Biological Design Dissertation Defense

Predictive Modeling of Nucleic Acids: From Sequence to Structure

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Abstract

The transition of nucleic acid nanotechnology from trial-and-error experimentation to predictive engineering requires the rigorous integration of computational modeling. In this work, we demonstrate how physics-based simulations and generative machine learning converge to enable the rational design of therapeutically active and proof-of principle nucleic acid structures. We begin by establishing the mechanical determinants of DNA origami function using the oxDNA coarse-grained molecular dynamics model. By implementing novel enhanced sampling techniques, we characterize the ”Hairygami” effect, revealing how the entropic forces of surface functionalization induce global conformational changes. These mechanical insights are then applied to the design of ”CytoDirect,” a shape-changing chemotherapy delivery platform, and a trivalent ”nanosynbody” capable of neutralizing SARS-CoV-2 by geometrically matching the viral spike protein. Extending beyond DNA, we further develop automated design pipelines for translationally active ssRNA origami, bridging the gap between structural nanotechnology and mRNA therapeutics. To address the challenge of scaling to higher order architectures, we introduce ”Polycubes,” an inverse design framework that utilizes SAT solvers to program the self-assembly of finite and crystal geometries, validated through rigorous thermodynamic characterization of dimerization energies. Finally, complementing these physical approaches, we explore the generative frontier of bioengineering. We demonstrate that machine learning models—ranging from Direct Coupling Analysis for cyclic peptides to the fine-tuning of genomic Large Language Models for aptamers—can efficiently navigate vast sequence spaces to discover high affinity binders. Collectively, these methods and experimental realizations provide a roadmap for the in-silico optimization of next-generation nanomedicines.

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