Viscoelastic Response of Folded Protein Chains under Tension: Insights from Titin and Ubiquitin

Shivprasad Patil, Harsh Rathod, Vedant Goankar, Manmat Sahoo

Indian Institute of Science Education and Research, Pune-411008
E-mail: s.patil@iiserpune.ac.in

The nanomechanical response of a folded single protein—the natural nanomachine responsible for myriad biological processes—offers crucial insights into its function. The conformational flexibility of the folded state, characterized by its viscoelasticity, enables proteins to adopt different shapes to carry out their biological roles. Despite extensive efforts, direct measurements of this property have only recently become possible[1, 2]. From a nanomechanical standpoint, both internal friction and stiffness can be directly probed by deforming a single protein at a defined strain rate. To characterize a protein's viscoelasticity, it must be periodically strained while monitoring the in-phase and out-of-phase components of the resulting stress. Such measurements provide quantitative values for both the molecular stiffness and internal friction coefficient. Particularly intriguing are tandem arrays of globular proteins—such as the tip links formed from cadherin tetramers or the titin molecules within muscle sarcomeres—that are subject to mechanical tension under physiological conditions.

Here, we present direct and simultaneous measurements of the stiffness and internal friction of an octamer of immunoglobulin-like (Ig) domains from titin, (I27)$_8$, and of polyubiquitin chains. We find that a chain of folded I27 domains exhibits measurable energy dissipation accompanied by a softening of the molecular chain. In contrast, polyubiquitin chains show neither dissipation nor corresponding softening. Interestingly, the stiffness of ubiquitin chains remains constant across different lengths—behaviour inconsistent with the predictions of freely jointed chain (FJC) or worm-like chain (WLC) models of entropic elasticity. For titin, similar behaviour is observed when all octamer units occupy the mechanical intermediate state. At forces around 100 pN, the polyprotein softens considerably upon further stretching. Simulations suggest that this behaviour arises from fluctuations between the native and intermediate states of individual domains. Such viscoelastic softening may underlie titin's distinctive "force-buffer" behaviour, wherein the force required to transition domains into intermediate states is largely independent of temperature and pulling speed.

The contrasting behaviour between tandem-domain proteins with and without mechanical intermediates is noteworthy. Further investigations are needed to elucidate the physiological significance of these intermediates in proteins subjected to mechanical tension.

References:

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