北京大学定量生物学中心
CENTER FOR QUANTITATIVE BIOLOGY

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第三届世界华人计算生物学大会

Online Meeting

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Monday, August 3rd

8:15-8:30	Opening: ZHANG, Zenghui & LAI, Luhua	
Session 1 (Chair: LI, Zhiyuan)		
8:30-9:10	**TANG, Lei-Han** Hong Kong Baptist University	Calibrated Intervention and Containment of the COVID-19 Pandemic
9:10-9:50	**DONG, Hao** Nanjing University	A stochastic particle dynamics model for predicting epidemics
9:50-10:15	**ZHU, Huaiqiu** Peking University	基于深度学习的病毒宿主预测方法
Break		
Session 2 (Chair: DONG, Hao)		
10:25-11:05	**DING, Qiang** Tsinghua University	Functional and Genetic Analysis of Viral Receptor ACE2 Orthologs Reveals a Broad Potential Host Range of SARS-CoV-2
11:05-11:45	**LUO, Haibin** Sun Yat-Sen University	Free energy perturbation-based virtual screening against COVID-19 and clinical validation
11:45-12:10	**ZHANG, Lu** Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences	Role of 1'-Ribose Cyano Substitution for Remdesivir to Effectively Inhibit both Nucleotide Addition and Proofreading in SARS-CoV-2 Viral RNA Replication
Break		
Session 3 (Chair: WANG, Yibo)		
13:30-14:10	**LAI, Luhua** Peking University	Prediction of targeted cancer drug resistance
14:10-14:50	**OUYANG, Defang** University of Macau	Integrated computer-aided formulation design: A case study of andrographolide/ cyclodextrin ternary formulation
14:50-15:15	**XIA, Kelin** Nanyang Technological University	Topology Data Analysis (TDA) Based Machine Learning Models for Drug Design
15:15-15:40	**WU, Ruibo** Sun Yat-Sen University	GM-DockZn: A Geometry Matching based Docking Algorithm for Zinc Proteins
Break		
Session 4 (Chair: WU, Ruibo)		
15:55-16:35	**WEI, Dongqing** Shanghai Jiao Tong University	人工智能与精准药物发现：大数据时代的个性化药物设计
16:35-17:15	**YANG, Yuedong** Sun Yat-Sen University	Effective Deep Learning for Protein-drug interactions
17:15-17:40	**LI, Zhe** Sun Yat-Sen University	Development of FEP-ABFE method and its applications in drug discovery
17:40-18:05	**WANG, Yibo** Changchun Institute of Applied Chemistry, Chinese Academy of Sciences	靶向跨膜蛋白-蛋白相互作用的药物发现
Break		
Session 5 (Chair: XIA, Kelin)		
19:30-20:10	**ZHAN, Changguo** University of Kentucky	Power of computational design in drug discovery and development: A journey from in silico to clinical studies
20:10-20:50	**ZHANG, Yingkai** New York University	Integrating Machine Learning and Molecular Modelling for Drug Design
20:50-21:30	**PEI, Jianfeng** Peking University	AI-Assisted Drug Design

Tuesday, August 4th

Session 1 (Chair: WANG, Binju)			
8:30-9:10	**ZHOU, Huanxiang** University of Illinois at Chicago	Correlated Segments and Fuzzy Membrane Association of Intrinsically Disordered Proteins	
9:10-9:50	**LIU, Yajun** Beijing Normal University	Tuning Color and Activity of Calcium-regulated Photoprotein Luminescence	
9:50-10:15	**MEI, Ye** East China Normal University	Adaptive QM/MM via the Reference-Potential Method	
Break			
Session 2 (Chair: MEI, Ye)			
10:25-11:05	**MU, Yuguang** Nanyang Technological University	OnionNet: a multiple-layer inter-molecular contact based convolutional neural network for protein-ligand binding affinity prediction	
11:05-11:45	**ZHAO, Yilei** Shanghai Jiao Tong University	Specific Regio- and Enantioselectivity of Fluostatin Conjugation	
11:45-12:10	**WANG, Binju** Xiamen University	Deciphering the Enigmatic Oxygen Activation and Methane Oxidation Mechanisms by Particulate Methane Monooxygenase	
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Session 3 (Chair: ZHU, Tong)			
13:30-14:10	**GAO, Yiqin** Peking University	From dinucleotide to chromatin, a domain segregation perspective for chromatin structure change in development, differentiation, senescence and certain diseases	
14:10-14:50	**LI, Guohui** Dalian Institute of Chemical Physics, Chinese Academy of Sciences	生物体系多尺度理论研究的方法发展及应用	
14:50-15:15	**HAN, Wei** Peking University Shenzhen Graduate School	Bottom-Up Derived Flexible Water Model with Dipole and Quadrupole Moments for Multiscale Molecular Simulations	
15:15-15:40	**XIU, Peng** Zhejiang University	A novel multiscale scheme to accelerate atomistic simulations of bio-macromolecules by adaptively driving coarse-grained coordinates	
Break			
Session 4 (Chair: HAN, Wei)			
15:55-16:35	**ZHANG, Zenghui** NYU Shanghai	蛋白质相互作用及自由能计算研究	
16:35-17:15	**ZHANG, Linfeng** Beijing Institute of Big Data Research	Learning assisted modeling for molecular simulation	
17:15-17:40	**ZHU, Tong** East China Normal University	Force Field Development for Metalloproteins with Artificial Neural Networks	
17:40-18:05	**ZHANG, Zhiyong** University of Science and Technology of China	Phase Separation of FUS-LC investigated by Multiscale Modeling	
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Wednesday, August 5th

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8:55-9:35	**HUANG, Xuhui** The Hong Kong University of Science and Technology	Memory Kernels of Protein Conformational Dynamics
9:35-10:00	**ZHU, Lizhe** The Chinese University of Hong Kong (Shenzhen)	Assessing the performance of Travelling-salesman based Automated Path Searching (TAPS) on complex biomolecular systems
Break		
Session 2 (Chair: ZHU, Lizhe)		
10:10-10:50	**SHAN, Yibing** D.E.Shaw Research	Structural modeling of large biomolecular assemblies--case studies on full-length JAK2 kinase and on Ras-Raf signalosome
10:50-11:30	**MA, Jianpeng** Fudan University	TBA
11:30-11:55	**LI, Jianing** The University of Vermont	Targeting Stress-Related GPCRs for Next-Generation Pain Treatments
11:55-12:20	**YU, Jin** University of California, Irvine	Simulating Protein Stepping along DNA
Break		
Session 3 (Chair: ZHAO, Suwen)		
13:30-14:10	**LI, Shuhua** Nanjing University	TBA
14:10-14:50	**CHEN, Haifeng** Shanghai Jiao Tong University	Environmental Specific Precise Force Field for Intrinsically Disordered and Ordered Proteins
14:50-15:15	**DUAN, Mojie** Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences	The Regulation of Phosphorylation on the Structures and Interactions of Intrinsically Disordered Proteins
15:15-15:40	**WANG, Beibei** University of Electronic Science and Technology of China	Release of empty nanodiscs from charged droplets in the electrospray ionization process: A molecular dynamics study
Break		
Session 4 (Chair: DUAN, Mojie)		
15:55-16:35	**MA, Jing** Nanjing University	A Data-Driven Accelerated (DA2) Sampling Method for Searching Functional States of Proteins
16:35-17:15	**LIU, Haiyan** University of Science and Technology of China	Statistical energy functions for de novo protein design
17:15-17:40	**ZHAO, Suwen** ShanghaiTech University	Discovery of universal activation mechanism of class A GPCRs by residue-residue contact score
17:40-18:05	**WANG, Yong** University of Copenhagen	Integrative Ensemble Modeling of a Mitochondria Chaperone-Membrane Protein Complex Using Incomplete and Ambiguous Experimental Information
Break		
Session 5 (Chair: SONG, Chen)		
19:30-20:10	**YANG, Wei** Florida State University	Energy Sampling of Long-Timescale Biomolecular Dynamics: the Energy Flow Viewpoint
20:10-20:50	**CHENG, Yuan-Chung** National Taiwan University	Theoretical study on the dynamics of light harvesting in the Photosystem II
20:50-21:30	**WEI, Guanghong** Fudan University	Molecular simulation study of peptide self-assembly and amyloid fibril inhibition by natural small molecules

Thursday, August 6th

Session 1 (Chair: GONG, Haipeng)		
8:30-9:10	**ZHOU, Yaoqi** Griffith University	Identifying molecular recognition features in intrinsically disordered regions of proteins by transfer learning
9:10-9:50	**XU, Jinbo** Toyota Technological Institute at Chicago	Latest development of deep learning for protein folding
9:50-10:15	**GONG, Xinqi** Renmin University of China	Multimer protein complex structure prediction by machine learning
Break		
Session 2 (Chair: GONG, Xinqi)		
10:30-11:10	**XU, Xin** Fudan University	New insights into the ion-π interactions
11:10-11:50	**GONG, Haipeng** Tsinghua University	Protein inter-residue distance prediction and enhanced sampling
11:50-12:15	**YUAN, Shuguang** Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences	Enhancing the Signaling of GPCRs via Orthosteric Ions
Break		
Session 3 (Chair: ZHANG, Lei)		
13:30-14:10	**LI, Hao** University of California, San Francisco	Deciphering the Genetic Determinants of Complex Human Traits through an Integrative Analysis of GWAS and Intermediate Molecular Trait Data
14:10-14:50	**HAO, Nan** University of California, San Diego	Divergent trajectories of single-cell aging
14:50-15:30	**OUYANG, Qi** Peking University	The free energy cost of oscillator synchronization
Break		
Session 4 (Chair: LI, Zhiyuan)		
15:45-16:25	**LIU, Chenli** Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences	Expanding at the right speed: an evolutionary stable strategy to colonize spatially extended habitats
16:25-17:05	**ZHANG, Lei** Peking University	Network design principle for dual function of adaptation and noise attenuation
17:05-17:30	**WANG, Weikang** University of Pittsburgh	Reconstruct cellular dynamics from single cell data
17:30-18:10	**LIN, Jie** Harvard University	Evolution of microbial traits under serial dilution
Break		
Session 5 (Chair: LIU, Chenli)		
19:30-20:10	**CHEN, Luonan** Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences	Constructing single cell specific networks
20:10-20:50	**TANG, Chao** Peking University	Oscillation, phase locking and Arnold tongues in pancreatic islets
20:50-21:00	Closing: TANG, Chao	

Calibrated Intervention and Containment of the COVID-19 Pandemic

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Abstract

Globally, one of the biggest challenges to determining the appropriate policy response to the 2019 Coronavirus Disease (COVID-19) has been the uncertainty of pre-symptomatic transmission and the lack of tools to quantify and predict its impact. A number of studies suggested that this group of viral carriers could contribute significantly to the spread of the SARS-CoV-2 virus. In East Asian countries, mask-wearing, contact-tracing and testing combined have been effective in containing early outbreaks, while western countries taking a lax approach have witnessed prolonged exponential growth of the pandemic and much slower decay.

We have developed a variant of the stochastic SEIR model with parameters calibrated against COVID-19 disease progression and transmission characteristics[1]. Due to its linear nature, the model, when applied to a large population, affords analytical solutions. The efficacy of various prevention measures can be evaluated

quantitatively. The seeding and initial growth of outbreaks, on the other hand, are dominated by chance events that require a different approach. Large social gatherings, for example, could set off an outbreak in an otherwise subcritical community. Statistical features of outbreaks with cluster infections are investigated numerically.

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[1] Liang Tian, Xuefei Li, Fei Qi, Qian-Yuan Tang, Viola Tang, Jiang Liu, Zhiyuan Li, Xingye Cheng, Xuanxuan Li, Yingchen Shi, Haiguang Liu, Lei-Han Tang, "Calibrated Intervention and Containment of the COVID-19 Pandemic", under review at Nature Communications (https://arxiv.org/abs/2003.07353).

A stochastic particle dynamics model for predicting epidemics

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Abstract

Pandemics, including COVID-19, have caused severe disasters in human history. Understanding both the trends and the details of epidemic transmission could provide useful clues for introducing efficient intervention measures. The widely used deterministic nonlinear compartmental models qualitatively capture some dynamic features of infectious disease epidemiology but present continuous “analytical” results with no room for spatiotemporal variation. To mimic the random and heterogeneous nature of the infectious disease transmission process in the real-world, here we propose a stochastic particle dynamics (SPD) based epidemic propagation model. This individual-based SPD model provides a unifying framework to represent the temporal and spatial variations and to track the motions of each one. The SPD model well reproduces the epidemic curves in different areas, discloses the local dynamics and heterogeneity of the outbreaks at the individual level, and explains the macroscopic trend of disease spreading from the microscopic perspective, which enables quantitative assessment of the potential impact of different intervention strategies. Seemingly, this SPD model is also applicable to study other stochastic processes at “meter-scale”.

Functional and Genetic Analysis of Viral Receptor ACE2 Orthologs Reveals a Broad Potential Host Range of SARS-CoV-2

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Abstract

The pandemic of Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major global health threat. Epidemiological studies suggest that bats are the natural zoonotic reservoir for SARS-CoV-2. However, the host range of SARS-CoV-2 and intermediate hosts that facilitate its transmission to humans remain unknown. The interaction of coronavirus with its host receptor is a key genetic determinant of host range and cross-species transmission. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor to enter host cells in a species-dependent manner. It has been shown that human, palm civet, pig and bat ACE2 can support virus entry, while the murine ortholog cannot. In this study, we characterized the ability of ACE2 from diverse species to support viral entry. We found that ACE2 is expressed in a wide range of species, with especially high conservation in mammals. By analyzing amino acid residues of ACE2 critical for virus entry, based on structure of SARS-CoV spike protein interaction with human, bat, palm civet, pig and ferret ACE2, we identified approximately eighty ACE2 proteins from

mammals that could potentially mediate SARS-CoV-2 entry. We chose 47 representative ACE2 orthologs among eighty orthologs for functional analysis and it showed that 43 of these mammalian ACE2 orthologs, including those of domestic animals, pets, livestock, and animals commonly found in zoos and aquaria, could bind SARS-CoV-2 spike protein and support viral entry. In contrast, New World monkey ACE2 orthologs could not bind SARS-CoV-2 spike protein and support viral entry. We further identified the genetic determinant of New World monkey ACE2 that restricts viral entry using genetic and functional analyses. In summary, our study demonstrates that ACE2 from a remarkably broad range of species can facilitate SARS-CoV-2 entry. These findings highlight a potentially broad host tropism of SARS-CoV-2 and suggest that SARS-CoV-2 might be distributed much more widely than previously recognized, underscoring the necessity to monitor susceptible hosts to prevent future outbreaks.

Free energy perturbation-based virtual screening against COVID-19 and clinical validation

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Abstract

Coronavirus disease 2019 (COVID-19) has become a global crisis, infected more than 14,000,000 patients and caused 60,000 deaths. There is no suitable therapeutic agent towards COVID-19. It is highly desirable to identify potential agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the FDA-approved drug database. Here we used a new virtual screening approach with accelerated free energy perturbation-based absolute binding free energy (FEP-ABFE) predictions to predict agents in targeting main protease Mpro. As a result, out of twenty-five drugs predicted, fifteen were confirmed as potent inhibitors of Mpro. The most potent agent Dipyridamole, which remarkably suppressed SARS-CoV-2 replication in vitro, has showed considerable therapeutic effects in clinical studies for treatment of 31 patients with COVID-19.1 Treatment with Dipyridamole improves coagulation profiles and suppresses the replication of virus simultaneously.

Reference

[1]. Xiaoyan Liu; Zhe Li; Shuai Liu; Jing Sun; Zhanghua Chen; Min Jiang; Qingling Zhang; Yinghua Wei; Xin Wang; Yi-You Huang; Yinyi Shi; Yanhui Xu; Huifang Xian; Fan Bai; Changxing Ou; Bei Xiong; Andrew M Lew; Jun Cui; Rongli Fang; Hui Huang; Jincun Zhao; Xuechuan Hong; Yuxia Zhang; Fuling Zhou; Hai-Bin Luo. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 2020, https://doi.org/10.1016/j.apsb.2020.04.008.

Role of 1'-Ribose Cyano Substitution for Remdesivir to Effectively Inhibit both Nucleotide Addition and Proofreading in SARS-CoV-2 Viral RNA Replication

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Abstract

COVID-19 has recently caused a global health crisis and an effective interventional therapy is urgently needed. SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) provides a promising but challenging drug target due to its intrinsic proofreading exoribonuclease (ExoN) function. Nucleoside triphosphate (NTP) analogues added to the growing RNA chain should supposedly terminate viral RNA replication, but ExoN can cleave the incorporated compounds and counteract their efficacy. Remdesivir targeting SARS-CoV-2 RdRp exerts high drug efficacy in vitro and in vivo. However, its underlying inhibitory mechanisms remain elusive. Here, we performed all-atom molecular dynamics (MD) simulations to elucidate the molecular mechanisms underlying the inhibitory effects of remdesivir in nucleotide addition (RdRp complex: nsp12-nsp7-nsp8) and proofreading (ExoN complex: nsp14-nsp10). We found that the 1'-cyano group of remdesivir possesses the dual role of inhibiting both nucleotide addition and proofreading. For nucleotide addition, we showed that incorporation of one remdesivir is not sufficient to terminate RNA synthesis. Instead, the presence of the polar 1'-cyano group of remdesivir at an upstream site causes instability via its electrostatic interactions with a salt bridge formed by Asp865 and Lys593, rendering translocation unfavourable. This may eventually lead to a delayed chain termination of RNA extension by three nucleotides. For proofreading, remdesivir can inhibit cleavage via the steric clash between the 1'-cyano group and Asn104. Our work provides plausible mechanisms at molecular level on how remdesivir inhibits viral RNA replication, and our findings may guide rational design for new treatments of COVID-19 targeting viral replication.

References:

[1] Lu Zhang*, Dong Zhang, Congmin Yuan, Xiaowei Wang, Yongfang Li, Xilin Jia, Xin Gao, Hui-Ling Yen*, Peter Pak-Hang Cheung*, Xuhui Huang*, *in preparation*

Prediction of targeted cancer drug resistance

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Abstract

Targeted therapies provide precision treatments for cancer patients. However, cancers acquire drug resistance over a certain period of time and new generations of drugs have to be developed again. Methods that can predict drug resistance mutations in advance will make us more prepared for life-threatening mutations. We developed a combined computational and experimental strategy to predict kinase drug resistance mutations and studied multiple factors that influence their clinical occurrence. Our computational method employs a genetic algorithm to simulate the evolution of drug-resistance mutations (EVER) with a specially designed scoring function. Using BCR-ABL as a model system, EVER successfully recaptured the clinically observed mutations that confer resistance to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib. By experimentally testing the predicted mutants *in vitro*, we found that although all mutants weakened drug binding strength as expected, the binding constants alone were not a good indicator of drug resistance. Instead, the half-maximal inhibitory concentration (IC_{50}) was shown to be a good indicator of the incidence of the predicted mutations, together with change in catalytic efficacy. EVER can be used to computationally predict potential drug-resistance mutations, which can be experimentally selected and serve as targets for next generation drug discovery and development.

Integrated computer-aided formulation design: A case study of andrographolide/ cyclodextrin ternary formulation

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Abstract

Current formulation development strongly relies on trial-and-error experiments in the laboratory by pharmaceutical scientists, which is time-consuming, high cost and waste materials.

This research aims to integrate various computational tools, including machine learning, molecular dynamic simulation and physiologically based pharmacokinetic (PBPK) modeling, to enhance andrographolide (AG) /cyclodextrins (CDs) formulation design.

The lightGBM prediction model which we built before was utilized to predict the binding free energy of AG/CDs inclusion. AG/γ-CD inclusion complexes showed the strongest binding affinity, which experimentally validated by the phase solubility study. The molecular dynamic simulation was used to investigate the inclusion mechanism between AG and γ-CD, which was experimentally characterized by DSC, FTIR and NMR techniques. PBPK modeling was applied to simulate the in vivo behavior of the formulations, which were validated by cell and animal experiments. Cell experiments revealed that the presence of D-α-Tocopherol polyethylene glycol succinate (TPGS) significantly increased the intracellular uptake of AG in MDCK-MDR1 cells and the absorptive transport of AG in MDCK-MDR1 monolayers. The relative bioavailability of the AG-CD ternary system in rats was increased to 2.6-fold and 1.59-fold compared with crude AG and commercial dropping pills, respectively.

In conclusion, this is the first time to integrate various computational tools to develop a new AG-CD ternary formulation with significant improvement of aqueous solubility, dissolution rate as well as the oral bioavailability. The integrated computational tool is a novel and powerful methodology to facilitate pharmaceutical formulation design.

Keywords: Integrated computer-aided formulation design; Machine learning; Molecular dynamic simulation; PBPK modeling; Andrographolide; Cyclodextrins.

Topology Data Analysis (TDA) Based Machine Learning Models for Drug Design

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Abstract

I will discuss topological data analysis (TDA) and its application in biomolecular data analysis, in particular, drug design. Persistent homology, which is one of the most important tools in TDA, is used in identification, classification and analysis of biomolecular structure, flexibility, dynamics, and functions. Properties from persistent homology analysis are used as features for learning models. Unlike previous biomolecular descriptors, topological features from TDA, provide a balance between structural complexity and data simplification. TDA-based learning models have consistently delivered the best results in various aspects of drug design, including protein-ligand binding affinity prediction, solubility prediction, protein stability change upon mutation prediction, toxicity prediction, solvation free energy prediction, partition coefficient and aqueous solubility, binding pocket detection, and drug discovery. Further, I will discuss our recently-proposed persistent spectral based machine learning (PerSpect ML) models. Different from all previous spectral models, a filtration process is introduced to generate multiscale spectral models. Persistent spectral variables are defined as the function of spectral variables over the filtration value. We test our models on the most commonly-used databases, including PDBbind-2007, PDBbind-2013, and PDBbind-2016. Our results are better than all existing models, for all these databases, as far as we know. This demonstrates the great power of our PerSpect ML in molecular data analysis and drug design.

GM-Dock$_{Zn}$: A Geometry Matching based Docking Algorithm for Zinc Proteins

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Abstract

Molecular docking is a widely used technique for large-scale virtual screening of the interactions between small-molecule ligands and their target proteins. However, docking methods often perform poorly for metalloproteins due to additional complexity from the three-way interactions among amino acid residues, metal ions, and ligands. This is a significant problem because zinc proteins alone comprise about 10% of all available protein structures in the protein databank. Here, we developed GM-DockZn that is dedicated for ligand docking to zinc proteins. Unlike the existing docking methods developed specifically for zinc proteins, GM-DockZn samples ligand conformations directly using a geometric grid around the ideal zinc coordination positions of 7 discovered coordination motifs, which were found from the survey of known zinc proteins complexed with a single ligand. In this work, GM-Dock$_{Zn}$ shows the best performance in sampling near-native poses with correct coordination atoms and numbers within the top 50 and top 10 predictions when compared to several state-of-the-art techniques. This is true not only for a nonredundant dataset of zinc proteins but also for a homolog set of different ligand and zinc-coordination systems for the same zinc proteins. Similar superior performance of GM-DockZn for near-native-pose sampling was also observed for docking to apo-structures and cross docking between different ligand complex structures of the same protein. The highest success rate for sampling neaest near-native poses within top 5 and top 1 was achieved by combining GM-DockZn for conformational sampling with GOLD for ranking. The proposed geometry-based sampling technique will be useful for ligand docking to other metalloproteins.

Reference

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人工智能与精准药物发现：大数据时代的个性化药物设计

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Abstract

基因突变包括单核苷酸多态性(SNP)、核苷酸序列重复、插入以及缺失等，其可能会引起编码蛋白的氨基酸序列改变，导致蛋白结构变化而影响活性，也有一些位于调控区的基因突变可能引起功能蛋白表达量的差异。现已发现多种编码药物代谢酶、转运蛋白以及作用靶点蛋白(如受体)的基因存在着基因多态性，其中药物代谢酶基因多态性可能影响到药物吸收、分布、代谢和排泄的药动学过程，导致患者出现严重毒性反应或治疗无效。

我们开发了分子模拟与计算机辅助药物设计软件 SAMM，构建细胞色素 P450 酶多态性基因型-表型相关性数据库。把支持向量机，神经网络，贝叶斯等非线性方法开发了统计预测模型以及基于 web 的软件工具并应用到药物构效关系，药物代谢以及毒理和基因表型相关性的研究中。 开发了 SNPs 及 ADMET 在线预测平台，并将其应用到各种典型体系，对个性化药物用药有一定的指导意义。

通过超大规模的高性能计算和虚拟筛选，我们发现花椒有效成分 WGX-50 有可能作为治疗阿尔兹海默症的候选药物。与本院乔中东教授以及睿智化学合作，通过大量的实验证实了 WGX-50 小分子能够结合到目标蛋白 α 7 烟碱乙酰胆碱受体（α 7 nAChR）上。同时 WGX-50 分子能够有效地抑制 Aβ 淀粉样蛋白（β-amyloid）诱导的神经胶质细胞的炎性因子的分泌，阻止细胞凋亡蛋白的表达，减少细胞凋亡，从而有效地保护神经细胞。除此以外，wgx50 能够直接作用于 Aβ 淀粉样蛋白（β-amyloid），使其解聚，从而抑制其对神经元的毒害作用。经过 WGX-50 处理之后的神经细胞中，细胞凋亡分子 Bax 的基因和蛋白表达量明显减少，进一步从蛋白和基因水平说明 WGX-50 是有神经保护作用的。

在动物水平，我们进行了 Morris 水迷宫（Morris water maze, MWM）实验，测试 WGX-50 对东莨菪碱急性引发的智力障碍的干扰作用。结果表明，WGX-50 无论是对小鼠穿越平台的次数（空间记忆），还是寻找有效路径的时间（方向位置），都可以有效地改善东莨菪碱所致的急性小鼠记忆获得性障碍。为进一步评价 WGX-50 对老年痴呆症的作用，我们采用了 ppr 转基因小鼠作为老年痴呆症的模型小鼠。选择了鼠龄为 10 周的同窝的 ppr+雄鼠及 ppr-雄鼠，随机各分为 2 组，双盲法注射 WGX-50 或生理盐水 10 天后，Morris 水迷宫法评价 WGX-50 对老年痴呆的影响。 WGX-50 可以有效地改善 ppr+转基因小鼠的记忆能力。因此，

WGX-50 可以通过激动α7 乙酰胆碱能受体及解聚β-amyloid 等途径，有效地治疗由β-amyloid 诱导的老年痴呆症。与 A 股上市公司合作申报国家一类新药。

Effective Deep Learning for Protein-drug interactions

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Abstract

Identifying novel drug–protein interactions is crucial for drug discovery. For this purpose, many machine learning-based methods have been developed based on drug descriptors and one-dimensional protein sequences. However, protein sequences cannot accurately reflect the interactions in three-dimensional space, while direct input of three-dimensional structure is of low efficiency due to the sparse three-dimensional matrix, and is also prevented by the limited number of co-crystal structures available for training. Here we propose an end-to-end deep learning framework to predict the interactions by representing proteins with a two-dimensional distance map from monomer structures (Image) and drugs with molecular linear notation (String), following the visual question answering mode. For efficient training of the system, we introduce a dynamic attentive convolutional neural network to learn fixed-size representations from the variable-length distance maps and a self-attentional sequential model to automatically extract semantic features from the linear notations. We validated the representative learning of the protein and molecule through protein sequence recovery and predictions of molecular properties. The experiments to predict protein-compound interactions demonstrate that our model obtains competitive performance against state-of-the-art baselines on the directory of useful decoys, enhanced (DUD-E), human and BindingDB benchmark datasets. Further attention visualization provides biological interpretation to depict highlighted regions of both protein and drug molecules.

Development of FEP-ABFE method and its applications in drug discovery

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Abstract

Accurate prediction of absolute protein-ligand binding free energy is essential for structure-based drug design, and free energy perturbation (FEP) has been proven to be a reliable method. We developed a Gaussian algorithm enhanced FEP (GA-FEP) protocol to enhance the FEP simulation performance, enabling to efficiently carry out the FEP simulations on annihilation of the whole ligand and, thus, predict the absolute binding free energies (ABFE). We further derived a new restraint energy distribution (RED) function which greatly accelerate the FEP-ABFE calculations. We will discuss the theoretical development of the FEP-ABFE method and introduce two typical application cases of the FEP-ABFE method in drug discovery. In the first application, the FEP-ABFE-guided lead optimization against phosphodiesterase-10 led to discovery of a subnanomolar inhibitor (IC_{50}=0.87 nM, ~2,000-fold improvement in potency). In the second application, we used FEP-ABFE method to screen the existing drug library in order to find anti COVID-19 drugs, and as a result, out of twenty-five drugs picked by virtual screening method, fifteen were confirmed as potent inhibitors of SARS-CoV-2 M^{pro}. The most potent one is dipyridamole (K_i=0.04 μM) which has showed promising therapeutic effects in subsequently conducted clinical studies for treatment of patients with COVID-19. We anticipate that the FEP-ABFE prediction-based drug design and virtual screening approach will be useful in many other drug discovery efforts.

靶向跨膜蛋白-蛋白相互作用的药物发现

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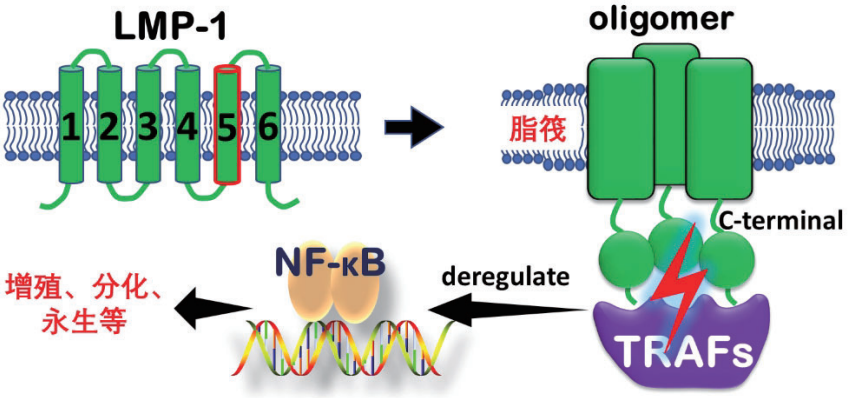
Abstract

蛋白-蛋白相互作用几乎是一切生命活动的基础。因此，蛋白-蛋白相互作用是至关重要的药物靶点。由于膜蛋白具有强疏水性，导致目前对其结构了解较少，严重制约了靶向跨膜蛋白-蛋白相互作用的药物发现研究。

Epstein-Barr 病毒作为第一个被发现的导致人类癌症的病毒，具有高度传染性。同时，该病毒也与许多恶性肿瘤高度相关。Epstein-Barr 病毒诱导宿主细胞癌变主要通过其编译的癌蛋白（潜在膜蛋白 1，LMP-1）寡聚化激活下游信号通路实现[1]。然而，由于 LMP-1 富集结晶困难，至今还未有相关结构报道。鉴于 LMP-1 寡聚化由第五跨膜域介导，本研究以第五跨膜域为靶标，进行靶向 LMP-1 寡聚化作用界面的小分子及多肽抑制剂理性设计，为治疗 Epstein-Barr 病毒诱导的恶性肿瘤提供潜在药物[2]。通过计算模拟与实验结合，本研究将小分子抑制活性（IC_{50}）由最初的 90.0±10.5 μM 优化提高到 0.7±0.2 μM，并设计了首个可破坏膜蛋白同源三聚化的多肽抑制剂，为相关疾病的药物开发提供了新思路。



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Power of computational design in drug discovery and development: A journey from *in silico* to clinical studies

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Abstract

Computational drug design has become a truly powerful tool for not only drug discovery stages, but also preclinical and clinical drug development stages. I will first give a brief overview of the roles of computational biology and molecular modeling in understanding molecular mechanisms of biological systems and modern drug design, discovery and development, and discuss the general trend of computational drug design, discovery, and development through specific examples of our recent efforts in drug design, discovery, and development (from computational design to clinical development). The presentation will show how the state-of-the-art computational modelling and design can effectively be integrated with wet experimental tests (*in vitro* and *in vivo*) and clinical studies for actual drug discovery and development. Appropriately integrated with wet experimental studies *in vitro* and *in vivo* as well as clinical studies, state-of-the-art computational design is of great value not only for small molecule drug discovery, but also for discovery and development of novel therapeutic proteins engineered from naturally occurring proteins. Integrated computational-experimental drug design and discovery efforts have led to exciting discovery of promising drug candidates, including multiple Investigational New Drugs (INDs) including two that have completed Phase II clinical trials; one has received the *Breakthrough Therapy* designation by the FDA. In addition, I will also briefly discuss our most recently developed new protocol, called DREAM-*in*-CDM (Drug Repurposing Effort Applying Integrated Modeling-*in vitro/vivo*-Clinical Data Mining), for successful drug repurposing.

Integrating Machine Learning and Molecular Modelling for Drug Design

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Abstract

Computational approaches have increasingly become an indispensable part in drug design and attracted much more attention. In this talk, I will present our most recent progresses along this direction by integrating machine learning and molecular modeling.

Correlated Segments and Fuzzy Membrane Association of Intrinsically Disordered Proteins

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Abstract

Intrinsically disordered proteins (IDPs) account for a significant fraction of any proteome and are central to numerous cellular functions. Yet how sequences of IDPs code for their conformational ensembles, conformational dynamics, and ultimately, functions is poorly understood. I will report advances from our computational and experimental studies of two membrane proteins containing intrinsically disordered regions (IDRs). For ChiZ (a component of the cell division machinery in *Mycobacterium tuberculosis*), our NMR data revealed non-uniform backbone dynamics along the sequence of the 64-residue N-terminal IDR (NT) [1]. Our molecular dynamics (MD) simulations traced the origin to correlated segments, which are stabilized by polyproline II stretches, salt bridges, cation-π interactions, and sidechain-backbone hydrogen bonds. Moreover, the extent of segmental correlation is sequence-dependent: segments (e.g., residues 11-29) where internal interactions are more prevalent manifest elevated "collective" motions on the 5-10 ns timescale and suppressed local motions on the sub-ns timescale. Our NMR experiments found that NT associates with acidic membranes, but most residues remain dynamic, exception for a subset of Arg residues. MD simulations provided crucial details on the fuzzy conformational ensemble, showing NT anchored to membranes in the midsection, in particular by Arg37. Lastly, we used MD simulations to investigate the mechanism of Ca^{2+}-bound synaptotagmin-1 triggering membrane fusion, and produced a promising model that reconciles many conflicting experimental observations [2]. Most importantly, a conserved acidic motif within an IDR competes with the vesicle membrane for interacting with the Ca^{2+}-binding loops of the C2B domain, and flips C2B over for association with the plasma membrane, thereby bringing the two membranes closer for fusion. These findings serve as paradigms for sequence-conformation-dynamics-function relations of IDPs.

Reference

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Tuning Color and Activity of Calcium-regulated Photoprotein Luminescence

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Abstract

Bioluminescence (BL) produced by calcium-regulated photoproteins (CaDP) is widely distributed in five phyla of marine organisms. The well-known CaDPs are aequorin and obelin, which emit light via the excited-state coelenteramide (CTD). CTD is formed via decomposition of a key high-energy intermediate dioxetanone (CDO), which is produced from coelenterazine (CTZ) oxidation. The light emitted by those CaDPs can be tuned by mutating the CaDPs and/or by modifying the substrate. To extend the color range of CTD fluorescence (FL), we theoretically designed six CTD analogues based on the regularity from investigating 42 CTD analogues. Together with the wild CTD, these seven ones emit the seven colors of rainbow. For obelin, His22-Phe88-Trp92 triad is crucial factor affecting BL color. By mutating obelin at His22-Phe88-Trp92 triad, we theoretically constructed nine mutants of emitting separable FL colors. Thirty years ago, Shimomura observed that the luminescence activity of aequorin was dramatically reduced when the substrate CTZ was replaced by its analog *v*-CTZ. The latter is formed by adding a phenyl ring to the π-conjugated moiety of CTZ. The decrease in luminescence activity has not been understood until now. Through QM/MM calculation and MD simulation, we clearly explain the reason. The microenvironments of CTZ in obelin and in aequorin are very similar, so we predicted that the luminescence activity of obelin will also dramatically decrease when CTZ is replaced by *v*-CTZ. This prediction has been verified by both theoretical and experimental studies.

Adaptive QM/MM via the Reference-Potential Method

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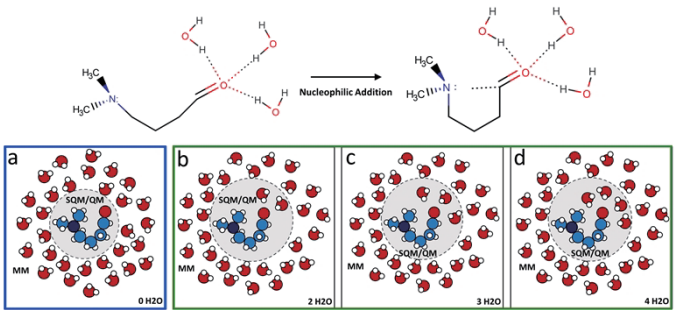
Abstract

Although QM/MM methods are now routinely applied to the studies of chemical reactions in condensed phase and enzymatic reactions, they may confront technical difficulties when the reactive region is varying. For instance, when the solvent molecules are participating the reaction, the exchange of water molecules between the QM and MM regions may occur on a time scale that is comparable to the reaction. Several adaptive QM/MM schemes have been proposed to cope with this situation. However, these methods either significantly increase the computational cost or introducing unrealistic restraints to the system. In this work, we developed a novel adaptive QM/MM scheme and applied it to a study of nucleophilic addition reaction. In this approach, the simulation was performed with a small QM region (without solvent molecules), and the thermodynamic properties under the potential energy functions with large QM regions (with different number of solvent molecules) are computed via the reference-potential method. The results show that this reweighting process is numerically stable, at least for the case studied. Furthermore, this method also offers an inexpensive way to check the convergence of the QM/MM calculation with respect to the size of the QM region.



OnionNet: a multiple-layer inter-molecular contact based convolutional neural network for protein-ligand binding affinity prediction

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Abstract

Computational drug discovery provides an efficient tool helping large scale lead molecules screening. One of the major tasks of lead discovery is identifying molecules with promising binding affinities towards a target, a protein in general. The accuracies of current scoring functions which are used to predict the binding affinity are not satisfactory enough. Thus, machine learning (ML) or deep learning (DL) based methods have been developed recently to improve the scoring functions. In this study, a deep convolutional neural network (CNN) model (called OnionNet) is introduced and the features are based on rotation-free element-pair specific contacts between ligands and protein atoms, and the contacts were further grouped in different distance ranges to cover both the local and non-local interaction information between the ligand and the protein. The prediction power of the model is evaluated and compared with other scoring functions using the comparative assessment of scoring functions (CASF-2013) benchmark and the v2016 core set of PDBbind database. When compared to a previous CNN-based scoring function, our model shows improvements of 0.08 and 0.16 in the correlations (R) and standard deviations (SD) of regression, respectively, between the predicted binding affinities and the experimental measured binding affinities. The robustness of the model is further explored by predicting the binding affinities of the complexes generated from docking simulations instead of experimentally determined PDB structures.

Specific Regio- and Enantioselectivity of Fluostatin Conjugation

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Abstract

Fluostatins, benzofluorene-containing aromatic polyketides in the atypical angucycline family, conjugate into dimeric and even trimeric compounds in the post-biosynthesis. The formation of the C–C bond involves a non-enzymatic stereospecific coupling reaction (Nature Communication, 2018, 9: 2088). In this work, the unusual regio- and enantioselectivities were rationalized by density functional theory calculations with the M06-2X(SMD, water)/6-311+G(d,p)//6-31G(d) method. These DFT calculations reproduce the lowest-energy C1-(R)-C10'-(S) coupling pathway observed in a nonenzymatic reaction. Bonding of the reactive carbon atoms (C1 and C10') of the two reactant molecules maximizes the HOMO–LUMO interactions and Fukui function involving the highest occupied molecular orbital (HOMO) of nucleophile p-QM and lowest unoccupied molecular orbital (LUMO) of electrophile FST□□. In particular, the significant π–π stacking interactions of the low-energy pre-reaction state are retained in the lowest-energy pathway for C–C coupling. The distortion/interaction-activation strain analysis indicates that the transition state (TScp-I) of the lowest-energy pathway involves the highest stabilizing interactions and small distortion among all possible C–C coupling reactions. One of the two chiral centers generated in this step is lost upon aromatization of the phenol ring in the final difluostatin products. Thus, the π–π stacking interactions between the fluostatin 6-5-6 aromatic ring system play a critical role in the stereoselectivity of the nonenzymatic fluostatin conjugation.

Deciphering the Enigmatic Oxygen Activation and Methane Oxidation Mechanisms by Particulate Methane Monooxygenase

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Abstract

The enzymatic oxidation of methane to methanol has been discovered in methanotrophs for over 110 years. Nevertheless, the mechanism of action of particulate methane monooxygenase (pMMO) remains elusive, especially regarding the issues of O_2 activation and the nature of the active-species of the enzyme. Starting from scratch, by incorporating the physiological reductant duroquinol (DQH_2), we deciphered the catalytic-cycle of pMMO. We demonstrate that O_2 activation is in fact initiated by a $Cu_C(II)-DQH^-$ species generated by deprotonation of DQH_2. Our simulations capture the exclusive pathway for the sequential formation of the intermediates, $Cu_C(II)-O_2^{\bullet -}$, $Cu_C(II)-OOH$ and H_2O_2, along O_2 reduction pathway. Further, H_2O_2 activation by $Cu_C(II)-DQH^-$ is initiated by dissociation of $DQH^\bullet$ to yield $Cu_C(I)$, followed by the $Cu_C(I)$-catalyzed O−O homolysis, *en-route* to the formation of the $Cu_C(II)-O^\bullet$ species, which is the one responsible for C−H oxidations. These findings uncover the important roles of the phenol co-substrate for O_2 activation, and help resolve the enigmatic mechanisms of pMMO.

From dinucleotide to chromatin, a domain segregation perspective for chromatin structure change in development, differentiation, senescence and certain diseases

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Abstract

The high-order chromatin structure and epigenetic modification plays an important role in gene regulation. The mechanism, especially the sequence dependence for the formation of varied chromatin structures in different cell states remain to be elucidated. In this talk, we try to touch on three questions: (1) What is the sequence dependence and chemical structure basis in the formation of high order chromatin structure? (2) How does the chromatin structure reflect the biological function of different cellular states and tissue-specificity? (3) How does this sequence-dependent chromatin structure formation manifest in different species? Based on the sequence properties, we divided the genome into two sequentially, epigenetically, and transcriptionally distinct regions. These two megabase-sized domains were found to spatially segregate, and to different extents in different cell types. They show enhanced segregation from each other in development, differentiation, and senescence, meanwhile the multi-scale forest-prairie spatial intermingling is cell-type specific and increases in differentiation, helping to define cell identity. We propose that the phase separation of the 1D mosaic sequence in the 3-D space serves as a potential driving force, and together with cell type specific epigenetic marks and transcription factors, shapes the chromatin structure in different cell types. Specifically, based on the analysis of latest published Hi-C data of post-implantation stages, we present a consistent view of the chromatin structural change and the corresponding sequence dependence. Chromatin shows systematic and overall increase of spatial segregation during embryonic development, but with notable mixing occurring at two stages, ZGA and implantation. The segregation level change largely coincides with the change of genetic and epigenetic properties, leading to a possible mechanism of functional realization during implantation was proposed. We will also discuss the possible chromatin structure changes and their influence on gene regulation in carcinogenesis.

生物体系多尺度理论研究的方法发展及应用

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Abstract

生物系统虽然由简单的氨基酸、核酸组成的大分子体系和小分子环境组成，但是由于它们排列组合空间巨大，使得它们之间的相互作用也是异常之复杂多样。现有的实验技术手段由于采用其他分子或外力作为辅助，导致所观察到的结果与真实生物学现象之间有很大差距，分子动力学模拟弥补了这些实验的局限性。

尽管分子动力学模拟已经取得了一定成功，但是对于生物学研究来讲它能够解析或回答的问题还很有限，除了生物体系本身的复杂性之外，更重要的是现有分子动力学模拟理论方法本身还存在着很多不足之处，无法实现中小体系的高精度模拟以及高效率研究巨大复杂体系，我们近几年在高精度分子模型和高效率模拟方法以及新型粗粒化分子模型等方面取得了一定进展。并针对重大疾病开展了相关药物筛选与设计以及生命科学领域重要体系功能机理的应用研究，取得了重要成果，在 Nature（2016, 2019）、Science（2018）、Nat. Plants(2019)、Mol. Cell(2018, 2019)等国际著名期刊发表 120 余篇论文，多次受邀担任国际会议主席和做邀请报告。

Bottom-Up Derived Flexible Water Model with Dipole and Quadrupole Moments for Multiscale Molecular Simulations

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Abstract

Coarse-grained (CG) water models offer opportunity to study molecular processes in water on spatial and temporal scales inaccessible to conventional atomistic simulations. A CG model that can properly describe structural, electrostatic and thermodynamic properties of liquid water is invaluable but difficult to derive. Here, we present a flexible three-site CG water model representing clusters of water molecules. This model, termed FlexDQ, is derived with a fully bottom-up approach in which atomistic information of water molecules is processed through a clustering technique based on both energy and geometry consideration and a mapping algorithm that encodes information of dipole and quadrupole moments of water clusters into CG interaction sites. Augmented by these processed data, the parameterization is conducted consistently and systematically. The resulting model reproduces not only dipolar and quadrupolar fluctuations of water clusters but also their spatial and orientational correlation. We demonstrate that the reproduction of structural correlation originates from explicit treatment of electrostatics. As a result, the model predicts, to a good extent, pressure-related properties and dielectric permittivity that are not targeted for parameterization. When combined with the MARTINI CG lipid model, our model describes reasonably well the dielectric behavior of water at water-membrane interface, yielding a positive internal electrostatic potential in membrane that has otherwise been difficult to reproduce originally with MARTINI. Furthermore, our coarse-graining framework is extended to the development of united-atom models for various solute molecules that are consistent with our water model, describing reasonably well water structures near these solutes and solvation free energy of nonpolar solute. Collectively, the CG water model shows promise for multiscale simulations in water.

A novel multiscale scheme to accelerate atomistic simulations of bio-macromolecules by adaptively driving coarse-grained coordinates

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Abstract

All-atom molecular dynamics (MD) simulations of bio-macromolecules can yield relatively accurate results while suffering from the limitation of insufficient conformational sampling. On the other hand, the coarse-grained (CG) MD simulations efficiently accelerate conformational changes of biomolecules but losing atomistic details and accuracy. Here we propose a novel multiscale simulation method, called the adaptively-driving multiscale simulation (ADMS) – it efficiently accelerates biomolecular dynamics by adaptively driving virtual CG atoms on the fly while maintaining the atomistic details and focusing on important conformations of the original system with irrelevant conformations rarely sampled. Herein the "adaptively driving" is based on the short-time-averaging response of the system (i.e., an approximate free energy surface of the original system), without requiring the construction of the CG force field. We apply the ADMS to two peptides (deca-alanine and Ace-GGPGGG-Nme) and one small protein (HP35) as illustrations. The simulations show that the ADMS not only efficiently captures important conformational states of biomolecules and drives fast interstate transitions but also yields, although might be in part, reliable protein folding pathways. Remarkably, a ~100-ns explicit-solvent ADMS trajectory of HP35 with three CG atoms realizes folding and unfolding repeatedly and captures the important states comparable to those from a 398-μs standard all-atom MD simulation.

蛋白质相互作用及自由能计算研究

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Abstract

In this talk, we will discuss some computational methods to study thermo- and interaction dynamics of proteins. This will include the prediction of the thermostability of a protein upon point mutation and how mutation changes the protein-ligand and protein-protein binding free energy. Effort to treat metalo-protein will also be discussed.

Learning assisted modeling for molecular simulation

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Abstract

In recent years, machine learning (ML) has emerged as a promising tool for dealing with the difficulty of representing high dimensional functions. This gives us an unprecedented opportunity to revisit theoretical foundations of various scientific fields, develop new schemes, and solve problems that were too complicated for conventional approaches to address. Here we identify a list of such problems in the context of multi-scale molecular modeling and propose ML-based strategies to boost simulations with *ab-initio* accuracy to much larger scales than conventional approaches. Our strategies follow two seemingly obvious but non-trivial principles: 1) ML-based models should respect important physical constraints like symmetry; 2) to build truly reliable models, efficient algorithms are needed to construct a minimal but truly representative training data set. We use these principles to develop ML-based models at different scales: electronic structure models (DeePHF, DeePKS), molecular dynamics models (DeePMD, Deep Wannier, etc.), and coarse-grained models (DeePCG). In the meanwhile, we develop efficient data generation and sampling strategies: Deep Potential Generator (DP-GEN) for generating an optimal data set on the fly, and Reinforced Dynamics for efficiently exploring the high-dimensional free energy landscape. Applications of these models and algorithms are presented for problems in chemistry, biology, and materials science. Finally, we present our efforts on developing related software packages, which have now been widely used worldwide by experts and practitioners in the molecular simulation community.

Force Field Development for Metalloproteins with Artificial Neural Networks

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Abstract

The question of whether molecular dynamics (MD) simulations can yield reliable structural and dynamical properties of metalloproteins highly depends on the accuracy of the force field. Artificial neural network provides the possibility to develop force fields with both the efficiency of the classical molecular mechanics and the accuracy of the quantum chemical methods. We developed an *ab initio* based neural network potential (NN/MM-RESP) to study the hydration of Zn^{2+}. In this approach, the interaction energy, atomic forces, and atomic charges of zinc ion and water molecules in the first solvent shell were described by a neural network potential trained with energies and forces generated from density functional calculations. The predicted energies and forces from the NN potential show excellent agreement with the quantum chemistry calculations. The experimentally observed zinc–water radial distribution function, as well as the X-ray absorption near-edge structure spectrum, is well-reproduced by the MD simulation. Recently, this method has been extended to metalloproteins. In the MD simulation the coordination geometry of metal-binding groups shows excellent agreement with the experimental measurements, demonstrating that the NN potentials are accurate enough to maintain the correct structural integrity of the metal-binding pocket and provide accurate interaction dynamics of metalloproteins. The salient features of NN force fields can shed light on the development of more accurate molecular potentials for metal ions in other molecular environments.

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Phase Separation of FUS-LC investigated by Multiscale Modeling

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Abstract

In human cells, there are many membraneless organelles, also known as biomacromolecules condensation, which can be reversibly assembled and disassembled to precisely regulate the specificity of intracellular biochemical reactions. There are many types of membraneless organelles, such as P granules, Stress granules (SG). Stress granules are formed by the combination of RNA and many proteins, they can respond to external environmental stimulation by covering untranslated mRNA. Proteins, such as FUS and G3BP1, are core protein of SG. In recent years, many studies have shown that liquid-liquid phase separation(LLPS) is considered to play important roles in membraneless organelle formation. The weak multivalent interactions between protein-protein and protein-RNA can drive the phase separation. Many kinds of chemical modification, such as, phosphorylation and acetylation could regulate the process of LLPS. Obtaining high-resolution structural information of proteins involved in the phase separation may be difficult, the methods of multiscale computational simulation are currently effective, which study the dynamic process of biological macromolecules on different spatial and temporal scales to complementary to experimental data. We used multiscale computational simulation to study the phase separation process of LC domain of FUS protein by phosphorylation. A NMR structure of FUS-LC was taken to start All-atom MD simulations, which clearly indicated that phosphorylating could destroy the nine-layers fiber structures and preventing LLPS. Coarse-graining (CG) method were performed to study the process of assembly and disaggregation of FUS-LC, which have shown that only WT could be assembled to nine-layers fiber structures from random initial conformation, we also predict critical folding temperature of FUS-LC by CG. The MM/PBSA method were used to analyze the inter-chain binding free energy of non-phosphorylated and phosphorylated FUS-LC and predict residues that play an important role in structural changes. Our study is expected to reveal the molecular mechanism of liquid-liquid phase separation by regulating of phosphorylation.

Functional plasticity and evolutionary adaptation of allosteric regulation

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Abstract

Allostery is a fundamental regulatory mechanism of protein function. Despite notable advances, understanding the molecular determinants of allostery remains an elusive goal. Our current knowledge of allostery is principally shaped by a structure-centric view which makes it difficult to understand the decentralized character of allostery. Our experimental collaborator (S. Raman, UW-Madison) developed a function-centric approach using deep mutational scanning to elucidate the molecular basis and underlying functional landscape of allostery. The results show that allosteric signaling exhibits a high-degree of functional plasticity and redundancy through myriad mutational pathways. Residues critical for allosteric signaling are surprisingly poorly conserved while those required for structural integrity are highly conserved, suggesting evolutionary pressure to preserve fold over function. The results suggest multiple solutions to the thermodynamic conditions of cooperativity, in contrast to the common view of a finely-tuned allosteric residue network maintained under selection. Motivated by these experimental findings, we have conducted extensive molecular dynamics simulations, free energy calculations and machine learning analyses to better understand the molecular basis of cooperativity and modulation of the free energy landscape by mutations as well as by inducer/DNA binding. Initial results of the analysis will be presented.

Memory Kernels of Protein Conformational Dynamics

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Abstract

Protein conformational dynamics play an important role in numerous biological processes. Markov State Models (MSMs) provide a powerful approach to study these dynamic processes by predicting long time scale dynamics based on many short molecular dynamics (MD) simulations. In an MSM, protein dynamics are modeled as a kinetic process consisting of a series of Markovian transitions between different conformational states at discrete time intervals (called “lag time”). To achieve this, a master equation must be constructed with a sufficiently long lag time to allow interstate transitions to become truly Markovian. This imposes a major challenge for MSM studies of proteins since the lag time is bound by the length of relatively short MD simulations available to estimate the frequency of transitions. Here, we show how one can employ the generalized master equation formalism to obtain an exact description of protein conformational dynamics without the time resolution restrictions imposed by the MSM lag time. Our developed quasi-MSM (qMSM) encodes the non-Markovian dynamics in a generally time-dependent memory kernel, whose characteristic decay time scale corresponds to the kernel lifetime. We have shown that qMSMs can be used to capture short-, intermediate-, and long-time dynamics of a variety of systems, including alanine dipeptide and the WW Domain Fip35, with a memory kernel lifetime that is 5–10 times shorter than the lag time, needed to obtain accurate MSM dynamics. Moreover, we applied qMSMs to elucidate memory kernels and mechanisms of the RNA polymerase clamp opening, a functional conformational change critical for gene transcription. We expect that qMSMs hold promise to be widely applied to study biomolecular conformational changes.

Assessing the performance of Travelling-salesman based Automated Path Searching (TAPS) on complex biomolecular systems

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Abstract

Though crucial for understanding biomolecular function, it remains challenging to locate the minimum free energy paths (MFEPs) between two conformational states of large biomolecular systems because of the often lack of prior knowledge about the system. To alleviate this issue, we have previously introduced a Travelling-salesman based path searching method (TAPS) and demonstrated its efficiency on simple peptide systems. Having implemented a parallel version of this method, here we access the performance of TAPS on three realistic systems (tens to hundreds of residues) in explicit solvents. We show that TAPS successfully located the MFEP for the ground/excited state transition of T4 lysozyme L99A variant, consistent with previous findings. Moreover, TAPS revealed unprecedented details of the loop-in/loop-out transition of Mitogen-activated protein kinase kinase MEK1 (role of salt bridges R227:L235, Y229:E255) and the Ltn40/Ltn10 interconversion of Lymphotactin (five salt bridges E31:R57 / E31:R61 / R35:T54 / T16:R43 / R23:S67 directing the process). These results present TAPS as a general and promising approach for studying the functional dynamics of complex biomolecular systems.

Structural modeling of large biomolecular assemblies--case studies on full-length JAK2 kinase and on Ras-Raf signalosome

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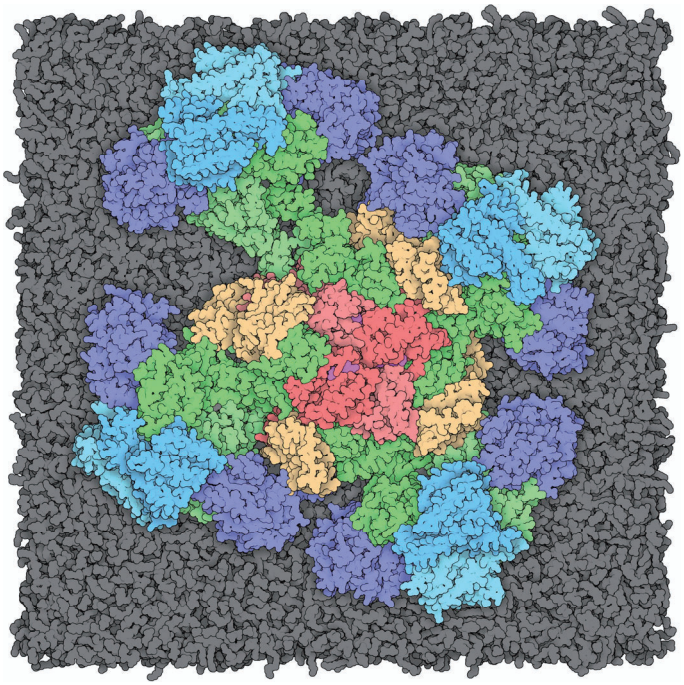
Abstract

Molecular dynamics (MD) simulations hold the potential in recapitulating the physical process of protein-protein and protein-small molecule binding and in predicting the native structure of the biomolecular complexes. Careful scrutiny of the simulation-generated structural models in light of existing biochemical, biophysical, and cellular data should largely eliminate the false models and lead to focus on the correct ones. Further model constructions, MD simulations, and experimental validation enable may produce atomic-detailed structural models of large biomolecular assemblies. We here discuss two projects: we modeled the four-domained structures of inactive and active (dimerized) JAK2 kinase and the megadalton membrane-anchored Ras-Raf signalosome that consists of many copies of K-Ras and C-Raf proteins, together with copies of several auxiliary proteins. These models illustrate that MD simulation is increasing a viable platform for the structural biology of large biomolecular assemblies.



Targeting Stress-Related GPCRs for Next-Generation Pain Treatments

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Abstract

Sustained stress is well known to facilitate maladaptive physiological and behavioral responses, and increase health risks. However, the molecular mechanisms underlying the stress effects are not fully understood, and thus targeting such mechanisms remains a great challenge. Herein, we demonstrate that G protein coupled receptors (GPCRs) may control stress-related signaling dynamics, with a showcase of a critical stress modulator GPCR — the PAC1R and its variants. Using extensive molecular simulations and the Markov state model, we examined the open-to-closed transition of PAC1R and an ensemble of transitional states, which elucidated the key details of PAC1R activation. Furthermore, we simulated different PAC1R variants and discovered that the Hop variant enhanced receptor internalization and sustained stress response. Building on the knowledge from *in silico* investigations, we have successfully designed peptides and small molecules that inhibit the receptor activation. These findings hold the great promise to rationally design new treatments to stress-related chronic pain, as well as potential solutions to the opioid crisis. Overall, our studies present an example of conjugated protein modeling, multiscale simulations, and cutting-edge computer-aided design in modern drug discovery.

Simulating Protein Stepping along DNA

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Abstract

Protein machinery consisting of enzymes and a variety of factors move along DNA and are responsible for regulating gene expression. Our team has computationally studied representative transcription engine, a viral RNA polymerase (RNAP), and several transcription factors (TFs), which demonstrate stepping from one to several base pairs (bps) per cycle during movements on the DNA. For an RNAP enzyme or motor that makes a transcription bubble along DNA for template-based polymerization, the 1-bp stepping or RNAP translocation appears Brownian but rectified or biased by cognate nucleotide incorporation. We examined such an RNAP translocation along with nucleotide incorporation and selection using all-atom molecular dynamics (MD) simulation and chemical master equation approaches, showing structural dynamics, energetics, and kinetic mechanisms of the RNAP selective ratcheting. Employing the structure-based MD simulations, we studied binding and diffusion of TFs on the DNA. A complete 1-bp stepping cycle during diffusion of a small plant TF, the WRKY domain protein, has been identified from our atomic equilibrium simulations. The simulations reveal non-synchronized hydrogen bonding breaking and reformation at the protein-DNA interface, as well as stochastic behaviors of protein slipping, directional reversal, and strand crossing. Preferential binding onto one strand of DNA becomes prominent when the protein domain binds onto specific DNA. We additionally implemented coarse-grained (CG) simulations to sample persistent protein diffusion on the DNA and sequence-dependent step size distributions etc. For a heterodimeric oncogenic protein Myc-Max, interestingly, we have identified inchworm stepping of the protein in the CG simulation as it diffuses along DNA, with two DNA binding basic regions (BRs) alternating stepping upon open and close transitions, and with occasional left-right BR swapping. These studies show great potential to computationally examine protein-DNA structural dynamics across scales to reveal physical and functional mechanisms in genetic and epigenetic regulations.

EnvironmentalSpecific Precise Force Field for Intrinsically Disordered and Ordered Proteins

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Abstract

Intrinsically disordered proteins (IDPs) or intrinsically disordered regions have not fixed tertiary structure, but play key roles in signal regulation, molecule recognition, and drug target. However it is difficult to study the structure and function of IDPs by traditional experimental methods because of their diverse conformations. Limitations of current generic protein force fields were reported in the previous simulations of IDPs. We have also explored to overcome these limitations by developing precise force fields to correct the dihedral distribution for eight disordered promoting residues, all 20 naturally occurring amino acids, and environmental specific residues to further improve the quality in the modeling of IDPs. Extensive tests of IDPs and unstructured short peptides show that the simulated Cα chemical shifts with the precise force field are in quantitative agreement with those from NMR experiment and are more accurate than the base generic force field. Furthermore, the simulation effectiveness is also higher than other force fields. These findings confirm that the newly developed precise force field can improve the conformer sampling of intrinsically disordered proteins.

The Regulation of Phosphorylation on the Structures and Interactions of Intrinsically Disordered Proteins

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Abstract

As a class of proteins without ordered secondary and tertiary structures, intrinsically disordered proteins (IDPs) play critical roles in the signal transport and regulation. The IDP functions are regulated by post-translational modifications (PTMs). As one of the most common PTMs, more than 2/3 phosphorylation are located on IDPs. Due to the high flexibility, it is hard to determine the structure transitions and regulations of the IDPs induced by PTMs based on current experimental technologies. In this study, the conformational changes of IDPs induced by phosphorylation were investigated by computational simulations and enhanced sampling technologies. Moreover, the binding process and mechanism induced by the phosphorylation were studied. Our study provides the detailed description of how phosphorylation regulates the folding and binding with their partners of IDPs. This work would help to understand the structure basis of the IDP functions.

Release of empty nanodiscs from charged droplets in the electrospray ionization process: A molecular dynamics study

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Abstract

Electrospray ionization (ESI) prevents the analyte from being split into fragments and is widely used to analyze biomolecules. Nanodiscs provide a native-like environment for membrane proteins, while making them accessible in solution for analysis. We used molecular dynamics simulations to provide atomistic insight in the release of intact nanodiscs from charged droplets. This process proceeds overall according to the charged residue model, i.e., solvent evaporates leaving a gaseous ion. We observed two distinct main scenarios, at-center and off-center. In the at-center process, the nanodisc stays well in the droplet interior, keeping its original geometry. As solvent evaporates, lipids turn over to protect the hydrophilic surface. In the off-center process, by contrast, the nanodisc migrates to the water/air interface, leading to lipids escaping from the dissociated dimer. The ESI charge states of the gaseous ions are higher than found experimentally. By extrapolating our data to lower charge states, our results are in excellent agreement with the experimental mass spectra. Further simulations without long-range electrostatic interactions or for neutral droplets confirmed that the electrostatic interactions play an essential role in the behavior of nanodiscs in the ESI process and the shape of the resulting gaseous ions

A Data-Driven Accelerated (DA2) Sampling Method for Searching Functional States of Proteins

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Abstract

Protein exhibits distinct characteristics in different functional states. The lack of structural information for proteins hinders the understanding of their functions. We proposed a data-driven accelerated (DA2) sampling method, which is capable of searching new functional states of protein from a known structure with high efficiency.[1] In DA2, no biased potential/force was applied, and principle component analysis was applied on-the-fly to extract the intrinsic motion from conventional molecular dynamics simulations. The capacity and accuracy of DA2 sampling were demonstrated by the simulation of transition from the open state of N-terminal calmodulin (nCaM) to the closed state. The closed state discovered by DA2 deviated a little from the crystal structure of nCaM in its closed state, with a root-mean-square deviation (RMSD) of only 1.8 Å. Interestingly, independent DA2 samplings disclosed different open-to-closed transition pathways for nCaM, which is likely to have implications for its biological functions. Therefore, DA2 sampling is expected to play important roles in exploring functional states of a broad spectrum of proteins at atomic level that are not easily determined experimentally. Other related DA2 versions will be also presented in this talk.

Reference

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Statistical energy functions for de novo protein design

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Abstract

Previously, we have developed and validated a statistical energy function, ABACUS, for the de novo design of amino acid sequences for given protein backbones. For the design of protein backbones from scratch, a general method to sample and optimize protein backbones without specific sequence information is much needed. A viable solution would be molecular simulations driven by an energy function that can faithfully recapitulate the characteristically coupled distributions of multiplexes of local and non-local conformational variables in designable backbones. It is desired that the energy surfaces are continuous and smooth, with easily computable gradients. We have developed an energy function named SCUBA, standing for Side-Chain-Unspecialized-Backbone-Arrangement. SCUBA uses neural networks (NN) learned from known protein structures to analytically represent high-dimensional statistical energy surfaces. Each NN term is derived by first estimating the statistical energies in a multi-variable space via neighbor-counting (NC) with adaptive cutoffs, and then training the NN with the NC-estimated energies. The weights of the different energy components are calibrated on the basis of SCUBA-driven stochastic dynamics (SD) simulations of natural proteins. We illustrate that SCUBA-optimized backbone structures can closely reproduce those of native proteins. We show an example that a de novo protein domain with its backbone designed using SCUBA and amino acid sequence designed using ABACUS fold into the desired structure. Our results suggest statistical energy functions can drive protein design with complete backbone flexibility. In addition, the NC-NN approach can be generally applied to develop continuous, noise-filtered multi-variable statistical models from structural data. The ABACUS and SCUBA protein design tools are available at http://biocomp.ustc.edu.cn/servers/abacus-design.php.

Discovery of universal activation mechanism of class A GPCRs by residue-residue contact score

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Abstract

Class A G protein-coupled receptors (GPCRs) influence virtually every aspect of human physiology. Understanding receptor activation mechanism is critical for discovering novel therapeutics since about one-third of all marketed drugs target members of this family. GPCR activation is an allosteric process that couples agonist binding to G protein recruitment, with the hallmark outward movement of TM6. However, what leads to TM6 movement and the key residue level changes of this trigger remain less well understood. Here, we developed a framework called residue-residue contact score to quantify conformational changes. By analysing the conformational changes in 234 structures from 45 class A GPCRs, we discovered a universal GPCR activation pathway comprising of 34 residue pairs and 35 residues. The pathway unifies previous findings into a universal activation mechanism and strings together the scattered key motifs such as CWxP, DRY, Na+ pocket, NPxxY and PIF, thereby directly linking the bottom of ligand-binding pocket with G protein coupling region. Through a detailed investigation of this pathway, we reveal the continuous and modular nature of the activation mechanism and provide insights into how specific residue-level changes, leads to transmembrane helix-level changes in the receptor. Site-directed mutagenesis experiments support the continuous and modular nature of the universal activation mechanism and reveal that rational mutations of residues in the universal activation pathway can be used to obtain receptors that are constitutively active or inactive. The universal activation pathway allows for the mechanistic interpretation of constitutively activating mutations, inactivating mutations and disease mutations. We suggest that the modular nature of the universal GPCR activation pathway allowed for the decoupling of the evolution of the ligand binding site, G protein binding region and the residues important for receptor activation. Such an architecture might have facilitated GPCRs to emerge as a highly successful family of proteins for signal transduction in nature.

Integrative Ensemble Modeling of a Mitochondria Chaperone-Membrane Protein Complex Using Incomplete and Ambiguous Experimental Information

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Abstract

Mitochondria contain approximately 1200 different proteins, 99% of which are synthesized on cytosolic ribosomes and need to be delivered into the right destination through the intermembrane space by transport machineries, such as the TIM chaperone. Currently, the mechanistic and structural details of how the TIM chaperone binds to these mitochondrial proteins remain elusive. To gain structural insight into the binding and chaperone mechanisms, we focused on the complex of the TIM9/10 chaperone and the mitochondrial GDP/GTP carrier membrane protein (Ggc1). Such complexes are difficult to study because they consist of a transiently formed, dynamic complex between two folded proteins and a membrane protein that should be solubilized and bound by the chaperone. X-ray crystallography has revealed the core structure of the free chaperone protein, but because of the dynamic nature and large size (~1400 amino acids) of the complex its structural features have remained elusive. Using an integrative approach that combines biochemical assays, NMR spectroscopy and SAXS it was, however, able to obtain detailed but ambiguous information on the structures of the complex (Weinhäupl, Lindau, et al; Cell, 2018). In particular, the experiments showed that the complex consists of two well-structured (TIM9)3/(TIM10)3 hexamers bound to a mostly-disordered Ggc1.

In this work, we developed a protocol to integrate such heterogeneous experimental data with a coarse-grained molecular model to provide a description of the conformational ensemble of the TIM9/10-Ggc1 complex. In particular, we used a hybrid structure-based model (to describe the intra-molecular interactions within the folded chaperone), an NMR-derived contact potential for chaperone-client interactions and a knowledge-based potential (to describe the inter-molecular interactions between the chaperones and chaperone-client interactions). We used molecular dynamics (MD) simulations to sample the conformational landscape of the complex, and the resulting coarse-grained conformational ensemble was subsequently converted into all-atom resolution and refined using a Bayesian/Maximum Entropy reweighting approach using the SAXS data. This allows us to generate a weighted ensemble in agreement with experimental measurement. Such integrative structural modeling method is useful to

generate a structural ensemble of large and dynamic proteins in a both efficient and reliable way.

Energy Sampling of Long-Timescale Biomolecular Dynamics: the Energy Flow Viewpoint

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Abstract

Biomolecules aimlessly fluctuate in their functional environments and occasionally undergo characteristic activated transitions; these rare conformational events usually play pivotal roles in biological functions. In the past decade, understanding rare activated events at the atomistic level, especially mapping the corresponding free energy landscapes via molecular dynamics (MD) simulation, has been an immense focus in the fields of theoretical chemistry and computational biophysics. Although a large number of reports have been published to claim success, it has been increasingly clear that such attempts seem to be still far reaching to the existing strategies. As is widely known, a major general challenge lies in the fact that a majority of biologically important conformational transitions occur at timescales above the ranges of hundreds of microseconds to milliseconds. In contrast, currently commonly accessible timescales for GPU-based MD simulations are around tens of nanoseconds to microseconds depending on system size. To overcome this challenge, a physics-based enhanced sampling strategy, the orthogonal space sampling scheme, was introduced and enriched in the past decade. Such scheme allows physically essential energy flows related to target events to be specifically accelerated and thereby lead to practically robust and efficient sampling. Recent mathematical and algorithmic developments and applications will be discussed in this talk.

Molecular simulation study of peptide self-assembly and amyloid fibril inhibition by natural small molecules

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Abstract

Peptide self-assembly and aberrant protein aggregation have been attracting great interest because of their various potential biotechnological/biomedical applications as well as their close association with many ageing-related degenerative diseases (such as Alzheimer's disease and type 2 diabetes). Inhibition of protein aggregation and destabilization of preformed protofibrils by natural small molecules are considered as two major effective strategies to interfere with amyloid fibril formation and treat amyloidoses. Understanding the microscopic mechanisms of peptide self-assembly and amyloid fibril inhibition is of paramount importance for the design of peptide-based bio-nanomaterials and the development of potent inhibitors targeting the early stages of the pathological self-assembly process of amyloid proteins. Molecular dynamic (MD) simulations play an essential role by allowing generation of sufficiently accurate conformational ensembles which can be used to interpret experimental observations, predict new nanostructures and reveal the molecular interaction mechanisms. Here, I present our recent MD simulation results of the self-/co-assembly of ultra-short peptides and the molecular mechanisms by which natural small molecules inhibit amyloid protein aggregation and disrupt preformed protofibrils [1-4].

Reference

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Identifying molecular recognition features in intrinsically disordered regions of proteins by transfer learning

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Abstract

Protein intrinsic disorder describes the tendency of sequence residues to not fold into a rigid three-dimensional shape by themselves. However, some of these disordered regions can transition from disorder to order when interacting with another molecule in segments known as molecular recognition features (MoRFs). Previous analysis has shown that these MoRF regions are indirectly encoded within the prediction of residue disorder as low confidence predictions [i.e. in a semi-disordered state P(D)~0.5]. Thus, what has been learned for disorder prediction may be transferable to MoRF prediction. Transferring the internal characterization of protein disorder for the prediction of MoRF residues would allow us to take advantage of the large training set available for disorder prediction, enabling the training of larger analytical models than is currently feasible on the small number of currently available annotated MoRF proteins. In this presentation, we describe a new method for MoRF prediction by transfer learning from the SPOT-Disorder2 ensemble models built for disorder prediction. We confirm that directly training on the MoRF set with a randomly initialized model yields substantially poorer performance on independent test sets than by using the transfer-learning-based method SPOT-MoRF, for both deep and simple networks. Its comparison to current state-of-the-art techniques reveals its superior performance in identifying MoRF binding regions in proteins across two independent testing sets, including our new dataset of >800 protein chains. These test chains share <30% sequence similarity to all training and validation proteins used in SPOT-Disorder2 and SPOT-MoRF, and provide a much-needed large-scale update on the performance of current MoRF predictors. The method is expected to be useful in locating functional disordered regions in proteins.

Multimer protein complex structure prediction by machine learning

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Abstract

CryoEM has advanced structural biology to multimer superlarge protein complex stuctures, but the underlying theoretical understanding and prediction of multimer protein complex structure is still difficult. We developed machine learning methods based on LSTM and U-net to predict the structures of trimer, tetramer and even large supercomplex with 80 monomer proteins.Our methods have good applications in experimental biology researches, and also help to explore the insights of multimer protein interaction complex mechanism.

New insights into the ion-π interactions

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Abstract

Ion-π interactions play a critical role in many important vital processes, such as gene expression, nicotine addiction, and ion channel etc., through recognizing specific ions by the receptors. While cation-π interaction has long been recognized as an important noncovalent bonding force in supramolecular chemistry and biology, anion-π interaction has just come to be greatly appreciated recently. Although it is generally accepted that both the electrostatic and ion-induced polarization effects play a significant role in the ion-π interactions, there has been a conscious effort to exploit and differentiate their nature in order to achieve more accurate descriptors that can be utilized to guide the screening or design of a specific ion-π system. Currently, the widely used models, such as electrostatic potential and quadrupole moment, treat ions as point charges, where the key role of information-carrying ions has been rarely discussed. Here, we shed light on the ion specificities in ion-π interactions by correlating binding energies to a new model, namely the orbital electrostatic energy (OEE), which describes the electrostatic properties of both ions and the π systems in detail via electron density distributions on orbitals. The OEE has been shown to be the only descriptor that always exhibits the strongest correlation to the trend of the binding energies, regardless of the shape of the given ion and binding sites on the aromatic rings. With this more detailed descriptor on electrostatics, new insights behind several important experimental and theoretical behaviors of ion-π interactions have been revealed, which shall provide a deeper understanding on molecular recognition and communication through ion-π interactions. On top of the OEE model, an ion-specific design strategy has been proposed.

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Protein inter-residue distance prediction and enhanced sampling

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Abstract

In this talk, I will introduce two of our recent works. In the first project, we developed lightweight protein inter-residue distance prediction method using the generative adversarial network (GAN), which is capable of capturing the delicate geometric relationship between residue pairs and thus could predict the continuous, real-valued distance rapidly and satisfactorily. Pipelined with structure modeling software like the CNS suite, this method could construct protein structure models with the state-of-theart quality. In the second project, we developed a novel enhanced sampling method, frontier expansion sampling (FEXS), which can accelerate protein conformational search by identifying novel seed structures for restart in molecular dynamics simulations. Validation in three protein systems support the effectiveness of this method in observing the large-scale conformational changes of proteins with at least the same level of efficiency as methods like structural dissimilarity sampling (SDS).

Enhancing the Signaling of GPCRs via Orthosteric Ions

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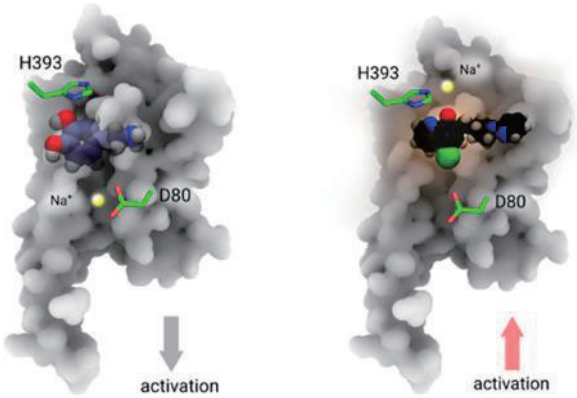
Abstract

G protein-coupled receptors play essential roles in cellular processes such as neuronal signaling, vision, olfaction, tasting, and metabolism. As GPCRs are the most important drug targets, understanding their interactions with ligands is of utmost importance for discovering related new medicines. In many GPCRs, an allosteric sodium ion next to the highly conserved residue D2.50 has been proposed to stabilize the inactive receptor state by mediating interactions between transmembrane helices. Here, we probed the existence of internal and functionally important sodium ions in the dopamine D2 receptor, using molecular dynamics simulations. Besides a new sodium ion at the allosteric ligand binding site, we discovered an additional sodium ion, located close to the orthosteric ligand binding site. Through cell-based activation assays, the signaling of D2 receptor with site-specific mutations was tested against a series of chemically modified agonists. We concluded an important structural role of this newly discovered orthosteric sodium ion in modulating the receptor signaling: It enables the coordination of a polar residue in the ligand binding site with an appropriately designed agonist molecule. This unique principle and strategy could be used to optimize the drug activity of GPCR. Our findings open a new mechanistic opportunity of GPCR signaling and help design the next generation of drugs targeting GPCRs.



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Deciphering the Genetic Determinants of Complex Human Traits through an Integrative Analysis of GWAS and Intermediate Molecular Trait Data

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Abstract

The rapid accumulation of Genome-Wide Association Studies (GWAS) and association studies of intermediate molecular traits provides new opportunities for comparative analysis of the genetic basis of complex human phenotypes. Using a newly developed statistical framework called Sherlock-II that integrates GWAS with eQTL (expression Quantitative Trait Locus) and metabolite-QTL data, we systematically analyzed 445 GWAS datasets, and identified 2114 significant gene-phenotype associations and 469 metabolites-phenotype associations. This integrative analysis allowed us to translate SNP-phenotype associations into functionally informative gene-phenotype association profiles. Genetic similarity analyses based on these profiles clustered phenotypes into sub-trees that reveal both expected and unexpected relationships and enabled us to identify sets of functionally related genes driving the similarity. Our approach can be used to assess genetic similarity and suggest mechanistic connections between phenotypes, and has the potential to improve the diagnosis and treatment of diseases by transferring the knowledge from one disease to another based on common molecular underpinnings.

Divergent trajectories of single-cell aging

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Abstract

Cellular aging is a complex process that involves many interwoven molecular processes. Studies in model organisms have identified many individual genes and factors that have profound effects on lifespan. However, how these genes and factors interact and function collectively to drive the aging process remains unclear. We investigated single-cell aging dynamics throughout the replicative lifespans of *S. cerevisiae*, and found that isogenic cells diverge towards two aging paths, with distinct phenotypic changes and death forms. We further identified specific molecular pathways driving each aging fate and revealed that these pathways interact and operate dynamically to enable an early-life switch that governs the aging fate decision and the progression towards death. Our work uncovers the interconnected molecular pathways that drives the aging process and opens up the possibility of designing interventions that simultaneously target multiple network nodes, instead of single genes, to more effectively extend the healthspan.

The free energy cost of oscillator synchronization

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Abstract

Oscillation is an important cellular process that regulates timing of different vital life cycles. However, under the noisy cellular environment, the oscillation can be highly inaccurate due to phase fluctuation. It remains poorly understood how biochemical circuits maintain their phase coherence, and what is the free energy cost of increasing the accuracy of timing. In this talk, we analyze the free energy partition between oscillatory cost and synchronization cost. Using simplified model, we found that an oscillatory system spends significant amount of free energy on synchronization. To confirm this finding, we studied a typical biological circadian clock: The Kai oscillatory system in cyanobacteria. We show that compared with the free energy that make the system oscillate, a significant among of free energy is consumed by the information exchange among individual oscillators so that the molecules can oscillated synchronously.

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Expanding at the right speed: an evolutionary stable strategy to colonize spatially extended habitats

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Abstract

In nature, organisms live in dynamical ecosystems where local habitats are created and destroyed repeatedly over time. Accordingly, the ability of a species to colonize newly available habitats is crucial to its overall fitness. Intuitively, fast expansion is expected to be beneficial to the colonization process and hence to organismal fitness. Here we apply a unique evolution protocol to investigate phenotypical requirements for colonizing habitats of different sizes during bacterial range expansion. Although the fitness of a clonal population indeed increases for faster expansion speeds, too fast an expansion speed makes that population unstable to invasion by mutants with slower speeds growing at the same rate. This phenomenon, a manifestation of frequency-dependent selection, was investigated via a mathematical model of the associated competition process involving the growth and expansion of multiple strains. Our analysis identified the origin of this effect, residing in interactions among pioneering cells located at the front of the expanding population, and led us to recognize a simple, evolutionary stable strategy for colonizing a habitat of a given size: to expand at a speed given by the product of the growth rate and habitat size. This prediction was verified by numerous additional sets of evolution experiments in a variety of conditions, showing that the expansion speeds evolve towards stable equilibria, the stable speeds depend linearly on habitat sizes, with the slope set by the population growth rate. These results establish the coordination between expansion and growth as an optimal strategy for colonizing spatially extended habitats, and more generally illustrates stability-to-invasion as a powerful principle for the selection of phenotype in complex competitive processes lacking a fixed fitness landscape. The unprecedented ability to predict the outcome of such complex processes provides a guide to discover additional rules governing the survival and fitness of interacting species in more complex ecosystems.

Network design principle for dual function of adaptation and noise attenuation

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Abstract

Many signaling systems execute adaptation under noisy circumstances. While the adaptation or noise attenuation has been studied separately, how to achieve these two competing functions simultaneously remains elusive. To explore such dual function, we first explore three-node enzymatic regulation networks, and identify an intrinsic trade-off existing between good sensitivity and noise attenuation in the three-node networks. Although fine-tuning timescales in three-node adaptive networks can partially mediate such trade-off, it introduces prolonged adaptation time and unrealistic parameter constraints. This trade-off can be minimized in four-node networks, in which the adaptation module and the noise attenuation module can be effectively decoupled to achieve dual function. There exist constraints on assembling the two modules in order to allow high performance of dual function. Maintaining the system sensitivity is a bottleneck and the time scales of the two modules need to be well coordinated. By scrutinizing seven biological systems, we find that adaptive networks are often associated with a noise attenuation module. The obtained design principles are then studied using two examples: *Dictyostelium discoideum* chemotaxis and p53 signaling network. Our approach may be applicable to finding network design principles for other dual and multiple functions.

Reconstruct cellular dynamics from single cell data

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Abstract

Recent advances of single cell techniques catalyzed quantitative studies on the dynamics of cell phenotypic transitions (CPT) emerging as a new field. Two grand technical challenges, however, impede further development of the field. Fixed cell-based approaches can provide snapshots of high-dimensional expression profiles but have fundamental limits on revealing temporal information, and fluorescence-based live cell imaging approaches provide temporal information but are technically challenging for multiplex long- term imaging. To tackle the challenges we developed an integrated experimental/computational platform for reconstructing single cell phenotypic transition dynamics.

We first developed a live-cell imaging platform that tracks cellular status change through combining endogenous fluorescent labeling that minimizes perturbation to cell physiology, and/or live cell imaging of high-dimensional cell morphological and texture features. With our platform and an A549 VIM-RFP EMT reporter cell line, recorded live cell trajectories reveal parallel paths of epithelial-to-mesenchymal transition missing from snapshot data due to cell-cell dynamic heterogeneity. Recognizing that CPTs are examples of rate processes, we introduced transition path analyses and the concept of reaction coordinate from the well-established rate theories into CPT studies, and applied on this EMT process. We modified a finite temperature string method to reconstruct the reaction coordinate from the trajectories, and reconstruct a corresponding quasi-potential. The potential reveals that the EMT process under study resembles a barrier-less relaxation rather than a barrier escaping process along a potential surface. Thus our work demonstrates the necessity of extracting dynamical information of phenotypic transitions and the existence of a unified theoretical framework describing transition and relaxation dynamics in systems with and without detailed balance.

Evolution of microbial traits under serial dilution

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Abstract

Selection of mutants in a microbial population depends on multiple cellular traits. In serial-dilution evolution experiments, three key traits are the lag time when transitioning from starvation to growth, the exponential growth rate, and the yield (number of cells per unit resource). Here we investigate how these traits evolve in laboratory evolution experiments using a minimal model of population dynamics, where the only interaction between cells is competition for a single limiting resource. We find that the fixation probability of a beneficial mutation depends on a linear combination of its growth rate and lag time relative to its immediate ancestor, even under clonal interference. The relative selective pressure on growth rate and lag time is set by the dilution factor; a larger dilution factor favors the adaptation of growth rate over the adaptation of lag time. The model shows that yield, however, is under no direct selection. We also show how the adaptation speeds of growth and lag depend on experimental parameters and the underlying supply of mutations. Finally, we investigate the evolution of covariation between these traits across populations, which reveals that the population growth rate and lag time can evolve a nonzero correlation even if mutations have uncorrelated effects on the two traits. Altogether these results provide useful guidance to future experiments on microbial evolution.

Constructing single cell specific networks

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Abstract

Single-cell RNA sequencing (scRNA-seq) is able to give an insight into the gene–gene associations or transcriptional networks among cell populations based on the sequencing of a large number of cells. However, traditional network methods are limited to the grouped cells instead of each single cell, and thus the heterogeneity of single cells will be erased. We present a new method to construct a cell-specific network (CSN) for each single cell from scRNA-seq data (i.e. one network for one cell), which transforms the data from‘unstable’ gene expression form to ‘stable’ gene association form on a single-cell basis. In particular, it is for the first time that we can identify the gene associations/network at a single-cell resolution level. By CSN method, scRNA-seq data can be analyzed for clustering and pseudo-trajectory from network perspective by any existing method, which opens a new way to scRNA-seq data analyses. In addition, CSN is able to find differential gene associations for each single cell, and even ‘dark’ genes that play important roles at the network level but are generally ignored by traditional differential gene expression analyses. In addition, CSN can be applied to construct individual network of each sample bulk RNA-seq data. Experiments on various scRNA-seq datasets validated the effectiveness of CSN in terms of accuracy and robustness.

Oscillation, phase locking and Arnold tongues in pancreatic islets

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Abstract

The Ca^{2+} modulated pulsatile secretions of glucagon and insulin by pancreatic α and β cells play a key role in glucose metabolism and homeostasis. However, how different types of cells in the islet couple and coordinate to give rise to various Ca^{2+} oscillation patterns and how these patterns are being tuned by paracrine regulation are still elusive. Here we develop a microfluidic device to facilitate long-term recording of islet Ca^{2+} activity at single cell level and find that islets show heterogeneous but intrinsic oscillation patterns. The α and β cells in an islet oscillate in antiphase and are globally phase locked to display a variety of oscillation modes. A coarse-grained mathematical model is constructed and compares well with the experiments. The model generates two-dimensional Arnold tongues and maps out the dependence of the oscillation modes on the paracrine interactions between α and β cells. Our study reveals the origin of the islet oscillation patterns and highlights the role of paracrine regulation in tuning them.

Accurate Predictions of Water Distribution at Strongly Charged Groups of Large Biomolecules with the Ion-Dipole Correction

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Abstract

The integration equation theory (IET) provides highly efficient tools for the calculation of structural and thermodynamic properties of molecular liquids. In recent years, the 3D reference interaction site model (3DRISM), the most developed IET for solvation, has been widely applied to study protein solvation, aggregation, and drug-receptor binding. In particular, the accurate prediction of water sites at biomolecules have been an important problem in the computer assisted drug design. But unfortunately, the performances of all grid-based methods including 3DRISM were poor, hence the most time consuming method, MD simulation, was still recommended for water site predictions [1]. In this work, we found that the inaccuracy of 3DRISM may happen at strong electrostatic interactions like hydrogen-bond and ion-dipole interactions. These interactions may be incompatible with the mean field treatment adopted in the 3DRISM that originally developed from hard-sphere models. In order to solve this issue, we introduced a correction that arises from the water polarization at strong electric field, namely the Ion-Dipole Correction (IDC). With this correction, the 3DRISM-IDC can accurately predict the density distribution of water at strong electric interaction regions of large biomolecules (ions, proteins or DNA), where both the locations and heights of solvation peaks overlap with the results sampled from MD simulations. We also demonstrated that the efficiency of our implementation of 3DRISM or 3DRISM-IDC is four orders of magnitude higher than MD simulations. Therefore, we anticipate the IDC would be widely applied in the water site prediction of large biomolecules.

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Degradation of nerve agents by PTE: QM/MM insight into the enzymatic mechanism

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Abstract

The nerve agents are belong to highly toxic organophosphorus compounds, and the wild-type phosphotriesterase (PTE) enzyme is capable of hydrolyzing these organophosphates but with a low catalytic efficiency. Here extensive QM/MM MD and MM MD simulations have been performed, and the plausible mechanisms for the chemical and nonchemical steps, the roles of water molecules and key residues have been discussed. The present work provides the mechanistic details for the enzymatic degradation of never agents by PTE and the understanding of stereochemical effects, which are improtant for improving the catalytic efficiency of PTE towards the detoxification of never agents.

Molecular Dynamics Simulations of Antibiotic Ceftaroline at the Allosteric Site of Penicillin-Binding Protein 2a (PBP2a)

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) tolerates β-lactam antibiotics by carrying out cell wall synthesis with the transpeptidase Penicillin-binding protein 2a (PBP2a), which cannot be inhibited by β-lactams. It has been proposed that PBP2a's active site is protected by two loops to reduce the probability of it binding with β-lactams. Previous crystallographic studies suggested that this protected active site opens for reaction once a native substrate binds at an allosteric domain of PBP2a. This opening was proposed for the new β-lactam ceftaroline's mechanism in successfully treating MRSA infections, i.e. by it binding to the allosteric site, thereby opening the active site to inhibition. In this work, we investigate the binding of ceftaroline at this proposed allosteric site using molecular dynamics simulations. Unstable binding was observed using the major force fields CHARMM36 and Amber ff14SB, and free energy calculations were unable to confirm a strong allosteric effect. Our study suggests that the allosteric effect induced by ceftaroline is weak at best.

Exploring the Interaction Mechanism between Antagonist and the Jasmonate Receptor Complex by Molecular Dynamics Simulation

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Abstract

Jasmonates induce the protein-protein interaction between the F-box protein CORONATINE INSENSITIVE 1 (COI1) and jasmonate ZIM-domain proteins (JAZs) in the presence of inositol phosphate, which made the degradation of JAZs and the release of the JAZ-repressed transcription factors. They are involved in the regulation of a wide range of physiology process, including plant growth, development and stress response. Coronatine-O-methyloxime (COR-MO) prevents the binding of COI1-JAZ, acting as an antagonist for jasmonate signaling pathway, while the understanding on the molecular basis of its action as an antagonist is still lacking at atomic level. In this study, we explored the interaction mechanism of jasmonate antagonists through molecular docking, molecular dynamics simulation, residue interaction network analysis and binding free energy calculation. Compared with the agonists, the conformation of JAZ1 is different in response to the binding with antagonist. Antagonists lost hydrogen bond interaction with Ala204 and Arg206 in JAZ1, and Arg496 in COI1, resulting that Arg206 swings and could not penetrate into COI1, so that it could not interact with 1,5-InsP8. It is indicated that the agonist is more closely associated with 1,5-InsP8 than the antagonist based on the residue interaction network analysis. The binding free energy of JA-Ile-MO/COR-MO with JAZ1 is higher than JA-Ile/COR. It is unfavorable for the binding of JAZ1 with COI1 in the presence of antagonists. This study provides a basis for the understanding of the interaction mechanism of jasmonate agonists/antagonists, which will contribute to the discovery of novel jasmonate agonists/antagonists.

Discovery of a species-specific novel antifungal compound against Fusarium graminearum through an integrated molecular modeling strategy

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Abstract

The cyanoacrylate fungicide phenamacril targeting fungal myosin I has been widely used for controlling Fusarium head blight (FHB) of wheat caused by the pathogenic fungus Fusarium graminearum worldwide. Therefore, there is great interest in the discovery and development of novel FgMyo1 inhibitors through structure-based drug design for the treatment of FHB. In this study, the binding mechanism of phenamacril with FgMyo1 was predicted by an integrated molecular modeling strategy. The predicted key phenamacril-binding residues of FgMyo1 were further experimentally validated by point mutagenesis and phenamacril sensitivity assessment. Four novel key residues responsible for phenamacril binding were identified, highlighting the reliability of the theoretical predictions. The subsequent optimization of phenamacril derivatives led to the discovery of a novel compound (10) which shows better activity than phenamacril against conidial germination of F. graminearum, but not against other fungal species. Moreover, 10 also inhibits conidial germination of phenamacril-resistant strains effectively. Further experiments illustrated that application of 10 could dramatically inhibit deoxynivalenol biosynthesis. Overall, our results further optimize and develop the binding model of phenamacril-myosin I. Furthermore, 10 was found and has the potential to be developed as a species-specific fungicide for management of FHB.

Deciphering Embryonic Morphogenesis with in vivo Cell Morphology and Phase Field Model

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Abstract

Morphogenesis is a precise and robust dynamic process during metazoan embryogenesis consisting of both cell proliferation and cell migration, which is also critical to a series of developmental events such as intercellular signaling transduction and body axis formation. However, unlike the progress in discovering molecular activity that regulates morphogenesis, general and extensible in silico model based on cell-level interaction has not been well established yet, especially for comprehensive reconstruction and prediction on morphological features observed in live embryo (e.g., cell shape, cell-cell contact relationship). Using Caenorhabditis elegans as model animal, in this work, we first collect three-dimensional time-lapse (4D) cellular morphological information from 1- to 12-cell stage, from the in vivo imaging experiments at ~1.5-minute interval in our previous works. Then, we refine the quantitative cell-resolved features including cell location, cell shape, cell volume, cell surface area, cell-cell contact relationship and area, and eggshell shape. Based on the developmental properties obtained, we build a phase field model and take a set of mechanical constrictions and interactions into account, including cell surface tension, cell volume consistency, cell-cell repulsion and attraction. After fitting and optimizing the systematic parameters, we simulate the morphogenesis procedure from 1- to 8-cell stage within a confined compressed eggshell. We not only successfully reconstruct the evolution of cell location, cell morphology and cell-cell contact relationship observed in real embryo, but also provide mechanical perspectives on several significant developmental events such as Wnt signaling from P2 to EMS, establishment of the three orthogonal body axes and spatial robustness against external compression. Last but not

least, three system-level strategies for self-organized morphogenesis are found by simulations, that is, control of cell division timing, cell division orientation and cell-cell attraction matrix. These components specify a multi-body system into a targeted developmental trajectory with high structural stability, by working together on the evolution of cell-cell contact map which is conceptualized as “mechanoconnectome”. Combined with in vivo cell morphology information, a computational framework based on phase-field methods is proposed and expected to facilitate toward deciphering morphogenesis in metazoan embryo development.

CADD in Biologics Drug Discovery

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Abstract

Computer Aided Drug Design (CADD) has been practiced by pharmaceutical industry for more than 30 years. With the expansion of the molecular modalities, the technology has been increasingly applied to biologics discovery by the pharma and biotech players across the board. At Hengrui, CADD has been a key driver for our biologics drug discovery effort. We have used it whenever possible. The talk will be divided in three parts. First I will introduce the computational technologies and infrastructures to enable the practice of CADD in our biologics drug discovery projects. Then the application of CADD in project setting will be illustrated using real world examples. The last part will focus on the emerging computational technologies for biologics drug discovery.

The difference of the FMO complex from different green sulfur bacteria: A QM/MM description with PPC charge

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Abstract

The Fenna-Mattews-Olson light-harvesting complex is one of the primary model systems for the study of excitation energy transfer (EET). The relation between structural differences and the difference of absorption spectra for the two-type Fenna-Matthews-Olson (FMO) complexes from Chlorobaculum tepidum (C-type) and Prosthecochloris aestuarii 2K (P-type) has not yet understood. To contribute the opinion, molecular dynamics simulations and the electrostatic-embedding quantum-mechanics/molecular-mechanics calculations have been employed utilizing the polarized protein-specific charge (PPC), which provides a more realistic description of the environment effect for excitation energy and its fluctuation than conventional mean-field charge scheme. Understanding the contributions of individual pigments to the FMO complex's absorption spectrum are of benefit to know the origin of the difference of absorption spectra. The absorption spectra of the two-type of FMO complex are both significantly modified when mutant occurs near BChl 6 (W183F) of C-type and BChl 6 (W184F) of P-type, respectively. Our result suggests that the BChl 6 is pointed out to be the origin of the spectral differences. According to the exciton model and the population dynamics, an optimal energy transfer efficiency is reproduced. Moreover, the obtained spectral density is used to describe the diverse local environment embedding each pigment.

Molecular simulation on identification of proteinogenic amino acids by coupling force and current signals

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Abstract

The diversity of residue types and properties makes nanopore sequencing exponentially challenging and detecting a one-dimensional signal has not been reported to recognize all the constituent 20 proteinogenic amino acids. Inspired by the conception that sensing multi-dimensional signals could enhance distinguishability, we performed proof-of-principle molecular dynamics simulation on the feasibility of detecting differentiable pulling force and ionic current signals simultaneously. Firstly, the force and current signals with distinguishability were detected by tailoring the geometry of graphene nanoslit sensor when sequencing the model peptides polymerized by Tyrosine and Alanine. Based on that, the characteristic force and current signals also obtained by sequencing 20 homogenous peptides with each polymerized by one type of amino acid. A pattern concerning the signals is that the larger or heavier amino acids have larger pulling forces and lower ionic currents. Further insights revealed that the signals are severely affected by the hydrophobicity and charge states of residues, and residues with similar properties could be grouped according to the signals. Generally, the geometry of graphene nanoslit could ensure the simultaneous sensing of differentiable force and current signals, which shows enhanced distinguishability of 20 constituent residues and could provide a new detecting mode of nanopore protein sequencing.

Studying the Selectivity of Protein Binding to Calcium ions and Magnesium ions Using a Reference-Potential

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Abstract

Calculate relative binding free energy difference between two ligands can be helpful for lots of work, such as drug design, drug selection and so on. In this work, we calculated relative binding free energy difference between Calcium ions and Magnesium ions combine with metall-protein by a method called Reference-potential. We first calculated the relative binding free energy deference at MM level, then we reweighted this difference to QM/MM level by reference potential. The results proved that our method can not only drive an accurate free energy difference with little stand error, but also cost less simulation time than calculate the free energy difference by a QM/MM simulation directly.

Cellular Morphological Reconstruction in Caenorhabditis elegans Embryo Using Nucleus Position and Voronoi Segmentation

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Abstract

Cellular morphology, such as cell-cell contact and cell volume, plays critical roles in metazoan development including intercellular signaling transduction, cell fate specification, division-orientation regulation, cell-packing arrangement, cellcycle control, etc. However, it's difficult to be captured directly by membrane-based fluorescence and imaging in most cases, because of the small cell size and the dim membrane signal. Many researches on model organism Caenorhabditis elegans used nucleus position and Voronoi segmentation to reconstruct the 3D time-lapse embryonic morphology at singlecell resolution, but the accuracy of predictive outcomes is still unknown. In this work, we first establish a standard computational pipeline based on nucleus position and Voronoi segmentation. Then, we collect 17 wild-type embryos with distinguishable membrane signal and following cell segmentation, which are generated in our recent works and serve as ground truth here. After setting eggshell boundary and excluding dramatic cytokinesis, we segment the embryos before gastrulation onset (i.e. 4- to 24-cell stage) and compare the results with ground truth, revealing prediction accuracy of 85% in cell-cell contact and goodness of fit of 0.90 in cell volume. The methods are applied on our previous public database that contains 1818 RNAi-treated embryos of 758 genes. The contact between MS and ABara, which is essential for Notch signaling and pharynx formation, is found to be lost with high probability after perturbing gsk-3 and further verified by experiments as an additional support for our methods. Last but not least, we build a graphical user interface named C. elegans Morphology Viewer (CMV) to allow users to access the segmented results

of all the mutants. Both the methods and resources in this work are expected to facilitate further research on developmental biology.

A New Energy Decomposition Analysis Approach and Its Application in the Study of Rhodopsin

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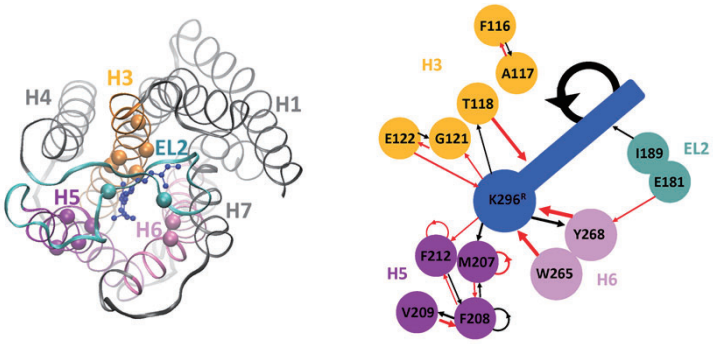
Abstract

Theoretical and computational approaches nowadays play an important role in the study of the structure and function of biomolecules. Especially, molecular dynamics simulations make it possible to unveil the dynamics and energy contributions at the atomic level when biomolecules perform their functions, and provide alternative approaches in protein/drug design. However, current energy decomposition approaches usually provide qualitative results, which hinder their wide-use in the study of biomolecules and protein/drug designs [1]. Recently, we proposed a new approach, which decomposes the energy along the reaction coordinate, established its theoretical foundation based on statistical mechanics, and systematically validated it on a model system [2]. Now, it is applied to study the relaxation of rhodopsin from bathorhodopsin to lumirhodopsin, and for the first time quantitatively analyzed the energy contributions at the reside-wise level, which are consistent with experimental results [3]. Thus, the proposed new energy decomposition approach is further demonstrated to be applicable to biomolecular systems and will be a powerful tool in the study of biomolecules and protein/drug designs.



Keywords: protein-ligand interaction, molecular dynamics, energy decomposition, rhodopsin

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Ligand Hydrophobicity and Rigidity Modulate Lipid Raft Affinity of Hydrophobic Nanoparticles: Insights from Molecular Dynamics Simulations

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Abstract

Lipid raft was reported to be important in many biological processes (e.g. signal transduction, endocytosis, etc.) in the cell. Hence, design functional nanoparticles to target lipid raft and regulate its dynamics will be helpful for the development of new nanomedicines. In the work, we designed a ligand-modified hydrophobic spherical nanoparticle with coarse-grained molecular dynamics simulations, which can be encapsulated into the hydrophobic region of the lipid membrane and specifically target either raft or non-raft membrane domains. The preferred localization of the nanoparticle can be tuned by adjusting not only ligand hydrophobicity but also ligand rigidity. The impact of nanoparticles with different ligand properties (e.g. hydrophobicity, rigidity, length) on the membrane domains were quantified in detail using a series of μs-scale molecular dynamics simulations. Our results may provide solid guidelines for designing functioned nanoparticles for targeting lipid rafts, which will provide new ideas for the diagnosis and treatment of diseases.

Atomistic Details of Charge/Space Competition in the RyR1 Ion Selectivity

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Abstract

Ryanodine receptors (RyR) control the release of Ca^{2+} from the sarco/endoplasmic reticulum and precisely regulate the Ca^{2+} concentration in the cytosol. A charge/space competition mechanism was proposed to explain the weak ion selectivity of RyR, but the molecular interaction details of this mechanism have yet to be fully elucidated. By utilizing a multi-site Ca^{2+} model developed in our group in molecular dynamic simulations, here we show that multiple cations accumulate in the highly charged upper selectivity filter of RyR1. The small size and high valence of Ca^{2+} make it preferable to K^+ in competition for space in this region. The presence of Ca^{2+} increases the energy barrier of K^+ permeation by about 1 kJ/mol. These results validate the charge/space competition mechanism in the RyR1 ion selectivity on the atomistic level, providing further microscopic and quantitative information.

Molecular simulations of polymer membranes for organic solvent nanofiltration

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Abstract

Organic solvent nanofiltration (OSN) through a membrane is an economically viable technology for the separation and recovery of organic solvents. The OSN performance is governed by many complex factors and quantitative understanding is experimentally challenging. To efficiently simulate membrane swelling in solvents, a molecular simulation protocol is developed. The new protocol is approximately one order of magnitude faster than normal simulation method. Based on this, the swelling of polymer membranes in different organic solvents are investigated, and then the OSN through the swollen membranes are examined. Many complex factors (e.g., solvent viscosity, pore size, polymer-solvent and polymer-polymer interactions) that govern OSN performance are analysed. We also design two new microporous polymer membranes (namely PILP-1 and PILP-3) and predict their OSN performance. From these simulation studies, the microscopic insights into the swelling of polymer membranes and the permeation of organic solvents are provided, which are useful for the development of new membranes for high-performance OSN.

Molecular mechanism of ligand bindings to Zika virus at SAM site

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Abstract

We investigated residue-specific binding free energies using computational alanine scanning with interaction entropy method to identify hot-spots and unravel molecular basis in 3 ligand bindings to Zika SAM binding site. This approach allows one to obtain quantitatively residue-specific contributions to protein-ligandbinding free energy. Our computational analysis identified four major residues, W87, I147, H110, and K105 that contribute most to the ZIKV bindings to both SAH and SFG ligands. There are two additional residues, R160 and R163, which also contribute significantly to the binding. Finally, the computed total binding free energies are in good agreement with experimentally measured data.

The Inhibitory Mechanism of Anthraquinone Derivative Purpurin on Tau Amyloidosis Segment

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Abstract

Alzheimer's disease involves two neuropathological hallmarks in patient brains: microtubule-associated protein tau tangles and amyloid-β plaques. The hexapeptide motif of VQIVYK is prone to be amyloidosis, and disruption of this motif hinders tau aggregation. The anthraquinone derivative purpurin is suggested to have a strong inhibitory effect on VQIVYK fbrillization, while the underlying mechanism at the atomistic level is unclear. In this work, we investigated the structural stability of protofibrillar oligomers of VQIVYK in different sizes, as well as the bind behavior of purpurin with different concentrations. We found that octamer is the smallest stable protofibrillar oligomer and the structural stability increases with oligomer size. Purpurin prefers to bind to the hydrophilic and aromatic Tyr, and has a low binding probability to the hydrophobic Val located in the middle of peptide. In addition, purpurin in molar ratio of 1:2 to peptide is the most effective in disrupting the protofibrillar octamer. The aromatic stacking contributes the most in the tau-purpurin interaction. Our work reveals the inhibitory mechanism of purpurin on the minimal stable oligomer of tau-derived VQIVYK peptide at the atomistic level, which may be helpful to the exploration of novel inhibitor targeting tau.

A De Novo Covalent Drug Design Protocol (Cov_FB3D) Integrating the BA-SAMP Strategy

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Abstract

De novo drug design actively seeks to use sets of chemical rules for the fast and efficient identification of structurally new chemotypes with the desired set of biological properties. Fragment-based de novo design tools have been successfully applied in the discovery of noncovalent inhibitors. Nevertheless, these tools are rarely applied in the field of covalent inhibitor design. Herein, we present a new protocol, called Cov_FB3D, which aims to the 'in silico' assembly of potential novel covalent inhibitors by identifying the active fragments in the covalently binding site of the target protein. In this protocol, we propose a BA-SAMP strategy, which combines the noncovalent moiety score with the X-score as MM level, and the covalent candidate score with the PM7 as QM level. The synthetic accessibility of each suggested compound could be further evaluated with machine-learning-based synthetic complexity evaluation (SCScore). An in-depth test of this protocol against the crystal structures of 15 covalent complexes consisting of BTK-inhibitors, KRAS-inhibitors, EGFR-inhibitors, EphB1-inhibitors, MAGL-inhibitors and MAPK-inhibitors revealed that most of these inhibitors could be de novo reproduced from the fragments by Cov_FB3D. The binding modes of most generated reference poses could accurately reproduce the known binding mode of most of the reference covalent adduct in the binding site (RMSD $\leqslant$ 2 Å). In particular, most of these inhibitors were ranked in the top 2% using the BA-SAMP strategy. Notably, the novel human ALDOA inhibitor (T1) with potent inhibitory activity (0.34 ± 0.03 μM) and greater synthetic accessibility was successfully de novo designed by this protocol. The positive results confirm the abilities of Cov_FB3D protocol.

OnionMHC: peptide - HLA-A*02:01 binding prediction using both structure and sequence feature sets

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Abstract

The peptide binding to Major Histocompatibility Complex (MHC) proteins is an important step in the antigen-presentation pathway. Thus, understanding the binding potential of peptides with MHC is essential for the design of peptide-based therapeutics. Most of the available machine learning based models predict the peptide-MHC binding based on the sequence of amino acids alone, not characterizing the structural features of the peptide-MHC complex.

Given the importance of structural information in determining the stability of the complex, we have considered both the peptide sequence as well as the complex structural features to predict peptide binding to HLA-A*02:01. We have applied machine learning techniques through the natural language processing (NLP) and convolutional neural network to design a model that outperforms the existing state-of-art models. Our model shows that, information from both sequence and structure domains would result in an enhanced performance in binding prediction compared to information from one domain alone. Our model has achieved the state-of-the-art result in most of the weekly benchmark datasets provided by Immune Epitope Database (IEDB).

Enzymatic Pictet-Spengler Reaction: Computational Study of Mechanism and Enantioselectivity of Norcoclaurine Synthase

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Abstract

The Pictet-Spengler (PS) reaction, i.e. the acid-catalyzed condensation between β-arylethylamine and an aldehyde or a ketone and the subsequent ring closure, is an important reaction in organic chemistry [1]. It is widely utilized for the synthesis of heterocyclic compounds of pharmaceutical importance. A number of enzymes (called Pictet-Spenglerases, PSases) have been identified to catalyze this reaction, usually with very high enantioselectivity, making these enzymes of potential value in biocatalysis. However, the reaction mechanisms and the origins of the selectivity are not fully understood. We have used the quantum chemical cluster approach to investigate the mechanism and enantioselectivity of norcoclaurine synthase (NCS), an enzyme that catalyzes the PS condensation between dopamine and 4-hydroxyphenylacetaldehyde (4-HPAA). A large model of the active site is designed on the basis of a recent crystal structure and it is used to calculate the detailed energy profile of the reaction [2]. Excellent agreement is obtained between the calculated energies and available experimental information. Both the “dopamine-first” and the “HPAA-first” binding modes of the two substrates reported in the literature are shown to be energetically accessible in the enzyme-substrate complex. However, it is demonstrated that only the “dopamine-first” pathway is associated with feasible energy barriers. Key active site residues are identified and their roles in the catalysis are discussed and compared to site-directed mutagenesis experiments. Very importantly, the calculations are able to reproduce and rationalize the observed enantioselectivity of NCS. A detailed analysis of the geometries of the intermediates and transition states helps to pinpoint the main factors controlling the selectivity. The presented results provide further support to the usefulness of the quantum chemical cluster approach in the study of enzymatic reaction mechanisms, including reproducing and rationalizing experimental enantioselectivities [3,4].

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Two-phase dynamics of DNA supercoiling from polymer physics

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Abstract

DNA supercoils are generated in crucial cellular processes, like transcription, replication and consideration while supercoiling in turn regulates the corresponding processes. Supercoiling also facilitates site juxtaposition for site-specific recombination and interactions on DNA. Under tension, DNA supercoil can present a coexistence state of plectonemic and stretched phases. In representing the dynamics of plectonemes under tension, we propose a further coarse-grained model of the extended DNA supercoiling from the physics of the worm-like chain model, called two-phase dynamic model. By comparing with the discrete worm-like chain model, we show that the two-phase dynamic model offers a reliable and highly efficient technique in describing supercoiling dynamics with trivial computational expense. The dynamics, including the nucleation, diffusion, and hopping of plectonemic coils, can be reproduced using the two-phase dynamic model. In addition, we extract the physical explanations for the statistics of plectoneme dynamics based on the two-phase dynamics and give the implications on juxtaposition of distant sites on DNA and gene expression.

A new adaptive QM/MM method via reference-potential approach

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Abstract

Hybrid Quantum Mechanical/Molecular Mechanical (QM/MM) methods are nowadays well accepted for the simulations of chemical reactions in condensed phase and enzymatic reactions.However, it brings technical difficulty in maintaining dynamic continuity when exchange of solvent molecules between the QM and the MM regions takes place, especially an abrupt repartitioning scheme of the QM and MM regions are adopted. In the adaptive QM/MM scheme, an effective QM/MM potential is adopted by weighted average of the potential from multiple partitionings of the system with varying combinations of solvent molecules. It is one of the schemes to overcome the problem and may significantly increase the computational expense. Fortunately, if we are only interested in thermodynamic properties, for instance the free energy profile, but not real dynamics, these properties can be calculated indirectly via the reference-potential approach. In this MsTP method, we can avoid sampling in the high level Hamiltonian, which can significantly reduce the computational complexity.

Classical molecular dynamics and metadynamics simulations decipher the mechanism of CBP30 selectively inhibiting CBP/p300 bromodomains

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Abstract

The selective modulation of individual bromodomains (BDs) by small molecules represents an important strategy for the treatment of various cancers, considering that the BD-containing proteins share common BD structures and distinct pharmacological functions. Small molecule inhibitors targeting BDs outside of the bromodomain and extraterminal domain (BET, including BRD2–4 and BRDT) family are particularly lacking. CBP30 exhibited excellent selectivity for the transcriptional coactivators CBP (CREB binding protein) and p300 bromodomains, providing a new opportunity for designing selective non-BET inhibitors. Here, we performed classical molecular dynamics (cMD) and metadynamics simulations to reveal the selective mechanism of CBP30 binding with CBP/p300 and BRD4-BD1/BD2 bromodomains. The cMD simulations combined with binding free energy calculations were performed to compare the overall features of CBP30 binding with CBP/p300 and BRD4-BD1/BD2 bromodomains. Arg1173/1137, as the unique residue for CBP/p300, was responsible for the selective binding to CBP30 via cation–π and hydrogen bond interactions. Metadynamics simulation, together with unbinding free energy profiles, suggested that the dissociation pathways of CBP30 from CBP/p300 and BRD4-BD1/BD2 bromodomains were different, with the unbinding of the former being more difficult. These findings will be helpful for novel CBP/p300-inhibitor design and rational structural modification of existing inhibitors to increase their selectivity.

Keywords: bromodomain; metadynamics; molecular dynamics

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The Recent Development of Ultra-Coarse-Grained Model for Protein

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Abstract

The coarse-grained model is widely used in the study of protein structure and function. The development of the coarse-grained model of protein provides an important theoretical tool for the multi-scale simulation of large biological systems. Recently, we focus on the development of ultra-coarse-grained (UCG) model of protein, which has a low resolution and is suitable for long time simulation. The recent development includes the newly developed optimization algorithms for coarse-graining and UCG models for function simulation. We will use the developed UCG models to simulate the conformational change of protein at the microsecond scale.

Keywords: ultra-coarse-grained model, algorithm development, CG simulation

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Molecular dynamics simulations on the role of Cys22-Cys27 disulfide bond in modulating the clotting activity of the serine protease domain of coagulation factor X

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Abstract

In addition to the classical ping pong reaction mechanism, a great many serine proteases are also common in the activation of their catalytic domain, which requires a conformational change to insert their N-terminal newly formed from a peptidyl cleavage. However, lacking of fully resolved structures, especially in the flexible loops around the activation pocket in the zymogen, prevented understanding the details in this dynamic conformational change and its regulations. A recently identified mutant p.Cys27Ser in a pedigree of congenital deficiency of a typical serine protease, coagulation factor X (FX) was compared with wild type enzymes with/without the Cys22-Cys27 disulfide bond by molecular dynamics simulations. The simulations showed that the broken disulfide bond resulted in a more flexibly wandering N-terminal segment reluctant to insert into the activation pocket and form a perfect active pocket for substrate binding. This result may somewhat explain the 1.33 and 22 fold lowered amidolytic and prothrombinase activity by FX, respectively, while the latter could be remedied to 4.77 fold in presence of the cofactor FV. The role of this solvent accessible disulfide bond in modulation of FX clotting activity may suggest a possible influence of the oxidation/reduction balance to coagulation and provide a new way to design drugs as clotting regulator.

A QMMM Study on Methyltransferase

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Abstract

Methyltransferases play key roles in various ways of post translational modifications. Recent discovery of a new type of transferase extended our knowledge in the functions of methyl transfer. We combine molecular dynamics simulation and quantum mechanical/molecular mechanical calculations to elucidate key residues and water molecules contributing to the catalysts and expect further improvement on the enzyme activity.

Accelerated Computation of Free Energy Profile at ab initio QM/MM

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Abstract

Path integral molecular dynamics (PIMD) is a computationally efficient approach to quantum mechanical nuclear motion such as tunneling, by recasting exponential-scaling quantum mechanical propagation into more accessible classical simulations, even though the notoriously expensive computational cost. In this work, the PIMD was combined with some enhanced sampling methods to accelerate the convergence. In addition, it is firstly attempted to obtain free energy at expensive Hamiltonian (e.g., ab initio Hamiltonian) from trajectories calculated at inexpensive Hamiltonian (e.g. Semi--empirical (SE) QM/MM) through the combination of PIMD and some free energy post-processing methods.

An integrated receptor-based screening strategy for flexible target: identify novel chemoprophylactic agents based on the dynamic behavior of PPARγ

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Abstract

Motivation: Receptor-based virtual screening (RBVS) has emerged as a predictive tool to accelerate the drug development. Nevertheless, accurate modeling of the receptor and accounting for receptor dynamics in RBVS still represent the severe issues, is in urgent need for the way of carrying out the balance between receptor flexibility and cost-effective. In addition, PPARγ is an attractive target for lung chemoprevention, and its highly dynamic nature has plagued the discovery of PPARγ agonists for decades.

Results: We presented an integrated RBVS strategy to identify PPARγ agonists and their binding profiles, with accounting for the dynamic behavior of PPARγ by using extend docking and conformational sampling methods. Our results showed that the conformational plasticity of PPARγ is markedly affected by binding of full / partial agonist, and should be carefully considered in docking and scoring. The platform sorted out potential chemoprophylactic agents ZINC03775146 (Gusperimus) and ZINC14087743 (Miltefosine), with the comforting accuracies and computational costs. In addition, the intrinsically dynamic behavior of PPARγ could offer enticing hope for PPARγ-targeted therapeutics to lung cancer chemoprevention, by blocking kinase accessibility to PPARγ. These results aid the development of novel chemopreventive drugs, and the integrated VS strategy is benefit for the rational drug design to highly flexible biomacromolecules.

Investigation on the fungicide resistance mechanism against FgMyoI inhibitor phenamacril by computational study

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Abstract

The pathogenic fungus Fusarium graminearum (F.graminearum) causes the fusarium head blight (FHB), which is a global problem for agricultural industry due to its infection strategies and uncontrollable characteristics. The cyanoacrylate fungicide phenamacril is one of the most powerful fungicides for controlling FHB by inhibiting the ATPase activity of the sole class I myosin of only a subset of F.graminearum (FgMyoI). F.graminearum is insensitivity to phenamacril owing to FgMyoI appears single point mutation at K216E, S217L, S217P, S418A or E420G. How these mutations affect the interaction mode between FgMyoI and phenamacril is not well understood. In the present study, we investigated the resistance mechanism against phenamacril at atomic level by analyzing the interaction mode between phenamacril and FgMyoIWT, FgMyoIK216E, FgMyoIS217L, FgMyoIS217P, FgMyoIE420G and FgMyoIS418A, using multiple computational methods, including homology modeling, molecular docking, molecular dynamics simulations, residue interaction network analysis, binding free energy calculation and principle component analysis (PCA). The binding free energy calculation suggests that the binding between FgMyoI and phenamacril is stronger in the wild type (WT) than that in the mutated types (MTs). Further, in comparison with the WT, the interaction mode between phenamacril and residues Lys216, Ser217, Ser418, Glu420 significantly alters in MTs. Mutations in the protein led to phenamacril resistance in the F.graminearum due to the inefficient binding. In summary, this study provides novel insight to understand the interaction mechanism between FgMyoI and phenamacril and useful information for the rational fungicide design.