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The three-dimensional structures of proteins often show a modular architecture comprised of discrete structural regions or domains. Cooperative communications between these regions is important to catalysis, regulation and efficient folding; lack of coupling has been implicated in the formation of fibrils and other misfiling pathologies. How different structural regions of a protein communicate and contribute to a protein’s overall energetics and folding, however, is still poorly understood. Here, we use a single-molecule optical tweezers approach to induce the selective unfolding of particular regions of T4 lysozyme and monitor the effect of other regions not directly acted on by force. We investigate how the topological organization of a proven (the order of structural elements along the sequence) affects the coupling and folding cooperatively between its domains. To probe the status of the regions not directly subjected to force, we determine the free energy changes during mechanical unfolding using Crooks’ fluctuation theorem. We pull on topological variants (circular per mutants) and find that the topological organization of the polypeptide chain critically determine the folding cooperativity between domains and thus what parts of the folding/unfolding landscape are explored. We speculate that proteins may have evolved to select certain topologies that increase coupling between regions to avoid areas of the landscape that lead to kinetic trapping and misfolding.

You’re invited to a reception for Professor Bustamante after his seminar, Kate & Michael Bárány Conference Room (117/119 Smith Hall).