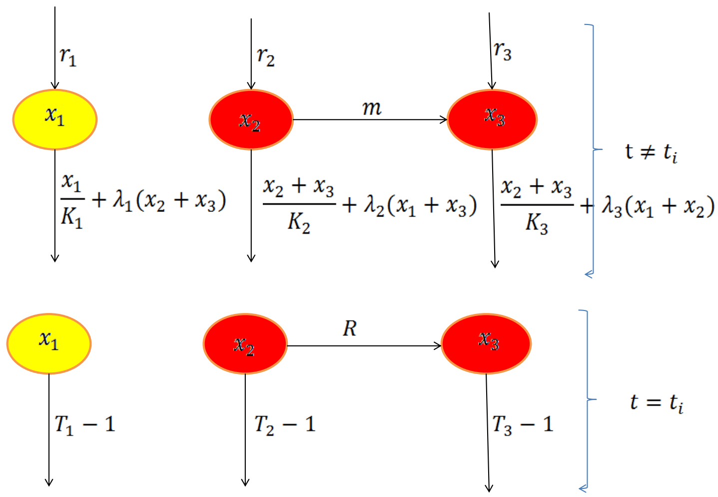

Figure 5.1: Schematic diagram of the cancer model with resistant tumor cells for $t \neq t_i$.

In view of the fact that $\lambda_2 K_1 < 1$ *and* $\lambda_3 K_1 < 1$ *(see [145]), we have*

$$T_1^{\frac{r_2 \lambda_2 K_1}{r_1}} > T_2 - R \tag{5.29}$$

and

$$T_1^{\frac{r_3 \lambda_3 K_1}{r_1}} > T_3. \tag{5.30}$$

If $\acute{e}_0 > 0$ *and* $\acute{i}_0 > 0$*, then* ζ *is stable as an equilibrium for the full system (5.21)-(5.26). In this case, we have*

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_2 \lambda_2 K_1}{r_1}} (T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2 K_1) - m} \text{ and } \frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_3 \lambda_3 K_1}{r_1}} T_3^{-1}\right)}{r_3(1 - \lambda_3 K_1)}.$$

So

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \min\left(\frac{\ln\left(T_1^{\frac{r_2 \lambda_2 K_1}{r_1}} (T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2 K_1) - m}, \frac{\ln\left(T_1^{\frac{r_3 \lambda_3 K_1}{r_1}} T_3^{-1}\right)}{r_3(1 - \lambda_3 K_1)}\right). \tag{5.31}$$

Using theorem 5.2, we deduce the following result.

Corollary 5.7. *If (5.29)-(5.31) are satisfied, then the trivial solution* $\zeta = (x_s, 0, 0)$ *is exponentially stable.*

If conditions (5.29), (5.30) are satisfied and

$$T_1^{\frac{K_1(r_2\lambda_2 - r_2\lambda_3 + m\lambda_3)}{r_1(1-\lambda_3 K_1)}} T_3^{\frac{r_2(1-\lambda_2 K_1)-m}{r_3(1-\lambda_3 K_1)}} < T_2 - R, \tag{5.32}$$

we have

$$\min\left(\frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2 K_1)-m}, \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3 K_1)}\right) = \frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2 K_1)-m}.$$

That is, the trivial solution is stable for

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2 K_1)-m}. \tag{5.33}$$

If conditions (5.29), (5.30) are satisfied and

$$T_1^{\frac{K_1(r_2\lambda_2 - r_2\lambda_3 + m\lambda_3)}{r_1(1-\lambda_3 K_1)}} T_3^{\frac{r_2(1-\lambda_2 K_1)-m}{r_3(1-\lambda_3 K_1)}} > T_2 - R, \tag{5.34}$$

we have

$$\min\left(\frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2 K_1)-m}, \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3 K_1)}\right) = \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3 K_1)}.$$

That is, we have stability of the trivial solution for

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3 K_1)}. \tag{5.35}$$

Remark 5.8. *Equality*

$$\tau_0 = \frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2 K_1)-m}, \tag{5.36}$$

corresponds to $e_0' = 0$ *and equality*

$$\tau_0 = \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3 K_1)}, \tag{5.37}$$

corresponds to $i_0' = 0$.

If (5.28)-(5.30), (5.32) and (5.36) are satisfied, we deduce that $\acute{e_0} = 0$ and $\acute{i_0} \neq 0$, and the conditions of Theorem 5.3 are satisfied. Further, for $\lambda_2 = 0$, we have $B = -(T_2 - R)\,(r_2 - m)\,e^{(r_2-m)\tau_0} < 0$ and

$$C = \frac{r_2(T_2 - R)e^{(r_2-m)\tau_0}}{k_2}\left\{\frac{e^{(r_2-m)\tau_0} - 1}{r_2 - m} + 2m\int_0^{\tau_0} I_1(u)du + \frac{-2\acute{h_0}\int_0^{\tau_0} I_2(u)du}{\acute{i_0}(1 - e^{-r_1\tau_0})^{\frac{-r_3\lambda_3 K_1}{r_1}}}\right\}.$$

where

$$I_1(u) = \int_0^u \frac{e^{r_3 u}((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1 - T_1))^{\frac{-r_3\lambda_3 K_1}{r_1}}}{e^{-(r_2-r_3-m)s}((T_1 - e^{-r_1\tau_0})e^{r_1 s} + (1 - T_1))^{\frac{(r_2\lambda_2 - r_3\lambda_3)K_1}{r_1}}}ds$$

and

$$I_2(u) = e^{r_3 u}((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1 - T_1))^{\frac{-r_3\lambda_3 K_1}{r_1}}$$

From conditions cited above $\acute{i_0} > 0$ and $\acute{h_0} < 0$ (see Appendix A, subsection 6.5), then $C > 0$. Therefore $BC < 0$. From Theorem 5.3, we have

Corollary 5.9. *If conditions (5.28)-(5.30), (5.32) and (5.36) hold, then there exist $\epsilon_0 > 0$, such that for all $|\lambda_2| < \epsilon_0$, the problem (5.21)-(5.26) has a nontrivial periodic solutions. More specifically, there exists $\beta > 0$, such that for all $0 < \alpha < \beta$, we have a nontrivial $(\tau_0 + \sigma(\alpha))$-periodic solution*
$$\Phi\left(.,\left(x_0 + \left(\frac{\acute{c_0}\acute{h_0}}{\acute{a_0}\acute{i_0}} - \frac{\acute{b_0}}{\acute{a_0}}\right)\alpha + z_1^*(\sigma(\alpha),\alpha), \alpha, -\frac{\acute{h_0}}{\acute{i_0}}\alpha + z_3^*(\sigma(\alpha),\alpha)\right)\right).$$

If (5.28)-(5.30), (5.34) and (5.37) are satisfied, we deduce that $\acute{e_0} \neq 0$ and $\acute{i_0} = 0$, and the condition of Theorem 5.3 are satisfied.
Further, for $\lambda_3 = 0$, we have $B = -r_3 T_3 e^{r_3\tau_0} < 0$ and $C = 2r_3\tau_0 K_3^{-1} T_3 e^{r_3\tau_0} > 0$. Therefore $BC < 0$.
From Theorem 5.3, we have

Corollary 5.10. *If conditions (5.28)-(5.30) (5.34) and (5.37) hold, then there exist $\epsilon_0 > 0$, such that for all $|\lambda_3| < \epsilon_0$, the problem (5.21)-(5.26) has a nontrivial periodic solutions. More specifically, there exists $\beta > 0$, such that for all $0 < \alpha < \beta$, we have a nontrivial $(\tau_0 + \sigma(\alpha))$-periodic solution*
$$\Phi\left(.,\left(x_0 + \left(\frac{-\acute{c_0}}{\acute{a_0}}\right)\alpha + z_1^*(\sigma(\alpha),\alpha), z_2^*(\sigma(\alpha),\alpha), \alpha\right)\right).$$

5.6 Conclusion

In this work, we have studied a nonlinear mathematical model describing evolution of cell population constituted by three kinds of cells (normal cells, sensitive tumor cells and resistant tumor cells) under periodic pulsed chemotherapeutic treatment. We have found sufficient conditions for exponential stability of trivial periodic solutions corresponding to eradication of the tumor. We have studied conditions of bifurcation of non trivial periodic solutions which corresponds to the onset of the tumor, that is the disease is eradicated but it is still viable, and it reappears for small perturbation on the treatment period τ. The results obtained are applied to particular cases corresponding to models of Panetta [145]. Bifurcation of nontrivial periodic solutions are studied in (**C1, C2 and C3**) corresponding to weak drug destruction rates of sensitive tumor cells, resistant tumor cells and the both tumor cells, respectively, that is the drug action on the tumor cells is not very efficient. Note that the case **(C3)** needs a more specific study of the higher derivatives of terms describing the evolution of the population and chemotherapy functions, it should be interesting to consider a dependence with respect to the drug dose treatment in order to study the perturbation in both parameters (dose treatment and period of administration), also a study in case of many drugs should be interesting these works is in preparation. In our model we consider an impulsive differential equations, it should be interesting and more realistic to consider a functional dependence like constant delays in the differential equations.

Chapter 6

Appendix of chapter 5

6.1 derivatives of $\Phi = (\Phi_1, \Phi_2, \Phi_3)$

From (5.11), for all $t \in [0, \tau]$, we have

$$\frac{d}{dt}\begin{pmatrix} \frac{\partial\Phi_1(t,X_0)}{\partial x_1} & \frac{\partial\Phi_1(t,X_0)}{\partial x_2} & \frac{\partial\Phi_1(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_2(t,X_0)}{\partial x_1} & \frac{\partial\Phi_2(t,X_0)}{\partial x_2} & \frac{\partial\Phi_2(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_3(t,X_0)}{\partial x_1} & \frac{\partial\Phi_3(t,X_0)}{\partial x_2} & \frac{\partial\Phi_3(t,X_0)}{\partial x_3} \end{pmatrix} = \begin{pmatrix} \frac{\partial F_1(\zeta(t))}{\partial x_1} & \frac{\partial F_1(\zeta(t))}{\partial x_2} & \frac{\partial F_1(\zeta(t))}{\partial x_3} \\ 0 & \frac{\partial F_2(\zeta(t))}{\partial x_2} & 0 \\ 0 & \frac{\partial F_3(\zeta(t))}{\partial x_2} & \frac{\partial F_3(\zeta(t))}{\partial x_3} \end{pmatrix} \times \begin{pmatrix} \frac{\partial\Phi_1(t,X_0)}{\partial x_1} & \frac{\partial\Phi_1(t,X_0)}{\partial x_2} & \frac{\partial\Phi_1(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_2(t,X_0)}{\partial x_1} & \frac{\partial\Phi_2(t,X_0)}{\partial x_2} & \frac{\partial\Phi_2(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_3(t,X_0)}{\partial x_1} & \frac{\partial\Phi_3(t,X_0)}{\partial x_2} & \frac{\partial\Phi_3(t,X_0)}{\partial x_3} \end{pmatrix},$$

with the initial condition $D_X(\Phi(0, X_0)) = I_{\mathbb{R}^3}$. Then we obtain

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_1} = 0, \tag{6.1}$$

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_2} = \exp\left(\int_0^t \frac{\partial F_2(\zeta(r))}{\partial x_2} dr\right), \tag{6.2}$$

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_3} = 0, \tag{6.3}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_1} = 0, \tag{6.4}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_2} = \int_0^t \exp\left(\int_u^t \frac{\partial F_3(\zeta(r))}{\partial x_3} dr\right) \frac{\partial F_3(\zeta(u))}{\partial x_2} \exp\left(\int_0^u \frac{\partial F_2(\zeta(r))}{\partial x_2} dr\right) du, \tag{6.5}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_3} = \exp\left(\int_0^t \frac{\partial F_3(\zeta(r))}{\partial x_3} dr\right), \tag{6.6}$$

$$\frac{\partial\Phi_1(t,X_0)}{\partial x_1} = \exp\left(\int_0^t \frac{\partial F_1(\zeta(r))}{\partial x_1} dr\right),$$

$$\begin{aligned} \frac{\partial\Phi_1(t,X_0)}{\partial x_2} &= \int_0^t \exp\left(\int_s^t \frac{\partial F_1(\zeta(r))}{\partial x_1} dr\right) \left\{ \frac{\partial F_1(\zeta(s))}{\partial x_2} \exp\left(\int_0^s \frac{\partial F_2(\zeta(r))}{\partial x_2} dr\right) \right. \\ &+ \left. \frac{\partial F_1(\zeta(s))}{\partial x_3} \int_0^s \exp\left(\int_u^s \frac{\partial F_3(\zeta(r))}{\partial x_3} dr\right) \frac{\partial F_3(\zeta(u))}{\partial x_2} \exp\left(\int_0^u \frac{\partial F_2(\zeta(r))}{\partial x_2} dr\right) du \right\} ds \end{aligned}$$

and

$$\frac{\partial \Phi_1(t,X_0)}{\partial x_3} = \int_0^t \exp\left(\int_u^t \frac{\partial F_1(\zeta(r))}{\partial x_1} dr\right) \frac{\partial F_1(\zeta(u))}{\partial x_3} \exp\left(\int_0^u \frac{\partial F_3(\zeta(r))}{\partial x_3} dr\right) du \qquad (6.7)$$

for all $0 \leq t \leq \tau$.
From (5.14), we have

$$\begin{pmatrix} \acute{a} & \acute{b} & \acute{c} \\ \acute{d} & \acute{e} & \acute{f} \\ \acute{g} & \acute{h} & \acute{i} \end{pmatrix} = \begin{pmatrix} 1 - \sum_{i=1}^{3} \frac{\partial \Theta_1}{\partial x_i} \frac{\partial \Phi_i}{\partial x_1} & -\sum_{i=1}^{3} \frac{\partial \Theta_1}{\partial x_i} \frac{\partial \Phi_i}{\partial x_2} & -\sum_{i=1}^{3} \frac{\partial \Theta_1}{\partial x_i} \frac{\partial \Phi_i}{\partial x_3} \\ -\sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \frac{\partial \Phi_i}{\partial x_1} & 1 - \sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \frac{\partial \Phi_i}{\partial x_2} & -\sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \frac{\partial \Phi_i}{\partial x_3} \\ -\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \frac{\partial \Phi_i}{\partial x_1} & -\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \frac{\partial \Phi_i}{\partial x_2} & 1 - \sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \frac{\partial \Phi_i}{\partial x_3} \end{pmatrix} \left(\tau_0 + \bar{\tau}, X_0 + \bar{X}\right).$$

For $\left(\bar{\tau}, \bar{X}\right) = (0,0)$, we have

$$\begin{pmatrix} \acute{a}_0 & \acute{b}_0 & \acute{c}_0 \\ \acute{d}_0 & \acute{e}_0 & \acute{f}_0 \\ \acute{g}_0 & \acute{h}_0 & \acute{i}_0 \end{pmatrix} = \begin{pmatrix} 1 - \frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1}{\partial x_1} & -\sum_{i=1}^{3} \frac{\partial \Theta_1}{\partial x_i} \frac{\partial \Phi_i}{\partial x_2} & -\frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1}{\partial x_3} - \frac{\partial \Theta_1}{\partial x_3} \frac{\partial \Phi_3}{\partial x_3} \\ 0 & 1 - \frac{\partial \Theta_2}{\partial x_2} \frac{\partial \Phi_2}{\partial x_2} & 0 \\ 0 & -\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \frac{\partial \Phi_i}{\partial x_2} & 1 - \frac{\partial \Theta_3}{\partial x_3} \frac{\partial \Phi_3}{\partial x_3} \end{pmatrix} (\tau_0, X_0).$$

6.2 The first partial derivatives of $Z^* = (z_1^*, z_2^*, z_3^*)$

(C1) $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$.
Let $\eta(\bar{\tau}) = \tau_0 + \bar{\tau}$, $\eta_1(\bar{\tau}, \alpha) = x_0 + \left(\dfrac{\acute{c}_0 \acute{h}_0 - \acute{b}_0 \acute{i}_0}{\acute{a}_0 \acute{i}_0}\right) \alpha + z_1^*(\bar{\tau}, \alpha)$, $\eta_2(\bar{\tau}, \alpha) = \alpha$ and $\eta_3(\bar{\tau}, \alpha) = -\dfrac{\alpha \acute{h}_0}{\acute{i}_0} + z_3^*(\bar{\tau}, \alpha)$.
From (5.16) and (5.17) we have

$$\begin{cases} \frac{\partial M_1}{\partial \bar{\tau}}(0,0) = 0, \\ \frac{\partial M_3}{\partial \bar{\tau}}(0,0) = 0, \end{cases}$$

then

$$\begin{cases} \frac{\partial}{\partial \bar{\tau}}(\eta_1 - \Theta_1 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))(0,0) = 0, \\ \frac{\partial}{\partial \bar{\tau}}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))(0,0) = 0. \end{cases}$$

Therefore

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} - \sum_{i=1}^{3} \frac{\partial \Theta_1(\Phi(\tau_0,X_0))}{\partial x_i} \left(\frac{\partial \Phi_i(\tau_0,X_0)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_1} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_3} \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} \right) = 0, \\ \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} - \sum_{i=1}^{3} \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_i} \left(\frac{\partial \Phi_i(\tau_0,X_0)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_1} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_3} \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} \right) = 0. \end{cases}$$

Since

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_3} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_1} = 0,$$

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial \bar{\tau}} = 0$$

and

$$\frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = 0,$$

we obtain

$$\begin{cases} \acute{a}_0 \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + \acute{c}_0 \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} = \frac{\partial \Theta_1(\Phi(\tau_0,X_0))}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}}, \\ \acute{i}_0 \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} = 0, \end{cases}$$

that is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} = \frac{1}{\acute{a}_0} \frac{\partial \Theta_1(\Phi(\tau_0,X_0))}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}}, \\ \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} = 0. \end{cases} \tag{6.8}$$

In the same way as above, we obtain

$$\begin{cases} \frac{\partial}{\partial \alpha}(\eta_1 - \Theta_1 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))(0,0) = 0, \\ \frac{\partial}{\partial \alpha}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))(0,0) = 0. \end{cases}$$

Therefore

$$\begin{cases} \left(\frac{\acute{c}_0 \acute{h}_0 - \acute{b}_0 \acute{i}_0}{\acute{a}_0 \acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial \alpha} \right) - \sum_{i=1}^{3} \frac{\partial \Theta_1(\Phi(\tau_0,X_0))}{\partial x_i} \left\{ \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_1} \left(\frac{\acute{c}_0 \acute{h}_0 - \acute{b}_0 \acute{i}_0}{\acute{a}_0 \acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial \alpha} \right) \right. \\ \qquad \left. + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_2} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_3} \left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*(0,0)}{\partial \alpha} \right) \right\} = 0, \\ \left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*(0,0)}{\partial \alpha} \right) - \sum_{i=1}^{3} \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_i} \left\{ \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_1} \left(\frac{\acute{c}_0 \acute{h}_0 - \acute{b}_0 \acute{i}_0}{\acute{a}_0 \acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial \alpha} \right) \right. \\ \qquad \left. + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_2} + \frac{\partial \Phi_i(\tau_0,X_0)}{\partial x_3} \left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*(0,0)}{\partial \alpha} \right) \right\} = 0. \end{cases}$$

Since

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_3} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_1} = 0$$

and

$$\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1}=0,$$

we obtain

$$\begin{cases} \acute{a}_0\frac{\partial z_1^*(0,0)}{\partial\alpha}+\acute{c}_0\frac{\partial z_3^*(0,0)}{\partial\alpha}=0,\\ \acute{i}_0\frac{\partial z_3^*(0,0)}{\partial\alpha}=0, \end{cases}$$

that is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\alpha}=0,\\ \frac{\partial z_3^*(0,0)}{\partial\alpha}=0. \end{cases} \tag{6.9}$$

(C2) $\acute{e}_0\neq 0$ and $\acute{i}_0=0$.

Let $\eta(\bar\tau)=\tau_0+\bar\tau,\ \eta_1(\bar\tau,\alpha)=x_0-\dfrac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar\tau,\alpha),\ \eta_2(\bar\tau,\alpha)=z_2^*(\bar\tau,\alpha)$ and $\eta_3(\bar\tau,\alpha)=\alpha$.

From (5.19) and (5.20) we have

$$\begin{cases} \frac{\partial M_1}{\partial\bar\tau}(0,0)=0,\\ \frac{\partial M_2}{\partial\bar\tau}(0,0)=0, \end{cases}$$

In the same way as above, we obtain

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\bar\tau}=\frac{1}{\acute{a}_0}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar\tau},\\ \frac{\partial z_2^*(0,0)}{\partial\bar\tau}=0. \end{cases} \tag{6.10}$$

and

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\alpha}=0,\\ \frac{\partial z_2^*(0,0)}{\partial\alpha}=0. \end{cases} \tag{6.11}$$

6.3 The first partial derivatives of f

(C1) $\acute{e}_0=0$ and $\acute{i}_0\neq 0$.

We have

$$\begin{aligned} \frac{\partial f}{\partial\bar\tau} &= \frac{\partial}{\partial\bar\tau}(\eta_2-\Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))\\ &= -\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar\tau}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial\bar\tau}\right). \end{aligned}$$

Since

$$\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1}=\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_3}=\frac{\partial\Phi_2(\tau_0,X_0)}{\partial\bar\tau}=0$$

and

$$\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1}=\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3}=0,$$

we obtain

$$\frac{\partial f(0,0)}{\partial \bar{\tau}} = 0.$$

Moreover,

$$\begin{aligned} \frac{\partial f}{\partial \alpha} &= \frac{\partial}{\partial \alpha}(\eta_2 - \Theta_2 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= 1 - \sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \left\{ \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{c_0' h_0' - b_0' i_0'}{a_0' i_0'} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \right. \\ &+ \left. \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \left(\frac{-h_0'}{i_0'} + \frac{\partial z_3^*}{\partial \alpha} \right) \right\}. \end{aligned}$$

Since

$$\frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_1} = \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_3} = 0,$$
$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_3} = 0$$

and

$$1 - \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} = e_0' = 0,$$

we obtain

$$\frac{\partial f(0,0)}{\partial \alpha} = 0.$$

Therefore $Df(0,0) = (0,0)$.
(C2) $e_0' \neq 0$ and $i_0' = 0$.
We have

$$\begin{aligned} \frac{\partial f}{\partial \bar{\tau}} &= \frac{\partial}{\partial \bar{\tau}}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= -\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \left(\frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \bar{\tau}} \right). \end{aligned}$$

Since

$$\frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_1} = 0$$

and

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial \bar{\tau}} = 0.$$

From (6.10), we have

$$\frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} = 0,$$

then

$$\frac{\partial f(0,0)}{\partial \bar{\tau}} = 0.$$

Moreover

$$\begin{aligned} \frac{\partial f}{\partial \alpha} &= \frac{\partial}{\partial \alpha}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= 1 - \sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \left\{ \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{-c_0'}{a_0'} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \left(\frac{\partial z_2^*}{\partial \alpha} \right) \right. \\ &+ \left. \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \right\}. \end{aligned}$$

We have

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_3} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_1} = 0,$$

$$\frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = 0$$

and

$$1 - \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} = \acute{i}_0 = 0.$$

From (6.11), we have

$$\frac{\partial z_2^*}{\partial \alpha}(0,0) = 0,$$

then

$$\frac{\partial f(0,0)}{\partial \alpha} = 0.$$

Therefore $Df(0,0) = (0,0)$.

6.4 Second partial derivatives of f

Let $A = \frac{\partial^2 f(0,0)}{\partial \bar{\tau}^2}$, $B = \frac{\partial^2 f(0,0)}{\partial \bar{\tau}\partial \alpha}$ and $C = \frac{\partial^2 f(0,0)}{\partial \alpha^2}$.
(C1) $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$.
Calculation of A**.** We have $\frac{\partial^2 f}{\partial \bar{\tau}^2} = \frac{\partial^2}{\partial \bar{\tau}^2}(\eta_2 - \Theta_2 \circ \Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\frac{\partial^2 f}{\partial \bar{\tau}^2} =$$

$$-\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2 \Theta_2}{\partial x_i \partial x_j}\left(\frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial \bar{\tau}}\right)$$

$$\times\left(\frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial \bar{\tau}}\right)$$

$$-\sum_{i=1}^{3}\frac{\partial \Theta_2}{\partial x_i}\left\{\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}^2} + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}\partial x_1}\frac{\partial z_1^*}{\partial \bar{\tau}} + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}\partial x_3}\frac{\partial z_3^*}{\partial \bar{\tau}}\right.$$

$$+\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial \bar{\tau}}\right)^2 + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1 \partial x_3}\frac{\partial z_1^*}{\partial \bar{\tau}}\frac{\partial z_3^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial \bar{\tau}^2}$$

$$\left.+\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\left(\frac{\partial z_3^*}{\partial \bar{\tau}}\right)^2 + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial^2 z_3^*}{\partial \bar{\tau}^2}\right\}.$$

We have

$$\frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_1^2} = \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_1} = \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_3} = 0,$$

$$\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_3} = 0$$

and

$$\frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial \bar{\tau}^2} = \frac{\partial \Phi_2(\tau_0,X_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_3(\tau_0,X_0)}{\partial \bar{\tau}} = 0.$$

From (6.1) and (6.8), we have $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1^2} = \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_1} = 0$ and $\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} = 0$, then $A = 0$.

Calculation of C. We have $\frac{\partial^2 f}{\partial\alpha^2} = \frac{\partial^2}{\partial\alpha^2}(\eta_2 - \Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\frac{\partial^2 f}{\partial\alpha^2} = -\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2}{\partial x_i\partial x_j}$$

$$\times\left\{\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\acute{c_0}\acute{h_0}-\acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\left(\frac{-\acute{h_0}}{\acute{i_0}}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}$$

$$\times\left\{\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\acute{c_0}\acute{h_0}-\acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\left(\frac{-\acute{h_0}}{\acute{i_0}}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}$$

$$-\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\left\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{\acute{c_0}\acute{h_0}-\acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}}+\frac{\partial z_1^*}{\partial\alpha}\right)^2+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_1}\left(\frac{\acute{c_0}\acute{h_0}-\acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}}+\frac{\partial z_1^*}{\partial\alpha}\right)\right.$$

$$+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_1}\left(\frac{-\acute{h_0}}{\acute{i_0}}+\frac{\partial z_3^*}{\partial\alpha}\right)\left(\frac{\acute{c_0}\acute{h_0}-\acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\partial^2 z_1^*}{\partial\alpha^2}\right)$$

$$\left.+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_2}\left(\frac{-\acute{h_0}}{\acute{i_0}}+\frac{\partial z_3^*}{\partial\alpha}\right)\frac{\partial z_2^*}{\partial\alpha}+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\left(\frac{-\acute{h_0}}{\acute{i_0}}+\frac{\partial z_3^*}{\partial\alpha}\right)^2\right\}.$$

From (6.1) and (6.3), we have $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_3} = \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3^2} = 0$.

For determining C, we must calculate the expressions $(E_1): \frac{\partial^2\Phi_2}{\partial x_2\partial x_1}$, $(E_2): \frac{\partial^2\Phi_2}{\partial x_2^2}$ and $(E_3): \frac{\partial^2\Phi_2}{\partial x_3\partial x_2}$ at (τ_0, X_0).

The second partial derivatives of Φ_2 can be obtained from the following differential equations

$$(E_1):\ \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_2\partial x_1}+\frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}+\frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_2\partial x_1}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_1}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_1}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_1}$$

then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}+\frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2\partial x_1} = 0$. We obtain

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1} = \int_0^t \exp\left(\int_0^t\frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left(\frac{\partial^2 F_2(\zeta(r))}{\partial x_2\partial x_1}\right)\exp\left(\int_0^r\frac{\partial F_1(\zeta(s))}{\partial x_1}ds\right)dr.$$

$$(E_2): \ \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_2^2} + \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2} + \frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_2^2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_2}$$

then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}$$

$$+\left(2\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + 2\frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2^2} = 0$. We obtain

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2} = \int_0^t \exp\left(\int_0^t \frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left\{2\frac{\partial^2 F_2(\zeta(r))}{\partial x_2\partial x_1}\frac{\partial\Phi_1(r,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(r))}{\partial x_2^2}\frac{\partial\Phi_2(r,X_0)}{\partial x_2}\right.$$

$$\left. + \ 2\frac{\partial^2 F_2(\zeta(r))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(r,X_0)}{\partial x_2}\right\} dr.$$

$$(E_3): \ \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_3\partial x_2} + \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2} + \frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}$$

$$+\left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_2}$$

then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2} + \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_3\partial x_2} = 0$. We obtain

$$\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\right) = \int_0^t \exp\left(\int_0^t \frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left(\frac{\partial^2 F_2(\zeta(r))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(r,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(r))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(r,X_0)}{\partial x_3}\right)dr.$$

From (6.9), we have $\frac{\partial z_1^*(0,0)}{\partial \alpha} = \frac{\partial z_3^*(0,0)}{\partial \alpha} = 0$. Therefore

$$C = -2\left\{ \frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2 \partial x_1} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} + \frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_3 \partial x_1} \left(\frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_2} + \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} \right) \right) \right\}$$

$$\times \left\{ \frac{\partial \Phi_1(\tau_0, X_0)}{\partial x_1} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} \right) + \frac{\partial \Phi_1(\tau_0, X_0)}{\partial x_2} + \frac{\partial \Phi_1(\tau_0, X_0)}{\partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} \right) \right\}$$

$$-2 \frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_3 \partial x_2} \left\{ \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_2} + \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} \right) \right\} \left(\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} \right)$$

$$- \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} \left\{ 2 \frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial x_2 \partial x_1} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} \right) + \frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial x_2^2} + 2 \frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial x_3 \partial x_2} \left(\frac{-\acute{h_0}}{\acute{i_0}} \right) \right\}$$

$$- \frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2^2} \left(\frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} \right)^2 - \frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_3^2} \left(\frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_2} + \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} \right) \right)^2 .$$

Calculation of B. We have $\frac{\partial^2 f}{\partial \bar{\tau} \partial \alpha} = \frac{\partial}{\partial \bar{\tau}} \left(\frac{\partial}{\partial \alpha} (\eta_2 - \Theta_2 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \right)$, then

$$\frac{\partial^2 f}{\partial \bar{\tau} \partial \alpha} =$$

$$-\sum_{j=1}^{3} \sum_{i=1}^{3} \frac{\partial^2 \Theta_2}{\partial x_i \partial x_j} \left(\frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \frac{\partial z_3^*}{\partial \bar{\tau}} \right)$$

$$\times \left\{ \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} + \frac{\partial z_3^*}{\partial \alpha} \right) \right\}$$

$$-\sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \left\{ \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau} \partial x_1} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2} \frac{\partial z_1^*}{\partial \bar{\tau}} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) \right.$$

$$+ \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3 \partial x_1} \frac{\partial z_3^*}{\partial \bar{\tau}} \left(\frac{\acute{c_0}\acute{h_0} - \acute{b_0}\acute{i_0}}{\acute{a_0}\acute{i_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial^2 z_1^*}{\partial \bar{\tau} \partial \alpha} + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau} \partial x_2}$$

$$+ \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1 \partial x_2} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3 \partial x_2} \frac{\partial z_3^*}{\partial \bar{\tau}} + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau} \partial x_3} \left(\frac{-\acute{h_0}}{\acute{i_0}} + \frac{\partial z_3^*}{\partial \alpha} \right)$$

$$\left. + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1 \partial x_3} \frac{\partial z_1^*}{\partial \bar{\tau}} \left(\frac{-\acute{h_0}}{\acute{i_0}} + \frac{\partial z_3^*}{\partial \alpha} \right) + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2} \frac{\partial z_3^*}{\partial \bar{\tau}} \left(\frac{-\acute{h_0}}{\acute{i_0}} + \frac{\partial z_3^*}{\partial \alpha} \right) \right\}.$$

From (6.8), we have $\frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} = \frac{1}{\acute{a_0}} \frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}}$ and $\frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} = 0$.
From equations (6.1), (6.3) and (6.2), we obtain $\frac{\partial^2 \Phi_2(t,X_0)}{\partial \bar{\tau} \partial x_1} = 0$, $\frac{\partial^2 \Phi_2(t,X_0)}{\partial \bar{\tau} \partial x_3} = 0$ and $\frac{\partial^2 \Phi_2(t,X_0)}{\partial \bar{\tau} \partial x_2} = \frac{\partial F_2(\zeta(t))}{\partial x_2} \exp \left(\int_0^t \frac{\partial F_2(\zeta(r))}{\partial x_2} dr \right)$, then

$$B = -\frac{\partial^2 \Theta_2(\Phi(\tau_0,X_0))}{\partial x_1 \partial x_2} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} \left(\frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}} + \frac{\partial \Phi_1(\tau_0,X_0)}{\partial x_1} \frac{1}{\acute{a_0}} \frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}} \right)$$

$$- \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} \left(\frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial \bar{\tau} \partial x_2} + \frac{\partial^2 \Phi_2(\tau_0,X_0)}{\partial x_1 \partial x_2} \frac{1}{\acute{a_0}} \frac{\partial \Theta_1}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}} \right).$$

(C2) $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$.
Calculation of A. We have $\frac{\partial^2 f}{\partial \bar{\tau}^2} = \frac{\partial^2}{\partial \bar{\tau}^2}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))$, then

$$\frac{\partial^2 f}{\partial \bar{\tau}^2} =$$

$$-\sum_{j=1}^{3}\sum_{i=1}^{3} \frac{\partial^2 \Theta_3}{\partial x_i \partial x_j} \left(\frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \bar{\tau}} \right)$$

$$\times \left(\frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \bar{\tau}} \right)$$

$$-\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \left\{ \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau}^2} + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau} \partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial \bar{\tau} \partial x_2} \frac{\partial z_2^*}{\partial \bar{\tau}} \right.$$

$$+\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2} \left(\frac{\partial z_1^*}{\partial \bar{\tau}} \right)^2 + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1 \partial x_2} \frac{\partial z_1^*}{\partial \bar{\tau}} \frac{\partial z_2^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \frac{\partial^2 z_1^*}{\partial \bar{\tau}^2}$$

$$\left. + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2} \left(\frac{\partial z_2^*}{\partial \bar{\tau}} \right)^2 + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial^2 z_2^*}{\partial \bar{\tau}^2} \right\}.$$

We have

$$\frac{\partial \Theta_3(\Phi(\tau_0, X_0))}{\partial x_1} = \frac{\partial^2 \Theta_3(\Phi(\tau_0, X_0))}{\partial x_1^2} = 0.$$

From (6.1), (6.4) and (6.10), we obtain

$$\frac{\partial \Phi_i(\tau_0, X_0)}{\partial x_1} = \frac{\partial^2 \Phi_i(\tau_0, X_0)}{\partial x_1^2} = 0,$$

$$\frac{\partial \Phi_i(\tau_0, X_0)}{\partial \bar{\tau}} = \frac{\partial^2 \Phi_i(\tau_0, X_0)}{\partial \bar{\tau}^2} = 0,$$

$$\frac{\partial^2 \Phi_i(\tau_0, X_0)}{\partial \tau \partial x_1} = 0,$$

for $i = 2, 3$ and

$$\frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} = 0.$$

From second partial derivative of equation (5.20), we obtain

$$\frac{\partial^2 z_2^*(0,0)}{\partial \bar{\tau}^2} \left(1 - \frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_2} \right) = \frac{\partial^2 z_2^*(0,0)}{\partial \bar{\tau}^2} \acute{e}_0 = 0,$$

then

$$\frac{\partial^2 z_2^*(0,0)}{\partial \bar{\tau}^2} = 0.$$

Thus $A = 0$.

Calculation of C. We have $\frac{\partial^2 f}{\partial \alpha^2} = \frac{\partial^2}{\partial \alpha^2}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3))$, then

$$\frac{\partial^2 f}{\partial \alpha^2} =$$

$$-\sum_{j=1}^{3}\sum_{i=1}^{3} \frac{\partial^2 \Theta_3}{\partial x_i \partial x_j} \left(\frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{-\acute{c_0}}{\acute{a_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \alpha} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \right)$$

$$\times \left(\frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{-\acute{c_0}}{\acute{a_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \alpha} + \frac{\partial \Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3} \right)$$

$$-\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \left\{ \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2} \left(\frac{-\acute{c_0}}{\acute{a_0}} + \frac{\partial z_1^*}{\partial \alpha} \right)^2 + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2 \partial x_1} \frac{\partial z_2^*}{\partial \alpha} \left(\frac{-\acute{c_0}}{\acute{a_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) \right.$$

$$+2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3 \partial x_1} \left(\frac{-\acute{c_0}}{\acute{a_0}} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1} \left(\frac{\partial^2 z_1^*}{\partial \alpha^2} \right) + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2} \left(\frac{\partial z_2^*}{\partial \alpha} \right)^2$$

$$\left. + 2\frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3 \partial x_2} \frac{\partial z_2^*}{\partial \alpha} + \frac{\partial \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2} \left(\frac{\partial^2 z_2^*}{\partial \alpha^2} \right) + \frac{\partial^2 \Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2} \right\}.$$

To determine C we must calculate the expressions (E_4): $\frac{\partial^2 z_2^*(0,0)}{\partial \alpha^2}$, (E_5): $\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_3 \partial x_1}$ and (E_6): $\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_3^2}$.
(E_4): From the second partial derivative of equation (5.20), we have

$$\left(1 - \frac{\partial \Theta_2(\tau_0,X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2}\right) \frac{\partial^2 z_2^*(0,0)}{\partial \alpha^2} = \acute{e}_0 \frac{\partial^2 z_2^*(0,0)}{\partial \alpha^2} = 0,$$

then

$$\frac{\partial^2 z_2^*(0,0)}{\partial \alpha^2} = 0.$$

(E_5): The term $\frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1}$ can be obtained from the following linear differential equation

$$\frac{d}{dt}\left(\frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1}\right) = \frac{\partial F_3(\zeta(t))}{\partial x_1} \frac{\partial^2 \Phi_1(t,X_0)}{\partial x_3 \partial x_1} + \frac{\partial F_3(\zeta(t))}{\partial x_2} \frac{\partial^2 \Phi_2(t,X_0)}{\partial x_3 \partial x_1} + \frac{\partial F_3(\zeta(t))}{\partial x_3} \frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1}$$

$$+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2} \frac{\partial \Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2 \partial x_1} \frac{\partial \Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3 \partial x_1} \frac{\partial \Phi_3(t,X_0)}{\partial x_3} \right) \frac{\partial \Phi_1(t,X_0)}{\partial x_1}$$

$$+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1 \partial x_2} \frac{\partial \Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2^2} \frac{\partial \Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3 \partial x_2} \frac{\partial \Phi_3(t,X_0)}{\partial x_3} \right) \frac{\partial \Phi_2(t,X_0)}{\partial x_1}$$

$$+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1 \partial x_3} \frac{\partial \Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2 \partial x_3} \frac{\partial \Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2} \frac{\partial \Phi_3(t,X_0)}{\partial x_3} \right) \frac{\partial \Phi_3(t,X_0)}{\partial x_1}$$

then

$$\frac{d}{dt}\left(\frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1}\right) = \frac{\partial F_3(\zeta(t))}{\partial x_3} \frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3 \partial x_1} \frac{\partial \Phi_3(t,X_0)}{\partial x_3} \frac{\partial \Phi_1(t,X_0)}{\partial x_1}$$

with the initial condition $\frac{\partial^2 \Phi_3(0,X_0)}{\partial x_3 \partial x_1} = 0$. We obtain

$$\left(\frac{\partial^2 \Phi_3(t,X_0)}{\partial x_3 \partial x_1}\right) = \int_0^t \exp\left(\int_0^t \frac{\partial F_3(\zeta(s))}{\partial x_3} ds\right) \left(\frac{\partial^2 F_3(\zeta(r))}{\partial x_3 \partial x_1}\right) \exp\left(\int_0^r \frac{\partial F_1(\zeta(s))}{\partial x_1} ds\right) dr.$$

(E_6): In the same way as above, we have

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}\right) = \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_3^2} + \frac{\partial F_3(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3^2} + \frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}$$

$$+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_3}$$

$$+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_3}$$

$$+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_3},$$

then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}\right) = \frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2} + \left(2\frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_3}$$

with the initial condition $\frac{\partial^2\Phi_3(0,X_0)}{\partial x_3^2} = 0$. We obtain

$$\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}\right) = \exp\left(\int_0^t \frac{\partial F_3(\zeta(s))}{\partial x_3}ds\right)\int_0^t\left(2\frac{\partial^2 F_3(\zeta(r))}{\partial x_3\partial x_1}\frac{\partial\Phi_1(r,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(r))}{\partial x_3^2}\frac{\partial\Phi_3(r,X_0)}{\partial x_3}\right)dr.$$

Therefore

$$C = -2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}\right) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right)\left(\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)$$

$$-2\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}\right) - \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3^2} - \frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2}\left(\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)^2.$$

Calculation of B. We have $\frac{\partial^2 f}{\partial\bar{\tau}\partial\alpha} = \frac{\partial}{\partial\bar{\tau}}\left(\frac{\partial}{\partial\alpha}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3)\right)$, then

$$\frac{\partial^2 f}{\partial\bar{\tau}\partial\alpha} =$$

$$-\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_3}{\partial x_i\partial x_j}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)$$

$$\times\left(\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0} + \frac{\partial z_1^*}{\partial\alpha}\right) + \frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\alpha} + \frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\right)$$

$$-\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\left\{\left(\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_1} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_1}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\left(\frac{-\acute{c}_0}{\acute{a}_0} + \frac{\partial z_1^*}{\partial\alpha}\right)\right.$$

$$+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar{\tau}\partial\alpha} + \left(\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_2}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\frac{\partial z_2^*}{\partial\alpha}$$

$$\left.+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial^2 z_2^*}{\partial\bar{\tau}\partial\alpha} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_3} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_3}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_3}\frac{\partial z_2^*}{\partial\bar{\tau}}\right\}.$$

From the second partial derivative of equation (5.20), we have

$$\left(1 - \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}\partial\alpha} = \acute{e}_0\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}\partial\alpha} = 0,$$

then

$$\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}\partial\alpha} = 0.$$

From equations (6.10), (6.1), (6.3), (6.4) and (6.6), we have

$$\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} = \frac{1}{\acute{a}_0}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}},$$

$$\frac{\partial z_2^*(0,0)}{\partial\bar{\tau}} = 0.$$

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_1} = 0,$$

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_3} = 0,$$

$$\frac{\partial^2\Phi_3(t,X_0)}{\partial\bar{\tau}\partial x_1} = 0$$

and

$$\frac{\partial^2\Phi_3(t,X_0)}{\partial\bar{\tau}\partial x_3} = \frac{\partial F_3(\zeta(t))}{\partial x_3}\exp\left(\int_0^t\frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right).$$

Therefore

$$B = -\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left\{\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_3}\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}}\right\}.$$

6.5 The cancer model cases

In the following, we calculate all parameters and partial differential equation terms in different cases.
Let

$$I_1(u) = e^{(r_2-r_3-m)u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{K_1(r_3\lambda_3-r_2\lambda_2)}{r_1}},$$

$$I_2(u) = e^{r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{1-\frac{r_3\lambda_3K_1}{r_1}},$$

$$I_3(u) = e^{(r_2-m)u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{1-\frac{r_2\lambda_2K_1}{r_1}},$$

Then, we have

$$\frac{\partial\Theta_i}{\partial x_j} = \begin{cases} T_i & if \quad i=j \text{ and } i\neq 2,\\ T_2-R & if \quad i=j=2,\\ 0 & if \quad i\neq j \text{ and } (i,j)\neq(3,2),\\ R & if \quad (i,j)=(3,2),\end{cases}$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1} = T_1^{-2}e^{-r_1\tau_0},$$

$$\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2} = T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0},$$

$$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} = T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3-r_3\lambda_3K_1)\tau_0},$$

$$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2} = \frac{me^{(1+\lambda_3K_1)r_3\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}I_1(u)du,$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3} = -\frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2(1-e^{-r_1\tau_0})^{2-\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0} I_2(u)du,$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2} = -\frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2(1-e^{-r_1\tau_0})^{2-\frac{r_2\lambda_2K_1}{r_1}}}\left(\int_0^{\tau_0} I_3(u)du + m\int_0^{\tau_0} I_2(u)\{\int_0^u I_1(p)dp\}du\right),$$

$$a_0' = T_1^{-1}(T_1 - e^{-r_1\tau_0}),$$

$$b_0' = \frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1(1-e^{-r_1\tau_0})^{2-\frac{r_2\lambda_2K_1}{r_1}}}\left(\int_0^{\tau_0} I_3(u)du + m\int_0^{\tau_0} I_2(u)\{\int_0^u I_1(p)dp\}du\right),$$

$$c_0' = \frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1(1-e^{-r_1\tau_0})^{2-\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0} I_2(u)du,$$

$$d_0' = 0,$$

$$e_0' = 1-(T_2-R)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0},$$

$$f_0' = 0,$$

$$g_0' = 0,$$

$$h_0' = -RT_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0} - \frac{mT_3e^{(1-\lambda_3K_1)r_3\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0} I_1(u)du$$

and

$$i_0' = 1 - T_3T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3-r_3\lambda_3K_1)\tau_0}.$$

(C1) $e_0' = 0$ and $i_0' \neq 0$. We have

$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_1} = \frac{r_2\lambda_2e^{(r_2-r_2\lambda_2K_1-m)\tau_0}}{r_1T_1^{\frac{r_1+r_2\lambda_2K_1}{r_1}}}(e^{-r_1\tau_0}-1),$$

$$\begin{aligned}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2} &= -\frac{r_1r_2\lambda_1\lambda_2k_1(T_1-e^{-r_1\tau_0})e^{r_2(1-\lambda_2k_1)\tau_0}}{e^{r_2m\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}T_1^{\frac{r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}\frac{\int_0^u I_2(s)ds}{e^{-r_1u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^2}du \\ &- \frac{r_2(1+\lambda_2k_2)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{r_2(1-\lambda_2k_1)\tau_0}}{k_2e^{r_2m\tau_0}(1-e^{-r_1\tau_0})^{\frac{-r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}\frac{I_2(u)}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}du,\end{aligned}$$

$$\begin{aligned}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2} &= \frac{2r_1r_2\lambda_1\lambda_2k_1e^{r_2(1-\lambda_2k_1)\tau_0}(T_1-e^{-r_1\tau_0})}{e^{m\tau_0}T_1^{\frac{r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}\frac{\int_0^u I_3(s)ds}{e^{-r_1u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^2}du \\ &+ \frac{2r_1r_2m\lambda_1\lambda_2k_1e^{r_2(1-\lambda_2k_1)\tau_0}(T_1-e^{-r_1\tau_0})}{e^{m\tau_0}T_1^{\frac{r_2\lambda_2K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}\frac{\int_0^u I_2(s)e^{-2r_3s}(\int_0^s I_1(r)e^{2r_3r}dr)ds}{e^{-r_1u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^2}du \\ &- \frac{r_2e^{(r_2(1-\lambda_2k_1)-m)\tau_0}T_1^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}\frac{I_3(u)}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}du \\ &- \frac{2r_2me^{(r_2-m)\tau_0}(T_1e^{r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}\frac{I_2(u)(\int_0^u I_1(s)ds)}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}du.\end{aligned}$$

We obtain

$$C = -(T_2 - R)\Bigg\{ 2\left(\frac{c_0' h_0' - b_0' i_0'}{a_0' i_0'}\right) \frac{r_2\lambda_2 e^{(r_2 - r_2\lambda_2 K_1 - m)\tau_0}}{r_1 T_1^{\frac{r_1 + r_2\lambda_2 K_1}{r_1}}} (e^{-r_1\tau_0} - T_1)$$

$$+ \frac{2r_1 r_2 \lambda_1 \lambda_2 k_1 (T_1 - e^{-r_1\tau_0})}{e^{(m - r_2(1-\lambda_2 k_1))\tau_0} T_1^{\frac{r_2\lambda_2 K_1}{r_1}}} \int_0^{\tau_0} \frac{\int_0^u \left(I_3(s) + m(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2 K_1}{r_1}} e^{-2r_3 s}(\int_0^s I_1(r) e^{2r_3 r} dr)\right) ds}{e^{-r_1 u}((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))^2} du$$

$$- \frac{r_2 e^{r_2(1-\lambda_2 k_1)\tau_0} T_1^{\frac{-r_2\lambda_2 K_1}{r_1}}}{k_2 e^{m\tau_0}(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2 K_1}{r_1}}} \int_0^{\tau_0} \frac{I_3(u) + 2m I_2(u)\int_0^u I_1(s)ds}{((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))} du$$

$$+2\left(\frac{-h_0'}{i_0'}\right) \frac{r_1 r_2 \lambda_1 \lambda_2 k_1 T_1^{\frac{-r_2\lambda_2 K_1}{r_1}} (T_1 - e^{-r_1\tau_0})}{e^{(m - r_2(1-\lambda_2 k_1))\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3 K_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1 u}\int_0^u I_2(s)ds}{((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))^2} du$$

$$-2\left(\frac{-h_0'}{i_0'}\right) \frac{r_2(1+\lambda_2 k_2) T_1^{\frac{-r_2\lambda_2 K_1}{r_1}}}{k_2 e^{(m - r_2(1-\lambda_2 k_1))\tau_0}(1-e^{-r_1\tau_0})^{\frac{-r_3\lambda_3 K_1}{r_1}}} \int_0^{\tau_0} \frac{I_2(u)}{((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))} du \Bigg\}.$$

$$\frac{\partial \Phi_1(\tau_0, X_0)}{\partial \bar\tau} = \dot{x}_s(\tau_0) = \frac{r_1 K_1 (1-T_1)(T_1 - e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2 (1-e^{-r_1\tau_0})^2},$$

$$\frac{\partial z_1^*(0,0)}{\partial \bar\tau} = \frac{r_1 K_1 (1-T_1) e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2},$$

$$\frac{\partial^2 \Phi_2(\tau_0, X_0)}{\partial\bar\tau \partial x_2} = \left(r_2 - m - \frac{r_2\lambda_2 K_1 (T_1 - e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right) T_1^{\frac{-r_2\lambda_2 K_1}{r_1}} e^{(r_2 - r_2\lambda_2 K_1 - m)\tau_0}.$$

We obtain

$$\begin{aligned} B &= -(T_2 - R)\left(r_2 - m - \frac{r_2\lambda_2 K_1 (T_1 - e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right) T_1^{\frac{-r_2\lambda_2 K_1}{r_1}} e^{(r_2 - r_2\lambda_2 K_1 - m)\tau_0} \\ &+ (T_2 - R)\frac{r_2\lambda_2 e^{(r_2 - r_2\lambda_2 K_1 - m)\tau_0}}{T_1^{\frac{r_1 + r_2\lambda_2 K_1}{r_1}}} \frac{K_1(1-T_1)(T_1 - e^{-r_1\tau_0})e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2}. \end{aligned}$$

(C2) $e_0' \neq 0$ and $i_0' = 0$. We have

$$\frac{\partial^2 \Phi_3(\tau_0, X_0)}{\partial x_3 \partial x_1} = -\frac{r_3\lambda_3 e^{(r_3 - r_3\lambda_3 K_1)\tau_0}}{T_1^{\frac{r_3\lambda_3 K_1}{r_1}} (1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3 K_1}{r_1} - 2}} \int_0^{\tau_0} \frac{e^{r_1 u}}{I_2(u)((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))} du,$$

$$\begin{aligned} \frac{\partial^2 \Phi_3(\tau_0, X_0)}{\partial x_3^2} &= -2r_3 K_3^{-1} \tau_0 e^{(r_3 - r_3\lambda_3 K_1)\tau_0} T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} \\ &+ \frac{r_1 r_3 \lambda_1 \lambda_3 K_1 (T_1 - e^{-r_1\tau_0})}{e^{-(r_3 - r_3\lambda_3 K_1)\tau_0} T_1^{\frac{r_3\lambda_3 K_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1 u}\int_0^u I_2(p)dp}{I_2(u)((T_1 - e^{-r_1\tau_0})e^{r_1 u} + (1-T_1))} du. \end{aligned}$$

We obtain

$$
\begin{aligned}
C &= \frac{2r_3\lambda_3 T_3 e^{(r_3-r_3\lambda_3K_1)\tau_0}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}-2}}\left(\frac{-\acute{c_0}}{\acute{a_0}}\right)\int_0^{\tau_0}\frac{e^{r_1u}}{I_2(u)((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}du \\
&+ 2r_3K_3^{-1}\tau_0T_3e^{(r_3-r_3\lambda_3K_1)\tau_0}T_1^{\frac{-r_3\lambda_3K_1}{r_1}} \\
&- \frac{r_1r_3\lambda_1\lambda_3K_1T_3(T_1-e^{-r_1\tau_0})}{e^{-(r_3-r_3\lambda_3K_1)\tau_0}T_1^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}\left(\frac{e^{r_1u}\int_0^u I_2(p)dp}{I_2(u)((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}\right)du.
\end{aligned}
$$

$$
\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} = \frac{r_1K_1(1-T_1)e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2},
$$

$$
\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} = r_3\left(1-\frac{\lambda_3K_1(T_1-e^{-r_1\tau_0})e^{r_1\tau_0}}{T_1(e^{r_1\tau_0}-1)}\right)T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3-r_3\lambda_3K_1)\tau_0}.
$$

We obtain

$$
\begin{aligned}
B &= -r_3\left(1-\frac{\lambda_3K_1(T_1-e^{-r_1\tau_0})e^{r_1\tau_0}}{T_1(e^{r_1\tau_0}-1)}\right)T_3T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3-r_3\lambda_3K_1)\tau_0} \\
&+ \frac{r_1r_3\lambda_3K_1(1-T_1)T_3e^{(r_3-r_1-r_3\lambda_3K_1)\tau_0}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}\frac{e^{r_1u}}{I_2(u)((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))}du.
\end{aligned}
$$

Part III

Contribution to the study of a deterministic model describing the role of prion in Alzheimer disease: molecular scale

Chapter 7

L^p, Distributions and Sobolev Spaces

Dealing with differential equations one cannot avoid to study functions in L^p-spaces (mainly L^2-spaces) all of whose derivatives of some order are in L^p. (The derivatives are sometimes taken in the weak sense.) This leads to the Sobolev spaces.

7.1 L^p Spaces

In this section we concentrate ourselves on the basic structural facts about the L^p spaces. Here, part of the theory, in particular the study of their linear functionals, is best formulated in the more general context of Banach spaces.

7.1.1 Definitions and basic properties

Definition 7.1. *Let $0 < p < 1$ and let $(X, \mathcal{M}, \mu)$ denote a measure space. If $f : X \to \mathbb{R}$ is a measurable function, then we define*

$$\|f\|_{L^p(X)} = \left(\int_X |f|^p dx\right)^{\frac{1}{p}}$$

and

$$\|f\|_{L^\infty(X)} = ess \sup_{x \in X} |f(x)|.$$

Note that $\|f\|_{L^\infty(X)}$ may take the value ∞.

Definition 7.2. *The space $L^p(X)$ is the set*

$$L^p(X) = \{f : X \to \mathbb{R} \setminus \|f\|_{L^p} < \infty\}.$$

The space $L^p(X)$ satisfies the following vector space properties:

(1) *For each* $\alpha \in \mathbb{R}$, *if* $f \in L^p(X)$ *then* $\alpha f \in L^p(X)$;

(2) *If* f, $g \in L^p(X)$, *then*

$$|f+g|^p \leq 2^{p-1}(|f|^p + |g|^p);$$

so that $|f+g| \in L^p(X)$.

(3) *The triangle inequality is valid if* $p \geq 1$.

The most interesting cases are $p = 1, 2, \infty$, *while all of the* L^p *arise often in nonlinear estimates.*

Definition 7.3. *The space* l^p, *called "small* L^p*", will be useful when we introduce Sobolev spaces on the torus and the Fourier series. For* $1 \leq p < \infty$, *we set*

$$l^p = \left\{ \{x_n\}_{n=1}^{\infty} \setminus \sum_{n=1}^{\infty} |x_n|^p < \infty \right\}.$$

7.1.2 Basic inequalities

Theorem 7.4. *(Hölder's inequality, [41]). Suppose that* $0 \leq p \leq \infty$ *and* $1 < q < \infty$ *with* $\frac{1}{p} + \frac{1}{q} = 1$. *If* $f \in L^p$ *and* $g \in L^q$, *then* $fg \in L^1$. *Moreover,*

$$\|fg\|_{L^1} \leq \|f\|_{L^p} \|g\|_{L^q}.$$

Note that $p = q = 2$, *gives the Cauchy-Schwarz inequality since* $\|fg\|_{L^1} = |(f,g)_{L^2}|$.

Definition 7.5. $q = \frac{p}{p-1}$ *or* $\frac{1}{q} = 1 - \frac{1}{p}$ *is called the conjugate exponent of* p.

Theorem 7.6. *(Minkowski's inequality, [41]). If* $1 \leq p \leq \infty$ *and* $f, g \in L^p$ *then*

$$\|f+g\|_{L^p} \leq \|f\|_{L^p} + \|g\|_{L^p}.$$

Corollary 7.7. *([41]) For* $1 \leq p \leq \infty$, $L^p(X)$ *is a normed linear space.*

7.1.3 The space $(L^p(X), \|.\|_{L^p})$ is complete

Recall that a normed linear space is a Banach space if every Cauchy sequence has a limit in that space; furthermore, recall that a sequence $x_n \to x$ in X if $\lim_{n\to\infty} \|x_n - x\|_X = 0$.

The proof of completeness uses the following two lemmas that are restatements of the Monotone Convergence Theorem and the Dominated Convergence Theorem (DCT), respectively.

Lemma 7.8. *([41]) If* $f_n \to L^1(X)$, $0 \leq f_1(x) \leq f_2(x) \leq \ldots$, *and* $\|f_n\|_{L^1} \leq C < 1$, *then* $\lim_{n\to\infty} f_n(x) = f(x)$ *with* $f \in L^1(X)$ *and* $\|f_n - f\|_{L^1} \to 0$ *as* $n \to 0$.

Lemma 7.9. *(DCT, [41]). If* $f_n \in L^1(X)$, $\lim_{n\to\infty} f_n(x) = f(x)$ *a.e., and if* $\exists g \in L^1(X)$ *such that* $|f_n(x)| \leq |g(x)|$ *a.e. for all* n, *then* $f \in L^1(X)$ *and* $\|f_n - f\|_{L^1} \to 0$.

7.1.4 Convergence criteria for L^p functions

If $\{f_n\}$ is a sequence in $L^p(X)$ that converges to f in $L^p(X)$, then there exists a subsequence $\{f_{n_k}\}$ such that $f_{n_k}(x) \to f(x)$ for almost every $x \in X$ (denoted by a.e.), but it is in general not true that the entire sequence itself will converge pointwise a.e. to the limit f, without some further conditions holding.

Example 7.10. *Set $X = \mathbb{R}$, and for $n \in \mathbb{N}$, set $f_n = 1_{[n,n+1]}$. Then $f_n(x) \to 0$ as $n \to \infty$, but $\|f_n\|_{L^p} = 1$ for $p \in [1, \infty)$; thus, $f_n \to 0$ pointwise, but not in L^p.*

Theorem 7.11. *([41]) For $1 \leq p < \infty$, suppose that $\{f_n\} \subset L^p(X)$ and that $f_n(x) \to f(x)$ a.e. If $\lim_{n\to\infty} \|f_n\|_{L^p} = \|f\|_{L^p}$, then $f_n \to f$ in $L^p(X)$.*

7.1.5 The space $L^\infty(X)$

Definition 7.12. *With $\|f\|_{L^\infty(X)} = \inf\{M \geq 0 \setminus |f(x)| \leq M a.e.\}$, we set*

$$L^\infty(X) = \{f : X \to \mathbb{R} \setminus \|f\|_{L^\infty} < \infty\}.$$

Theorem 7.13. *([41]) $(L^\infty(X), \|.\|_{L^\infty})$ is a Banach space.*

Lemma 7.14. *(L^p comparisons, [41]). If $1 \leq p < q < r \leq \infty$, then*

(a) $L^p \bigcap L^r \subset L^q$,

(b) $L^q \subset L^p + L^r$.

Theorem 7.15. *([41]) If $\mu(X) \leq \infty$ and $q > p$, then $L^q \subset L^p$.*

Lemma 7.16. *([41]) If $p \in [1, 1)$, then the set of simple functions $f = \sum_{i=1}^n a_i 1_{E_i}$, where each E_i is an element of the σ-algebra $\mathcal{A}$ and $\mu(E_i) < \infty$, is dense in $L^p(X, \mathcal{A}, \mu)$.*

7.2 Distributions

A distribution is a linear functional on a space of test functions. Distributions include all locally integrable functions and have derivatives of all orders (great for linear problems) but cannot be multiplied in any natural way (not so great for nonlinear problems). One can use many different spaces of test functions. We consider here distributions on space $\mathcal{D}(\Omega)$ of smooth compactly supported test functions where $\Omega \subset \mathbb{R}^n$ is an open set (which we call simply "distributions").

7.2.1 Test functions

If $\Omega \subset \mathbb{R}^n$ is an open set (possibly equal to $\mathbb{R}^n$), then the space $\mathcal{D}(\Omega)$ consists of all smooth functions ϕ whose support *supp* ϕ is a compact subset of Ω (i.e. $\mathcal{D}(\Omega) = C_c^\infty(\Omega)$ as a set).
The topology on $\mathcal{D}(\Omega)$ corresponds to the following notion of convergence of

test functions: $\phi_n \to \phi$ in $\mathcal{D}(\Omega)$ if there exists a compact set $K \subset \Omega$. such that *supp* $\phi_n \subset K$ for every $n \in \mathbb{N}$ and $\partial^\alpha \phi_n \to \partial^\alpha \phi$ uniformly on for every multi-index $\alpha \in \mathbb{N}^n$.
The space $\mathcal{D}(\Omega)$ is a topological vector space, but its topology is not metrizable. Nevertheless, somewhat remarkably, sequential continuity of a functional is equivalent to continuity.

7.2.2 Distributions in $D'(\Omega)$

A distribution $T \in \mathcal{D}'(\Omega)$ is a continuous linear functional

$$T : \mathcal{D}(\Omega) \to \mathbb{C}, \quad \phi \mapsto \langle T, \phi \rangle$$

Here, continuity means that

$$\langle T, \phi_n \rangle \to \langle T, \phi \rangle \quad \text{if} \quad \phi_n \to \phi \quad \text{in} \quad \mathcal{D}(\Omega).$$

Example 7.17. *If $\phi \in L^1_{loc}(\Omega)$, then T_f defined by*

$$\langle T_f, \phi \rangle = \int_\Omega f \phi dx$$

is a distribution, called a regular distribution. The function f is determined by the distribution T_f up to pointwise a.e. equivalence. We typically identify T_f with the function f and write $T_f = f$.

We shall define the derivative of a distribution in such a way that it agrees with the usual notion of derivative on those distributions which arise from continuously differentiable functions. That is, we want to define $\partial^\alpha : \mathcal{D}'\Omega) \to \mathcal{D}'(\Omega)$ so that

$$\partial^\alpha(T_f) = T_{D^\alpha f}, \quad |\alpha| \leq m, \quad f \in C^m(\Omega).$$

But a computation with integration-by-parts gives

$$T_{D^\alpha f}(\varphi) = (-1)^{|\alpha|} T_f(D^\alpha \varphi), \quad \varphi \in C_c^\infty(\Omega),$$

and this identity suggests the following.

Definition 7.18. *The α^{th} partial derivative of the distribution T is the distribution $\partial^\alpha T$ defined by*

$$\partial^\alpha T(\varphi) = (-1)^{|\alpha|} T(D^\alpha \varphi), \quad \varphi \in C_c^\infty(\Omega),$$

Since $D^\alpha \in L(C_c^\infty(\Omega), C_c^\infty(\Omega))$, it follows that $\partial \alpha^T$ is linear. Every distribution has derivatives of all orders and so also then does every function, e.g., in $L^1_{loc}(\Omega)$, when it is identified as a distribution. Furthermore, by the very definition of the derivative ∂^α it is clear that ∂^α and D^α are compatible with the identification of $C_c^\infty(\Omega)$ in $\mathcal{D}'(G)$.

Theorem 7.19. *([41])*

(a) *If S is a distribution on $\mathbb{R}$, then there exists another distribution T such that $\partial T = S$.*

(b) *If T_1 and T_2 are distributions on $\mathbb{R}$ with $\partial T_1 = \partial T_2$, then $T_1 - T_2$ is constant.*

Theorem 7.20. *([41]) If $f : \mathbb{R} \to \mathbb{R}$ is absolutely continuous, then $g = Df$ defines $g(x)$ for almost every $x \in \mathbb{R}$, $g \in L^1_{loc}(\mathbb{R})$, and $\partial f = g$ in $D^*(\mathbb{R})$. Conversely, if T is a distribution on $\mathbb{R}$ with $\partial T \in L^1_{loc}(\mathbb{R})$, $T(= T_f) = f$ for some absolutely continuous f, and $\partial T = Df$.*

7.3 Sobolev spaces

In this section, we give a brief overview on basic results of the theory of Sobolev spaces and their associated trace and dual spaces.

Definition 7.21. *For integers $k \geq 0$ and $1 \leq p \leq \infty$,*

$$W^{k,p}(\Omega) = \{u \in L^1_{loc}(\Omega) \setminus D^\alpha u \text{ exists and is in } L^p(\Omega) \text{ for } |\alpha| \leq k\},$$

Definition 7.22. *For $u \in W^{k,p}(\Omega)$ define*

$$\|u\|_{W^{k,p}(\Omega)} = \left(\sum_{|\alpha| \leq k} \|D^\alpha u\|^p_{L^p(\Omega)} \right)^{\frac{1}{p}} \quad \text{for } 1 \leq p < \infty,$$

and

$$\|u\|_{W^{k,\infty}} = \sum_{|\alpha| \leq k} \|D^\alpha u\|_{L^\infty}.$$

The function $\|.\|_{W^{k,p}(\Omega)}$ is clearly a norm since it is a finite sum of L^p norms.

Definition 7.23. *A sequence $u_j \to u$ in $W^{k,p}(\Omega)$ if*

$$\lim_{j \to \infty} \|u_j - u\|_{W^{k,p}} = 0.$$

Theorem 7.24. *([1]) $W^{k,p}(\Omega)$ is a Banach space.*

Definition 7.25. *For integers $k \geq 0$ and $p = 2$, we define*

$$H^k(\Omega) = W^{k,2}(\Omega).$$

$H^k(\Omega)$ is a Hilbert space with inner-product $(u; v)_{H^k(\Omega)} = \sum_{|\alpha| \leq k} (D^\alpha u, D^\alpha v)_{L^2(\Omega)}$.

7.3.1 Morrey's inequality

Theorem 7.26. *(Morrey's inequality, [1]). For $n < p \leq \infty$, let $B(x,r) \subset \mathbb{R}^n$ and let $y \in B(x,r)$. Then*

$$|u(x) - u(y)| \leq C r^{1-\frac{n}{p}} \|Du\|_{L^p(B(x,2r))} \quad \forall u \in C^1(\mathbb{R}).$$

Theorem 7.27. *(Sobolev embedding theorem for $k = 1$, [1]). There exists a constant $C = C(p,n)$ such that*

$$\|u\|_{C^{0,1-\frac{n}{p}}(\mathbb{R}^n)} \leq C \|u\|_{W^{1,p}(\mathbb{R}^n)}.$$

7.3.2 The Gagliardo-Nirenberg-Sobolev inequality

Theorem 7.28. *(Gagliardo-Nirenberg inequality, [1]). For* $1 \le p < n$*, set* $p^* = \frac{np}{n-p}$*. Then*

$$\|u\|_{L^{p^*}(\mathbb{R}^n)} \le C_{p,n} \|Du\|_{L^p(\mathbb{R}^n)}.$$

Theorem 7.29. *([1]) Suppose that* $u \in H^1(\mathbb{R}^2)$*. Then for all* $1 \le q < \infty$*,*

$$\|u\|_{L^q(\mathbb{R}^2)} \le C\sqrt{q}\|u\|_{H^1(\mathbb{R}^2)}.$$

7.3.3 Sobolev extensions and traces

Let $\Omega \subset \mathbb{R}^n$ denote an open, bounded domain with C^1 boundary.

Theorem 7.30. *([1]) Suppose that* $\tilde{\Omega} \subset \mathbb{R}^n$ *is a bounded and open domain such that* $\Omega \subset\subset \tilde{\Omega}$*. Then for* $1 \le p \le \infty$*, there exists a bounded linear operator*

$$E : W^{1,p}(\Omega) \to W^{1,p}(\mathbb{R}^n)$$

such that for all $u \in W^{1,p}(\Omega)$*,*

(1) $Eu = u$ *a.e. in* Ω*,*

(2) $spt(u) \subset \tilde{\Omega}$*,*

(3) $\|Eu\|_{W^{1,p}(\mathbb{R}^n)} \le C\|u\|_{W^{1,p}(\Omega)}$ *for a constant* $C = C(p, \Omega, \tilde{\Omega})$*.*

Theorem 7.31. *([1]) For* $1 \le p < \infty$*, there exists a bounded linear operator*

$$T : W^{1,p}(\Omega) \to L^p(\Omega)$$

(1) $Tu = u|_{\partial\Omega}$ *for all* $u \in W^{1,p}(\Omega) \bigcup C^0(\bar{\Omega})$*,*

(2) $\|Tu\|_{L^p(\partial\Omega)} \le C\|u\|_{W^{1,p}(\Omega)}$ *for a constant* $C = C(p, \Omega)$*.*

7.3.4 The subspace $W_0^{1,p}(\Omega)$

Definition 7.32. *We let* $W_0^{1,p}(\Omega)$ *denote the closure of* $C_0^\infty(\Omega)$ *in* $W^{1,p}(\Omega)$*.*

Theorem 7.33. *([1]) Suppose that* $\Omega \subset \mathbb{R}^n$ *is bounded with* C^1 *boundary, and that* $u \in W^{1,p}(\Omega)$*. Then*

$$W_0^{1,p}(\Omega) \quad \textit{iff} \quad Tu = 0 \quad \text{on} \quad \partial\Omega.$$

We can now state the Sobolev embedding theorems for bounded domains

Theorem 7.34. *(Gagliardo-Nirenberg inequality for* $W^{1,p}(\Omega)$*, [1]). Suppose that* $\Omega \subset \mathbb{R}^n$ *is open and bounded with* C^1 *boundary,* $1 \le p < n$*, and* $u \in W^{1,p}(\Omega)$*. Then*

$$\|u\|_{L^{\frac{np}{n-p}}(\Omega)} \le C\|u\|_{W^{1,p}(\Omega)} \quad \text{for a constant} \quad C = C(p, n, \Omega).$$

Theorem 7.35. *(Gagliardo-Nirenberg inequality for $W_0^{1,p}(\Omega)$, [1]). Suppose that $\Omega \subset \mathbb{R}^n$ is open and bounded with C^1 boundary, $1 \leq p < n$, and $u \in W_0^{1,p}(\Omega)$. Then for all $1 \leq q \leq \frac{np}{n-p}$,*

$$\|u\|_{L^q(\Omega)} \leq C\|Du\|_{L^p(\Omega)} \quad \textit{for a constant} \quad C = C(p, n, \Omega).$$

For additional details on L^p, distributions and Sobolev spaces, the books of Adams and Fournier [1], Brezis [41], Demengel [60] and Evans [72] are excellent sources.

Chapter 8

Alzheimer's disease: analysis of a mathematical model including the role of the prion protein

We introduce a model accounting for the *in vivo* dynamics of Alzheimer's disease including the role of the prion protein onto the memory impairment. We use a size-structured equation to describe the formation of β-amyloid plaques coupled with three differential equations on the concentration of Aβ oligomers, PrP^C proteins and A$\beta - \times - PrP^C$ complex since this latter has been considered, in some recent findings, to be responsible for the synaptic toxicity. We prove well-posedness of the problem and stability results of the unique equilibrium, when the polymerization rate of β-amyloid is constant and then when it is described as power law.

8.1 Introduction

What is the link between Alzheimer disease and the prion proteins? Alzheimer's disease (AD) is to our knowledge one of the most widespread age-related dementia with an estimation of about 35.6 million people worldwide being affected in 2009, as reported by the World Alzheimer Report 2010 [169]. By the 2050's, this same report has predicted three or four times more people living with AD. This syndrome affects memory, thinking, behavior, ability to perform activities and eventually leads to death. Apart from social side-effects for patients, another notable consequence of AD is its cost valued at \$422 billions in 2009 [169]. Considering this situation, the stake being so much important to understand and cure Alzheimer disease that research has been very prolific. Amongst these results, recent findings in AD imply cellular prion protein (PrP^C) into the memory impairment [88, 126]. This phenomenon caught our attention since memory loss is one of the most painful syndrome related to this disease. Thus, contributing to the understanding of the dynamics behind this process seemed to us quite challenging and at the same time would help to enlighten the biologists to find ways to cure the patients, at least for this aspect of the disease.

The pathogenesis of AD is related to a gradual build-up of β-amyloid (Aβ) plaques in the brain [98].β-amyloid plaques are formed from the Aβ peptides obtained from the amyloid protein precursor (APP) protein cleaved at a bad position. There exist different forms of β-amyloids , from soluble monomers to insoluble fibrillar aggregates [130, 131, 162, 165]. It has been revealed that the toxicity depends on the size of the structure and recent evidences suggest that oligomers (small aggregates) play a key role in memory impairment rather than β-amyloid plaques (larger aggregates) formed in the brain [154]. More specifically, Aβ oligomers cause spatial memory impairment via synaptic toxicity onto neurons. This phenomenon seems to be induced by a membrane receptor and there are some evidences that this rogue is the PrP^C protein [140]. We remind that this protein, when misfolded in a pathological form called PrP^{Sc} is responsible for Creutzfeldt-Jacob disease . It is believed indeed that there is a high affinity between PrP^C and Aβ oligomers, moreover the prion proteins has also been identified as an APP regulator which confirms that both are highly related [140, 50]. Thanks to this discovery, it could be expected f a new therapeutic target to recover memory in AD, or at least stopping the memory depletion, without however being able to stop death.

What is our objective? Our objective here is to introduce and study a brand new in vivo evolution model of AD mediated by PrP^C proteins. To the best of our knowledge, no model such as the one proposed here has ever been set-up. There exist some models specifically designed for Alzheimer's disease and their treatment, such the one studied in [56, 57]. Nevertheless, the prion protein has never been taken into account. The model studied here could be a starting point to design new treatments.

This paper is organized as follows. We present the model in section 8.2, and provide a well-posedness result in the particular case where β-amyloids are formed at a constant rate. Then, the third section is dedicated to a theoretical study of our model in a more general context with power law rate of polymerization, i.e. the polymerization or build-up rate depends on the size. Finally, in the fourth section we propose a numerical scheme for the system and test it in particular cases.

8.2 The model

8.2.1 A model for β-amyloid formation with prion

The model deals with four different species. First, the concentration of Aβ oligomers consisting of aggregates of few Aβ peptides, then the concentration of the PrP^C protein, third we have the concentration of the complex formed

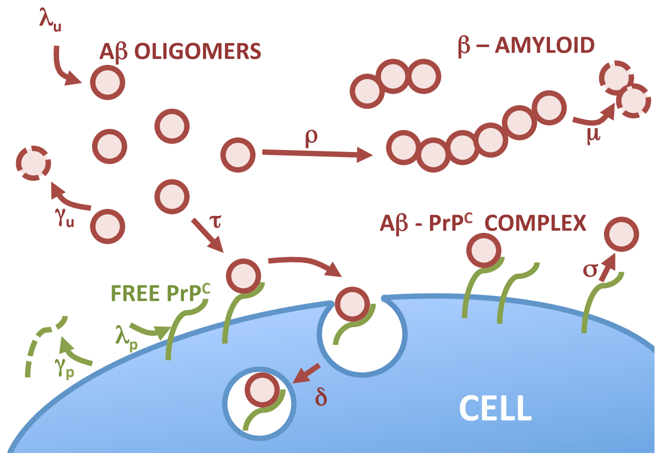

Figure 8.1: Schematic diagram of the evolution processes of β-amyloid plaques, Aβ-oligomers (bounded and unbounded), and PrP^C in the model.

from one Aβ oligomer binding onto one PrP^C protein. These quantities are soluble and their concentration will be described in terms of ordinary differential equations. Finally we have the insoluble β-amyloid plaques described by a density according to their size. Note that the size x is an abstract variable that could be the volume of the aggregate. However we consider here that aggregates lengthen like fibrils (one dimension). A 2D or 3D model would be more biologically accurate but the model would be technically and numerically more complex. This present model is a first step to upcoming 2D and 3D versions of the problem. The size x belongs thus here to the interval $(x_0; +\infty)$, where x_0 stands for a critical size below which the plaques become unstable and break into oligomers. To summarize we denote, for $x \in (x_0; +\infty)$ and $t \geq 0$,

- $f(t,x) \geq 0$: the density of Aβ plaques of size x at time t,
- $u(t) \geq 0$: the concentration of soluble Aβ oligomers (unbounded oligomers) at time t,
- $p(t) \geq 0$: the concentration of soluble cellular prion proteins PrP^C at time t,
- $b(t) \geq 0$: the concentration of A$\beta - \times - PrP^C$ complex (bounded oligomers) at time t.

Note that β-amyloid plaques are formed from the clustering of Aβ oligomers. The rate of agglomeration depends on the concentration of soluble oligomers and the structure of the amyloid which is linked to its size. Actually, it consists in a mass action between plaques and oligomers at a non-negative rate given by

$\rho(x)$ where x is the size of the plaque. This is the reason why the deliberate misused word "size" considered here (and described above) accounts for the mass of Aβ oligomers that form the polymer. We assume indeed, that the mass of one oligomer is given by a sufficiently small parameter $\varepsilon > 0$. Thus the number of oligomers in a plaque of mass $x > 0$ is x/ε which justifies that we assume the size of the plaques to be continuous. Moreover, amyloids have a critical size

$$x_0 = \varepsilon n > 0,$$

where $n \in \mathbb{N}^*$ is the number of oligomers in the critical plaque. The amyloids are prone to be damaged at a non-negative rate μ, possibly depending on the size x of the plaques. All the parameters for Aβ oligomers, PrP^C and complex, as production, binding and degradation rate are non-negative and described in table 8.1. Then, writing evolution equations for these four quantities, we get

Parameter/Variable	Definition	Unit
t	Time	days
x	Length of βamyloid fibrils	–
x_0	Critical mass of βamyloid plaques	–
n	Number of oligomers in a plaque of size x_0	–
ε	Mass of one oligomer	–
λ_u	Source of Aβ oligomers	days^{-1}
γ_u	Degradation rate of Aβ oligomers	days^{-1}
λ_p	Source of PrP^C	days^{-1}
γ_p	Degradation rate of PrP^C	days^{-1}
τ	Binding rate of β oligomers onto PrP^C	days^{-1}
σ	Unbinding rate of $A\beta - \times - PrP^C$	days^{-1}
δ	Degradation rate of $A\beta - \times - PrP^C$	days^{-1}
$\rho(x)$	Conversion rate of oligomers into a fibril	(SAF/sq)$^{-1}$ *·days^{-1}
$\mu(x)$	Degradation rate of a fibril	days^{-1}

∗ SAF/sq means Scrapie-Associated Fibrils per square unit and is explained in detail by Rubenstein et al. [152]
(we consider plaques as being fibrils here).

Table 8.1: Parameters description of the model

for any $t > 0$

$$\frac{\partial}{\partial t} f(x,t) + u(t)\frac{\partial}{\partial x}\big[\rho(x) f(x,t)\big] = -\mu(x) f(x,t), \quad \text{over } (x_0, +\infty) \tag{8.1}$$

$$\dot{u} = \lambda_u - \gamma_u u - \tau u p + \sigma b - n N(u) - \frac{1}{\varepsilon} u \int_{x_0}^{+\infty} \rho(x) f(x,t) dx, \tag{8.2}$$

$$\dot{p} = \lambda_p - \gamma_p p - \tau u p + \sigma b, \tag{8.3}$$

$$\dot{b} = \tau u p - (\sigma + \delta) b. \tag{8.4}$$

The term N accounts for the formation rate of a new β-amyloid plaque with size x_0 from the Aβ oligomers. In order to balance this term, we add the boundary condition

$$u(t)\rho(x_0) f(x_0, t) = N(u(t)), \quad \text{for any } t \geq 0. \tag{8.5}$$

The integral in the right-hand side of equation (8.2) is the total polymerization with parameters $1/\varepsilon$ since dx/ε counts the number of oligomers into a unit of length dx. Finally, the problem is completed with non-negative initial data

$$f(x, t = 0) = f^{in}(x) \geq 0, \ \forall x \geq x_0, \tag{8.6}$$

and,

$$u(t = 0) = u^{in} \geq 0, \ p(t = 0) = p^{in} \geq 0 \text{ and } b(t = 0) = b^{in} \geq 0. \tag{8.7}$$

where f^{in}, u^{in}, p^{in} and b^{in} are given data. In Figure 8.2.1 we give a schematic representation of these processes.

8.2.2 An associated ODE system

In this section we are interested in a constant polymerization and degradation rate, *i.e* independent of the structure of the plaque involved in the process, so we assume that

$$\rho(x) := \rho \text{ and } \mu(x) := \mu,$$

are positive constants. Moreover, without loss of generality we let $\varepsilon = 1$ even if it means to rescale the equations. Then we assume a pre-equilibrium hypothesis for the formation of β-amyloid plaques, as formulated in [150] for filament formation, thus we let

$$N(u) = \alpha u^n.$$

The formation rate is given by $\alpha > 0$ and the number of oligomers necessary to form a new plaque is an integer, $n \geq 1$. Doing these assumptions we are able to closed the system (8.1-8.4) with respect to (8.5) into a system of four differential equations. Indeed, integrating (8.1) over $(x_0, +\infty)$ we get formally an equation over the quantity of amyloids at time $t \geq 0$

$$A(t) = \int_{x_0}^{+\infty} f(x,t) dx.$$

This method has already been employed on prion model in first approximation in [90]. Now the problem reads

$$\begin{cases} \dot{A} &= \alpha u^n - \mu A, \\ \dot{u} &= \lambda_u - \gamma_u u - \tau u p + \sigma b - \alpha n u^n - \rho u A, \\ \dot{p} &= \lambda_p - \gamma_p p - \tau u p + \sigma b, \\ \dot{b} &= \tau u p - (\sigma + \delta) b. \end{cases} \tag{8.8}$$

The mass of βamyloid plaques is given by $M(t) = \int_{x_0}^{+\infty} x f(x,t)dx$ which satisfies an equation (formal integration of (8.1)) that can be solved independently since

$$\dot{M} = n\alpha u^n + \rho u A - \mu M. \tag{8.9}$$

Notice that initial conditions for A and M are given by $A^{in} = \int_{x_0}^{+\infty} f^{in}(x)dx$ and $M^{in} = \int_{x_0}^{+\infty} x f^{in}(x)dx$, while the ones on u, p and b are unchanged. The next section is devoted to the analysis of the system (8.8).

8.2.3 Well-posedness and stability of the ODE system

We first state, in the following proposition, existence and uniqueness of a global solution to the system (8.8) which derived from classic argument on differential equations.

Proposition 8.1 (Well-posedness)**.** *Assume that λ_u, λ_p, γ_u, γ_p, τ, σ, δ, ρ and μ positive, moreover, let $n \geq 1$ be an integer. For any $(A^{in}, u^{in}, p^{in}, b^{in}) \in \mathbb{R}_+^4$ there exists a unique non-negative bounded solution (A, u, p, b) to the system (8.8) defined for all time $t > 0$,* i.e *the solution A, u, p and b belong to $\mathcal{C}_b^1(\mathbb{R}_+)$ and remains in the stable subset*

$$S = \left\{ (A, u, p, b) \in \mathbb{R}_+^4, nA + u + p + 2b \leq nA_0 + u^{in} + p^{in} + 2\ b^{in} + \frac{\lambda}{m} \right\} \tag{8.10}$$

with $\lambda = \lambda_u + \lambda_p$ and $m = \min\{\mu, \gamma_u, \gamma_p, \delta\}$. Furthermore, let $M(t = 0) = M^{in} \geq 0$, then there exist a unique non-negative solution M to (8.9), defined for all time $t > 0$.

Proof. Let $F : \mathbb{R}^4 \mapsto \mathbb{R}^4$, given by

$$F(A, u, p, b) = \begin{pmatrix} F_1 := \alpha u^n - \mu A \\ F_2 := \lambda_u - \gamma_u u - \tau u p + \sigma b - \alpha n u^n - \rho u A \\ F_3 := \lambda_p - \gamma_p p - \tau u p + \sigma b \\ F_4 := \tau u p - (\sigma + \delta) b \end{pmatrix}.$$

F is obviously $\mathcal{C}^1$ and locally Lipschitz on $\mathbb{R}^4$. Moreover, if $(A, u, p, b) \in \mathbb{R}_+^4$, $F_1 \geq 0$ when $A = 0$, $F_2 \geq 0$ when $u = 0$, $F_3 \geq 0$ when $p = 0$ and $F_4 \geq 0$ when $b = 0$, thus the solution remains in $\mathbb{R}_+^4$. Finally, remarking that

$$\frac{d}{dt}(nA + u + p + 2b) \leq \lambda - m(nA + u + p + 2b),$$

with $\lambda = \lambda_u + \lambda_p$ and $m = \min\{\mu, \gamma_u, \gamma_p, \delta\} > 0$, Gronwall's lemma ensures that

$$nA(t) + u(t) + p(t) + 2b(t) \le nA^{in} + u^{in} + p^{in} + 2b^{in} + \frac{\lambda}{m}.$$

This provides the global existence of a unique non-negative bounded solution (A, u, p, b). We get straightforward the result on the mass M. □

We are interested in the steady state to get the asymptotic of the problem (8.8). It is to compute A_∞, u_∞, p_∞, b_∞ solving the problem

$$\mu A_\infty - \alpha {u_\infty}^n = 0 \tag{8.11}$$

$$\lambda_u - \gamma_u u_\infty - \tau u_\infty p_\infty + \sigma b_\infty - \alpha n u_\infty^n - \rho u_\infty A_\infty = 0 \tag{8.12}$$

$$\lambda_p - \gamma_p p_\infty - \tau u_\infty p_\infty + \sigma b_\infty = 0 \tag{8.13}$$

$$\tau u_\infty p_\infty - (\delta + \sigma) b_\infty = 0 \tag{8.14}$$

From the structure of the second equation, we cannot give an explicit steady state to this problem. To get u_∞ we have to solve an algebraic equation which involves a polynomial of degree n. However we can prove that it exists, and u_∞ is given implicitly. The next proposition states it and establish a local stability.

Theorem 8.2 (Linear stability). *Under hypothesis of proposition 8.1. There exists a unique positive steady state A_∞, u_∞, p_∞ and b_∞ to* (8.8) *with*

$$A_\infty = \frac{\alpha}{\mu} u_\infty^n, \quad p_\infty = \frac{\lambda_p}{\tau^* u_\infty + \gamma_p}, \quad b_\infty = \frac{1}{\sigma} \frac{\lambda_p(\tau - \tau^*)}{\tau^* u_\infty + \gamma_p} u_\infty,$$

where $\tau^* = \tau(1 - \sigma/(\delta + \sigma)$ and u_∞ is the unique positive root of Q, defined by

$$Q(x) = \gamma_p \lambda_u + ax - P(x), \ \forall x \ge 0$$

with $a = \tau^*(\lambda_u - \lambda_p) - \gamma_u \gamma_p$ and

$$P(x) = \tau^* \gamma_u x^2 + \alpha \gamma_p n x^n + (\alpha \tau^* n + \rho \gamma_p \frac{\alpha}{\mu}) x^{n+1} + \rho \tau^* \frac{\alpha}{\mu} x^{n+2}$$

Moreover, this equilibrium is locally linearly asymptotically stable.

Proof. First, equation (8.11) gives A_∞ with respect to u_∞. Then combining (8.14) and (8.14) we get p_∞ and b_∞ function of u_∞. Now replacing p_∞ and b_∞ in (8.12) we get u_∞ as the root of Q. We get straightforward that Q has a unique positive root. Indeed it is the intersection between a line and a monotone polynomial on the half plan. Now, let us linearize the system in A_∞, u_∞, p_∞ and b_∞. Let $X = (A, u, p, b)^T$ the linearized system reads

$$\frac{d}{dt} X = DX,$$

such that

$$D = \begin{pmatrix} -\mu & \alpha n {u_\infty}^{n-1} & 0 & 0 \\ -\rho u_\infty & \gamma_u - \tau p_\infty - \alpha n^2 {u_\infty}^{n-1} - \rho A_\infty & -\tau u_\infty & \sigma \\ 0 & -\tau p_\infty & -(\gamma_p + \tau u_\infty) & \sigma \\ 0 & \tau p_\infty & \tau u_\infty & -(\sigma + \delta) \end{pmatrix}.$$

The characteristic polynomial is of the form

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4,$$

with the $a_i > 0$, $i = 1 \dots 4$ given in appendix. Moreover it satisfies

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

Then, according to the Routh-Hurwitz Criteria (see [5], Th. 4.4, page 150), all the roots of the characteristic polynomial P are negative or have negative real part, thus the equilibrium is locally asymptotically stable. □

To go further, we give a conditional global stability result when no nucleation is considered, *i.e.* $\alpha = 0$.

Proposition 8.3 (Global stability)**.** *Assume that $\alpha = 0$. Under the condition*

$$\left(1 + 2\frac{\delta + \gamma_u}{\sigma}\right) > \frac{\delta}{2\gamma_p} > \frac{\gamma_p}{\sigma},$$

the unique equilibrium given by

$$A_\infty = 0, \quad p_\infty = \frac{\lambda_p}{\tau^* u_\infty + \gamma_p}, \quad b_\infty = \frac{1}{\sigma}\frac{\lambda_p(\tau - \tau^*)}{\tau^* u_\infty + \gamma_p} u_\infty,$$

and u_∞ be the unique positive root of $Q(x) = \gamma_p\lambda_u + ax - \tau^*\lambda_u x^2$, with $a = \tau^*(\lambda_u - \lambda_p) - \gamma_u\gamma_p$, is globally asymptotically stable in the stable subset defined in (8.10)*.*

Proof. The proof is given by a Lyapunov function Φ stated in appendix. It is positive when the condition above is fulfilled and its derivative along the solution to the system (8.8) is negative definite. Thus, from the LaSalle's invariance principle we get that the equilibrium of (8.8) is globally asymptotically stable. □

8.3 The case of a power law polymerization rate

In the previous section, we investigated the case when the degradation rate and the polymerization rate of an amyloid are constants. The equations can be reduced to an ODE system that can be analyzed using classical tools on ODE. This kind of coefficients are not always physically relevant. Because of that we study here the case when $\rho(x) \sim x^\theta$ and in the following we restrict our analysis to $\theta \in (0, 1)$. We will see that we are able to obtain a result of existence and uniqueness of solution for this more general case.

The last subsection will be devoted to a brief analysis of the long time behavior of this solution. Indeed, this asymptotic will be obtained almost for free, thanks in particular to the stability analysis performed in subsection 8.2.3, as well as a stability estimate given by proposition 8.10 hereafter.

8.3.1 Hypothesis and main result

We are interested in non-negative solutions to the system (8.1-8.4) with the boundary condition (8.5), completed by initial data (8.6) and (8.7). Moreover, we require the solution searched to preserve the total mass of βamyloid : this is biologically relevant. Hence the solution f will be sought in the natural space $L^1(x_0, +\infty; xdx)$, since xdx measures the mass at any time. Let us present now exactly the mathematical assumptions we make, in order both to ensure that system (8.1-8.4) is biologically relevant and to allow its theoretical study.

$$\text{(H1)} \quad \left| \begin{array}{l} f^{in} \in L^1(x_0, +\infty; xdx) \\ \text{and,} \\ f^{in} \geq 0, \ a.e. \ x > x_0. \end{array} \right.$$

$$\text{(H2)} \quad \left| \begin{array}{l} \rho \geq 0\,, \quad \text{and } \rho \in W^{2,\infty}([x_0, \infty)) \\ \text{and,} \\ \mu \geq 0\,, \quad \text{and } \mu \in W^{1,\infty}([x_0, \infty)). \end{array} \right.$$

$$\text{(H3)} \quad \left| \begin{array}{l} N \geq 0\,, \ N \in W^{1,\infty}_{loc}(\mathbb{R}_+) \\ \text{and } N(0) = 0. \end{array} \right.$$

$$\text{(H4)} \quad | \ \lambda_u,\, \gamma_u,\, \lambda_p,\, \gamma_p,\, \tau,\, \sigma,\, \delta > 0.$$

Some comments on the hypothesis:

- Note that (H2) implies there exists a constant $C > 0$ such that $\rho(x) \leq Cx$, with for example, $C = 2\|\rho'\|_{L^\infty} + \rho(x_0)/x_0$. Indeed for any $x \geq x_0$, it holds

  $$\rho(x) \leq \|\rho'\|_{L^\infty}(x + x_0) + \rho(x_0) \leq \left(2\|\rho'\|_{L^\infty} + \frac{\rho(x_0)}{x_0}\right) x.$$

  We remark that this kind of regularity of the rate ρ contains the power laws $\rho(x) \sim x^\theta$ with $\theta \in (0; 1)$. It will also be crucial to perform estimates in the next subsection.

- Moreover hypothesis (H3) implies there exists a constant $K_M > 0$ such that

  $$N(w) \leq K_M w, \ \text{for any } w \in [0, M].$$

  This will also be used in the computations of the next subsection.

- Finally, non negativity of the parameters of table 8.1, that is hypothesis (H4), is a natural assumption, regarding their biological meaning.

Before stating our existence result, we now introduce the definition of what will be called a solution to system (8.1-8.4).

Definition 8.4. *Consider a function f^{in} satisfying (H1) and u^{in}, p^{in}, b^{in} be three non-negative real data. Assume ρ, μ, N and all the parameters of table 8.1 verify assumptions (H2) to (H4), and let $T > 0$. Then a quadruplet (f, u, p, b) of non-negative functions is said to be a* solution *on the interval $(0, T)$ to the system (8.1-8.4) with the boundary condition* (8.5) *and the initial data* (8.6) *and* (8.7)*, if it satisfies, for any $\varphi \in \mathcal{D}'([0,T] \times [x_0, +\infty))$ and $t \in (0, T)$*

$$\int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx + \int_0^t N(u(s))\varphi(x_0,s)ds$$
$$+ \int_0^t \int_{x_0}^{+\infty} f(x,s)\left[\frac{\partial}{\partial t}\varphi(x,s) + u(s)\rho(x)\frac{\partial}{\partial x}\varphi(x,s) - \mu(x)\varphi(x,s)\right] dxds,$$

and,

$$u(t) = u^{in} + \int_0^t \left[\lambda_u - \gamma_u u - \tau up + \sigma b - x_0 N(u) - u\int_{x_0}^{+\infty} \rho(x) f(x,s)dx\right] ds$$
$$p(t) = p^{in} + \int_0^t \left[\lambda_p - \gamma_p p - \tau up + \sigma b\right] ds,$$
$$b(t) = b^{in} + \int_0^t \left[\tau up - (\sigma + \delta)b\right] ds,$$

with the regularity:

$$f \in L^\infty\left(0, T; L^1(x_0, +\infty; xdx)\right) \text{ and } u, p, b \text{ belong to } C^0(0, T).$$

We are now able to state the well-posedness result.

Theorem 8.5 (Well-posedness)**.** *Let f^{in} be a non-negative function satisfying (H1), u^{in}, p^{in} and b^{in} be non-negative real numbers, and assume hypothesis (H2) to (H4). Let $T > 0$, then there exists a unique non-negative solution (f, u, p, b) to (8.1-8.4) with* (8.5) *and initial conditions given by* (8.6) *and* (8.7)*, in the sense of definition 8.4, such that*

$$f \in C^0\left([0,T], L^1(x_0, +\infty; x^r dx)\right), \quad \forall r \in [0,1].$$

and,

$$u, p, b \in C_b^1(0, T).$$

The proof of the theorem 8.5 is decomposed into two part. First, we study under hypothesis (H1) to (H3) and in subsection 8.3.2, when $u \in \mathcal{C}_b^0(\mathbb{R}_+)$ is a given non-negative data, the initial boundary value problem

$$\frac{\partial}{\partial t}f(x,t)+u(t)\frac{\partial}{\partial x}\big[\rho(x)f(x,t)\big]=-\mu(x)f(x,t) \text{ on } (x_0,+\infty)\times\mathbb{R}_+, \quad (8.15)$$

$$u(t)\rho(x_0)f(x_0,t)=N(u(t)), \quad \forall t\geq 0, \quad (8.16)$$

$$f(x,0)=f^{in}(x)\,, \quad \forall x\geq x_0. \quad (8.17)$$

Namely, we prove in the next subsection the following proposition:

Proposition 8.6. *Consider $u\in\mathcal{C}_b^0(\mathbb{R}_+)$ a given function, f^{in} satisfying (H1) and assume hypothesis (H2) to (H3). For any $T>0$, there exists a unique non-negative solution f to (8.15-8.17) in the sense of distributions, such that*

$$f\in C^0\left([0,T],L^1(x_0,+\infty;x^r dx)\right), \quad \forall r\in[0,1].$$

The proof is in the spirit of [51] for the Lifshitz-Slyozov equation. It consists in a mild formulation (definition with the characteristic) which is proved to be the unique solution in the sense of the distributions with the additional requirement to be continuous in time into $L^1(xdx)$ space.

The second step of the proof of theorem 8.5 is performed in subsection 8.3.3. Precisely, once we have the existence of a unique density f when u is a given data we are able to construct the operator

$$\begin{array}{rcccl} S & : & C^0([0,T])^3 & \mapsto & C^0([0,T])^3 \\ & & (u,p,b) & \mapsto & (S_u,S_p,S_b)=S(u,p,b), \end{array} \quad (8.18)$$

defines by

$$\begin{aligned} S_u &= u^{in}+\textstyle\int_0^t\left[\lambda_u-\gamma_u u-\tau up+\sigma b-x_0N(u)-u\int_{x_0}^{+\infty}\rho(x)f(x,s)dx\right]ds,\\ S_p &= p^{in}+\textstyle\int_0^t\left[\lambda_p-\gamma_p p-\tau up+\sigma b\right]ds,\\ S_b &= b^{in}+\textstyle\int_0^t\left[\tau up-(\sigma+\delta)b\right]ds, \end{aligned}$$

where f is the unique solution associated to u given by proposition 8.6. Thus, theorem 8.5 is finally proved in subsection 8.3.3 thanks to the Banach fixed point theorem applied to the operator S.

8.3.2 Existence of a solution to the autonomous problem

This section is devoted to the proof of proposition 8.6. Thus, in the following, we let $u\in\mathcal{C}_b^0(\mathbb{R}_+)$ a given function and we use the notations

$$a(x,t)=u(t)\rho(x) \text{ and } c(x,t)=-u(t)\rho'(x),\ \forall(x,t)\in[x_0,+\infty)\times\mathbb{R}_+.$$

From (H2) and remarking that $\rho(x) \leq Cx$, we get that for any $t > 0$

$$a(t,x) \leq Ax, \text{ for } x > x_0, \tag{8.19}$$
$$|a(t,x) - a(t,y)| \leq A|x-y|, \text{ for } x,y > x_0, \tag{8.20}$$
$$|c(t,x)| \leq B, \tag{8.21}$$

where $A = \max\left(C\|u\|_{L^\infty}, \|u\|_{L^\infty}\|\rho'\|_{L^\infty}\right)$ and $B = \|u\|_{L^\infty}\|\rho'\|_{L^\infty(x_0,+\infty)}$. In order to establish the mild formulation of the problem, we define the characteristic which reaches $x \geq x_0$ at time $t \geq 0$, that is the solution to

$$\begin{aligned} &\frac{d}{ds}X(s;x,t) = a(t, X(s;x,t)), \\ &X(t;x,t) = x. \end{aligned} \tag{8.22}$$

From property (8.20), their exist a unique characteristic which reach (x,t). It is important to note that it makes sense as long as $X(s;x,t) \geq x_0$. Thus, we define the starting time of the characteristic as follows

$$s_0(x,t) := \inf\left\{s \in [0,t] : X(s;x,t) \geq x_0\right\}.$$

The characteristic will be defined for any time $s \geq s_0$ and takes its origin from the initial or the boundary condition respectively if $s_0 = 0$ or $s_0 > 0$. We recall the classical properties for the characteristics,

$$\begin{aligned} &X(s; X(\sigma;x,t),\sigma) = X(s;x,t) \\ &J(s;x,t) := \frac{\partial}{\partial x}X(s;x,t) = \exp\left(\int_s^t c(\sigma, X(\sigma;x,t))d\sigma\right) \\ &\frac{\partial}{\partial t}X(s;x,t) = -a(t,x)J(s;x,t). \end{aligned}$$

Also, remarking that $s_0(X(t;x_0,0),t) = 0$, then by monotonicity and continuity of X for any $t > 0$, we get

$$x \in (x_0, X(t;x_0,0)) \iff s_0(x,t) \in (0,t).$$

and for any $x \in (x_0, X(t;x_0,0))$ we have $X(s_0(x,t);x,t) = x_0$, it follows that

$$I(x,t) := -\frac{\partial}{\partial x}s_0(x,t) = J(s_0(x,t);x,t)/a(s_0(x,t),x_0), \quad \forall x \in (x_0, X(t;x_0,0)).$$

Regarding the derivative of $f(s, X(s;x,t))$ in s, and integrating over (s_0,t) we obtain the mild formulation

of the problem. The mild solution is defined *a.e.* $(x,t) \in (x_0,+\infty) \times \mathbb{R}_+$ by

$$f(x,t) = \begin{cases} f^{in}(X(0;x,t))J(0;x,t)\exp\left(-\int_0^t \mu(X(\sigma;x,t))d\sigma\right), \ x \geq X(t;x_0,0) \\ N(u(s_0(x,t)))I(x,t)\exp\left(-\int_{s_0(x,t)}^t \mu(X(\sigma;x,t))d\sigma\right), \ x \in (x_0, X(t;x_0,0)). \end{cases} \tag{8.23}$$

It infers from the formulation (8.23) that $a.e\ (x,t) \in [x_0, +\infty) \times \mathbb{R}_+$, f is non-negative since J and I are non-negative, and f^{in} satisfies (H1). We recall some useful properties that are derived in [51, Lemma 1].

Lemma 8.7. *Let $u \in \mathcal{C}_b^0(\mathbb{R}_+)$ be a given data and assume that (H2) holds true. Then for any $x \geq x_0$ and $t > 0$, as long as the characteristic curves $s \mapsto X(s;x,t)$ defined in (8.22) exists* i.e. *$s \geq s_0(x,t)$, we have*

$$\begin{aligned}
&\text{for } s_1 \leq s_2,\ X(s_1;x,t) \leq X(s_2;x,t) \leq X(s_1;x,t)e^{A(s_2-s_1)} \\
&\text{if } x_n \to +\infty,\ \text{then for all } t \geq s \geq 0,\ X(s;x,t) \to +\infty \\
&\text{for } s \geq t,\ X(s;x,t) \leq xe^{A(s-t)}
\end{aligned}$$

Proof. We refer to [51, Lemma 1], were the result follows from the fact that for any $x \geq x_0$, $t > 0$ and $s_0(x,t) \leq s_1 \leq s_2$, we have

$$\begin{aligned}
x_0 \leq X(s_2;x,t) &= X(s_1;x,t) + \int_{s_1}^{s_2} a(s, X(s;x,t))ds \\
&\leq X(s_1;x,t) + A\int_{s_1}^{s_2} X(s;x,t)ds
\end{aligned}$$

where A is given by (8.19). □

In the sequel we will repeatedly refer to the changes of variables,

$$y = X(0;x,t) \text{ over } x \in (X(t,x_0,0), +\infty),\ \text{with Jacobian } J(0;x,t),$$

and

$$s = s_0(x,t) \text{ over } x \in (x_0, X(t;x_0,0)),\ \text{with Jacobian } -I(x,t).$$

The first one is a $\mathcal{C}^1$ - diffeomorphism from $(X(t,x_0,0), +\infty)$ into $(x_0, +\infty)$, and the second from $(x_0, X(t;x_0,0))$ into $(0,t)$. Integrating f defined by (8.23) over $(0,R)$ with $R > X(t;x_0,0)$, using the change of variable above and with the help of lemma 8.7, taking the limit $R \to +\infty$ we get

$$\begin{aligned}
\int_{x_0}^{+\infty} x|f(t,x)|dx &\leq \int_{x_0}^{+\infty} X(t;y,0)|f^{in}(y)|dy + \int_0^t X(t;s,x_0)|N(u(s))|ds \\
&\leq e^{At}\left(\int_{x_0}^{+\infty} y|f^{in}(y)|dy + \int_0^t x_0|N(u(s))|ds\right)
\end{aligned} \tag{8.24}$$

when splitting the integral into two parts and using both the previous changes of variables. We conclude that for any $T > 0$, $f \in L^\infty\left(0,T;L^1(x_0,+\infty;xdx)\right)$ and therefore in $L^\infty\left(0,T;L^1(x_0,+\infty;x^r dx)\right)$, for any $r \in [0,1]$. In the lemma right after we claim that f defined by (8.23) is a weak solution.

Lemma 8.8. *Let f be the mild solution defined by* (8.23)*, then for any $t > 0$*

$$\int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx + \int_0^t N(u(s))\varphi(x_0,s)ds$$
$$+ \int_0^t \int_{x_0}^{+\infty} f(x,s)\left[\frac{\partial}{\partial t}\varphi(x,s)u(s)\rho(x)\frac{\partial}{\partial x}\varphi(x,s) - \mu(x)\varphi(x,s)\right]dxds$$

for all $\varphi \in \mathcal{D}'([0,T] \times [x_0,+\infty))$.

Proof. Since f belongs to $f \in L^\infty\left(0,T;L^1(x_0,+\infty;xdx)\right)$, it is possible to multiply the mild solution f against a test function $\varphi \in \mathcal{D}'([0,T] \times [x_0,+\infty))$ and integrate over $(x_0,+\infty)$, then

$$\int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} f^{in}(y)\varphi(X(t;y,0))e^{-\int_0^t \mu(X(\sigma;y,0))d\sigma}dy$$
$$- \int_0^t N(u(s))\varphi(X(t;x_0,s),t)e^{-\int_s^t \mu(X(\sigma;x_0,s))d\sigma}ds \quad (8.25)$$

by the same change of variable made above for (8.24). Furthermore, we have

$$\int_0^t \int_{x_0}^{X(s;x_0,0)} f(x,s)\left[\partial_t\varphi(x,s) + a(s,x)\partial_x\varphi(x,s) - \mu(x)\varphi(x,s)\right]dxds$$
$$= \int_0^t \int_{x^0}^{+\infty} f^{in}(x)\frac{d}{ds}\left(\varphi(X(s;x,0),s)e^{-\int_0^s \mu(X(\sigma;x,0))d\sigma}\right)dxds$$
$$= \int_{x_0}^{+\infty} f^{in}(x)\varphi(X(t;x,0),t)e^{-\int_0^t \mu(X(\sigma;y,0))d\sigma}dx - \int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx \quad (8.26)$$

still using the change of variable mentioned above and

$$\int_0^t \int_{X(s;x_0,0)}^{\infty} f(x,s)\left[\partial_t\varphi(x,s) + a(s,x)\partial_x\varphi(x,s) - \mu(x)\varphi(x,s)\right]dxds$$
$$= -\int_0^t \int_0^s N(u(z))\frac{d}{ds}\left(\varphi(X(s;x_0,z),s)e^{-\int_z^s \mu(X(\sigma;x_0,z))d\sigma}\right)dzds$$
$$= -\int_0^t N(u(s))\varphi(X(t;x_0,s),t)e^{-\int_s^t \mu(X(\sigma;x_0,s))d\sigma}dzds - \int_0^t N(u(s))\varphi(x_0,s)ds \quad (8.27)$$

Finally, combining (8.25), (8.26) and (8.27) we obtain that f is a weak solution. □

The aim of the following is to state that the moments of f less than 1 are continuous in time.

Lemma 8.9. *Consider hypothesis (H1) to (H3). Let f be the mild solution given by* (8.23)*. Then for any $T > 0$,*

$$f \in C^0\left([0,T], L^1(x_0,+\infty; x^r dx)\right), \quad \forall r \in [0,1].$$

Proof. Let $T > 0$ and $r \in [0,1]$, since $f \in L^\infty_{loc}\left(\mathbb{R}_+, L^1(x_0,+\infty; x^r dx)\right)$, we have for any $t > 0$ and $\delta t > 0$ such that $t + \delta t \leq T$

$$\int_{x_0}^{+\infty} x^r \left|f(x,t+\delta t) - f(x,t)\right| dx = I_1 + I_2 + I_3,$$

where

$$I_1 = \int_{x_0}^{X(t;x_0,0)} x^r \left|f(x,t+\delta t) - f(x,t)\right| dx,$$
$$I_2 = \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} x^r \left|f(x,t+\delta t) - f(x,t)\right| dx,$$
$$I_3 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \left|f(x,t+\delta t) - f(x,t)\right| dx.$$

The aim is to prove that each term goes to zero when δt goes to zero. We first bound I_3, that can be written from the initial condition since $x \geq X(t+\delta t; x_0, 0) \geq X(t; x_0, 0)$, as follows

$$I_3 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \Big| f^{in}(X(0;x,t+\delta t))J(0;x,t+\delta t)e^{-\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma}$$
$$-f^{in}(X(0;x,t))|J(0;x,t)e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}\Big| dx.$$

Let f^{in}_ε be $\mathcal{C}^\infty_0$ with compact support $supp(f^{in}_\varepsilon) \subset (0, R_\varepsilon)$ converging in $L^1([x_0,+\infty), xdx)$ to f^{in}. We write I_3 as follows

$$I_3 = I_3^1 + I_3^2 + I_3^3, \tag{8.28}$$

where

$$\begin{aligned} I_3^1 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \big| f^{in}(X(0;x,t+\delta t)) - f^{in}_\varepsilon(X(0;x,t+\delta t))\big| \\ &\qquad \times J(0;x,t+\delta t)e^{-\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma}dx, \\ I_3^2 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \big| f^{in}_\varepsilon(X(0;x,t+\delta t))J(0;x,t+\delta t)e^{-\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma} \\ &\qquad - f^{in}_\varepsilon(X(0;x,t))J(0;x,t)e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}\big| dx, \\ I_3^3 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r |f^{in}_\varepsilon(X(0;x,t)) - f^{in}(X(0;x,t))| \\ &\qquad \times J(0;x,t)e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}dx. \end{aligned}$$

$$I_3^1 + I_3^3 \leq 2e^{AT}\int_{x_0}^{+\infty} y^r |f^{in}(y) - f^{in}_\varepsilon(y)| dy = C_3^1(T,\varepsilon), \tag{8.29}$$

with the help of lemma 8.7. Let us bound now I_3^2 by

$$\begin{aligned} I_3^2 \quad \leq \quad & \textstyle\int_{X(t+\delta t;x_0,0)}^{+\infty} x^r |f_\varepsilon^{in}(X(0;x,t+\delta t)) - f_\varepsilon^{in}(X(0;x,t))| J(0;x,t+\delta t) dx \\ & + \textstyle\int_{X(t+\delta t;x_0,0)}^{+\infty} x^r f_\varepsilon^{in}(X(0;x,t)) |J(0;x,t+\delta t) - J(0;x,t)| dx \\ & + \textstyle\int_{X(t+\delta t;x_0,0)}^{+\infty} x^r f_\varepsilon^{in}(X(0;x,t)) J(0;x,t) \\ & \qquad \times |e^{-\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma} - e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}| dx \end{aligned}$$

and we denote each integrals by J_3^1 to J_3^3, respectively. Remarking that $J(0,x,t) \leq e^{BT}$ since (8.21) and

$$\begin{aligned} J_3^1 &\leq e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{C_\varepsilon} x^r |X(0;x,t+\delta t) - X(0;x,t)| dx \\ &\leq \delta t e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{C_\varepsilon} x^r \sup_{s\in[t,t+\delta t]} \left| \frac{\partial}{\partial t} X(0;x,s) \right| dx \\ &\leq \delta t A e^{2BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{x_0}^{C_\varepsilon} x^{r+1} dx, \end{aligned} \tag{8.30}$$

where C_ε depends on T, A and R_ε *i.e.* the compact support of f_ε^{in}. Then

$$J_3^2 \leq e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{R_\varepsilon} x^r |e^{G(t,\delta t,x)} - 1| dx$$

with

$$\begin{aligned} |G(t,\delta t,x)| &= \Big| \int_0^{t+\delta t} c(\sigma, X(\sigma;x,t+\delta t)) d\sigma - \int_0^t c(\sigma, X(\sigma;x,t)) d\sigma \Big| \\ &\leq \int_0^{t+\delta t} \Big| \rho'(X(\sigma;x,t+\delta t)) - \rho'(X(\sigma;x,t)) \Big| u(\sigma) d\sigma + \int_t^{t+\delta t} \Big| c(\sigma, X(\sigma;x,t)) \Big| d\sigma. \end{aligned}$$

Thus, with (8.19) and (8.21),

$$\begin{aligned} |G(t,\delta t,x)| &\leq K \|u\|_{L^\infty} \int_0^T \Big| X(\sigma;x,t+\delta t) - X(\sigma;x,t) \Big| d\sigma + \delta t B \\ &\leq \delta t K \|u\|_{L^\infty} \int_0^T \sup_{s\in[t,t+\delta t]} \left| \frac{\partial}{\partial t} X(\sigma;x,s) \right| d\sigma + \delta t B \\ &\leq \delta t \left(K \|u\|_{L^\infty} A T e^{BT} x + B \right) \end{aligned}$$

where K is the lipchitz constant of ρ'. Since $x \leq R_\varepsilon$, let $C_G(T,\varepsilon) = K\|u\|_{L^\infty} A T e^{BT} R_\varepsilon + B$, and remarking that if $|x| \leq y$, then

$$|e^x - 1| \leq |e^y - 1| + \left| e^{-y} - 1 \right|,$$

thus we get

$$J_3^2 \leq e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \left(\left| e^{\delta t C_G(T,\varepsilon)} - 1 \right| + \left| e^{-\delta t C_G(T,\varepsilon)} - 1 \right| \right) \int_{x_0}^{R_\varepsilon} x^r dx \tag{8.31}$$

For J_3^3, since μ is non-negative,

$$J_3^3 \leq e^{BT}\|f_\varepsilon^{in}\|_{L^\infty}\int_{X(t+\delta t;x_0,0)}^{R_\varepsilon} x^r \left|e^{-\left(\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma-\int_0^t\mu(X(\sigma;x,t))d\sigma\right)}-1\right|dx$$

Exactly as above,

$$\Big|\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma-\int_0^t\mu(X(\sigma;x,t))d\sigma\Big| \leq \delta t MATe^{BT}x+\delta t\|\mu\|_{L^\infty}$$

with M the lipschitz constant of μ, and then denoting by $C_M(T,\varepsilon)=MATe^{BT}R_\varepsilon+\|\mu\|_{L^\infty}$, we get

$$J_3^3 \leq e^{BT}\|f_\varepsilon^{in}\|_{L^\infty}\left(\left|e^{\delta tC_M(T,\varepsilon)}-1\right|+\left|e^{-\delta tC_M(T,\varepsilon)}-1\right|\right)\int_{x_0}^{R_\varepsilon}x^r dx \tag{8.32}$$

From estimations (8.29), (8.30), (8.31) and (8.32) we can conclude that for any $\varepsilon>0$,

$$I_3(\delta t)\leq C_3^1(T,\varepsilon)+C_3^2(T,\delta t,\varepsilon), \tag{8.33}$$

with $\lim_{\varepsilon\to 0}C_3^1(T,\varepsilon)=0$ and $\lim_{\delta t\to 0}C_3^2(T,\delta t,\varepsilon)=0$.

Concerning I_1, f can be written from the boundary condition. Let u^ε be $\mathcal{C}_0^\infty$ such that

$$u^\varepsilon \longrightarrow u, \text{ uniformly on } [0,T].$$

Then we write I_1 as follows

$$\begin{aligned} I_1 \leq & \int_{x_0}^{X(t+\delta t;x_0,0)} x^r|N(u(s_0(x,t+\delta t))-N(u^\varepsilon(s_0(x,t+\delta t))|I(x,t+\delta t)dx \\ & +\int_{x_0}^{X(t;x_0,0)} x^r\Big|N(u^\varepsilon(s_0(x,t+\delta t))I(x,t+\delta t)e^{-\int_{s_0(x,t+\delta t)}^t\mu(X(\sigma;x,t+\delta t))d\sigma} \\ & \qquad -N(u^\varepsilon(s_0(x,t))I(x,t)e^{-\int_{s_0(x,t)}^t\mu(X(\sigma;x,t))d\sigma}\Big|dx \\ & +\int_{x_0}^{X(t;x_0,0)} x^r|N(u(s_0(x,t))-N(u^\varepsilon(s_0(x,t))|I(x,t)dx \end{aligned}$$

With the help of (H3) we get similarly to I_3 that there exist two constant $C_1^1(T,\varepsilon)$ and $C_1^2(T,\delta t,\varepsilon)$

$$I_1(\delta t)\leq C_1^1(T,\varepsilon)+C_1^2(T,\delta t,\varepsilon), \tag{8.34}$$

with $\lim_{\varepsilon\to 0}C_1^1(T,\varepsilon)=0$ and $\lim_{\delta t\to 0}C_1^2(T,\delta t,\varepsilon)=0$. Finally, we deal with I_2.

It is a mixed of the two forms of f,

$$\begin{aligned} I_2 = & \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} x^r\Big|N(u(s_0(x,t+\delta t)))I(x,t+\delta t)e^{-\int_{s_0(x,t+\delta t)}^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma} \\ & \qquad -f^{in}(X(0;x,t))J(0;x,t)e^{-\int_{s_0(x,t)}^t\mu(X(\sigma;x,t))d\sigma}\Big|dx \end{aligned}$$

Using the lipschitz constant of N denoted by K_N, from the definition of I and with the help of lemma 8.7, we get

$$I_2 \le x_0^r e^{(rA+B)T} K_N \left| X(t+\delta t; x_0, 0) - X(t; x_0, 0) \right| l$$
$$+ x_0^r e^{rAT} \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} \left| f^{in}(X(0;x,t)) J(0;x,t) \right| dx$$

Still using the regularization f_ε^{in} of f^{in}, there exist two constant $C_2^1(T,\varepsilon)$ and $C_2^2(T,\delta t,\varepsilon)$ such that for any $\varepsilon > 0$,

$$I_2(\delta t) \le C_2^1(T,\varepsilon) + C_2^2(T,\delta t,\varepsilon), \tag{8.35}$$

with $\lim_{\varepsilon \to 0} C_2^1(T,\varepsilon) = 0$ and $\lim_{\delta t \to 0} C_2^2(T,\delta t,\varepsilon) = 0$. To conclude, gathering from (8.33), (8.34) and (8.35), we get for any $\varepsilon > 0$ and $\delta t > 0$,

$$\int_{x_0}^{+\infty} x^r |f(x,t+\delta t) - f(x,t)| dx \le C^1(T,\varepsilon) + C^2(T,\delta t,\varepsilon),$$

where $C^1(T,\varepsilon)$ and $C^2(T,\delta t,\varepsilon)$ are two constants such that $\lim_{\varepsilon \to 0} C^1(T,\varepsilon) = 0$ and $\lim_{\delta t \to 0} C^2(T,\delta t,\varepsilon) = 0$. Noticing that the proof remains the same when δt is negative, taking the lim sup in δt we get

$$0 \le \limsup_{\delta t \to 0} \int_{x_0}^{+\infty} x^r |f(x,t+\delta t) - f(x,t)| dx \le C^1(T,\varepsilon), \text{ for any } \varepsilon > 0,$$

The proof is ended when taking the limit ε goes to zero that leads to $f \in \mathcal{C}^0([0,T], L^1([x_0,+\infty), x^r dr)$ for all $r \in [0,1]$. □

We finish this section with a useful estimate for the uniqueness investigation.

Proposition 8.10. *Let $T > 0$ and u_1, $u_2 \in \mathcal{C}_b^0(0,T)$ be two given functions. Let f_1 and f_2 be two mild solutions to* (8.15)-(8.17)*, associated respectively to u_1 and u_2 with initial data f_1^{in}, f_2^{in}, that is given by formula* (8.23)*. Then, for any $t \in (0,T)$*

$$\begin{aligned}
\int_{x_0}^{+\infty} x \left| f_1(x,t) - f_2(x,t) \right| dx \quad &\le \int_{x_0}^{+\infty} x \left| f_1^{in}(x) - f_2^{in}(x) \right| dx \\
&- \int_0^t \int_{x_0}^{+\infty} \mu(x) x \left| f_1^{in}(x,s) - f_2^{in}(x,s) \right| dx ds \\
&+ A_1 \int_0^t \int_{x_0}^{+\infty} x \left| f_1(x,s) - f_2(x,s) \right| dx ds \\
&+ \int_0^t \left(K_{1,2} + C \| f_2(\cdot,s) \|_{L^1(xdx)} \right) \left| u_1(s) - u_2(s) \right| ds,
\end{aligned}$$

where A_1 is given by (8.19) *for u_1 and $K_{1,2}$ is the lipschitz constant of N on $[0,R]$ with $R = \max(\|u_1\|_{L^\infty(0,T)}, \|u_2\|_{L^\infty(0,T)})$. Finally $C > 0$ denotes the constant such that $\rho(x) < Cx$.*

Proof. This estimation is obtained from classical argument of approximation. Indeed, let $h = f_1 - f_2$ thus

$$\begin{aligned}\int_{x_0}^{+\infty} h(x,t)\varphi(x,t)dx = &\int_{x_0}^{+\infty} h^{in}(x)\varphi(x,0)dx \\ &+ \int_0^t \left(N(u_1(s)) - N(u_2(s))\right)\varphi(x_0,s)ds \\ + \int_0^t \int_{x_0}^{+\infty} h(x,s)&\left[\frac{\partial}{\partial t}\varphi(x,s) + a_1(s,x)\frac{\partial}{\partial x}\varphi(x,s) - \mu(x)\varphi(x,s)\right]dxds \\ &+ \int_0^t \int_{x_0}^{+\infty} \left(a_1(s,x) - a_2(s,x)\right) f_2(x,s)\frac{\partial}{\partial x}\varphi(x,s)dxds.\end{aligned}$$

Let h_ε be a regularization of h and S_δ a regularization of the $Sign$ function. Let us take $\varphi(x,s) = S_\delta(h_\varepsilon(s,x))g(x)$ with $g \in \mathcal{C}_c^\infty([x_0,+\infty))$. Then passing to the limit $\delta \to 0$ and then $\varepsilon \to 0$, we get

$$\begin{aligned}\int_{x_0}^{+\infty} |h(x,t)|g(x)dx = &\int_{x_0}^{+\infty} |h^{in}(x)|g(x)dx \\ &+ \int_0^t |N(u_1(s)) - N(u_2(s)))\, Sign(h_0(x_0))g(x_0)ds \\ &+ \int_0^t \int_{x_0}^{+\infty} |h(x,s)|\left[a_1(s,x)\frac{\partial}{\partial x}g(x) - \mu(x)g(x)\right]dxds \\ &+ \int_0^t \int_{x_0}^{+\infty} \left(a_1(s,x) - a_2(s,x)\right) f_2(x,s)Sign(h(s,x))\frac{\partial}{\partial x}g(x)dxds.\end{aligned}$$

Finally, we approach the identity function with a regularized function $\eta_R \in \mathcal{C}_c^\infty([x_0,+\infty))$ such that $\eta_R(x) = x$ over $(0,R)$, then passing to the limit $R \to +\infty$ ends the proof. □

We get straightforward from proposition 8.8 that f defined by (8.23) is a weak solution and the only one from 8.10. Indeed, getting $u_1 = u_2$ and $f_1^0 = f_2^0$ in proposition 8.10 leads to the uniqueness. Finally, proposition 8.9 provide the continuity in time of the moments with order less or equal to one. This concludes the proof of proposition 8.6

8.3.3 Proof of the well-posedness

In this section we prove the theorem 8.5, we first study the operator S in (8.18).

Lemma 8.11. *Consider hypothesis (H2) to (H4). Let u^{in}, p^{in} and b^{in} be non-negative real numbers accounting for initial data, and f^{in} satisfying (H1). Let $M > 0$ large enough such that $u^{in}, p^{in}, b^{in} < M/2$ and define*

$$X_M = \left\{(u,p,b) \in \mathcal{C}^0([0,T])^3 : 0 \le u,p,b \le M\right\}$$

where $\mathcal{C}^0([0,T])^3$ is equipped with the uniform norm. Then, there exists $T > 0$ (small enough) such that

$$S : X_M \mapsto X_M, \text{ is a contraction.}$$

Proof. Let M sufficiently large such that $\max(u^{in}, p^{in}, b^{in}) < M/2$, and $T > 0$ small enough such that

$$(\gamma_u + \tau M + \sigma + x_0 C_1(M) + C_2(M,T))MT \le M/2, \tag{8.36}$$
$$(\gamma_p + \tau M)MT \le M/2, \tag{8.37}$$
$$(\sigma + \delta)MT \le M/2, \tag{8.38}$$

and,

$$(\lambda_u + \sigma M)T \le M/2, \tag{8.39}$$
$$(\lambda_p + \sigma M)T \le M/2, \tag{8.40}$$
$$\tau M^2 T \le M/2, \tag{8.41}$$

where $C_1(M)$ is the lipschitz constant of N on $(0, M)$ and

$$C_2(M,T) = Ce^{MCT}\left(\|f^{in}\|_{L^1(xdx)} + C_1(M)MT\right) \tag{8.42}$$

where C is the constant such that on $\rho(x) \le Cx$, see (8.24). This assumptions ensure that for any $(u,p,b) \in X_M$, then $S(u,p,b) \in X_M$, *i.e* the solution remains bounded by M and non-negative. It remains to prove that S is a contraction. Let (u_1, p_1, b_1) and (u_2, p_2, b_2) belong to X_M. Then

$$\|S_{u_1} - S_{u_2}\|_\infty \le \gamma_u T\|u_1 - u_2\|_\infty + \tau T\|u_1p_1 - u_2p_2\|_\infty + \sigma T\|b_1 - b_2\|_\infty$$
$$+ x_0 T C_1(M)\|u_1 - u_2\|_\infty$$
$$+ T \sup_{t\in[0,T]} \left| u1 \int_{x_0}^{+\infty} \rho(x) f_1(x,s)dx - u2 \int_{x_0}^{+\infty} \rho(x) f_2(x,s)dx \right| \tag{8.43}$$

Remarking that,

$$\|u_1p_1 - u_2p_2\|_\infty \le M\|u_1 - u_2\|_\infty + M\|p_1 - p_2\|_\infty \tag{8.44}$$

and

$$\sup_{t\in[0,T]} \left| u1 \int_{x_0}^{+\infty} \rho(x) f_1(x,s)dx - u2 \int_{x_0}^{+\infty} \rho(x) f_2(x,s)dx \right|$$
$$\le C_2(M,T)\|u_1 - u_2\|_\infty + CM \sup_{t\in[0,T]} \left| \int_{x_0}^{+\infty} x|f_1(x,t) - f_2(x,t)|dx \right| \tag{8.45}$$

and from proposition 8.10,

$$\sup_{t\in[0,T]} \left| \int_{x_0}^{+\infty} x|f_1(x,t) - f_2(x,t)|dx \right| \leq T\left(C_1(M) + CC_2(M,T)\right) \|u_1 - u_2\|_\infty \tag{8.46}$$

We get similar bounds for $|S_{p_1} - S_{p_2}|_\infty$ and $|S_{b_1} - S_{b_2}|_\infty$. It infers that there exists a constant $C(M,T)$ depending only on M and T such that

$$\|(S_{u_1}, S_{p_1}, S_{b_1}) - (S_{u_2}, S_{p_2}, S_{b_2})\|_\infty$$

$$\leq C(M,T)T\|(u_1,p_1,b_1) - (u_2,p_2,b_2)\|_\infty \tag{8.47}$$

with $C(M,T)T \to 0$, when T goes to 0. Hence, if T is small enough such that $C(M,T)T < 1$, then S is a contraction. □

Now, with the help of proposition 8.11, we have a local non-negative solution on an interval of time $[0,T]$ which is unique when it is ensured that the solution (u,p,b) remain bounded by the constant M. The solution satisfy $f \in C^0(0,T;L^1(xdx))$ and $u,p,b \in C^0(0,T)$. Futhermore from (H3), N is continuous and from (H2), $\rho(x) \leq Cx$ where C is a positive constant, thus $\rho f \in C^0(0,T;L^1(dx))$. We conclude that u,p and b defined in definition 8.4 have continuous derivatives.

Now we remark that the solutions satisfies on $[0,T]$

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}(u+p+2b) &= \lambda_u + \lambda_p - \gamma_u u - \gamma_p p - \delta 2b - nN(u) - \frac{1}{\varepsilon}u\int_{x_0}^{+\infty}\rho(x)f(x,t)dx \\ &\leq \lambda - m(u+p+2b)\end{aligned}$$

with $m = \min(\gamma_u, \gamma_p, \delta)$ and $\lambda = \lambda_u + \lambda_p$. Using Gronwall's lemma, the solutions remain bounded, at any time by, namely

$$u + p + 2b \leq u^{in} + p^{in} + 2b^{in} + \frac{\lambda}{m}. \tag{8.48}$$

From this global bound on u,p and b, we can construct the solution on any interval of time $[0,T]$, $[T,2T]$, *etc.* This ends the proof of the theorem.

We just obtained a global in time existence of solution. Therefore we question in the next subsection the long time behavior of this solution, as well as a possible estimate of the rate of convergence towards some equilibrium. It is the subject of the next subsection.

8.3.4 Asymptotic profile and equilibrium.

Since we aim at investigating the long time behavior of the solution (f,u,p,b) to (8.1-8.7), we start by considering the steady formulation of (8.1). Namely, assume that ρ and μ satisfy (H2). Let $u_\infty > 0$, then we are interested in f_∞, verifying for all x in $(x_0, +\infty)$,

$$\begin{cases} \dfrac{d}{dx} f_\infty(x) & = -\dfrac{\mu(x) + u_\infty \rho'(x)}{u_\infty \rho(x)} f_\infty(x), \\ u_\infty \rho(x_0) f_\infty(x_0) & = N(u_\infty). \end{cases} \tag{8.49}$$

If $\inf_{x \in [x_0, +\infty)} \rho(x) > 0$ it follows from (H2) that the flow is globally lipschitz. Thus, there exists a unique solution $f_\infty \in \mathcal{C}^0([x_0, \infty))$, to (8.49). Actually, this solution is given explicitly by,

$$f_\infty(x) = \frac{N(u_\infty)}{u_\infty \rho(x)} \exp\left(- \int_{x_0}^{x} \frac{\mu(y)}{u_\infty \rho(y)} dy \right). \tag{8.50}$$

It appears that $f_\infty \in L^1(xdx)$, so we can define rigorously

$$F(u_\infty) := \int_{x_0}^{\infty} \rho(x) f_\infty(x) dx,$$

where the dependency with respect to u_∞ is contained in the function f_∞. Note that if ρ is assumed to be constant as in the first part of the chapter, we have $F(u_\infty) = \rho A_\infty$, where A_∞ is the quantity of amyloids, defined in subsection 8.2.2. Hence, as in the stability analysis of the ODE model, we are now interested in solving the following system. We search $(u_\infty, p_\infty, b_\infty)$, satisfying

$$\lambda_u - \gamma_u u_\infty - \tau u_\infty p_\infty + \sigma b_\infty - x_0 N(u_\infty) - u_\infty F(u_\infty) = 0, \tag{8.51}$$

$$\lambda_p - \gamma_p p_\infty - \tau u_\infty p_\infty + \sigma b_\infty = 0, \tag{8.52}$$

$$b \tau u_\infty p_\infty - (\sigma + \delta) b_\infty = 0, \tag{8.53}$$

If there exist a solution to the above system, we get the equilibrium of problem (8.1-8.4), as done in subsection 8.2.2, on the ODE model. Indeed, we can prove the following proposition.

Proposition 8.12. *Let (f, u, p, b) be the solution to the problem (8.1-8.7). Assume that $(u_\infty, p_\infty, b_\infty)$ is a triplet of non negative numbers, solution to (8.51-8.53), where $f_\infty \in L^1([x_0, +\infty))$ is given by* (8.50). *Moreover, we suppose that there exists $\lambda > 0$ such that*

$$|u(t) - u_\infty| e^{\lambda t} \to_{t \to +\infty} 0. \tag{8.54}$$

Then, f tends, when t goes to $+\infty$, to the function f_∞ in the following sense:

$$\int_{x_0}^{+\infty} x \left| f(x,t) - f_\infty(x) \right| dx \to_{t \to +\infty} 0, \tag{8.55}$$

and the convergence rate is exponential.

Proof. It is a straightforward consequence of proposition 8.10, applied to $f_1 = f$ and $f_2 = f_\infty$. The exponential rate of convergence comes from equation (8.54). □

Chapter 9

Appendix of chapter 8

9.1 Characteristic polynomials of the linearized ODE system

Here we give the coefficient a_i, $i = 1, \dots, 4$ for the characteristic polynomial of the linearized system in proposition 8.2. They are:

$$
\begin{aligned}
a_1 &= \left(\mu + \gamma_u + \tau\frac{\lambda_p}{\tau^*\bar{u} + \gamma_p} + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n + \gamma_p + \tau\bar{u} + \sigma + \delta\right), \\
a_2 &= \left(\mu + \gamma_u + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n\right)(\gamma_p + \tau\bar{u} + \sigma + \delta) + \gamma_p\sigma + (\gamma_p + \tau\bar{u})\delta \\
&\quad + \mu\left(\gamma_u + \tau\frac{\lambda_p}{\tau^*\bar{u} + \gamma_p} + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n\right) + \rho\alpha n\bar{u}^n + \tau(\gamma_p + \delta)\frac{\lambda_p}{\tau^*\bar{u} + \gamma_p}, \\
a_3 &= \left(\mu + \gamma_u + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n\right)(\gamma_p\sigma + (\gamma_p + \tau\bar{u})\delta) + (\gamma_p\delta + (\gamma_p + \delta)\mu)\tau\frac{\lambda_p}{\tau^*\bar{u} + \gamma_p} \\
&\quad + \left\{\mu\left(\gamma_u + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n\right) + \rho\alpha n\bar{u}^n\right\}(\gamma_p + \tau\bar{u} + \sigma + \delta), \\
a_4 &= \mu\gamma_p\delta\tau\frac{\lambda_p}{\tau^*\bar{u} + \gamma_p} + \left\{\mu\left(\gamma_u + \alpha n^2 \bar{u}^{n-1} + \rho\frac{\alpha}{\mu}\bar{u}^n\right) + \rho\alpha n\bar{u}^n\right\}(\gamma_p\sigma + (\gamma_p + \tau\bar{u})\delta).
\end{aligned}
$$

9.2 Lyapunov function

In order to derived the global stability in proposition 8.3 we consider Lyapunov to the system (8.8) be the function

$$\begin{aligned}\Phi =&\frac{1}{2}\left(\frac{2\gamma_p}{\delta}\right)s_1\theta_1^2+\frac{1}{2}\left(1+2\frac{\delta+\gamma_u+\rho(A_\infty+\theta_1)}{\sigma}\right)\theta_2^2+\frac{1}{2}\left(\frac{2\gamma_p}{\delta}\right)\theta_3^2+\frac{1}{2}\left(\frac{\sigma}{\gamma_p}\right)\theta_4^2\\&+\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\theta_1\theta_2+\theta_1\theta_3+\theta_2\theta_3\\&+\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1+\frac{\rho}{\tau}\right)\theta_1\theta_4+2\theta_2\theta_4+\left(\frac{2\gamma_p}{\delta}\right)\theta_3\theta_4,\end{aligned}$$

where $\theta_1=A-A_\infty$, $\theta_2=u-u_\infty$, $\theta_3=p-p_\infty$, $\theta_4=b-b_\infty$, with $s_1=\max(T_1,T_2)$ such that

$$\begin{aligned}T_1=\frac{\rho^2\delta u_\infty^2(1+2\frac{1+\delta}{\sigma})}{8\mu\gamma_p}+\frac{(\gamma_p+\mu)^2(\frac{\delta}{2\gamma_p})^2}{4\gamma_p\mu}\\+\frac{[(\delta+\mu)(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1)+(\sigma+\delta+\mu)\frac{\rho}{\tau}+2\rho u_\infty]^2}{8\mu\sigma}\end{aligned}$$

and,

$$\begin{aligned}T_2=&\frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)^2\left(\frac{2\sigma+\delta}{2\gamma_p}\right)}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}+\frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\left[2+4\frac{\rho}{\tau}\frac{\delta+\gamma_u}{\sigma}\right]}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}\\&+\frac{\left(\frac{\delta}{2\gamma_p}\right)^3\left[\frac{\rho}{\tau}\left(2+\frac{\rho}{\tau}\right)+\frac{\sigma}{\gamma_p}+2\frac{\delta+\gamma_u}{\gamma_p}\right]}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}+\frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(1+\frac{\rho}{\tau}\right)\left[1+2\frac{\delta+\gamma_u}{\sigma}\right]\frac{\rho}{\tau}}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}\\&+\left(\frac{\delta}{2\gamma_p}\right)\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)^2\left(\frac{1}{1+2\frac{\delta+\gamma_u}{\sigma}}\right)+\frac{\left(1+2\frac{\delta+\gamma_u}{\sigma}\right)\left(\frac{\delta}{2\gamma_p}\right)^2}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)}.\end{aligned}\tag{9.1}$$

This Lyapunov function Φ is positive when $\left(1+2\frac{\delta+\gamma_u}{\sigma}\right)>\frac{\delta}{2\gamma_p}>\frac{\gamma_p}{\sigma}$. Its derivative along the solutions to the system (8.8) is

$$\begin{aligned}\dot{\Phi}=&-\left(\mu s_1+\rho u\frac{\rho\frac{\delta}{2\gamma_p}p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\theta_1^2-\rho u_\infty\left(1+2\frac{\gamma_u+\rho(A_\infty+\theta_1)+\delta}{\sigma}\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_2\\&-\left(\frac{2(\gamma_u+\rho(A_\infty+\theta_1)+\tau p)(\gamma_u+\rho(A_\infty+\theta_1)+\delta)}{\sigma}+\gamma_u+\rho(A_\infty+\theta_1)\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_2^2\\&-\left((\delta+\mu)\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1\right)+(\sigma+\delta+\mu)\frac{\rho}{\tau}+2\rho u_\infty\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_4\\&-\left(\frac{\delta\tau u}{2\gamma_p}+\gamma_p\right)\theta_3^2-\delta\left(\frac{\sigma}{\gamma_p}\frac{\delta}{2\gamma_p}\right)\theta_4^2-(\gamma_p+\mu)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_3\end{aligned}$$

$\dot{\Phi}$ is non-positive. Furthermore, $\dot{\Phi} = 0$ if and only if $\theta_1 = \theta_2 = \theta_3 = \theta_4 = 0$.

Conclusion and perspectives

In this work, we have considered several problems involving inclusion and differential equations with and without impulses. We have succeeded in formulating our problems in such a way that results from nonlinear analysis can be applied to prove existence of solutions and to analyze the problems under consideration. We have made several contributions to the theory. Some results have been published [100] and others are submitted for publications [101, 123]. Yet, there are many subjects which need further investigation. We can name a few:

- mathematical model describing the dynamic of chronic myeloid leukemia,
- stability and bifurcation theory for general impulsive differential equations,
- extension and simulation of mathematical model including the role of prion in Alzheimer's disease,
- impulsive differential inclusion with state dependent instants of impulse,
- boundary value problems subject to impulsive effects,
- impulsive delay differential equations.

Bibliography

[1] Adams R. A. and Fournier J.J.F., *Sobolev spaces. Second edition. Pure and Applied Mathematics*, **140**. Elsevier Academic Press, Amsterdam, 2003.

[2] Agarwal R. P., and O'Regan D., *Multiple solutions for second order impulsive differential equations*, Appl. Math. Comput. **114** 2000, 51-59.

[3] Agur Z., Cojocaru L., Mazaur G., Anderson R. M. and Danon Y. L., *Pulse mass measles vaccination across age cohorts,* Proc. Nat. Acad. Sci. USA., **90** 1993, 11698-11702.

[4] Ahmed N. U., *Optimal control for impulsive systems in Banach spaces*, Int. J. Differ. Equ. Appl. **1** 2000, 37-52.

[5] Allen L. J. S., *An Introduction to Mathematical Biology,* Prentice Hall, 2007.

[6] Ambrosetti A. and Prodi G., *A Primer of Nonlinear Analysis,* Cambridge University Press, Cambridge, 1993.

[7] Andres J. and Górniewicz L., *Topological Fixed Point Principles for Boundary Value Problems,* Kluwer, Dordrecht, 2003.

[8] Aubin J. P., *Impulse Differential Inclusions and Hybrid Systems: a Viability Approach*, Lecture Notes Université Paris-Dauphine, 2002.

[9] Aubin J. P. , *Neural Networks and Qualitative Physics: A Viability Approch*, Cambridge University Press, 1996.

[10] Aubin J. P. and Cellina A., *Differential Inclusions,* Springer-Verlag, Berlin-Heidelberg, New York, 1984.

[11] Aubin J. P. and Frankowska H., *Set-Valued Analysis,* Birkhauser, Boston, 1990.

[12] Avgerinos E. P., Papageorgiou N. S., *Topological properties of the solution set of integrodifferential inclusions,* Comment. Math. Univ. Carolinae, **36(3)** 1995, 429-442.

[13] Aysagaliev S.A., Onaybar K.O. and Mazakov T.G., *The controllability of nonlinear systems*, Izv. Akad. Nauk. Kazakh-SSR.-Ser. Fiz-Mat **1** 1985, 307-314.

[14] Azbelev N. B., Maximov V. P., and Rakhmatulina L. F., *Introduction to the Functional Differential Dquations*, Russian, Nauka, Moscouw, 1991.

[15] Bainov D. D., *Impulsive differential equations*, Longman 1993.

[16] Bainov D. D. and Dishliev A. B., *Conditions for the absence of the phenomenon 'beating' for systems of impulse differential equations*, Bull. Inst. Math. Acad. Sin. **13(3)**, 1985, 237-256.

[17] Bainov D. D. and Milusheva S., *Justification of the averaging method for a system of differential equations with fast and slow variables with impulses*, Z. Angew. Math. Phys. **32**, 1981, 237-254.

[18] Bainov D. D. and Simeonov P. S., *Systems with impulsive effect; Stability, theory and applications*, John Wiley and Sons, New York 1989.

[19] Bainov D. D. and Simeonov P. S., *Systems with Impulse Effect*, Ellis Horwood Ltd., Chichister, 1989.

[20] Bainov D. D. and Simeonov P. S., *Impulsive differential equations: periodic solutions and applications*, Pitman Monographs and Surveys in Pure and Applied Mathematics, 66, Longman Scientific & Technical and John Wiley & Sons, Inc., New York, 1993.

[21] Ballinger G. and Liu X., *Permanence of population growth models with impulsive effects*, Math. Comput. Modelling **26** 1997, 59-72.

[22] Barnet S. *Introduction to Mathematical Control Theory*, Clarendon Press, Oxford, 1975.

[23] Bellomo N. and Forni G., *Dynamics of tumor interaction with the host immune system*, Math. Comput. Modelling **20**, 1994, 107-122.

[24] Benchohra M., Boucherif A., and Ouahab A., *On nonresonance impulsive functional differential inclusions with nonconvex valued right hand side*, J. Math. Anal. Appl. **282** 2003, 85-94.

[25] Benchohra M., Górniewicz L., Ntouyas S.K. and Ouahab A., *Controllability results for impulsive functional differential inclusions,* Reports on Mathematical Physics, **54** 2004, 211-227.

[26] Benchohra M. , Graef J., Ntouyas S. K., and Ouahab A., *Upper and lower solutions method for impulsive differential inclusions with nonlinear boundary conditions and variable times*, Dyn. Contin. Discrete Impuls. Syst., Ser. A, **12** 2005, 383-396.

[27] Benchohra M. , Henderson J. and Ntouyas S. K., *An existence result for first order impulsive functional differential equations in Banach spaces*, Comput. Math. Appl. **42** 2001, 1303-1310.

[28] Benchohra M. , Henderson J. and Ntouyas S., *Impulsive Differential Equations and Inclusions, Contemporary Mathematics and Its Applications*, Hindawi Publishing, New York, 2006.

[29] Benchohra M. , Henderson J. and Ntouyas S. K., *Impulsive neutral functional differential equations in Banach spaces*, Appl. Anal. **80** 2001, 353-365.

[30] Benchohra M., Henderson J., Ntouyas S. K., and Ouahab A., *Impulsive functional differential equations with variable times and infinite delay*, Inter. J. Appl. Math. Sci. **2** 2005, 130-148.

[31] Benchohra M., Nieto J. J., and Ouahab A., Existence results for functional integral inclusions of Volterra type, Dyn. Syst. Appl., **14**, 2005, 57-70.

[32] Benchohra M. and Ouahab A., *Impulsive neutral functional differential inclusions with variable times*, Electr. J. Differ. Equ., 2003, 1-12.

[33] Bensoussan A. and Lions J. L., *Novelle formulation de problmes de controle impulsionnel et applications*, C.R. Acad. Sciences **276**, 1189-1192.

[34] Bensoussan A. and Lions J. L., *Controle Impulsionnel et Inquations Quasi-variationnelles*, Dunod, Paris, 1982.

[35] Bensoussan A. and Lions J. L., *Impulse Controle and Quasivaritionnelles Inequalites*, Gauthier-Villars, 1984.

[36] Bressan A. and Colombo G., *Extensions and selections of maps with decomposable values,* Studia Math. **90** 1988, 70-85.

[37] Bressan A. and Colombo G., *Generalized Baire category and differential inclusions in Banach spaces*, J. Differential Equations **76** 1987, 135-158.

[38] Bressan A. and Colombo G., *Boundary value problems for lower semicontinuous differential inclusions*, Funkcial. Ekvac. **36** 1993, 359-373.

[39] Bressloff P. C. and Coombes S., *A dynamic theory of spike train transitions in networks of integral and fire oscillators*, SIAM J. Applied Analusis 98, 1998.

[40] Brézis H., *Analyse Fonctionnelle. Théorie et Applications*, Masson, Paris, 1983.

[41] Brézis H., *Functional analysis, Sobolev spaces and partial differential equations*, Universitext. Springer, New York, 2011.

[42] Browder F. E. and Gupta G. P., *Topological degree and nonlinear mappings of analytic type in Banach spaces*, J. Math. Anal. Appl. **26** 1969, 730-738.

[43] Brown R. F., Furi M., Górniewicz L., and Jiang B., *Handbook of Topological Fixed Point Theory*, Springer, Dordrecht, 2005.

[44] Burger R. A., Grosen E. A., Ioli G. R., Van Eden M. E., Brightbill H. D., Gatanaga M., DiSaia P. j., Granger G. A. and Gatanaga T., *Host tumor interaction in ovarian cancer spontaneous release of tumor necrosis factor and interleukin-1 inhibitors by purified cell populations from human ovarian carcinoma in vitro*, Gynecologic oncology, **55**, 1994, 294-303.

[45] Cabada A. and Liz E., *Discontinuous impulsive differential equations with nonlinear boundary conditions*, Nonlinear Anal. **28** 1997, 1491-1499.

[46] Cabada A. and Liz E., *Boundary value problem for higher order ordinary differential equations with impulses*, Nonlinear Anal. **32** 1998, 775-786.

[47] Castaing C. and Valadier M, *Convex Analysis and Measurable Multifunctions, Lecture Notes in Mathematics*, Springer-Verlag, Berlin-Heidelberg-New York, **580**, 1977.

[48] Chang Y. K. and Li W. T., *Existence results for second order impulsive functional differential inclusions*, J. Math. Anal. Appl. **301** 2005, 477- 490.

[49] Chow S. N. And Hale J., *Methods of bifurcation theory,* Springer Verlag 1982.

[50] Cisse M. and Mucke L., *A prion protein connection*, Nature, 457:1090-1991, Feb. 2009.

[51] Collet J.F. and Goudon T., *On solutions of the Lifshitz-Slyozov model. Nonlinearity*, **13(4)**:1239-1262, July 2000.

[52] Colombo G. and Goncharov V., *The sweeping processes without convexity*, Set-Valued Anal. **7** 1999, 357-374.

[53] Colombo G. and Monterio Marques M. D. P., *Sweeping by a continuous prox-regular set*, J. Differential Equations **187** 2003, 46-62.

[54] Cornil I., Theodorescu D., Man S., Herlyn M., Jambrosic J. and Kerbel R. S., *Fibroblast cell interactions with human melanoma cells affect tumor cell growth as a function of tumor progression*, Proc. Natl. Acad. Sci. USA, **88**, 1991, 6028-6032.

[55] Covitz H. and Nadler Jr. S. B., *Multi-valued contraction mappings in generalized metric spaces,* Israel J. Math. **8** 1970, 5-11.

[56] Craft D. L., Wein L. M. and S. D. J., *The Impact of Novel Treatments on $A\beta$ Burden in Alzheimers Disease: Insights from A Mathematical Model,* In M. L. Brandeau, F. Sainfort, and W. P. Pierskalla, editors, Operations Research and Health Care, volume **70** of International Series in Operations Research & Management Science, pages 839-865. Kluwer Academic Publishers, Boston, 2005.

[57] Craft D. L., Wein L. M. and Selkoe D. J., *A mathematical model of the impact of novel treatments on the A beta burden in the Alzheimer's brain, CSF and plasm,* Bulletin of mathematical biology, **64(5)**:1011-31, Sept. 2002.

[58] Day R. H., *Multiple-phase economic dynamics in Nonlinear and Convex Analysis in Economic Theory*, Tokyo, 1993, T. Maruyama and W. Takahashi, Eds., pp. 25-45, Lecture Notes in Econom. and Math. Systems, Vol. **419**, Springer, Berlin, 1995.

[59] Deimling K., *Multi-valued Differential Equations*, De Gruyter, Berlin-New York, 1992.

[60] Demengel F. and G.F. Demengel, *Function spaces. Usage for the solution of partial differential equations. (Espaces fonctionnels. Utilisation dans la résolution des équations aux dérivées partielles.) (French)*, Savoirs Actuels. Les Ulis: EDP Sciences; Paris: CNRS Éditions, 2007.

[61] Djebali S., Górniewicz L. and Ouahab A., *Filippov's Theorem and Structure of Solution Sets for First Order Impulsive Semilinear Functional Differential Inclusions,* Topo. Meth. Nonl. Anal., **32**, 2008, 261-312.

[62] Djebali S., Górniewicz L., and Ouahab A., *First order periodic impulsive semilinear differential inclusions existence and structure of solution sets,* Math. Comput. Modeling , **52** 2010, 683-714.

[63] Djebali S., and Ouahab A., *Existence results for ϕ-Laplacian Dirichlet BVPs of differential inclusions with application to control theory*, Discuss. Math. Differential Inclusions **30** (2010), 23-49.

[64] S. Djebali, L. Gorniewicz and A. Ouahab, *Existence and Structure of Solution Sets for Impulsive Differential Inclusions*, Lecture Notes, Nicolaus Copernicus University No 13 , 2013.

[65] Dieudonne J., *Foundations of Modern Analysis,* Academic Press, New York, 1964.

[66] Dordan O., *Analyse Qualitative*, Masson, 1992.

[67] Dotto G. P., Weinberg A. and Ariza A., *Malignant transformation of mouse primary keratinocytes by Harvey sarcoma virus and its modulation by surrounding normal cells*, Proc. Acad. Sci. USA **85**, (1988), 6389-6393.

[68] Dugundji J. and Granas A., *Fixed Point Theory,* Springer-Verlag, New York 2003.

[69] Dunford N. and Schwartz J., *Linear Operators, Part I: General Theory,* Wiley-Interscience, New York, 1964.

[70] Erbe L.,H., Kong Q., and Zhang B. G., *Oscillation Theory for Functional Differential Equations*, Pure and Applied Mathematics, Marcel Dekker, New York, 1994.

[71] Erbe L. and Krawcewicz W., *Existence of solutions to boundary value problems for impulsive second order differential inclusions*, Rocky Mountain J. Math. **22** 1992, 519-539.

[72] Evans C., Lawrence, *Partial differential equations. (English) Graduate Studies in Mathematics*, **19**. Providence, RI: American Mathematical Society 1998.

[73] Filippov A. H., *On some problems of optimal control theory*, *Vestnik Moskowskogo Univesiteta, Math.*, **2** 1958, 25-32.

[74] Filippov A. F., *Differential Equations with Discontinuous Right-hand Sides*, Kluwer Academic Publishers, Dordrecht, 1988.

[75] , Franco D. , Liz E., Nieto J. J., and Rogovchenko Y. V., *A contribution to the study of functional differential equations with impulses*, Math. Nachr. **218** 2000, 49-60.

[76] Frankowska H., *Set-Valued Analysis and Control Theory,* Centre de Recherche de Mathématique de la Décision, Université Paris-Dauphine, 1992.

[77] Frankowska H., *A priori estimates for operational differential inclusions, J. Differential Equations,* **84** 1990, 100-128.

[78] Frigon M., *Fixed point results for multivalued contractions on gauge spaces, set valued mappings with applications in nonlinear analysis*, 175-181, Ser. Math. Anal. Appl., **4**, Taylor & Francis, London, 2002.

[79] Frigon M. and Granas A., *Théorèmes d'existence pour des inclusions différentielles sans convexité,* C. R. Acad. Sci. Paris, Ser. I **310** 1990, 819-822.

[80] Frigon M. and O'Regan D., *Existence results for first order impulsive differential equations*, J. Math. Anal. Appl. **193** 1995, 96-113.

[81] Frigon M. and O'Regan D., *Boundary value problems for second order impulsive differential equations using set-valued maps*, Appl. Anal. **58** 1995, 325-333.

[82] Fryszkowski A. and Gòrniewicz L., *Mixed semicontinuous mappings and their applications to differential inclusions*, Set-Valued Anal. **8** 2000, 203-217.

[83] Gao S., Chen L., Nieto J. J. and Torres A., *Analysis of a delayed epidemic model with pulse vaccination and saturation incidence*, VACCINE, **24** 2006 6037-6045.

[84] Graef J. R. and Ouahab, *Some existence and uniqueness results for first-order boundary value problems for impulsive functional differential equations with infinite delay in Fréchet spaces*, Int. J. Math. Math. Sci. **16** 2006, 0161-1712.

[85] Graef J. R. and Ouahab, *A class of second order impulsive functional differential equations*, submitted.

[86] Graef J. R. and Ouahab, *Second order impulsive functional differential inclusions with infinite delay in Banach spaces*, preprint.

[87] Gatenby R. A., *Population ecology issues in tumor growth,* Cancer Res. **51**, 1991, 2542-2547.

[88] Gimbel D. A., Nygaard H. B., Coffey E. E., Gunther E. C., Laurn J., Gimbel Z. A., and Strittmatter S. M, *Memory impairment in trans-genic Alzheimer mice requires cellular prion protein*, The Journal of Neuroscience, **30(18)**:6367-74, May 2010.

[89] Granas A. and Dugundji J., *Fixed Point Theory*, Springer-Verlag, New York, 2003.

[90] Greer M. L., Pujo-Menjouet L., and Webb G. F., *A mathematical analysis of the dynamics of prion proliferation,* Journal of Theoretical Biology, **242(3)**:598-606, Oct. 2006.

[91] Górniewicz L., *Topological Fixed Point Theory of Multi-valued Mappings, Mathematics and its Applications*, **495**, *Kluwer Academic Publishers, Dordrecht*, 1999.

[92] Górniewicz L., *Topological Approach to Differential Inclusions, Topological Methods in Differential and Inclusions (A. Granas and M. Frigon,eds.)*, NATO ASI Series C, Vol. **472**, Kluwer Academic Publishers, Dordrecht, 1995.

[93] Graef J. R. and Ouahab A., *Impulsive differential inclusions with parameter*, Submitted.

[94] Guo H. and Chen L., *The effects of impulsive harvest on a predator-prey system with distributed time delay*, Commun Nonlinear Sci Numer Simulat. **14** 2009, 2301-2309.

[95] Guo M., Xue X. and Li R., *Controllability of impulsive evolutions inclusions with nonlocal conditions*, Z. Optim. Theory Appl. **120** 2004, 355-374.

[96] Halanay A. and Wexler D., *Teoria Calitativa a systeme cu Impulduri*, Editura Republicii Socialiste Romania, Bucharest, 1968.

[97] Hale J. K. and Verduyn Lunel S. M., *Introduction to Functional Differential Equations*, Applied Mathematical Sciences. **99**, Springer-Verlag, New York, 1993.

[98] Hardy J. and Selkoe D. J, *The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics*, Science, **297(5580)**:353-6, July 2002.

[99] He M., Li Z. and Chen F., *Permanence, extinction and global attractivity of the periodic Gilpin-Ayala competition system with impulses*, Nonlinear Analysis: Real World Applications **11**, 2010, 1537-1551.

[100] **Helal M.** and Ouahab A., *Existence and solution sets of impulsive functional differential inclusions with multiple delay*, Opuscula Mathematica, **32/2** 2012, 249-283.

[101] **Helal M.**, Hingant E., Pujo-Menjouet L. and Webb G. F., *Alzheimer's disease, analysis of a mathematical model including the role of the prion protein*, Journal of Mathematical Biology, submitted February 2013.

[102] Henderson J., *Boundary Value Problems for Functional Differential Equations*, World Scientific, Singapore, 1995.

[103] Henderson J. and Ouahab A., *Local and global existence and uniqueness results for second and higher order impulsive functional differential equations with infinite delay,* Aust. J. Math. Anal. Appl. **4** 2007, 149-182.

[104] Henderson J. and Ouahab A., *Global existence results for impulsive functional differential inclusions with multiple delay in Fréchet spaces*, PanAmerican Math. J. **15** 2005, 73-89.

[105] Hodgkin A. L. and Huxley A. F., *A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. [***117** 1952, 467-472.

[106] Hu Sh. and Papageorgiou N., *Handbook of Multivalued Analysis, Volume I: Theory*, Kluwer, Dordrecht, 1997.

[107] Hu Sh. and Papageorgiou N. S., *Handbook of Multi-valued Analysis, Volume I: Theory*, Kluwer, Dordrecht, 1997.

[108] Hu Sh. and Papageorgiou N. S., *Handbook of Multi-valued Analysis. Volume II: Applications,* Kluwer, Dordrecht, The Netherlands, 2000.

[109] Hu S., Papageorgiou N. S. and Lakshmikantham V., *On the properties of the solutions set of semilinear evolution inclusions,* Nonlinear Anal., **24**, 1995, 1683-1712.

[110] Iooss G., *Bifurcation of maps and applications, Study of mathematics,* North Holland 1979.

[111] Jiao J., Meng X. and Chen L., *A new stage structured predator-prey Gomportz model with time delay and impulsive porturbations*, Appl. Math. Comput. **196** 2008, 705-719.

[112] Kamenskii M., Obukhovskii V. and Zecca P., *Condensing multivalued Maps and Semilinear Differential Inclusions in Banach Spaces*, Walter de Gruyter & Co. Berlin, 2001.

[113] Kato T., *Perturbation Theory for Linear Operators,* Springer-Verlag, BerlinHeidelbergNew York, 1984.

[114] Kielhfer H., *Bifurcation Theory, An Introduction with Applications to Partial Differential Equations,* Second Edition. Springer New York Dordrecht Heidelberg London Volume. **156** 2012.

[115] Kisielewicz M., *Differential Inclusions and Optimal Control*, Kluwer, Dordrecht, The Netherlands, 1991.

[116] Korobov V.I., *Reduction of a controllability problem to a boundary value problem*, Different. Uranen. **12** 1976, 1310-1312.

[117] Kruger-Thiemr E. *Formal theory of drug dosage regiments,* J. Theo. Biol., **13** 1966, 212-235.

[118] Kruger-Thiemr E., *Formal theory of drug dosage regiments,* II. J. Theoret. Biol. **23** 1969, 169-190.

[119] Kyritsi S., Matzakos N. and Papageorgiou N. S., *Nonlinear boundary value problems for second order differential inclusions*, Czechoslovak Math. J. **55** 2005, 545-579.

[120] La Rocca S. A. , Grossi M., Fallone G., Alem S. and Tato F., *Interaction with normal cells suppresses the transformed phynotype of v-myc-transformed quail muscle cells*, Cel **58**, 1989, 123-131.

[121] Lakmeche A. and Arino O., *Nonlinear mathematical model of pulsed-therapy of hetergenous tumor, Nonlinear Anal*, Real World Appl. **2** 2001 455-465.

[122] Lakmeche A. and Arino O., *Bifurcation of non trivial periodic solutions of impulsive differential equations arising in chemotherapeutic treatment*, Dynamics Cont. Discr. Impl. Syst., **7**, 2000, 265-287.

[123] Lakmeche Ah., **Helal M.** and Lakmeche A., *Periodically pulsed chemotherapy with resistant tumor cells*, Acta Universitatis Apulensis, submitted April 2012.

[124] Lakshmikantham V., Bainov D. D. and Simeonov P. S., *Theory of Impulsive Differential Equations*, World Scientific, Singapore, 1989.

[125] Lasota A. and Opial Z., *An application of the Kakutani-Ky Fan theorem in the theory of ordinary differential equations,* Bull. Acad. Pol. Sci. Ser. Sci. Math. Astronom. Phys. **13** 1965, 781-786.

[126] Laurrn J., Gimbel D. A. , Nygaard H. B., Gilbert J. W. and Strittmatter S. M., *Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers*, Nature, **457(7233)**:1128-32, Feb.2009.

[127] Ledzewicz U., Naghnaeian M. and Schattler H., *Optimal response to chemotherapy of mathematical model of tumor-immune dynamics*, Journal of Mathematical Biology, **64**, 2012 557-577 in press, DOI/ 10.1007/S00285-011-424-6.

[128] Liotta A. L., *Cancer cell invasion and metastasis*, Scientific American, 1992, 54-63.

[129] Liz E. and Nieto J.,J., *Positive solutions of linear impulsive differential equations*, Commun. Appl. Anal. **2 (4)** 1998, 565-571.

[130] Lomakin A., *On the nucleation and growth of amyloid beta-protein fibrils: Detection of nuclei and quantitation of rate constants*, Proceedings of the National Academy of Sciences, **93(3)**:1125-1129, Feb. 1996.

[131] Lomakin A., *Kinetic theory of fibrillogenesis of amyloid beta-protein*, Proceedings of the National Academy of Sciences, **94(15)**:7942-7947, July 1997.

[132] Ma T. and Wang S., *Bifurcation theory and applications.*, Word scienrific series on nonlinear science. 53, 2005

[133] Meng X., Jiao J., Chen L., *The dynamics of an age structured predator-prey model with disturbing pulse and time delays*, Nonlinear Anal. **9** 2008, 547-561.

[134] Michelson S. and Leith J. T., *Growth factors and growth control of heterogeneouscell populations*, Bull. Math. Bio. **57**, 1993, 345-566.

[135] Michelson S. and Leith J. T., *Unexpected equilibria resulting from differing growth rates of subpopulations within heterogeneous tumors*, Math. Biosci. **91**, 1988, 119-129.

[136] Milman V. D. and Myshkis A. A., *On the stability of motion in the presence of impulses (in Russian),* Sib. Math.J. **1** 1960, 233-237.

[137] Milman V. D. and Myshkis A. A., *Randorn impulses in linear dynamical systems, in "Approximante Methods for Solving Differential Equations,"* Publishing house of the Academy of Sciences of Ukainian SSR, Kiev, in Russian, 1963 64-81.

[138] Mishkis A. D. and Samoilenko A. M., *Systems with impulses at prescribed moments of time*, Maths. Sb. in Russian **74** n^0**2**, 1967, 202-208.

[139] Musielak J., *Introduction to Functional Analysis,* in Polish. PWN, Warszawa 1976.

[140] Nygaard H. B. and Strittmatter S. M., *Cellular Prion Protein Mediates the Toxicity of -Amyloid Oligomers: Implications for Alzheimer Disease*, Archives of Neurology, **66(11)**:1325-1328, Nov. 2009.

[141] Ouahab A., *Local and global existence and uniqueness results for impulsive differential equtions with multiple delay*, J. Math. Anal. Appl. **323** 2006, 456-472.

[142] Ouahab A., *Existence and uniqueness results for impulsive functional differential equations with scalar multiple delay and infinite delay,* Nonlinear Anal. T.M.A., **67** 2006, 1027-1041.

[143] Ouahab A., *Local and global existence and uniqueness results for impulsive functional differential equations with multiple delay*, J. Math. Anal. Appl. **323** 2006, 456-472.

[144] Pandit S. G. and Deo S. G., *Differential Systems Involving Impulses,* Lecture Notes in Mathematics, **954** Springer-Verlag, 1982.

[145] Panetta J. C., *A mathematical model of periodically pulsed chemotherapy: tumor recurrence and metastasis in a competition environement*, Bulletin of mathematical Biology, Vol. **58(3)** 1996, 425-447.

[146] Papageorgiou N. S. and Yannakakis N., *Nonlinear parametric evolution inclusions,* Math. Nachr. **233/234** 2002, 201-219.

[147] Pei Y., Liu S., Li C., and Chen L., *The dynamics of an impulsive delay SI model with variable coefficients*, Appl. Math. Modell. **33** 2009, 2766-1776.

[148] Petruşel A., *Operatorial Inclusions,* House of the Book of Science, Cluj-Napoca, 2002.

[149] Pierson-Gorez C., *Problemes aux Limites Pour des Equations Differentielles avec Impulsions*, Ph.D. Thesis, Univ. Louvain-la-Neuve, 1993 (in French).

[150] Portet S. and Arino J., *An in vivo intermediate filament assembly model*, Mathematical Biosciences and Engineering, **6(1)**:117-134, Jan. 2009.

[151] Ricceri B. *Une propriété topologique de l'ensemble des points fixe d'une contraction multivoque à valeurs convexes*, Atti Accad. Naz. Linei Cl. Sci. Fis. Mat. Natur. Rend. Lincei **9** Mat. Appl. 1987, 283-286.

[152] Rubenstein R., Merz P., Kascsak R., Scalici C., Papini M., Carp R., and Kimberlin R., *Scrapie-infected spleens: analysis of infectivity, scrapie-associated fibrils, and protease-resistant proteins*, J. Infect. Dis., 164:29-35, 1991.

[153] Samoilenko A. M. and Perestyuk N. A., *Impulsive Differential Equations,* World Scientific, Singapore, 1995.

[154] Selkoe D. J., *Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior.* Behavioural brain research, **192(1)**:106-13, Sept. 2008.

[155] Shimokawa T., Pakdaman K., Satos S., *Time-scale matching in the response, of a leaky integale-and-fire neuron model to periodic stimulation with additive noise*, Physical Review E **59** 1999, 3427-3443.

[156] Smirnov G. V., *Introduction to the Theory of Differential Inclusions,* Graduate Studies in Mathematics **41**, American Mathematical Society, Providence, 2002.

[157] Song X. and Guo H., *Extinction and permanence of a kind of pest-predator models impulsive effect and infinite delay*, J Korean Math Soc. **44** 2007, 327-342.

[158] Tang S. and Cheke R. A., *State-dependent impulsive models of integrated pest management(IPM) stratgies and their dynamic consequences*, J. Math. Biol. **50** 2005, 257-292.

[159] Tolstonogov A. A., *Differential Inclusions in Banach Spaces*, Kluwer Academic Publishers, Dordrecht, 2000.

[160] Tolstonogov A. A., *Approximation of attainable sets of an evolution inclusion of subdifferential type,* Sibirsk. Mat. Zh., **44**, 2003, 883-904.

[161] Tolstonogov A. A., *Properties of attainable sets of evolution inclusions and control systems of subdifferential type,* Sibirsk. Mat. Zh., **45**, 2004, 920-945.

[162] Urbanc B., Cruz L., Buldyrev S. V., Havlin S., Irizarry M. C., Stanley H. E., and Hyman B. T., *Dynamics of plaque formation in Alzheimer's disease*, Biophysical journal, **76(3)**:1330-4, Mar. 1999.

[163] Vatsala A. S., and Sun Y., *Periodic boundary value problems of impulsive differential equations*, Appl. Anal. **44** 1992, 145-158.

[164] Wagner D., *Survey of measurable selection theorems,* SIAM J. Control Optim. **15** 1977, 859-903.

[165] Walsh D. M., *Amyloid-beta Protein Fibrillogenesis. Detection of a protofibrillar intermediate*, Journal of Biological Chemistry, **272(35)**:22364-22372, Aug. 1997.

[166] Wang L., Chen L. and Nieto J. J., *The dynamics of an epidemic model for pest control with impulsive effect*, Nonlinear Analysis: Real World Applications **11**, 2010, 1374-1386.

[167] Ważewski T., *On an optimal control problems*, Proc. Conference differential equations and third application, Pragu, 1962, 222-242.

[168] Wei H. C., Hwang S. F., Lin J. T. and Chen T. J., *The role of initial tumor biomass size in a matematical model of periodically pulsed chemotherapy*, Computers and Mathematics with Applications **61**, 2011, 3117-3127.

[169] Wimo A. and Prince M., *World Alzheimer Report 2010: The global economic impact of dementia*, Technical report, Alzheimer's Disease International, 2010.

[170] Yosida K., *Functional Analysis,* 6^{th} ed. Springer-Verlag, Berlin, 1980.

[171] Yujun D., *Periodic boundary value problems for functional differential equations with impulses,* J. Math. Anal. Appl. **210** 1997, 170-181.

[172] Yujun D. and Erxin Z., *An application of coincidence degree continuation theorem in existence of solutions of impulsive differential equations*, J. Math. Anal. Appl. **197** 1996, 875-889.

[173] Zhu Q. J., *On the solution set of differential inclusions in banach space,* J. Diff. Eq. **93(2)** 1991, 213-237.