BP 21: Focus Session: Sequence Spaces, Populations and Evolution

Evolutionary processes are central in the living world: they leave patterns in sequence databases and underlie phenomena such as cancer progression and antibiotic resistance. Achieving a quantitative understanding of evolution relies on two key components: variation and selection. The first component - variation - arises from random mutations in genotypic sequences that lead to selectable changes in phenotype and fitness. Thus, variation depends on how phenotype and fitness are distributed in biological sequence spaces. The second component - selection * shapes the composition of future generations and thus acts at the population level. Since these components jointly shape evolutionary processes, this focus session will encompass both: variation in sequence spaces and selection on the population level.

Organized by Nora Martin (Centre for Genomic Regulation, Barcelona) and Paula Garcia Galindo (University of Cambridge)

Time: Wednesday 15:00–17:30 Location: HÜL/S386

Invited Talk BP 21.1 Wed 15:00 HÜL/S386

Microbial Behavior in Context — •Fernanda Pinheiro — Human Technopole, Milan, Italy

Predicting microbial responses to antibiotics, nutrient shifts, or invading species requires models linked to metabolic pathways and cellular functions. In this talk, I present quantitative approaches for characterizing microbial behavior, from growth kinetics to coarse-grained models of cell metabolism and empirical growth laws. I will connect growth parameters to resource allocation and physiological constraints, and I will show how growth perturbations reveal layers of organization, from cellular physiology to ecological interactions and evolutionary change. In a broader context, I will discuss how metabolic models linking systems biology, ecology, and evolution can become tools for prediction.

BP 21.2 Wed 15:30 HÜL/S386

Insertions and Deletions make important contributions to the arrival of phenotypic variation — •Manuela Giraud[1,2] and Nora Martin[1] — [1]CRG (Barcelona Collaboratorium for Modelling and Predictive Biology), Dr. Aiguader 88, Barcelona 08003, Spain — [2]Universitat Pompeu Fabra (UPF), Barcelona, Spain.

In evolution, phenotypic variation is a prerequisite for selection and arises from random genotypic mutations. An extensive mapping of genotypes to their corresponding phenotype (GP map) provides us with a quantitative model for variation, thus informing evolutionary predictions. The features of GP maps and their relevance for evolutionary processes have been analyzed for different model systems, but these analyses have largely been limited to short substitutions. Insertions and deletions (InDels) of different lengths have been neglected despite their presence in natural sequence families. In this study, we analyze InDels in computational GP maps modelling RNA secondary structure, enzyme functionality, and a toy-model for protein quaternary structure self-assembly. We find that InDels are more likely to preserve the phenotype than expected from null models. These phenotype-conserving indels imply large sequence changes, affecting the effect of subsequent mutations: after a phenotype-conserving InDel, the distribution of accessible phenotypes shifts increasingly with the mutation size. Evolutionary simulations indicate that such phenotype-conserving indels can fix and strongly affect the number of encountered phenotypes. These results imply that InDels, even if rare, can make an important contribution to the arrival of phenotypic variation.

BP 21.3 Wed 15:45 HÜL/S386

Bias toward simplicity and symmetry in protein self-assembly — •Prarthana Agrawal — University of Oxford

Symmetry is ubiquitous in protein complexes and other biological assemblies and is often attributed to natural selection. Algorithmic information theory offers an alternative explanation: when structures are generated by simple local rules, outcomes that require less information to specify are intrinsically more likely [1]. Because symmetry enables reuse of the same assembly instructions, symmetric structures typically have low algorithmic (Kolmogorov) complexity and are therefore strongly favored.

We test this idea using a three-dimensional polycube self-assembly model as an abstract representation of protein quaternary structure. By sampling interaction rule spaces, we find a strong bias toward low-complexity assemblies, with symmetric structures occurring far more frequently than asymmetric ones. We further show that not all symmetries are equally accessible: some symmetry operations reduce assembly complexity more effectively than others and are therefore disproportionately likely.

These results indicate that biases toward simple and symmetric structures in self-assembly arise from intrinsic generative constraints rather than natural selection alone, suggesting that evolutionary outcomes are shaped not only by selection but also by how phenotypic variation is generated.

[1] Johnston et al., Proc. Natl. Acad. Sci. U.S.A. 119, e2113883119 (2022)

15 min. break

Invited Talk BP 21.4 Wed 16:15 HÜL/S386

The navigability of fitness landscapes shaped by global and universal epistasis — •Joachim Krug — Institute for Biological Physics, University of Cologne, Germany

Epistasis is the dependence of the effect of a mutation on the genetic context in which it occurs. Epistatic interactions shape the topography of the fitness landscape, the mapping from genotype to reproductive success. Global epistasis refers to interactions that arise when a nonlinear phenotype-fitness map acts on a lower-dimensional set of non-epistatic phenotypes, and has been argued to be a common occurrence at different scales of biological organization. It is therefore of interest to ask what features characterize fitness landscapes when epistasis is purely global. Here I show that, under certain conditions, global epistasis implies universal negative epistasis [1], an order relation on sequence space that is closely related to submodularity of set functions [2]. Universal epistasis makes fitness landscapes easily navigable, because any fitness peak is accessible through combinatorially many fitness-increasing mutational paths. I will discuss the theoretical results within the context of recent studies of large-scale empirical fitness landscapes that have found that rugged landscapes may also be highly navigable.

[1] Krug, J. & Oros, D.: Evolutionary accessibility of random and structured fitness landscapes. J. Stat. Mech. 034003:2024

[2] Pahujani, S. & Krug, J.: Complexity and accessibility of random landscapes. arXiv:2502.05896

BP 21.5 Wed 16:45 HÜL/S386

Adaptive Response of Quantitative Traits to a Moving Fitness Landscape — •Sakshi Pahujani, Yuna Zhang, Markus G. Stetter, and Joachim Krug — University of Cologne, Cologne, Germany

Phenotypic adaptation to long term persistent changes in the environment is typically studied using moving optimum models which consider a fitness landscape traversing the phenotypic space over time. Invoking the strong-selection-weak-mutation regime, we study adaptation as a walk towards the moving fitness optimum described by a continuous-state-discrete-time stochastic process. In this framework, at a critical speed of the optimum, we elucidate a transition, from a regime where the phenotypic gap of the adapting population from the optimum attains a stationary mean value to one where it increases indefinitely. Through a special case of the problem, we provide an alternative description of this transition in terms of a force that drives the adaptive process and a corresponding potential that switches from being confining to non-confining at the critical speed. Further analysis of this case suggests that adaptation is rather successfully carried out, until the population becomes limited by the maximum rate at which it can adapt. Remarkably, despite the simplicity of this special case, its predictions align well with observations from the original, more complex model [1].

[1] Sakshi Pahujani, Yuna Zhang, Markus G. Stetter, Joachim Krug, Adaptive Dynamics of Quantitative Traits in a Steadily Changing Environment, bioRxiv 2025.09.28.679017

BP 21.6 Wed 17:00 HÜL/S386

A simplified Rough Mount Fuji model clarifies how local adaptive walks can reach the highest peaks in rugged fitness landscapes

— •Kye E Hunter[1,2] and Nora Martin[1] — [1]CRG (Barcelona Collaboratorium for Modelling and Predictive Biology) — [2]Facultat de Física, Universitat de Barcelona (UB)

Adaptive evolution selects random genotypic mutations according to their fitness. This can be modeled using a fitness landscape, a network of possible genotypes with a fitness value associated to each sequence. In the simplest models of adaptive evolution, populations move through this network in fitness-increasing steps until reaching a genotype whose fitness exceeds that of all its neighbors—a fitness peak. In evolutionary simulations on their empirical folA landscape, Papkou et al. (Science 2023) found that such fitness-increasing walks are likely to reach the globally-highest-ranked peaks among a large number of peaks, despite only being based on local rules. Similar results were found in a mathematical model of fitness landscapes, the Rough Mount Fuji model (Li & Zhang MBE 2025).

We use a simplified Rough Mount Fuji model to find simple analytical explanations for how a landscape can have both a large number of peaks and populations that reach the highest-ranked peaks. Our explanation proceeds by dividing the landscape into different regions, and considering the number of peaks relative to the total number of genotypes in each region. We then identify the degree to which those same arguments apply in the empirical folA landscape.

BP 21.7 Wed 17:15 HÜL/S386

Mean adaptive basin size for fitness peaks in the House of Cards landscape

— •Daniel Oros and Joachim Krug — Institute for Biological Physics - University of Cologne

Fitness landscapes have been studied extensively in evolutionary theory. In a simple form, the fitness landscape maps the genotype of an organism to its reproductive success, denoted by fitness. While being a drastic simplification of biology, the concept is useful for understanding how evolution navigates such a landscape. When the time between mutations is much larger than the fixation time, one can think of a genetically homogeneous population moving one mutation at a time. The fitness value increases at each step and the population eventually reaches a fitness peak, a genotype having larger fitness than all its single mutant neighbors. The adaptive basin of a peak is composed of all genotypes which have a monotonically increasing fitness path to it.

Large scale fitness landscape measurements show that the basins of high fitness peaks contain a large fraction of all genotypes, a finding that has been argued to be inconsistent with existing fitness landscape models [1]. In House of Cards (HoC) landscapes fitness values are assigned independently at random, resulting in a maximally rugged landscape. Building on previous work on accessibility percolation [2] we show that typical peak adaptive basins in the HoC landscape contain a positive fraction of all genotypes, and derive an explicit expression for the mean basin size.

[1] Papkou A et al. 2023 *Science* **382** eadh3860

[2] Schmiegelt B and Krug J 2023 *J. Math. Biol.* **86** 46