INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

# *Project-Team masaie*

# *Tools and models of nonlinear control theory for epidemiology and immunology*

*Nancy - Grand Est*

Theme : Observation and Modeling for Environmental Sciences

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# 1. Team

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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 modellers, 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 subsaharian 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 [21] 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 [24]. 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 [22], [23]. 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

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

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

$$\dot{\widehat{x}}(t) = g(\widehat{x}(t), y(t), u(t)), \tag{2}$$

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

$$\|x(t) - \widehat{x}(t)\| \leq c\, \|x(0) - \widehat{x}(0)\|\, e^{-a\,t}\ ,\ \ \forall t > 0.$$

or at least $\|x(t) - \widehat{x}(t)\|$ 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. [25]) 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].

## 3.6. Dealing with heterogeneity using Complex Model

### *3.6.1. Modeling and analysis of epidemiological models*

We are considering general classes of models to address some epidemiological peculiarity. For example we consider and analyze a class of models [3], [4] under the general form

$$\begin{cases} \dot{x} = \varphi(x) \; - \; x \, \langle \beta \mid C \, y \rangle \\ \dot{y} = x \, P \;\; \mathrm{diag}(\beta) \, C \, y + \; A \, y - u \, x \;\; \mathrm{diag}(\beta) \, C y \end{cases} \tag{3}$$

where $x \in \mathbb{R}_+$ represents the concentration of susceptible individuals or target cells, $y \in \mathbb{R}_+^n$ represents the different class of latent, infectious and removed individuals. The matrix $C$ is a nonzero $k \times n$ nonnegative matrix, $\beta \in \mathbb{R}_+^k$ is a positive vector, $P$ denotes a linear projection, $A$ is a stable Metzler matrix and $\langle . \mid . \rangle$ denotes a scalar product in $\mathbb{R}^n$. The function $\varphi(x)$ describes the recruitment (or the demography) of susceptible individuals or cells and the quantity $x\langle \beta \mid C \, y \rangle$ represents the infection transmission. For some diseases, a bilinear infection transmission function $x\langle \beta \mid C \, y \rangle$ is not adequate so we have to replace in equation (3) the expression $C \, y$ by a more general non-linear incidence function $C \, f(y)$. The parameter $u$ takes only the value 0 or 1.

The model (3) represents either the transmission of a directly transmitted disease (i.e transmitted by adequate contact, Ebola, Tuberculosis, ...), in this case $u = 0$, or represents the intra-host dynamics of a parasite with target cells. To illustrate this claim we will give two examples.

The system (3) can represent the so called DI, SP or DISP models. In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been made. In the staged-progression (SP) hypothesis, the infected individuals sequentially pass through a serie of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity for many years, and finally becoming gradually more infectious as their immune system breaks down and they progress to AIDS. Based on other clinic findings and blood serum level studies, another hypothesis is the differential infectivity (DI) hypothesis, where infected individuals enter one of several groups $j$ ($j = 1...n$) with probability $\pi_j$, depending on their infectivity, and stay in that group until they develop AIDS. If we denote by $S$ the density of susceptible individuals, $I_i$ the density of the different classes of infectious individuals, the DI model can be represented by a compartmental model:

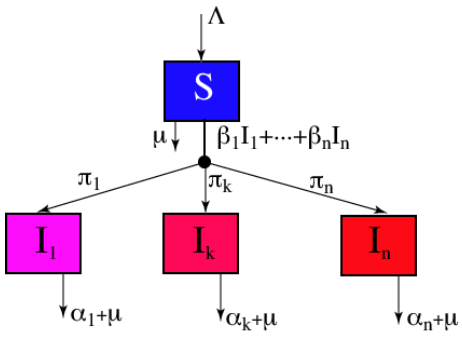


*Figure 1. DI model flow graph*

which gives the differential equation

$$\begin{cases} \dot{S} = \Lambda - \mu\, S - S \sum_{j=1}^{n} \beta_j\, I_j \\ \dot{I}_1 = \pi_1\, S \sum_{j=1}^{n} \beta_j\, I_j \; - \; (\mu + \alpha_1)\, I_1 \\ \vdots \\ \dot{I}_j = \pi_j\, S \sum_{j=1}^{n} \beta_j\, I_j \; - (\mu + \alpha_j)\, I_j \\ \vdots \\ \dot{I}_n = \pi_n\, S \sum_{j=1}^{n} \beta_j\, I_j \; - (\mu + \alpha_n)\, I_n \end{cases} \tag{4}$$

where $\Lambda$ is an input flow (or a recruitment rate) which is supposed to be constant, $\mu$ is the natural death rate of the population. For each $j$ the parameter $\beta_j$ is the contact rate, i.e., the rate at which susceptibles meet infectious individuals belonging to the class $j$, the parameter $\alpha_j$ is the disease-related death rate of the class $j$ and $\sum_{j=1}^{n} \pi_j = 1$

Similarly the SP model can be represented by

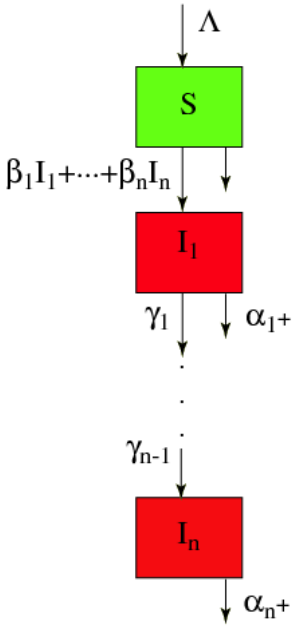


*Figure 2. SP model flow graph*

The parameter $\gamma_j$ denotes the fractional rate of transfer of infected from the stage $j$ to the stage $j+1$. The dynamical progression of the disease can be represented by the differential equation:

$$\begin{cases} \dot{S} = \Lambda - \mu\, S - S \sum_{j=1}^{n} \beta_j\, I_j \\ \dot{I}_1 = S \sum_{j=1}^{n} \beta_j\, I_j \; - \; (\gamma_1 + \mu + \alpha_1)\, I_1 \\ \dot{I}_2 = \gamma_1\, I_1 - (\gamma_2 + \mu + \alpha_2)\, I_2 \\ \vdots \\ \dot{I}_j = \gamma_{j-1}\, I_{j-1} - (\gamma_j + \mu + \alpha_j)\, I_j \\ \vdots \\ \dot{I}_n = \gamma_{n-1}\, I_{n-1} - (\mu + \alpha_n)\, I_n \end{cases} \tag{5}$$

The DISP is the combination of these two structures. These models are easily put under the general form. (3). This general form can also represents intra-host models : We sketch the example of malaria [4]. 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. Hence to model the dynamics of parasitized erythrocytes, it is natural to introduce different classes. Then we propose the following model

$$\begin{cases} \dot{x} = \varphi(x) - \beta x\, m \\ \dot{y}_1 = \beta x\, m - \alpha_1\, y_1 \\ \dot{y}_2 = \gamma_1\, y_1 - \alpha_2\, y_2 \\ \dots \\ \dot{y}_k = \gamma_{k-1}\, y_{k-1} - \alpha_k\, y_k \\ \dot{m} = r\, \gamma_k\, y_k - \mu_m\, m - \beta\, x\, m \end{cases} \tag{6}$$

where the variable $x$ denotes the concentration of uninfected RBC, the variable $y_j$ is the concentration of parasitized red blood cell (PRBC) of class $j$, and $m$ is the concentration of the free merozoites in the blood. The example of malaria gives an example where stages in modeling are created for biological reasons. We have seen before that continuous delays are important to be modeled. The process of converting time-delay integro-differential equations in a set of ODE is coined by MacDonald [23] as the linear chain trick. In other community this is also known as the method of stages. Actually any distribution can be approximated by a combination of stages in series and in parallel (Jacquez). This process consists to insert stages in the model. This is an example of stages created to take into account a behavior. This added stages have no biological meaning. Our general model is also well suited for this process.

The general model (3) can take into account the case of different strains for the parasites and can be adapted to cope with vector transmitted diseases. Then we have a building block to model complex systems. System (3) describes the basic model which can be extended, by introducing interconnections of blocks of the form (3), to describe more complex systems : more classes of susceptible can be introduced, the recruitment of susceptible individuals can be replaced by an output of an explicit model of the population dynamics, each sub-system describes what happens in a patch, inflows and outflows can be introduced to model the population movement between patches, different strains for the pathogen can be introduced, others systems can bring input in these models (e.g. the immune system) ...

This general form will be used to model some well-identified diseases for which we have data and expert collaborators (e.g. malaria, dengue, Ebola ...). This form has to be tailored to the particular case considered. For example the matrix $A$ represents connections and the structure of this matrix $A$ (triangular, Hessenberg, sparse ...) depends on the disease.

# 4. Application Domains

## 4.1. Modeling the building of immunity to malaria

In modeling the reaction of the immune system to a *Plasmodium falciparum* infection. Malaria infection gives rise to host responses which are regulated by both the innate and acquired immune system as well as by environmental factors. Acquired immunity is species- and stage-specific. A malaria infection initiates a complicated cascade of events. The regulation of this complex system with numerous feedbacks is intricately balanced. The objective is to build a computer model which allows to test the dynamics of malaria infection. This research is conducted in collaboration with immunologists. We collaborate also with B. Cazelles and

J.F. Trape of the research unity 77 “Afro-tropical epidemiology" of IRD in Sénégal. The steady increase of *Plasmodium falciparum* resistance to cheap first line antimalarials over the last decades has resulted in a dramatic increase in malaria-associated morbidity and mortality in sub-Saharan Africa. Research in recent years has established that resistance to chloroquine (CQ), pyrimethamine has been controlled and constantly monitored for more than a decade, coinciding to the time period of expansion of CQ- and SP-resistance across Africa.

The longitudinal active case detection study launched in Dielmo in 1990 by the UR77 of IRD, a rural Senegalese village, is probably the only place where drug use has been controlled and constantly monitored for more than a decade, coinciding to the time period of expansion of CQ- and SP-resistance across Africa. This is an unprecedented opportunity to quantify the impact of a strictly controlled use of antimalarials on drug resistance. Furthermore, first line treatment was changed in 1995, allowing to explore its consequences on dynamics of spreading of drug resistance.

## 4.2. 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 examplearises 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.

# 5. Contracts and Grants with Industry

## 5.1. 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. MASAIE will provide a compartmental model capable of predicting the range of adult populations of Anopheles arabiensis in two study sites in the North of Sudan.

# 6. Other Grants and Activities

## 6.1. Regional Initiatives

MASAIE has obtained a two year grant from Région Lorraine for an emerging project : “Modélisation et simulation de maladies transmissibles par vecteurs"

## 6.2. International Initiatives

### *6.2.1. SARIMA*

MASAIE is involved with the SARIMA project (Soutien aux Activités de Recherche en Informatique et Mathématiques en Afrique). G. Sallet and A. Iggidr have given lectures in Saint-Louis at master level.

### *6.2.2. AIRES-SUD project IRD*

A “AIRES-SUD" projet has been accepted with MASAIE and the LANI (Laboratoire d’Analyse Numérique et Informatique) laboratory of the university Gaston Berger of Saint-Louis for 2008-2011.

### *6.2.3. University Gaston Berger Saint-Louis*

G. Sallet has a special expatriation appointment in the university of Saint-Louis (Sénégal) (September 2009-August 2011)

### *6.2.4. CAPES-COFECUB*

MASAIE has applied to a cooperation program with Brazil and has obtained a project “new methods in epidemiology and early detection of events" for 4 years, starting in January 2011. CAPES and COFECUB finance the exchange of Brazilian and French researchers (who perform job missions) and Brazilian and French graduate students (through scholarships).

### *6.2.5. EPLS*

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

# 7. Dissemination

## 7.1. Animation of the scientific community

G. Sallet and A. Iggidr with J. Arino (university of Manitoba) have organized a **MITACS-CDM-INRIA-IRD Summer School** on Mathematical Epidemiology "Mathematical Modeling of ÊInfectious Diseases" in Saint-Louis, July 19-27, 2010. This school has been funded by MITACS-Centre for Disease Modelling, IRD, University Gaston Berger of Saint-Louis.

A. Iggidr has organized with K. Niri (university Ain Chock, Casablanca) and S. Touzeau (INRA) EPICASA 2010 in Casablanca, April 5–16, 2010. https://colloque.inra.fr/epicasa09

G. Sallet was invited speakers in the “Summer 2010 Thematic Program on the Mathematics of Drug Resistance in Infectious Diseases", August 3-13, 2010 Theme Weeks on Transmission Heterogeneity organized in Fields Institute (Toronto) http://www.fields.utoronto.ca/programs/scientific/10-11/drugresistance/transmission/index.html

G. Sallet was invited speaker in JOBIM Montpellier 2010, September 6, 2010. http://www.jobim2010.fr/?q=fr/node/24

## 7.2. Teaching

G. Sallet has given a 20 hours lecture in Saint-Louis at master 2 level.

G. Sallet has given a 10 hours lecture in Yaoundé at master 2 level.

A. Iggidr has given a 6 hours lecture in EpiCasa.

## 7.3. Phd Thesis

A. Fall defended his thesis "Etude de quelques modèles épidémiologiques : Application à la transmission du virus de l'hépatite B en Afrique subsaharienne (cas du Sénégal)". March 18, 2010.

A. Fall has obtained a post-doc position in the Mathematical Biosciences Institute (Ohio State University).

A. Iggidr defended his HDR, December 9, 2010, University of Nice Sophia-Antipolis : "Analyse, observation et contrôle de certains bio-systèmes"

# 8. Bibliography

## Major publications by the team in recent years

[1] P. ADDA, J.-L. DIMI, A. IGGIDR, J.-C. KAMGANG, G. SALLET, J.-J. TEWA. *General models of host-parasite systems. Global analysis.*, in "Discrete Contin. Dyn. Syst., Ser. B", 2007, vol. 8, n$^{o}$ 1, p. 1-17.

[2] P. AUGER, E. KOUOKAM, G. SALLET, M. TCHUENTE, B. TSANOU. *The Ross-Macdonald model in a patchy environment*, in "Mathematical Biosciences", 2008, vol. 216, n$^{o}$ 2, p. 123–131.

[3] A. A. FALL, A. IGGIDR, G. SALLET, J.-J. TEWA. *Epidemiological models and Lyapunov techniques*, in "Mathematical Modelling of Natural Phenomena", 2007, vol. 2, n$^{o}$ 1, p. 55-72.

[4] A. IGGIDR, J.-C. KAMGANG, G. SALLET, J.-J. TEWA. *Global analysis of new malaria intrahost models with a competitive exclusion principle.*, in "SIAM J. Appl. Math.", 2006, vol. 67, n$^{o}$ 1, p. 260-278.

[5] A. IGGIDR, J. MBANG, G. SALLET. *Stability analysis of within-host parasite models with delays.*, in "Math. Biosci.", 2007, vol. 209, n$^{o}$ 1, p. 51-75.

[6] A. IGGIDR, J. MBANG, G. SALLET, J.-J. TEWA. *Multi-compartment models*, in "Discrete Contin. Dyn. Syst.", 2007, n$^{o}$ Dynamical Systems and Differential Equations. Proceedings of the 6th AIMS International Conference, suppl., p. 506–519.

[7] D. NGOM, A. IGGIDR, A. GUIRO, A. OUAHBI. *An Observer for a Nonlinear Age-Structured Model of a Harvested Fish Population*, in "Mathematical Biosciences and Engineering", 2008, vol. 5, n$^{o}$ 2, p. 337 –354.

## Publications of the year

### Doctoral Dissertations and Habilitation Theses

[8] A. A. FALL. *Etude de quelques modèles épidémiologiques : application à la transmission du virus de l'hépatite B en Afrique subsaharienne (Sénégal).*, UPV-Metz, March 2010, http://www.theses.fr/2010METZ003S.

[9] A. IGGIDR. *Analyse, observation et contrôle de certains bio-systèmes.*, Université de Nice Sophia Antipolis, décembre 2010, HDR, http://tel.archives-ouvertes.fr/docs/00/55/75/88/PDF/hdrigg1Hal.pdf.

### Articles in International Peer-Reviewed Journal

[10] B. BONZI, A. A. FALL, A. IGGIDR, G. SALLET. *Stability of differential susceptibility and infectivity epidemic models.*, in "Journal of Mathematical Biology", February 2010, vol. Online First [*DOI :* 10.1007/s00285-010-0327-y], http://www.springerlink.com/content/0612425711325kh4/, http://hal.inria.fr/inria-00544315/en.

[11] A. IGGIDR, K. NIRI, E. OULD MOULAY ELY. *Fluctuations in a SIS epidemic model with variable size population*, in "Applied Mathematics and Computation", 2010, vol. 217, n° 1, p. 55-64 [*DOI :* 10.1016/j.amc.2010.03.040], http://www.sciencedirect.com/science/article/B6TY8-4YKGJ16-3/2/994381a120a4a11cfc4e5726c8c5cff3, http://hal.inria.fr/inria-00551771/en.

[12] D. NGUYEN NGOC, R. B. DE LA PARRA, M. A. ZAVALA, P. AUGER. *Competition and species coexistence in a metapopulation model: Can fast asymmetric migration reverse the outcome of competition in a homogeneous environment?*, in "Journal of Theoretical Biology", 9 2010, vol. 266, n° 2, p. 256–263, http://www.sciencedirect.com/science/article/B6WMD-50CVR8K-1/2/bd208973d2ce7736a94055d06679a5dd.

### International Peer-Reviewed Conference/Proceedings

[13] P. AUGER, G. SALLET, M. TCHUENTE, B. TSANOU. *Multiple endemic equilibria for the multipatch Ross-Macdonald with fast migrations*, in "Proc. 10th Biennal CARI Congress.", Côte d'Ivoire, Yamoussoukro, 2010, http://www.cari-info.org/cari2010.php.

[14] D. BICHARA, A. A. FALL, G. SALLET, P. ADDA. *A SIR model with differential mortality and constant population*, in "Proc. 10th Biennal CARI Congress.", Côte d'Ivoire, Yamoussoukro, 2010, http://www.cari-info.org/cari2010.php.

[15] G. RIVEAU, G. SALLET, L. TENDENG. *A transmission Model of Bilharzia*, in "Proc. 10th Biennal CARI Congress.", Côte d'Ivoire, Yamoussoukro, 2010, http://www.cari-info.org/cari2010.php.

### Workshops without Proceedings

[16] P. ADDA, L. N. NKAMBAA, G. SALLET, L. CASTELLI. *A SVEIR model with Imperfect Vaccine*, in "CMPD 3 Conference on Computational and Mathematical Population Dynamics.", France Bordeaux, June 2010, http://www.sm.u-bordeaux2.fr/CMPD3/Programme.html.

[17] D. BICHARA, A. IGGIDR, G. SALLET. *A competitive exclusion principle for sis and sir models with n strains.*, in "CMPD 3 Conference on Computational and Mathematical Population Dynamics.", France Bordeaux, June 2010, http://hal.inria.fr/inria-00552158/en.

[18] A. A. FALL, A. IGGIDR, G. SALLET. *A compartimental model of hbv with vertical transmission*, in "CMPD 3 Conference on Computational and Mathematical Population Dynamics.", France Bordeaux, June 2010, http://hal.inria.fr/inria-00552188/en.

[19] A. GUIRO, A. IGGIDR, D. NGOM. *On the regulation of a harvested fish population*, in "Troisième Conférence Internationale de la SFBT - SFBT2010", Tunisia Tunis, June 2010, http://hal.inria.fr/inria-00552193/en.

[20] A. IGGIDR, K. NIRI, G. SALLET. *Analysis of a sis epidemic model in a patchy environment*, in "Troisième Conférence Internationale de la SFBT - SFBT2010", Tunisia Tunis, June 2010, http://hal.inria.fr/inria-00552197/en.

## References in notes

[21] H. BOGREAU, F. RENAUD, H. BOUCHIBA, P. DURAND, S.-B. ASSI, M.-C. HENRY, E. GARNOTEL, B. PRADINES, T. FUSAI, B. WADE, E. ADEHOSSI, P. PAROLA, M. A. KAMIL, O. PUIJALON, C. ROGIER. *Genetic diversity and structure of African Plasmodium falciparum populations in urban and rural areas.*, in "Am J Trop Med Hyg", 2006, vol. 74, n$^{o}$ 6, p. 953–959.

[22] J. A. JACQUEZ, C. P. SIMON. *Qualitative theory of compartmental systems with lags*, in "Math. Biosci.", 2002, vol. 180, p. 329-362.

[23] N. MACDONALD. *Time lags in biological models*, Lecture Notes in Biomath., Springer-Verlag, 1978, n$^{o}$ 27.

[24] D. SILJAK. *Large-scale dynamic systems. Stability and structure*, system science and engineering, Elsevier North-Holland, 1978.

[25] J. X. VELASCO-HERNÁNDEZ, J. A. GARCÍA, D. E. KIRSCHNER. *Remarks on modeling host-viral dynamics and treatment.*, in "Mathematical approaches for emerging and reemerging infectious diseases: An introduction. Proceedings of a tutorial Introduction to epidemiology and immunology", IMA Vol. Math. Appl., Springer, 2002, vol. 125, p. 287-308.