

Colloquium Announcement

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ABSTRACT: Relationships Between Protein Function, Structure, (Mis)Folding, and Aggregation

Soluble proteins undergo a large number of structural changes through their cellular life cycle. Some changes are needed for the function and regulation of the protein. I will discuss an emerging idea that considers the regulation of protein structure in terms of modest changes in free energy between several fluctuating structures. At least for some proteins, this seems to provide a better explanation of conformational changes than the traditional ideas of allostery. I will show examples from our work on glucose/galactose binding protein (GGBP).

GGBP functions as part of a larger system of proteins for molecular recognition and signalling in enteric bacteria. The thermodynamics of conformational equilibrium distributions of GGBP are observed as three fluorescence components that appear at zero glucose concentration and systematically transition to three components at high glucose concentration. Fluorescence anisotropy correlations, fluorescent lifetimes, thermodynamics, computational structure minimization, and previous work are used to identify the three components as open, closed, and twisted conformations of the protein.

The existence of three states at all glucose concentrations indicates that the protein continuously fluctuates about its conformational state space via thermodynamically driven state transitions, and the glucose biases the populations by reorganizing the free energy profile. These results and their implications are discussed in terms specific and non-specific interactions GGBP has with cytoplasmic membrane proteins.

Other structural changes are deleterious. Many proteins or protein fragments can aggregate into cross β -amyloid fibrils. These fibrils accumulate into insoluble plaques in vivo and are associated with the progression of neurodegeneration in Alzheimer's, Parkinson's and Creutzfeldt-Jakob's diseases. Transmissible spongiform encephalopathies in cows (mad cow), deer and elk (chronic wasting syndrome), sheep and hamsters (scrapie) also show accumulation of β - amyloid during their progression. Many mechanistic intermediates have been proposed for the assembly of amyloid fibrils from soluble precursor proteins and peptides. However, few of these proposed intermediates have been observed directly. I will discuss the aggregation of β -lactoglobulin into β -amyloid fibrils and our efforts to characterize the structural and size distributions through all stages of the assembly using a combination of bulk and single molecule methods.

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12:30 p.m. – 1:45 p.m.

Campbell Hall 274

Refreshments served at 12:00 p.m. in CH 361