UIC COLLOQUIUM
Department of Physics

Wednesday, September 18, 2019

"Three-color Single-molecule FRET Studies of Binding and Folding of Intrinsically Disordered Proteins"

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Intrinsically disordered proteins (IDPs) play important roles in various dynamic cellular processes such as gene transcription and signal transduction. IDPs are unstructured but usually fold during binding to target proteins. In contrast to interactions between folded proteins, this additional folding step makes the binding process more complex. Understanding the mechanism of coupled binding and folding of IDPs requires analysis of binding transition paths that involve formation of the transient complex (TC). However, experimental characterization of the transition path is challenging because it only appears for a very brief period during binding. We use single-molecule fluorescence spectroscopy to probe the transition path and understand the mechanism of IDP binding and folding. We investigated binding of a disordered protein, the transactivation domain (TAD) of p53 and one of its binding partners, nuclear coactivator binding domain (NCBD) of CBP. Interestingly, these two proteins bind in a diffusion-limited manner. Diffusion-limited association of IDPs is a counterintuitive phenomenon because it suggests that a disordered protein should fold almost immediately after it encounters with a binding target, which seems very unlikely. We found that TC is unexpectedly long lasting (lifetime of several hundred μs) due to the stabilization by non-native electrostatic interactions. The long lifetime of TC allows for unstructured TAD to fold without dissociation once it encounters with NCBD, which makes diffusion-limited association possible. Diffusion limited-association also implies that binding pathways are heterogeneous. To probe this heterogeneity, we have developed fast three-color single-molecule FRET spectroscopy. The analysis of three-color photon trajectories requires a large amount of time for the likelihood calculation. We implemented co-parallelization of CPU-GPU processing, which leads to a significant reduction of the computation time. The three-color FRET experiment shows that there is one major binding transition path, along which about a half of transitions occur, and the rest of the transition paths are highly diverse as predicted.

The Department of Physics Colloquium will be held at 3pm in 238 SES.

**Refreshments will be served from 2:45 pm to 3pm outside of room 238 SES*