EuroMediterranean 3+3 Program

Call for Projects 2012, Renewal 2014

Deadline for receipt of proposal: ***September 30, 2011***

PROJECT

Acronym: **M3CD**

Full title: **Mathematical Models and Methods in Cell Dynamics**

With updated program and list of members, January 2014 (18 pages)

Keywords :
Mathematical modelling, Cell population dynamics, Adaptive dynamics, Cytoskeleton dynamics, Multiscale coupling, Numerical analysis and simulation

Abstract *(1/2 page max.)*

The aim of this project is to establish a network working on mathematical and computational models in cell dynamics. This network consists of five groups, which have already established close bilateral relations. Those are the INRIA teams Bang and Dracula in Paris and Lyon, France, the teams IAC-CNR in Rome *and Polito in Turin*, Italy, the laboratory of Mathematical Population Dynamics (LMDP) from the university of Marrakech in Morocco, *the University of Valladolid, Spain* and the team of Mathematical Modelling and Computing in Biology (MoMinBi) from the Pasteur Institute in Tunis.

Modelling cell dynamics and related processes is one of the main subjects of interest for the partners for many years. The issues addressed in the present project can be divided into five parts:

1) Analysis of structured models in cell population dynamics ;

2) Dynamics of normal and pathological haematopoiesis ;

3) Dynamics of Darwinian adaptation, in particular by drug resistance in competing cell or parasite populations, healthy and pathological / pathogenic (cancer, bacteria, parasites) ;

4) Dynamics of chemical and physical determinants of filament formation and intracellular spatial organisation of the cytoskeleton conformation ;

5) Coupling of the molecular mechanisms of control of the cell division cycle and cell proliferation.

6) Evolutionary dynamics of cancer cells under different selective pressure (environment, immune cells, therapeutical agents).

7) Numerical analysis and simulation of structured models in cell population dynamics

The first part has been developed for many years by all the partners in this project. It tackles issues related to cell dynamics and biological mechanisms, physiological and chemical properties of cells and cell populations. The other four aspects of the project have been studied in the past by the INRIA teams "Bang" and "Dracula" (2, 4, 5) and the IAC-CNR team (Rome), or are a rapidly emergent theme in Bang (3, cell Darwinism) with possible and natural connections with the other teams, in particular IAC-CNR and MoMinBi in Tunisia. Themes (2, 4, 5) have also been initiated (for their fundamental part) in a recent collaboration between Dracula and the teams from Morocco and Tunisia. Theme 7 has been dealt for some years in collaboration among "Dracula" team and team from University of Valladolid.

The objectives of the present project are to pursue and deepen the study of cell proliferation dynamics and cellular mechanisms using structured models that take into account some new structure variables. The development of computer models will also be investigated in this project.

Training and research activities related to these topics are currently underway between the INRIA teams and the teams from Marrakech and Tunis, and between the Italian team and Bang. Two co-supervised theses are currently in progress, a Spring school on this subject will be organised by the partners in 2012.

I - PARTNERS

Partner 1 (Global Coordinator of the project)

Country : .France.....

Name of the Institution : INRIA Research Centre Paris-Rocquencourt, project-team BANG

(http://www-roc.inria.fr/bang/index_en.html)

Full address of the Institution : Domaine de Voluceau, BP 105, 78153 Rocquencourt, France

Name/Surname of the scientific leader for this project :

Jean Clairambault.

Title or function: PhD, MD, INRIA Research Director

Phone n°: .+33 1 44 27 91 70 or +33 1 39 63 55 43

e-mail : jean.clairambault@inria.fr

Partner 2

Country : Italy

Name of the Institution: Consiglio Nazionale delle Ricerche- Istituto per le Applicazioni del Calcolo Mauro Picone

Full address of the Institution:

Via dei Taurini 19, I-00185 Rome (Italy)

Name/Surname of the scientific leader for this project :

Roberto Natalini

Title or function:

Dr, Research Director

Phone n°:

0039 06 49270961-66

e-mail :

roberto.natalini@cnr.it

Partner 3

Country: …**France** ……..

Name of the Institution: …**INRIA – DRACULA Team**.

Full address of the Institution: INRIA Antenne Lyon la Doua
66, Boulevard Niels Bohr, 69603 Villeurbanne
(http://www.inria.fr/equipes/dracula)

Name/Surname of the scientific leader for this project:

Mostafa Adimy
Title or function: PhD, Reasearch Director.. .....

Phone n°: 33 (0) 4 72 43 74 88 **e-mail**: Mostafa.Adimy@inria.fr

Partner 4

Country: ……**Morocco**……..

Name of the Institution: Cadi Ayyad University, Faculty of Sciences, **Mathematical Population Dynamics Laboratory**, Marrakech.

Full address of the Institution: Bd du Prince Moulay Abdellah, BP 2390, Marrakech, Morocco.

Name/Surname of the scientific leader for this Project:

Moulay Lhassan HBID

Title or function: PhD, Professor (Director of the Math. Populations Dynamics Laboratory).

Phone n°: .+212 661087942 **e-mail**: hbid@ucam.ac.ma or hassan.hbid@gmail.com.

Partner 5

Country: ……Tunisia……..

Name of the Institution: Pasteur Institute
Full address of the Institution: Institut Pasteur de Tunis
Ad: BP 37, 1002 Tunis Belvedere, Tunisia.
http://www.pasteur.tn/

Name/Surname of the scientific leader for this Project:

Slimane Ben Miled

Title or function: PhD - Maître de Conférence (=assistant professor).....

Phone n°: 216 71 843755 ext: 464 e-mail: slimane.benmiled@gmail.com, slimane@ipeit.rnu.tn

Partner 6

Country : .Italy.....

Name of the Institution : Politecnico di Torino - Department of Mathematical Sciences

http://www.disma.polito.it/en/research/research_groups/models_and_methods_in_mathematical_physics

Full address of the Institution : Corso Duca degli Abruzzi 24, 10129, Torino, Italy

Name/Surname of the scientific leader for this project :

Marcello Delitala

Title or function: PhD, Assistant Professor (Maître de Conférence)

Phone n°: .+39 011 0907537

e-mail : marcello.delitala@polito.it

Partner 7

Country : Spain.....

Name of the Institution : Universidad de Valladolid - ETSIT - Department of Applied Mathematics

Full address of the Institution : Pso. Belén 15, 47011 Valladolid, Spain

Name/Surname of the scientific leader for this project :

Óscar Angulo

Title or function: PhD, Assistant Professor (Maître de Conférence)

Phone n°: .+34 983 423 000 ext 5835

e-mail : oscar@mat.uva.es

II - DEFINITION AND DESCRIPTION OF THE PROJECT

1 – Scientific objectives

Describe the project for the full period of two years, indicate the scientific interest of the collaboration

Project Description:

The objectives of the present project are to continue and deepen the study of cell proliferation dynamics and cellular mechanisms by using mathematical models, together with computer models, that take into account structure variables. The questions addressed have been divided into five parts, as listed in the abstract:

1) Analysis of structured models in cell population dynamics ;

2) Dynamics of normal and pathological hematopoiesis ;

3) Dynamics of adaptation, in particular by drug resistance, in competing cell or parasite populations, healthy and pathological or pathogenic (cancer, bacteria, parasites) ;

4) Dynamics of chemical and physical determinants of filament formation and intracellular spatial organisation of the cytoskeleton conformation ;

5) Coupling of the molecular mechanisms of control of the cell division cycle and cell proliferation.

6) Evolutionary dynamics of cancer cells under different selective pressure (environment, immune cells, therapeutical agents).

7) Numerical analysis and simulation of structured models in cell population dynamics

1) Structured models in cell population dynamics: modelling and mathematical analysis.

Structured cell population models produce a sequence of mathematical problems that has not been answered yet and therefore requires the development of new tools. Various issues concerning the ongoing dynamic models come up repeatedly in the fields of applications. These include: the treatment of non-local terms of partial differential equations, the use of stochastic equations in the context of Lagrangian approaches to the treatment of multiple spatial and temporal scales, taking into account the variability in time; nonlinear analysis problems are also studied, the treatment of discontinuities of the coefficients in differential equations, the theory of extrapolation, integrated semigroup theory, bifurcation theory for the qualitative study of evolution problems and ordinary differential equations, delay equations and state-dependent equations.

The main objective of structured models of cell proliferation is to determine an asymptotic distribution of the population (in terms of the structure variable, e.g. age in the cell division cycle). This distribution, that can generally be observed in data is expressed in terms of parameters such as mortality and division rate. In this case, the model allows us to reconstruct the unknown values of the parameters from the asymptotic distribution. Therefore, it implies solving inverse problems. Several models have been obtained and analysed by the partners of this project. These models are given by PDE and / or delay equations or state-dependent delay equations. Such results have been produced by all researchers involved in this project, tackling mathematical questions related to search for special solutions, bifurcation and stability properties.

2) **Dynamics of normal and pathological haematopoiesis**

The production and regulation of blood cells is a very complex process, called haematopoiesis. It involves a population of haematopoietic stem cells (HSC), able to differentiate and self-renew, in order to maintain a HSC population. The Dracula team at INRIA has as its principal theme multiscale modelling of the haematopoietic system.

Adimy et al. (SIAP 2010), have proposed a mathematical model describing the dynamics of a hematopoietic stem cell population. Assuming that the number of cells influences the durations of cell cycle phases modifies the nature of the time delays in Mackey's models, yielding a state-dependent delay system. The authors have performed a complete stability analysis of this system. Y. Bourfia's PhD thesis project, co-supervised by J. Clairambault, M. Adimy and H. Hbid, will be dedicated to extending this work in various directions using PDE models and distributed state-dependent delay models.

3) Dynamics of Darwinian adaptation, in particular by drug resistance in competing cell populations, healthy and pathological / pathogenic (cancer, bacteria, parasites), using physiologically based models

Cancer initiation, promotion, and progression have the hallmarks of a complex system: multiple levels (genes, gene networks, signalling networks, cells, tissue…), dynamically changing endogenous and exogenous environments, cascades (chains of events) and feedbacks. These factors affect different contingencies in cell fate (survival, population expansion), and cell phenotype and function (dormancy, proliferation, migration). This theme is central to a French multisciplinary research consortium on Cell Darwinism and cancer (with involvement of the Bang team) and is also already a theme of research in the IAC-CNR team.

An important conceptual breakthrough in understanding cancer lies in Darwinian and ecological theories: cancer is a disease associated with clonal evolution and competition within the body. Specifically, somatic cellular selection and evolution are the fundamental processes leading to malignancy, metastasis and resistance to therapies. Tumours can be viewed as collections of individual cells that accumulate genetic and epigenetic changes, and through their interactions with the environment (selection), adaptively evolve. Examples include stressful microenvironments affecting the evolution of the invasive phenotypes, and the evolution of resistance to toxic insults (drugs) during tumour growth, providing a competitive advantage with wild-type cells.

A major challenge in understanding cancerogenesis is relating process to pattern in malignant and pre-neoplastic lesions. While a full description of tumorigenesis will require taking into account an enormous set of variables concerning both the intrinsic characteristics of cancer cells and their interactions with the environment, there remains a number of crucial issues that can be addressed by studying simple model systems, amenable both to biological analysis and to mathematical modelling.

4) Dynamics of chemical and physical determinants of filament formation and intracellular spatial organisation of the cytoskeleton conformation

Modelling the dynamics of chemotactic and mechanotactic determinants of filament formation and organisation of the cytoskeleton: mechanotactic reaction-diffusion modelling (local effects) and mixed local-nonlocal effects (mechanical properties of filaments). The cells contain a protein skeleton called the cytoskeleton. The cytoskeleton is composed of various types of interconnected networks of proteins, and its functions are varied. One of its main functions, however, can be isolated: the cytoskeleton ensures the physical integrity of the cell, gives it its shape. It is also responsible for signal transduction from the external environment to the inside of the cell toward the nucleus. It is assumed by biologists that the conformation of the cytoskeleton is a reaction to environmental conditions. Local effects are modeled via a reaction-diffusion model representing force fields by concentration fields of soluble units, diffusion representing the growth of filaments. Mixed local/nonlocal effects linked to the physical properties of filaments will be represented by a hyperdiffusion term. This part will be shared between teams 3 (LMDP, Marrakech) and 4 (Dracula, Lyon).

5) Coupling of the molecular mechanisms of control of the cell division cycle and cell proliferation.

After an "all-molecular" supremacy period for modelling, a revival of interest in population dynamics has now emerged. It is essential in this perspective to determine the asymptotic distribution of the population according to the different cell cycle phases, or even better depending on the cyclin content of cells, which means exploring the individual-population relation to identify the determinants of the passage from the individual level of molecular processes to the level of populations, in particular: a) modelling the cell population dynamics structured by its position in the cell division cycle (i.e., its “age” in the different phases), the progression of which varies under the action of growth factors, and by dispersion of a random nature, e.g., modelled by a second order operator; b) modelling nucleocytolasmic transport, with application to the intracellular dynamics of protein p53, to represent the influence of drug-induced DNA damage on cell cycle blockade, apoptosis launching or DNA repair. This share of the project is the subject of Luna Dimitrio’s PhD thesis, co-supervised by Roberto Natalini (IAC-CNR, Rome) and Jean Clairambault (INRIA, Paris); it comes as a missing link between intracellular processes and blockade of the cell cycle (and subsequent events) in proliferating cell populations.

6) Evolutionary dynamics of cancer cells under different selective pressure (environment, immune cells, therapeutic agents).

Cell competition for resources and survival is studied as a process of Darwinian evolution, which involves different sub-populations and leads, case by case, to the selection of the fittest ones within the biological contexts at hand.

Applications to biology and medicine are developed, such as the dynamics of cancer cells and the role played by specific therapeutic agents, the action of the immune system and the competition between T-cells and tumour cells. In general, aspects of complexity in the biological sciences are object of study and modelling. In more detail, the focus is on evolutionary aspects related to iterative selection, that is,

- Cancer cell development under different environmental pressures; genetic/epigenetic alterations and competition for resources.

- Competition phenomena involving tumor-immune interactions and immune response against cancer; selection of specific cancer clones (e.g. able to escape immune surveillance) as a consequence of the immune pressure and the action exerted by the immune system over cancer cells; effects of intra-tumor heterogeneity on immune response; selective recognition process and clonal expansion of immune cells with adaptation and learning aspects of the immune system.

- Effects of therapeutic agents and immunotherapies on the evolutionary dynamics of tumour cells (e.g. selection of the fittest cancer clones); virtual analysis of different therapeutic protocols (e.g. metronomic approach, MTD, bang-bang) and optimal combination of different anti-cancer drugs.

The reference mathematical formalism is the one of continuous structured populations, which allows to define more realistic models as well as to inspect interesting features of the systems under study (e.g. intra-tumor heterogeneity). Besides modelling activity, numerical simulations and qualitative analyses of mathematical problems are performed, aiming at verifying adherence to the biological reality of the proposed models and exploring possible emergent behaviors.

This objective (6) is strictly related to the objective (3) of the project (Dynamics of adaptation… in competing cell … populations…). In this context, T. Lorenzi during his PhD thesis, supervised by Marcello Delitala (POLITO-Italy) has spent a visiting research period at UPMC-Paris under the supervision of and Jean Clairambault (INRIA, Paris) and B. Perthame (UPMC, Paris).

7) Numerical analysis and simulation of structured models in cell population dynamics

In general, size-structured models in cell population dynamics cannot be solved analytically and require numerical integration to obtain an approximation to the solution. However, numerical methods cannot be indiscriminately applied, because they could lead to inaccurate results and, therefore, wrong conclusions.

The main objective is to propose new “ad hoc” numerical schemes in order to solve such size-structured cell models, with the commintment of circumvent the serious numerical challenges they include. We will analyse the good properties of such methods as consistency, stability and convergence. One of the main features is to give a description of the asymptotic behaviour of the population. It is useful in the study of bifurcation theory.

This objective is related with objective (1) and (2). And it was started in collaboration with “Dracula” team in the study of age-structured hematopoietic cell models.

2 – Work programme and schedule

Research work:
The proposed scientific work programme takes as its starting point existing mathematical models, developed to describe cell population dynamics, with a focus on disruptions of normal and pathological haematopoiesis. In the course of their development, the models will be improved with several innovations. The detailed scientific research work program is as follows:

- We will continue our analysis of structured PDEs and delay differential equations by focusing in particular on the asymptotic behaviour of the system (stability, bifurcation, oscillations).
- We will establish numerical simulations of nonlocal transport PDEs.
- We will study and compare models of healthy and pathological haematopoiesis by taking into account the cell cycle, the maturity of cells and the role of growth factors.

Each of these tasks represents an important field of research. They will be pursued throughout the whole duration of the project. In order to meet these challenges we plan to:

- - work in close collaboration (several meetings between the partners will be programmed during the two years): the fact that there exist already collaborations between the partners will represent the pending advantage for the success of the project.
- - take advantage of the long experience of each partner and use their best methods to develop new models.

Training:
During this 2-year programme, the 2 PhD theses will be continued (or terminated for Luna Dimitrio's thesis work), with the perspective of proposing postdoctoral positions in other teams of the network. In the years of their PhD theses, the students will increase the frequence of exchange visits between Paris and Marrakech, and Paris and Rome, with possible extensions to other bilateral exchanges.

Dissemination: Organisation of a Workshop and of presentations/seminars:
Dissemination activities will be carried out by all Partners throughout the whole project duration and will include:
a) information about the project and its aims to institutions, universities and research centers;

b) presentation of final results in national and international specialised publication organs and peerreviewed journals in the relevant areas. Papers will be elaborated and submitted in common, bilaterally or more, by members of the network, on the five themes described in the project.

c) presentations of interim and final results at national and international conferences in the area, in the form of papers/posters;

d) organisation of workshops, presentations and seminars to sustain awareness about the project and its results;
A workshop will be organised in Spring 2012 on the initiative of teams LMNDP (Marrakech), Dracula (Lyon) and MoMinBi (Tunis). It will include Partners and selected participants from the relevant scientific, industrial and health care target groups. This rhythm of 1 workshop a year will hopefully be reconducted during the following years of the programme, according to funding by the 3+3 programme and by other solicited resources.

3 – Scientific interest of the collaboration and complementarities of the partners

The project aims at establishing an active network to design mathematical and computational models and methods in cell dynamics. This network consists of five teams that have already established very close bilateral relations: Teams DRACULA and BANG from INRIA (France), the team IAC-CNR in Rome, the LMDP team based in Marrakech, Morocco, and the MoMinBi team from Pasteur Institute in Tunis. Bilateral cooperation activities include research, training and communication of results in regular meetings. They have been developed within bilateral exchange programs. Collaborative activities have led to theses, publications and organisation of meetings. Training and research activities are currently underway between INRIA teams and teams from Marrakech and Tunis, and between the IAC-CNR team (Rome) and the INRIA BANG team (Paris). Two co-supervised theses are currently in progress (Rome-Paris / Marrakech-Paris), and a Summer school will be organised by the partners of the network.

Objectives of the project

• Develop the art of cellular dynamics modelling, and improve mathematical methods and tools related to physiologically structured population dynamics.

• Establish a multi-disciplinary methodological guidance through a set of training opportunities that falls within the academic environment of the project partners and to make recognize the expertise of the network through publications, participation in and organisation of conferences, workshops and schools.

• More precisely: the multidisciplinary orientation of the network relies on the experience of its teams in the domain of mathematical modelling in cell dynamics and related processes. We recall the five themes of this project: 1) Analysis of structured models in cell population dynamics; 2) Dynamics of normal and pathological haematopoiesis; 3) Dynamics of Darwinian adaptation, in particular by drug resistance in competing cell or parasite populations, healthy and pathological / pathogenic (cancer, bacteria, parasites); 4) Dynamics of chemical and physical determinants of filament formation and intracellular spatial organisation of the cytoskeleton conformation; 5) Coupling of the molecular mechanisms of control of the cell division cycle and cell proliferation. In more details:

1. All partners are developing models according to the line of structured cell population dynamics.

- 2. Haematopoiesis modelling, is the main subject of team Dracula (Lyon), and has been a subject of collaboration between teams Dracula and LMNDP (Marrakech). It is also in development with clinical applications in the Bang team (Paris), who have detached a Postdoc, Annabelle Ballesta, for 18 months in the experimental and clinical team of Jean-Pierre Marie (INSERM-UPMC) in St Antoine hospital in Paris.

- 3. Darwinian adaptative dynamics in cell populations (healthy and cancer) is an emergent theme in the Bang team, who are presently included in a 10-team French multidisciplinary research consortium (DarEvCan, Darwinian evolution and cancer, in which Bang and Dracula are committed). This aspect is already in development within team IAC-CNR (Rome) along the line of evolutionary game theory and cancer, using a PDE formalism. It could also lead to fruitful interactions with team MoMinBi (Tunis) about leishmaniosis.

- 4. Dynamics of cytoskeleton conformation in relation to chemotaxis and mechanotaxis is a theme that is currently being developed between teams Dracula (Lyon) and LMNDP (Marrakech)

- 5. Coupling the intracellular level and the cell population level in proliferating cell populations is a theme that has been continuously tackled since 2003 by the Bang team (Paris), as shown in http://www-roc.inria.fr/bang/JC/JCarticles.html, and is also reinforced as a perspective, via p53 modelling, in the subject of Luna Dimitrio's PhD thesis on nucleocytoplasmic transport, within the scope of this programme.

III - PRESENTATION OF THE PARTNERS
One page for each partner

Partner 1: INRIA MAMBA (ex-BANG) project-team, Paris *(Global Coordinator of the project)*

Presentation of the team

The BANG research project-team at Paris-Rocquencourt is a joint INRIA- Pierre-et-Marie-Curie University (UPMC) team that belongs to the INRIA theme Computational Sciences for Biology, Medicine and the Environment , subtheme: "Observation, Modeling, and Control for Life Sciences".

The physiological or physical modelling of the complex and multiscale phenomena under study leads to the mathematical analysis of partial differential equations and to the development of effective and reliable numerical methods.
Of particular interest for the BANG project are problems of mathematical biology related to cell movements and cell population growth, in particular for healthy or cancer cells, subject to intact or disrupted physiological control, and to the possible restoration of this normal control by drugs.

(extract from http://www-roc.inria.fr/bang/index_en.html

List of the members involved in this Project *(Name, title)*

Jean Clairambault, PhD, MD, INRIA DR

Benoît Perthame, PhD, IUF Senior member, Professor, UPMC

Tommaso Lorenzi, UPMC Postdoc

Rebecca Chisholm, INRIA Postdoc

Xavier Dupuis, INRIA Postdoc, Team

Jan Elias, UPMC PhD student

Ex-members, until 2012: Annabelle Ballesta, PhD, INRIA Postdoc, Frédérique Billy, PhD, INRIA Postdoc, Luna Dimitrio, INRIA PhD student

Significant publications related to the Project at he submission of the project (September 2011)

- Ballesta, A., Dulong, S., Abbara, C., Cohen, B., Okyar, A., Clairambault, J., Levi, F. A Combined Experimental and Mathematical Approach for Molecular-based Optimization of Irinotecan Circadian Delivery. PLoS Comput Biol 7(9): e1002143. doi:10.1371/journal.pcbi.1002143, 2011.

- Billy, J. Clairambault, O. Fercoq, S. Gaubert, T. Lepoutre, and T.Ouillon, Synchronisation and control of proliferation in cycling cell population models with age structure, submitted 2011 / *In a shorter form as: Billy, F., Clairambault, J., Fercoq, O., Gaubert, S., Lepoutre, T., Ouillon, T.* Proliferation in cell population models with age structure. *In: Proceedings of ICNAAM 2011, pp. 1212-1215, Kallithea Chalkidikis (Greece), Sep. 2011.*

- Clairambault, J. Modelling physiological and pharmacological control on cell proliferation to optimise cancer treatments. Mathematical Modelling of Natural Phenomena, 4(3):12-67, 2009.

- Bekkal Brikci, F., Clairambault, J., Ribba, B., Perthame, B. An age-and-cyclin-structured cell population model for healthy and tumoral tissues, Journal of Mathematical Biology, 57(1):91-110, 2008.

- Adimy, M., Bernard, S., Clairambault, J., Crauste, F., Génieys, S., Pujo-Menjouet, L. Modélisation de la dynamique de l'hématopoïèse normale et pathologique. Hématologie, 14(5):339-350, 2008.

Partner 2: IAC-CNR, Rome

Presentation of the team

The IAC-CNR unit is coordinated by Dr. Roberto Natalini, Research Director with a wide experience in the following research fields: nonlinear partial differential equations, hyperbolic and parabolic problems, numerical approximation of shock and diffusive waves, mathematical models in biomathematics. The IAC unit is composed by Dr. Andrea Tosin, winner of a Researcher position at IAC-CNR, Emiliano Cristiani, winner of a Researcher position at IAC-CNR, Dr. Gabriella Bretti, Researcher of IAC-CNR. The IAC-CNR unit had a significant scientific production in several problems of applied mathematics mainly focused on the analysis and numerical approximation of systems of nonlinear conservation laws, biomedical mathematical modelling, traffic flows on networks, crowd dynamics, optimization and control.

List of the members involved in this Project

Roberto Natalini, Dr – IAC-CNR Reserach Director

Garbiella Bretti, Dr- IAC-CNR Researcher

Andrea Tosin, Dr- IAC-CNR Researcher

Emiliano Cristiani- Dr- IAC-CNR Researcher

Significant publications related to the project

1. Boccabella, Astridh; Natalini, Roberto; Pareschi, Lorenzo. On a continuous mixed strategies model for evolutionary game theory. *Kinet. Relat. Models* 4 (2011), no. 1, 187--213.
2. A. Cangiani, R. Natalini, A spatial model of cellular molecular trafficking including active transport along microtubules. JOURNAL OF THEORETICAL BIOLOGY, vol. 267; (2010). p. 614-625, ISSN: 0022-5193, doi: 10.1016/j.jtbi.2010.08.017
3. F. Clarelli, R. Natalini, A pressure model of immune response to mycobacterium tuberculosis infection in several space dimensions, MATHEMATICAL BIOSCIENCES AND ENGINEERING Volume: 7 Issue: 2 Pages: 277-300 Published: APR 2010
4. F. Guarguaglini, C. Mascia, R. Natalini, M. Ribot, Global stability of constant states and qualitative behavior of solutions to a one dimensional hyperbolic model of chemotaxis, Discrete and Continuous Dynamical Systems - Series B, 12, 2009, 39-76.
5. Davide Vergni, Filippo Castiglione, Maya Briani, Silvia Middei, Elena Alberdi, Klaus G. Reymann, Roberto Natalini, Cinzia Volonté, Carlos Matute, Fabio Cavaliere, A Model of Ischemia-Induced Neuroblast Activation in the Adult Subventricular Zone, PLoS ONE, 23Feb. 2009, http://dx.plos.org/10.1371/journal.pone.0005278.

Partner 3: INRIA team Dracula, Lyon

Presentation of the team.

Dracula is a joint research team between INRIA, University of Lyon 1 (UCBL) and CNRS (ICJ, UMR 5208 and CGMC UMR 5534). It belongs to the INRIA theme “Computational Sciences for Biology, Medicine and the Environment”, subtheme: "Observation, Modeling, and Control for Life Sciences".

The Dracula project is devoted to multi-scale modelling in biology with application to normal and pathological hematopoiesis (blood cell production). Multi-scale modelling implies simultaneous modelling of intra-cellular networks (molecular level), of cell behaviour (cellular level), of the dynamics of cell populations (organ or tissue) with the control by other organs (organism).
The team carries out multi-scale modelling of the biological phenomena on the basis of coupled DPD-PDE-ODE models, where dissipative particle dynamics (DPD) is used in order to describe individual cells and relatively small cell populations, partial differential equations (PDE) is used to describe concentrations of bio-chemical substances in the extra-cellular matrix, and ordinary differential equations (ODE, deterministic or stochastic) for intra-cellular regulatory networks. Partial differential equations (PDE) are also used to describe cell populations considered as continuous medium. The team studies reaction-diffusion-convection equations with or without hydrodynamics and transport equations *(hyperbolic PDEs)* in which the structure can be age, size, maturity, protein concentration, etc. In some particular cases, transport equations are reduced to delay differential equations (DDE) which are less difficult to investigate analytically. (See more at http://dracula.univ-lyon1.fr/)

List of the members involved in this project

Mostafa ADIMY, INRIA DR

Fabien Crauste, CNRS CR

Thomas Lepoutre, INRIA CR

Laurent Pujo-Menjouet, Univ Lyon I, MCF

Vitaly Volpert, CNRS DR

Léon M. Tine, Univ Lyon I, MCF

Loïc Barbarroux, PhD student

Abdennasser Chekroun, PhD student

Marine Jacquier, PhD student

Significant publications related to the project

- M. Adimy, F. Crauste, H. Hbid and R. Qesmi. Stability and hopf bifurcation for a cell population model with state-dependent delay. SIAM J. Appl. Math, 70 (5), 1611-1633 (2010).

- M. Adimy and F. Crauste. Mathematical model of hematopoiesis dynamics with growth factor-dependent apoptosis and proliferation regulation. Mathematical and Computer Modelling, 49, 2128-2137 (2009).

- F. Crauste, I. Demin, O. Gandrillon, and V. Volpert. Mathematical study of feedback control roles and relevance in stress erythropoiesis. Journal of Theoretical Biology 263 303-16 (2010).

- I. Demin, F. Crauste, O. Gandrillon and V. Volpert. A multi-scale model of erythropoiesis. Journal of Biological Dynamics 4, 59-70 (2010).

- Adimy, M., Bernard, S., Clairambault, J., Crauste, F., Génieys, S., Pujo-Menjouet, L. Modélisation de la dynamique de l'hématopoïèse normale et pathologique. Hématologie, 14(5):339-350, 2008.

Partner 4: LMDP team, Marrakech, Morocco

Presentation of the team

The LMDP team deals with modelling and analysis of biological, natural and social complex systems. It is focused on the study of relations between the evolution of a population and that of individuals (or groups) within it.

Since the 90s, the LMDP researchers contribute to the development of structured models in various applications including: marine population dynamics, cell population dynamics, urban dynamics, epidemiology. Mathematical methods and tools related to partial differential equations and dynamic systems as well as delay differential equations have been used to discuss and to analyse such models. More than 100 publications have been produced and 20 PhDteam theses defended by reseachers from LMDP in the last quadriennal.

The LMDP contribute also to the development of these issues in Morocco and the region through the organisation of international meetings:

- A workshop on the dynamics of marine populations in March 2005 was attended by more than 40 researchers.

- An international conference on differential equations and applications in June 2006 was attended by over 200 researchers from 26 countries.

- An International Conference on Biomathematics in June 2011 was attended by over 160 researchers coming from Europe, the United States and Africa.

Since the last decades the LMDP coordinate and participate in the Masters program on applied mathematics including courses on modelling and mathematical analysis of biological, natural and social complex systems

There are 10 Professors and 4 Assistant professors members of the LMDP. 20 PhD Students prepare their theses in the laboratory.

List of the members involved in this Project *(Name, title)*

Name	Title
Ait Dads El Hadi	**Professor**
Bouslous Hammadi	**Professor**
Ezzinbi Khalil	**Professor**
Hbid My Lhassan	**Professor**
Khaladi Mohamed	**Professor**
Maniar Lahcen	**Professor**
Ouhinou Aziz	**Assistant professor**
Taoudi Mohamed Aziz	**Assistant professor**
Bourfia Youssef	**PhD student**

Significant publications related to the project

M. Adimy, F. Crauste, My L. Hbid et R. Qesmi. Stability and Hopf bifurcation for a cell population model with state-dependent delay. SIAM J. Appl. Math, 70 (5), (2010), 1611-1633

N. Bacaër and E. Ait Dads, Genealogy with seasonality, the basic reproduction number, and the influenza pandemic accepted for publication Journal of Mathematical Biology. (On line 2010), Vol 62, (2011), 741 – 762.

A.Kebir, S. Ben Miled, M.L. HBID and R. Bravo de La Parra, Effects of density dependent sex allocation on the dynamics of a simultaneous hermaphroditic population: Modelling and analysis. Journal of Theoretical Biology, Volume 263, Issue 4, 21 (2010), 521-529.

M.L. Hbid, M. Louihi and E. Sanchez, Existence and Asymptotic Stability of solutions for a Functional Equation with Sate-Dependent Delay Arising in Marine Populations Dynamics. J. Evol. Equ. 10, N°. 4, (2010), 905—928

K. Ezzinbi, S. Ghnimi, M.A. Taoudi, Existence and regularity of solutions for neutral partial functional integrodifferential equations with infinite delay, Nonlinear Analysis: Hybrid Systems, Vol. 4(1), (2010), 54-64.

Partner 5: MoMinBi team, Pasteur institute, Tunis

Presentation of the team

The research program at the mathematical modelling and bio-informatics group (MoMinBi) of Pasteur Institute in Tunis is a multidisciplinary functional genomics approach to study fundamental biological processes relevant to human health and to develop tools of biomathematics and bioinformatics in systems biology. It will decipher the complex regulatory networks that control basic cellular processes in the context of intracellular pathogen infections as a paradigm of host/pathogen conflict of genomes. This project models the innate immune response of macrophages from two species (humans, mice) to an intracellular pathogenic parasite, Leishmania. This model is one of the most intensively investigated at the levels of parasite, host immune response and genetics, and allows testing and validating theoretical models in the light of already available and more expected data. In a combined strategy of experimental and theoretical work, we will systematically capture data on different levels of cellular information using state-of-the-art multiparametric molecular technologies.
The relationship between the different levels of regulation will give a picture of the fine control in the different phases of the infection. These data will be used to populate computer models of the relevant signalling pathways and regulatory motifs. The computer models will be designed as independent modules covering gene regulation, gene expression, protein expression and modification, protein interactions and signalling. The modularisation will be used to mimic the different types of innate macrophage responses and to map theoretical predictions to the experimental data. The project is based on a strong interaction between two SMEs and five key research institutes in the field of immunology, computational analysis and molecular biology research. It will reinforce R/D in the SMEs, allow valorisation of fundamental research and strengthen European competitiveness in the new field of systems biology and related areas. The project will constitute a template for further analyses of similar kind.

List of the members involved in this Project *(Name, title)*

Slimane Ben Miled, PhD, Habilité, Assistant professor
Alia Benkahla, PhD, Assistant professor
Ines Abdeljaoued, PhD, Assistant professor
Amira Kebir, PhD, Assistant professor

Kais Ghdira, PhD student
Sondos Smandi, PhD Student
Sonda Walha, master Student
Rym Jaroudi, master student

Significant publications related to the project

Alia Benkahla, I. Guizani, H. Mardassi, B. Bouhaouala, S. Ben Abderrazak, S. Ben Miled, L. Chargui, M. Chenik, S. Abdelhak, A. Ben Abdeladhim, and K. Dellagi (2009). Sustaining capacity building and implementing bioinformatics at institut pasteur de tunis. Infection genetics and evolution, 9(3) :383-384.

Kebir, A., BenMiled, S., Hbid, M. L., & de La Parra, R. B. (2010). Effects of density dependent sex allocation on the dynamics of a simultaneous hermaphroditic population: Modelling and analysis. Journal of Theoretical Biology, 263(4):521-529. doi: DOI: 10.1016/j.jtbi.2009.12.013.

BenMiled, S., Kebir, A., & Hbid, M. L. (2010). Mathematical modeling describing the effect of fishing and dispersion on hermaphrodite population dynamics. Math. Mod. of Nat. Phenom., 5(6):159-179.

BenMiled, S ., Kebir, A., & Hbid, M. L. (2010). Individual based model for grouper populations. Acta Biotheoretica, 58(2-3):247-264.

Benkahla A, L Guizani-Tabbane, I Abdeljaoued-Tej, S Ben Miled and K Dellagi (2009). Systems Biology and infectious diseases. Handbook of Research on Systems Biology Applications in Medicine, Andriani Daskalaki Ed., Publisher: Medical Information Science Reference, pp. 377-402.

Partner 6:

Presentation of the team

The Polito unit coordinated by Marcello Delitala has experience in dealing with several problems of applied mathematics and integrates mathematical modeling, qualitative analysis and numerical simulations. The theoretical work has been so far coupled with applications in the following fields: biological systems, as for instance multicellular systems from an evolutionary viewpoint and various applications related to biology and medicine; traffic flow systems; dynamics of socio-economic systems, such as the process of opinion formation in social groups.

List of the members involved in this Project

Marcello Delitala, Dr – Politecnico di Torino, Researcher

Tommaso Lorenzi, Dr – Politecnico di Torino, Post-doc – UPMC Paris, ex-PhD student supervised by M. Delitala

Significant publications related to the project

M. Delitala, T. Lorenzi, Evolutionary Branching Patterns in Predator-Prey Structured Populations, Discrete Contin. Dyn. Syst. Ser. B, 18, 2267-2282, 2013.

M. Delitala, U. Dianzani, T. Lorenzi, M. Melensi, A mathematical model for immune and autoimmune response mediated by T-cells, Comput. Math. Appl., 66, 1010-1023, 2013.

M. Delitala, T. Lorenzi, Recognition and learning in a mathematical model for immune response against cancer, Discrete Contin. Dyn. Syst. Ser. B, 18, 891-914, 2013.

M. Delitala, T. Lorenzi, A mathematical model for the dynamics of cancer hepatocytes under therapeutic actions, J. Theoret. Biol., 297, 88-102, 2012.

M. Delitala, T. Lorenzi, A mathematical model for progression and heterogeneity in colorectal cancer dynamics, Theor. Popul. Biol., 79, 130–138, 2011.

Partner 7:

Presentation of the team

The University of Valladolid Unit, coordinated by Óscar Angulo, has experience in dealing with the numerical analysis and simulations of population models since nineties. We have a deep collaboration with Dracula team.

List of the members involved in this Project

Óscar Angulo, Dr – Universidad de Valladiolid, Researcher
Juan Carlos López-Marcos, Dr – Universidad de Valladiolid, Researcher
Miguel Ángel López-Marcos, Dr – Universidad de Valladiolid, Researcher
Luis M. Abia, Dr – Universidad de Valladiolid, Researcher
Julia Martínez-Rodríguez, Dr – Universidad de Valladiolid, Researcher
Lourdes Gómez, Dr – Universidad de Valladiolid, Researcher

Significant publications related to the project

M. Adimy, O. Angulo, J. C. López-Marcos, M.A. López-Marcos, Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics, International Journal of Computer Mathematics, in press, 2013

O. Angulo, J. C. López-Marcos, M.A. López-Marcos, A semi-lagrangian method for a cell population model in a dynamical environment, Mathematical and Computer Modelling 57, 1860–1866 ,2.013.

L.M. Abia, O. Angulo, J. C. López-Marcos, M.A. López-Marcos, Numerical study on the proliferation cells fraction of a tumour cord model, Mathematical and Computer Modelling, 52, 992-998, 2.010.

L.M. Abia, O. Angulo, J. C. López-Marcos, M.A. López-Marcos, Numerical schemes for a Size-Structured Cell Population Model with Equal Fission, Mathematical and Computer Modelling, 50, 653-664, 2.009.

M. Adimy, O. Angulo, F. Crauste, J. C. López-Marcos, Numerical integration of a mathematical model of hematopoietic stem cell dynamics, Computers and Mathematics with Applications, 56, 594-606, 2.008.

(This page intentionally left blank in prevision of new teams joining the program in 2014-2015)

Previous collaborations between partners of the project

1. A long tradition of collaboration between the members of the two INRIA teams Bang and Dracula has existed even before the creation of the Dracula team. This collaboration has led in particular to common work inside the
- INRIA ACI "ModLMC" (modeling chronic myelogenous leukaemia, 2007-2009) and to a joint publication in the French journal *Hématologie:*
- Adimy, M., Bernard, S., Clairambault, J., Crauste, F., Génieys, S., Pujo-Menjouet, L. Modélisation de la dynamique de l'hématopoïèse normale et pathologique. Hématologie, 14(5):339-350, 2008.
- Jean Clairambault (Paris) and Vitaly Volpert (Lyon) are committed together in the ANR project "Bimod": Hybrid models of cell populations. Application to cancer modelling and treatment

2. In the same way, a long tradition of collaboration exists between the teams LMDP (Marrakech) and Dracula (Lyon), leading in particular to common publications:

- M. Adimy, F. Crauste, My L. Hbid et R. Qesmi. Stability and Hopf bifurcation for a cell population model with state-dependent delay. SIAM J. Appl. Math, 70 (5), (2010), 1611-1633.

- Fabien Crauste, M. Lhassan Hbid, - Abdelaziz Kacha, A delay reaction-diffusion model of the dynamics of botulism in fish, Mathematical Biosciences, Volume 216, Issue 1, (2008) 17-29.

3. Youssef Bourfia (Marrakech) is currently co-supervised in his PhD thesis by Hassan Hbid (Marrakech), Jean Clairambault (Paris) and Mostafa Adimy (Lyon).

4. - Luna Dimitrio (Paris) is currently co-supervised in her PhD thesis by Roberto Natalini (Rome) and Jean Clairambault (Paris).
- Thomas Lepoutre (Lyon) has been a PhD student in the INRIA team Bang before joining the INRIA team Dracula. There have been several papers published in common between Thomas Lepoutre, Benoît Perthame, Jean Clairambault and others (see http://www-roc.inria.fr/bang/JC/JCarticles.html)

5. Active and regular collaborations between teams LMNDP (Marrakech) and MoMinBi (Tunis) have in particular produced common publications:
- Kebir, A., BenMiled, S. , Hbid, M. L., & de La Parra, R. B. (2010). Effects of density dependent sex allocation on the dynamics of a simultaneous hermaphroditic population: Modelling and analysis. Journal of Theoretical Biology, 263(4), 521-529. doi: DOI: 10.1016/j.jtbi.2009.12.013.
- BenMiled, S ., Kebir, A., & Hbid, M. L. (2010). Mathematical modeling describing the effect of fishing and dispersion on hermaphrodite population dynamics. Math. Mod. of Nat. Phenom. 5: 159-179, 2010.
- BenMiled, S ., Kebir, A., & Hbid, M. L. (2010). Individual based model for grouper populations. In revision, Acta Biotheoretica.

6. A collaboration exists between the teams "Dracula" (Lyon) and the team of Valladolid, leading in particular to common publications:

M. Adimy, O. Angulo, J. C. López-Marcos, M.A. López-Marcos, Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics, International Journal of Computer Mathematics, in press, 2013

M. Adimy, O. Angulo, F. Crauste, J. C. López-Marcos, Numerical integration of a mathematical model of hematopoietic stem cell dynamics, Computers and Mathematics with Applications, 56, 594-606, 2008.