Elucidating the feedback between micro-mechanical environments and the nano-scale dynamics of biofilaments

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In principle, the mechanical environment around a cell can be described by using a semi-continuum or coarse-grained (CG) description. The response of a cell to such mechanical cues is carried out mainly by proteins, where molecular dynamics (MD) simulation can reveal atomistic details. While MD simulation employs force fields based on physical and chemical principles, parameters for the CG models are based mainly on simplifying and phenomenology-driven assumptions. Establishing the link between these two levels of descriptions is a major challenge in understanding the behavior of cells in a hierarchical manner. By using the link, it is possible to elucidate the effect of the mesoscale mechanical environment on local protein conformational dynamics. Conversely, the link allows one to predict how protein dynamics influences or modifies the cellular environment.

As a first step towards mending the gap between the meso- and atomistic scale dynamics, we study the conformational behavior and interaction between biofilaments. Mainly two example systems are analyzed: collagen and amyloid. At the smallest scale, we show that both 'hydrophobic' and 'hydrophilic' forces arise from the interactions between the ubiquitously formed hydration shells around the filament surfaces. Water molecules also actively control the conformation of collagen sub-domains that interact with other collagen-associated proteins, in particular, matrix metalloproteinase (MMP). MMPs cleave collagen and play key roles in cancer metastasis and adaptation/mal-adaptation of collagenous tissues in cardiovascular diseases. We find that a reduction in surface-bound water bridges leads to torsional relaxation of a collagen triple helix, which is essential for the cleavage by MMP. We then develop a local fluctuation analysis method that uses MD simulation of biofilaments to build the 'flexibility map,' as an atomistic simulation-based CG modeling framework. Finally, we show the importance of non-bonded attractions as they limit the validity of describing a biofilament as an idealized chain. The conformational behavior in the atomistic-parameter based CG models can then be used to understand the load-dependence of collagen catabolism by MMP.