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Computer-aided drug design for Alzheimer's disease

Mai Suan Li
Institute of Physics Polish Academy of Sciences, Poland

In the first part of this talk I shall present our new method for finding the optimal path to pull a ligand from the binding pocket by the steered molecular dynamics (SMD). The optimal path corresponds to the minimal hindrance introduced as a scoring function to ligand displacement. Contrary to the existing caver method, our approach takes into account the geometry of ligand leading to much better correlation between experimental inhibition constants and mechanical works estimated by SMD. In the second part the virtual screening, improved SMD and MM-PBSA methods are applied to search for potential drugs for the Alzheimer's disease (AD) from large data bases of natural and synthesized compounds. The design strategy is based on the amyloid cascade hypothesis which posits that AD is caused by aggregation of amyloid beta (Aβ) peptides. Oligomers and protofibrils were taken as drug targets as they seem to be more cytotoxic than mature fibrils. Some of top-hit compounds predicted by our *in silico* study have already passed *in vitro* tests for inhibition activity, blood-brain barrier crossing and non-toxicity to cells. Concerning peptide-based inhibitors, we have shown that presence of tryptophan and proline residues in tripeptides is crucial for their tight binding to Aβ fibrils as well as for extensive fibril depolymerization. Fullerenes and their derivatives were found to have high binding affinity to Aβ and ability to block Aβ aggregation. The binding free energy linearly scales with the size of fullerenes.

masli@ifpan.edu.pl

Toward whole-cell models for science and engineering

Jonathan Karr
Mount Sinai School of Medicine, USA

A central challenge in biology is to understand how phenotype arises from genotype. Despite decades of research which have produced vast amounts of data, a complete, predictive understanding of biological behavior remains elusive. Computational techniques are needed to assemble this data into a unified understanding. We have developed the first comprehensive whole-cell model. The model predicts the cell cycle dynamics of the gram-positive bacterium *Mycoplasma genitalium* from the level of individual molecules and their interactions including its metabolism, transcription, translation and replication. We validated the model by comparing its predictions to a wide range of experimental data across several biological processes and scales. We have demonstrated that the model can guide biological discovery. We have used the model to determine how the metabolic network controls the *M. genitalium* cell cycle in the absence of genetically encoded regulators, enumerate the modes and frequency of *M. genitalium* stochastic death and determine the kinetic parameters of several *M. genitalium* metabolic enzymes. We believe that gene-complete models will accelerate bioengineering and medicine by enabling rapid, low cost *in silico* experimentation, facilitating experimental design and interpretation and ultimately guiding rational biological design.

jkarr@alumni.stanford.edu

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