**Computational Game Theory for Antibody Design**

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Computational methods are becoming increasingly important in the design of drugs and vaccines.  However, the design of vaccines against chronic or seasonal infections, such as HIV and influenza, presents a major challenge because of evolutionary adaptation of the pathogen to the immune response.  An important first step in the design of vaccines is protein-level design of antibodies, with the goal of identifying antibodies which exhibit good neutralization properties against specific targets.

To date, the major way to consider such evolutionary response in antibody design is to develop polyspecific antibodies, that is, antibodies which can be shown to neutralize a collection of known viral variants. Moreover, a common approach to design is to use computational protein modeling tools, such as Rosetta, in combination with stochastic optimization, such as simulated annealing. Two major challenges that arise are (a) the computational burden associated with evaluating binding (as a proxy for neutralization), and (b) the limited evaluation of evolutionary viral response from a fixed panel of viral variants. An additional challenge is that current multistate design techniques typically become difficult to apply when the panel of possible targets is relatively large.

We propose using a combination of machine learning, integer linear programming, and computational game theory, to address these problems. First, we are able to significantly extend effectiveness of multistate design by learning a proxy model of antibody-virus interaction which is then used in a mixed-integer linear program to compute an optimal antibody in terms of binding breadth to a fixed panel of viruses. We show that the resulting method is able to design antibodies which are stable and broadly binding.

To consider the issue of evolutionary viral escape, we model the pathogen-immunity interaction using game theory. Specifically, we consider the antibody design within a Stackelberg game framework, in which the pathogen (e.g., HIV) responds to the antibody by mutating to escape it.  We developed a number of computational approaches both to predict viral response to immunity, as well as to antibody design based on this model, and show that preliminary computational evidence suggests that this approach is very promising in developing novel antibodies which have neutralization breadth beyond that for known broadly neutralizing antibodies that have previously been experimentally analyzed.