Antibiotic Resistance: Adaptive Evolution & Dissemination of Resistance Genes

Bacteria can avoid extinction during antimicrobial exposure by becoming resistant. They achieve this either via adaptive mutations or horizontally acquired resistance genes. If resistance emerges in clinical relevant species, it can lead to treatment failure and ultimately result in increasing morbidity and mortality as well as an increase in the cost of treatment. Understanding how bacteria respond to antibiotic exposure gives the foundations for a rational approach to counteract antimicrobial resistance.

In the work presented in this thesis, I explore the two fundamental sources of antimicrobial resistance: (1) adaptive mutations and (2) horizontal acquisition of resistance genes from antibiotic gene reservoirs. By studying the geno- and phenotypic changes of E. coli in response to single and drug-pair exposures, I uncover the evolutionary trajectories leading to adaptive resistance. I find, in contrast to a general assumption of independent responses, that there is a high degree of interactions between the evolutionary responses to the individual drugs, which is manifested in collateral changes in drug susceptibility. Specifically, I show that collateral sensitivity can be exploited to rationally design drug combinations that limit the evolution of antibiotic resistance due to counteracting evolutionary trajectories. My results highlight that an in-depth knowledge about the genetic responses to the individual antimicrobial compounds enables the prediction of responses to drug combinations.

In the second study I focus on horizontal gene transfer as a way of achieving resistance. More specifically, I focus on gene acquisition from environmental reservoirs. The study investigates the resistance gene reservoirs in several wastewater treatment plants (WWTPs) sampled over a two years period. I find, that although the resistance gene reservoir is highly shared across different WWTPs, there is only a small overlap with resistance genes from other environments. This finding suggests, that there is a dissemination barrier preventing the spread of functional resistance genes across environmental niches.