INVITED TALKS

I1. Co-evolutionary fitness landscapes for sequence design

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Recent work has shown that it is possible to use the correlations between sequence variations at different positions in related proteins in order to infer which residues are in contact. It is also possible to use the energy from the underlying statistical model as a score for the evolutionary fitness of a given protein sequence, and this energy has been found to be correlated with the stability of the folded state of each sequence. We have used this information first to infer the number of proteins which can fold to a given structure, a longstanding problem which had not been quantitatively addressed. Secondly, we tested how predictive these sequence models could be of stable, foldable sequences. We found that for each of three protein folds, we were able to design sequences which folded to the target structure, verified by solving the NMR structure of the resulting designs. Thus coevolutionary information could be used to complement more traditional protein design efforts. Lastly, we are investigating potential evolutionary pathways between different protein folds by combining statistical models for each fold.

I2. Entropy and Enzyme Adaptation

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The speed of chemical reactions in water and in enzymes varies with temperature, depending on how the free energy of activation is partitioned into enthalpy and entropy. In enzymes, this partitioning is also optimized as a consequence of the organism's adaptation to the environment. We will show how the temperature dependence of chemical reaction rates can be obtained from brute force computer simulations. Such calculations shed new light on entropic effects in enzyme catalysis and on how protein structures have evolved in differently adapted species.

I3. Energetic costs, precision, and transport efficiency of molecular motors

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An efficient molecular motor would deliver cargo to the target site at a high speed and in a punctual manner while consuming a minimal amount of energy. However, according to a recently formulated thermodynamic principle, known as the thermodynamic uncertainty relation, the travel distance of a motor and its variance are constrained by the free energy being consumed. Here we use the principle underlying the uncertainty relation to quantify the transport efficiency of molecular motors for varying ATP concentration ([ATP]) and applied load (f). Our analyses of experimental data find that transport efficiencies of the motors studied here are semi-optimized under the cellular condition. The efficiency is significantly deteriorated for a kinesin-1 mutant that has a longer neck-linker, which underscores the importance of molecular structure. It is remarkable to recognize that, among many possible directions for optimization, biological motors have evolved to optimize the transport efficiency in particular.

I4. Folding of knotted proteins under nascent conditions and unfolding of entangled neurotoxic polypeptydes in proteasomes

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There is an abundance of topological features associated with proteins and their complexes. In multi-chain protein complexes, there is a possibility that two chains are natively entangled so that when one pulls at both termini of each chain simultaneously then the chains lock together and cannot be separated. The individual protein chains themselves may have non-trivial topologies. In particular, there are proteins that have a knot, typically with three intersections, like the trefoil knot, but sometimes even with six intersections, like the stevedore stopper knot. The interesting questions to ask are: what is the biological role of the knots, how do they form during folding, and how do they affect thermal and mechanical stabilities. We elucidate many knot-related physics by employing a coarse-grained structure-based molecular dynamics model which allows for studies of large conformational changes. In particular, we show that knotting is facilitated by formation of a slipknot during the very process of the protein assembly at the ribosome, especially in the case of the deeply knotted proteins, in which the knot ends are distant from the termini. The presence of the covalent disulfide bonds may introduce other topologically interesting motifs such as cystine knots and lasso. We show that the cystine knot motif yields particularly large resistance to unraveling through stretching. Knotted structures may also arise in intrinsically disordered peptide chains, such as polyglutamine tracts, but their nature is transient. These tracts are fused in huntingtin protein which is associated with Huntington disease, a well-known genetically-determined neurodegenerative disease. We show that the presence of a knot in the tract hinders and sometimes even jams translocation, leading to toxicity.

I5. Modeling and analyzing the flow of molecular machines in gene expression

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Gene expression is a fundamental cellular process by which proteins are synthesized based on the information encoded in the genetic material. During this process macromolecules such as ribosomes or RNA polymerases scan the genetic material in a sequential manner. I will describe various computational/mathematical models for the flow of such macromolecules. These models can be simulated efficiently, and some are suitable for rigorous mathematical analysis. I demonstrate how these models can be used to predict various aspects related to the expression levels of genes, and to study important biological phenomena, such as competition for finite resources, the evolution of genomes, and intracellular traffic jams. These models can also be used for optimization of gene expression for various biotechnological objectives.

I6. Protein escape at the ribosomal exit tunnel

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How fast a post-translational nascent protein escapes from the ribosomal exit tunnel is relevant to its folding and protection against aggregation. Here, by using simple models and Langevin dynamics, we show that folding and diffusion are key factors determining the protein escape at the tunnel. In particular, the protein escape is accelerated by the formation of non-local tertiary contacts outside the tunnel, but is slowed down by the formation of local contacts corresponding to alpha-helices inside the tunnel. Foldable proteins generally escape much faster than same-length self-repulsive homopolymers at low temperatures, and beta-sheet proteins escape faster than alpha-helical proteins. A simple diffusion model described by the Smoluchowski equation can be used to map out the escape time distribution. For the tunnel's model as a hollow cylinder, it is shown that protein diffusion at the tunnel is much slower if the tunnel length is larger than a crossover length related to the protein length. Simulations with a realistic tunnel shape provide further details on how folding and diffusion influence the escape process of nascent proteins.

I7. Domain topology, stability, and translation speed determine co-translational folding force generation on the ribosome

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The concomitant folding of a nascent protein domain with its synthesis can generate mechanical forces that act on the ribosome and alter translation speed. Such changes in speed can affect the structure and function of the newly synthesized protein as well as cellular phenotype. The domain properties that govern force generation have yet to be identified and understood, and the influence of translation speed is unknown as all reported measurements have been carried out on arrested ribosomes. Here, using coarse-grained molecular simulations and statistical mechanical modeling of protein synthesis, we demonstrate that force generation is determined by a domain's stability and topology, as well as translation speed. These results indicate that force measurements on arrested ribosomes will not always accurately reflect what happens in a cell, especially for slow-folding domains, and suggest the possibility that certain domain properties may be enriched or depleted across the structural proteome of organisms through evolutionary selection pressures to modulate protein synthesis speed and post-translational protein behavior.

I8. Protein aggregation and neurodegenerative diseases

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Protein aggregation is associated with a large group of major human diseases, including Alzheimer's disease, prion disorders, type 2 diabetes etc [1]. Therefore, understanding the key factors that govern this process is of paramount importance. Because the time scales of fibril formation are of order of hours or longer the all-atom study of kinetics of this process is beyond present computational facilities. To overcome this problem, we have developed a simple lattice model [2] which allows one to understand the fibrillogenesis of polypeptide chains depends on their sequences. It was shown that, in agreement with experiments, fibril formation times are strongly correlated with hydrophobicity, charges, mechanical stability of fibril [3] and population of the so called fibril-prone conformation in monomer state [2]. The higher is the population the faster is the fibril elongation and this dependence may be described by a single exponential function. Our results open a new way to understand the self-assembly of bio-molecules at the monomer level as shown by all-atom molecular dynamics simulations of amyloid beta (Aβ) peptides and *in vitro* experiments.
Recent research reveals that soluble complexes of Aβ peptides and copper are efficient catalysts in dioxygen activation and, therefore, are potentially dangerous species triggering an irreversible oxidative pathway in Alzheimer's disease. We have shown [4] that in the presence of Cu the β-content of monomer is reduced substantially compared with the wild-type Aβ42 suggesting that, in accord with experiment, metal ions facilitate formation of amorphous aggregates rather than amyloid fibrils with cross-β structures. For the Cu:Aβ stoichiometric ratios of 1:1 Cu delays the Aβ dimerization process as observed in a number of experiments. The mechanism underlying this phenomenon is associated with decreased hydrophobicity of monomer upon Cu-binding. We built statistical models of oligomeric Cu-Aβ42 complexes up to octamers. The simulations of these models show that in all cases there is a significant pool of configurations with Cu largely exposed to the water solvent. The burying of Cu within the protein assembly appears disfavoured in transient Aβ oligomers with Cu:Aβ 1:1.

References

[1] J. Nasica-Labouze, *et al.*, Amyloid beta-protein and Alzheimer's disease: when computer simulations complement experimental studies , *Chemical Reviews* **115**, 3518-3563 (2015).

[2] Mai Suan Li, N.T. Co, G. Reddy, C-K Hu and D. Thirumalai, Factors governing fibrillogenesis of polypeptide chains revealed by lattice models, *Phys. Rev. Lett.* **105**, 218101 (2010).

[3] M. Kouza et al, Kinetics and mechanical stability of the fibril state control fibril formation time of polypeptide chains: A computational study, J. Chem. Phys. **148**, 215106 (2018)

[4] P.D.Q. Huy *et al*., Impact of Cu(II) binding on structures and dynamics of Aβ42 monomer and dimer: Molecular dynamics study, ACS Chem. Neurosci. **10**, 1348 (2016).

I9. Improved physical models enable the investigation of molecular recognition in intrinsically disordered proteins at atomistic resolution

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Molecular dynamics (MD) simulation can serve as a valuable complementary tool to experiments in characterizing the structural and dynamic properties of intrinsically disordered proteins. By comparing long-timescale simulations of ordered and disordered proteins to experimental data, we have systematically identified limitations in current physical models and have developed new force fields that provide substantially improved accuracy in simulations of disordered proteins while maintaining state-of-the-art accuracy for folded proteins. These new force fields have enabled us to study mechanisms of molecular recognition in intrinsically disordered proteins in atomistic detail. In unbiased MD simulations of an intrinsically disordered protein and its physiological binding partner, for example, we observe a large number of spontaneous folding-upon-binding events, allowing us to carefully dissect and characterize the observed binding mechanisms. In a second application, unbiased MD simulations of the intrinsically disordered protein α-synuclein with a small molecule ligand reproduce a binding interaction observed by NMR spectroscopy experiments. These simulations have enabled us to rationalize the molecule's affinity for the experimentally observed binding site using a dynamic binding mechanism model in which α-synuclein remains flexible as it interacts with the small molecule in a variety of binding modes. Based on this mechanism, we have conducted a computational screen of small molecules selected to modify the bound ensemble and the affinity of the interaction. NMR measurements of a representative series of small molecules are in line with predictions of relative binding affinities and have provided support for details of the simulated binding mechanism and its perturbations. We are currently exploring the possibility of using dynamic binding mechanisms observed in MD simulations to rationally design molecules that exhibit improved binding to intrinsically disordered proteins.

I10. Role of metal ions in disordered biological systems: The perspective of modeling

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Ions have an essential role in many biological processes. In particular when the charge density is high (Mg, Ca, Zn) and when it changes according to microenvironmental conditions (Fe, Cu, Mn). Metal ions often interact with disordered proteins. The affinity is high enough to compete with structured proteins, but the structural and catalytic activity of the metal center is often out of control and, therefore, potentially dangerous for cells. In this talk I shall summarize this role with two examples. In the first example, we investigate the interactions between osteopontin and nucleic acids [1], describing the role of Mg in modulating protein association. In the second example, we apply a high-throughput modelling of Cu-amyloid beta complex in contact with dioxygen, with the aim at providing a tool to dissect the structural features that characterize dangerous catalysts in neurodegeneration [2,3]. The latter is a paradigmatic example where the oxidative pathway induced by sporadic copper catalysts triggers cell death.

References

[1] http://dx.doi.org/10.3389/fchem.2018.00002

[2] http://dx.doi.org/10.1002/chem.201704654

[3] http://dx.doi.org/10.1021/acs.jpcb.8b03983

I11. Molecular dynamics study of amyloid-β aggregates

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Amyloids are insoluble and misfolded fibrous protein aggregates and associated with more than 40 serious human diseases. For example, amyloid-β peptides (Aβ) form amyloid fibrils that are associated with Alzheimer's disease. To investigate the oligomerization process of Aβ, we developed Hamiltonian replica-permutation molecular dynamics (MD) method and applied this method to Aβ in explicit water solvent. We will show the oligomerization process of Aβ. We also performed MD simulations of Aβ fibrils in explicit water. We discovered that molecular structure is different between two ends: The two β-sheets β1 and β2 are close to each other at the even end. On the other hand, at the odd end the Aβ fluctuates more and takes an open form, too. Our theoretical prediction was proved by experiment after our MD simulations. We further performed nonequilibrium MD simulations with sinusoidal pressure and visualized this process with movies to describe the disruption of amyloid-β fibrils by ultrasonic cavitation. When the pressure is negative, a bubble was formed. When the pressure became positive, the bubble collapsed, and water molecules crashed against the hydrophilic residues to disrupt the amyloid.

I12. Development and application of nonequilibrium molecular dynamics simulation methods

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In recent years, we have developed a number of nonequilibrium molecular dynamics simulation methods aimed at unraveling the hidden complexity of dynamical processes of large nanostructures, which are otherwise not feasible with the current all-atom equilibrium simulation methods. I will present first the development of the laser-induced simulation method, which is essentially based on the resonance between the laser field and vibrational modes of the studied systems. The method is then applied to explain the experimental findings of the dissociation mechanism of the Alzheimer's disease related amyloid fibrils, and to provide proof-of-concepts showing the potential applications of the method such as recycling peptide nanotubes, killing viruses and dissolving celluloses in the pretreatment step of the biofuel production. I will then present the ultrasound-induced bubble cavitation molecular dynamics simulation method, and its applications to the clearance of amyloid fibrils, and formation of pores in the cell membranes. We show that the fusion of the lipid-coated bubble with the membrane, following by the bubble cavitation is the mechanism of the pore formation.

I13. Folding and self-assembly of peptides using coarse-grained on-lattice and off-lattice simulations

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I shall present where OPEP coarse-grained simulations coupled to advanced sampling techniques stand in the context of fast and accurate peptide structure determination, and the self-assembly of amyloid proteins associated with Alzheimer's disease.

I14. Aggregation and Coacervation of the Tau Peptide

Joan-Emma Shea

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Tau is an intrinsically disordered peptide that plays an important role in the cell by binding to microtubules. Under pathological conditions, Tau can form fibrillar aggregates, a process that has been linked with Alzheimer's disease. In addition to forming fibrils, the Tau protein can also phase separate into a protein rich and a protein depleted phase, a process known as liquid-liquid phase separation (LLPS), or coacervation. I will present field theoretic simulations that map out the phase diagram for Tau coacervation. The phase diagram is then used to predict the conditions under which Tau can be driven towards coacervation under live cell coculturing conditions. The theoretical predictions are corroborated by experiments.

I15. New tools for fast modeling of protein flexibility and protein-peptide docking

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During the talk, I will present the newly developed tools (standalone software packages and web servers) for fast modeling of protein flexibility and flexible protein-peptide docking [1-3]. The tools are enhanced versions of well-established CABS-flex and CABS-dock approaches [4-6]. Apart from the means for efficient simulations of protein/peptide flexibility, the presented tools offer numerous options for guiding & controling the conformational search, pipeline modifications according to users needs and also for results analysis and visualization.

References

[1] CABS-flex standalone: a simulation environment for fast modeling of protein flexibility. Bioinformatics, bty685, 2018

[2] CABS-flex 2.0: a web server for fast simulations of flexibility of protein structures. Nucleic Acids Res 46:W338–W343, 2018

[3] Protein-peptide docking using CABS-dock and contact information. Briefings in Bioinformatics, bby080, 2018

[4] Coarse-Grained Protein Models and Their Applications. Chemical Reviews, 116, 7898-7936, 2016

[5] CABS-dock web server for the flexible docking of peptides to proteins without prior knowledge of the binding site. Nucleic Acids Res, 43, W419-W424, 2015

[6] CABS-flex: server for fast simulation of protein structure fluctuations. Nucleic Acids Res. 41, W427-W431, 2013

I16. Computational approach to investigate protein complex formation and dissociation

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"Formation and dissociation of protein complexes are essential processes in biological systems, however, observation of these processes is challenging. Molecular simulations are useful methods to investigate molecular mechanisms of protein dissociation and association in silico. We recently developed efficient molecular simulation methods to investigate the mechanisms, which include a combination of parallel cascade selection molecular dynamics (PaCS-MD) and Markov state model [1] and concentrated ligand docking (ColDock) [2]. Our recent results on this topic will be reported in the conference.

References

[1] D.P. Tran et al., J. Chem. Theory Comput., 14 (1), 404–417 (2018).

[2] K. Takemura et al., J. Phys. Chem. B, 122 (29), 7191–7200 (2018).

I17. Chromatin and transcription factor dynamics via coarse-grained molecular simulations

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In eukaryotic genome, chromatin structures are known to play major roles in regulating gene expression. In particular, nucleosomes can be major bottlenecks for transcription factors to find their cognate sites, serving as general repressor. While nucleosomes are intrinsically stable, they are known to be dynamic and can move either spontaneously or driven by remodeler, which can affect transcription. Developing new protein-DNA coarse-grained model we study various aspects of interplay between chromatin and transcription. We further utilize Markov state modeling to quantify long-time dynamics and free energy landscape. Here, we based on these studies, we discuss nucleosome sliding dynamics, nucleosome assembly/disassembly process, transcription factor binding dynamics, and their interplay.

References

[1] S. Sainsbury, C. Bernecky, P. Cramer, Mol. Cell Biol., 16, 129-143, 2015

[2] C. Plaschka, et al, Nature, 533, 353-358, 2016

I18. Towards Simulating Eukaryotic Cells at Single Molecule Resolution

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Abstract: One of the key unsolved challenges at the interface of physical and life sciences is to formulate comprehensive computational modeling of the whole eukaryotic cell, at a single molecule resolution, which would deeply integrate reaction-diffusion, mechanical-structural and transport processes of cell's salient mechanochemical modules. Towards addressing this problem, we have developed a unique reactive mechanochemical force-field and software, called MEDYAN (Mechanochemical Dynamics of Active Networks: http://medyan.org). MEDYAN integrates dynamics of multiple mutually interacting phases: 1) a spatially resolved solution phase is treated using a reaction-diffusion master equation; 2) a polymeric gel phase is both chemically reactive and also undergoes complex mechanical deformations; 3) flexible membrane boundaries interact mechanically and chemically with both solution and gel phases. The above-mentioned computational components constitute the fundamental ingredients for minimal modeling of eukaryotic cells at a single molecule resolution. In this talk, I will outline our recent progress in simulating multi-micron scale cytosolic/cytoskeletal dynamics at 1000 seconds timescale, and also highlight the outstanding challenges in bringing about the capability for routine molecular modeling of eukaryotic cells.

I19. Protein-Drug Interaction in Dilute Solution and Cellular Environments

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Prediction of molecular interaction between a drug and a protein receptor is essential for in-silico drug discovery. Vast effort has been paid, so far, for rigid-body docking simulations as well as flexible drug-binding simulations. A drug-binding process is able to divide into two: one is the barrier crossing process toward the binding pocket and the other is diffusion from the bulk solution to the surface of a receptor. Recent simulation studies, these two processes are simulated individually using different computational methods and molecular models.

In our laboratory, we utilize one of the generalized-ensemble methods, gREST/REUS, for the first process and perform brute-force molecular dynamics simulations for the second one. gREST/REUS is the two-dimensional replica-exchange method, where generalized solute tempering is applied to the first dimension (gREST) and replica-exchange umbrella sampling (REUS) along the distance between a drug and the binding pocket. We obtain potential of mean force (PMF) of a drug binding from the surface of a protein to the binding pocket and investigate the binding mechanisms on the free-energy landscape. In brute-force molecular dynamics simulations, we study diffusion of a drug in dilute solution and cellular crowding environments. This simulation suggests slightly different binding pathways toward the binding pocket as well as different interactions between drug and protein surface in different environments.

I20. Recent computational biomedicine and biophysical research at the VNU Key Laboratory on Multiscale Simulation of Complex systems, Vietnam National University, Hanoi

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Abstract: In this talk, I will introduce different computational biomedical and biophysical research being done at the VNU Key Laboratory on Multiscale Simulation of Complex systems, Vietnam National University. Our overall research theme of computational research spans different scales from quantum mechanical to atomistic to coarse-grain modelings, many time linked together and with coordinated collaboration with experimental research to address problems in molecular biomedicine. Current projects include DNA system, TSPO translocator protein, Gout diseases, Metal-Organic-Frame, ... These are done with international collaborations as well as with other mutli-disciplinary computational and experimental research groups in Vietnam.

CONTRIBUTED TALKS

C1. Studies of proteins with disulfide bonds with molecular modeling tools

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Disulfide bonds and other cross-links play important role in protein folding, protein structure stabilization and often are responsible for the function of proteins and peptides. Although over 23% of the proteins stored in the PDB database contains at least one disulfide bond, their presence in biophysical and bioinformatical studies is often omitted due to technical difficulties.[1] For example, in most of the existing force fields disulfide bonds can be present (usually in form of a restraint function clipping two sulfur atoms at the desired distance) or absent for the whole time of the simulation and their formation or reduction cannot be studied. Examples of the disulfide-bond treatment will be presented based on the recent studies using mostly Gō[2] and coarse-grained models[3-4], which allows to study their formation and disruption associated with structural changes of the proteins.

References

1. Krupa P. TASK Quarterly 2016; 20(4):393-398.

2. Qin M. et al. Biophys J. 2006; 90(1):272–286.

3. Qin M. et al. Proc Natl Acad Sci U.S.A. 2015; 112(36):11241-6.

4. Krupa P. et al. J Chem Theory Comput. 2017; 13(11):5721-5730.

C2. Impact of surface roughness on aggregation process: Lattice model study

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Protein misfoding and aggregation into cross-β fibril structures may be associated with severe chronic neurodegenerative diseases such as the Alzheimer's disease, Huntington disease etc.. Because understanding the fibril formation kinetics plays a key role in developing effective therapies to cope with these diseases, much of progress has been achieved in exploring mechanisms and factors that govern the fibril growth. In vivo the protein aggregation often occurs on membrane surfaces the roughness and topology of which strongly affect the aggregation kinetics. Because the estimation of the fibril formation rate is not feasible using all-atom models, in this paper, we employed the homemade lattice model [1,2]. We have shown that the aggregation rate of peptides drastically depend on the roughness of both hydrophobic and hydrophilic surfaces. Surfaces with a small roughness catalyze the self-assembly, while those with a large roughness retard the aggregation and even block if the roughness is above a threshold value. Our results agree with the experiment of Vcha *et. al.* [3].

References

1. M. S. Li, D. K. Klimov, J. E. Straub, and D. Thirumalai. Probing the mechanisms of fibril formation using lattice models. J. Chem. Phys., 129:175101, 2008

2. M. S. Li, N. T. Co, C. K. Hu, J. E. Straub, and D. Thirumalai. Determination of factors governing fibrillogenesis of polypeptide chains using lattice models. Phys.Rev. Lett., 105:218101, 2010

3. Robert Vcha, Sara Linse, and Mikael Lund. Surface effects on aggregation kinetics of amyloidogenic peptides. Journal of the American Chemical Society, 136(33):11776–11782, 2014. PMID: 25068615

C3. Understanding Intrinsically Disordered Membrane Proteins in Alzheimer's Disease via Molecular Simulation

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"The Alzheimer’s amyloid disease pathway has been investigated for many years. Modern efforts to treat Alzhimer's Disease focus on prevention of genesis of 42- and 43-residue long fragments of amyloid beta peptide (Abeta), generated by cleavage of the 99-residue long C-terminal fragment of the Amyloid Precursor Protein (C99) in cellular membranes by gamma secretase (GS). Shorter, nontoxic Abeta fragments may be generated in cellular environments featuring longer lipids, which modify the structural ensemble of C99, environmentally selecting configurations of C99 that result in formation of different lengths of Abeta. Via molecular dynamics (MD) simulations, we have recently shown membrane thickness may determine the secondary and tertiary structure of the intrinsically disordered N- and C-terminal extramembrane regions of C99, which feature sites of many familial Alzhimer's Disease mutations, phosphorylatable residues, and interactions sites with intra- and extra-cellular proteins. These extra-membrane domains display many discrete, metastable conformational states between which there are many transitions. In addition to the cellular membrane, formation of C99 homodimers prevents formation of toxic lengths of Abeta by preventing C99 cleavage by GS. The structure of the transmembrane domain of C99 in homodimers is well-understood, but the effect of homodimerization on C99 N- and C-terminal remains unresolved. Currently, we are performing more detailed simulations of C99 in explicit solvent membranes to better-resolve the structural ensemble of the N- and C-terminal domains in the monomeric and dimeric state of C99. The novelty of this work is not limited to the domain of Alzheimer's Disease research, but also opens new understanding of intrinsically disordered proteins at the interface of cellular membranes and the role played by intrinsically disordered domains in the formation of protein dimers in the cell membrane."

C4. Flexible peptide docking using CABS-dock

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The characterization of protein-peptide interactions is a challenge for computational molecular docking. Protein-peptide docking tools face at least two major difficulties: efficient sampling of large-scale conformational changes induced by binding and the selection of the best models from a large set of predicted structures. Here we present the CABS-dock standalone application, developed to address both these issues. CABS-dock allows for highly efficient modeling of full peptide flexibility and significant flexibility of the protein receptor. Upon CABS-dock docking, the peptide folding and binding process is explicitly simulated and no information about the peptide binding site or its structure is used. CABS-dock methodology has been made available in 2015 as a web service dedicated solely to the prediction of structures of protein-peptide complexes. Presently we have released a standalone application, which significantly extends the range of applications of the method.

C5. A topological order parameter for describing folding free energy landscapes of proteins

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We studied the refolding free energy landscape of 26 proteins using the Go-like model. The distance between the denaturate state and the transition state, X_F, was calculated using the Bell theory and the nonlinear Dudko-Hummer-Szabo theory and its relation to the geometrical properties of the native state was considered in detail. We showed that none of the structural parameters, such as the contact order, protein length and radius of cross section, correlate with X_F for all classes of proteins. To overcome this problem we have introduced the nematic order parameter P_{02}, which describes the ordering of the structured elements of the native state. Due to its topologically global nature, P_{02} is better than other structural parameters in describing the folding free energy landscape. In particular, P_{02} displays a good correlation with X_F extracted from the nonlinear theory for all three classes of proteins. Therefore, this parameter can be used to predict X_F for any protein, if its native structure is known.

References

[1] Pham Dang Lan, Maksim Kouza, Andrzej Kloczkowski, and Mai Suan Li, A topological order parameter for describing folding free energy landscapes of proteins, J Chem Phys (accepted).

[2] Maksim Kouza, Pham Dang Lan, A. M. Gabovich, A. Kolinski, and Mai Suan Li, Switch from thermal to force-driven pathways of protein refolding , J. Chem. Phys. 146, 135101 (2017).

C6. Multi-scale modeling of cell biology

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Despite advances in technologies in studying complex biological systems, every experimental technique has a blind spot. For example, omic technologies can reveal molecular identities but not functions, biochemistry can reveal functions but not spatiotemporal details, light microscopy can provide high temporal resolution but not high spatial resolution, and electron microscopy can provide high spatial resolution but not real-time dynamics. While experimental insights might suggest conceptual models, these models need to be verified and therefore having them tested in silico brings us closer to the truth, stimulates new sets of experiments, and even inspires new fields of study. For this reason, we have been developing 3D multi-scale mathematical modeling methods to advance the knowledge of complex biological systems – an active soft matter. The approach is to use all available experimental data (e.g. from structure determination methods, imaging, genetics and biochemistry) to first build a detailed 3D model of a system, then use this model to simulate mechanistic hypotheses about individual molecules, hypotheses which are then validated or refuted by experiments in an iterative process of refinement. For a couple of highlights, I will first show how we have used our approach to offer a new understanding of how enzymes remodel the bacterial cell wall, the largest macromolecule in cell (Nguyen et al., PNAS 2015). Next, taking advantages of input from our Cryo-EM data that show the structure of rings of actin filaments in native state for the first time (Swulius, Nguyen et al., PNAS 2018), our simulations revealed detailed mechanics of the ring and how it constricts the membrane to divide cells (Nguyen et al., MBoC 2018).

C7. Modeling of protein interaction with charged polymers: from model polymers and nucleic acids to posttranslational modifications of amyloid proteins

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Interaction of proteins with charged macromolecules is involved in many processes in cells. First, there are many natural charged polymers such as DNA and RNA, polyphosphates, sulfated glycosaminoglycans etc. as well as pronouncedly charged proteins such as histones or actin. Electrostatic interactions are important also for "usual" proteins, which generally are not considered as polyanions or polycations. Herein we present few examples of atomistic molecular dynamic simulations (MD) applications to elucidate the role of charge-charge interactions in the mentioned processes. First, we adopted MD simulations to elucidate the mechanism of chaperone-like action of charged polymers. Then we performed modeling of interaction of different polymers with prion protein and observed a difference in the binding and prion protein structural changes induced by the binding of two types of sulfated polyanions, whose effect on amyloid aggregation was opposite. Compared to linear polyanions, the predicted binding site of cationic pyridinium dendrimers was more "local" and covered the region which is crucial for amyloid conversion of prion protein. Electrostatic interaction of the protein can be altered due to posttranslational modifications such as glycation, sulfation or phosphorylation, which change local charge of the protein region. We have analyzed the binding of glyceraldehyde-3-phosphate dehydrogenase with nucleic acid and amyloidogenic protein alpha-synuclein. Both macromolecules have been shown to interact with anion-binding groove of glyceraldehyde-3-phosphate dehydrogenase, and the interaction is determined mainly by charge-charge interaction. We investigated an impact of protein glycation, which is associated with modification of positively charged groups of lysine (and, in less extent, arginine) to neutral or negatively charged ones. The affinity of the binding and specificity to anion-binding groove have been shown to decrease when alpha-synuclein glycation level increased. Glycation of glyceraldehyde-3-phosphate dehydrogenase influenced the binding in the same manner. These results corroborated by experimental data demonstrate the importance of posttranslational modifications associated with local charge changes. These results are of special interest since glycation of amyloidogenic proteins can be associated with progression of neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease.

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POSTERS

P1. Erythromycin leads to differential protein expression through differences in electrostatic and dispersion interactions with nascent proteins

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Abstract. The antibiotic activity of erythromycin, which reversibly binds to a site within the bacterial ribosome exit tunnel, against many gram positive microorganisms indicates that it effectively inhibits the production of proteins. Similar to other macrolides, the activity of erythromycin is far from universal, as some peptides can bypass the macrolide-obstructed exit tunnel and become partially or fully synthesized. It is unclear why, at the molecular level, some proteins can be synthesized while others cannot. Here, we use steered molecular dynamics simulations to examine how erythromycin inhibits synthesis of the peptide ErmCL but not the peptide H-NS. By pulling these peptides through the exit tunnel of the *E.coli* ribosome with and without erythromycin present, we find that erythromycin directly interacts with both nascent peptides, but the force required for ErmCL to bypass erythromycin is greater than that of H-NS. The largest forces arise three to six residues from their N-terminus as they start to bypass Erythromycin. Decomposing the interaction energies between erythromycin and the peptides at this point, we find that there are stronger electrostatic and dispersion interactions with the more C-terminal residues of ErmCL than with H-NS. These results suggest that erythromycin slows or stalls synthesis of ErmCL compared to H-NS due to stronger interactions with particular residue positions along the nascent protein.

References

1. Nguyen, Hoang Linh, Pham Dang Lan, E.P. O'Brien, and Mai Suan Li, Erythromycin leads to differential protein expression through differences in electrostatic and dispersion interactions with nascent proteins, *Scientific Reports* **8**: 6460 (2018).

P2. Erythromycin, Cethromycin and Solithromycin Exhibit Similar Binding Affinities to the E. coli's Ribosome

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Abstract. Macrolide antibiotics bind to the exit tunnel of the ribosome inhibiting the synthesis of protein by blocking its translocation. By this way antibiotics including the known macrolide Erythromycin (ERY) exhibit activity against bacteria. However, nowadays some bacteria show resistance to drug, necessitating the development of new powerful antibacterial agents. One possible way is to use the ERYstructure, but change its side chains, while the size of the lactone ring can remain unchanged or change. In this work we consider Cethromycin (CET) and Solithromycin (SOL) which are ketolides with quinolylallyl group at C6 and aminophenyl at C11, respectively (both of them have the same lactone ring as ERY). Experiments have shown that these ketolides have improved efficacy against pathogens but their binding affinity to the E.coli's ribosome is almost identical. To clarify this issue we studied in detail the binding mechanisms of ERY, CET and SOL using the docking and molecular dynamic simulations. In agreement with the experiments, we showed that these compounds exhibit similar binding affinities. Cladinose group plays an important role in the interaction between ERY and ribosome. The keto group and alkyl-aryl arm in Solithromycin balance each other, whereas in Cethromycin they compensate the contribution from the lactone. The alkyl-aryl arm of both ketolides strongly interacts with A752 and U2609. In addition, the presence of macrolides in the exit tunnel may fluctuate the conformation of U2585, which is a residue in the peptidyl transferase center. Therefore, the side chain of ketolides affects not only the binding site but also other residues possibly leading to a high effect on the protein synthesis process.

P3. Probing Binding Affinity by Jarzynski's Non-equilibrium Binding Free Energy and Rupture Time

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Abstract. Binding affinity of small ligand to receptor is the important quantity in drug design and it might be characterized by different quantities. The most popular one is the binding free energy which can be estimated by several methods in conventional molecular dynamics simulation. So far in steered molecular dynamics (SMD) one can use either the rupture force or non-equilibrium pulling work as a measure for binding affinity. In this paper we have shown that the non-equilibrium binding free energy $\Delta G_{\mathrm{neq}}^{\mathrm{Jar}}$, obtained by Jarzynski's equality at finite pulling speed, has good correlation with experimental data on inhibition constants implying that this quantity can be used as a good scoring function for binding affinity. A similar correlation has been also disclosed for binding and unbinding free energy barriers. Applying the SMD method to unbinding of 23 small compounds from the binding site of beta-lactamase protein, a bacterial produced enzyme, we have demonstrated that the rupture or unbinding time strongly correlates with experimental data with correlation level $R \approx 0.84$. As follows from the Jarzynski's equality, the rupture time depends on the unbinding barrier exponentially. We show that $\Delta G_{\mathrm{neq}}^{\mathrm{Jar}}$, the rupture time as well as binding and unbinding free energy barriers are good descriptors for binding affinity. Our observation may be useful for fast screening of potential leads as the SMD simulation is not time consuming. Based on non-equilibrium simulation we disclosed that, in agreement with experiment, the binding time is much longer than the unbinding one.

References

1. Truong, Duc Toan, and Mai Suan Li. "Probing Binding Affinity by Jarzynski's Non-Equilibrium Binding Free Energy and Rupture Time." *The Journal of Physical Chemistry B* **122** (17), 4693–4699 (2018).

P4. Picosecond melting of peptide nanotubes using an infrared laser: A nonequilibrium simulation study

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Abstract. Self-assembled functional peptide biomaterials are emerging with a wide range of envisioned applications in the field of nanotechnology. Currently, methods and tools have been developed to control and manipulate as well as to explore new properties of self-assembled structures. However, considerably fewer studies are being devoted to developing efficient methods to degrade or recycle such extremely stable biomaterials. With this in mind, here we suggest a theoretical framework, inspired by the recent developed mid-infrared free-electron laser pulse technology, to dissociate peptide nanotubes. Adopting a diphenylalanine channel as a prototypical example, we find that the primary step in the dissociation process occurs due to the strong resonance between the carboxylate bond vibrations of the diphenylalanine peptides and the tuned laser frequencies. The effects of laser irradiation are determined by a balance between tube formation and dissociation. Our work shows a proof of concept and should provide a motivation for future experimental developments with the final aim to open a new and efficient way to cleave or to recycle bio-inspired materials.

References

1. Man Hoang Viet, Phan Minh Truong, Philippe Derreumaux, Mai Suan Li, Christopher Roland,Celeste Sagui and Phuong H. Nguyen, Picosecond melting of peptide nanotubes using an infrared laser: a nonequilibrium simulation study, *Physical Chemistry Chemical Physics* 17 (2015): 27275-27280.

P5. Protocol for fast screening of multi-target drug candidates: Application to Alzheimer's disease

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Abstract. The treatment of many diseases may require drugs that are capable to attack multiple targets simultaneously. Obviously, the virtual screening of multi- target drug candidates is much more time consuming compared to the single-target case. To overcome this difficulty, we propose a simple protocol which is relied on the fast steered molecular dynamics simulation [1,2] and on available experimental data on binding affinity of reference ligand to a given target. Applying our new protocol to five targets including amyloid beta fibril, peroxisome proliferator-activated receptor γ, retinoic X receptor α, β- and γ-secretases, we have found two potential drugs [3] (CID 16040294 and CID 9998128) for AD from the large PubChem database. We have probed capability of small CID 9998128 compound *in silico* and *in vitro* experiments. *In silico*, by all-atom simulation and MM-PBSA method [4] we have demonstrated that this compound strongly binds to both amyloid beta 42 ($A\beta_{42}$) fibrils and β-secretase and the van der Waals interaction is dominating over the electrostatic interaction in binding affinity. *In vitro* experiments have shown that CID 9998128 [5] inhibits the $A\beta_{42}$ amyloid fibrillization and is capable to clear $A\beta_{42}$ fibrils. Moreover, compound dose-dependently decreases β-site amyloid precursor protein cleaving enzyme (BACE-1) activity with EC50 value in micromolar range. Thus, our study has revealed that CID 9998128 is a good candidate for AD treatment through preventing production of Aβ peptides and degrading their aggregates. For drug design we predict that the chemical structure of potent AD multi-target inhibitors should not contain indazole.

References

1. Nguyen Quoc Thai, Nguyen Hoang Linh, Huynh Quang Linh, and Mai Suan Li, Protocol for fast screening of multi-target drug candidates: Application to Alzheimer's disease. Journal of Molecular Graphics and Modelling, 77, 121-129 (2017).
2. Nguyen Quoc Thai, Z. Bednarikova, M. Gancar, Huynh Quang Linh, Chin-Kun Hu, Mai Suan Li, and Z. Gazova, CID 9998128 compound is a potential multi-target drug for Alzheimer's disease. ACS Chemical Neuroscience, (2018), DOI: 10.1021/acschemneuro.8b00091

P6. Molecular insight of how Aβ42-G37V reduces toxicity: An *in vitro* and *in silico* study

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Aggregation of β-amyloid (Aβ) peptides is a hallmark of the Alzheimer's disease. Aβ peptide, which contains a Glycine zipper motif at the C-terminus may have high impact on formation of toxic oligomers. Particularly, the Gly37Leu substitution dramatically reduces Aβ toxicity *in vivo* and *in vitro* and thereby advocating the hypothesis that deduction of Glycine zipper formation could prevent assembly of toxic Aβ oligomers. The decreased toxicity under mutation is presumably caused by deletion of Glycine or by the effect of Leucine but this problem has not been considered. To gain the molecular insight on the effect of glycine zipper motif on Aβ properties, we substituted Leucine by Valine - an amino acid, which have similar properties as Leucine (nonpolar and hydrophobic), using *in silico* and *in vitro* experiments. The Aβ-Gly37Val monomer was studied by the replica exchange molecular dynamics simulation with the OPLS-AA force field and implicit water model. We have found that this mutation changes the aggregation rate of Aβ42 although the total β-content alters slightly. This is because under mutation the β-turn and β-hairpin at position 36-37 increased tremendously. This result suggests that the Gly37Val mutation makes Aβ42 behavior to become "*super*" Aβ42 by stabilizing the β turn at the C-terminus. The thioflavin-T aggregation assay confirmed this prediction showing the different morphologies of Aβ42-WT and Aβ42- Gly37Val aggregates. In our *in vitro* study, the G37V mutation did not accelerate the aggregation rate, instead its aggregates showed an ellipse shape instead of a network-like fibril, which was observed in Aβ42 or Aβ42-G37L and reduced the toxicity.

P7. Screening potential inhibitors for cancer target LSD1 from natural products by steered molecular dynamics

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Abstract. LSD1 is one of the important proteins which help transcriptional machine to access to DNA though open or close DNA around histone. It can also demethylate p53 at specific lysines altering the p53-mediated transcriptional process which could lead to the inhibition of the role of p53 in promoting apoptosis. Thus, inhibition of LSD1 activity by small compounds becomes a promising cancer therapy. Combining the Lipinski's rule with docking and steered molecular dynamics simulation we have found from the traditional Chinese medicine database four compounds that are good candidates for inhibiting LSD1 activity.

References

1. Thai, Nguyen Quoc, Ngan Quy Nguyen, Chuong Nguyen, Truong Quy Nguyen, Kiet Ho, Trung Tin Nguyen, and Mai Suan Li, Screening potential inhibitors for cancer target LSD1 from natural products by steered molecular dynamics, *Molecular Simulation* **44** (2018): 335-342.

P8. Fullerenol $C_{60}(OH)_{16}$ prevents amyloid fibrillization of $A\beta_{40}$ – *in vitro* and *in silico* approach

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The generation of Aβ amyloid aggregates in the form of senile plaques in the brain is one of the pathological hallmarks of Alzheimer's disease (AD). There is no cure for AD and one of the recent treatment strategies is focused on the inhibition of amyloid fibrillization of Aβ peptide. Fullerene C_{60} has been proposed as a candidate for destroying Ab aggregates but it is not soluble in water and its toxicity to cells remains largely ambiguous. To overcome these drawbacks, we synthesized and studied the effect of water-soluble fullerenol $C_{60}(OH)_{16}$ (fullerene C_{60} carrying 16 hydroxyl groups) on the amyloid fibrillization of Ab 40 peptide in vitro. Using a Thioflavin T fluorescent assay and atomic force microscopy it was found that $C_{60}(OH)_{16}$ effectively reduces the formation of amyloid fibrils. The IC 50 value is in the low range (μg ml -1) suggesting that fullerenol interferes with Ab_{40} aggregation at stoichiometric concentrations. The in silico calculations supported the experimental data. It was revealed that fullerenol tightly binds to monomer Ab_{40} and polar, negatively charged amino acids play a key role. Electrostatic interactions dominantly contribute to the binding propensity via interaction of the oxygen atoms from the COO - groups of side chains of polar, negatively charged amino acids with the OH groups of fullerenol. This stabilizes contact with either the D23 or K28 of the salt bridge. Due to the lack of a well-defined binding pocket fullerenol is also inclined to locate near the central hydrophobic region of Ab_{40} and can bind to the hydrophobic C-terminal of the peptide. Upon fullerenol binding the salt bridge becomes flexible, inhibiting Ab aggregation. In order to assess the toxicity of fullerenol, we found that exposure of neuroblastoma SH-SY5Y cells to fullerenol caused no significant changes in viability after 24 h of treatment. These results suggest that fullerenol $C_{60}(OH)_{16}$ represents a promising candidate as a therapeutic for Alzheimer's disease.

References

1. Bednarikova, Z.; Huy, P. D. Q.; Mocanu, M.-M.; Fedunova, D.; Li, M. S.; Gazova, Z., PCCP **2016**, 18, 18855–18867.
2. Huy, P. D. Q.; Li, M. S., PCCP, **2014**, 16, 20030–20040.

P9. Cryo-EM flexible fitting for large bimolecular systems

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Flexible fitting is a powerful technique to build the three-dimensional structure of a biomolecule from its density map obtained by single-particle cryo-electron microscopy (cryo-EM). One popular method is a cross-correlation-coefficient-based approach, where the cross-correlation coefficient between the experimental and simulated density maps is included as a biasing potential and flexible fitting is carried out via molecular dynamics (MD) simulation with the biasing potential. Here, we propose efficient parallelization schemes for the cross-correlation coefficient calculation to accelerate atomic- and domain-decomposition MD simulations with flexible fitting. These schemes are tested for small, medium, and large biomolecules using not only multiple CPUs but also hybrid CPU+GPU clusters. The parallel scheme for the atomic-decomposition MD is suitable for the flexible fitting of the small system like Ca2+-ATPase with the all-atom Go-model, while that for the domain-decomposition MD is better for larger systems like ribosome with the all-atom Go or the all-atom explicit solvent models. These parallelization schemes developed here allow flexible fitting of cryo-EM data for various biological systems including membrane proteins and large protein/RNA complexes with reasonable computational cost. This approach also connects high-resolution structure refinements with investigation of protein structure-function relationship.

P10. In silico study of Bombyx Mori Fibroin N Terminal Domain by Graphene

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We reported the best bound conformation of graphene to the Bombyx Mori Fibroin by using high concentration docking method together with Markov State Model for selection. The calculated binding free energy at tens of kcal/mol indicating the strong binding. By comparing the RAMAN spectra of free standing graphene and the bound structure, we found that there is change in molecular orbitals upon the bound.