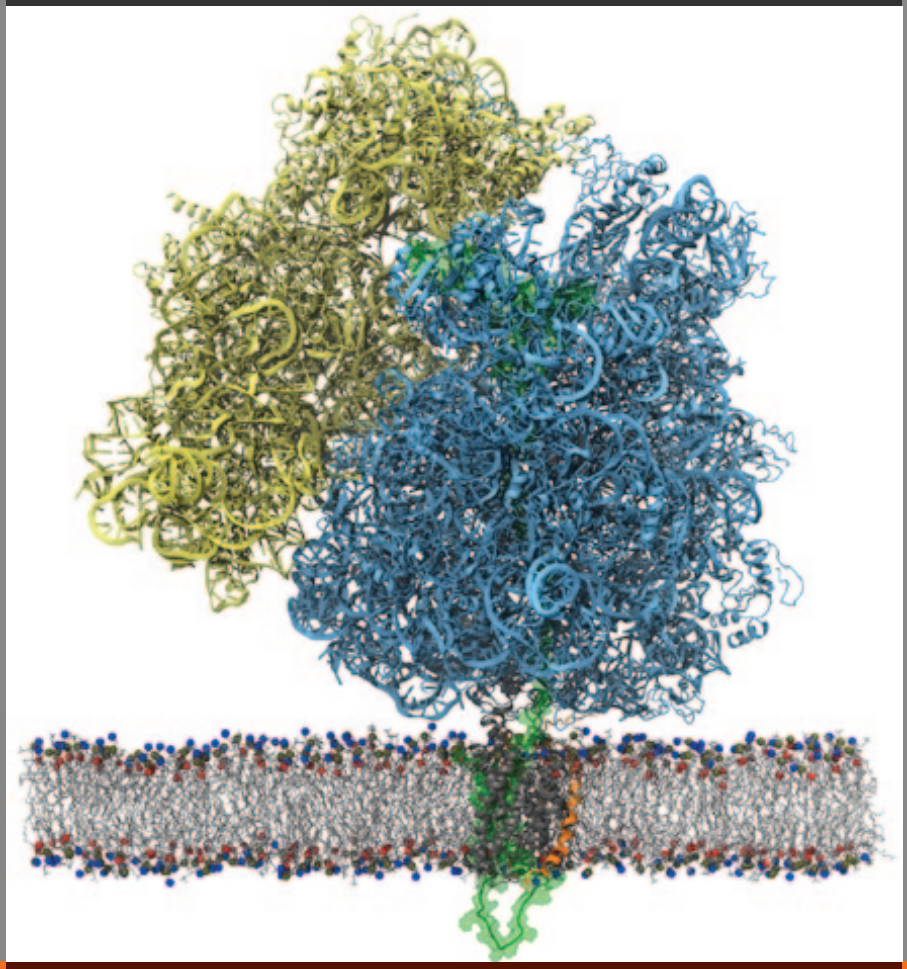


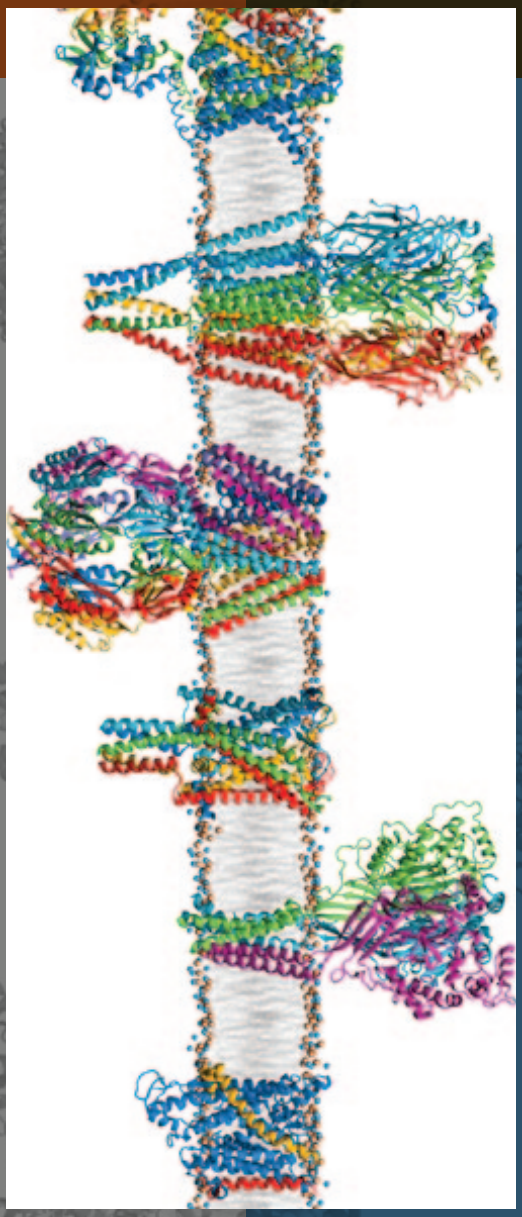
Highlights 2006 – 2011

Theoretical and Computational Biophysics Group

www.ks.uiuc.edu

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

NIH Center for Macromolecular Modeling and Bioinformatics



Highlights
June 2006 – December 2011

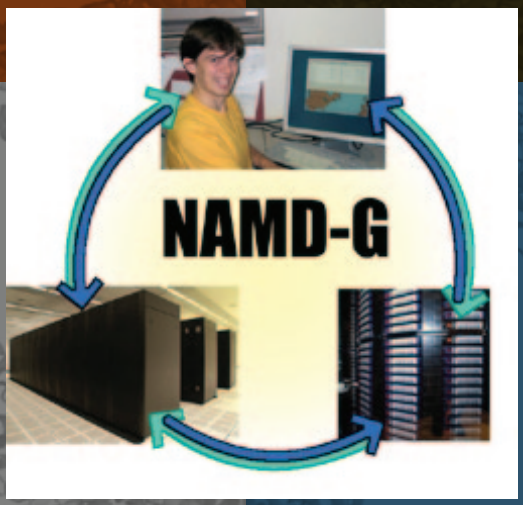
Motivated by biomedically relevant problems and collaborating closely with experimental laboratories, the Theoretical and Computational Biophysics Group exploits advances in physical theory and computing to model living organisms across many levels of organization, from molecules to cells to networks. Over the years, the group has pioneered the modeling of very large biomolecular structures, as well as the combination of quantum mechanical and classical mechanical simulations. Highlights of our group's research and software tool development are presented each month on our website and are represented here.
www.ks.uiuc.edu

Director Professor Klaus Schulten (Physics)
Professor Emad Tajkhorshid (Biochemistry)
Professor Alek Aksimentiev (Physics)
Professor Zaida Luthey-Schulten (Chemistry)
Professor Laxmikant Kale (Computer Science)

Research of the TCB Group is funded by the National Institutes of Health, the National Science Foundation, and the University of Illinois.

Linux Clusters the Easy Way
June 2006

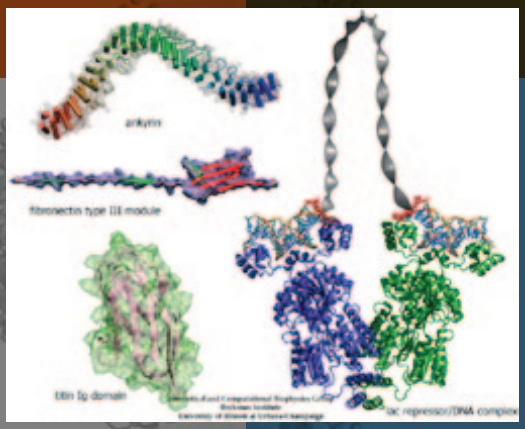
For hard-working scientists, the task of maintaining a single desktop computer is an unwelcome distraction. But what if your work requires the power of 10 or 100 machines? Our recent series of workshops has given nearly 100 participants hands-on experience installing and using low-cost Linux clusters. Students were taught to eliminate many sources of complexity, such as hard drives, and to automate what remained with cluster management software and a queuing system. Lectures on cluster design stressed the importance of knowing which applications would be run and choosing cost-effective hardware to meet those specific needs, as well as less-obvious aspects of cluster acquisition such as electrical power, cooling, and the purchasing process. After assembling and installing small, four-node clusters, students ran both the molecular dynamics program NAMD and a more typical parallel application that they compiled from scratch. Most participants were motivated by concrete plans to build clusters for their own groups in the near future and felt better equipped to do so following their experience.



NAMD-G: A Nanny for NAMD
June 2006

Many proteins store or react with gases like oxygen, carbon dioxide, and nitric oxide. The gases are conducted into the protein through access routes that exist only in passing and as a result of a protein's fluctuations. Accordingly, access routes are difficult to establish, but researchers are now able to image gas access pathways inside proteins computationally. The new method has many implications for biotechnology and science. Imaging gas access systematically over whole protein families, i.e., the family of myoglobins, requires a large number of calculations that need to be run and monitored. The traditional means of doing so are very wasteful of researchers' time. To solve this problem, NAMD-G, a grid-based automation engine for biomolecular simulations running the NAMD software, has been developed in collaboration with the National Center for Supercomputing Applications. From the researchers' workstations, NAMD-G "farms out" a large number of calculations, in parallel, to supercomputers on the TeraGrid. NAMD-G monitors and manages multiple sequences of calculations at distant sites, and performs the necessary data transfers and backups on an as-needed basis. While the gas transport simulations provide a clear scientific driver for the development, NAMD-G is quite general and will aid any NAMD user with access to the TeraGrid. The result? Less time spent babysitting runs and more time for science.

Michelle Gower, Jordi Cohen, James Phillips, Richard Kufrin, and Klaus Schulten. **Managing biomolecular simulations in a grid environment with NAMD-G.** In Proceedings of the 2006 TeraGrid Conference, 2006. (7 pages).

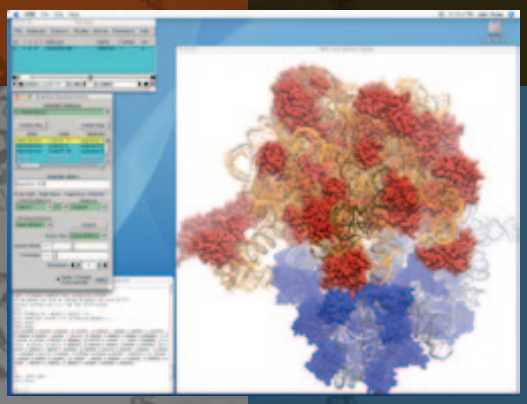


Life Under Tension

July 2006

The living state of biological cells manifests itself through mechanical motion on many length scales. Behind this motion are processes that generate and transform mechanical forces of various types. As with other cell functions, the machinery for cellular mechanics involves proteins. Their flexible structures can be deformed and restored, and are often essential for handling, transforming, and using mechanical force. For instance, proteins of muscle and the extracellular matrix exhibit salient elasticity upon stretching; mechanosensory proteins transduce weak mechanical stimuli into electrical signals; and so-called regulatory proteins force DNA into loops controlling, thereby, gene expression. In a recent review, the structure-function relationship of four protein complexes with well-defined and representative mechanical functions has been described. The first protein system reviewed is titin, a protein that confers passive elasticity on muscle. The second system reviewed is the elastic extracellular matrix protein fibronectin and its cellular receptor integrin. The third protein system covered is the proteins cadherin and ankyrin involved in the transduction apparatus of mechanical senses and hearing. The last system surveyed is the lac repressor, a protein that regulates gene expression by looping DNA. In each case, molecular dynamics simulations using NAMD provided insights into the physical mechanisms underlying the associated mechanical functions of living cells.

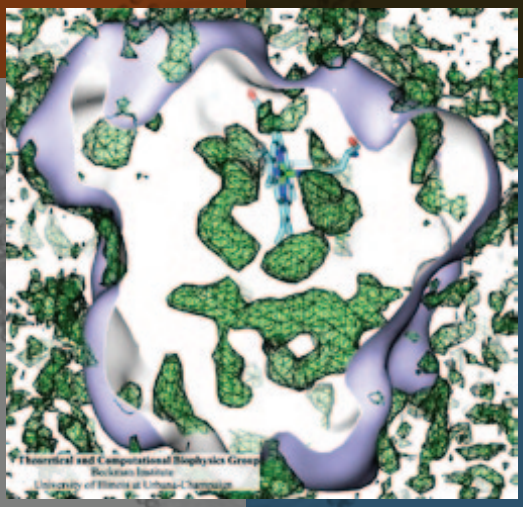
Mu Gao, Marcos Sotomayor, Elizabeth Villa, Eric Lee, and Klaus Schulten. **Molecular mechanisms of cellular mechanics.** *Physical Chemistry - Chemical Physics*, 8:3692-3706, 2006.



New Horizon for Molecular Biologists

August 2006

How far and how well molecular biologists can look into the living cell depends as much on microscopes and observations as it does on computers and their software. The premiere software for looking into the molecular world of the cell, VMD, has made a big leap forward in broadening the molecular horizon of life scientists through its new release, VMD 1.8.5. Researchers are now offered a fresh view through a modern unified bioinformatics environment, MultiSeq, combining sequence and structure analysis for proteins and amino acids. VMD, now literally more colorful, lets scientists quickly exchange VMD views through integration of BioCoRE, calculate APBS electrostatics maps, call on NAMD to calculate energies, build and mutate structures, easily determine force field parameters, and navigate through proteins with a flying camera. VMD 1.8.5, though only a minor version number different from the previous release, includes now many new structure building and analysis tools that make it easier for modelers to set up, run, and analyze computer simulations of biomolecules.

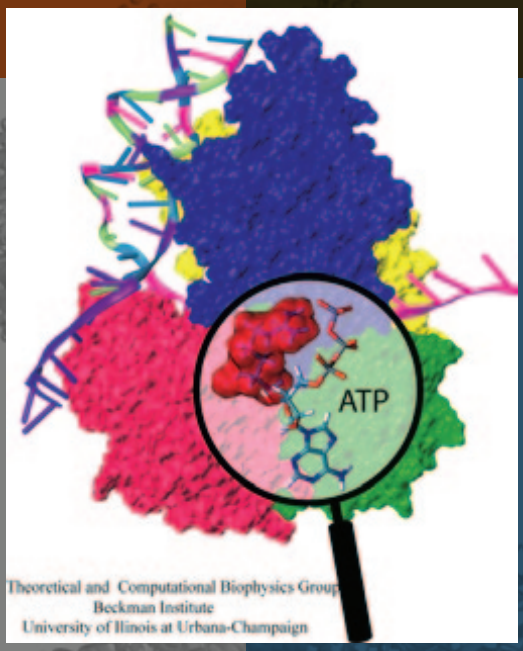


A Protein with Many Doors

August 2006

Many proteins interact with gas molecules such as oxygen to perform their functions. In most cases, the gas molecules must reach active sites buried deep inside the proteins that bind the molecules, with no obvious way in. Understanding how, for example, oxygen enters the protein, and mapping out which pathways it takes has been a long-standing challenge. Computational biologists, inspired by previous work on the hydrogenase enzyme, have developed a method, called implicit ligand sampling, that maps the pathways taken by gas molecules inside proteins. The mapping is determined by monitoring fluctuations of the protein, surprisingly, in the absence of the gas molecules. The mapping method is available in the program VMD used for structure and sequence analysis of proteins. The researchers applied the method to myoglobin, an oxygen-storing protein present in muscle cells, and determined detailed three-dimensional maps of oxygen and carbon monoxide pathways inside the protein. While some details of these pathways were already known from experiment, the implicit ligand maps revealed a large number of new pathways and suggest that oxygen enters myoglobin using many different entrance doors.

Jordi Cohen, Anton Arkhipov, Rosemary Braun, and Klaus Schulten. **Imaging the migration pathways for O2, CO, NO, and Xe inside myoglobin.** *Biophysical Journal*, 91:1844-1857, 2006. (PMC: 1544290)



Molecular Motor Scooting along DNA

September 2006

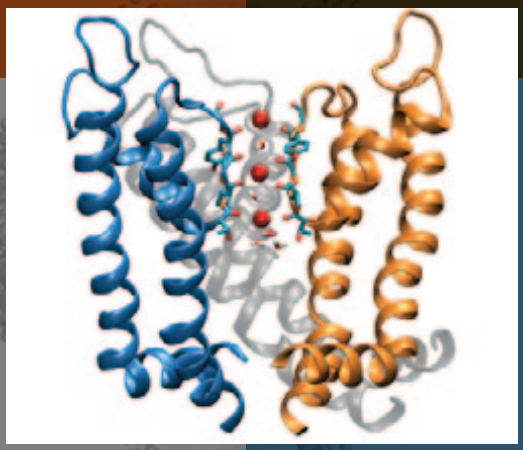
DNA – with its famous double helix structure – stores the genetic information of all life forms known. In order that this information is read, the double helix needs to be first unwound and separated into single helices or strands. This is achieved by cellular motor proteins called helicases that operate on already separated DNA strands. The helicases specialize in unwinding and separating the DNA double helix by scooting along one of DNA's single strands against the point where the two strands merge into the double helix; pushing against this point unwinds and separates the double helix further. The helicases are driven by energy stored in molecules of ATP, which bind to the protein and get released in their so-called hydrolyzed, lower energy, form. Based on atomic resolution structures, researchers have now studied one of the smallest helicases known, PcrA, from the electronic to the functional level carrying out quantum mechanical/molecular mechanical simulations, as well as a combination of classical molecular dynamics simulation, using NAMD, and stochastic modeling calculations. This resulted in an overall explanation of how ATP's hydrolysis powers helicase activity. The researchers discovered that PcrA moves with two "hands" along single-stranded DNA; when ATP binds, one hand moves along the DNA; when ADP and Pi (the hydrolysis products of ATP) unbind, the other hand moves; through a molecular "trick" both hands move in the same direction. Amazingly, the hand movement arises mainly from an increase in random mobility of the hands—it is not enforced. Physicists refer to the underlying mechanism as a ratchet mechanism that was indeed long suspected to drive molecular motors. Interestingly, the helicase motor is very closely related to a wide class of other biological motors, for example FoF1-ATP synthase.

Markus Dittrich and Klaus Schulten. **PcrA helicase, a prototype ATP-driven molecular motor.** *Structure*, 14:1345-1353, 2006.

Jin Yu, Taekjip Ha, and Klaus Schulten. **Structure-based model of the stepping motor of PcrA helicase.** *Biophysical Journal*, 91:2097-2114, 2006. (PMC: 1557568)

Jin Yu, Taekjip Ha, and Klaus Schulten. **How directional translocation is regulated in a DNA helicase motor.** *Biophysical Journal*, 93:3783-3797, 2007. (PMC: 2084242)

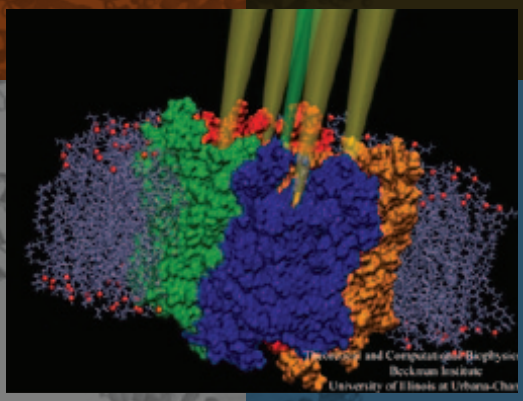
Markus Dittrich, Jin Yu, and Klaus Schulten. **PcrA helicase, a molecular motor studied from the electronic to the functional level.** Topics in *Current Chemistry*, 268:319-347, 2006.



Movies of Potassium Ion Permeation
September 2006

Biological cells, in particular neurons, maintain an inside-outside voltage gradient through active transport of ions (Na+, K+, Cl-, and others) across their membranes. The flow of the ions down their gradients through membrane channels is highly selective for each ion. The high selectivity permits nerve cells to signal each other through voltage spikes, which are produced through transient changes of channel conductivities for Na+ ions (channels open and close in about 1 ms) and K+ ions (channels open and close in about 10 ms). Crucial for the generation of voltage spikes is the selective, yet quick, conduction of ions, but as one knows from experience at border crossings, high selectivity and quick crossing seem to be mutually exclusive. Yet biological ion channels reconcile selectivity and speed. Prior experimental work, primarily that of 2003 Nobelist MacKinnon, as well as computational work, suggested how potassium channels achieve selectivity and speed. But until recently no high resolution atomic structure of a potassium channel was known in the open form and the suggested mechanism could not be tested under natural conditions through atomic level simulations. Last year's solution of the structure of the potassium channel Kv1.2 in its open form made it finally possible to simulate, using NAMD, the conduction of ions through Kv1.2 driven by a voltage gradient. The results reported confirmed indeed the high selectivity-high speed mechanism suggested earlier, namely a billiard-type motion of two and three ions, the last ion kicking the first ion out. The simulations revealed for the first time, through movies, the overall permeation process, including the jumps of ions between energetically favorable binding sites and the sequence of multi-ion configurations involved in permeation.

Fatemeh Khalili-Araghi, Emad Tajkhorshid, and Klaus Schulten. **Dynamics of K+ ion conduction through Kv1.2.** *Biophysical Journal*, 91:L72-L74, 2006. (PMC: 1557577)



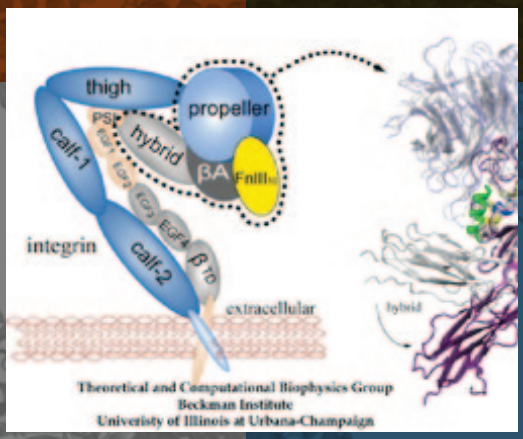
Aquaporin and the Cambridge Five
October 2006

Sometimes analogies go a long way—surprisingly long. Aquaporins are ubiquitous water channels in living cells, known to be tetrameric, each unit contributing one pore. This much is certain and this is where an analogy begins, namely with a British spy ring that passed information to the Soviet Union during World War II and into the 1950s. The ring is often referred to as the Cambridge Four since the spies, when recruited, were undergrads at Cambridge Trinity College and there were four of them (cryptonyms Stanley, Homer, Hicks, and Johnson). But a fifth man was long suspected, yet never formally identified. Here the analogy continues: aquaporin was suspected to sport a fifth pore, supposedly at its center, where its four subunits join (hence known as the tetrameric pore). Strong but not yet completely conclusive evidence has now been put forward that the central pore, actually quite plainly visible to the eye when aquaporins are inspected by molecular graphics – with VMD – is an ion channel gated by a common cellular signaling molecule, cGMP. The evidence stems from a combined computational (molecular dynamics using NAMD) and experimental (verifying computationally suggested mutants) study. But the analogy goes further. Today it is suspected that the Cambridge Five actually had more than five members and the same holds for the pores of aquaporin. An ongoing investigation has lead to evidence that the further pore members conduct gases, for example carbon dioxide. Hopefully, we will know one day with certainty all members of the Cambridge Five and all pores of aquaporin.

Jin Yu, Andrea J. Yool, Klaus Schulten, and Emad Tajkhorshid. **Mechanism of gating and ion conductivity of a possible tetrameric pore in Aquaporin-1.** *Structure*, 14:1411-1423, 2006.

NAMD More Powerful
October 2006

The computer processor is the workhorse of biomolecular modeling, with NAMD the plow to which a single processor or a team of thousands may be hitched. The recent release of NAMD 2.6 has extended the drawbar to harness the power of several thousand processors: 2000 on a Cray XT3 and 8,000 on an IBM Blue Gene/L. This permits the efficient simulation of an entire ribosome, the cell's protein factory, comprising 3,000,000 atoms when solvated. But the features and increased performance of NAMD 2.6 are also available to the scientist with only a laptop, on which a domain of the muscle protein titin (10,000 atoms solvated) can be readily simulated. NAMD has also become more versatile, supporting more force fields (OPLS, CHARMM with CMAP cross terms), calculating free energies, and executing customizable replica exchange simulations. In addition, NAMD can now be called from the structure analysis program VMD to calculate, for example, interaction energies between protein domains. Like increased horsepower in transportation, increased simulation power opens new routes—routes to study entire systems of biopolymers like the ribosome, not just isolated pieces.

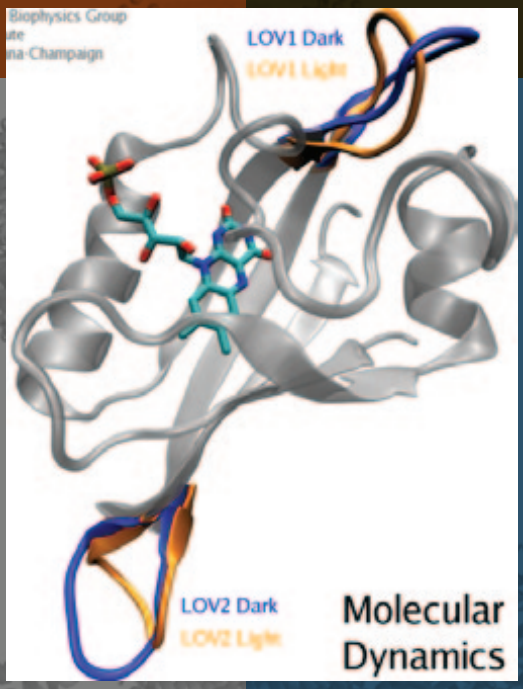


Hook and Sensor of Cells
November 2006

Mammalian cells adhere to each other forming tissues. The adhesion is due to a network of proteins, so-called extracellular matrix proteins, "gluing" the cells together. The cell membranes are too soft to provide anchoring points for the extracellular matrix proteins; rather, the cells furnish on their outer surface specialized hooks for anchoring the extracellular matrix proteins. The hooks, in the form of surface proteins, are linked directly through the membranes to the intracellular cytoskeleton that stabilizes and shapes cells. Integrins are an important family of such surface proteins that form hooks specific for certain types of extracellular matrix proteins. The hooks are flexible – they can be open for contacts or closed, the switch being induced by signals from inside or outside the cell through interactions with other proteins. The interactions between integrins and extracellular matrix proteins are rather complex, as the proteins are composed of many subunits; fortunately, their overall structures are presently being solved through crystallography. In a recent report a major component of an integrin and an extracellular matrix protein have been investigated through molecular modeling using NAMD, including steered molecular dynamics. The study described in detail how the extracellular matrix protein induces a transition in integrin, potentially strengthening its adhesion property.

Eileen Puklin-Faucher, Mu Gao, Klaus Schulten, and Viola Vogel. **How the headpiece hinge angle is opened: new insights into the dynamics of integrin activation.** *Journal of Cell Biology*, 175:349-360, 2006. (PMC: 2064575)

Wei Chen, Jizhong Lou, Jen Hsin, Klaus Schulten, Stephen C. Harvey, and Cheng Zhu. **Molecular dynamics simulations of forced unbending of integrin $\alpha_V\beta_3$.** *PLoS Comput. Biol.*, 7(2):e1001086, 2011. (PMC: 3040657)

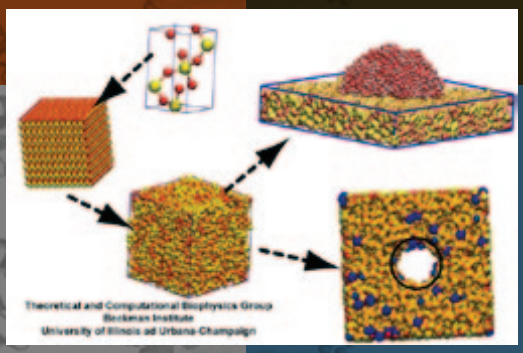


LOV in Motion
November 2006

Most forms of life need to detect and respond to changes in their environment for survival and optimal growth. For this purpose organisms rely on receptors that are based on sensory proteins. In plants, several sensory proteins detect the ambient light for optimal exposure of their photosynthetic apparatus. One class of plant light sensors, the phototropins, influence photosynthesis and induce the transition between root and stem growth when seedlings emerge out of the ground. Induction is activated through several protein domains, two of which actually absorb light – and, for their sensitivity to light, oxygen, and voltage, are called LOV1 and LOV2 domains. Understanding the LOV domains' involvement in activation is important for studying the signaling mechanisms of other types of sensory proteins. Strangely, light absorbed by LOV domains is observed to lead to a distinct, but only very minute, structural change that does not explain how activation might come about. NAMD-based molecular dynamics simulations of the LOV domain have now revealed that photoactivated LOV domains exhibit altered patterns of motion that can induce a signal for plant cells.

Peter L. Freddolino, Markus Dittrich, and Klaus Schulten. **Dynamic switching mechanisms in LOV1 and LOV2 domains of plant phototropins.** *Biophysical Journal*, 91:3630-3639, 2006. (PMC: 1630464)

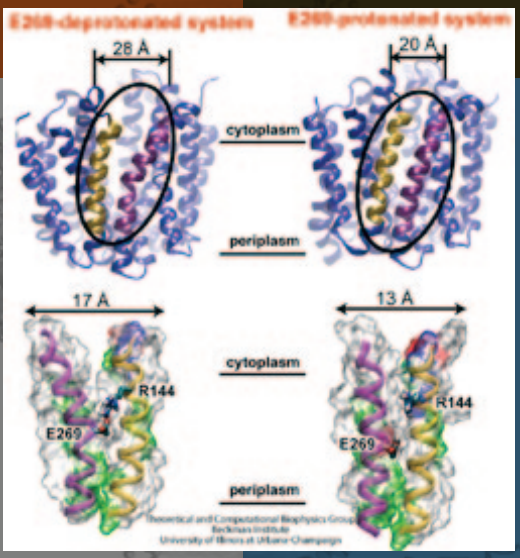
Sang-Hun Song, Peter Freddolino, Abigail Nash, Elizabeth Carroll, Klaus Schulten, Kevin Gardner, and Delmar S. Larsen. **Modulating LOV domain photodynamics with a residue alteration outside the chromophore binding site.** *Biochemistry*, 50:2411-2423, 2011. (PMC: PMC3068209)



Transistor Meets DNA II
December 2006

Bionanotechnology involves a marriage of two different materials: inorganic solids, like silica, and biomolecules, like DNA. The new combinations of materials have to be mastered on the laboratory bench as well as in computer simulations. On the bench, devices are manufactured and tested. In simulations, they are imaged and designed. So far, inorganic solids and biomolecules were simulated successfully, but only separately. To join the materials requires as much effort in simulations as on the bench. Even just the interaction of inorganic solids (like silica) with physiological solutions (water and ions) demands challenging descriptions of silica surface properties. Researchers have now succeeded in describing accurately the wetting (by water) of amorphous silica, an essential material for nanoelectronics, clearing a major hurdle to simulating bionanotechnological devices, for example, those suggested for rapid and economical sequencing of DNA.

Eduardo R. Cruz-Chu, Aleksei Aksimentiev, and Klaus Schulten. **Water-silica force field for simulating nanodevices.** *Journal of Physical Chemistry B*, 110:21497-21508, 2006. (PMC: 2517990)



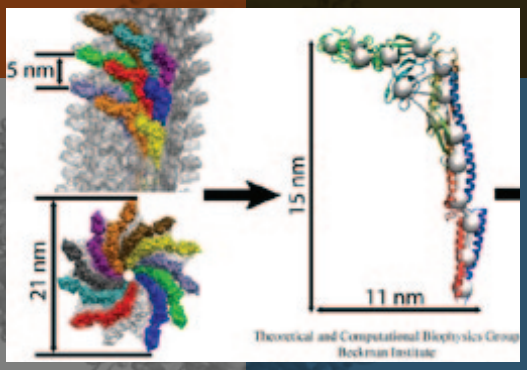
Bacterium's Sweet Tooth

December 2006

Escherichia coli are bacteria living in the intestines of mammals as part of healthy gut flora. However, they also cause disease outside of the gut. The bacteria import from their environment nutriments (for example, molecules of lactose, a sugar). For this purpose Escherichia coli employs in its cell membrane a protein channel, lactose permease, that translocates the sugar outside-in. This is the bacterium's "sweet tooth." To establish the unidirectional sugar transport, the bacterium utilizes an electrical potential maintained in the form of a trans-membrane proton gradient (more protons on the outer cellular than on the inner cellular side of the membrane). Protons – very small ions – that enter the channel from the outside one at a time, open the outer channel entrance. This permits access of lactose that gets bound inside the channel. Release of the proton to the cell interior closes the outer channel entrance and opens the inner channel entrance, such that the bound lactose can enter the cell. Despite extensive and elegant biochemical studies, the physical mechanism that couples unidirectional proton and sugar translocation is not yet known in detail. A crystallographic structure of lactose permease permitted investigations into this mechanism by means of molecular dynamics simulations using NAMD. The simulations, reported recently, showed one step of the proton-sugar translocation, namely how binding and unbinding of the proton activates a spring-like bond, a so-called salt bridge, that closes and opens the inner channel exit.

Ying Yin, Morten Ø. Jensen, Emad Tajkhorshid, and Klaus Schulten. **Sugar binding and protein conformational changes in lactose permease.** *Biophysical Journal*, 91:3972-3985, 2006. (PMC: 1635680)

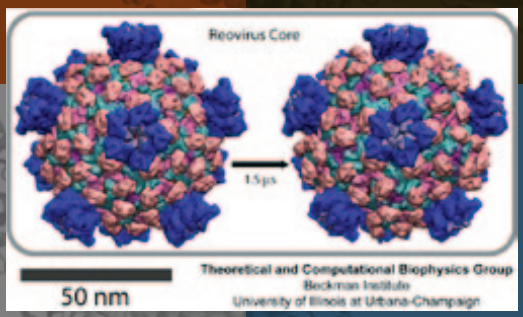
Morten Ø. Jensen, Ying Yin, Emad Tajkhorshid, and Klaus Schulten. **Sugar transport across lactose permease probed by steered molecular dynamics.** *Biophysical Journal*, 93:92-102, 2007. (PMC: 1914442)



Bacteria Swim and Tumble
January 2007

The bacterial flagellum is a large biomolecular assembly used by many types of bacteria as a helical propeller for forward swimming and turning. The flagellum is remarkable in that its properties differ greatly depending on the direction in which it is rotated, allowing the bacterium to switch between swimming straight ("running") and turning ("tumbling"). The mechanics of the flagellum are of interest both to biologists and mechanical engineers, as the molecular mechanisms of the transition in the flagellum between running and tumbling modes are unknown. Because of the flagellum's size (several micrometers in length) and composition (made up of 30,000 protein subunits) it presents a challenge to computational modeling. Researchers have now achieved an advance describing the flagellum in both its running and tumbling state. For this purpose, the researchers developed a computational model of the system that glosses over atomic level detail, but resolves the shapes of all proteins making up a bacterial flagellum, simulating a simplified version of the system using the program NAMD. The results, reported recently, showed that the flagellum's transition between swimming straight and tumbling is triggered by friction due to the water around the bacterium.

Anton Arkhipov, Peter L. Freddolino, Katsumi Imada, Keiichi Namba, and Klaus Schulten. **Coarse-grained molecular dynamics simulations of a rotating bacterial flagellum.** *Biophysical Journal*, 91:4589-4597, 2006. (PMC: 1779929)

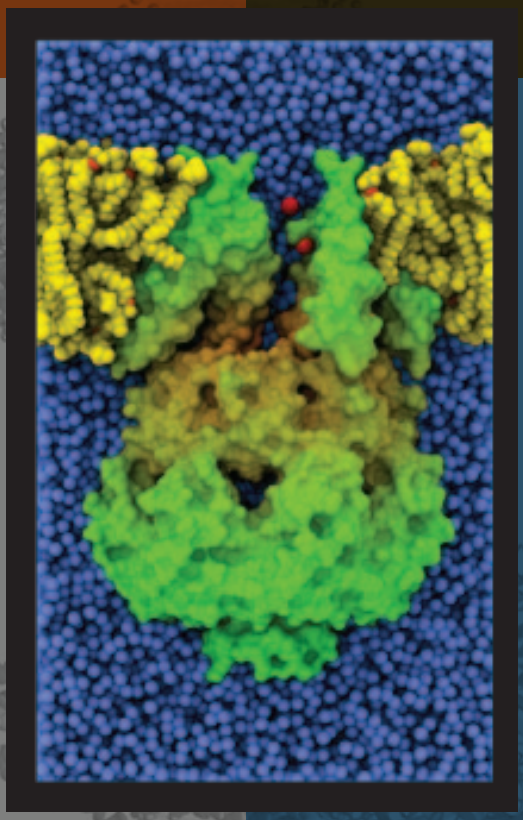


Viruses Up Close
January 2007

Viruses are the cause of many human diseases, from the common cold to AIDS, and medicine is continuously searching for better ways to battle viruses through vaccination or medication. Detailed knowledge of the life cycles of viruses should be useful in the treatment of viral diseases. A key focus of investigations is the virus capsid, a protein coat that not only protects the viral genome, but also triggers release of the genome and other viral factors upon contact with the body's cells. X-ray crystallography has resolved the average structures of many types of virus capsids, providing the basis for detailed investigations—for example, by means of molecular dynamics methods of capsid dynamical properties, i.e., in assembly and disassembly. Unfortunately, due to their large size most virus capsids are beyond the reach of molecular dynamics simulations, with one notable exception. An earlier simulation allowed researchers to develop and test a method for coarse-grained molecular dynamics simulations that glosses over atomic detail and thereby permits microsecond descriptions of entire viral particles. Such simulations, employing the program NAMD, were applied to the empty capsids of several viruses. These simulations revealed a variety of behaviors, from rapid collapse to high stability, depending on the strength of interactions between the proteins from which capsids are built. The new method offers unprecedented views of capsid dynamics that may assist in battling viral diseases.

Anton Arkhipov, Peter L. Freddolino, and Klaus Schulten. **Stability and dynamics of virus capsids described by coarse-grained modeling.** *Structure*, 14:1767-1777, 2006.

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.



Observing and Modeling a Crucial Membrane Channel
February 2007

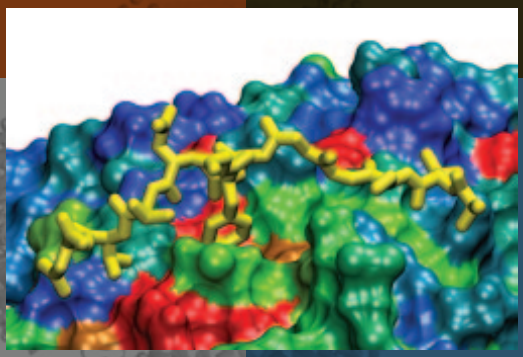
Bacteria employ membrane proteins as crucial safety valves that release water and small solutes under challenging osmotic conditions. There are valves for balancing small pressure differences between the inside and outside of bacterial cells, that open and close readily, but there are also ones for protection against large pressure differences as a safety measure of last resort. The valves for balancing small pressure differences, like the one shown in the figure, include a filter that presumably keeps the most valuable molecules inside the cell interior, though this is not understood yet in detail. To reveal the function of such channels a combination of X-ray crystallography, physiological measurements, and molecular dynamics simulations using NAMD was employed. Crystallography, in a prior study, captured the channel in a halfway open state. Now a team of physiologists and modelers reported the details on valve opening and closing. The experiments, using a pipette small enough to measure currents from a single channel, MscS, along with the simulations, revealed that the channel conducts both positive and negative ions when subjected to tension and voltage. The unprecedented comparison of experimental and computational results open a new era of quantitative cell biology that borrows successful research strategies from physics.

Marcos Sotomayor, Valeria Vasquez, Eduardo Perozo, and Klaus Schulten. **Ion conduction through MscS as determined by electrophysiology and simulation.** *Biophysical Journal*, 92:886-902, 2007. (PMC: 1779981)

Valeria Vasquez, Marcos Sotomayor, Julio Cordero-Morales, Klaus Schulten, and Eduardo Perozo. **A structural mechanism for MscS gating in lipid bilayers.** *Science*, 321:1210-1214, 2008. (PMC: 2897165)

Valeria Vasquez, Marcos Sotomayor, D. Marien Cortes, Benoit Roux, Klaus Schulten, and Eduardo Perozo. **Three dimensional architecture of membrane-embedded MscS in the closed conformation.** *Journal of Molecular Biology*, 378:55-70, 2008. (PMC: 2703500)

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. (PMC: 1440732)



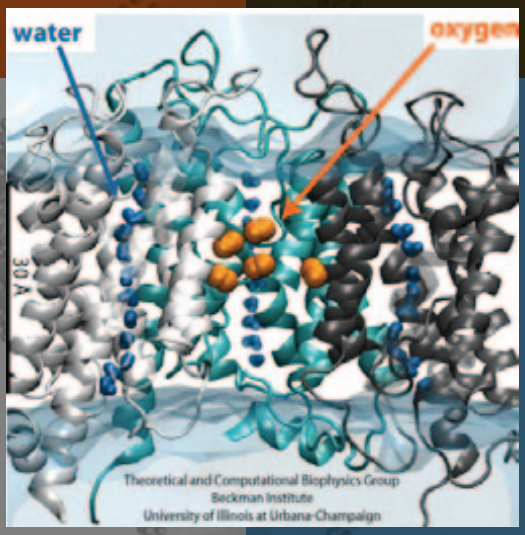
The Ins and Outs of the Nucleus
February 2007

The nucleus is responsible for storing the genome of eukaryotic cells, isolating it from the cellular cytoplasm. Partitioning the genetic material is very important in protecting it from cellular processes or foreign molecules. However, the nucleus also needs to provide access for the rest of the cell to the information stored in the genome. Numerous nuclear pores in the nuclear envelope offer communication pathways between the nucleoplasm and cytoplasm. The pathways are restricted to so-called transport receptors, proteins that taxi molecules into and out of the nucleus. If a molecule wishes to enter or leave the nucleus, it associates with a transport receptor. The complex passes through the pore and then dissociates. The question is why transport receptors can pass the nuclear pores while other proteins cannot. The answer lies in the role of FG-repeat proteins lining the pores and filling much of their free volume. These proteins are disordered peptides, consisting of repeating phenylalanine-glycine (FG) residues separated by a sequence of hydrophilic linker residues. Only proteins that interact favorably with the FG-repeat regions can pass through, while other proteins are excluded. A recent report used molecular dynamics via NAMD to examine the way in which the transport factor NTF2 interacts with the FG-repeats. The study described binding spots for FG-repeat peptides on the surface of NTF2, confirming known binding spots discovered previously via experimental means, and suggesting the existence of further binding spots. The new binding spots may play a role in steering NTF2, upon import or export, along a particular path through the nuclear pore.

Timothy A. Isgro and Klaus Schulten. **Association of nuclear pore FG-repeat domains to NTF2 import and export complexes.** *Journal of Molecular Biology*, 366:330-345, 2007.

Lingling Miao and Klaus Schulten. **Transport-related structures and processes of the nuclear pore complex studied through molecular dynamics.** *Structure*, 17:449-459, 2009. (PMC: 2701619)

Lingling Miao and Klaus Schulten. **Probing a structural model of the nuclear pore complex channel through molecular dynamics.** *Biophysical Journal*, 98:1658-1667, 2010. (PMC: 2865169)

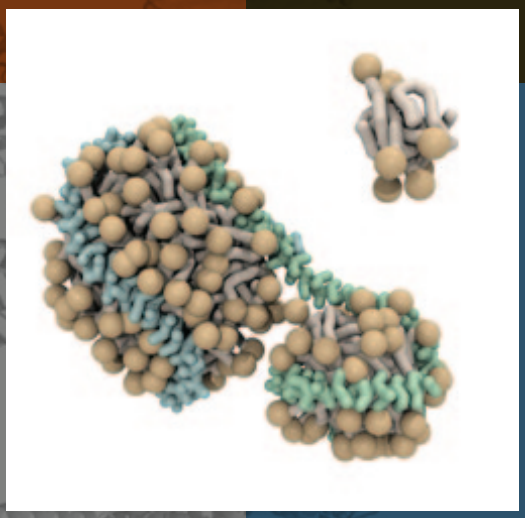


Gas Molecules Commute into Cell
March 2007

Every morning, many people drive to work, while others may bike or take the bus or metro. Similarly, various biomolecules in the human body reach their destinations in diverse manners. For example, to cross the cellular membrane, small hydrophobic gas molecules diffuse through the lipid bilayer, while water molecules pass through specialized channel proteins named aquaporins (AQPs). Interestingly, just like one may get to work both by bus and by car, it has been found recently that some gas molecules may have more than one way to cross the membrane—besides diffusion through lipids, oxygen and carbon dioxide may also pass through AQPs. However, the pathways these gas molecules take remained elusive. Using molecular dynamics performed with NAMD, researchers have investigated the gas permeability of AQP1 in a recent study with two complementary methods (explicit gas diffusion simulation and implicit ligand sampling). The simulation results suggest that while the four monomeric pores of AQP1 function as water channels, the central pore of AQP1 may serve as a pathway for gas molecules to cross the membrane.

Yi Wang, Jordi Cohen, Walter F. Boron, Klaus Schulten, and Emad Tajkhorshid. **Exploring gas permeability of cellular membranes and membrane channels with molecular dynamics.** *Journal of Structural Biology*, 157:534-544, 2007.

Jordi Cohen, Anton Arkhipov, Rosemary Braun, and Klaus Schulten. **Imaging the migration pathways for O2, CO, NO, and Xe inside myoglobin.** *Biophysical Journal*, 91:1844-1857, 2006. (PMC: 1544290)

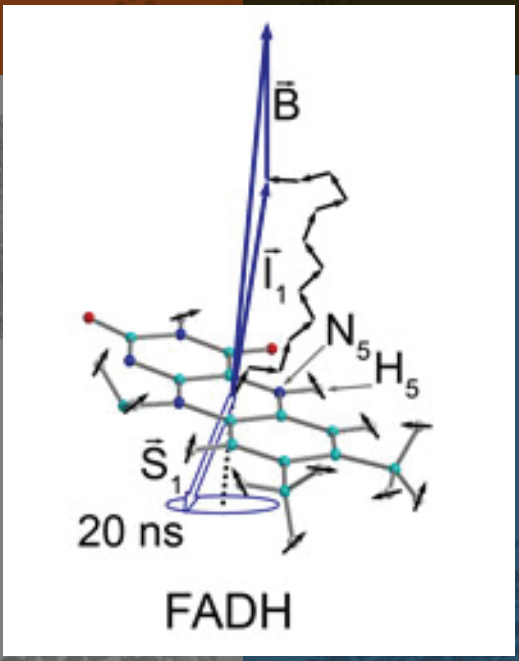


Mopping Up Lipids in the Blood
March 2007

High-density lipoproteins (HDLs), otherwise known as the "good cholesterol," are the body's way of naturally removing cholesterol in the blood stream. Since lipid and cholesterol molecules are not soluble in blood, lipoproteins are needed to collect and transport them. The proteins wrap themselves around the hydrophobic portions of lipids and cholesterol, effectively shielding them from the aqueous environment and allowing them to be transported through the bloodstream to the liver for degradation. HDLs exhibit a variety of shapes and sizes and presently cannot be imaged through experimental observations. Computational methods, however, can provide detailed images of HDL particles, even showing how these particles form in the body. As recently reported, so-called coarse-grained molecular dynamics simulations using NAMD discovered how lipid molecules are corralled by lipoproteins to form disc-like high-density lipoprotein particles. The simulations show in remarkable detail the aggregation of proteins and lipids, starting from a random arrangement of lipids that are mopped up by two lipoproteins, eventually forcing the lipids into a disc shape surrounded on its circumference by belt-like lipoproteins.

Amy Y. Shih, Peter L. Freddolino, Anton Arkhipov, and Klaus Schulten. **Assembly of lipoprotein particles revealed by coarse-grained molecular dynamics simulations.** *Journal of Structural Biology*, 157:579-592, 2007.

Amy Y. Shih, Anton Arkhipov, Peter L. Freddolino, Stephen G. Sligar, and Klaus Schulten. **Assembly of lipids and proteins into lipoprotein particles.** *Journal of Physical Chemistry B*, 111:11095-11104, 2007.

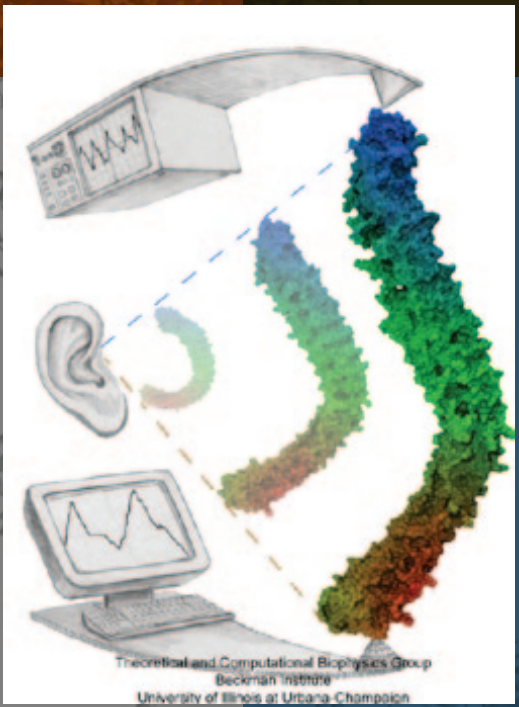


Animal Magnetic Sense Protein Shared by Plant

April 2007

The five human senses are based on amazingly sensitive molecular processes: smell and taste are based on molecular recognition, hearing and touch on molecular mechanics, and vision on molecular electronic excitation. Some animals have additional sensory capabilities. For example, some possess a magnetic sense used for orientation by means of the geomagnetic field. The magnetic sense has long been poorly understood since the underlying molecular process could not be identified, but recently some progress has been made. Surprisingly, animal vision has been implicated and evidence has been accumulated that animals can see the geomagnetic field. A long-hidden receptor in the eye, a protein aptly called cryptochrome, is likely involved. Unfortunately, cryptochrome exists only in minute amounts in animal eyes, i.e., those of migratory birds, so that only behavioral measurements on animals can be taken, but not physical measurements directly on cryptochromes. Fortunately, cryptochromes exist also in plants, where they control hypocotyl growth inhibition in seedlings. Experimentalists have observed that cryptochrome-dependent responses in Arabidopsis thaliana seedlings are magnetic-field-dependent. Researchers have now also computationally demonstrated that light activation of plant cryptochrome is magnetic field dependent. A recent report showed that light excitation leads to cascading electron transfer in which electron spins are influenced by weak magnetic fields; the spin dynamics was found to influence the activation of cryptochrome. Arabidopsis thaliana cryptochrome can be produced in quantities large enough for physical measurements so that the door is now wide open for cracking the secret behind the long-mysterious magnetic sense of animals.

Ilia A. Solov'yov, Danielle E. Chandler, and Klaus Schulten. **Magnetic field effects in Arabidopsis thaliana cryptochrome-1.** *Biophysical Journal*, 92:2711-2726, 2007. (PMC: 1831705)

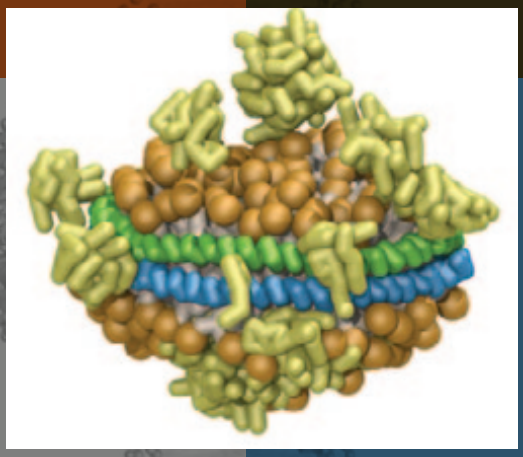


Computational Force Microscope

May 2007

Mechanical forces are everywhere in human life. Strong forces power machines and cars, our body's forces let us labor and move, soft forces are sensed through touch, and even softer ones through hearing. Forces are also ubiquitous in the living cell, driving its molecular machines and motors as well as signaling ongoing action in its surroundings. Man-made, force-bearing machines rely on extremely strong materials not found in the cell. How can the cell bear substantial forces? Also, how do cells sense extremely weak forces as in hearing, surpassing most microphones? Single molecule measurements, reviewed in a recent issue of Science, begin to answer these questions, offering information on biomolecules' mechanical responses and action. However, the information offered by these measurements is not enough to relate the biomolecular function to the biomolecular architecture. Computational modeling comes to the rescue. It can simulate the measurements and, in doing so, can reveal the physical mechanisms underlying cellular mechanics at the atomic level. In as far as observed data are available, the simulations show impressive agreement with actual measurements. While initially only following experiments or, at best, guiding experiments, modeling has advanced now further and through simulated measurements discovered on its own entirely novel mechanical properties that were later verified by experimental measurements.

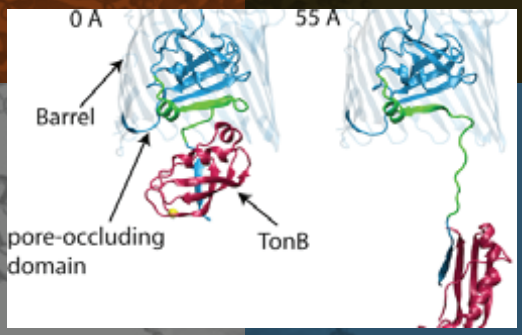
Marcos Sotomayor and Klaus Schulten. **Single-molecule experiments in vitro and in silico.** *Science*, 316:1144-1148, 2007.



Molecular Sushi Roll
June 2007

We all know sushi rolls, but just to be sure here is an easy definition: a wrapper encircles rice which holds a precious bit of fish. To make a sushi roll is an art and the same holds true for molecular sushi that is made of two lipoproteins as wrapper, lipids as rice, and membrane proteins as filling. Sushi rolls are for eating. Molecular sushi roles are for holding membrane proteins in place for physical analysis; they actually come only in sliced form, one disc at a time. Due to their size, the discs are called nanodiscs. Since membrane proteins are notoriously difficult to study experimentally due to their need to be in a "native" membrane environment, nanodiscs are a great tool, furnishing a membrane environment that has been used to embed a variety of membrane proteins for biochemical assay, including cytochrome P450s, rhodopsin, bacterial chemoreceptors, blood clotting factors, and translocation proteins. Unfortunately, it is difficult to make either real or molecular sushi rolls (nanodiscs). In either case one needs to lay down the ingredients first. In the case of nanodiscs, one starts with the raw ingredients, which are solubilized by the detergent cholate. Removing the detergent allows the nanodiscs to self-assemble. However, the assembly process is difficult to quantify experimentally, thus researchers rather studied the disassembly process, i.e., how detergent disassembles preformed nanodiscs. One can watch a sushi chef make rolls, but watching the disassembly and assembly of nanodiscs is harder due to the small size. Fortunately, a computer can image the process. In a recent publication, nanodisc disassembly through the addition of increasing concentrations of cholate was monitored through computer simulations using NAMD and verified through experimental small-angle X-ray scattering. The study showed how cholate molecules insert themselves at the interface between the lipids and lipoproteins towards complete disassembly. The simulations employed a new method called residue-based coarse-graining.

Amy Y. Shih, Peter L. Freddolino, Stephen G. Sligar, and Klaus Schulten. **Disassembly of nanodiscs with cholate.** *Nano Letters*, 7:1692-1696, 2007.



Unraveling Outer Membrane Transport
July 2007

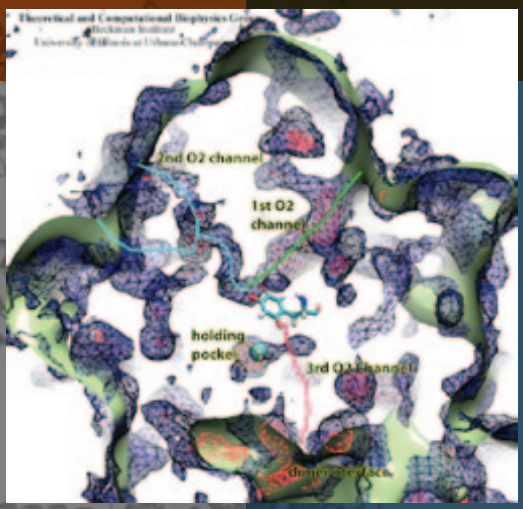
Like all organisms, bacteria have to eat. However, bringing nutrients in from the outside world is not an easy task for many bacteria that are surrounded by an extra membrane. The second membrane, called the outer membrane, offers additional protection but at a cost: no energy can be generated or stored at the outer fringes of the cell. So, to import large, rare nutrients that cannot cross by diffusion alone, bacteria have evolved a unique transport system that couples the inner, energy-generating membrane to the passive outer membrane, known as the TonB-dependent transport system. TonB, an inner membrane-associated protein, transfers energy across the periplasm to a variety of outer-membrane transporters. These transporters have a large, beta-barrel structure, which is blocked in the middle by a plug called the 'luminal domain.' How TonB transfers energy to the transporter and causes the luminal domain to come out is still a mystery, however. Now with the help of computer simulations using NAMD and a recent crystal structure of TonB coupled to BtuB, the transporter responsible for vitamin B12 transport, researchers have shown that TonB can mechanically activate the transporter by pulling on the luminal domain, causing it to leave the barrel. Using steered molecular dynamics, it was found that TonB stayed firmly attached to the luminal domain of BtuB, even though the contact between the two is limited to just a handful of residues. Furthermore, this pulling initiates unfolding of the luminal domain, opening a transport pathway for the substrate. These results, the subject of a recent publication, demonstrate how a mechanical coupling can bridge the gap between the two membranes, thus enabling outer membrane transport.

James Gumbart, Michael C. Wiener, and Emad Tajkhorshid. **Mechanics of force propagation in TonB-dependent outer membrane transport.** *Biophysical Journal*, 93:496-504, 2007. (PMC: 1896255)

Passport for the Cell's Nucleus
August 2007

The cells of higher organisms store their genetic material, the genome, in the so-called nucleus, where they organize transcription of DNA into messenger-RNA, the blueprint for proteins. The messenger-RNA leaves the cell to be decoded by ribosomes that synthesize the respective protein. Transcription factors, also proteins, control in the nucleus which parts of the cells' genomes are transcribed. Naturally, the access to the nucleus and exit from it must be restricted to transcription factors and related biomolecules. This is achieved by the nuclear pores – wide channels lined with brushes of polymers. The polymers are disordered proteins and prevent passage for most cellular proteins, except for so-called transport factors, which bus transcription factors, messenger-RNA, and certain larger biomolecule into and out of the nucleus. How transport factors are permitted to pass the nuclear pores, despite many studies, has been largely unknown. Molecular dynamics simulations using NAMD, based on relevant crystallographic structures, provided a comprehensive picture on the passage mechanism. The simulations, analyzed with VMD, revealed that transport factors are dotted rather regularly on their surface with spots that bind to the brushes of nuclear pore proteins. While any protein may accidentally exhibit such a binding spot or two, only transport factors offer a regular pattern of such spots on their surface that apparently is their passport permitting them movement into and out of the nucleus—helping them to glide through the pores' protein brushes.

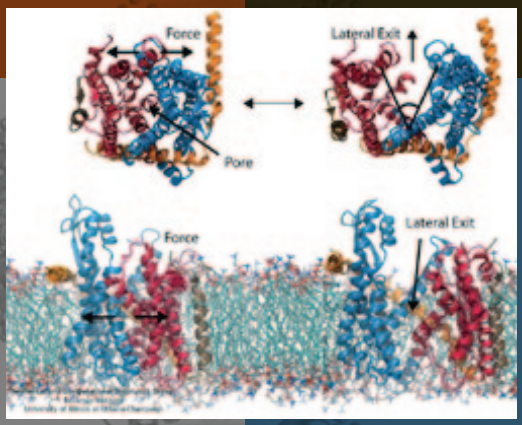
Timothy A. Isgro and Klaus Schulten. **Cse1p binding dynamics reveal a novel binding pattern for FG-repeat nucleoporins on transport receptors.** *Structure*, 15:977-991, 2007.



Bringing Oxygen into an Enzyme
August 2007

Because oxygen gas is very reactive, it is frequently employed by the cell as a reagent by proteins called enzymes, which build the organic compounds that the cell needs. One such enzyme belongs to the copper amine oxidase family. These proteins transform amine-containing compounds into molecules needed by the cell, by reacting the compounds with oxygen. Researchers have long been interested in finding out how the various reagents reach the buried copper active site before the final oxidation reaction can occur. While copper amine oxidases exhibit an obvious channel for capturing the amine compounds to be modified, it had been unclear until now how oxygen molecules make their way through the enzyme. With the help of computer simulations using NAMD, researchers have identified the routes taken by oxygen inside various copper amine oxidases from different species. In order to accomplish this, they analyzed simulations of the motions of four copper amine oxidases, using the VMD analysis and visualization software, which can predict the probability of finding oxygen molecules anywhere inside the simulated proteins. This analysis found numerous oxygen conduction routes inside each copper amine oxidase. Oxygen can enter the protein through many routes, as it would in a sponge.

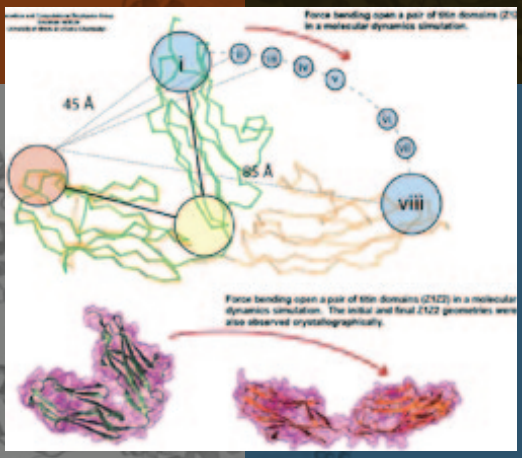
Bryan J. Johnson, Jordi Cohen, Richard W. Welford, Arwen R. Pearson, Klaus Schulten, Judith P. Klinman, and Carrie M. Wilmot. **Exploring molecular oxygen pathways in Hanseluna Polymorpha copper-containing amine oxidase.** *Journal of Biological Chemistry*, 282:17767-17776, 2007.



Protein Passage into the Membrane
September 2007

Everyone knows oil and water don't mix. Proteins observe this rule, too – some choosing to stay in the watery cytoplasm and others choosing the oily membrane. But getting into the membrane is not easy, and most newly formed proteins require another protein, the membrane-bound translocon, to help them insert into the membrane. The translocon, surprisingly also serves as a conduit for proteins across the membrane, thus carrying out a unique dual function. The structure of the translocon showed evidence of a likely "lateral gate," i.e., an exit from the channel into the membrane. How the channel opened to the membrane and how it closed afterwards were not clear from the structure alone. Now, molecular dynamics simulations performed with NAMD, discussed in a recent publication, have permitted researchers to understand how the channel opens laterally, how it closes, and how the oily lipids are prevented from invading the water-filled pore. Furthermore, the novel simulation technique, residue-based coarse graining, allowed the researchers to simulate the lipid-channel interactions for up to one microsecond, clearly illustrating that the lipids do not want to mix with the channel interior.

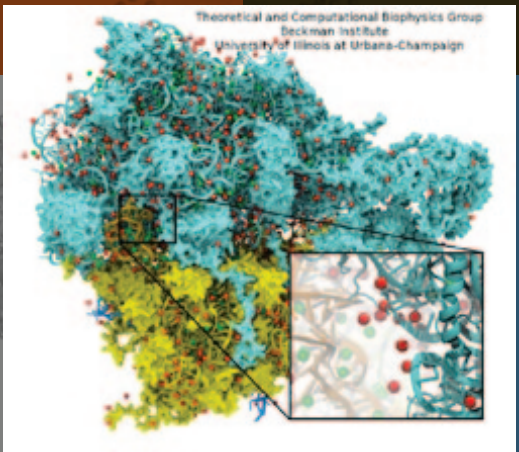
James Gumbart and Klaus Schulten. **Structural determinants of lateral gate opening in the protein translocon.** *Biochemistry*, 46:11147-11157, 2007.



Muscle Protein Plays Accordion
September 2007

Muscle fibers, in contracting and extending, generate tremendous force that needs to be buffered to protect muscle from damage. This role falls to the protein titin—with about 27,000 amino acids the longest protein in human cells. Titin functions as a molecular rubber band, but unlike uniform rubber bands, titin is made from more than 300 different protein domains strung into a chain. While experiments have found that the individual domains of titin feature remarkable resilience against mechanical stretching, little is known about the elasticity of the overall titin chain. Crystallographers teamed up with computational biologists to investigate this elasticity, focusing on two adjacent titin domains. Molecular dynamics simulations using NAMD suggest, as reported recently, that the overall elasticity of the titin chain stems in part from a zigzag – an accordion-like, motion. As titin is contracted and extended, energy is stored and released in the angular tilt of adjacent domains.

Eric H. Lee, Jen Hsin, Olga Mayans, and Klaus Schulten. **Secondary and tertiary structure elasticity of titin Z1Z2 and a titin chain model.** *Biophysical Journal*, 93:1719-1735, 2007. (PMC: 1948054)

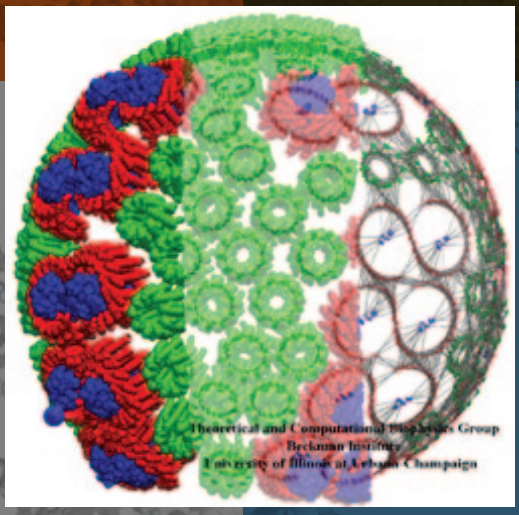


Graphics Processors Speed Up Simulations

October 2007

Modern computers include a massively parallel graphics processing unit (GPU) designed to perform geometry and lighting calculations at blistering speeds. State-of-the-art GPUs can perform 0.5 teraFLOPS with their hundred cores. The tremendous computational power of GPUs was untapped by scientific computations because it could only be accessed with difficulty until now. As reported in the Journal of Computational Chemistry, recent advances allowing GPUs to be used for general purpose computing have boosted the performance of a number of molecular modeling applications, including NAMD simulations and VMD electrostatic potential calculations. The accelerated versions of these applications run 5 to 100 times faster than on the best CPU-based hardware, allowing a single desktop computer equipped with a GPU to provide processing power equivalent to an entire, large computing cluster.

John E. Stone, James C. Phillips, Peter L. Freddolino, David J. Hardy, Leonardo G. Trabuco, and Klaus Schulten. **Accelerating molecular modeling applications with graphics processors.** *Journal of Computational Chemistry*, 28:2618-2640, 2007.

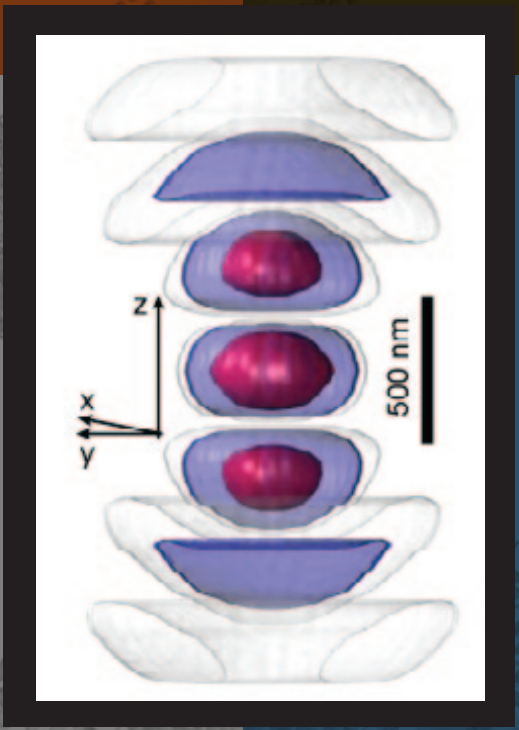


Life's Solar Battery

October 2007

Life on Earth learned, through billions of years of evolution, to make do with renewable energy. Indeed, evolution discovered early on that sunlight is an excellent renewable energy source. To harvest sunlight, many different types of biological solar batteries are used. One of the simplest ones is found in so-called purple bacteria. Their cells contain about 100 bulbous invaginations of the cell membrane, pointing into the cell. The spherical bulbs contain six different kinds of proteins adding up to a total of about 250 proteins. The primary function of the bulbs is to absorb sunlight and electrically charge their spherical membrane; the charge then being used to synthesize fuel for the bacterium's energy needs. The structures of the individual proteins were determined earlier through X-ray crystallography. In a recent paper, a team of experimental and computational biologists reported the atomic level architecture of the entire bulb. The team used atomic force microscopy on flattened bulbs to measure the height profile of the proteins, reconstructing from the data the bulbous protein assembly. The result is a detailed picture of the bulb, showing more than 4,000 chlorophyll molecules being held in the bulb, absorbing sunlight, and transferring its energy to reaction centers that convert the sunlight into an electrical membrane voltage. Indeed, the team could calculate, using quantum and thermal physics, from the architecture the amazing efficiency of the bacterial solar battery.

Melih K. Sener, John D. Olsen, C. Neil Hunter, and Klaus Schulten. **Atomic level structural and functional model of a bacterial photosynthetic membrane vesicle.** *Proceedings of the National Academy of Sciences*, USA, 104:15723-15728, 2007. (PMC: 2000399)

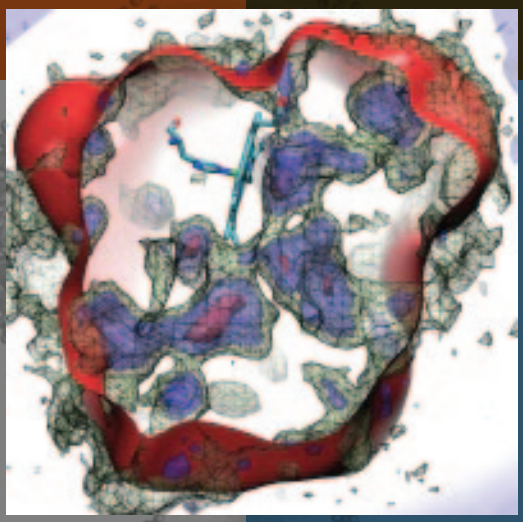


Microscopy and Computing Sharpen the Focus

November 2007

Since Leeuwenhoek introduced it to biology 300 years ago, the light microscope has brought about multiple discoveries, many achieved through improving over time the instrument's resolution. However, in 1873 Abbe recognized that the resolution has a limit, given by the wavelength of light. This limit was considered absolute, until in 1992 Hell suggested a microscope that breaks the limit postulated by Abbe. This is achieved by sending coherent light through two opposing objectives, the resulting interference pattern squeezing the radiation into spots significantly smaller than the light's wavelength. This improvement has already permitted biologists to see a new level of detail in living cells. However, the pattern of light in the Hell microscope is rather complex and certain quantitative measurements require a computational analysis to take advantage of the full benefits of the instrument. Such analysis has been accomplished and validated in a recent study, the validation involving measurements on known systems. The developed numerical algorithms harness the computational power of modern processors. In particular, they resort to exploiting the computational power of graphics processors. The new methodology combined with the new microscopes opens the avenue to unprecedented measurements in living cells.

Anton Arkhipov, Jana Hüve, Martin Kahms, Reiner Peters, and Klaus Schulten. **Continuous fluorescence microphotolysis and correlation spectroscopy using 4Pi microscopy.** *Biophysical Journal*, 93:4006-4017, 2007. (PMC: 2084225)

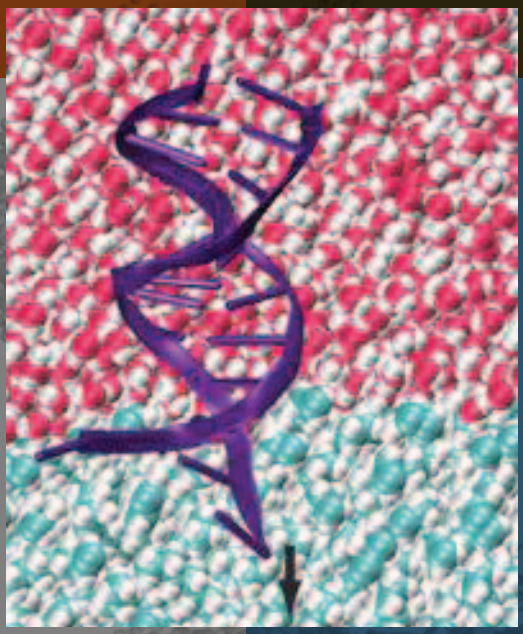


Spelunking Inside Myoglobin
November 2007

Globins are oxygen-storing proteins, vital to life. In our blood, hemoglobins carry oxygen from our lungs to every cell in our body. In our muscles, myoglobins keep reserves of oxygen to make sure it is available when needed. In some plants, leghemoglobins capture oxygen molecules that would otherwise be harmful to the production of ammonium necessary for the plant's survival. All these globins possess an iron-containig "heme," that grabs on to oxygen for a short time, and share the same protein architecture, despite large variations in their sequences. Since the heme group is buried inside a globin, scientists wondered how oxygen makes its way inside the protein to reach it. Exploring the motion and energies of globins using the program NAMD, researchers learned to gather data that permitted them to visualize, utilizing the VMD software, all the pathways taken by oxygen migrating inside whale myoglobin. However, when the researchers turned their attention to the rest of the globin family to compute their oxygen pathways, they found – on their computational spelunking trip – something surprising. Given the conserved architecture of all globins, they expected to see similar oxygen pathways throughout the globin family—but they saw the opposite! Aside from a conserved pocket right at the heme binding site, the distribution of oxygen pathways showed very little similarity from one globin to the next. This result was described in a recent report, which shows that oxygen-pathways are not conserved by evolution, and that their location is not determined by a protein's overall architecture, but rather by its local amino acids. The researchers also learned which amino acids are found more often than others lining oxygen pathways, recognizing that bulky side groups are not hindering, but favoring oxygen passage.

Jordi Cohen and Klaus Schulten. **O2 migration pathways are not conserved across proteins of a similar fold.** *Biophysical Journal*, 93:3591-3600, 2007. (PMC: 2072066)

Jordi Cohen, Kenneth W. Olsen, and Klaus Schulten. **Finding gas migration pathways in proteins using implicit ligand sampling**. In Robert K. Poole, editor, *Globins and other NO-reactive Proteins in Microbes, Plants and Invertebrates*, volume 437 of *Methods in Enzymology*, pp. 437-455. Elsevier, 2008.

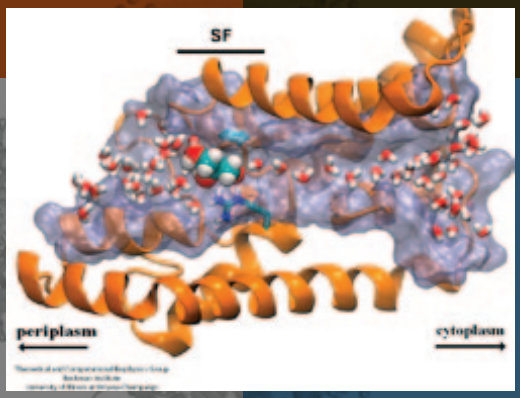


Oil and Water Split DNA

December 2007

Ever since the 1953 discovery of DNA's double helix structure, researchers wondered how the double strands are separated so that genetic information stored inside the helix can be delivered from generation to generation. A class of proteins known to achieve this separation are DNA helicases, molecular motors that operate at a fork where a double-stranded DNA separates into two single-stranded DNAs. Helicases translocate along one of the single-stranded DNAs, pushing forcefully into the fork to further split apart the double-stranded DNA. Helicases seem to work, though, both through force and through persuasion, exposing to the double-stranded DNA a surface that is apparently conducive for strand separation. This property suggests itself on account of the fact that many of the amino acid side groups at the relevant surface are highly conserved among species or evolved from species to species through pair-wise mutation. But what chemical strategy evolution had in mind in molding the surface was not realized. Recently, however, researchers seeking artificial means of splitting apart double-stranded DNA might have found a key clue. They pulled double-stranded DNA at one of its single strands by means of an atomic force microscope from DNA's native saltwater environment into a so-called non-polar solvent. The force-distance curve measured suggested that the DNA actually split apart, but there existed no direct experimental means of viewing the splitting. The researchers employed molecular dynamics simulations, using NAMD, that indeed clearly revealed the splitting of the DNA strands at a water-oil (octane) interface. Their study suggests how helicases achieve the splitting of DNA strands, namely by altering the local environment of DNA, from water-like (hydrophilic) to oil-like (hydrophobic).

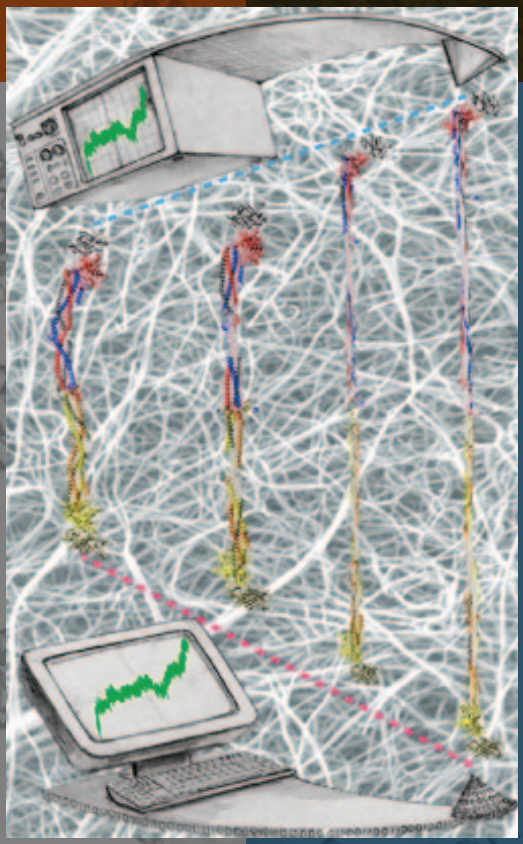
Shuxun Cui, Jin Yu, Ferdinand Kühner, Klaus Schulten, and Hermann E. Gaub. **Double stranded DNA dissociates into single strands when dragged into a poor solvent.** *Journal of the American Chemical Society,* 129:14710-14716, 2007.



Molecular Obstacle Course
January 2008

Biological cells protect their interior through their cellular membranes, yet rely on import of nutrients. They have evolved for this import of nutrients fast conduction channels that include reliable checkpoints distinguishing desirable and undesirable compounds. A checkpoint puts up a veritable obstacle course that only the right compounds can pass quickly. Understanding the channel design is difficult due to lack of detailed experimental data on nutrient dynamics. Presently, the most detailed information comes from viewing channel dynamics computationally, starting from static crystallographic structures. Glycerols, small nutrient molecules needed by some bacteria, pass through checkpoints realized through the membrane protein aquaporin. Aquaporin furnishes four parallel channels that were monitored computationally using NAMD and a novel algorithm that explores the channel energetics quickly enough to be methodologicaly feasible on today's computers. The results show how the physical characteristics of glycerol—for example, the molecule's ability to form so-called hydrogen bonds, its electrical dipole moments, its diffusive mobility, and intrinsic flexibility—are probed along the channel, discriminating glycerol from other molecules.

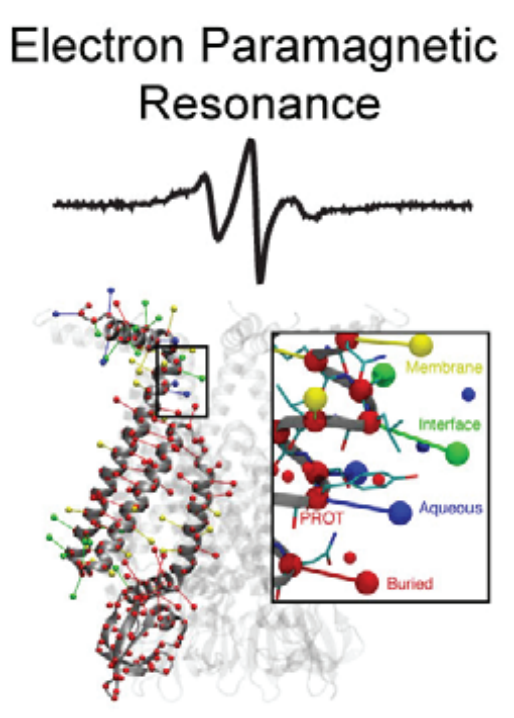
Jerome Henin, Emad Tajkhorshid, Klaus Schulten, and Christophe Chipot. **Diffusion of glycerol through Escherichia coli aquaglyceroporin GlpF.** *Biophysical Journal*, 94:832-839, 2008. (PMC: 2186255)



Closer Look at Blood Clots
February 2008

Bleeding through physical injury is stopped in animals through the formation of blood clots. Such clots, actually arising often in blood vessels without injury, can rupture due to blood's sheer force and obstruct smaller upstream vessels, leading to life-threatening stroke, pulmonary embolism, and heart attack. Thus, a blood clot must be both mechanically stable to stop a bleeding yet elastic enough to avoid rupture. Fibrin, the main component of a blood clot, possesses the stated mechanical properties in healthy individuals, but in pathological circumstances needs to be managed through medication. Unfortunately, preventive treatment of blood clots is still a black art since the molecular basis of fibrin elasticity is unknown. Clinicians at the Mayo Clinic teamed up with computational biologists at the University of Illinois to investigate this elasticity, focusing on the protein fibrinogen, the building block of fibrin. The clinical researchers stretched individual fibrinogen molecules, measuring the force needed to extend the molecules. They found a characteristic force-extension relationship and its dependence on blood pH and calcium concentration, but they could not interpret the finding chemically, a prerequisite for improving blood clot chemical management. They joined forces with computational biologists who could reproduce the measured force-extension relationship in steered molecular dynamics using NAMD. The simulations starting from known crystallographic structures of fibrinogen offered a full (atomic resolution) chemical picture of fibrinogen elasticity. The insights by clinical and computational researchers have opened new avenues for blood clot treatment. For example, it was found that pH and calcium concentrations alter the stiffness of blood clots, thereby opening pharmacological avenues for controlling the incidence of pathological blood clots.

Bernard Lim, Eric H. Lee, Marcos Sotomayor, and Klaus Schulten. **Molecular basis of fibrin clot elasticity.** *Structure*, 16:449-459, 2008.

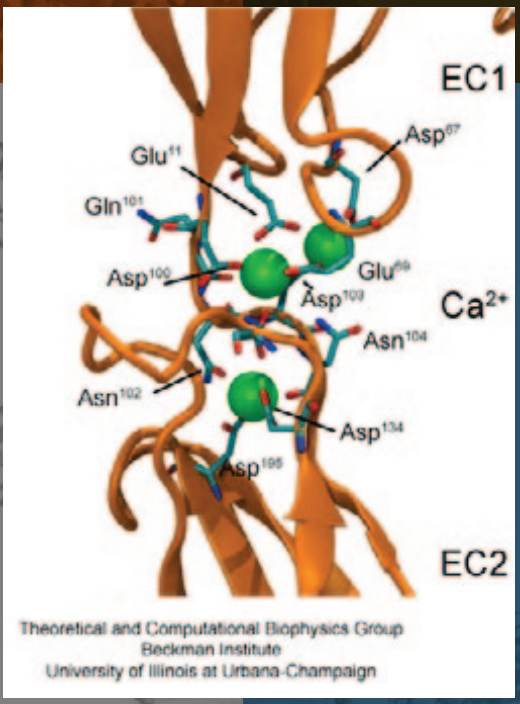


Observation and Simulation Depict Cell's Safety Valve
March 2008

The environment of cells can undergo drastic changes – for example, from dry to wet – in which case cells shrivel or swell. However, they are protected from bursting by a system of safety valves in their cellular membranes that open and release cellular content. Some of the valves open already at low membrane tension, but only a little, and others open only at higher tension, but wide and without filtering outflow. The mechanosensitive channel of small conductance, MscS, is a low pressure safety valve in bacterial cells. MscS is able to rescue cells about to burst by releasing small solutes through a large and transient opening in the cell membrane, thereby relieving internal pressure. The only way to learn how MscS performs this vital task is by determining its atomic-level structure under native conditions. However, the only structure available for MscS was obtained for the purified and crystallized protein; inspection of the structure left doubt that it shows a functional protein, i.e., a closed safety valve. A team of experimentalists and modelers has now examined the structure of MscS in its natural membrane environment. In their approach, simulations incorporate information from so-called paramagnetic resonance measurements experiments. This finding is yet another case where the combination of modeling and observation offers entirely new close-up views of living cells.

Valeria Vasquez, Marcos Sotomayor, D. Marien Cortes, Benoit Roux, Klaus Schulten, and Eduardo Perozo. *Three dimensional architecture of membrane-embedded MscS in the closed conformation. Journal of Molecular Biology*, 378:55-70, 2008. (PMC: 2703500)

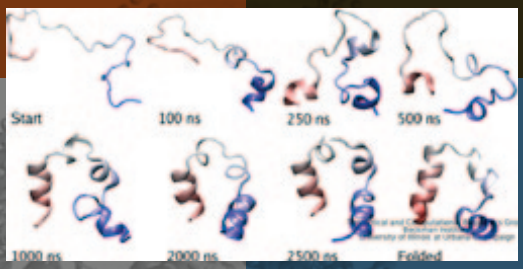
Valeria Vasquez, Marcos Sotomayor, Julio Cordero-Morales, Klaus Schulten, and Eduardo Perozo. **A structural mechanism for MscS gating in lipid bilayers**. *Science*, 321:1210-1214, 2008. (PMC: 2897165)



Cells Get Sticky with Calcium
April 2008

Adhesion between human cells organizes our body into its organs and parts. The adhesion comes about through an intricate system of molecules that perform their tasks in a highly selective manner such that the body's different types of cells will find the right cells and stick to them. This selectivity leads to tissue differentiation and the organization of organs as complicated as the brain. Cadherin proteins form a particular family of such adhesion molecules. Interestingly, they glue cells together only in the presence of calcium. How cadherins selectively bind to each other and the role of calcium was not well understood, but now molecular dynamics simulations have offered magnificent insight into calcium's role. The simulations took advantage of parallel supercomputers and NAMD's ability to harness their power. The simulations revealed that in the absence of calcium cadherins stick out of cell surfaces like ends of loose rope; in the presence of calcium cadherin molecules turn into stiff hooks that link cells together. The calcium-induced links can withstand the strong mechanical forces that arise between cells much larger than cadherin.

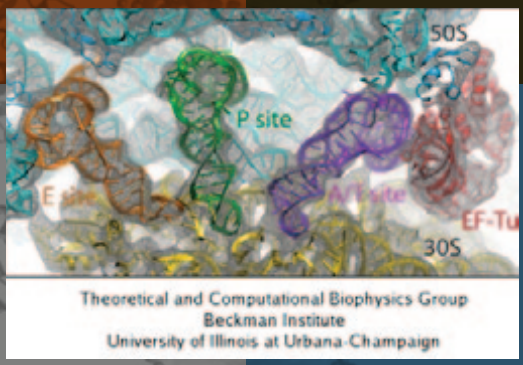
Marcos Sotomayor and Klaus Schulten. **The allosteric role of the Ca++ switch in adhesion and elasticity of C-cadherin.** *Biophysical Journal*, 94:4621-4633, 2008. (PMC: 2397358)



Longest Ever Protein Folding Movie
May 2008

Proteins carry out most functions in living cells, from import of food substances to chemical synthesis to motion to signaling. Proteins are chains of amino acids like GLSDGEWQLVLNVWGKVEAD... where each letter stands for one of twenty amino acids that are the building blocks of proteins—G for glycine or L for leucine, for example. In general, sequences of proteins native to cells fold into unique three-dimensional structures capable of executing the proteins' specific function. Living cells store the amino acid sequences of their many different proteins in the form of DNA sequences, safeguarding them in the cells' genome. On demand, the DNA sequences are translated according to the famous genetic code into amino acid sequences. The amino acid chains of newly synthesized proteins have to fold into the proper structure, an essential process scrutinized by biologists for decades. The folding process often takes milliseconds or longer, but recently proteins were identified that fold within microseconds. This was still a time too long to be simulated through molecular dynamics, which could reveal folding in atomic-level detail. However, improvements of NAMD have now made simulations of 10 microseconds possible, allowing experimental and computational biologists to engage in a joint study of seeing a protein segment, known as the WW domain, fold over this timescale. The great increase in simulation time revealed intricate details of WW domain folding, but also points to a need to further improve the computational model (force field) used to simulate proteins.

Peter L. Freddolino, Feng Liu, Martin Gruebele, and Klaus Schulten. **Ten-microsecond MD simulation of a fast-folding WW domain.** *Biophysical Journal*, 94:L75-L77, 2008. (PMC: 2367204)



Seeing Molecular Machines in Action
June 2008

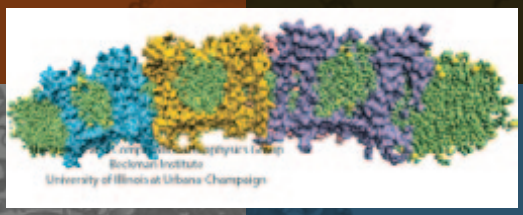
Living cells are brimming with activity, much of it due to their manifold molecular machines pulling cargo, importing and exporting molecules, digesting food molecules and transforming their energy, reading and copying genetic messages, or synthesizing proteins from these messages (the latter done by the ribosome). Static structures of the molecular machines have been resolved through crystallography—machines pressed into the confinement of crystals and frozen into inactivity reveal their atomic-level geometry through this methodology. However, many machines – for example the ribosome – undergo large conformational transitions during their cyclic action, but active motions are hard to view in atomic detail. A way out is offered by electron microscopy, which freeze-shocks machines into states characteristic for action cycle intermediates. Unfortunately, the method does not yield atomic resolution images, leaving the chemical detail needed for a comprehension of the mechanisms blurred. Computational methods can be used to bridge the resolution gap—atomic level structures of non-functional states of the machines captured in crystals are deformed, accounting for biomolecules' natural flexibility, to match electron microscopy images. Until recently, this method worked well only for very small machines. A team of electron microscopists and computational biologists using NAMD extended the method to common size machines and achieved its successful application to the ribosome, providing astonishing detail about ribosome dynamics and function.

Leonardo G. Trabuco, Elizabeth Villa, Kakoli Mitra, Joachim Frank, and Klaus Schulten. **Flexible fitting of atomic structures into electron microscopy maps using molecular dynamics.** *Structure*, 16:673-683, 2008. (PMC: 2430731)

Molecular Flow Sensor Triggers Wound Healing
July 2008

Ouch! You cut your finger with a knife. Blood immediately starts flowing from the wound, and in a panic you search through your drawer for a bandage. However, well before you can find the bandage, and even before the "ouch" came out – just about the time you sensed the pain – your body's self-healing mechanism was turned on. A multistep signaling cascade involving a dozen different proteins in the blood began calling for platelet cells to clog around the wound and form a plug to stop the bleeding. How does our body sense a wound so fast? One possible answer is that the platelet cells carry on their surface a sensitive molecular flow sensor, a protein called GP1b, which senses erroneous blood flow caused by a cut in the blood vessel. It has been hypothesized that a small segment located on the alpha-subunit of GP1b, called the ß-switch, transforms from a random coil to a ß-hairpin in the presence of shear flow. The ß-switch, in its ß-hairpin form, is able to bind to a protein called von Willerbrand factor, which will then anchor the platelet to the damaged site. To test this hypothesis, researchers resorted to computer simulation using the program NAMD and mimicked blood flow around GP1b. Researchers have discovered that a long-suspected part of GP1b indeed changes shape under flow conditions, the likely trigger of the body's self-healing system.

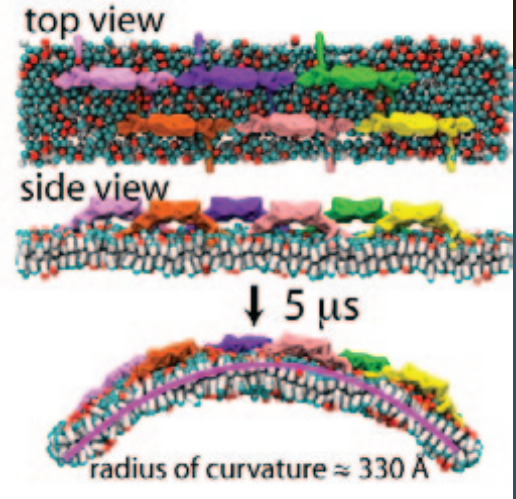
Zhongzhou Chen, Jizhong Lou, Cheng Zhu, and Klaus Schulten. **Flow induced structural transition in the ß-switch region of glycoprotein Ib.** *Biophysical Journal*, 95:1303-1313, 2008. (PMC: 2479615)



How Proteins Build Their Cellular Houses
August 2008

Chromatophores are the photosynthetic machineries of bacteria. Each chromatophore contains, embedded in a membrane, all the photosynthetic proteins needed to absorb sunlight and turn it into chemical fuel. Chromatophores come in different shapes: while some chromatophores are spherical, others are flat or tubular. It has puzzled scientists how all these different geometries arise, and a hypothesis has developed that it is the photosynthetic proteins that render the shape of the chromatophore membrane. Computational biologists using NAMD took an atomistic look at how the chromatophore proteins bend the membrane. Simulations showed that the most numerous photosynthetic proteins dome the membrane, building arched membrane patches that can then be assembled into a spherical chromatophore. These simulations demonstrated that photosynthetic proteins construct their individual membrane environment, and when many of such proteins come together in the bacterial membrane, they can build functional cellular units with unique geometries. In other words: photosynthetic proteins first build their house in the cell and then do their work.

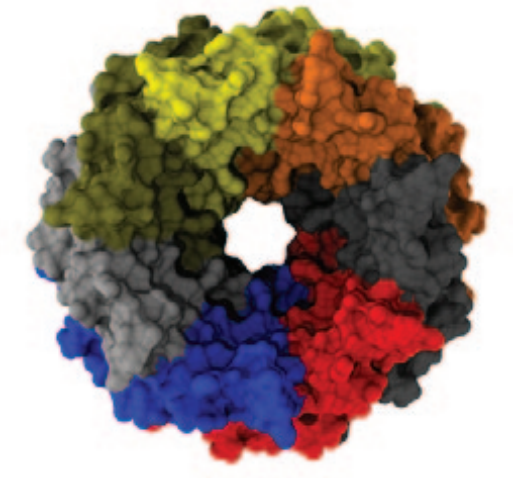
Danielle Chandler, Jen Hsin, Christopher B. Harrison, James Gumbart, and Klaus Schulten. **Intrinsic curvature properties of photosynthetic proteins in chromatophores.** *Biophysical Journal*, 95:2822-2836, 2008. (PMC: 2527265)



Proteins Sculpting Cell Interior
September 2008

Living cells organize many functions: molecular import and export, signaling, transcription of genes into proteins, movement, building, repair, and more. These functions are realized through a complex architecture of the cell interior reflected in a system of labyrinthine membranes forming manifold cellular organelles from tubes, vesicles and many other shapes. Accordingly, cells need to sculpt their membrane in never ceasing processes and have at their disposal a wide range of mechanisms. A key sculpting mechanism is furnished by proteins – so-called BAR domains – that apparently form lattice-like scaffolds adhering to membrane surfaces. Such scaffolds have been observed through electron microscopy and are now also being described through molecular dynamics simulations using NAMD. Simulations carried out at four different levels of resolution (from an atomic to a continuum level), have revealed that different arrangements of BAR domains lead to different curvatures. The simulations help to explain why BAR domains working in teams, i.e., in lattice formation, sculpt intracellular membranes into different shapes, depending on the exact arrangement. An arrangement of BAR domains that is particularly efficient in bending membranes was identified.

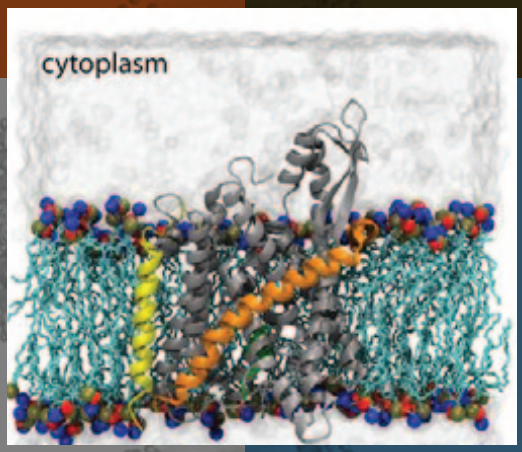
Anton Arkhipov, Ying Yin, and Klaus Schulten. **Four-scale description of membrane sculpting by BAR domains.** *Biophysical Journal*, 95:2806-2821, 2008. (PMC: 2527247)



Gatekeeper Protein
October 2008

Biological cells are surrounded by a highly versatile, yet very feeble, cellular membrane, and need to balance differences between the cell's interior and exterior that otherwise would burst the membrane. For example, the osmotic pressures inside and outside the cell need to be closely balanced. Thousands of proteins in the membrane act as gatekeepers, opening pores that can also act as safety valves, helping to reduce the interior-exterior difference in pressure rapidly. One such protein, the mechanosensitive channel of small conductance, MscS, opens in response to cellular membrane tension generated due to a drastic imbalance in osmotic pressure as it arises when a bacterial cell suddenly finds itself in fresh water, rather than a highly saline physiological medium. The MscS channel widens then to jettison molecules out of the cell and quickly reduce tension on the cellular membrane. Researchers have combined experimental data from electron paramagnetic measurements and computer modeling to reveal in atomic detail how MscS opens and closes its channel. Combining measurement and modeling, the researchers established a highly resolving computational microscope, unmatched by existing microscopes.

Valeria Vasquez, Marcos Sotomayor, Julio Cordero-Morales, Klaus Schulten, and Eduardo Perozo. **A structural mechanism for MscS gating in lipid bilayers.** *Science*, 321:1210-1214, 2008. (PMC: 2897165)



Patching a Leaky Channel
November 2008

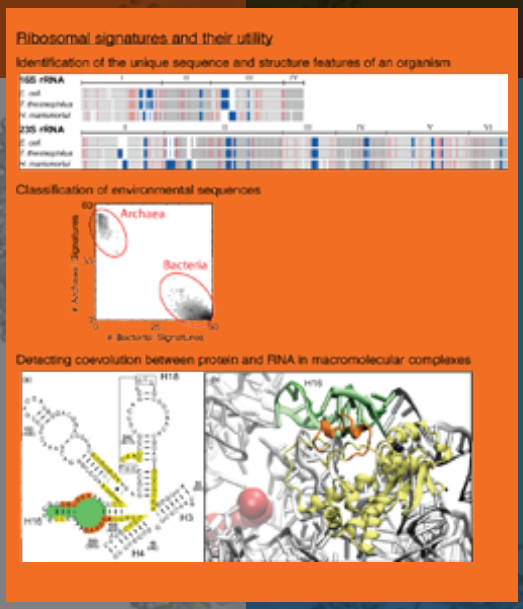
When you have a leaky roof, you need to plug the hole quickly to avoid further damage. Similarly, cells do not tolerate open holes in their enveloping membranes for long. However, cell membranes do require channels for various molecules to get across, and proteins are no exception. The protein-conducting channel SecY, a membrane-bound protein itself, is the pathway used by other proteins to cross the membrane. When it's not in use, it needs to have a water-tight seal, which is provided by two elements in the channel, a bulky plug and a constrictive pore ring. But do these two elements – plug and pore ring – function separately to provide two independent barriers, or together, providing a single barrier? Molecular dynamics simulations on the channel and two mutants in which a portion of the plug was deleted have provided the answer: both components work together to prevent leaks in the channel.

James Gumbart and Klaus Schulten. **The roles of pore ring and plug in the SecY protein-conducting channel.** *Journal of General Physiology*, 132:709-719, 2008. (PMC: 2585858)

Tapping Teenager Computer Power
December 2008

The most powerful compute engine in your laptop and home computer is what? The central processing unit, of course. Wrong—it is the graphics processing unit (GPU)! Since GPUs are specialized for graphics and games, popular uses of modern computers, their development benefitted from strong market forces. Modern GPUs reach Teraflop speed, passing entire computer clusters filling a room. Unfortunately, GPUs lie dormant when computers are employed for intensive biological computing like biomolecular simulations. GPUs are now getting a wake-up call from biomedical researchers who then enjoy many-fold speed-ups of their laptop computations, vendors already now hawking GPU-powered "desktop supercomputers." The next challenge is to bring the GPU from the laptop to computer centers, speeding up the world's fastest supercomputers. Building on previous development experience of NAMD and VMD, NAMD was made to run at an impressive speed on a GPU cluster. The advance suggests techniques, useful also for programmers of other applications to efficiently accelerate computer clusters through GPUs. The GPU-based speed-ups will permit biomolecular simulations, which were largely unfeasible so far, namely for studies of entire virus particles and cellular organelles.

James C. Phillips, John E. Stone, and Klaus Schulten. **Adapting a message-driven parallel application to GPU-accelerated clusters.** In SC '08: Proceedings of the 2008 ACM/IEEE Conference on Supercomputing, Piscataway, NJ, USA, 2008. IEEE Press.

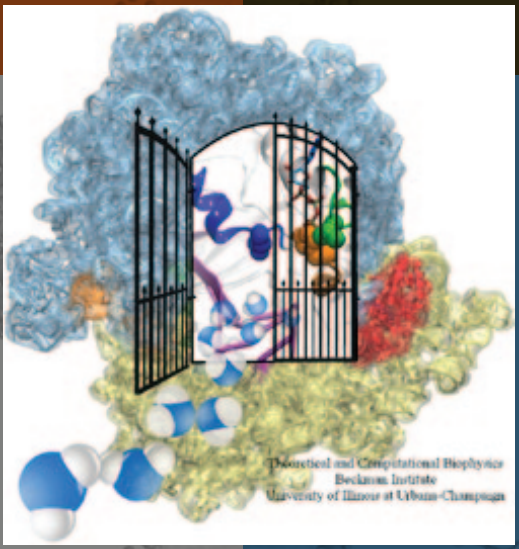


Evolution's Clock

December 2008

Life on Earth today is based on two fundamental classes of molecules, the molecules of the genetic material, RNA and DNA, and the molecules of life's machines, proteins. At the dawn of life billions of years ago, RNA apparently reigned pretty much by itself, DNA and proteins coming on board later. Eventually, early living organisms began to specialize and then split into the three domains, Bacteria, Archaea, and Eucarya. From there, life continued to evolve, branching out into the many and diverse forms that surround us today. Life itself gave scientists the clock to study this process of evolution. The clock is nothing less but the central machine of all living cells, the ribosome, that reads genetic information and translates it into proteins. The first to read this clock and establish the modern science of evolution was Carl Woese. The ribosome differs greatly from other cellular machines in that it is made mainly of RNA, only to a smaller extent of proteins, the latter being added in the course of evolution. A study using the MultiSeq tool of VMD investigated the interaction between RNA and proteins in the ribosome. The researchers examined the details of how RNA and proteins evolved together and showed how such details can lead to better understanding of the ribosome as a machine.

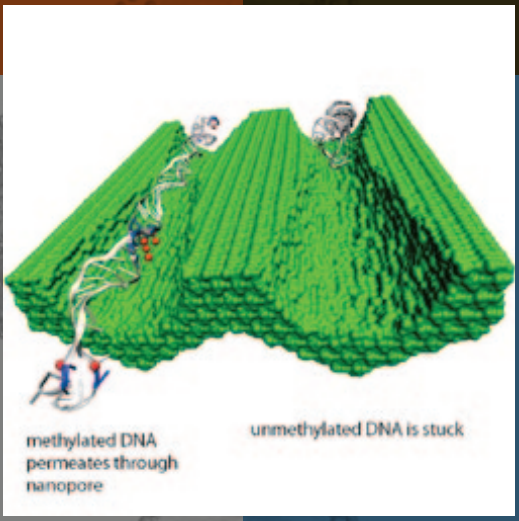
Roberts, Elijah; Sethi, Anurag; Montoya, Jonathan; Woese, Carl R.; Luthey-Schulten, Zaida. **Molecular signatures of ribosomal evolution.** *Proceedings of the National Academy of Sciences*, vol. 105, issue 37, pp. 13953-13958.



Open Sesame
January 2009

The ribosome is one of the largest molecular machines, present in hundreds to thousands of copies in every cell, in charge of synthesizing every protein in the cell faithfully from genetic instructions. For this purpose the ribosome "reads" the sequence of bases on so-called messenger RNA, three bases at a time, and—depending on the base triple, the codon—elongates a nascent protein by one of 20 possible amino acids, avoiding to an impressive degree adding a wrong amino acid. So far one knew that the reading is done by transfer RNA molecules that have a "foot" which matches the possible codons and a "head" that brings along the associated amino acid. Each amino acid has its transfer RNA, the transfer RNAs checking if the next codon is "theirs," and if it is they add the proper amino acid to the nascent protein, elongating it. But how does the ribosome make the critical decision at the decoding center, namely if the transfer RNA "foot," the so-called anticodon, matches the codon? The answer is not known, but a key detail has now been discovered through a combination of electron microscopy and molecular dynamics simulation using NAMD, VMD, and a method called flexible fitting. It was known that a third molecular system is involved, called the elongation factor Tu (EF-Tu), which generates a key signal to the ribosome and transfer RNA through a chemical reaction. This reaction involves chemically attacking a substrate of EF-Tu, the molecule guanosine-triphosphate (GTP), with water, breaking a bond, and turning GTP into guanosine-diphosphate (GDP). The puzzle was that EF-Tu is far away from the decoding center. A collaboration between experiment and simulation revealed that "correct recognition" through anticodon-codon binding opens a gate in the EF-Tu that allows water access to the GTP inducing the signaling reaction. The finding promises to now establish how the decision at the decoding center is made and how an "open sesame" order is transmitted to EF-Tu.

Elizabeth Villa, Jayati Sengupta, Leonardo G. Trabuco, Jamie LeBarron, William T. Baxter, Tanvir R. Shaikh, Robert A. Grassucci, Poul Nissen, Måns Ehrenberg, Klaus Schulten, and Joachim Frank. **Ribosome-induced changes in elongation factor Tu conformation control GTP hydrolysis.** *Proceedings of the National Academy of Sciences, USA*, 106:1063-1068, 2009. (PMC: 2613361)

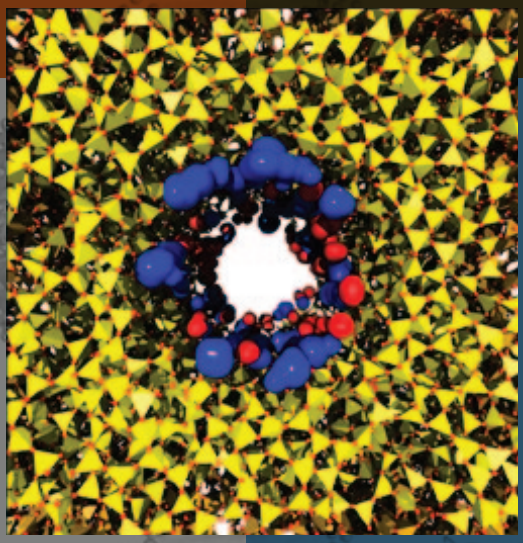


Bumpy DNA
February 2009

All cells making up the human body contain the same DNA in their nucleus, the DNA entailing about 30,000 genes and each gene containing instructions for a protein. Despite this sameness, the cells in different parts of our body are very different due to many factors, a key one being that the level of expression of genes into protein is highly regulated and differs strictly from cell to cell. One rather common regulation mechanism involves methylation of one of the four bases of DNA, cytosine. Researchers find that the long DNA in human cells show spots of methylated cytosines, the methylation being correlated with the expression level of the genes near the spots. In fact, medical researchers relate several cancers to improper methylation of DNA. Despite the common occurrence of regulation by methylation, researchers have little understanding of how methylation—which swaps out an H (hydrogen atom) for a CH_3 (methyl group) here and there (i.e. just adds small bumps on a rather bulky DNA molecule)—affects the physical properties of DNA such that expression levels are altered. It was found that there are proteins that can recognize the CH_3 groups, i.e. the bumps, on the DNA, but researchers have a hunch that methylation affects DNA properties directly – without protein markers – but do not know which properties. In a collaboration between bioengineers measuring the passing of DNA through nanopores and computational biologists simulating this process with NAMD, first hints emerge that methylation does in fact alter DNA's ability to stretch itself through a nanopore. A study found that pulling DNA electrostatically through nanopores is easier for methylated than for unmethylated DNA, as seen both in experiment and simulation. The findings promise insight into an important chapter in the field of genetic control.

Utkur M. Mirsaidov, Winston Timp, Xueqing Zou, Valentin Dimitrov, Klaus Schulten, Andrew P. Feinberg, and Greg Timp. **Nanoelectromechanics of methylated DNA in a synthetic nanopore.** *Biophysical Journal*, 96:L32-L34, 2009. (PMC: 2717226)

Aleksei Aksimentiev, Robert Brunner, Jordi Cohen, Jeffrey Comer, Eduardo Cruz-Chu, David Hardy, Aruna Rajan, Amy Shih, Grigori Sigalov, Ying Yin, and Klaus Schulten. **Computer modeling in biotechnology, a partner in development.** In *Protocols in Nanostructure Design, Methods in Molecular Biology*, pp. 181-234. Humana Press, 2008. (PMC: 2688837)

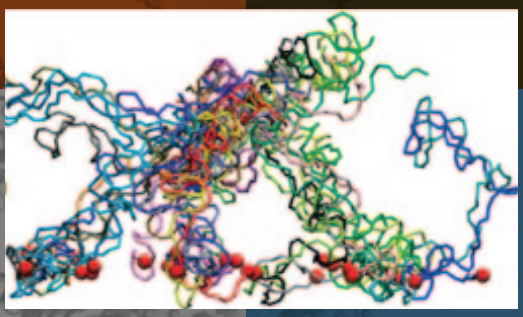


Silica Nanopores
March 2009

Nanotechnology develops small devices with dimensions less than 100 nm, one hundred times smaller than the diameter of a human hair. Nanodevices can be used for a wide range of applications, such as biomedical sensors or tools for studying DNA properties. In building and controlling such small devices, researchers run into problems such as surface effects and significant thermal fluctuations. Furthermore, properties arising from the discrete nature of matter start to dominate at the nanoscale, producing phenomena not observed in larger devices. For instance, when immersed in electrolytic solution and under the influence of an electric field, nanopores act as diodes for ionic currents, conducting in one voltage polarity better than the other, a behavior that has been proposed as the basis for developing nanoelectronic devices. Researchers have studied this so-called rectification behavior by means of molecular dynamics simulations using the program NAMD, the ionic rectification inside the nanopore being described in atomic detail.

Eduardo R. Cruz-Chu, Aleksei Aksimentiev, and Klaus Schulten. **Ionic current rectification through silica nanopores.** *Journal of Physical Chemistry C*, 113:1850-1862, 2009. (PMC: 2658614)

Aleksei Aksimentiev, Robert Brunner, Jordi Cohen, Jeffrey Comer, Eduardo Cruz-Chu, David Hardy, Aruna Rajan, Amy Shih, Grigori Sigalov, Ying Yin, and Klaus Schulten. **Computer modeling in biotechnology, a partner in development.** In *Protocols in Nanostructure Design, Methods in Molecular Biology*, pp. 181-234. Humana Press, 2008. (PMC: 2688837)

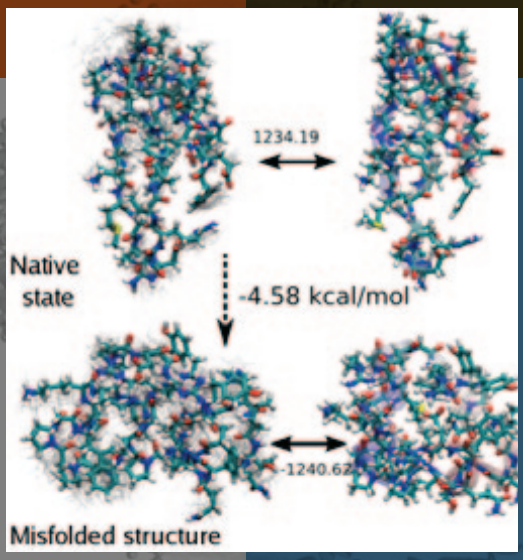


Amazing Filter
April 2009

Many living cells, so-called eukaryotic ones, organize their genetic materials in the cell's nucleus, enveloped by a double membrane with guarded access through pores that involve an amazing filter. Like an ordinary filter it permits passage of small particles (biomolecules), but not of large particles (e.g. proteins). However, certain large particles, proteins called transport receptors, can pass. The filter is made of long "finger" proteins anchored inside the pores. The transport receptors can intermittently widen the filter. But to observe how this is achieved is difficult since the finger proteins are highly disordered. Simulations using NAMD now suggest a simple and elegant answer: the finger proteins bundle in groups of 2-6 and form a brush, filling the nuclear pores with its bristles. The bristles are bundles of finger proteins and have two key properties: (i) on the surface they are dotted with spots of amino acid pairs, phenylalanine and glycine, that are known to interact favorably with transport receptors; (ii) the bristles are also interconnected, namely where finger proteins change from one bundle to another bundle, which they do with some frequency. It appears then that the bristles of the nuclear pore filter form an energetically favorable environment for transport receptors. Research using new simulations shows that transport receptors are pulled into the bristles of the nuclear pore filter.

Lingling Miao and Klaus Schulten. **Transport-related structures and processes of the nuclear pore complex studied through molecular dynamics.** *Structure*, 17:449-459, 2009. (PMC: 2701619)

Lingling Miao and Klaus Schulten. **Probing a structural model of the nuclear pore complex channel through molecular dynamics.** *Biophysical Journal*, 98:1658-1667, 2010. (PMC: 2865169)

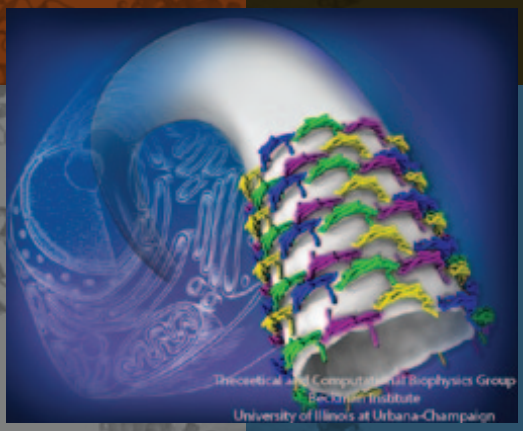


Cracks in the Mirror
May 2009

Computational modeling seeks to simulate biomolecules, particularly proteins. The dream of computational biologists is that their simulations realistically mirror the structure and dynamics of proteins, which act as molecular machines in living cells. Indeed, when researchers tried to simulate how a nascent protein folds into its known shape, the chosen protein, called WW domain, did not fold properly. Historically, simulations could follow protein movement for about 0.0000001 seconds and the computational mirror seemed to work well. Recently, however, simulations with the program NAMD began to follow proteins for almost 0.0001 seconds, a thousand times longer, and the mirror showed cracks. Thus, a question arose as to what went wrong and how the distortion could be repaired. It was unclear whether the simulations still did not last long enough, or whether the physical interactions in the protein were poorly described in the computer model that was used. A study of the phenomenon indicates the interactions show subtle errors, significant enough to throw off the energy balance in the folding protein. Fortunately, the results suggest ways to improve the computation of physical interactions to fold proteins more accurately, repairing the cracks in the mirror.

Peter L. Freddolino, Sanghyun Park, Benoit Roux, and Klaus Schulten. **Force field bias in protein folding simulations.** *Biophysical Journal*, 96:3772-3780, 2009. (PMC: 2711430)

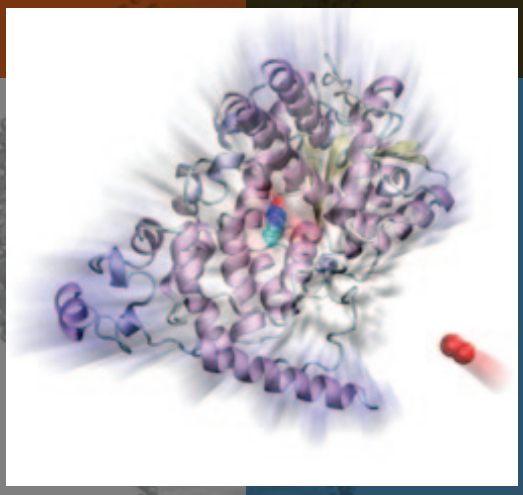
Peter L. Freddolino, Christopher B. Harrison, Yanxin Liu, and Klaus Schulten. **Challenges in protein folding simulations.** *Nature Physics*, 6:751-758, 2010. (PMC: 3032381)



Protein Teamwork
June 2009

Living cells are characterized by a great diversity of separate internal spaces, the boundaries of which are made of membranes forming convoluted surfaces of manifold shapes. Sculpting these shapes is achieved in many cases by proteins. A single protein is too small to bend the membrane into useful shapes, such as spheres or tubes, that measure 10-100 nm, or more, in diameter. Indeed, the proteins work in teams, but exactly how remained a mystery. A computational study elucidated the membrane-sculpting process for proteins called amphiphysin N-BAR domain. Simulations performed with NAMD had revealed a first glimpse earlier. The new study showed that multiple N-BAR domains form lattices maintained through electrostatic interactions. Positively charged, banana-shaped surfaces of individual proteins bend the negatively charged membrane, while the lattice formation ensures a uniform bending force across a wide membrane surface. In a dramatic example of computational "microscopy" the 200 microsecond sculpting of a large flat membrane into a complete tube was observed.

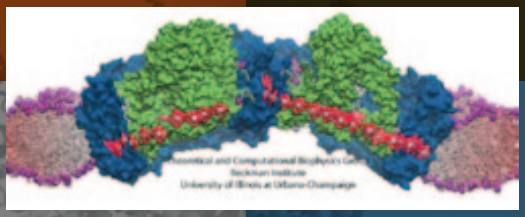
Ying Yin, Anton Arkhipov, and Klaus Schulten. **Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains.** *Structure*, 17:882-892, 2009. (PMC: 2743466)



Where's North? Ask Superoxide!
July 2009

Many animals have a magnetic sense that tells them north from south. Migratory birds, salmon, or sea turtles migrate thousands of miles relying on this sense, and animals that stay closer to home like honeybees, newts, or lobsters also use it. Most likely, the animal magnetic sense is based on two types of receptors, one based on magnetite, another one on a protein called cryptochrome found in animal and human eyes. So why do we humans not enjoy the magnetic sense? In sensing the Earth's magnetic field, cryoptochrome relies on so-called redox reactions, which exchange electrons between molecules. Such reactions are crucial for life but can also be damaging; antioxidants are used by organisms, but also in pharmacology and as dietary supplements to keep the reactions in check. Apparently, cryptochrome recruits as a reaction partner in its magnetosensitive behavior a special form of molecular oxygen—namely its negatively charged brethren superoxide. For this purpose, cryptochrome requires superoxide in low doses—which is good since superoxide, though arising in organisms and used in signaling elsewhere in the body, is actually toxic. The human body has an extremely efficient enzyme, superoxid dismutase, which keeps superoxide at a very low concentration level, apparently too low for human cryptochromes to capture and tell north from south. Humans, somewhere in evolution, might have lost the magnetic sense, but gained longevity.

Ilia A. Solov'yov and Klaus Schulten. **Magnetoreception through cryptochrome may involve superoxide.** *Biophysical Journal*, 96:4804-4813, 2009. (PMC: 2712043)

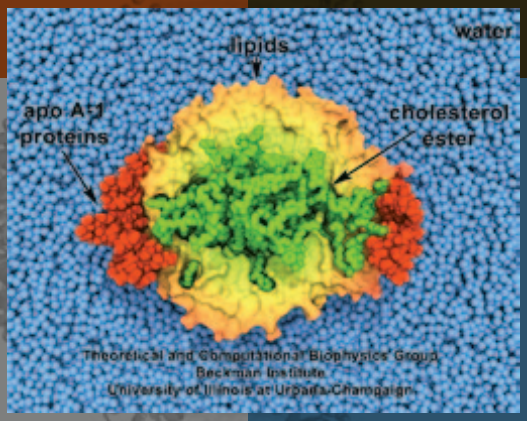


Multi-tasking Proteins
August 2009

Proteins are the workers in cells; they carry out designated cellular functions tirelessly throughout their lifetimes. Some proteins can even hold two different jobs. One example of a dual-duty protein is the bacterial photosynthetic core complex. The photosynthetic core complex performs the first steps of photosynthesis: absorption of sunlight and processing of light energy. Besides providing solar power, the core complex acts as an architect of the cell by shaping membranes in the interior of photosynthetic bacteria. Combining computational modeling and electron microscopy data using the Molecular Dynamics Flexible Fitting method, computational biologists have recently reported studies of both functions of the core complex, namely, the light-absorbing features and the membrane-sculpting properties.

Jen Hsin, James Gumbart, Leonardo G. Trabuco, Elizabeth Villa, Pu Qian, C. Neil Hunter, and Klaus Schulten. **Protein-induced membrane curvature investigated through molecular dynamics flexible fitting.** *Biophysical Journal*, 97:321-329, 2009. (PMC: 2711417)

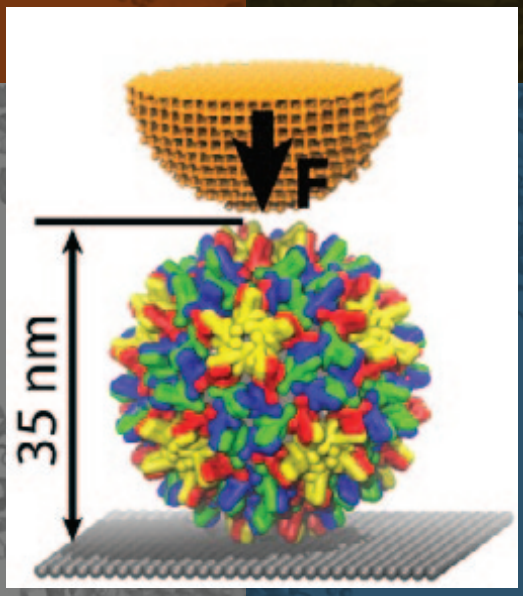
Melih K. Sener, Jen Hsin, Leonardo G. Trabuco, Elizabeth Villa, Pu Qian, C. Neil Hunter, and Klaus Schulten. **Structural model and excitonic properties of the dimeric RC-LH1-PufX complex from Rhodobacter sphaeroides.** *Chemical Physics*, 357:188-197, 2009. (PMC: 2678753)



Bagging Cholesterol
September 2009

Cholesterol maintains a healthy body, but too much cholesterol can lead to atherosclerosis and heart disease. Lipoproteins can bag superfluous cholesterol in the arteries and transport it to the liver for removal. One such lipoprotein is high-density lipoprotein (HDL), which self-assembles into discoidal particles and then bags cholesterol. Molecular dynamics simulations using NAMD revealed that discoidal HDL particles, teaming up with the enzyme LCAT, first turn cholesterol chemically into cholesterol ester and then suck it into the interior of the particle; in the course of this process, the HDL particle swells into a sphere.

Amy Y. Shih, Stephen G. Sligar, and Klaus Schulten. **Maturation of high-density lipoproteins.** *Journal of the Royal Society Interface*, 6:863-871, 2009. (PMC: 2805102)

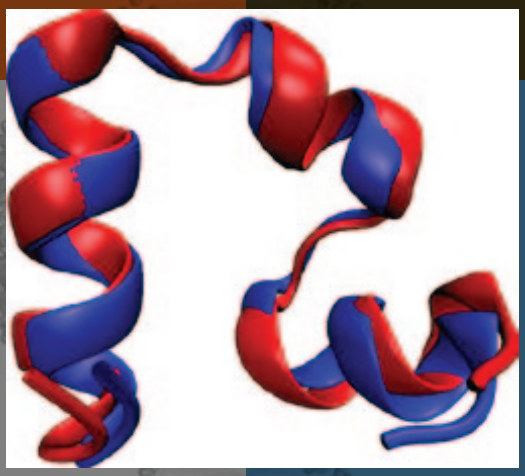


Squeezing a Virus
October 2009

Viruses are the simplest life forms known. In fact, one can question if they are life forms at all, as they cannot exist without infecting a host cell and using its machinery for replication. The virus is indeed just a package material surrounding a genetic message that instructs the host cell to replicate the virus. It looks like a soccer ball, but is a million times smaller. The infection, for instance, that of human cells by a flu virus, involves the virus approaching a human cell and docking onto it, becoming internalized by the cell, bursting its package, (called the capsid), and releasing the genetic message. The virus capsid needs to be sturdy and impermeable up to the approach to the cell, but then become brittle and porous to release the genetic material. Thus, the virus capsid must have very distinct mechanical properties to function. To investigate these properties, experimental and computational biophysicists teamed up. The experimentalists placed empty capsids of the hepatitis B virus onto a small chip and mechanically squeezed the capsid with an extremely small tip, measuring how much force is needed to squeeze the spherical capsid down repeatedly. Computational researchers using NAMD repeated the experiment in simulation. A simulation gave the same forces as the experiment, and also yielded a detailed picture of the capsid mechanics.

Anton Arkhipov, Wouter H. Roos, Gijs J. L. Wuite, and Klaus Schulten. **Elucidating the mechanism behind irreversible deformation of viral capsids.** *Biophysical Journal*, 97:2061-2069, 2009. (PMC: 2756377)

Wouter H. Roos, Melissa M. Gibbons, Anton Arkhipov, Charlotte Uetrecht, Norman Watts, Paul Wingfield, Alasdair C. Steven, Albert J.R.Heck, Klaus Schulten, William S. Klug, and Gijs J.L. Wuite. **Squeezing protein shells: how continuum elastic models, molecular dynamics simulations and experiments coalesce at the nanoscale.** *Biophysical Journal*, 99:1175-1181, 2010. (PMC: 2920642)



Protein Folding
November 2009

Proteins are molecular machines inside living cells that carry out tasks from chemical synthesis to cellular motion. Each protein is a linear polymer made of units that are one of twenty amino acids, A(1) to A(20), for example from a sequence A(5) - A(12) - A(1) - A(5) - ... - A(17). Random sequences lead to disordered, non-functional proteins. A central feature of life is that evolution has given rise to protein sequences that fold into functional proteins. The process through which the disordered linear polymer folds into its final structure, however, remains mysterious, since it is very difficult to observe experimentally. Unfortunately, simulations of protein folding are very computationally demanding and have uncertain outcomes, which has historically limited their utility. Now, researchers have used NAMD to simulate the complete folding process of a small protein, villin headpiece. In a series of atomic resolution molecular dynamics simulations, covering a total of 50 microseconds, multiple folding events were observed. Importantly, the simulations provided a glimpse at the prevalent intermediate conformations visited by villin during folding. A key transition between two intermediates was recognized as rate-limiting in the villin folding process.

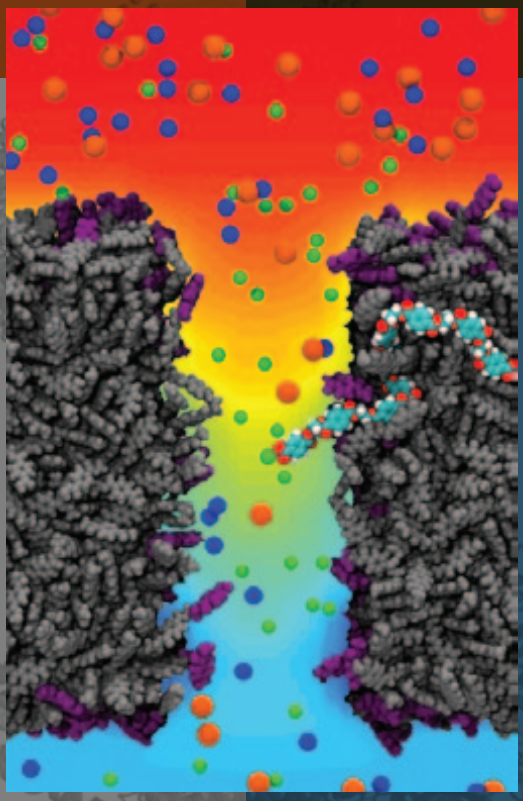
Peter L. Freddolino and Klaus Schulten. **Common structural transitions in explicit-solvent simulations of villin headpiece folding.** *Biophysical Journal*, 97:2338-2347, 2009. (PMC: 2764099)

Aruna Rajan, Peter L. Freddolino, and Klaus Schulten. **Going beyond clustering in MD trajectory analysis: an application to villin headpiece folding.** *PLoS One*, 5:e9890, 2010. (12 pages). (PMC: 2855342)

Peter L. Freddolino, Christopher B. Harrison, Yanxin Liu, and Klaus Schulten. **Challenges in protein folding simulations.** *Nature Physics*, 6:751-758, 2010. (PMC: 3032381)

20th Anniversary
November 2009

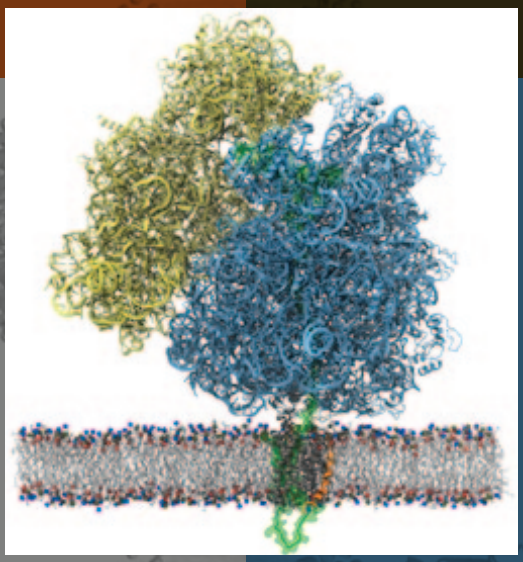
Twenty years ago the Beckman Institute opened on the campus of the University of Illinois and the Theoretical and Computational Biophysics Group (TCBG) was the first to move into the beautiful new building. The group advanced computational biology through widely used software and exciting discoveries. Thus, it was time to celebrate, which TCBG did with the symposium, "Computational Biology of the Cell: The Next Decade." Rather than looking backward, the symposium glanced into the future that promises as many great opportunities as the last two decades realized: computational power for millisecond atomic resolution simulations, coarse-graining methods to describe true cellular size and times scales, better force fields, closer collaboration with experiment, and partnership with nanotechnology. Bringing together many of today's leading thinkers and practitioners of biomolecular modeling lectures led to lively debates regarding the future of computational biology.



Plastic Nanopore
December 2009

Nanotechnology is flourishing today, witnessed by the building of entire chemistry laboratories on a small chip. In doing so, nanoengineers experiment with different materials, the latest of which is good old plastic, chemically known as polyethylene terephthalate, or PET. Presently, nanometer-size pores, so-called nanopores, are built from silicates and PET membranes. To image how nanopores filter ions or affect DNA mechanics one can employ molecular dynamics (MD) simulations using NAMD. Such simulations provide a realistic representation of the devices, which can be employed to improve the technical uses of nanopores. MD simulations revealed that the conduction properties of PET nanopores are controlled by chemical properties of the inner surfaces of the nanopores—for example, if surface groups sticking into the nanopore are protonated or not. The studies show once more the value of molecular dynamics simulations as computational microscopes, providing to nanoengineers the atomic-level visualization of extremely small devices.

Eduardo R. Cruz-Chu, Thorsten Ritz, Zuzanna S. Siwy, and Klaus Schulten. **Molecular control of ionic conduction in polymer nanopores.** *Faraday Discussion*, 143:47-62, 2009.



Managing the Protein Assembly Line

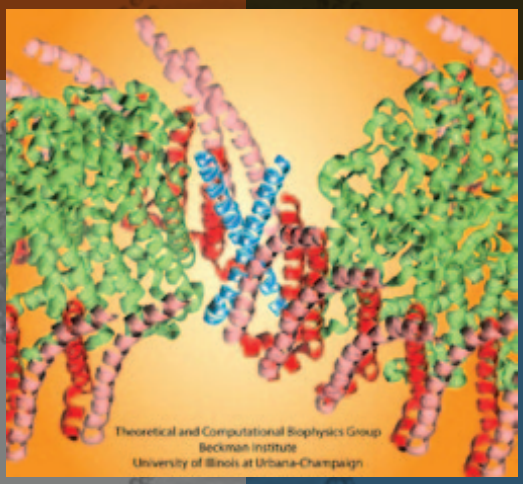
December 2009

Living cells contain millions of proteins composed of sequences of different amino acids that typically fold spontaneously into well-defined three-dimensional conformations and then carry out their role as molecular machines serving manifold functions in the cells. The synthesis of the proteins is carried out by the ribosome, one of the largest molecular machines present in all cells, which reads the cell's genetic information for the purpose. Three researchers were awarded the 2009 Nobel Prize in Chemistry for the determination of the ribosome's structure. The physical mechanism of the ribosome, the cell's protein factory, is still largely unknown. Just as in any factory, there are multiple directions and controls on the protein assembly line. Sometimes the protein products need to be redirected to different parts of the cell, and other times assembly needs to be halted altogether. Now, significant new insights into both of these aspects of protein assembly have been made by combining electron microscopy with molecular dynamics simulations using the recently developed Molecular Dynamics Flexible Fitting method. This combination allowed researchers to visualize the complexity of the ribosome and a protein-conducting channel that directs proteins into and across membranes. Despite the evolutionary distance between mammals and bacteria, both complexes are remarkably similar. Simulations of the bacterial ribosome-channel complex, among the largest simulations ever performed, revealed the steps in the process that directs proteins through the protein-conducting channel. In a third study, researchers determined how TnaC, as a protein newly synthesized by the ribosome, can stall the ribosome during its own assembly, creating an impediment that controls the expression of other genes.

Thomas Becker, Shashi Bhushan, Alexander Jarasch, Jean-Paul Armache, Soledad Funes, Fabrice Jossinet, James Gumbart, Thorsten Mielke, Otto Berninghausen, Klaus Schulten, Eric Westhof, Reid Gilmore, Elisabet C. Mandon, and Roland Beckmann. **Structure of monomeric yeast and mammalian Sec61 complexes interacting with the translating ribosome.** *Science*, 326:1369-1373, 2009. (PMC: 2920595)

James Gumbart, Leonardo G. Trabuco, Eduard Schreiner, Elizabeth Villa, and Klaus Schulten. **Regulation of the protein-conducting channel by a bound ribosome.** *Structure*, 17:1453-1464, 2009. (PMC: 2778611)

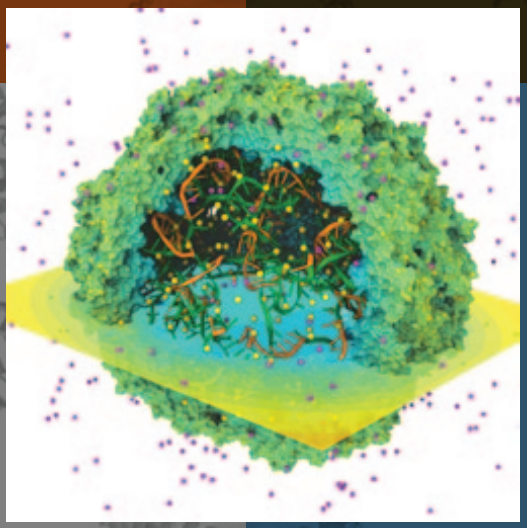
Birgit Seidelt, C. Axel Innis, Daniel N. Wilson, Marco Gartmann, Jean-Paul Armache, Elizabeth Villa, Leonardo G. Trabuco, Thomas Becker, Thorsten Mielke, Klaus Schulten, Thomas A. Steitz, and Roland Beckmann. **Structural insight into nascent polypeptide chain-mediated translational stalling.** *Science*, 326:1412-1415, 2009. (PMC: 2920484)



A Mysterious Protein in Photosynthesis
January 2010

Bacteria contain the simplest photosynthetic machineries found in nature. Higher organisms like algae and plants practice photosynthesis in a more elaborate but principally similar manner as bacteria. But even for its simplicity, the bacterial photosynthetic unit is not without its unsolved mysteries. Take, for example, the crucial photosynthetic core complex, which performs light absorption and the initial processing of the light energy. In certain bacterial species, the core complex contains two copies of an additional small protein (made of about 80 amino acids) called PufX, whose role in photosynthesis is still a puzzle and whose location within the core complex is yet to be pinpointed. Numerous imaging studies have been published, yielding two opinions on what the role of PufX is and where exactly it resides. One opinion assigns the protein the role of gatekeeper, the other the role of coordinator. A computational investigation supports the second role. Since PufX comes as a pair, two copies of PufX were placed side-by-side in a biological membrane and they were seen to adhere to each other strongly, but with their cylindrical (helical) shape an angle of 38 degrees. This geometry is perfectly suited for PufX to join the two parts of the symmetrical core complex together in the middle and to impose on the parts the tilt that was actually observed in the imaging studies. The needed simulations were done with NAMD.

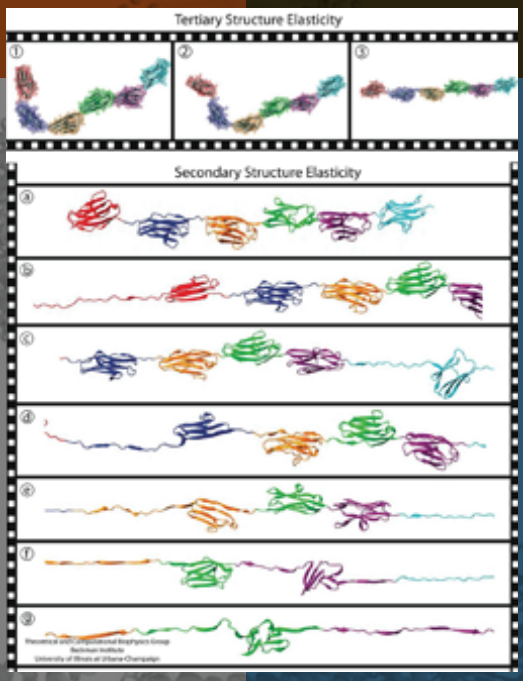
Jen Hsin, Chris Chipot, and Klaus Schulten. **A glycophorin A-like framework for the dimerization of photosynthetic core complexes.** *Journal of the American Chemical Society*, 131:17096-17098, 2009.



VMD 1.8.7 Unleashes Graphics and Computation
February 2010

As the size and complexity of structurally resolved biomolecules continue to increase, researchers require ever more powerful visualization and analysis tools to gain understanding of their function and dynamics. VMD, the leading molecular dynamics visualization tool, has unleashed the computational power of graphics processing units (GPUs) and multi-core CPUs to enable researchers to interactively study large biomolecular complexes on desktop computers as a matter of daily routine. VMD 1.8.7 includes many new and improved graphics algorithms, enabling fast rendering of high-resolution photorealistic molecular scenes. New graphical representations and coloring features enable visualization of carbohydrates, nanodevice structures, and results of quantum chemistry simulations. Fast GPU electrostatics algorithms reduce or eliminate the need for batch mode calculations, i.e., for computing electrostatics of large systems, accelerating them by a factor of 22-44. The latest improvements to the MultiSeq plugin enable processing of up to 100,000 sequences on a desktop computer. New and updated structure building tools ease construction of large all-atom and coarse-grained molecular models.

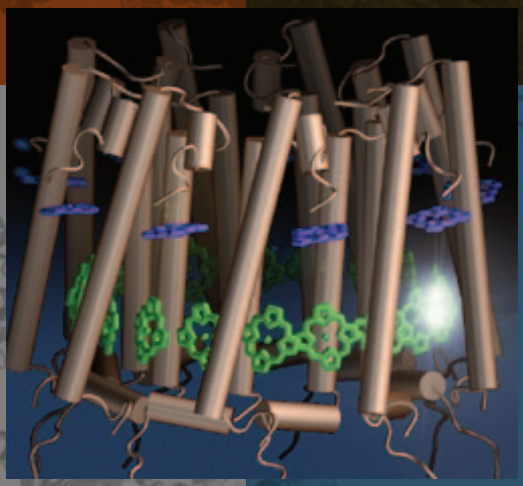
John E. Stone, David J. Hardy, Ivan S. Ufimtsev, and Klaus Schulten. **GPU-accelerated molecular modeling coming of age.** *Journal of Molecular Graphics and Modelling*, 29:116-125, 2010. (PMC: 2934899)



The Fantastic Elastic Muscle Protein
March 2010

A smart strategy usually involves a plan B. As it turns out, the muscle proteins in our bodies responsible for physical motions like running or the beating of our hearts, are also on a backup strategy. When contracting and extending, muscle fibers generate tremendous forces that need to be buffered to protect muscle from damage. This role falls to the muscle protein titin, which is composed of a chain of linked domains, making it a molecular rubber band. When a small force is applied, titin employs its plan A and stretches apart without unraveling its individual domains. When a stronger force is applied, plan B kicks in and more elasticity is generated by the unraveling of the protein domains one at a time. By practicing two modes of response to different levels of forces, titin provides the elasticity that muscle needs at a minimal structural cost. A computational-theoretical investigation provided a molecular view on how titin's two plans work. The needed simulations were performed using NAMD. Principles described in this study can also be found in other mechanical proteins.

Eric H. Lee, Jen Hsin, Eleonore von Castelmur, Olga Mayans, and Klaus Schulten. **Tertiary and secondary structure elasticity of a six-Ig titin chain.** *Biophysical Journal*, 98:1085-1095, 2010.



Light Capture
April 2010

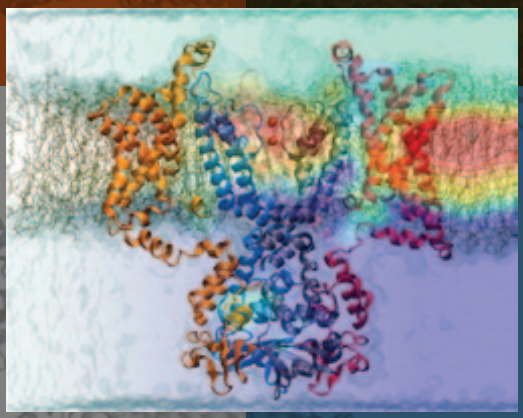
Photosynthetic organisms fuel their energy needs by harvesting sunlight. Photosynthetic bacteria called purple bacteria live in the darkest places in ponds and lakes and as a result, every photon of sunlight they receive must be efficiently collected and converted into chemical energy for the cell. Incoming photons are absorbed by proteins that contain many molecules of chlorophyll. The chlorophylls capture light energy and transfer that energy between them. Such transfer, a quantum mechanical process, happens multiple times before the energy is converted into chemical energy and is governed by thermal interactions between chlorophylls and protein. Research shows that the surrounds thermalize, or randomize, the light excitation migration within one picosecond (one trillionth of a second), after which the typically coherent quantum process looks incoherent. The finding explains the great success of earlier simpler descriptions suggested sixty years ago by U.S. physicist Robert Oppenheimer and German chemist Theodor Förster, who postulated the now established incoherence.

Johan Strümpfer and Klaus Schulten. **Light harvesting complex II B850 excitation dynamics.** *Journal of Chemical Physics*, 131:225101, 2009.

Shutting Down the Protein Factory
May 2010

The ribosome is the protein factory of all cells. While proteins are being synthesized, they must travel through a tunnel inside the ribosome before reaching their required location in the cell. This tunnel recognizes certain sequences of nascent proteins and responds to them in various ways. For example, certain protein sequences recognized in the tunnel can shut down the ribosome, stopping protein synthesis. An often studied example is the bacterial protein TnaC, which by shutting down its own synthesis turns on the synthesis of proteins involved in the degradation of a molecule called tryptophan. The structure of TnaC inside the ribosome was previously determined through crystallography, electron microscopy, and computer modeling. Simulation of TnaC dynamics inside the ribosome using NAMD and VMD has revealed the mechanism by which TnaC shuts down the ribosome, as recently reported. The questions of how the ribosome recognizes the sequence of TnaC and why many proteins that have sequences similar, but not identical, to that of TnaC do not shut down the ribosome have also been answered.

Leonardo G. Trabuco, Christopher B Harrison, Eduard Schreiner, and Klaus Schulten. **Recognition of the regulatory nascent chain TnaC by the ribosome.** *Structure*, 18:627-637, 2010.



Nerve Signals
June 2010

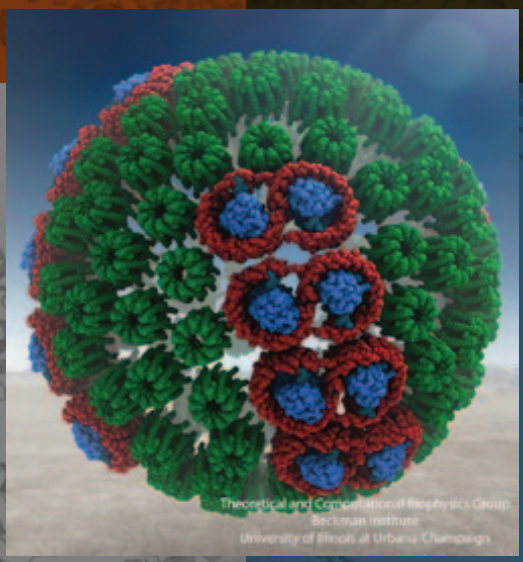
Nerve cells, through their electrical signals, control the intelligent actions of higher organisms. The signals result mainly from potassium and sodium ion channels in cells; when the cells are stimulated electrically, they send an all- (in case of sufficient stimulation) or-nothing signal to other nerve cells or organs like muscle. As shown in groundbreaking work by 1963 Nobelists Hodgkin and Huxley, cast into mathematical equations, nerve cells establish these signals through voltage gating of channels. The nature of the gating, monitored through the so-called gating current, has been elusive for decades, despite a detailed characterization of the ion conductivity itself rewarded through a 2003 Nobel Prize to MacKinnon. The riddle is that the channel involves a protein with few charged amino acids that seem to be only weakly coupled energetically to an electrical potential gradient across the cell membrane. A sweeping modeling study using NAMD employing the most powerful computers available to researchers today has led to an explanation of voltage-gating. Simulations revealed that the potential gradient is focused by the channel protein to a very narrow region, such that its value is much larger than anticipated. The protein was also seen to arrange its charged amino acids (sensing the gradient) in an unusual helix—a so-called 3_{10} helix—that aligns charges perfectly and at the same time induces a motion that opens and closes the channel. Proof of the veracity of the computational model is that the calculated gating current perfectly fits the observation.

Fatemeh Khalili-Araghi, Vishwanath Jogini, Vladimir Yarov-Yarovoy, Emad Tajkhorshid, Benoit Roux, and Klaus Schulten. **Calculation of the gating charge for the Kv1.2 voltage-activated potassium channel.** *Biophysical Journal*, 98:2189-2198, 2010.

A Compass in the Eye
July 2010

Animals as varied as salmon, honeybees, and migratory birds have a magnetic sense that sees the Earth's magnetic field and allows them to distinguish north, south, east, and west. In migratory birds the magnetic sense is apparently based on a protein called cryptochrome that acts in the retina, the light-sensitive part of the eye. Cryptochromes rely on light-dependent reactions, which depend on the protein's orientation in the geomagnetic field. The product of the reaction in cryptochrome is said to affect the sensitivity of light receptors in the retina of a bird's eye such that a bird literally "sees" the geomagnetic field. However, cryptochrome in the eye most likely is not perfectly aligned with the retina, even if bound to ordered membrane structures found in the outer segments of the eye's light receptors. Researchers have shown that birds' vision-based compass is surprisingly insensitive to cryptochrome disorder, and suggest a cloud-like pattern in the visual field that points a bird to the correct orientation.

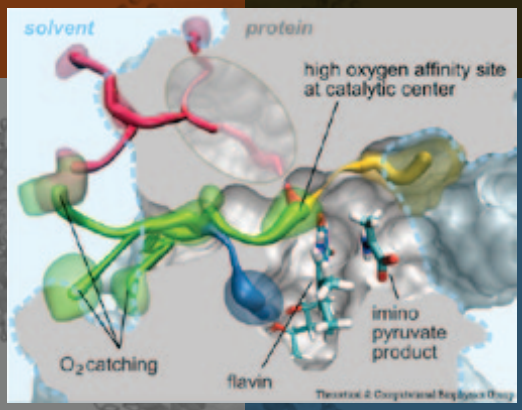
Ilia A. Solov'yov, Henrik Mouritsen, and Klaus Schulten. **Acuity of a cryptochrome and vision based magnetoreception system in birds.** *Biophysical Journal*, 99:40-49, 2010.



Bacterial Solar Energy Engineering
August 2010

The energy of the sun feeds life on Earth and is harvested by molecules of chlorophylls and carotenoids. In the case of certain photosynthetic bacteria, thousands of these molecules are fitted into spheres smaller than 1/10000 of a millimeter. Naturally, it is crowded in these spheres! Researchers have now established the composition and arrangement of the light harvesting system – the chlorophylls and carotenoids held by hundreds of ring-shaped proteins. Utilizing the sun's energy optimally is a difficult balancing act in molecular engineering; on the one hand, the proteins must pack together closely to share light energy absorbed by any chlorophyll or carotenoid, and on the other hand, roadways must be kept open between proteins for passing chemical substances that capture the light energy in chemical form and deliver it to the rest of the bacterial cell. Research indicates that the bacterial cell manages the balance through ingenious utilization of quantum electronics.

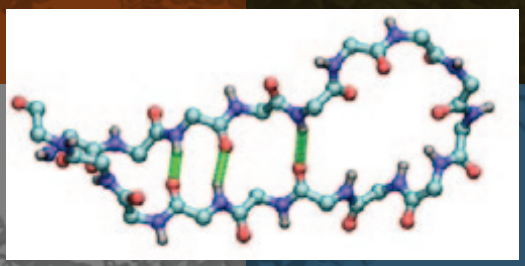
Melih Sener, Johan Strumpfer, John A. Timney, Arvi Freiberg, C. Neil Hunter, and Klaus Schulten. **Photosynthetic vesicle architecture and constraints on efficient energy harvesting.** *Biophysical Journal*, 99:67-75, 2010.



Oxygen Gas in Protein
September 2010

Cells contain numerous enzymes that use molecular oxygen for their reactions. Often, their active sites are buried deep inside the protein, which raises the question of whether there are specific access channels guiding oxygen to the site of catalysis. Localizing oxygen molecules in proteins is difficult. Oxygen is very mobile and difficult to locate by most experimental techniques. However, computer modeling comes to the rescue. Computational biologists using NAMD identify the D-amino acid oxidase regions where oxygen molecules most likely reside. D-amino acid oxidase is considered essential for understanding catalysts that involve flavin moieties in proteins. Findings reveal a channel system through which oxygen molecules diffuse from the protein surface to the protein's catalytic center. Indeed, the channel ends at a site in the protein that constitutes the ideal location for oxygen to react with flavin. The computational results are verified through so-called site directed mutagenesis experiments.

Jan Saam, Elena Rosini, Gianluca Molla, Klaus Schulten, Loredano Pollegioni, and Sandro Ghisla. **O2-reactivity of flavoproteins: Dynamic access of dioxygen to the active site and role of a H+ relay system in D-amino acid oxidase.** *Journal of Biological Chemistry*, 285:24439-24446, 2010.

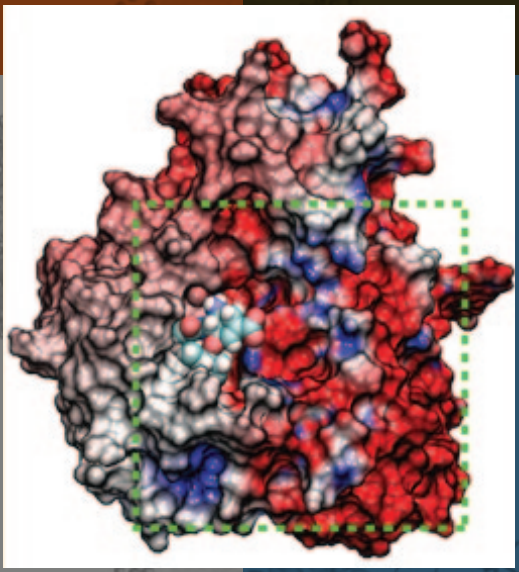


Biological Flow Sensor
September 2010

The human body is protected by self-healing mechanisms, one of them being instant blood clotting at the site of a blood vessel injury. However, what triggers the formation of a blood clot? Researchers have found that a protein on blood platelets, called GPIbα, functions as a sensor of so-called high shear flow caused by bleeding. A loop-shaped, 17-amino-acid-long segment of GPIbα, the ß-switch, acts as the flow sensor. When a blood vessel is injured, bleeding increases shear stress due to blood flow at the wound, which in turn induces the ß-switch to change from a loose, loop shape to an elongated, hairpin shape, the latter referred to by researchers as a ß-hairpin. This conformational change makes GPIbα adhere better to the damaged vessel and eventually leads to clotting, which heals the vessel. In a prior study, molecular dynamics simulations using NAMD and VMD provided a microscopic view of the flow-induced loop to ß-hairpin transition. Researchers extended the investigation of the remarkable biological flow sensor, detailing the flow rate needed to trigger it and identifying the detailed sensor mechanism. A combination of simulation and mathematical analysis revealed the ß-switch as a system of two stable states—one disordered, with loop geometry and one ordered, with ß-hairpin geometry. Normal flow prefers the disordered state; high shear flow prefers the ordered state, thereby inducing the life saving transition.

Zhongzhou Chen, Jizhong Lou, Cheng Zhu, and Klaus Schulten. **Flow-induced structural transition in the ß-switch region of glycoprotein Ib.** *Biophysical Journal*, 95:1303-1313, 2008.

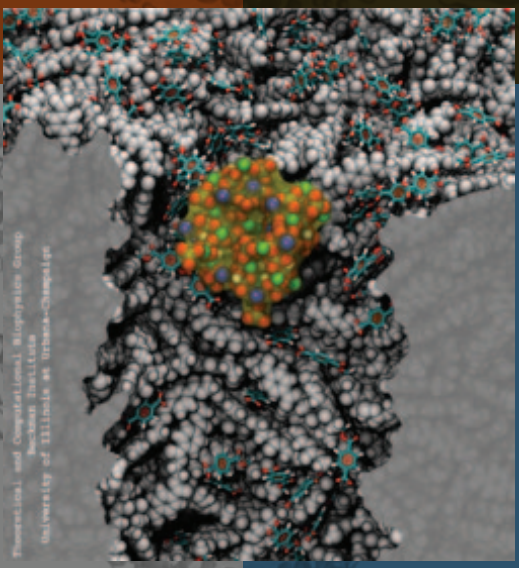
Xueqing Zou, Yanxin Liu, Zhongzhou Chen, Gloria Ines Cardenas-Jiron, and Klaus Schulten. **Flow-induced beta-hairpin folding of the Glycoprotein Ibα beta-switch.** *Biophysical Journal*, 99:1182-1191, 2010.



Molecular Mechanism of Influenza Drug Resistance
October 2010

Fever, chills, sore throat, coughing, aches, and pains? Ah… you have the flu! As a measure of prevention, vaccines against seasonal influenza are distributed and administered each fall. Last year though, the outbreak of the H1N1pdm influenza virus – the "swine" flu – caught health workers by surprise as this flu virus not only infected individuals during the spring and summer months, but also seemed to be particularly virulent towards otherwise healthy young people. Even more alarming was increasing evidence that H1N1pdm had acquired resistance to the frontline anti-flu drug, Tamiflu. In response to this, computational biologists at the University of Illinois and the University of Utah teamed up to uncover the basis for influenza drug resistance through quantum chemistry, and molecular dynamics simulations with NAMD. The results of this study have uncovered a two-stage binding pathway for Tamiflu in H1N1pdm "swine" and H5N1 "avian" flu proteins, as well as a possible mechanism through which genetic mutations can induce drug resistance in one of the two stages. Subsequent efforts at drug design against influenza could take advantage of this discovery, which was made possible through use of so-called GPU computing.

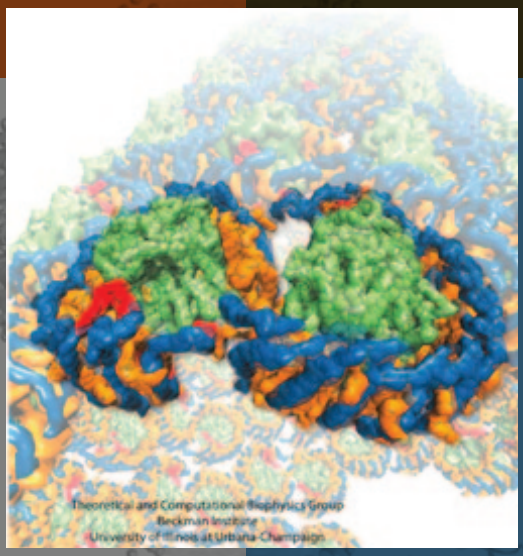
Ly Le, Eric H. Lee, David J. Hardy, Thanh N. Truong, and Klaus Schulten. **Molecular dynamics simulations suggest that electrostatic funnel directs binding of Tamiflu to influenza N1 neuraminidases.** *PLoS Computational Biology*, 5:e1000939, 2010.



Smallest Grain of Salt
October 2010

Nanopores are promising new sensors, which may soon sequence DNA in a cheap, fast way and control the flow of ions in nanodevices. In measurements, DNA molecules and ions pass through nanopores that are only a nanometer (0.000001 mm) wide. Unfortunately, researchers have to battle clogging of the very narrow nanopores. For example, it was found that small concentrations of so-called divalent cations produce clogging of nanopores drilled in a common plastic material called PET. To determine how to prevent clogging, researchers needed a microscopic view of the process. Such a view was furnished through molecular dynamics simulations, based on NAMD, of ion-conducting nanopores. An atomic-level view of the clogging process reveals the formation of tiny ionic crystals inside the nanopore and suggests a remedy against nanopore clogging.

Eduardo R. Cruz-Chu and Klaus Schulten. **Computational microscopy of the role of protonable surface residues in nanoprecipitation oscillations.** *ACS Nano*, 4:4463-4474, 2010.

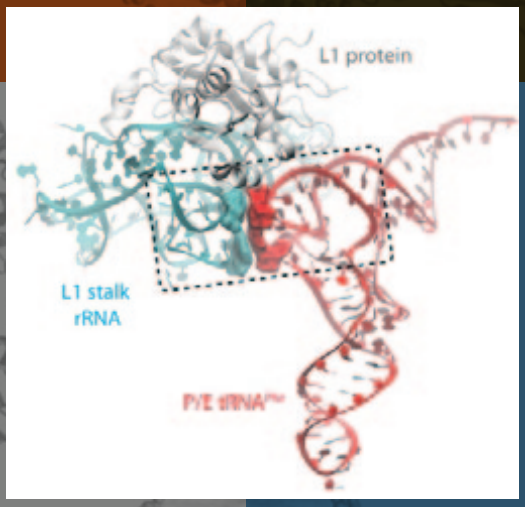


Light-Capturing Rod
November 2010

The process of photosynthesis fuels life on Earth. Its first step is capturing the energy in sunlight. Light-capturing proteins in photosynthetic organisms are often seen closely crowded together in the cellular membrane, forming hundred nanometer-sized patches. Such "photosynthetic membranes" can be flat or spherical, depending on bacterial species; in case of a certain mutant bacterium the membrane forms the cylindrical surface of a rod. This membrane is actually an ideal case for scientific investigation, since it contains only one type of protein complex organized in an orderly fashion, such that placement of all proteins is known with atomic precision. Researchers have used the cylindrical photosynthetic membrane as a model system to elucidate in great detail how light is captured, and how the light energy is passed around the light-capturing proteins until it is utilized to charge the membrane through electron transfer.

Jen Hsin, Johan Strumpfer, Melih Sener, Pu Qian, C. Neil Hunter, and Klaus Schulten. **Energy transfer dynamics in an RC-LH1-PufX tubular photosynthetic membrane.** *New Journal of Physics*, 12:085005, 2010.

Jen Hsin, Danielle E. Chandler, James Gumbart, Christopher B. Harrison, Melih Sener, Johan Strumpfer, and Klaus Schulten. **Self-assembly of photosynthetic membranes.** *ChemPhysChem*, 11:1154-1159, 2010. (PMC: 3086839)



Computational Microscopy of the Ribosome
November 2010

The ribosome is a molecular machine ubiquitous in all living cells and translates genetic information into proteins. Proteins are made of twenty different amino acids, strung in a linear sequence. The amino acids are coded for by the genes in DNA, but for the purpose of protein synthesis genes are transcribed into a working copy, a messenger RNA. The latter is translated by the ribosome into proteins with the help of transfer RNAs, which bring the individual amino acids. There is a transfer RNA for each of the twenty amino acids. Much progress has been made regarding the static structure of the ribosome, transfer RNA, and nascent protein components. Now researchers are looking into the inner workings of the whole system combining various experiments and computational modeling using NAMD and VMD. The combination yielded unprecedented detailed views of the ribosome in action, as reported recently, namely, how a dynamic part of the ribosome helps guide transfer RNAs on their way out of the ribosome, and explains why transfer RNAs behave differently, dependent upon whether they start the synthesis of a protein or if they elongate a protein.

Leonardo G. Trabuco, Eduard Schreiner, John Eargle, Peter Cornish, Taekjip Ha, Zaida Luthey-Schulten, and Klaus Schulten. **The role of L1 stalk-tRNA interaction in the ribosome elongation cycle.** *Journal of Molecular Biology*, 402:741-760, 2010.

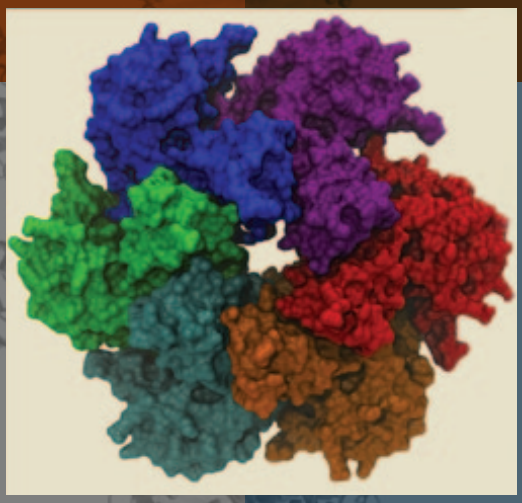
Wen Li, Leonardo G. Trabuco, Klaus Schulten, and Joachim Frank. **Molecular dynamics of EF-G during translocation.** *PROTEINS: Structure, Function, and Bioinformatics*, 79:1478-1486, 2011.

Opposites Attract in a Motor Protein
December 2010

Motor proteins are fascinating cellular machines that convert chemical energy into mechanical work. They are employed in a wide range of cellular functions like muscular contraction, transportation of proteins and vesicles, and cell motility. Myosin VI is an example of a motor protein. It "walks" along actin filaments (kind of like cellular highways), performing tasks such as delivering materials across the cell. Primarily, myosin VI functions as a dimer (i.e. two myosin VI proteins are associated and form a functional complex), but the structure of the myosin VI dimer—particularly how a myosin VI associates with another one—is still debated. Teaming up with experimentalists, computational biologists investigated how two myosin VI assemble and pull their cargo together. The investigation focused on a segment of myosin VI that forms a long, rigid alpha-helix that is notably decorated with a distinct ring of positively and negatively charged amino acids. Carrying out single-molecule experiments along with molecular dynamics simulations using NAMD, it was found that two myosin VI proteins attract each other electrostatically through the charge-ring proteins, shifting them such that oppositely charged amino acids from different helices face each other.

HyeongJun Kim, Jen Hsin, Yanxin Liu, Paul R. Selvin, and Klaus Schulten. **Formation of salt bridges mediates internal dimerization of myosin VI medial tail domain.** *Structure*, 18:1443-1449, 2010.

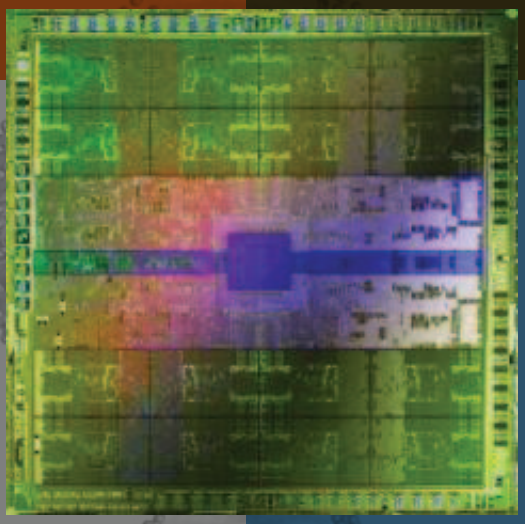
Yanxin Liu, Jen Hsin, HyeongJun Kim, Paul R Selvin, and Klaus Schulten. **Extension of a three-helix bundle domain of myosin VI and key role of calmodulins**. *Biophysical Journal*, 100:2964-2973, 2011.



NAMD 2.7 Extends Free Energy Capability
December 2010

The eagerly awaited 2.7 release of NAMD includes GPU acceleration, downloadable binaries for Linux clusters with InfiniBand networks, grid-based forces and extra bond/angle/torsion conformational restraints for molecular dynamics flexible fitting (MDFF), and a major enhancement of both alchemical and conformational free energy methods. Alchemical calculations gradually alter the chemical structure of a molecule during a simulation, monitoring the consequences of creating and deleting atoms via free energy perturbation or thermodynamic integration. A soft-core correction may be employed to circumvent singularities when atoms are created. Conformational calculations can probe structural rearrangements along an arbitrary number of collective variables, including distances between atoms or groups of atoms, distances projected along an axis or in a plane, angles, torsions, eigenvectors, gyration radii, coordination, root mean-square displacements, orientations, and alpha-helicity. New variables can be introduced without recompilation. Free energy surfaces or potentials of mean force can be constructed using meta-dynamics, the adaptive biasing force method, umbrella sampling, and steered molecular dynamics. The collective variables capability of NAMD has allowed the simulation of the illustrated hexameric helicase. In the simulation, a single strand of DNA passes through the central core while the hexamer translocates or "walks" along the DNA, a mechanical process driven by the energy of ATP hydrolysis.

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. (PMC: 2486339)



GPU Molecular Modeling Coming of Age
January 2011

A recent review explores how the Graphics Processing Units (GPUs) found in commodity high-end video cards are increasingly being used not only for interactive molecular graphics, but also for molecular simulation and analysis. NAMD and VMD both support GPU-acceleration using NVIDIA CUDA, enabling computationally demanding simulation, visualization, and analysis tasks (e.g., of the electrostatics of Tamiflu binding) to be run with shorter turnaround on modestly priced GPU clusters, desktop, and laptop computers. This affordable computational power is particularly compelling for interactive modeling, with a recent report detailing how interactive molecular dynamics simulations with haptic feedback are now possible on GPU-accelerated desktop computers. Three recent book chapters detail the application of GPU computing techniques to the calculation of electrostatic potentials, interactive display of molecular orbitals, and more general molecular modeling algorithms. In August 2010 the Resource held its first workshop on GPU programming for molecular modeling to bring the benefits of GPU computing to a broader range of molecular modeling tools and magnify the impact of our GPU computing research.

John E. Stone, David J. Hardy, Ivan S. Ufimtsev, and Klaus Schulten. **GPU-accelerated molecular modeling coming of age**. *Journal of Molecular Graphics and Modelling*, 29:116-125, 2010. (PMC: 2934899)

Ly Le, Eric H. Lee, David J. Hardy, Thanh N. Truong, and Klaus Schulten. **Molecular dynamics simulations suggest that electrostatic funnel directs binding of Tamiflu to influenza N1 neuraminidases**. *PLoS Comput. Biol.*, 5:e1000939, 2010. (13 pages). (PMC: 2944783)

John E. Stone, Axel Kohlmeyer, Kirby L. Vandivort, and Klaus Schulten. **Immersive molecular visualization and interactive modeling with commodity hardware**. *Lecture Notes in Computer Science*, 6454:382-393, 2010. (PMC: 3032211)

David J. Hardy, John E. Stone, Kirby L. Vandivort, David Gohara, Christopher Rodrigues, and Klaus Schulten. **Fast molecular electrostatics algorithms on GPUs**. In Wen-Mei Hwu, editor, *GPU Computing Gems*, chapter 4, pp. 43-58. Morgan Kaufmann Publishers, 2011.

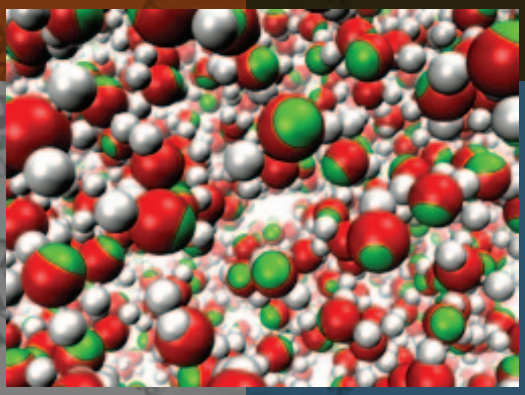
John E. Stone, David J. Hardy, Jan Saam, Kirby L. Vandivort, and Klaus Schulten. **GPU-accelerated computation and interactive display of molecular orbitals**. In Wen-Mei Hwu, editor, *GPU Computing Gems*, chapter 1, pp. 5-18. Morgan Kaufmann Publishers, 2011.

John E. Stone, David J. Hardy, Barry Isralewitz, and Klaus Schulten. **GPU algorithms for molecular modeling**. In Jack Dongarra, David A. Bader, and Jakub Kurzak, editors, *Scientific Computing with Multicore and Accelerators*, chapter 16, pp. 351-371. Chapman & Hall/CRC Press, 2011.

Placing New Proteins
February 2011

Constructing and correctly placing new proteins is a complicated task for living cells. Starting with nothing more than a sequence of DNA, the cell has to translate the genetic code, stitch together the constituent amino acids, then place the newly constructed protein where its function is needed. To accomplish these feats, the cell uses tools such as the ribosome, a protein factory, and the protein-conducting channel, a switching station within the membrane. All instructions for making a nascent protein and localizing it (e.g., to the watery cytoplasm or the oily membrane), are carried within its DNA sequence, but how it is read and then executed has long been unclear. Now, two research advances picture these processes in astonishing detail. The first advance, from a collaboration between cryo-electron microscopists and computational biologists using MDFF, shows an atomic level structure that caught the ribosome in the act of inserting a protein into a membrane. The structure reveals the newly forming protein transiting from within the ribosome to the channel and then through an open gate in the protein-conducting channel into the membrane. The second advance, accomplished with the simulation program NAMD, explained how the ribosome and the protein-conducting channel manage to pay the energy price of inserting a new protein – one amino acid at a time – into the membrane.

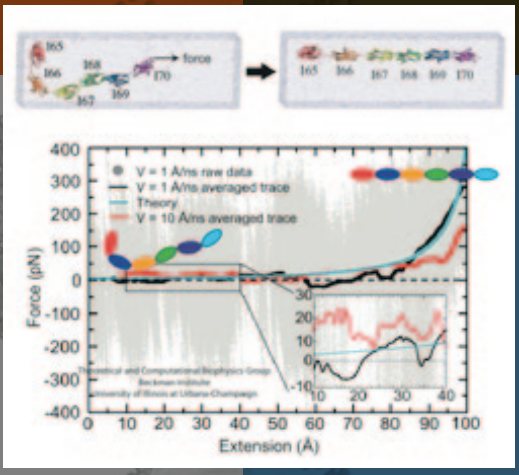
Jens Frauenfeld, James Gumbart, Eli O. van der Sluis, Soledad Funes, Marco Gartmann, Birgitta Beatrix, Thorsten Mielke, Otto Berninghausen, Thomas Becker, Klaus Schulten, and Roland Beckmann. **Cryo-EM structure of the ribosome-SecYE complex in the membrane environment**. *Nature Structural & Molecular Biology*, 18:614-621, 2011.



More Faithful Molecular Modeling
March 2011

Molecular modeling simulates the motion of cellular biomolecules at the atomic level. To make the simulations faithful, the physical forces acting between atoms need to be described accurately. Electric field effects between atoms, so-called atomic polarizabilities, are especially difficult to model well in a computationally cost-effective way. There is an ongoing effort in the molecular modeling community to develop such models that more faithfully represent the microscopic properties of biomolecules due to the ambient electric field effects. Recent development work has added support in the simulation program NAMD for one of these advanced modeling efforts. The new algorithms used in NAMD achieve good parallel computing performance, with a cost that is not more than twice that of the standard model, not accounting for atomic polarizabilities. The new model is demonstrated to reproduce many physical properties better than the standard model—including more accurate bulk density and surface tension at the interface between liquids and more accurate diffusive behavior of ions in a solution.

Wei Jiang, David Hardy, James Phillips, Alex MacKerell, Klaus Schulten, and Benoit Roux. **High-performance scalable molecular dynamics simulations of a polarizable force field based on classical Drude oscillators in NAMD**. *Journal of Physical Chemistry Letters*, 2:87-92, 2011. (PMC: 3092300)

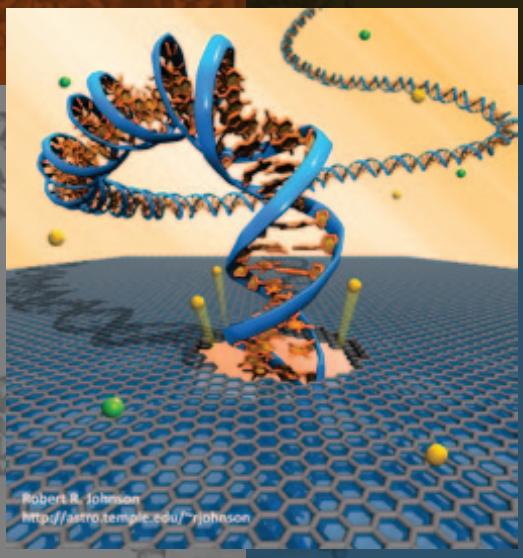


Slower is Better in Studying Cells
April 2011

A cell that is alive can be recognized typically under a microscope through cell motion, streaming of inner cell fluids, and other mechanical cell activities. These activities are the result of mechanical forces that arise in the cell, but even though the effect of the forces on cells are tremendous, the magnitude of the forces when measured by physical instruments are extremely small: 1/1000000000000 of the force felt when lifting a kilogram. Sensing such small force requires extremely high precision in research techniques, and for more than a decade, computational biologists, using NAMD, have exploited the all-atom resolution of molecular dynamics modeling to successfully explain the molecular level effect of small forces in cells. But simulations, too, are challenged by the small magnitude of cellular forces, mainly because precise simulation requires extremely extensive simulations that cover a duration as close as possible to the biological time scale. Advances in computational biology have now permitted, in the case of the muscle protein titin, a simulation of unprecedented accuracy that clearly resolved the relationship between molecular structure of titin and its ability to sustain the forces that arise in muscle function. For this purpose a key element of titin was stretched at a velocity slow enough that hydrodynamic drag, which came about as an unwanted byproduct of earlier simulations, was negligible compared to titin's intrinsic force-bearing properties. The new simulations opened an unveiled view on muscle elasticity.

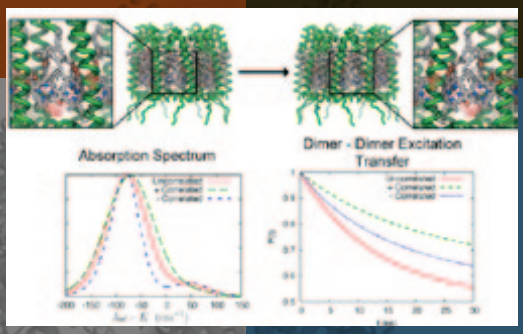
Jen Hsin and Klaus Schulten. **Improved resolution of tertiary structure elasticity in muscle protein**. *Biophysical Journal*, 100:L22-L24, 2011. (PMC: 3037604)

Jen Hsin, Johan Strümpfer, Eric H. Lee, and Klaus Schulten. **Molecular origin of the hierarchical elasticity of titin: simulation, experiment and theory**. *Annual Review of Biophysics*, 40:187-203, 2011.



VMD 1.9 Even More Powerful
May 2011

The molecular graphics program VMD has evolved to version 1.9, featuring new and improved tools for molecular cell biology. A new tool in VMD permits visual diagnosis of the long-time dynamics of large structures. Improved computer power now permits simulation of processes like protein folding that stretch over microseconds to milliseconds. While short in human time, the process measured in terms of basic molecular motion, like bond vibration, is seemingly endless, involving hundreds of gigabytes of data and long hours of human attention if not automated. Now, with the Timeline tool, VMD offers a convenient way to scan such data for key "events" that signal successful process steps. Timeline can likewise assist in monitoring the dynamics of large cellular machines involving millions of atoms. VMD 1.9 sports other new tools like ParseFEP for analyzing so-called free energy perturbation calculations determining the energy arising in reaction processes as calculated with VMD's sister program NAMD. VMD now also includes a lightening-fast tool to detect spatial regularities in the arrangement of small molecules in order to detect if they constitute disordered or ordered arrangements. By calculating the so-called radial distribution function the tool could identify plug formation in nanopore sensors due to precipitates that go undetected by density or visual inspection. Pleasing to the eye, molecular graphics features in VMD have been enhanced, enabling faster ray tracing, new shading features, and X3D molecular scene export for display in WebGL-capable browsers including Chrome, Firefox, and Safari.

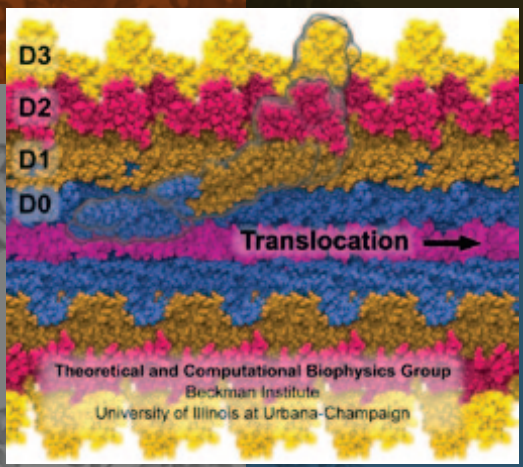


Bottling the Energy of Sunlight
May 2011

Photosynthetic life forms bottle the energy of sunlight. How do they do it? Fast! Indeed, the first nanosecond after absorption of sunlight is crucial in photosynthetic light harvesting. During this time, absorbed solar energy is in its least stable form—that of electronically excited molecules which decay by re-emitting a photon (fluorescence) at a rate of 1 every nanosecond (1 every 0.000000001 seconds). Fluorescence would be wasteful to the organism and to avoid it the molecular excitation energy is transported over tens to hundreds of nanometers through an energy transfer network to so-called photosynthetic reaction centers, where it is converted into a more stable form of energy. This fast transport is achieved by transferring excitation energy between clusters of strongly interacting pigment molecules that act as stepping stones, and as a result the excitation energy is used in about 0.1 nanoseconds—i.e., within 10% of the fluorescence decay time—thus bottling sunlight with an efficiency of 90%. The thermal motion of the pigment molecules and their protein scaffold greatly influence the excitation transport. A recent study showed that correlated thermal fluctuations that arise in pigment clusters affect the excitation transfer greatly, typically slowing it down. Pigment clusters that avoid correlated thermal motion increase the efficiency of light harvesting.

Melih Sener, Johan Strümpfer, Jen Hsin, Danielle Chandler, Simon Scheuring, C. Neil Hunter, and Klaus Schulten. **Förster energy transfer theory as reflected in the structures of photosynthetic light harvesting systems**. *ChemPhysChem*, 12:518-531, 2011. (PMC: PMC3098534)

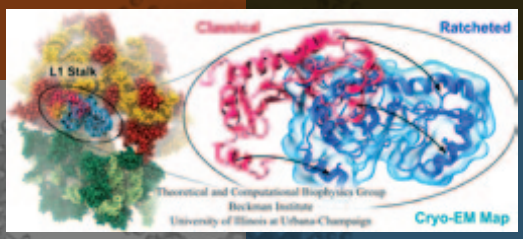
Johan Strümpfer and Klaus Schulten. **The effect of correlated bath fluctuations on exciton transfer**. *Journal of Chemical Physics*, 134:095102, 2011. (9 pages). (PMC: 3064689)



Growing a New Whip
June 2011

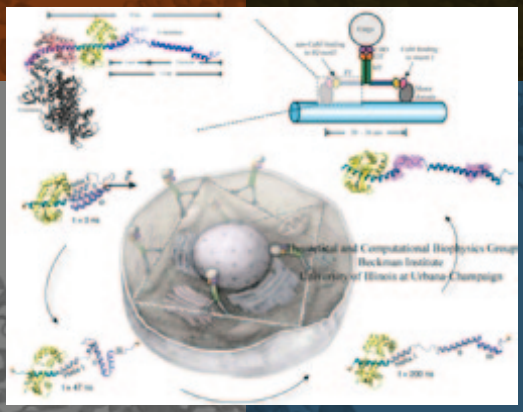
Bacterial cells can swim, and for this purpose use one or more flagella – whip-like appendages that exceed the length of the cell several-fold. The flagella are made of thousands of copies of a protein called flagellin arranged in a helical fashion such that the flagella are hollow inside, forming a very long channel. When the flagella are rotated counter clockwise by the cell, the cell swims straight; when they are rotated clockwise, the cell turns in a new direction. Through swimming and turning the cell searches its habitat for food and avoids trouble. But sometimes a flagellum breaks and needs to grow back. This begins an amazing process: the cell makes new flagellin and pumps the unfolded protein into the flagellar channel, extending its length. This is like squeezing toothpaste out of a tube, except in reverse – like pumping toothpaste into the tube at the factory – and the tube is extremely long. Now researchers have described the process that makes flagella grow step-by-step through a combination of mathematics, physics, and molecular modeling using NAMD. As reported, the researchers reproduce the time course of growth as well as the length of the growth, and also explain how friction of the protein paste is kept extremely low to make the flagella grow many times the length of the cell itself.

David E. Tanner, Wen Ma, Zhongzhou Chen, and Klaus Schulten. **Theoretical and computational investigation of flagellin translocation and bacterial flagellum growth**. *Biophysical Journal*, 100:2548-2556, 2011.



NAMD 2.8 Cures Hydrophobia
June 2011

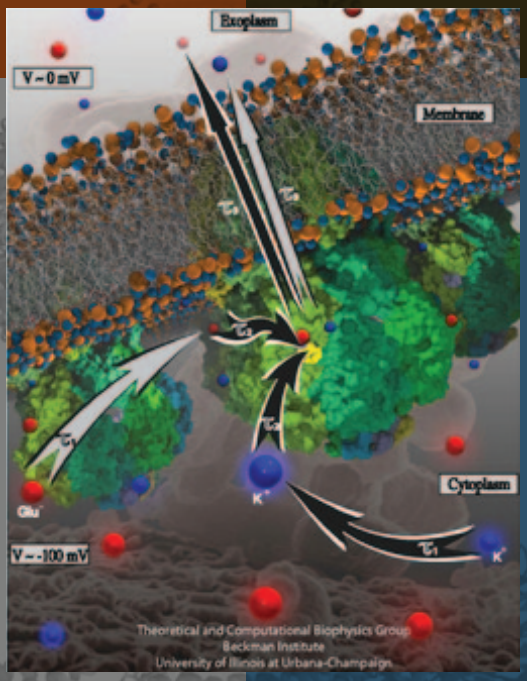
Water is the essential solvent that shapes protein structure and function, but for researchers using molecular dynamics flexible fitting (MDFF) to fit large biomolecular models to data from cryo-electron microscopy (such as fitting the classical ribosome into the ratcheted map) it was a mixed blessing. Since the network of hydrogen bonds that gives water its unique properties must rearrange as the solute moves, water molecules not only increase the size of the simulation but also slow the fitting process. Leaving water out completely was a common practice, relying on the MDFF fitting potential to prevent the dehydrated protein from shriveling. The 2.8 release of NAMD provides a better option: a new implementation of the generalized Born implicit solvent model that scales to thousands of cores for large biomolecular aggregates—thanks to NAMD's unique parallel structure and measurement-based load balancing system. By eliminating explicit water molecules from the simulation, an implicit solvent model helps shape protein structure while adapting immediately to new conformations. With this best-of-both-worlds option now available in NAMD, biomedical researchers using MDFF need fear water no longer.



Large Step With a Short Leg
July 2011

Motor proteins transport cargos from one place in living cells to another—for example, transport cell components along the long axons of nerve cells. A motor protein such as myosin VI has to "walk" or "run" along the cellular highway of actin filaments to perform the transport. In the case of myosin VI, snapshots from crystallography revealed that the protein's "legs" are too short to explain the size of step taken. Computational and experimental biophysicists have now solved the mystery of how myosin VI dimers realize their large step size despite their short legs. The investigation, based on the program NAMD, demonstrates that the answer lies in the flexibility of the legs. Myosin VI is able to triple the length of each leg, made of a short bundle of up-down-up connected alpha-helices, by extending the bundle to a stretched-out down-down-down geometry of segments, like turning a letter z into a single long line. In the telescoping process, myosin VI also gets help from its well-known binding partners, namely calmodulins. The calmodulins direct the telescoping of the protein legs as well as strengthen the extended legs. Together with an earlier study of the "neck" region of the molecule, scientists have established how walking myosin VI achieves its wide stride.

Yanxin Liu, Jen Hsin, HyeongJun Kim, Paul R Selvin, and Klaus Schulten. **Extension of a three-helix bundle domain of myosin VI and key role of calmodulins**. *Biophysical Journal*, 100:2964-2973, 2011.

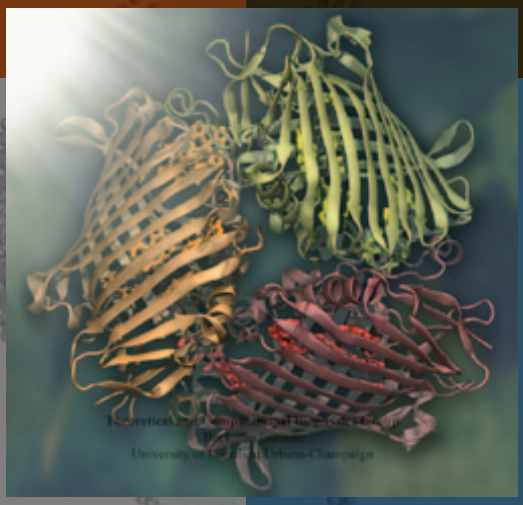


Smart Bacterial Safety Valve

July 2011

Bacterial cells enclose themselves with a cell membrane to maintain an optimal interior ion concentration and interior electrical potential. The potential is about -0.1 V inside versus 0 V outside, the potential difference amounting to an important energy reservoir for the cell. Closing itself off from the outside can be dangerous for a cell though, particularly when sudden changes outside the cell can cause it to burst. This can happen when ions outside the cell are washed away suddenly: outside water pushes itself into the cell – as the water prefers to be near ions only found inside the cell – a behavior called osmosis. The osmotic push can be so strong that the cell can burst. To prevent such a burst, cells evolved safety valves, one the mechanosensitive channel of small conductance or MscS. Under pressure, the valve, i.e., MscS, opens and enough ions leave the cell to keep water from pushing in too hard. But since the electrical potential inside is negative, primarily negative ions leave the cell, discharging its potential and leaving it without energy. A theoretical and computational study, the latter carried out using NAMD, reports now that MscS developed an ingenious solution: ions going through the MscS valve must pass a balloon-like filter that manages to mix positive and negative ions so that only a 1:1 mixture leaves a cell under osmotic shock, thereby providing protection against the shock without compromising the cell's electrical potential.

Ramya Gamini, Marcos Sotomayor, Christophe Chipot, and Klaus Schulten. **Cytoplasmic domain filter function in the mechanosensitive channel of small conductance**. *Biophysical Journal*, 101:80-89, 2011.



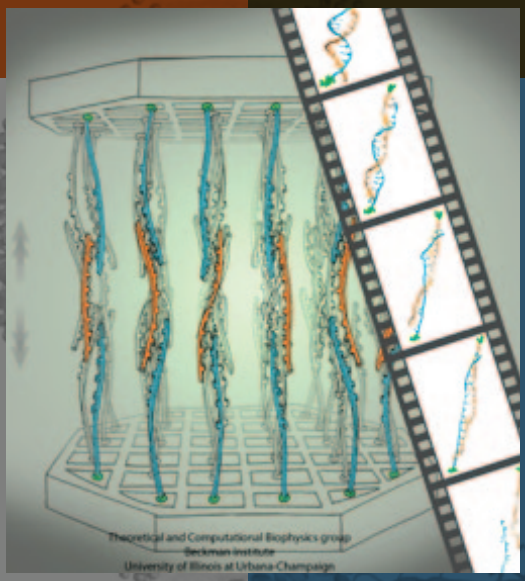
Energy Faucet
August 2011

Green sulfur bacteria are life forms that use sunlight as a main food source. They harvest the light by absorbing the sun's photons with their chlorosome system, an assembly of thousands of chlorophyll molecules. Absorption produces electronic excitation of the chlorophyll molecules, but the excitation is short-lived (lifetime of about 1 nanosecond) and needs to be turned quickly enough into a more stable form of energy. The latter is achieved in a protein complex called the reaction center, but for this purpose the electronic excitation needs to travel from the chlorosome to the reaction center through a protein complex called the Fenna-Matthews-Olson (FMO) protein. FMO is a crucial bottleneck, acting as an energy faucet, through which the short-lived excitations need to flow in a fraction of a nanosecond. Electronic excitations are quantum phenomena highly sensitive to thermal noise. Biophysicists spend much effort to measure thermal effects on FMO electronic excitation flow. Now researchers have complemented measurements through calculations and have shown why FMO function is actually robust against thermal noise. Using a combination of classical and quantum mechanical calculations they quantified the thermal noise present in FMO, and determined that thermal noise greatly reduces quantum coherent excitation in the transport through FMO, but that does not seem to be detrimental to excitation flow.

Carsten Olbrich, Johan Strümpfer, Klaus Schulten, and Ulrich Kleinekathoefer. **Quest for spatially correlated fluctuations in the FMO light-harvesting complex**. *Journal of Physical Chemistry B*, 115:758-764, 2011. (PMC: 3140161)

Carsten Olbrich, Johan Strümpfer, Klaus Schulten, and Ulrich Kleinekathoefer. **Theory and simulation of the environmental effects on FMO electronic transitions**. *Journal of Physical Chemistry Letters*, 2:1771-1776, 2011. (PMC: 3144632)

Carsten Olbrich, Thomas L. C. Jansen, Jörg Liebers, Mortaza Aghtar, Johan Strümpfer, Klaus Schulten, Jasper Knoester, and Ulrich Kleinekathoefer. **From atomistic modeling to excitation transfer and two-dimensional spectra of the FMO light-harvesting complex**. *Journal of Physical Chemistry B*, 115(26):8609-8621, 2011.

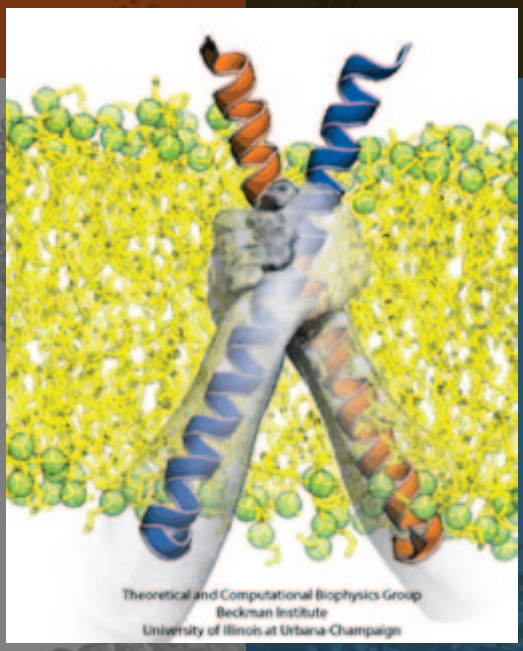


Diet and DNA
September 2011

The genes of organisms, like plants and animals, offer the blueprint, not only to build the organism anew from a seed or fertilized egg cell, but also to adapt the living organism to its habitat and life experience. For example, a type of tree growing in an arid or wet region will adapt expression of its genes for root growth optimal to circumstances. A child living on a scarce or abundant diet or with little or much physical activity will adapt body growth accordingly. The adaptation of an individual's gene expression is the subject of epigenetics. One control element in epigenetics is that cytosine bases of an organism's DNA become methylated at the 5-position in a chemical reaction in which the hydrogen atom is replaced by a methyl group (CH3). DNA methylation patterns depend on an organism's individual history; aberrant methylation patterns can be the cause of diseases, for example, of certain cancers. It is known that the proteins involved in gene expression can recognize methylated sites of DNA and, thereby, direct gene expression; DNA methylation also affects the packing of DNA in the chromosomes. However, methylation may also affect gene expression directly; experiment and computational modeling with NAMD suggest now an intriguing third way how methylation can regulate gene expression. Methylation is shown to make it more difficult to separate the two strands of DNA, as is necessary during gene expression. An earlier experimental-computational study had revealed already that methylated DNA can pass narrow synthetic nanopores more readily than unmethylated DNA can. The two experimental-computational findings advance our understanding of methylation-based epigenetics and of how our body adapts to our life style and diet.

Philip M.D. Severin, Xueqing Zou, Hermann E. Gaub, and Klaus Schulten. **Cytosine methylation alters DNA mechanical properties**. *Nucleic Acids Research*, 2011.

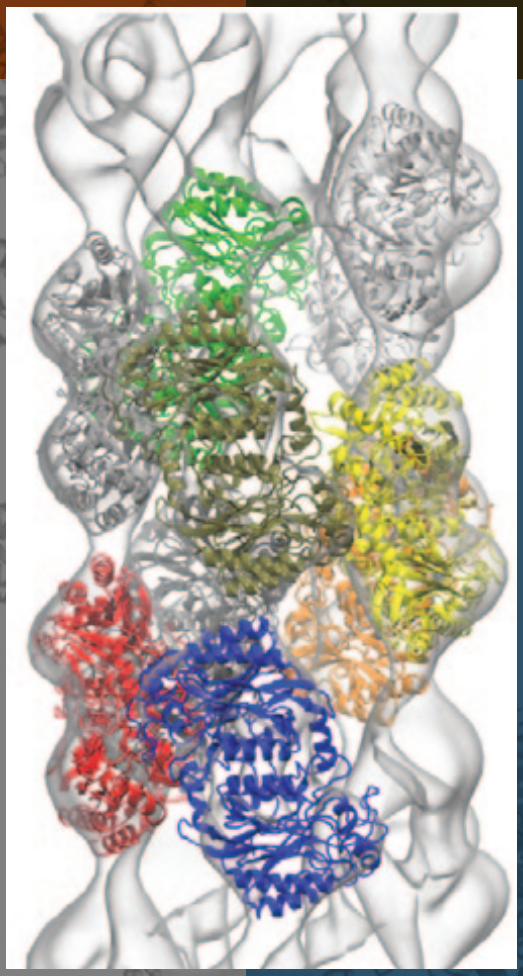
Utkur M. Mirsaidov, Winston Timp, Xueqing Zou, Valentin Dimitrov, Klaus Schulten, Andrew P. Feinberg, and Greg Timp. **Nanoelectromechanics of Methylated DNA in a Synthetic Nanopore**. *Biophysical Journal*, 96:L32-L34, 2009. (PMC: 2717226)



Protein Twins Hold Hands
October 2011

Bacteria contain the simplest photosynthetic machineries found in nature. Higher organisms like algae and plants practice photosynthesis in a more elaborate but principally similar manner as bacteria. But even for its simplicity, the bacterial photosynthetic unit is not without its unsolved mysteries. Take, for example, the crucial photosynthetic core complex, which performs light absorption and the initial processing of the light energy. In certain bacterial species, the core complex are each ring-shaped singlets, but in some other bacterias they can be 8-shaped doublets, formed by the association of two ring-shaped core complexes. The question arises: What holds doublets together. It turned out that doublets arise when bacteria bacterial contain two copies, i.e., twins, of an additional small protein called PufX. Recently, computational biologists and biochemists have come together to study PufX from different bacteria. They found an interesting trend showing that bacterial species with PufX that associates with another PufX protein also contain core complexes that form 8-shaped doublets. On the other hand, bacteria whose PufX is incapable of associating with another PufX have only singlets of ring-shaped core complexes. These new results resonate with a proposed role of PufX as the protein that holds two core complexes together to form 8-shaped doublets. Bacteria with PufX that cannot perform this role therefore only have singlets of ring-shaped core complexes. The needed simulations were done with NAMD.

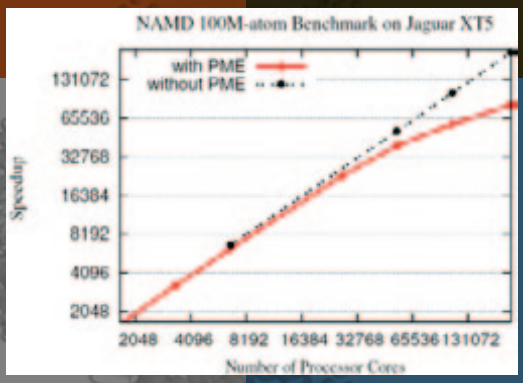
Jen Hsin, Loren LaPointe, Alla Kazy, Christophe Chipot, Alessandro Senes, and Klaus Schulten. **Oligomerization state of photosynthetic core complexes is correlated with the dimerization affinity of a transmembrane helix.** *Journal of the American Chemical Society*, **133:14071-14081, 2011. doi: 10.1021/ja204869h. (PMC: 3168531)**



Symmetry Helps
October 2011

Inorganic nature brings about symmetry that one can admire, for example when one sees a polished diamond. Living nature, too, brings about symmetric structures; for example, many processes in living cells are carried out by highly symmetric protein complexes. In case of living cells symmetry comes about partially out of physical or geometrical necessity, but also partially out of its usefulness for the intended purpose. Hence, understanding symmetry in biology goes beyond related studies of the beauty of symmetry in the physical and mathematical sciences as one also asks: Does symmetry help? Put it another way: Symmetry in living cells is beautiful and useful! The proteins in symmetric complexes are often imaged by electron microscopy (EM), but unfortunately not at a resolution high enough to recognize chemical detail, as is needed in most cases, e.g., in case of the study of a symmetric multi-enzyme system. Computational biologists have developed a method to solve the resolution problem, using high resolution images obtained through X-ray scattering of related molecules and matching them through molecular dynamics using NAMD to the image seen in EM. This method is called molecular dynamics flexible fitting (MDFF). MDFF has now been extended to determine the atomic-level structure of symmetric multi-protein systems. MDFF has been applied successfully to three highly symmetric multi-protein systems: (i) GroEL-GroES, a protein complex that assists proteins to fold properly into their native conformation; (ii) a nitrilase multi-enzyme system that converts massive amounts of molecules into forms more suitable for a bacterial cell; (iii) Mm-cpn, a protein complex supposedly involved in assisting protein folding in so-called archaebacteria. In all cases the symmetry of the protein complexes plays a key role.

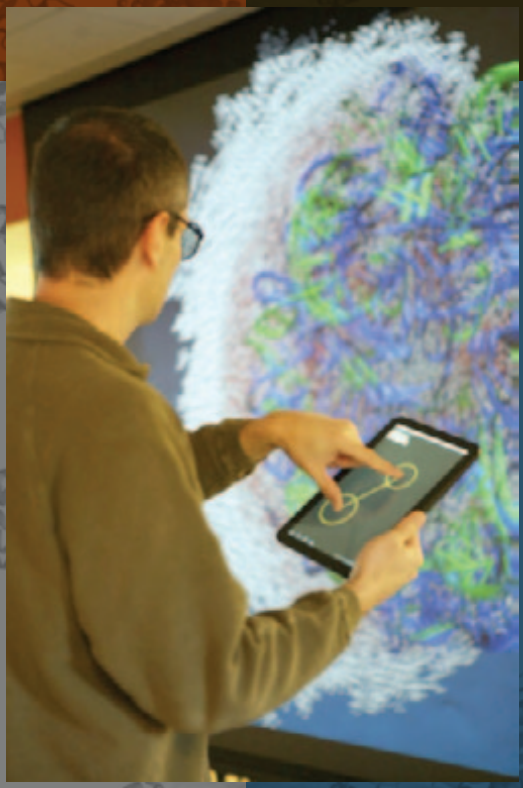
Kwok-Yan Chan, James Gumbart, Ryan McGreevy, Jean M. Watermeyer, B. Trevor Sewell, and Klaus Schulten. **Symmetry-restrained flexible fitting for symmetric EM maps.** *Structure*, **19:1211-1218, 2011. (NIHMS: 317172)**



Expanding Simulation Size
November 2011

The NAMD molecular dynamics program excels at simulating, in atomic detail, the complex molecular machinery of living cells. NAMD now enables hundred-million-atom simulations using the full capabilities of the nation's fastest supercomputers due to parallel programming innovations reported at the SC11 supercomputing conference. While parallel supercomputers have massive amounts of memory in aggregate, any part of the machine can directly access only a small fraction. To fit the molecular blueprint of cellular structures such as the chromatophore in the memory of such machines, a compressed data format was developed that exploits the repetitive nature of proteins, nucleic acids, lipid membranes, and solvent. This format requires only a small amount of data to be copied to all parts of the supercomputer, while the remainder is read from disks in parallel and distributed across the machine. Simulation output and the balancing of work loads are similarly distributed. The Charm++ parallel programming system, on which NAMD is built, was also extended to allow the molecular structure and other data to be shared among the increasing number of cores in modern processors. A hundred-million-atom simulation can now run on supercomputers with only 2 gigabytes of memory per node, such as the IBM BlueGene/P. The enhancements are available to computational biologists world-wide in special memory-optimized versions of NAMD 2.8.

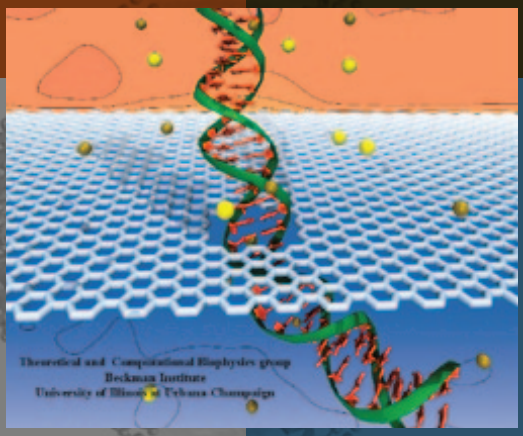
Chao Mei, Yanhua Sun, Gengbin Zheng, Eric J. Bohm, Laxmikant V. Kalé, James C. Phillips, and Chris Harrison. **Enabling and scaling biomolecular simulations of 100 million atoms on petascale machines with a multicore-optimized message-driven runtime. In Proceedings of the 2011** *ACM/IEEE conference on Supercomputing*, **Seattle, WA, November 2011.**



A Movie per Second
November 2011

Computer simulations of the biomolecular processes in human cells guide better understanding of health and disease as well as development of dietary supplements and pharmacological treatments. Such simulations are extremely demanding and, in fact, all too often still limited by technological feasibility. However, technological advances are being brought to bear on computer simulations in biomedicine through highly dedicated biomedical engineers, who have often speerheaded uses of new computer technologies such that they became available in biomedicine much sooner than in other fields. A case in point is solid state disk (SSD) technology that can serve as extremely fast and large computer memory. Conventional RAM (random access memory) is fast, but limited in size due to cost; the well known hard disks (HDs) can hold large data sets at an affordable price, but are slow. The new SSDs are in the middle ground, faster than HDs, slower than RAM, offering large data storage at an affordable price. Modern uses of SSDs in smart phones and tablets attest to the usefulness of SSDs. The biomolecular visualization and analysis software VMD in its next release (VMD 1.9.1) makes the power of SSDs as a huge, yet fast storage medium available to biomedical researchers. This will allow them to view and analyze through VMD on the fly Gigabytes-to-Terabytes of simulation data, that are being raked into a computer at the rate of up to 4 Gigabytes per second (one high definition video of a long movie per second!).

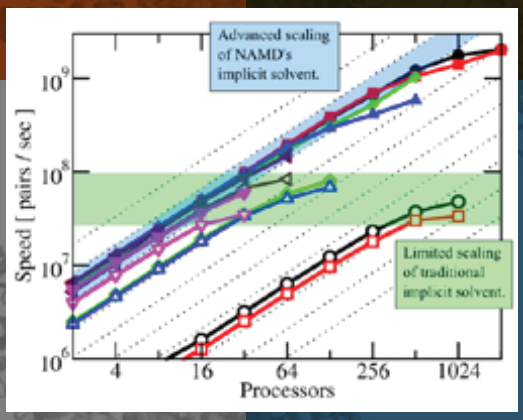
John E. Stone, Kirby L. Vandivort, and Klaus Schulten. **Immersive out-of-core visualization of large-size and long-timescale molecular dynamics trajectories.** *Lecture Notes in Computer Science*, **6939:1-12, 2011. (PMC: 3032211)**



DNA Through Graphene Pore
December 2011

Threading DNA electrically through nanometer-sized pores, so-called nanopores, holds promise for detecting and sequencing DNA. Nanopore measurements tend to be the more sensitive the smaller the pores are. The material graphene, which is just one atom thick and looks like a two-dimensional ``honeycomb" made up of carbon atoms, offers the ultimate physical resolution for measuring DNA (the stacking distance between base-pairs in DNA is about 0.35 nm). Molecular dynamics simulations using NAMD revealed the motion of DNA being threaded through graphene nanopores at atomic level resolution. Simulations not only agree qualitatively with previous experiments on DNA translocation through graphene nanopores, but go one step further than the experiments and suggest how individual base pairs can be discriminated. The recent computational study is one further example for the guidance that molecular dynamics simulations provide in nanosensor development.

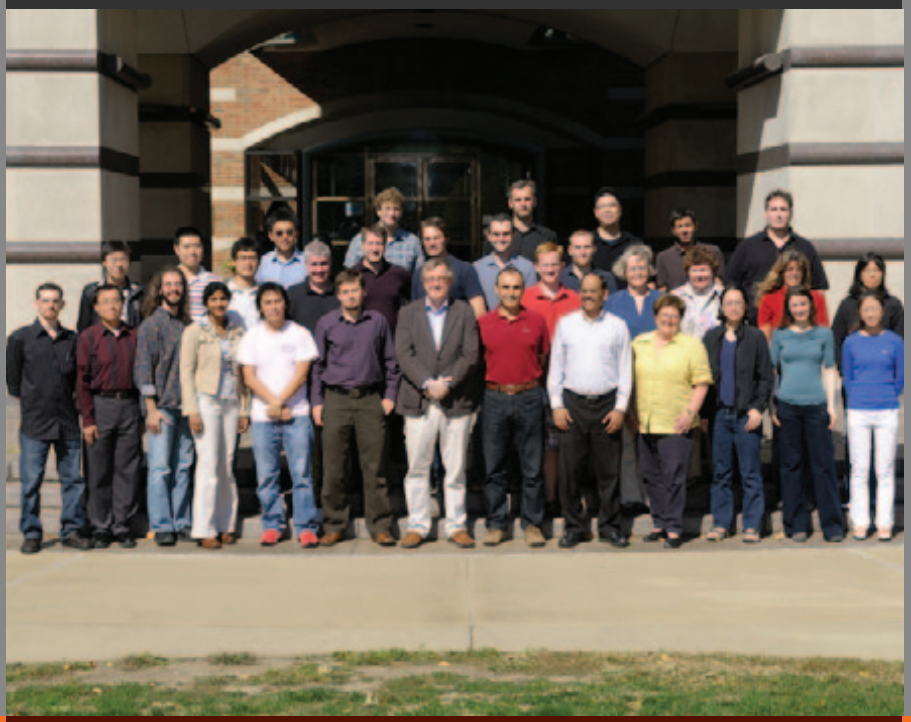
Chaitanya Sathe, Xueqing Zou, Jean-Pierre Leburton, and Klaus Schulten. **Computational investigation of DNA detection using graphene nanopores.** *ACS Nano*, 5:8842-8851, 2011. (PMC: 3222720)



Water, Water, Every Where
December 2011

Water is ubiquitous; living cells and the cells' biomolecules are greatly influenced by water. Accounting for water in computational modeling, a key access route to imaging cell processes, comes at a stiff price: up to 90% of the simulation volume needs to be a water bath embedding simulated biomolecular machinery. The sheer number of water molecules arising here, sometimes millions, and the strong hydrodynamic drag resisting biomolecular dynamics, slows down simulations tremendously. Computational biologists had invented a means to replace water by a kind of continuous ether, so-called implicit solvent, that accounts for key electrostatic features of water around biomolecules, but does not slow down simulations. Computational hinderance through explicit water is getting worse with increasing size of biomolecular machines, but so far the implicit solvent description could not be effectively employed to model large systems using supercomputers. Now, the situation has been repaired and the use of an implicit solvent in molecular dynamics simulations of systems as large as the whole ribosome (containing 300,000 ribosome atoms and eliminating 2,700,000 water atoms) have been documented.

David E. Tanner, Kwok-Yan Chan, James Phillips, and Klaus Schulten. **Parallel generalized Born implicit solvent calculations with NAMD.** *Journal of Chemical Theory and Computation*, 7:3635-3642, 2011. (PMC: 3222955)



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