Departmental Seminar

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Title:

"Protein Design with Rigorous Alchemical Calculation of Folding Free Energies"

Protein design is a blossoming field with exciting applications in medicine, green chemistry, and nanotechnology. There is a gap between current computational design methods, which sometimes fail to produce viable initial designs due to insufficient accuracy, and experimental design methods like directed evolution that require some initial level of function for optimization. Alchemical free energy methods, which utilize molecular dynamics simulations to produce more accurate free energy predictions, have the potential to bridge this gap. Multisite λ dynamics (MSλD) is an emerging alchemical free energy method that is uniquely suited to computational protein design because of its scalability to massive protein design sequence spaces arising from multiple mutations. In this talk I will highlight recent developments that enable MSλD to be applied to protein design and are also bearing fruit in computer aided drug design. Retrospective protein design calculations of T4 lysozyme folding free energies have demonstrated the accuracy of MSλD through unprecedented agreement with experimental measurements. Ongoing prospective protein design studies of ribonuclease H are demonstrating the ability of MSλD to design within spaces of over 30,000 sequences with 15 mutations.