enzyme. In addition, these studies can provide fundamental insights into how ligand binding regulates protein function. Such information has direct applications in the areas of drug discovery, regulation of metabolic pathways and other signal transduction processes.

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Dynamics of Amyloid Beta-Peptide (21-30) and its Iowa Mutation under Confinement and Crowding: A Molecular Dynamics Study
Srinivasa Rao Jampani, Luis Cruz.
Drexel University, Philadelphia, PA, USA.
We present long time all-atom molecular dynamics simulations of the wild type (WT) and Iowa mutation of the amyloid β-protein (Aβ) fragment (21-30) under confinement and crowding. To study the effects of confinement, we model the protein and solvent system to be confined inside spherical pores of varying sizes (12-24Å) composed of both, hydrophilic and hydrophobic walls. We discuss the dynamics of folding, and mechanisms of unfolding from a preformed β-hairpin under both confinement types by varying the size of the confined pore. Simulation results show that the dynamics of the WT and Iowa Aβ(21-30) in confinement (hydrophobic and hydrophilic) exhibit considerable variations from the corresponding bulk simulations. Also, the unfolding of preformed β-hairpin structures follow different mechanisms based on the pore type and closeness to the confined wall. These differences in mechanism are also reflected in the lifetimes of the preformed β-hairpin structures. We present effects of crowded environments on the dynamics of the WT Aβ(21-30) by modeling the crowders as C70 and $C60(OH)_{20}$ spherical fullerenes in explicit solvent. Results and detailed comparisons between the two systems will be presented.

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Power-Law Trappings Cause Anomalous Diffusions of Water Molecules on Membrane Surfaces
Eiji Yamamoto[1], Takuma Akimoto[1], Yoshinori Hirano[2], Masato Yasui[3], Kenji Yasuoka[1].
[1]Department of Mechanical Engineering, Keio University, Yokohama, Japan, [2]Quantitative Biology Center (QBiC), RIKEN, Kobe, Japan, [3]Department of Pharmacology, School of Medicine, Keio University, Tokyo, Japan.
Cell membranes provide unique local environments for biological reactions, where diffusion of biomolecules as well as water molecules plays critical roles. In this study, molecular dynamics simulations for a system of water molecules / lipid bilayer were performed at temperatures from 250 K to 350 K to examine dynamics of water molecules around the surface of the lipid bilayer. Our analysis introduces a mean exit time approach which allows characterizing diffusive properties of water molecules around the surface of lipid bilayers. Using this method, we show that translational motions of water molecules around the surface of lipid bilayers are slower than those in bulk. Moreover, we find that trapping times of water molecules onto membrane surfaces are distributed according to power-law distributions depending on temperature and that water molecules on the membrane surfaces exhibit subdiffusions in translational as well as rotational motions. We provide evidence that not only an enhancement of the viscosity but also subdiffusions of water molecules on membrane surfaces originates from power-law trappings in translational motions on membrane surfaces.

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Photoisomerization Control Mechanisms in Protonated Schiff Bases
Lela Vukovic[1,2], Carl F. Burmeister[1], Petr Kral[2], Gerrit Groenhof[1].
[1]Max Planck Institute for Biophysical Chemistry, Goettingen, Germany, [2]University of Illinois at Chicago, Chicago, IL, USA.
We have performed *ab initio* excited-state molecular dynamics simulations of an isolated photo-excited protonated Schiff base (C_1-N_2=C_3-C_4=C_5-C_6) to search for mechanisms that control its photoisomerization outcome, such as the bond selectivity and (trans, cis) conformation. We observe that the photo-excited molecule twists around the N_2C_3 bond (~80% cases of the thermal ensemble) or the C_4C_5 bond, and relaxes back to the ground electronic state with either a trans or cis outcome. First, we show that a significant initial distortion of several selected dihedral angles can preferentially guide the excited-state dynamics towards twisting of the C_4C_5 bond. Next, we examine if the bond selectivity can be controlled by the vibrational pre-excitation of the molecule along individual normal modes. We find that pre-excitation of only one of the modes, which contains a prominent propelling motion of the C_4C_5 bond with respect to the neighboring C_3C_4 single bond, leads to twisting of the C_4C_5 bond. Normal mode decomposition of the ground state thermal ensemble shows that in starting structures in which this same mode is pre-excited by 1-2 k_BT thermal energy, the twisting of C_4C_5 occurs with a 30-50% probability. Finally, we find that the (trans, cis) outcome of the reaction can be controlled by selective pre-twisting of several dihedral angles, while keeping other degrees of freedom thermally excited. This choice was justified by the observed pre-twisting of retinal chromophore in rhodopsin, which exhibits 65% cis to trans transition. In the thermal ensemble with such pre-twisted dihedrals, we observe on the excited state potential energy surface synchronized twisting of CN_2C_3C and HN_2C_3H torsional angles surrounding the isomerizing N_2C_3 bond, which significantly increases the fraction of reactive (cis to trans) trajectories. These observations provide crucial understanding of natural photoisomerization mechanisms and their potential use in synthetic molecules.

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Dependency of Percolation Threshold of Water Cluster on Flexibility of Ice Nucleation Protein
Daisuke Murakami, Kenji Yasuoka.
Keio Universiry, Yokohama, Japan.
Ice nucleation protein is a planar hydrophilic protein buried in the outer cell membrane of ice nucleating active bacteria. This protein is said to induce a phase transition from liquid water to ice surfaced on it. However, the mechanism of the phase transition has not been clarified. We investigated characteristics of water clusters on the protein and interactions between water clusters and the protein by molecular dynamics simulations. We also focused on the percolation theory to analyze those clusters. As a result, behavior of water molecules depended on the existence of percolation clusters. The flexibility of the protein helped to form percolation clusters.

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Molecular Dynamics Study of the Effect of the Interface Structure on the Kinetics of Ice Crystal Growth
Dmitri Rozmanov, Peter G. Kusalik.
University of Calgary, Calgary, AB, Canada.
Understanding the mechanisms of molecular spontaneous self-assembly is essential for the ability to predict structures of folded proteins and other complex biological structures. Precise control of material crystal structure and, therefore, its mechanical properties is another field where detailed knowledge of self-assembly is of principal interest.
Our current knowledge of the mechanisms and kinetics of such processes is still limited. In this work the spontaneous growth of ice (freezing) is studied by molecular dynamics simulations in the isoconfigurational ensemble at three different temperatures below the melting point. Ice is a molecular crystal where water molecules are held in place by hydrogen bonding, an interaction similar to interactions in biological systems. This similarity and relative simplicity of this system, at the same time, make it a perfect subject for uncovering details of ordering and disordering processes during self-organization of matter.
It is shown that specific structures determine local thermodynamics at a growing interface and directly influence kinetics of growth at a time scale of 1-2 ns due to fluctuations. The structural effect on the growth behaviour can be characterized in terms of relative growth propensities.
The topology of the initial interfaces is obtained using a structural order parameter and compared with the observed growth behaviour. Critical interfacial features specific to the observed growth patterns are identified in some cases. The work clearly indicates that local structure determines, to a large degree, the tendency of an interface to grow or melt.
This structural effect upon the ordering kinetics should be a universal behaviour and can be expected in more complex biologically relevant ordering processes.

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Effect of Monovalent Ion Concentration in Molecular Simulation of Electroporation
Ming-Chak Ho[1], Zachary A. Levine[1], P. Thomas Vernier[2].
[1]Department of Physics and Astronomy, Dornsife College of Letter, Arts, and Sciences, University of Southern California, Los Angeles, CA, USA, [2]Ming Hsieh Department of Electrical Engineering. Viterbi School of Engineering, University of Southern California, Los Angeles, CA, USA.
Monovalent ion concentration gradients, regulated by ion pumps and leak channels, are critical components of many cellular functions. This dynamic balance is disturbed by the electroporative permeabilization of the cell membrane, which bypasses the normal membrane barriers to transmembrane ion flux. A better understanding of ion transport during and after electroporation will enable more efficient and more effective utilization of this method in biomedicine and biotechnology.
Molecular dynamics (MD) simulations provide a view of the behavior of ions and biomolecular structures at the molecular level. Previous MD studies

have demonstrated some of the effects of monovalent ions on phospholipid bilayers, including decreased area per lipid, higher ordering in head group vertical orientations, and decreased lateral lipid mobility [1-4]. MD simulations of porated membranes have also shown that the binding of monovalent cations to phospholipids can increase pore line tension, which leads to a decrease in pore lifetime [5]. In this work we employ MD simulations to systematically study the effects of varying the concentration of Na^+, K^+, and Cl^- in POPC lipid bilayer systems during different stages of electropore formation.

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Conduction and Selectivity of Ions through a Sodium Channel

Leticia Stock[1], Lucie Delemotte[2], Vincenzo Carnevale[2], Werner Treptow[1,2], Michael L. Klein[2].
[1]Universidade de Brasilia, Brasilia, Brazil, [2]Temple University, Philadelphia, PA, USA.

The NavAb (a bacterial voltage-gated Na^+ channel) atomic structure has been recently resolved. Because NavAb is a possible ancestor of the vertebrate Nav and Cav - voltage dependent Na^+ and Ca^{++} channels, respectively - such a structure provides a unique opportunity to deepen our understanding on these closely related channels. Strikingly, the NavAb structure displays a selectivity filter much wider than the one observed in the well characterized K^+ channels, and therefore raises relevant questions concerning the conduction and selectivity mechanism in this channel. We follow from an ongoing project aiming at studying the conduction mechanism and selectivity on sodium channels. For that purpose, the Free-Energy surface (FES) of the permeation events of two Na^+ ions was assessed by means of a 180 ns long metadynamics calculation. In such method, two reaction coordinates are defined for each ion: the axial distance (z) along the pore axis and the radial distance (x, y) plane. The resulting four-dimensional FES is employed to retrieve the minimum energy pathway covered by the ions. In order to investigate channel selectivity, the present work extends the above mentioned studies to the two-ions constructs: sodium-potassium and potassium-potassium. Our findings point to a dynamical process in which ions transit between favorable interaction sites. Also, subtle differences in the process free-energy landscape may lead to significantly altered permeation rates. Taken together, these results are likely to provide a rationalization for selectivity.

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The Electric Fingerprint of Membrane Voltage Sensor Domains

Cristiano Amaral, Caio S. Souza, Letícia L. Stock, Werner Treptow.
Universidade de Brasilia, Brasilia, Brazil.

Voltage-sensor domains (VSDs) are electrically-charged constructs controlling the voltage-dependent activity of ion channels in excitable cells. Four packed transmembrane (TM) helices, S1 through S4, form the domain in which S4 contains 4 to 7 positively charged basic amino acids, mostly arginines. VSDs operate essentially by transferring the S4 charges across the transmembrane electric field (**E**), giving rise to the observable Q, the so-called ''gating charge''. Mostly supported by structure-function studies on voltage-gated potassium (Kv) channels, a focused **E** has been identified as one key electric property of the VSD machinery. The recent increasing availability of other VSD-containing ion channel structures, including the x-ray structures for the NavAb and NavRh voltage-gated Na^+ channels, provides us with the opportunity to extend the structure-based investigation of the domain electrostatic properties over a larger set of distinct conformations and isoforms. Using all-atom MD simulations in combination with electrostatic calculations, founded on an energetic formalism, we show that, over the entire set of available VSD structures, a specific hydration of the voltage sensor focuses **E** over a narrow TM region across the domain, at the vicinity of the so-called catalytic center. Furthermore, its focalization and shape is largely preserved over distinct conformations of the construct. Our results support that a focused and conformation-independent TM field is a robust electric feature of the VSD machinery, despite sequence variations or local structural modifications of the domain. This electric fingerprint seems to favor a highly conserved sensing mechanism for VSDs over the large family of voltage-gated cation channels.

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Skeletal Calsequestrin - Calcium Interaction: Role of Acidic C-Terminus

Naresh C. Bal[1], Amit Kumar[2], Harapriya Chakravarty[3], Tuniki Balaraju[3], Chandralata Bal[3], Nivedita Jena[1], Ashoke Sharon[3], Muthu Periasamy[1].
[1]The Ohio State University, Columbus, OH, USA, [2]Science and Technology Park, Pula, Italy, [3]Birla Institute of Technology, Ranchi, India.

Skeletal isoform of calsequestrin (CASQ1) is expressed primarily in fast twitch skeletal muscles in all vertebrates and buffers Ca^{2+} inside the sarcoendoplasmic reticulum (SR), the intracellular Ca^{2+} store. CASQ1 has a very unique C-terminus composed sole of aspartic acid residues. Presence of more than 10 consecutive aspartic acid residues in a protein sequence [referred as consecutive aspartate stretch (CAS)] is a very rare feature that is found only in about 20 proteins in the human genome. However, the role of CAS in CASQ1 function has not been investigated. Here we applied computational approach to understand the role of CAS in Ca^{2+}-binding. The recent structure of CASQ1 has resolved the structure of its whole protein except for the CAS. We prepared the model by adding the CAS residues and performed molecular dynamics simulations for 50 nanoseconds in the presence of various Ca^{2+} concentrations. Our study shows that the CAS assumes a compact structure at higher Ca^{2+} concentrations and indicates that the CAS might work as a metal sensor. We found that the CAS undergoes maximal Ca^{2+}-binding before the rest of the surface is saturated. The study revealed various Ca^{2+}-binding sites with differing affinities and geometry. Interestingly, some sites are Ca^{2+}-concentrations dependent while some others are independent of Ca^{2+} concentration. The low affinity sites of CASQ1 bind Ca^{2+} transiently that is mediated by water molecules and can dissociate quickly to support Ca^{2+}-release during contraction. These studies collectively indicate the CAS works as a Ca^{2+}-sensor that may be a novel metal sensing motif. We propose the term ''D_n-motif'' for CAS.

Single Molecule Techniques I

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Single-Molecule DNA Curtains Reveals the Details of KOPS Targeting, Translocation, and Collision with Protein Roadblocks of DNA Translocase FtsK

Ja Yil Lee[1], Ilya J. Finkelstein[1,2], Estelle Crozat[3,4], David J. Sherratt[3], Eric C. Greene[1,5].
[1]Department of Biochemistry and Molecular Biophysics Columbia University, New York, NY, USA, [2]Department of Chemistry and Biochemistry, Austin, TX, USA, [3]Department of Biochemistry, University of Oxford, Oxford, United Kingdom, [4]Institut de Genetique Microbienne, Universite Paris Sud 11, Orsay, France, [5]Howard Hughes Medical Institute Columbia University, New York, NY, USA.

In E coli cell division, two daughter chromosomes often form a dimer, which impedes a proper segregation of chromosomes. The chromosome dimer can be resolved by XerCD-mediated site specific recombination at dif site. The alignment of two dif sites and activation of XerCD require FtsK translocation, which is directed by a short DNA sequence called KOPS (FtsK Orienting Polar Sequences). KOPS targeting and translocation activities of FtsK were examined using single-molecule DNA curtains, which enables to visualize the protein-DNA interaction in real time. We show that FtsK preferentially locates KOPS through 3D collision within our resolution and non-hydrolysable nucleotides enhance the FtsK loading on KOPS. We also reveal that KOPS determines the orientation of FtsK translocation, but only upon initial binding to KOPS. During the translocation, FtsK abruptly pauses and/or changes its direction independently of KOPS, suggesting that FtsK cannot identify KOPS once it begins to translocate. Next we investigated the collision of FtsK with various protein roadblocks including XerCD through two-color labeling in DNA curtains. Interestingly, the FtsK, which has a hexameric ring structure, changes its direction and bypasses the roadblocks, and can also push them along the DNA. Our single-molecule results help reveal how FtsK might function in the crowded environments expected to be found in physiological settings.

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Single-Molecule Dissection of KRas and EGFR Signaling Dynamics in Individual Cancers

Hong-Won Lee[1], Min Kwon Cha[1], Seung-Hyo Lee[2], Tea-young Yoon[1].
[1]Department of Physics, KAIST, 335 Gwahak-ro, Yuseong-gu, Daejeon, Korea, Republic of, [2]Graduate School of Medical Science and Engineering, KAIST, 335 Gwahak-ro, Yuseong-gu, Daejeon, Korea, Republic of.

At the molecule level, individual cancers are driven by their own sets of dysregulated protein-protein interactions. Due to the lack of PCR technique for