L24EEDs Workshop

Abstract Booklet

Invited speakers

Bansept, Florence (Aix-Marseille Université) - Host-associated microbial communities: stories of migration

Multispecies communities and dynamics

Friday 12th July 09:00-10:00

What is the role of microbial migration in the establishment and maintenance of host-associated microbial communities?

In addition to being widely spread in nature, bi-phasic life cycles - in which microbes spend part of their time in a host, part of their time in the environment - are thought to represent a first step towards host association. We aim at understanding what selection pressures apply to microbes following such a life style. By combining mathematical modeling and experimental evolution, we uncover the contribution of migration to microbial fitness. In particular, we derive predictions that are consistent with experimental observations of an increased ability to form biofilms in bacteria evolved in biphasic conditions with C. elegans.

Feeding is an important source of microbial migration for the gut microbiome. In community ecology, immigration is considered a key factor to maintain the diversity of a local community; furthermore, a diverse gut microbiome is usually considered an important determinant of health. Thus, questions arise: do hosts adapt their feeding behavior so as to manipulate microbial immigration in a way that facilitates the maintenance of a diverse flora? What fluctuations are to be expected in the community composition from feeding intermittence, and should sampling be controlled for it? We develop mathematical models of microbial communities with birth, death and intermittent migration to study these questions. So far, we have shown that intermediate feeding frequencies facilitate coexistence in a multi-species community, and that a food more concentrated in microbes relaxes the constraint around the optimal feeding frequency. We will compare our theoretical results with experimental studies in different animals, as we expect this effect to depend on host characteristics, like typical carrying capacity or transit time.

Beardmore, Robert (University of Exeter) - Observations about the world of antibiotics and its datasets from a mathematical perspective

Antibiotic treatments, experiments, and resistance

Wednesday 10th July 16:15-17:15

In the field of mathematics we are taught to think carefully about the use of theory, how theoretical assumptions leads to the development of models and how those models subsequently interact with data. However, it is relatively rare in infection medicine that a mathematical model and its predictions impinge on the lives of patients, or are used as the basis of clinical trial design or form the basis of treatment policy. There is the opportunity that these things could eventually happen in infection medicine and there are positive signs whereby the properties of antibiotics are subject to increasingly quantitative methodologies, but many gaps remain.This talk will look at some of the quantitative oddities of the antibiotics world, like the algorithm that is used to define something called an ECOFF, a variable used in the making of treatment decisions, yet the algorithm doesn't really converge where it is supposed to. We'll look at the use of models in (unsuccessful?) clinical trials which predict that randomly allocating antibiotics to patients is the best strategy, despite optimal control theory making very different predictions. We'll consider the mutant selection window hypothesis which predicts that resistance accrues at far higher dosages than it actually does.

This talk will provide several stories whereby quantitative scientists have seemingly played too small a role in the development of theoretical and data analysis techniques in the field of antibiotics and it calls for more to become involved; those opportunities do exist. For instance, we are currently applying data-driven ML-type techniques to understand whether, or not, it is rational that Europe and the USA have different recommended treatment dosages for many antibiotics, it so far appears that it is not rational given the available, often sparse, data.

In summary, mathematicians have constructed a world with strong foundations that the next generation can build upon, we need the field of antibiotics to have that kind of foundation too.

Bitbol, Anne-Florence (EPFL) - Impact of population spatial structure on mutant fixation, from models on graphs to the gut

Evolution, cooperation, and drug resistance

Tuesday 9th July 11:00-12:00

Microbial populations often have complex spatial structures, with homogeneous competition holding only at a local scale. Population structure can strongly impact evolution, in particular by affecting the fixation probability of mutants.I will first discuss a general model for describing structured populations on graphs. I will show that by tuning migration asymmetry in the rare migration regime, the star graph transitions from amplifying to suppressing natural selection. Next, I will discuss the impact of increasing migration rates. In particular, I will show that suppression of selection is pervasive in the regime of frequent migrations.

Then I will show that the specific structure of the gut, with hydrodynamics and gradients of food and bacterial concentrations, can increase the fixation probability of neutral mutants. Our results can be rationalized by introducing an active population, which consists of those bacteria that are actively consuming food and dividing. Thus, the specific environment of the gut enhances neutral bacterial diversity.

Bottery, Michael (University of Manchester) - Interspecies interactions and their effect on antibiotic efficacy

Antibiotic treatments, experiments, and resistance

Thursday 11th July 09:15-10:15

Accumulating evidence suggests that the response of bacteria to antibiotics is significantly affected by the presence of other interacting microbes. These interactions are not typically accounted for when determining pathogen sensitivity to antibiotics. Resistance and the evolutionary responses to antibiotic treatments should not be considered only a trait of an individual bacterial species but also an emergent property of the microbial community in which pathogens are embedded. Interspecies interactions can affect the responses of individual species and communities to antibiotic treatment, and ultimately alter the trajectory of resistance evolution. Here, I will present examples of how co-occurring pathogens can alter the efficacy of antibiotic treatments and the evolution of resistance within the polymicrobial setting of cystic fibrosis lung infections. Acknowledging the ecological context, i.e., the interactions that occur between pathogens and within communities, is critical in understanding the diverse outcomes of antibiotic treatments within a community setting.

Gjini, Erida (University of Lisbon) - Understanding cooperation and competition in co-colonization systems with multiple strains

Multispecies communities and dynamics

Thursday 11th July 11:30-11:55

Explaining the forces generating and shaping diversity in microbial ecosystems remains a fascinating challenge. For this, tractable models are needed, that bridge the gap between pattern observations and underlying mechanisms. In a series of papers, we develop a mathematical modeling framework where colonization systems with multiple interacting strains can be studied. In our model N similar strains grow, propagate and interact in co-colonization via micro-scale environmental modification, which can range from pairwise cooperation to competition. Using time-scale separation, we simplify the model and obtain an explicit replicator equation for strain frequency dynamics. Starting from our original epidemiological motivation, I will present this framework and highlight some key mathematical and biological features that enhance our understanding of multi-strain microbial consortia. Applications may range from epidemiology and coinfection dynamics, to microbiota or social evolution.

Möbius, Wolfram (University of Exeter) – Geometry as a predictor for evolutionary dynamics of populations undergoing range expansions in fragmented environments

Spatial microbial models

Wednesday 10th July 11:45-12:45

Evolution of microbial populations expanding into fragmented environments is a complex process shaped by the interplay of local population dynamics, mutation, migration, and environmental heterogeneity. Understanding the effects of environmental structure is challenging not least due to the vast number of different environments a population may encounter.

In a series of projects, we followed a bottom-up approach to uncover the consequences of environmental heterogeneity on neutral evolution as well as the dynamics of mutation and selection in the presence of unfavourable patches. Guided by simulations, we developed coarsened models which are closely associated with geometrical arguments. These highlight general principles and allow one to predict the dynamics in complex environments from the dynamics around individual heterogeneities. In addition to the theoretical work, we present experiments and experimental approaches that highlight the effects of environmental structure on microbial ecology and evolution.

Shou, Wenying (UCL) - The evolution of Cooperative Communities

Evolution, cooperation, and drug resistance

Tuesday 9th July 14:00-15:00

I will discuss experimental and theoretical work on the evolution of two-species cooperative communities. Audience participation is encouraged and appreciated.

Täuber, Uwe (Virginia Tech) - Stochastic Population Dynamics of Competing Species in Driven and/or Spatially Inhomogeneous Systems

Spatial microbial models

Wednesday 10th July 09:00-10:00

Agent-based Monte Carlo simulations of simple lattice models constitute a versatile tool to investigate stochastic population dynamics subject to time- and/or space-dependent rate parameters. I will address two topics: (1) To represent seasonal oscillations in resource availability, we implement a periodically varying carrying capacity in a two-dimensional Lotka-Volterra predator-prey model. We find that two-species coexistence is enhanced through this periodic drive. The fast- and slow switching regimes can be described through different effective static environments. Yet we observe intriguing resonant features when the external switching rate matches the internal population oscillation frequency, inducing persistent spatial correlations. (2) Stochastic population dynamics in finite systems often ultimately terminates in an absorbing state. However, in sufficiently large spatially extended models, the time to reach species fixation or extinction becomes exceedingly long, effectively permitting coexistence. Yet tuning certain control parameters, e.g., increasing the predation rate in predator-prey systems or enhancing asymmetries in cyclic dominance models, may render coexistence states in finite systems highly vulnerable against stochastic fluctuations. Intriguingly, though, they can be efficiently stabilized through continuous influx from the

system's boundaries, which is generated via diffusive coupling of the vulnerable region to an adjacent stable patch. I will discuss (semi-)quantitative criteria that delineate the conditions for this remarkable boundary flow stabilization of finite-size absorbing-state instabilities in stochastic population dynamics with either cyclic or hierarchical competition.

Waclaw, Bartlomiej (Polish Academy of Sciences) - The physics of growth and evolution in microbial biofilms

Spatial microbial models

Wednesday 10th July 14:30-15:30

Microbes in biofilms interact with each other and the environment in many ways, including mechanical repulsion, adhesion, and friction. In the last 10 years, these physics-like interactions have been shown to be as important for biofilm growth and evolution as biochemical interactions. In this talk, I will discuss mechanistic spatial models and experiments aimed at explaining how physical interactions affect population dynamics of genetic variants in the biofilm. I will also show how the physics of a growing biofilm can be used against it to reduce the chance that an undesired variant, e.g., an antibiotic-resistant mutant, spreads in the biofilm.

Contributed speakers

Aagren, Jonathan (Roskilde University) - Using the Lotka-Volterra competition model to predict co-existence from extinction

Multispecies communities and dynamics

Thursday 11th July 12:30-12:55

Bacterial communities exhibit cooperative behaviour such as the production of population beneficial secretions known as public goods. Quorum sensing (QS) is the communication system coordinating this cooperative behaviour. QS-defiant mutants show cheating behaviour benefiting from the communities public goods without contributing to the production. This behaviour leads to competition between cooperating strains and cheating strains. The emergence of such cheaters in bacterial communities are theorised to lead to extinction of the cooperating strains known as the tragedy of the commons. This has been confirmed in in-vitro experiments. However, recent in-vitro studies indicate, that cheaters and cooperators might be able to co-exist under certain conditions. Our research goal is to increase the understanding of the dynamics leading to either extinction or co-existing.

We use in-vitro competition experiments of Pseudomonas Aeruginosa (PA) with a high time resolution to study the early dynamics between the cooperating wild-type reference strain PA01 and a cheating QS-defiant lasR-mutant. To quantify the dynamics we infer the Lotka-Volterra

competition model from the experimental data. This model is one of the simplest models able to predict both extinction and co-existence depending on parameters and initial conditions.

A crucial model characteristic in order to make reliable predictions is that of identifiability, i.e. to have a one-to-one relation between model parameters and model predictions. Due to the sparsity in observables for bacterial competition experiments, many models describing the QSsystem are not identifiable. We show that the Lotka-Volterra competition model is structural identifiable given growth measurements (optical density at 600nm) by employing a Lie derivative method known as strike-goldd. Further, we show that the model is practical identifiable given our data using the profile likelihood method. This underlines that the model has the mathematical properties necessary to predict co-existence from extinction. The quantification of competition and verification of model predictions for varying growth conditions are still work-in-progress.

Allen, Rosalind (Friedrich Schiller University Jena) - Effect of spatial partitioning of a microbial population on collective antibiotic resistance

Spatial microbial models

Wednesday 10th July 10:00-10:25

Spatial partitioning is a common feature of many environments inhabited by microbes, including the human body. Yet microbiological measurements to assess antibiotic susceptibility are almost always made for large well-mixed populations of microbes. Here we investigate theoretically how spatial partitioning can alter antibiotic resistance. For a population of bacteria that produce an antibiotic-degrading beta-lactamase enzyme, our model predicts that spatial partitioning into multiple small populations can strongly enhance the collective benefits of enzymatic degradation of the antibiotic, such that partitioned populations can survive antibiotic concentrations that would be more than sufficient to kill a non partitioned population. This "partitioning enhancement" is a purely stochastic effect, originating from variation in the initial bacterial densities among different subpopulations. We also present preliminary experimental data in which we track the response of partitioned populations of beta-lactamase producing *E. coli* bacteria, encapsulated in thousands of microfluidic droplets, to the antibiotic ampicillin. While the experimental results are more complex than the theoretical predictions, they can be understood using similar principles. Our results have implications for the development of effective antibiotic treatment protocols for strongly partitioned infections.

N. Verdon, O. Popescu, S. Titmuss & R. J. Allen (2024) Spatial partitioning of a microbial population enhances collective enzymatic defence BioRxiv 2024.03.20.585867

Asker, Matthew (University of Leeds) - Population Bottlenecks in Spatially Structured Microbial Populations

Spatial microbial models

Wednesday 10th July 10:50-11:15

Microbial populations evolve within spatially structured and dynamically changing environments, a reality often overlooked by classical modelling approaches. From microbial infections spreading across host organs to environmental pollutants altering ecological niches, understanding the effects of and interplay between spatial structure and environmental change is essential for developing insights into the evolutionary dynamics of microbial communities. Here, we present a comprehensive analysis of a two-species metapopulation model, incorporating selection bias, to investigate how microbial species evolve while competing for a varying level of resources. Our analytical framework provides insights into the fixation probability and mean fixation time across network structures in one dimension. Additionally, stochastic simulations offer a deeper understanding of the complex dynamics on a two-dimensional lattice, extending beyond the scope of analytical predictions. By combining analytical and computational methodologies, we uncover the rich dynamics underlying microbial population evolution in spatially structured and dynamically changing environments.

Bali, Yogesh (Johannes Guntenberg Universität Mainz) - Phenotype-driven Mathematical Approaches for T-cell activation

Antibiotic treatments, experiments, and resistance

Thursday 11th July 10:15-10:40

T cells actively scan lymphoid tissues for antigens presented by specialized cells such as APCs, a crucial step in immune response initiation mediated by TCR recognition of antigens on MHC molecules. Various phenotypic models have been proposed to elucidate this process, starting with the KPR scheme introduced by McKeithan et al. (1995)[1], which posits a series of biochemical modifications in the TCR-pMHC complex. However, to address T-cell activation sensitivity, subsequent models like the KPR model with limited signal duration and the KPR model with sustained signaling were proposed. Additionally, Dushek et al. (2014) [2], suggested an induced rebinding model incorporating TCR clustering to enhance sensitivity while maintaining specificity. These diverse models aimed to elucidate certain observable experimental characteristics of T cells, including the prolonged half-lives of potent pMHC, the incapacity of TCRs to transmit signals for downregulation to neighbouring TCRs, suggesting that each downregulated TCR must directly engage with pMHC, and the presence of an intermediate dwell time crucial for efficient downstream signaling. While each model accounted for certain experimental results, none fully captured all observed characteristics.

One notable model addressing key characteristics is the TCR with negative signaling model, proposed by Francois et al.[3] explored qualitatively by Rendall et al. [4]. This model revealed the multiplicity of steady states and non-monotonicity of the response function.

My talk aims to address two main issues: firstly, comparing all proposed phenotypic models based on experimentally observed parameter values to determine which model best explains observable characteristics of T cell activation. Secondly, reproducing the mathematical results of Alan et al. using parameter values derived from experimental setups. This classification and analytical observation of T-cell activation models aim to provide insights into their phenotypic characteristics and mathematical properties.

[1] T. W. McKeithan, “Kinetic proofreading in t-cell receptor signal transduction.,” Proceedings of the national academy of sciences, vol. 92, no. 11, pp. 5042–5046, 1995.

[2] O. Dushek and P. A. Van der Merwe, “An induced rebinding model of antigen discrimination,” Trends in immunology, vol. 35, no. 4, pp. 153–158, 2014.

[3] P. Fran¸cois, G. Voisinne, E. D. Siggia, G. Altan-Bonnet, and M. Vergassola, “Phenotypic model for early t-cell activation displaying sensitivity, specificity, and antagonism,” Proceedings of the National Academy of Sciences, vol. 110, no. 10, pp. E888–E897, 2013.

[4] A. D. Rendall and E. D. Sontag, “Multiple steady states and the form of response functions to antigen in a model for the initiation of t-cell activation,” Royal Society Open Science, vol. 4, no. 11, p. 170821, 2017.

Berríos-Caro, Ernesto (Max Planck Institute for Evolutionary Biology) - Adaptation of bacterial populations exposed to periodic bottlenecks and antibiotic drug pressure

Antibiotic treatments, experiments, and resistance

Thursday 11th July 10:40-11:05

Bacterial populations face bottlenecks during the infection of hosts caused by the transmission step itself, the host’s immune response, or the spread of small subpopulations from one tissue to another. The combined effect of bottlenecks and antibiotic selection can have crucial consequences for microbial growth dynamics and adaptation. Through modelling, we investigate how the bottleneck size and the strength of antibiotic selection affect the evolution of resistance. Our model is built upon recent experimental data [1] in Pseudomonas aeruginosa subjected to several conditions varying in the bottleneck size and the antibiotic concentration. We model bacterial growth by means of the Baranyi–Roberts growth model with Lotka-Volterra competition, considering as traits: maximum growth rate, lag time, transition rate of the lag phase, and carrying capacity.

Analysis of the experimental data reveals that treatments with a small bottleneck size select mainly for a larger maximum growth rate, while the carrying capacity is mainly selected for treatments with a large bottleneck size. We find that large bottleneck sizes tend to select for longer times of the lag phase but with a reduced transition rate, and vice versa for small bottleneck sizes.

By parameterising the model using the experimental data, we conduct stochastic simulations to dissect the adaptive process into its components: the rate of appearance of resistance mutations, their establishment probabilities, the product of the two (i.e., the rate at which ‘successful’ mutants appear), and the fixation time. Overall, we find that high antibiotic pressure increases the establishment probability of mutants and decreases the fixation time. The bottleneck size has little effect on the fixation time. We observe that the timing at which successful mutants emerge does not substantially change with the bottleneck size when selection is weak but exhibits considerable variation when selection is strong.

Furthermore, we focus on the adaptation of 'fictitious mutants' by allowing traits to vary beyond the experimental conditions. We study why some traits are more selected than others when changing the bottleneck size and the antibiotic pressure. We do this by looking at how much the traits must change in order to achieve a particular selection coefficient. In general, we find that the lag time and the maximum growth rate are the traits with more influence on adaptation, which is in good agreement with the experimental outcome.

We further investigate how stochasticity affects the emergence of low– and high–fitness mutants. We find that low–fitness mutants can only evolve when the bottleneck size is low, regardless of the antibiotic concentration. This result contrasts with predictions from fully deterministic approaches and highlights the role that stochasticity plays in the mutant variability in resistance evolution.

Our study points out the relevance of the interplay of bottleneck size and antibiotic concentration for the emergence of resistant mutants, which paves the way for informed strategies in combating antibiotic resistance. At the end of this presentation, I will discuss several model extensions that may inspire new experiments.

[1] Mahrt, N., Tietze, A., K¨unzel, S., Franzenburg, S., Barbosa, C., Jansen, G., Schulenburg, H., Bottleneck size and selection level reproducibly impact evolution of antibiotic resistance. Nature Ecology & Evolution, 5(9), pp.1233-1242, 2021.

Constable, George (University of York) - Maternal transmission as a microbial symbiont sieve and the absence of lactation in male mammals

Multispecies communities and dynamics

Friday 12th July 11:20-11:45

Gut microbiomes of mammals carry a complex symbiotic assemblage of microorganisms. Feeding newborn infants milk from the mammary gland allows vertical transmission of the parental milk microbiome to the offspring's gut microbiome. This has benefits, but also has hazards for the host population. Using mathematical models, we demonstrate that biparental vertical transmission enables deleterious microbial elements to invade host populations. In contrast, uniparental vertical transmission acts as a sieve, preventing these invasions. Moreover, we show that deleterious symbionts generate selection on host modifier genes that keep uniparental transmission in place. Since microbial transmission occurs during birth in placental mammals, subsequent transmission of the milk microbiome needs to be maternal to avoid the spread of deleterious elements. This paper therefore argues that viviparity and the hazards from biparental transmission of the milk microbiome, together generate selection against male lactation in placental mammals.

Fontanarrosa, Pedro (UCL) - MIMIC: A Comprehensive Python Package for Simulating, Inferring, and Predicting Microbial Community Interactions

Evolution, cooperation, and drug resistance

Tuesday 9th July 17:00-17:15

The study of microbial communities is vital for understanding their impact on environmental, health, and technological domains. The Modelling and Inference of MICrobiomes Project (MIMIC) introduces a Python package designed to advance the simulation, inference, and prediction of microbial community interactions and dynamics. Addressing the complex nature of microbial ecosystems, MIMIC integrates a suite of mathematical models, including previously used approaches such as Generalized Lotka-Volterra (gLV), Gaussian Processes (GP), and Vector Autoregression (VAR) plus newly developed models for integrating multiomic data, to offer a comprehensive framework for analysing microbial dynamics. We show that by leveraging Bayesian inference and machine learning techniques, MIMIC accurately infers the dynamics of microbial communities from empirical data, facilitating a deeper understanding of their complex biological processes, unveiling possible unknown ecological interactions, and enabling the design of microbial communities. Such insights could help to advance microbial ecology research, optimizing biotechnological applications, and contributing to environmental sustainability and public health strategies. MIMIC is designed for flexibility and ease of use, aiming to support researchers and practitioners in microbial ecology and microbiome research. This software package contributes to microbial ecology research and supports ecological predictions and applications, benefiting the scientific and applied microbiology communities.

Hernández-Navarro, Lluís (University of Leeds) - Eco-evolutionary dynamics of cooperative antimicrobial resistance

Evolution, cooperation, and drug resistance

Tuesday 9th July 12:25-12:50

Antimicrobial resistance is a global threat responsible for millions of deaths [1]. There is a pressing need to better understand how microbial populations respond to antimicrobial drugs, and to find mechanisms to possibly eradicate antimicrobial-resistant cells. The inactivation of antimicrobials by resistant microbes can often be viewed as a cooperative behavior leading to the coexistence of resistant and sensitive cells in large populations and static environments. This picture is however greatly altered by the fluctuations arising in volatile environments, in which microbial communities commonly evolve. In this presentation I will discuss the eco-evolutionary dynamics of a population consisting of an antimicrobial resistant strain and microbes sensitive to antimicrobial drugs in a time-fluctuating environment, modeled by a carrying capacity randomly switching between states of abundance and scarcity [2, 3] (https://eedfp.com/), and inspired by a chemostat laboratory set-up. We assume that antimicrobial resistance is a shared public good when the total number of resistant cells exceeds a certain threshold, which fully inactivates the antimicrobial drug and protects sensitive cells. Eco-evolutionary dynamics is thus characterized by demographic noise (birth and death events) coupled to environmental fluctuations that can cause population bottlenecks. By combining analytical and computational means, we determine the environmental conditions for the long-lived coexistence and fixation of both strains, and characterize a fluctuation-driven antimicrobial resistance eradication mechanism, where resistant microbes experience

bottlenecks leading to extinction. Finally, I will discuss the possible applications of our findings to drug-treatments, and I will briefly present our most recent results on a metapopulation variant of this model with spatial migration.

[1] O'Neill J. (2016). *Tackling drug-resistant infections globally: final report and recommendations.* Government of the United Kingdom, Analysis and Policy Observatory. See https://apo.org.au/node/63983.

[2] Hernández-Navarro, L., Asker, M., Rucklidge, A. M., & Mobilia, M. (2023*). Coupled environmental and demographic fluctuations shape the evolution of cooperative antimicrobial resistance.* Journal of the Royal Society Interface, 20(208), 20230393.

[3] Asker, M., Hernández-Navarro, L., Rucklidge, A. M., & Mobilia, M. (2023). *Coexistence of Competing Microbial Strains under Twofold Environmental Variability and Demographic Fluctuations.* New Journal of Physics, 25(12), 123010.

Jain, Paras (Indian Institute of Science) - Cell-state transitions and frequency-dependent interactions among subpopulations together explain the dynamics of spontaneous epithelial-mesenchymal heterogeneity in breast cancer

Multispecies communities and dynamics

Thursday 11th July 16:45-17:00

Individual cells in a tumor can be distributed among Epithelial (E) and Mesenchymal (M) cell states, as characterized by the levels of canonical E and M markers. Even after E and M (E-M) subpopulations are isolated and then cultured independently, E-M heterogeneity can re-equilibrate in each population over time, sometimes regaining the initial distribution of the parental cell population. However, it remains unclear which population-level processes give rise to the dynamical changes in E-M heterogeneity observed experimentally, including 1) differential growth, 2) cell-state switching, and 3) frequency-dependent growth or state-transition rates. Here, we analyse the necessity of these three processes in explaining the dynamics of E-M population distributions as observed in PMC42-LA and HCC38 breast cancer cells. We find that growth differences among E and M subpopulations, with and without any frequency-dependent interactions (cooperation or suppression) among E-M sub-populations, are insufficient to explain the observed population dynamics. This insufficiency is ameliorated by including cell-state transitions, albeit at slow rates, in explaining both PMC42-LA and HCC38 cells data. Further, our models predict that treatment of HCC38 cells with TGFβ signalling and JAK2/3 inhibitors could significantly enhance the transition rates from M state to E state, but does not prevent transitions from E to M. Finally, we devise a selection criterion to identify the next most informative time points for which future experimental data can optimally improve the identifiability of our estimated best fit model parameters. Overall, our study identifies the necessary population-level processes shaping the dynamics of E-M heterogeneity in breast cancer cells.

Juhász, János (Pázmány Péter Catholic University) - Agent-based modelling of multi-strain yeast colony development in inhomogeneous environmental conditions

Spatial microbial models

Wednesday 10th July 10:25-10:50

Saccharomyces cerevisiae (budding yeast) is a widespread model organism to study eukaryotic cellular behaviours and an important contributor in many processes of biotechnology and food industry. Yeast colonies can be grown both in well mixed liquid batches and on solid media. Different strains can show different growth characteristics, for example different lag phase times or nutrient preferences. They can exhibit various growth patterns like budding or filamentous division strategies in the cellular and smoother or complex (biofilm-like) colony structures in the macroscopic level. Some strains can produce toxins against their competitors establishing complex multi-strain interactions in addition to the competition for the shared nutrient sources. Yeast cells also can enter a passive, stationary phase during unfavourable conditions in order to survive, as a response for starving for example. They reduce their metabolism, nutrient uptake and halt their cell division in this state.

We developed a two-dimensional agent-based and differential equation-based hybrid computational model to capture these cellular processes and simulate yeast colony development on solid agar surfaces. Agents of the model represent yeast cell groups. They take up nutrient from their environment, store some of it (growth) and divide into two daughter cells after reaching a certain energy level. The position of the daughter cells can be random around the mother cell (budding) or aligned to it (filamentous behaviour). Active cell can also emit toxins or extracellular materials into their environment. The energy levels of the agents decrease in nutrient depleted conditions, and they enter a stationary (G0) stage after their energy level has dropped below a threshold. It slows down the process of losing energy and let the agents survive until nutrient supply or die later without it. The remaining energy of dead agents returns to their environment. The simulation framework can handle multiple strains with different parameters and lifestyles enabling the study of interactions in diverse communities. Nutrients, toxins, and extracellular matrix components are defined in the models as diffusive materials. Their spread and potential decay is simulated on separate two-dimensional grids. The width of the agar medium is modelled with two nutrient layers. The upper one is directly connected with the agents and the lower one serves as a supply layer from which material can flow upward guaranteeing more uniform nutrient supply for the agents.

The model was used to simulate the growth of colonies with various initial cell distributions; interactions between communities of the same or different yeast strains; the effects of changing medium humidity, and unequal nutrient gradients. The model can help predicting the outcomes of *in vitro* experiments and facilitate laboratory work in this way. The flexible and expandable framework can be capable of describing the growth of other microbes as well, for example the colony formation and spread patterns of pathogens in various, inhomogeneous environments. It proposes the applicability of the model in additional fields, like healthcare or pathogen surveillance.

The model is available at the following link:

https://github.com/CsikaszNagyLab/yeast_colony_growth_model

Lee, Julian (Soongsil University) - Inference of Causal Interaction Network of Gut Microbiota

Multispecies communities and dynamics

Friday 12th July 10:00-10:25

Understanding the complex dynamics of gut microbiota interactions is essential for unraveling their influence on human health. In this study, we employed transfer entropy analysis to construct a causal interaction network among gut microbiota genera, from the time-series data of bacterial abundances. The reconstructed network provides us with valuable insights into the ecosystem of gut microbiota, and allows us to a identify some key microbial hubs that play pivotal roles in shaping the network structure.

Lepper, Hannah (University of Edinburgh) - Multi-serotype models of mechanisms of coexistence of antibiotic resistant strains and dynamics of *Streptococcus pneumoniae* following vaccine introduction

Evolution, cooperation, and drug resistance

Tuesday 9th July 12:00-12:25

Background: *Streptococcus pneumoniae* (pneumococcus) infections are a leading cause of mortality attributable to antibiotic resistance worldwide. However, it is not understood how both sensitive and resistant strains are stably maintained in the pneumococcal population. Multiple plausible models have been proposed to explain these dynamics, but more models are needed that simultaneously capture pneumococcal serotype dynamics as well as resistance. Resistance frequency varies by serotype, and the introduction of pneumococcal conjugate vaccines (PCV) alters selection pressures on vaccine- and non-vaccine-type pneumococci. Multi-serotype models of sensitive/resistant strain competition are needed to explain current resistance epidemiology and predict post-vaccine changes in resistant carriage.

Methods and results: We developed a suite of individual-based mathematical models that capture the serotype-specific dynamics of sensitive and resistant pneumococcal strains before PCV introduction. Each model uses a different mechanism for co-existence of sensitive and resistant types. These models were used to predict resistant carriage after the introduction of PCV. While each mechanism can generate co-existence between sensitive and resistant of multiple serotypes in pre-vaccine dynamics, they resulted in diverging predictions of resistance frequency after vaccine introduction. We will ultimately confront these predictions with genomic data from a cluster-randomised controlled trial of PCV to test the plausibility of each model.

Implications: This work expands our understanding of strain competition and coexistence of sensitive and resistant strains of pneumococcus, and can inform predictions of resistant carriage after vaccine introduction.

Li, Bowen (Newcastle University) - NUFEB 2.0 - A massively parallel simulator for individual-based modelling of microbial communities

Spatial microbial models

Wednesday 10th July 12:45-13:10

NUFEB 2.0 (https://github.com/nufeb/NUFEB-2) is an open-source software for modelling 3D dynamics of microbial communities. The tool implements the Individual-based Modelling (IbM) approach, allowing users to explicitly model the dynamics of microbes, including cellular processes that result in microbial growth, decay, and motility.

NUFEB 2.0 enables the study of population behaviours that emerge from the interactions between individuals and their environment. The novelty of NUFEB lies in its parallelisation and generic model specification, which enables realistic modelling and simulation of systems with over 10 million microbes. It also offers a wide range of biological, physical, and chemical processes.

In this talk, I will give an overview of NUFEB functionalities and showcase the types of systems that NUFEB can be used to model and simulate. Examples include Anammox biofilm formation, plasmid dynamics, and biofilm deformation and detachment under fluid flow.

Liu, Ming (University of Oxford) - What makes microbial communities stable?

Evolution, cooperation, and drug resistance

Tuesday 9th July 15:50-16:15

What determines the stability of communities is a major question in ecology. However, despite a large body of theory on the topic, the fundamental drivers of ecological stability in microbial systems remain unclear. A key challenge is that the models are very abstract and not amenable to direct empirical testing. We, therefore, developed a new body of theory grounded in the biology of microbial communities, which can be both compared to previous theory and, importantly, empirically tested. As a first test case, we have focused on the much-debated relationship between species diversity and stability. I will both present the new theory and empirical tests using communities of human gut bacteria. Our work both reveals the relationship between diversity and stability, and underlines that the way natural systems are perturbed is critical for assessing ecological stability.

Liu, Xiaoyuan (University of York) - Eco-evolutionary modelling of environmentally triggered sex and hibernation

Evolution, cooperation, and drug resistance

Tuesday 9th July 15:00-15:25

Environmentally triggered sex is observed empirically in a range of organisms, including the green algae C. reinhardtii, fission yeast S. pombe and daphnia (water fleas). They switch to sexual reproduction in response to environmental adversity (i.e nitrogen limitation) and revert to their default asexual reproductive mode when the environment becomes ideal again. Existing theories for the evolution of environmentally triggered sex include the red queen hypothesis which speculates that the advantage of sex lies in its ability to generate genetic diversity more rapidly, which hastens adaptation in fluctuating environments. Another theory known as Muller's ratchet specifies that sex evolved since it prevented deleterious mutations from accumulating. What these theories don't explain is why sex and hibernation evolved to occur in tandem. Here, accounting for ecological realism in the population dynamics, we provide a novel mathematical explanation for the evolution of simultaneous sex and hibernation as a response to environmental adversity. In addition to analytical predictions, we provide stochastic simulations of evolutionary trajectories, which reveal richer dynamical behavior beyond what is predictable by our analytics.

López, Roberto Corral (University of Granada) - Deciphering Dysbiosis: Modeling the Ecological Dynamics of the Gut Microbiome

Multispecies communities and dynamics

Friday 12th July 11:45-12:00

Recent advancements in gut microbiome research have highlighted the emergence of dysbiotic microbial community states with profound implications for host health. Despite abundant data, current knowledge primarily stems from correlation studies and the mechanistic basis of these observations largely remains unexplored. To date, no theoretical model has comprehensively explained the emergence of dysbiotic states from a bottom-up mechanistic approach. In this study, we introduce a novel model of the gut microbiome that not only reproduces well-known empirical observations such as functional redundancy but also demonstrates alternative stable states characterized by distinct ecological behaviors associated with healthy or dysbiotic gut conditions.

These associations are underscored by differences in Shannon index (alpha diversity), longitudinal beta diversity, and the abundance of functional pathways, mirroring the disparities observed empirically between healthy and unhealthy individuals. Our analysis reveals that, contrary to initial expectations, the healthy (more diverse) state is predominated by competitive interactions, whereas the dysbiotic (less diverse) state is mainly governed by cross-feeding interactions.

Moreover, we explore potential triggers for transitions to dysbiotic states, particularly how dramatic species loss--akin to antibiotic treatment--can facilitate such shifts. We also discuss effective strategies for reverting from dysbiotic states, including the application of probiotic cocktails, Fecal Microbiota Transplant (FMT), and specific dietary interventions.

This research not only advances our understanding of microbial community dynamics but also paves the way for a deeper mechanistic insight into dysbiotic states as well as novel therapeutic approaches for maintaining gut health and preventing dysbiosis.

Maull, Victor (Universitat Pompeu Fabra) - A synthetic microbial Daisyworld: planetary regulation in the test tube

Multispecies communities and dynamics

Thursday 11th July 16:30-16:45

The idea that the Earth system self-regulates in a habitable state was proposed in the 1970s by James Lovelock, who conjectured that life plays a self-regulatory role on a planetary-level scale. A formal approach to such hypothesis was presented afterwards under a toy model known as the Daisyworld. The model showed how such life-geosphere homeostasis was an emergent property of the system, where two species with different properties adjusted their populations to the changing external environment. So far, this ideal world exists only as a mathematical or computational construct, but it would be desirable to have a real, biological implementation of Lovelock's picture beyond our one biosphere. Inspired by the exploration of synthetic ecosystems using genetic engineering and recent cell factory designs, here we propose a possible implementation for a microbial Daisyworld. This includes: (i) an explicit proposal for an engineered design of a two-strain consortia, using pH as the external, abiotic control parameter and (ii) several theoretical and computational case studies including two, three and multiple species assemblies. The special alternative implementations and their implications in other synthetic biology scenarios, including ecosystem engineering, are outlined.

Maull, V., Pla, J., Conde, N. and Solé, R., 2024. A synthetic microbial Daisyworld: planetary regulation in the test tube. Royal Society Interface. 21, 211.
https://royalsocietypublishing.org/doi/full/10.1098/rsif.2023.0585

Meacock, Oliver (University of Lausanne) - Three sides of the same coin: Unifying context-dependencies of ecological interactions

Multispecies communities and dynamics

Thursday 11th July 15:40-16:05

Dynamical ecosystem models allow ecologists to investigate how community-level properties such as stability and resistance to invasion emerge from elementary ingredients. In recent decades, approaches originally developed by theoretical ecologists have been taken up by researchers hoping to understand microbial communities. An early ambition was to measure the mutual impact of species on each other's growth – their interactions – and use these to predict and ultimately control community-level outcomes. Unfortunately, such simple bottom-up approaches have recently run into difficulties. A particularly thorny problem is that interaction measurements have proven to be contingent on multiple factors, including

environmental conditions and the spatio-temporal context of the measurement. Given this shaky foundation, it has been difficult to build on top of it to a more holistic view of complex communities.

Here, I will discuss new theoretical and experimental results that both explain and predict these context-dependencies, providing a firmer platform on which to build bottom-up approaches. Our key insight is to develop a modified interaction concept that is more appropriate for systems in which interactions are mediated by feedbacks between organisms and their environment, such as microbial ecosystems. Changes in multiple environmental factors by a partner may impact the growth rate of a focal species, and the net balance of positive and negative impacts – set by the current environmental state – determines the net interaction value. This environmental dependency can then give rise to temporal and spatial dependencies as organisms modify the environment over time and space. We apply our approach to predict changes in interaction values in an experimental model based on antibiotic degradation, as well to as relate time and spatial dependencies in crossfeeding communities. Ultimately, we hope to apply these insights to the bottom-up community engineering problem, rationally manipulating interaction values through environmental change to bring about desired co-existence outcomes.

Moser, Niklas (University of Jyväskylä) - A general likelihood-based method for the inferential analysis of agent-space reactant-catalyst-product models

Spatial microbial models

Wednesday 10th July 15:30-15:55

While agent-based models (ABMs) have been shown to be suitable for simulating complex system dynamics, the model behaviour is oftentimes too complicated so that the microscopic master equation cannot be solved analytically. Common workarounds for the inferential analysis use treatments of the master equations on different scales: (1) microscopic in approximation frameworks such as Bayesian variational inference, (2) mesoscopic where linear noise approximation or moment closure methods are used to derive pseudo-likelihoods or to compare simulated moments with those extracted from the data, as it is common in pattern-oriented modelling, and (3) solutions to the deterministic macroscopic equation are used. Most approaches within (1) – (3) approximate the true likelihood without quantification of the error introduced due to the approximation and are thus based on heuristic choices. Here we propose an analytical avenue to derive an asymptotically exact likelihood equation of ABMs. We consider a broad range of ABMs that can be defined as spatio-temporal point processes, specifically the reactant-catalyst-product models that operate in continuous space and time. We mathematically describe the system of interest by spatial and spatio-temporal moments and cumulants of any order without being constrained by heuristic moment closure methods. We apply a perturbation expansion that enables us to include information beyond the mean field approximation. This results in a general, rigorously derived and asymptotically exact expression of the conditional density for any agent type at any location given information about the locations of other agents of any type, for systems in transient and stationary regimes. Most importantly, in the first-order perturbation expansion the expression for the conditional density of agents includes information on the length scale at which agents interact and thus

enables to infer such spatial information from data. We utilize the conditional density predictions to construct a composite likelihood and a Bayesian parameter estimation framework. We use simulated case studies of both single- and multi-species communities as well as empirical data on the distribution and evolution of cancer cells to illustrate the general suitability of this approach for ecological research and beyond.

Pawar, Samraat (Imperial College London) - Predicting the assembly and functioning of bacterial communities in thermally fluctuating environments

Multispecies communities and dynamics

Thursday 11th July 14:30-14:55

Bacteria are the second-most abundant organisms on Earth and play a dominant role in decomposing organic matter, recycling nutrients, and releasing greenhouse gases. Therefore, predicting (and engineering) the assembly, stability, and functioning of bacterial communities (or microbiomes) is necessary for a range of applications, from biosynthesis and bioremidiation to predicting how Earth's biogeochemical cycles will change in an increasingly unpredictable global climate. However, predicting the dynamics of bacterial communities, which typically contain complex networks of hundreds of interacting taxa ("strains") and trillions of cells, is one of the greatest contemporary challenges in biology. This challenge is amplified by the fact that, in the real world, temperature, nutrients, and chemical conditions (e.g., through pollution) are constantly fluctuating. Temperature is particularly important because of its universal thermodynamic effects on cellular physiology and associated metabolic rates (functional traits), from resource uptake and processing, to allocation and growth.

I will present a trait-based theoretical framework to predict the effects of temperature change on the dynamics of microbial community assembly, stability, and functioning, and focus on a recent, empirically validated result based on this framework: that thermal sensitivity of microbial community respiration increases as species interactions change from competition to facilitation (for example, commensalism, cooperation and mutualism). This is because facilitation disproportionately increases positive feedback between the thermal sensitivities of species-level metabolic and biomass accumulation rates at warmer temperatures. We experimentally validated our theoretical predictions in a community of eight bacterial taxa and showed that a shift from competition to facilitation, after a month of co-adaptation, caused a 60% increase in the thermal sensitivity of respiration relative to de novo assembled communities that had not co-adapted.

Sayyar, Golsa (University of Szeged) - Evolution into chaos - implications of the trade-off between transmissibility and immune evasion

Evolution, cooperation, and drug resistance

Tuesday 9th July 16:45-17:00

The prediction of viral evolution poses a substantial challenge and represents a paramount public health imperative. In response to this challenge, we develop a pioneering model for viral evolution that integrates considerations of the trade-off between immunity evasion and transmissibility. Our findings demonstrate that when the pathogen exhibits high transmissibility, evolution tends to favor immune evasion, whereas lower transmissibility favors heightened transmission rates. Moreover, we illustrate the long-term evolutionary patterns following the emergence of new strains with maximum invasion fitness modeled by a difference equation. We provide sufficient criteria for when evolution converges, and subsequent strains exhibit similar transmissibility. Furthermore, we identify scenarios characterized by a biennial pattern in subsequent strains, indicating a sequence wherein a highly transmissible strain is succeeded by a less immune-evasive strain, and vice versa. This cyclic pattern recurs iteratively. Visualization through bifurcation diagrams illustrates our analytical findings, elucidating rich dynamic phenomena encompassing the existence of various periodic solutions, extending to chaotic behavior. This comprehensive analysis provides valuable insights into the complexities of viral evolution in the light of the trade-off between immunity evasion and transmissibility.

Taitelbaum, Ami (Hebrew University of Jerusalem) - Population Dynamics in a Changing Environment: The effect of the noise properties

Multispecies communities and dynamics

Thursday 11th July 14:55-15:20

Environmental changes greatly influence the evolution of populations. Here, we study the dynamics of a population of two strains, one growing slightly faster than the other, competing for resources in a varying environment. We conduct several comparisons between different types of noises and elucidate the similarities and differences of the evolution subject to these noises. First, we examine time-varying binary carrying capacity switching either randomly or periodically between the two states. The population size distribution is generally found to be broader under intermediate and fast random switching than under periodic variations, which results in markedly different asymptotic behaviors between the fixation probability of random and periodic switching [1]. Second, we compare the competition dynamics under discretely-varying environmental noise with the dynamics under continuously-varying environmental noise. Here we study how the noise characteristic influence the population size and fixation properties. Notably, we show that the slow strain fixation probability can be greatly enhanced for a continuously varying environment compared to binary switches [2], even when the first two moments of the carrying capacity coincide. Finally, we study the consequences of power-law correlated environment on the dynamics of competing populations. We reveal the emergence of a novel intermediate phase that lies between the adiabatic noise (or quenched) and white noise (or annealed) regimes [3]. Within this phase, dynamics are primarily driven by rare, yet not exceedingly rare, long periods of almost-steady environmental conditions.

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Vilk, Ohad (Hebrew University of Jerusalem) - Non-Markovian zero-sum rock-paper-scissors game

Multispecies communities and dynamics

Thursday 11th July 16:05-16:30

Rock-paper-scissors (RPS) games are used to model cyclic dominance in ecology and microbiology. When the dynamics are Markovian, with exponentially-distributed inter-event waiting time distribution (WTD), it is well established that the species that has the smallest reproduction-predation rate is most likely to prevail. In large populations, the fixation probability of this species asymptotically approaches one while the other species go extinct. This yields a counterintuitive zero-one fixation behaviour often referred to as the ``law of the weakest" (LOW), that has been found in a number of variants of the RPS model, and also in recent microbial experiments. Here we consider a general zero-sum RPS game with non-exponential WTD between all reactions. We systematically study how the fixation and survival behavior of the RPS dynamics with non-Markovian dynamics is influenced by power-law and gamma WTDs. In particular, we show that the LOW is dramatically altered when the coefficent of variation of the WTD of the species with the smallest reproduction-predation rate is increased.

Zaherddine, Jana (ASTEK - DRI) - Stochastic Models of Regulation of Transcription in Biological Cells

Evolution, cooperation, and drug resistance

Tuesday 9th July 15:25-15:50

We study an important global regulation mechanism of transcription of biological cells using specific macro-molecules, 6S RNAs. The functional property of 6S RNAs is of blocking the transcription of RNAs when the environment of the cell is not favorable. We investigate the efficiency of this mechanism with a scaling analysis of a stochastic model. The evolution equations of our model are driven by the law of mass action and the total number of polymerases is used as a scaling parameter. Two regimes are analyzed: exponential phase when the environment of the cell is favorable to its growth, and the stationary phase when resources are scarce. In both regimes, by defining properly occupation measures of the model, we prove an averaging principle for the associated multi-dimensional Markov process on a convenient timescale, as well as convergence results for “fast” variables of the system. An analytical expression of the asymptotic fraction of sequestrated polymerases in stationary phase is in particular obtained. The consequences of these results are discussed.

Zhang, Xiaotong (University of Manchester) - Can pairwise cocultures predict complex microbiome dynamics?

Multispecies communities and dynamics

Friday 12th July 10:25-10:50

There has been a rising trend to quantitatively describe and predict microbial community dynamics, due to the desire for accurate microbiome manipulations for therapeutic and bioremediation needs. One increasingly common approach has been to fit generalized Lotka-Volterra (gLV) equations to complex community data, in theory enabling us to directly infer how individual microbes are interacting with one another within the community context. However, it is still uncertain how well this approach can identify true biological interactions and, more importantly, how well it can predict the dynamics of novel communities. Here we apply Bayesian gLV-inference to data from an artificial cheese rind community data, in order to predict the microbial interactions occurring between seven co-existing bacterial and fungal species. We find that our inferred interaction network can well recapitulate novel microbiome dynamics if we train the model with multi-taxa coculture data. However, the inferred interactions often cannot be validated with simple coculture experiments. In contrast, interaction networks derived from co-culture experiments cannot accurately forecast multi-taxa community dynamics. Together our results suggest higher-order interactions may be playing an important role within our model system, and indicate that care must be taken when using pairwise based approaches to predict community dynamics.

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The organisers would like to extend their sincerest thanks to the team at Maths Reception for their help and in particular to Dave Stones for his assistance in the behind-the-scenes work for this event.

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