



INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team ANUBIS

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

Futurs

THEME BIO

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1. Team

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2. Overall Objectives

2.1. Overall Objectives

The ANUBIS team is joint to INRIA and MAB, UMR CNRS-universités Bordeaux 1-2 5466. It is located in Bordeaux (Bordeaux 1 and Bordeaux 2 universities) and in Pau (université de Pau et des Pays de l'Adour). The team was created in July 2004.

This team is dedicated to developing tools for solving general partial differential equation problems, and more specifically those coming from modelling in Biology. The target is twofold : - provide methods with increased speed and precision to obtain a better interactivity of simulations; -allow the use of more complex and so more realistic models. The proposed way insists on the links with automatic control. We shall study problems naturally formulated in terms of optimal control (optimization, game theory, inverse problems, data assimilation) but also problems where the state equation can be rewritten as an optimal control problem in time or space. The general idea is then to transpose methods and algorithms from automatic control to numerical analysis. We expect numerical methods with properties of stability, robustness and with computing localization from this transposition. The team will investigate biomathematical modelling and simulation more specifically.

The biological problems investigated are coming from population dynamics (demography, epidemiology, hematology) and from neuroscience.

3. Scientific Foundations

3.1. 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. It 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.

This point of view developed independently, is not completely original as some of the ideas were presented in the book [28], but they seem to have been forgotten since. It is also investigated in the framework of submarine acoustics in [33] (cf infra). Recently M. Gander from Mc Gill university in Montreal has worked on similar ideas and we want to collaborate with him.

At the moment the method has been applied and fully justified in the case of a cylinder [9]. 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 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. Two situations are possible : these surfaces have or not an edge. In the second case one can consider for example a family of surfaces starting at the boundary of the domain and shrinking to a point. The difficulty comes from the singularity at that point [27] and to the initialization of the “climbing phase”. It is now well understood in the case of a disk. The directions of investigation aim at giving this methodological tool its larger generality:

1. Maria do Céu Soares’s PhD at the new university of Lisbon, supervised jointly with B. Louro, aims at implementing the method in the case of a circular domain, swept over by a family of concentric circles. Two possible situations have been dealt with : the family of circles are decreasing from the boundary of the domain or increasing from the origin. In the later case the singularity is met at the initialization of the descent phase. With this formulation one can obtain the Dirichlet-Neumann operator at the boundary which is useful, for example, for domain decomposition methods. More generally we want to deal with the case of star-shaped domains where the subdomains are obtained by homotethy.
2. study of slender domains We aim at studying domains defined by their plane sections evolving smoothly along an axis. Various ways are possible : either by defining an Hilbert basis of the functions on the section, which limits the possible evolutions of this section ; either by using a geometrical transform for each section such that we are lead back to the cylinder case ; either by reasoning in the physical domain. In that later case the difficulty comes from the fact that the spaces of functions defined on sections depend on these sections. We intend to use techniques developed in shape optimization (velocity method of Sokolowski-Zolesio [36]). The factorization obtained depends on the method used.

3. multiple parameter invariant embedding. It could allow a continuous analogous of the complete Gauss factorization in the discrete case. This needs the study and the factorization of non local kernels linked to operators of the kind previously mentioned (Dirichlet-Neumann, for example);
4. study of other types of equation (parabolic, hyperbolic) with space invariant embedding. It should be noticed the pioneering computation of J.L. Lions [32] for the heat equation on the half infinite domain \mathbb{R}^+ ;
5. obtaining transparent boundary conditions for unbounded domains. This very important problem for the simulation of wave propagation relies on the computation of a Dirichlet-Neumann operator for the neglected part of the domain. Now it can be addressed analogously to the optimal stationary feedback and the algebraic Riccati equation;
6. domain decomposition. The classical presentation of iterative substructuring methods (Schwarz without overlap) uses the Steklov-Poincaré operator at the interface of subdomains [35]. Now it can be directly expressed with the Dirichlet-Neumann operators in each of the neighbouring domains. The Riccati equation furnished by the factorization method allows to let evolve the Steklov-Poincaré operator when the interface is moved. This may be useful for load balancing in a parallel computation ;
7. study of boundary control problems where the spatial decoupling (as previously explained) can be done jointly with the decoupling of the optimality system ;
8. study of a QR like factorization. As for the Gauss factorization, the QR factorization can be extended to the continuous problem as the product of an orthogonal operator and a Cauchy problem of the same order as the initial problem. One of the interests of this parallel vision of boundary value problems on one side and optimal control problems on the other is that results in one domain can “bounce back” to the other : for example, for linear quadratic control problems, the QR factorization gives rise to an optimal proportional integral feedback;
9. study of non linear problems. If a general approach through a Hamilton-Jacobi equation seems out of reach, we may think to study a linearized problem within a Newton method. This will lead to quasi-Riccati equation. For quasi-linear systems (which are frequently used in population dynamics) it is possible to iterate without recomputing the solution of the Riccati equation;
10. robust simulation. For ill modelled problems, one can introduce a modelization error as a bounded perturbation which transforms the control problem into a differential game problem. Using a second Riccati equation one can obtain a worst case design simulation.

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

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 multiphysics 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 and we intend to contribute to it.

3.2. Structured population modelling

3.2.1. Structured populations

Population dynamics aims at describing the evolution of sets of individual of various nature : humans, animals, vegetals, parasites, cells, viruses,.. These descriptions are of interest in various domains : epidemiology, ecology, agriculture, fishing, In medicine that kind of models can be used in immunology, cancer therapy,... First the models are studied qualitatively, particularly in view of the asymptotic behaviour : extinction or persistence of a species, or oscillating behaviour. These topics are also those of automatic control. For example a theoretical tool as Lyapounov functions has long been used in population dynamics. Similarly, the recent trend in automatic control consisting in using families of model giving a finer or coarser representation of the reality can be found in population dynamics : models describing the evolution of interacting populations are quite numerous, ranging from individual centered models to models governed by ordinary or partial differential equations. The choice of the structuring variables is essential to describe the population evolution well. It depends also on the final goal, mathematical analysis or numerical simulation.

For space distributed models, multimodelling techniques could be useful where the model can change from one region to another. The methods presented in section 3.1 could then be used to give interface conditions.

In demography the most significant variable is age for an individual ([37], [31]). This theme, although already intensively studied in our team in the past (see for example [2], [6], [8], [10]) will be central for our future research. Independently of the space variable, other kind of structuration will be considered (size of individuals (fishing), weight,...).

For interacting populations or subpopulations additional 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 (models SI, SIS, SIR, SIRS, SEIRS,...); another relevant variable is the age of the disease or the infection age for an individual [6], [13].

In previous works, rather strong assumptions are made on demographic and diffusion coefficients (e.g. identical or independent of age) to obtain qualitative results. In recent works (as [1] J.-M. Naulin's Ph D thesis or works in progress), it becomes possible to weaken these conditions.

3.2.2. Prey-predator models in highly heterogeneous environment

We consider prey-predator models in highly heterogeneous environment allowing certain spatial periodicities at scales that are small compared to the size of the domain. For example this is the case for the dynamics of ladybugs and green flies in orchards with hundreds of trees. The dynamics of the original problem (before going to the limit of small scale) is not known and it is impossible to study the influence of various biological parameters on the system. Nevertheless the limit problem is well posed. We intend to go on investigating this way and determining global dynamics for this kind of problems.

3.2.3. Invasion process in island environment

In a series of joint works with F. Courchamp and G. Sugihara, e.g. [5], we are concerned by invasion models in island environment by species introduced at purpose or by chance, and their control. They highlight singular differential system with unusual dynamics : a finite time extinction may coexist with a Hopf bifurcation. It is important to take into account a space variable as heterogeneities are rather frequent in that environment (e.g. Kerguelen islands). A work has begun jointly with D. Pontier with the PhD thesis of S. Gaucel. In another work we deal with the invasion of a host population by a virus.

3.2.4. Aggregation/fragmentation of groups of individuals in a given population

In this section we are interested by individuals or groups of individuals aggregation/fragmentation phenomena. This question is up to date in works in animal ecology [30], but also in other domains as physiology and medicine.

Phenomena of alignment of fish shoals, of gathering of certain animal species, of cell aggregation are part of this class of problems and we intend to invest in the modelling and simulation of these phenomena which play an important role for understanding the dynamics of the concerned populations. A first work in this direction is

[3] where we consider a model structured with respect to a given character (infectiousness, social character,...) diffusing in space and having a non local renewal process. Interactions between individuals are supposed of Boltzman type. For example to model the proliferation of phytoplankton piles we use as structuring variable the size of the piles. Then the research is oriented towards the development of transport-projection numerical techniques. This work is done in the framework of the GDR GRIP.

3.2.5. Space dependent epidemiologic models

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 place, influence the dynamics of the infected population. Various ways can be experienced. In a first possibility we could assume that individuals are randomly distributed in space [13]. We would obtain a reaction diffusion system whose reaction term would depend on space. In another way, we could define patches where the population dynamics is governed by ordinary differential equation (cf. works by Auger et al.).

3.2.6. Host-parasites systems

This research theme has been present in our team for many years with investigations on virus of carnivorous animals (foxes *Vulpes vulpes*, domestic cats *Felis catus*) [4], or on macroparasites (*Diplectanum aequens*) infesting of sea-perches (*Dicentrarchus labrax*) populations. It will remain a main theme due to its importance for the biologists with whom we are working and the new opportunity opened after the drastic reduction of simulation time for these problems (cf the PhD of J.-M. Naulin, and joint work with ScalApplix team).

New problems are opened, in particular with the models with indirect transmission through the ground or environment ([4]) or with *interspecific* transmission. Then now we can speak of parameter identification, control,....., and even more with reaction-diffusion systems coupled with ordinary differential systems which arise in [4], [7], [13], and whose mathematical treatment is not straight forward.

3.2.7. Generating process for blood cells

The process of production of blood elements, called hematopoiesis, is a complex phenomenon, based on self renewal and differentiation of stem cells. For human, it occurs in the bone marrow. Every day billions of cells are produced to face unequal life durations and different renewal rates of blood cells. Mathematical modelling of hematopoiesis is not a new topic. It mainly incorporates models proposed by the team of M.C. Mackey [34], [29] and uses partial differential equations structured in age and maturity. Maturity in these models is different from size (classically used for models of mitosis) it is a variable describing the level of development of a cell (quantity of DNA or RNA synthesized, rate of mitochondry,...). There exists cells with maturity as small as one may want in the bone marrow (multipotent primitive stem cells). These cells determine the behaviour of the whole population of blood cells. One can incorporate delays in these equations due to the duration of the cell cycle, nonlinearities due to the piling of cells in the population and stochastic features. Among blood diseases some exhibit oscillations in the production of blood cells. They are called cyclic hematologic diseases. They can affect only one kind of cells (periodic auto-immune hemolytic anemia) or all the kinds of cells. It is the case for periodic chronic myeloid leucemia, where the period can vary between 30 and 100 days which is much longer than the duration of the cell cycle (less than one week). In previous works [17], [16], we have shown the existence of oscillating solutions through Hopf bifurcations for simplified models of hematopoiesis. We intend to go on investigating these questions. Yet the study of these diseases allow a better understanding of regulation phenomena that are acting in hematopoiesis : the periodic nature of these diseases brings evidence of a control on bone marrow proliferation which is still unknown. This question has been investigated by M.C. Mackey's team who developed experiments and numerical approaches for simplified models. Nevertheless this team did not develop the mathematical analysis of these equations sufficiently. Generally speaking the problems arising in hematopoiesis are twofold : differential equation with delay (which may be stochastic) or degenerated hyperbolic partial differential equations. There exists data on maturation velocity or mortality rates which allow the numerical resolution of these equations. Differential equations with delay are solved numerically by adapting Runge-Kutta methods and by using interpolation methods. Solving numerically hyperbolic partial

differential equations with delay needs new tools based on one dimensional finite difference or finite element methods or characteristic method or decentered finite volume method more adapted to hyperbolic equations. Implementing these methods needs the use of servers capable of managing heavy computations.

3.2.8. *Modeling in neurobiology*

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 3.1. 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.

3.2.9. *Kinetic models in microbiology*

In this work we are interested in developing kinetic models of social behaviour of several cell populations. It consists in a system of several kinetic equations satisfied by the population densities. These equations are coupled by integral source terms expressing the meeting rate of individuals.

3.2.10. *Predator-prey models with chemotaxy*

We consider predator-prey systems in which we take into account a spatial displacement due to chemotaxy. We assume that predators are chasing their preys by smelling out their scent and reciprocally preys are escaping predators by detecting their approach. So we build nonlinear models of the Keller and Segel type. Displacement velocities are functions of the species density gradient. The main work consists in developing finite volume numerical techniques for these equations.

3.3. **Optimal control problems in biomathematics**

The controls in population dynamics are of various kinds and generally speaking are due to the action of man on his environment. Prophylaxis, sterilization, vaccination, detecting, quarantine, elimination, re-introduction, capture, hunting, fishing, pesticides are examples of control processes at man's disposal. It is then important to know what is the impact of such actions on the considered population and to distinguish between what is feasible and what is not in terms of optimal management of resources. A rather rich literature exists on this topic ranging from resource management in ecology to applications of Pontryaguin's maximum principle to mathematical biology problems.

One important significant variable is often ignored : the space variable. Its importance is due to space inhomogeneities of the environment and of the control structure which is often localized to small part of the domain. This point is linked to the cost of control and the ability of the controller to access to the individuals.

The other important variable ignored in works on population control is the age of individuals which, in the domains under investigation (demography, ecology, epidemiology, cell growth,...), plays a leading part also. In the framework of this research team-project we will investigate control problems for structured models (size, weight, age, health state, position of individuals, age of the disease,...) from biomathematics. We will use both individual based models and models using densities. The techniques to be used are mainly those from automatic control and the factorization methods described in section 3.1.

But control theory can also be a way to model the evolution itself of the population. For example, for age structured populations the birth rate can be considered as a feedback control for an optimal control problem whose objective is to be determined. Such optimal control formulation of the model can shed a new light on it.

3.3.1. Control of fisheries

The problem of management of fish harvesting is very hard from the socio-economical point of view. Determining the quotas depends on the evolution of the stock of fish in the considered area. Most of the models used to determine these quotas are only time dependent although the fishing effort is size dependent due to the techniques of fishing. We intend to use techniques coming from automatic control in order to maximize the income of fishers with bounds on the fishing effort and its derivative. Models will be structured by the age, size and position of the fishes. This last variable is important for migrating fishes and those who spawn at specific areas.

3.3.2. 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 badness 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.

3.3.3. Controlling the size of a population

This is a classical problem in demography. Various kinds of control can be used : control by migration, by elimination (animal populations), by the policy of birth,... 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 applied directly. 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,...).

3.3.4. 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. For certain problems the ill-posedness can be related by the factorization method to the ill-posedness of the backward integration of a parabolic equation. Then we can apply the well-known quasi-reversibility method to that case.

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).

The setting in position of programs of vaccination, prophylaxy, detection needs an a priori study of feasibility. This study after a modelling 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.

4. New Results

4.1. Age structured population dynamics as a problem of control

Participant: Jacques Henry.

We consider the usual linear model (Sharpe - Lotka - McKendrick) for the evolution of an age structured population. Usually the birth rate $v(t)$ is given through a birth law with a fertility rate. From the point of view of automatic control theory, this can be viewed as feedback mechanism. We derive a reformulation of this "closed loop" model as an open loop optimal control problem. In other words we consider the birth rate as a control and we look for an objective function such that the corresponding optimal control in closed loop form gives exactly the birth law. The quadratic cost function is given as the sum of two terms corresponding to the gap to a given feedback law and the difference with a desired population distribution. We distinguish the homogeneous and non homogeneous cases. In some cases an explicit derivation of this cost function is obtained. This could 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.

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

Participants: Jacques Henry, Maria do Céu Soares, Maria Orey, Kapil Sharma.

We are pursuing the development of the theory of factorization of boundary value problems as described in 3.1. With Angel Ramos we are trying to find simpler methods to justify the computation leading to the Riccati equation which is non classical. We studied directly this Riccati equation in a Hilbert-Schmidt framework. The result is still not as general as one could hope as we need the existence of a fixed basis of eigenfunctions of the restricted operator on the moving surface. Maria Orey is using the same framework for studying the QR factorization. With Bento Louro and Luis Trabuco we studied the factorization of the Laplacian on slender domains (cylinder with a section of small area) in view of applying it to rods. The fact that non constant Dirichlet data on the section gives rise to a boundary layer in order to recover the Neumann boundary data on the section is related to singular term in the expansion of the Dirichlet to Neumann operator. Other problems of factorization of linear elliptic boundary value problems have been studied : the various way of factorizing systems of elliptic operators and the Stokes model. This last problem leads to new kinds of operator Riccati equations with divergence free constraint. Kapil Sharma begun his postdoctoral period by studying the "computing zoom" technique applied to the elasticity equations.

4.3. Deep brain stimulation modeling

Participants: Jacques Henry, Bedr'Eddine Ainseba, Alejandro Pascual, Julien Modolo.

Rubin and Terman have proposed an explanation of the effect of the treatment of Parkinson's disease by deep brain stimulation based on a model of the thalamus and subthalamic nuclei model. In this model each structure is represented by a small number of neurons modeled by a Hodgkin Huxley like model. The thalamus should relay the sensori-motor inputs to the cortex. Subthalamic nuclei are tuning this relay. During his internship Alejandro Pascual has deeply studied this model. He concluded that although it furnishes valuable explanations to the biologists it is not completely satisfactory : it cannot explain the parkinsonian tremor. Furthermore the benefit of deep brain stimulation which is clearly obtained in a simplified model is more difficult to assess and more unstable in the full model. We pursue the study of this problem with the beginning of the PhD of Julien Modolo at a higher level : we consider now populations of neurons structured by the potential. This work is done jointly with Anne Beuter.

4.4. Invasion processes

Participants: Bedr'Eddine Ainseba, Michel Langlais, Fabien Marpeau, Cédric Wolf, Arnaud Ducrot.

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 [20] [19] [18], controllability with B. Ainseba), (2) derivation of models and model analysis within a collaborative work with C. Wolf and the team of D. Pontier (feline retroviruses, rodents viruses possibly transmitted to humans) [25], (3) numerical simulations of complex host–parasite systems within a collaboration with H. Malchow (and his group) [23] [24], and (4) the impact of alien species on native prey populations [21].

- 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) [23] [24]. This problem can be investigated from a theoretical point of view. In particular we prove the existence of travelling wave solutions together with some qualitative properties. The sign of the wave speed can be characterised in function on the different parameters arising in the problem.
- A new result obtained through model analysis and numerical simulations is related to rodent populations experiencing periodic dynamics and a hantavirus: in some circumstances the hantavirus can take advantage of the cyclicity to invade neighbouring human populations within which it can be lethal [25] [13].
- New results concerning the transmission of parasites between host populations living on distinct spatial domains are derived in [20] [19] [18] [12].
- New results concerning the impact of invading alien predators and competitors on native prey populations are discussed in [21] and [22] [11].
- Some modelling concerning the impact of nuclear disposal leaks on populations is studied in [12].
- Some modelling concerning the propagation of brucellosis within an ovine population and its transmission to humans, (magister thesis of C. Benosman).
- Concerning the analysis of an epidemiological age and space population dynamics diffusion system when the demographic functions and the diffusion coefficients are distinct already studied by B. Ainseba, some first results on the existence of travelling wave solutions are investigated. For the moment, we only consider the simplest case where demographic functions and diffusion coefficients are identical.

4.5. The blood production system

Participants: Mostafa Adimy, Fabien Crauste.

4.5.1. Proliferation of hematopoietic stem cells mediated by growth factors

Hematopoiesis is a complex biological process that leads to the production and regulation of blood cells. It consists of mechanisms triggering differentiation and maturation of hematopoietic stem cells. Located in the bone marrow, hematopoietic stem cells are undifferentiated and unobservable cells with unique capacities of differentiation (the ability to produce cells committed to one of blood cell types) and self-renewal (the ability to produce an identical cell with the same properties). Under the action of growth factors (molecules acting like hormones playing an activator/inhibitor role), hematopoietic stem cells produce differentiated cells throughout cell divisions until blood cells (white cells, red blood cells, and platelets) are formed and ready to enter the bloodstream.

We proposed in [14] a mathematical approach of this process to carry out explanation on some blood diseases, characterized by oscillations in circulating blood cells. We assumed that the growth factors act on the rate of introduction from the resting to the proliferating phase, and in [14], we considered the action of growth factors on the mortality rate of the proliferating phase, known as apoptosis (a programmed cell death).

We studied the stability of the steady states of a reduced model and we proved the existence of a Hopf bifurcation that can destabilize the system and lead to the appearance of oscillating solutions. In previous mathematical studies of hematopoietic stem cells dynamics, oscillating solutions have shown their importance in the understanding of some diseases affecting blood cells, known to exhibit oscillations of circulating blood cells. We showed that the influence of growth factors, which are exterior to the process of hematopoiesis, should not be neglected in stem cells dynamics, since it adds some information on the behavior of hematopoietic stem cells, and the action of growth factors can lead to the existence of oscillating solutions in the stem cell population. Numerical simulations demonstrated that long period oscillations in the circulating cells are possible even with short cell cycle durations. Thus, we were able to characterize some hematological diseases, especially those exhibit a periodic behavior of all the circulating blood cells.

4.5.2. Malignant proliferation of hematopoietic stem cells

To understand the dynamics of chronic myelogenous leukemia, we considered in [15], [17], [16] models for the regulation of stem cell dynamics and investigated the influence of parameters on oscillations period when the model becomes unstable and starts to oscillate. Taking 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, and assuming that cells divide at different ages, we proposed a system of differential equations with distributed delay to model the dynamics of hematopoietic stem cells. Stability and Hopf bifurcation were studied. Numerical simulations showed that periodic solutions occur after the bifurcation, with periods increasing as the bifurcation parameter (the sensitivity) increase. We obtained periodic oscillations with periods around 45 days, and amplitudes of the oscillations range from low values to normal values. When the sensitivity continues to increase, longer oscillations periods was observed with amplitudes varying from low values to high values. This situation characterizes periodic chronic myelogenous leukemia, with periods in the order of two months (70 days).

4.6. Spreading of a fungal disease over a vineyard

Participants: Jean-Baptiste Burie, Michel Langlais.

4.6.1. 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 ScAIApplix 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, and the role of a dual short and long range dispersal of the disease [26].

In a more distant future we will have interactions with other members of the project:

- with M. Adimy and his collaborators, we would like to compare delay equation models with epidemiological models based on classical ODEs in the phytopathologic domain.
- with J. Henry et al., in the spatial case we plan to use transparent boundary conditions to simulate an unbounded domain.

4.7. Integrated Pest Management in vineyard

Participants: Ahmed Noussair, Bedr'Eddine Ainseba, Jacques Henry, Sarah Ardit, 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).

4.7.1. Prediction of Grapevine Moth Dynamics

The prediction of damages caused by the grape moths *Lobesia botrana* and *Eupoecilia ambiguella* 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 modifies 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. The model will include all these parameters in order to develop a tool of computer aided decision for a better phyto-sanitary management.

4.7.2. Mating Disruption for Insect Control

Pheromone are volatile chemical odors 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. 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.

4.7.3. Biocontrol in Vineyard

Biological control is narrowly defined here as the use of predators, parasites, pathogens, competitors, or antagonists to control a pest. Here we consider predator-prey models in the vineyard geometry taking into account the highly heterogeneous spatial environment allowing periodicities at scales that are small compared to the size of the domain.

4.8. Hyperbolic and Kinetic models in Mathematical Ecology

Participant: Ahmed Noussair.

4.8.1. 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. 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 demonstrates how seasons can play a dominant role in shaping population development.

4.8.2. Energy Budget Model for Structuring Populations

The Energy budget model consists of a set of simple, mechanistically inspired, rules for the uptake and use of substrates (food) by an individual organism. It specifies the key processes of feeding, assimilation, development, maintenance, growth, reproduction (or division) and ageing quantitatively. These processes can

by specified realistically for animals, feeding on other animals, with only one internal reserve and structural body mass as state variables.

4.8.3. Generalized Boltzmann Models in Mathematical Biology

This work is based on the idea that Boltzmann-like modelling methods can be developed to design, with special attention to applied sciences, kinetic-type models which are called generalized kinetic models. The evolution is determined both by interactions among individuals and by external actions. Generalized kinetic models can play an important role in dealing with several interesting systems in applied sciences: population dynamics and socio-economic behaviours, models of biology and immunology.

4.8.4. Coagulation-Fragmentation Equations

We consider a model equations describing the coagulation process of a microorganism 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.

4.8.5. Hyperbolic Model with Chemotaxis.

Here we study hyperbolic models with chemotaxis. For example we consider predator-prey systems in which we take into account a spatial displacement due to chemotaxy. We assume that predators are chasing their preys by smelling out their scent and reciprocally preys are escaping predators by detecting their approach. Displacement velocities are functions of the species density gradient. Finite volume numerical techniques for these equations are developed.

5. Contracts and Grants with Industry

5.1. National Grants

M. Langlais is funded by the GDR MoMas for a study on the impact on populations of a nuclear waste contamination.

6. Other Grants and Activities

6.1. Other Grants and Activities

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.

J. Henry has a PAI grant PESSOA with CMAF of the university of Lisbon (B. Louro and L. Trabucho) on “Boundary problems factorization and application to the elasticity theory and to control”.

M. Langlais has a joint grant with C.-H. Bruneau on the “Impact of a contamination by radionucleides on population dynamics” supported by GDR MOMAS from ANDRA, BRGM, CEA, CNRS and EDF.

M. Langlais belongs to a french-japanese PICS program on “Mathematical Understanding of Invasion Processes in Life Sciences” (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 unit. 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 22nd IFIP TC 7 Conference on System Modeling and Optimization Turin, Italy, July 18-22, 2005.
- B.E. Aïnseba is member of the scientific committee of the International workshop on differential equations in mathematical biology Le Havre July 11-13, 2005.
- B.E. Aïnseba is a co-organiser with P. Magal and S. Ruan of a special session on "Dynamical Systems and Control in Biology" in the AIMS' Sixth International Conference on Dynamical Systems, Differential Equations and Applications which will be held in Poitiers (France) from June 25 to June 28, 2006.
- M. Langlais was a co-organiser with H. Malchow of a mini-symposium on at the *European Conference on Mathematical and Theoretical Biology*, Dresden, July 2005.
- M. Langlais was a member of the scientific committee of the conference "*Mathematical Analysis of Complex Phenomena in Life Sciences*" held in Tokyo, October 2005.

7.2. Academic Teaching

M. Langlais teaches basic deterministic mathematical modelling techniques in Demography and Life Sciences at the Master level in Bordeaux 2 university; 15h per year.

6h lecture by M. Langlais during the Summer School "Mathematical Models in Biology and Population Dynamics", held in Dourdan on July 5–9 2004, organised by CNRS and GRIP GDR.

In the Master 2 MAM (Mathematics and Applications of Mathematics) of the university of Pau, M. Adimy taught in 2004-2005 a course named "*Models and methods in populations dynamics*".

J. Henry is teaching a course on numerical methods of optimization at the Master 1 level at the university Bordeaux 2.

B.E. Aïnseba is teaching a course on Mathematical Control in Biology and a course on optimization at the Master level at the university Bordeaux 2.

7.3. Participation to conferences, seminars

M. Adimy and F. Crauste presented two works at the "*International Workshop on Differential Equations in Mathematical Biology*, (Le Havre), July 11-13, 2005. They gave a presentation at the "*9th Applied Mathematics Days of Pau-Zaragossa*", Jaca (Spain), September, 19-21, 2005.

C. Benosman gave a talk entitled "Modelling Brucellosis" at the "*International Workshop on Differential Equations in Mathematical Biology*, (Le Havre), July 11-13, 2005.

J. Henry gave a talk entitled "For which objective is birth process an optimal feedback for age structured population dynamics?" at the "*International Workshop on Differential Equations in Mathematical Biology*, (Le Havre), July 11-13, 2005. He gave a presentation on the same subject at the workshop "Functional methods in biomathematics" held from August 10 to August 16, 2005, at Galanesti, Romania. At this workshop Fabien Marpeau gave a talk on "impact on populations of a nuclear waste contamination".

M. Langlais gave a talk at *Systèmes de Réaction-Diffusion en Sciences de la Vie*. Orsay, March 2005. He gave a talk at *Mathematical Models and Methods in Biology and Medicine*. Bedlewo, Pologne, May-June 2005.

M. Langlais was a main speaker at International Workshop on *Differential Equations in Mathematical Biology*. Le Havre, July 2005. He gave a talk at *Mathematical Analysis of Complex Phenomena in Life Sciences*. University of Tokyo, October 2005. M. Langlais was a main speaker at the INRA workshop *Architecture and Epidemiology*, held in Rennes November 7–8 2005, organised by B. Tivoli.

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