A Monte Carlo Protein Folding Simulation using Energy Optimization with Novel Applications to Alzheimer's Disease Research

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Alzheimer's Disease (AD) is a growing problem worldwide and has no treatment. Tau protein misfolding is linked to AD. Tau is an intrinsically disordered protein, hence natively unfolded in solution. Thus, conventional techniques (crystallography/spectroscopy) cannot be used to predict tau structures, and alternative modeling techniques are required. The purpose of this research is to apply Monte Carlo methods to simulate tertiary folding patterns of intrinsically disordered htau40, 441-residue tau isoform. The simulation developed takes as input pH, primary sequence, and torsional angle distributions to predict tertiary structures based on optimal/minimal Solvation Potentials, Electrostatic Potentials, and Lennard-Jones Potentials. It calculates Volume-Surface Area Ratios and Radii of Gyration of predicted protein structures. To verify accuracy of the simulation, it was run against 30 proteins from literature whose structural properties are known. Statistical tests revealed that the simulation yielded similar results to original published data for those 30 proteins; this validated the simulation and allowed advancement to simulation of htau40, whose structure is unknown. Correlations between biological parameters, structural properties, and energies were calculated for 300 predicted htau40 structures. The most significant result was a strong, positive correlation between pH and Energy, indicating that increased pH corresponds to increased Energy, and increased tau instability. This is notable as researchers have observed elevated hippocampal pH levels in AD patients, meaning the results of the simulation offer a possible explanation for tau abnormality in AD patients. In conclusion, based on this finding, future AD research can be geared towards targeting pH.

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