# BP 1: Systems and Network Biophysics

Time: Monday 9:30–12:45 Location: H 0112

**Invited Talk** BP 1.1 Mon 9:30 H 0112

**Co-evolution of RNA viruses and the human immune system** — •Richard Neher — Biozentrum, University of Basel, Switzerland

Human influenza viruses and SARS-CoV-2 rapidly accumulate mutations to evade recognition by the human immune system, which allows these viruses to repeatedly infect individuals. Since circulation of a viral variant generates immunity against that variant, the resulting dynamics has features of rapid adaptive evolution as well as features of ecological interactions. With extensive surveillance of these human viruses, we can now track emerging variants in detail and quantify their competition. We also have more and more data on the diversity of human immune responses and molecular basis of viral immune escape. These data provide an opportunity to understand the co-evolutionary dynamics of humans and their viruses in quantitative terms. I will discuss the relative importance of adaptation and ecological dynamics for viral evolution and how it depends on the immunological diversity of the host population. Lastly, I will discuss implications of host diversity and ecological dynamics on predictability of the evolution of SARS-CoV-2 and influenza virus.

BP 1.2 Mon 10:00 H 0112

**Non-determinism and Boltzmann ensembles in genotype-phenotype maps** — •Nora S. Martin[1], Paula García-Galindo[2], and Sebastian E. Ahnert[2,3] — [1]CRG (Barcelona Collaboratorium for Modelling and Predictive Biology), Barcelona Institute of Science and Technology, Dr. Aiguader 88, Barcelona 08003, Spain — [2]Department of Chemical Engineering and Biotechnology, University of Cambridge, Philippa Fawcett Drive, Cambridge CB3 0AS, UK — [3]The Alan Turing Institute, 96 Euston Road, London NW1 2DB, UK

Over the last decades, analyses of genotype-phenotype (GP) maps have greatly contributed to our quantitative understanding of variation and its role in evolutionary processes. While the GP map of RNA secondary structure is maybe the best-studied example, many concepts have subsequently been applied to a range of further biological systems. However, most analyses neglect one key aspect of RNA folding that is also relevant in other systems: a genotype does not simply fold into a single structure (i.e. phenotype). Instead, its folding is more accurately described as a Boltzmann ensemble, i.e., a distribution of structures. This defines a different type of GP map, referred to as a "non-deterministic" map. In this contribution, I will describe definitions required for characterising these "non-deterministic" maps, and what patterns they reveal.

BP 1.3 Mon 10:15 H 0112

**Unraveling the Influence of Geometry, Binding and Diffusion on Proteins in the Presynaptic Region** — •Simon Dannenberg, Sarah Mohammadinejad, and Stefan Klumpp — Institut für Dynamik komplexer Systeme Georg-August-Universität Göttingen Friedrich-Hund-Platz 1 37077 Göttingen, Germany

The mobility of a protein is a key factor determining its availability for chemical reactions in a cell. It is influenced by many factors including the diffusion coefficient, binding to membranes and the geometry of the environment. In the presynaptic region of neurons, the latter varies widely between different synapses. Combined with the tremendous biological importance of this region it becomes a compelling quest to investigate mobility here. In our work we use simulations to disentangle the interplay of the aforementioned factors. We demonstrate that the binding to synaptic vesicles and the cytoplasmic diffusion of the protein give rise to a specific length scale that determines whether the recovery of protein material is dominated by protein redistribution inside the synapse or via fluxes from the axon. This length scale is comparable to the size of the presynaptic region, which makes the interpretation of common experimental techniques for mobility measurements such as FRAP challenging. However, our simulations enable suggestions to circumvent pitfalls in Experiments.

BP 1.4 Mon 10:30 H 0112

**Elucidating the genetic determinants of antibiotic resistance evolution** — •Gabriela Petrungaro, Theresa Fink, and Tobias Bollenbach — Institute for Biological Physics, University of Cologne, Germany

Biological evolution of bacterial populations under strong antibiotic selection can quickly lead to resistant populations that pose a threat to public health. To understand the evolutionary dynamics that lead to resistance, a thorough statistical characterization of this stochastic process is needed, which requires many repeats of the same experiments under tightly controlled conditions. Here, we report the results of 864 parallel automated evolution experiments with tight feedback control of population size and selection pressure. We investigate how the genetic background of an initially susceptible population constrains its ability to evolve resistance. To this end, we systematically compared 258 Escherichia coli strains that initially differ in single gene-deletions and evolve for two to three weeks under three clinically relevant antibiotics, one at a time. We find that evolution is highly parallel at the phenotypic and genotypic level, but the degree of parallelism varies among antibiotics. The evolutionary paths to resistance can be rationalized as biased random walks on a fitness landscape in genotype space. We find that certain gene deletions drastically alter these evolutionary paths, making new fitness peaks accessible and hampering others. Our results contribute to the understanding of repeatability in the evolution of antibiotic resistance and to the identification of possible targets for strategies to combat resistance.

**15 min. break**

BP 1.5 Mon 11:00 H 0112

**Fluctuation-response relations for integrate-and-fire models with an absolute refractory period** — •Benjamin Lindner[1,2] and Friedrich Puttkammer[1,2] — [1]Institut für Physik, Humboldt-Universität zu Berlin — [2]Bernstein Center for Computational Neuroscience Berlin

For many systems in statistical physics it is known, that their spontaneous fluctuations and their response to a time-dependent perturbation are related via a fluctuation-dissipation theorem. For spike-generating nerve cells (neurons) such relations have been uncovered only recently (Lindner, PRL 2022) but these fluctuation-response relations (FRRs) were limited to a special class of stochastic neuron models, namely, integrate-and-fire (IF) neurons without a refractory period. Here we relax this restriction and derive FRRs for IF neurons with an absolute refractory period and a stereotypical spike shape for the action potential. The derived relations are exact for the case of an uncorrelated (white) intrinsic noise but only approximate if the intrinsic fluctuations are temporally correlated. All results are tested by comparison with stochastic simulations and reveal that even a small but nonvanishing refractory period leads to a significantly modified relation between fluctuation statistics and response statistics.

BP 1.6 Mon 11:15 H 0112

**Nonrenewal spiking in Calcium signaling** — •Lukas Ramlow[1,2,3], Martin Falcke[2,3], and Benjamin Lindner[1,2] — [1]Bernstein Center for Computational Neuroscience, Berlin, Germany — [2]Department of Physics, Humboldt University, Berlin, Germany — [3]Max Delbrück Center for Molecular Medicine, Berlin, Germany

Inositol 1,4,5-trisphosphate-induced $Ca^{2+}$ signaling is a second messenger system used by almost all eukaryotic cells. The agonist concentration that stimulates $Ca^{2+}$ signaling is encoded in the sequence of $Ca^{2+}$ concentration spikes. In response to the onset of stimulation, the times between spikes, the interspike intervals (ISIs), exhibit a distinct transient during which they gradually increase. In the steady state, this slow adaptation correlates the intervals and spiking is a nonrenewal process. We propose a stochastic model that can reproduce both stationary and transient statistics of experimentally observed ISI sequences. We derive approximate analytical expressions for the stationary ISI statistics and consider the response to the onset of a constant stimulus to estimate the length of the transient and the strength of the adaptation of the ISI. We show that the adaptation determines the coefficient of variation, in agreement with current ideas derived from experiments. Finally, we fit our model to reproduce the transient statistics of experimentally observed ISI sequences in stimulated HEK cells. The fitted model is able to qualitatively reproduce the relationship between stationary interval correlations and transient interval statistics.

BP 1.7 Mon 11:30 H 0112

**Analysing biological systems via maximally informative representations** — •Roberto Menichetti[1,2], Riccardo Aldrigo[1], and Raffaello Potestio[1,2] — [1]Physics Department, University of Trento, Trento, Italy — [2]INFN-TIFPA - Trento Institute for Fundamental Physics and Applications, Trento, Italy

The main challenge of an in silico investigation of biological systems is nowadays shifting from the generation of data to the problem of developing techniques enabling their rational interpretation. Often, the noise/signal discrimination passes through dimensionality reduction strategies; while such coarsening is necessary to interpret high-dimensional simulation datasets, it inevitably results in a loss of information on the system that critically depends on the choice of the low-dimensional projection [1]. We here discuss a recent workflow aimed at identifying simplified representations of a system that retain the largest amount of information on its statistical properties while reducing the observational level of detail [1,2]. The protocol is applied to proteins and memory-retrieving neural networks; in both cases, the resulting representations are shown to single out biologically relevant regions of the system, either in the form of functional chemical fragments in the analysed proteins or of strongly coupled neurons in the network. Our results suggest that this scheme can be employed to extract insight from large simulation datasets, further shedding light on the relation between dimensionality reduction and information loss. [1] Giulini M. et al., Front. Mol. Biosci. 8, 676976 (2021). [2] Giulini M. et al., J. Chem. Theory Comput. 16, 6795 (2020).

**15 min. break**

BP 1.8 Mon 12:00 H 0112

**The beginning of olfactory signal transduction: A theoretical model on the synergist-agonist threshold of G-protein-coupled receptors** — •Won Kyu Kim — Korea Institute for Advanced Study, Seoul 02455, South Korea

We present a chemical reaction network theory for olfactory sensing processes of G-protein-coupled receptors (GPCRs) as olfactory receptors (ORs). The theory is applicable to mixtures of odorants and any number of ORs. It explicitly considers reactions of ORs with G-proteins, with and without odorants. The theory introduces an odor activity vector, representing strengths of odorant-induced signals from ORs relative to those from background G-protein activity. Each vector component follows a Michaelis-Menten form, accounting for cooperation or competition effects between different odorants. The theory's main features are illustrated for a two-odorant mixture, quantitatively describing known and potential mixture effects, such as suppression, shadowing, inhibition, and synergy. The effects of rate constants, basal activity, and G-protein concentration are also demonstrated.

BP 1.9 Mon 12:15 H 0112

**A stochastic conductance-based model of the hawkmoth Manduca sexta olfactory receptor neuron** — •Mauro Ariel Forlino, Aditi Vijayan, Katrin Schröder, Anna Schneider, Monika Stengl, and Martín García — Kassel University, Kassel, Germany

The long trichoid sensillum in male hawkmoths, Manduca sexta, is innervated by two olfactory receptor neurons (ORNs) that respond to the pheromone released by female moths to attract conspecific mates. In the absence of odor stimuli, pheromone-sensitive ORNs in hawkmoths exhibit non-randomly distributed spontaneous spikes. Analyzing spike distribution is crucial for identifying different mechanisms at play. The random opening and closing of ion channels introduce internal fluctuations in neurons, known as channel noise, which contributes to the variability in spike distribution and determines whether a single spike or a burst occurs. Furthermore, insect ORNs serve as endogenous peripheral circadian clock neurons, leading to the expression of daytime-dependent rhythmic spike distributions. In this study, we present a novel conductance-based model that incorporates the olfactory receptor coreceptor (ORCO) as a pacemaker ion channel with linear conductance dependent on cAMP concentration. Our model takes into account that cAMP express daytime-dependent rhythms with concentration being maximal during activity phase. By utilizing stochastic differential equations based on the microscopic Markovian states of ion channels, our model can reproduce the observed spike distribution with its circadian oscillations.

BP 1.10 Mon 12:30 H 0112

**Inference of dynamical networks in biology with recurrent neural networks** — •Pablo Rojas[1], Marie Kempkes[1], Claudia Arbeitman[1,2], and Martin Garcia[1] — [1]Theoretical Physics, University of Kassel, Kassel, Germany — [2]CONICET, Argentina

The inference of networks in dynamical systems is crucial to the mechanistic understanding of complex systems. Biological systems often rely on the emergent behaviour resulting from the interaction of multiple units. Inferring the existence of links between nodes of a network from measured time series is an inverse problem that becomes more complex under the presence of non-equilibrium, strong nonlinearity, noise, delays and large number of interacting nodes - frequent conditions in experimental time series. In this work, we present a method that uses recurrent neural networks to learn the underlying connections in a dynamical system from its multivariate time series. A key aspect of the method is that it does not assume a mathematical model, i.e. equations, defining the dynamics of the network. Thus, the method is model-free, which makes it applicable to a broader range of systems. We apply this method to a range of biological systems under far-from-ideal conditions to evaluate its performance. We sketch a comparison against other neural network architectures to showcase its advantages.