



INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team ANUBIS

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

Futurs

THEME BIO

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R *eport*

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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. It is created in the framework of IMB (Institut de Math matiques de Bordeaux), UMR CNRS 5251 and Bordeaux 1 and 2 universities.

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 ([28]), 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. [27]. 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. [46], [50]. 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. [37], [49]. This age-structure although already intensively studied in our team in the past, cf. [3], [8], [51], 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 phenomenon 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. [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. [27], [29]. 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. [34].

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. [44]. Isolated environments we had in mind were mostly remote islands in Southern Indian Ocean, e.g., Kerguelen Archipelago. 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. [44]; see also [34]).

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 [36]. 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. [34], [30], or on macroparasites (*Diplectanum aequens*) infesting sea-bass (*Dicentrarchus labrax*) populations, cf. [31]. It remains a main research theme through new developments of a collaborative effort with D. Pontier for zoonosis and anthroozoonosis, 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. [30], [22], 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. [33].

Pathogens of vineyards and transmission 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. [30], [19].

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 [13].

3.3. Developing 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 [38]. 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 multiphysic 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 ([43]). 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. 3.4.4.2). 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 [14]. 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 preconditioning as corresponding to suboptimal feedbacks in the framework of optimal control. It is a matter of defining sparse approximations of the Dirichlet-Neuman operator and to use these approximations to obtain preconditioning 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 [24], [25], [26], [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 [24], [25], [26], [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. Aïnseba, 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. Contamination of a trophic chain by radionuclides

Contamination of a food chain by radionuclides is a study conducted within the auspices of CNRS GdR MOMAS . F. Marpeau's PhD. is dedicated to a first comprehensive approach for modeling, numerical simulations and mathematical analysis of the whole process. That means starting from the transport of radionuclides in porous media emanating from a leaking underground storage device to the contamination of a trophic chain made of various species living on the ground and contaminated by a source.

This is not an infectious disease but this is closely related to the problem of section 3.1.3. At the trophic chain level interactions are modelled by predator-prey systems. Indirect contamination of individuals by the source resembles indirect transmission of parasites. Direct contamination of susceptible predators by contaminated preys is also feasible.

3.4.2. Blood cells

(M. Adimy, B. Ainseba, A. Ducrot, A. Noussair)

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 [45]) 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 [39]).

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 [40]). 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 [24], [25], [26], , 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 particular, 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 [40], 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 research 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, see [23]. This new class of models of population dynamics with stochastic interaction, 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. 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. Noussair, 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 [42], [47], and [48]. 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 ScAIApplix 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 [17]. Moreover in the 1D spatial case we have developed new tools to exhibit traveling fronts for complex models [32].

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 homogenization techniques for the mathematical study of the disease spreading in periodic environments;
- extend these models to the study of diseases in other examples of periodic environments 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 Odyssee 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 : we want to participate to the challenge of elucidating the mechanisms of the treatment by deep brain stimulation of Parkinson's disease. As a matter of fact, while the treatment is recognized as very efficient, the way it is acting is still not completely clear. Tentative modeling of the problem have been tried but the relevant level of description is still unclear. We are trying the level of population of neurons.

Our goal is to bring our know how in excitable tissues modeling and in integration (passing from small scales (neurons) to large scales (brain)).

3.4.4.1. *The biological model of aplysia*

To start with a realistic but yet affordable model, we decided with R. Nargeot (Univ. Bordeaux 1) to focus our research on the mollusc *aplysia* whose neuronal network of its ganglion is almost perfectly known. All its chemical and anatomical structures are known. A first work of modeling of spatial effects has been done by Léonie Deméryère in her DEA thesis. The resulting spatio-temporal systems are rather complex and need to solve a transmission type problem with discontinuous state and normal derivative at the interfaces, at each time step. A toy program has been implemented in Scilab which has to be rewritten in order to be able to simulate realistic situations where the size of neurons is much smaller than the size of the ganglion. Then unstructured meshes should be used and the factorization method should be tested. We wish to be able to model and simulate the learning by reinforcement processes which is at the heart of R. Nargeot's research.

3.4.4.2. *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. O. Faugeras (Odyssee project) 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 [35] 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.

3.4.4.3. *Inverse problem for Aplysia's ganglion model*

It seems sensible to introduce constraints in the inverse problem on the way the electric activity is generated and propagated in the brain but very little is known for the human brain. In order to go further on this problem and test the advantage of introducing a priori knowledge on the generating of electric activity in order to stabilize the inverse problem, we intend to study a much more simple biological system, considered as a model system, the oral ganglion of the mollusc *aplysia*. We think that a neural network of about a hundred neurons would be sufficiently realistic. R. Nargeot has numerous recordings of these neural networks. So *aplysia* is an experimental lab with which we can model, test and validate any assumption and algorithm.

In this research we will resume the inverse EEG problem for the oral ganglion of *aplysia* with the introduction of an electric activity generating model.

3.4.4.4. Modeling of the treatment of Parkinson's disease by deep brain stimulation

Deep brain stimulation of subthalamic nuclei is an efficient intervention for alleviating motor symptoms associated with Parkinson's disease. Nevertheless the understanding of the action of such stimulation remains poor. For example the ablation by surgery of the same nuclei was recognized to have some efficiency although it has been abandoned due to the risks of that surgery. Some mathematical models have been proposed to try to solve this paradox. The one of Terman and Rubin includes pertinent physiological knowledge and seems able to give clues to understand this phenomenon. Nevertheless after experimenting it, we found that additional research need to be done : we intend to extend the model to incorporate additional physiological knowledge to be able to simulate the resulting tremor which can be easily recorded. An important feature of the research in that context is that we model the considered brain tissues as a structured population of neurons. Each neuron is described by a 2D Izhikevich model. The population is structured with respect to the two state variables. This description is sufficient to study the synchronization/desynchronization phenomena of the firing of neurons of the same population and it is insensitive to the number of neurons (as opposed to a direct simulation). Many problems are still open for this kind of modeling : study of boundary conditions related to firing, synaptic coupling with scale-free connectivity, spatial structure including gap junctions and glial cells,... This research is done jointly with Anne Beuter at the "institut de cognitique" at Bordeaux 2 [41]. This collaboration will last till the end of 2008.

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. In the case of the "computing zoom" the factorization is used as a tool to continuously eliminate the unknowns outside the region of interest.

The simplest case for presenting the theory of factorization of boundary value elliptic problems is the Poisson problem in a cylinder where the spatial invariant embedding is easy to use. Nevertheless the mathematical study of the resulting Riccati equation is not easy due to the unboundedness of the Dirichlet to Neumann operator. In previous works its well posedness was studied through a Galerkin approach in finite dimension and within the framework of Hilbert-Schmidt operators. Both methods need quite long developments. With N. Belaib, B. Louro and M. Orey we proposed a direct study of this Riccati equation using a Yosida regularization. This way is much simpler and we hope to be able to apply it to study more complex Riccati equations coming from the same theory.

The QR factorization is a well known factorization for rectangular matrices in the product of an orthogonal and triangular matrices, for overdetermined linear problems. Formally it has already been extended to the continuous case in the factorization of boundary value problems, and the study of this method is the subject of Maria Orey's thesis. In the framework of linear quadratic optimal control problems governed by a parabolic equation it has been shown in a previous work that this leads to an optimal feedback which is of the proportionnal and derivative form : the optimal control is expressed by a linear combination of the present state and its time derivative which are supposed to be measured. If these measurements are compatible with the state equation the formula reduces to the classical optimal state feedback formula. In the case of incompatible data the formula gives the optimal control in the sense that the state equation is satisfied in the least square sense. This year we studied the dual problem that is the filtering problem leading to the Kalman filter. We consider only the deterministic framework. Then the QR factorization leads to the study of underdetermined problems where there is no information on the initial condition. The state is chosen as the minimum norm one. Then a four Riccati equations filter is derived providing an optimal state estimate in this context.

4.2. New results in dynamical systems theory

Participants: Arnaud Ducrot, Pierre Magal.

In a joint paper (Ducrot-Liu-Magal) to appear in JMAA, we study of the essential growth rate of some class of semigroup generated by bounded perturbation of some non-densely defined problem. We extend some previous results due to Thieme to a class of non-densely defined Cauchy problems in L^p . In particular in the context the integrated semigroup is not operator norm locally Lipschitz continuous. We overcome the lack of Lipschitz continuity of the integrated semigroup by deriving some weaker properties that are sufficient to give information on the essential growth rate.

In another study by the same authors we present the explicit formulas for the projectors on the generalized eigenspaces associated to some eigenvalues for linear neutral functional differential equations (NFDE) in L^p spaces by using integrated semigroup theory. The analysis is based on the main result theorem 1.2 established by Ducrot, Liu and Magal and the results on non-densely defined Cauchy problem by Magal and Ruan. We formulate the NFDE as a non-densely defined Cauchy problem and obtain some spectral properties, from which we then derive explicit formulas for the projectors on the generalized eigenspaces associated to some eigenvalues. Such explicit formulas are important in studying bifurcations in some semi-linear problems.

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

Participants: Jacques Henry, Fadhel Jday.

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. There is a long tradition of studying this problem at the laboratory LAMSIN of ENIT in Tunis. Within the “équipe associée” Enée 06 led by A. Ben Abda and J. Henry, F. Jday investigates the data completion problem formulated as a control in the Kohn-Vogelius setting with two states. He uses the factorization method to decouple simultaneously the two states and two adjoint states, but only two Riccati equations must be integrated. This leads to the operator of a linear problem that provides the best estimate of the lacking data from the measurement ones. This is of particular interest in quasi-stationary problems as the inverse EEG problem, where one has to solve a set of independent inverse problems indexed by time. From the numerical experiments of F. Jday it appears that the integration of the Riccati equations is ill-conditioned but in the case of a cylinder an analytic solution exists that provides precise results for the data completion problem.

4.4. Deep brain stimulation modeling

Participants: Jacques Henry, Julien Modolo.

The treatment of Parkinson’s disease by deep brain stimulation is known to be efficient but is still poorly understood. In Parkinson’s disease synchronous firing of certain populations of neurons in subthalamic nuclei which is stopped by the stimulation. In our approach to understand this phenomenon we consider populations of similar neurons. Each neuron is governed by the integrate and fire Izhikevich’s 2D model. The population is described by its state density distribution function. This function satisfies a Fokker-Planck equation in a 2D domain. Due to the discontinuity of the model, this equation satisfies an unusual relation linking one boundary condition and a source term. Simulations of this approach have been compared to a direct simulation of a large number of Izhikevich neurons done by A. Garenne at INSERM E 358 in Bordeaux 2 university [21]. The comparison shows discrepancy due to numerical diffusion in the numerical integration of the Fokker-Planck equation. Solution to this problem are sought by using a second order Lax-Wendroff scheme with flux limiter. This scheme needs some adaptation due to the particular boundary conditions. Couplings within the same population and due to external populations by activating synapses have been introduced and some preliminary results on the phenomenon of synchronization of two populations of neurons have been observed. The PhD thesis of J. Modolo is supervised jointly with A. Beuter at Institut de cognitive Bordeaux 2.

4.5. Invasion processes and modeling in epidemiology

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

Our research program is mostly dedicated to mathematical population dynamics, i.e., predator–prey systems or host–parasite systems in heterogeneous environments. Four main aspects are considered: (1) basic mathematical analysis (global existence and qualitative properties of ODEs or PDEs systems with W.-E. Fitzgibbon [18] , controllability with B. Ainseba and S. Anița , front propagation with J. Burie and A. Ducrot), (2) derivation of models and model analysis for epidemic problems within a collaborative work with the team of D. Pontier [22] and A. Calonnec , (3) numerical simulations of complex host–parasite systems within a collaboration with H. Malchow and F. Hilker [20], and (4) the impact of alien species on native prey populations [19].

- A new result obtained through numerical simulations shows a parasite can slow down and reverse the invasion process of a host population whose dynamic exhibits a Allee effect (bistable dynamics) [20].
- A new result obtained through model analysis and simulation is related to rodent populations experiencing periodic dynamics and a hantavirus [22].
- New results concerning the transmission of parasites between host populations living on distinct spatial domains are derived in [18].
- New results concerning the stabilisation of both species in a predator-prey system.
- New results concerning the impact of invading alien predators and competitors on native prey populations are discussed in [19].
- New results concerning the spread of a fungal disease in a vineyard are derived.

4.5.1. Travelling waves in invasion processes with pathogens

This work is devoted to the study of a singular reaction–diffusion system arising in modelling the introduction of a pathogen within an invading host population. In absence of the pathogen the host population dynamics exhibits a bistable dynamics (or Allee effect). Earlier numerical simulations of the singular SI model under consideration have exhibited stable travelling waves and also, under some circumstances, a reversal of the wave front speed due to the introduction of the pathogen. Here we prove the existence of such travelling wave solutions, study their linear stability and give analytical conditions yielding an actual reversal of the wave front speed.

4.5.2. Malaria epidemiological modeling

P. Zongo is a PhD student at the university of Ouagadougou. He spent three months in the team to work on a model of malaria development in endemic areas, with the financial support of the associated team Enée06. The model he has developed take into account different new features, that are epidemiologically very important. Indeed it is well known that children are more sensitives than adults to malaria. He incorporated a discrete stucturation with respect to age to take care about this. Moreover emigration of susceptible individuals is also considered. He started with A. Ducrot to understand the dynamics of this ODE model by using basic reproduction number theory as well as bifurcation theory. The resulting work is still in progress. He also plans to take care of the heterogeneous spatial motion of mosquitoes (and human population) to understand its role into the dynamics of the disease.

4.6. Control in biomathematics

Participant: Bedr'Eddine Ainseba.

The internal zero-stabilization of the nonnegative solutions to some parabolic equations modelling biological processes in heterogeneous domains is still under investigation. In our last results , we provide a necessary and a sufficient condition for nonnegative stabilizability in terms of the sign of the principal eigenvalue of a certain elliptic operator. This principal eigenvalue is related to the rate of the convergence of the solution. We give some evaluations of this principal eigenvalue with respect to the geometry of the domain and of the support of the control. A stabilization result for an age-dependent population dynamics with diffusion is also established.

The main question of this study is in finding the positions and shapes of ω the domain of control and Ω the whole domain, which maximize a certain eigenvalue denoted $\lambda_1^{\omega, \Omega}$.

The proof is based on optimal shape design techniques and uses rearrangement techniques. We have treated the particular case when ω is a ball.

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

This joint work with E. Augeraud from the university of La Rochelle started two years ago and is still in progress. In this work we analyze 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 affects 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 studied 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 showed how the level of economic development, the price of the screening campaign and the price of medications affects the dynamic of public intervention. A fortran code has been developed for computing this optimal balance. This work has been presented to CMPD conference in Campinas Brazil 2007.

4.7. The blood production system

Participants: Mostafa Adimy, Arnaud Ducrot.

4.7.1. Numerical integration of a mathematical model of hematopoietic stem cell dynamics

A mathematical model of hematopoiesis, describing the dynamics of a stem cell population, was investigated. This model is represented by a system of two nonlinear age-structured partial differential equations, describing the dynamics of resting and proliferating hematopoietic stem cells. It differs from previous attempts to model the hematopoietic system dynamics by taking into account a cell age-dependence of the coefficients that prevents a usual reduction of this system to an unstructured delay differential system. We proved existence and uniqueness of a solution to our problem, and we investigated the existence of stationary solutions. A numerical scheme adapted to the problem was presented. We showed the effectiveness of this numerical technique in the simulation of the dynamics of the solution. Numerical simulations show that long-period oscillations can be obtained in this model, corresponding to a destabilization of the system. These oscillations can be related to observations of some periodical hematological diseases (such as cyclic pancytopenia or CML).

4.7.2. Discrete maturity-structured model of cell differentiation with applications to acute myelogenous leukemia

We proposed and analyzed a mathematical model of hematopoietic stem cell dynamics, that takes two cell populations into account, an immature and a mature one. All cells are able to self-renew, and immature cells can be either in a proliferating or in a resting compartment. The resulting model was a system of age-structured partial differential equations, whose analysis was reduced to the one of a system of delay differential equations, with several distributed delays. We investigated the existence of positive, and axial, steady states for this system, and we obtained conditions for their stability. Numerically, we concentrated on the influence of variations in differentiation rates on the behavior of the system. In particular, we focused on applications to acute myelogenous leukemia, a cancer of white cells characterized by a quick proliferation of immature cells that invade the circulating blood. We showed that the result of a blocking of differentiation at an early stage of immature cell development could be the over-expression of very immature cells, with respect to the mature cell population.

4.7.3. Mathematical model of hematopoiesis dynamics with growth factor-dependent apoptosis and proliferation regulations

We considered a nonlinear mathematical model of hematopoietic stem cell dynamics, in which proliferation and apoptosis are controlled by growth factor concentrations. Cell proliferation is positively regulated, while apoptosis is negatively regulated. The resulting age-structured model was reduced to a system of three differential equations, with three independent delays, and existence of steady states was investigated. The stability of the trivial steady state, describing cell's dying out with a saturation of growth factor concentrations was proven to be asymptotically stable when it was the only equilibrium. The stability analysis of the unique positive steady state allowed to determine a stability area, and showed that instability may occur through a Hopf bifurcation, mainly as a destabilization of the proliferative capacity control, when cell cycle durations are very short. Numerical simulations were carried out and result in a stability diagram that stressed the lead role of the introduction rate compared to the apoptosis rate in the system stability.

4.7.4. Mathematical model of leukemia development with spatial cell distribution

In a joint study of A. Ducrot with V. Volpert, a mathematical model to describe the evolution of leukemia in the bone marrow is proposed. The model is based on a reaction-diffusion system of equations in a porous medium. We show the existence of two stationary solutions, one of them corresponds to the normal case and another one to the pathological case. The leukemic state appears as a result of a bifurcation when the normal state loses its stability. The critical conditions of leukemia development are determined by the proliferation rate of leukemic cells and by their capacity to diffuse. The analytical results are confirmed and illustrated by numerical simulations.

4.8. Spreading of a fungal disease over a vineyard

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

4.8.1. Spreading of a fungal disease over a vineyard

This part is mostly an application of 3.3 (Disease control).

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 prove 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 is 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 [17].

Moreover in the 1D spatial case we have developed new tools to exhibit traveling fronts for complex models [32]. This allows to analyse the influence of the various models parameters on the epidemic spreading speed. Another article on this subject with a different approach is in preparation. It is entitled 'On the existence of travelling wave solutions for some models in phytopathology' and is to be submitted before the end of 2007.

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 homogenization techniques for the mathematical study of the disease spreading in 2D periodic environments;
- extend these models to the study of diseases in other examples of periodic environments such as orchards.

4.9. Prediction of Grapevine Moth Dynamics (Eudemis)

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

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. Studies here might develop a better understanding of the mechanisms by which the biocontrol agent suppresses pests. This research is done in collaboration with INRA Villenave d'Ornon (S. Savary and D. Thiery).

The prediction of damages caused by the grape moths *Lobesia botrana* is always problematic in the vineyards where these insects occur. The objective of our work is to progress in the risk assessment of this pest by predicting the offspring size of the n generation at the $(n-1)$ generation. *L. botrana* is a species in which the larva is polyphagous. 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 consequence on the temporal dynamics of oviposition and thus grape damages. Multistructured models are constructed and describe the distribution of individuals throughout different stages. A work on parameters estimation is still in progress.

4.10. Pheromone-Taxis and Mating Disruption Model for Insect Control

Participants: Ahmed Noussair, Damien Chapon, Julien Hubert.

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. We develop here a two coupled models: the first simulate the convection diffusion of the artificially synthesized pheromone in the vineyard geometry taking into account the wind effect. The second describe the moth population dynamic with chemotaxis. A numerical code in fortran have developped for monitoring integrated pest management using mating disruption approach. This research is done in collaboration with INRA Villenave d'Ornon (S. Savary and D. Thiery).

4.11. Direct movement of population

Participants: Bedr'Eddine Ainseba, Ahmed Noussair.

We are concerned with a system of nonlinear partial differential equations modeling the Lotka Volterra interactions of predator-prey in the presence of prey taxis and spatial diffusion. The spatial and temporal variations of the predator's velocity are determined by the prey gradient. The existence of weak solutions is proved by using Schauder fixed-point theorem. The linearized stability around equilibrium is also studied. A finite volume scheme is built and numerical tests are shown.

4.12. Hyperbolic and Kinetic models in Mathematical Ecology

Participant: Ahmed Noussair.

4.12.1. Kinetic models of Physiologically structured population

The kinetic growth here is described using the physiological age: the age of an individual expressed in terms of the chronological age of a normal individual showing the same degree of anatomical and physiological development. The model answers the question how population is going to change in the near future, given its current status and environmental conditions that the population is exposed to. Rules for the resource uptake and use of substrates (food) by an individual organism have also been integrated in the model via Energy budget approach.

Several types of numerical methods are developed, Eulerian methods, implicit method and the method of characteristics. Existence of global weak solutions are proved via these schemes, and numerical solutions demonstrate how seasons can play a dominant role in shaping population development.

4.12.2. Coagulation-Fragmentation Equations

We consider a model equation describing the coagulation process of a micro-organism on a surface. The problem is modeled by two coupled equations. The first one is a nonlinear transport equation with bilinear coagulation operator while the second one is a nonlinear ordinary differential equation. The velocity and the boundary condition of the transport equation depend on the supersaturation function satisfying the nonlinear ode. We first prove global existence and uniqueness of solution to the nonlinear transport equation then, we consider the coupled problem and prove existence in the large of solutions to the full coagulation system.

5. Contracts and Grants with Industry

5.1. National Grants

M. Langlais is funded by the GDR MoMas from ANDRA, BRGM, CEA, CNRS and EDF for a study on the impact on populations of a nuclear waste contamination. This funding has been renewed.

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*".

M. Adimy is head for the french part of a UE grant INTERREG III A with Spain on "development of a passive ocean tracer model" for the period 2005-2007. He is also responsible for a Brancusi PAI project with Rumania (polytechnic university of Bucarest) on "stability, bifurcation and control for delay differential equations coming from Biology."

The team is associated with a Brancusi PAI project *Reaction-diffusion systems in population dynamics* (2007-2008) between the team of V. Volpert in Lyon and the one of N. Apreutesei in Iasi.

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.

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).

7. Dissemination

7.1. Services to the scientific community, organization of conferences

J. Henry is in charge of International relations for INRIA Futurs-Bordeaux research center. J. Henry is vice chairman of IFIP TC7. He is member of INRIA's COST committee for incentive actions.

- J. Henry is vice chairman of the International Program Committee of the 23rd IFIP TC 7 Conference on System Modeling and Optimization Cracow, Poland, July 23-27, 2007.
- A. Noussair is organizing a bimonthly working group at Bordeaux 2 on population dynamics.
- M. Langlais was a member of the Scientific Committee for the *Second Conference on Computational and Mathematical Population Dynamics (CMPD2)*, Campinas, Brazil, July 16-20, 2007.
- M. Langlais was a member of the Scientific Committee for META 2007, *Modeling of Tropical & Amazonian Ecosystems*, Kourou, Guyane october 2007.

7.2. Academic Teaching

- M. Langlais teaches a course on "basic PDEs" – 20 hours – and a course on "Deterministic mathematical models in demography and epidemiology" – 30 hours – at the Master level, Bordeaux 1 and 2 Universities.
- M. Langlais teaches a course on "Mathematical models and complex systems" – 15 hours – at the Master level in Cognitive Sciences, Bordeaux 2 University.
- M. Langlais gave a 12 hours lecture on "Structured models in epidemiology" at Chaire UNESCO special semester on "Mathematics and development", Tunis, April 2007
<http://www.tn.refer.org/unesco/semestre5/semestre5-fr.html>.
- M. Langlais gave a 9 hours lecture at EpiCasa, "Training in Epidemiology", Casablanca, November 2007,
<https://colloque.inra.fr/epicasa07/>.

In the Master 2 of the university of Bordeaux, M. Adimy teaches in 2007 a course entitled "*Cancer Modelling*".

J. Henry gave a course on "factorisation des problèmes aux limites elliptiques linéaires" at the university Bordeaux 2 at the research level.

7.3. Participation to conferences, seminars

B. Aylaj and A. Noussair *State Trajectories Analysis for a kinetic model of Tumor Immune System Interactions* TAMTAM07 Alger 3^eme colloque sur les Tendances dans les Applications Mathématiques en Tunisie, Algérie, Maroc Alger, 16-18 Avril 2007.

B. Aylaj and A. Noussair *Asymptotic Behavior of State Trajectories for a kinetic model of Tumor Immune System Interactions* Euro-mediterranean Conference on Biomathematics, Cairo, 26-28 June 2007.

B. Aylaj and A. Noussair *BV compactness and convergence of a numerical scheme to a nonlinear kinetic model of Tumor-Immune cell interactions* II Conference on Computational and Mathematical Population Dynamics (CMPD2) Campinas Brazzil 16-22 july 2007.

J.-B. Burie gave a talk entitled "Analysis of a powdery midew simulator with a SEIR model" at the "II Conference on Computational and Mathematical Population Dynamics", Campinas (Brazil), July 16–20, 2007.

A. Ducrot gave a talk at *Colloque IXXI*, Lyon, june 18-22, 2007. He gave a talk at *Conference on computational and mathematical population dynamics*, Campinas, Brasil, july 16-20, 2007. He gave a talk at the workshop *Modelling of blood disease*, Lyon, november 5-8, 2007.

M. Adimy presented two works at the "*Euro-Mediterranean Conference on Biomathematics*", (Cairo, Egypt), June 26-28, 2007. He gave a presentation at the "*First IXXI workshop on mathematical models in biology and medicine*", Lyon, June 18-22, 2006.

J. Henry gave a talk the "23rd IFIP TC 7 Conference on System Modeling and Optimization" Cracow, Poland, July 23-27, 2007, on "A robust extension of the Kalman filter for parabolic systems in the deterministic framework".

M. Langlais gave a talk at GdR MABEM, Lyon, june 2007,

M. Langlais gave a talk at *Second Conference on Computational and Mathematical Population Dynamics (CMPD2)*, Brasil, july 2007.

M. Langlais gave a talk at Workshop "ReaDiLab", LIA franco japonais, Orsay, september 2007.

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- [16] M. ADIMY, A. ELAZZOUI, K. EZZINBI. *Bohr-Neugebauer type theorem for some partial neutral functional differential equations*, in "Nonlinear Analysis, TMA.", vol. 66, 2007, p. 1145-1160.
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