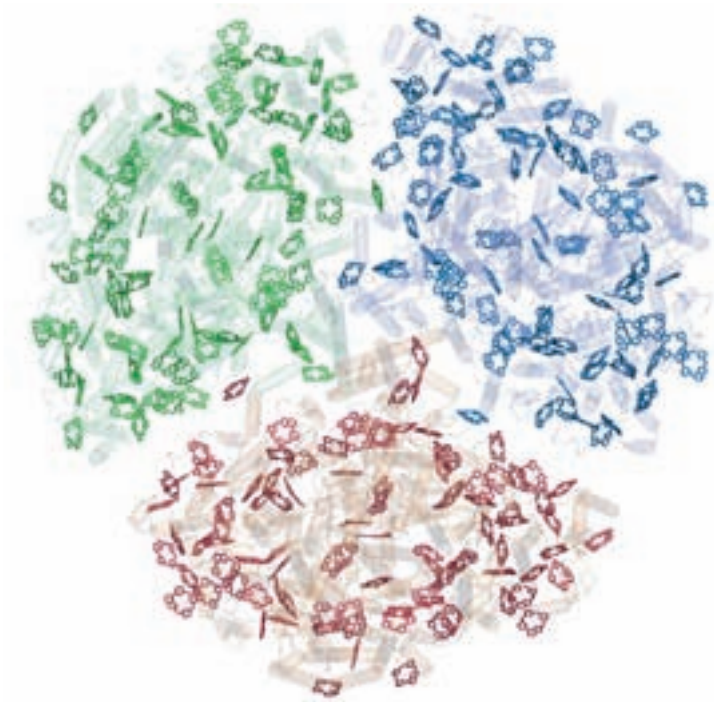


Recent Highlights



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

Theoretical and Computational Biophysics Group

NIH Resource for Macromolecular Modeling and Bioinformatics





Motivated by biomedically relevant problems and collaborating closely with experimental laboratories, the Theoretical and Computational Biophysics Group exploits advances in physical theory and computing to model living organisms across many levels of organization, from molecules to cells to networks. During the past three years, the group has pioneered the modelling of very large biomolecular structures and has embarked on an innovative computational tool, steered and interactive molecular dynamics. Highlights of our group's research program, software tool development, and outreach to the wider community are presented each month on our web site. In the following we present the recent highlights from the years 2001 to 2004.

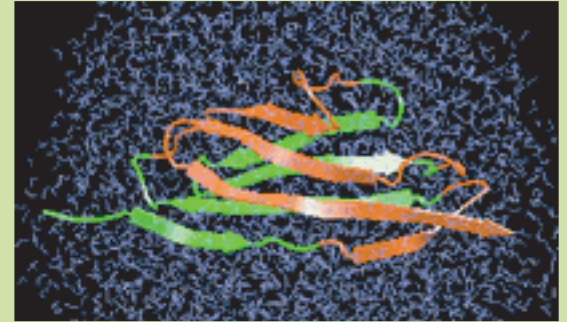
Recent Highlights

<http://www.ks.uiuc.edu>



Jan 2001 Stretching Muscle

Water can act as a conformational lubricant for protein folding. The giant muscle protein titin is a roughly 30,000 amino acid long filament which plays a number of important roles in contraction and elasticity. For example, upon stretching in muscle some of titin's protein domains can unfold one-by-one permitting titin to retain elastic properties in muscle over a very wide range of length. To examine in atomic detail the dynamics and structure-function relationships of this behavior, SMD simulations of force-induced titin domain unfolding were performed in close collaboration with atomic force microscopy observations. The simulations led to the discovery that water molecules play an essential role in breaking sets of hydrogen bonds that control the unfolding of titin's domains.

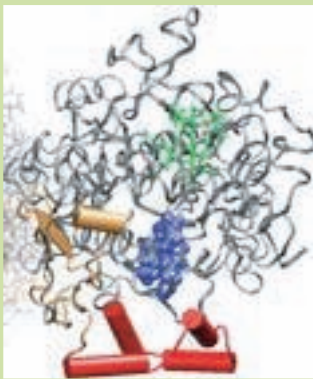


H. Lu and K. Schulten
Biophysical Journal, 79:51-65, 2000

Feb 2001 Commodity Supercomputing

We have installed a low-cost cluster of 32 PCs with 1.1GHz Athlon processors, 256MB of RAM, and switched fast ethernet. On this new platform, the freely available simulation code NAMD runs 1 ns of our 92K atom ApoA1 PME benchmark in 8 days with 70% efficiency, the equivalent of a 100 processor Cray T3E. The new machine will be useful for simulations such as the stretching of the muscle protein titin. This work seeks to examine in atomic detail the dynamics and structure-function relationships of this 30,000 amino acid long filament in muscle contraction and elasticity. The cluster also provides a powerful engine for interactive simulations. The Linux-based Scyld Beowulf operating system makes the entire cluster appear to computational biologists as a single machine.





F. Molnar, L. S. Norris, and K. Schulten
Progress in Reaction Kinetics and Mechanism, 25:263-298, 2000

Mar 2001 A Captive Audience

Our UIUC College of Engineering 2001 Open House event featured a simulation of the regulation of genetic expression in bacteria using NAMD and VMD. We showed a model of a repressor protein that shuts down an active DNA site by forcing the DNA to adopt a looped form. The combination of a detailed all-atom model for the protein with a coarse-grained model for the DNA loop helps us to reduce the computational time required to simulate the behavior of this protein-DNA system. With a second project we illustrated how through Interactive Molecular Dynamics (IMD) one can manipulate manually, with force feedback, simulated biomolecules for the purpose of drug design. IMD, via a haptic input device, relies on researchers' sense of touch in their quest to understand how biomolecules work. Finally, we presented BioCoRE, a collaborative research environment for structural biology within which researchers can visualize information, share resources and interact with each other and with structural biology tools via a common infrastructure and across time zones and continents.

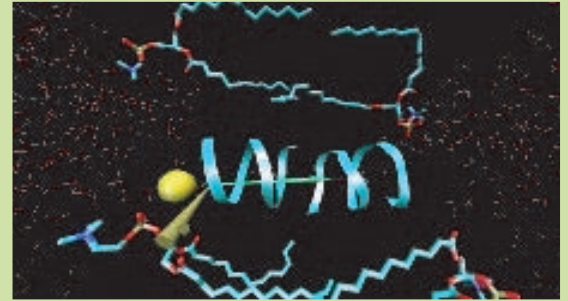
Mar 2001 Superaspirin - Simulated

Aspirin, the widely used pain killer, has revealed many beneficial effects such that it has attracted renewed attention. It has become known that aspirin acts as an inhibitor to prostaglandin synthase. Pharmacological researchers have succeeded to improve aspirin's effect by synthesizing analogue compounds, so-called superaspirins, that target the right type of prostaglandin synthase in the body. The continuing effort has been supported by basic research on the properties of prostaglandin synthases. Molecular dynamics simulations, carried out with our molecular dynamics program NAMD, have investigated how prostaglandin synthases select their substrates, arachidonic acid, through a binding channel that acts as a filter for compounds with the right stereochemical properties. The figure, taken from a recent publication, and made with our graphics program VMD, shows one monomeric subunit (in a cartoon/ribbon representation) of the ovine PGHS-1 homo dimer.



Apr 2001 Putting Your Hands on a Protein

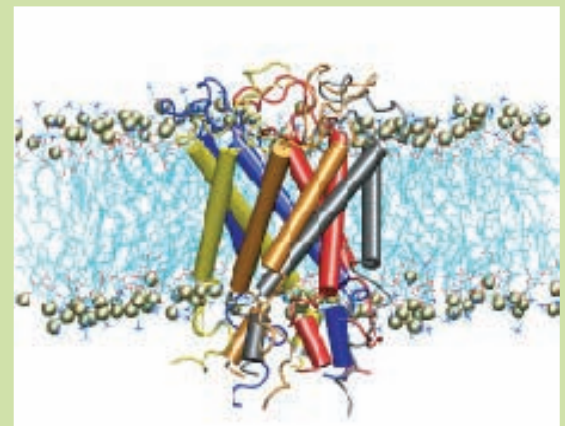
"If I could just get my hands on that protein!" Single molecule manipulation techniques like atomic force microscopy have brought us closer to this frequently expressed wish. These techniques, however, do not "see" the atomic level detail needed to relate mechanism to protein architectures. True, computational methods do illuminate the elusive protein structures, but are limited to static structures, or trajectories yielded by weeks-long simulations. Now, with the advent of inexpensive, high-performance computing, interactive manipulation of molecular dynamics simulations has become a reality. Linking advanced molecular graphics with ongoing molecular dynamics simulations, and utilizing a haptic device to connect forces from a user's hand with forces in the simulation, researchers can interact with "live" proteins. The new methodology is described in a recent publication and the figure shown here demonstrates a Cl⁻ ion being pulled through a gramicidin A channel.



J. Stone, J. Gullingsrud, P. Grayson, and K. Schulten. 2001 *ACM Symposium on Interactive 3D Graphics*, pages 191-194, New York, 2001. ACM SIGGRAPH

May 2001 How Cells "Feel" Mechanical Tension and Osmotic Stress

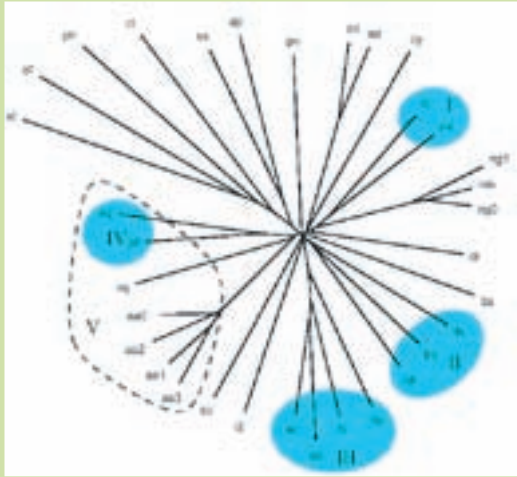
"How do you feel?" Biologists now have an answer that may surprise you. Our sense of touch relies upon the fact that cells in our fingertips can sense the pressure from a tabletop and transmit a signal to the brain. But until recently, the molecular mechanism for turning the stretching of a cell membrane into a cellular signal was unknown. An important step in understanding this process was the discovery of a protein known as a the mechanosensitive channel of large conductance, or MscL. Though this protein has been studied primarily in bacteria, homologues exist in all major kingdoms of life. Researchers in the Theoretical Biophysics Group have used molecular dynamics simulations to study, at the atomic level, how MscL opens in response to pressure changes. Models of MscL will give us new insight, not only into how we feel, but also how our hearts beat and how we keep our balance. Feel better now?



J. Gullingsrud, D. Kosztin, and K. Schulten
Biophysical Journal, 80:2074-2081, 2001

Recent Highlights

<http://www.ks.uiuc.edu>



C. Forst and K. Schulten
Journal of Molecular Evolution,
52:471-489, 2001 2001

Jun 2001 Phylogenetic Analysis of Metabolic Pathways Shows How Organisms Evolve

Organisms evolve according to the Darwinian principle by optimizing their traits through mutations of their genomes. In the past this principle had been rather narrowly applied to single genes and the associated single proteins. Knowledge of the sequences of the entire genomes of organisms encourages today a broader perspective: evolution should improve the entire context in which proteins function in organisms, for example, entire metabolic or signaling pathways. A new method describing the tree of evolution of organisms includes accordingly entire groups of genes that consolidate a cellular reaction network. The new phylogenetic analysis of metabolic networks has been applied in a recent publication to electron-transfer and amino acid biosynthesis networks yielding a more comprehensive understanding of similarities and differences between organisms.

Jul 2001 More Commodity Supercomputing

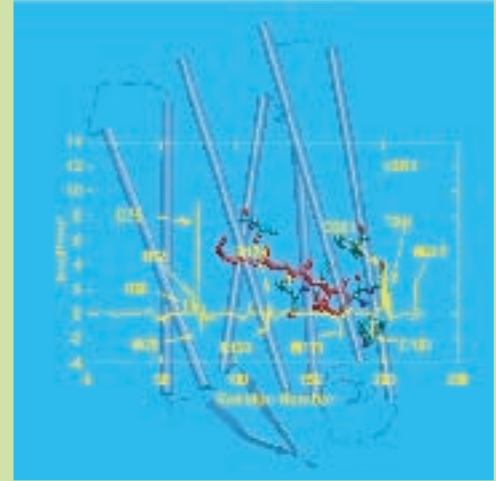
Our low-cost cluster of 32 Athlon PCs (see February 2001 highlight) has been in constant use by local users, providing a substantial and very cost-effective boost to our group's large-scale simulation capabilities. To satisfy demand, we have added two additional 32-processor clusters with higher performance at an even lower cost. On this platform, the freely available simulation code NAMD can complete a 1 nanosecond simulation of the 60,000 atom aquaporin-1 water channel with full electrostatics and constant pressure in a single week. We have given three tutorials, both filled to capacity, introducing participants to cluster hardware and software with the aid of a hands-on session assembling and installing four-processor clusters (see photo).





Aug 2001 Why We Can Enjoy a van Gogh Painting

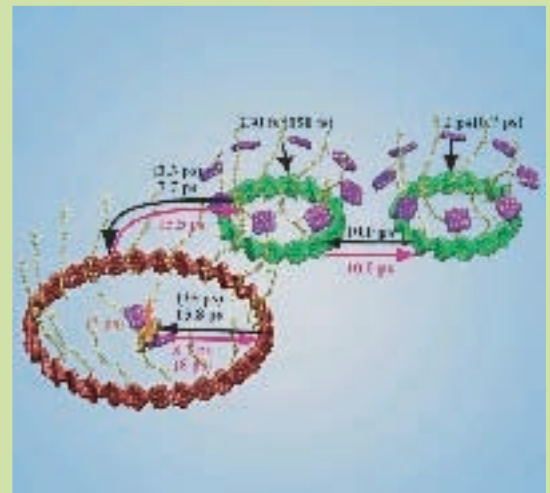
Perception of light and color permits humans to enjoy art, though the sense evolved more likely to better find ripe fruits. The recognition, centuries ago, that the wondrous sense of color comes from three visual receptors to which is added in the eye a fourth black & white one is one of the major achievements in the history of science. The visual receptors of all animals rely on one molecule for light absorption, retinal. How do the receptors tune then their spectral sensitivity? Exploiting a similarity of visual receptors to proteins in an archaebacterium, *Natronobacterium pharaonis*, researchers have finally been given an opportunity to answer this question quantitatively. In the bacterium, two structurally almost identical proteins absorb maximally light of 497 nm and 568 nm wavelength. X-ray crystallography and advanced quantum chemical studies could explain the difference and pinpoint to the protein side groups (see figure) that actually tune the spectra.



S. Hayashi, E. Tajkhorshid, E. Pebay-Peyroula, A. Royant, E. M. Landau, J. Navarro, and K. Schulten
J. Physical Chemistry, 105:10124-10131, 2001

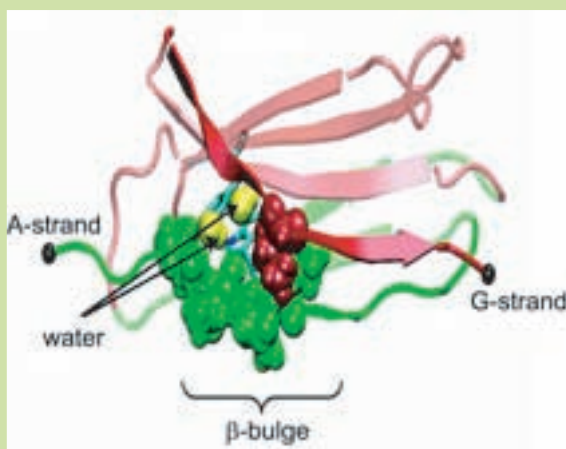
Sep 2001 A Solar Cell Engineered by Biological Evolution

Most of energy consumed by living species on earth stems ultimately from the sunlight harvested by photosynthetic cells. The light harvesting apparatus works like a solar cell, and optimizing its efficiency for the various habitats of life forms was a key strategy for survival of the fittest. After exploring for decades the role of individual molecules in light harvesting, chlorophylls, carotenoids, and small aggregates of these, researchers in the Theoretical Biophysics Group have now been able to put their findings together to calculate the overall efficiency and operational characteristics of a particular light harvesting system, that of purple bacteria. Based on structural biology, spectroscopy, and quantum mechanical calculations, a kinetic scheme was devised to show how evolution, like a good engineer, optimized the overall function of the system. The results are described in a recent paper, as well as in a review article .

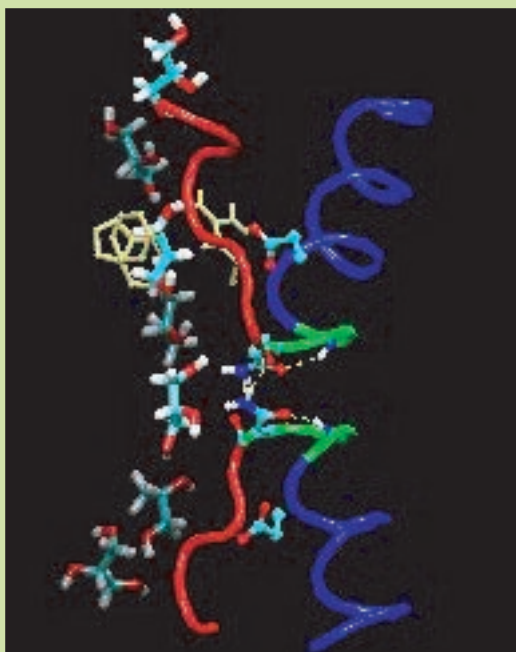


T. Ritz, S. Park, and K. Schulten
J. Physical Chemistry, 105:8259-8267, 2001

X. Hu, T. Ritz, A. Damjanovic, and K. Schulten
Quarterly Review of Biophysics, 35:1-62, 2002



D. Craig, A. Krammer, K. Schulten, and V. Vogel
Proc. Natl. Acad. Sciences, USA,
98:5590-5595, 20001



M. Jensen, E. Tajkhorshid, and K. Schulten
Structure, 9:1083-1093, 2001

Oct 2001 Mechanical Forces Rule Cells and Their Molecules

Mechanical force is seen today as a key component of molecular processes in cells: forces can be signals as in touch receptors, products as in muscle action, and substrates as in the matrix surrounding moving cells. This view of molecular processes is the result of a series of ground-breaking investigations that have become possible only recently and is rapidly turning into a new field, mechanobiology. A collaboration with V. Vogel and coworker (U. Washington, Seattle) has investigated structural changes accompanying stretch-induced unfolding events in type III fibronectin, a protein of the extracellular matrix, explaining the design of these proteins.

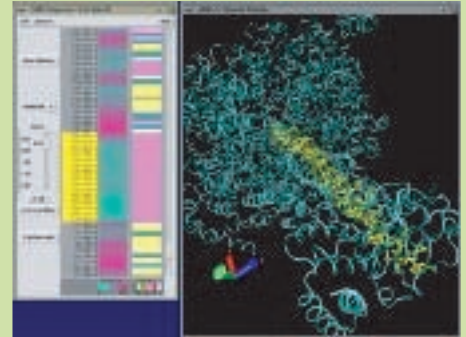
Nov 2001 How Cells Make Super Conductors

Aquaporins are channel proteins abundantly present in all life forms, for example, bacteria, plants, and in the kidneys, the eyes, and the brain of humans. These proteins conduct water and small molecules, but no ions, across the cell walls. Their defective forms are known to cause diseases, e.g., diabetes insipidus, or cataracts. The molecular modeling program, NAMD, along with large parallel computers at the Pittsburgh and Illinois supercomputing centers, permitted researchers now to model aquaporins in the natural environment of membrane and water in one of the largest molecular dynamics simulations ever (over 100,000 atoms). The simulations revealed in unprecedented detail how cells conduct water and glycerol, a molecule that serves cells' metabolism. The simulations provided a movie of the entire conduction process.



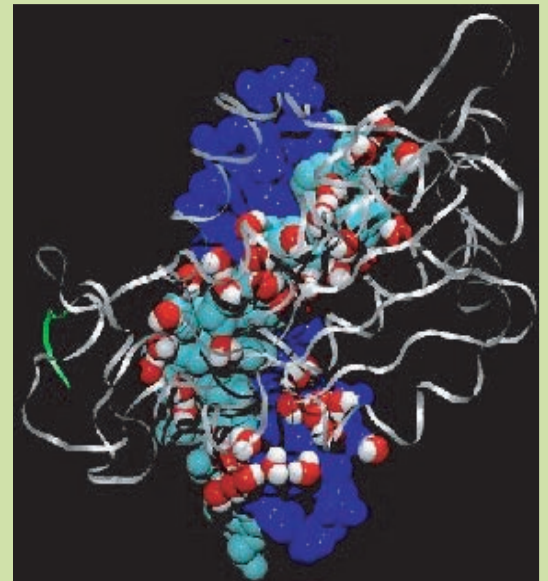
Dec 2001 VMD Integrates Sequence and Structure Display

Sequence and structure are complementary properties of proteins that are critical for our understanding of the molecular machinery of living cells. VMD now makes the study of both easier than ever by integrating its structure viewing capabilities with a new sequence viewing window. Protein residues selected in the structure window can be highlighted in the new sequence window; conversely, the three-dimensional structure of segments selected from the new sequence window can be displayed in the structure window. With its powerful molecular graphics capabilities and its existing and planned sequence viewing tools, VMD has become an essential tool in biomedicine.



Jan 2002 Putting Pressure on Protein-DNA Recognition

Deciphering the processes by which proteins recognize and bind to DNA is critical in our quest to understand cellular functions. To reach this goal, a collaboration with the group of Stephen Sligar, UIUC, explored the factors involved in protein-DNA recognition using hydrostatic pressure to perturb the binding of the BamHI endonuclease to cognate DNA. Our joint resulting publication outlines a new technique of high-pressure gel mobility shift analysis to test the effects of elevated hydrostatic pressure on the binding of BamHI (so-called restriction enzyme) to a specific DNA sequence. Upon application of a hydrostatic pressure of 500 bar, recognition between BamHI and the DNA sequence was weakened nearly 10-fold, suggesting an important role of water. An advanced 65,000 atom nanosecond molecular dynamics simulations with NAMD, at both ambient and elevated pressures, complemented the experiments and revealed how water-mediated interactions between BamHI and DNA control sequence recognition.



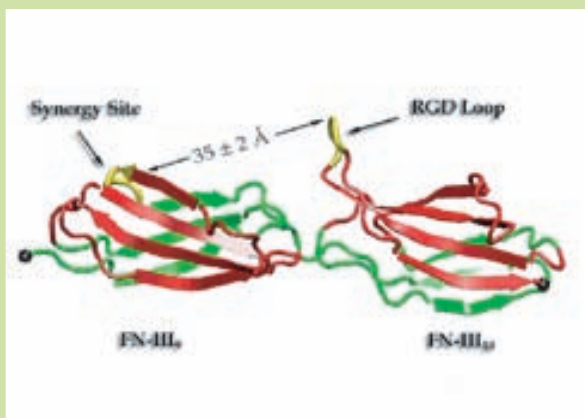
T. W. Lynch, D. Kosztin, M. A. McLean,
K. Schulten, and S. G. Sligar
Biophysical Journal, 82:93-98, 2002

Recent Highlights

<http://www.ks.uiuc.edu>



E. Tajkhorshid, A. Aksimentiev, I. Balabin, M. Gao, B. Isralewitz, J. C. Phillips, F. Zhu, and K. Schulten.
Adv. Protein Chemistry 66: 195-247, 2003.



A. Krammer, D. Craig, W. E. Thomas, K. Schulten, and V. Vogel
Matrix Biology, 21: 139-147, 2002

Feb 2002 Teraflops Harnessed for Biomedical Research

Adenosine triphosphate (ATP) is the fuel of life; every living cell must use ATP to carry out its functions, and the human body synthesizes its own weight in ATP every day. The ubiquitous molecular motor ATP synthase catalyzes the creation of ATP by precisely directing electrochemically generated torque. A detailed understanding of how this system functions can impact areas ranging from neurodegenerative disease research to nanotechnology development. Running at the Pittsburgh Supercomputing Center on LeMieux, the most powerful computer system in the world for open research, the freely available simulation code NAMD can simulate a solvated all-atom model of ATP synthase with full electrostatics at 65% efficiency on 1000 processors. This achievement in scalability places NAMD an order of magnitude ahead of comparable packages for molecular dynamics simulation.

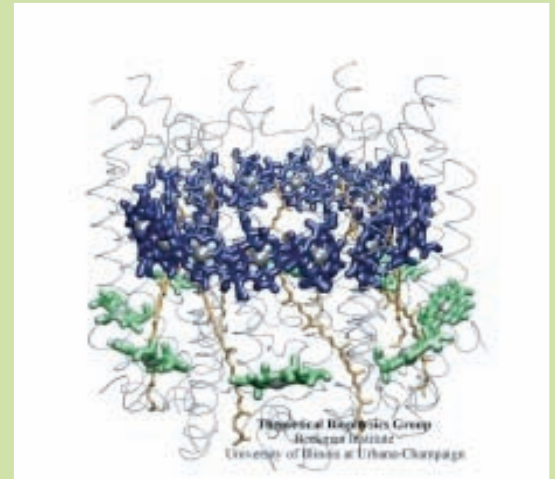
Mar 2002 Cells Sense Push and Pull

Cells in animals adhere to dynamic, seemingly random assemblies with other cells that make up tissues like skin, organs, and brain. The cell's adhesion and motion is controlled by the extracellular matrix, with the protein fibronectin being a key component. The proteins have optimal mechanical elasticity and also signal to cell surface receptors, integrins, the tension exerted on them. How this is achieved is the subject of an ongoing collaboration with the research group of Viola Vogel of the Department of Bioengineering at the U. of Washington in Seattle (see also Oct 2001 highlight). The most recent publication from this effort reports a 97,884 atom steered molecular dynamics simulation using NAMD. It is revealed now that stretching two consecutive domains of fibronectin deforms two sites, the so-called RGD and synergy sites as well as their distance. This weakens binding to cell receptors and, as a result, integrins can function as gauges that signal the magnitude of exterior forces to a cell.



Mar 2002 Exciting Biology and Hot Physics Meet

Most life forms exist near temperatures of about 300 Kelvin where thermal disorder is significant. Understanding how life copes with this disorder, in fact, most often exploits it, poses a deep intellectual challenge. Two recent publications investigate thermal disorder for electronically excited bioelectronic systems that harvest sun light and funnel its energy into the metabolism of so-called purple bacteria. One study borrows mathematics (supersymmetric calculus) from the physics of elementary particles to describe the optical properties of randomly distributed, but otherwise immobile, aggregates of chlorophylls. The second study goes a step further and investigates optical properties affected by thermal motion. The paper draws its insights from a pioneering 87,055 atom molecular dynamics simulation of a membrane-protein-chlorophyll system that monitored thermal motion of atoms and electrons and extends a mathematical description, the polaron model, used in advanced solid state physics.

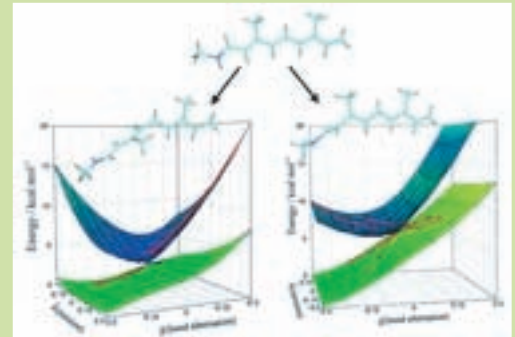


M. Sener and K. Schulten
Physical Review, 65:031916, 2002

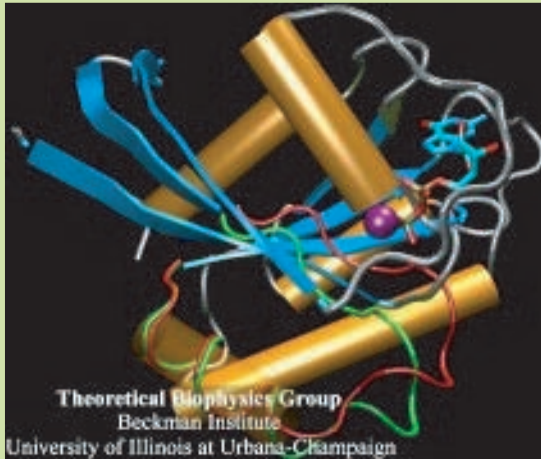
A. Damjanovic, I. Kosztin, U. Kleinekathoefer, and K. Schulten
Physical Review, 65:031919, 2002

Mar 2002 The First 0.000000000001 Second of Vision

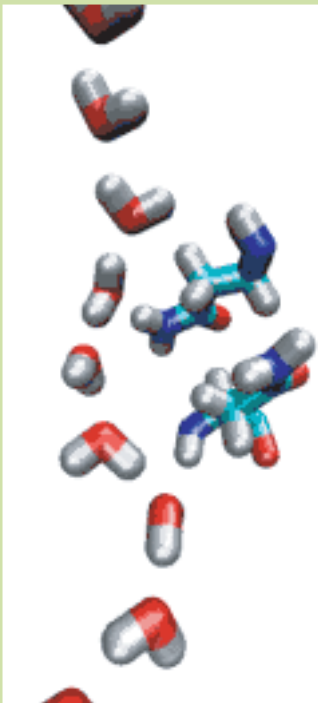
Since Newton, vision has attracted physicists seeking to explain how light is sensed by organisms. Recently, the structure of a visual receptor protein has been solved crystallographically and physicists have a new opportunity to explain vision in atomic level detail. Vision starts with optical excitation of retinal, located in the receptor protein, and the subsequent vibrational - torsional motion in retinal's electronically excited state. Retinal reaches within less than a picosecond (0.000000000001 s) geometries for which excited state and ground state merge energetically, the so-called conical intersections. Here retinal converts back to the ground state and becomes trapped into a new stable geometry. A recent study by the Theoretical Biophysics Group explains how the conical intersections of retinal steer retinal towards the right trapped geometry, one that is capable of triggering a visual signal.



M. Ben-Nun, F. Molnar, K. Schulten, and T. J. Martinez
Proc. Natl. Acad. Sciences, USA,
99: 1769-1773, 2002



I. Kosztin, R. Bruinsma, P. O'Lague, and K. Schulten
Proc. Natl. Acad. Sciences, USA, 99:
3575-3580, 2002



E. Tajkhorshid, P. Nollert, M. Jensen, L. Miercke, J. O'Connell, R. M. Stroud, and K. Schulten
Science, 296: 525-530, 2002

Apr 2002 Forceful Signaling

Biological cells process numerous types of information, for optimal control of their life cycles or to adapt to their environment, and recruit for this purpose signaling proteins. The best known among the latter are the G-proteins, involved in numerous diseases and related to many targets of drugs. G-proteins are closely related to motor proteins: G-proteins get switched on and off through the binding of GTP and its hydrolysis to GDP; motor proteins generate mechanical force through binding of ATP and its hydrolysis to ADP. A recent publication reports a 19,463 atom computer simulation using NAMD that reveals a "power stroke" in G-proteins likewise found in motor proteins. The stroke switches on and off G-proteins' ability to interact with other signaling proteins, with a power stroke that transforms the protein from an ordered into a disordered conformation.

May 2002 Filtering a Bathtub of Water a Day

Human kidneys need to filter about a bathtub of water a day through cells that contain membrane channels made of proteins called aquaporins. Crystallographers from the University of California at San Francisco (R. Stroud and coworkers) that discovered the structure of one type of aquaporins, aquaglyceroporins, have teamed up with UIUC researchers to determine how these channels achieve their very high water throughput, yet prevent the cells' electrical potential from discharging by not permitting any flow of ions or conduction of protons. The team, combining 106,000 atom simulations using NAMD and crystallography, found that the channels achieve the impressive filtering function by conducting water single file and keeping the water molecules strictly oriented: water molecules enter the channel oxygen atom first and leave the channel oxygen atom last. Aquaporins are ubiquitous in mammals, plants, and bacteria and the finding, published recently in *Science* magazine, has implications for many biological functions as well as for human diseases, e.g., cataract of the eye, loss of hearing, or diabetes insipidus.

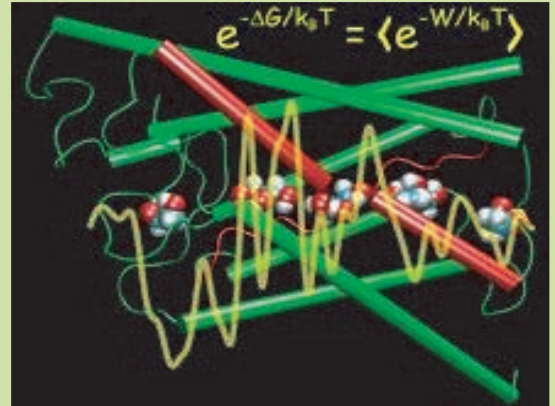
Recent Highlights

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Jun 2002 A Molecular Sieve

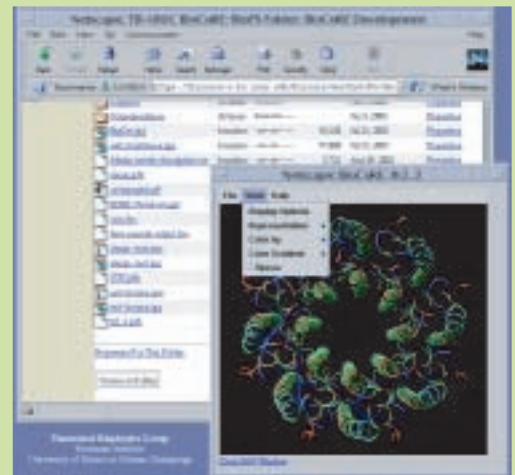
Living cells rely on nutrients absorbed through their cell membranes, for example on glycerol that is key to the cells' metabolism. Proteins, so-called aquaporins, in the membranes form channels that act as sieves permitting passage of water, glycerol, and like molecules, but prevent other molecules of similar size from entry and clogging. For this purpose the channels interact strongly with molecules attempting to pass. In a recent publication, the energetics of the conduction process of glycerol for the aquaporin GlpF was measured in a molecular dynamics simulation, carried out with NAMD, that pulled glycerol through the channel, monitoring the forces needed to advance along the channel axis. An analysis that discounted the irreversible work done on glycerol, a difficult prerequisite, yielded the energy profile that glycerol experiences along the channel and that reflects how the protein decides which molecules are allowed to pass the sieve.



M. Jensen, S. Park, E. Tajkhorshid, and K. Schulten
Proc. Natl. Acad. Sciences, USA,
 99: 6731-6736, 2002

Jul 2002 Proteins Through the Looking Glass

The building blocks of living cells are biomolecules so small that no light microscope can see them, yet viewing them is essential to decipher the inner workings of cells. The best looking-glass for biomolecules (such as proteins) available today is computers running molecular graphics software that translates experimental data into the molecular graphics. Now the wide availability of molecular graphics has taken a step forward with our new visualization package, JMV (Java Molecular Viewer). JMV borrows several key features from our visualization tool for large scale biomolecules, VMD. The JMV applet places the picture of a protein in your web browser, shown in a 3-D view, ready to be rotated, scaled, and colored according to physical properties. JMV will serve the next generation of bioinformatics web tools, like BioCoRE, through its great adaptability and will turn every molecular picture in electronic text books or web sites into an interactive looking-glass.



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Aug 2002 Unbreakable Biological Solar Cell

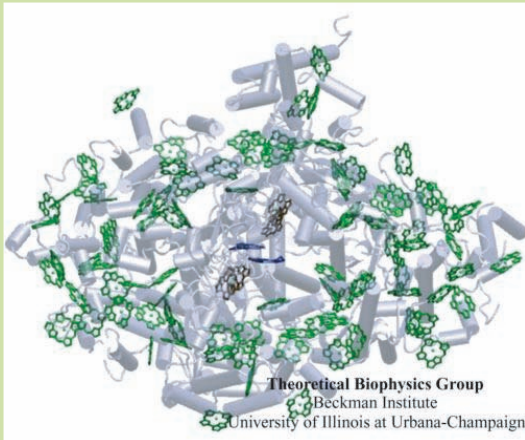
Light is fundamental for life. Through many photosynthetic life forms, its energy fuels the major part of Earth's biosphere. The familiar green color of plants, so ubiquitous in our surroundings, stems from chlorophylls, molecules that help plants, algae, and some bacteria to harvest the sunlight. Recently, the structure of an apparatus that harvests sunlight in cyanobacteria, and actually in a similar fashion in plants, has been discovered, showing 96 chlorophylls being held at close distances by a protein complex. The chlorophylls absorb sunlight and deliver its energy to a central chlorophyll pair that utilizes it to electronically charge a cell membrane, the whole functioning like an extremely efficient biological solar cell. Quantum physics and a theoretical analysis of the energy utilization of the system, reported in a recent publication, have revealed that this system has been designed with a high degree of fault tolerance and optimality: pruning single and even multiple chlorophylls hardly affects the efficiency of the apparatus; altering the chlorophylls' arrangement though leads to a reduction of efficiency. Since the apparatus is naturally exposed to intense radiation and subject to continuous damage, its robustness is crucial for the organism.

Sep 2002 Nailing the Mechanism of a Protein

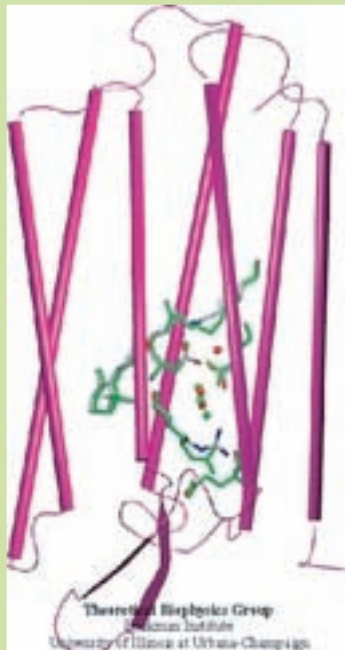
Resolving the physical processes that underly the biological function of a protein can be an elusive goal even with extremely detailed observations available. An example is the protein bacteriorhodopsin, a light driven proton pump in archaeobacteria. This protein is a close relative to human G-protein coupled receptors that are the target for many pharmacological interventions and, hence, knowledge of bacteriorhodopsin's dynamics is of great medical interest. Despite the availability of highly resolved structures and spectroscopic observations of the protein and its functional intermediates, as they arise within 10-12 s of light absorption triggering its function, the physical mechanism remained ill understood. A recent computational modeling study that combined a quantum mechanical simulation of the protein's active site with a classical mechanical simulation of the remainder of the protein succeeded to fill in the elusive detail that reveals a complete picture of how the protein initiates proton pumping, a key step to explain entirely the biological function.

Recent Highlights

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M. K. Sener, D. Lu, T. Ritz, S. Park, P. Fromme,
and K. Schulten
J. Physical Chemistry, 106: 7948-7960, 2002



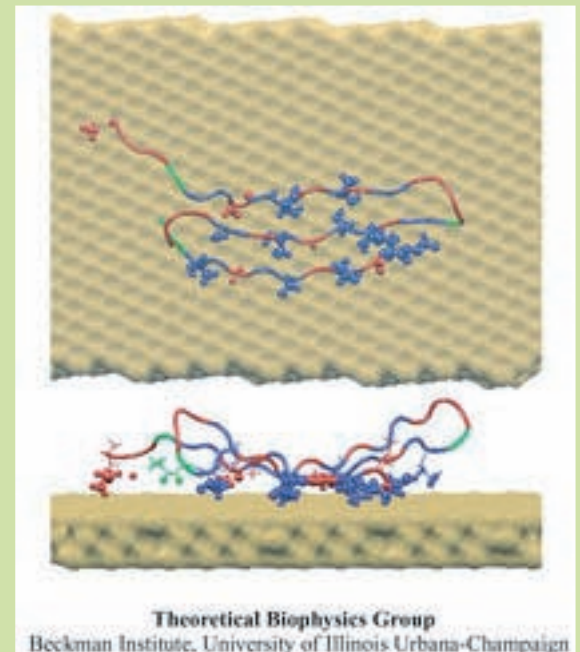
S. Hayashi, E. Tajkhorshid, and K.
Schulten
Biophysical Journal, 83: 1281-1297,
2002



Oct 2002 Seeking Gold

The biological control of inorganic crystal formation, morphology and assembly is of interest to biologists and biotechnologists studying hard tissue growth and regeneration, as well as to materials scientists using biomimetic approaches for control of inorganic material fabrication and assembly. A molecular-level understanding of the natural mechanisms involved in these processes can be derived from the use of metal surfaces to study surface recognition by proteins together with combinatorial genetics techniques for selection of suitable peptides.

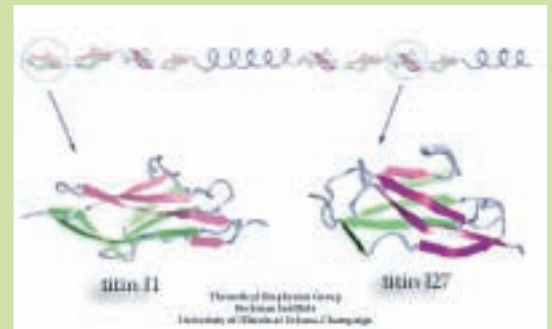
In a recent study, the structure of a genetically engineered gold binding protein has been determined computationally, and the ability of the protein to recognize gold crystal surfaces has been explained. Molecular dynamics simulations were carried out with the program NAMD using the solvated protein at the gold surface to assess the dynamics of the binding process and the effects of surface topography on the specificity of protein binding.



R. Braun, M. Sarikaya, and K. Schulten
Journal of Biomaterials Science, 13: 747-758, 2002

Nov 2002 The Longest Gene

What kind of function does the longest gene in the human genome code for? The answer is a bit mundane: a very long molecular spring that provides muscle with passive elasticity. Nature adjusts the protein, called titin, for many types of muscle, e.g., skeletal or cardiac muscle, as well as for other cellular functions. The molecular spring contains hundreds of elastic elements in series like beads on a string. One type of bead is the immunoglobulin domain, which can stretch to ten times its normal length. For a long time only one of the immunoglobulin domains was structurally known, permitting only a single peek into nature's design library. Recently, a second domain became structurally known and protein crystallographers and modelers joined forces to discover how nature designs its beads along titin, as described in a recent publication.



M. Gao, M. Wilmanns, and K. Schulten
Biophysical Journal, 83: 3435-3445, 2002



Dec 2002 Gordon Bell Award for NAMD

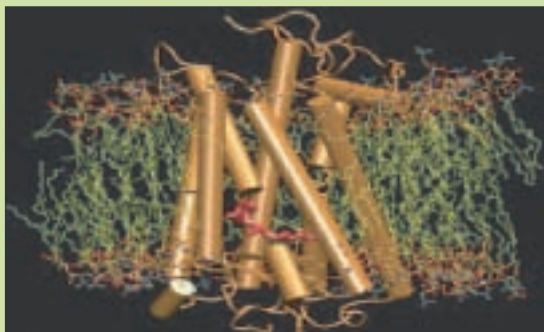
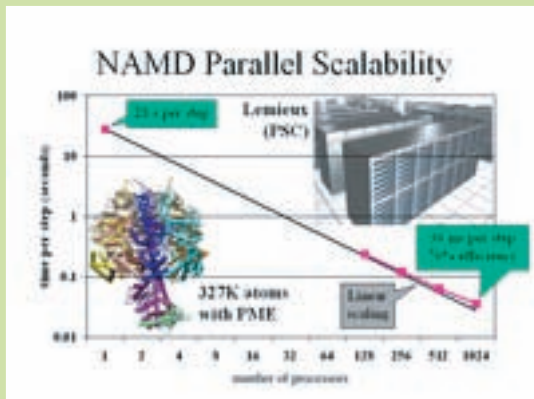
The parallel molecular dynamics program NAMD, and its sister visualization program VMD, have helped researchers at Illinois discern how muscles stretch, nerves sense pressure, and kidneys filter water. The latter project, for example, used simulations of 106,000 atoms to discover how aquaporins, which are ubiquitous in mammals, plants, and bacteria, allow water to pass while preventing the conduction of protons or ions. Our years of work developing this software to apply the nation's fastest supercomputers to understand the tiny components of living cells were recognized at the SC2002 High Performance Networking and Computing conference with a Gordon Bell Award for unprecedented parallel performance on a challenging computational problem. NAMD and VMD are distributed, free of charge, to thousands of scientists in industry and academia around the world, quickening the pace of drug discovery and other vital research to unravel biological processes.

Jan 2003 Information is Everything

Scanning their environment for information such as food resources, signs of danger, and illumination is crucial for the well being of biological cells. Evolution has developed for this purpose a great variety of membrane proteins, so-called receptors, that receive physical cues from the external environment through encounters with molecules or absorption of photons and send respective signals into the cell. A common type of receptor sends its signal through interaction with intracellular G-proteins that convey the signal further; proteins of this type are called G protein coupled receptors (GPCRs). GPCRs exist in lower as well as higher life forms and, in fact, the human genome codes for over 1300 GPCRs that detect ions, organic odorants, amines, peptides, proteins, lipids, nucleotides and photons. As about half of modern drugs act on GPCRs, learning how they become activated once they receive their signal is highly relevant. In a recent study, advanced computer simulation techniques using NAMD and VMD have been employed to investigate the first key steps of activation of a GPCR, the visual receptor rhodopsin.

Recent Highlights

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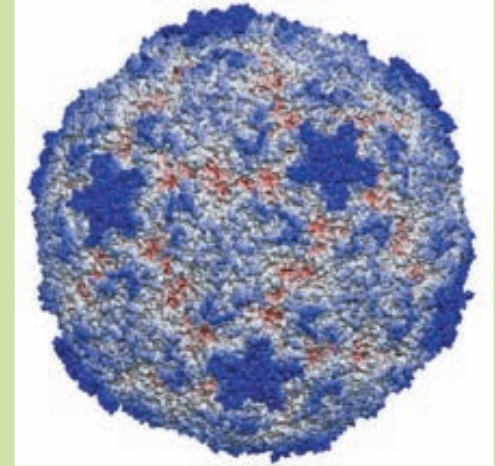


J. Saam, E. Tajkhorshid, S. Hayashi, and K. Schulten
Biophysical Journal, 83: 3097-3112, 2002



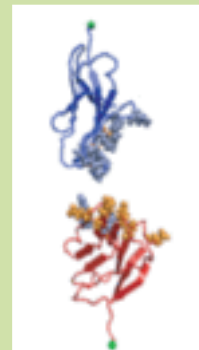
Feb 2003 Displaying the Invisible

This month the number of entries in the protein data base passed the 20,000 mark. The data provide microscopic images of the building blocks and functional units of living systems, an invaluable intellectual resource for biomedical researchers. The microscope used is built from software that reads the data base and drives computer graphics, widely available today. Our group's VMD is a leading visualization program for viewing static as well as dynamic structures of proteins and other biomolecules. Now downloaded by more researchers than ever, VMD features ease-of-use for beginners with greater power and flexibility for experts. Running on Apple's MacOS X alongside all other common platforms (e.g., Windows, Linux), VMD 1.8 offers extensive visualization and analysis capabilities for structures as well as sequences. VMD is easily updated and exceptionally user friendly. VMD integrates closely with its sister programs, the molecular modeling tool NAMD, and the collaborative suite BioCoRE.



Mar 2003 Strengthening the Immune System

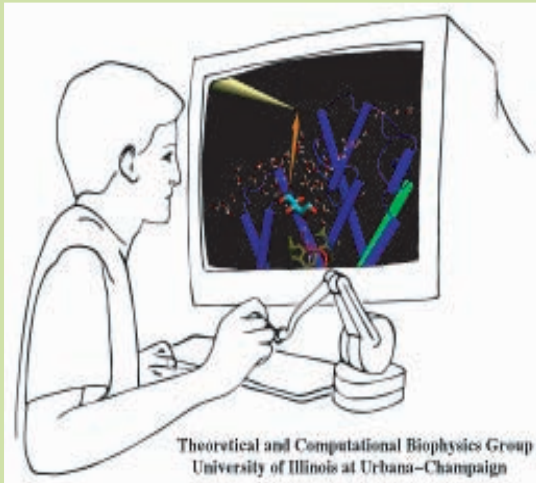
Infections are battled best by the human immune system when there exists a memory from a previous disease or vaccination. The first step in using this line of defense is recognition: Cells of the immune system capture antigens, e.g., microbes in the respiratory tract, then mature in the lymph system, and finally present on their surface pieces of the antigen to T-cells that may recognize the antigen and become activated. The recognition of the antigen by T-cells is dramatically enhanced through surface receptors, CD2 and CD58, on the T-cell and the antigen presenting cell. The receptors stick out from their cell, adhere to one another, and conjoin the T-cell and antigen presenting cell long enough to enable recognition and activation. The molecular basis of this adhesion has been probed in a recent collaborative study with UIUC chemical engineer D. Leckband. Starting from the available crystallographic structure of the CD2-CD58 complex the researchers carried out 90,000 and 100,000 atom simulations using NAMD and pulled the complex apart in steered molecular dynamics simulations. An analysis of the simulations with VMD revealed in atomic level detail how the human immune system is strengthened through elastic adhesion.



M. V. Bayas, K. Schulten, and D. Leckband
Biophysical Journal, 84: 2223-2233, 2003

Recent Highlights

<http://www.ks.uiuc.edu>



P. Grayson, E. Tajkhorshid, and K. Schulten
Biophysical Journal, 85: 36-48, 2003

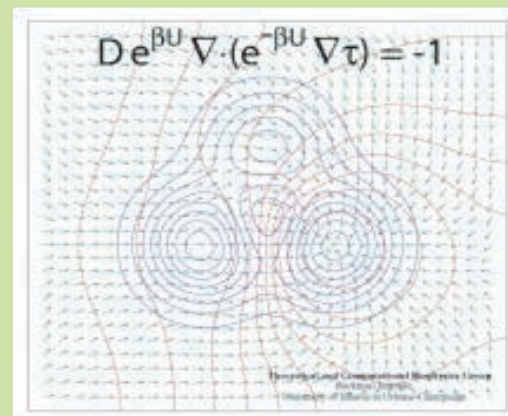
Apr 2003 Interactive Molecular Dynamics

The import of material into biological cells needs to be highly selective. Which physical interactions are the best capable of differentiating suitable from unsuitable imports? How can one keep import traffic fast despite strong selection? As one knows from border crossing, fast traffic and high security can be conflicting objectives. A recent investigation employed a new simulation method to answer the above questions for import of glycerol through a membrane channel. Linking the renown molecular graphics program VMD with the simulation program NAMD permits researchers to view "live" proteins, e.g., the membrane channel, and employing computer game technology, namely, a device that permits one to pull glycerol through the simulated channel, researchers can feel the mechanical resistance of the pulled glycerol, guide it through the channel, and directly observe the selection process involving glycerol's shape, capability for hydrogen bonding, and electric dipoles. The new methodology, interactive molecular dynamics, will revolutionize computational biology and is one of the first tools that take advantage of fast (TeraGrid) computer networks in linking local graphics workstations (running VMD) with a distant supercomputer (running NAMD).



May 2003 Finding the Path

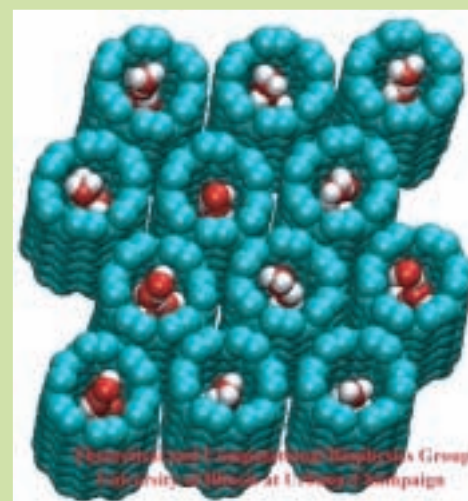
Processes in living cells are based on molecular transformations linking reactant and product states. To understand such processes, one needs to know the paths linking reactants and products. Brownian dynamics, as it occurs in cells at physiological temperature, finds any path, as long as it does exist, even if it may take billions of vibrational periods in a protein. But on the nanosecond time scale of computational modeling such paths are too rare to detect, even for the most powerful computers available today. Steered or interactive molecular dynamics, pioneered in our group, can accelerate motion along a reaction path within reach of available computational power, but only if the path is known beforehand. Principles for finding reaction paths are therefore the most desirable goals of theoretical biology. A recent study has formulated a new mathematical principle for determining reaction paths that is based on the mean first-passage time linking any intermediate state of the system to the product state. The principle has proven already its worth in describing pathways of light harvesting in photosynthesis, the process that energetically fuels life on earth.



S. Park, M. K. Sener, D. Lu, and K. Schulten
Journal of Chemical Physics,
 119: 1313-1319, 2003

Jun 2003 Nanoengineering Meets Molecular Biology

Biological cells have evolved highly optimized molecular devices made from nanometer size proteins that are the basis for all cellular processes. Engineers seek to conquer the domain of such nanodevices and naturally they look to nature for guidance. In turn, biologists look to nanoengineers for new tools to manipulate cells. A recent study attempts a third type of exchange at the cell - nanotechnology frontier, use of nanodevices that mimic proteins for better understanding of the functions of both: the engineered system can be much simpler than the protein and much easier to comprehend, whereas the protein is more evolved and can reveal the design principles for optimized function. The study links two renowned devices, nanotube and membrane channel. Using the molecular dynamics program NAMD, water flow through nanotubes is simulated and compared with earlier studies of aquaporin water channels in bacteria.



F. Zhu and K. Schulten
Biophysical Journal, 85: 236-244, 2003



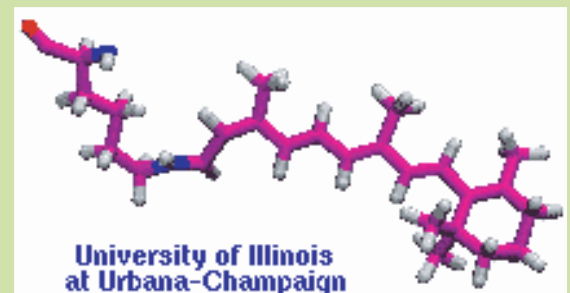
Jun 2003 Learning by Doing

Modeling the molecular processes of biological cells is a craft and an art. Techniques like theoretical and computational skills can be learnt by training, but meaningful applications are achieved only with experience and sensitivity. A summer school in Theoretical and Computational Biophysics attempted to teach both the craft and art of modeling through learning by doing: nearly hundred participants from all over the world came for two weeks to the Beckman Institute in Illinois to stretch proteins, pull water through molecular channels, mine genomic data, build their own computer cluster, and study their favorite biomolecules. After lectures and discussions in the morning, afternoon and evening were devoted to learning by doing, assisted through 300 pages of tutorials, in computer laboratories humming with computational biology software, e.g., VMD, NAMD, and GAMESS, and linked to NCSA's fast pentium machines. The school lasted two weeks, but will go on much longer: all school materials remain available on the web; participants will use BioCoRE to stay in touch and continue the scholarship and friendship experienced in Illinois.



Jul 2003 Quantum Biology Modeling Breakthrough

Retinal proteins are photoreceptors found in many living organisms. They possess a common chromophore, retinal, that upon absorption of light isomerizes and, thereby, triggers biological functions ranging from light energy conversion to phototaxis and vision. The photoisomerization of retinal is extremely fast, highly selective inside the protein matrix, and characterized through optimal sensitivity to incoming light. Photoisomerization takes place while the molecule (retinal) is in its short-lived electronically excited state when internal forces differ strongly from those in the prevalent ground state. Simulation of photoisomerization inside a protein has been a key goal, but unattainable so far since the forces of excited state molecules, largely unknown, need to be described by so-called *ab initio* quantum mechanical calculations and updated extremely frequently. A recent report describes that this goal has finally been achieved for retinal inside bacteriorhodopsin, a microbial retinal protein that functions as a light-driven proton pump, i.e., a pump driven by photoisomerization and thermal re-isomerization. The description unveils in complete detail the photoisomerization process and the essential role of the protein for the characteristic kinetics and high selectivity of the biomolecular reaction. Supported by comparison with dynamic spectral modulations observed in femtosecond spectroscopy, the results identify the principal molecular motion during photoisomerization that initiate proton pumping.



S. Hayashi, E. Tajkhorshid, and K. Schulten
Biophysical Journal, 85: 1440-1449, 2003

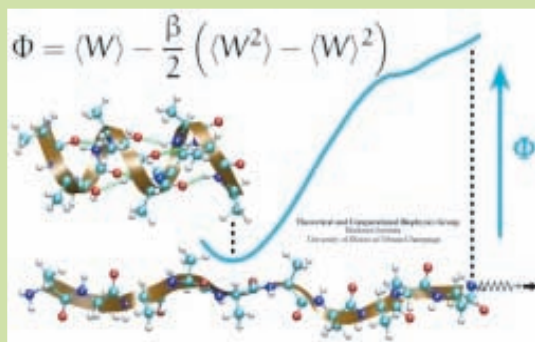


Aug 2003 Ubiquitous Computing Through BioCoRE

Biomedical researchers collaborating on a project are often separated by great distances. However, their projects demand continuous sharing of computer files, whether the files be protein data files, trajectories, or written documents. BioCoRE is a web-based collaboration tool for sharing all kinds of data, co-authoring papers, running applications on remote supercomputers, sharing molecular visualization over the Internet, chatting, and keeping an on-line lab book. The newest addition to BioCoRE is the BioFS (BioCoRE File System)-- a way of sharing data that brings ubiquitous computing one step closer to reality. Employing a technology called WebDAV, the BioFS makes files stored centrally within BioCoRE directly available to researchers as if they were stored on their local computer. This provides an intuitive interface, allowing researchers to see folders and files in their native format on their computer desktop. A scientist in Boston can use Word for Windows to edit an upcoming journal article stored in the BioFS. Then a collaborator in Seattle can immediately load the same article on his Macintosh for revision, and another in Germany can complete it on her Linux laptop.

Aug 2003 Mathematics for Proteins

Many proteins in living cells are nanomachines that undergo mechanical transformations. Modern modeling methods permit the manipulation of such proteins to discover the physical mechanism behind their function. Applying forces, one can induce geometrical changes characteristic of the proteins' role in the cell and, beyond obtaining qualitative insight, calculate the work W done during a machine cycle. Unfortunately, the manipulations realized in computer modeling include irreversible work which needs to be discounted for comparison with the energetics of naturally occurring, i.e., slower, machine cycles. A recent report suggests how this can be achieved mathematically by means of statistical physics. The new methodology is demonstrated on the most simple mechanical transformation of a protein, the stretching of a so-called alpha-helix which behaves like a coiled spring.



S. Park, F. Khalili-Araghi, E. Tajkhorshid, and K. Schulten
Journal of Chemical Physics,
119:3559-3566, 2003

S. Park, F. Khalili-Araghi, E. Tajkhorshid, and K. Schulten
Journal of Chemical Physics,
120:5946-5961, 2004

Recent Highlights

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Sep 2003 Protein & Membrane Mechanics

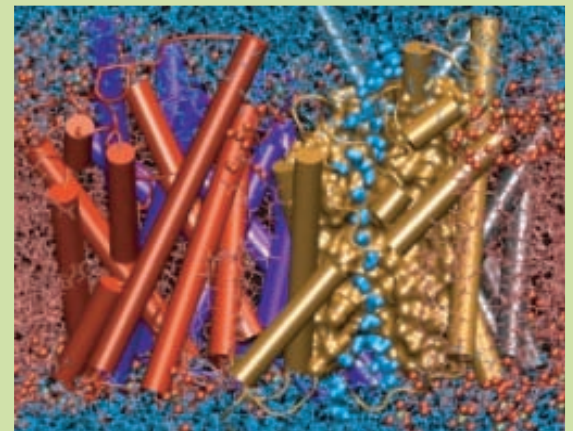
Living cells sense their environment and respond to its changes through proteins integrated into their outer membrane. These proteins mediate a broad range of cellular activities, including active and passive transport of materials across the membrane as well as response to osmotic shock, which can strain the cell membrane to the point of catastrophic bursting. Cells protect themselves through so-called mechanosensitive channels that open before the membrane tension grows too large. Molecular dynamics simulations and advanced analysis using NAMD and VMD have revealed in a recent report how the joint mechanics of membrane and protein opens a mechanosensitive channel called MscL. The finding promises to revolutionize the modern view of membrane - protein interaction: the membrane, far from being a homogeneous elastic sheet, exhibits a dramatic variation of tension across its thickness that proves to be decisive for the opening of MscL.



J. Gullingsrud and K. Schulten
Biophysical Journal, 85: 2087-2099,
2003

Oct 2003 Channel Nobel Prize

This year's Nobel prize in chemistry goes to Peter Agre and Roderick MacKinnon for their groundbreaking work on membrane channels. We join all in congratulating our two colleagues who have advanced knowledge on membrane channels. Foremost, this advance was made possible through great achievements in experimental methodology by several distinguished researchers, but computational and theoretical investigations of the channels the two new Nobelists investigated, contributed significantly. Our group feels fortunate to have participated in the exciting development through modeling studies of the aquaporin channel (see previous highlights June and April 2003, June and May 2002, and November 2001). Our investigations were based on molecular dynamics simulations of channels in their native membrane environment and demonstrate the widening role of computing in modern life science: using the most advanced computers at the NSF centers in Pittsburgh and Urbana, we could establish the mechanisms of conduction and selectivity in aquaporins in a series of studies that are summarized and in three recent publications showing how the molecular architecture of channels is optimally designed for their function.



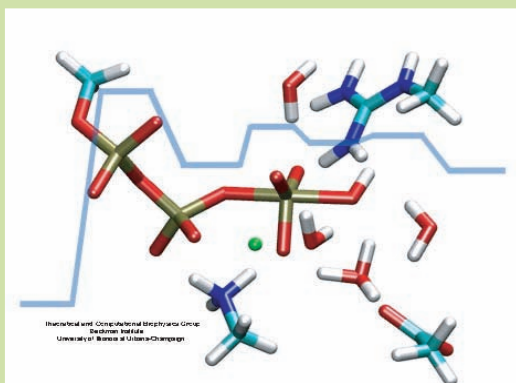
M. Jensen, E. Tajkhorshid, and K. Schulten
Biophysical Journal, 85: 2884-2899, 2003

D. Lu, P. Grayson, and K. Schulten
Biophysical Journal, 85: 2977-2987, 2003

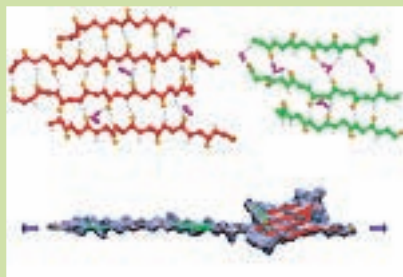
F. Zhu, E. Tajkhorshid, and K. Schulten
Biophysical Journal, 86: 50-57, 2004

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<http://www.ks.uiuc.edu>



M. Dittrich, S. Hayashi, and K. Schulten
Biophysical Journal, 85:2253-2266, 2003



M. Gao, D. Craig, O. Lequin, I. D. Campbell,
V. Vogel, and K. Schulten
Proc. Natl. Acad. Sciences, USA
100:14784-14789, 2003

Nov 2003 Fuel of Life

Adenosine triphosphate (ATP) is the fuel of life; every living cell needs ATP to carry out its functions. The human body actually synthesizes its own weight in ATP every day. This is achieved by ATP synthase, a protein complex of two joined rotating molecular motors. A detailed understanding of how this system functions will impact our fundamental understanding of life, but also the treatment of neurodegenerative diseases or the development of biomimetic nanodevices. Presently, biomedical science still lacks a sufficient understanding of how ATP synthase efficiently stores energy in ATP. A recent report suggests a new chemical mechanism for this energy storage reaction, the discovery being based on quantum-chemical calculations conducted in the presence of the reaction environment in ATP synthase. The suggestion could constitute an important step towards an understanding of one of the most ubiquitous reactions in all living cells, the synthesis of ATP and its use as cellular fuel.

Dec 2003 Body's Glue

Tissues of the human body are composed of specialized cells held together by a connective fabric of proteins, that form the knots of a net glueing cells together. Upon stretching tissues, the knots unravel, rendering the net larger, but mysteriously also firmer. A protein called fibronectin-III-1 plays a particularly important role in the latter respect. Atomic force microscopy revealed that under mechanical tension fibronectin-III-1 stretches to ten times its initial length; but it does so in two steps, the first stretching step leading to net strengthening. It had been discovered earlier that other fibronectins found between cells are made of two sheets packed like a sandwich, but the structure of fibronectin-III-1 remained elusive. In an experimental-computational collaboration reported recently, the structure has now been resolved that at first sight looked similar to the sandwich structure of the other fibronectins, but on closer inspection showed a weak and a strong sheet. Simulations using NAMD revealed that stretching of the protein unravels readily the weak sheet, and only thereafter the strong sheet. It turns out that the strong sheet of fibronectin-III-1 by itself, known as anastellin, inhibits tumor growth. Stretching of fibronectin-III-1, as it occurs naturally in tissue, unravels apparently half of the protein to render it extremely adhesive, strengthening a protein net that prevents metastasis of cancer cells and also assists wound healing.

Recent Highlights



Jan 2004 Genetic Switch

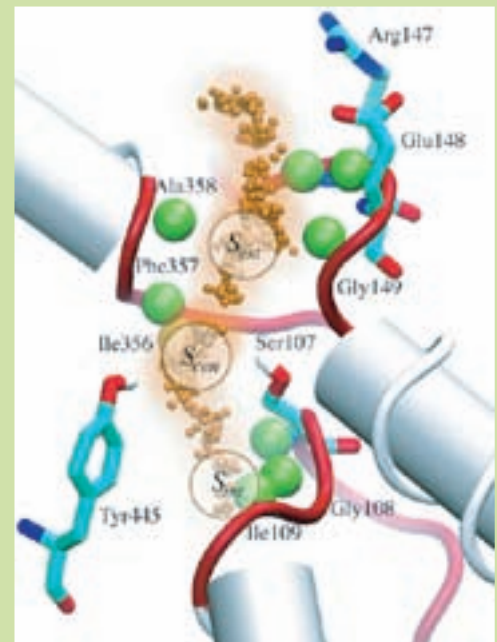
Bacteria must respond quickly to food sources in their environment. A common source of food for the bacterium *E. coli* is lactose; the bacterium's DNA contains genes for proteins needed for import and metabolic degradation of lactose and related sugar molecules. When lactose is lacking, a regulatory protein called lac repressor prevents the needless expression of lactose processing proteins; in doing so, lac repressor is assisted by a second protein, called catabolic activator protein (CAP). To understand the roles of the two proteins in regulating DNA, a recent report employed an advanced mathematical model for the flexibility of DNA and showed how lac repressor and CAP force DNA to form a loop such that the local genetic information cannot be expressed; the loop is held at its ends by the lac repressor and CAP inserts itself into the loop, adjusting and stabilizing it. Together, lac repressor and CAP form a genetic switch, in fact, the first such switch discovered long ago and explained now in detail through mathematics. When lactose appears around the bacterium, the lac repressor becomes deactivated by the molecule and loses its grip on the DNA. In this case the DNA loop opens and the CAP present assists in the expression of the genes needed for lactose processing.



A. Balaeff, L. Mahadevan, and K. Schulten
Structure, 12:123-132, 2004

Feb 2004 Biological Ion Conduction

When their environment gets high in hydrochloric acid, bacteria must protect themselves from chloride ions leaking into the cells. Some bacteria rely on so-called CIC chloride channels to quickly evacuate these ions without letting other small particles pass through. A recent paper investigates the mechanism of chloride transport in a CIC channel from the bacterium *E. coli*. By means of computer simulations using NAMD, researchers visualized the pathway taken by chloride ions as they pass through the channel and identified how the channel's protein architecture optimizes ion conduction. The relevant architectural features have also been observed in aquaporin water channels (see October 2003 highlight) and the potassium ion channel, but are rarely seen in other proteins. The new discovery demonstrates how much computer simulations are contributing to the emerging picture of life's membrane channel design that is critical for functions of biological cells ranging from the maintenance of our body's hydration to electrical signaling in the brain.



J. Cohen and K. Schulten
Biophysical Journal, 86:836-845, 2004.

Recent Highlights

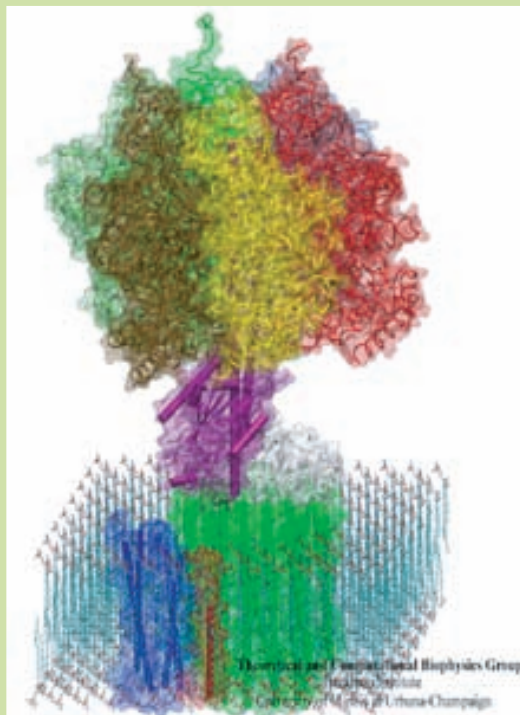
<http://www.ks.uiuc.edu>



Mar 2004

Biological Motor Running a Million Years

How will car motors look like in a million years? It's hard to tell, but biological cells seem to have found an ideal engine that they use since the early days of evolution. A spoonful of their engines generates about as much total torque as the strongest car engine today. The engine is called FoF1-ATP synthase and synthesizes the molecule ATP by combining two generator-like motors, Fo-ATPase and F1-ATPase, coupled through a single axle, one motor (Fo) that converts the cell's electrical energy into rotation, another one (F1) that converts rotation into chemical synthesis (see November 2003 highlight). ATP synthase, found throughout the whole kingdom of life, can also work in reverse, turning ATP into electrical energy. Cells typically use the energy of sun light or of food to generate an electrical potential by pumping protons that carry a positive charge across their cell membrane. The energy stored drives the protons back through Fo-ATPase enforcing rotation of the axle; the rotation in turn induces ATP synthesis in F1-ATPase. In one of the largest computational and mathematical biomodeling projects undertaken to this day and reported recently, researchers build from available disjoint structural data a model of Fo-ATPase and demonstrated its function as a motor turning proton conduction into rotation of a cylindrical protein complex. By linking nanosecond molecular modeling to a mathematical model of the motor's key elements, they could follow Fo-ATPase function properly, even when the load arising from driving synthesis in F1-ATPase was added. FoF1-ATP synthase being one of the largest molecular machines in biological cells, modelers needed to employ for its study the most advanced tools, NAMD and massively parallel computers, along with a new approach that combined molecular dynamics and stochastic mathematics.



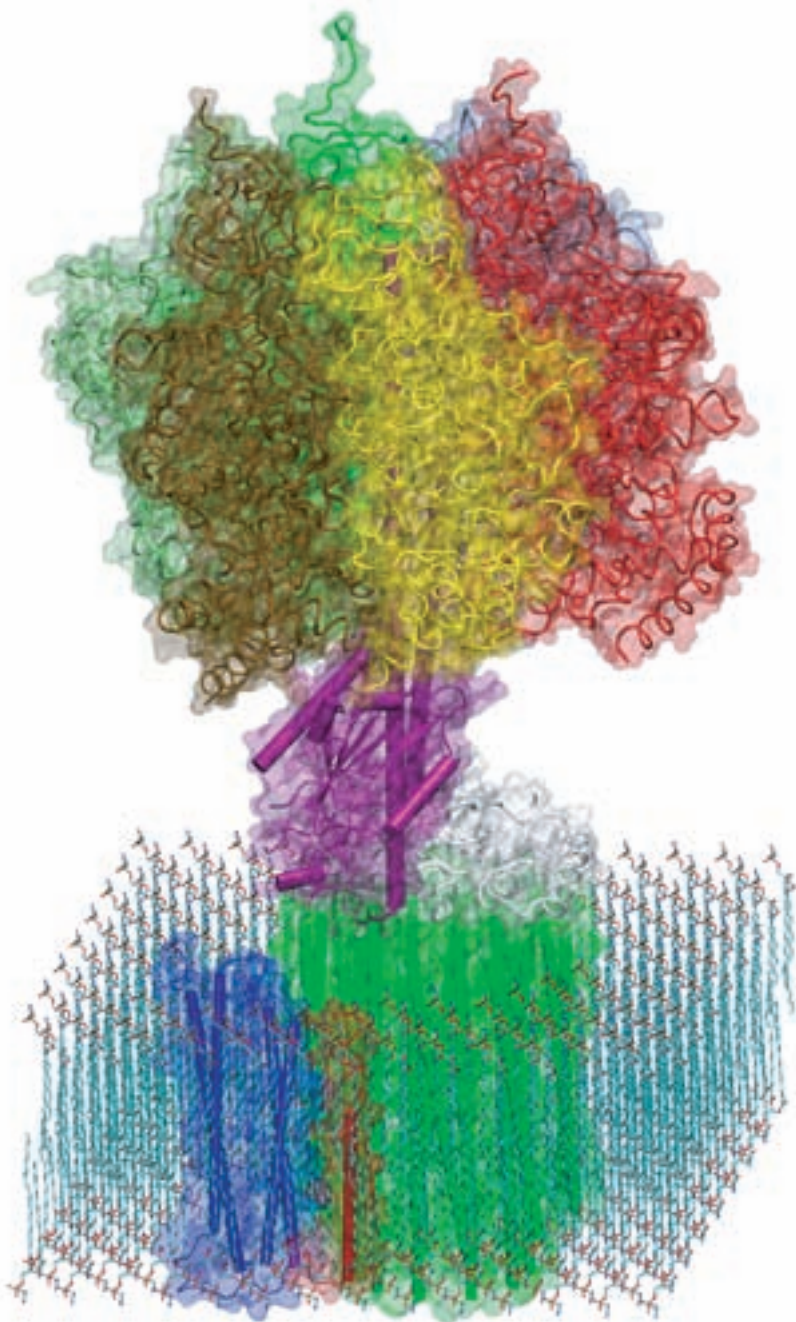
A. Aksimentiev, I. Balabin, R. Fillingame, and
K. Schulten
Biophysical Journal, 86:1332-1344, 2004



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

Recent Highlights

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The cover figure shows the cyanobacterial photosystem I, a protein complex that harvests sun light and transforms it into an electrical membrane potential. The figure to the left shows ATP synthase, a protein complex that converts an electrical membrane potential into the synthesis of ATP, a fuel driving processes in living cells.

The research of the Theoretical and Computational Biophysics Group is funded by the National Institutes of Health, the National Science Foundation, and the University of Illinois.

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