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Structure-Based Prediction of Unstable Regions in Proteins: Applications to Protein Misfolding Diseases WILL GUEST, NEIL CASHMAN, STEVEN PLOTKIN, UBC — Protein misfolding is a necessary step in the pathogenesis of many diseases, including Creutzfeldt-Jakob disease (CJD) and familial amyotrophic lateral sclerosis (fALS). Identifying unstable structural elements in their causative proteins elucidates the early events of misfolding and presents targets for inhibition of the disease process. An algorithm was developed to calculate the Gibbs free energy of unfolding for all sequence-contiguous regions of a protein using three methods to parameterize energy changes: a modified Gō model, changes in solvent-accessible surface area, and solution of the Poisson-Boltzmann equation. The entropic effects of disulfide bonds and post-translational modifications are treated analytically. It incorporates a novel method for finding local dielectric constants inside a protein to accurately handle charge effects. We have predicted the unstable parts of prion protein and superoxide dismutase 1, the proteins involved in CJD and fALS respectively, and have used these regions as epitopes to prepare antibodies that are specific to the misfolded conformation and show promise as therapeutic agents.

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