LAUFER CENTER
FOR PHYSICAL AND QUANTITATIVE BIOLOGY

Lecture 2015

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Tuesday October 13, 2015

2:00 PM

Laufer Center Lecture Hall 101

Host: Joe Morrone

Towards predictive pharmacodynamics simulations with recent developments in enhanced sampling

How, when and why does a drug leave the binding pocket of a host protein? What are the roles played by water molecules and protein flexibility? Using molecular dynamics (MD) simulation to answer such questions is a desirable but difficult task primarily due to the long timescales involved. Recent progress in enhanced sampling [1] has now made it possible to address this with full atomistic resolution, recovering thermodynamic and kinetic information at timescales previously unattainable in MD simulations. In this talk, I will briefly highlight the underlying theory and some recent applications calculating thermodynamics and kinetics of ligand unbinding for model hydrophobic systems [2], trypsin-benzamidine [3] and an FDA-approved anti-cancer drug as it unbinds from Src-kinase. I will also address a longstanding theoretical and practical challenge in furthering the widespread applicability of enhanced sampling methods; namely, a computationally efficient protocol for choosing collective variables (CVs) for biasing. For this, I will introduce a Maximum Caliber based spectral gap estimation technique (MaxSpec), that suggests optimal collective variables to bias in enhanced sampling simulations, given limited prior information about the system and a set of candidate CVs. Practical examples of this new approach will be shown.

[1]Tiwary & Parrinello, Phys. Rev. Lett. 111 230602 (2013)
[2]Tiwary, Mondal, Morrone & Berne, Proc. Nat. Acad. Sci. (in press)
[3]Tiwary, Salvalaglio, Limongelli & Parrinello, Proc. Nat. Acad. Sci. 112 E386 (2015)

Refreshments following seminar

Laufer Hub 110

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