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Directly measuring single molecule heterogeneity in proteins and RNA using force spectroscopy MICHAEL HINCZEWSKI, Case Western Reserve University, CHANGBONG HYEON, Korea Institute for Advanced Study, DEVARAJAN THIRUMALAI, Institute For Physical Science and Technology, University of Maryland, College Park — One of the most intriguing results of single molecule experiments on proteins and nucleic acids is the discovery of functional heterogeneity: the observation that complex cellular machines exhibit multiple, biologically active conformations. The structural differences between these conformations may be subtle, but each distinct state can be remarkably long-lived, with stochastic interconversions occurring only at macroscopic timescales, fractions of a second or longer. Though we now have proof of functional heterogeneity in a handful of systems—enzymes, motors, adhesion complexes—identifying and measuring it remains a formidable challenge. We show that evidence of this phenomenon is more widespread than previously known, encoded in data collected from some of the most well-established single molecule techniques: AFM or optical tweezer pulling experiments. We present a theoretical procedure for analyzing distributions of rupture/unfolding forces recorded at different pulling speeds. This results in a single parameter, quantifying the degree of heterogeneity, and also leads to bounds on the equilibration and conformational interconversion timescales. Our work suggests experimental approaches for estimating the timescales of these fluctuations with unprecedented accuracy.

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