



IN PARTNERSHIP WITH:  
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Activity Report 2011

## **Project-Team MASAIE**

Tools and models of nonlinear control theory  
for epidemiology and immunology

IN COLLABORATION WITH: Laboratoire de mathématiques et applications de Metz (LMAM)

RESEARCH CENTER  
**Nancy - Grand Est**

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



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# Project-Team MASAIE

**Keywords:** Control Theory, Epidemiology

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## 2. Overall Objectives

### 2.1. Overall Objectives

The overall objective of MASAIE is to develop and apply methods and tools of control theory and dynamical systems for the mathematical modeling in epidemiology and immunology. The problem at issue is twofold. The first objective is to obtain a better understanding of epidemiological and immunological systems. The second objective is to mathematically study problems arising naturally when addressing questions in the fields of epidemiology and immunology. In our opinion our two endeavors operate in a synergic way : new problems will appear in control theory and their study will give new tools to epidemiology and immunology.

In this regard the first step is modeling. Modeling has always been a strong activity in control theory, however modeling in epidemiology and immunology has some specificities not encountered in engineering. The systems are naturally complex and have highly nonlinear parts. A second characteristic is the paucity of data. These data, when existing, are often imprecise or corrupted by noise. Finally rigorous laws seldom exists, this is a major difference with engineering. In this situation modeling is a back and forth process between the "mathematician" and the "biologist." When modeling, it is necessary to decide what is important and what can be neglected. This is not an easy task. A term or a structure, that can be discarded by the biologist modeler, turns out to give an unexpected behavior to the system. On the other side the biologist wants the more complete model possible, which can be difficult for the mathematical tractability. In MASAIE a close collaboration with researchers in epidemiology and immunology (IMTSSA, INRA, IRD, Institut Pasteur, University of Tübingen) is essential and will be developed.

Beyond the stage of modeling we have the validation, simulation and mathematical analysis of the models. This is also a part of modeling. For example some models can be rejected for inappropriate behavior while others are accepted for their agreement with data. Once again the role of data and the collaboration with researchers in these fields are certainly crucial, but the mathematical analysis cannot be neglected.

Emerging and reemerging diseases have led to a revived interest in infectious diseases and immunology. Our final objective is to propose and study epidemiological and immunological models for

1. analysis of the spread and control of infectious disease,
2. a better understanding of the dynamics and behavior of epidemics,
3. clarification of hypotheses, variables and parameters,
4. proposition of conceptual results (thresholds, sensitivity analysis ...),
5. simulation as an experimental tool for building and testing theories,
6. effective evaluation of field and outbreak data,
7. planning and evaluation of intervention campaigns.

## 2.2. Research themes

1. Building models in epidemiology and immunology. Studies of models and their global behavior. We will concentrate primarily on models for disease transmitted by blood-sucking insect vectors (malaria, dengue, chikungunya, yellow fever) but we will also consider some diseases for which we have collaborations and data such as Ebola haemorrhagic fever, Hepatitis B or Meningitis.
2. Modeling and model validation guided by field data.
3. Design of observers (software sensors for biological systems): observers are auxiliary dynamical systems that use the model together with the available measurement data in order to reconstruct the unobservable variables (that are not measured directly) and to estimate some parameters of the system. Observers are related to observability and, therefore, also determine data collection plans.
4. Establishing control strategies for the considered systems that can help to determine some policies in public health and fishery.

In our project, Africa has a special place:

Our research focuses on infectious diseases caused by bacteria, parasites in humans and animals. The populations of less developed countries are specially affected by these diseases. "End users" with whom we work are specialists in tropical diseases. This explains the interest in our project for African collaborations. A strong partnership exists with the network EPIMATH in central Africa. The objective of EPIMATH is to promote collaboration between different communities: Specialists in Health Sciences on the one hand and modelers, mathematicians, computer and automation on the other. Another objective is to encourage mathematicians from Africa to work in the field of mathematical epidemiology. This partner explains the strong set of data we have and also the number of Phd's students coming from sub-Saharan Africa.

## 2.3. Fields of application

1. Intra-host models for malaria.
2. Metapopulation models considering the dynamics of *Plasmodium falciparum* causing tropical malaria in human populations, and the development of drug resistance.
3. Modeling the dynamics of immunity in human populations in endemic areas. Models describing the intra-host parasite dynamics, considering the development and loss of immunity.
4. Spread of epidemics of arbovirus diseases (dengue, chikungunya ...)
5. Disease leading to structured model to allow to take in account the effect of asymptomatic carriers, differential infectivity or differential susceptibility (HBV, Meningitis ...)

One of the challenge of the project is to ensure the relevance of these models. It is Important to closely involve the “end users” (specialists in the fields, experimenters, observers, physicians, epidemiologists, entomologists, etc.) and “providers” (Mathematicians, numerical, statisticians, computer scientists,...). Users are able to bring a critical evaluation on the quality of results, to validate them or exploit them further. For example we want to understand the genetic diversity and structure of African *Plasmodium falciparum* population. The spread of drug resistance is due to gene flow and the scale of *P. falciparum* population structure. A better understanding of *P. falciparum* population genetics is necessary to adjust control measures. The findings of Rogier et al [13] provide evidence for support structured *P. falciparum* populations in Africa, and suggest that malaria epidemiology in urban areas depends on local transmission, geographic isolation, and parasite flow between the city and the surrounding rural areas. The molecular geneticists use many different statistical measure of distance. (For example  $F_{st}$ , Nei’s distance ...). It is important in our modeling process to understand how these measures can be obtained as output of our models. This explains why our team is composed of "control theorist" "applied mathematician" and "statisticians" (A. Maul, B. Cazelles).

## 3. Scientific Foundations

### 3.1. Description

Our conceptual framework is that of Control Theory : the system is described by state variables with inputs (actions on the system) and outputs (the available measurements). Our system is either an epidemiological or immunological system or a harvested fish population. The control theory approach begins with the mathematical modeling of the system. When a “satisfying” model is obtained, this model is studied to understand the system. By “satisfying”, an ambiguous word , we mean validation of the model. This depends on the objectives of the design of the model: explicative model, predictive model, comprehension model, checking hypotheses model. Moreover the process of modeling is not sequential. During elaboration of the model, a mathematical analysis is often done in parallel to describe the behavior of the proposed model. By behavior we intend not only asymptotic behavior but also such properties as observability, identifiability, robustness ...

### 3.2. Structure and modeling

Problems in epidemiology, immunology and virology can be expressed as standard problems in control theory. But interesting new questions do arise. The control theory paradigm, input-output systems built out of simpler components that are interconnected, appears naturally in this context. Decomposing the system into several sub-systems, each of which endowed with certain qualitative properties, allow the behavior of the complete system to be deduced from the behavior of its parts. This paradigm, the toolbox of feedback interconnection of systems, has been used in the so-called theory of large-scale dynamic systems in control theory [16]. Reasons for decomposing are multiple. One reason is conceptual. For example connection of the immune system and the parasitic systems is a natural biological decomposition. Others reasons are for the sake of reducing algorithmic complexities or introducing intended behavior ...In this case subsystems may not have biological interpretation. For example a chain of compartments can be introduced to simulate a continuous delay [14], [15]. Analysis of the structure of epidemiological and immunological systems is vital because of the paucity of data and the dependence of behavior on biological hypotheses. The issue is to identify those parts of models that have most effects on dynamics. The concepts and techniques of interconnection of systems (large-scale systems) will be useful in this regard.

In mathematical modeling in epidemiology and immunology, as in most other areas of mathematical modeling, there is always a trade-off between simple models, that omit details and are designed to highlight general qualitative behavior, and detailed models, usually designed for specific situations, including short-terms quantitative predictions. Detailed models are generally difficult to study analytically and hence their usefulness for theoretical purposes is limited, although their strategic value may be high. Simple models can be considered as building blocks of models that include detailed structure. The control theory tools of large-scale systems and interconnections of systems is a mean to conciliate the two approaches, simple models versus detailed systems.

### 3.3. Dynamic Problems

Many dynamical questions addressed by Systems Theory are precisely what biologist are asking. One fundamental problem is the problem of equilibria and their stability. To quote J.A. Jacquez

A major project in deterministic modeling of heterogeneous populations is to find conditions for local and global stability and to work out the relations among these stability conditions, the threshold for epidemic take-off, and endemicity, and the basic reproduction number

The basic reproduction number  $\mathcal{R}_0$  is an important quantity in the study in epidemics. It is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible. The basic reproduction number  $\mathcal{R}_0$  is often considered as the threshold quantity that determines when an infection can invade and persist in a new host population. To the problem of stability is related the problem of robustness, a concept from control theory. In other words how near is the system to an unstable one ? Robustness is also in relation with uncertainty of the systems. This is a key point in epidemiological and immunological systems, since there are many sources of uncertainties in these models. The model is uncertain (parameters, functions, structure in some cases), the inputs also are uncertain and the outputs highly variable. That robustness is a fundamental issue and can be seen by means of an example : if policies in public health are to be taken from modeling, they must be based on robust reasons!

### 3.4. Observers

The concept of observer originates in control theory. This is particularly pertinent for epidemiological systems. To an input-output system, is associated the problem of reconstruction of the state. Indeed for a given system, not all the states are known or measured, this is particularly true for biological systems. This fact is due to a lot of reasons : this is not feasible without destroying the system, this is too expensive, there are no available sensors, measures are too noisy ...The problem of knowledge of the state at present time is then posed. An observer is another system, whose inputs are the inputs and the outputs of the original system and whose output gives an estimation of the state of the original system at present time. Usually the estimation is required to be exponential. In other words an observer, using the signal information of the original system, reconstructs dynamically the state. More precisely, consider an input-output nonlinear system described by

$$\begin{cases} \dot{x} = f(x, u) \\ y = h(x), \end{cases} \quad (1)$$

where  $x(t) \in \mathbb{R}^n$  is the state of the system at time  $t$ ,  $u(t) \in U \subset \mathbb{R}^m$  is the input and  $y(t) \in \mathbb{R}^q$  is the measurable output of the system.

An observer for the the system (1) is a dynamical system

$$\dot{\hat{x}}(t) = g(\hat{x}(t), y(t), u(t)), \quad (2)$$

where the map  $g$  has to be constructed such that: the solutions  $x(t)$  and  $\hat{x}(t)$  of (1) and (2) satisfy for any initial conditions  $x(0)$  and  $\hat{x}(0)$

$$\|x(t) - \hat{x}(t)\| \leq c \|x(0) - \hat{x}(0)\| e^{-at}, \quad \forall t > 0.$$

or at least  $\|x(t) - \hat{x}(t)\|$  converges to zero as time goes to infinity.



The problem of observers is completely solved for linear time-invariant systems (LTI). This is a difficult problem for nonlinear systems and is currently an active subject of research. The problem of observation and observers (software sensors) is central in nonlinear control theory. Considerable progress has been made in the last decade, especially by the “French school”, which has given important contributions (J.P. Gauthier, H. Hammouri, E. Busvelle, M. Fliess, L. Praly, J.L. Gouze, O. Bernard, G. Sallet ) and is still very active in this area. Now the problem is to identify relevant class of systems for which reasonable and computable observers can be designed. The concept of observer has been ignored by the modeler community in epidemiology, immunology and virology. To our knowledge there is only one case of use of an observer in virology ( Velasco-Hernandez J. , Garcia J. and Kirschner D. [17]) in modeling the chemotherapy of HIV, but this observer, based on classical linear theory, is a local observer and does not allow to deal with the nonlinearities.

### 3.5. Delays

Another crucial issue for biological systems is the question of delays. Delays, in control theory, are traditionally discrete (more exactly, the delays are lags) whereas in biology they usually are continuous and distributed. For example, the entry of a parasite into a cell initiates a cascade of events that ultimately leads to the production of new parasites. Even in a homogeneous population of cells, it is unreasonable to expect that the time to complete all these processes is the same for every cell. If we furthermore consider differences in cell activation state, metabolism, position in the cell cycle, pre-existing stores of nucleotides and other precursors needed for the reproduction of parasites, along with genetic variations in the parasite population, such variations in infection delay times becomes a near certainty. The rationale for studying continuous delays are supported by such considerations. In the literature on dynamical systems, we find a wealth of theorems dealing with delay differential equations. However they are difficult to apply. Control theory approaches (interconnections of systems), is a mean to study the influence of continuous delays on the stability of such systems. We have obtained some results in this direction [5].

## 4. Application Domains

### 4.1. Metapopulation models

Heterogeneity plays an important role in many infectious disease processes. For instance, spatial heterogeneity is a strong determinant of host-parasite relationships. In modeling spatial or geographic effects on the spread of a disease, a distinction is usually made between diffusion and dispersal models. In diffusion models, spread is to immediately adjacent zones, hence the phenomenon of traveling waves can appear. These models traditionally use partial differential equations. However, there are some important situations that cannot be modeled by PDE. This is the case when the space considered is discrete. For example, when we have to consider sparsely populated regions, the human population is located in patches. The organization of human-hosts into well-defined social units such as families, villages or cities, are good examples of patches. Another example arises in the study of the human African Trypanosomiasis. The vector is the tse-tse fly, and it is known that flies take fewer blood meals in villages than in coffee plantations where the villagers work during the day. For such situations where human or vectors can travel a long distance in a short period of time, dispersal models are more appropriate. These models consider migration of individuals between patches. The infection does not take place during the migration process. The situation is that of a directed graph, where the vertices represent the patches and the arcs represent the links between patches. Recently, there has been increased interest in these deterministic metapopulation disease models. We have generalized to  $n$  patches the Ross-Macdonald model which describes the dynamics of malaria. We incorporate in our model the fact that some patches can be vector free. We assume that the hosts can migrate between patches, but not the vectors. The susceptible and infectious individuals have the same dispersal rate. We compute the basic reproduction ratio  $\mathcal{R}_0$ . We prove that if  $\mathcal{R}_0 \leq 1$ , then the disease-free equilibrium is globally asymptotically stable. When  $\mathcal{R}_0 > 1$ , we prove that there exists a unique endemic equilibrium, which is globally asymptotically stable on the biological domain minus the disease-free equilibrium.

MASAIE is developing, in the framework of the CAPES-COFECUB project (see international program), a metapopulation model for dengue. This model is for the state of Rio and is using the data of foundation FIOCRUZ.

## 4.2. Estimating total parasite load in falciparum malaria patients

We give a brief review of the biological features of malaria. Malaria in a human begins with an inoculum of *Plasmodium* parasites (sporozoites) from a female *Anopheles* mosquito. The sporozoites enter the liver within minutes. After a period of asexual reproduction in the liver, the parasites (merozoites) are released in the bloodstream where the asexual erythrocyte cycle begins. The merozoites enter red blood cells (RBC), grow and reproduce over a period of approximately 48 hours after which the erythrocyte ruptures releasing daughter parasites that quickly invade a fresh erythrocyte to renew the cycle. This blood cycle can be repeated many times, in the course of which some of the merozoites instead develop in the sexual form of the parasites : gametocytes. Gametocytes are benign for the host and are waiting for the mosquitoes. An important characteristic of *Plasmodium falciparum*, the most virulent malaria parasite, is sequestration. At the half-way point of parasite development, the infected erythrocyte leaves the circulating peripheral blood and binds to the endothelium in the microvasculature of various organs where the cycle is completed. A measurement of *Plasmodium falciparum* parasitaemia taken from a blood smear therefore samples young parasites only. Physician treating malaria use the number of parasites in peripheral blood smears as a measure of infection, this does not give the total parasite burden of the patient. Moreover antimalarial drugs are known to act preferentially on different stages of parasite development. Our work consists in developing tools for estimating the sequestered parasites and hence the total parasite burden of the patient.

## 5. New Results

### 5.1. Metapopulation

In the framework of metapopulation models we have obtained some new results. We have studied a metapopulation model with  $n$  patches. The migration model is with residents and travelers and the epidemic model is of SIS type. In particular, we have proved analytically the conjecture of Arino and van den Driessche [12]. The global behavior of the system is addressed in [10].

We are also currently studying, with our brazilian partners in the framework of the CAPES-COFECUB project (see international program), a metapopulation model for studying the propagation of dengue in the state of Rio. We use data provided by the foundation FIOCRUZ. These data concern different epidemics in RIO between 1986 to 2006. The effects of transportation system are taken into account.

We have considered a reduced system represented by Figure 2. The outputs of the model compare favorably with the actual data (Figure 3).

### 5.2. Identification and state estimation

We identify some unknown parameters using the framework of observers.

We have used numerical observers to identify the transmission parameters of bilharzia.

We also have used observers for models with unknown inputs to identify the transmission parameters for intra-host models of malaria. We have developed a method for estimating total parasite load in *falciparum* malaria patients using the clinical observations of peripheral parasitaemia. We have applied this method using the data from malariatherapy. The results are illustrated in Figure 4.

### Public transport flow in Rio



Figure 1. Transportation system in Rio

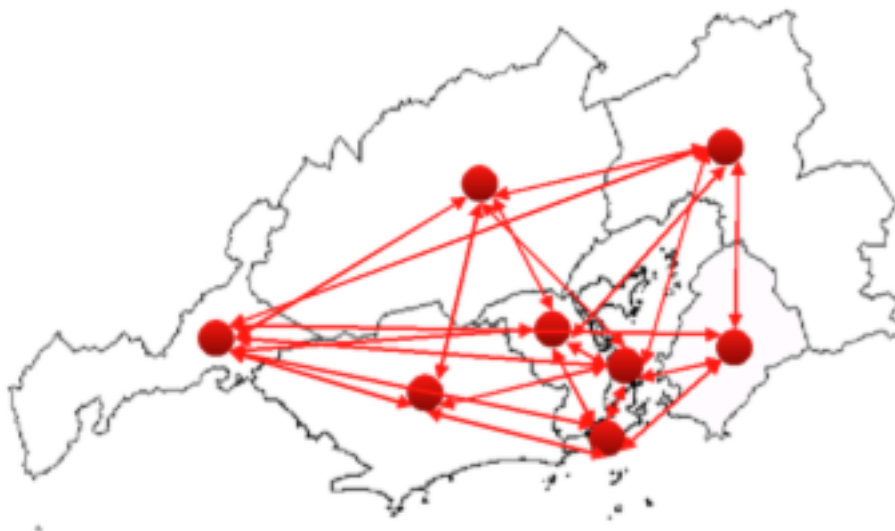


Figure 2. Reduced metapopulation model

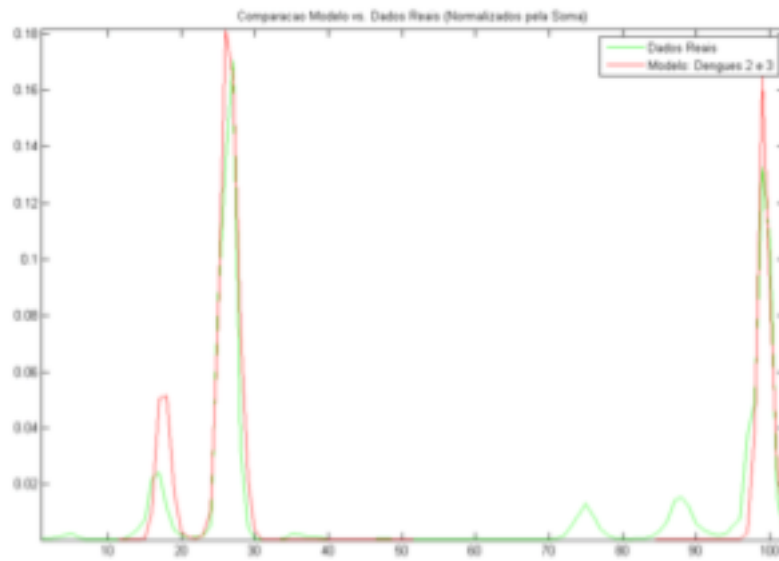


Figure 3. Model vs data

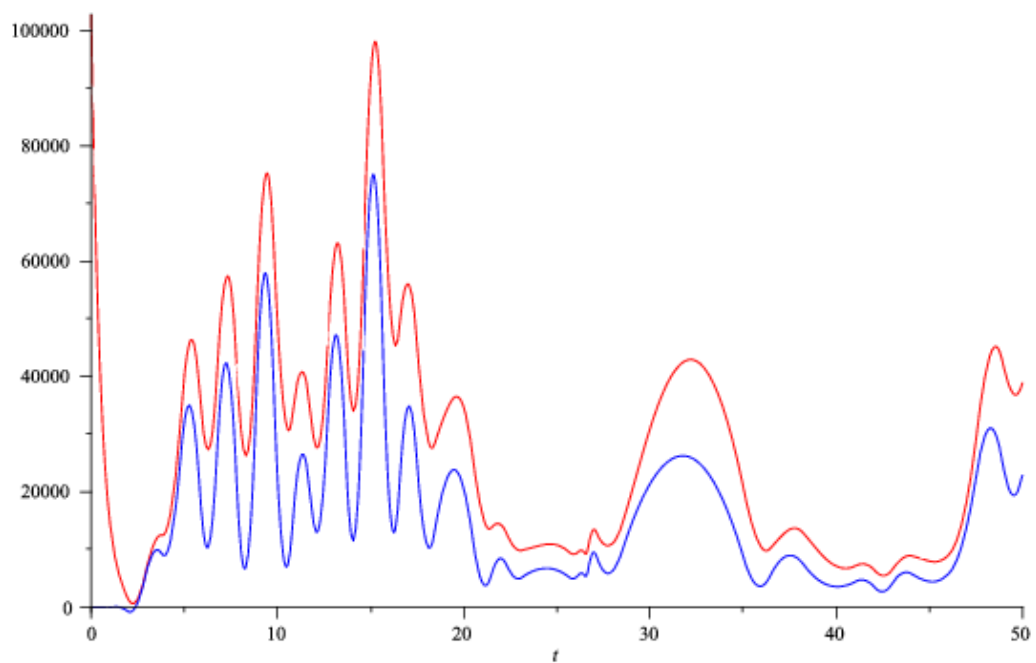


Figure 4. Estimated total parasite load (red) and parasitaemia measures (blue)

## 6. Contracts and Grants with Industry

### 6.1. Contract with IAEA

*Anopheles arabiensis* is the target of a sterile insect technique (SIT) program in Sudan. Success will depend in part upon reasonable estimates of the adult population in order to plan the sizes of releases. It is difficult to obtain good estimates of adult population sizes for this mosquito because of the low density of the populations and also because the temporal and spatial distribution of *Anopheles arabiensis* is very dynamic. We have developed a compartmental model capable of predicting the range of adult populations of *Anopheles arabiensis* in two study sites in the North of Sudan. We have provided a software that is “user friendly” and that is able to give an estimate of the whole male and female population for the two geographical areas. A screenshot of the soft user interface is presented in Figure 5.

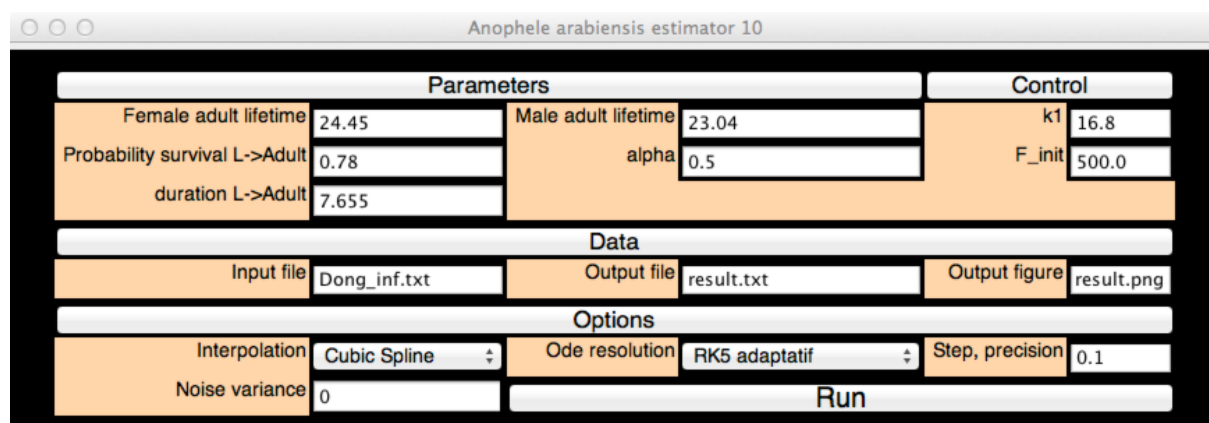


Figure 5. *Anopheles estimator*: screenshot of the soft user interface

## 7. Partnerships and Cooperations

### 7.1. Regional Initiatives

MASAIE has obtained a grant from Région Lorraine for a research project : “Dynamique des populations de pathogènes”.

### 7.2. International Initiatives

#### 7.2.1. Participation In International Programs

MASAIE is involved in a cooperation program with Brazil. This project, funded by CAPES-COFECUB, “new methods in epidemiology and early detection of events” for 4 years, has begun in January 2011.

A. Iggidr and G. Sallet have spent 3 weeks in Brazil and M-L Penna (UFF) and M. De Souza (UFF) has visited MASAIE in 2011. This program includes Federal University Fluminense (Rio), Unicam (Caminas), UPFE (Recife) , Foundation Fiocruz (Brazilian Ministry of Health), Foundation Getulio Vargas and IMPA. A research program on dengue has been established and a common paper is under writing. The common research team is constituted half by mathematicians and computer scientist and half by public health researchers.

### 7.2.1.1. EPLS

MASAIE has developed a cooperation with Pasteur Institute and EPLS to model Bilharzia on Senegal river basin.

## 8. Dissemination

### 8.1. Animation of the scientific community

G. Sallet was invited speaker in "Exploratory Workshop on Emerging Infectious Diseases and Mathematical Modelling" July 11 to 15, 2011, CRM Barcelona (<http://www.crm.es/>)

G. Sallet has organized with D. Bekollé and R. Walo a CIMPA School in Kinshasa (RDC) "Systèmes Dynamiques dans des Variétés et Applications " <http://www.cimpa-icpam.org/spip.php?article311>

G. Sallet has organized a workshop in Kenya on "mathematical epidemiology" October 29-November 6. (<http://www.ambafrance-ke.org/spip.php?rubrique407> gazette 11, décembre 2011)

### 8.2. Teaching

Master: Systèmes dynamiques monotones et applications, 29h, M2, Université Paul Verlaine, Metz, France (Abderrahman Iggidr);

Master: Equations différentielles et applications à l'épidémiologie, 30h, M2, Université Polytechnique de Bobo-Dioulasso, Burkina Faso (Abderrahman Iggidr);

Mathematical epidemiology, 2h, Pasteur Institute, Paris (Gauthier Sallet).

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## Publications of the year

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