Hidden correlations and symmetries determine per-residue interaction free energy contributions of protein: Small molecule/biomolecule binding

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Protein interaction free energy is the lynchpin to understanding, identifying, and targeting cancer. Despite the common practice of describing key interactions in terms of ionic, polar, hydrogen bonding, and hydrophobic contacts, the interactions are too numerous, varied, weak and delicately balanced to allow meaningful prediction of per-residue contributions to interaction free energy. All-atom physics-based (molecular dynamics and free energy perturbation) simulations have struggled to provide per-residue contributions as well. The ideas presented here constitute an alternative physics-based approach to describe protein interaction energies without resorting to atomistic methods or rationales. Dilation symmetry, simple accommodations of protein backbone fluctuations and renormalization-based approaches provide a straight forward description of the individual and correlated effects of per-residue contributions to interaction free energy. This approach enables protein residues to be mapped according to how 'hot' or 'sticky' each residue is. Protein interiors are dominated by hot residues and exteriors are dominated by cool residues. Hot patches on protein surfaces correspond to the substrate binding surfaces of enzymes (Bcl kinase), protein-protein interfaces (Mcl-1/Bim), and protein-peptide interfaces (MHCs). Additionally, the model can be used to classify mutations as primarily impacting ground state conformations (Class I mutation) or ground and/or excited state conformations (Class II mutation) and to compute protein stability (*ddG*, lysozyme). The data suggest that sequence space – so abundant in the wake of the genomic revolution – can be converted into energy space and that it may be possible to navigate and interpret genomic and protein structure data directly in terms of interaction energy signatures.

Speaker Biography

Lawrence J Williams completed his PhD at the University of Arizona and held Post-doctoral fellowships at MIT and Memorial Sloan-Kettering where he studied molecular structure and synthesis of natural and engineered peptides and tumor-associated glycopeptides for immune activation. His independent research has focused on developing synthetic methods and strategies to understand structure, reactivity, materials and biological function of complex organic molecules, especially natural products, peptides and proteins. Recently, he has worked in the fields of antibody drug conjugates, biomarker diagnostics and protein biophysics.

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