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Mathematical Biology Modelling days of Besançon 2018

Book of abstracts

19-22 June 2018

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5 List of abstracts by theme

5.1 "Fluid flow in biology" Theme

Modeling final stochastic fruit ripening process

Time slot: Wednesday 20 at 14:45–15:35
Author(s): Trang Hoang[1]
Affiliation(s):
[1] Dong A University, 33 Xo Viet Nghe Tinh, Da Nang city, Vietnam

In this paper, a biomathematics model will be applied in computational software R to get insights into ripening process of fruit and vegetables at postharvest period. Inside the fruit cells at postharvest shelf-life, a balanced conversion from 1-aminocyclopropane-1-carboxylic acid (ACC) to ethylene and from ACC to N-malonyl-ACC (MACC) is stochastically happening. MACC has long been believed to be a conjugated stable product to store ACC in cells, so that ACC cannot transfer to ethylene to stimulate ripening of fruits. In this work, we will use stochastic system to model MACC production in two hypotheses: MACC will be converted to other substances and MACC is the dead-end product. Simulating models on R gives controversial results. The theory that MACC is the dead-end product is more significant to reject than it will be degraded. MACC produced seems to be forward in two ways: stored in cells until a milestone moment to convert back to ACC or degrade to other conjugated compounds. Future perspectives are opened. First, one could consider investigating effects of postharvest intercellular and extracellular factors on Yang ripening cycle. Another perspective is to study the case MACC being converted back into ACC and parallely degraded to some other substances.

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A mathematical model of the human gut microbiota in its fluidic environment

Time slot: Tuesday 19 at 11:15–11:40
Author(s): Béatrice Laroche[1], Simon Labarthe[1], Bastien Polizzi[22], Thuy Phan[3], Thierry Goudon[4], Magali Ribot[3]
Affiliation(s):
[1] MaIAGE, INRA, Paris-Saclay University, Jouy-en-Josas, France
[2] IMFT, CNRS-INPT-Paul Sabatier University, Toulouse, France
[3] IDP, Université d'Orléans-CNRS, Orleans, France
[4] LJAD, Université Côte d'Azur, Inria, CNRS, Nice, France

The human gut hosts a commensal microbial population that colonizes the digestive tract at birth. It is now established that it plays an important role on the health and well-being of the host by engaging a symbiotic dialog, emphasizing the importance of understanding the gut bacterial ecology. Among the ecological drivers of this microbiota, the spatial structure of the gut is of special interest: spatio-temporal mechanisms can lead to the constitution environmental niches that impact the overall colonization of the gut. We propose a mathematical model of the large intestine microbial ecosystem based on the explicit coupling of a population dynamics model of microbial populations involved in fiber degradation with a fluid dynamics model of the gut content. Exploiting the geometric characteristics of the problem, a simplified model together with an efficient numerical implementation are obtained through a first order asymptotic approximation. This detailed modeling framework allows studying the main drivers of the spatial structure of the microbiota, specifically focusing on the dietary fiber intake, the epithelial motility, the microbial active swimming and viscosity gradients in the digestive track. A sensitivity analysis highlights that their relative importance varies along the gut.

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2. El Bouti, T. *et al.* A mixture model for the dynamic of the gut mucus layer. *ESAIM: Proceedings and Surveys* **55,** 111–130 (2016).
3. Labarthe, S. *et al.* A mathematical model to investigate the key drivers of the biogeography of the colon microbiota. (2018).

Fluid-poroelastic interface modelling for an implantable medical device: Application to brain tumours treatment

Time slot: Tuesday 19 at 11:40–12:05
Author(s): Julien Yves Rolland[1], Alexei Lozinski[1], Jean-Christophe Gimel[2], Florence Franconi[2], Laurent Lemaire[2], Brice Calvignac[2]
Affiliation(s):
[1] Laboratoire de Mathématiques de Besançon - UMR 6623, UBFC - Besançon - France
[2] Micro & Nanomédecines Translationelles - UNIV Angers, INSERM U1066, CNRS 6021 - Angers - France

In order to overcome biological barriers and improve the local delivery of drugs for the treatment of solid tumours such as glioblastoma, the use of an innovative medical injection device composed by microneedles array as been proposed by MINT. This work will focus on the mathematical modelling of the drug transport and diffusion in the region of interest.
Mathematically, the injection of a drug into the brain can be described by the system of equations comprising the Biot equations - for displacements of the elastic matrix and for the intraporous flow - and the Stokes equations - for fluid flow inside the needle and in the gap between the wall and the poroelastic tissue. These equations are coupled by Biot-Darcy interface conditions and a dynamic contact condition at the triple line defined by the tissue, the fluid and the wall of a needle.
We have developed a monolithic scheme using continuous finite elements to discretise both the Biot and Stokes systems. The choice of finite elements space and the implementation of the Biot-Stokes interface conditions allow us to avoid stabilisation terms, unlike other approaches available in the recent literature[1].
The critical difficulty is the triple line treatment. Our modelling assumption is that each point at the edge of the tissue-wall interface is either:

- attached to the wall, if the normal component of the force exerted on the wall by the tissue is opposite to the normal outgoing wall,
- detached from the wall; in this case, the fluid is assumed to fill the created gap.

Numerically, unknowns are represented on two dynamic meshes: One for elastic displacements and pressure in the tissue, the other for the fluid velocity. The former evolves in time by moving the initial mesh nodes, the latter is reconstructed at each time step to allow for geometric evolution of the fluid domain.
This system allows us to model the crucial phenomena of "backflow"[2]: Under specific conditions, the triple line may creep up the needle wall, exit the region of interest and thus, would lead to an inefficiency of the locoregional drug delivery in the brain.

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Cardiovascular modeling and simulations. Applications to some clinical studies

Time slot: Thursday 21 at 16:30–17:15
Author(s): Adélia Sequiera[1]
Affiliation(s):
[1] Instituto Superior Técnico, Department of Mathematics and CEMAT, University of Lisbon, Portugal

Mathematical modeling and numerical simulations can provide an invaluable tool for the interpretation and analysis of the circulatory system functionality, in both pathological and healthy situations. However, although many substantial achievements have been made, most of the difficulties are still on the ground and represent major challenges for the coming years.

In this talk we introduce some mathematical models of the cardiovascular system and comment on their significance to yield realistic and accurate numerical results. They include fluid-structure interaction (FSI) models to account for blood flow in compliant vessels, analysis of absorbing boundary conditions to deal with the numerical spurious reflections due to the truncation of the computational domain and the geometrical multiscale approach to simulate the reciprocal interactions between local and systemic hemodynamics.

Results on the simulation of some image-based patient-specific clinical applications will also be presented.

5.2 "Cellular heterogeneity and dynamics" Theme

Inter-individual variability in CD8 T cell immune responses explained by mathematical modeling

Time slot: Thursday 21 at 14:45–16:00

Author(s): Chloe Audebert[1,2], Jacqueline Marvel[3], Christophe Arpin[3], Olivier Gandrillon[1,4], Fabien Crauste[1,2]

Affiliation(s):

[1] Inria, Villeurbanne, France

[2] Institut Camille Jordan, CNRS UMR 5208, Villeurbanne, France

[3] CIRI, Inserm U1111, CNRS UMR5308, ENS, Université Claude Bernard Lyon 1, Lyon, France

[4] Laboratory of Biology and Modelling of the Cell, ENS, Lyon, France

Following an infection by an intracellular pathogen, the immune system triggers different mechanisms that lead to the activation and expansion of killer CD8 T cells, that will eliminate the pathogen. In the present work, we analyze the CD8 T cell immune response to an antigen that cells never encountered before (primary response). For this we rely on quantitative experimental data. The data correspond to antigen specific CD8 T cell counts measured at different times on groups of infected mice. CD8 T cell counts display a very significant inter-individual mice-to-mice variability. The purpose of this work is to explain such an inter-individual variability by accounting for parameter variability in a mechanistic model of the CD8 T cell response.

A mathematical model based on ordinary differential equations has been proposed to describe an average behavior of CD8 T cells in response to a pathogen infection[1]. It is based upon the description of different cell compartments and their interactions. To describe inter-individual heterogeneity, we aim at estimating the variability of the model parameters within the population. To do so, instead of performing parameter estimation for each individual, we estimate for each relevant parameter of the model a distribution. This distribution is characterized by a mean and a standard deviation so that each individual can be seen as a deviation from an average individual within a single population. The estimations were performed with stochastic approximation expectation-maximization algorithm implemented in the Monolix software[2].

We first generated synthetic data in order to better understand how the variability might emerge from variability in the parameters. Then, we estimated the parameters from the experimental data, for two different responses to the same antigen: one where the antigen is carried by a pathogen and one where it is carried by cancer cells. Altogether, this study will enable us to identify the parameters that vary the most within the population, and to compare parameter mean and variance between those two conditions. Finally, the consequences for vaccine development will be discussed.

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Modelling oscillatory behavior in asymmetric division of *C.elegans* embryo

Time slot: Thursday 21 at 14:45–16:00
Author(s): Anca Caranfil[1,2,3], Yann Le Cunff[1,2], Charles Kervrann[3], Jacques Pecreaux[1]
Affiliation(s):
[1] Institute of Genetics and Development of Rennes, CNRS UMR 6290
[2] University of Rennes 1
[3] INRIA Rennes Bretagne Atlantique

Asymmetric cell division is a complex process that is not yet fully understood. A very well-known example of such a division is *C.elegans* embryo's first division. To improve our understanding of this process, we used mathematical modelling to study *C.elegans* embryo's first division, both on wild type cells and under a wide range of genetic perturbations. Asymmetry is clearly visible at the end of the anaphase, as the mitotic spindle is off-center. The study of the mitotic spindle dynamics is, thus, a useful tool to gain insights into the general mechanics of the system used by the cell to correctly achieve asymmetric division. The overall spindle behavior is led by the spindle poles behavior. We proposed a new dynamic model for the posterior spindle pole that explains the oscillatory behavior during anaphase and confirms some previous findings, such as the existence of a threshold number of active force-generator motors required for the onset of oscillations. We also confirmed that the monotonic increase of motor activity accounts for their build-up and die-down. By theoretically analyzing our model, we determined boundaries for the motor activity-related parameters for these oscillations to happen. This also allowed us to describe the influence of the number of motors, as well as physical parameters related to viscosity or string-like forces, on features such as the amplitude and number of oscillations. Lastly, by using a Bayesian approach to confront our model to experimental data, we were able to estimate distributions for our biological and bio-physical parameters. These results give us insights on variations in spindle behavior during anaphase in asymmetric division, and provide means of prediction for phenotypes related to misguided asymmetric division. This model will be instrumental in probing the function of yet undocumented genes involved in controlling cell division dynamics.

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Modelling approach for cells in a chemostat

Time slot: Thursday 21 at 14:00–14:45
Author(s): Coralie Fritsch[1]
Affiliation(s):
[1] Université de Lorraine, CNRS, Inria, IECL, Nancy

The first difficulty for the modelling of biological problems is in choosing the type of model which is appropriate for the problem (stochastic or determinisic model, discreet or continuous model,...). In this talk, I will present a variety of models for cells modelling and the links between them.

At a microscopic scale, that is the scale of individuals, it is more judicious to describe the population by an individual based model (IBM). These models describe the behavior of each individual and can represent the stochasticity of the population. It is also a good way to discuss with biologists; in fact these models are constructed describing the biological mechanisms by basic rules before the description by mathematical equations. When the number of individuals in the population is very large, these models can however be very costly to compute. It is then important to link IBMs with other models. Under suitable assumptions, we can obtain the convergence of IBMs, in large population size, toward deterministic partial differential equations (PDEs) models, which correspond to the macroscopic model associated to the microscopic one. At an intermediate scale we can also derive stochastic PDEs by central limit theorems. These models are easier to compute than IBM, but still represent stochasticity of the population.

I will present the links between these models through convergence theorems for growth-fragmentation chemostat models and I will propose a modelling approach based on these mathematical results as well as numerical simulations. Finally, I will present how to derive results on the PDE, like variations of the main eigenvalue w.r.t. model parameters, through probabilistic methods using the stochastic microscopic interpretation. I will apply these results to an adaptive dynamics model of chemostat.

Regulation of cellular heterogeneity by uneven molecular partitioning during the CD8 T-cell immune response

Time slot: Thursday 21 at 14:45–16:00

Author(s): Simon Girel[1,2], Jacqueline Marvel[3] , Christophe Arpin[3] , Olivier Gandrillon[1,4], Fabien Crauste[1,2]

Affiliation(s):

[1] Inria, Villeurbanne, France

[2] Institut Camille Jordan, CNRS UMR 5208, Villeurbanne, France

[3] CIRI, INSERM U1111, ENS, Université Lyon 1, Lyon, France

[4] Laboratory of Biology and Modelling of the Cell, ENS, Lyon, France

The lymph-node resident naive CD8 T-cells are activated upon infection by an intra-cellular pathogen. Activated CD8 T-cells then mount an immune response, characterised by a program of cell proliferation, migration, differentiation and death. It is now well known that responding CD8 T-cells develop heterogeneous phenotypes, associated with heterogeneous intra-cellular molecular contents. Which mechanisms regulate that heterogeneity and how it impacts the immune response dynamics remain a matter of debate. To address this question, we mathematically studied the contribution of uneven partitioning of molecular content at cell division to the regulation of molecular heterogeneity.

In a recent work[1], we designed an impulsive differential equation, where impulses are associated with cell division, to model the concentration of Tbet protein in a single dividing CD8 T-cell. High and low Tbet levels may be associated with two antagonistic cell fates: either cytotoxic effector or long-lived memory. Through the analysis of the impulsive equation, we studied the impact of uneven molecular partitioning on the emergence of effector and memory fates and discuss how variations in the degree of unevenness and in the cell cycle length affect the regulation and reversibility of the differentiation process.

In parallel, a hybrid discrete-continuous agent-based model of the early CD8 T-cell immune response has been developed in our team[2, 3]. It couples the discrete description of CD8 T-cell population dynamics with a continuous description of a molecular regulatory network, including Tbet protein. Based on our results from[1], we enriched this model to introduce an additional state of differentiation (memory) and employed it to evaluate the contribution of uneven molecular partitioning to the immune response dynamics.

Quite interestingly, both the molecular and multi-scale descriptions converged toward the idea that an intermediate amount of noise, or unevenness, was providing an optimal solution for the immune response outcome.

References

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2. Prokopiou, S. A. *et al.* Multiscale modeling of the early CD8 T-cell immune response in lymph nodes: an integrative study. *Computation* **2,** 159–181 (2014).
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Inferring gene regulatory networks from single-cell data: a mechanistic approach

Time slot: Poster session
Author(s): Ulysse Herbach[1,2,3], Arnaud Bonnaffoux[1,2,4], Thibault Espinasse[3], Olivier Gandrillon[1,2]
Affiliation(s):
[1] Laboratory of Biology and Modelling of the Cell, ENS de Lyon, Lyon
[2] Inria Team Dracula, Inria Center Grenoble Rhône-Alpes
[3] Institut Camille Jordan, Université Claude Bernard Lyon 1, Villeurbanne
[4] The CoSMo company, Lyon

The behaviour of a cell population largely depends on decisions made at the individual level, resulting from a complex interaction network between genes within each cell. Gene network inference, i.e. reconstruction of both structure and underlying dynamics from data, has been a major challenge in systems biology for years. So far, most studies have been based on population-averaged data: now that new technologies enable to observe mRNA levels in individual cells, a revolution in terms of precision, this problem paradoxically remains more challenging than ever. Besides, gene expression being fundamentally stochastic, any relevant modelling framework must have a probabilistic base to fully exploit such single-cell data, where biological stochasticity is preserved from averaging. We will focus on the construction of a dynamical model for a set of interacting genes, that should be relevant both from a mathematical and from a biological perspective. The starting point is a simple yet rich model of single gene expression, the well known "two-state model", for which one can compute analytically and infer the stationary distribution. The production of mRNA and proteins will be described with a two-state-like model, the paramaters of which will now depend on other genes. The result is a general network model where each link between two genes is directed and has an explicit biochemical interpretation, in terms of chemical reactions. The network distribution can then be approximately computed and used to derive a promising statistical model for the data, where stochasticity is not just noise but also contains information. This work should eventually provide an efficient way to infer gene networks from single-cell transcriptomics data[1].

References

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Bifurcations and critical transitions in cell population dynamics: Why cancer treatment can backfire...

Time slot: Tuesday 19 at 10:00–10:45
Author(s): Sui Huang[1]
Affiliation(s):
[1] Institute of Systems Biology of Seattle, USA

Drug resistance in cancer is to some extent driven by a treatment-induced cell state transition, namely from a drug-sensitive to a resilient, stem-cell-like state, instead of solely being the result of Darwinian selection of mutant cells that "happen" to be drug resistant. At the basis of this drug-induced phenotype switching is a transition from one stable high-dimensional attractor state in gene expression space into another. We postulate that this process is not "just" a jump between attractor states due to stochastic fluctuations in gene expression in individual cells (too rare an event) but requires the destabilization of the original attractor. Then cells will, without overcoming an "energy barrier", enter the new attractor state ("alternative regime") that encodes the gene expression profile conferring the new resistant, stem-like phenotype. Thus, we propose that in general, a cell state transition between stable attractors is a bifurcation event, and therefore, would be observable as a critical transition. I will show single-cell resolution gene expression profile measurements in cell populations undergoing such cell state transitions that are consistent with two predictions from the theory: (i) appearance of the equivalent of "Early Warning Signals" that precede critical transitions and (ii) the emergence of "rebellious cells". The latter are cells that due the particular multi-attractor nature of the "epigenetic landscape" (e.g. associated with a pitchfork bifurcation) and the heterogeneity of cell populations have entered an alternative attractor and not the one "intended by the signal". This alternative fate can be manifest as a phenotype change in the "direction opposite to the one desired" after their attractor has vanished. This would explain why cancer therapy, which seeks a state transition of tumor cells to the apoptotic state, can, as predicted by theory, also generate stem-cell-like cells –the source of drug resistance. Theoretical considerations and experimental results will be presented and practical implications discussed, including on theoretical limits of "curability" of cancer.

Cell motility in structured environments without focal adhesion

Time slot: Thursday 21 at 17:15–18:05
Author(s): C. Giverso[1], Gaspard Jankowiak[2], D. Peurichard[3], L. Preziosi[1], C. Schmeiser[4]
Affiliation(s):
[1] Politecnico di Torino
[2] TU Wien
[3] Inria
[4] Universität Wien

Although it has been a subject of research for years (e.g. biophysict Victor Small) mechanisms allowing living cells to move around the body are not completely understood. These differ between cell type and a given cell can be sport several of them. For example leukocytes can move on a surface by sticking to it at several locations (focal adhesion) and rolling forward, similarly as bulldozer tracks.

Concerning this particular mechanism, recent experiments at the IST (Reversat & Sixt), leukocytes were engineered and stripped from their adhesion capabilities. When placed in appropriately structured media, these cell are still able to move around the environment. A good image to understand the physical setting would be a climber in an iced chimney, which would offer zero traction.

I will discuss the experiments and both discrete and continuous variants of a new mechanical model describing this behaviour, based on simple physical considerations. The two main, non standard ingredients are the treatment of the polymerization and cortex internal viscosity, which when combined, create motion.

The resulting system of parabolic equations is of integro-differential type and involves high-order in space differential operators. It can be analysed partially, and existence results will be given in simple situations.

I will also discuss some numerical experiments and extensions which are currently under study.

5.3 "Ecosystem structure and dynamics" Theme

Model & Data-based inference approach of biological invasions

Time slot: Wednesday 20 at 9:30–10:45
Author(s): Candy Abboud[1,2], Olivier Bonnefon[1], Eric Parent[2], Samuel Soubeyrand[1]
Affiliation(s):
[1] Biostatistique et Processus Spatiaux, INRA, 84914 Avignon
[2] AgroParisTech, UMR 518 Math. Info. Appli., Paris

Population dynamics of pathogens invading new regions continues to be of primary concern for both biologists and mathematicians. Extensive researches are mainly carried out throughout mathematical modeling to reconstruct the past dynamics of the alien species. In this talk we will present a mechanistic-statistical approach that will allow us to date and localize the invasion of an alien species and describe other epidemiological parameters as per example, the diffusion, the reproduction and the mortality parameter. The used approach is based on (i) a coupled reaction-diffusion-absorption sub-model that describes the dynamics of the epidemics in a heterogeneous domain and (ii) a stochastic sub-model that represents the observation process. Then, we will jointly estimate the initial conditions (date and site) and the epidemiological parameters using a Bayesian framework through an adaptive multiple importance sampling algorithm. We will show the results obtained in this framework on the basis of abundant post-introduction data gathered to draw up a surveillance plan on the expansion of Xylella fastidiosa, a phytopathogenic bacterium detected in South Corsica in 2015. Nevertheless, this approach could be applied to other post-emergent species in order to endorse a fast reaction.

References

1. Cornuet, J., Marin, J.-M., Mira, A. & Robert, C. P. Adaptive multiple importance sampling. *Scandinavian Journal of Statistics* **39,** 798–812 (2012).
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Toward a mixed effects model of the *in vitro* erythroid differentiation

Time slot: Poster session
Author(s): Ronan Duchesne[1,2], Anissa Guillemin[1], Fabien Crauste[2,3], Olivier Gandrillon[1,2]
Affiliation(s):
[1] Laboratory of Biology and Modelling of the Cell, École Normale Supérieure de Lyon
[2] Dracula team, Inria
[3] Institut Camille Jordan, Université Claude Bernard Lyon 1

Mixed Effect Models (MEM) are being increasingly used to describe temporal data involving an important amount of variability in diverse fields such as econometrics, human sciences and biology [1]. This is due to their accounting for the whole variability of a dataset instead of simply averaging it out. A MEM for a dynamical process is a model (for instance, a deterministic ODE) whose usually constant parameters are modeled by distributions of random variables. Different samples from these random variables model the measurement of the same process on different individuals. It allows the model to adopt a range of behaviours, and to reproduce the distribution of an observed variable over time, instead of simply fitting its mean.

However, it might be difficult to recover full parameter distributions from small datasets. We address this issue through the example of a MEM for the dynamics of the *in vitro* erythropoiesis. Erythropoiesis is the process by which red blood cells are produced by the differentiation of immature progenitors in the bone marrow. These progenitors can either keep self-renewing, or engage into differentiation [2]. A variety of mathematical models have already described the dynamics of erythropoiesis *in vivo* [3, 4], yet no modelling work has ever focused on the kinetics of cell populations growing *in vitro*.

In this work, we build a MEM for *in vitro* erythropoiesis. We use experimental countings of different cell populations, at regularly spaced time points during erythroid differentiation. The population of individuals to be fitted by the model is made of repeated samples of this experiment, each repetition giving qualitatively similar though quantitatively different results due to inter-individual heterogeneity. We will illustrate the difficulty of fitting whole parameter distributions from such experimental datasets. Then, using artificial data, we will suggest experimental approaches that could lead to the recovery of these distributions.

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Stationary fronts in competition-diffusion models in stochastically fluctuating environments

Time slot: Wednesday 20 at 9:30–10:45
Author(s): Merlin Christopher Köhnke[1], Horst Malchow[1]
Affiliation(s):
[1] Institute of Environmental Systems Research, School of Mathematics/Computer Science, Osnabrück University

The spatio-temporal intra- and interspecific competition of two competing and diffusing populations is considered. Nonspatial conditions for spatial segregation without mixing are identified. Furthermore, the impact of environmental noise on the spatial segregation is studied. Here, a particular focus is set on the form of the density-dependent noise. The obtained results are associated with a biological case study of two competing invasive thistle species[1].

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Competitive invasion, infection and noise in a heterogeneous habitat

Time slot: Wednesday 20 at 8:45–9:30
Author(s): Horst Malchow[1], Ivo Siekmann[2], Michael Bengfort[3]
Affiliation(s):
[1] Institute of Environmental Systems Research, Osnabrück University, Germany
[2] Department of Applied Mathematics, Liverpool John Moores University, UK
[3] Energy & meteo systems, Oldenburg, Germany

Stochastic reaction-diffusion equations are a popular modelling approach for studying interacting populations in a heterogeneous environment under the influence of environmental fluctuations. Although the theoretical basis of alternative models such as Fokker-Planck diffusion is not less convincing, movement of populations is most commonly modelled using the diffusion law due to Fick. An interesting feature of Fokker-Planck diffusion is the fact that for spatially varying diffusion coefficients the stationary solution is not a homogeneous distribution - in contrast to Fick's law of diffusion. Instead, concentration accumulates in regions of low diffusivity and tends to lower levels for areas of high diffusivity. Thus, the stationary distribution of the Fokker-Planck diffusion can be interpreted as a reflection of different levels of habitat quality.

Furthermore, the most common model for environmental fluctuations, multiplicative noise with linearly density-dependent noise intensity, is based on the assumption that individuals respond independently to stochastic environmental fluctuations. For large population densities the assumption of independence is debatable and the model further implies that noise intensities can increase to arbitrarily high levels. Therefore, instead of the commonly used linear multiplicative noise model, the environmental variability is implemented by an alternative nonlinear noise term which never exceeds a certain maximum noise intensity. With Fokker-Planck diffusion and the nonlinear noise model replacing the classical approaches, a simple invasive system is investigated based on the Lotka-Volterra competition model. It is found that the heterogeneous stationary distribution generated by Fokker-Planck diffusion generally facilitates the formation of segregated habitats of resident and invader. However, this segregation can be broken by nonlinear noise leading to coexistence of resident and invader across the whole spatial domain, an effect that would not be possible in the non-spatial version of the competition model for the parameters considered here[1–3].

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Sensitivity analysis of a grassland vegetation model: Responses to drivers depend on species richness

Time slot: Wednesday 20 at 9:30–10:45
Author(s): Thibault Moulin[1], Antoine Perasso[1], François Gillet[1]
Affiliation(s):
[1] Laboratoire Chrono-environnement - UMR 6249 - Université de Franche-Comté / CNRS, Besançon, France

We address in this study a general issue that could be raised in any modelling work: the appropriate choice of the level of detail of one model, i.e. the number of state variables and associated parameters to be taken into account for describing the dynamical system. We applied this question to grassland ecosystems. Indeed semi-natural grasslands are the plant communities with the word records for species richness at fine scale. Besides the size of the initial species pool could have consequences on the outcome of the simulated ecosystem dynamics in terms of grassland productivity, diversity, and stability.
To address these issues, we developed a system of ordinary differential equations, *Dynagram*, designed to simulate seasonal changes in both aboveground biomass production and species composition of managed permanent grasslands under various soil, climate and management conditions[1]. We compared simulation results from alternative instances of *DynaGraM* that only differ by the identity and number of state variables describing the green biomass, here plant species. We performed a sensitivity analysis, using uni- variate and multivariate regression trees[2] and dynamic trees, of each instance of the model to key forcing parameters accounting for climate, soil fertility, and defoliation disturbances.
We compared results of 10-year simulations under various climate, fertility and defoliation conditions. We showed that the sensitivity to forcing parameters of community structure and species evenness differed markedly among alternative models, showing a progressive shift from high importance of soil fertility (fertilisation level, mineralization rate) to high importance of defoliation (mowing frequency, grazing intensity) as the size of the species pool increased. By contrast, the key drivers of total biomass production were independent of species richness and only linked to resource supply (nitrogen and water).

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5.4 "Ecotoxicology" Theme

Implementation of toxicokinetics-toxicodynamics models with Bayesian inference - calibration of ordinary differential equations with JAGS and Stan

Time slot: Wednesday 20 at 12:00–12:25
Author(s): Virgile Baudrot[1], Sandrine Charles[1]
Affiliation(s):[1] Univ. Lyon 1, Laboratoire de Biométrie et Biologie Évolutive, France

Toxicokinetic-toxicodynamic (TKTD) models proved to be of particular interest in strengthening the Environmental Risk Assessment (ERA) of chemicals compounds[1]. TKTD models describe the time-course of processes leading to toxicity at the level of organisms. These models may include all mechanisms from the toxicokinetics part describing the compound fate from external concentration to internal kinetics (e.g., exposure, uptake, elimination, biotransformation, internal distribution), and translate the internal concentration into toxicodynamics covering alteration of cells and organs functioning that can eventually lead to a toxic effect at the organism level (e.g., mortality, reduced reproduction, abnormal behavior) then affecting the population dynamic. For survival analysis of organisms in response to a chemical stressor, the General Unified Threshold model of Survival (GUTS) is today recognized as a powerful TKTD framework incorporating two complimentary death mechanisms: Stochastic Death (GUTS-SD) and Individual Tolerance (GUTS-IT), from which a large range of existing models can be derived[1, 2]. While an integrative mathematical framework as GUTS offers an efficient theoretical approach, its practical use for parameter estimation is challenging especially with time-variable exposure. Faced with this difficulty, Bayesian approach for GUTS models has multiple advantages as (i) using all data provided by the experiments, (ii) taking into account the knowledge from experts and/or previous studies, (iii) being still relevant for complex model with small data set, and (iv) handling uncertainties by providing distributions of parameter posteriors[3, 4]. To facilitate the access to Bayesian fitting of GUTS models based on ordinary differential equations, we implemented GUTS models within two R packages (*morse*[5] and *rstanguts*) using respectivelly two languages dedicated to Bayesian statistics in connections with the widespread statistical language R (JAGS and Stan). In this presentation, we compare the result from both implementations (goodness-of-fit and speedup) and provide some guidelines for using Bayesian approach in ecotoxicology.

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Mathematical modelling in ecotoxicology: an overview

Time slot: Wednesday 20 at 11:15–12:00
Author(s): Sandrine Charles[1], Virgile Baudrot[1], Christelle Lopes[1]
Affiliation(s):
[1] Laboratoire de Biométrie - Biologie Évolutive, Université de Lyon, CNRS UMR 5558, Villeurbanne, France

Across the levels of biological organization, effects of chemicals can be very diverse, from DNA-damages within cells to shifts in trophic chains within ecosystems. When only focusing on intermediate levels, namely individual, population and community levels, environmental risk assessors already meet challenging issues, like the influence of chemical substances on individual life-history traits according to their mode of ac- tion, the resulting changes in species population dynamics and ecological interactions, until the potential repercussions in community structure and ecosystem functioning. These questions are today still made more complex due to increasingly numerous man-made chemicals at which living organisms are exposed, at low mixture concentrations hardly detectable and in combination with other environmental stress factors.

To unravel these inextricable situations, modelling is today become essential making environmental risk assessment of chemicals entering a new era. Indeed, reviews recently published by EFSA and OECD highlight the necessity of modelling, and specifically of mechanistic models, to conduct assessments that are not only ecologically relevant, but also more integrative and effective. For example, among mecha- nistic models recently developed at the individual level, toxicokinetic-toxicodynamic (TKTD) models are promoted to describe effects of chemical substances over time. TKTD models have many advantages in terms of mechanistic understanding of the chemical mode of action, deriving time-independent parameters, interpreting time-varying exposure profiles and making predictions under untested situations. Neverthe- less, the population growth rate is today recognized as a more robust endpoint for assessing ecological risks of chemicals. Hence, capitalizing on the predictive power of TKTD models, they can be coupled with population dynamic models to predict chemical impacts at the population level. The final step consists in accounting for ecological interactions between species when the protection goal is to prevent a decrease in ecosystem services. For that purpose, large dynamical systems are required for which a large number of parameter needs to be valued, a particular big challenge at a scale where expriments are difficult, indeed impossible.

In this presentation, I will give an overview of several modelling approaches that revealed successful to answer scientific questions in the field of ecotoxicology, as well as to support the daily work of risk assessors in providing them with operational tools. I will illustrate my words based on examples at the individual, population and community levels, and suggest new challenging research questions for the future.

5.5 "Epidemiology" Theme

Modelling epidemics dynamics due to Aedes mosquitoes : the example of Rio de Janeiro. How to approximate an epidemic attractor and to estimate the infectivity rate

Time slot: Tuesday 19 at 14:45–16:00

Author(s): Stefanella Boatto[1], Catherine Bonnet[2], Bernard Cazelles[3] , Frédéric Mazenc[2], Le Ha Vy Nguyen[2]

Affiliation(s):

[1] Dep. Applied Math. IM, Universidade Federal de Rio de Janeiro, Brazil

[2] Inria-CNRS-CentraleSupélec, Gif sur Yvette, France

[3] ENS-UPMC-IRD, France

Migratory fluxes of humans and of insects of various species have favoured the spreading of diseases world-wise. In particular the Ae. Agypti and Ae. Albopcitus mosquitoes of the Aedes family, are vectors able to transmit and spread among humans a variety of diseases : Dengue, Zika, Chikungunya, Yellow fever and, the newly discovered, Mayaro[1]. The Ae. Albopictcus, able to survive even at low temperature, is already well established in Europe, while the Ae. Aegypti, traditionally present in tropical regions are now starting colonising part of Europe. The overlapping of the two mosquitoes is worrisome since it could increase the spreading of the concerned diseases. In France recent cases of locally transmitted Chikungunya have been reported (22 August 2017, `http://outbreaknewstoday.com/france-reports-two-locally-transmitted-chikungunya-cases-south-45270/`) in addition to locally transmitted cases of Dengue virus type 1 (DENV-1) already registered in Nimes, south of France, in 2015 (`https://www.e-sciencecentral.org/upload/eurosurv/pdf/eurosurv-21-21-22485.pdf`)
Dengue is rather invasive epidemic due to the fact that already four different serotypes are present. It is important to stress that those epidemics can have strong social and economical impacts if not seriously controlled. Only in 2010 in Brazil, one million infected individual of which 80,000 where hospitalised.
I shall present the SIR-Network model, introduced in[2], and revisite the SIR model with birth and death terms and time-varying infectivity parameter $\beta(t)$. In the particular case of a sinusoidal parameter, we show that the average Basic Reproduction Number R_o , already introduced in Bacaër et al.[3] is not the only relevant parameter and we emphasise the role played by the initial phase, the amplitude and the period. For a quite general slowly varying $\beta(t)$ (not necessarily periodic) infectivity parameter all the trajectories of the system are proven to be attracted into a tubular region around a suitable curve, which is then an approximation of the underlying attractor. Numerical simulations are given and comparison with real data from Dengue epidemics in Rio de Janeiro allow us to estimate the infectivity rate and make predictions about what are the periods more at risk of infection.

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Modeling the spread of airborne pathogens by dispersal networks

Time slot: Poster session
Author(s): Maria Choufany[1] , Samuel Soubeyrand[1], Davide Martinetti[1], Cindy Morris[2]
Affiliation(s):
[1] Biostatistique et Processus spatiaux, INRA, 84914 Avignon France
[2] Recherches de Pathologie Végétale, INRA, 84143 Montfavet cedex, France

Surveillance of air-mass trajectories allow the anticipation of plant disease spread. In this poster, we present an approach to develop pathogen surveillance strategies based on this concept in order to reduce impacts of airborne plant diseases. In this framework, a dispersal network based on graph theory and other statistical tools will be inferred. Graphs are mathematical presentation of the relationship between objects. Within the context of this study, nodes represent a part of the territory and the edges represent the possibility of pathogen diffusion. After defining the nodes, the air mass trajectories are built with "Hysplit", a model used to compute air parcel trajectories. Then the relationship between the chosen nodes are computed using a statistical model. We thus obtained the so-called contact matrix between the nodes, that we can exploit to improve existing strategies of surveillance and help in the prediction of long-range spread of bacterial pathogens with airborne dissemination. We will illustrate this approach in the case of the dissemination of pseudomonas syringae in the Durance river basin.

Modelling the spread of Japanese Encephalitis virus in swine farms in Cambodia: Exploring for control strategies and cost-effectiveness

Time slot: Tuesday 19 at 14:45–16:00

Author(s): Alpha Oumar II Diallo[1,2,3,4,5,6], Benoit Durand[4], Raphaël Duboz[1,2,3], Julien Cappelle[1,2,5], Didier Fontenille[6], Véronique Chevalier[1,2,3]

Affiliation(s):

[1] CIRAD, UMR ASTRE, Phnom Penh, Cambodia

[2] ASTRE, UNiv Montpellier, CIRAD, INRA, Montpellier, France

[3] Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia

[4] Unité d'Epidémiologie, Agence Française de Sécurité Sanitaire des Aliments, Maisons-Alfort, France

[5] UMR EpiA, INRA, VetAgro-Sup, F-69280, Marcy l'étoile, France

[6] Institut Pasteur du Cambodge (IPC), Phnom Penh, Cambodia

Despite human vaccination, Japanese Encephalitis (JE) remains the most important cause of human encephalitis in Southeast Asia. JE virus is a *Flavivirus* transmitted from pigs to human by mosquito bites. Direct transmission between pigs can occur via direct contact. Causing abortions, JE may negatively affect swine production. Beside human vaccination, several control measures may reduce JE incidence in pigs, thus the risk of human disease: (i) vaccination of sows, that may not be sustainable alone due to a rapid turnover in pigs and a high cost; (ii) herd management that may help raising a high proportion of immune pigs thus, reducing viral circulation, and (iii) vector control. In a previous study, we proposed a deterministic compartmental model of JE transmission in pigs taking into account direct and indirect transmission. Starting from this model, we developed a new one incorporating pig batch management. It is a hybrid model assuming continuous-time for virus spreading and discrete-time for pig dynamics. We assessed the effect of combinations of control on JE incidence and abortions in pigs (JE-IAP), as well as on the risk of transmission to farmers and workers of slaughterhouses (FWS). A sensitivity analysis was performed to determine which parameters mostly influence model outputs. We identified the relative cost-efficacy of control measures. Results showed that herd management had a low impact on JE incidence in pigs. Although vaccination alone led to a disappearance of abortions (as expected), its effect on JE incidence in pigs and on the transmission risk to human (FWS) was low. However, a high level of vector control (around 80% of reduction in mosquitoe population) led to a 100% annual reduction in JE-IAP. Paradoxically, a reduction of 20-70% of the population of mosquitoes without the implementation of vaccination increased by 15% the incidence of abortions.

Gene-for-gene epidemic models, systemic acquired resistance, and the evolution of plant parasites

Time slot: Tuesday 19 at 16:30–17:15
Author(s): Frédéric Hamelin[1], Pauline Clin[1,2], Florence Val[1], Frédéric Grognard[2]
Affiliation(s):
[1] IGEPP, Agrocampus Ouest, INRA, Université de Rennes 1, Université Bretagne-Loire, Rennes, France
[2] Université Côte d'Azur, Inria, Biocore, Sophia-Antipolis, France

Many plant parasites interact with their host through gene-for-gene interactions. Considerable polymorphism for virulence (defined as the ability to overcome a resistance gene) and resistance occurs in agricultural and wild ecosystems. Fitness costs of resistance and virulence are required for polymorphism to be maintained in the long run[1]. A previous study[2] showed that there exist virulence costs in the Great Famine pathogen (*Phytophthora infestans*). These costs are mainly due to a lower spore production. However, virulent genotypes have a shorter latent period (time-to-sporulation). The latter observation is intriguing as virulent genotypes are expected to benefit from shorter latent periods.

A key component of plant immunity is termed systemic acquired resistance (SAR): this is a partial resistance response that occurs following an earlier exposure to a pathogen.

Through an adaptive dynamics approach, we show that SAR, by increasing the latent period of subsequent infections, may indeed select for shorter latent period in virulent genotypes. This way, we provide an original and possibly testable hypothesis to explain previously puzzling observations.

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Chaos and Noise in Population Biology: mathematical modelling, data analysis and intervention methods in dengue fever epidemiology, a case study

Time slot: Tuesday 19 at 14:00–14:45
Author(s): Nico Stollenwerk[1], Maíra Aguiar[2]
Affiliation(s):
[1] Centro de Matemática, Aplicações Fundamentais e Investigação Operacional (CMAF-CIO), Faculdade de Ciências, Universidade de Lisboa, Portugal
[2] Centre for Mathematics and Applications, Faculty of Sciences and Technology, NOVA University of Lisbon, Portugal

We investigate epidemiological models describing the difference between primary and secondary infection in dengue fever, which show complex dynamics, like Hopf and torus bifurcations into chaotic dynamics with positive Lyapunov exponents, in wide parameter regions.

These models describe surprisingly well long term empirical time series of dengue hospitalized cases, e.g. from Thailand, Brasil and Indonesia. Statistical methods for such complex dynamics are developed, including parameter estimation via iterated filtering and Bayesian model comparison.

We finally investigate some recent advances in control measures, namely the newly licensed first dengue vaccine and its distinctive efficacy and relative risk for seronegative versus seropositive hosts, via Bayesian analysis. This ties in well into the initial modeling assumptions of differences in primary and secondary infection as empirical confirmation.

5.6 "Food webs and interactions between species" Theme

The relationship between biodiversity and ecosystem-functioning under temperature change: a model and experimental results

Time slot: Thursday 21 at 11:15–12:00
Author(s): Louis-Félix Bersier[1]
Affiliation(s):
[1] Department of Biology, University of Fribourg, Switzerland

The relationship between biodiversity and ecosystem functioning (BEF) has received much theoretical and experimental attention. Yet, little is known about how increased temperature will impact this BEF relationship. First, a BEF theory based on mechanistic population dynamic models is developed. Second, the effect of temperature is included in the model for physiologically mild situation (i.e., in the rising part of the performance-temperature curve). This model predicts that temperature increase will intensify competition and consequently the BEF relationship will flatten or even become negative. Interestingly, negative BEF relationships are impossible with classical BEF models. Finally, a laboratory experiment with natural microbial microcosms is presented. The results are in agreement with the model predictions. The experimental results also reveal that an increase of both temperature average and variation has a more intense effect than an increase of temperature average alone.

A metagenomic-data based model of the gut microbiota

Time slot: Poster session
Author(s): Léo Darrigade[1], Simon Labarthe[1], Béatrice Laroche[1]
Affiliation(s):
[1] INRA Jouy-en-Josas, Unité MaIAGE

The human gut is engaged in a symbiosis with a complex bacterial community, the gut microbiota. Ecology of this microbial organ is crucial for host development and health. For example, the metabolites produced by the microbiota impact host physiology. As biologists shed light on these interactions, mathematical models become promising tools to study drivers of eubiosis or dysbiosis. We couple a PDE population dynamics model of meta-populations with defined metabolic abilities for dietary fibre degradation to a fluid mechanic model of intestinal content[1, 2]. The metabolic abilities are inferred from functionnal metagenomic data through NMF (non-negative matrix factorization[3]). Simplified FBA models are used to determine metabolite consumptions and growth rates of the meta-populations, and are plugged to the PDE population dynamics model to account for interactions between bacteria and with the colonic ecosystem. Taxonomic composition of a meta-population can be assessed by comparing its metabolic traits with the genome of 190 bacterial strains of the human gut microbiota which are among the most common. This approach makes comparisons possible between the model output and metagenomic data.

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Modelling spatially distributed refuge areas and sterile insect releases in a *Bt* sugarcane agroecosystem

Time slot: Thursday 21 at 9:55–10:45
Author(s): Linke Potgieter[1], Dirk J Human[1]
Affiliation(s):
[1] Department of Logistics, Stellenbosch University, Stellenbosch, South Africa

Genetically engineered crops that produce insecticidal toxins from Bacillus thuringiensis (*Bt*) are increasingly being developed and used for pest control. Unfortunately, insects develop resistance over time and as a result the toxins' efficacy are reduced, rendering this method of control ineffective as a longterm strategy. One way of delaying pest resistance to *Bt* crops is the use of refuge areas of non-*Bt* host plants or crops where susceptible insects reside. If resistance is inherited as a recessive trait, hybrid progeny resulting from matings between susceptible insects and resistant insects will also be killed by *Bt* crop, thereby resulting in a slower evolution of resistance. In this talk, we present an agent-based simulation approach to modelling resistance development in an Eldana *saccharina Walker* (Lepidoptera: Pyralidae) population for different spatially distributed or sized refuge areas in a *Bt* sugarcane scenario[1]. Results from computer simulations indicate that the spatial distribution and size of refuge areas have a direct impact on the longterm success of using *Bt* sugarcane. The economic viability of differently sized refuge areas are also considered. Apart from using refuge areas, sterile insect releases have been shown as an alternative strategy to delay pest resistance to *Bt* crops[2]. Sterile insect release has also been indicated as a viable pest control method against Eldana infestation in a sugarcane agroecosystem depending on the spatial distribution of releases. However, the economic viability of this technique remains a concern[3, 4]. Combining the use of *Bt* sugarcane, refuge areas and sterile insect releases in a sugarcane agroecosystem as an integrated strategy against Eldana infestation is also considered in this talk.

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Dynamics of predator-prey interactions : from age-structured to delay differential equations models

Time slot: Thursday 21 at 9:55–10:45
Author(s): Quentin Richard[1], Antoine Perasso[2]
Affiliation(s):
[1] Laboratoire de Mathématiques de Besançon, Université Bourgogne Franche-Comté
[2] Chrono-Environnement, Université Bourgogne Franche-Comté

The relationships between a predator and a prey are subject of numerous studies in ecology. In order to describe such trophic interactions, A. Lotka[1] and V. Volterra[2] introduced in the 20s a mathematical model of Ordinary Differential Equations (ODEs) which is still widely studied in populations dynamics. For a better modelling, it can be interesting to take into account a continuous age variable as proposed by M. Gurtin and D. Levine[3]. As shown by Sharpe and Lotka[4] then by McKendrick[5], structuring individuals according to their age leads to the formulation of a PDE of transport type. In this talk we will give some time asymptotic results obtained in[6], such as the extinction of the populations. The fact that the predation also depends on the age of the prey will enable the total quantity of individuals to explode in infinite time. We will show some numerical simulations where the populations can converge to a coexistence equilibrium. Finally, we will consider a particular case where the model can rewrite as a delay predator-prey model and for which we will study the stability of the nontrivial equilibrium.

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A laboratory-data-supported mathematical model for water purification

Time slot: Thursday 21 at 9:10–9:55
Author(s): Iulia Martina Bulai[1], Federica Spina[2], Giovanna Cristina Varese[2], Ezio Venturino[3]
Affiliation(s):
[1] Departement of Information Engineering, University of Padova, Padova, Italy
[2] Dipartimento di Scienze della Vita e Biologia dei Sistemi, Università di Torino, Torino, Italy
[3] Dipartimento di Matematica Università di Torino, Torino, Italy

The ever increasing worldwide scarcity of clean water renders wastewater treatment of paramount importance to satisfy the drinking and industrial needs. Mathematical models represent relatively cheap means of simulating the behavior of complex systems, if enough computing power is available. We present here a mathematical system that models the decolourisation process of waters flowing out of textile industrial plants.

In particular, we consider the Remazol Brilliant Blue Reactive dye (RBBR) as pollutant, and employ a selected white rot fungus, which is known to be able to degrade a wide range of recalcitrant compounds. We focus on the important role that carbon (glucose) plays in this action. Indeed, it can help fungal metabolism and growth.

The dynamical system thus contains three major actors, the pollutant, the fungi and glucose, which represent the time-dependent variables, whose behavior is then compared with the results of experimental data obtained in the laboratory experiments especially designed for this purpose. Then best fitting allows us to assess the value of the various parameters describing the growth and the chemical reactions rates in this closed system.

A more general mathematical model is finally introduced, to simulate real industrial purification reactors, that allows for a constant pollutant and nutrients input.

5.7 "Genome evolution" Theme

Models for demo-genetic viral dynamics that will be used for inferring transmission links

Time slot: Poster session
Author(s): Maryam Alamil[1], Karine Berthier[2], Gaël Thebaud[3], Samuel Soubeyrand[1]
Affiliation(s):
[1] BioSP, INRA PACA, Avignon, France
[2] PV, INRA PACA, Avignon, France
[3] Plant Health and Environment, INRA, Montpellier, France

Fast-evolving viruses can cause epidemics of high impact in developing and developed countries. Inferring transmission links, for such pathogens, using viral genetic data is crucial to make epidemiological predictions and to design control strategies. In order to determine "Who infected whom" from genetic data, classical approaches exploit consensus sequences. Such sequencing data provide only a limited amount of information, whereas high-throughput sequencing methods (e.g NGS) give more accurate information at the within-host level. Our long-term aim is precisely to develop a statistical approach based on such data and a pseudo-evolutionary model to infer infectious disease transmissions and to infer the relationship between disease spread and environnemental factors. To calibrate and validate this approach, we need a simulator generating sets of sequences from different hosts at different times and taking into-account within- and between-hosts demographic and evolutionary dynamics.
In this poster, we will present the stochastic model for the pathogen population demography and evolution that we have constructed to generate sets of different viral variants and their frequencies under various conditions. In the intents of inferring transmission links later, we measured the within-host genetic diversity by several indices that depend on the variant frequencies resulting from our model. We used these indices to show the impact of genetic and demographic factors on the within-host genetic diversity. These results can then be exploited to design sampling strategies that will allow to efficiently infer transmission links.

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Metastability property of a model for the evolution of a fungal pathogen

Time slot: Wednesday 20 at 14:45–15:35
Author(s): Jean-Baptiste Burie[1], R. Djidjou-Demasse[2], A. Ducrot[1]
Affiliation(s):
[1] Université de Bordeaux, CNRS IMB UMR 5251
[2] INRA Villenave d'Ornon, UMR SAVE

In this talk we will consider an integro-differential model for the genetic adaptation of a fungal pathogen. The pathogen population asymptotically concentrates around the optimal value of the fitness function. But, in some specific configurations, we are able to describe the existence of a long transient regime during which the pathogen population remains far from this optimal value. Thus we exhibit a property of metastability for a pathogen strain ill adapted to its host which may act as a barrier of evolution very long to bypass.

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Embedding and clustering gene sequences for evolution analysis using Laplacian eigenmaps and a stochastic gradient based PCA

Time slot: Thursday 21 at 17:15–18:05
Author(s): Jean-Claude Charr[1], Stéphane Chrétien[2], Christophe Guyeux[1], Olivier Ho[3]
Affiliation(s):
[1] National Physical Laboratory, Teddington, UK
[2] FEMTO-ST Institute, UMR 6174 CNRS, France
[3] LMB, Université de Bourgogne Franche-Comté, France

Being able to predict how chloroplastic genomes evolve over time makes it possible to reconstruct their ancestors. By doing so, it is possible to infer the old DNA sequence of their last common ancestor: if this latter is close enough from a cyanobacteria, the origin of plant photosynthesis will then be established. A first important step in this ancestral reconstruction is the so-called gene prediction stage, in which coding sequence locations are detected: indeed, with such a knowledge, it is possible to deduce the evolution of gene content and ordering over time. This can be achieved by collecting a large amount of chloroplastic sequences from the NCBI, clustering them by similarity, and then inferring a consensus gene. The main contribution of the paper is to introduce a bespoke embedding methodology based on the Laplacian eigenmap approach for gene sequence embedding and clustering. Laplacian eigenmaps have been extremely successful in many different problems from Data Science[1]. Application of Laplacian eigenmaps to gene sequence analysis and clustering was first proposed in[2]. The main bottleneck of the Laplacian eigenmap approach is the need to compute the entries of a very large affinity matrix and it first few eigenvectors. Moreover, the affinity matrix for gene sequences being computed using the Needleman-Wunsch algorithm, the computation of the affinity matrix is even more cumbersome in our setting of interest. The main novelty of our work is to propose a principled approach to reduce the number of pairwise affinities that need to be computed in the context of gene sequences. Moreover, we devise a new stochastic gradient algorithm for computing the most significant eigenvectors. Numerical simulation experiments show the relevance of the approach for large genomic datasets that were not previously amenable to this kind of analysis.

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5.8 "Oncology" Theme

Mathematical Modeling of Tumor-Tumor Distant Interactions Supports a Systemic Control of Tumor Growth

Time slot: Friday 22 at 11:20–12:05
Author(s): Sébastien Benzekry[1,2,3], Clare Lamont[2], Dominique Barbolosi[3] , Lynn Hlatky[2] , Philip Hahnfeldt[2]
Affiliation(s):
[1] Inria Bordeaux Sud-Ouest and Institut de Mathematiques de Bordeaux, Talence, France
[2] Center of Cancer and Systems Biology, Tufts University School of Medicine, Boston, USA
[3] SMARTc team, Centre de Recherche en Cancerologie de Marseille (Inserm 1068), Marseille, France

Interactions between different tumors within the same organism have major clinical implications, especially in the context of surgery and metastatic disease. Three main explanatory theories (competition, angiogenesis inhibition, and proliferation inhibition) have been proposed, but precise determinants of the phenomenon remain poorly understood. In this talk, I will present a formalized version of these theories into mathematical models and the results of biological experiments that were performed to test them against empirical data.

The main experimental finding was that in syngeneic mice bearing two simultaneously implanted tumors, growth of one and only one of the tumors was significantly suppressed (61% size reduction at day 15, $P < 0.05$). At the theoretical level, the competition model had to be rejected, whereas the angiogenesis inhibition and proliferation inhibition models were able to describe the data.

The proliferation inhibition model was identifiable and minimal (four parameters), and its descriptive power was validated against the data, including consistency in predictions of single tumor growth when no secondary tumor was present. This theory may also shed new light on single cancer growth insofar as it offers a biologically translatable picture of how local and global action may combine to control local tumor growth and, in particular, the role of tumor-tumor inhibition. This model offers a depiction of concomitant resistance that provides an improved theoretical basis for tumor growth control and may also find utility in therapeutic planning to avoid postsurgery metastatic acceleration.

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Reduced Google matrix approach for the analysis of directed biological networks

Time slot: Friday 22 at 10:00–10:50
Author(s): José Lages[1], Dima L. Shepelyansky[2], Andrei Zinovyev[3]
Affiliation(s):
[1] Institut UTINAM, Observatoire des Sciences de l'Univers THETA, CNRS, Université de Bourgogne Franche-Comté, Besançon, France
[2] Laboratoire de Physique Théorique, IRSAMC, Université de Toulouse, CNRS, UPS, Toulouse, France
[3] Institut Curie, PSL Research University, Mines Paris Tech, Inserm, U900, Paris, France

Signaling pathways represent parts of the global biological network which connects them into a seamless whole through complex direct and indirect (hidden) crosstalk whose structure can change during development or in pathological conditions. We suggest a novel methodology, called Googlomics, for the structural analysis of directed biological networks using spectral analysis of their Google matrices, using parallels with quantum scattering theory, developed for nuclear and mesoscopic physics and quantum chaos. We introduce the reduced Google matrix method for the regulatory biological networks and demonstrate how its computation allows inferring hidden causal relations between the members of a signaling pathway or a functionally related group of genes. We investigate how the structure of hidden causal relations can be reprogrammed as the result of changes in the transcriptional network layer during cancerogenesis. The suggested Googlomics approach rigorously characterizes complex systemic changes in the wiring of large causal biological networks.

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In vivo and in vitro experiments validate mathematical predictions for brain tumor behaviour

Time slot: Friday 22 at 9:15–10:00

Author(s): Alicia Martínez-González[1], JM Ayuso[2] , GF Calvo[1] , LJ Fernández[2] , J Frontiñán[3] , LA Pérez Romasanta[4] , I Ochoa[2] , VM Pérez García[1]

Affiliation(s):

[1] Mathematics Department, Mathematical Oncology Laboratory, Universidad de Castilla-La Mancha, Spain

[2] Group of Applied Mechanics and Bioengineering. (CIBER-BBN), Zaragoza, Spain

[3] Dpto. de Ciencias Médicas, Facultad de Medicina, Universidad de Castilla-La Mancha, Spain

[4] Servicio de Oncología Radioterápica, Hospital General Universitario de Salamanca, Spain

Glioblastoma (GBM) is the most frequent and lethal malignant brain tumor in adults. Combined mathematical simulations and on-chip validation of malignant cellular structures formation in GBM has confirmed their usability to better understand the tumor behavior. In addition, mathematical model results predicted a synergistic decrease in tumor volume when both, cytotoxic therapies and antioxidants were applied. In vitro and in vivo results have confirmed this benefit not only in terms of tumor reduction but also in terms of toxicity reduction. Considering the excellent results, a clinical trial has been designed.

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Towards data integration for Triple Negative Breast Cancer

Time slot: Friday 22 at 10:00–10:50
Author(s): Renaud Seigneuric[1]
Affiliation(s):
[1] Cancer and adaptive immune response (CADIR) team / CGFL, UMR INSERM 1231 Lipids, Nutrition, Cancer, University of Burgundy / Franche-Comté, Dijon, France

Breast cancer is the most frequently diagnosed cancer in women. Approximately 15% of all breast tumors are considered triple-negative breast cancer (TNBC), which is characterized by the lack of immune-histochemical (IHC) expression of estrogen receptor (ER), progesterone receptor (PR) and HER2. High-throughput techniques including gene expression profiling with DNA microarrays have demonstrated the heterogeneity of breast cancer by distinguishing subtypes with different therapeutic implications. Yet, many challenges remain, including regarding drug resistance. A bioinformatics approach aiming at integrating data expression of hundreds of patients using pathways, networks and drugs databases in order to contribute to a better treatment selection will be presented.