SUMMARY of PhD THESIS

MGHAMES RAGHEB

Title:***"Delay differential equations and partial differential equations modelling of biological processes with applications to hematological diseases and solid tumors"***

Scientific advisor: **Prof.dr. Andrei HALANAY**

Key words: **Delay differential equations- Partial differential equations- Mathematical modeling- stability-critical case- Cahn–Hilliard equation- Acute Lymphoblastic Leukemia- Solid tumor.**

Table of Contents

Mathematical modeling is used to study the effects of different components and allows us to predict their behavior. The theory of mathematical modeling has been studied extensively in delay differential equations (DDEs) and partial differential equations (PDEs) models over 250 years. The importance of hereditary effects in these models was emphasized by the end of the 19^{th} century. Mathematical models are used in several fields of study such as the natural sciences, engineering, social sciences...etc.

This thesis deals with mathematical models for application in biology. The content of the thesis is arranged in two parts and a total of seven chapters.

In the first part, we introduce a delay-differential equations mathematical model for Acute Lymphoblastic Leukemia (ALL) under treatment. This model consists of a compartment for erythropoiesis, a compartment for leukopoiesis and a compartment for lymphopoiesis coupled with the dynamics of 6-MP used in the maintenance therapy. We obtain the equilibrium points of each compartment and perform the stability analysis. The second part deals with some generalizations of the Cahn–Hilliard equation with mass source endowed with Neumann Boundary conditions for biological applications. In this part, we discuss the stationary problem of the Cahn–Hilliard equation with mass source. We were able to prove the existence of a unique solution of the problem. Then, we consider a numerical scheme of the model based on a finite element discretization in space and Backward Euler scheme in time for the evolution problem of the Cahn–Hilliard equation with mass source. Furthermore, after obtaining some error estimates on the numerical solution, we prove that the semi discrete scheme converges to the continuous problem. In addition to that, we prove the stability of our scheme which allows us to obtain the convergence of the fully discrete problem to the semi discrete one.

Finally, we perform the numerical simulations that confirm the theoretical results and demonstrate the performance of our scheme for cancerous tumor growth model and image inpainting model.

Part One: Analysis of a DDEs model for Acute Lymphoblastic Leukemia under treatment

This part is formed of three chapters (1,2 and 3). In this part we introduce a delay-differential equations mathematical model for Acute Lymphoblastic Leukemia (ALL) under treatment. This model consists of a compartment for erythropoiesis,a compartment for leukopoiesis and a compartment for lymphopoiesis coupled with the dynamics of 6-MP used in the maintenance therapy. We obtain the equilibrium points of each compartment and we perform the stability analysis.

Chapter 1. Mathematical Background. In this chapter we give a brief introduction into the theory of delay differential equations. We recall the main theorems necessary for studying the stability of delay differential equations using the characteristic equation and Lyapunov-Krasovskii functional.

Chapter 2. Biological aspects. In this chapter we present the biological aspects and processes which are used in constructing the models, as well as the main delay differential equations that influence the constructed models.

Chapter 3. The mathematical model. In this chapter we introduce a model for erythropoiesis, a model for leukopoiesis and a model for lymphopoiesis coupled with the dynamics of 6-MP used in the maintenance therapy.

The state variables are cells populations and we cannot talk about negative densities of cells, therefore the positivity of the solution corresponding to the system is a very important characteristic for the model. The first important result corresponds to the positivity of the solution.

The erythropoiesis model consists of seven DDEs with two delays. This model describes the dynamics of the stem-like short-term erythroid cells, the erythrocytes, the concentration of erythropoietin, the amount of 6-MP in Gut, the amount of 6-MP in plasma and the concentration of 6-TGN (tioguanine nucleotide) in red blood cells (RBCs).

The model that takes into consideration the response of the treatment becomes:

$$\dot{z} = f_i(z, z_{\tau_j}), i = \overline{1,7}, j = \overline{1,2} \tag{1}$$

$$\begin{aligned}
\dot{z}_1 = \quad & -\tfrac{\gamma_0}{1+z_3^\alpha} z_1 - \tfrac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} z_1 - (\eta_{1e} + \eta_{2e}) k_e(z_3) z_1 - (1 - \eta_{1e} - \eta_{2e}) \beta_e(z_1, z_3) z_1 \\
& + 2z_4(1 - \eta_{1e} - \eta_{2e}) \beta_e(z_{1\tau_1}, z_{3\tau_1}) z_{1\tau_1} + \eta_{1e} z_4 k_e(z_{3\tau_e}) z_{1\tau_1} \\
\dot{z}_2 = \quad & -\gamma_2 z_2 + \tilde{A}_e k_e(z_{3\tau_2}) z_{1\tau_2} \\
\dot{z}_3 = \quad & -k z_3 + \tfrac{a_1}{1+z_2^n} \\
\dot{z}_4 = \quad & z_4 \left(-\tfrac{\gamma_0}{1+z_3^\alpha} - \tfrac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} + \tfrac{\gamma_0}{1+z_{3\tau_1}^\alpha} + \tfrac{\tilde{R}_m z_{7\tau_1}}{\tilde{R}_{50}+z_{7\tau_1}} \right) \\
\dot{z}_5 = \quad & -b_1 z_5 + a_2 \\
\dot{z}_6 = \quad & b_1 z_5 - e_1 z_6 - \tfrac{c_1(1-e_2)}{c_2+z_6} z_6 - \tfrac{m_2 e_2}{m_1+z_6} z_6 \\
\dot{z}_7 = \quad & \tfrac{b_2 c_1 (1-e_2)}{c_2+z_6} z_6 - e_3 z_7.
\end{aligned}$$

The erythropoiesis compartment has two equilibrium points E_1 and E_2.

The characteristic equation corresponding to E_1 has a critical case ($\lambda = 0$). This situation is treated, for the case of ordinary differential equations, in the book [**?**]. In what follows we extend this result to the case of delay differential equations. The following theorems that generalize the one from [?], give a stability criterion in the critical case.

Theorem 0.0.1. *Consider the following nonlinear system with time delays:*

$$\begin{aligned} \dot{x}(t) &= A_0x(t) + \sum_{j=1}^{m} A_jx(t-\tau_j) + F[x(t), x(t-\tau_1), ..., x(t-\tau_m), y(t)] \\ \dot{y}(t) &= G[x(t), x(t-\tau_1), ..., x(t-\tau_m), y(t)], \end{aligned} \tag{2}$$

where $A_j \in M_n(R)$, $\tau_j > 0$ *for all* $1 \leq j \leq m$, $G(0,0,...,0,y) = F(0,0,...,0,y) = 0$, $\forall y \in R$, *F takes values in* R^n *and G is scalar. F and G contain only powers of the variables with sum greater or equal to two. Then, for every* $\delta > 0$, *there exist* $M_1(\delta)$ *and* $M_2(\delta)$ *with* $\underset{\delta\to 0}{lim} M_1(\delta) = \underset{\delta\to 0}{lim} M_2(\delta) = 0$ *so that, whenever* $||x(t)|| \leq \delta, ||x(t-\tau_j)|| \leq \delta, 1 \leq j \leq m, |y| \leq \delta$,

$$\begin{aligned} &\|F\left(x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t)\right)\| \leq \\ &\leq M_1(\delta)\left(\|x(t)\| + \|x(t-\tau_1)\| + \cdots + ||x(t-\tau_m)||\right) \\ &|G((x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t))| \leq \\ &\leq M_2(\delta)(||x(t)|| + ||x(t-\tau_1)|| + \cdots + ||x(t-\tau_m)||). \end{aligned} \tag{3}$$

Theorem 0.0.2. *Suppose that the linear system*

$$\dot{x}(t) = A_0x(t) + \sum_{j=1}^{m} A_jx(t-\tau_j) \tag{4}$$

is asymptotically stable, that is, if λ *is a root of the characteristic equation then* $Re(\lambda) < 0$. *Then the zero solution of (??) is simple stable and, if* φ *is the initial data of (??) in* $C\left([-\tau, 0]; \mathbb{R}^{n+1}\right)$ *with* $\tau = \max_{1\leq j\leq m} \tau_j$, *there exist* $\delta > 0$ *so that, if* $\sup\left\{||\varphi(t)||_2 / t \in [-\tau, 0]\right\} < \delta$ *,then*

$$\lim_{t\longrightarrow\infty} x_i(t) = 0, i = 1, ..., n \text{ and } \exists \lim_{t\longrightarrow\infty} y(t) = \tilde{y}.$$

The analysis of the critical case shows that the stability of E_1 depends on the study of the transcendental terms in its characteristic equation. we determined necessary and sufficient parameter conditions for the stability of this equilibrium point.

The characteristic equation corresponding to E_2 is complicated and its stability analysis can be studied numerically.

The leukopoiesis model consists of six DDEs with two delays. The model describes the dynamics of short-term stem-like white blood cells precursors, the adult leukocytes, the amount of 6-MP in Gut, the amount of 6-MP in plasma and the concentration of 6-TGN (tioguanine nucleotide) in leukocytes.

The model that takes into consideration the response of the treatment becomes:

$$\dot{x} = \tilde{f}_i(x, x_{\tau_j}), i = \overline{1,6}, j = \overline{3,4} \qquad (5)$$

$$\begin{aligned}
\dot{x}_1 = \;& -\gamma_{1l}x_1 - T_1 l_1(x_6)x_1 - \eta_{1l}k_l(x_2)x_1 - \eta_{2l}k_l(x_2)x_1 - (1-\eta_{1l}-\eta_{2l})\beta_l(x_1)x_1 + \\
& +2e^{-\gamma_{1l}\tau_3}x_3(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3})x_{1\tau_3} + \eta_{1l}e^{-\gamma_{1l}\tau_3}x_3 k_l(x_{2\tau_3})x_{1\tau_3} \\
\dot{x}_2 = \;& -\gamma_{2l}x_2 + \tilde{A}_l k_l(x_{2\tau_4})x_{1\tau_4} \\
\dot{x}_3 = \;& x_3 T_1[l_1(x_{6\tau_3}) - l_1(x_6)] \\
\dot{x}_4 = \;& -b_1 x_4 + a_2 \\
\dot{x}_5 = \;& b_1 x_4 - e_1 x_5 - \tfrac{c_1(1-e_2)}{c_2+x_5}x_5 - \tfrac{m_2 e_2}{m_1+x_5}x_5 \\
\dot{x}_6 = \;& \tfrac{b_2 c_1(1-e_2)}{c_2+x_5}x_5 - c_3 x_6.
\end{aligned}$$

The leukopoiesis compartment has two equilibrium points $\tilde{E}_1$ and $\tilde{E}_2$.

From analyzing the characteristic equations corresponding to the linearization of the system around $\tilde{E}_1$ and $\tilde{E}_2$, we determined necessary and sufficient parameter conditions for the stability of these equilibrium points.

The lymphoblasts model consists of two delay differential equations with two delays, the model studies the evolution of Acute Lymphoblastic Leukemia cell population and describes the dynamics of the Stem-Like progenation and mature cells (see [?]).

The model of lymphoblasts becomes,

$$\dot{u} = \hat{f}_i(u, u_{\tau_{jll}}), i = 1, 2,\ j = 1, 2 \tag{6}$$

$$\begin{aligned}
\dot{u}_1 = &\quad -\gamma_{1ll} u_1 - (\eta_{1ll} + \eta_{2ll}) k_{ll}(u_2) u_1 + \eta_{1ll} e^{-\gamma_{1ll}\tau_{1ll}} k_{ll}(u_{2\tau_{1ll}}) u_{1\tau_{1ll}} \\
\dot{u}_2 = &\quad -\gamma_{2ll} u_2 + A_{ll}(2\eta_{2ll} + \eta_{1ll}) k_{ll}(u_{2\tau_{2ll}}) u_{1\tau_{2ll}}.
\end{aligned}$$

The lymphoblasts compartment has $\hat{E}$ the only meaningful biological equilibrium point. The stability analysis of the characteristic equation corresponding to the linearization of the system around the equilibrium point $\hat{E}$ shows that the point is locally asymptotically stable. So the model ensures the healing, at least when the leukemic burden is not very high.

When modeling the hematopoiesis process using the three compartments, we considered two types of cell division (symmetric and asymmetric). The treatment consists in oral administration of 6-MT (mercaptopurine).

Part two: A fourth-order PDE for biological applications

This part is formed of four chapters (4, 5, 6 and 7). In this part we consider the Cahn–Hilliard equation with mass source endowed with Neumann boundary conditions. The mathematical results come from the study of the well possedness of the stationary problem and the numerical analysis of the associated evolution problem endowed with Neumann boundary condition.

Chapter 4. Mathematical framework. In this chapter we give a brief introduction into the origin of Cahn–Hilliard equation. We present the mathematical theory related to the study of such equations, their applications and the related previous results.

Chapter 5. Well Posedness of the stationary problem.

With $g(x,u) = h(x)L(u)$ the following mixed problem will be studied:

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + g(x,u) = 0, \qquad \text{in } \Omega \times [0,T], \tag{7}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial}{\partial \nu}(\Delta u) = 0, \qquad \text{on } \Gamma, \tag{8}$$

$$u|_{t=0} = u_0, \qquad \text{in } \Omega. \tag{9}$$

The stationary problem associated to (**??**-**??**) is given as follows:

$$\Delta^2 u - \Delta f(u) + h(x)L(u) = 0, \qquad \text{in} \qquad \Omega, \tag{10}$$

$$\frac{\partial u}{\partial v} = \frac{\partial}{\partial v}(\Delta u) = 0, \qquad \text{on} \qquad \Gamma. \tag{11}$$

In this chapter, we consider the well posedness of the stationary problem associated to the Cahn–Hilliard equation with mass source endowed with Neumann boundary conditions. Using the subsequent strategy we prove the existence of a weak solution, and its uniqueness is attained under certain assumptions.

Chapter 6. Numerical study of the evolution problem.

Consider the following equation:

$$\frac{\partial u}{\partial t} + \Delta^2 u - \Delta f(u) + g(x,u) = 0. \tag{12}$$

Here, $g(x,u) = h(x)L(u)$, where $h \in L^\infty(\Omega)$ and $L(u)$ is a polynomial of odd degree.

In this chapter we consider the problem (**??**) as follows:

$$u_t = \Delta w + g(x,u), \text{ in } \Omega \tag{13}$$

$$w = f(u) - \Delta u, \text{ in } \Omega \tag{14}$$

$$\frac{\partial u}{\partial v} = \frac{\partial \Delta u}{\partial v} = 0, \text{ on } \partial\Omega. \tag{15}$$

We study the Numerical analysis of (**??**-**??**) with mass source term endowed with Neumann boundary conditions. We propose a finite element semi-discrete scheme, and prove the convergence of the semi-discrete problem to the continuous problem. Then we prove the stability of the backward Euler scheme.

Chapter 7. Numerical Simulation. In this chapter we give numerical simulations that confirm the theoretical results, and show the efficiency of our scheme. These simulations were done using Freefem++.

Bibliography

[1] A. K. Abass, A. H. Lichtman, S. Pillai Cellular and Molecular Immunolgy, 7th edition, Elsevier ,2012.

[2] R. Adams, Sobolev spaces, Academic Press, 1970.

[3] M. Adimy, Y. Bourfia, M. L. Hbid, C. Marquet, Age-structured model of hematopoiesis dynamics with growth factor-dependent coefficients, Electr. J. of Diff. Eq., (2016), 1-20.M.

[4] Adimy, F. Crauste, Modeling and asymptotic stability of a growth factor-dependent stem cell dynamics model with distributed delay, Discrete Contin. Dyn. Syst. Ser. B 8 (2007), no. 1, 19-38.

[5] M. Adimy, F. Crauste, Mathematical model of hematopoiesis dynamics with growth factor-dependent apoptosis and proliferation regulations, Math. Comput. Modelling 49 (2009), no. 11-12, 2128-2137.

[6] M. Adimy, F. Crauste, Delay differential equations and autonomous oscillations in hematopoietic stem cell dynamics modeling, Mathematical Modelling of Natural Phenomena 7 (2012), 1-22.

[7] M. Adimy, F. Crauste, A. Halanay, M. Neamtu, D. Opris , Stability of Limit Cycles in a Pluripotent Stem Cell Dynamics Model, Chaos, Solitons&Fractals, 27(4), 1091-1107(2006).

[8] M. Adimy, F. Crauste, S. Ruan, A mathematical study of the hematopoiesis process with application to chronic myelogenous leukemia, SIAM J. Appl. Math., 65(4), (2005), 1328–1352.

[9] M. Adimy, F. Crauste, S. Ruan, Modelling hematopoiesis mediated by growth factors with applications to periodic hematological diseases, Bull. Math. Biol. 68 (2006), no. 8, 2321-2351. MR 2293845 (2007k:92034).

[10] I. Akushevich,G. Veremeyeva, G. Dimov, S. Ukraintseva, K. Arbeev, A. Akleyev, A. Yashin, Modeling hematopoietic system response caused by chronic exposure to ionizing radiation, Radiat Environ Biophys, May (2011), 50(2): doi:10.1007/s00411-011-0351-3.

[11] S.M. Allen and J.W. Cahn, A macroscopic theory for antiphase boundary motion and its application to antiphase domain coarsening, Ada Metall 27 (1979), 1085-1095.

[12] A.C. Aristotelous, O.A. Karakashian, and S.M. Wise, Adaptive, second order in time, primitive-variable discontinuous Galerkin schemes for a Cahn–Hilliard equation with a mass source, IMA J. Numer. Anal 35 (2015), 1167–1198.

[13] I. Badralexi, A. Halanay, A Complex Model for Blood Cells' Evolution in Chronic Myelogenous Leukemia, 20th International Conference on Control Systems and Computer Science (CSCS), 611 - 617(2015).

[14] I. Badralexi, A. Halanay, Stability and oscillations in a CML model, AIP Conference Proceedings 2017 Jan 27, 1798(1), 020011(2017).

[15] I. Badralexi, A. Halanay, R. Mghames, A Delay Differential Equations model for maintenance therapy in acute lymphoblastic leukemia, U.P.B. Sci. Bull. Series A, (to appear).

[16] I. Badralexi, A. Halanay, R. Radulescu, A Lyapunov-Krasovskii functional for a complex system of delay-differential equations, U.P.B. Sci. Bull., Series A, 77(2), 9-18(2015).

[17] S. Balea, A. Halanay, D. Jardan, M. Neamtu, C. A. Safta, Stability Analysis of a Feedback Model for the Action of the Immune System in Leukemia, Math. Model. Nat. Phenom., 9(1), 108-132(2014) DOI: 10.1051/mmnp/20149108.

[18] S. Balea, A. Halanay, M. Neamtu, A feedback model for leukemia including cell competition and the action of the immune system, 10th ICNPAA 2014, 1637(1), AIP Publishing, (2014).

[19] S. Bernard, J. B'elair, M.C. Mackey, Oscillations in cyclical neutropenia: New evidence for origins based on mathematical modeling, (2003), J. Theor. Biol., 223, 283-298.

[20] R. Bellman, K. L. Cooke, Differential-Difference Equations, Academic Press New York, (1963).

[21] A. Bertozzi, S. Esedoglu, and A. Gillette, Inpainting of binary images using the Cahn–Hilliard equation, IEEE Trans. Imag. Proc. 16 (2007), 285–291.

[22] A. Bertozzi, S. Esedoglu, and A. Gillette, Analysis of a two-scale Cahn–Hilliard model for binary image inpainting, Multiscale Model. Simul. 6 (2007), 913–936.

[23] M. Burger, L. HE and C.B Schönlieb, Cahn-Hilliard inpainting and a generalization for grayscale images, SIAM Journal on Imaging Sciences 2, no. 4 (2009): 1129-1167.

[24] J.W. Cahn and J.E. Hilliard, Free energy of a nonuniform system I. Interfacial free energy, J. Chem. Phys. 28 (1958), 258–267.

[25] D. Candea, A. Halanay, I.R. Radulescu, Stability analysis of some equilibria in a time-delay model for competition of leukemia and healthy cells in CML, Bull. Math. Soc. Sci. Math. Roum, 59(2), 135-150(2016).

[26] D. Candea, A. Halanay, I.R. Radulescu, R. Talmaci, Parameter estimation and sensitivity analysis for a mathematical model with time delays of leukemia, AIP Conference Proceedings 2017, 1798(1), 020034(2017), AIP Publishing.

[27] V. Chalupecki, Numerical studies of Cahn-Hilliard equations and applications in image processing, Proceedings of Gzech-Japanese Seminar in Applied Mathematics, 4-7 August, 2004, Czech Technical University in Prague, (2004).

[28] L. Cherfils, H. Fakih, and A. Miranville, Finite-dimensional attractors for the Bertozzi–Esedoglu–Gillette–Cahn–Hilliard equation in image inpainting, Inv. Prob. Imag. 9 (2015), 105–125.

[29] L. Cherfils, H. Fakih, and A. Miranville, On the Bertozzi–Esedoglu–Gillette–Cahn–Hilliard equation with logarithmic nonlinear terms, SIAM J. Imag. Sci. 8 (2015), 1123–1140.

[30] L. Cherfils, H. Fakih, and A. Miranville, A Cahn–Hilliard system with a fidelity term for color image inpainting, J. Math. Imag. Vision 54 (2016), 117–131.

[31] L. Cherfils, H. Fakih, and A. Miranville, A complex version of the Cahn-Hilliard equation for grayscale image inpainting, Multi. Modeling Simul. 15 (2017), 575–605.

[32] L. Cherfils, A. Miranville, and S. Zelik, The Cahn–Hilliard equation with logarithmic potentials, Milan J. Math. 79 (2011), 561–596.

[33] L. Cherfils, A. Miranville, and S. Zelik, On a generalized Cahn–Hilliard equation with biological applications, Discrete Cont. Dyn. Systems B 19 (2014), 2013–2026.

[34] L. Cherfils, M. Petcu, and M. Pierre, A numerical analysis of the Cahn–Hilliard equation with dynamic boundary conditions, Discrete Cont. Dyn. Systems 27 (2010), 1511–1533.

[35] A. Childhood, Collaborative Group. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukemia: overview of 42 trials involving 12,000 randomized children, Lancet, (1996), 1783-1788.

[36] P.G. Ciarlet, The Finite Element Method for Elliptic Problems, Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, (2002).

[37] D. Cohen and J.M. Murray, A generalized diffusion model for growth and dispersion in a population, J. Math. Biol. 12 (1981), 237-248.

[38] C. Colijn, M. C. Mackey, A Mathematical Model for Hematopoiesis: I. Periodic Chronic Myelogenous Leukemia, J. Theor. Biol., (2005), 117-132.

[39] K. Cooke, Z. Grossman, Discrete Delay, Distribution Delay and Stability Switches. J. Math. Anal. Appl., (1982), 592-627.

[40] K. Cooke, P. van den Driessche, On Zeroes of Some Transcendental Equations. Funkcialaj Ekvacioj, (1986), 29, 77-90.

[41] J. Dockery and I. Klapper , Role of cohesion in the material description of biofilms, Phys. Rev. E 74 (2006), 0319021.

[42] I.C. Dolcetta, S.F. Vita, and R. March, Area-preserving curve-shortening flows: from phase separation to image processing, Interfaces Free Bound. 4 (2002), 325–343.

[43] C. M. Elliott, The Cahn-Hilliard model for the kinetics of phase separation, in Mathematical models for phase change problems, Birkhuser Basel, (1989), 35-73.

[44] C.M. Elliott, D.A. French, and F.A. Milner, A second order splitting method for the Cahn–Hilliard equation, Numer. Math. 54 (1989), 575–590.

[45] L.E. El'sgol'ts, S.B. Norkin, Introduction to the theory of differential equations with deviating arguments, (in Russian). Nauka, Moscow, (1971).

[46] A. Ern and J.L. Guermond, Elements finis: theorie, applications, mise en oeuvre, Springer-Verlag, Berlin, (2002).

[47] H. Fakih, Asymptotic behavior of a generalized Cahn–Hilliard equation with a mass source, Applicable Analysis. 96 (2016), 324–348.

[48] H. Fakih, A Cahn–Hilliard equation with a proliferation term for biological and chemical applications, Asympt. Anal. 94 (2015), 71–104.

[49] H. Fakih, R. Mghames, N. R. Nasereddine,On the Cahn-Hilliard equation with mass source for biological applications, Communications on Pure and Applied Analysis, (2019), (to appear).

[50] Aristide Halanay, Differential Equations. Stability, Oscillations, Time Lags, Academic Press, New York, (1966).

[51] A. Halanay. Stability analysis for a mathematical model of chemotherapy action in hematological diseases. Bull. Sci. Soc. Roumaine Sci. Math. 53 (101) (2010), no. 1, 3-10.

[52] A. Halanay, Treatment induced periodic solutions in some mathematical models of tumoral cell dynamics. Mathematical Reports, 2(62) (2010), no. 4, 329-339.

[53] A. Halanay, Periodic Solutions in Mathematical Models for the Treatment of Chronic Myelogenous Leukemia.Math. Model.Nat.Phenom, 7 (2012), no.1, 235-244.

[54] A. Halanay, D. Candea, R. Radulescu, Existence and stability of limit cycles in a two-delays model of hematopoiesis including asymmetric division, Math. Model. Nat. Phenom., (2013), 32-52.

[55] A. Halanay, C. Safta, A critical case for stability of equilibria of delay differential equations and the study of a model for an electrohydraulic servomechanism, submited.

[56] J. Hale. Theory of Functional Differential Equations. Springer, New York, (1977).

[57] J. Hale, S. M. Verduyn Lunel, Introduction to Functional Differential Equations. Springer, New York, (1993).

[58] F. Hecht, New development in FreeFem++, J. Numer. Math. 20 (2012), 251–265.

[59] D. Jayachandran, A. E. Rundell, R. Hannemann, T. A. Vik, D. Ramkrishna, Optimal Chemotherapy for Leukemia : A model-Based Strategy for Individualized Treatment, PLOS ONE, (2014), vol. 9, issue 10, e109623. doi:10.1371/journal.pone.0109623.

[60] I.M. Khalatnikov and L.D. Landau , On the theory of superconductivity, Collected Papers of L.D. Landau (ed. D. Ter Haar) Pergamon, Oxford, (1965), 546-568.

[61] R.V. Kohn and F. Otto, Upper bounds for coarsening rates, Commun. Math. Phys. 229 (2002), 375-395.

[62] E. Khain and L.M. Sander, A generalized Cahn–Hilliard equation for biological applications, Phys. Rev. E 77 (2008), 51–129.

[63] V. L. Kharitonov, A. P. Zhabko, Lyapunov-Krasovskii approach to the robust stability analysis of time-delay systems, Automatica, (2003), 15-20.

[64] Y. Kuang. Delay Differential Equations With Applications in Population Dynamics. Mathematics in Science and Engineering Vol.191, Academic Press Limited, San Diego, CA, (1993).

[65] J.S. Langer, Theory of spinodal decomposition in alloys, Ann. Phys. 65 (1975), 53-86.

[66] T.L. Lin, M.S. Vala, J.P. Barber, J.E. Karp, B.D. Smith, W Matsui and R.J. Jones, Induction of acute lymphocytic leukemia differentiation by maintenance therapy,Leukemia, (2007), 1915-1920. doi:10.1038/sj.leu.2404823.

[67] M.C. Mackey, L. Glass, Oscillation and chaos in physiological control systems, Science,Vol. 197, (1977), 287-289.

[68] S. Maier-Paape and T. Wanner, Spinodal Decomposition for the Cahn-Hilliard Equation in Higher Dimensions. Part I: Probability and Wavelength Estimate, Communications in Mathematical Physics 195 (1998), 435-464.

[69] S. Maier-Paape and T. Wanner, Spinodal Decomposition for the Cahn-Hilliard Equation in Higher Dimensions: Nonlinear Dynamics, Archive for Rational Mechanics and Analysis 151 (2000), 187-219.

[70] I. G. Malkin, Theory of stability of motion (in Russian), Nauka, Moskow, English translation: Atomic Energy Comm. Translation AEC–TR–3352, 1966.

[71] R. Mghames, H. Fakih, N. R. Nasereddine,Well-Posedness of the steady state problem for the Cahn–Hilliard equation with mass source, DIMACOS2019, Hammamet, Tunisia, October, (2019), 250-251.

[72] A. Miranville, Asymptotic behavior of the Cahn–Hilliard–Oono equation, J. Appl. Anal. Comp. 1 (2011), 523–536.

[73] A. Miranville, Asymptotic behavior of a generalized Cahn–Hilliard equation with a proliferation term, Appl. Anal. 92 (2013), 1308–1321.

[74] A. Miranville, Existence of solutions to a Cahn–Hilliard type equation with a logarithmic nonlinear term, Mediterr. J. Math. 16 (2019), 1–18.

[75] A. Miranville, The Cahn–Hilliard equation and some of its variants, AIMS Math. 2 (2017), 479–544.

[76] A. Novick-Cohen and L.A. Segal, Nonlinear Cahn–Hiliard equation, Proc. Roy. Soc. London Ser. A 422 (1989), 261–278.

[77] Y. Oono and S. Puri, Computationally efficient modeling of ordering of quenched phases, Phys. Rev. Lett. 58 (1987), 836–839.

[78] C. H. Pui, W. E. Evans, Treatment of acute lymphoblastic leukemia. New England Journal of Medicine, (2006), 166–178.

[79] I.R. Radulescu , D. Candea , A. Halanay , A study on stability and medical implications for a complex delay model for CML with cell competition and treatment, Journal of Theoretical Biology, 363, (2014), 30-40.

[80] I.R. Radulescu, D. Candea, A. Halanay , A control delay differential equations model of evolution of normal and leukemic cell populations under treatment, IFIP Advances in Information and Communication Technology, 443, (2014), 257-266.

[81] J.C. Robinson, Infinite-dimensional dynamical systems: an introduction to dissipative parabolic PDEs and the theory of global attractors, Cambridge University Press, 28, (2001).

[82] K. Schmiegelow , I. Al-Modhwahi ,M.K. Andersen, M. Behrendtz , E. Forestier et al., Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study, (2009), Blood 113: 6077.

[83] C.B. Schönlieb and A. Bertozzi, Unconditionally stable schemes for higher order inpainting, Commun. Math. Sci. 9 (2011), 413–457.

[84] R. Temam, Infinite-dimensional dynamical systems in mechanics and physics, Springer Science and Business Media, Vol. 68 (2012).

[85] S. Villain-Guillot, Phases modulées et dynamique de Cahn–Hilliard, Habilitation thesis, Université Bordeaux 1, (2010).

[86] J. Zajac, L. E. Harrington, Immune Response to Viruses: Antibody-Mediated Immunity, University of Alabama at Birmingham, Birmingham, AL, USA, Elsevier Ltd, (2008).