Estimating HIV evolutionary pathways and the genetic barrier to drug resistance

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Drug resistance presents a major obstacle to successful treatment of HIV infected patients. HIV's high mutation rate and turn-over facilitate the development of drug resistant mutants in response to antiretroviral therapy. The fixation of resistance mutations in the virus population results in therapy failure and limits future treatment options. Hence, understanding this evolutionary process is important for the design of effective treatment strategies. The development of drug resistance is characterized by the accumulation of amino acid changes in those parts of the viral genome that are under selective drug pressure. These drug resistance mutations tend to occur in preferred evolutionary pathways. We present statistical and computational methods for modeling the development of drug resistance in HIV and for the design of effective antiretroviral drug combinations.
Mutagenetic trees, a family of probabilistic graphical models, are applied to describe the evolution of drug resistance. The basic building block of these models is a tree, which encodes certain constraints on the order in which mutations can occur. Two major extensions of the single tree model are presented. First, we introduce a mixture model of trees that allows for modeling more involved evolutionary scenarios as they often occur in nature. Second, we present a mutagenetic tree hidden Markov model which is designed to model longitudinal and clonal samples from the virus population, rather than one sequence per patient and time point. While the single tree can be learned from data by an efficient combinatorial algorithm that solves the maximum weight branching problem, we devise Expectation Maximization algorithms for both extended models. We apply our methods to sequence data from clinical trials involving different inhibitors of the HIV reverse transcriptase enzyme.
The genetic barrier quantifies the difficulty for the virus to escape from the selective pressure of a drug by developing escape mutations. Based on the mutagenetic tree models, we define the genetic barrier as the probability of viral escape, and we show how to estimate this quantity from observed data. The predictive power of the genetic barrier for therapy outcome is analyzed on clinical trials data and on large sets of observational cohort data. We find that the evolutionary potential of the virus population, as encoded by the genetic barrier, is an independent prognostic marker of treatment failure. We discuss and evaluate different methods for selecting optimal drug combinations based on this evolutionary information.
In conclusion, we develop evolutionary models for the development of drug resistance in HIV and use the model predictions for optimizing individual drug combinations. Thus, we support the design of personalized therapies.

References

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