UNIVERSITA' DEGLI STUDI - L'AQUILA
DIPARTIMENTO DI INGEGNERIA E SCIENZE DELL'INFORMAZIONE E MATEMATICA
Via Vetoio Loc. Coppito - 67100 L'Aquila - Tel. (0862) 43.3124/25/33 - Fax (0862) 43.3180
C.F./P.I.: 01021630668

Report on the Ph.D. thesis

Understanding Cell Dynamics in Cancer from Control and Mathematical Biology Standpoints - Particular Insights into the Modeling and Analysis Aspects in Hematopoietic Systems and Leukemia, by Walid Djema

Reviewer: Pierdomenico Pepe, University of L'Aquila, Italy

Contribution

The thesis deals with the very interesting problems of modelling cancer dynamics and providing analysis tools for stability and control. The objective of the thesis is therefore twofold: first improving the results in the literature about modelling, for instance by introducing new factors in the models, previously not taken into account; then making an analysis of possible equilibria by advanced mathematical tools for nonlinear systems mainly described by partial differential equations. These equations are suitably transformed into retarded functional differential equations coupled with continuous time difference equations. Then a stability analysis of these equations is provided by means of sophisticated Lyapunov-Krasovskii functionals. At any step, insights into the meaning of provided results in the cancer evolution are provided. The thesis provides significant improvements in both the biological models and in the mathematical analysis. Very impressive, the results suggest control strategies in order to improve cancer cells treatment by medical therapies.

Chapters Analysis

Chapter 1

In the introductory chapter 1, it is pointed out which are the main tasks of the research project: better understanding by mathematical tools the behavior of healthy and unhealthy blood cell dynamics; suggesting, in cooperation with medicine scientists, new anti-leukemic chemotherapies. Population dynamical models are introduced. The role of retarded functional differential equations is evidenced. The main mathematical tool for stability, based on Lyapunov-Krasovskii functionals, is recalled.

Chapter 2

In chapter 2 an interesting overview of biological dynamics is given. Biological notions of stem cells, cancer stem cells, dedifferentiation, transdifferentiation, cancer dormancy, regulation of hematopoietic cell growth, pathological blood disorders are introduced, allowing non-experts of the sector to better capture the biological problems at hand. Current therapies for Acute Myeloid Leukemia are briefly described. Finally, the importance of engineering-mathematical tools for dealing with the introduced biological principle is highlighted. It is pointed out how the use of mathematical tools may allow a better understanding of healthy and unhealthy blood cell dynamics, as well as may provide suggestions in the elaboration of medical therapies.

Chapter 3

In chapter 3 strict Lyapunov-Krasovskii functionals are provided for stability analysis of extended versions of biological models available in the literature. Robust stability with respect to non-vanishing perturbations is also provided. Biological models are described by retarded functional differential equations with distributed delay. The positivity of the solutions and the existence of equilibria are studied. Conditions for the global asymptotic stability and the global exponential stability are provided. The interesting case of time-varying parameters (time-varying differentiation rates) is also investigated. Regions of attraction are estimated.

Chapter 4

In chapter 4, in order to take into account of unlimited time quiescent cells, a model of retarded differential equation with infinite distributed delay is investigated. Stability analyses are performed by means of novel Lyapunov-Krasovskii functionals. A model of partial differential equations, with suitable boundary conditions is firstly illustrated. Then a resulting system of retarded functional differential equations with distributed delay is provided, obtained by the partial differential equations model. The Student here does not provide insights about how this transformation is performed. I guess it would be helpful to the reader, here and in other parts of the thesis, to report in details how the model of partial differential equations is transformed into a retarded differential equation, also providing explanations about, for instance, exact or not coincidence of solutions. The last sentence in

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Theorem 9 does not fit well with the statement, a better formulation may be needed. Conditions of stability are provided by means of involved Lyapunov-Krasovskii functionals. A glimpse into the medical experience is provided.

Chapter 5

In chapter 5 a model of hematopoietic system recently introduced in the literature is analyzed. The model consists of coupled delay differential and functional difference equations. Exponential stability of equilibria are investigated and basins of attraction estimated. Comparison methods and positive systems theory are used. An estimate of the decay rate is also provided. The assumption after model (5.1) that solutions are piece-wise continuous may be better explained (highlighting whether the biological system at hand may present possible non piece-wise continuous initial conditions), given the previous sentence about existence and uniqueness. Positivity of the solutions is exploited in the analysis. A natural exponential stability result (Lemma 1, nice proof, typo in (5.7)) for scalar continuous time difference equations is used later in order to get stability of the entire system, whenever exponential stability of the first (differentiated) variable is proved by linear, because of positivity, Lyapunov-Krasovskii functionals. In Theorem 11 and proof, a typo occurs, concerning a still undefined system (6.8), which should be system (5.1). Interesting necessary and sufficient stability conditions for the stability of the origin are given in Theorem 11. Then positive equilibria are analyzed. First existence results are provided. Then exponential stability analysis is issued by means of comparative positive system approach and linear Lyapunov functionals. Analysis by quadratic functionals is also issued, and basin of attractions estimated. Again, last sentence in Theorem 12 may be better written. It is not very meaningful to say that a basin of attraction can be determined, in the statement of the theorem. Anyway, the basin of attraction is clearly reported in a window later. Fig. 5.10 concerns still system (6.8) which should be system (5.1).

Chapter 6

The mathematical involvement increases in Chapter 6, since this chapter concerns nonlinear systems described by coupled delay differential and difference equations. Stability results are provided, and positive steady states describing cancer dormancy are extensively studied, and therapeutic strategies discussed. A deep analysis of the conditions guaranteeing existence of positive steady states is provided in notable Proposition 6. Global exponential stability of the origin is proved by means of Lyapunov-Krasovskii functionals which are linear in the Euclidean part and nonlinear in the integral terms. A decay rate estimation is provided. Local stability issues are also addressed for positive steady states such as dormancy, by means of first order approximation methods and related Linear Matrix Inequalities. Finally, possible therapeutic strategies for cancer dormancy are discussed.

Chapter 7

Chapter 7 concerns very complicated models, nonlinear, delayed, and switching (due to drug infusion or body reaction to infection). Stabilization issues by means of artificial intelligence planning tools are addressed. Therapeutic strategies are suggested. Many numerical simulations are provided. The models (Tables 7.1, 7.2), resulting in nonlinear delay differential equations, include growth factor depending parameters. Algorithms for finding stabilizing switches path are provided, in order to achieve best therapeutic strategy. Nice comparison with robotics is given. As highlighted in the conclusions, the identification of the parameters involved in acute myeloid leukemia models may need further investigations.

Evaluation

I think this thesis is very interesting, in both the difficult argument which is dealt with, and in the contribution with respect to the state of the art. The results are an in important improvement with respect to the literature, in both the mathematical analysis of past and new models, and in the biological aspects. The Student has had to keep together two very different science arenas, i.e. the medicine one and the engineering-mathematical one. Having reached such a high level of interaction is, in my opinion, notable. The thesis is excellently written, in both organization and structure, with many pictures and windows allowing the reader to easy capture the main messages. Part of the thesis results have been already published in world leading journals and proceedings of top level conferences on automatic control. I am definitely in favor of the final defense of this thesis, by the Ph.D. Student W. Djema.

L'Aquila, 7 November 2017

Pierdomenico Pepe
University of L'Aquila, Italy