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Project-Team ANUBIS

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

IN COLLABORATION WITH: Institut de Mathématiques de Bordeaux (IMB)

RESEARCH CENTER
Bordeaux - Sud-Ouest

THEME
**Observation, Modeling, and Control
for Life Sciences**

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Project-Team ANUBIS

Keywords: Population Dynamics, Inverse Problem, Optimal Control, Computational Neurosciences, Computational Biology

The Anubis project team ends at the end of the year 2011. The research on cardiac electrophysiology will be gathered in the newly created Carmen team.

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2. Overall Objectives

2.1. Overall Objectives

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

As we face the great problems arising in the field of population dynamics (for instance : new epidemics, optimization of the treatment of leukemia, understanding the mechanisms of interaction between neuron populations, etc.) there is a great need to develop more realistic models and mathematical tools to analyse them. Up to now most models used in population dynamics are mainly qualitative : they try to reproduce qualitative behaviours such as extinction of species, propagation of epidemics, synchronization of neurons, ... to validate underlying assumptions. There is still a great need of such qualitative studies to analyze the mechanisms of interaction. New models using integro-differential or other non local operators instead of parabolic equations for spatial interactions should be investigated. But there is also a need for more quantitative simulations of biological phenomena. In particular one may wish not only to simulate the phenomenon but to act on it: stop the propagation of an epidemic, improve the protocol of brain stimulation in Parkinson's disease treatment or of drug administration in leukemia, fight against pests of vineyard, ... Tools from automatic control theory have already been used in this field as optimal control ([21]), parameter identification or feedback design, but there still remain many open questions we intend to investigate. For instance optimal control is useful not only to describe an external action on the population but also internal interactions that can be seen as optimizing certain criteria.

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

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

3. Scientific Foundations

3.1. Structured population modeling

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

Spatial structures are widely used to assess the impact of heterogeneities or variable local densities in population dynamics, cf. [3]. This leads to systems of reaction diffusion for continuous models, or to networks of systems of ordinary differential equations in the discrete case. Discrete spatial models are also in order, cf. [12], [13]. A new set of models is dedicated towards analyzing the transmission of parasites between populations distributed over distinct spatial models.

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

In demography the most significant variable is the chronological age of individuals, cf. [27], [31]. This age-structure although already intensively studied in our team in the past, cf. [2], [8],[14], will be central in our future research. Discrete age structures are also in order.

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

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

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

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

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

Various ways can be experienced. In a first approach we could assume that individuals are randomly distributed in space, cf. [3], [5]. We would obtain a reaction-diffusion system whose reaction term would depend on space. In an alternate approach we could define patches where the population dynamics is governed by ordinary differential equation yielding large size systems of ODEs, cf. [9].

3.2. Optimal control problems in biomathematics

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

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

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

3.2.1. Disease control

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

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

In particular, a somewhat "inverse problem" is one consisting in controlling an invading alien species by using a pathogen. Field experiments have been conducted, and simple mathematical models derived, cf. [6], [25].

3.2.2. *Controlling the size of a population*

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

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

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

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

Optimal control of systems governed by partial differential equations has a long past history at INRIA going back to the pioneering work of J.L. Lions [28]. Now Commands and Corida team-projects are investigating this area. First we want to be users of results from these researches. We want to use the automatic control tools not only as a way of optimizing the action on a system but also as a modeling help. For instance Lyapunov functions have long been used as a theoretical tool in population dynamics. Similarly, the recent trend in automatic control consisting in using families of model giving a finer or coarser representation of reality can be found in population dynamics: models describing the evolution of interacting populations are quite numerous, ranging from individual based models to models governed by systems of ordinary or partial differential equations.

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

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

A classical way to tackle inverse problems is to set them as optimal control problems. This method has proved to be efficient and is widely used in various fields. Nevertheless we are persuaded that important methodological progresses are still to be done in order to generalize its use. With JP Yvon, we have worked on the numerical stability of these methods, seeking to redefine the mismatch criterion in order to improve the conditioning of the Hessian of the optimization problem ([29]). In the same way a simple idea to explore is to use a total least square approach for this criterion.

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

For certain problems the ill-posedness can be related by the factorization method to the ill-posedness of the backward integration of a parabolic equation. Then we can apply the well-known quasi-reversibility method to that case. The setting in position of programs of vaccination, prophylaxy, detection needs an a priori study of feasibility. This study after a modeling step will go through a step of model tuning to the data. Yet,

initial data are badly known or completely unknown, demographic parameters are often unknown and disease transmission mechanisms are subject to discussion between biologists to determine their nature but their exact form and value is unknown. We intend to use parameter estimation techniques for these biomathematics problems.

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

3.3.2. Dynamic programming and factorization of boundary value problems

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

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

At the moment the method has been applied and fully justified for the Poisson equation in the case of a cylinder [10]. Indeed, the invariant embedding can be done naturally in the direction of the cylinder axis and allowing the factorization of the second order operator in the product of operators of the first order with respect to the coordinate along the cylinder axis. It needs the computation of an operator solution of a Riccati equation. This operator relates two kinds of boundary conditions on the mobile boundary for the same solution (for example the operator relating Neumann and Dirichlet boundary conditions). Furthermore the same method applied to the finite difference discretized problem is nothing else but the Gauss block factorization of its matrix. Therefore the method can be seen as the infinite dimensional generalization of the Gauss block factorization. We look for a generalization of the method to open sets of arbitrary shape and also to families of surfaces sweeping over the domain of arbitrary shape.

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

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

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

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

1. the interpretation of the block Gauss factorization as a possible discretization of the continuous factorization suggests new schemes : we have already studied an explicit discretization of the factorized system in the privileged space direction. Many other variants are possible;

2. following the analogy with control problems, we can see incomplete factorization preconditioning as corresponding to suboptimal feedbacks in the framework of optimal control. It is a matter of defining sparse approximations of the Dirichlet-Neumann operator and to use these approximations to obtain preconditioning operators.
3. the factorization puts into play a family of surfaces depending on a space variable sweeping over the domain. Then we have to describe these surfaces and their displacement, as well as the effect of operators acting on functions defined on these surfaces. In the framework of the finite element method a discretization of the family of surfaces as the “fronts” of the meshing and the block (related to the front) LU factorization as the integration of first order equations. The method needs only the meshing of a family of surfaces instead of a volume meshing. Then mesh size adaption methods may give rise to an alteration of the front velocity and so to an alteration of the mesh.

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

4. Application Domains

4.1. Application fields and collaborations with biologists

We present here collaborations on specific biological modeling problems.

4.1.1. Epidemiology

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

4.1.1.1. Nosocomial diseases

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

In the last 15 years, various mathematical models have been proposed to describe the transmission dynamics of antibiotic-resistant bacteria in hospitals or communities, we refer to the survey on this topic [26]. In [30], we formulated a two-level population model to quantify key elements in nosocomial infections. The objectives were to study the effect of antibiotic treatments of the dynamic elements of nonresistant and resistant bacteria strains in hospital environments and to provide understanding of measures to avoid the endemicity of resistant antibiotic strains in hospitals in USA (and also in the rest of the world). The theoretical analysis was reported in [24]. Most recently, in [23] we used an individual based model (so called Monte-Carlo simulations in mathematics) which is formulated by individuals and includes the interaction with the healthcare workers. The main point in this paper is that we derive a model in which all the parameters are expressed in terms of observable quantities. An important conclusion for this paper is that the average time of visit of patient by healthcare workers plays a key role in such a problem, while this parameter has not been considered before.

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

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

Participants: Jean-Baptiste Burie, Michel Langlais.

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

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

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

But still disease features have to be investigated at a higher level. This will be done thanks to epidemiological models based on ODE or PDE systems that will focus on a particular characteristic of the disease propagation mechanism. These models will also be used to quantify key parameters of the infection using outputs of the mechanistic model or directly with the real field data available. In particular we are currently investigating the interaction between the date of primary infection and growth of the host, the role of a dual short and long range dispersal of the disease and the effects of the spatially periodic structure of vineyards [7]. Moreover in the 1D spatial case we have developed new tools to exhibit traveling fronts for complex models [22].

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

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

4.1.3. Modeling in neurobiology

Participants: Jacques Henry, Gregory Dumont, Oana Tarniceriu.

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

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

4.1.4. Modeling in electrocardiology

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

This is a new field of application we are starting to develop this year. This new orientation is mainly due to the initiative of Pr Michel Haissaguerre an internationally renowned cardiologist, head of the cardiology department at the hospital "Haut Leveque" in Pessac near Bordeaux. He is applying for the creation in Bordeaux of an IHU (a new prestigious structure for medical research). His proposal "Liryc" will mix intimately research in cardiac rhythmology and mathematical modeling and computer simulation. Based on a previous experience of J. Henry in the field, we decided to reshape a part of the research activity of the team to this domain. The main objectives of this institute in which we will be involved are the improvement of the management of cardiac arrhythmias. More specifically Pr Haissaguerre's team made important progresses in the discovery of the role of pulmonary veins in the triggering of atrial fibrillation and its curative treatment by thermoablative therapy. Nevertheless there remain many open questions to fully understand the mechanisms at the origin of the atrial fibrillation and to improve its treatment. For example it is important to make the distinction between paroxysmic and permanent fibrillation. The institute will also tackle the prevention of sudden death by ventricular fibrillation. This needs efficient diagnosis tools. Electrocardiographic imaging consists in reconstructing an epicardial map of potential from measurements on torso. From the mathematical viewpoint this is an inverse problem. Our targets in that domain are i) lead theoretical investigations on the nature of fibrillation ii) improve the existing monodomain and bidomain models to have a more realistic modeling of the cardiac tissue and its inhomogeneities which will be applied in a first step at the atrial level iii) improve the numerical methods to solve these models iv) enhance the precision of the resolution of the ECG inverse problem. These researches will be lead in collaboration with the teams of the former Cardiosense 3D project of INRIA.

5. New Results

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

Participants: Jacques Henry, Fadhel Jday, Maria Orey.

We are pursuing the development of the theory of factorization of boundary value problems as described in 3.1. Maria Orey who suspended her PhD thesis for a while due to health reason, has resumed her work on extending the method of factorization to the analogous in infinite dimension of the QR algorithm for matrices. This passes through the factorization of the normal equation for the least squares problem. This problem is solved and this allows a clear definition of the Q and R operators. She will defend her thesis in 2012.

F. Jday has obtained also a clear formulation for the factorization of the Stokes equation.

A progress has been made in the attempt to extend the factorization method to parabolic evolution equation. It appears that it is not the evolution problem that can be factorized with respect to space but the evolution operator $S(t)$ that transfers the solution from time 0 to t . The corresponding Riccati equation has been obtained but a full mathematical justification remains to be done.

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

Participants: Jacques Henry, Fadhel Jday.

F. Jday is continuing his thesis co-supervised by A. Ben Abda and J. Henry. The use of the method of factorization for the data completion problem has been presented in a paper in Inverse Problems when the domain is a cylinder, both Dirichlet and Neumann data are known on one face and are to be estimated on the other. Dirichlet boundary conditions were assumed on the lateral boundary. In relation to the inverse problem in electrocardiology one has to take into account more complex geometries. F. Jday considered the domain limited by two concentric spheres. The method still applies considering the family of concentric spheres deduced by homothety.

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

Participants: Jacques Henry, Gregory Dumont, Oana Tarniceriu.

During the second year of his PhD thesis G. Dumont continued to develop and refine a simulator of a population of leaky integrate and fire neurons, with a finite jump of potential response to a synaptic stimulation in order to compare with the results from another approach, the Fokker-Planck approach. It would be interesting to show that the Fokker Planck approach can be seen as a limiting case, for high frequency small jump of potential, of the one of B. Knight, L. Sirovich and L. Omurtag. At least it is suggested by the simulations. The second year focused on the study of mathematical aspects of the equation. The methods were inspired by the book of Benoit Perthame: Transport equation in biology. With these tools, the mathematical properties of the model of population density have been established: the existence and uniqueness of a solution. G. Dumont has also been able to establish that in special cases the equation has no solution, or more precisely that the solution blows up, assuming that there is no conduction delay of the spikes within the considered population. This blow up can be related to a synchronization. In case of a conduction delay the condition of existence of a solution are much larger. The situation of inhibiting synapses has also been studied. This has been submitted to the Journal of Mathematical Biosciences.

Using the principles of entropy, G. Dumont has shown that under certain circumstances the solution of the equation converges to a stationary solution and this can be interpreted as the desynchronization of the population of neurons.

Similar studies have been done on the thetaneuron model which accounts for self spiking neurons.

The question of the synchronization of a population of neurons is also studied in collaboration with O. Tarniceriu. We consider a population of identical self firing neurons that are weakly coupled and we study the long term evolution of the repartition of phases. We are now focusing on a population of 1D leaky integrate and fire neurons and we expect more precise results for this simple model.

5.4. Modeling in electrocardiology

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

5.4.1. Modeling the electrical activity of the atria

The first year of the PhD thesis of Simon Labarthe has been dedicated to three main activities :

- a review of medical and mathematical literature about anatomy and physiology of atria and atrial fibrillation, numerical simulation of cardiac activity, mathematical analysis of cardiac models.
- the numerical implementation of simulation tools has been developed : the software is able to take into account a real 3D or 2D manifold geometry with realistic fibre orientation to simulate the bidomain or monodomain problem. Geometrical tools facilitating the fibre orientation construction have been added.
- numerical and theoretical studies of the modeling and the influence of fibre orientation in the atria and the pulmonary veins have been initiated.

5.4.2. Inverse problem in electrocardiology

The PhD thesis of Alejandro Lopez is devoted to improving the resolution of the inverse problem to recover the potential map on the heart from the measured potentials on the torso.

To have a best solution of the inverse problem many steps were taken. First, a software to solve the finite element method in 3d for the Poisson equation was created, and compared to an analytical solution. Also a software for the heat equation was created to prepare the the monodomain equation. The improvement of the forward solution helps to improve the inverse solution. An article explaining the software was included in the book "VEHÍCULOS AEROESPACIALES" (aerospace vehicles) published by the Sociedad Mexicana de Ciencia y Tecnología Aeroespacial (Mexican Society of Aerospace Science, and Technology) [19].

The second step was to develop a static solution of the inverse problem constructing a transfer matrix (heart to thorax), and solving with conjugate gradient. An article describing this software was accepted in the 22nd International Conference on Electronics, Communications and Computers.

As a third step the boundary element method was implemented to see the advantages and disadvantages in comparison with the finite element method.

The next step was to implement the monodomain model of the heart, to try to solve the problem of identification of parameters (in progress).

5.5. Invasion processes and modeling in epidemiology

Participants: Jean-Baptiste Burie, Arnaud Ducrot.

We have derived a homogenized version of our model of a fungal of disease of vine(see [7]) that takes into account the periodic row structure of vineyards. We used two-scale homogenization of Ngüentseng and Allaire (see e.g. [20]): the macroscopic scale is the vineyard scale while the microscopic one is the plant scale. We have proved a result of convergence towards the homogenized model and numerical simulations have demonstrated a significant gain in computing time and stability.

These results have been presented at ECMTB2011 in Krakow (and also, at the Exploratory Workshop on Emerging Infectious Diseases and Mathematical Modelling, Barcelona 2011 and seminars at Franche-Comté University, Tamkang and National Taiwan University).

An article is to be submitted in SIAM J. Multiscale Modeling and Simulation in early 2012.

6. Contracts and Grants with Industry

6.1. Contracts with Industry

The society CardioInsight Inc. is developing a new technology for a non invasive cardiac electrical mapping in close collaboration with the IHU Liryc. Measuring the surface potential on the torso it provides a map of the potential on the epicardium by solving an ill-posed inverse problem. The research on improvement of the inversion method is an objective of the thesis of Alejandro Lopez Rincon. Preliminary discussion with CardioInsight were done to collaborate on the project.

7. Partnerships and Cooperations

7.1. Regional Initiatives

- G. Dumont is partly supported for his PhD thesis by a grant from region Aquitaine and partly from scholarship of CNRS.
- S. Labarthe is partly supported for his PhD thesis by a grant from region Aquitaine.

7.2. National Initiatives

M Langlais, B Ainseba and A. Noussair were members of the proposal ADHOC 2010, Co-viability modeling of fisheries and marine biodiversity, funded in 2009 by ANR "La 6me extinction" with L Doyen as principal investigator.

7.3. European Initiatives

7.3.1. Major European Organizations with which you have followed Collaborations

There exists a long collaboration with A. Ramos, head of the department of applied mathematics at the Complutense university of Madrid on the theory of factorization of boundary value problems.

The same long term collaboration exists with B. Louro at the new university of Lisbon with whom J. Henry is co supervising the thesis of M. Orey.

7.4. International Initiatives

7.4.1. Visits of International Scientists

The team invited Pr Tayeb Benouaz from Tlemcen university in december 2011. Pr A.M. Ramos was invited in March 2011.

7.4.2. Participation In International Programs

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

8. Dissemination

8.1. Animation of the scientific community

- JB Burie and P Magal coorganize a weekly seminar on population dynamics.
- J. Henry is chairman of IFIP TC7.

9. Bibliography

Major publications by the team in recent years

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Articles in International Peer-Reviewed Journal

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