Stochastic models of evolving populations: from bacteria to cancer

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Posters

Baumdicker, Franz

The evolution of the CRISPR defense memory in bacteria and archaea

The evolutionary dynamics of prokaryotes are shaped by fundamentally different mechanisms compared to the ones in eucaryotes. For example, many bacteria and archaea are under constant attack by a myriad of viruses that try to infect them. Remarkably, many prokaryotes harbor a so called CRISPR system, an immune system against such viral attacks. This system includes an array of spacer sequences that encode an inheritable memory of previous infections. Short sequence samples from viral attacks are stored in the spacer sequences and provide a specific immunity against the corresponding virus. The insertion of new spacer sequences is an example of Lamarckian evolution, since spacers acquired from repelled viral infections are passed to the offspring. Notably, new spacer sequences are always inserted at the beginning of the array such that the order of spacers represents the chronological infection history of the host. In contrast, deletion of spacers is frequent and can occur at any position in the array. A sample of n bacterial CRISPR arrays will thus be a set of n spacer sequences, where some spacers can be present in only a subset of the sequences. We showed how to calculate the distribution of the number of different spacers between identical spacers present in all n arrays. In particular, it is possible to use the order of spacers in a sample of n spacer arrays to estimate the rate of spacer deletions independently of the spacer acquisition rate.

Berríos, Ernesto

Multi-drug resistance in bacteria: theoretical and numerical approaches

A theoretical and numerical study is presented of multi-drug resistance (MDR) in bacteria, supported by experiments of *Escherichia coli* (str. K-12 substr. BW25113), submitted to a combination therapy of two antibiotics. Using simple numerical simulations based on binomial probability distributions, we can predict the temporal evolution of bacteria which have developed MDR to one or two antibiotics (single and double resistant bacteria, respectively), under different drug concentrations applied. Further, with the initial condition of no resistant bacteria at the therapy initiation, we can estimate the probability of single and double resistant bacteria appearance, as a function of time. This probability has been verified numerically. Moreover, including a hypermutator derivative, i.e., bacteria with higher mutation rates, we study the dependence of single and double resistant bacteria with the initial proportion of hypermutators. Partial results show good agreement with experimental data.

Ghafari, Mahan

How fast can sexual populations cross a fitness plateau?

In this work, we mathematically model a sexual population on a fitness plateau that can escape via a complex adaptation. We provide a complete description of the rate of adaptations that require three mutations to function. We identify and examine multiple plateau-crossing regimes for a population with low and high recombination rates. We also provide, for the first time, an analytical prediction for the rate at which a highly recombinant population spreads and escapes a wide fitness-plateau. We find that rare recombination can increase the rate of adaptation by 2 orders of magnitude compared to that of an asexual population, but if recombination is frequent relative to selection, the rate would be similar to that of an asexual population when the plateaus are tight. However, through

the stochastic tunnelling of some (small) number of mutant lineages on the background of (many) other fixed alleles, populations with frequent recombination cross wider plateaus by an order of magnitude faster than asexual populations. We also demonstrate that this mixed regime of stochastic tunnelling with sequential fixations makes the plateau-crossing by almost an order of magnitude faster compared to the pure sequential fixation.

Grajzel, Daniel
Tissue size regulation leads to a threshold proliferation rate for the survival of mutant cells
Our cells go through many divisions during our lifetime. When a division occurs, it is possible that the dividing cell collects a mutation. This mutation could give the cell a slight advantage in the growth opposed to the wildtype cells. The proliferation rate of a mutant cell is 1 minus the ratio of the death and birth rates.

Our model considers a hierarchical tissue with birth, death and differentiation processes. Cells interact with each other through regulation, the strength and direction of which depends on the difference between the number of cells present at a given time in the tissue and the desired homeostatic state. Regulation acts by modifying the rate of cell division and differentiation at each level of the hierarchy such that it tries to maintain the tissue at its homeostatic size.

Our results suggest that the tissue size regulation creates a threshold proliferation rate for mutant cells below which they are washed out of the tissue by differentiation from below. Above the threshold the probability of the survival probability of the mutants rises steeply. Without the regulation there is no such a threshold, even with a small advantage there is a non-zero probability for the mutants to spread and remain in the system. (Joint with Imre Derényi and Gergely J. Szöllősi ELTE-MTA "Lendulet" Biophysics Research Group, Department of Biological Physics, Eötvös University)

Herrerías-Azcué, Francisco
Stirring does not make populations well mixed – the effect of motion on fixation probability
In evolutionary dynamics, the notion of a "well-mixed" population is usually associated with all-to-all interactions at all times. This assumption simplifies the mathematics of evolutionary processes, and makes analytical solutions possible. At the same time the term "well-mixed" suggests that this situation can be achieved by physically stirring the population. Using simulations of populations in chaotic flows, we show that in most cases this is not true: conventional well-mixed theories do not predict fixation probabilities correctly, regardless of how fast or thorough the stirring is. We propose a new analytical description in the fast-flow limit. This approach is valid for processes with global and local selection, and accurately predicts the suppression of selection as competition becomes more local. It provides a modelling tool for biological or social systems with individuals in motion.

Huss, Elisabeth
Modifiers of mutation rate in selectively fluctuating environment
We study a mutation-selection model with a fluctuating environment. More precisely, individuals in a large population are assumed to have an A-locus determining the mutation rate at a second, B-locus with alleles $u \in \{0,1\}$. The goal of our study is to quantify the optimal mutation rate, in the sense that the fixation probability for states in the A -locus is maximized. In order to obtain this, we use limit results for fast fluctuating environments and small fitness differences. This is joint work with Franz Baumdicker and Peter Pfaffelhuber (both Freiburg).

Kimmel, Gregory
The influences of spatial heterogeneity and nonlinear functions on the dynamics of the public goods game.
Ecological and evolutionary dynamics can be strongly affected by population assortment. It is often difficult to identify the key drivers of these dynamics. A particular challenge is to disentangle global ecological effects from local, often frequency-dependent, effects. Here we implement a logistic

growth and death model, coupled to frequency-dependent growth rates influenced by a public goods game between cooperators and defectors. For each individual, the public good is only effective within a neighborhood, and the public good–growth rate relationship can be nonlinear. At low numbers of cooperators, increases of public good accumulate synergistically; at high numbers, they only provide diminishing returns. We observed complex behavior in the evolutionary dynamics' equilibria, determined by the relative magnitude of frequency-dependent to constant (background) growth benefits of the nonlinear public goods population game. We predict neighborhood-size-driven state changes, hysteresis between polymorphic and monomorphic equilibria, and observed that type-dependent differences in neighborhood sizes can destabilize monomorphic cooperative states, but also increase coexistence of producers and defectors. Stochastic neighborhood size fluctuations also led to coexistence and could stabilize the purely cooperative equilibrium. Our results quantify the role of both assortment through neighborhood-size effects and nonlinearity of the gains function in eco-evolutionary dynamics that are relevant for a variety of microbial and cellular public goods games.

Kiss, Máté

Minimizing the number of cell divisions accumulating in meristems

Protecting genetic information from mutations is an essential task of all living cells. These mutations arise largely from replication errors during cell division and if they accumulate they can cause the development of cancerous tumours. For this reason the self-renewing and growing tissues which have to produce a large number of functional cells during the lifetime of an organism are subject to increased risk. To mitigate this risk there must be a biological mechanism fine-tuned by natural selection that is capable of keeping the number of divisions low along any individual cell lineage.

We have constructed a mathematical model describing the cell division dynamics of spatially constrained tissues and have derived analytical results on the optimal pattern of division rates. Our results explain the low rates of somatic evolution observed in constantly growing tissues.

In particular, we know that the number of mutational differences between cells located on distant branches of large plants can be remarkably low despite the series of branchings that must also correspond to cell divisions. [1] We developed a simple in silico model of the meristem and used a genetic algorithm to find the optimal set of division rates and patterns of cell division during the branching of such tissues. We found that with the proper set of parameters it is possible to greatly reduce the number of cell divisions accumulated during the lifetime of the organism.

[1] Sarkar, N., Schmid-Siegert, E., Iseli, C., Calderon, S., Gouhier-Darimont, C., Chrast, J. Reymond, P. (2017). Low Rate of Somatic Mutations in a Long-Lived Oak Tree. doi:10.1101/149203

Lupo, Cosimo

V-gene insertions and deletions during the affinity maturation process in BCR repertoires

The ability of the immune system to recognize and kill a huge range of external pathogens is ensured by a high diversity in the binding sites of membrane Receptors in B-Cell lymphocytes (BCR). The resulting repertoire of BCRs is updated and increased via a 2-step stochastic process for the creation (recombination) and the evolution (affinity maturation) of each nucleotide sequence forming the receptors. The common picture of the recombination process involves a random choice of the genes from the germline DNA forming the sequence, plus some nucleotides deletions and insertions (briefly, indels) at the junctions of such genes. Instead, the affinity maturation of the sequence involves some context-dependent point mutations, namely the exchange of some nucleotide bases. Our analysis focuses on the possibility of experiencing indels not just at the junctions between the germline genes, but directly in the bulk of the most variable (V) gene in the chain, further enhancing the variability of the repertoire. These indels appear prominently in the BCR of both healthy people and HIV responding broadly neutralising antibodies. We evaluate the probability of such indels, developing a likelihood-based approach for their inference from real data and for the generation of more reliable synthetic sequences.

Márton, Demeter

Structural and dynamical properties of differentiation hierarchies that minimise somatic selection

Cancer development is a somatic evolutionary process where cells must divide and as a result mutations that can ultimately lead to neoplastic progression may accumulate. Our previous results demonstrated that hierarchically organized tissues can greatly reduce divisional load, the number of divisions along cell lineage trees [Derenyi and Szollosi 2017 Nat.Comm.]. These results, however, did not consider the selective effects of mutations.

Here we explore the role of selection by introducing mutations that change the rate of different types of cell divisions and differentiation events implementing the tissue hierarchy. We derive a generic threshold value that determines the critical number of mutations necessary for cancer initiation in hierarchically organized tissues. Using extensive stochastic simulations we show that we are able to analytically estimate the probability of neoplastic progression in our model using the theory of birth death processes and the statistical characteristics of the cell-linage tree.

Our results demonstrate that hierarchically organized tissues optimized to reduce the accumulation of mutations with selective effects, i.e. to reduce to probability of tumor progression, are not identical to those that minimize divisional load. In particular we find that in tissues with a physiologically realistic parameters the division rate of stem cells is higher than the extremely low rates required to minimize divisional load. This suggest that the optimum induced by selection supports an elevated functional diversity of tumor cells due to an increased propensity for neoplastic progression in less differentiated levels of the hierarchy.

Park, Su-Chan

Speed of adaptation of spatial population in the presence of both beneficial and deleterious mutations

We investigate the speed of adaptation of a spatial asexual population, with the focus on how much beneficial mutations alter the Muller's ratchet. At first, we present how the Muller's ratchet for one- and two-dimensional populations is operating. Unlike the well-mixed population, which has an equilibrium distribution under infinite population size limit, the spatially local competition among individuals enables the ratchet to operate even in infinite population limit, once the deleterious mutation probability U_d is larger than a certain threshold value U_c. It has been well noted that the speed of the Muller's ratchet for the spatial population is described by the critical exponents of the directed percolation. We will show our simulation results which reconfirm this connection. After presenting the dynamics of the Muller's ratchet for spatial population, we will discuss how much the speed of adaptation is affected by the presence of beneficial mutations. At the threshold value $U_d = U_c$, the speed increases with the beneficial mutation probability U_b as U_b^{ξ}, where ξ is a nontrivial exponent whose numerical values are found to be 0.76 and 0.72 for one and two spatial dimensions, respectively. When the probability U_d of having deleterious mutations is larger than U_c (the regime where Muller's ratchet is operating), we observed that a mere presence of beneficial mutations cannot alter the direction of the Muller's ratchet and sufficiently large value of U_c is required to halt the Muller's ratchet. It turned out that when U_b is larger than $(U_d - U_c)^{\tau}$ with τ to be a nontrivial exponent, the Muller's ratchet does not operate and the population accumulates beneficial mutations and evades the mutational meltdown. We will discuss the biological implications of our finding.

Tibély, Gergely

Subclonal structure in tumors

Intratumor heterogeneity appears as a consequence of imperfect DNA copying during division of tumor cells, leading to a somatic evolutionary process. (1) argues that tumor evolution, apart from the driver mutations, can be well fitted by assuming a neutral model, and gives estimates for the mutation rate. Along the question of robustess of the results against measurement noise, the study implies that the number of subclonal mutations is much larger than expected, compared to current estimates of the human somatic mutation rate, assuming neutrality of mutations (1, 2). We hypothesize that the elevated number of mutations are caused either by a significantly higher mutation rate, or to prevalent cell death which lengthens lineage lines, resulting in more cell divisions

along each lineage. We are developing tools to estimate the likelihood of generative models having different mutation rate-cell death rate parameter values. Preliminary test results show that the real parameters can indeed be found. (Joint with Gergely Szöllősi, Imre Derényi, ELTE-MTA "Lendulet" Biophysics Research Group, Department of Biological Physics, Eötvös University)

(1) Williams M J, Werner B, Barnes C P, Graham T A, Sottoriva A. Identification of neutral tumor evolution across cancer types. Nat Genet 2016; 48:238-244.
(2) Martincorena I, Campbell P J. Somatic mutation in cancer and normal cells. Science 2015; 349:1483-1489.

Widder, Stefanie

A switch in the organization of the airway microbiome links homoeostasis and lung exacerbation in cystic fibrosis.

The lung microbiome of person with cystic fibrosis (CF) is a dynamical ecosystem and a model system for the study of evolving community processes in complex environments. The microbiome establishes and evolves individually in every patient due to genetically-borne deficiencies in mucociliary clearance of the airways. The disease is characterized by recurrent lung exacerbations that lead to irreversible lung function decline and death. Exacerbation events caused by overshooting immune response present instances of system perturbation that initiate a reassembly of the microbial community and their interaction patterns. Our preliminary analyses suggest that community metabolism is re-established after every exacerbation, thereby re-defining robustness and re-establishing communication. These accumulating instances of independent evolution ‘runs’ together with decade-long clinical observation provide ideal, high-resolution data ideally support the study of evolving, functional populations. Here, we will present our analyses on the underlying community structure derived from a large patient cohort. We will furthermore show how keystone species impact population robustness and can be used in an applied sense, for the prediction of drug targets.