**426p Molecular Simulation and Energy Landscape Analysis of Mechanical Unfolding of the Titin Protein**

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Molecular simulations and an energy landscape analysis are carried out for the Immunuoglobulin 27 (Ig27) domain of the titin protein as it is stretched. Titin is a muscle protein, and the mechanical response of titin plays a role in controlling muscle function. Stretching the protein breaks hydrogen bonds near the termini of the protein, and leads to an unfolding of the native state.

This mechanical unfolding process is studied in terms of the underlying energy landscape. Stretching destroys energy minima and creates new energy minima, such that energy minima exist only for small intervals of elongation (~2 Å). The destruction of energy minima leads to metastability limits of folded states of the protein, since the protein cannot exist in a folded state if such energy minima do not exist. The present results show that the metastability limits of the folded states of Ig27 are very similar to the thermodynamic stability limits found previously by molecular dynamics simulation. Structural changes leading to unfolding occur either by the gradual weakening of hydrogen bonds while in a single energy minimum, or by the sudden breaking of hydrogen bonds – the mode of structural change that occurs (gradual or sudden) is related to the local stiffness of the relevant interactions. In general, these results show that the creation and destruction of energy minima must be considered in energy landscape descriptions of proteins in time-dependent environments, such as the environments relevant to muscle proteins and cell adhesion proteins.