A115 · Customizing protein evolution with Fitness Landscape Design (FLD)

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Evolutionary adaptation is often visualized as a population's stochastic climb toward the top of a fitness landscape. While there exist approaches to design or synthetically evolve proteins into desired structures, there is a lack of methodology for quantitatively designing or tuning the fitness landscapes themselves on which protein evolution takes place. Here, we introduce computational protocols for fitness landscape design (FLD) to customize the structural peaks and valleys of fitness landscapes with quantitative accuracy, offering robust control of long-term evolutionary outcomes. Given a user-defined target fitness landscape, our FLD algorithms use stochastic optimization of an in vitro-, in silico-, and epidemiologically validated biophysical fitness model to consistently discover optimal antibody ensembles which force the target protein to evolve according to the predefined fitness penalties. We derive tight theoretical bounds on FLD, which we then validate using a recently published experimental dataset of binding affinities between over 62,000 antibody variants and each of three glycoprotein antigens. Using two classes of FLD algorithms, demonstrate applications to 1) suppression the fitnesses of two SARS-CoV-2 genotype neutral networks and 2) discovery of proactive vaccines that preemptively restrict escape variant fitness trajectories before they arise. Our results suggest the feasibility of engineering quantitatively programmable fitness landscapes for laboratory protein evolution experiments. More broadly, by thinking several steps ahead of pathogen evolution, FLD opens the door to proactive vaccine, antibody, and peptide design, offering potential solutions to immune evasion of pathogens and cancers as well as improved biosecurity and pandemic preparedness.

Customizing protein evolution with Fitness Landscape Design (FLD)

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Evolving populations stochastically climb toward the top of fitness landscapes like physical particles funneling toward the bottom of an energy landscape. Directed evolution and other laboratory evolution methods have allowed local optimization on fitness landscapes to improve the structure or function of proteins. However, while directed evolution (and *de novo* protein design) methods have enabled the design of specific proteins, there is still a lack of methodology to tune and control protein *evolution itself*. Here, we introduce computational protocols to enable **fitness landscape design (FLD)**[1,2]: namely, the problem of customizing the structural peaks and valleys of fitness landscapes with quantitative accuracy, offering robust control of long-term evolutionary outcomes. As applications, we tackle the problem of viral escape, developing algorithms which can identify antibodies that proactively block of viral escape mutations before they can even emerge.

Viruses constantly face pressure from human adaptive immunity to mutate, allowing escape mutants to emerge which cause increased infections and deaths. Even if vaccination efforts are rapid—like the development of the first SARS-CoV-2 mRNA vaccine—by the time vaccines are adequately and widely deployed, viral escape mutations typically will have already emerged, seeding yet another wave of infections. Numerous investigations report methods predict fitness from biophysical interaction or evolutionary time series data; here, we distinguish FLD as the *inverse problem*, where those evolutionary outcomes are modifiable based on target fitness landscapes which are specifically designed for anti-viral defense (**Fig. 1A**). Our FLD algorithms use a statistical physics-based fitness oracle—validated on *in vitro,* epidemiological, and *in silico* data[1]—to discover antibodies that transform a viral surface protein's biophysical fitness landscape into an "evolutionary trap" which blocks dangerous mutations (**Fig. 1B**). By modifying antibody residues which contact the viral surface protein (**Fig. 1C**)**,** we develop physics-based stochastic optimization algorithms (**Fig. 1D**) which discover antibodies that can achieve a desired target landscape.

We derive tight theoretical bounds on FLD, which we then validate using a recently published experimental dataset of binding affinities between over 62,000 antibody variants and each of three glycoprotein antigens[2]. Subsequently, demonstrate the applicability of our FLD optimization algorithm to suppression the fitnesses of two SARS-CoV-2 genotype neutral networks, showing that we can turn a dangerous SARS-CoV-2 mutation into a deleterious mutation which would have been unfavorable for viral evolution had the appropriate antibodies been deployed prior to its appearance[1]. In a second application, we tackle the problem of vaccine design: as an alternative to standard vaccine design protocols which target a viral strain as it emerges (**Fig. 1E**), we propose an iterative FLD algorithm (**Fig. 1F**), which—like a chess bot—uses the experimentally validated physics-based fitness oracle to iteratively calculate multiple steps ahead of viral escape, discovering the optimal antibody and target antigen that would suppress viral peak fitness even if escape takes place[1]. FLD-designed antibodies impose a lower fitness ceiling on viral escape compared to standard vaccine antibodies (**Fig. 1G**)[1].

By thinking several steps ahead of pathogen evolution, FLD enables new strategies for proactive vaccine, antibody, and peptide design, offering potential solutions to immune evasion of pathogens and cancers and improved biosecurity and pandemic preparedness[1,2].

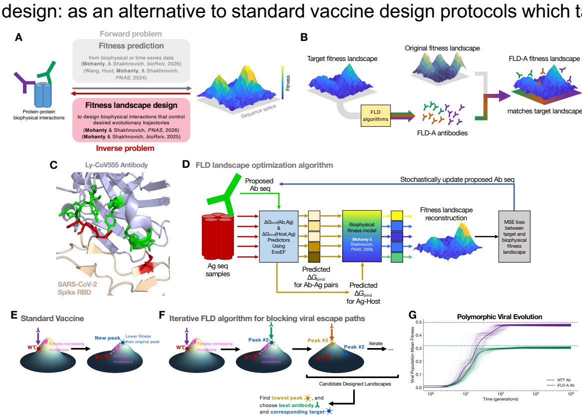

Figure 1. *Overview of Fitness Landscape Design (FLD) and applications to proactive suppression of viral escape mutations.*

References

[1] Mohanty & Shakhnovich, Biophysical fitness landscape design traps viral evolution. *PNAS*, 2026.

[2] Mohanty & Shakhnovich, Phase diagrams for biophysical fitness landscape design. *bioRxiv*, 2025.