APPLIED MATHEMATICS COLLOQUIUM

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Unraveling the Mechanism of Chaperone-Mediated Protein Folding

Abstract: Chaperones are special proteins that aid in the folding, unfolding, assembly and disassembly of other proteins. Chaperones rely on a large and diverse set of co-chaperones that regulate their specificity and function. How these co-chaperones regulate protein folding and whether they have chaperone-independent biological functions is largely unknown. In this talk, I will begin by discussing a previously unresolved puzzle on how Hsp90, a molecular chaperone, regulates the folding of protein kinases, possibly the most important drug targets for cancer therapy. Using computational graphical modeling and robust sparse regression methods, we identify a striking association between the binding specificity and a structural motif that includes deeply-buried hydrophobic residues in the kinase core region. Computation-guided mutagenesis validates the role of this motif in binding and suggests that Hsp90 recognizes intermediate kinase conformations by sensing the thermostability of the kinase core region. We anticipate our new results will advance the understanding of the role of Hsp90 in cancer drug development. I will conclude by presenting how computational approaches allow us to more generally study the chaperone/co-chaperone/client interaction network in a systematic way, finding biological signals from noisy experimental data. We delineate the relationship between the Hsp70 and Hsp90 chaperone systems, uncover novel co-chaperones and clients, and establish a surprisingly distinct network of protein-protein interactions for co-chaperones. Our results provided a rich resource for exploring how this network changes in the context of development and disease.

Monday March 3, 2014
4:30 PM
Building E17, Room 122

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