

MIT Chemical Engineering Department

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Analysis and Engineering of Multivalent Biomolecular Interactions



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ABSTRACT: Multivalency represents a powerful tool in nature's toolbox, providing a general strategy for enhancing affinity and specificity of biomolecular interactions relative to monovalent counterparts. However, these emergent **biochemical** properties and their mechanistic underpinnings have proven difficult to determine as a function of the biophysical properties of the multivalent binding partners. In this talk, I will describe the approaches that our lab has developed to understand and engineer multivalent biomolecular interactions. First, I will show how a structurally-informed mechanistic model can accurately predict the binding kinetics and equilibria of protein-protein interactions as a function of the kinetics of monomer-monomer binding, the properties of the linkers connecting monomer subunits, and the valency of each interacting partner. Given the combinatorial complexity of multivalent interactions and the correspondingly large number of species that can comprise the binding ensemble, the model provides insights into the molecular microstates that drive noncanonical binding dynamics observed in these systems and elucidates strategies to modulate these dynamics. Applications of this model to guide therapeutic design and engineer novel protein-protein interactions will also be discussed. In a second vignette, I will demonstrate how, without detailed structural information, directed evolution can be used to identify key DNA binding determinants of a multivalent recombinase. Furthermore, using data-driven modeling, we can rationally design DNA sequences with predictable recombinase activity for genome engineering and synthetic biology applications.