**Steffen Schaper**, University of Oxford, Oxford, UK
Ard A. Louis, University of Oxford, Oxford, UK

## Predicting and preventing evolution from the knowledge of neutral spaces

In recent years, our understanding of molecular processes in medicine has exploded. One of the promises of this advance is the ability to tailor compounds for the treatment of specific pathogens. On the other hand, many drugs eventually stop being effective when pathogens evolve resistance. In this talk, we give a description of the evolutionary race to resistance, focusing on the importance of molecular details through the genotype-phenotype (GP) map. This map determines how the outcome of mutations at the genotype level induces phenotypic variation and thus triggers natural selection.

Often, single mutations do not change the phenotype but instead connect genotypes with the same phenotype to form a neutral space. These neutral spaces can be vast even for very small molecular systems; reasonably large molecules will most likely have neutral spaces that are much bigger than most reasonable populations. The discovery of an advantageous phenotype (the 'target') is then a search problem in a vast space (the 'source'). We characterize this search in terms of the frequency of the target in the mutational neighborhood of the source space. We study a simple model ignoring correlations between genotypes and find that the difficulty of the search problem is simply related to the inverse of this frequency.

Under low mutation rates, genetic drift leads to a localization of the population in genotype space. Thus exploration is limited to the immediate neighborhood of the population, and transitions between neighborhoods only occur when a neutral mutant goes to fixation. Between two fixations, large enough populations will thus repeatedly produce the currently accessible phenotypes. Intuitively such bursts increase the probability of that an advantageous mutant is fixed once it is discovered. Consequently, we probably cannot prevent the evolution of drug resistance when adaptive phenotypes are readily available. Instead we should aim to prevent the discovery of the target.

The effect of bursts is even stronger in realistic GP maps, which show strong correlations between similar genotypes. As an example, we study the folding of RNA sequences into secondary structures where the biophysical details are relatively well understood. We show how Watson-Crick base-pairing causes the fragmentation of neutral spaces into disjoint components. Furthermore, we find that the components can have intricate internal structure, and that connections to alternative phenotypes are not homogeneously distributed. While averages of the evolutionary process are still described reasonably well by our theory, fluctuations become more important in the presence of genotype correlations. In particular, both the size and temporal separation between bursts can increase.

All these findings underline the central role of the GP map for evolutionary dynamics. They also suggest how the course of evolution may be influenced. We discuss one possible approach to prevent, or at least delay, the evolution of resistance to drugs. When adaptive mutants are not immediately accessible, we can delay their discovery by a drug that removes genotypes on the path to discovery from the neutral space. This result suggests that drugs should be designed not only to be effective against the pathogens in their current state, but that evolutionary pathways can and should be taken into account.