Design of Single-Chain Polymer Nanoparticles to Mimic Globular Proteins

Tianyi Jin (he/him)

While globular proteins exhibit an impressive range of precise functionalities, their sensitivity to environmental changes has motivated scientists to pursue two complementary strategies: (1) engineering and designing proteins directly or indirectly, and (2) exploring synthetic alternatives with higher stability. Single-chain polymer nanoparticles (SCNPs) based on random heteropolymers (RHPs) have emerged as a promising platform serving both as protein stabilizers and mimetics. However, theoretical understanding of the origins underlying their functional versatility has not kept pace with experimental advances. Unlike globular proteins, which rely on well-defined sequences and three-dimensional structures, RHPs achieve their functions through ensembles of sequences and structures.

In this thesis, I use multiscale molecular simulation techniques to uncover the molecular origins of the versatile, protein-mimetic functions of RHPs. This work is motivated by recent experimental findings showing that four-monomer methacrylate-based (MMA-based) RHPs can function as catalysts, proton channels, and chaperonins. By comparing the behavior of MMA-based RHPs with that of globular proteins, I provide fundamental physicochemical insights and design principles for SCNPs as protein mimetics and stabilizers. I highlight the significance of chemical polarity and nuances in materials design.

In Part I, I study the self-assembly and dynamics of MMA-based RHPs in both melt and solution. I show that MMA-based RHPs collapse into compact globular structures characterized by dynamical heterogeneity and slow dynamics due to a glassy backbone. Properties such as compactness, monomer hydration, and potential to stabilize membrane protein are largely insensitive to sequence but strongly depend on composition. At the core of their behavior lies a phenomenon known as hydration frustration, where polar groups become dehydrated while hydrophobic groups remain hydrated, a key feature also observed in globular proteins. In MMA-based RHPs, hydration frustration originates from a negative Flory–Huggins interaction parameter (χ) between methyl methacrylate and polyethylene glycol. Guided by these insights, I design a biodegradable, polyester-based RHP that exhibits similar properties *in silico*. I further map the potential energy landscape of these RHPs through microsecond-scale simulations.

In Part II, I study the adsorption and stabilization behaviors of MMA-based RHPs on both synthetic and biological surfaces. I show that adsorption onto graphene and non-specific binding to β-barrel membrane proteins are primarily mediated by side-chain interactions, with limited backbone reconfiguration. The transition from a globular to a wrapped morphology is hindered by internal friction arising from deformation of the glassy backbone. I demonstrate that population-based stabilization of β-barrel proteins is achieved through loop-specific contacts that reduce fluctuations in flexible regions.

The findings of this thesis provide a comprehensive framework for understanding and designing synthetic protein mimetics and stabilizers. MMA-based RHPs present a promising alternative to natural proteins, offering greater resilience, improved cost-effectiveness, and enhanced scalability. The structural and functional parallels between RHPs and globular proteins suggest that the principles uncovered here may extend to a broad class of biomimetic and bio-synthetic hybrid systems. This thesis lays the foundation for the rational design of SCNPs for emerging applications.

Thesis Supervisor: Alfredo Alexander-Katz
Title: Michael (1949) and Sonja Koerner Professor of Materials Science and Engineering

Thesis Supervisor: Connor W. Coley
Title: Class of 1957 Career Development Professor; Associate Professor of Chemical Engineering, Electrical Engineering and Computer Science