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INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team anubis

Tools of automatic control for scientific computing, Models and Methods in Biomathematics

Bordeaux - Sud-Ouest

Theme : Observation, Modeling, and Control for Life Sciences

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Anubis is an INRIA Project-Team joint with University of Bordeaux and CNRS (IMB, UMR 5251). The team became an INRIA project on January the 1st, 2009. By decision of INRIA's direction it will stop on december 31st, 2011.

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2. Overall Objectives

2.1. Introduction

This team is dedicated to modeling and controlling the spatio-temporal evolution of biological populations.

As we face the great problems arising in the field of population dynamics (for instance : new epidemics, optimization of the treatment of leukemia, understanding the mechanisms of Parkinson's disease treatment by deep brain stimulation, etc.) there is a great need to develop more realistic models and mathematical tools to analyse them. Up to now most models used in population dynamics are mainly qualitative : they try to reproduce qualitative behaviours such as extinction of species, propagation of epidemics, oscillations of blood cells number in some leukemias, synchronization of neurons, ... to validate underlying assumptions. There is still a great need of such qualitative studies to analyze the mechanisms of interaction. New models using integro-differential instead of parabolic equations for spatial interactions should be investigated. But there is also a need for more quantitative simulations of biological phenomena. In particular one may wish not only to simulate the phenomenon but to act on it: stop the propagation of an epidemic, improve the protocol of brain stimulation in Parkinson's disease treatment or of drug administration in leukemia, fight against pests of vineyard, ... Tools from automatic control theory have already been used in this field as optimal control ([44]), parameter identification or feedback design, but there still remain many open questions we intend to investigate. For instance optimal control is useful not only to describe an external action on the population but also internal interactions that can be seen as optimizing certain criteria.

A long term goal would be to forecast by simulation the evolution of a population in for instance epidemiology. Although in many cases models are not sufficiently reliable at present, we think we can begin to investigate the question of estimating the initial data for the simulation: this is the well known problem of data assimilation which is intensively studied in geophysics, oceanology and meteorology. Based on Kalman filtering, new techniques have been developed in these fields as the ensemble Kalman filtering. To our knowledge no similar research is done in population dynamics. One of our goals is to transfer, adapt and develop techniques of data assimilation to population dynamics.

These studies make it possible to develop specific softwares that are intended to be useful to our biologist partners. Developing these softwares and experimenting with the results of the numerical simulations are an important part of our workload. Till now those developments have been specific to each problem, but our team is thinking about common elements of our studies with a view to defining common software tools.

2.2. Highlights

The team organized the Conference on Computational and Mathematical Population Dynamics (CMPD3) from May 31 to June 4, in the university Bordeaux 2 (La Victoire).

3. Scientific Foundations

3.1. Structured population modeling

The introduction of one or several structuring variables is important when one wants to more precisely describe the evolution of populations. Besides large time behavior this concerns transient behaviors, e.g., describing epidemic curves at the onset of an epidemic or the initial development of cell growth and tumors. It also depends on the final goals of modeling, i.e., mathematical analysis, numerical simulations or experiments, or both.

Spatial structures are widely used to assess the impact of heterogeneities or variable local densities in population dynamics, cf. [43]. This leads to systems of reaction diffusion for continuous models, or to networks of systems of ordinary differential equations in the discrete case. Discrete spatial models are also in order, cf. [64], [67]. A new set of models is dedicated towards analyzing the transmission of parasites between populations distributed over distinct spatial models.

Multimodeling techniques could be useful when the model changes from one region to another. Methods presented in section 3.3 could then be used to give interface conditions.

3.1.1. Structured modeling in demography and epidemiology

In demography the most significant variable is the chronological age of individuals, cf. [57], [66]. This age-structure although already intensively studied in our team in the past, cf. [2], [8], [68], will be central in our future research. Discrete age structures are also in order.

Lot of models in epidemiology couple spatial and age structures to take care of the spreading rate of individuals together with the vital dynamics of the population. This structuration can lead to complex patterns formation and waves. A new problem we would like to investigate is the propagation phenomenom that, like in the classical reaction-diffusion framework, arises due to travelling waves. More specifically the description of the wave speed in function of the demography characteristics of the population is of particular interest for biologists.

In addition to spatial and age variables, other continuous structuring variables will be considered, i.e., size of individuals (fishing), weight, age of the disease for an infected individuals, cf.[8].

For interacting populations or subpopulations additional discrete structures can be put forth. In the study of disease propagation (microparasites) usually a structure linked to the health status or parasitic state of individuals in the host population is used, i.e., SIS, SIR, SIRS, SEIRS models.

In previous works, rather strong assumptions were made on demographic and diffusion coefficients (e.g. identical or independent of age) to obtain qualitative results. In recent works it becomes possible to weaken these conditions, cf. [1].

With M. Iannelli, we intend to study the impact of the spatial location (developed or underdeveloped country) on the propagation of an infectious disease (tuberculosis, AIDS ...). Then we have to model the way that the infectiveness rate or the recovery rate, which are dependent on the location, influence the dynamics of the infected population.

Various ways can be experienced. In a first approach we could assume that individuals are randomly distributed in space, cf. [43], [45]. We would obtain a reaction-diffusion system whose reaction term would depend on space. In an alternate approach we could define patches where the population dynamics is governed by ordinary differential equation yielding large size systems of ODEs, cf. [52].

3.1.2. Invasion processes in fragile isolated environments

In a series of joint works with F. Courchamp and G. Sugihara, e.g., [7], we were concerned by ecological models designed to model the fate of native species living in isolated environments after the introduction of alien predator or competitor species, cf. [62]. Isolated environments we had in mind were mostly remote islands in Southern Indian Ocean, e.g., Kerguelen Archipelageo. Native species were seabirds while purposely or accidentally introduced species were small predators, i.e., domestic cats, or small rodents, i.e., rats and rabbits.

Singular systems of ODEs with unusual dynamics were derived. Typically finite or infinite time extinction of state variables may coexist, a Hopf bifurcation being also observed. This has important ecological implications and requires a detailed mathematical and numerical analysis.

It is also important to introduce a spatial structure, spatial heterogeneities being rather frequently observed in these environments (cf. [62]; see also [52]).

Control problems related to overcome finite or infinite time extinction of endangered native species emerge. In collaboration with H. Malchow we deal with the impact of a virus on an invasive population which is another way of controlling an invading species [55]. A comprehensive analysis is required. More specifically for spatially distributed systems with three populations the emergence of spatial heterogeneities and pattern formations must be understood.

3.1.3. Indirectly transmitted diseases

Host–parasite systems have been present in our team for many years with studies on viruses of carnivorous animals (foxes *Vulpes vulpes*, domestic cats *Felis catus*), cf. [52], [46], or on macroprarasites (*Diplectanum*

aequens) infesting sea-bass (*Dicentrarchus labrax*) populations, cf. [47]. It remains a main research theme through new developments of a collaborative effort with D. Pontier for zoonosis and anthropozoonosis, of a new collaboration with A. Callonec on pathogens of vineyards and of new proposals concerning interspecific transmission of toxoplasma with E. Fromont (mainland France) and P. Silan (French Guyana).

New important problems arise occurring in the generic setting of emerging diseases, invasion and persistence of parasites. Typically a parasite is transmitted from a population 1 wherein it is benign to a population 2 wherein it is lethal. It becomes important to assess and control the impact of the parasite on the host population 2.

This involves models dedicated to indirect transmission of parasites either via vectors, or through the contaminated ground or environment, cf. [46], [63], or through predation. In that case spatial structuration of species yields systems of reaction-diffusion equations posed on distinct spatial domains that may be coupled to ordinary differential equations, cf. [51].

Pathogens of vineyards and transmision of toxoplasma within multicomponent host-pathogens systems yield complex biological systems. Analyzing their actual dynamics requires a dedicated effort that is to be developed in collaborative efforts with our biologists colleagues.

3.2. Optimal control problems in biomathematics

Controls in population dynamics can take various forms and generally speaking are governed by the anthropization of the environment, i.e., by the action of human populations on their environment. Prophylaxis, sterilization, vaccination, screening, quarantine, culling, re-introduction, capture, hunting, fishing, pesticides are examples of widely used control processes. It is then important to assess the impact of such actions on the considered population and to distinguish between what is actually feasible and what is not in terms of optimal management of resources.

A rather rich literature is available on this topic ranging from resource management in ecology to applications of Pontryaguin's maximum principle to mathematical biology problems.

In the framework of this research team-project, we investigate control problems for structured models (size, weight, age, health status, spatial location of individuals, age of the disease) from a biomathematical point of view. We will use both individual based models (IBM) and models using densities. Techniques to be used are mainly those from automatic control and the factorization methods described in section 3.3.2.

3.2.1. Disease control

Some problems of prevention against disease propagation can be modelled as optimal control problem with control acting on subdomains and/or on certain cohorts. Then several optimization programs can take place depending on the severity of the disease and the cost of the control. The problem consists in minimizing or maximizing an objective function with constraints on the control and on the state.

For some of these problems concerning animal populations the objective consists in finding the smallest domain that can prevent the propagation of the disease : the reduced level of healthy individuals or the absence of any infected prevents the propagation. This is a control problem coupled to a shape optimization problem.

In particular, a somewhat "inverse problem" is one consisting in controlling an invading alien species by using a pathogen (see below and the end of subsection 3.1.2). Field experiments have been conducted, and simple mathematical models derived, cf. [46], [53].

3.2.2. Controlling the size of a population

This is a classical problem in demography. Various kinds of control can be used : control by migration, elimination (animal populations) or designing birth policies. Numerical and mathematical difficulties come from the existence of non local terms in the equation due to the mortality and renewal processes of the population.

Classical results of automatic control theory cannot be directly applied. Our last results on the topic show that one can control (after a time equivalent to one generation) a population (except the smallest age classes) by acting only on age classes of small size and localized on small domains. These studies could be extended to systems (populations structured by sex, prey-predator systems) and to other fields than demography but with similar difficulties (cell growth, epidemiology with sanitary structuration).

A study with S. Anita on the control of a predator population upon acting either on preys or on predators has been initiated. This is to be further developed toward a predator-prey system with species living on distinct spatial domains. In this new setting the question of where to act and on which species is more realistic.

3.2.3. Public prevention of epidemics in an optimal economic growth model

In this field (done within the proposal for :" projet thématique prioritaire du CNRS Méthodes et décision pour le développement durable"), we address the question of whether or not economics can affect or be affected by the spread of a disease within a population. Ill individuals often stop working and affect the production function, diminishing the capital accumulation per capita. The public health policies are not only an immediate cost but also affect the future wealth of the economy. The social costs of the disease are not devoted to investment, but the reduction of the epidemics increases the labor population and the capital per capita. In a first approach with E. Augeraud (University of La Rochelle) and H. D'Albis (University Toulouse 1), we introduce a dynamical economic model of Ramsey type, where the labor population is affected by an infectious disease like HIV or TB (Tuberculosis). To control the spread of this disease, the government has the possibility to set up a screening procedure. We will study the optimal balance between the economical problem consisting in the maximization of the discounted sum of instantaneous utility and the classical social problem consisting in minimizing the number of infected individuals. Using the Pontryagin's maximum principle we will see how the level of economic development, the price of the screening campaign and the price of medications affects the dynamic of public intervention.

3.2.4. Age structured population dynamics as a problem of control

For some evolution problems, one can consider that a part of the dynamics comes from a state feedback. This is naturally the case for age structured populations for whose dynamics the birth rate depends on the breakdown of the present population by age. Then one can consider the birth rate as a control. There remains to determine the criterion and therefore the observation of the system in order that the optimal feedback corresponds exactly to the natural fertility rate. This problem leads to a functional equation which has to be studied and solved numerically. This could allow to transform population evolution problems to an open loop control problem and may be a clue to numerical problems linked to birth rates. Possibly for control problems in population dynamics (fishing, epidemiology,....) such an approach could provide a smooth transition between the phase under optimization and a desired asymptotic behaviour [12].

3.3. Developping mathematical methods of optimal control, inverse problems and dynamical systems; software tools

Optimal control of systems governed by partial differential equations has a long past history at INRIA going back to the pioneering work of J.L. Lions [59]. Now Commands and Corida team-projects are investigating this area. First we want to be users of results from these researches. We want to use the automatic control tools not only as a way of optimizing the action on a system but also as a modeling help. For instance Lyapunov functions have long been used as a theoretical tool in population dynamics. Similarly, the recent trend in automatic control consisting in using families of model giving a finer or coarser representation of reality can be found in population dynamics: models describing the evolution of interacting populations are quite numerous, ranging from individual based models to models governed by systems of ordinary or partial differential equations.

The method of virtual controls has been set forth by J.-L. Lions and O. Pironneau. It aims at providing methods for domain decomposition, model coupling, and multipyshic model based on optimal control techniques. Yet interactions (between domains or models) are considered as control variables and the problem is solved by minimizing a criterion. This approach suits well with the framework described here particularly for inverse problems and we intend to contribute to it.

3.3.1. Inverse problems : application to parameter identification and data assimilation in biomathematics

A classical way to tackle inverse problems is to set them as optimal control problems. This method has proved to be efficient and is widely used in various fields. Nevertheless we are persuaded that important methodological progresses are still to be done in order to generalize its use. With JP Yvon, we have worked on the numerical stability of these methods, seeking to redefine the mismatch criterion in order to improve the conditioning of the Hessian of the optimization problem ([61]). In the same way a simple idea to explore is to use a total least square approach for this criterion.

An other idea we want to investigate consists in defining a measure of match (positive) and one of mismatch (negative) between the output of the model and the measurements, and to take into account only the positive part in the criterion. This point of view inspired from methods used in genomic sequences comparison (Waterman's algorithm) aims at a better robustness of the method by eliminating from the criterion the effect of unmodelled phenomena. It also leads to free boundary problems (part of the observation taken into account).

For certain problems the ill-posedness can be related by the factorization method to the ill-posedness of the backward integration of a parabolic equation. Then we can apply the well-known quasi-reversibility method to that case. The setting in position of programs of vaccination, prophylaxy, detection needs an a priori study of feasibility. This study after a modeling step will go through a step of model tuning to the data. Yet, initial data are badly known or completely unknown, demographic parameters are often unknown and disease transmission mechanisms are subject to discussion between biologists to determine their nature but their exact form and value is unknown. We intend to use parameter estimation techniques for these biomathematics problems.

Also, even though the models used nowadays are mainly qualitative, we want to investigate on forecasting simulations. For that purpose data assimilation is an important method. It has benefited of many recent developments in the field of meteorology and oceanography as reduced state Kalman filtering or ensemble Kalman filtering. To our knowledge these tools have not been used in the present context. We intend to explore the use of these tools and adapt them. Furthermore the efficiency of the "robust" Kalman filter issued from our research on QR factorization will also be evaluated (cf. section 3.3.2).

3.3.2. Dynamic programming and factorization of boundary value problems

We propose a method to solve elliptic boundary value problems inspired by optimal control theory. We use here spatially the technique of invariant embedding which is used in time to compute optimal feedback in control. In the symmetric case we consider the state equation as the optimality system of a control problem, one space variable playing the role of time. The problem is embedded in a family of similar problems defined over subdomains of the initial domain. These subdomains are limited by a family of surfaces sweeping over the initial domain. This technique allows to decouple the optimality system as for the derivation of the optimal feedback. So one can factorize a second order elliptic boundary value problem in two first order Cauchy problems of parabolic type. These problems are decoupled : one can solve one problem in one space direction ("descent phase") then the other problem in the opposite direction ("climbing phase"). This decoupling technique also works in the nonsymmetric case.

The goal is to provide Cauchy problems equivalent to boundary value problems in a manner as general as possible. We expect from this an interesting theoretical tool : it has already established a link between certain uniqueness results for the Cauchy problem for the considered operator and backward uniqueness for the parabolic problem in the factorized form.

At the moment the method has been applied and fully justified for the Poisson equation in the case of a cylinder [13]. Indeed, the invariant embedding can be done naturally in the direction of the cylinder axis and allowing the factorization of the second order operator in the product of operators of the first order with respect to the coordinate along the cylinder axis. It needs the computation of an operator solution of a Riccati equation. This operator relates two kinds of boundary conditions on the mobile boundary for the same solution (for example the operator relating Neumann and Dirichlet boundary conditions). Furthermore the same method applied to the finite difference discretized problem is nothing else but the Gauss block factorization of its matrix. Therefore the method can be seen as the infinite dimensional generalization of the Gauss block factorization. We look for a generalization of the method to open sets of arbitrary shape and also to families of surfaces sweeping over the domain of arbitrary shape.

There are many ways of extending the method for instance to other elliptic equations, equations of different type, QR factorisation, nonlinear equations ... and of applying it to other problems as obtaining transparent conditions for unbounded domains, domain decomposition, inverse problems, singular perturbation analysis,...

Besides this theoretical tool, giving equivalent formulation to the continuous problem may give rise to new numerical methods based on these formulations (cf. 3.3.3).

3.3.3. Applications of the factorization method to devise new numerical methods

The factorization method yield an equivalent formulation to the original boundary value problem. One can use it numerically in various ways :

1. the interpretation of the block Gauss factorization as a possible discretization of the continuous factorization suggests new schemes : we have already studied an explicit discretization of the factorized system in the privileged space direction. Many other variants are possible;
2. following the analogy with control problems, we can see incomplete factorization preconditionning as corresponding to suboptimal feedbacks in the framework of otimal control. It is a matter of defining sparse approximations of the Dirichlet-Neuman operator and to use these approximations to obtain preconditionning operators.
3. the factorization puts into play a family of surfaces depending on a space variable sweeping over the domain. Then we have to describe these surfaces and their displacement, as well as the effect of operators acting on functions defined on these surfaces. In the framework of the finite element method a discretization of the family of surfaces as the “fronts” of the meshing and the block (related to the front) LU factorization as the integration of first order equations. The method needs only the meshing of a family of surfaces instead of a volume meshing. Then mesh size adaption methods may give rise to an alteration of the front velocity and so to an alteration of the mesh.

Generally speaking in any situation where the Dirichlet-Neumann operator is used (transparent boundary conditions, domain decomposition, wave guide matching,..) the factorization method which provides the equation satisfied by this operator may permit advances. We will also make progress by transposing results obtained in one domain to connected domains. In this framework we wish to develop and promote the concept of “computing zoom”: during a simulation the user defines a region of interest and the software recomputes the solution only in the region of interest (with the same number of unknowns i.e. with a better resolution) allowing variation of the data in this region. For that purpose we need to compute boundary conditions on the boundary of the region of interest which sums up the behaviour of the solution outside exactly. This can be done by integrating a Riccati equation from the boundary of the initial domain to the boundary of the region of interest.

3.3.4. Differential equations with delay modeling cellular replication

Mathematical systems for a variety of cellular models are most appropriately framed as differential equations or partial differential equations with delay (see for example [40], [41], [42]). In this circumstance, the natural delay is the duration of the cell cycle. Several classes of these systems can be reformulated as abstract functional differential equations. Our aim in this part is to provide a qualitative theory and applications for such equations from dynamical systems point of view.

As in [40], [41], [42], we will concentrate our study on the fundamental theory of existence, uniqueness, continuation, continuous dependence, compactness, spectral decomposition of the state space, invariant manifolds, Hopf bifurcation, dissipativeness and existence of attractors, stability of the limit cycles yielded by the bifurcation using the normal form theory and the center manifold theorem.

3.3.5. Tools for modeling and control in biomathematics

Within the framework of this project team, we intend to implement an epidemic propagation simulation software based on a spatially distributed mathematical model. This software should allow data assimilation, parameter identification and optimal vaccination strategy determination. So we hope to be able to supply our biologists and physicians colleagues with a working tool to test hypothesis and determine vaccination campaign planning rules.

A more precise scheduling of this work will depend on the human means of our project team. It may also be developed in collaboration with other INRIA teams interested by this topic (Comore, Mere) and with M. Iannelli's team.

4. Application Domains

4.1. Application fields and collaborations with biologists

We present here collaborations on specific biological modeling problems.

4.1.1. Epidemiology

Participants: Bedr'Eddine Aïnseba, Arnaud Ducrot, Michel Langlais, Pierre Magal.

4.1.1.1. Brucellosis

This is a collaboration with CHU of the university of Tlemcen (Algeria). Brucellosis is a highly contagious infectious disease in domestic livestock and many other species and is communicable to humans by contact with infected animals or by infected products (milk, meat, ...). This disease is not transmitted between humans but is a major disease in developing countries because of its severity in human cases and the economically caused damage to the livestock. Our goal is to study the disease within an ovine population. Infection usually occurs after contact with tissues, urine, vaginal discharges, aborted fetuses and placentas,... When infected for a first time the female aborts and the infected fetus remains in the environment still highly contaminating for several months. The pioneering works on the subject focused only on direct transmission mechanisms and did not take in account the indirect transmission by the contaminated environment.

4.1.1.2. HIV-1 Infection in tissue culture

Since the 80's there has been a big effort made in the mathematical modeling of the human Immunodeficiency Virus type 1, the virus which causes AIDS. The major targets of HIV-1 infection is a class of lymphocytes or white blood cells known as $CD4^+$T-cells which are the most abundant white blood cells in the immune system. It is thought that HIV-1, although attacking many different cells, wreaks the most havoc on the $CD4^+$T-cells by causing their destruction and decreasing the body's ability to fight infection. Many mathematical models have been introduced to describe the dynamics in HIV-1 infection in the bloodstream (see the works of Leenheer *et al.*, Nowak *et al.*, Kirshner, May, Perelson *et al.*, ...). For tissue culture (lymph nodes, brain, ...) the cell to cell mode contact is much more important for the infection than the cell-free viral spread (see Culshaw *et al.*, Philips, Dimitrov, ...). Following these pioneering works we propose a model of the SI type with delay, modeling the interaction between healthy cells, infected cells, and infected cells that are still not infectious .

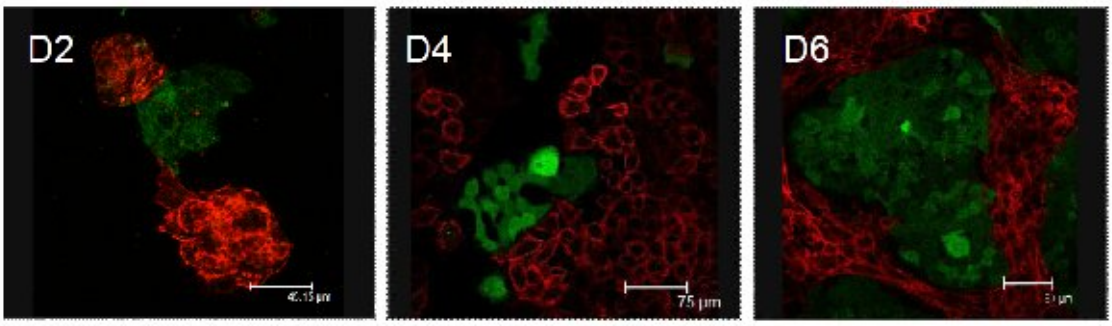

Figure 1. Confocal imaging of cell-to-cell interactions in the human breast cancer cell line, MCF-7. MCF-7 were cytosol-tagged with the persistent probe CellTracker Green (green fluorescence, ctgMCF-7) or membrane-tagged with a phycoerythrin-conjugate antibody directed against a specific surface protein (red fluorescence, peMCF-7). A mixture of 50:50 of ctgMCF-7 and peMCF-7 was co-cultured over 6 days. Images were obtained by confocal laser scanning microscopy. Photos was taken at day 2 (D2), day 4 (D4), and day 6 (D6). Note that cells get organized in well-delimited islets.

4.1.1.3. Resistance to chemotherapeutic treatments and P-gp

We are interested by co-culture of resistant and sensitive cancer cells in a dish. The line of cells considered are the so called MCF7, which are nothing but breast cancer cells. In this problem, our goal is to understand how cancer cells exchange a protein P-glycoprotein (P-gp for short). This protein turns to be responsible for multidrug resistance of cancer cells, in particular it is responsible for resistance against chemotherapy treatments. Our goal is to understand how sensitive cancer cells may acquire resistance by transfers of P-pg from cells over expressing P-pg (resistant cells). This type of mechanisms has been recently discovered by Levchenko [58] and investigated and modeled in [56].

Figure 1 shows the complexity of the describing the spatial distribution of cells in a co-culture of cells. The red cells correspond to the resistant cells, and the green cells correspond to sensitive cells. It is clear that the motion process is not just a diffusion process. Moreover, since the direct transfers occur at the boundary of the islets (red or green islet), we need a good model to describe the spatial motion of cancer cells

4.1.1.4. Nosocomial diseases

Nosocomial infections caused by antibiotic-resistant pathogens are a global public health problem, in both developed and developing countries, including China, France, and USA. For example in USA, every year approximately 2 million people acquire a clinically significant hospital infection, which cause about 20,000 deaths and cost hospitals $20 billions per year. A recent estimate showed that there were 18,650 deaths in patients with invasive methicillin-resistant Staphylococcus aureus (MRSA) in the US in 2005, exceeding the total number of deaths due to HIV/AIDS in the same year.

In the last 15 years, various mathematical models have been proposed to describe the transmission dynamics of antibiotic-resistant bacteria in hospitals or communities, we refer to the survey on this topic [54]. In [65], we formulated a two-level population model to quantify key elements in nosocomial infections. The objectives were to study the effect of antibiotic treatments of the dynamic elements of nonresistant and resistant bacteria strains in hospital environments and to provide understanding of measures to avoid the endemicity of resistant antibiotic strains in hospitals in USA (and also in the rest of the world). The theoretical analysis was reported in [50]. Most recently, in [49] we used an individual based model (so called Monte-Carlo simulations in mathematics) which is formulated by individuals and includes the interaction with the healthcare workers. The main point in this paper is that we derive a model in which all the parameters are expressed in terms of

observable quantities. An important conclusion for this paper is that the average time of visit of patient by healthcare workers plays a key role in such a problem, while this parameter has not been considered before.

In China, one special groups of health care workers (HCWs), volunteers, are widely used in many tertiary care hospitals. The relationship between this kind of healthcare mode and the transmission of antibiotic-resistant bacteria has not been investigated in detail. Proper infection control measures are needed to attenuate the nosocomial infection involving volunteers. Our goal in this part is to construct some mathematical models which are suitable tools to study the transmission dynamics of antibiotic-resistant bacteria in hospitals and to design effective infection control programs in China.

4.1.2. Blood cells

Participants: Bedr'Eddine Aïnseba, Arnaud Ducrot.

Hematological diseases have attracted a significant amount of modeling attention because a number of them are periodic in nature . Some of these diseases involve only one blood cell type and are due to the destabilization of peripheral control mechanisms, e.g., periodic auto-immune hemolytic anemia. Such periodic hematological diseases involve periods between two and four times the bone marrow production/maturation delay. Other periodic hematological diseases, such as cyclical neutropenia , involve oscillations in all of the blood cells and very long period dynamics on the order of weeks to months and are thought to be due to a destabilization of the pluripotent stem cell compartment from which all types of mature blood cells are derived.

We focus, in particularly, on chronic myelogenous leukemia (CML), a cancer of the white cells, resulting from the malignant transformation of a single pluripotential stem cell in the bone marrow . Oscillations can be observed in patients with CML, with the same period for white cells, red blood cells and platelets. This is called periodic chronic myelogenous leukemia (PCML). The period of the oscillations in PCML ranges from 30 to 100 days , depending on patients.

We have studied in a delay model that describes the dynamics of a pluripotent stem cell population involved in the blood production process in the bone marrow. The delay describes the cell cycle duration. We established stability conditions for the model independent of the delay. We have also observed oscillations in the pluripotent stem cell population through Hopf bifurcations. With parameter values given by Mackey [60], our calculations indicate that the oscillatory pluripotent stem cell population involves a period of 46 days.

It will be interesting to study the dynamics of the hematopoietic cells throughout different compartments modeling various stages of the maturation of cells. This resarch is joint with INSERM teams E 217 in Bordeaux 2 and U 590 in Lyon.

4.1.3. Modeling in viticulture : Spreading of a fungal disease over a vineyard (collaboration with INRA)

Participants: Jean-Baptiste Burie, Michel Langlais.

This is a joint research with different groups of UMR "Santé végétale" of INRA, Villenave d'Ornon.

This part is mostly an application of section 3.2.1. We aim at investigating the spreading of powdery mildew upon vine within a growing season to help having a better management of the disease. Indeed fungicide treatments have a financial and environmental cost. This is a collaborative work with A. Calonnec and P. Cartolaro from INRA in Villenave d'Ornon (UMR INRA-ENITA en santé végétale). The ultimate goal is to provide a diagnosis tool to help the vine producer treating the disease.

Until now a mechanistic model has been built that takes into account the interaction between host growth, pathogen development and climatic conditions. This mechanistic model is being extended at the vineyard scale using the knowledge in high performance computations of some INRIA ScAlApplix members: G. Tessier and J. Roman.

But still disease features have to be investigated at a higher level. This will be done thanks to epidemiological models based on ODE or PDE systems that will focus on a particular characteristic of the disease propagation mechanism. These models will also be used to quantify key parameters of the infection using outputs of the mechanistic model or directly with the real field data available. In particular we are currently investigating the interaction between the date of primary infection and growth of the host, the role of a dual short and long range dispersal of the disease and the effects of the spatially periodic structure of vineyards [6]. Moreover in the 1D spatial case we have developped new tools to exhibit traveling fronts for complex models [48].

In a more distant future this study will give rise to new developments within the project-team:

- compare delay equation models with epidemiological models based on classical ODEs in the phytopathologic domain;
- in the spatial case improve the code by the use of transparent boundary conditions to simulate an unbounded domain;
- include the effects of fungicide treatments in the models;
- use homogeneization techniques for the mathematical study of the disease spreading in periodic environnments;
- extend these models to the study of diseases in other examples of periodic environnments such as orchards.

4.1.4. Modeling in neurobiology

Participant: Jacques Henry.

As an other medical field of application of mathematical modeling we have chosen neurophysiology. Our interest is at two levels : the global electric and magnetic activities generated by the cortex as measured by EEG and MEG. At this level we are mainly interested by the inverse problem which is also studied by the Odyssée and Apics teams. Our approach is based on the factorization methods described in section 3.3.2. We are also interested in modeling the neural activity at the level of interacting populatios of neurons. Our main collaborations is with the "Basal Gang" team of UMR 5227 at the Bordeaux 2 university.

Our approach for modeling neuron populations is based on structured population dynamics and gives a description of the activity of the tissue at a higher level, through the density function of neurons in the state space. It is based on realistic models at the level of the neuron: each neuron is described by a 2D Izhikevich model. The synchronization or desynchronization of neurons can be represented in this description. This modeling has the advantage of being insensitive to the number of neurons (as opposed to a direct simulation). Whether this kind of modeling can give insight into the functioning of the sensori-motor pathways in the brain has still to be investigated. This methodology has not been fully utilized in computational neurosciences and we believe that classical tools in population dynamics, as for instance the renewal process formulation, could be applied with benefit. Will they help to build a bridge using aggregation techniques with models used at a larger scale in time and space as firing rate models? This would give a basis at the neuron level for these models.

4.1.5. Modeling in electrocardiology

Participants: Jacques Henry, Bedr'Eddine Aïnseba.

This is a new field of application we are starting to develop this year. This new orientation is mainly due to the initiative of Pr Michel Haissaguerre an internationally renowned cardiologist, head of the cardiology department at the hospital "Haut Leveque" in Pessac near Bordeaux. He is applying for the creation in Bordeaux of an IHU (a new prestigious structure for medical research). His proposal "Liryc" will mix intimately research in cardiac rhythmology and mathematical modeling and computer simulation. Based on a previous experience of J. Henry in the field, we decided to reshape a part of the research activity of the team to this domain. The main objectives of this institute in which we will be involved are the improvement of the management of cardiac arrhytmias. More specifically Pr Haissaguerre's team made important progresses in the discovery of the role of pulmonary veins in the triggering of atrial fibrillation and its curative treatment by

thermoablative therapy. Nevertheless there remain many open questions to fully understand the mechanisms at the origin of the atrial fibrillation and to improve its treatment. For example it is important to make the distinction between paroxystic and permanent fibrillation. The institute will also tackle the prevention of sudden death by ventricular fibrillation. This needs efficient diagnosis tools. Electrocardiographic imaging consists in reconstructing an epicardial map of potential from measurements on torso. From the mathematical viewpoint this is an inverse problem. Our targets in that domain are i) lead theoretical investigations on the nature of fibrillation ii) improve the existing monodomain and bidomain models to have a more realistic modeling of the cardiac tissue and its inhomogeneities which will be applied in a first step at the atrial level iii) improve the numerical methods to solve these moodels iv) enhance the precision of the resolution of the ECG inverse problem. These researches will be lead in collaboration with the teams of the former Cardiosense 3D project of INRIA.

5. Software

5.1. Software

Participant: Youcef Mammeri.

A generic model for the spread of a powdery mildew epidemic in a growing vine stock has been integrated by Y. Mammeri (et al.) [36] in the Open Alea platform (http://openalea.gforge.inria.fr/dokuwiki/doku.php?id=openalea) developed by the EPI Vplants. In a near future this integration will be extended to the case of an apple scab epidemic. This work has been achieved in the framework of the ARC INRIA M2A3PC.

6. New Results

6.1. New results in the theory of factorization of boundary value problems

Participants: Jacques Henry, Fadhel Jday.

We are pursuing the development of the theory of factorization of boundary value problems as described in 3.1. The method has been extended to non cylindrical domains: we consider domains generated by its sections that are continuously deformed when moving along an axis. We consider also a regularization of the Laplace operator which is of fourth order and that results from the optimality conditions of the control problem of a parabolic equation in a non cylindrical domain. Results of J. P. Zolesio apply to this problem. A joint paper with M Soares and B Louro has been submitted to the “comptes rendus de l’académie des sciences”.

An extension of the factorization method to the stationnary Stokes problem in a cylinder has been studied with F. Jday. Here the difficulty comes from the incompressibility relation and its Lagrange multiplier, the pression. Nevertheless the general framework apply: the factorization is obtained through the solution of a (more complicated) operator Riccati equation.

6.2. Data completion problems for elliptic equations using the theory of factorization

Participants: Jacques Henry, Fadhel Jday.

F. Jday is continuing his thesis co-supervised by A. Ben Abda and J. Henry as a consequence of the collaboration initiated within the “équipe associée” Enée 06. A paper using the factorization method for the data completion problem for elliptic equations in a cylinder has been submitted to the journal “Inverse problems”. This paper presents a characterization of the compatibility of the data for solving the Cauchy problem; it explores the dependency of the ill-posedness with respect to the length of the cylinder and proposes an alternative regularization. In relation to the inverse problem in electrocardiology and in order to take into account the movement of the heart, the effect of small perturbation of the faces of the cylinder in the data completion problem is studied.

6.3. New results in dynamical systems theory applied to population dynamics

Participants: Arnaud Ducrot, Pierre Magal.

In a joint work of A. Ducrot, P. Magal and K. Prevost we investigate some mathematical properties of a class of linear abstract Cauchy problem involving almost sectorial operators by using the theory of integrated semigroups. Some results of well posedness as well as some perturbation result of linear operators are obtained. This work has been published in Journal of Evolution Equations (2010).

A methodology to compute the projectors on the generalized eigenspaces for some neutral functional differential equations in L^p-spaces has been derived by A. Ducrot, Z. Liu and P. Magal in some article published in Canadian Journal of Mathematics (2010).

A. Ducrot, P. Magal and S. Ruan generalized the above methodology in the context of partial differential equation with delay in some article published in the Field Institue Communication (2010).

These results as well as an introduction of integrated semigroup theory and bifurcation problems has reviewed in a survey paper published in Gazette des mathématiciens (2010).

6.4. Modeling the activity of populations of neurons: study of synchronization

Participants: Jacques Henry, Gregory Dumont, Oana Tarniceriu.

In 2010, we implemented a simulator for a population of neurons. The mathematical equation describing the population is written as conservation law, where the behavior of the population is directly derived from the characteristics of a single neuron. In our case, we choose the Izhikevich model for the dynamics of a single neuron. The numerical schemes we used to resolve the equation are the recent WENO scheme mainly introduced by Shi-Wang Shu. In order to validate the numerical results obtained with our simulator, we have compared our results with the results that biologists get from Monte Carlo method. The simulator and its results were presented in the CMPD3 (Conference of Mathematic for Population dynamic) .

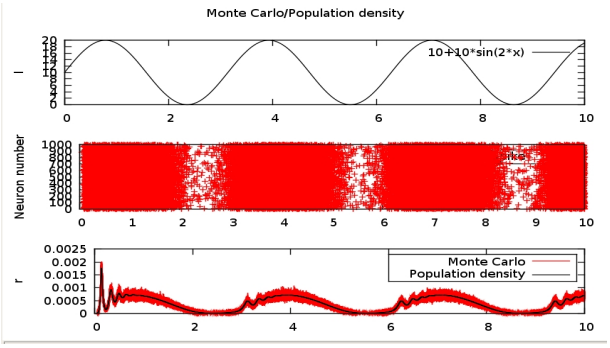

Figure 2. Raster plot of a Monte Carlo simulation

We are now able to observe two different types of behavior, synchronization and desynchronization, behavior also observed by biologists. In the future, we hope to be able to explain and predict such behavior. For us, the desynchronization can be interpreted as an asymptotic convergence to a stationary state. And the synchronization as a Hopf bifurcation due to nonlinearity of our equation.

6.5. Invasion processes and modeling in epidemiology

Participants: Bedr'Eddine Ainseba, Michel Langlais, Arnaud Ducrot, Pierre Magal, Charhazed Benosman.

6.5.1. Model analysis

Arnaud Ducrot defended his "Habilitation à Diriger des Recherches" on june 25 2010 at the university Bordeaux 2 on "Ondes de reaction-diffusion et equations d'evolution en dynamique des populations".

- The existence of travelling wave solution for an epidemic system including criss-cross transmission spatially structured as well as taking into account the age since infection has been considered by A. Ducrot, P. Magal and S. Ruan. (Arch. Rational Mech. Anal. 2010).
- M. Alfaro and A. Ducrot studied the generation and propgation of interface for the Fisher-KPP equation leading to free boundary problems describing the long-time behavior of spatial invasion of invasive species (to appear in CPAA 2011).
- A species invasion model has been studied by A. Ducrot. The model under consideration takes into account spatial dispersal of the individuals and the birth process is driven by the size (or age) of the individuals that is considered as a structuring variable. The emergence of spatio-temporal patterns (including oscillations) is proved to exist and to propagate through the spatial domain (J. Diff. Eq. 2011).
- The existence of component-wise nonnegative solutions for cross-diffusion model systems was worked out by M. Bendahmane and M. Langlais (J. Evol. Eq. 2010).
- The dynamics of solutions to a predator-prey system posed on non coincident spatial domains was analyzed by A Ducrot, V. Guyonne and M. Langlais. An interesting feature is the impact of the distributed numerical response to predation on existence of stationary solutions, their stability and the occurence of waves (DCDS-S, 2011).
- A comprehensive analysis of the spatially structured SI model with logistic dynamics and vertical transmission, including the existence of wave fronts, was developed by A. Ducrot, M. Langlais and P. Magal (CPAA, 2011).
- The complex dynamics of solutions to a singular reaction-difusion system arising in modeling predator-prey systems in a fragile environment (Courchamp and Sugihara model) begins to be understood by A. Ducrot and M. Langlais for distinct diffusivities. This will extend known results for the underlying ODE systems and the case of the singular reaction-difusion system with identical diffusivities (Gaucel and Langlais, DCDS-B 2007). This is also part of the Orchid EGIDE program with Taiwan.

6.5.2. Hantaviruses

Models for the spread and persistence of Hantavirus with seasonality are analyzed by L. Allen, M. Langlais and C. Wesley (M.B.E. 2010), supplying a sound mathematical analysis to earlier works by C. Wolf et al. (2006) in the periodic case, e.g. computing R_0.

6.5.3. Toxoplasma gondii

Together with E. Gilot-Fromont, M.L. Poulle and M. Lélu (T.P.B. 2010), M. Langlais derived invasion and persistence criteria in simple ODE models for Toxoplasma *gondii* spread involving cat and rodent populations and contamination through the environment. The case of spatially distributed populations over fragmented domains is currently analyzed : quite complex dynamics occur. New results were presented at two dedicated workshops at NIMBioS in May and November 2010 by M. Langlais.
This topics of fragmented populations dynamics is also related to ANR ADHOC program.

6.5.4. Blue Tongue Virus

Together with P. Ezanno, M. Charron and H. Segeers, M. Langlais derived invasion and persistence criteria in a single cattle herd / midge population system depending on whether this herd is a fattening one or one with insemination. Vertical transmission and vaccination play important roles. Results were presented at CMPD3 in Bordeaux by M. Charron.

6.5.5. Root network development

A rather conceptual model system for the growth or a root network is built in a collaborative framework by A. Bonneu, Th. Fourcaud, A. Ducrot, M. Langlais (IEEE CS, 2010).

6.5.6. Plant-pathogen systems

Participants: Jean-Baptiste Burie, Michel Langlais, Youcef Mammeri.

Model building, simulation and analysis was further developed for the powdery mildew epidemic by JB Burie and M. Langlais in collaboration with A. Calonnec. A reliable aggregated model at the plant scale is now available (AoB, 2010). This is part of ANR ARCHIDEMIO.

First results for the powdery mildew/vine pathosystem show that the plant growth (leaf emergence rate) is the key factor for the development of the pathogen. This confirms the relevancy of our modelisation approach that takes explicitly into account the growth of the host. The mathematical analysis of the aggregated model also indicates when the risk is maximal for the development of the pathogen: at the beginning of the growing season and after the shoot toppings. After shoot topping, the risk can be minimized by keeping the vigour of the vine at a low level.

In the frame work of ARC INRIA M2A3PC the apple scab system is under consideration, as well as using OpenAlea platform in Montpellier to ease numerical simulations and produce dedicated animations and visualization. Available results were presented by Y. Mammeri at the FSPM Conference at UC Davis in September 2010. Model building, simulation and analysis was further developed for the powdery mildew epidemic by JB Burie and M. Langlais in collaboration with A. Calonnec (INRA). Models are derived at two different spatio-temporal scales. First at a local scale, the wine tree level, the building and analysis of a sharply detailed discrete model allows to better understand the local contamination out of a primary focus at the beginning of Spring. A reliable aggregated model at the plant scale is now available (AoB, 2010). This is part of ANR ARCHIDEMIO. Next at a meso scale, the plot level, a Reaction-Diffusion model for short and long distances dispersal of spores coupled to a system of ODEs for local production of spores is derived and analysed with A Calonnec, J Burie and A Ducrot to understand the global dynamics over a year.
In the frame work of ARC INRIA M2A3PC the apple scab system is under consideration, as well as using OpenAlea platform in Montpellier to ease numerical simulations and produce dedicated animations and visualization. Available results were presented by Y. Mammeri at the FSPM Conference at UC Davis in September 2010. Model building, simulation and analysis was further developed for the powdery mildew epidemic by JB Burie and M. Langlais in collaboration with A. Calonnec. A reliable aggregated model at the plant scale is now available (AoB, 2010). This is part of ANR ARCHIDEMIO.

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In the frame work of ARC INRIA M2A3PC the apple scab system is under consideration, as well as using OpenAlea platform in Montpellier to ease numerical simulations and produce dedicated animations and visualization. Available results were presented by Y. Mammeri at the FSPM Conference at UC Davis in September 2010.

6.5.7. A mathematical model of of HIV-1 infection

Participants: Bedr'Eddine Aïnseba, Mahiedine Kouche.

Figure 3. Simulation of a growing vinestock contaminated by powdery mildew using OpenAlea platform (work of Y. Mammeri et al.)(the leave colour from green to red indicates the severity of the disease).

In this work we derive a model describing the dynamics of HIV-1 infection in tissue culture where the infection spreads directly from infected cells to healthy cells trough cell-to-cell contact. We assume that the infection rate between healthy and infected cells is a saturating function of cell concentration. Our analysis shows that if the basic reproduction number does not exceed unity then infected cells are cleared and the disease dies out. Otherwise, the infection is persistent with the existence of an infected equilibrium. Numerical simulations indicate that, depending on the fraction of cells surviving the incubation period, the solutions approach either an infected steady state or a periodic orbit.

6.5.8. Resistance to chemotherapeutic treatments and P-gp

Participant: Pierre Magal.

In order to understand further the transfer mechanisms in the resistance phenomena to chemotherapeutic treatments, some new biological experimentations have been developed. The conclusions of these new biological experiments show that we need to understand two types of transfers processes: 1) direct transfers by local contacts (in space) between cells; 2) indirect transfers through released of P-gp into the culture liquid contains in the dish. The first process (direct transfers) occurs through tunneling nanotubes, and it becomes now clear that the space variable is necessary to understand such a transfers processes. In the second process (indirect transfers) the cells release P-gp in the liquid used for the culture of cells, then P-gp diffuses into the liquid, and finally is recaptured by the cells (in particular by sensitives cancer cells).

Next, our goal is to understand how to model such a transfer processes in space. Ultimately, our goal is to include both direct and indirect transfers and to fit the measure with the derived models.

6.6. The blood production system

Participants: Bedr'Eddine Ainseba, Chahrazed Benosman.

6.6.1. Global dynamics of hematopoietic stem cells and differentiated cells in a chronic myeloid leukemia model

We consider a mathematical model describing evolution of normal and leukemic hematopoietic stem cells (HSC) and differentiated cells in bone marrow.We focus on chronic myeloid leukemia (CML), a cancer of blood cells resulting from a malignant transformation of hematopoietic stem cells. The dynamics are given by a system of ordinary differential equations for normal and leukemic cells. Homeostasis regulates the

proliferation of normal HSC and leads the dynamics to an equilibrium. This mechanism is partially efficient for leukemic cells. We define homeostasis by a functional of either hematopoietic stem cells, differentiated cells or both cell lines. We determine the number of hematopoietic stem cells and differentiated cells at equilibrium. Conditions for regeneration of hematopoiesis and persistence of CML are obtained from the global asymptotic stability of equilibrium states.We prove that normal and leukemic cells can not coexist for a long time. Numerical simulations illustrate our analytical results. The study may be helpful in understanding the dynamics of normal and leukemic hematopoietic cells. This work has been published in the Journal of Marthematical Biology.

6.6.2. Optimal control for resistance and suboptimal response in CML

The mathematical modelling of hematopoiesis received a significant attention in the last few years. However, the treatment of hematological diseases is less investigated by optimal control tools. In this paper, we consider the dynamics of chronic myeloid leukemia based on a four dimensional model. First we analyze the global dynamics of normal and cancer hematopoietic stem cells and differentiated cells using the principle of BendixsonDulac. Then we introduce some nonlinear effects of imatinib treatment over a fixed period of time. We represent therapy effects as an optimal control problem to minimize the cost of treatment and the level of cancer cells. The influence of imatinib onto the division and the mortality rates of cancer cells produces the suboptimal response, resistance and recovery forms. This work has been published in Mathematical Biosciences.

6.6.3. CML dynamics: optimal control in an age-structured stem cell population

We build an age-structured model for the growth of hematopoietic stem cells HSC in case of CML. Imatinib treatment is analyzed as an optimal control problem. The control represents the drug dosage over a fixed treatment period. We show that optimal control is maximal at the beginning of treatment and declines over time for patients in initial stages of the disease.

6.7. Modeling in electrocardiology

Participants: Bedr'Eddine Ainseba, Jacques Henry, Simon Labarthe, Alejandro Lopez Rincon.

6.7.1. Modeling the electrical activity of the atria

The PhD thesis of Simon Labarthe, just starting, is oriented in a first step towards the simulation of the atrial fibrillation. It has started with a numerical implementation of a monodomain model on a 2D, square domain using the finite element method. The anisotropy due to the orientation of the fibers has been incorporated to the simulation. Furthermore a numerical implementation of the main models of the ionic activity of the myocardial cells (Beeler-Reuter, Luo-Rudy and Courtemanche-Ramirez-Nattel model) has been carried out.

6.7.2. Electrocardiographic imaging

The PhD thesis of Alejandro Lopez is devoted to improving the resolution of the inverse problem to recover the potential map on the heart from the measured potentials on the torso. He is starting by solving the direct electrostatic problem in the chest in 2D by a P1 finite element method.

6.8. Nosocomial diseases

Participants: Pierre Magal, Arnaud Ducrot, Ousmane Seydi.

Supervised by P. Magal and A. Ducrot, O. Seydi started his Phd thesis in October 2010. The topics he is working on are concerned with singular perturbation theory for partial differential equations with applications to nosocomial infection transmission. A manuscript dedicated to singular perturbation analysis for some age structured model is in preparation. This work has been initiated during a mission in China july-august 2010 supported by Egide and INRIA. . More recently, we have been working with X. Lu (MD and PU at Beijing Tongren Hospital) on the spread of multi-drug resistant in Beijing Tongren Hospital.

7. Other Grants and Activities

7.1. National Initiatives

- M Langlais was a co-investigator (partner 6 and single non INRA member) of the proposal ARCHIDEMIO 2009-12, Modelling of the interactions between plant development, canopy architecture and fungal aerial diseases epidemics for a sustainable crop management, funded by ANR SYSTERRA with B Tivoli as principal investigator.
- M Langlais was the principal investigator of ARC INRIA M2A3PC 2009-10, Modelling the airborne dispersal of a pathogen over a highly structured and anthropized perennial plant cover crop, a collaborative program with 3 EPI INRIA and 5 INRA teams.
- M Langlais was a member of the proposal ADHOC 2010, Co-viability modeling of fisheries and marine biodiversity, funded in 2009 by ANR “La 6me extinction" with L Doyen as principal investigator.
- M Langlais was a member (and single non INRA member) of the INRA network EpiArch, dedicated to plant architecture and plant-pathogen systems, chaired by B. Tivoli.
- M Langlais is the co-advisor with T Fourcaud of the Ph.D A Bonneu dedicated to *modelling the growth of tree roots*. This is supported by CIRAD at UMR AMAP in Montpellier.
- M Langlais is a co-advisor with H Seegers, P Ezzanno of the Ph.D of M Charron dedicated to *modelling the spread of the blue-tongue disease*. This is supported by an ASC position from INRA at Ecole Nationale Vétérinaire in Nantes.
- G. Dumont is partly supported for his PhD thesis by a grant from region Aquitaine and partly from scholarship of CNRS.
- S. Labarthe is partly supported for his PhD thesis by a grant from region Aquitaine.

7.2. International Initiatives

- A. Ducrot and M. Langlais belong to a french-japanese program, LIA - 197 CNRS France-Japon (2007/2010), ReaDiLab, Biomathematics Modelling and Analysis Laboratory co-chaired by D. Hilhorst (Paris 11) et J. Demongeot (Grenoble), M. Mimura (Meiji U.) et H. Matano (Tokyo U.).
- J.B. Burie, A. Ducrot and M. Langlais won an Orchid collaboration program for 2010-11 on “Singular reaction-diffusion systems and persistence phenomena" with Guo Jong-Shenq, Fu Sheng Chen, Tsai Je-Chiang and Wu Chin-Chin at the National Taiwan Normal University.

8. Dissemination

8.1. Animation of the scientific community

- M Langlais was a member of the AERES evaluation committee for INRIA Grenoble Rhône-Alpes on March 2010.
- M Langlais was a member of the AERES evaluation committee for Grenoble 3 University on June 2010.
- M Langlais was a member of a hiring committee for a Maître de Conférences / Chaire CIRAD in Mathematics at Ile de la Réunion University.
- M Langlais organized 2 meetings in Bordeaux and Montpellier within the framework of ARC INRIA M2A3PC.

- M. Langlais co-organized with A. Calonnec the yearly meeting of ANR ARCHIDEMIO with its Scientific Board in Bordeaux in March 2010.
- M Langlais is a member of the Editing Committee of Journal of Biological Dynamics.
- M Langlais was a co-organizer of a NIMBioS Investigative Workshop on “Mathematical modeling of life cycle, stage conversion, and clonal expansion of *Toxoplasma gondii*", May 13-15, 2010. See the website http://www.nimbios.org
- JB Burie was the treasurer of CMPD3 (3rd conference on Computational and Mathematical Population Dynamics) held in Bordeaux in June 2010.
- JB Burie and P Magal coorganize a weekly seminar on population dynamics.
- B. Ainseba is head of the UFR “sciences et modélisation” at the university Bordeaux 2
- B. Ainseba is head of the IMB UMR CNRS 5251 Team "Life modelling".
- B. Ainseba was head of the CMPD3 Conference, May 31, June 4, 2010.
- B. Ainseba was a member of a hiring committee for a Professor in Mathematics at Bordeaux 2 univeristy.
- J. Henry is chairman of IFIP TC7.

8.2. Participation to conference, seminars

- G. Dumont presented the joint work with J. Henry and O. Tarniceriu “A numerical solver for the population density function for neural network” at the conference CMPD3, Bordeaux, may 31-june 4.
- O. Tarniceriu presented the joint work with J. Henry and G. Dumont “Analysis of synchronization in a neural population by a population density approach” at the conference CMPD3, Bordeaux, may 31-june 4.
- M. Langlais gave a talk at “Colloquium en Dynamique de Populations", ENIT Tunis, 5-6 March 2010.
- M. Langlais gave a talk at Department of Mathematics, Nashville (TN), May 11 2010.
- M. Langlais gave a talk at NIMBioS Investigative Workshop on “Mathematical modeling of life cycle, stage conversion, and clonal expansion of *Toxoplasma gondii*", Knoxville (TN), 13-15 May 2010.
- M. Langlais gave a talk at “Journées Scientifiques" of LMDP, Marrakech, 25-26 June 2010.
- M. Langlais gave a talk at Journées SM2A, session “Biomaths", Rabat, 28-30 June 2010.
- M. Langlais gave a talk at the 2010 General Meeting of INRA MIA Department, La Grande Motte, 06 october 2010.
- M Langlais gave a talk at the Workshop “Reaction-Diffusion Systems: Experiments, Modeling, and Analysis", Paris 11(Orsay), October 21-22 2010.
- M. Langlais gave a talk at NIMBioS Investigative Workshop on ‘Modeling Wildlife and Virus Zoonoses", Knoxville (TN), 8-10 November 2010.
- A. Ducrot gave a seminar at the University of Montpelier 2, February 2010.
- A. Ducrot gave a seminar at National Taiwan University (Taiwan), March 2010.
- A. Ducrot gave a seminar at National Chung Cheng University (Taiwan), March 2010.
- A. Ducrot gave a plenary lecture at CMPD 3 that held in Bordeaux, May 31 to June 4 2010.
- JB Burie gave a talk at CMPD3, Bordeaux, June 2010, entitled : ’Modeling and simulated a fungal disease epidemic over a heterogeneous plot’.

- JB Burie gave a seminar at Taida Institute for Mathematical Sciences, Taiwan National University in april 2010 entitled: 'A reaction-diffusion system for the modeling of the propagation of a fungal disease over a vineyard'.
- JB Burie gave a seminar at the Institute of Environmental Systems Research, University of Osnabrück, Germany in june 2010 entitled: 'Some models for the propagation of a fungal disease of vine: from the plant scale to the vineyard scale'.
- JB Burie presented the ARC INRIA M2A3PC at the "Journées nationales des ARC, ADT et Actions exploratoires", december 2010, at INRIA-Rocquencourt.
- J. Henry gave a talk at the "session plénière de l'académie Hassan II :Risques d'épidémies ou de pandémies - maladies émérgentes ou réémergentes - anthropozoonoses" Rabat 17-19 février 2010 on "modélisation mathématique en épidémiologie, maladies nosocomiales,résistance aux antibiotiques, d'après les travaux de P. Magal".
- J. Henry gave a talk at the BCAM-INRIA Bordeaux meeting in Bordeaux september 22-23, on "Factorization of linear elliptic boundary value problems in non cylindrical domains; Expansion to non linear cases"

8.3. Teaching

- A. Ducrot gave a series of lectures at École-Atelier sur l'Épidémiologie INRIA-IRD-MITACS at Saint-Louis (Senegal), 19-27 July 2010.
- M. Langlais teaches a course on "Deterministic mathematical models in demography and epidemiology" – 30 hours – at the Master level, Universities Bordeaux 1 and 2.
- M. Langlais teaches a course on "Mathematical Modelling" – 10 hours – at the Master level, University Bordeaux 2

9. Bibliography

Major publications by the team in recent years

[1] B. AINSEBA. *Age-dependent population dynamics diffusive systems*, in "Discrete and Continuous Dynamical Systems- Series B", 2004, vol. 4, n^{o} 4, p. 1233–1247.

[2] B. AINSEBA, S. ANITA, M. LANGLAIS. *Internal stabilizability of some diffusive models*, in "Journal of Mathematical Analysis and Applications", 2002, vol. 265, p. 91–102.

[3] B. AINSEBA, F. HEISER, M. LANGLAIS. *A mathematical analysis of a predator-prey system in a highly heterogeneous environment*, in "Differential and Integral Equations", 2002, vol. 15, n^{o} 4, p. 385-404.

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