

BIOENGINEERING SEMINAR

at 4:00 PM on May 30th, 2014 (Friday)

MRDG Seminar Hall, 1st Floor, Biological Sciences Building

Exploring the HIV fitness landscape

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The development of a quantitative understanding of the evolution of drug resistance in HIV-1 is a formidable challenge given the large number of available drugs and drug resistance mutations. I will first talk about recent work based on the analysis of a large dataset measuring the in vitro fitness of ~70,000 virus samples isolated from HIV-1 subtype B infected individuals undergoing routine drug resistance testing. In vitro replicative capacity of the virus samples was measured in the absence of drugs as well as in the presence of 15 individual drugs. Using a machine learning algorithm we estimated main fitness effects and epistatic interactions of ~1,900 single amino acid variants found within the HIV-1 protease and reverse transcriptase sequences. Models including epistatic interactions predict an average of 54.8% of the variance in replicative capacity across the 16 different environments and substantially outperform models based on main fitness effects only. This argues that replicative fitness of HIV-1 is characterized by strong epistasis among mutations in protease and reverse transcriptase.

In the second part of the talk I will use the predictive model of in-vitro replicative fitness of HIV-1 to explore general properties of the resulting fitness landscape. The concept of fitness landscapes is central to evolutionary theory, but suffers from the lack of explicit examples for large-scale biologically realistic fitness landscapes. We find that the HIV-1 fitness landscape is characterized by a large correlation length, considerable neutrality and high ruggedness. While the relative extent to which mutations affect fitness on their own (main effects) or in combination (epistasis) strongly affects these properties, the landscape is considerably less rugged, less neutral, and more correlated than expected from the distribution of main effects and epistasis. Overall this study demonstrates both the complexity and unpredictability of adaptation on such landscapes as well as the importance of the high dimensionality of the genetic space in which adaptation takes place.

About the speaker:

Sebastian Bonhoeffer is full professor at the ETH Zurich. Being originally trained as a physicist he did his PhD with Martin Nowak and Robert May at the University of Oxford. His research interest span broadly across the evolution and population biology of infectious diseases. He is Deputy Editor in Chief of the PLoS Computational Biology, serves as a member of the Research Council of the Swiss National Science Foundation and has recently been elected to the European Molecular Biology Organization.