Enhancing self-assembly with time-dependent protocols and liquid-liquid phase separation

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1. Abstract

The self-limited assembly of protein subunits into finite-sized structures with well-defined architectures underlies essential functions of cells and the pathogens that infect them. Recently, advances in DNA origami and protein design have enabled engineering synthetic subunits that are programmed for self-limited assembly, with atomic-scale precision rivaling that of natural proteins. Yet, achievable sizes of assembled structures fall far short of nature, because self-limited assembly is highly susceptible to kinetic traps that reduce target yields and constrain assembly rates. In this talk I will discuss (time permitting) two approaches to significantly increase target yields and robustness to variation in control parameters.

The first develops nonequilibrium assembly protocols in which system parameters change over time to avoid kinetic traps. To make finding optimal protocols computationally tractable, we develop a framework to use Markov State Model (MSM) analysis to construct an optimal time-dependent protocol that maximizes yield of the target structure at a finite time. MSMs are a powerful tool for coarse-graining the dynamics of complex molecular systems into a reduced-order representation that is tractable to analysis. We show that MSMs enable simulating self-assembly reactions on timescales that are orders of magnitude longer than those accessible to straightforward simulations. Then, by constructing an MSM for a system as a function of its control parameters, an adjoint-based gradient descent method can be used to efficiently optimize the assembly protocol. We show that the resulting protocols can increase yields and rates by orders of magnitude compared to equilibrium assembly protocols.

The second approach exploits a prominent form of spatial control in cells – liquid-liquid phase separation. Using a simulation model, we show that coupling between self-assembly and liquid-liquid phase separation can dramatically accelerate assembly and enhance robustness against parameter variations.