

LECTURE

Professor Krzysztof Kuczera

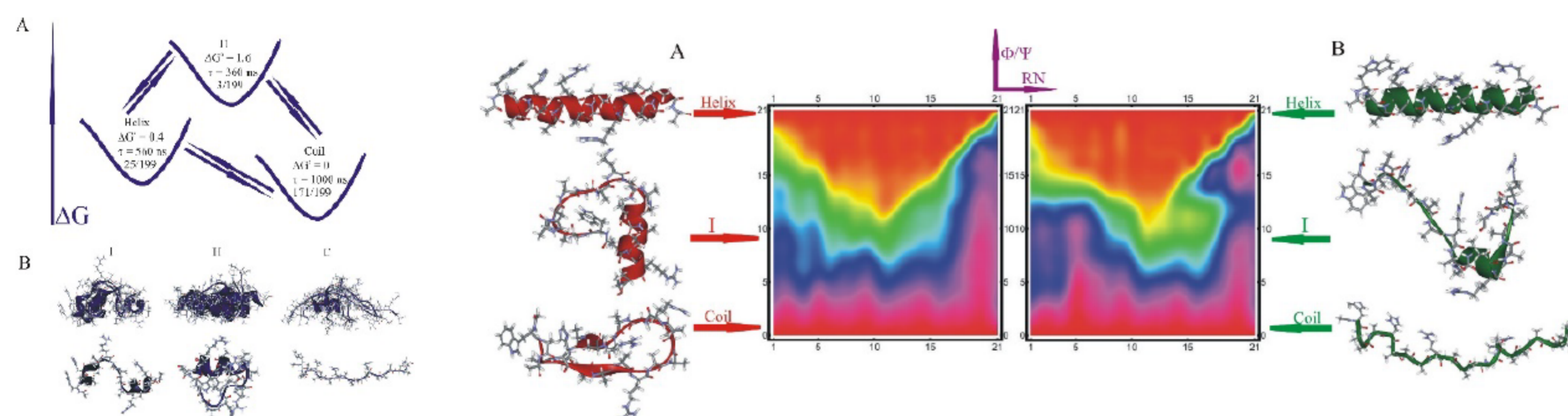
Department of Chemistry and Department
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will deliver a lecture titled:

Multiple timescales of peptide folding from computer simulations

DATE: **Thursday, 9 January | 11:00** VENUE: **CNBCh UW, room 0.38**

Long-term molecular dynamics simulations and a novel kinetic coarse-grained analysis were carried out to model the mechanism of formation of the helix-coil transition in a 21-residue peptide. A 12 microsecond molecular dynamics trajectory in explicit solvent yielded structural and dynamic properties in good agreement with available experimental data. Clustering and optimal dimensionality reduction were applied to produce low-dimensional coarse-grained models of the underlying kinetic network in terms of 2-5 metastable states. In accord with the generally accepted understanding of the multiple conformations and high entropy of the unfolded ensemble of states, the "coil" metastable set contains the largest number of structures. Interestingly, the helix metastable state was also found to be structurally heterogeneous, consisting of the completely helical form and several partly folded conformers which interconvert at a time scale faster than global folding. The intermediate states contain the fewest structures, have lowest populations and have the shortest lifetimes. As the number of considered metastable states increases, more intermediates and more folding paths appear in the coarse-grained models. One of these intermediates corresponds to the transition state for folding, which involves an "off-center" helical region over residues 11-16. The simulation data further suggest that the experimentally observed fast kinetic time scale should be assigned to correlated breaking/formation of blocks of several adjacent helical hydrogen bonds. The same computational analysis was also applied to a 13-microsecond molecular dynamics trajectory of the peptide with the neutral form of its histidine residue, corresponding to a higher pH. The loss of the histidine proton induces significant changes in the free energy landscape. This form has a higher helix content than the protonated peptide, in accord with experimental observations. Additionally, the kinetic network and folding pathway are also markedly different.



G.S. Jas and K. Kuczera. Helix-Coil Transition Courses Through Multiple Pathways and Intermediates: Fast Kinetic Measurements and Dimensionality Reduction. *J Phys Chem B*, **122**:10806-10816.(2018).

G.S. Jas, E.W. Childs and K. Kuczera. Kinetic pathway analysis of an alpha-helix in two protonation states: Direct observation and optimal dimensionality reduction. *J Chem Phys*, **150**:074902 (2019).



Research field:

Computational chemistry and biochemistry.

Research interest and experience:

to determine detailed microscopic effects of the environment on peptide structure, dynamics and interactions with proteins. Our studies employ molecular dynamics, replica-exchange and free energy simulations, as well as kinetic network modeling, to provide microscopic insights into influence of temperature, pH, viscosity and presence of co-solvents on peptide folding pathways. Our work involves extensive collaborations with experimental groups.

