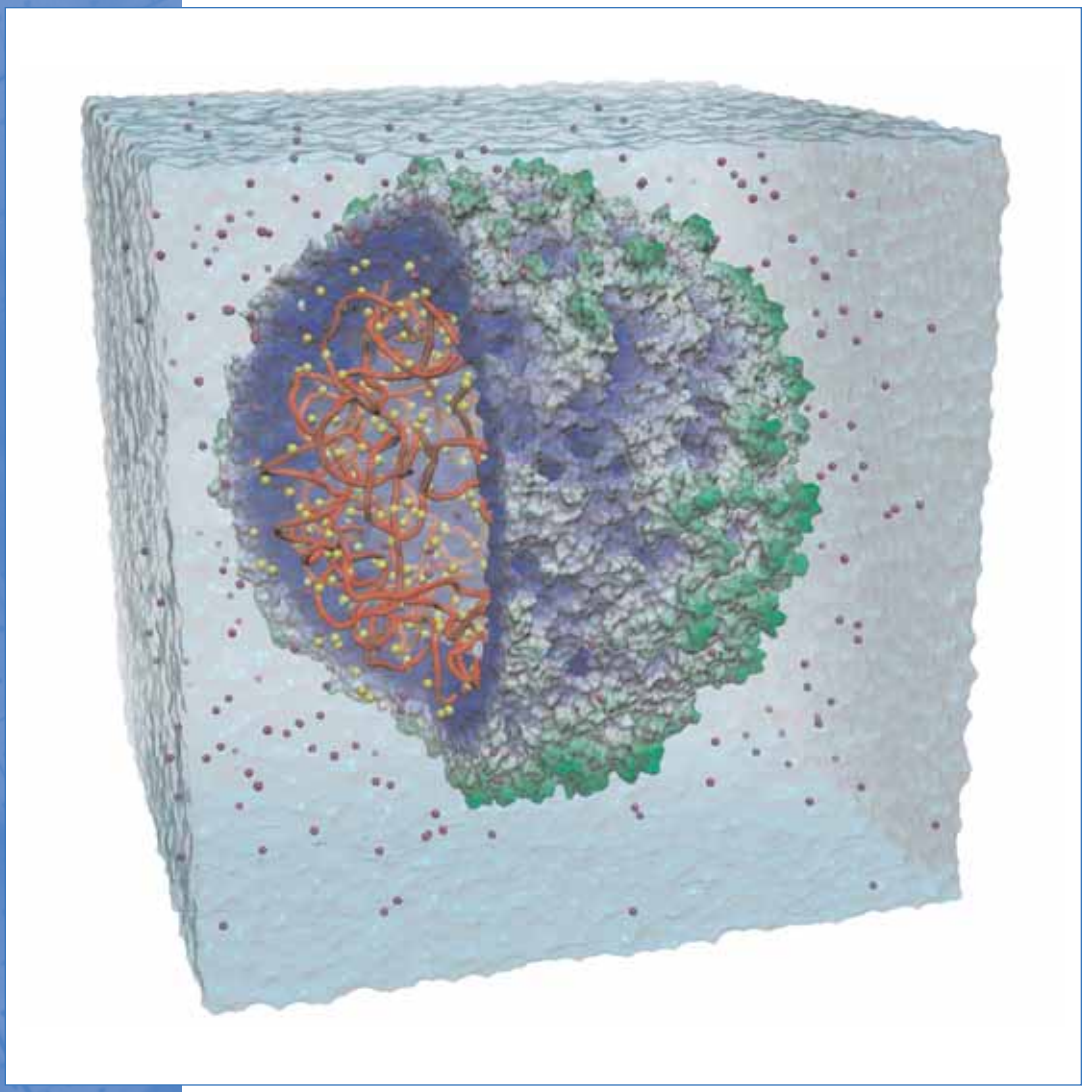
[Highlights 2004-2006]

Theoretical and Computational Biophysics Group



University of Illinois at Urbana-Champaign
Beckman Institute for Advanced Science and Technology

TCBG

Theoretical and Computational Biopysics Group

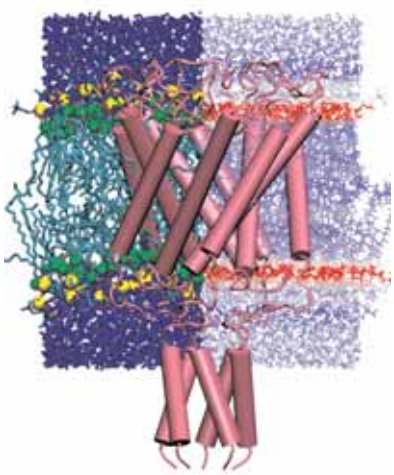
Motivated by biomedically relevant problems and collaborating closely with experimental laboratories, the Theoretical and Computational Biophysics Group exploits advances in physical theory and computing to model living organisms across many levels of organization, from molecules to cells to networks. During the past three years, the group has pioneered the modeling of very large biomolecular structures, as well as the combination of quantum mechanical and classical mechanical simulations, and has embarked on an innovative computational tool, steered and interactive molecular dynamics. Highlights of our group's research program, software tool development, and outreach to the wider community are presented each month on our web site. In the following pages we present highlights from April 2004 through May 2006.

Theoretical and Computational Biophysics Group
http://www.ks.uiuc.edu

[Apr 2004]

Bricks and Mortar of Living Cells

Far from playing only the role of bricks and mortar as a mere divider between the inside and outside of cells or between parts of the cell, lipid bilayers are an active, tightly regulated cellular component whose physical properties are critical for the proper function of the membrane proteins contained within them. Lipid bilayers are the preeminent domain of computational biology since despite their considerable stability and impenetrability they form disordered films that are best described through computer modeling, albeit tested by observation. One of the largest molecular modeling projects achieved so far has been recently reported that employed NAMD to investigate the mechanical properties of cellular membranes. The systems simulated were made of lipids and water, composed of about 40,000 atoms, and simulated for over 100 nanoseconds. The simulations revealed that membranes, in terms of their mechanical properties, are far from being homogenous films; rather, they exhibit a delicate multi-lamellar structure of layers that alternatively tend to shrink and expand the membrane, inducing strong forces on all proteins and molecules entering. The lamellar character of the cell's membranes plays a key role for cellular processes such as osmotic regulation and may explain even the action of anaesthetics.

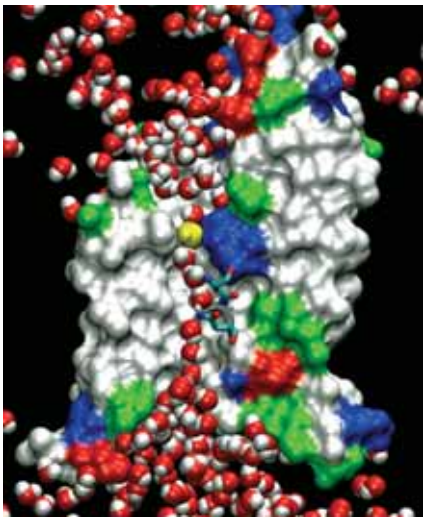


Justin Gullingsrud and Klaus Schulten. **Lipid bilayer pressure profiles and mechanosensitive channel gating**. *Biophysical Journal*, 86:3496-3509, 2004.

[May 2004]

Leaving the Cellular Battery Charged

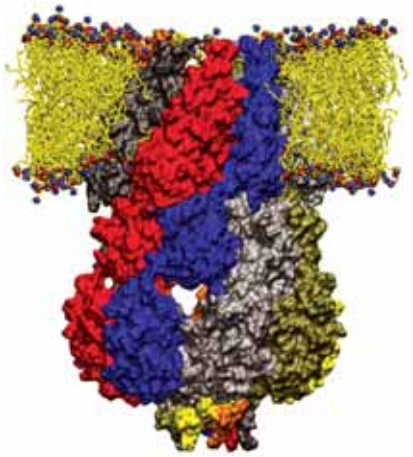
Biological cells are batteries charged by a voltage across their cell membrane. The voltage is maintained through a gradient of protons; the latter push back into the cell driving key cellular processes, e.g., the synthesis of ATP. But leakage of protons back into the cell is lethal. This generates a problem for water channels that exist in cell walls, e.g., in human tissues and plants, and conduct each about 10 million water molecules a second. Since protons are found in physiological solutions at a fraction of 1/10 million each channel should pass along with the water a proton per second, draining the cellular battery. The cells' water channels amazingly prevent this leakage. The underlying mechanism was suspected to be connected with an orientation pattern of water in the channel enforced by an internal electrostatic field that neither allows protons to hop through the channel, overtaking the water transport speedwise, nor permits protons to flow along with the water. Now two collaborative studies have confirmed the suggestion, finding an energy barrier high enough to reduce the chance of proton passage to less than a proton per day.



Boaz Ilan, Emad Tajkhorshid, Klaus Schulten, and Gregory A. Voth. **The mechanism of proton exclusion in aquaporin channels**. *PROTEINS: Structure, Function, and Bioinformatics*, 55:223-228, 2004.

[Jun 2004]

New Era in Computational Biology

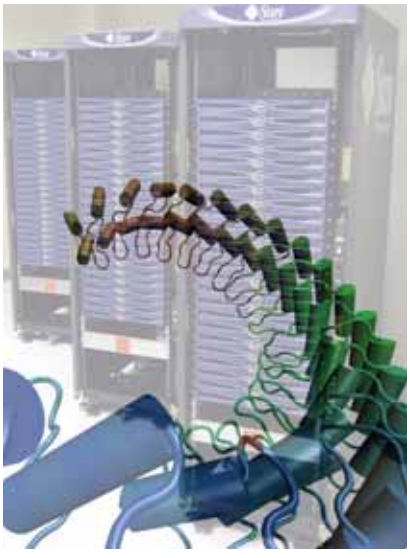


Emad Tajkhorshid, Aleksij Aksimentiev, Ilya Balabin, Mu Gao, Barry Isralewitz, James C. Phillips, Fangqiang Zhu, and Klaus Schulten. **Large scale simulation of protein mechanics and function**. In Frederic M. Richards, David S. Eisenberg, and John Kuriyan, editors, *Advances in Protein Chemistry*, volume 66, pp. 195-247. Elsevier Academic Press, New York, 2003.

Computational and experimental biologists investigate jointly the physical mechanisms underlying the function of the molecular machines in cells. Simulations used to encompass biomolecular systems of 10,000 atoms, but recently the size increased tenfold. For example, simulations of aquaporins, a water channel, published during 2001-2003, involved about 100,000 atoms and had been cited in connection with last year's chemistry Nobel prize; simulations of cadherin, a cell adhesion protein, and of ATPase, a key metabolic protein complex, published 2004 included a similar number of atoms. Simulations of over 200,000 atoms for a protein, lac repressor, that regulates genes, and for a protein, MscS, that is a mechanically gated membrane channel will be published later this year. Simulations involving over 300,000 atoms, on a protein, ankyrin, acting as an elastic spring in hearing, have been completed. The increase in the size of simulated systems is prompted by a revolutionary advance in crystallography that resolves ever larger structures of biomolecules and simulations are made possible through the great increase of computer resources at the NSF centers (PSC, NCSA). This marks the beginning of a new era in which systems like virus capsids and the ribosome, entailing 1-3 million atoms, will be studied, too. NAMD is ready for the challenge posed by simulations needing 250-500 processors today and 1,000-10,000 processors in the future, to keep up with the developments in the biology laboratories.

[Jul 2004]

Nanoscale Imaging with Molecular Dynamics

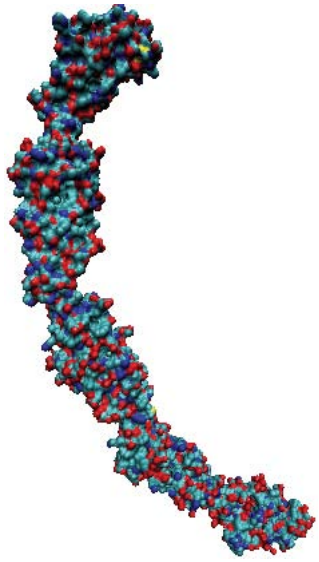


Since Leuwenhook, microscopic images of living matter have been produced with radiation, from light to X-rays. With the advent of ever more reliable computational methodologies, molecular dynamics has reached the status of a trusted research instrument. This instrument is particularly powerful for imaging nanoscale, i.e., 10-100 nanometersize, systems. This month our group brought three computers on-line that can serve to image nanoscale systems, three 48-processor rack-mount Xeon clusters (pictured) running our MD program NAMD. One such cluster, a nanoscale system of 300,000 atoms imaged over a nanosecond at the most advanced simulation conditions possible today, requires four days of computing. The Clustermatic software from Los Alamos National Laboratory makes each cluster of 48 processors appear to biomedical researchers as a single machine and allows interactive simulations to temporarily displace long-running NAMD jobs. The clusters have been used already for a study of balance and hearing in the human inner ear. These senses are intrinsically mechanical, relying on hair cells to convert vibration to ion channel modulation. Ankyrin, a protein formed by repeats of a 33-amino-acid domain, is thought to act as a molecular spring in mechanotransduction channels. Explaining the mechanism of ankyrin elasticity requires large simulations of 340,000 atoms that apply repeatedly stretching forces to the protein and monitor its response, revealing a mechanical behavior ideally suited for its biological function. The clusters are presently also used to design artificial nanopores for sequencing of DNA.

[Aug 2004]

Nature's Velcro

One of life's great achievements is the development and maintenance of multi-cellular organisms, from an embryo to adulthood. Multitudes of cells need to be sorted and resorted into tissues, organs, and body of living beings. One strategy towards this end is to endow cells with so-called adhesion proteins that connect a mechanical framework inside cells through the cell membrane with other cells. A key type of adhesion protein is cadherin (calcium-dependent adherent protein) that stretches through the cell surface five-tandem domains. The outermost domain can stick to a cadherin molecule from an adjacent cell. Crystallography provided the molecular structures of cadherin pairs and resolved in atomic detail the cadherin-cadherin contact between cells. This prompted a collaboration that aimed at probing the adhesion strength of cadherin pairs through steered molecular dynamics simulations stretching the pairs apart. Results of the simulations were reported in a recent publication that employed NAMD as well as VMD. As shown by crystallography, the cadherins each insert a tryptophan residue into the other protein. The link thereby established can be broken only through strong forces that induce a step-wise slippage of the residues first out of their binding pockets and then along the protein surface. This scenario suggests a mechanism for selectivity among cadherins, i.e., why among the various cadherins found on the surfaces of cells some adhere much better to each other than others.

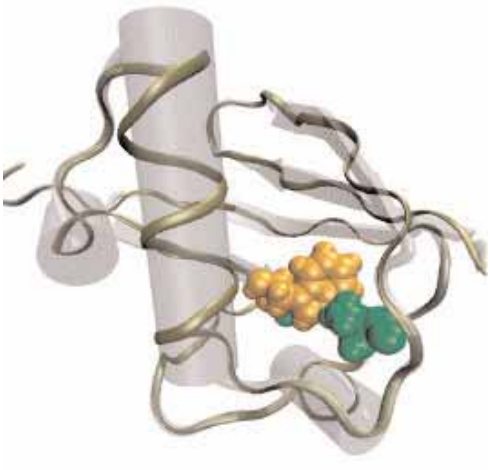


M. V. Bayas, K. Schulten, and D. Leckband. **Forced dissociation of the strand dimer interface between C-cadherin ectodomains**. *Mechanics and Chemistry of Biosystems*, 1:101-111, 2004.

[Sep 2004]

Cold Protein in Slow Motion

Proteins perform the many functions of biological cells. This ability arises from the particular three-dimensional structure into which proteins fold at physiological temperature. The quick and precise folding of proteins depends on their molecular environment, e.g., water or lipid membrane, and is being investigated in many laboratories today. A new study from a computational – experimental collaboration investigated the folding and resulting structure of a protein, ubiquitin, in ethylene-glycol, commonly known as antifreeze, mixed with water. In this mixture the folding could be monitored at very low temperature in "slow motion" and resolved in great detail. Computational modeling using NAMD and VMD suggested that adding antifreeze to water leaves ubiquitin folding unaffected and this was born out indeed by further observation. Antifreeze is offering now a wider window into the study of the amazing abilities of other proteins.



E. Larios, J. S. Li, K. Schulten, H. Kihara, and M. Gruebele. **Multiple probes reveal a native-like intermediate during the low-temperature refolding of ubiquitin**. *Journal of Molecular Biology*, 340:115-125, 2004.

[Sep 2004]

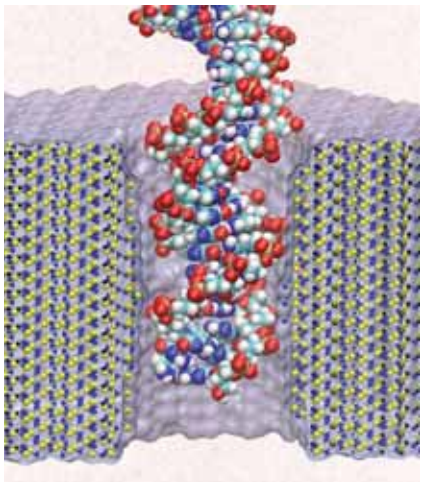
Protein Energy from Sun Light

Shigehiko Hayashi, Emad Tajkhorshid, Hideki Kandori, and Klaus Schulten. **Role of hydrogen-bond network in energy storage of bacteriorhodopsin's light-driven proton pump revealed by ab initio normal mode analysis**. *Journal of the American Chemical Society*, 126:10516-10517, 2004.

Sun light offers abundant energy fueling life on earth. Primary users of this energy are photosynthetic life forms. Remarkable in this regard are certain halophilic bacteria that developed a protein, bacteriorhodopsin(bR), which acting as a light driven proton pump turns sun light into a voltage gradient across the cell wall. Each photon absorbed primes bR to transfer of a proton. The bR pump had been discovered 30 years ago, yet the mechanism of the pump is still basically unknown. A key step towards establishing the mechanism would be identification of the initial energy form stored after light absorption. While some researchers suggest energy is stored highly localized in bR, others recognized that given the soft nature of proteins storage should be spread over many degrees of freedom. Widely accepted candidates are torsions of retinal, the linear molecule in bR that actually absorbs the light. A collaboration between computational and experimental groups carrying out unprecedented calculations and spectroscopic observations of water inside bR has now reported that a key fraction of light energy is stored in a geometrically distorted so-called hydrogen bond network involving retinal, three water molecules, and three amino acid side groups of bR. The results demonstrate dramatically that, in order to reveal mechanisms underlying protein function, structural details at the sub-Angstrom level need to be resolved; only computational modeling guided by observation is presently capable of such resolution.

[Oct 2004]

Transistor Meets DNA



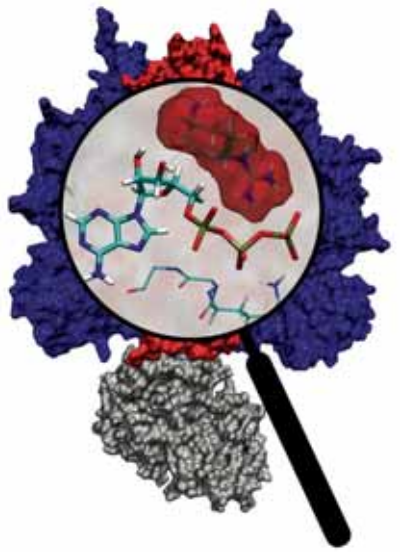
Aleksij Aksimentiev, Jiunn Benjamin Heng, Gregory Timp, and Klaus Schulten. **Microscopic kinetics of DNA translocation through synthetic nanopores**. *Biophysical Journal*, 87:2086-2097, 2004.

Electrical devices on computer chips built from silicon compounds have reached the small length scales of the building blocks in biomolecules, namely, the amino acids in proteins and the bases in DNA. Using beams of electron microscopes, electrical engineers drill nanometer wide pores into silicon wafers that contain a central layer only a few atoms thick. The engineers surround these pores with transistors and electrodes that can detect charges moving in the nanopore. Electrical fields across such synthetic nanopores can thread charged molecules like DNA through, and electrical signals stemming from single molecules transiting the pores can be recorded. Since the size of the nanopores compares with the dimension of DNA bases, the signals should eventually become precise enough to distinguish DNA bases, such that nanopores can become recording heads reading off sequences of DNA. While such ultrafast recording of DNA sequences is still a distant goal, the manufactured nanopores have been used already for sizing short strands of DNA as reported recently. Molecular dynamics simulations with NAMD and molecular graphics with VMD played a crucial role in imaging the dynamic events involved in recording single molecules of DNA and for optimizing the design of nanopores towards efficient threading and accurate recording. The landmark collaboration between computational biologists and device engineers promises to further unlock the great potential of biomedical nanotechnology.

[Nov 2004]

Nature's Sparkplug

Molecular motors are efficient nanoscale machines destined to make any human designed engine look clumsy. F1-ATPase is such a machine – so powerful that a spoonful of it could produce as much torque as your car's engine. As part of the enzyme ATP synthase, the protein can work as an engine but also operate in reverse as a generator. In the latter mode it is responsible for the synthesis of the energy-rich molecule ATP that serves as fuel driving many processes in biological cells. It can also convert the energy stored in ATP into mechanical rotation. A recent study suggests that the analogy to a car's engine goes even further! A quantum chemical description of the reaction of ATP combined with a simulation of the protein revealed that an amino acid side group of the protein, called the "arginine finger", controls the progression of the catalytic event, much like a spark plug controls the combustion process in a car engine. The very extensive simulation made use of a powerful computer, the Jonas Cluster at the Pittsburgh Supercomputing Center. The investigation is yet another example for the important role of computational biology unraveling the secret behind the function of the machinery of living cells.

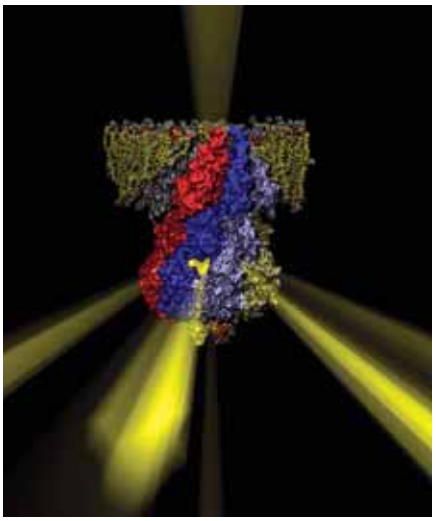


Markus Dittrich, Shigehiko Hayashi, and Klaus Schulten. **ATP hydrolysis in the β_{TP} and β_{DP} catalytic sites of F1-ATPase**. *Biophysical Journal*, 87:2954-2967, 2004.

[Nov 2004]

Japanese Lantern Protein

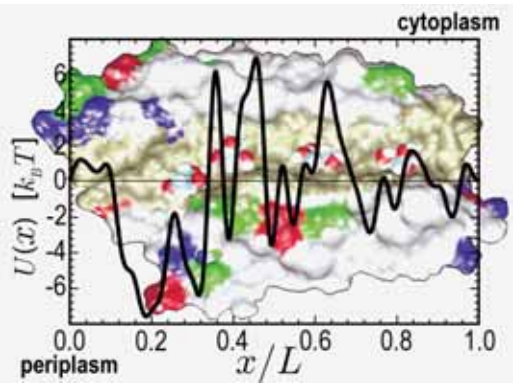
Many bacteria hang into their cellular membranes proteins that look like a Japanese lantern. These proteins have a flexible cylinder (pore) that crosses the membrane and opens and closes depending on membrane tension; from the cylinder hangs a balloon with seven small openings around its equator (see figure). The apparent function of the Japanese lantern protein, aptly called mechanosensitive channel of small conductance(MscS), is to protect the bacterial cell against osmotic stress: when a bacterium finds itself suddenly in an aqueous environment entering water can burst the cell. Before this happens the cell membrane experiences tension that opens the protein pore, permitting passage of water and ions, the efflux being controlled through the protein balloon. A recent study explores the dynamical properties of MscS, e.g., pore closure and opening as well as ion conduction, by means of molecular dynamics simulations using NAMD. Embedding the large protein into a lipid bilayer and water led to a simulation encompassing 220,000 atoms. Surprisingly, the protein balloon was found to control the arrangement of positive and negative ions through a peculiar pattern of charged, polar, and non-polar amino acids on its internal and external surfaces. This suggests that the Japanese lantern protein has a yet unknown second function in the bacterial cell.



Marcos Sotomayor and Klaus Schulten. **Molecular dynamics study of gating in the mechanosensitive channel of small conductance MscS**. *Biophysical Journal*, 87:3050-3065, 2004.

[Dec 2004]

Why Do Cells Sing?

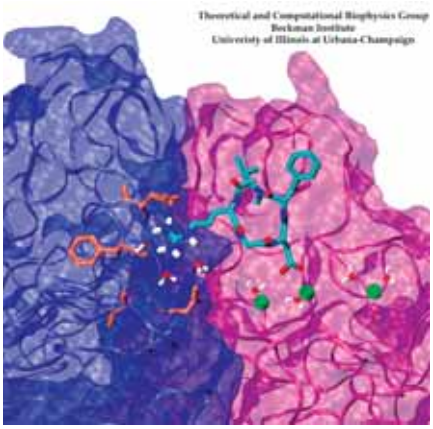


Ioan Kosztin and Klaus Schulten. **Fluctuation-driven molecular transport through an asymmetric membrane channel**. *Physical Review Letters*, 93:238102, 2004.

Atomic force microscopy measurements of the surfaces of cells lead to a bizarre discovery: single cells twitch with their surfaces. When the microscope feeds a microphone one hears the murmur, shrieking, or singing of cells. But why do cells sing? A recent report (covered in a news report) suggests that the twitching motion of cell membranes can help cells directionally transport nutriments across their cell wall. Earlier results of computer simulations that described the energetics of glycerol (a nutriment for E. coli) conduction across an aquaglyceroporin membrane channel combined with a mathematical analysis of channel transport concludes that the twitching motion of cells leads the channel to act as a ratchet: the twitching moves the glycerol, the channel energetics discourages backslip such that the glycerol moves in one direction. The direction is outside–in when glycerol is in short supply, and inside–out when there is too much of it. The finding has deep implications for other biological channels showing how they can use energy from pulsating membranes to drive solutes through.

[Dec 2004]

Snap Fastener on Biological Cells



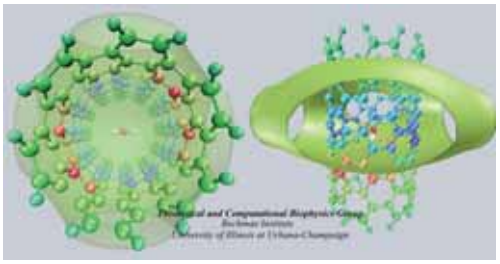
David Craig, Mu Gao, Klaus Schulten, and Viola Vogel. **Structural insights into how the MIDAS ion stabilizes integrin binding to an RGD peptide under force**. *Structure*, 12:2049-2058, 2004.

Biological cells must be capable of attaching themselves to their surroundings. For this purpose they utilize fibrillar proteins, such as fibronectins, that grasp cells through cell surface receptors integrins. The latter act as snap fasteners to the extra-cellular fibrils. The growth, movement, and survival of cells are all dependent on the ability of integrins to fasten cells upon intra-cellular signals or to signal inwards that something has become fastened on the cell surface. The major fastener on integrins are simple divalent ions like Mg^{++} or Ca^{++} that can adhere to specific molecules with amazing strength, even though the interaction at the cell surface is exposed to water. Computer simulations using NAMD, reported recently, revealed a dynamic picture of the interactions used by cells to link themselves to the extra-cellular matrix. They showed that it is actually a brave water molecule that is recruited by integrins as a protective shield for the interaction. The simulations provide for the first time a detailed view of how cell tissues are stabilized through surface ions against mechanical stress.

[Jan 2005]

Nanotubes, Tool for Nanomedicine

Carbon nanotubes are becoming universal tools and building blocks in nanomedicine, being proposed as nanodevices for drug delivery, DNA transfection, and biosensing. They can also be employed as nanopores that conduct protons, ions, and small molecules, or as reaction vessels for new types of chemical reactions. Studying carbon nanotubes can assist in designing improved nanodevices. One approach to studying nanotubes is furnished by molecular dynamics simulations. However, such simulations must account for one key property of nanotubes, their large polarizability due to the mobility of electrons over the tube walls. Until recently this polarizability could only be calculated through expensive quantum chemical calculations that could not be linked to simulations imaging molecular processes around carbon nanotubes. Recent studies report now an empirical model that can be efficiently implemented into molecular dynamics simulations to take into account the polarization effect. The model reproduces results of more expensive quantum chemistry calculations very well. A first application of the new model studied the transport of water molecules through nanotubes. Water has a strong dipole moment that polarizes the nanotube wall and, therefore, provides a stringent test for the new methodology.

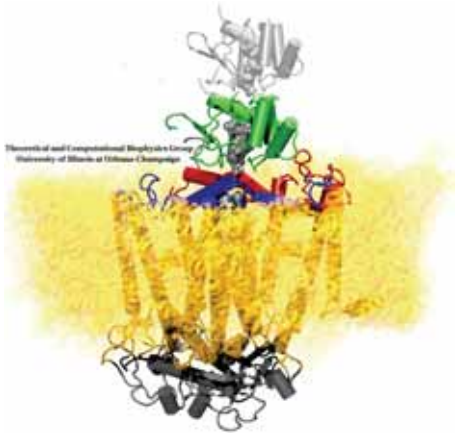


Deyu Lu, Yan Li, Umberto Ravaioli, and Klaus Schulten. **Empirical nanotube model for biological applications.** *Journal of Physical Chemistry B,* 109:11461-11467, 2005.

[Jan 2005]

Bioelectric Extension Cord

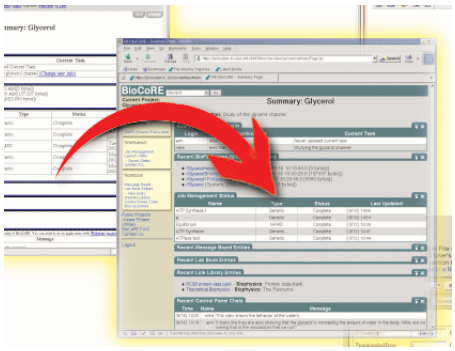
Energy for most of the earth's biosphere is gained when sun light absorbed drives electrons across a membrane through a protein called the photosynthetic reaction center (RC), leaving behind positive electron holes. The electrons join protons to become hydrogen atoms and move, bound pairwise to a quinone molecule, to another protein, the so-called bc1 complex. Here electrons and protons move together back over the membrane and become separated again, thereby establishing an electro-osmotic potential that fuels many cellular processes. However, the electrons need to return to the RC to fill the electron holes left behind. Nature employs for this purpose a kind of bioelectric extension cord in the form of a third protein, cytochrome c2, that shuttles the electrons back from the bc1 complex to the RC. A recent paper reports molecular dynamics simulations using NAMD that investigated how cytochrome c2 plugs into the RC. Landing on a broad face of the RC, interactions steer the protein such that its electron carrying heme group comes close to RC's chlorophylls with electrons missing, a chain of water molecules providing an electrical conduit. The study is yet another example of how simulations provide today complete views of the fundamental processes underlying life.



Felix Autenrieth, Emad Tajkhorshid, Klaus Schulten, and Zaida Luthey-Schulten. **Role of water in transient cytochrome c2 docking**. *Journal of Physical Chemistry B*, 108:20376-20387, 2004.

[Jan 2005]

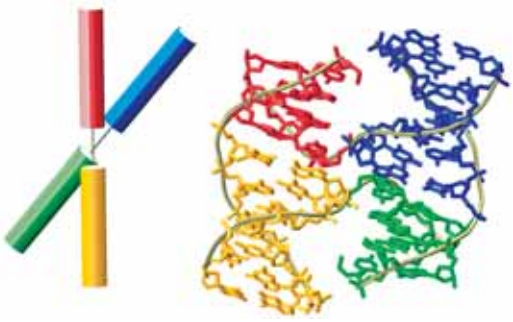
Better Science Through Collaboration



The interdisciplinary nature of modern science calls for collaborations across the campus, across the country, and even across the globe. Computer networks are ideally suited to assist researchers in this regard and this month a brand new release of the BioCoRE collaborative environment for biomedicine has taken a huge step towards getting researchers working together over small and large distances. BioCoRE sports a new, beautiful, and very responsive web interface and BioCoRE's control panel now has integrated Google®; searches as well as mathematical expression solving, and private conversations with collaborators are intuitively displayed. To ensure further improvements, BioCoRE's programming interface and computer code have been redesigned to permit development of instant messaging and easier programming by third parties. All of this promises to make BioCoRE the next best thing to doing research together in the same room.

[Feb 2005]

Atomic Level View of Sexual Reproduction



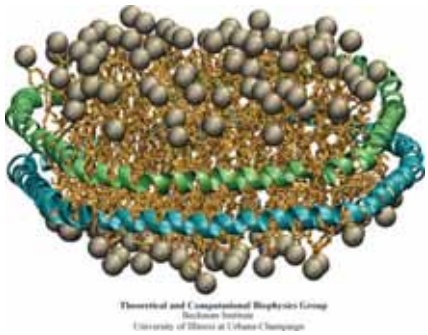
Jin Yu, Taekjip Ha, and Klaus Schulten. **Conformational model of the Holliday junction transition deduced from molecular dynamics simulations**. *Nucleic Acids Research*, 32:6683-6695, 2004.

An important means for generating genetic diversity to provide raw material for evolution and maintain genomic stability is sexual reproduction. At the molecular level, the genes of two individuals are mixed through a process called homologous recombination. This process is found also in many simple life forms, even bacteria. At the beginning of recombination, two DNA duplexes, e.g., from mother and father, are aligned next to one another as the result of homology search, i.e., like strands are brought together with like strands. The four single DNA strands, two in each duplex, cross reciprocally two of the strands between the duplexes. The result is a joint molecule that contains DNA crossovers, named Holliday junctions. The Holliday junction is highly polymorphic in moving along two DNA duplexes, exchanging their DNA. Researchers are now investigating the physical mechanism of Holliday junction migration. The polymorphic, dynamic character of this migration-makes observations difficult and the researchers resorted to molecular dynamics simulations using NAMD. The results, reported recently, resolved the dynamics of maternal-paternal DNA exchange through Holliday junction transitions in unprecedented detail providing an atomic level view of sexual reproduction.

[Feb 2005]

Membrane Nanodiscs

Biological cells, the basic units of life, are organized assemblies of nanodevices. Nanobiotechnology can adapt Nature's solutions for its own purposes, using computational biology to redesign Nature's nanodevices. In the case of Nanodiscs, bioengineers thought to construct the smallest possible environment that mimics the native environment of membrane proteins. Researchers borrowed the amino acid sequence of a naturally occurring class of proteins, lipoproteins, which are involved in the transport of lipids and cholesterol. The lipoprotein found in humans, apolipoprotein A-1, was used to synthetically engineer "belts" that surround a discoidal lipid bilayer, shielding the hydrophobic lipid tail groups from water. As recently reported, molecular dynamics simulations using NAMD showed an atomic level image of the structure of such a nanodevice. The predicted discoidal shape, diameter, and thickness of Nanodiscs simulated were experimentally corroborated through so-called small angle X-ray scattering.

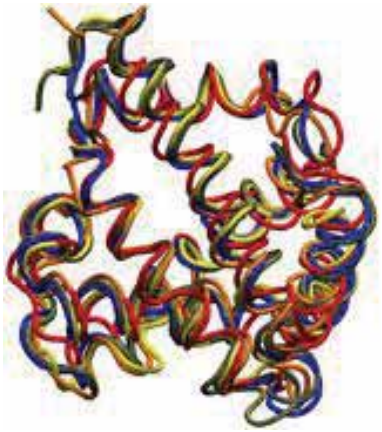


Amy Y. Shih, Ilia G. Denisov, James C. Phillips, Stephen G. Sligar, and Klaus Schulten. **Molecular dynamics simulations of discoidal bilayers assembled from truncated human lipoproteins**. *Biophysical Journal*, 88:548-556, 2005.

[Mar 2005]

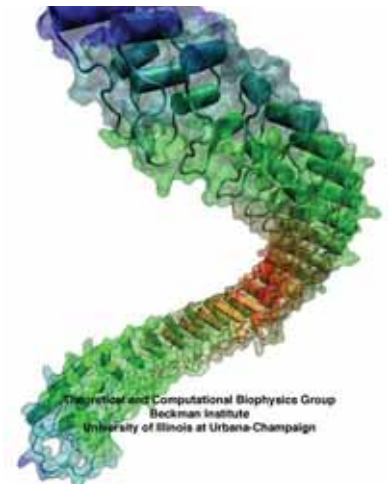
Visual Molecular Dynamics

Biological evolution left its many traces in the form of organisms as well as in "fine print" in the form of gene sequences and associated protein structures. From the "fine print" researchers can draw conclusions about the inner workings of living cells and derive opportunities to battle disease. Researchers enjoy easy access to sequence and to structure information, but so far mainly separately, i.e., either for sequence or for structure. VMD, our widely used structure viewing and analysis program, has already offered a glimpse of the viewed protein's sequence, but with its latest release has taken a key step further, assisting in viewing and aligning multiple structures and sequences with few mouse clicks. Users of VMD 1.8.3 find themselves routinely comparing their protein of interest with analogous ones getting VMD to color the protein by similarity in structure, in sequence, and showing conserved amino acids. VMD 1.8.3 surprises with numerous further features, including a new cartoon representation that follows the actual molecular structure closely and offers superb, publication quality images. VMD continues to work together with the molecular dynamics program NAMD, permitting viewing and analysis of huge trajectory files by supporting 64-bit processors.



[Apr 2005]

Hearing: Turning Sound into Voltage



Marcos Sotomayor, David P. Corey, and Klaus Schulten. **In search of the hair-cell gating spring: Elastic properties of ankyrin and cadherin repeats**. *Structure*, 13:669-682, 2005.

The ear is a sensitive and robust device, able to perceive the faint sound of flowing water and the thunderous blast of an air plane. Like a microphone, the ear transforms a complex, mechanical stimulus (sound), into an electrical signal, a voltage change in a nerve cell, that can be understood by our brain. This transformation is called ”mechanotransduction” and is accomplished by a series of amazingly minute devices that each connect a soft spring to an ion channel, both located in specialized sensory cells, the hair cells of the inner ear. The springs, through their vibrations agitated by particular sound frequencies, control ion currents passing through the channels, thereby, modifying the hair cell internal electrical potential. This leads to neural signaling to the acoustic cortex of the brain. Recently reported molecular dynamics simulations using NAMD, some of the most extensive simulations accomplished to date both in size and duration, showed that the mechanical characteristics of hair cell signaling may be traced to a single protein, ankyrin, that acts as a helical spring. Imagine a soft spring that is extended several inches by the weight of a feather! Ankyrin is such a spring, but a billion times finer.

[May 2005]

Gene Lock

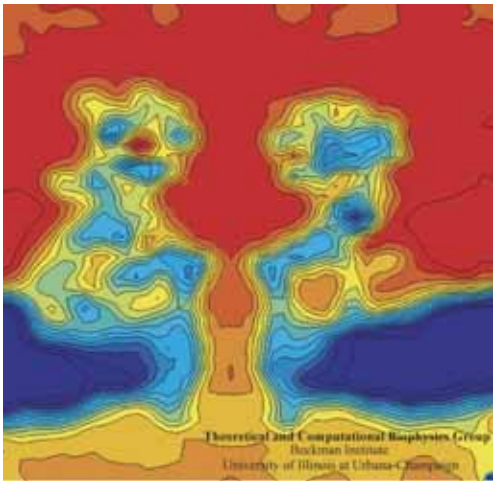
Elizabeth Villa, Alexander Balaeff, and Klaus Schulten. **Structural dynamics of the Lac repressor-DNA complex revealed by a multiscale simulation**. *Proceedings of the National Academy of Sciences,* USA, 102:6783-6788, 2005.

When Escherichia coli bacteria enjoy lactose and related food molecules in their environment, the cells quickly furnish proteins needed for import and metabolic digestion of the food. A set of genes, called the lac operon, is transcribed into messenger RNA that directs the synthesis of these proteins. When lactose is not available, the protein synthesis would be wasteful and, indeed, is prevented by locking the lac operon. This is achieved by a protein called lac repressor that forces the segment of the lac operon needed to initiate transcription into a loop, but that can be unlocked by a lactose molecule binding to the protein as soon as the food becomes available again. A recent study of the lac repressor combines a 314,000-atom protein simulation using NAMD with a multiscale simulation technique coupling the protein to the DNA loop. The calculations reveal how the lac repressor stretches out two “hands” grabbing the genomic DNA and then keeps a tight grip on the DNA wrestling it into a loop. The discovery is described on our website as well as in a popular article.

[Jun 2005]

Computational Patch Clamp Measurement

In a biological cell, membrane channels act like miniature valves regulating the flow of ions and other solutes between intracellular compartments and across the cell's boundary. Assembled in complex circuits, they generate, transmit, and amplify signals orchestrating cell function. To investigate how membrane channels work, life scientists, using an extremely fine pipette, isolate a tiny patch of a cell membrane and, in so-called patch clamp measurements, determine electric currents in response to applied electric potentials. Dramatic increase in computational power and its efficient utilization by NAMD allows one today to reproduce such studies computationally, calculating the permeability of a membrane channel to ions and water directly from its atomic structure. In what is one of the largest molecular dynamics simulation to date, one copy of the membrane channel alpha-hemolysin, submerged in a lipid membrane and water, was subjected to an external electric field that drove ions and water through the channel. The calculations produced also an image of the electrostatic potential across the channel (see figure).

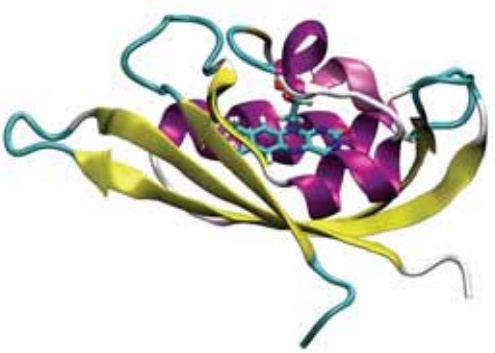


Aleksij Aksimentiev and Klaus Schulten. **Imaging alpha-hemolysin with molecular dynamics: Ionic conductance, osmotic permeability and the electrostatic potential map**. *Biophysical Journal*, 88:3745-3761, 2005.

[Jul 2005]

When Light Falls in LOV

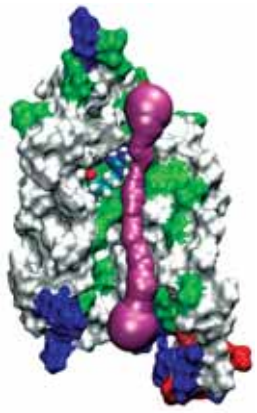
Plants and other photosynthetic organisms convert sunlight into various forms of metabolic energy. To expose themselves optimally to the sun while at the same time avoiding damaging overexposure to light, these organisms employ molecular photosensing systems that control, for example, the orientation of their leaves. Common photosensing systems include photoreceptors of the so-called phot family that are sensitive to blue light and contain Light, Oxygen, and Voltage (LOV) sensitive protein domains as photoactive elements. Light absorbed by a flavin molecule leads to bond formation with the protein (LOV domain), thereby, initiating signaling until the flavin-protein bond breaks spontaneously. A study of the photosensing events in the LOV domain of the algae C. reinhardtii (see figure) employed computer simulations that combined quantum mechanical and classical simulation methods to study photoexcitation and subsequent processes. It emerged that formation of the flavin-protein bond is initiated by a unique light-driven transfer of a hydrogen atom between the LOV domain and the flavin molecule.



Markus Dittrich, Peter L. Freddolino, and Klaus Schulten. **When light falls in LOV: A quantum mechanical/molecular mechanical study of photoexcitation in Phot-LOV1 of Chlamydomonas reinhardtii**. *Journal of Physical Chemistry B*, 109: 13006-13013, 2005.

[Aug 2005]

Channel Design

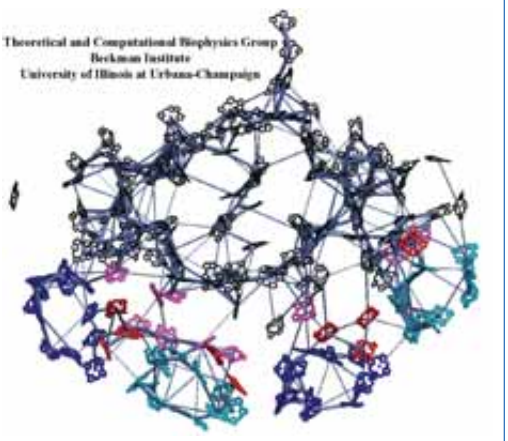


Yi Wang, Klaus Schulten, and Emad Tajkhorshid. **What makes an aquaporin a glycerol channel: A comparative study of AqpZ and GlpF**. *Structure*, 13:1107-1118, 2005.

The import of nutriments over their cellular membranes is one of the main tasks of all living cells. Even though a major part of the cell's molecular machinery is devoted to this task, principles of selective membrane transport are not yet well understood, mainly due to the fact that the membrane proteins responsible are notoriously difficult to resolve in their structure, the latter a prerequisite for a full physical description of the function. Recently, cell biology got very lucky in having the structures of two closely related membrane proteins solved. Two highly homologous aquaporins from the same bacterium, Eschericha coli, have become structurally known: one that conducts only water, called AqpZ, and one that conducts water as well as the nutriment glycerol, called GlpF. The discoveries have permitted us through structure analysis with VMD and molecular modeling with NAMD to look over nature's shoulder in the evolutionary design of two similar import channels of different conductivity. In making a water channel also a glycerol channel, nature has turned to a very basic principle, namely adjusting the overall pore size of the channel from a very narrow channel, just wide enough for water, to one wide enough also for glycerol.

[Sep 2005]

Evolution Shaped by Physics



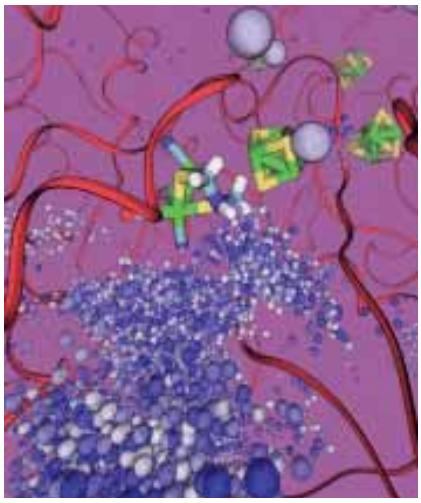
Melih K. Sener, Craig Jolley, Adam Ben-Shem, Petra Fromme, Nathan Nelson, Roberta Croce, and Klaus Schulten. **Comparison of the light harvesting networks of plant and cyanobacterial photosystem I**. *Biophysical Journal*, 89:1630-1642, 2005.

Sun light is the primary source of energy for Earth's biosphere made available through photosynthetic organisms. In the cells of such organisms, so-called photosynthetic units form in which about a hundred interacting chlorophylls are assembled into a molecular network. The network (see figure) absorbs through its individual chlorophylls light and transfers the ensuing electronic excitation and with it the light energy efficiently along the network connections to a center where the energy is transformed into a membrane potential that subsequently fuels the machinery of the organisms' cells. The biological evolution that lead to such energy transfer networks had to obey physical constraints that act upon the network assembly and all stages of the light harvesting process. With the availability of atomic level structures of two networks, one in plants and one in cyanobacteria, it became possible to compare the energy transfer networks from two related species that are separated by more than a billion years of evolution. The comparison answers many questions about how living systems evolved extremely efficient solar cells for their energy needs, while still leaving a puzzle behind to be answered: despite a huge evolutionary distance the plant and bacterial photosystems maintained an amazing identity as the positions and geometry of about eighty chlorophylls remained unchanged for over a billion years. For most of these chlorophylls, repositioning would have had little effect on the efficiency of the light harvesting processes as calculations show, yet evolution chose to freeze the chlorophyll ensemble geometry-wise.

[Sep 2005]

Hydrogen Fuel from Protein

In an optimistic future, cars and appliances will be powered by renewable energy produced by burning hydrogen gas, with water being the only waste product. To supply this hydrogen gas, scientists are turning their attention to an enzyme called hydrogenase that is found in certain microorganisms, which produce hydrogen gas from sunlight and water. This enzyme, however, is sensitive to oxygen gas, which irreversibly deactivates its hydrogen-producing active site. Understanding how oxygen reaches the active site will provide insight into how hydrogenase's oxygen tolerance can be increased through protein engineering, and in turn make hydrogenase an economical source of hydrogen fuel. In a recent paper, the programs NAMD and VMD are used to analyze the gas diffusion process inside hydrogenase, and how it correlates with the protein's internal fluctuations, thereby creating a map of the oxygen pathways. The calculations revealed two distinct pathways for oxygen to reach the active site. Gases participate in physiological processes of many organisms and the new computational strategy developed promises to image gas diffusion pathways for many relevant proteins. In fact, the researchers are currently inspecting hundreds of proteins for their ability to internally transport gas molecules.

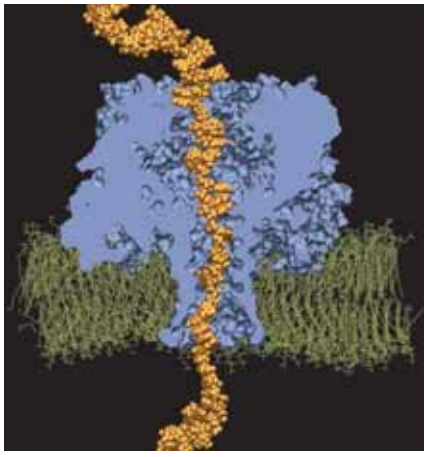


Jordi Cohen, Kwiseon Kim, Paul King, Michael Seibert, and Klaus Schulten. **Finding gas diffusion pathways in proteins: Application to O2 and H2 transport in CpI [FeFe]-hydrogenase and the role of packing defects**. *Structure*, 13:1321-1329, 2005.

[Oct 2005]

DNA Smooth and Rough

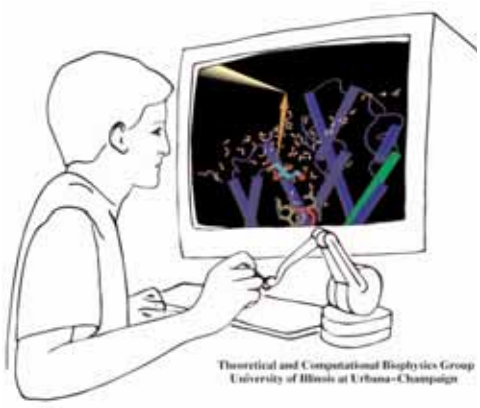
For the sequence of DNA, the genetic instructions of cells, to be read, the double helix of DNA is split open, exposing single DNA strands to DNA binding proteins. Once bound to DNA, the proteins, in carrying out their functions, will crawl along the DNA strand in one of two directions, towards DNA's 3' or 5' end. A recent study of DNA discovered a surprising property of single DNA strands that seems to explain how DNA binding proteins recognize the right direction on DNA strands. By measuring the translocation of DNA through alpha-hemolysin, a membrane protein with a narrow pore, researches discovered that directed single stranded DNA moves much faster when entering the pore 3' end first, rather than 5' end first. The underlying mechanism of this directionality was discovered through molecular dynamics simulations using NAMD and VMD.The simulations revealed that, in a narrow pore, DNA bases tilt collectively towards the 5' end, transforming a wide space directionless DNA brush into a tight space DNA ratchet. The 360,000-atom MD simulation did not only reveal how the DNA bases align and move faster in the "smooth" direction, but did also predict how the directional DNA movement can be discerned by means of direction-sensitive ionic currents through the channel blocked by translocating DNA strands.



Jerome Mathé, Aleksei Aksimentiev, David R. Nelson, Klaus Schulten, and Amit Meller. **Orientation discrimination of single stranded DNA inside the α-hemolysin membrane channel**. *Proceedings of the National Academy of Sciences*, USA, 102:12377-12382, 2005.

[Oct 2005]

Ten Years of NAMD

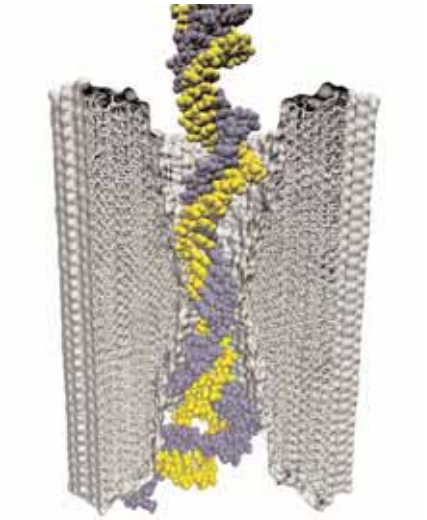


James C. Phillips, Rosemary Braun, Wei Wang, James Gumbart, Emad Tajkhorshid, Elizabeth Villa, Christophe Chipot, Robert D. Skeel, Laxmikant Kale, and Klaus Schulten. **Scalable molecular dynamics with NAMD.** *Journal of Computational Chemistry*, 26:1781-1802, 2005.

It was 1995 when NAMD was introduced as a parallel molecular dynamics code enabling interactive simulation by linking to the visualization code VMD. In 1999, a major improvement was accomplished in NAMD 2, scaling to 200 processors at the time. NAMD has since matured, adding many features and scaling to thousands of processors, garnering accolades and users in the process. This progress is now collected in a NAMD review paper that presents, in a manner accessible to the novice researcher, the concepts and algorithms behind NAMD, features for steered and interactive MD and for free energy calculation, the elements of the NAMD design that enable parallel scaling, performance comparisons of a variety of platforms, and advice for productive use of NAMD on modern research projects. Case studies ranging from the typical to the elaborate demonstrate the capabilities and flexibility of NAMD. This new reference provides an excellent foundation for working with NAMD.

[Nov 2005]

Stretchable DNA



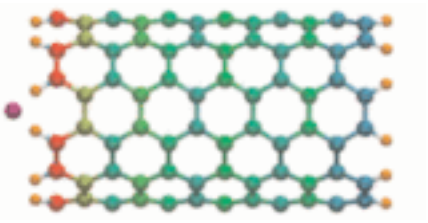
J. B. Heng, A. Aksimentiev, C. Ho, P. Marks, Y. V. Grinkova, S. Sligar, K. Schulten, and G. Timp. **The electromechanics of DNA in a synthetic nanopore**. *Biophysical Journal*, 90:1098-1106, 2006.

The most celebrated molecule of living cells, DNA, owes its fame to its role as a carrier of genetic information. But DNA is also impressive through other amazing properties, for example its mechanical flexibility. At first sight, it might seem a dull question to ask what is the smallest pore DNA can be squeezed through, as the obvious answer is that the diameter of that pore should be slightly larger than the diameter of a DNA helix. However, recent studies in asking the stated question discovered that double stranded DNA can permeate, without loosing its structural integrity, pores smaller in diameter than a DNA double helix. The discovery was initiated through molecular dynamics simulations, carried out using NAMD and VMD. The simulations demonstrated that if an electrical field, driving negatively charged DNA through a nanopore, exceeds some critical value, the force exerted on DNA stretches DNA to twice its equilibrium length, reducing thereby its diameter and allowing it to squeeze through narrow pores. The simulations predicted precise values of pore radii and associated critical fields. The predictions were validated experimentally by counting the number of DNA copies that passed at different electric fields through synthetic nanopores.

[Dec 2005]

Nanotube Oscillator

A pendulum swinging back and forth every second due to the law of gravity is a common sight. By going down to nanometer dimensions new phenomena emerge under different physical laws. According to a recent report, a potassium ion is found to swing back and forth inside a nanoscale tube at a terahertz frequency (a trillion times a second). Unlike the pendulum, the ion's oscillation is driven by electrostatic interactions with electrons inside the nanotube wall as shown in the figure. The tube, a carbon nanotube, is composed of a cylindrical hexagonal lattice of carbon atoms; the ion induces through a so-called dielectric response charges in the nanotube wall that interact back with the ion. This dielectric response of the nanotube electrons, ordinarily, can be described only through time-consuming calculations, but based on previous work (see Jan 2005 highlight) the response can now be calculated very quickly, in effect, on-the-fly along with the ion motion. The calculations revealed that carbon nanotubes attract ions into their inside and make them oscillate at Terahertz frequency. The Terahertz oscillator may serve as a detector in future imaging devices.

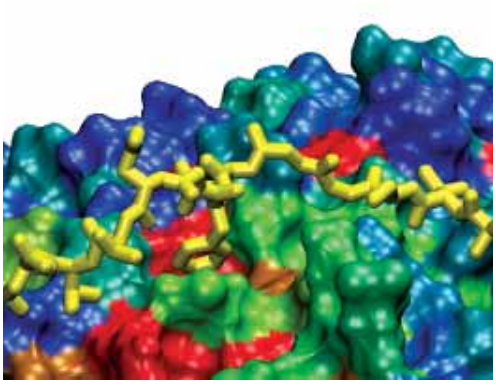


Deyu Lu, Yan Li, Umberto Ravaioli, and Klaus Schulten. **Ion-nanotube terahertz oscillator**. *Physical Review Letters*, 95:246801, 2005.

[Jan 2006]

Gateway to the Nucleus

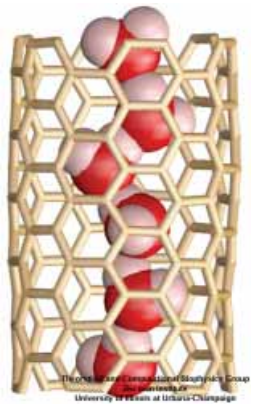
Eukaryotic cells envelop their genetic material in the cell nucleus whose boundary contains numerous pores. Only small molecules can pass through these nuclear pores unhindered. For all larger ones, passage is highly selective and controlled. The control involves import and export proteins (transport receptors) that load and release cargo on the proper side of the nucleus upon interaction with signaling proteins. Researchers are presently solving the structure of the nuclear pore and its transport receptors with increasing resolution, and the first atomic level investigation into the mechanism of nuclear pore selectivity has recently been reported. The study inspected the interaction between the transport receptor importin-β with key nuclear pore proteins that appear disordered near the center of the pore and contain characteristic phenylalanine-glycine sequence repeats. Molecular dynamics simulations using NAMD and analyzed using VMD revealed a key insight into the selectivity mechanism. The simulations showed that the key sequences of the repeat-proteins interact strongly with certain spots on the surface of importin-β. The study confirmed spots that had previously been identified experimentally and, moreover, found numerous binding spots not yet seen in experiment. Further experiments and simulations promise an understanding of the selectivity of entry and exit from the nucleus, a key element of the cell's genetic control.



Timothy A. Isgro and Klaus Schulten. **Binding dynamics of isolated nucleoporin repeat regions to importin-β**. *Structure*, 13:1869-1879, 2005.

[Feb 2006]

Molecular Modeling for Bionanotechnology

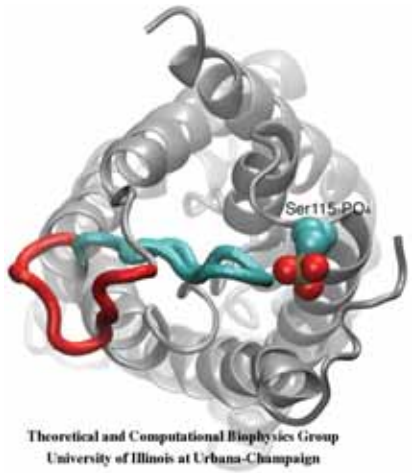


Deyu Lu, Aleksei Aksimentiev, Amy Y. Shih, Eduardo Cruz-Chu, Peter L. Freddolino, Anton Arkhipov, and Klaus Schulten. **The role of molecular modeling in bionanotechnology**. *Physical Biology*, 3:S40-S53, 2006.

Molecular modeling with NAMD promises to become a key methodology for research and development in bionanotechnology. Molecular modeling provides nanoscale images at atomic and even electronic resolution, predicts the nanoscale interaction of yet unfamiliar combinations of biological and inorganic materials, and can evaluate strategies for redesigning biopolymers for nanotechnological uses. The methodology's value has been reviewed for three uses in bionanotechnology. The first involves the use of single-walled carbon nanotubes as biomedical sensors where a computationally efficient, yet accurate description of the influence of biomolecules on nanotube electronic properties and a description of nanotube-biomolecule interactions were developed. The second case study involves the use of nanopores manufactured into electronic nanodevices based on silicon compounds for single molecule electrical recording, in particular, for DNA sequencing. The third case involves the development of nanoscale lipid bilayers for the study of embedded membrane proteins and cholesterol. In entirely new technological areas like bionanotechnology qualitative concepts, pictures, and suggestions are sorely needed; the three exemplary applications document that molecular modeling can serve as a critical "imaging" method for bionanotechnology, even though it may still fall short on quantitative precision.

[Feb 2006]

Cellular Faucets



S. Törnroth-Horsefield, Y. Wang, K. Hedfalk, U. Johanson, M. Karlsson, E. Tajkhorshid, R. Neutze, and P. Kjellbom. **Structural mechanism of plant aquaporin gating**. *Nature*, 439:688-694, 2006.

Your favorite flower pot would not survive a weekend in your office without watering, if it wasn't for a sophisticated cellular mechanism evolved in land plants to conserve water under drought conditions. Water exchange between cells and their environment is facilitated by a group of highly specialized membrane proteins called aquaporins. Although present in all life forms, plants are particularly dependent on their function. While in most species these channels function as always-open "cellular pipes" allowing water in and out of the cell, in plants they evolved into "cellular faucets" whose water permeability can be controlled by the cell. Nearly all plant aquaporins can be gated in response to drought or even flooding conditions, through basic biochemical signals, e.g., phosphorylation and change of pH. A recent Nature paper reporting a collaborative study between crystallographers who succeeded in solving the first structure of a plant aquaporin from spinach, and modelers provides the most detailed view of the mechanism of gating for a membrane channel. Molecular dynamics simulations of the channel performed by NAMD reveals a dual gating mechanism in which phosphorylation of certain protein residues unleashes a long cytoplasmic loop that physically blocks water access to the pore.

[Mar 2006]

Good Cholesterol

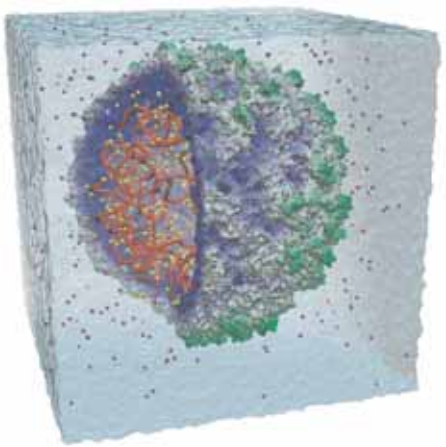
Lipoproteins are protein-lipid particles which circulate in the blood collecting cholesterol, fatty acids, and lipids. Low levels of one such lipoprotein particle, called high-density lipoprotein (HDL) or “good cholesterol”, has been implicated in the increased risk of coronary heart disease. The ability of lipoproteins to transport lipid and cholesterol through the blood is amazing since these types of particles are not generally soluble in blood plasma. However, when HDLs assemble, proteins wrap themselves around the lipids and cholesterol, shielding the lipid tails from the aqueous environment. Native HDL exhibit a variety of shapes and sizes, for example forming a discoidal particle. Conventional high-resolution imaging techniques, such as NMR and X-ray crystallography, cannot resolve how lipid and cholesterol are being accommodated by HDL, but the assembly and geometry of HDL discs can be captured using computer simulations. Unfortunately, the long time scales required for HDL assembly was a major stumbling block. Now a new simulation method, coarse-grained modeling in conjunction with the molecular dynamics program NAMD, has permitted the simulation of HDL assembly as recently reported. The simulations show that lipids quickly aggregate into a bilayer from their initial spherical “micelle” shape and that the two proteins subsequently attach to either side forming a belt surrounding the lipid core.

Amy Y. Shih, Anton Arkhipov, Peter L. Freddolino, and Klaus Schulten. **A coarse grained protein-lipid model with application to lipoprotein particles**. *Journal of Physical Chemistry B*, 110:3674-3684, 2006.

[Mar 2006]

Simulating an Entire Life Form

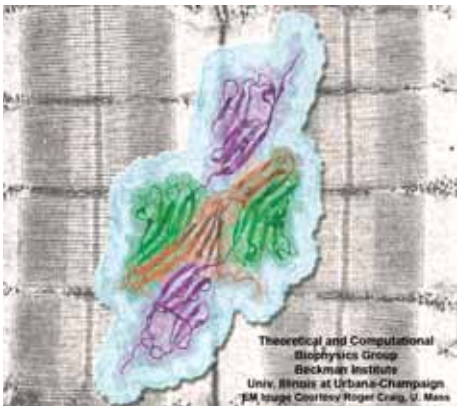
Viruses, the cause of many diseases, are the smallest natural organisms known. They are extremely primitive and parasitic such that biologists refer to them as “particles”, rather than organisms. Viruses contain in a protein shell, the capsid, their own building plan, the genome, in the form of DNA or RNA. Viruses hijack a biological cell and make it produce from one virus many new ones. Viruses have evolved elaborate mechanisms to infect host cells, to produce and assemble their own components, and to leave the host cell when it bursts from viral overcrowding. Because of their simplicity and small size, computational biologists selected a virus for their first attempt to reverse-engineer in a computer program, NAMD, an entire life form, choosing one of the tiniest viruses for this purpose, the satellite tobacco mosaic virus. As described in a recent report, the researchers simulated the virus in a small drop of salt water, altogether involving over a million atoms. This provided an unprecedented view into the dynamics of the virus for a very brief time, revealing nevertheless the key physical properties of the viral particle as well as providing crucial information on its assembly. It may take still a long time to simulate a dog wagging its tail in the computer, but a big first step has been taken to simulate living organisms. Naturally, this step will assist modern medicine.



Peter L. Freddolino, Anton S. Arkhipov, Steven B. Larson, Alexander McPherson, and Klaus Schulten. **Molecular dynamics simulations of the complete satellite tobacco mosaic virus**. *Structure*, 14:437-449, 2006.

[Mar 2006]

Gluing Molecules the Right Way

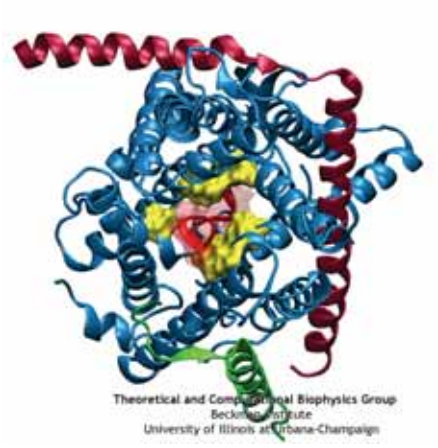


Eric H. Lee, Mu Gao, Nikos Pinotsis, Matthias Wilmanns, and Klaus Schulten. **Mechanical strength of the titin Z1Z2/ telethonin complex**. *Structure*, 14:497-509, 2006.

Muscle fibers, through their so-called thick and thin filaments, contract and extend in doing their work. To render the fibers elastic and protect them from overstretching, the thick filaments are connected through a long and thin elastic protein, titin, to the base of the fibers. Titin, by far the longest protein in human cells, is a molecular bungee cord and, like such cord, must be affixed firmly to the base. How this is done was a mystery until crystallographers took the first atomic resolution image of the system: it turns out that two titins are spliced together at their ends like ropes. The splicing involves a third small protein, the titin-telethonin-titin system forming a U. The U apparently is thrown over a bollard-like cellular structure to hold the thick filaments much like boats are held by bollards and ropes at their mooring place. The crystallographers teamed up with computational biologists to investigate the mechanical strength of the titin – telethonin – titin cord by means of molecular dynamics simulations using NAMD. As reported recently, the cord has great mechanical strength due to an extended network of hydrogen bonds between beta-strands, common structural features in proteins, that in the present case form a sheet extending through all three proteins. This discovery explains how living cells can splice cellular proteins together through a system of hydrogen-bonded beta-strands that extend through several proteins. Interestingly, such beta-strands were seen previously in cases of diseases like Alzheimers where the feature leads, however, to pathological assembly of proteins. What needs to be understood now is how the telethonin glue is applied only to the right spots in the cell and how the cells prevent telethonin from splicing together the wrong proteins.

[Apr 2006]

Threading a Needle



James Gumbart and Klaus Schulten. **Molecular dynamics studies of the archaeal translocon**. *Biophysical Journal*, 90:2356-2367, 2006.

Anyone who has attempted to fit a long piece of thread through a needle's eye realizes how difficult fitting something so small and flexible into such a small hole can be. Yet this action is carried out every second in every living cell. Flexible polypeptides, proteins, often have to cross a cellular membrane to get to their correct location, whether that location is an organelle within the cell or even outside of it. To accomplish this, they are pushed through a protein pore in an unfolded conformation much like a long string. The channel that accepts the string-like proteins, the protein translocon, allows only certain proteins to pass, while restricting access to molecules even much smaller than the macromolecular proteins. As reported in a recent publication, computer simulations using the molecular dynamics program NAMD helped to answer the question of how such a small channel could achieve this feat, demonstrating how the channel itself can be flexible yet resilient during a protein-crossing event and also elucidating in part how it can maintain such tight control over what is permitted to cross.

[Apr 2006]

DNA Loops and Garden Hoses

One of the most fascinating aspects of molecular biology is how objects of very different sizes are involved in the intricate biological machinery of living cells. A small protein may bind to DNA many times larger than itself and fold the DNA into a loop to regulate nearby genes. Understanding of such processes requires coupling of the dynamics of an individual protein to the dynamics of a long, looped DNA double helix. This can be achieved best through a so-called multi-scale approach that describes the protein motion at atomic resolution and the larger DNA in a less resolved manner as an elastic rod, i.e., a physical object behaving much like a twisted garden hose. Mathematical equations can be devised that capture the behavior of the DNA "hose" bent into a loop by a bound protein, predicting the conformation of the DNA as well as the energy that the protein has to muster to keep the DNA looped (DNA prefers energetically to be straight). A recent publication studies in detail mathematically and computationally the elastic rod model of DNA, taking for a case study the DNA loop folded by the lac repressor, a celebrated protein regulating the expression of DNA in E. coli. The study explores how physical characteristics built into the elastic rod model influence the energy and conformation of looped DNA and describes the possible ways of coupling the looped DNA to all-atom protein simulations of the lac repressor or other regulatory proteins in order to achieve the multi-scale description of a protein-DNA complex.

Alexander Balaeff, L. Mahadevan, and Klaus Schulten. **Modeling DNA loops using the theory of elasticity**. *Physical Review E*, 73:031919, 2006. (23 pages).

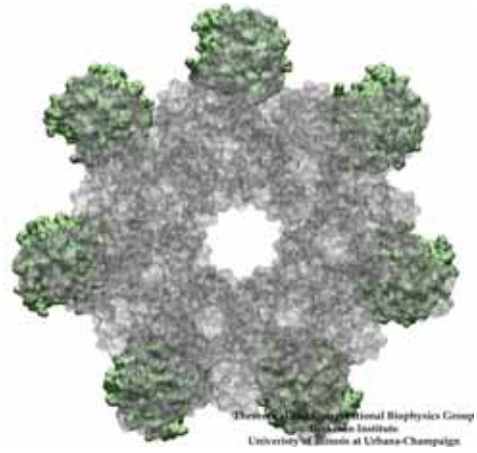
[Apr 2006]

New Generation Hands-on Workshop

Computational tools, like the molecular graphics program VMD and molecular dynamics program NAMD, move rapidly from theoretical to experimental biology. To train researchers in the proper use of computational tools, a series of hands-on workshops was organized in the US and Australia in 2003-2005 (see July 2005 highlight). This year the first European hands-on workshop started a new generation of training with three novel features. First, the workshop addressed mainly bench scientists in need of computational methods. Second, the workshop introduced a key expansion of VMD that turned a mainly structurally oriented visualization program into a structure and sequence analysis program. This is achieved through a multiple sequence analysis tool in VMD, called multiseq. Third, all training material has been extended to multiple platforms and participants could bring their own laptops for the training sessions. As in the previous series, participants enjoyed workshop lectures that introduced concepts and good uses of biocomputing software, but were most enthusiastic about practical tutorials that provided opportunities to learn by example and to apply newly mastered tools to their own research. The participants carried all lecture material and software home on a DVD; others can obtain the same material through our web site.

[May 2006]

Killers' Entry Route

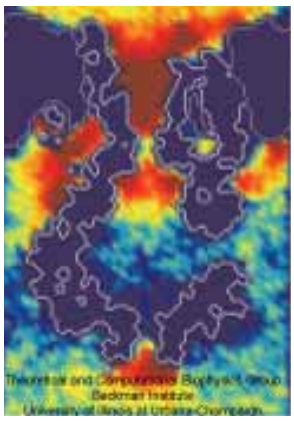


Mu Gao and Klaus Schulten. **Onset of anthrax toxin pore formation**. *Biophysical Journal*, 90:3267-3279, 2006.

Bacillus anthracis, the cause of anthrax, is one of the most lethal bacteria. In addition to its ability to infect animal and human cells, the bacterium attacks also the cells of the host's immune system, the so-called macrophages. For this purpose the anthrax bacterium releases three types of proteins, or toxins, into the blood stream of the host: protective antigen, lethal factor, and edema factor, referred to as PA, LF, and EF, respectively. LF and EF team up with PA, which transports them into a host macrophage cell. Once inside the cell, LF depletes the energy source of the cell by catalyzing the consumption of ATP, while EF disrupts various cellular signaling pathways. These attacks cause the death of macrophages and some other cells, essentially shutting down the host's immune system and often leading to death of the host. To invade macrophages, the toxins take an intricate entry route that involves binding to a cell receptor, capillary morphogenesis protein 2 (CMG2), inducing the cell to internalize the toxins in a bubble like membrane (endosome), the bubble wall being then punctured by seven PAs forming a channel upon a chemical (acidifying) trigger from the host; the channel permits then their lethal cargo, LFs and EFs, to slip into the cell. How exactly the PAs punctured the endosome wall remained a mystery. In a recent report the entry route has been resolved now in greater detail through molecular dynamics simulations using NAMD. The report reveals how acidic conditions in the endosome trigger conformational changes of the PA complex necessary for pore formation, and provides structural insights into the role of unusual interactions between the PAs and its receptor CMG2.

[May 2006]

Electrical Safety Valve



Marcos Sotomayor, Trudy A. van der Straaten, Umberto Ravaioli, and Klaus Schulten. **Electrostatic properties of the mechanosensitive channel of small conductance MscS**. *Biophysical Journal*, 90:3496-3510, 2006.

Bacterial cells, like those of Escherichia coli, protect themselves against sudden inside-out pressure differences that arise osmotically from changes in a cell's environment, through so-called mechanosensitive channels in their cell membrane. One such channel, that dissipates like a safety valve pressure differences across the Escherichia coli cell membrane, is contributed by the protein MscS. Upon tension in the cell membrane, that can also be applied systematically in the laboratory, the channel opens and permits molecules to pass, as best measured through an ion current leaking through the stretched membrane. MscS is a channel with a balloon-like filter, the function of the latter being still a mystery (see Nov 2004 highlight, "Japanese lantern protein"). Now computational biologists using NAMD teamed up with device engineers using BioMoca to study MscS as reported recently. The team monitored the mysterious MscS computationally over several microseconds, a record time for protein simulations. MscS was found to permit water passage, but to also exhibit strong electrostatic forces that focus ions streaming through its filter balloon and channel. This suggests MscS to be both a hydrostatic and an electrical safety valve. Even though now better known, MscS' entire function remains shrouded in mystery.

TCBG

Theoretical and Computational Biopysics Group

The Theoretical and Computational Biophysics Group is directed by Professor Klaus Schulten (Physics) and assistant director Dr. Emad Tajkhorshid, who are joined by Professor Alek Aksimentiev, Professor Zaida Luthey-Schulten, and Professor Laxmikant Kale. The group presently has four administrative staff members, five software developers, three postdoc associates, and twenty-six graduate students from the departments of physics, computer science and the biophysics program.

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