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IN SILICO VACCINE DESIGN THROUGH EMPIRICAL FITNESS LANDSCAPES AND POPULATION DYNAMICS

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EXECUTIVE SUMMARY

The hepatitis C virus (HCV) affects 170 million people worldwide, and kills 700,000 annually. Vaccination provides the most realistic and cost-effective hope of controlling this epidemic, but no vaccine is available. Computational models can offer rational precepts to inform and accelerate vaccine design. We have developed a computational tool to translate databases of viral sequences into "fitness landscapes," mapping the replicative capacity of the virus as a function of its genome. These landscapes represent the mutational playing field over which the virus evolves. By integrating these landscapes with agent-based models of viral mutation and host immune response, we have explicitly modeled the host–pathogen dynamics over its empirically defined fitness landscape. (Agent-based models simulate the actions and interactions of autonomous agents to assess their effects on the system as a whole.) Using this simulator, we have employed the hardware resources of Blue Waters to perform computational screening of candidate vaccine components to identify those best able to cripple viral fitness and block immune escape. These findings can inform next-generation HCV vaccine design.

RESEARCH CHALLENGE

HCV continues to pose a global threat to public health. Despite the availability of efficacious drug treatments in the developed world, the high cost of these therapies make them effectively unavailable in the developing world where the preponderance of infections occur. A prophylactic vaccine represents the most cost-effective and realistic strategy to combat the epidemic, but despite 25 years of research, a vaccine is still not available. A challenge in vaccine design is the identification of promising targets within the virus that can be targeted by a vaccine that simultaneously cripple viral fitness and are not subject to facile mutational escape, whereby a microorganism defends itself from host immune responses by making mutations in its genotype and phenotype. Computational models of viral infection and the host immune response can systematically identify promising targets that may be translated into rational precepts for experimental development and testing of HCV vaccines.

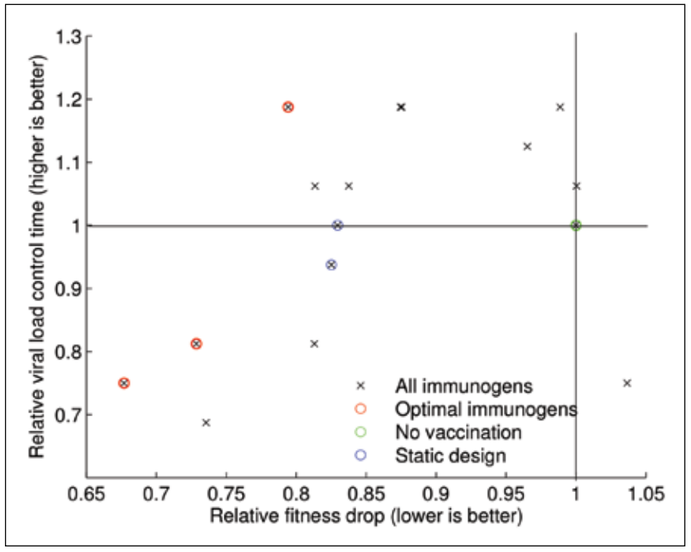

Figure 1: The black crosses characterize the immune response of the inoculated host relative to no vaccination (green circle). Red circles indicate the Pareto optimal vaccine candidates. Blue circles indicate previously identified vaccine candidate. Candidates in the upper-left quadrant provide superior strength and length of control relative to no vaccination.

METHODS & CODES

The simulations of the viral mutational evolution over our viral fitness landscapes is implemented via an agent-based model comprising 50,000 distinct viral sequences. The host immune response is described by a set of ordinary differential equations modeling the dynamics of the host T-cells as they recognize the virus, activate, mature, proliferate, and die. The coupling to the viral dynamics occurs through a term imposing a penalty on the fitness of viral strains that are recognized and attacked by particular members of the T-cell population, and through a recognition term in which T-cells that recognize particular viral strains are primed to activate and proliferate. The relatively small T-cell populations within our control volume mean that fluctuations are important, and we implement a stochastic integration protocol via Gillespie dynamics to explicitly capture these effects.

RESULTS & IMPACT

We considered two representative hosts in detail and used our simulator to predict the efficacy of the ensemble of all possible vaccine candidates consistent with the immunological genotypes of the hosts. In each case, we identified a number of promising vaccine candidates that led to strong and durable responses by priming T-cells that imposed strong fitness penalties upon the viral population for long periods of time. Interestingly, we also found vaccine candidates that led to poorer immune responses compared to no vaccination by priming the "wrong" T-cell responses to attack regions of the virus from which mutational escape is facile. These results lay the foundation for large-scale simulations of vaccine candidates for all representative hosts in the North American population for the particular protein considered, and for extending this work to 10 HCV proteins.

WHY BLUE WATERS

The scale and parallelism available within Blue Waters support the computational intensity of each single simulation and also enable the range of simulations to evaluate large numbers of vaccine candidates in a variety of hosts. Furthermore, the volume of data generated is also significant as the viral sequences present at each time point must be written to disc.

PUBLICATIONS & DATA SETS

Hart, G.R., and A.L. Ferguson, Computational design of hepatitis C virus immunogens from host-pathogen dynamics over empirical viral fitness landscapes. To be submitted (2018).