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Molecular architecture governs the kinetics of single molecule unfolding under force¹

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Proteins are a paradigm of complexity due to the broad energy scales involved in holding their folded structure intact under thermal fluctuations. Moreover, a subset of all proteins is known to withstand stretching forces on the order of 100 pN on the timescale of seconds. The dynamic mechanism by which these proteins support stress on the molecular level remains largely unknown. With the advent of single molecule techniques using the atomic force microscope (AFM), we measure the kinetics of unfolding as a function of a constant force for the archetypal mechanically stable proteins: the degradation protein ubiquitin and the 27th immunoglobulin domain (I27) in muscle. Instead of filtering the data, we develop a maximum likelihood method to analyze all force-clamp unfolding dwell times in order to deduce the underlying kinetics. We find that the large pool of data for both proteins is best fit with stretched exponential distributions, whose exponent depends on the molecular architecture of the protein. Our analysis of previously published kinetic data on ubiquitin as a function of force [PNAS, Garcia-Manyes et. al., 2009] follows stretched exponential kinetics at all forces. Rescaling the data by the exponent shows that the characteristic timescale for the rupture of the molecules increases slower than exponentially with the force, challenging the Bell model. The observed complex kinetics may therefore be of evolutionary importance, as it increases the protein's mechanical resilience. We discuss competing microscopic mechanisms by which the complex kinetic profiles may arise.

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