Participants: (left to right) Ilaria Dorigatti, Davide Liessi, Dimitri Breda, Jordi Ripoll, Martina Conte, Rafael Bravo de la Parra, Silvia Cuadrado, Ahmed Noussair, Pierre Magal, Mimmo Iannelli, Glenn Webb, Fabio Milner, Lorenzo Pellis, Julia Kroos, Nicole Cusimano, Argyrios Petras, Havva Yoldas, Isabella Marinelli, Gabriela Capo-Rangel, Luca Gerardo-Giorda, Tomás Alarcón, Oscar Angulo, and Sandeep Kumar
Speakers

Plenary
1. Oscar Angulo (Valladolid, Spain)
2. Tomás Alarcón (CRM Barcelona, Spain)
3. Rafael Bravo de la Parra (Alcalá de Henares, Spain)
4. Dimitri Breda (Udine, Italy)
5. Silvia Cuadrado (Barcelona, Spain)
6. Ilaria Dorigatti (Imperial College, UK)
7. Luca Gerardo-Giorda (BCAM, Spain)
8. Mimmo Iannelli (Trento, Italy)
9. Pierre Magal (Bordeaux, France)
10. Ahmed Noussair (Bordeaux, France)
11. Lorenzo Pellis (Warwick, UK)
12. Jordi Ripoll (Girona, Spain)
13. Glenn Webb (Vanderbilt, USA)

Semi-Plenary
1. Martina Conte (Parma, Italy)
2. Davide Liesi (Udine, Italy)
3. Isabella Marinelli (BCAM, Spain)

Other Participants
1. Gabriela Capo-Rangel (BCAM, Spain)
2. Nicole Cusimano (BCAM, Spain)
3. Julia Kroos (BCAM, Spain)
4. Sandeep Kumar (BCAM, Spain)
5. Fabio Milner (Arizona State, USA)
6. Argyrios Petras (BCAM, Spain)
7. Havva Yoldas (BCAM, Spain)
Program

Tuesday, July 4, 2017

9:00-9:10. Opening and Welcome

9:10-12:40 Session 1: Population Dynamics

Chair: Luca Gerardo-Giorda

09:10-10:00 Jordi Ripoll
On the reproduction number of a gut microbiota model

10:00-10:50 Silvia Cuadrado
Asymptotic profile in selection mutation equations: Gauss versus Cauchy distributions

10:50-11:20 Coffee Break

11:20-12:10 Dimitri Breda
Numerical analysis of delay equations for structured populations

12:10-12:40 Davide Liessi
Pseudospectral methods for the stability of linear periodic delay models

12:40-14:10 Lunch

14:10-18:00 Session 2: Disease Models

Chair: Silvia Cuadrado

14:10-15:00 Glenn Webb
Spatial spread of epidemic diseases in geographical settings: Seasonal influenza epidi-
emics in Puerto Rico

15:00-15:50 Rafael Bravo de la Parra
Discrete eco-epidemiological models with two time scales

15:50-16:20 Coffee Break

16:20-17:10 Ilaria Dorigatti
Modelling immunogenicity, efficacy, risks and benefits of the Sanofi-Pasteur dengue
vaccine

17:10-18:00 Tomás Alarcón
Mathematical modelling in oncology: Multi-scale modelling of tumour growth

20:45-??? Social dinner
Wednesday, July 5, 2017

9:00-13:15 Session 3: Ecology and Epidemics

Chair: Fabio Milner

09:00-9:50 Oscar Angulo
Hierarchically structured population models: Numerical integration and forest dynamics application

9:50-10:40 Lorenzo Pellis
Multi-scale models of HIV infection and evolution

10:40-11:10 Coffee Break

11:10-12:00 Pierre Magal
Final size of a multi-group SIR epidemic model: Irreducible and non-irreducible modes of transmission

12:00-12:30 Isabella Marinelli
Estimation of age-specific rates of reactivation and immune boosting of the varicella zoster virus

12:30-14:00 Lunch

14:00-16:40 Session 4: Potpourri of Cancer, Control and the Skin

Chair: Ilaria Dorigatti

14:00-14:50 Ahmed Noussair
A model for transfers of P-glycoproteins in MCF-7 breast cancer cell line with multiple transfers rules

14:50-15:20 Martina Conte
Kinetic-based models for tumor-immune system competition

15:20-15:50 Luca Gerardo-Giorda
Modeling uncertainty in invasive species dispersal through geographically accurate landscapes

15:50-16:40 Mimmo Iannelli
A basic model for the description of skin structure: Well-posedness analysis, numerics and simulations

16:40-16:50 Closing
Abstracts
A spatially-structured linear model of the growth of intestinal bacteria is analysed from two generational viewpoints. Firstly, the basic reproduction number associated to the bacterial population, i.e. the expected number of daughter cells per bacterium, is given explicitly in terms of biological parameters. Secondly, an alternative quantity is introduced based on the number of bacteria produced within the intestine by one bacterium originally in the external media. The latter depends on the parameters in a simpler way and provides more biological insight than the standard reproduction number, allowing the design of experimental procedures. Both quantities coincide and are equal to one at the extinction threshold, below which the bacterial population becomes extinct. Optimal values of both reproduction numbers are derived assuming parameter trade-offs.
Asymptotic profile in selection mutation equations: Gauss versus Cauchy distributions

Silvia Cuadrado

Department of Mathematics, Autonomous University of Barcelona, Spain

Selection mutation equations are mathematical models of Darwinian evolution. In this talk we will analyze the behavior for large time and small mutation rate of a selection-mutation-competition model for a population structured with respect to a phenotypic trait.

We assume that the reproduction is asexual, and that mutations can be described by a linear integral operator.

We are interested in the interplay between the time variable $t$ and the rate $\varepsilon$ of mutations. We will show that depending on $\alpha > 0$, the limit $\varepsilon \to 0$ with $t = \varepsilon^{-\alpha}$ can lead to population number densities which are either Gaussian-like (when $\alpha$ is small) or Cauchy-like (when $\alpha$ is large). So, on the one hand we analyze transient dynamics, which could be important in many biological situations (invasions, infections...) and, on the other hand, we determine the asymptotic profile of the densities, which shows heavy tails. This could also be relevant for the survival of the population under environmental changes.

This is joint work with Àngel Calsina, Laurent Desvillettes and Gaël Raoul.
Numerical analysis of delay equations for structured populations

Dimitri Breda

Department of Mathematics, Computer Science and Physics, University of Udine, Italy

Renewal and delay differential equations play a prominent role in modeling structured populations. Recently, they have been coupled for describing consumer-resource interaction, leading to problems of increasing difficulty. This is witnessed, for instance, by the presence of external ordinary equations to define vital rates like fertility and survival probability.

On the one hand, practical limitations often prevent an exact analysis of the dynamics. On the other hand, the same limitations have fostered a certain interest in efficient numerical methods to address stability and bifurcation. Among others, pseudospectral approaches arise as particularly promising. In this talk I will try to give an overview of problems, methods and open directions, touching on several aspects which might deserve a substantial development in the future, also in response to the growing request of the bio-math community for automatic and user-friendly tools.
Pseudospectral methods for the stability of linear periodic delay models

Davide Liessi

Department of Mathematics, Computer Science and Physics, University of Udine, Italy

Realistic models of structured populations are often based on delay equations. Due to the complexity of such models, their dynamics usually cannot be studied analytically and must be approximated numerically. A method based on pseudospectral collocation for approximating the eigenvalues of evolution operators of linear delay differential equations has been recently developed in [1, 2]. The method can be applied, in particular, to the monodromy operator of linearized problems to study the local asymptotic stability of periodic solutions. I present an extension of that method to coupled renewal equations and delay differential equations, along with examples and a sketch of the proof of convergence.

References

Spatial spread of epidemic diseases in geographical settings:  
Seasonal influenza epidemics in Puerto Rico

Glenn Webb

Department of Mathematics, Vanderbilt University, Knoxville, USA

Deterministic models are developed for the spatial spread of epidemic diseases in geographical settings. The models are focused on outbreaks that arise from a small number of infected hosts imported into sub-regions of the geographical settings. The goal is to understand how spatial heterogeneity influences the transmission dynamics of the susceptible and infected populations. The models consist of systems of partial differential equations with diffusion terms describing the spatial spread of the underlying microbial infectious agents. Applications are given to seasonal influenza epidemics in Puerto Rico.
Discrete eco-epidemiological models with two time scales

Rafael Bravo de la Parra

Department of Mathematics, University of Alcalá, Spain

In this talk we present some discrete eco-epidemic models. The community interactions, predator-prey or competition, are represented by discrete Leslie-Gower models. The disease dynamics follows a discrete SIS epidemic model with frequency-dependent transmission. We focus on the case of disease only affecting one of the species. We assume that parasites provoke density- and trait-mediated indirect interactions in the community that occur on a shorter time scale. This is included in the model considering that in each time unit there exist a number $k$ of episodes of epidemic changes followed by a single episode of demographic change, all of them occurring separately. The construction of this kind of systems, together with a reduction method that simplifies their analysis, is reviewed in [1,2].

The proposed models take the form of three-dimensional systems of difference equations with two time scales. The application of the reduction method to the proposed systems yields two-dimensional ones representing a kind of more general community models that include the effects of the disease in its parameters. The analysis of these reduced models allows us to examine the effects of parasites on the long-term community interactions. Conditions for the disease to drive extinct some of the species are obtained. Also, the influence of disease on populations sizes is described.

References

Modelling immunogenicity, efficacy, risks and benefits of the Sanofi-Pasteur dengue vaccine

Ilaria Dorigatti

Department of Mathematics, Imperial College, London, UK

CYD-TDV, the dengue vaccine developed by Sanofi Pasteur, is the first dengue vaccine ever licensed and is characterised by a complex efficacy profile. In this talk I will revisit the key stages of development of CYD-TDV and present the mathematical and statistical models that were developed to describe the immunogenicity of the vaccine and to explore the benefits and risks of large scale vaccination with CYD-TDV. I will also discuss the statistical challenges associated with the computation of the vaccine efficacy from a relatively small subset of the subjects enrolled in the trials and how machine learning can be employed to refine the existing vaccine efficacy estimates.
Mathematical modelling in oncology: Multi-scale modelling of tumour growth

Tomás Alarcón
Centre de Recerca Matemàtica, Barcelona, Spain

In recent years multi-scale modelling of tumour growth has become an emergent area in Mathematical Biology. Multi-scale models seek to integrate different mathematical descriptions of phenomena characterised by a widely varying time and length scales, whereby the global behaviour of the tumour is an emergent property of the non-linear coupling between scales. In this talk, I will present a review of multi-scale models of tumour growth as well as recent advancements in coarse-grained models and hybrid simulation techniques that allow to simulate this very complex models more efficiently.
Hierarchically structured population models: Numerical integration and forest dynamics application

Oscar Angulo

Department of Applied Mathematics, University of Valladolid, Spain

We will study the numerical integration of a nonlinear model which describes the dynamics of a hierarchical size-structured population. More precisely, we consider a model with contest competition

\[ u_t + (g(x, B(x, t))u)_x = -\mu(x, B(x, t))u, \quad x_m < x < x_M, t > 0, \quad (1) \]

\[ g(x_m, B(x_m, t))u(x_m, t) = C(t) + \int_{x_m}^{x_M} \alpha(x, B(x, t))u(x, t)dx, \quad t > 0, \quad (2) \]

\[ u(x, 0) = \phi(x), \quad x_m < x < x_M, \quad (3) \]

\[ B(x, t) = \int_{x_m}^{x_M} w(\sigma)u(\sigma, t)d\sigma, \quad x_m < x < x_M, t > 0. \quad (4) \]

The independent variables \( x \) and \( t \) represent, respectively, size and time, where \( x_m \) and \( x_M \) are, respectively, the minimum and maximum value reached by a given population. The function \( u(x, t) \) is the population density with size \( x \) at time \( t \). The population dynamics is determined by the growth rate \( g \), the mortality rate \( \mu \), the reproduction rate \( \alpha \) and the external inflow \( C \). The vital functions (growth, mortality and reproduction rates) depend on the structuring variable and on the functional \( B(x, t) \), used to describe the competition among individuals for available resources. In this case, contest competition, no individual in a class of smaller size can affect the amount of resource available to an individual of greater size. Therefore, we have a nonlinear partial differential equation which has a functional dependence on nonlocal terms, with a nonlocal and nonlinear boundary condition with functional dependence on nonlocal terms. Existence and uniqueness of solutions for this model has been studied by Kraev [1].

We have carried out the numerical integration of equations (1)-(4) by means of a method that integrates along the characteristic curves and uses a constant number of grid nodes. The integral terms are approximated by means of second order quadrature rule. Finally, we will apply it to the solution of a model that describes the dynamics of models of size-structured tree populations that takes into account the effect of competition for light [2]. In this case the size is given by the diameter at breast height (d.b.h.) and \( B(x, t) \) represents the cumulative basal area of trees greater in size than \( x \) and expresses the shading effect under light competition.

References


This is joint work with Luis M. Abia, Juan Carlos López-Marcos and Miguel Ángel López-Marcos.
Multi-scale models of HIV infection and evolution

Lorenzo Pellis
University of Warwick, Coventry, UK

HIV infection is characterised by an initial burst in viral load, lasting a few months, followed by a long arms race between the immune system and the virus. The roughly stable viral load during this long chronic phase is called set-point viral load (SPVL). SPVL can vary by orders of magnitude between individuals, but homogeneously mixing models of within-host viral dynamics struggle to explain such an extreme amount of variation. I will show how a metapopulation model can give rise to substantial more heterogeneity in SPVL without the need for other ad-hoc explanations. Similarly, standard ODE-based HIV epidemic models struggle in capturing the implications of the variation in SPVL on the evolution of the virus, and I will present a multiscale model of within- and between-host evolutionary epidemiology based on integral equations, and discuss its assumptions, limitations and future extensions.
A model for transfers of P-glycoproteins in MCF-7 breast cancer cell line with multiple transfers rules

Pierre Magal
Bordeaux Mathematics Institute, University of Bordeaux, France

The objective of this talk is to analyse a population dynamics model for a distribution of cells with respect to a quantity of protein called P-glycoprotein (P-gp). We consider a direct protein transfer process between cells. Assuming that cells continually encounter each other, and from some hypotheses on cell to cell rules of transfer, we derive discrete and continuous Boltzmann-like integrodifferential equations. The novelty of this model is to take into account multiple transfers rules. This new transfer model is used to fit the experimental data of cell-to-cell protein transfer in breast cancer.
Estimation of age-specific rates of reactivation and immune boosting of the varicella zoster virus

Isabella Marinelli

BCAM, Bilbao, Spain

Studies into the impact of vaccination against the Varicella zoster virus (VZV) have increasingly focused on herpes zoster (HZ), which is believed to be increasing in vaccinated populations with decreasing infection pressure. This idea can be traced back to Hope-Simpson’s hypothesis, in which a person’s immune status determines the likelihood that he/she will develop HZ. Immunity decreases over time, and can be boosted by contact with a person experiencing varicella (exogenous boosting) or by a reactivation attempt of the virus (endogenous boosting). Here we use transmission models to estimate age-specific rates of reactivation and immune boosting, exogenous as well as endogenous, using zoster incidence data from the Netherlands (2002–2011, n = 7,026). The boosting and reactivation rates are estimated with splines, enabling these quantities to be optimally informed by the data. The analyses show that models with high levels of exogenous boosting and estimated or zero endogenous boosting, constant rate of loss of immunity, and reactivation rate increasing with age (to more than 5% per year in the elderly) give the best fit to the data. Estimates of the rates of immune boosting and reactivation are strongly correlated. This has important implications as these parameters determine the fraction of the population with waned immunity. We conclude that independent evidence on rates of immune boosting and reactivation in persons with waned immunity are needed to robustly predict the impact of varicella vaccination on the incidence of HZ.

This is joint work with Alies van Lier, Hester de Melker, Andrea Pugliese, and Michiel van Boven.
A model for transfers of P-glycoproteins in MCF-7 breast cancer cell line with multiple transfers rules

Ahmed Noussair
Bordeaux Mathematics Institute, University of Bordeaux, France

In this presentation a model of an epidemic outbreak incorporating multiple subgroups of susceptible and infected individuals is investigated. The asymptotic behavior of the model is analyzed and it is proved that the infected classes all converge to 0. A computational algorithm is developed for the cumulative final size of infected individuals over the course of the epidemic. The results are applied to the SARS epidemic in Singapore in 2003, where it is shown that the two-peak evolution of the infected population can be attributed to a two-group formulation of transmission.

This is joint work with Pierre Magal.
A mathematical model, based on a mesoscopic approach, describing the competition between tumor cells and immune system in terms of kinetic integro-differential equations is presented. Four interacting populations are considered, representing, respectively, tumors cells, cells of the host environment, cells of the immune system, and interleukins, which are capable to modify the tumor-immune system interaction and to contribute to destroy tumor cells. A closed set of autonomous ODEs is then derived by a moment procedure; two three-dimensional reduced systems of ODEs are obtained in some partial quasi-steady state approximation and their qualitative analysis is performed.
Modeling uncertainty in invasive species dispersal through geographically accurate landscapes

Luca Gerardo-Giorda

BCAM, Bilbao, Spain

One of the main difficulties in the modeling and numerical simulation of the spread of an infectious disease or invasive species in wildlife is to properly take into account the heterogeneities of the landscape. Forests, plains and mountains present different levels of hospitality, while large roads, lakes and major waterways can provide strong natural barriers to the epidemic (invasive species) spread. A canonical approach has been to discretize both population and geography into geopolitical units and consider the movement of individuals from unit to unit (multi-patch models). This approach, however, does not well represent the biological realities of animal movement, since animals do not move at the scale of geopolitical units.

We propose an alternative based on combining a standard SEI epidemiological model with a diffusion process to account for movement as a continuous process across a continuous region. This results in a system of parabolic reaction-diffusion equations with nonlinear reaction term. Landscape heterogeneities are accounted for by including in the computational domain the significant geographical features of the area. We discretize the resulting model in time by an IMEX scheme and in space by finite elements. To show the effectiveness of the method, we present numerical simulation for rabies epidemics among raccoons in New York State using data collected between 1990 and 2007.

We also show the results of applying the same detailed terrain description to the invasive spread of cane toads in Australia. Native to South and mainland Middle America, they were introduced from Hawaii in June 1935 by the Bureau of Sugar Experiment Stations, now the Sugar Research Australia, in an attempt to control the native grey-backed cane beetle (*Dermolepida albohirtum*) and Frenchi beetle (*Lepidiota frenchi*).

Finally, a discussion of some extensions of the method to stochastic simulations will be presented, replacing constant model parameters by distributed ones.
A basic model for the description of skin structure: well-posedness analysis, numerics and simulations

Mimmo Iannelli
Department of Mathematics, University of Trento, Italy

The epidermis (the outermost part of the skin) is a stratified epithelium formed by multiple layers of cells that undergo a continuous renewal process. In the innermost layer—the basal cells layer—cell proliferation occurs. Progenitor cells produce quiescent differentiated cells (post-mitotic keratinocytes) that detach from the underlying basement membrane and move outward forming the suprabasal layers. Suprabasal cells undergo a progressive maturation, called keratinization and, at the end of this process, cells filled of keratin die, and the dead cells (corneous cells or corneocytes) form the stratum corneum. The inner cells of the stratum corneum adhere each other, but, when the corneocytes are pushed to the surface by newly formed cells, they lose their adhesion and eventually are shed from the surface, through a process named desquamation.

To describe the process outlined above, we propose a model with age and space structure, including different types of cells (proliferating cells, differentiated cells, corneous cells, and apoptotic cells) that move with the same velocity, under the constraint that the local volume fraction occupied by the cells is constant in space and time.

The stationary state of the model corresponds to the spatial organization of the normal, homeostatic epidermis, or the state that may be reached after prolonged and time-invariant damaging. This state should also be the limit of the time evolution of the skin after any perturbation. Existence of a solution, both in the stationary and in the dynamic case, requires conditions that can be viewed as parameters restrictions for skin formation. A numerical scheme to compute the solution of the model is proposed and simulations are provided for realistic values of the parameters.
List of Participants

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