Evolutionary Dynamics for HIV Vaccine Design

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Vaccination saves countless lives and has eradicated multiple diseases. However, to date, no effective vaccine exists against HIV, which continues to devastate many parts of the world. This is partly because the virus's high mutability and replication rate enable it to evade immune recognition, thus complicating traditional empirical approaches to vaccine design. HIV protein sequences are constrained by the "fitness landscape" – that is, the fitness of the virus as a function of its sequence, with explicit account of epistatic interactions between mutations – which past work has elucidated and validated. This dissertation describes my work exploiting knowledge of this landscape to design a T cell-based vaccine that is currently undergoing pre-clinical animal studies. To do this, I present two simple algorithms and several simulation tools designed to quantify the effect of vaccine-directed immune pressure on in vivo viral evolution. The importance of dynamics are further explored in an examination of clinical trial data on cross-reactive monoclonal antibodies administered as a therapeutic for HIV. With experimental collaborators, we uncovered a mechanism through which these antibodies enhance the clearance rate of infected cells. Finally, although such antibodies show great promise as a therapeutic, they remain difficult to obtain through vaccination. Therefore, motivated by recent studies that tested alternatives to the traditional prime-boost method using single antigen variants, I present a theoretical framework for optimizing time-dependent vaccination protocols to elicit cross-reactive antibodies. By combining immunology, statistical physics, stochastic dynamics, and computational modeling, this thesis research provides avenues to enable rational design of vaccines against complex evolving pathogens.

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