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

Activity Report

2006

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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 [34], but they seem to have been forgotten since. It is also investigated in the framework of submarine acoustics in [38] (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.

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 multipyshic model based on optimal control techniques. Yet interactions (between domains or models) are considered as control variables and the problem is solved by minimizing a criterion. This approach suits well with the framework described here 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 immmunology, 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 ([40], [37]). 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].

In previous works, rather strong assumptions are made on demographic and diffusion coefficients (e.g. indentical 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 [36], but also in other domains as physiology and medecine.

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. 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 macroprarasites (*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], 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 [39], [35] 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 [15], [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. Reproductive strategy for age structured population and least regret control

Participant: Jacques Henry.

Continuing the point of view of considering the birth rate as an open loop control for the evolution of an age structured population, we considered the reproductive strategy of insects subject to environmental perturbations. The objective is to maximize the number of individuals in the pupae phase at the end of the year in order to maximize the survival of the species for the next year. A simple linear-quadratic control problem is considered with a Lotka - McKendrick model for the evolution of the age structured population. The control is a modulation of the “natural” birth rate. To take into account the perturbation of the environment as an increase of the mortality rate, both the worst case and the least regret (as proposed by J. L. Lions) approaches have been considered. Owing to the linear-quadratic formulation, the optimal control can be expressed as a linear state feedback. So this study leads to a modification of the fertility rate which now becomes time depending.

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. 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 postdoctoral period of Kapil Sharma was dedicated to the study of “computing zoom” technique where the invariant embeding is done by the use of an homothety. First he derived the equation giving the transparent boundary conditions for the elastiticity equation in the case of a circular domain. Then he made numerical experiments for the Poisson equation. The problem was discretized by Q1 finite elements. Both cases of homogeneous and non homogeneous problems outside the region of interest were studied. Two possible discretization for the Dirichlet to Neumann operator depending on the basis chosen in the space where it is acting and on its range. For the rectangular domains that we studied the discretization at the corners did not seem to make problem. The result were satisfactory in terms of the precision of the computation within the region of interest and the gain in time of computation in limiting the computation to the region of interest. The overhead for computing the transparent boundary conditions does not seem too heavy in the cases studied.

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. This method has been applied to linear quadratic optimal control problems governed by a parabolic equation. In the classical calculus the decoupling by invariant embeding (factorization) of the optimality system leads to the optimal feedback giving the optimal control as a linear function of the present state through a Riccati equation. In the case of the QR factorization the optimal control is given as a function of both the state and its time derivative. This could seem to be redundant as once the control is chosen, the derivative of the state is given by the state equation as a function of the state. In fact if the state equation is exactly satisfied the optimal control is the one given by the classical method. But this method is robust in the sense that if perturbations are not taken into account in the state equation, it gives an optimal control using the additional observation of the time derivative, the state equation being verified in the least square sense.

4.3. Deep brain stimulation modeling

Participants: Jacques Henry, Julien Modolo.

After exploring Rubin and Terman's model of the treatment of Parkinson's disease by deep brain stimulation we decided to turn to models encompassing large numbers of neurons. We consider populations of similar neurons governed by Izhikevich's 2D model. This model can simulate various behaviours of a neuron. The state variables are the potential and a recovery variable. The model is of the integrate and fire kind and so it exhibits a discontinuity when the neuron fires. 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. The conservativeness has been studied theoretically and by simulation. 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. The comparison is satisfactory which gives confidence for further use of this approach which is much less demanding in terms of computaion. Couplings within the same population and due to external populations by activating synapses have been introduced. The phenomenon of synchronization of two populations of neurons has been observed on simulations which a necessary first step in simulating Parkinson's disease in which such a synchronization occurs in subthalamic nuclei. The PhD thesis of J. Modolo is supervised jointly with A. Beuter at Institut de cognitique Bordeaux 2.

4.4. Invasion processes and modeling in epidemiology

Participants: Bedr'Eddine Ainseba, Michel Langlais, Arnaud Ducrot, Mahieddine Kouche, Abdel Bourassi.

Our research programm 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 [24], controllability with B. Ainseba and S. Aniţa, front propagation with J. Burie and A. Ducrot), (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) [30] [25] [29], (3) numerical simulations of complex host–parasite systems within a collaboration with H. Malchow (and his group) [27] [28], and (4) the impact of alien species on native prey populations.

- 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) [27].
- 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 letal [30] [29].
- New results concerning the transmission of parasites between host populations living on distinct spatial domains are derived in [24].
- New results concerning the impact of invading alien predators and competitors on native prey populations are discussed.
- New results concerning the spread of a fungal disease in a vineyard are derived in [22].
- Some modelling concerning the impact of nuclear disposal leaks on populations is studied within the auspices of GdR CNRS MoMaS.

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

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.

4.4.2. Brucellosis

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 communicable between humans but is a major disease in development countries because of its severity in human cases and the damaged caused economically to the livestock. In the magister thesis of B. Chahrazed at the university of Tlemcen, our goal was to first study the disease within an ovin population. Infection usually occurs after contact with tissues, urine, vaginal discharges, aborted fetuses and placentas, ... When infected for a first time the female abort and the infected fetus in the environment still highly contaminating for several months. The pioneer works on the subject focused only on direct transmission mecanisms and didn't take in account the indirect transmission by the contaminated environment.

4.4.3. 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 decline 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 and al, Nowak and 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 that the cell-free viral spread (see Culshaw et al, Philips, Dimitrov, ...). Following these pioneers work 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.

4.4.4. Travelling wave propagation in age-structured models

Lot of models in epidemiology couple spatial and age structures to take care of the spreading rate of individuals together with the vital dynamics of the population. This structuration can lead to complex patterns formation and waves. A new problem we would like to investigate is the propagation phenomenom that, like in the classical reaction-diffusion framework, arises due to travelling waves. More specifically the description of the wave speed in function of demography characteristics of the population is of particular interest for biologists. A first study concerning this kind model can be found in [23] where a very simple epidemiological model with only intercohort interactions has been investigated. The study of more realistic models including multi-group interactions and inter-cohort infectivity ar still in progress.

Other structurartions are also interesting in epidemic models. The age since the infection is known to be a significant variable for some diseases with long incubation. A joint work with P. Magal (Le Havre university) is in progress to understand wave propagation for a SI model coupling spatial spread of individuals and the age since the infection.

4.5. The blood production system

Participant: Mostafa Adimy.

4.5.1. Discrete maturity structured system of hematopoietic stem cell dynamics

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). 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 and analyzed a mathematical model of hematopoietic stem cell dynamics. This model takes into account a finite number of stages in blood production, characterized by cell maturity levels, which enhance the difference, in the hematopoiesis process, between dividing cells that differentiate (by going to the next stage) and dividing cells that keep the same maturity level (by staying in the same stage). It is described by a system of n nonlinear differential equations with n delays. We studied some fundamental properties of the solutions, such as boundedness and positivity, and we investigated the existence of steady states. We determined some conditions for the local asymptotic stability of the trivial steady state, and obtained a sufficient condition for its global asymptotic stability by using a Lyapunov functional. Then we proved the instability of axial steady states. We studied the asymptotic behavior of the unique positive steady state and obtain the existence of a stability area depending on all the time delays. We gave a numerical illustration of this result for a system of four equations.

4.5.2. Periodic Oscillations in Leukopoiesis Models

The term leukopoiesis describes processes leading to the production and regulation of white blood cells. It is based on stem cells differentiation and may exhibit abnormalities resulting in severe diseases, such as cyclical neutropenia and leukemias. We consider a nonlinear system of two equations, describing the evolution of a stem cell population and the resulting white blood cell population. Two delays appear in this model to describe the cell cycle duration of the stem cell population and the time required to produce white blood cells. We establish sufficient conditions for the asymptotic stability of the unique nontrivial positive steady state of the model by analyzing roots of a second degree exponential polynomial characteristic equation with delay-dependent coefficients. We also prove the existence of a Hopf bifurcation which leads to periodic solutions. Numerical simulations of the model with parameter values reported in the literature demonstrate that periodic oscillations (with short and long periods) agree with observations of cyclical neutropenia in patients.

4.6. Spreading of a fungal disease over a vineyard

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

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 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 [22].

Moreover in the 1D spatial case we have developped new tools to exhibit traveling fronts for complex models [21]. This allows to analyse the influence of the various models parameters on the epidemic spreading speed.

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

- compare delay equation models with epidemiological models based on classical ODEs in the phytopathologic domain;
- in the spatial case improve the code by the use of transparent boundary conditions to simulate an unbounded domain;
- include the effects of fungicide treatments in the models;
- use homogeneization techniques for the mathematical study of the disease spreading in 2D periodic environnments;
- extend these models to the study of diseases in other examples of periodic environnments such as orchards.

4.7. 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.

4.8. 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).

4.9. 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.

4.10. Hyperbolic and Kinetic models in Mathematical Ecology

Participant: Ahmed Noussair.

4.10.1. 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 environemental conditions that the population is exposed to. Rules for the ressoure uptake and use of substrates (food) by an individual organism have also been intgrated in the model via Energy budget approach.

Several types of numerical methods are developped, Eulerian methods, implicit method and the method of charactertics. 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.

4.10.2. 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 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 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.

M. Langlais belongs to a french-japonese 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 23rd IFIP TC 7 Conference on System Modeling and Optimization Cracow, Poland, July 23-27, 2007.
- J. Henry was a member of the organizing committee of the day honoring the memory of Jean-Pierre Kernévez in Compiègne (october 2, 2006).
- B.E. Ainseba 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.
- A. Noussair is organizing a bimonthly working group at Bordeaux 2 on population dynamics.
- M. Langlais was co-organiser with E. Venturino of a minisession on *Mathematical population dynamics, Mathematical epidemiology and other biomedical applications* at the Italian-French conference, Mathematics and its Applications, Turin, July 2006.
- M. Langlais was a member of the Scientific Committee for the *Conférence francophone sur la Modélisation Mathématique en Biologie et en Médecine*, Craiova, Roumanie July 2006. (http://lma.univ-pau.fr/meet/craiova2006/).

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.

In the Master 2 MAM (Mathematics and Applications of Mathematics) of the university of Pau, M. Adimy teached in 2005-2006 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.

Within the associated team Enée06, J. Henry gave a 6h course on “factorisation des problèmes aux limtes elliptiques linéaires” at LAMSIN in Tunis (june 2006).

B.E. Ainseba 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

J.-B. Burie gave a talk entitled “Travelling wave analysis of a reaction-diffusion model describing a powdery mildew epidemic over a vineyard” at the “*World Conference on Differential Equations and Applications”*, Marrakech (Marocco), June 15–20, 2006. He gave a talk on the same subject at the “*AIMS’ 6th International Conference on Dynamical Systems, Differential Equations and Applications*”, Poitiers (France), 25–28 June, 2006 and at the Meeting “*Mathematics and its Applications*”, Torino (Italy), July 3–7, 2006. He was also invited to give a talk on this subject at the “*Workshop Modelization and Simulation in Agro Food technologies*”, Madrid (Spain), November 24, 2006.

A. Noussair gave a talk entitled " Kinetic models of physiologically structured population in several physiological character space dimension " (Seminar University Cady Ayad Marakech), Mars 2006.

A. Noussair gave a talk entitled " Mating Disruption Model for Insect. " (Marrakech World Conference on Differential Equations and Applications), July 15-20, 2006.

A. Noussair gave a talk entitled " Global weak solution to Coagulation-Fragmentation Equations " Workshop: " Renormalisation en EDP et Applications " ENSAM Meknes 30 oct-2nov, 2006.

A. Ducrot gave a talk at *RTN Front-singularities*, Nottingham, March 2006. He gave a talk at *Marrakech World Conference on Differential Equations and Applications*, Marrakech, June 15-20, 2006. He gave a talk at *AIMS' Sixth International Conference on Dynamical Systems, Differential Equations and Applications* Poitiers, France, June 25-28, 2006. He gave at talk at *Conférence Francophone sur la Modélisation Mathématique en Biologie et en Médecine*, Craiova, Roumania 12-14 july 2006. He gave a talk at *Mathematics and its applications*, Torino, Italy, July 3-7 2006.

M. Adimy presented a work at the "*French-Speaking Conference on Mathematical Modelling in Biology and Medicine*", (Craiova, Romania), July 12-14, 2006. He gave a presentation at the "*AIMS' 6th International Conference on Dynamical Systems, Differential Equations and Applications*", Poitiers, June 25-28, 2006. He also presented a work at the "*Marrakesh World Conference on Differential Equations and Applications*", (Marrakesh, Morocco), June 15-20, 2006.

J. Henry gave a talk entitled " Reproductive strategy for age structured populations and least regret control." (Marrakech World Conference on Differential Equations and Applications), July 15-20, 2006. He gave a talk on “On a proportinal and derivative robust optimal feedback for linear-quadratic control problems” at the “*AIMS' 6th International Conference on Dynamical Systems, Differential Equations and Applications*”, Poitiers (France), 25–28 June, 2006. He gave a talk on ”Vers un modèele mathématique du traitement de la maladie de Parkinson par stimulation électrique profonde” at the day honoring the memory of Jean-Pierre Kernevez in Compiègne (october 2, 2006). He gave also a seminar at the laboratory LaMSID of EDF-Clamart on “factorisation de problèmes aux limites elliptiques linéaires et technique du zoom de calcul”, (march 19, 2006).

M. Langlais gave a talk at *Biomathematics and BioComplexity in Africa 2006*, University of Cape Town, January 2006.

M. Langlais gave a plenary talk at *Marrakesh world conference on differential equations and applications* Marrakesh, June 2006, (http://euromedbiomath.free.fr/m2006/).

M. Langlais gave a talk at *Conférence francophone sur la Modélisation Mathématique en Biologie et en Médecine*, Craiova, Roumanie July 2006. (http://lma.univ-pau.fr/meet/craiova2006/).

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