Special Session 21: Dynamical Systems and Control in Biology

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In this session we expect to have talks either about differential equations (in the large sense), or on control problems arising mathematical biology. Theoretical aspects of models in biology (Population dynamics, Cell proliferation, Epidemiology, ...) will be presented. Some papers will focus on modelling and mathematical analysis of problems arising in biology while others will examine control methods for infectious diseases or population dynamics.

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The control of some population dynamics. Dependence on the support of the control

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This paper concerns some internal optimal control and internal stabilization problems related to population dynamics. The main goal is to investigate the magnitude of the control as well as the dependence of these problems on the position and shape of the support of the control. Algorithms to approximate the optimal position or optimal shape of the support of the control are indicated.

Key words: Population dynamics; Epidemic system; Optimal control; Stabilization

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The basic reproduction number R0 for infectious diseases in a periodic environment

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We would like to present: - a definition of the basic reproduction number R0 for vector-borne diseases with a periodic vector population or for directly tranmitted diseases with a periodic contact rate; - a numerical scheme to compute R0, which is the spectral radius of a linear integral operator on a space of periodic functions; - approximate formulas for R0 when the vector population or the contact rate is sinusoidal; - an estimation of R0 for an epidemic of cutaneous leishmaniasis in Morocco; - an estimation of R0 for an epidemic of chikungunya in France.

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Travelling waves analysis of a reaction-diffusion model describing a powdery mildew epidemics over a vineyard

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In this talk we investigate the structure of travelling waves for a model of a fungal disease over a vineyard. This model is based upon a set of ODEs of SIR-type coupled with two reaction-diffusion equations describing the dispersal inside and over the vineyard of the spores produced by the fungus. An estimate of the order of magnitude of the various biological parameters of the model leads to a singular pertubation analysis, and we are able to compute the speed and shape of the travelling waves. Numerical simulations are presented as well.

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Bacteriophage dynamics: an age of infection structured model

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Bacteriophage are a yet promising, largely forgotten, weapon in the fight against antibiotic-resistant bacterial infections, for instance in biocontrol of farm chicken salmonellosis. The prey-predator dynamics virus-bacteria, including delays due to the latency period, the interaction with hosts immune system, the evolutionary dynamics of the mentioned latency period, the

optimal doses in therapeutic using, both for acute and for chronic diseases, the mutation-selection induced resistance to adsorption by the bacteria and the corresponding co-evolution of the viruses to overcome such resistances, etc. are topics which deserve a great effort of mathematical modelisation and analysis. The presentation will be an attempt to propose and analyse a model of phage-bacteria population dynamics taking into account the distribution of infected bacteria with respect to the age of infection and assuming a random latency time with a given probability distribution. The long term goal of this research would be twofold: in the theoretical biology field, to understand the evolutionarily stable values of the latency period, by considering it as a function valued trait; in the therapeutic field, to design optimal therapeutic policies related to the probably oscillating dynamics and hopefully, to the selected bacterial resistance to phage infection.

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On the effects of nonlinear boundary conditions in diffusive logistic equations on bounded domains

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In this talk we consider the diffusive logistic problem

$$\frac{\partial u}{\partial t} = d\nabla^2 u + ru(1-u) \quad \text{in } \Omega \times (0,\infty) \qquad (1)$$

$$\alpha(u)\nabla u \cdot \vec{\eta} + (1-\alpha(u))u = 0 \quad \text{on } \partial\Omega \times (0,\infty), \qquad (2)$$

where $u = u(x,t)$ designates the density of a biological species at spatial location x and time t, Ω designates a focal patch of habitat for the species in question, and the diffusion rade d and intrinsic per capita growth rate r are constant within Ω. Motivated by empirical studies on edge-mediated mechanisms producing an Allee effect in the Glanville fritillary butterfly, we posit that the function α in (2) be density dependent and nondecreasing in u and satisfy

$$\alpha([0,1]) \subseteq [0,1]. \qquad (3)$$

We find that this density dependence in (2) allows for a far richer range of asymptotic outcomes in (1)-(2) than would be the case where $\alpha = \alpha^* \in [0,1]$. By refining (3), we show in particular that (1)-(2) can exhibit Allee and/or threshold type effects as well as multiple equilibria.

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Modelling and Asymptotic Stability of a Growth Factor-Dependent Stem Cells Dynamics Model with Distributed Delay

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Under the action of growth factors, proliferating and non-proliferating hematopoietic stem cells differentiate and divide, so as to produce blood cells. Growth factors act at different levels in the differentiation process, and we consider their action on the mortality rate (apoptosis) of the proliferating cell population. We propose a mathematical model describing the evolution of a hematopoietic stem cell population under the action of growth factors. It consists of a system of two age-structured evolution equations modelling the dynamics of the stem cell population coupled with a delay differential equation describing the evolution of the growth factor concentration. We first reduce our system of three differential equations to a system of two nonlinear differential equations with two delays and a distributed delay. We investigate some positivity and boundedness properties of the solutions, as well as the existence of steady states. We then analyze the asymptotic stability of the two steady states by studying the characteristic equation with delay-dependent coefficients obtained while linearizing our system. We obtain necessary and sufficient conditions for the global stability of the steady state describing the cell population's dying out, using a Lyapunov function, and we prove the existence of periodic solutions about the other steady state through the existence of a Hopf bifurcation.

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Travelling wave solutions for an age-structured equation in epidemiology

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This talk is devoted to the study of travelling wave solutions for a reaction-diffusion equation with a structuration with respect to the age of the individuals. We present an existence result of solution together with some qualitative properties. More particularly we prove that these travelling waves are monotonic with respect to the propagation direction.

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Epidemics in an optimal economic growth model

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We present an economic model of optimal growth in which the population dynamics is affected by an infectious disease. The disease we are concerned with is AIDS. The objective of the social planner is assumed to be the discounted value of the utility of consummers. Control variables are consumption, as usually in economic growth models and health expenditures. The dynamics of the state variables take into account the fact that infected people are not able to work. Health expenditures affect the population dynamics. We show the existence of an optimal solution and analyze it. We give conditions under which an optimal path of public health intervention yields ultimately to the disappearance of the epidemics.

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Modelling and analysis of RSV-infection of cells

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The aim is a mathematical modelling and analysis of the dynamics resulting from the infection of cells by RSV virus. Infected cells produce virons and interferon, both of which are taken up by target cells. Viron uptake results in infection of target cells, interferon uptake in their becoming resistant. At first instance we analyze stability of the equilibria for the resulting five dimensional (three cell populations, virus, interferon) ODE model. Then we structure the infected cells by infection-age with the aim to study the effects of delay of either interferon or viron production.

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Stability and bifurcation analysis for a structured metapopulation model with an application to evolution of mutualism

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Structured metapopulation models were introduced about 15 years ago and they ahve been analysed and applied to a variety of ecological problems ever since. However, questions concerning stability and bifurcation have been treated rather intuitively than rigorously. In particular, up to now, there has been no rigorous proof of the principle of linearized (in)stability for structured metapopulation models. In this talk I give such a proof, based on recent joint results with O. Diekmann and Ph. Getto. As an application, I consider the evolution of mutualism in a plant-endophyte metapopulation.

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Selection-Mutation dynamics

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We investigate non linear selection-mutation models where the selection rate is very high with respect to the mutation rate. This typically induces the population to concentrate around a few traits which may then evolve.

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Stability of Equilibria for Piecewise Linear Models of Genetic Regulatory Networks

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A formalism based on piecewise-linear (PL) differential equations has been shown to be well-suited to modelling genetic regulatory networks. The discontinuous vector field inherent in the PL models leads to the approach of Filippov, which extends the vector field to a differential inclusion. We study the stability of equilibria (called singular equilibrium sets) that lie on the surfaces of discontinuity. We prove several theorems that characterize the stability of these singular equilibria directly from the state transition graph, which is a qualitative representation of the dynamics of the system. We also study some control problems.

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A model of Salmonella infection in industrial hen houses

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Salmonella is one of the major sources of toxi-infection in humans. Incidences of human salmonellosis have greatly increased over the past 20 years and this can largely be attributed to epidemics of S. enteritidis phage type 4 within poultry. The main concern with this bacterium is the existence of silent carriers, i.e. animals harbouring S. enteritidis without expressing any visible symptoms. In this talk, we will present a model for S. enteritidis transmission in hen houses, considering both the hens and the environmental bacterium contamination. By considering the hen's individual development of the disease, we build a model for the production of eggs contaminated by S. enteritidis. The objectives are to analyze the dynamic of the disease, and to provide understanding of measures to avoid the endemicity of S. enteritidis in industrial hen houses. Keywords: salmonella infection; models; reproductive number; asymptotic behaviour.

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From molecules to cellular regulation: Mathematical pathway analysis

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The talk will present some recent results from mathematical analysis of biological pathways. On one hand there is currently much research on master equations describing molecular interactions (for example in the proteome) in case only a low number of molecules are present. On a systems level there is a need to dissect for example metabolic pathways into smaller units. Here a concept from the chemical literature (extremal currents) proves to be very versatile and leads to complex mathematical questions. Both concepts will be tested and explained with the help of an example, the famous lac-operon of E. coli. We will discuss extensions to a spatial context and to cell population aspects using structured population models.

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Dynamic analysis for a competitive periodic stage structured system

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In this paper we derive a model describing the dynamics of HIV infection in tissue culture where the infection spreads from infected cells to healthy cells. The intracellular incubation period is modeled by the introduction of a distributed delay term in the growth of the infected cells. We assume in the model that there is a saturation effect in the proliferation process which occurs accordingly to the Michaelis-Menten law. The basic reproduction number R_0 for our model is derived by means of next generation matrix. Our analysis shows that if $R_0 \leq 1$, then the healthy equilibrium is globally attractive and if $R_0 > 1$, the infection is persistent. If the endemic equilibrium E^* is unstable we prove that infective oscillations may occur. Finally we give a parameter regions in which the endemic equilibrium E^* is globally attractive.

Keywords: Global attractors, Periodic solution, Permanence, Poincaré map, Spectral radius, Stage structure

AMS Subject Classifications: 34C11, 34C25, 34K12, 34K13, 34K25

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The effects of random dispersion in competing species models

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The main goal is to prove that random dispersion enhances permanence of competing species making precise evaluations on how this phenomenology occurs. Both, analytical and numerical results will be discussed.

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A Model of Antibiotic Resistant Bacterial Epidemics in Hospitals

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The development of drug-resistant strains of bacteria is an increasing threat to society, especially in hospital settings. Many antibiotics that were formerly effective in combating bacterial infections in hospital patients are no longer effective due to the evolution of resistant strains. The evolution of these resistant strains compromises medical care worldwide. In this article, we formulate a two-level population model to quantify key elements in nosocomial infections. At the bacteria level patients infected with these strains generate both nonresistant and resistant bacteria. At the patient level susceptible patients are infected by

infected patients at rates proportional to the total bacteria load of each strain present in the hospital. The objectives are to analyze the dynamic elements of nonresistant and resistant bacteria strains in epidemic populations in hospital environments and to provide understanding of measures to avoid the endemicity of resistant antibiotic strains.

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Stability and periodic oscillations in a mathematical model of hematopoiesis

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The hematopoiesis is the process by which the population of blood cells is produced and regulated. It is based upon a succession of complex differentiation of stem cells. These different differentiations, occurring in the bone marrow, are mainly regulated by the population of mature cells (there is a feedback control from the mature cells to the hematopoietic stem cells). In this work, we consider a system of delay differential equations modelling the evolution of hematopoietic stem cells and the population of mature cells. The delay describes the cell cycle duration of hematopoietic stem cells. Our aim is to show oscillations in such models due to the destabilization of the feedback loop between mature cells and hematopoietic stem cells.

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Fitness control by a parameter of asymmetry in a cell division model

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General models of cell division have been known for a long time. Although the most classical case is division in two equal new cells, it is now well established that this is not always the case. We can explain this by adaptive dynamic. In some cases, the symmetric division is not the best fitted way of division. The natural model to study it, is a cell division model in which the density of cells $n(t,y)$ is structured by their size y and evolution is describes by the master equation

$$\frac{\partial n}{\partial t}(t,y)+\frac{\partial nV(y)}{\partial y}(t,y)+B(y)n(t,y)= \frac{1}{\sigma}B(\frac{y}{\sigma})n(t,\frac{y}{\sigma})+\frac{1}{1-\sigma}B(\frac{y}{1-\sigma})n(t,\frac{y}{1-\sigma}), \quad (1)$$

where a cell of size y gives birth to a cell of size $y\sigma$ and an another of size $(1-\sigma)y$, with $\sigma \in]0,1[$. The asymptotic behavior of $n(t,y)$ gives the invasive capacity of the population and thus a fitness measure of populations under different rates and probabilities in (1). We fix $V=1$ and we study two cases, B has a compact support and $B(y)=y^p$. We show that the symmetric division is not all the time the best fitted division, it depends on the birth rate B.

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Global analysis of Differential infectivity and staged progression models: Application to an EBOLA model

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We provide a global analysis of general DISP models. Differential infectivity (DI) and staged progression models have been considered for modeling HIV transmission. Variations in infectiousness over time can be explained as part of a Markov chain, or staged-progression (SP), model in which infected individuals sequentially pass through a series of stages, with different kind of infectivity. Based on other clinic findings another hypothesis is the differential infectivity (DI) hypothesis, where infected individuals enter one of several groups, depending on their infectivity, and stay in that group until they develop AIDS. When the two models are combined a DISP model is obtained. Another rationale for considering DISP models is the introduction of continuous delays with probability function a convex combination of gamma distributions.

We compute the basic reproduction ratio $\mathcal{R}_0$ of the model. We prove that if $\mathcal{R}_0 \leq 1$ the disease free equilibrium is globally asymptotically stable on the nonnegative orthant, if $\mathcal{R}_0 > 1$ then a unique endemic equilibrium exists and is globally asymptotically stable on the nonnegative orthant minus the stable manifold of the disease free equilibrium.

We give an application to an EBOLA model.

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Periodic solution of a slow and fast switched system describing the dynamic of a population in a fluctuating environment.

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Dynamical system described by a combination between

discrete and continuous dynamics are called hybrid system which can be seen as a continuous system with switching events. This type of hybrid systems are called switched systems, the switching events are governed by a switching signal. In this communication, we consider the following singularly perturbed switched system

$$\left\{ \begin{array}{ll} \varepsilon \frac{dx}{dt}(t) = & f_u(x(t), y(t), \varepsilon) \\ \frac{dy}{dt}(t) = & g_u(x(t), y(t), \varepsilon), \end{array} \right. \quad (1)$$

where $(x,y) \in \mathbb{R}^n \times \mathbb{R}^m$, ε is a positive and small real parameter, f_u, g_u, $u \in \{0,1\}$ are vectorial functions and $u : \mathbb{R} \to \{0,1\}$, the switching signal, is a piecewise constant, fast and periodic function of the time t. For that purpose, we define u as follows: we suppose given a positive and small real parameter α such that $\varepsilon = o(\alpha)$, a continuous 1-periodic real function $\Theta : \mathbb{R} \to [0,1]$ and a positive integer $N \in \mathbb{N}_0^*$. Let $\theta_i = \Theta(\frac{i}{N})$, for $i = 0..N-1$, the switching times in the interval $[0,1)$.
Now we have a P-periodic switching signal u define over one period $P := \alpha N$ by

$$u(t) = \left\{ \begin{array}{ll} 0 & \text{if } t \in [\alpha i, \alpha(i+\theta_i)), i = 0..N-1, \\ 1 & \text{if } t \in [\alpha(i+\theta_i), \alpha(i+1)), i = 0..N-1, \end{array} \right.$$

so that the system (1) becames a P-periodic switched and singularly perturbed differential system. Using the Tykhonov's theory on slow-fast systems, we describ the geometry of the phase portrait of system (1). A method of averaging allows us to describe the behavior of the solutions of the switched system (1) and to give somes conditions of the existence of periodic solution. We conclude this study by giving differents examples some of them modelising population dynamics in a fluctuating environment.

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Dynamical systems methods in pathogen competition and coexistence

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Persistence theory and certain Lyapunov type functions are used to study competition between different strains of a micro-parasite which provide complete cross-protection and cross-immunity against each other. Competition selects for maximal basic replacement ratio, R_0, if, in the absence of the disease, the host population is exclusively limited in its growth by a nonlinear population birth rate. For mass action incidence, the principle of R_0-maximization can be extended to exponentially growing populations, if the exponential growth rate is small enough that the disease can limit population growth. For standard incidence, though not in full extent, it can be extended to populations which, without the disease, either grow exponentially or are growth-limited by a nonlinear population death rate, provided that disease prevalence is low and there is no immunity to the disease. If disease prevalence is high, strain competition rather selects for low disease fatality.

A strain which is horizontally (and possibly also vertically transmitted) and a second strain which is only vertically transmitted can coexist if the first strain has a sufficiently high horizontal transmission coefficient and is more virulent than the vertically transmitted second strain.

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Dynamics of semelparous populations

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A semelparous organism reproduces only once in its life and dies thereafter. If there is only one opportunity for reproduction per year, and all individuals born in a certain year reproduce k years later, then the population can be divided into year-classes according to the year of birth modulo k. The dynamics is described by a discrete time nonlinear Leslie matrix model, where the nonlinearity enters through the density dependent fertility and mortality rates. Parameters in the model are, apart from the basic reproduction ratio, the age dependent impact on and sensitivity to the environment. In parameter space we intend to classify, depending on the life-cycle length k, the attractors with emphasis on the Single Year Class state (all but one year class are not present), Multiple Year Class patterns (with some year classes present), heteroclinic cycles and invariant tori. When the reproduction ratio is close to one, the full-life-cycle map can be approximated by a differential equation, which is of Lotka-Volterra type, and which inherits the cyclic symmetry that is present in the full-life-cycle map. In this talk we give the detail of this differential equaion for k=3, and an almost complete picture for k=4, with some open problems left. We pay special attention to heteroclinic cycles and periodic orbits.

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A multi structured epidemic problem with direct and indirect transmissions in heterogeneous environment

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We analyse a deterministic epidemic mathematical model motivated by a Hantavirus - bank vole system.

The host population is split into juvenile and adult individuals because sexual maturation of juveniles depends on the density of adults.

First we analyze a disease-free model modeling the interactions between juveniles and adults. For the resulting age dependent reaction-diffusion system with discontinuous dispersion rates we give global existence, uniqueness and global boundedness results.

Hantavirus is benign in the host population and there is no vertical transmission. It propagates via direct transmission (contacts between individuals) and indirect transmission through the contaminated environment (by infected individuals). Newly infected individuals highly excrete the virus and are more infectious than chronically infected individuals. We derived a SI epidemic model with six population classes (susceptible, newly infected and chronically infected juveniles and adults) and an equation for the contaminated environment. Then we studied the resulting age dependent reaction-diffusion system and give global existence, uniqueness and global boundedness results.

Finally we study a model with transmission of the virus to Human (we distinguished susceptible, infected and recovered individuals for Human's populations) with possible lethal consequences and give global existence, uniqueness and global boundedness results.

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