Structural entanglements in proteins and their complexes

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There is an abundance of topological features associated with proteins and their complexes. In multi-chain protein complexes, there is a possibility that two chains are natively entangled so that when one pulls at both termini of each chain simultaneously then the chains lock together and cannot be separated. In fact, we have identified about 900 entangled systems in a subset of the Protein Data Bank - the databank that stores experimentally determined protein structures. The individual protein chains themselves may have non-trivial topologies. In particular, there are proteins that have a knot, typically with three intersections, like the trefoil knot, but sometimes even with six intersections, like the Stevedore stopper knot. The interesting questions to ask are: what is the biological role of the knots, how do they form during folding, and how do they affect thermal and mechanical stabilities. We elucidate many knot-related physics by employing a coarse-grained structure-based molecular dynamics model which allows for studies of large conformational changes. In particular, we show that knotting is facilitated by formation of a slipknot during the very process of the protein assembly at the ribosome, especially in the case of the deeply knotted proteins, in which the knot ends are distant from the termini. The presence of the covalent disulfide bonds may introduce other topologically interesting motifs such as cystine knots and lasso. We show that the cystine knot motif yields particularly large resistance to unraveling through stretching. Knotted structures may also arise in intrinsically disordered peptide chains, such as polyglutamine tracts, but their nature is transient. These tracts are fused in huntingtin protein which is associated with Huntington disease, a well-known genetically-determined neurodegenerative disease. We show that the presence of a knot in the tract hinders and sometimes even jams translocation, leading to toxicity.