NAMD as a tool for *in silico* force spectroscopy

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The concept of employing mechanical forces to shape macroscopic materials can be considered of universal knowledge. The outcome of applying mechanical forces into to a material is recognizably dependent on the direction of the force application. For instance, a transverse force can easily bend an iron bar, while a much higher longitudinal force is needed to deform it. A far more intriguing question is how mechanical forces affect single biomolecules. In fact, the chemistry at high forces can be really surprising. Recently, we have shown that an array of hydrogen bonds can be as strong as a covalent bond when a macromolecular system is designed such that all hydrogen bonds must be broken at the same time to separate a protein-peptide complex [1]. Nevertheless, if force is applied in an unfavorable geometry, the protein complex can become relatively weak. Indeed, the directionality of force loading can regulate key biological activities. For instance, some genetic diseases are associated to single mutations in mechanoactive proteins. This mutations affect how these proteins behave under force load, causing significant phenotypic differences in humans. Still, studying different force-loading geometries on the single-molecule level is not straightforward and little is known about how protein complexes behave under mechanical load [2]. Experimentally, modern force spectroscopy investigates these issues by taking advantage of atomic force microscopes, and of both magnetic and optical tweezers. In my talk I will show how, boosted by a GPU-accelerated NAMD [3], we are employing a wide-sampling approach on molecular dynamics simulations to acquire atomistic details to these experimental approaches. Steered molecular dynamics simulations, when carefully performed and combined with single-molecule atomic force spectroscopy experiments, can predict and explain the behavior of highly mechanostable protein complexes [4]. A great example of highly mechanostable protein complexes is found in the adhesion mechanism of staphylococcal bacteria to its human host. Our joint computational-experimental approach revealed not only how strong this protein complex is, but also the molecular details that are responsible for such strength [1]. The mechanism proposed provides an atomistic understanding of why these adhesins can adhere to their hosts so resiliently, from which possible routes to inhibit it and impede staphylococcal adhesion may be derived.

References

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