SOME CURRENT THEMES IN COMPUTATIONAL MOLECULAR BIOPHYSICS

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Aspects of the physics and chemistry of biological macromolecules are discussed from the viewpoint of atomistic computer simulations. The combination of neutron scattering with simulation is used to understand dynamical aspects of the protein glass transition (1,2), anomalous internal subdiffusion (3), binding phenomena, protein:protein interactions (2) and protein folding (5). Energy landscape approaches to describing kinetically metastable states of proteins are described (4). The scaling of molecular dynamics simulation and ligand binding screening to ~100k cores on the ORNL Jaguar XT5 supercomputer is described (5,6). Applications of simulation methods to biofuel research and mercury detoxification are detailed (9,10).

1. MEINHOLD et al PRL 99 (13):138101 (2007); PNAS 104 44 17261-17265 (2007).

2. KURKAL-SIEBERT et al PRL 100 13 138102 (2008).

3. NEUSIUS et al PRL 100 18 188103 (2008); PRE. 83, 021902 (2011)

4. NOE et al PNAS In press.

5. DAIDONE et al PNAS 104 39 15230 (2007); PLoS Comp. Biol. 6(1) e1000645 (2010).

6. SCHULZ et al J. Chem. Theo. Comp. 5, 2798–2808 (2009).

7. COLLIGNON et al J Comp. Chem. In Press.

8. YANG et al PNAS 23 10395–10400 (2010)

9. PARKS et al JACS 131, 13278-13285 (2009)

10. SAHARAY et al PLoS ONE 5 (10) e12947 (2010)

Extending the Time Scales of Biomolecular Simulations on Emerging Computing Architectures

Xiaolin Cheng

Abstract:

One of the significant challenges faced with molecular dynamics (MD) simulation is to extend its attainable time scale. There are two ways to do this: to make each sequential step run faster by using fast algorithms, and to improve the parallel efficiency so that more processors can be used. In this talk, I will discuss more scalable treatment of long-range electrostatic interactions in simulation using Ewald-mesh based explicit models and Poisson-Boltzmann based implicit models.

Narrowing the gap in understanding protein structure and function through computer simulations

Hong Guo

Results of molecular dynamics (MD) and free energy simulations with quantum mechanical/molecular mechanical (QM/MM) potentials are reported for different enzyme systems. It is demonstrated how computer simulations may lead to important insights into biological structure and function. One family of the enzymes to be discussed is serine-carboxyl peptidases (sedolisins) which was recently characterized but is poorly understood. The members of the family also include tripeptidyl-peptidase (TPP1) for which the loss of the activity as a result of mutations in the TPP1 gene is the cause of one of the most common devastating neurodegenerative disorders of childhood. Our results on sedolisins suggest that unlike classical serine peptidases the members of this family may stabilize the tetrahedral intermediates primarily through general acid-base mechanism. Moreover, the existence of dynamic substrate-assisted catalysis (DSAC) is proposed, and it is shown that DSAC may contribute to the relatively high activities of the enzymes towards certain substrates and could have a general implication for enzyme catalysis and substrate specificity. Other enzymes are discussed as well, including protein lysine methyltransferases (PKMTs) that catalyze the methylation of certain lysine residues in the N-terminal tails of the core histone proteins in nucleosome. The biological consequences of histone lysine methylation (e.g., gene activation and repression) depend on the methylation states of the lysine residue (mono-, di- or tri-methylated). Therefore, it is of fundamental importance to understand why different PKMTs have their unique product specificity (i.e., the ability to direct specific degrees of lysine methylation). The results of the simulations suggest that the relative efficiencies of the chemical steps involving three methyl transfers in PKMTs from S-adenosyl-L-methionine (AdoMet) to the ε-amino group of the target lysine may determine how the epigenetic marks of lysine methylation are written. Two energy triplets are propose d as important parameters for the prediction of product specificity of PKMTs through computer simulations.

Efficient methods for electrostatics in the presence of dielectric interfaces

Zhenli Xu

In this talk, I will discuss some recent results on efficient treatment methods of electrostatic surface polarization charges in the presence of dielectric sphere, dielectric cylinder, dielectric multiple spheres, and dielectric irregular interface, in both salt-free and ionic solvents, which could be useful to be incorporated into fast algorithms in molecular simulations of biological and soft matter systems. Simulation results from the Poisson-Boltzmann model, reaction-field model to the primitive model of electrolytes will be presented.

Induced Fit or Conformational Selection for RNA/U1A recognition

Haifeng Chen

The hairpin II of U1 snRNA can bind U1A protein with high affinity and specificity. NMR spectra suggest that the loop region of apo-RNA is largely unstructured and undergoes a transition from unstructured to well folded upon U1A-binding. However, the mechanism that RNA folding coupled protein binding is poorly understood. To get an insight into the mechanism, we have performed explicit-solvent molecular dynamics (MD) to study the folding kinetics of bound and apo-RNA.

Room-temperature MD simulations suggest that the conformation of bound RNA has significant adjustment and becomes more stable upon U1A-binding. Kinetic analysis of high-temperature MD simulations shows that bound and apo-RNA unfold via a two-state process, respectively.

Both kinetics and free energy landscape analyses indicate that bound RNA folds in the order of RNA contracting, U1A binding and the tertiary folding. The predicted phi-values suggest that A8, C10, A11, and G16 are key bases for bound RNA folding. Mutant Arg52Gln analysis shows that electrostatic interaction and hydrogen bonds between RNA and U1A (Arg52Gln) decrease. These results are in qualitative agreement with experiment. Furthermore, this method could be used to other study about biomolecule folding upon receptor-binding.

Theoretical Exploration of Protein S-Nitrosylation

Yilei Zhao

Abstract: Nitric oxide plays important roles in biology, while its chemistry is yet clear up to now. One of the most interesting is how protein S-nitrosylation occurs, which connects cell signal transductions and thereby many diseases. Recently, hundreds SNO proteins have been reported in proteomic experiment. Bioinformatic analysis indicates that these proteins appear structural similarity at certain level. Using quantum chemistry, we have made several efforts for protein S-nitrosylation, such as: 1) Dimeriation of nitric oxide under aromatic surrounding, 2)reactivity of nitric oxide dimer, 3) electronic properties of peroxynitrite, 3) reaction of cystein and nitric oxide.

Structural Bioinformatics, Chinese Traditional Medicine Database For Drug Design, Ion Channels and Personalized Medicine

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Structural bioinformatics tools and databases have been developed and applied to study diversified biological problems. Molecular modeling tools were developed to generate 3D structure from sequences of novel gene. It allows us pursue structure based drug design. Applications were made to drug design for SARS, H5N1 and HIV. A octapeptide AVLQSGFR designed by us was synthesized and its antiviral potential against SARS coronavirus (BJ-01) was assessed, which demonstrates that AVLQSGFR is the most active in inhibiting replication of the SARS coronavirus compared with other compounds reported so far(EC50 is 2.7×10-2mg/L, and its selectivity index is more than 3704). We have built an effective component Database of the Traditional Chinese Medicine(TCMD), which contains 3-D structures of 10000 different compounds from various sources of traditional Chinese medicines. The database is screened with various cheminformatics tools, many promising molecules were obtained, for example, agaritine and gx-50 was singled out through similarity search, molecular docking and molecular dynamics simulations. Experimental studies were carried out to test the effectiveness of these molecules.

Two alternative binding sites of adamantane-type drugs in the influenza A M2 channel have been suggested, one with the drug binding inside the channel pore, and the other with four drug molecules binding to the C-terminal surface of the transmembrane domain. Recent computational and experimental studies have suggested that the pore-binding site is more energetically favorable but the external surface-binding site may also exist. Nonetheless, which drug binding site leads to channel inhibition in vivo and how these sites are affected by drug resistant mutations are not completely understood. We applied molecular dynamics simulation and potential of mean force calculations to examine the structures and free energies associated with these putative drug binding sites in M2-lipid bilayer system. We found that, at biological pH (~7.4), the pore-binding site is more thermodynamically favorable than the surface-binding site by about 7 kcal/mol, hence would lead to more stable drug-binding and channel inhibition. This result is in excellent agreement with several recent studies. More importantly, a novel finding of ours is that binding to channel pore requires overcoming a much higher energy barrier of about 10 kcal/mol than binding to the C-terminal channel surface, indicating the latter site is more kinetically favorable. Our study is the first computational work that provides both kinetic and thermodynamic energy information on these drug binding sites. Our results provide a theoretical framework to interpret and reconcile existing and often conflicting results regarding these two binding sites, thus help expand our understanding of M2-drug binding and may help guide the design and screening of novel drugs to combat the virus.

In our structural bioinformatics studies, the three-dimensional (3D) structures of selected enzymes were built, for example, 2C19, 2E1. By a series of docking studies and MD simulations, the binding affinities of existing drugs with various CYP enzymes were analyzed to understand role of SNPs, which accord well with the results obtained from photo-affinity labeling studies, and will be very useful for conducting mutagenesis studies, providing useful information for drug metabolism and personalization of drug treatments, as well as stimulating novel strategies for finding desired personalized drugs.

Biography

Prof. Dong-Qing Wei, obtained his Ph.D. at the age 24, is the deputy head at the Department of Bioinformatics and Biostatistics, College of Life Science and Biotechnology, Shanghai Jiaotong University, Shanghai, China, editor-in-Chief, “Interdisciplinary Sciences- Computational Life Sciences”, chairman, International Association of Scientists in the Interdisciplinary Areas(IASIA). Prof. Wei’s research is in the general area of structural bioinformatics and computational physics. He has made many important contributions to sciences. With more than 100 journal papers and SCI 2700 citations, he is becoming a leading figure in the area of structural bioinformatics and computational physics.