Stochastic models of evolving populations: from bacteria to cancer

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Abstracts

Alexander, Helen

Stochastic establishment of antibiotic-resistant bacteria: theory and experiments

The evolution of antibiotic resistance is a critical challenge in the treatment of bacterial infections. Resistance first arises (e.g. by de novo mutation) in individual bacterial cells, whose lineages may be lost due to demographic stochasticity when rare. These stochastic population dynamics have been widely modelled by branching processes, which predict that the probability of establishing a surviving lineage is sensitive to birth (i.e. cell division) and death rates. These rates in turn should depend on environmental variables in a way that cannot easily be predicted by theory. However, stochastic establishment has rarely been investigated empirically, and is largely overlooked in the antibiotic resistance literature. A prevailing paradigm in medical microbiology is that resistance will be selected at antibiotic concentrations within the "mutant selection window" (MSW) between the standardized minimum inhibitory concentrations (MICs) of sensitive and resistant strains, at which their respective net growth rates reach zero. Therefore, remaining above the MSW is a priority for optimal dosing. However, this view neglects the stochastic nature of establishment of rare resistant cells, which we furthermore predict may be hindered by the presence of antibiotics, even within the MSW. We investigated this process using high-replicate experiments with a streptomycin-resistant strain of the clinically relevant bacterium Pseudomonas aeruginosa, combined with a likelihood-based statistical framework to infer from these data the per-cell probability of establishment in a stochastic model. We find that establishment probability sharply drops off with streptomycin concentration and already approaches zero well below the upper bound of the MSW. We additionally test whether these data support a simple relationship between population size and establishment probability predicted by independence among individuals, as commonly assumed in branching processes, or whether there is evidence of density-dependent interactions. Finally, we obtain time courses of population dynamics, which suggest that models of bacteria exposed to antibiotics will need to be parameterized by time-varying birth and death rates. These results suggest that the stochastic nature of resistance emergence should be taken into account when optimizing antibiotic dosing. Furthermore, the experimental and theoretical approaches developed in this system could be transferred to other evolving populations.

Altrock, Philipp

Evolutionary dynamics of non-Hodgkin's lymphoma CAR T cell therapy

Non-Hodgkin Lymphoma (NHL) is the most common hematologic malignancy in the United States with an estimated 72,000 new cases (4.3% of all cancer cases) and 20,000 deaths (3.4% of all cancer deaths) in 2017; the median 5-year survival rate is 71%. Despite a possible cure, with front-line chemotherapy, there exist patients that do not response or relapse and develop refractory disease. These patients have a median overall survival of less than seven months. Chimeric antigen receptor (CAR) T-cell therapy for refractory NHL relies on expansion of engineered T- cells that specifically target tumor cells expressing CD19. Here we use statistical and mathematical modeling to elucidate the key mechanisms that drive evolutionary dynamics of anti-CD19 CAR T-cell therapy. To this end, we integrate patient specific tumor burden profiles, inflammatory cytokine profiles and CAR T cell population dynamics into an eco-evolutionary model. The success of CAR T cell therapy may depend on dynamic regulation of inflammatory cytokines in the tumor microenvironment, as well as on specific properties of the heterogeneous CAR T cell population that competes with wildtype T cells.

The relative abundances of juvenile and effector T cells are key factors that drive the tumor-killing rate and thus the treatment response in the clinic. Our framework elucidates the short-term dynamical properties of CD19-specific CAR T immunotherapy that determine toxicity and patient survival and can also be used to predict long-term tumor eradication rate based on clinically relevant parameters.

Ashcroft, Peter
Evolutionary dynamics in hierarchical populations
The hematopoietic system is an archetypal example of a hierarchical population structure. Multipotent stem cells, which have the potential to reconstitute the full complement of blood-based cells, lie at the top of this hierarchy. A complex division tree then provides diversification and amplification of the progenitor and terminally-differentiated cells, and also a large degree of invasion protection. Mathematical modelling, combined with in vivo data, can help to unpick this population structure, and the dynamics within. The information that can be extracted is dependent on the labelling protocol used. More systematic analysis of these models can be used to address how resistant they are to mutant invasion. This analysis sheds light on the conditions required for a mutant to be successful, including at what stage of differentiation the mutant can emerge, what the effect of the mutation is, and how selection acts to promote it. These findings are also discussed in relation to other hierarchical systems, such as colonic crypts. (Peter Ashcroft*, Roland R. Regoes, Markus M. Manz, Sebastian Bonhoeffer)

Beardmore, Robert
Building a rig to observe spatial selection for copy number variation in a clinically important antibiotic resistance operon, acr
We take an evolutionary ecology modelling approach to a standard hospital assay, namely the disk diffusion test, which provides a visual readout on how susceptible a microbial population is to an antibiotic drug. Surprisingly, perhaps, the pharmacological literature and textbooks make contradictory statements on what the relationship is between the antibiotic dosage given and the resulting zone of inhibition where the microbes are unable to grow on an agar plate. So we study this, given its clinical importance.

First, a linear diffusion theory of microbial killing makes dose-dependent predictions that are consistent with images of the agar plate assays but the images also indicate certain intricacies, in the form of rings that hint at a nonlinear theory. Spatial ecological models explain these ringed patterns as selective hotspots of scalable resistance mechanisms in the genome of the microbe and so we study the spatio-temporal dynamics of the antibiotic efflux operon, acr, in the genome of E.coli MG1655 experimentally. We use a homemade fluorescence imaging rig built around an Arduino controller to quantify gradients of an AcrB::GFP fusion protein (validated by qPCR) and show how genomic amplifications of the acr operon form a wave of advance into regions of high drug dose, not unlike a Fisherian wave. PCR data and the images show acr has tripled in the genome within 48h where growth is visually detected as close as possible to the source of the drug.

This adaptation, which incidentally contradicts the well-known 'mutation selection window' hypothesis, equates to a 20% variation in the DNA content of the bacterial cells from the sides of the agar plate to the centre, illustrating just how much novelty can arise in a hospital assay of relatively short duration! (Joint work with Carlos Reding with substantial help from Rafael Pena-Miller, Michael Sieber, Tobias Bermueller, Ayari Fuentes-Hernandez and Ivana Gudelj).

Beerenwinkel, Niko
Learning tumor phylogenies from single-cell data
Cancer progression is an evolutionary process characterized by the accumulation of mutations and responsible for tumor growth, clinical progression, and drug resistance development. We discuss how to reconstruct the evolutionary history of a tumor from single-cell sequencing data. The tumor

phylogeny problem is challenging because of sequencing errors and the high rate of allelic drop-out in single-cell DNA sequencing experiments. We present probabilistic models and efficient inference algorithms for mutation calling and learning tumor phylogenies from such data.

Berestycki, Julien
Branching Brownian motion with decay of mass and the non-local KPP equation
The non-local variant of the celebrated Fisher-KPP equation describes the growth and spread of population in which individuals diffuse, reproduce and – crucially – interact through a non-local competition mechanism. This type of equation is intrinsically harder to study than the classical Fisher-KPP equation because we lose such powerful tools as the comparison principle and the maximum principle. In this talk, I will show how this equation arises as the hydrodynamic limit of a particle system – the branching Brownian motion with decay of mass, and use this to study front propagation behaviours. (This is based on joint work with Louigi Addario-Berry and Sarah Penington).

Bovier, Anton
Adapting models of adaptive evolution to modelling of immunotherapy
Stochastic individual based model have been successful over the last decade to capture in a mathematically rigorous way key features of adaptive dynamics. In collaboration with colleagues from our medical school we have applied modifications of these models to model and reproduce experiments on immunotherapy of melanoma in a mouse model. I will discuss the modelling results as well as some interesting new challenges brought to the mathematical analysis.

Carballo-Pacheco
Evolution of drug resistance in the presence of a phenotypic lag
Spontaneous mutations that create drug resistance is a critical problem in the treatment of both infectious diseases and cancer. Typically, statistical physics and population genetics models assume that mutations have an immediate effect. However, experiments suggest that mutations need time to manifest themselves, i.e., a phenotypic lag exists. Here, we model using computer simulations and analytical calculations the effect of different mechanisms of phenotypic lags on the evolution of resistance. We also provide the theoretical background for which experiments can be performed to differentiate between the possible mechanisms. Finally, we create a simple model to include phenotypic lag in evolutionary models.

Cheek, David
Mutation frequencies in a birth-death branching process
First we revisit a classic two-type branching process which describes cell proliferation and mutation; widespread application has been seen in cancer and bacteria modelling. We prove convergence and exact results for the number of mutants, mutation times, and clone sizes. Then we extend the model to keep track of mutations at multiple sites along the genome. We characterise the site frequency spectrum, and recover a power-law distribution which is commonly observed in cancer genetic data.

Our multiple-sites description does not make use of the ubiquitous but disputed infinite-sites assumption. Similarities and differences to infinite-sites models will be discussed.

Constable, George W A
Demographic stochasticity selects against the emergence of large complexes in early multicellularity
The evolution of multicellularity has long been recognised as one of the major transitions in evolution. It has been suggested that this transition should be considered in three stages; the formation, maintenance, and finally transformation of multicellular units of selection. While there are many

theoretical studies addressing the latter two stages, significantly less theoretical work has aimed at understanding how multicellular complexes might initially form and evolve. John Bonner discussed a distinction between two different modes of multicellular complex formation, staying together (ST) and coming together (CT). These distinct modes of multicellular construction were subsequently described mathematically in [1], where it was shown that each strategy faced very different evolutionary challenges. In this talk I extend the models in [1] to account for finite population sizes. I will show that in the absence of additional selective pressures favouring the formation of large complexes, and in the presence of extrinsic environmental mortality factors, both multicellular strategies are selected against relative to their unicellular ancestors, while CT is selected for over ST for large swathes of parameter space. These selection effects are only apparent in models that account for finite population size, and are essentially the result of the increased demographic stochasticity experienced by genotypes that concentrate their biomass in fewer individuals.

[1] CE Tarnita, CH Taubes, MA Nowak. Evolutionary construction by staying together and coming together. *Journal of theoretical biology* **320**, 10-22

Doekes, Hilje

Quantifying natural selection at all spatial scales

Evolution often involves processes occurring on various spatial scales. Selection pressures at these different scales are not necessarily aligned. Consider, for example, models of the evolution of costly public good production. Locally, such production is typically selected against because of the associated fitness costs, whereas globally it is favoured because areas with a higher mean production tend to have a higher mean fitness. Here, a new mathematical framework is presented that quantifies the selection pressures acting at different spatial scales. We combine the Price equation and kernel estimates to define the kernel selection differential (KSD): a measure of the selection pressure acting on a trait in a given local environment, or kernel. For any scale, the KSD can be used to split selection into contributions acting within and among environments of that scale. This decomposition is reminiscent of the within- and among-group components of selection defined in classical group selection approaches. However, whereas these approaches generally define groups a priori and assume that ecological interactions happen at either the within- or among-group level, our method does not require distinct groups or a correspondence between the range of ecological interactions and the scale of the local environments. Rather, it allows one to identify the spatial scales relevant to natural selection. We illustrate the use of these mathematical tools in the context of two simple spatial simulations modelling (i) the evolution of infectivity in an SI-system, and (ii) the evolution of cooperation. In both models, our analysis clearly demonstrates that selection pressures within and among environments point in opposing directions. We then consider the scale at which this difference between selection within and among environments is maximal, and show that this scale of natural selection directly relates to the scales of the emergent ecological patterns in the population. (Joint with Reinder Bosman and Rutger Hermsen, Theoretical Biology, Department of Biology, Utrecht University).

Derenyi, Imre

Cancer risk and the somatic cell-lineage tree

All the cells of an organism are the product of cell divisions organized into a single binary tree. This somatic cell-lineage tree is not uniform in the sense that its lineages have different lengths. As cell divisions are accompanied by replication errors, longer cell lineages are more prone to the accumulation of mutations and, thereby, to somatic evolution, which can potentially lead to the development of cancer. By mapping the accumulation of driver mutations along a somatic cell-lineage tree into a graph theoretical problem, we have been able to derive an analytical formula for the probability of carcinogenesis in an arbitrary cell-lineage tree with a given rate of driver mutations per cell division. The result is consistent with epidemiological data and highlights the significance of the longest cell lineages. We also show how tissues can minimize the length of their longest lineages through differentiation hierarchies [Derenyi & Szollosi, *Nat. Commun*. (2017)].

Durrett, Rick

Spatial evolutionary games

Recently, a rigorous mathematical theory has been developed for spatial games with weak selection, i.e., when the payoff differences between strategies are small. The key to the analysis is that when space and time are suitably rescaled, the spatial model converges to the solution of a partial differential equation (PDE). This approach can be used to analyze all 2 x 2 games, but there are a number of 3 x 3 games for which the behavior of the limiting PDE, a system of reaction-diffusion equations is not known. In this talk, we give rules for determining the behavior of a large class of 3 x 3 games and show their validity using simulation. In words, the effect of space is equivalent to making changes in the payoff matrix, and once this is done, the behavior of the spatial game can be predicted from the behavior of the replicator equation for the modified game.

Fisher, Daniel S

Ecology and evolution in high dimensions

The great complexities of organisms, environments, and their effects on each other, mean that even "simple" short-term evolution occurs in a very high dimensional "space". And dynamics in high-dimensions is strikingly different than intuition from low-dimensions would suggest. Focusing on short term evolution, microdiversity, and ecological feedbacks, approaches that take advantage of the complexities will be discussed and some surprising results obtained.

Foo, Jasmine

Understanding epigenetically-driven drug resistance in cancer

Glioblastoma, also known as glioblastoma multiforme (GBM), is an extremely fast-growing and lethal form of brain cancer. The standard treatment regimen for GBM involves surgery followed by radiation and adjuvant chemotherapy using the drug Temozolomide (TMZ). However, initial response to treatment is usually followed by tumor recurrence, which is driven by the development of resistance to TMZ. It has been shown that epigenetic processes, which alter the expression of a gene without changing the genetic code itself, play an important role in the development of TMZ resistance. I will introduce this problem and describe a mathematical model of the evolutionary dynamics driving GBM response to treatment. We will use this model to investigate the how these epigenetic processes impact tumor population dynamics in GBM recurrence. (joint work with K. Storey)

Frey, Erwin

Ecological feedback in quorum-sensing microbial populations

Bacteria and other microbes can communicate with each other using chemical languages. They release small signaling molecules called autoinducers into their surroundings and sense the levels of the autoinducers in the environment. The response to these autoinducers – known as quorum sensing – can regulate how whole communities of microbes grow and behave; for example, autoinducers can alter the ability of microbes to infect humans or enable the microbes to collectively switch on light production. Recent experiments suggest that, in a population of genetically identical microbes, some individuals may produce autoinducers while others do not. The coexistence of these different phenotypes in one population may enable different individuals to perform different roles, or act as a bet-hedging strategy that helps the population to survive if it is later exposed to a stressful situation. It is not clear how microbes regulate autoinducer production so that only some individuals produce these molecules. In this talk a theoretical model will be presented that addresses this question. In the model, the microbes shape their environment by producing autoinducers and can respond to this self-shaped environment by changing their level of autoinducer production. The coupling between ecological and population dynamics through quorum sensing can induce phenotypic heterogeneity in microbial populations, suggesting an alternative mechanism to stochastic gene expression in bistable gene regulatory circuits.

Galla, Tobias

Evolutionary dynamics in switching environments

In this talk I will discuss the stochastic dynamics of finite populations in switching environments. This includes the success of invading mutants in evolutionary games with time-varying payoff matrix, as well as bet-hedging strategies of bacterial populations and phenotypic switching. I will also highlight recent theoretical work on stochastic processes subject to fast external environments. Deriving reduced dynamics of such open systems leads to effective master equations with negative transition 'rates. I will discuss the origin of these unphysical features and describe how reduced processes can be simulated and analysed effectively using stochastic differential equations capturing both intrinsic demographic noise, and extrinsic noise resulting from fast-switching external environments.

References:

Peter Ashcroft, Philipp M Altrock, Tobias Galla. Fixation in finite populations evolving in fluctuating environments. *J. R. Soc.* Interface:201411 20140663 (2014)

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Gifford, Danna

Bacterial mutators facilitate multi-drug resistance evolution

Combination therapy, the practice of giving multiple drugs simultaneously, is gaining support as a strategy for preventing antibiotic resistance. However, we argue that the motivation behind combination therapies neglects important aspects of treating infections; chiefly, antibiotic concentrations are not always fully-inhibitory during the course of treatment and resistance mutation rates are heterogeneous within bacterial populations. Using stochastic simulations, corroborated with laboratory experimental resistance evolution, we show that the presence of bacterial 'mutator' sub-populations permit evolution of multi-drug resistance (MDR) through sequential acquisition of resistance mutations under a gradually-increasing antibiotic regime. This effect holds over mutator frequencies commonly observed clinically (5-60%). In contrast, populations without mutators evolved only resistance to single drugs. Given that mutators are particularly common in chronic infections, which are frequently treated with multiple antibiotics, our results suggest that combination therapies are unlikely to be a panacea for the multi-drug resistance crisis. (Joint work with Ernesto Berrios, Christine Joerres, Tobias Galla, Christopher G Knight)

Gudelj, Ivana

The impact of microbial community interactions on the evolution of virulence and antibiotic resistance

Existing theory, empirical, clinical and field research all predict that reducing the virulence of individuals within a pathogen population will reduce the overall virulence, rendering disease less severe. Here, we show that this seemingly successful disease management strategy can fail with devastating consequences for infected hosts. We deploy cooperation theory and a novel synthetic system involving the rice blast fungus *Magnaporthe oryzae*. In vivo infections of rice demonstrate that *M. oryzae* virulence is enhanced, quite paradoxically, when a public good mutant with low virulence is present in a population of high-virulence pathogens. We reason that during infection, the fungus engages in multiple cooperative acts to exploit host resources. We establish a multi-trait cooperation model which suggests that the observed failure of the virulence reduction strategy is caused by the interference between different social traits. In addition we show that interactions between multiple traits such as resource consumption and antibiotic resistance play a critical role in determining pathogen community composition during drug treatment. In particular we demonstrate

that single species antibiotic dose response is a poor predictor of multispecies community dynamics because it cannot foresee the tipping points that cause irreversible changes in resistance that persist, even when treatment stops.

Hallatschek, Oskar
The role of jackpot events in the dynamics of evolution
Luria and Delbrück discovered that mutations that occur early during a growth process lead to exceptionally large mutant clones. These mutational "jackpot" events are thought to dominate the genetic diversity of growing cellular populations, including biofilms, solid tumors and developing embryos. We show that jackpot events can be generated not only when mutations arise early but also when they occur at favourable locations, which exacerbates their role in adaptation and disease. We will also consider the impact of recurrent jackpot events, which lead to a bias favoring alleles that happen to be present in the majority of the population. This peculiar rich-get-richer phenomenon is a general feature of evolution driven by rare events.

Hoyle, Andy
Combining mathematics, computing & biology to optimise antibiotic dosage regimens
For too long have antibiotic dosage regimes followed the traditional approach of a giving a fixed dose X per day for N days. With the rise of antibiotic resistance, the need to find better, more efficient strategies is essential. Here we combine mathematical modelling of a bacterial infection (including resistance), with genetic algorithms from computational optimisation, to find optimal dosage regimes. These regimes improve the treatment success while also giving the option to minimise total antibiotic usage.

Kareva, Irina
Primary and metastatic tumor dormancy as a result of population heterogeneity
Existence of tumor dormancy, or cancer without disease, is supported both by autopsy studies that indicate presence of microscopic tumors in men and women who die of trauma (primary dormancy), and by long periods of latency between excision of primary tumors and disease recurrence (metastatic dormancy). Within dormant tumors, two general mechanisms underlying the dynamics are recognized, namely, the population existing at limited carrying capacity (tumor mass dormancy), and solitary cell dormancy, characterized by long periods of quiescence marked by cell cycle arrest. Here we focus on mechanisms that precede the avascular tumor reaching its carrying capacity, and propose that dynamics consistent with tumor dormancy and subsequent escape from it can be accounted for with simple models that take into account population heterogeneity. We evaluate parametrically heterogeneous Malthusian, logistic and Allee growth models and show that 1) time to escape from tumor dormancy is driven by the initial distribution of cell clones in the population and 2) escape from dormancy is accompanied by a large increase in variance, as well as the expected value of fitness-determining parameters. Based on our results, we propose that parametrically heterogeneous logistic model would be most likely to account for primary tumor dormancy, while distributed Allee model would be most appropriate for metastatic dormancy. We conclude with a discussion of dormancy as a stage within a larger context of cancer as a systemic disease.

Komarova, Natalia
To follow

Krug, Joachim
Interference of deleterious and beneficial mutations in spatial habitats
The effect of spatial structure on the initiation and spreading of mutant clones is of key importance in microbial evolution as well as in the dynamics of cancers. If all mutations are deleterious both spatial and well-mixed populations are subject to an irreversible fitness decline caused by the operation of Muller's ratchet. However, the fitness decline is much more severe in spatial populations,

in that it proceeds at finite speed even in the limit of infinite habitat size when the deleterious mutation rate exceeds a critical threshold. In the talk I discuss to what extent the ratchet can be reversed by a small supply of beneficial mutations. Based on a previously observed connection between the spatial ratchet and directed percolation, a scaling theory for the speed of adaptation will be developed and compared to extensive simulations for one- and two-dimensional habitats. The talk is based on joint work with Philipp Klatt, Jakub Otwinowski and Su-Chan Park.

Leder, Kevin

Optimal chemoradiotherapy for metastatic cancer

A common goal when designing optimal radiotherapy and chemoradiotherapy treatment schedules is to design the schedules to minimize the number of viable cells at the primary site. In this talk I will consider how optimal treatment schedules change when one instead is interested in somehow controlling a metastatic tumor population. In pursuit of this I will first develop a stochastic model for the evolution of metastatic cancer and then look at optimal treatment schedules for increasingly complex versions of the stochastic model.

Miedema, Daniël

Lineage tracing experiments and stochastic modelling reveal the growth mode of colorectal cancer xenografts

Cancer is a disease of abnormal cell growth. Tumor growth is thought to originate from a single cell but comprises over a billion cells by the time of detection. Which malignant cells contribute to tumor growth, and under which conditions, remains largely unclear. Moreover, the amount of heterogeneity in the malignant cell population that arises during tumor growth can, so far, not be quantified, while molecular heterogeneity underlies resistance to (targeted) therapy. We report on quantitative lineage tracing of primary colorectal cancer xenograft tissue, in conjunction with stochastic modelling and spatially resolved simulations. We use multiple fluorescence based lineage tracing techniques to study the growth dynamics of established cancer tissues. To derive the tumor growth mode from the quantitative experimental data we developed stochastic models for tumor growth and apply simulation models of tumor growth. We find that the tumor microenvironment drives growth of malignant cells in established cancer tissues, while in contrast no evidence for a cancer stem cell hierarchy was found.

Moebius, Wolfram

Another level of survival of the luckiest: How isolated features in the habitat shape genetic diversity and the fate of mutations during spatial spread of a population

Despite many natural environments being highly heterogeneous, the effect of environmental heterogeneity on the evolutionary dynamics of spreading populations remains poorly understood so far – not least due to the large variety of environmental heterogeneity found in nature. We here address its effect using theory and simulations and thereby focus on large isolated structures. In particular, we consider regions which hinder or accelerate the invasion in a flat environment as well as bumps out of an otherwise flat environment. We find that all those structures have characteristic effects on genetic diversity and the fate of mutations occurring at the time of spatial spread. We observe an effect of 'geometry-enhanced genetic drift' – complementary to, yet qualitatively different from founder effects occurring in the presence of 'spatial bottlenecks'. Based on these findings, we can predict the consequences of more complex habitat structure onto the evolutionary dynamics and test those predictions using simulations.

Nelson, David

Microorganisms living on highly viscous liquids generate buoyant flows that alter colony morphology and evolutionary dynamics

The interplay between fluid flows and living organisms plays a major role in the competition and organization of microbial populations in liquid environments. Hydrodynamic transport leads to the dispersion, segregation or clustering of biological organisms in a wide variety of settings. To explore

such questions, we have created microbial range expansions in a laboratory setting by inoculating two identical strains of *S. cerevisiae* (Baker's yeast) with different fluorescent labels on a nutrient-rich fluid 10^4 to10^5 times more viscous than water. The yeast metabolism generates intense flow in the underlying fluid substrate many times larger than the unperturbed colony expansion speed. These flows dramatically impact colony morphology and genetic demixing, triggering in some circumstances a fingering instability that allows these organism to spread across an entire Petri dish within two days. We argue that yeast colonies create fluid flow by consuming nutrients from the surrounding fluid, decreasing the fluid's density, and ultimately triggering a baroclinic instability when the fluid's pressure and density contours are no longer parallel. Our results suggest that microbial range expansions on viscous fluids will provide rich opportunities to study the interplay between advection and spatial population genetics.

Nicholson, Michael

Competing pathways in growing populations over fitness valleys

Our interest is in when, and how, a particular cell type emerges in a stochastically growing population. Motivated by the fitness cost of resistance, and sensitive cells in contact with drugs, we focus on the setting where the initial cell type has largest growth rate. Simple formulas are obtained which can yield insight on a variety of scenarios in cancer and bacterial systems. We demonstrate their usefulness by considering the impact of imperfect drug penetration.

Patel, Swati

Feedbacks between genetics within one population and the community it lives in

Most populations live in biotic communities, in which they interact with other populations around them. These interactions can impose selection pressures and as a focal population evolves, this may, in turn, alter the populations and selection pressures around it, generating feedbacks between ecology and evolution. Here, we investigate how the densities of two prey populations affect the internal genetics and evolution of a focal predator population and vice versa. In particular, we analyze an explicit two locus population genetics model coupled to a Lotka–Volterra community model.

We show that linkage between the two loci and the magnitude of the effects of each locus affect the persistence of alleles and the cycling of the predator and the prey. Importantly, our work highlights that aspects of genetics and evolution within one species play an important role in population dynamics of interacting species. (Joint with Reinhard Burger)

Pflug, Florian

Correctly counting molecules with a little help from a well-known population model

Counting molecules using next-generation sequencing (NGS) suffers from polymerase chain reaction (PCR) amplification bias, which reduces the accuracy of many quantitative NGS-based experimental methods such as RNA-Seq. This is true even if molecules are made distinguishable using unique molecular identifiers (UMIs) before PCR amplification, and distinct UMIs are counted instead of reads: Molecules that are lost entirely during the sequencing process will still cause underestimation of the molecule count, and amplification artefacts like PCR chimeras create phantom UMIs and thus cause over-estimation. To quantify and correct these biases, we re-use tools from mathematical population modeling, and treat PCR amplification as a Galton-Watson branching process. We show that we can effectively estimate all process parameters from real data, and observe that the data fits our model remarkably well. The data in particular shows traces of effects that are particular to branching processes and not explained by generic stochastic models, which we take as evidence that our Galton-Watson model indeed captures the main stochastic properties of PCR amplification. We then use this model to detect & correct biases, and demonstrate that corrected molecule counts are more precise. We also use the model to study the amplification reaction, and in particular its behaviour during early cycles that is hard to observe otherwise.

Reiter, Johannes

The evolution of pancreatic cancer: from precursor lesions to metastases

Most adult carcinomas develop from noninvasive precursor lesions, a progression that is supported by genetic analysis. We analyzed the somatic variants of co-existing pancreatic cancers and precursor lesions sampled from distinct regions of the same pancreas. After inferring evolutionary relationships, we found that the ancestral cell had initiated and clonally expanded to form one or more lesions, and that subsequent driver gene mutations eventually led to an invasive pancreatic cancer. We estimate that this multi-step progression generally spans many years. Utilizing multi-region sequencing of primary tumors and many spatially-distinct metastases, we found that the identical driver gene mutations were present across all analyzed cancer samples of each patient. These new data refine the step-wise progression model of pancreatic cancer by illustrating independent, high-grade pancreatic precursor lesions which represent a single neoplasm that accumulated spatial and genetic divergence and colonized the ductal system.

Schweinsberg, Jason

Rigorous results for a population model with selection

We consider a model of a population of fixed size in which each individual acquires beneficial mutations at a constant rate. Each individual dies at rate one, and when a death occurs, an individual is chosen with probability proportional to the individual's fitness to give birth. We obtain rigorous results for the rate at which mutations accumulate in the population, the distribution of the fitnesses of individuals in the population at a given time, and the genealogy of the population. Our results confirm predictions of Desai and Fisher (2007), Desai, Walczak, and Fisher (2013), and Neher and Hallatschek (2013).

Swain, Peter

Predicting metabolic adaptation from networks of mutational paths

Although cells respond specifically to environments, how environmental identity is encoded intracellularly is not understood. I will discuss this organization of information in budding yeast by estimating the mutual information between environmental transitions and the dynamics of nuclear translocation for ten transcription factors. Using a new method of estimation that is general, scalable, and based on decoding from single cells, we find that the dynamics of the transcription factors are necessary to encode the highest amounts of extracellular information and that information is transduced through two channels. Transcription factors are either generalists, which can encode the nature of multiple stresses but only if stress is high, or specialists, which encode one particular stress, but do so more quickly and for a wider range of magnitudes. Further, each transcription factor reports differently, and it is only their collective response that provide sufficient information to distinguish between multiple environmental states. I will argue that changes in the dynamics of the localization of transcription factors thus constitute a precise, distributed internal representation of extracellular change.

Traulsen, Arne

From game theory to neutrality: Modelling the ecology of microbiomes

The microbes strongly associated animals and plants often have fundamental roles in the functioning of their hosts, from metabolic functions to contributing to development. The multi-stability of microbiomes can be understood in terms of game theoretical models, but it is challenging to assess the associated parameters from experimental data. On the other hand, many microbes will randomly vary in their abundance, such that stochastic models are more appropriate to describe them.

Such neutral models are well established in theoretical ecology and they can be directly applied to the microbiomes of a wide variety of host organisms. Neutral models allow to identify key taxa, which are not necessarily those that are found in particularly high abundance.