

On May 15, 2013, PED Seminar Series Presents

"Optimal" fitness landscapes and evolvability in antibiotic resistance

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The evolution of antibiotic resistance is a complex problem in which human behavior and microecology combine to select for the molecular mechanisms conferring resistance. Although these resistance mechanisms have been well characterized in vitro, their contributions to microbial fitness in situ are often unknown in quantitative terms. I'll discuss how the multi-scale synthesis of molecular details into a quantitative fitness landscape has revealed optimal evolutionary strategies for bacteria facing drug treatment. The fitness landscape is the result of an experimentally validated mathematical model that predicts the growth rates of bacterial strains carrying arbitrary degrees of resistance, exposed to arbitrary drug concentrations. The model contains only a few parameters (e.g. binding constants of known values), and thus provides a general fitness landscape for antibiotic resistance without ad hoc fitting parameters. I'll talk briefly about the model and how biochemical details determine certain universal features of the fitness landscape, such as its saddle-node bifurcation and overall shape. The shape of this landscape conforms to one of two simple geometries, each predicted to afford profoundly different adaptation rates for bacteria in a drug-treatment microhabitat. I will present computational and theoretical results demonstrating the effects of geometry on adaptation rate, and I'll identify geometric characteristics of an "optimal" fitness landscape in general (even independent of the model described above), touching on an unexpected role for fitness in evolvability. Then using the antibiotic resistance model, I'll show the simple biochemical criteria required for maximizing or minimizing adaptation rate--and I'll discuss ways to use this knowledge to minimize evolvability of drug resistance during treatment. Time permitting, I'll discuss implications for the evolution of evolvability.