New and Notable

Advances in the Theory of Single-Molecule Force Spectroscopy: Bond Potentials and Mobilities

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In biological systems, conventional concepts of affinity and standard kinetic constants have been shown to be insufficient. For example, so-called catch bonds increase bond lifetimes with increasing force, like a Chinese finger trap. These type of bonds allow cells to regulate their integrin-mediated adhesions, an effect that can only be revealed by direct force application. For roughly two decades, measuring the forces required to pull single-molecule bonds apart has been used to reveal information about the binding-energy landscape of said molecules. These data, gathered by instruments such as the atomic force microscope, optical tweezers, or magnetic tweezers, have revealed details of chemical bonds, DNA polymerases, protein folding, etc. To derive meaningful information from the experimental data, a theoretical framework is necessary. Based on a model by Bell (1), Evans and Ritchie (2) wrote a breakthrough article in 1997 with the main idea that external force lowers the free activation barrier, consequently increasing the probability for the bond under force to break. Since then this has been the backbone of force spectroscopy analysis, although it should be mentioned that many experimental data did not agree with the theoretical expectations (summarized in Fuhrmann and Ros (3)). Some discrepancies can be simply explained as experimental data containing multiple molecule events, instead of truly single-molecule data; however, these cannot be as easily detected as previously thought, and this can significantly bias the data (4,5). On the theoretical side, additions were made to the form of the potential barrier (6) while still assuming one molecular bond, on one dimension. But biological bonds are highly complex, formed of multiple noncovalent interactions such as H-bonds, and thus, in reality, are multidimensional problems.

Chang et al. (7) take the theory of single-molecule force spectroscopy one level up. They use a sophisticated inference method based on Bayesian field theory to obtain the energy landscape. This model integrates the complexity of large molecule interactions by introducing a position-dependent diffusion coefficient that introduces roughness to the potential barrier. For the experimentalist, the novelty of this approach becomes impressively visible in Fig. 1 (7), where single-molecule force spectroscopy force trajectories are simulated. Due to the complex energy landscape and diffusivity, each pulling curve looks a bit different as the experimental parameters slightly change, just as one would expect in a real experiment. While much more complex, the beauty of this approach is that not only can it reveal these complex energy landscapes but also that it requires much less data from the experimentalist. While high-resolution single-molecule force spectroscopy, required for this kind of analysis, is becoming a reality thanks to innovations such as small or T-shaped cantilevers, this model has yet to be proven on a real experimental problem. In summary, this approach offers the opportunity to reconstruct the energy and mobility profiles of large bimolecular complexes with multiminimum energy and diffusivity profiles.

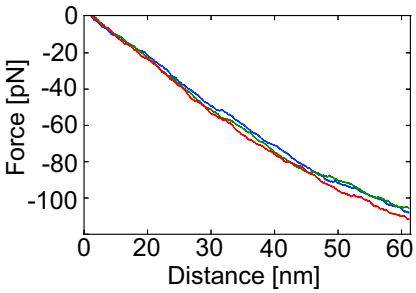

FIGURE 1 Three simulated force-distance curves over the same molecular complex. Using the software and data provided in Chang et al. (7) (and kind help from J.C. Chang), force curves are plotted using typical single-molecule force spectroscopy parameters. The difference in each individual curve, as one can expect in real experiments, highlights the novelty of this approach. To see this figure in color, go online.

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