Book of Abstracts

BioHasard 2019
International Conference on
Stochastic Models for Biology
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Contents

Schedule

MONDAY			TUESDAY			WEDNESDAY			THURSDAY		
Chair: Jürgen Angst			Chair: Solenn Stoeckel			Chair: Fred Hamelin			Chair: Jürgen Angst		
	1340	Solenn STOECKEL	Welcome introduction and practical information	09:00	Maria ORIVE	Adaptation to environmental change under partial clonality: the effect of environmental variation	09:00	Linda ALLEN	Stochastic Epidemic Models of Zoonotic Spillover	09:00	Florent MAUBIEU	On the ergodicity of Piecewise Deterministic Markov Processes in Biology
	1400	Vincent BANSAYE	Stochastic functional responses and some multi-scale models in population dynamics									
				09:45	Loren COQUILLE	Crossing a fitness valley as a metastable transition in a stochastic population model	09:45	Aline MARQUET	Inheritance and variability of kinetic gene expression parameters in microbial cells	09:45	Charline SMADI	Multidimensional Lambda-Wright-Fisher processes with general frequency-dependent selection
	1445	Camille CORON	Infering marmosets neuroscience parameters using vocalization time datasets									
	1530		Coffee Break	10:30		Coffee Break	10:30		Coffee Break	10:30		Coffee Break
Vincent Bansaye	1600	Aurélien VELLERET	Quasi-Stationary Distribution and related topics in ecology: the adaption of populations to a changing environment	11:00	Nathalie KRELL	Non-parametric estimation of the spiking rate in systems of interacting neurons	11:00	Gaël BEAUNEE	Inference for a meta-population model via a composite-likelihood approximation	11:00	Yann LE CUNFF	Modelling oscillatory behavior in asymmetric division of *Caloglyphus* embryo
	1630	Raphaël FORIEN	The stepping stone model in a random environment : the effect of spatial heterogeneities on isolation by distance patterns	11:30	Patrick HOSCHEIT	Lambda-coalescents as priors in phylodynamical analysis	11:30	Driss KOUACH	Dynamics of modified SIRS model with stochastic influences : stationary distribution, persistence in the mean and extinction	11:30	Vincent CLUEDE-VILLE	Insights into age-structured biological population models
	1700		Discussion (Chair: Solenn Stoeckel)	12:30		Lunch	12:00	Hélène CECILIA	Predicting the risk of Rift Valley Fever outbreaks in West African Sahel	12:00	Anjela DAVIDOVIC	Calibration of stochastic biochemical models using single-cell video-microscopy experiments
	1830		End of the conference day	14:00	Nicolas BACAER	Quelques modèles stochastiques de population dans un environnement périodique ou aléatoire	Autonomous lunch and afternoon: enjoying Rennes or visiting Saint-Malo			12:30		Lunch
				14:45	Hélène GUERIN	Interacting Zigzag processes to model collaborative bacteria				14:00	Vitushkã BOKIL	Stochastic models for competing species in the presence of disease with applications to bacterial competition and killing
				15:30		Coffee Break				14:45	Romain YVINEC	Stochastic population dynamics applied to ovarian follicles development
				16:00	Philippe CARMONA	Pathogen emergence in seasonal environments				15:30		Coffee Break
				16:30	Nik CUNNIFFE	Co-infections by non-interacting pathogens are not independent and require new tests of interaction				16:00	Floor BIEMANS	A stochastic model of the within-herd transmission of paratuberculosis in an Irish dairy herd
				17:00	Brady BOWEN	Density dependence in vector influenzes control: Aedes aegypti as a case study				16:30	Sébastien PICAULT	A mechanistic model for comparing detection methods and control measures in Bovine Respiratory Disease
				17:30		Discussion (Chair: Solenn Stoeckel)				17:00		Discussion (Chairs: Gaël Beaunée & Fred Hamelin)
				18:30		End of the conference day				18:00		End of the conference
				19:30		Gala dinner in Rennes city center						

Invited Talks

Stochastic Epidemic Models of Zoonotic Spillover

Linda J. S. Allen
Department of Mathematics & Statistics, Texas Tech University

Zoonotic infectious diseases are spread from animals to humans. It is estimated that over 60% of human infectious diseases are zoonotic. Many emerging or re-emerging infectious diseases are viral zoonoses, including avian influenza, rabies, Ebola, and hantaviruses. Spillover of infection from animals to humans depends primarily on the contact between animals and humans. Environmental factors, such as seasonal variations in temperature, humidity, and rainfall also impact the spread of zoonotic diseases. A new time-nonhomogeneous stochastic process is formulated for infectious disease spread from animals to humans when transmission and recovery rates are time-periodic. Application of a branching process approximation shows that the probability of the first spillover event from animals to humans is also a periodic function which depends on the time when the infection begins in the animal population. It is shown that the highest risk of the first spillover event generally does not coincide with the time of peak animal-to-human transmission. Applications to rabies and hantaviruses are discussed. This is joint work with Aadrita Nandi and Kaniz Fatema Nipa.

Quelques modèles stochastiques de population dans un environnement périodique ou aléatoire

Nicolas Bacaër
IRD Paris

On présentera un résumé de quelques travaux sur des processus de naissance et de mort avec un ou plusieurs types dans un environnement périodique ou aléatoire. Il sera question notamment de la durée moyenne jusqu'à l'extinction dans des modèles épidémiques de type S-I-S, de la probabilité d'extinction dans des modèles linéaires surcritiques et du taux d'extinction dans les modèles linaires sous-critiques.

Stochastic functional responses and some multi-scale models in population dynamics

Vincent Bansaye
École Polytechnique

The objective of this work is to take into account at the individual level complex interactions within populations and to reduce associated models in large populations. First, we will present a unified probabilistic framework for functional responses, which quantify interactions in biology and ecology. It is based on renewal theory and provides a deterministic approximation and Gaussian fluctuations describing the number of interactions. In a second step we will consider two populations governed by such interactions, with two scales of different sizes and a large time scale. We will focus on predator prey systems and describe their macroscopic approximation by dynamic systems. The proof will be based on martingale techniques and averaging developed by Tom Kurtz. In some regimes, we can also describe the fluctuations around the dynamic system, inherited from the renewal theorem.

Stochastic models for competing species in the presence of disease with applications to bacterial competition and killing

Vrushali Bokil

Oregon State University

The presence of a disease among multiple competing species has important ecological implications, in particular with respect to a change in the competitive outcomes. Alternatively, if a pathogen becomes established, there may be a drastic reduction in species numbers. Stochastic variability in the birth, death and disease transmission processes plays an important role in determining the success of species or pathogen invasion. We investigate these phenomena using stochastic models in the form of continuous-time Markov chains and stochastic differential equations. Branching process theory is applied to the continuous-time Markov chain model to estimate probabilities for pathogen extinction or species invasion. We apply our results to the case of bacterial competition involving killing of adjacent competitors via the T6SS secretion system and consider conditions for competitive exclusion or coexistence.

Crossing a fitness valley as a metastable transition in a stochastic population model

Loren Coquille
Université Grenoble-Alpes

We consider a stochastic model of population dynamics where each individual is characterised by a trait in $\{0, 1, \dots, L\}$ and has a natural reproduction rate, a logistic death rate due to age or competition and a probability of mutation towards neighbouring traits at each reproduction event. We choose parameters such that the induced fitness landscape exhibits a valley: mutant individuals with negative fitness have to be created in order for the population to reach a trait with positive fitness. We focus on the limit of large population and rare mutations at several speeds. In particular, when the mutation rate is low enough, metastability occurs: the exit time of the valley is random, exponentially distributed. This is a joint work with Anton Bovier and Charline Smadi.

Inferring marmosets neuroscience parameters using vocalization time datasets

Camille Coron
Université Paris-Sud

We use marmosets (*ouistitis*, in French) vocalization data, and more specifically the beginning and ending time of all sounds produced by each marmoset during a several minutes recording. Our hypothesis is that these beginning and ending time correspond to the reaching time of some threshold by a 2-dimensional stochastic diffusion process whose equation is known and whose dynamics changes during vocalization. Our aim is to estimate the parameters of the model using these vocalization time data. We also investigate the evolution of these parameters and of the behaviour of marmosets during their life.

Interacting Zigzag processes to model collaborative bacteria

Hélène Guérin
Université du Québec à Montréal

The Zigzag process has been recently introduced to model the behavior of flagelated bacteria, as E-Coli, in their environment. Indeed the behavior of such bacteria is composed of run phases with constant velocity and of tumble phases where we observe a quick change of the velocity. Under some good assumptions this process converges exponentially fast to an explicit invariant measure.

In this talk we will consider a system of Zigzag particles attracted by the mean position of the system to model bacteria with collaborative behavior. The question of propagation of chaos will be studied and properties of the nonlinear limit process such as its long time behavior will be discussed.

This is a joint work with N. Fétique and F. Malrieu.

Inheritance and variability of kinetic gene expression parameters in microbial cells

Aline Marguet
Inria Grenoble Rhône-Alpes

Modern experimental technologies enable monitoring of gene expression dynamics in individual cells and quantification of its variability in isogenic microbial populations. Among the sources of this variability is the randomness that affects inheritance of gene expression factors at cell division. Known parental relationships among individually observed cells provide invaluable information for the characterization of this extrinsic source of gene expression noise. Starting from a transcription and translation model of gene expression, we propose a stochastic model for the evolution of gene expression dynamics in a population of dividing cells. Based on this model, we develop a method for the direct quantification of inheritance and variability of kinetic gene expression parameters from single-cell gene expression and lineage data. We demonstrate that our approach provides unbiased estimates of mother-daughter inheritance parameters, whereas indirect approaches using lineage information only in the post-processing of individual cell parameters underestimate inheritance. Finally, we show on yeast osmotic shock response data that daughter cell parameters are largely determined by the mother, thus confirming the relevance of our method for the correct assessment of the onset of gene expression variability and the study of the transmission of regulatory factors.

Adaptation to environmental change under partial clonality: the effect of environmental variation

Maria E. Orive[1], James H. Peniston[2], Michael Barfield[2], and Robert D. Holt[2]

[1]Department of Ecology and Evolutionary Biology, University of Kansas;
[2]Department of Biology, University of Florida

We develop a general model for phenotypic evolution under both sexual and clonal reproduction (partial clonality), and show that the effects of clonal reproduction on changes in mean phenotype partition into two portions: one that is phenotype-dependent and one that is genotype-dependent (Orive et al. 2017). This partitioning is governed by the association between the non-additive genetic plus random environmental component of phenotype of clonal offspring and their parents (ρ). Analytical results, combined with individual-based simulations allowing for both demographic and genetic stochasticity, demonstrate that the response of partially clonal populations to rapid environmental change depends on both the magnitude of the change, and on the whether the population experiences that change as a single step or as continual change. Increased clonality increases the probability of population persistence following a single abrupt change in the environment, while increasing the risk of population extinction under continual change. Additional simulations allowing for fluctuations in the optimum phenotype show that these general patterns hold in noisy environments. However, uncorrelated fluctuations decrease the benefit of increasing clonal reproduction (r_c) following an abrupt change. Conversely, under positively autocorrelated environmental variability, the benefit of increased offspring-parental association (ρ) becomes greater (Peniston et al., in prep).

On the ergodicity of Piecewise Deterministic Markov Processes in Biology

Florent Malrieu
Institut Denis Poisson, Tours

The evolution of a PDMP is very intuitive: a deterministic motion punctuated by random jumps. Despite this simplicity, the long time behavior of these processes is sometimes surprising. With several basic examples motivated by biological concerns, I will present some counter-intuitive results and their consequences.

Multidimensional Lambda-Wright-Fisher processes with general frequency-dependent selection

Charline Smadi[1] and Adrian Gonzalez Casanova[2]
[1]IRSTEA, Clermont-Ferrand; [2]UNAM, Mexico

We construct a multitype constant size population model allowing for general selective interactions as well as extreme reproductive events. Our multidimensional model aims for the generality of adaptive dynamics and the tractability of population genetics. It generalizes the idea of (Krone and Neuhauser 1997), and (Gonzalez Casanova and Spano 2018), who represented the selection by allowing individuals to sample several potential parents in the previous generation before choosing the 'strongest' one, by allowing individuals to use any rule to choose their real parent. The real parent can even not be one of the potential parents, which allows modelling mutations. Via a large population limit, we obtain a generalisation of Lambda-Fleming Viot processes, with a diffusion term and a general frequency-dependent selection, which allows for non transitive interactions between the different types present in the population. We provide some properties of these processes related to extinction and fixation events, and give conditions for them to be realised as unique strong solutions of multidimensional stochastic differential equations with jumps. Finally, we illustrate the generality of our model with applications to some classical biological interactions. This framework provides a natural bridge between two of the most prominent modelling frameworks of biological evolution: population genetics and eco-evolutionary models.

Keywords: Lambda-Fleming Viot processes, Frequency-dependent selection, Multidimensional processes, Duality, Ancestral Processes.

Stochastic population dynamics applied to ovarian follicles development

Romain Yvinec
INRA Tours

I will present several stochastic population dynamical models applied to ovarian follicles development in mammals. The ovarian follicles are the basic anatomical and functional units of the ovaries. One ovarian follicle consists of a population of somatic cells sheltering the germ cell.

We first present models describing the growth of a single follicle, by focusing on the somatic cell population dynamics along the first developmental stages of an ovarian follicle. We present both analytical results on those models as well as parameter calibration based on available data.

Then, we present a multiscale model describing the evolution of the population of follicles within the ovaries, focusing on the interactions between follicles all along the reproductive life. We performed a model reduction based on a separation of time scale, and show qualitative adequacy with biological data of our reduced model.

Contributed Talks

Inference for a metapopulation model via a composite-likelihood approximation

Gaël Beaunée[1], Pauline Ezanno[1], Alain Joly[2], Pierre Nicolas[3], and Elisabeta Vergu[3]

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Processes related to the spatio-temporal spread of pathogens in metapopulations are most often partially observed, and available data are usually incomplete, spread over time and heterogeneous. Moreover, the representation of this type of biological systems often leads to complex models. In this case, classical inference methods (i.e. maximum likelihood) are not usable because the likelihood function can not be specified. Bovine paratuberculosis (agent *Mycobacterium avium* subsp. *paratuberculosis* - Map) is a worldwide enzootic disease of economic importance whose screening in the field is difficult due to its long incubation period and the low sensitivity of routine diagnostic tests.

Our objective was to develop a new inference procedure for complex mechanistic epidemiological models and sparse and heterogeneous observed data, in order to estimate key parameters of a multiscale dynamic model of Map spread from a longitudinal and spatial dataset collected in Brittany (Western France), and to provide additional knowledge on the propagation of Map.

Our approach is based on a stochastic mechanistic model of Map spread between dairy herds through animal trade movements. Comprehensive data on cattle movements in 12,857 dairy herds in Brittany and partial data on animal infection status (2,013 herds sampled from 2005 to 2013) were available. Inference was performed with a Monte-Carlo approximation of a composite likelihood coupled to a numerical optimization algorithm (Nelder-Mead Simplex-like). The seven estimated key parameters of this model are: (i) the proportion of initially infected herds, (ii and iii) their infection level (distribution of within-herd prevalence), (iv and v) the probability of purchasing infected cattle from outside the metapopulation and the trend of this probability, (vi) the indirect local transmission rate, and (vii) the sensitivity of the diagnostic test.

Empirical identifiability was verified on simulated data. The optimization algorithm converged after appropriate tuning. Point estimates and profile likelihoods indicate a very large proportion (> 0.90) of infected herds with a low within-herd prevalence on average at the initial time (2005), a moderate and constant risk of

introducing an infected animal from outside the meta population (~ 0.10) and a low sensitivity of the diagnostic test (~ 0.21).

Estimations of previously unknown key parameters provide new insights on Map spread at the regional scale, mainly showing a high prevalence in the number of infected herds, in agreement with qualitative opinions of experts. These estimates of previously unknown parameters provide new insights on Map status in Western France. The inference framework could easily be applied to datasets from other regions concerned by paratuberculosis and adapt to estimate key features of other spatio-temporal infection dynamics, most often imperfectly observed, especially for long-lasting endemic diseases. It is of particular interest when ABC-like inference methods fail due to difficulties in defining relevant summary statistics.

Keywords: parameter estimation, composite likelihood, mechanistic stochastic epidemic model, metapopulation model.

A stochastic model of the within-herd transmission of paratuberculosis in an Irish dairy herd

Floor Biemans[1,2], Simon J. More[1] and Pauline Ezanno[2]

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[2]BIOEPAR, INRA, Oniris, 44307, Nantes, France

Paratuberculosis (Johne's disease) is a chronic bacterial infection of the intestine caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP). Paratuberculosis is widely spread among industrial dairy farms worldwide and causes economic losses to farmers. Clinical signs (decreased milk production, weight loss, diarrhea) usually do not appear until after the first calving or even at much older ages. Diagnostic tests have a poor sensitivity for detecting infected animals that do not show clinical signs, therefore, herd prevalences could be much higher than expected. The main pathways of MAP transmission at farm scale and their drivers associated to the farming system are not fully understood yet.

In Ireland, the milk production system is pasture based, meaning that most herds adhere to a compact spring calving period, so that grass supply matches the intake demand of cattle. A consequence of the seasonal calving pattern is that contacts between age groups also are seasonal. These specificities may influence MAP transmission, as MAP is transmitted from infected adult cows to young susceptible calves (<1-year-old) via contaminated colostrum and milk, via an environment that contains contaminated faeces, and via in utero transmission.

To assess the transmission and persistence of MAP in a typical Irish dairy cattle farm, a stochastic individual-based model has been developed which accounts for both seasonal herd demographics and infection processes. We investigated MAP persistence, prevalence, and incidence in Irish dairy cattle herd, and assessed which are the main transmission routes. Using a sensitivity analysis of the model, we evaluated the effect of the calving system on model predictions both in a MAP-free herd in which the infection was introduced once and in an endemically infected herd.

Most infections occurred in utero or via a contaminated environment; colostrum and milk were minor transmission routes. Highest incidences were observed when large numbers of highly susceptible calves resided in an environment where the infectious pressure was high, for example indoors in the calving pen where newborn calves share the environment with cows or outdoors when young calves and cows share part of the pasture.

Density dependence in vector influences coinfection in plant pathogens

Brady Bowen[1], Vrushali Bokil[1], Margaret-Rose Leung[2] and Elizabeth T. Borer[3]
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Interactions among pathogen species within a host, resulting in cross protective immunity, synergistic mortality, or alterations of host infectivity or transmission can alter the dynamics of both host and pathogen populations. Whereas most coinfection models assume a constant vector population, many vectors experience density-dependent population regulation. Here we develop and parameterize a model based on a well-studied multi-pathogen, multi-vector system, barley and cereal yellow dwarf viruses (B/CYDV). Our model, a system of nonlinear ordinary differential equations, describes a single host, two pathogen strains, and n vector species with a single parameter describing pathogen relatedness. We examine basic and type reproductive numbers, linear stability, parameter sensitivity, and the relative importance of pathogen similarity and vector population regulation on pathogen prevalence and coinfection. We demonstrate numerically that the basic reproduction number describes the disease-free equilibrium stability, whereas type reproduction numbers better describe coinfection dynamics. A sensitivity analysis for two different vector growth functions indicates that infection equilibria of both formulations are sensitive to disease transmission rates, but vector birth and death rates are important only for the logistic formulation. Cross protection is influential only for the constant vector formulation. Thus, empirical determination of the degree and form of vector density dependence is critical for effective predictions about coinfection in natural host populations.

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

Anca Caranfil[1,2,3], Yann Le Cunff[1,2], Charles Kervrann[3], and Jacques Pécréaux[1]

[1]INRIA Rennes Bretagne Atlantique; [2]Institute of Genetics and Development of Rennes;[3]University of Rennes 1

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* embryos first division. To improve our understanding of this process, we used mathematical modelling to study *C. elegans* embryos 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.

Keywords: asymmetric cell division, spindle dynamics, spindle oscillations modelling, Bayesian statistics.

Pathogen emergence in seasonal environments

Philippe Carmona[1] and Sylvain Gandon[2]
[1]Université de Nantes; [2]CNRS, Montpellier

Many infectious diseases exhibit seasonal dynamics driven by periodic fluctuations of the environment. We study the impact of seasonality on the probability of pathogen emergence under different epidemiological scenarios. When the period of the fluctuation is large relative to the duration of the infection, the probability of emergence varies dramatically with the time at which the pathogen is introduced in the host population. We use this theoretical framework to compare the impact of different control strategies on the average probability of emergence. We show that, if pathogen eradication is not attainable, the optimal strategy is to act intensively in a specific time interval. Interestingly, the optimal control strategy is not always the strategy minimizing the basic reproduction ratio of the pathogen. This analysis has very practical implications on the control of emerging infectious diseases in seasonal environments. For instance, we discuss how these results could be used to improve the evaluation of the risk of Zika virus emergence across different geographic locations and at different points in time.

Keywords: time varying branching processes, extinction probability.

Predicting the risk of Rift valley fever outbreaks in West African Sahel

Hélène Cecilia[1], Raphaëlle Métras[2], Frédéric Huard[3], Annelise Tran[2,4], Renaud Lancelot[2] and Pauline Ezanno[1]

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[3]US Agroclim, INRA, Avignon; [4]TETIS, CIRAD, Sainte-Clotilde, Réunion

When studying the epidemiology of an infectious disease, it is critical to assess the risk of this disease spreading at large demographic scale, creating outbreaks. Quantifying this risk in time and space is essential to design efficient surveillance strategies. Indeed, knowing where and when a pathogen is likely to spread if introduced making a huge difference for health services who need to react quickly to limit the extent of the epidemic. The basic reproduction number R0 is a convenient metric for such a purpose, commonly used in epidemiology. R0 represents the average number of secondary cases arising after one infected individual is introduced in an entirely susceptible population.

Rift valley fever (RVF) virus is a vector-borne zoonosis present throughout Africa and part of the Middle East, listed by the World Health Organization (WHO) as a top-10 emerging disease. Mosquitoes are the main vectors of RVF virus, which is transmitted to a variety of hosts, including cattle and small ruminants, causing abortion storms and a high mortality in young animals. Vectors, hosts and their relation to their environment form a complex biological system still poorly understood. In addition to vectorial transmission, Aedes vectors are suspected to be capable of vertical transmission, while direct transmission between animals can occur after farrowing, making it difficult to anticipate RVF virus spread.

In West African Sahel, RVF outbreaks occurred in two contrasted ecosystems. Along the Senegal River, water, vectors (mainly Culex) and hosts are in contact all year long. In dryer areas such as the Ferlo region of Senegal, life is regulated by seasons. When the rain comes, temporary ponds are flooded and Aedes mosquitoes massively emerge, thanks to eggs layed on the pond border the year before. In the meantime, vegetation grows and creates the right conditions for nomadic herds to stop during their transhumance pathway, thus putting vectors and hosts in contact.

We provided a new formula for R0 considering both vector genus (Culex and Aedes), two host species (cattle and small ruminants), and the three potential transmission routes (vectorial, transovarian, host-to-host). We assessed R0 sensitivity to parameter variations. Then, we mapped R0 in Senegal during the rainy season, using remotely sensed data on temperature, rain, and water bodies locations, as well as outputs from published models for vector and host densities. We highlighted areas and periods with the highest risk of outbreak occurrence.

Such results provide a better understanding of underlying processes contributing to RVF risk. This knowledge is needed when trying to implement targeted control measures with a strong impact. In future work, these results will provide the starting situation for predicting RVF virus spread at large scale, using a mechanistic, stochastic spatio-temporal model of RVF virus transmission dynamics.

Keywords: Rift valley fever, Senegal, basic reproduction number, vector-borne disease.

Co-infections by non-interacting pathogens are not independent and require new tests of interaction

Frédéric M. Hamelin[1], Linda J.S. Allen[2], Vrushali A. Bokil[3], Louis J. Gross[4], Frank M. Hilker[5], Michael J. Jeger[6], Carrie A. Manore[7], Alison G. Power[8], Megan A. Rúa[9], Nik J. Cunniffe[10]

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If pathogen species, strains or clones do not interact, intuition suggests the proportion of co-infected hosts should be the product of the individual prevalences. Independence consequently underpins the wide range of methods for detecting pathogen interactions from cross-sectional survey data. Surprisingly, however, the results of the very simplest of epidemiological models challenge the underlying assumption of statistical independence. Even if pathogens do not interact, death and/or clearance of co-infected hosts causes net prevalences of individual pathogens to decrease simultaneously. The induced positive correlation between prevalences means the proportion of co-infected hosts is expected to be higher than multiplication would suggest. By modeling the dynamics of multiple non-interacting pathogens, we develop a pair of novel tests of interaction that properly account for this hitherto overlooked coupling. Which test is appropriate for any application depends on the form of the available data, as well as the extent to which the co-infecting pathogens are epidemiologically similar. Our tests allow us to reinterpret data from a number of previous studies, including pathogens of plants and animals, as well as papillomavirus and malaria in humans. We find certain reports of interactions have been overstated, and in some cases are not supported by the available data. Our work demonstrates how methods to identify interactions between pathogens can be updated to account for epidemiological dynamics.

Keywords: co-infection, multiple pathogens, SIS epidemic, statistical independence, pathogen association.

Calibration of stochastic biochemical models using single-cell video-microscopy experiments

Andjela Davidovic[1], Gregory Batt[2,1] and Jakob Ruess[2,1]

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Biochemical reaction networks are often represented at the cellular level by stochastic models. Video-microscopy data provide rich longitudinal information on the behavior of single cells and can be used for the calibration of these models. In combination with optogenetic approaches, one can even apply different perturbations (i.e. different light input profiles) to different cells in parallel. These parallelized single-cell video-microscopy experiments can potentially be very informative. To fully exploit this rich information for model calibration, one has to be able to compute efficiently likelihoods of the data given model parameters. Exact methods rely on the computation of the full state probability distribution, which is generally not tractable. Approximate methods, most notably using the linear noise approximation (LNA), have been applied with some success. However, their use is limited for two reasons. Firstly, they rely on Gaussian approximations of state probability distributions and are very inaccurate when this assumption is violated. This is notably the case for systems admitting bimodal distributions. Secondly, their computational times increases significantly with the number of measurement time points. Here, we propose a method that addresses these two issues by combining LNA with Kalman filters. The use of a Kalman filter allows us to employ LNA only between two measurements points, that is, over short time horizons. We demonstrate the benefits of the proposed method with respect to the classical, full time horizon LNA using several in-silico test cases. More specifically, we show on examples that the former provides more accurate likelihood estimates and scales better with respect to the duration of the experiments. We also consider parallelized single-cell video-microscopy experiments as performed in Chait et al. (Nature Communications, 2017) and demonstrate with our approach that applying different light patterns to individual cells renders the calibration process more robust and allows to use data from fewer cells. Lastly, we use actual experimental data generated using the microscopy platform of Chait and colleagues to investigate temporal fluctuations of cells responsiveness to light.

Keywords: parameter inference, stochastic models of single cells, biochemical reaction networks, linear noise approximation, microscopy data, optogenetic gene expression system.

The stepping stone model in a random environment - the effect of spatial heterogeneities on isolation by distance patterns

Raphaël Forien
INRA Avignon

I will present a mathematical model for the genetic evolution of a population which is divided in discrete colonies along a linear habitat, and for which the population size of each colony is random but constant in time. I will show that, under reasonable assumptions on the distribution of the population sizes, over large spatial and temporal scales, this population can be described by the solution to a stochastic partial differential equation with constant coefficients. These coefficients describe the effective diffusion rate of genes within the population and its effective population density, which are both different from the mean population density and the mean diffusion rate of genes at the microscopic scale. This means that inference methods based on the assumption of a homogeneous environment will be biased if the population violates this assumption. To show this, I will present a duality technique and a new convergence result for coalescing random walks in a random environment.

Lambda-coalescents as priors in phylodynamical analysis

Patrick Hoscheit[1], Oliver Pybus[2], and Timothy Vaughan[3]
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A variety of methods based on coalescent theory have been developed to infer demographic history from gene sequences sampled from natural populations. The "skyline plot" and related approaches are commonly employed as flexible prior distributions for phylogenetic trees in the Bayesian analysis of pathogen gene sequences.

In this work we extend the classic and generalised skyline plot methods to phylogenies that contain one or more multifurcations (i.e. hard polytomies). We use the theory of Lambda-coalescents (specifically, Beta(2-alpha, alpha)-coalescents) to develop the "multifurcating skyline plot", which estimates a piecewise constant function of effective population size through time, conditional on a time-scaled multifurcating phylogeny. We implement a smoothing procedure and extend the method to serially-sampled (heterochronous) data, but we do not address here the problem of estimating trees with multifurcations from gene sequence alignments. We validate our estimator on simulated data using maximum likelihood and find that parameters of the Beta(2-alpha, alpha)-coalescent process can be estimated accurately.

Further, we apply the multifurcating skyline plot to simulated trees generated by tracking transmissions in an individual-based model of epidemic superspreading. We find that high levels of superspreading are consistent with the high variance assumptions underlying Lambda-coalescents and that the estimated parameters of the Lambda-coalescent model contain information about the degree of superspreading.

Keywords: Phylodynamics, Phylogenetics, Viral Evolution, Random Trees, Coalescents.

Dynamics of modied SIRS model with stochastic influences: stationary distribution, persistence in the mean and extinction

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This study presents a susceptible-infected-recovered-susceptible (SIRS) model for the dynamics of epidemics in a non-closed human population. We consider the vertical transmission of the disease and incorporate varying periods of immunity of the individuals in the population. The dynamics of our model are driven by two independent Brownian motions. The ergodicity of the perturbed system is proved by employing a new approach different from the Lyapunov method. Under the same condition of the existence of the unique ergodic stationary distribution, the persistence in the mean of disease is shown. Moreover, sufficient conditions for the extinction of disease are also obtained. Computer simulations illustrate our results and provide evidence to back up our theory.

Keywords: Epidemic model, Stochastic dynamics, Stationary distribution, Persistence in mean, Extinction.

Non-parametric estimation of the spiking rate in systems of interacting neurons

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I will present a work that I have done with Pierre Hodara and Eva Löcherbach, which is devoted to the statistical study of certain Piecewise Deterministic Markov Processes (PDMP) modeling the activity of a biological neural network.

Our model can be interpreted as Hawkes process with memory of variable length. We consider a model of interacting neurons where the membrane potentials of the neurons are described by a multidimensional PDMP with values in R^N, where N is the number of neurons in the network. A deterministic drift attracts each neuron's membrane potential to an equilibrium potential m. When a neuron jumps, its membrane potential is reset to a resting potential, here 0, while the other neurons receive an additional amount of potential $\frac{1}{N}$. We are interested in the estimation of the jump (or spiking) rate of a single neuron based on an observation of the membrane potentials of the N neurons up to time t.

We study a Nadaraya-Watson type kernel estimator for the jump rate and establish its rate of convergence in L^2. This rate of convergence is shown to be optimal for a given Hölder class of jump rate functions. We also state two important probabilistic tools that are needed in order to obtain the statistical results. The first one is the uniform positive Harris recurrence of process. The second one is the existence of a regular density function of the invariant measure of a single neuron.

In the present work we had to work with two difficulties. The first is the fact that our process is multidimensional, presenting real interactions between the neurons, which made it impossible to use the very powerful tool "many-to-one formula" (which allows to express the occupation time measure of the whole system in terms of a single "typical" particle). This is not the case in the present paper - and it is for this reason that we have to work under the relatively strong condition of uniform ergodicity which is implied by compact state space - a condition which is biologically meaningful. The second, more important, difficulty is the fact that the transition kernel associated to jumps is degenerate which leads to real difficulties in the study of the regularity of the invariant density of a single neuron. We will use (Löcherbach 2016) to solve the problem.

We also show some theoretical simulation which illustrate our results.

Keywords: Piecewise deterministic Markov processes, Kernel estimation, Non-parametric estimation, Biological neuronal nets.

A mechanistic model for comparing detection methods and control measures in Bovine Respiratory Disease

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Bovine Respiratory Disease (BRD) dramatically affects fattened young beef bull pens. How collective treatment (metaphylaxis) and sensor-based early detection help balance disease duration and antibiotics usage remains unclear. Our goal was to determine efficient control strategies, assessed on disease duration, antibiotics doses, and true positives, for various infection forces accounting for BRD pathogen diversity. A stochastic mechanistic individual-based model combined infectious processes, detection methods, and treatment protocols in a realistic simulated small-size pen. To enable veterinary experts to assess and revise model assumptions, a new artificial intelligence framework, EMULSION, was used to describe model features in an explicit and intelligible form. Parameter values and distributions were calibrated from observed data. Overpassing on-farm reference scenario using boluses required to very early detect the first case while using longer hyperthermia for subsequent detections. Metaphylaxis was efficient only for high pathogen transmission. Besides concrete recommendations to farmers, EMULSION could easily be used to design stochastic models of other farming systems, treatments, and diseases.

Insights into age-structured biological population models

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Population Balance Models aim at discriminating a population with respect to inner coordinates, which are assumed to perfectly describe each and every individual. In biology, two variables have been of practical interest over the last 50 years: size and age, the latter being closely intertwined with the notion of interdivision time. Size-structured models cannot be solved analytically because the generational redistribution of size-related features has not been thoroughly understood yet and only data-fitting kernels have been suggested to model this process. Age-structured models rely on the McKendrick-von Foerster equation and the literature is rife with analytical results in both batch and continuous cultures. One of these seminal articles was published in 1956 by Powell and has been cited more than 370 times to date. Even before Population Balance Equations were formulated, Powell realised that a population's mean interdivision time is necessarily less than the doubling time coming from an unstructured model, with experimental data to underpin his assertion. Indeed, if interdivision time is a distributed quantity, when measurements are carried over a certain time interval, some cells will have given birth to several offspring whereas some will have yet to divide. Therefore, as the majority of the renewal is the doing of the most active elements, the measured interdivision time will come "quick" in comparison with the average over the whole population. This interpretation is not a consensus view though, since in 1967 Painter & Marr proved the reverse inequality coming from Powell's framework and their article is still the inspiration behind experimental works even today. In fact, two definitions for the interdivision time PDF have been proposed in the literature. One of them stands for the age-at-rupture PDF and is experimentally observable, whereas the other relates to the probability that a cell divides at a certain age and is unobservable because such a division may not occur over the course of an experiment. Thus, a unequivocal demonstration is provided hereinafter to dissipate this confusion.

Keywords: Biological population dynamics, age-structured models.

Quasi-Stationary Distribution and related notions to describe the adaption of populations to a changing environment

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Given any model of ecology or eco-evolution that takes into account the stochasticity in the population size, one must deal with events of extinction. In such a context, many theoretical analysis argue apparently that the extinction is sufficiently negligible for a probabilistic equilibrium to be rapidly achieved. For instance, in many classical results of large deviation, the authors intend to quantify the observed fluctuations around some deterministic equilibrium in the limit of large population size. In fact, the order of these fluctuations is usually related to a proxy for the population size, vanishing to zero as population gets larger. My aim is to present some general criteria ensuring such analysis of fluctuations at equilibrium while extinction is not considered negligible anymore. This means that they can hold for finite population size or when we include Brownian fluctuations in the model of infinite population. In practice, these conditions ensure the existence and uniqueness of a quasi-stationary distribution (QSD). This law of probability is left invariant by the temporal dynamics of the process, taking into account the exponential decay due to the extinction. The range of fluctuations is then directly related to the dispersion of this QSD. Furthermore, these conditions imply, for the law of the process, its exponential convergence towards the QSD. This rate describes in a way the speed at which the process loses the memory of its ancestral state. Sustainable evolution appears then characterized by the fact that the rate of convergence is much quicker than the rate of extinction at the QSD. Numerically, one can evaluate this condition. I plan to illustrate these theoretical aspects with a model of adaptation. I will consider an asexual population submitted to a progressive change of its environmental conditions. This effect is assumed to be (at least partly) compensated by the occurrence of (genetic) mutations that invade regularly the population. The question is then to study how efficiently these mutations manage to keep the population adapted and thus in a viable regime. Extinction is a key component of this problem in a perspective of natural selection among populations : since only the surviving ones are observed, does this bias lead to an overestimation of their future ability to adapt?

Keywords: adaptation, changing environment, quasi-stationarity.

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Author Index