INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team ANUBIS

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

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 1^{st}, 2009.

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2. Overall Objectives

2.1. Overall Objectives

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 ([41]), 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.

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. [40]. 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. [60], [64]. 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. [51], [63]. This age-structure although already intensively studied in our team in the past, cf. [3], [9], [65], 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.[9].

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. [2].

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. [40], [42]. 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. [47].

3.1.2. Invasion processes in fragile isolated environments

In a series of joint works with F. Courchamp and G. Sugihara, e.g., [8], 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. [57]. 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. [57]; see also [47]).

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 [50]. 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. [47], [43], or on macroprarasites (*Diplectanum* *aequens*) infesting sea-bass (*Dicentrarchus labrax*) populations, cf. [44]. 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. [43], [59], 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. [46].

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.

3.1.4. Direct movement of population

The classical chemotaxis model introduced by Keller and Segel (1971) demonstrates the emergence of endogenous patterns, including travelling waves. The appearance of advection-driven heterogeneity in relation to single and multispecies ecological interactions was studied by Levin (1977), Levin and Segel, (1976), Okubo (1980), Mimura and Murray (1978), Mimura and Kawasaki (1980), Mimura and Yamaguti (1982), and many other authors. These studies form a theoretical basis for modeling complex spatio-temporal dynamics observed in real systems.

Several field studies measuring characteristics of individual movement confirm the basic hypothesis about the dependence of acceleration on a stimulus gradient. For example, acceleration vectors of individuals in fish schools (Parrish and Turchin, 1997) and in swarms of flying insects (Okubo and Chiang, 1974; Okubo *et al.*, 1977) are directed towards the centroid of such dynamically stable formations. The acceleration increases with distance from this point, being maximal on the edges (where the density gradient is maximal) and equal to zero at the centroid position (where the density gradient is zero).

We will focus our attention to study chemotaxis phenomena of bacteria population, we also investigate the effect of prey-taxis and the effect of pursuit-evasion in prey-predators interactions.

We will consider a system of partial differential equations describing two spatially distributed population in “predator-prey” relationship with each other. Assuming that, locally (i.e., at each point and each instant), predators attack prey following the familiar Lotka-Volterra interaction term, we intend to investigate how the heterogeneities induced by the behavioural mechanisms affect the functional relationships between the population abundances.

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. [43], [48].

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 [14].

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 [52]. 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 ([56]). 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 (cf. 3.4.4.1). 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 [15]. 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 [37], [38], [39], [1]). 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 [37], [38], [39], [1], 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.

3.4. Application fields and collaborations with biologists

We present here collaborations on specific biological modeling problems.

3.4.1. Epidemiology

(B. Ainseba, A. Ducrot, M. Langlais)

3.4.1.1. 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.

3.4.1.2. 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 .

3.4.1.3. Toxoplasma gondii

Toxoplasma gondii (T. gondii) is a most successful parasite infecting a wide range of intermediate hosts (mammals, rodents and birds). Up to 30Toxoplasmosis can cause life-threatening encephalitis in immunocompromised persons (AIDS patients, recipients of organ transplants, cancer chemotherapy). Infection acquired during pregnancy may cause severe problems to the fetus (babys eyes, nervous system, skin, and ears). Toxoplasmosis may also lead to neuropsychiatric disorders, e.g. schizophrenia.

This is a pluridisciplinary and collaborative work with Ecole Vétérinaire de Lyon, CERFE and French National Reference Center for Toxoplasmosis at University of Limoges and Reims, funded by AFSSET. A multipatch model coupling SIR epidemic models and predator-prey systems is currently under study.

3.4.1.4. Blue Tongue Virus

Bluetongue (BT) is a vector-borne disease of ruminants transmitted by biting midges (Culicoïdes). BT virus (BTV) serotypes spreading in southern Europe before 2006 could infect ruminants, cattle being subclinically infected. Since 2006, BTV8 infected cattle may show clinical signs. Current epizootics have a large socioeconomic impact on the international trade of animals and their productivity. Strategies to control their consequences and the spread of the virus were set up such as vaccination. In Europe, vaccination against BTV8 was recommended in 2008. However, a partial coverage and waning immunity weaken the efficacy of such a strategy.

This is a pluridisciplinary and collaborative work with Ecole Vétérinaire de Nantes, funded by INRA. A large ODE model at a single cattle herd scale is currently studied before tackling the more realistic spatial problem.

3.4.2. Blood cells

(M. Adimy, B. Ainseba, A. Ducrot, A. Noussair) Due to the departure of M. Adimy to Lyon to create the team MAIA, this research is decreasing in our team.

3.4.2.1. Generating process for blood cells (Hematopoiesis)

Cellular population models have been investigated intensively since the 1960's (see, for example, Rubinow and Lebowitz [58]) and still interest a lot of researchers. This interest is greatly motivated, on one hand, by the medical applications and, on the other hand, by the biological phenomena (such as oscillations, bifurcations, traveling waves or chaos) observed in these models and, generally speaking, in the living world (Mackey and Glass [53]).

Hematopoiesis is the process by which primitive stem cells proliferate and differentiate to produce mature blood cells. It is driven by highly coordinated patterns of gene expression under the influence of growth factors and hormones. The regulation of hematopoiesis is about the formation of blood cell elements in the body. White and red blood cells and platelets are produced in the bone marrow whence they enter the blood stream. Abnormalities in the feedback are considered as major suspects in causing periodic hematological diseases, such as auto-immune hemolytic anemia, cyclical neutropenia, chronic myelogenous leukemia.

Cell biologists classified stem cells as proliferating cells and resting cells (also called G_0-cells) (see Mackey [54]). Proliferating cells are committed to undergo mitosis a certain time after their entrance into the proliferating phase. Mackey supposed that this time of cytokinesis is constant, that is, it is the same for all cells.

Based on [37], [38], [39], , we propose a more general model of hematopoiesis. We take into account the fact that a cell cycle has two phases, that is, stem cells in process are either in a resting phase or actively proliferating. However, we do not suppose that all cells divide at the same age, because this hypothesis is not biologically reasonable. We obtain a system of two nonlinear partial differential equations. Due to cellular replication, the system exhibits a retardation of the maturation variable and temporal delay depending on this maturity.

3.4.2.2. *Malignant proliferation of hematopoietic stem cells*

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 [54], 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.

3.4.2.3. *Socio-biological activities of the Immune-System cells*

In recent years, much effort has been put into the mathematical foundation of models of Tumor-Immune System Interaction. The aim is the description of the cell distribution as a function of time and a physiological state which includes both mechanical and socio-biological activities. . This new class of models of population dynamics with stochastic interation, is characterized by a mathematical structure similar to the one of the Boltzmann equations. In this theory it is assumed that the system under consideration consists of a very large number of cells that can interact. This is the case in immunology problems and in particular in the competition between tumors and immune system. The motivation is that the stage of the early growth of a tumor belongs to the so-called free cells regime, in which the tumor cells are not yet condensed in a macroscopically observable spatial structure and the interactions between tumor and immune system, occur at a cellular level. This makes the kinetic approach particularly appropriate.

However the development of numerical schemes which gives precise calculations of these class of models, is desirable and hopefully the work envisaged here is a step towards obtaining such algorithms (see B. Aylaj and A. Noussair *State trajectory analysis of a nonlinear kinetic model of multi-species population dynamics* MCM in press doi:10.1016/j.mcm.2008.07.022). The question of how to discretize a given model, in particular the treatment of the discrete encounter operator together with the special treatment of the nonlocal boundary condition, represents an interesting part. Convergence properties of numerical schemes for these models seem to be a rather unexplored area. Least squares technique must be developed for identifying unknown parameters of the models. Convergence results for the parameters must be investigated and established. Ample numerical simulations and statistical evidence will be provided to demonstrate the feasibility of this approach.

3.4.3. Modeling in viticulture; collaboration with INRA

(B. Ainseba, J.B. Burie, J. Henry, M. Langlais, A. Noussair)

This is a joint research with different groups of UMR “Santé végétale” of INRA, Villenave d’Ornon.

3.4.3.1. Integrated Pest Management in viticulture.

Integrated Pest Management (IPM) is an approach to solving pest problems by using knowledge on the pest to prevent them from damaging crops. Under an IPM approach, actions are taken to control insects, disease or weed problems only when their numbers exceed acceptable levels. The goal is to promote and coordinate research on integrated control strategies in viticulture which reduce inputs of pesticides and maximize the effects of natural enemies, thereby minimizing impacts on the environment.

A first objective of our work here is to progress in the risk assessment of the moth Lobesia botrana. Host plant and grape varieties eaten by the larvae modify the protandry between males and females, the female fecundity, the egg fertility and thus the demography of the offspring, with its consequences on the temporal dynamics of oviposition and thus grape damages see [55], [61], and [62]. We are developing models and numerical methods including parameter estimation procedures to follow the level of the population in a vineyard.

A second objective to develop a numerical code to model a " Mating disruption technic" for insect control: Pheromone are volatile chemical scents involved in communication between individuals of the same species. One type that is used in pest management is called sex pheromone. Individuals of one gender produce and liberate the chemical to attract individuals of the other sex. One novel insect control approach, ”pheromone mediated mating disruption”, interrupts the reproductive cycle so that no eggs are produced. The main consequence of mating disruption is a decrease of female active space. A last biological control is narrowly defined here as the use of predators, parasites, pathogens, competitors, or antagonists to control a pest.

3.4.3.2. Spreading of a fungal disease over a vineyard

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 [7]. Moreover in the 1D spatial case we have developped new tools to exhibit traveling fronts for complex models [45].

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.

3.4.4. Modeling in neurobiology

(B. Ainseba, J. 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.

3.4.4.1. MEG-EEG inverse problem

One of the goals of MEG-EEG is to reconstruct human functional brain activity images with a much better time resolution than functional MRI. Starting from electric potential and magnetic field external measurements, it consists in recovering internal electric dipoles which generated them. The Odyssée project-team animates a multidisciplinary group on this research theme. We intend to go on participating in these researches especially with respect to the methodology of inverse problem. On the one hand one has to set the problem in an as less instable as possible form. On the other hand the factorization method can be used twice : the optimality system for the inverse problem set as a control is linear and includes two coupled elliptic problems. By a space invariant embedding as previously, one can obtain a factorization in first order Cauchy problems and decouple state and adjoint state as in [49] at the same time. Due to the linearity of the problem, the resolution of the optimality system is transformed in a Cauchy problem on a family of surfaces starting from the electrodes and sweeping over the domain to the surface of dipoles. At each time an inverse problem is to be solved for the measured data and so there is a family of inverse problem to be solved indexed by time. The factorization computation being done once for all, the method should be quite efficient. This research is carried on within the Enée 06 associated team with A. Ben Abda at LAMSIN in Tunis.

3.4.4.2. Modeling populations of neurons by a population density approach

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. New Results

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

Participants: Jacques Henry, Maria Orey.

We are pursuing the development of the theory of factorization of boundary value problems as described in 3.1. One of the main mathematical difficulties of this theory from the mathematical standpoint is that the full justification of the computation needs the study of a Riccati equation for unbounded operators. In previous papers it has been done by a Galerkin method or within the Hilbert-Schmidt framework. Both method are lengthy and technical. The Yosida regularization has been used successfully in the case of the Laplacian in a cylinder but the generalization to other operators and domains seems difficult. A new method has been investigated: a regularization of the original problem using the square of the operator tangential to the moving surface leads to a problem that can be directly interpreted as the optimality system for the optimal control of a parabolic equation. The justification of the Riccati equation for such a problem is now clearly established. This is also the case in non cylindrical domains from a paper by J. P. Zolesio. This work has been presented at the IFIP TC-7 conference in Buenos Aires.

As explained in 3.1 boundary value problems factorisation can be viewed as an infinite dimensional extension of the block Gauss factorisation for matrices. The block are related to the variable section. A natural question that arises then is what is the extension of the full Gauss factorisation. A preliminary investigation of this question on the Laplacian in a rectangle leads to a solution that needs the factorisation of the operator solution of the Riccati equation. This is also related to the spatial factorisation of parabolic problems.

The study of the QR factorization of boundary value problems, which is the subject of Maria Orey's thesis is pursued. A chapter of a book to be published in 2010 by Intech has been written jointly by M. Orey, B. Louro and J. Henry. Improved derivation and justification of the calculation of the factorisation of the normal equation of the problem set in the least squares sense is presented there.

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

Participants: Jacques Henry, Fadhel Jday.

This is the topic of F. Jday's thesis co-supervised by A. Ben Abda and J. Henry within the "équipe associée" Enée 06. The data completion problem for elliptic equations consists in finding the best approximation of lacking boundary data on certain part of the boundary using extra measurements on other parts of the boundary. F. Jday investigates the data completion problem in a cylindrical domain where the factorisation method is most easily applied. It is formulated as a control in the Kohn-Vogelius setting with two states. There is no need to introduce adjoint variables in this case as the cost function can be expressed directly in terms of the control variables with the use of the operators furnished by the factorisation. New boundary conditions as the Fourier conditions have been studied. Numerical results show the benefits of the method when the same problem has to be solved with various data.

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

Participants: Arnaud Ducrot, Pierre Magal.

4.3.1. Size structured populations and integrated semigroup theory

A joint work of P. Magal, J. Chu, S. Ruan and A. Ducrot studied the possibility to have Hopf bifurcations for some size structured model with random noise by using the theory of integrated semigroup. After reformulating the problem in term of abstract Cauchy problem, the authors studied the characteristic equation associated to the problem to study bifurcations in the dynamical system. This work provides a fine description of the resulting dynamics. This study leads to the appearance of new bifurcation phenomena. It has been published by Journal of Differential Equations [27].

In a joint work of P. Magal and S. Ruan, the existence and smoothness of the center manifold for abstract non-densely defined Cauchy problems is investigated. This is allows in particular to study the existence the bifurcation properties of the various class of infinite dimensional dynamical system, such as delay differential equations, age-structured models, and some class of parabolic problems with non-linear and non-local boundary conditions. In this work an application to the existence of Hopf bifurcation to a class of age structured model has been studied. The work has been published in 2009 the Memoirs of American Mathematical Society.

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 will appear in Journal of Evolution Equations [30].

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

Participants: Jacques Henry, Gregory Dumont, Oana Tarniceriu.

Modeling of the interaction of neuron population between basal ganglia is going on within the collaboration with the team “Basal Gang” of UMR 5227. The research of this team is focused at studying the basal ganglia and in particular the mechanisms of selection of action. This joint research is sponsored by the “neuroinformatique” program of CNRS.

The master 2 internship of Gregory Dumont was dedicated to study the numerical approximation to population density equation for the Izhikevich model. It has already been studied by Julien Modolo during his PhD thesis but the numerical scheme he used showed an important numerical diffusion. This is incompatible with the objective of simulating synchronization phenomena which are represented by a concentration of the population density around a point in the state space. G. Dumont tested various numerical schemes on the population density equation in the case of uncoupled neurons. In that case if the initial condition consists in all the neurons being in the same state (Dirac mass) the solution should remain a Dirac mass moving in the state space. This is quite difficult to obtain numerically in particular due to the stiffness of the Izhikevich model where the velocity varies of several porder of magnitude. G. Dumont has experimented a variable discretization in potential and a refinement with respect to the recovery varaiable. The method was of finite volume type with flux limitation. The most satisfactory results were obtained with a WENO scheme of order 5. G. Dumont has now begun a PhD thesis in the team on the modeling on the cortico-basal ganglia-thalamo loop with a financial support of CNRS and Région Aquitaine.

During her one year postdoc O. Tarniceriu investigated the issue of synchronisation of a population of neuron weakly coupled using the population density approach based on the Izhikevich model. Considering neurons having the same rhythmic activity, the model was first transformed to phase density population. Then by analogy to the Malkin’s Theorem, a slow phase deviation equation for the weakly coupled population was derived. Sufficient conditions for the stability of the syncrhonized solution were obtained.

4.5. Invasion processes and modeling in epidemiology

Participants: Bedr’Eddine Ainseba, Michel Langlais, Arnaud Ducrot, Pascal Zongo, Mahieddine Kouche, Pierre Magal, Chahrazed Benosman.

The research program in mathematical population dynamics as presented in 3.1 is mostly dedicated to predator-prey sytems or host-parasite sytems in heterogeneous environments. The new results include :

- A quasi comprehensive description of the complex intertwined dynamics for a SI epidemic model with density dependent incidence and a host population exhibiting an Allee effect is derived in a joint work with H Malchow and F Hilker. Typically we showed that unforeseen tri-stability dynamics, oscillations, limit cycles and Bogdanov-Takens bifurcation can occur. A a consequence the host population can also go extinct for SI models with density dependent incidence. This may have profound implications for biological conservation as well as pest management.
- A comprehensive analysis of the spatially structured SI model with logistic dynamics and vertical transmission, including the existence of wave fronts, is currently developed with A. Ducrot and P. Magal.

Related analysis for cross-diffusion systems is worked out with M. Bendahmane.

- New results with S Anita and W.E. Fitzgibbon concerning the stabilisation of predators in a spatially distributed predator-prey system show that reducing the prey density may drive predators to extinction. This includes the case of non coincident spatial domains; in that case locally reducing prey density is closely related to herd management to prevent prey from unwelcome wild predators.
- The underlying dynamics of solutions to this predator-prey system posed on non coincident spatial domains without controllability effects is analysed with A Ducrot. 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.
- New results concerning the spread of a fungal disease in a vineyard 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 with A Calonnec et al. allows to better understand the local contamination out of a primary focus at the beginning of Spring. 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.
  This is also the core of ANR ARCHIDEMIO and of the ARC INRIA M2A3PC. A friendly user interface for the discrete model at the plant scale was designed by two M1 students supported by ANR and ARC.

4.5.1. *Toxoplasma gondii*

With E. Gilot-Fromont, M.L. Poulle and M. Lélu we look for invasion and persistence criteria in simple ODE models featuring cat and rodent populations spatially distributed over spatial domains. First results were presented at EPIDEMICS 2 in Athens, december 09.

4.5.2. *Blue Tongue Virus*

With P. Ezanno, M. Charron and H. Segeers we look for 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. First results were presented at EPIDEMICS 2 in Athens, december 09.

4.5.3. *Travelling waves for epidemic models*

With P. Magal we investigate the existence of travelling wave solution for an age structured Kermack and McKendricks model with diffusion where both infectivity and recovery can depend on the duration of infection . We prove in [34] that the basic reproduction number leads to the existence or non-existence of such particular solutions. Moreover, when such solutions exist, there is a continuum of admissible wave speed.

With P. Magal and S. Ruan, we extend a previous work to a more general framework of multigroup interactions [28]. This means that a disease may circulate within several species and can be transmitted from one species to an other one. Together with some irreductibility assumptions on the graph of transmission, we provide the existence a travelling wave solutions in this context. Here again, the global basic reproduction number leads to the existence and non-existence of such solutions.

4.5.4. *Malaria epidemiological modeling*

P. Zongo is a PhD student at the university of Ouagadougou, co supervised by A. Ducrot. He defended his PhD in May 2009. He has an AUF financial support. He works on a model of malaria development in endemic areas. New results obtained with A. Ducrot to understand the dynamics of the ODE model by using basic reproduction number theory as well as bifurcation theory have been published in Journal of Biological dynamics [29].

With A. Ducrot and J. Arino, P. Zongo studies a new metapopulation model for malaria development. The main idea is to understand what is the effect of migration on malaria epidemics. Moreover we aim to understand the role of the migration from rural to urban area on the transmission of malaria. This work has been submitted to Journal of Mathematical biology.

4.5.5. Brucellosis

Brucellosis is a serious animal (ovine, bovine,...) disease that can be transmitted to humans. This disease causes important economical damages in north Africa and south America. In this work , we construct and analyse an ovine brucellosis mathematical model. In this model, the population is divided into susceptible and infected subclasses. Susceptible individuals can contract the disease in two ways: (i) direct mode - caused by contact with infected individuals; (ii) indirect mode - related to the presence of virulent organisms in the environment. We derive a net reproductive number and analyse the global asymptotic behaviour of the model. We also perform some numerical simulations, and investigate the effect of a slaughtering policy. (Journal of Biological Dynamics, Volume 4, Issue 1 2010 , pages 2 - 11)

4.5.6. Modeling transfers of proteins in cancer cells

In a joint work with P. Hinow, F. Le Foll, G. F. Webb, P. Magal studies the problem of transfer in a population structured by a continuum variable corresponding to the quantity being transferred. The transfer of the quantity occurs between individuals according to specified rules. The model is of Boltzmann type with kernels corresponding to the transfer process. We prove that the transfer process preserves total mass of the transferred quantity and the solutions of the simple model converge weakly to Radon measures. We generalize the model by introducing proliferation of individuals and production and diffusion of the transferable quantity. It is shown that the generalized model admits a globally asymptotically stable steady state, provided that transfer is sufficiently small. We discuss an application of our model to cancer cell populations, in which individual cells exchange the surface protein P-glycoprotein, an important factor in acquired multi-drug resistance against cancer chemotherapy. The work has been published in 2009 SIAM J. Appl. Math.

4.6. Control in biomathematics

Participants: Bedr'Eddine Ainseba, Arnaud Ducrot.

4.6.1. Fishery ressource

With P. Auger, A. Ducrot proposes a model of fisheries involving the management of the stock by using infinite distributed delay differential equations. They prove that such a delay may induce some sustained oscillations for the density of fishes. This work will be published in Phi. Trans. Roy. Soc. A.

4.7. The blood production system

Participants: Mostafa Adimy, Arnaud Ducrot.

4.7.1. Optimization of the treatment of the Chronic Myeloid Leukemia by Imatinib

Imatinib is the main treatment of the Chronic Myeloid Leukemia (CML), with posology varying from 400 to 1000 mg per day. Some affected individuals respond to the treatment with various levels being hematologic, cytogenetic and molecular. The treatment fails in two cases. In the first case, the patient takes a long time to react, then suboptimal response occurs. In the second case, the patient resists after an initial response. We approach the effects of therapy as an optimal control problem to minimize the cost of treatment and the level of leukemic cells. Suboptimal response, resistance and recovery forms are obtained through the influence of imatinib onto the division and mortality rates of leukemic cells.

4.7.2. 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. This work has been submitted to Mathematics and Computers in Simulation.

4.8. Modeling in viticulture

This is a collaborative research with INRA Villenave d'Ornon (UMR Santé Végétale).

4.8.1. Spreading of a fungal disease over a vineyard

Participants: Jean-Baptiste Burie, Michel Langlais, Arnaud Ducrot.

This is a joint work with A. Calonnec. Using a suitable re-formulation in the form of a nonlinear integral equation with measure kernel convolutions, we were able to prove existence of travelling fronts for the previous models we considered in [7]. In particular, this framework applies to reaction-diffusion systems coupled with ordinary differential equations with or without time delay. It also applies to integro-differential system of equations. This allows to prove the existence of travelling fronts for more general models of disease propagation than the ones considered so far: the spores dispersal is not necessarly modelized by Fickian diffusion [26].

In the framework of M. Charron's Master degree internship, the code used for simulations in [7] has been improved by using a more efficient discretization method and it now also handles spatial heterogeneity. It has been used to compare the results of the mathematical model with those of the mechanistic model and with field data. This work will be the subject of a future publication.

With Pierrick Legrand (EPI Alea, Bordeaux Sud ouest), using Matlab we started to build a user-friendly front end to the code used for the simulations at the vineyard scale. It allows to easily define spatial heterogeneities for the vinestock vigors and test various cases of primary infections.

4.8.2. Prediction of insect dynamics over a vineyard

Participants: Ahmed Noussair, Bedr'Eddine Ainseba, Jacques Henry, Delphine Picart.

This research is done in collaboration with D. Thiery (INRA Villenave d'Ornon). The goal is to promote and coordinate research on integrated control strategies in viticulture which reduce inputs of pesticides. This collaboration ended in february with the defense of Delphine Picart PhD thesis.

4.9. Interactions within populations

4.9.1. Emulsion polymerization process

Participant: Ahmed Noussair.

Roughly speaking, polymerization is the formation of huge molecules (the molecules of the polymer) from smaller ones (the molecules of the monomer). In the case of emulsion polymerization this process takes place in an aqueous medium in the presence of appropriate auxiliary substances. We derive a model of coupled equations describing the emulsion polymerization process with size structure . The nonlinear size growth is modelled with a transport equation with bilinear polymerization operator while the concentrations of monomers , of appropriate emulsifier substance and the supersaturation satisfies a nonlinear system of ordinary differential equations. The inflow boundary condition is a nonlocal condition and depend on the above concentrations and on the surface coverage. We first prove global existence and uniqueness of solution to the nonlinear transport equation then and prove the existence of solutions to the full system. This research is related to the developpement of polymer-based nanotechnology delivery system for antibiotic.

4.9.2. Binary interactions in proliferating multispecies cells population

Participant: Ahmed Noussair.

We examine existence and uniqueness of a global solution and some basic mathematical issues associated with the development of a numerical scheme for a model of a binary interactions between of multispecies cells. The system consists of nonlinear transport equations with bilinear operator of type similar to Boltzmann's and with a nonlocal boundary condition. We construct a numerical schemes and we prove the convergence via Bv compactness argument. A Numerical code in Fortran is available.

5. Contracts and Grants with Industry

5.1. National Grants

J. Henry was funded for the second year by the “neuroinformatique” program of CNRS for a study on modelling of the activity of basal ganglia through a population density approach, jointly with the team basal gang of UMR 5227 at univesity Bordeaux 2.

M Langlais is 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 a co-investigator (partner 6 and single non INRA member) of the proposal ARCHIDEMIO, Modelling of the interactions between plant development, canopy architecture and fungal aerial diseases epidemics for a sustainable crop management, funded in 2008 by ANR SYSTERRA with B. Tivoli as principal investigator. M. Langlais is also 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 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 is 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 is a co-organizer of a NIMBioS working group on “Mathematical modeling of life cycle, transmission, and clonal expansion of Toxoplasma gondii" that is funded for 2010.

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 Normale Vétérinaire in Nantes.

6. Other Grants and Activities

6.1. Other Grants and Activities

M. Adimy is responsible for a CNRS grant (CNRS/CNRST convention) project with Morocco (university of Marrakesh) on "*The study of differential equations with delay in finite and infinite dimensional spaces with applications to models of population dynamics*".

The Enée06 associated team gathers the group of A. Ben Abda at Lamsin (ENIT) in Tunis and the Anubis team. It also associates the groups of H. Hbid in Marrakesh and M. Bouguima in Tlemcen and the Poems and Apics INRIA teams. In 2009 a support for one extra year was used mainly to supervise the thesis of F. Jday.

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.) (see section 7.1). A. Ducrot and M. Langlais with J.B. Burie won an Orchid collaboration program with Taiwan on “Singular reaction-diffusion systems and presistence phenomena". The collaboration is with Fu Sheng-Chen, Guo Jong-Shenq , Tsai Je-Chiang and Wu Chin-Chin at the National Taiwan Normal University. P. Magal has a France-China (PFCC) collaboration contract with Rong Yuan at the Beijing Normal University.

7. Dissemination

7.1. Services to the scientific community, organization of conferences

- J. Henry is chairman of IFIP TC7 and chairman of the International Program Committee of the 24th IFIP TC 7 Conference on System Modeling and Optimization Buenos Aires, Argentina, July 27-31, 2009.
- B. Ainseba is head of the UFR “sciences et modélisation” at the university Bordeaux 2.
- J. Henry was member of the local organizing committee of the conference Neurocomp held in Bordeaux september 16-18 2009.
- J.B. was organizing a bimonthly working group at Bordeaux 2 on population dynamics.
- M Langlais was a member of the AERES evaluation committee for UMR CNRA CAMS at EHESS on February 2009.
- M Langlais was a member of a hiring committee for a Professor in Mathematics at Bordeaux 2 University.
- M Langlais organized 3 meetings in Bordeaux and Montpellier within the framework of ARC INRIA M2A3PC.
- M Langlais is a member of the Editing Committees of Communications in Pure and Applied Analysis (until December 2009) and Journal of Biological Dynamics.
- M. Langlais was member of the Scientific Committee for Models of Population Dynamics and Evolution (MPDE 9), Leicester, UK, May 11-13, 2009.

7.2. Academic Teaching

- Bedr’Eddine Ainseba gave a course on the control in biomathematics at the CIMPA School (January 2009, Guadeloupe).
- Bedr’Eddine Ainseba gave a course on the control of population dynamics at Algiers (June 2009).
- M. Langlais teaches a course on "Deterministic mathematical models in demography and epidemiology" – 30 hours – at the Master level, Universities Bordeaux 1 and 2.
- J. Henry teaches a course on "Système dynamique et neurosciences" at the Master MIMSE1, Universities Bordeaux 1 and 2 for the year 2009-2010.
- J. Henry taught a one week course at the universidad complutense of Madrid on “Mathematical modeling in neurosciences” at the doctoral level.
- M. Langlais gave a 9h series of lectures at CIMPA SCHOOL in Guadeloupe, January 2009.

7.3. Participation to conferences, seminars

- Bedr’Eddine Ainseba, gave a talk at Beijing Normal School, Population dynamics and their control (December 2009).
- Bedr’Eddine Ainseba, gave a talk at the university of Annaba, Modelling insect growth in a vineyard (February 2009).
- M. Langlais gave a talk at the workshop ‘Populations en interaction" (modèles déterministes et probabilistes), March 23 2009 at Marseille-Luminy.
- M. Langlais gave a talk at the Workshop RTP M3D, RTP CNRS “Mathématiques et décision pour le développement durable", Cargese, France, April 2009.
- M. Langlais gave a talk at “Partial Differential Equations and Applications", International Workshop for the 60th birthday of Michel Pierre, Vittel, 22-24 October 2009.

- M Langlais gave a joint talk with A. Calonnec at a workshop INRA-INRIA, Sophia Antipolis, December 10-11 2009.
- M. Langlais gave a talk at White Workshop on Mathematical Biology, Trento, 15-17 December 2009.
- J. Henry gave a talk at the IFIP TC7 conference on Sustem modeling and optimization, Buenos Aires July 27-31, 2009, on “Factorization of linear elliptic boundary value problems in non cylindrical domains”.
- J. Henry gave a talk at the International Workshop on Biomathematics and Biomechanics, Tozeur, 20-23 November 2009 on “Analysis of Synchronization of Neurons through a Density Population Approach”.
- J. Henry gave a seminar at the new univeristy of Lisbon in may on “mathematical modeling in neurosciences”.
- A. Ducrot participated to the Summer School "Mathematical and informatic modelling in epidemiology and immunology" in Yaounde (Cameroon) 10 -20 august.
- A. Ducrot gave a talk at the worshop "Reaction-Diffusion systems: Modeling and analysis" at Orsay university 2-5 june.
- JB Burie gave a talk entitled ’Modelling of a powdery mildew over a vineyard’ at the annual meeting of the Society of mathematical biology in Vancouver, Canada, July 27-30, 2009.
- JB Burie presented a poster ’Effect of crop growth and susceptibility on the dynamics of a plant disease epidemic: powdery mildew of grapevine’ at PMA 09: 3rd intern. symposium on Plant Growth Modeling, Simulation, Visualization and Applications - Beijing (CHINA), Nov. 09-13, 2009

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