

# Center for Molecular Biophysics

2006-2011



CMB is affiliated with the Biosciences Division of the Energy and Engineering Sciences Directorate at ORNL and with the Department of Biochemistry and Molecular and Cellular Biology in the College of Arts and Sciences at UT, and we thank these organizations for putting up with us and our griping over the last five years! Everything we have accomplished was enabled by our systems administrators, Michael Galloway and Steve Moulton, and our secretary, Julia Cooper.

# Welcome!

The University of Tennessee (UT) / Oak Ridge National Laboratory (ORNL) Center for Molecular Biophysics (CMB), was founded in October 2006. With an approximately 50/50 UT/ORNL personnel mix, we have now built up a vibrant research atmosphere.

Thematically, our research is heavily influenced by the 'mission space' of ORNL and DOE. Supercomputing and neutron scattering constitute central toolsets that we integrate into our investigations in bioenergy and subsurface biogeochemistry. At the same time, we also have programs in biomedical sciences, including drug design. Our research is strongly interdisciplinary, incorporating elements of theoretical physics, quantum chemistry, statistical mechanics and simulation methodologies through to molecular and synthetic systems biology.

Our team of principal investigators comprises myself, three other UT professors and three ORNL Staff Scientists. We have two UT Assistant Professors: Jerome Baudry, who specializes in ligand binding and computational biochemistry, and Tongye Shen, who is more physics-oriented. Jerome and Tongye have, in a relatively short period of time, already established productive programs and published several significant papers. Hong Guo, an Associate Professor who I first met twenty-eight years ago in Martin Karplus' group at Harvard, specializes in enzyme reaction mechanisms.

The first ORNL staff scientist to be hired, in 2008, was Xiaolin Cheng, and two more have been recently appointed, Jerry Parks and Loukas Petridis. Again, these three have complementary expertise, with Xiaolin experienced in simulation methodologies and ion channels, Loukas coming from polymer physics, and Jerry a quantum chemist.

The above team of principal investigators has worked together with our postdoctoral fellows, graduate and undergraduate students to produce 17 successful grant proposals and about 130 peer-reviewed publications in the last five years. The publications include reports on a number of breakthroughs in fields of research of national importance, and some of the corresponding press releases by UT or ORNL are reprinted here. Our research, as well as the challenges ahead, is discussed here in an informal style from the point of view of the young scientists who actually did the work.

I hope you find our five-year report a stimulating read!

**Jeremy C. Smith, Director, CMB.**



**Hanging:** *Jeremy Smith*

**Standing:** *Zheng Yi, Xiaolin Cheng, Tongye Sheng, Hong Guo, Qin Xu, Vonel Teragene, Ricky Nellas, Richard Lindsay, Derek Cashman, Jerome Baudry, Ryan Johnson, Barmak Mostofian, Hao-Bo Guo, Jerry Parks, Demian Riccardi, John Eblen, Goundla Srinivas, Steve Moulton, Nikolai Smolin*

**Sitting:** *Julia Cooper, Barbara Collignon, Xianghong Qi, Liang Hong, Amandeep Sangha, Loukas Petridis, Yinglong Miao*

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# Principal Investigators

## OF THE CENTER FOR MOLECULAR BIOPHYSICS



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### **Jerome Baudry**

Assistant Professor, Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee, Knoxville

Jerome received a Ph.D. in molecular biophysics from the University of Paris-VI. After his postdoctoral work in the group of Klaus Schulten at the University of Illinois, Dr. Baudry worked in the pharmaceutical industry and as Research Faculty in the School of Chemical Sciences at the University of Illinois, Urbana-Champaign. Jerome joined the Center for Molecular Biophysics as tenure-track faculty in 2008. His group conducts research on the biophysics of protein/ligand and protein/protein interactions and develops supercomputing tools to accelerate drug discovery, using these tools in specific health and environmental discovery projects. Jerome is also active in obtaining fundamental understanding of intermolecular interactions.



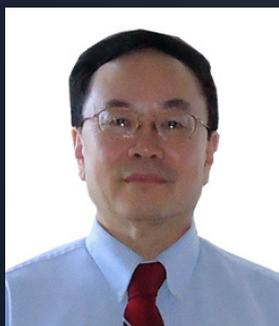
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### **Xiaolin Cheng**

Staff Scientist and Joint Assistant Professor, ORNL Computer Science and Mathematics Division

Xiaolin is a Staff Scientist in the Computer Science and Mathematics Division at Oak Ridge National Laboratory. He is also a joint Assistant Professor in the Department of Biochemistry & Cellular and Molecular Biology at the University of Tennessee, Knoxville. He received his Ph.D. from the State University of New York at Stony Brook, and his postdoctoral training at University of California, San Diego. Moving to ORNL in early 2008 Xiaolin's research has been focused on developing more scalable and multi-scale algorithms for molecular simulation on emerging computer architectures and the application of molecular

simulations to understanding biomass recalcitrance, gating mechanisms in ion channels and drug resistance of HIV integrase.



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### **Hong Guo**

Associate Professor, Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee

Hong obtained his Ph.D. from Harvard University in 1991. He was an International NSERC Fellow at the University of Waterloo, Canada in 1991-1993, a Research Associate at CERCA/University of Montreal, 1994-1997 and returned to Harvard as a scientist 1998-2001. He has lead a research group at Department of Biochemistry & Cellular and Molecular Biology, University of Tennessee since 2002. He has performed and directed research in computational studies of proteins, the catalytic mechanisms of enzymes, the role of hydrogen bonding and other interactions on protein structure and stability, and structural and vibrational properties of small molecules.



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## ***Jerry M. Parks***

Staff Scientist, ORNL Biosciences Division

Jerry received a Ph.D. in Chemistry in 2008 from Duke University. Previously a postdoctoral researcher at ORNL from 2008 to 2009, his research interests include using computer simulation to study the structure and dynamics of biomolecules, bioinorganic chemistry of mercury, and enzyme mechanisms.



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## ***Loukas Petridis***

Staff Scientist, ORNL Biosciences Division

Loukas received a Ph.D. in physics from the University of Cambridge in 2006. He was a postdoctoral fellow at ORNL, 2007-2009. His research focus is computer simulation of biological macromolecules, neutron scattering and polymer theory with emphasis in bioenergy and his current projects include the dynamic visualization of lignocellulose, a simulation model of lignocellulosic biomass deconstruction, and incorporating molecular-scale mechanisms stabilizing soil organic carbon into terrestrial carbon cycle models.



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## ***Tongye Shen***

Assistant Professor, Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee Knoxville

Tongye received a Ph.D. in physics from the University of California-San Diego in 2002. He was a postdoctoral researcher at the Center for Theoretical Biological Physics at UCSD, 2003-2007 and a postdoctoral associate at the Center for Nonlinear Dynamics/Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, 2007-2009. Tongye has constructed physical models and performed theoretical calculations and simulations on various biomolecular systems, ranging from the internal conformational dynamics of proteins and polysaccharides and protein-ligand association, to larger cellular structures. As

of 2011, Tongye has published 40+ peer-reviewed scientific articles.



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## ***Jeremy C. Smith***

UT/ORNL Governor's Chair and Director of the Center for Molecular Biophysics

Jeremy received a Ph.D. from the University of London in 1985. He was a postdoctoral fellow at Harvard University, 1985-1989. He previously lead research groups in biomolecular simulation at the Centre D'Etudes Nucleaires at Saclay, France, 1989-1998 and as Chair of Computational Molecular Biophysics at the University of Heidelberg, Germany, 1998-2006. He sticks his nose into a lot of research performed at CMB including the high-performance computer simulation of biological macromolecules, neutron scattering in biology, the physics

of proteins, drug design, bioenergy, subsurface biogeochemistry and the analysis of structural change in proteins. As of 2011 Smith has published close to 300 peer-reviewed scientific articles.

# Research Highlights

## Bioenergy

Lignin surface structure

Hydrogen-bonding in cellulose deconstruction

Catalytic mechanism of cellulose degradation by a cellulase

Solvent-free coarse-grain model for cellulose fibrils

Acetate- and ethanol-tolerant biomass-degrading microbe strains

## Folding & Function

Dehydration-driven solvent exposure of hydrophobic surfaces drives folding

Loop-closure kinetics and structured folding pathways

Accurate peptide partitioning and folding into lipid bilayers

Sugar recognition by ricin-like domains

Hydration, energetic roughness and peptide dynamics

Ion Channels and the Nicotinic Acetylcholine Receptor

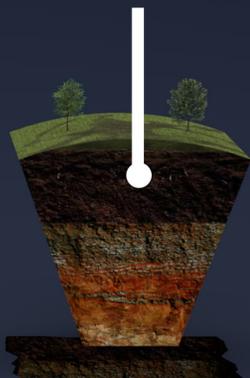
## Multiscale

REACH – coarse-graining biomolecular dynamics

Transition networks, metastable states and dynamical fingerprints of proteins

Treecode fast electrostatics

# Subsurface Biogeochemistry



Catalytic mechanism of an organomercurial lyase

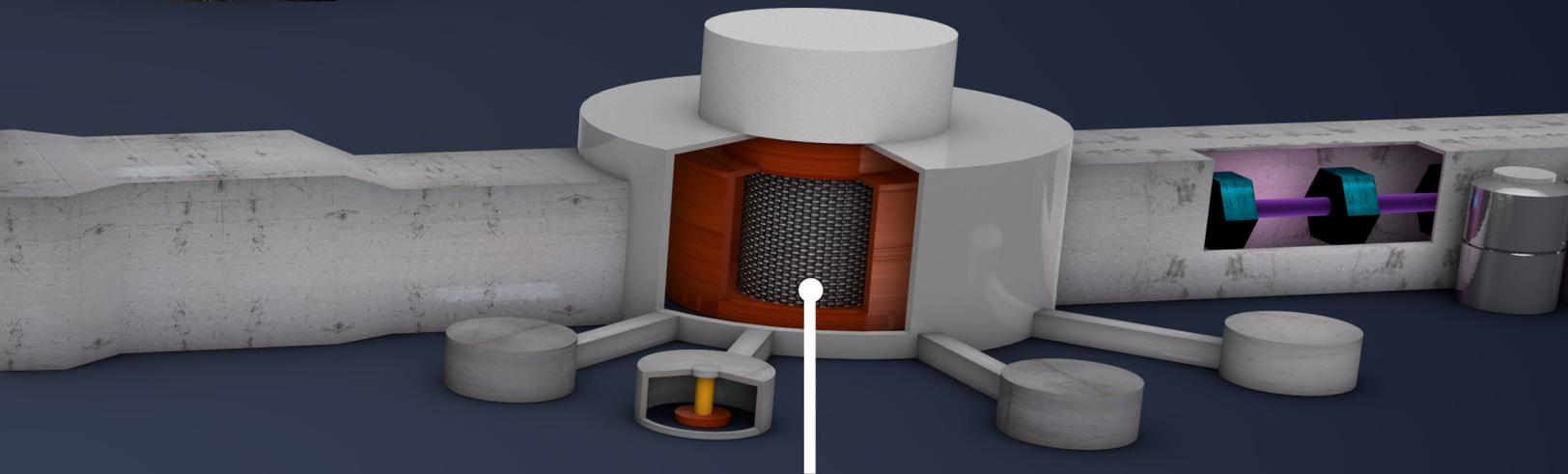
Dynamic mechanisms of bacterial mercury-resistance proteins

# Supercomputing



Scaling of biological simulations on a petascale supercomputer

Multimillion-atom simulations of biomass



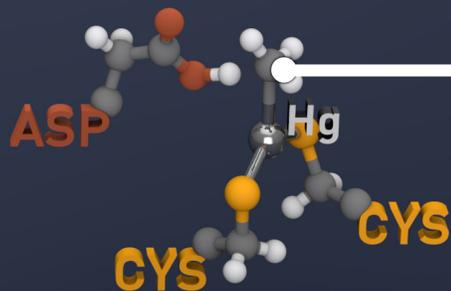
# Neutron Scattering

Lattice dynamics of a protein crystal

Subdiffusion and fractal configuration space

Three classes of motion in the neutron-scattering spectrum of a globular protein

Activity and dynamics of a very dry enzyme



# Catalysis

Catalytic mechanisms of

- a carboxyl peptidase
- xyloglucan endotransglycosylases/hydrolases
- a methyl transferase



# Medicine

Rapid docking of ligands on supercomputers and cloud architectures

Molecular origin of Gerstmann-Sträussler-Scheinker syndrome

# Bioenergy

## THE RECALCITRANCE OF PLANTS

*Bioenergy is of critical national importance as we strive to develop viable alternatives to fossil fuels. Our efforts in computer simulation and neutron scattering are aimed at understanding "biomass recalcitrance".*

### Cellulose as a fuel source

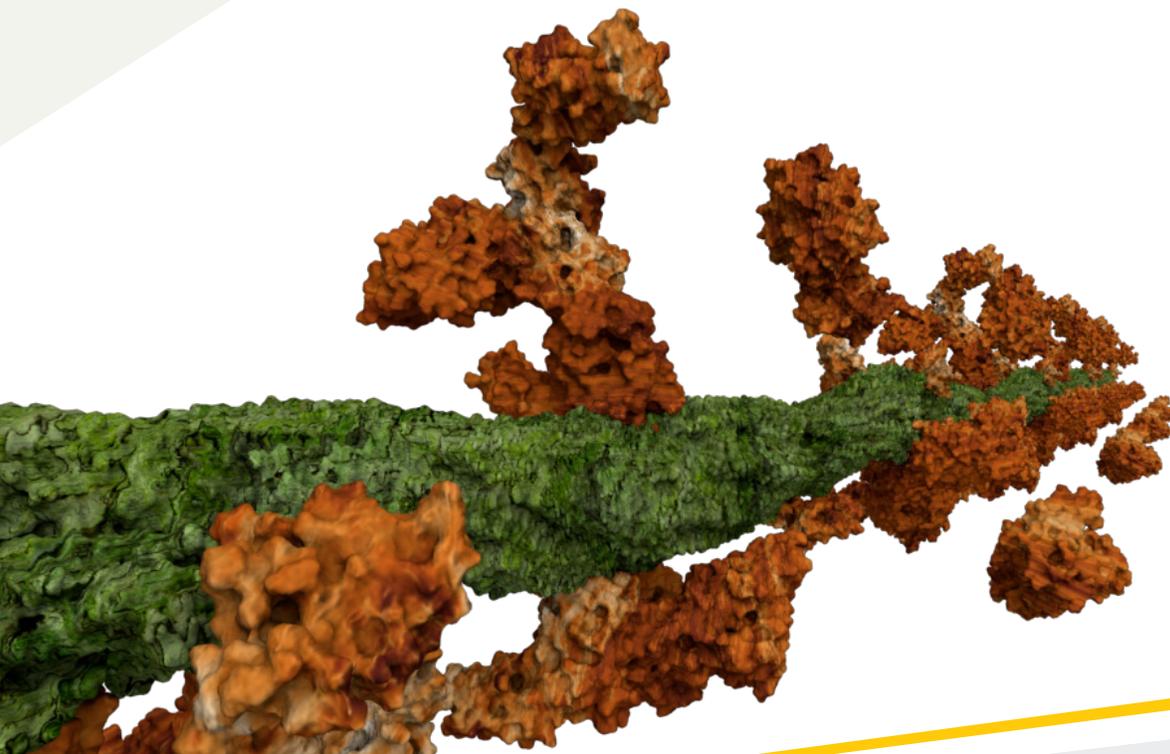
"Biofuels serve as a substitute for a very important part of our current technology: combustion driven engines", says graduate student Benjamin Lindner, who is performing simulations of biomass with the ORNL Jaguar supercomputer. "This work is also relevant when you consider national security, because it ensures that fuel will always be available albeit at a limited rate. Energy efficiency is another important aspect and a necessity for a sustainable economy. Cellulose-based biofuels have a significant advantage over first-generation biofuels, because they are more scalable,

don't compete with the food market, and allow the use of specially designed energy plants. However, it is unlikely that all our energy demands can be met by using biofuels. I see cellulose-based biofuels as an important ingredient in a sustainable and ecologically friendly energy mix."

### Bioenergy barrier

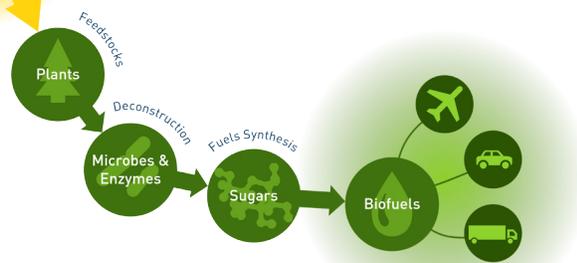
"Lignin is the major "undesirable" component of biomass in the conversion process", adds Amandeep Sangha, a postdoctoral fellow. "The presence of lignin, along with other factors, makes the breakdown of polysaccharides into sugars difficult. Understanding the origin of biomass recalcitrance to hydrolysis is one of the major challenges in improving the efficiency of the conversion process."

According to Barmak Mostofian, also a graduate student, one of the main is-



CMB model of Lignocellulose. Cellulose (green) from plant cell walls binds strongly to other cell wall molecules such as lignin (in brown). Removal of lignin is essential for efficient biomass deconstruction.

Road to energy independence:  
Harnessing the sun to power  
greener vehicles and herald more  
efficient energy production.



sues, besides the frequently mentioned competition with food crops for available land and other logistics, is the development and proper implementation of technologies that produce affordable fuel in a more effective way. "While the enzymatic approach exploits the capabilities of natural catalysts to liberate sugars, which are then subsequently transformed into ethanol in a fermentation/distillation process, purely chemical routes do not rely on expensive enzymes or on the use of genetically altered microbes for enhanced alcohol production. Instead high-energy organic compounds can be synthesized directly from lignocellulose using solid catalysts, for instance. It is conceivable that the different approaches to tackle the natural resistance of biomass deconstruction will result in a multi-faceted bioenergy industry".

## ORNL Biofuels Science Focus Area and the Bioenergy Science Center

CMB is part of the Bioenergy Science Center (BESC), which integrates experts from a wide range of scientific disciplines to understand biomass recalcitrance. According to Loukas Petridis, "Most of the chemical data used to construct our lignocellulose (biomass) models are derived from experiments performed at BESC. Also, many fruitful ideas have arisen from interactions with experimentalists at BESC. For ex-

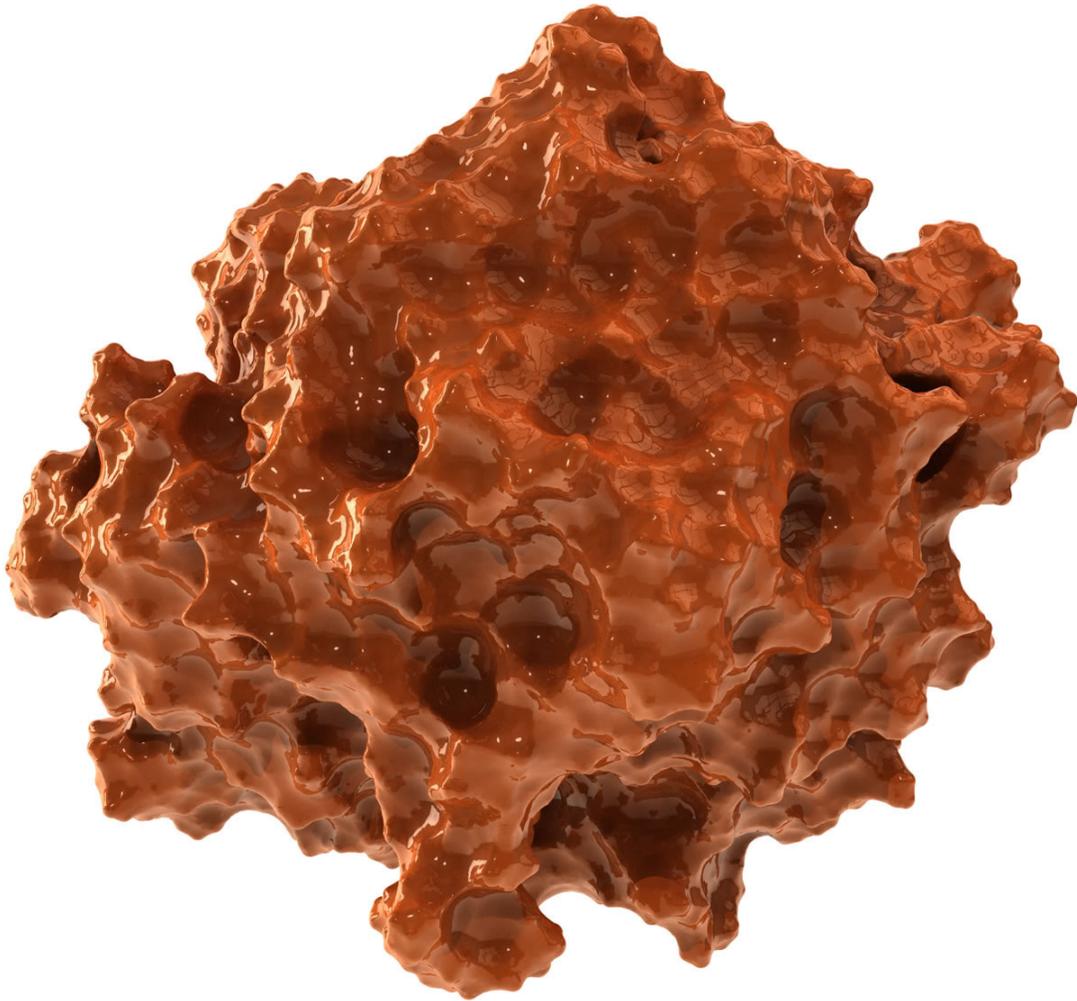
ample, it was during a BESC retreat that I first saw beautiful images of lignin aggregates forming after dilute acid pretreatment of biomass. The subsequent study of lignin aggregation by computer simulation has been one of the main focus areas of bioenergy research performed in the first 5 years of CMB" (see press release on following page).

BESC and the ORNL Biofuels Science Focus Area aim to provide breakthroughs that will allow viable cellulosic biofuel production. Significant steps in this direction have already been achieved. CMB has participated in high-profile studies, commented on by Secretary Chu, identifying and characterizing a single microbial gene linked to increased ethanol tolerance. Also, Sangha and Jerry Parks have been performing quantum chemical calculations aiming at understanding lignin polymerization, and CMB has also performed calculations to understand cellulase catalysis and cellulosome function.

According to Petridis, "In the next five years, BESC will use its achievements in order to viably produce biofuels. The way simulation can help is by providing detailed molecular-level understanding of mutated microbial proteins, or transgenic switchgrass. Such understanding enables rational improvement of these systems and thus helps us achieve improved bioethanol yield."

# ***ORNL neutrons, simulations reveal details of bioenergy barrier***

Source: [http://www.ornl.gov/info/press\\_releases/get\\_press\\_release.cfm?ReleaseNumber=mr20110615-00](http://www.ornl.gov/info/press_releases/get_press_release.cfm?ReleaseNumber=mr20110615-00)



*New molecular models of lignin aggregates are helping scientists understand a limiting factor in the production of ethanol. (Image courtesy of <http://www.scistyle.com>)*

OAK RIDGE, Tenn., June 15, 2011 — A first of its kind combination of experiment and simulation at the Department of Energy's Oak Ridge National Laboratory is providing a close-up look at the molecule that complicates next-generation biofuels.

Lignin, a major component of plant cell walls, aggregates to form clumps, which cause problems during the production of cellulosic ethanol. The exact shape and structure of the aggregates, however, have remained largely unknown.

A team led by ORNL's Jeremy Smith revealed the surface structure of lignin aggregates down to 1 angstrom—the equivalent of a 10 billionth of a meter or smaller than the width of a carbon atom. The team's findings were published in *Physical Review E*.

"We've combined neutron scattering experiments with large-scale simulations on ORNL's main supercomputer to reveal that pretreated softwood lignin aggregates are characterized by a highly folded surface," said Smith, who directs ORNL's Center for Molecular Biophysics and holds a Governor's Chair at University of Tennessee.

Lignin clumps can inhibit the conversion of biofuel feedstocks—for example, switchgrass—into ethanol, a renewable substitute for gasoline. When enzymes are used to release plant sugars necessary for ethanol production, the lignin aggregates bind to the enzymes and reduce the efficiency of the conversion.

Lignin's highly folded surface creates more opportunities to capture the passing enzymes than a smooth surface would. An improved understanding of the lignin aggregates will aid scientists in efforts to design a more effective pretreatment process, which in turn could lower the cost of biofuels.

"Nature has evolved a very sophisticated mechanism to protect plants against enzymatic attack," said ORNL team member Loukas Petridis. "We're trying to understand the physical basis of biomass recalcitrance—resistance of the plants to enzymatic degradation."

The complementary techniques of simulation on ORNL's Jaguar supercomputer and neutron scattering at the lab's High Flux Isotope Reactor enabled Smith's team to resolve lignin's structure at scales ranging from 1 to 1,000 angstroms. Smith's project is the first to combine the two methods in biofuel research. "This work illustrates how state-of-the-art neutron scattering and high-performance supercomputing can be integrated to reveal structures of importance to the energy biosciences," Smith said.

The research was supported by DOE's Office of Science and used the resources of the Leadership Computing Facility at ORNL under a DOE INCITE award. Team members include ORNL's Sai Venkatesh Pingali, Volker Urban, William Heller, Hugh O'Neill and Marcus Foston and Arthur Ragauskas from Georgia Institute of Technology.

ORNL is managed by UT-Battelle for the Department of Energy's Office of Science.



Ethanol tolerance in *Clostridium thermocellum* was traced to two mutations in a single gene encoding an alcohol dehydrogenase. A model of the enzyme with the mutation sites highlighted is shown here.



# Supercomputing

## TOWARDS THE EXASCALE

*Supercomputing is a key element of the ORNL mission, alluded to by President Obama in his 2011 State of the Union speech. Also, UT recently joined the elite ranks of NSF supercomputing institutions with its Kraken machine. As molecular simulation is a CPU-hungry enterprise, CMB is keenly involved with the development and application of highly parallel codes and we are major users of the local supercomputers, having received several awards for supercomputing time, including from the prestigious DOE INCITE program.*

*Here we ask John Eblen, a post-doctoral fellow, and Roland Schulz and Sally Ellingson, both graduate students, about their experiences with petaflop supercomputers and prospects as we move towards the exascale.*

### **What is the most powerful computation you have ever performed?**

**Ellingson:** I recently ran a high-throughput docking screen on the Jaguar machine that included over one million chemical compounds. We used an MPI (message passing interface) version of Autodock4 (virtual docking software) that distributes the docking tasks.

**Schulz:** As part of our INCITE allocation, I am simulating lignocellulosic biomass. A realistic model requires several million atoms. Our largest model constitutes 22 million atoms and runs on 45,000 cores. Additionally, I run larger tests to improve software performance for current and future projects, and the largest of these was run on 150,000 cores. As far as I know this is a world record for this type of calculation.

### **D.E. Shaw has made a special purpose supercomputer for molecular simulation. How does ORNL's Jaguar machine compare with it?**

**Schulz:** The Shaw Anton special purpose machine is about 100 times faster for simulating the molecular dynamics of small biological systems, such as small proteins containing e.g. 20,000 atoms. This is partly achieved by a network that is significantly faster. Jaguar allows us to run more flexible codes

and is more suitable for our very large simulations.

### **Are supercomputers easy to use for the average computational scientist?**

**Ellingson:** When everything works right they are fairly easy to use. The hard part is figuring out what went wrong when it doesn't work right.

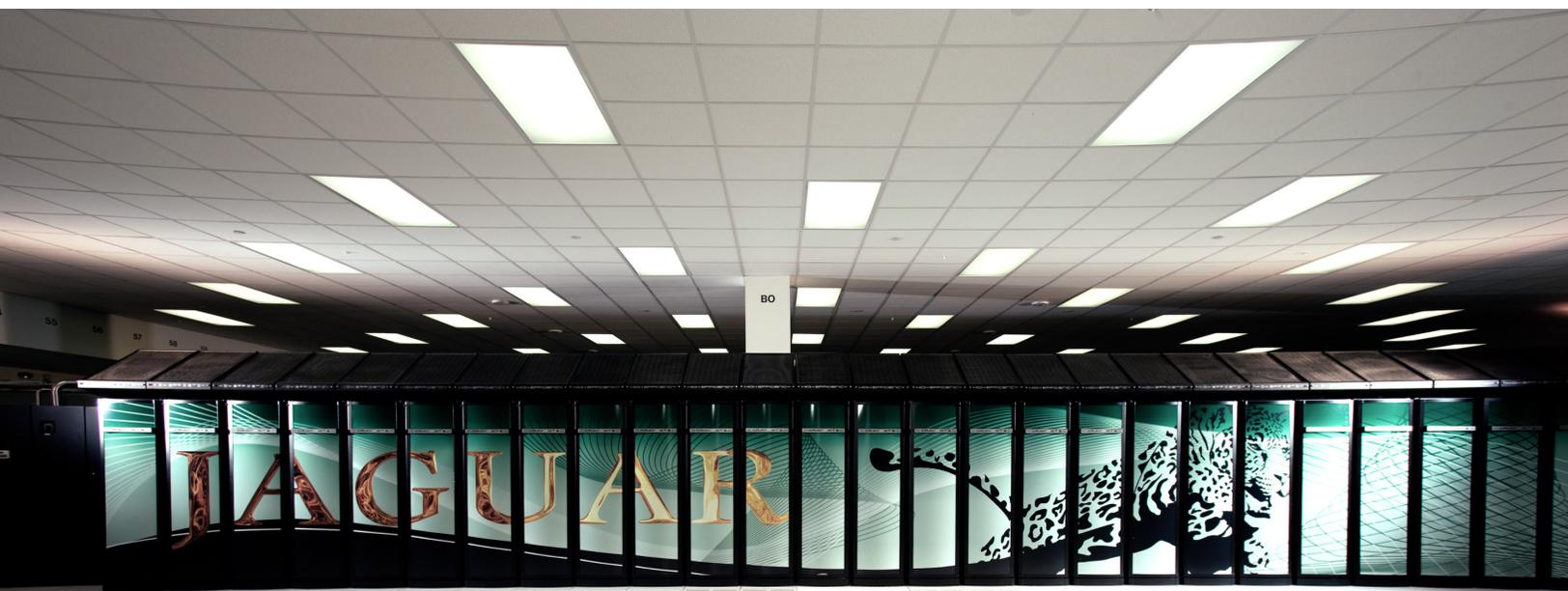
### **What tools are you developing to help get programs to work on supercomputers?**

**Eblen:** I'm focused on improving software development on supercomputers, a goal of the Eclipse Parallel Tools Platform (PTP) synchronized projects. Modern IDEs, such as Eclipse, offer many features to speed up software de-

velopment. We want to make sure that these tools are available to those developing the most complex applications – those that run on supercomputers. Most people are not free to work directly on their favorite supercomputer with an IDE. They should be able to use the IDE on their personal computer, though, and have it work as if they were sitting at the supercomputer.

### **What have you done so far with the UT/ORNL supercomputers and what is the future for supercomputers in biomolecular simulation?**

**Schulz:** We have performed enormous simulations of biomass that wouldn't have been possible any other way. Analyzing the results is taking quite some time...



With a peak speed of 2.33 petaflops (over two thousand trillion calculations per second), "Jaguar," a Cray XT5 supercomputer located at Oak Ridge National Laboratory, is one of the world's fastest supercomputers for unclassified research. Capable of simulating physical systems with heretofore unfeasible speed and accuracy, Jaguar has led ORNL into the era of petascale computing and beyond.

**Ellingson:** I have done many smaller drug-design screenings to prepare for the million compound screen we recently completed. I think that we may see more special purpose computers, such as Anton, for biomolecular simulations. However, since special purpose computers are built around the code that runs on them, they will not be able to handle everything, and multi-purpose supercomputers will still be very important. Many multi-purpose supercomputers are going toward hybrid architectures which include GPUs for part of the processing power. It will be important to learn how to correctly utilize these architectures to improve the speed of simulation code.

### **How can we advance the state of software development, especially for supercomputing?**

**Eblen:** Historically, leaps in what humans can do with computers come from newer and better tools. The purpose of a tool is to take care of the mundane activities, so that we can focus on the bigger issues. What has changed over time is what is considered "mundane." Assemblers automate the mundane task of having to translate operations to bits and bytes. Compilers automate the mundane task of translating common operations to a series of assembly commands, such as adding multi-byte numbers or creating loops. IDEs automate still more complex operations. Each new class of tools frees us to tackle bigger, more ambitious projects. Unfortunately, this process has some inertia. People become familiar with their tools and aren't eager to learn new ways of doing things. For example, some of our programming languages are long

overdue for a remake. Now I love C++. It is my favorite of the commonly used languages. What other language allows both raw, system-level access and tons of useful, high-level features, such as classes and well-developed standard libraries? C++ is a good example of a tool that pushed the industry ahead. It suffers from its C heritage, though, which makes the language overly complex and error prone. Now there is a wonderful, relatively new language, called the D programming language, which has been carefully designed and well-engineered over about a decade now. It is a systems language that is just as powerful and feature-rich as C++ while fixing many of its problems. But I don't know anyone trying to use it for supercomputing. So that is one example of a possible initiative that could advance our tools and increase even more of what we humans can do with our computers.

### **Mere mortals find computers extremely annoying when they don't do what they want. Is it the same with you hot-shots?**

**Ellingson:** Getting computers to do what you want is the fun part. If they always did exactly what you wanted the first time you tried, it wouldn't be as rewarding when you finally get your programs working right.

**Eblen:** Of course! Often, I know why it's not working like I want. So as a developer myself, depending on my mood and whatever the problem is, I may feel sympathetic to the poor programmer or feel... displeased because he or she should have known better!

# Neutron Scattering

## STRUCTURE AND DYNAMICS OF BIOMOLECULAR SYSTEMS

Neutrons are unique probes of condensed materials, furnishing both structural and dynamic information, and neutron scattering has been a sustained interest of Jeremy Smith's since he published his first papers on the subject as a Ph.D. student at the Institut Laue-Langevin in Grenoble, France in 1986. The advent of the Spallation Neutron Source at ORNL now promises to take neutron scattering research to new heights, and we have therefore established a program aiming at developing methodologies for neutron research, integrating high-performance simulation with neutron scattering, and applying a range of neutron techniques to systems of interest in biology and the energy biosciences.

The methodological work has produced a number of breakthroughs. Among these is the first calculation of the lattice dynamics of a protein crystal at atomic resolution, which we hope can at some point be tested experimentally using triple-axis instrumentation. Just this year, work performed principally by postdoctoral fellow Liang Hong, in collaboration with Alexei Sokolov, another Governor's Chair, demonstrated how the dynamic neutron susceptibility of a protein can be simply interpreted in terms of three classes of motion (see press release). Complementary theoretical work with graduate student Thomas Neusius demonstrated that the subdiffusive behavior of peptide dynamics has a fractal origin.

Also, postdoctoral fellows Yi Zheng and Yinglong Miao have been working with Jerome Baudry and Nitin Jain, an Associate Professor in the UT Department of Biochemistry and Cellular and Molecular Biology, to perform and interpret neutron scattering experiments on cytochrome P450 – this work has led to a new method for analyzing elastic scattering that yields not only the average mean-square displacement of hydrogen atoms in a protein but also the variance.

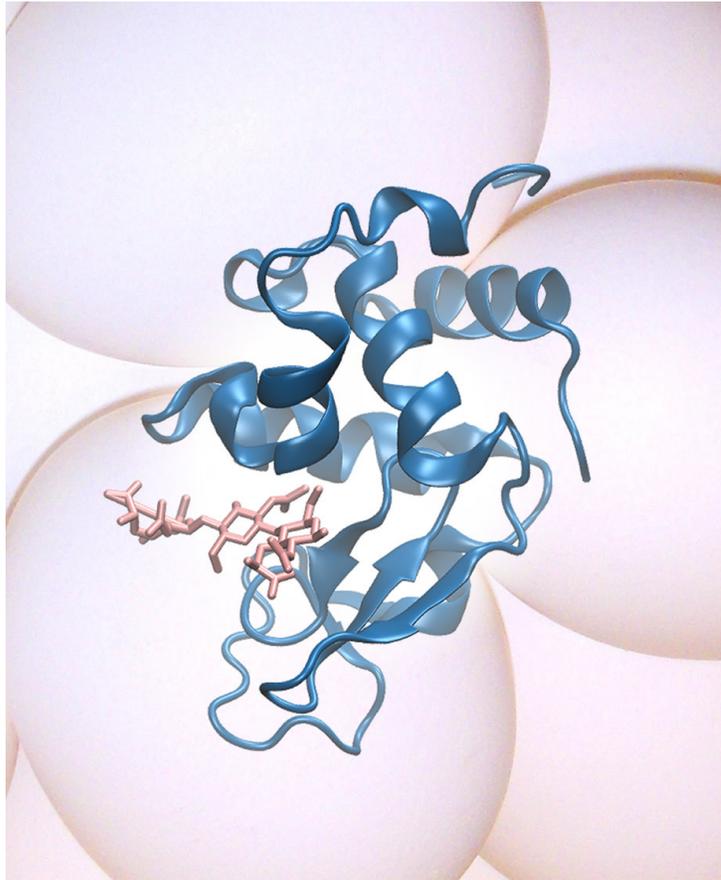
Two growth areas for the future have been identified. One of these is the application of neutron spin-echo spectroscopy to characterize functional domain motions of biomolecules, an area that postdoctoral fellow Nikolai Smolin has been concentrating on, and the second is the application of neutrons to the energy biosciences, and, in particular, the structure and dynamics of lignocellulosic biomass. Finally, Jeremy would like to realize a vision of unifying exascale supercomputing with high-performance neutron scattering in which molecular simulations are performed using the full power of the exascale machinery and are used to plan and interpret experiments at SNS in real time. We are quite a way from achieving that goal, but a first step has been taken by graduate student Benjamin Lindner, who has efficiently parallelized software for scattering calculations. Given the resources, the unification dreamed for will happen.

# ***High-performance simulation, neutrons uncover three classes of protein motion***

Source: [http://www.ornl.gov/info/press\\_releases/get\\_press\\_release.cfm?ReleaseNumber=mr20110930-00](http://www.ornl.gov/info/press_releases/get_press_release.cfm?ReleaseNumber=mr20110930-00)

OAK RIDGE, Tenn., Sep. 30, 2011 — Molecular motion in proteins comes in three distinct classes, according to a collaboration by researchers at the Department of Energy's Oak Ridge National Laboratory and the University of Tennessee, in research reported in *Physical Review Letters*.

The research team, directed by ORNL-UT Governor's Chairs Jeremy Smith and Alexei Sokolov, combined high-performance computer simulation with neutron scattering experiments to understand atomic-level motions that underpin the operations of proteins.



*Lysozyme (shown in blue) -- a natural enzyme found in tears, saliva and egg whites -- can break down bacterial cell walls (shown in pink). ORNL researchers have combined computational simulation and neutron experiments to clarify the complicated motions of proteins such as lysozyme into three distinct classes.*

"The analysis and interpretation of neutron scattering spectra are always difficult for complex molecules such as proteins," said Smith, who directs ORNL's Center for Molecular Biophysics. "We've performed experiments and then shown that simulation can provide a clear view of them. It allows us to see through the complexity and find out what motions are going on."

Defining the motions present -- localized diffusion, methyl group rotations and jumps -- is important as it allows scientists to think about how the motions determine the functions of proteins that are critical to all life.

"First, we found that experiment and simulation agreed perfectly with each other, which is remarkable," Smith said. "Second, the simulations told us that this type of neutron scattering can be interpreted in a very simple way."

Although the team performed its research on a particular protein called lysozyme, a natural antibacterial enzyme found in tears, saliva and egg whites, the researchers anticipate the technique will have a much broader impact in the neutron scattering community, aiding research in areas such as biofuel design or environmental remediation.

The combined simulation and neutron scattering approach should also be of use in the characterization of non-biological materials such as polymers. Smith notes that approximately half

the neutron scattering experiments at ORNL's Spallation Neutron Source involve the study of motions in materials.

"These methods are of general applicability," Smith said. "Many experimentalists can now come to the ORNL's Spallation Neutron Source, measure a spectrum of whatever sample they have, and then apply this analysis in terms of three classes of motion to interpret their results."

The research was primarily conducted by ORNL's Liang Hong, with the support of Benjamin Lindner and Nikolai Smolin from ORNL. They performed neutron scattering experiments at ORNL's Spallation Neutron Source on the BASIS instrument and at the National Institute of Standards and Technology Center for Neutron Research. The work was published as "Three classes of motion in the dynamic neutron scattering susceptibility of a globular protein."

The simulation component of the work was supported by ORNL's Laboratory Directed Research and Development program, while the neutron scattering component was supported by an Experimental Program to Stimulate Competitive Research (EPSCOR) grant to the University of Tennessee from the DOE Office of Science.

ORNL is managed by UT-Battelle for the Department of Energy's Office of Science.

# Subsurface Biogeochemistry

## TRANSPORT AND TRANSFORMATION OF MERCURY

*The fate of mercury as a subsurface contaminant is of particular interest in Oak Ridge because of contamination from cold-war activities at the Y12 weapons plant in the 1950s and 1960s. It turns out that following mercury in the environment has some fascinating aspects. Mercury interacts with and is transformed by organic matter in streams and sediments, and bacteria are able to methylate mercury, rendering it more toxic, and also to demethylate and thus detoxify it. The transport and transformation of mercury in these bacterial cells has become a subject of intense interest for CMB, in the framework of an ORNL Science Focus Area and a university-led project through UT.*

*Among the methods applied are semi-empirical quantum mechanical/molecular mechanical (QM/MM) calculations, which postdoctoral fellow Demian Riccardi has been working at streamlining, MD simulations and subsequent structural analysis, which Jerry Parks and postdoctoral fellow Hao-Bo Guo have performed. Also,*

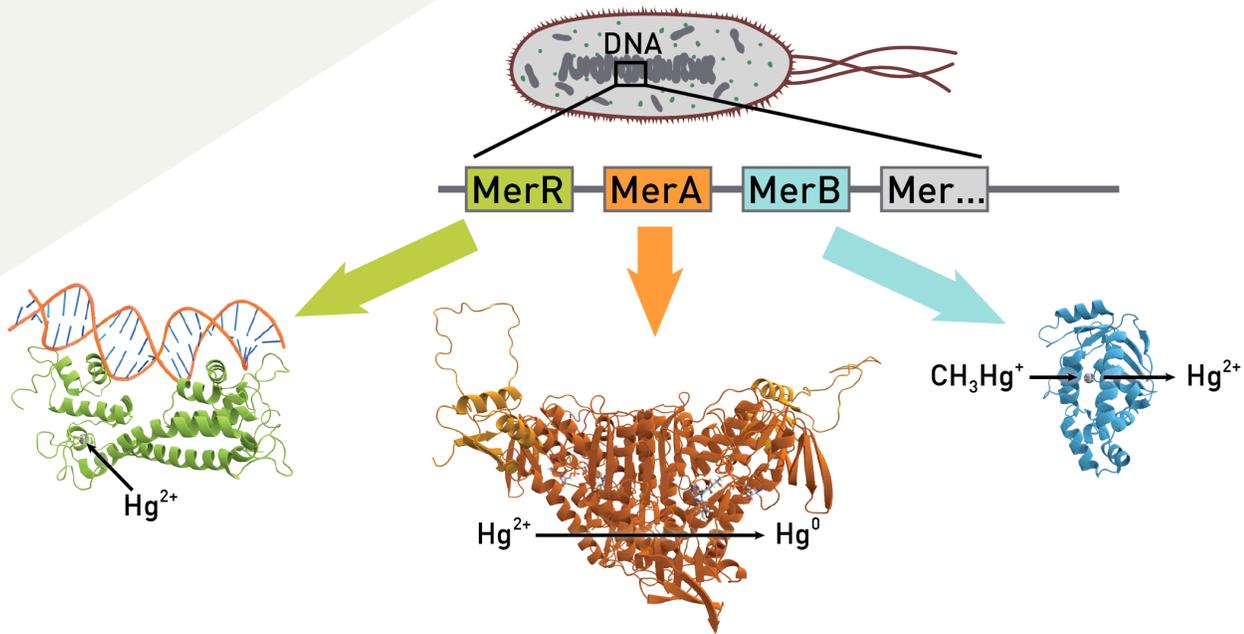
*Hong Guo and postdoctoral fellow Qin Xu are examining the chemistry of the reduction of mercury in a protein active site. All this work has involved intense (and sometimes heated!) collaboration with Profs. Anne Summers from the University of Georgia and Sue Miller of the University of California, San Francisco.*

### Why is mercury research important?

**Parks:** Mercury is interesting in itself because it's a really shiny liquid metal that sticks to just about everything. Unfortunately, it also happens to be an environmental toxin. It really likes to interact with sulfur, which is one reason it is harmful to living organisms. Lots of bacteria are resilient and can live happily in mercury-rich environments. They have genes that allow them to take up harmful forms mercury from the environment and turn it into a less toxic form. But there are other types of bacteria that make the more toxic form called methylmercury. We need to understand the fate of mercury thoroughly – how it gets converted from one form to another by sunlight, bacteria, and so on. Mercury transformation not a one-time event - there is a complex global mercury cycle. So here's how it works - There's already some mercury hanging around, then more of it gets into the air from things like power plants, then it floats halfway around the world, falls back to the ground during a rainstorm, then it



Mercury is an environmental toxin due to its unusually strong affinity for thiols and other functional groups.



Binding of Hg<sup>2+</sup> to MerR induces conformational changes required to initiate transcription of *Mer* genes, which encode proteins and enzymes involved in mercury resistance. Two other major components of the Mer system are the organomercurial lyase, MerB, which converts methylmercury to Hg<sup>2+</sup>, and the mercuric reductase, MerA, which reduces Hg to Hg(0).

gets oxidized, then methylated, then demethylated, and then reduced and the whole process starts over again.

of this dynamics, and this may yield insight into other biological systems with similar dynamics.

### What have you discovered about bacterial mercury transformation?

**Hao-Bo Guo:** "Mer" proteins are genetically encoded by the mer operon. These proteins transport and transform mercury in resistant bacteria. We have looked at the highly toxic form methylmercury – methylmercury – and how it is broken down by an enzyme called MerB. Another part of the molecular machinery is MerR, which turns on transcription of mer genes when mercury binds to it. Our recent work with X-rays, neutrons and MD simulations has shown that the primary motion of MerR involves two DNA-binding domains approaching and departing from each other. We successfully determined the end-states

### What other aspects are worth pursuing?

**Riccardi:** The behavior of mercury is intimately related to its oxidation state and affinity for various ligands. We're considering investigating how the oxidation state affects mercury transfer among ligands and across lipid membranes, and constructing model computational systems of naturally occurring organic matter to which mercury binds in streams. We're also using structural bioinformatics to characterize both observed and potential sites of mercury interaction with biological molecules in vitro and in the crystalline state. All of these are very interesting research directions and could have broad scientific and environmental impacts.

# Biomedical Research

*Biomedical research expands in several directions at CMB. Using the ORNL and UT supercomputers to design new drugs is an important and exciting field. However, we are also researching bacterial chemotaxis, active site solvation and ion channel function:*

## Drug Design

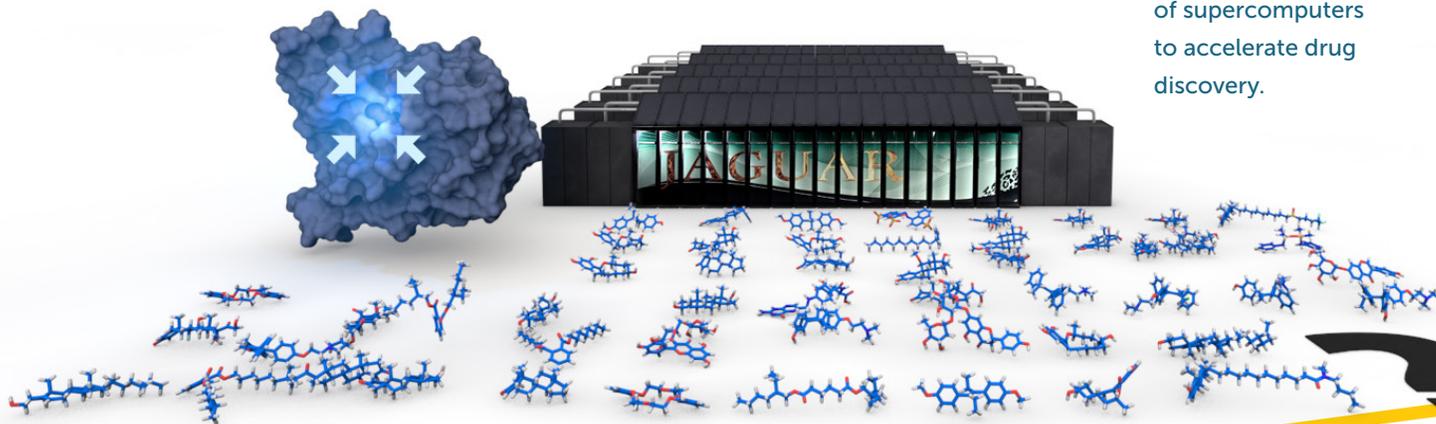
### Supercomputing and Docking

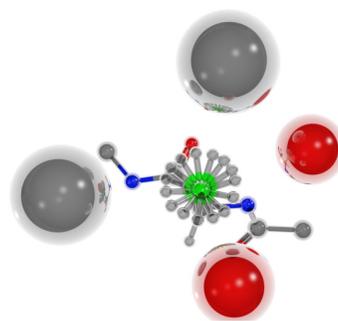
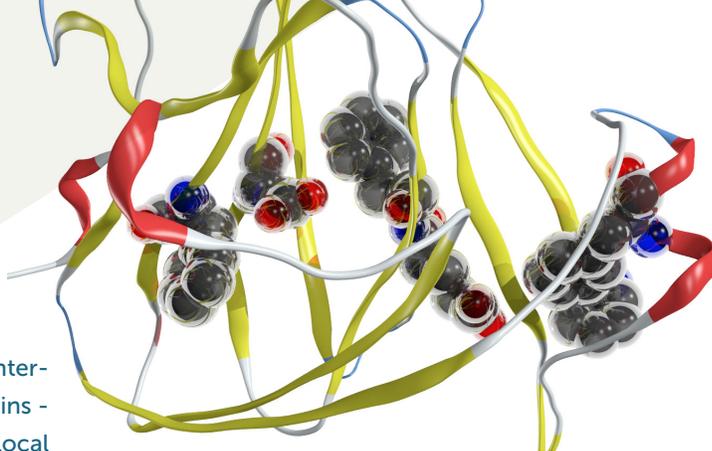
CMB uses molecular modeling and computational chemistry to investigate how medically relevant biomolecules interact with each other. We are particularly interested in molecular discovery, i.e. how to select and/or design small molecules, like pharmaceuticals, that will interact in a specific and potent way with much larger molecules, like proteins. Small

molecules may sometimes enhance, or sometimes inhibit, the functioning of the proteins to which they bind. To discover or design a new drug against a disease, we must understand a great deal about what the target proteins look like and how they function, such as where possible binding cavities are located in the protein, how these cavities change their shapes with time, and how the atoms in the proteins interact with those of the pharmaceuticals.

The availability of thousands of processors, either localized together in a supercomputer, or delocalized as in cloud computing, can be used to perform virtual screening of massive databases of chemicals against protein targets. To take advantage of these giant computers, Jerome Baudry, postdoctoral fellow Barbara Collignon, Roland Schulz and Sally Ellingson have developed efficient, well validated computer programs for docking (see press release). Sally

Using the power of supercomputers to accelerate drug discovery.

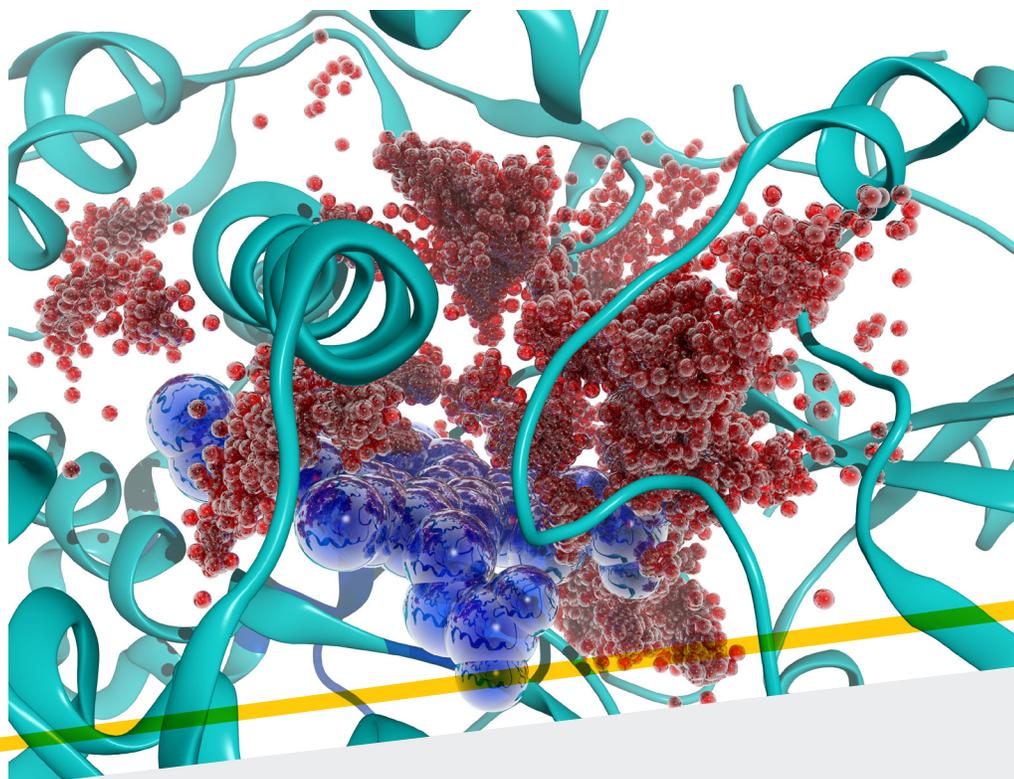




Detailed analysis of interactions within proteins - methyl groups probe local environments.

Ellingson is continuing this work and developing it for Cloud architectures and to allow multiple protein targets to be used efficiently in the docking process. It is now possible to investigate computationally how millions of compounds would bind in a given protein, or in multiple proteins of a biochemical pathway. These approaches are used in collaboration with experimental laboratories to discover novel classes of molecules against several endocrine cancers and infectious diseases. With the advent of the exascale in supercomputing, it may become possible to screen essentially complete ligand databases against all known classes of protein in about one day.

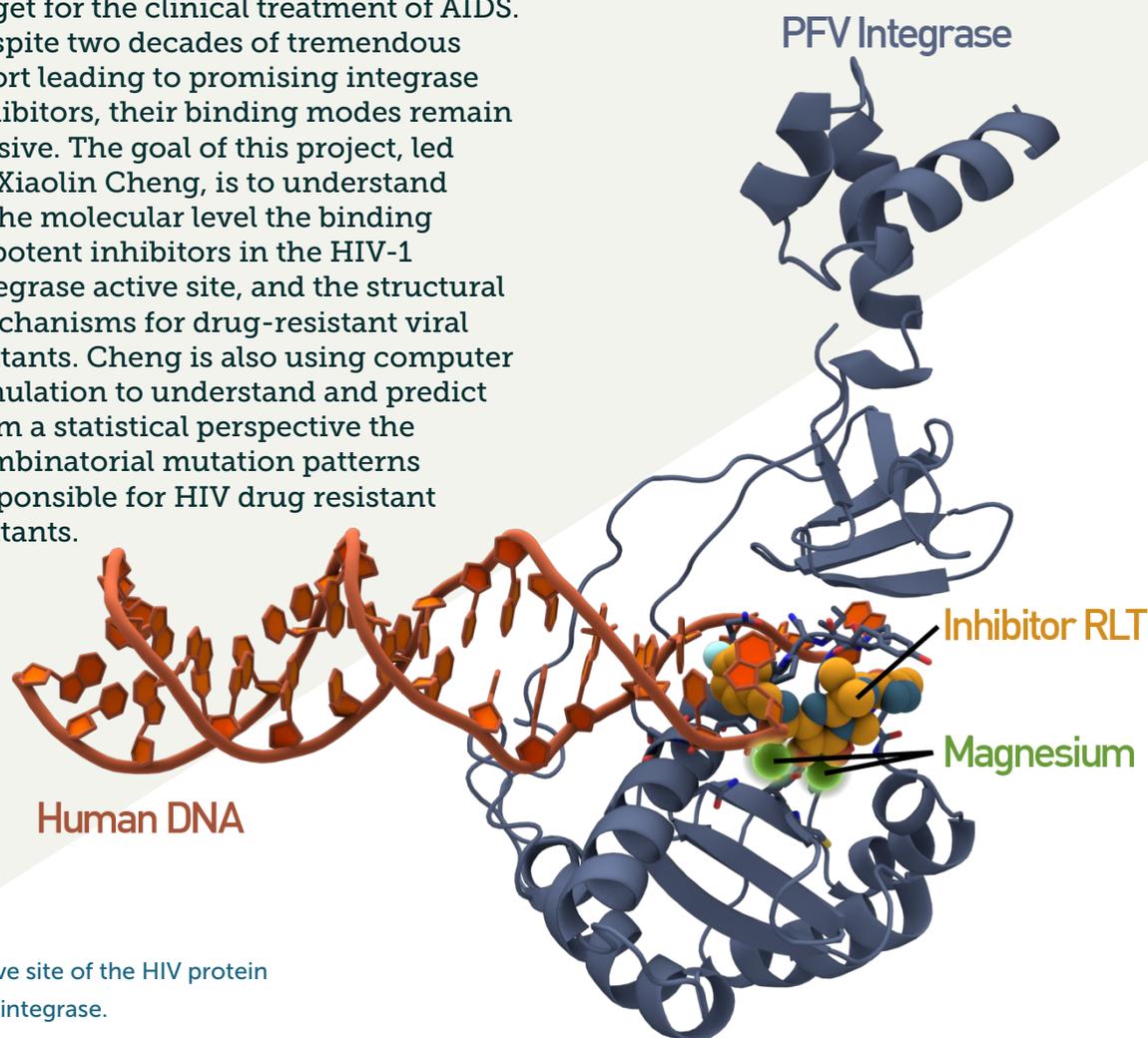
To improve the efficiency of drug design, it is very important to understand how drugs and proteins interact with each other at the atomistic scale. We are developing new views on how non-bonded interactions control the dynamics and the energetics of protein/ligand complexes through facilitation of molecular rotations and anion/ $\pi$ -interactions. We are also characterizing how medically and pharmaceutically important proteins are behaving, to understand how drugs may affect them: we are building the "protein skyscrapers" that control how bacteria look for food and we are following each and every water molecule that flushes a P450 enzyme's active site to help detoxify drugs.



Detoxifying-enzymes cytochrome P450s "flush" their active site to ensure catalytic efficiency.

## AIDS Drug Design

HIV-1 integrase is an important enzyme in viral HIV replication with apparently no human counterpart, making it an attractive therapeutic target for the clinical treatment of AIDS. Despite two decades of tremendous effort leading to promising integrase inhibitors, their binding modes remain elusive. The goal of this project, led by Xiaolin Cheng, is to understand at the molecular level the binding of potent inhibitors in the HIV-1 integrase active site, and the structural mechanisms for drug-resistant viral mutants. Cheng is also using computer simulation to understand and predict from a statistical perspective the combinatorial mutation patterns responsible for HIV drug resistant mutants.



Active site of the HIV protein  
PFV integrase.

## Interactions in Proteins

The Baudry group is also interested in the effect of nonbonded interactions in protein-protein and protein-ligand complexes. Undergraduate student William Hembree has used quantum chemistry to investigate how the rotational dynamics of methyl groups, an important marker

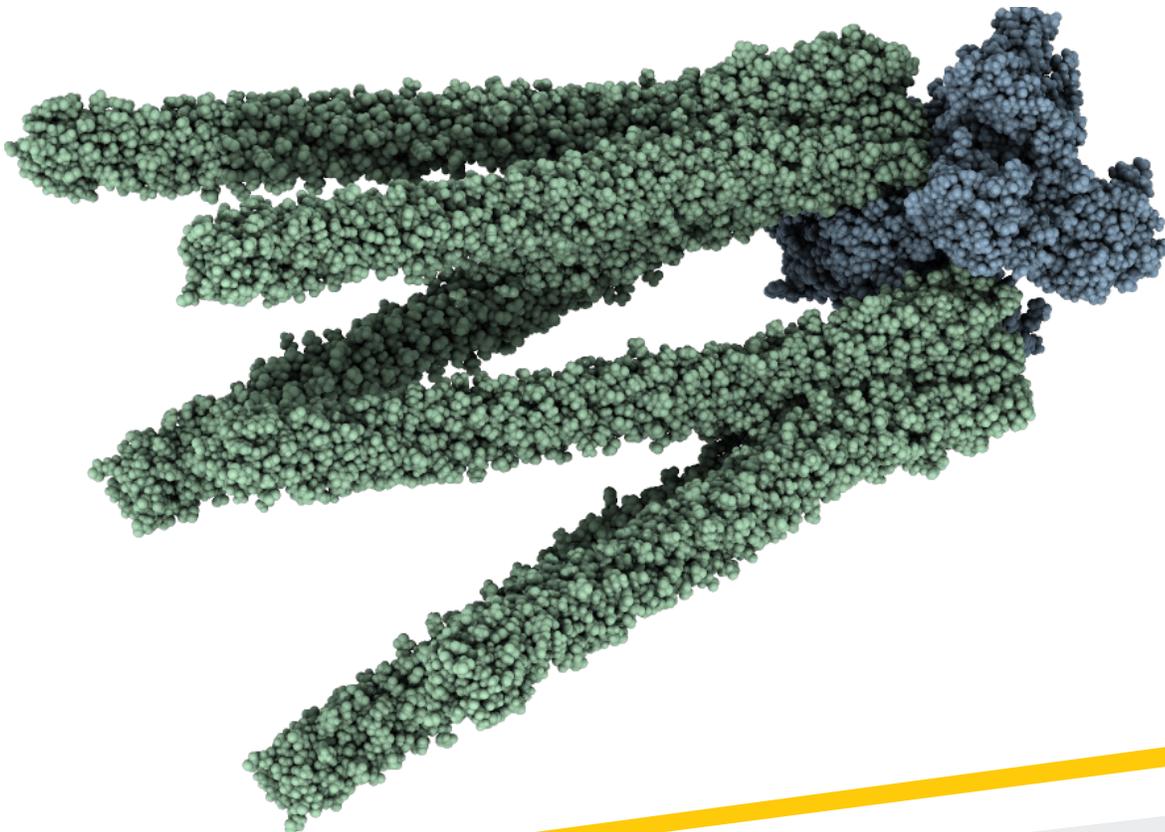
in chemistry, is affected by their micro-environment. In collaboration with the groups of Dr. Howell and Dr. Hinde at the University of Tennessee, the group, along with graduate student Jason Harris, is also investigating how anion/ $\pi$ -interactions in proteins and protein-ligand complexes contribute to protein stability and dynamics.

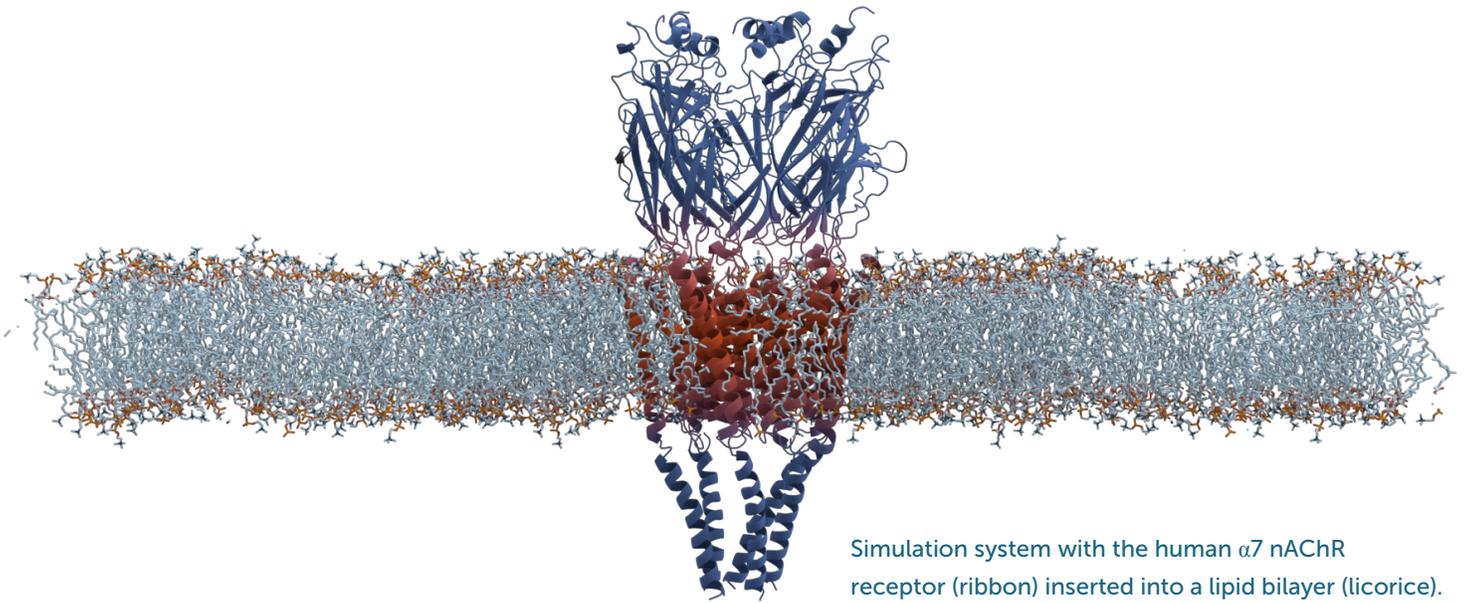
## Chemotaxis - Ligand based signaling pathways

Postdoctoral researcher Derek Cushman is working collaborative project involving the groups of Jerome Baudry and Igor Zhulin that involves the integration of bioinformatics with biophysical studies. The first step involves creating a natural classification of chemotaxis proteins based on phylogenetic analysis and identifying conserved residues within evolutionarily related subgroups, and co-variance analysis of co-evolving residues. This information is then integrated with

machine learning analysis of surface patches on each protein to predict potential sites for protein-protein interactions, leading to molecular docking and computational simulations to test the protein-protein interactions of each model. These results will then be used to drive further experimental and systems biology research by our collaborators and other laboratories. The principles learned through these studies will provide insight into about signal transduction mechanisms, and will aid in the design of new therapeutics targeting the signaling pathways that control virulence in human pathogens.

The structural basis of bacterial chemotaxis. A hypothetical model of the bacterial chemoreceptor (MCP, shown in green) interacting with the scaffolding protein, CheW, and histidine kinase, CheA (both shown in blue). These proteins are part of a signal transduction cascade that responds to stimuli in the environment and transfers a signal to the bacterial flagellar apparatus to control the cell's swimming behavior in response to that stimulus.





Simulation system with the human  $\alpha 7$  nAChR receptor (ribbon) inserted into a lipid bilayer (licorice).

## Solvation of Active Sites

P450 proteins are very important enzymes responsible in the human body that are responsible for processing many pharmaceuticals. Jerome Baudry and Postdoctoral researcher Yinglong Miao have used computer simulation to reveal the highly dynamic nature of CYP101 P450 hydration. Water molecules enter and leave the active site on the nanosecond timescale, sustaining the efficiency of the enzyme.

## Channel gating and ligand recognition in pentameric ligand gated ion channels

The nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion channel. Binding of neurotransmitter mol-

ecules to nAChR induces structural rearrangements of the membrane-spanning domain, which permits the influx of cations and leads to message propagation. Due to their essential roles in synaptic transmission, nAChRs have emerged as attractive therapeutic targets for the treatment of pain, cognitive impairment, neurodegenerative disease, schizophrenia, epilepsy, anxiety, and depression. Fundamental steps in receptor activation include neurotransmitter recognition, coupling of recognition to opening of the ion pore, and passive flow of ions through the pore. Xiaolin Cheng has performed extensive molecular dynamics simulations to understand the molecular mechanisms underlying all three of these fundamental steps. Cheng's calculations probe the energy barriers to ion conduction and origins of ion selectivity in the channel.

# UT Scientist Uncovers Trigger to Fatal Neurodegenerative Disease

Source: <http://www.utk.edu/tntoday/2011/06/22/jeremy-smith-gss-protein>

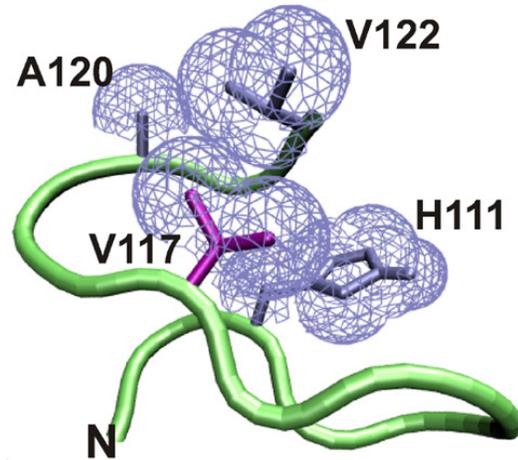
Jeremy Smith, Governor's Chair for Molecular Biophysics at the University of Tennessee, Knoxville, has helped reveal a key trigger of Gerstmann–Sträussler–Scheinker (GSS) syndrome, a rare but deadly neurodegenerative disease. The finding could have far-reaching implications for the treatment of other neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's.

Smith conducted his research with two collaborators in Italy: Isabella Daidone, a former postdoctoral researcher of his who is now at the University of L'Aquila, and Alfredo Di Nola of Sapienza – Università di Roma.

Most GSS patients begin developing symptoms in their late fifties. Symptoms include loss of memory, difficulty speaking, and unsteadiness and lead to progressive dementia, and then death within a few months or years. There is presently no cure or treatment. The disease results from a single, tiny mutation in a protein, resulting in it having a wrong shape—through “misfolding”—then aggregating to form amyloid plaques in the brain.

“Ever since the ‘mad cow’ scare in Britain in the 1990s, which led to several hundred human deaths and 4.4 million cattle being destroyed, I’ve been interested in finding out more about these fascinating diseases of wrongly shaped proteins,” said Smith, who was born in England.

The team compared high-performance computer simulations of the struc-



tures of the normal and the GSS–mutant proteins. They found the GSS protein looks dramatically different from the normal form and revealed how its shape is primed for plaque formation.

“This research shows how computer simulation can be used to pinpoint changes in molecular structure that lead directly to disease,” said Smith. “We think that a similar line of investigation should prove beneficial in understanding the origins of other amyloid diseases such as Alzheimer's, Parkinson's, and rheumatoid arthritis. Once the origin is understood at molecular detail, strategies to rationally prevent and cure a disease can be conceived.”

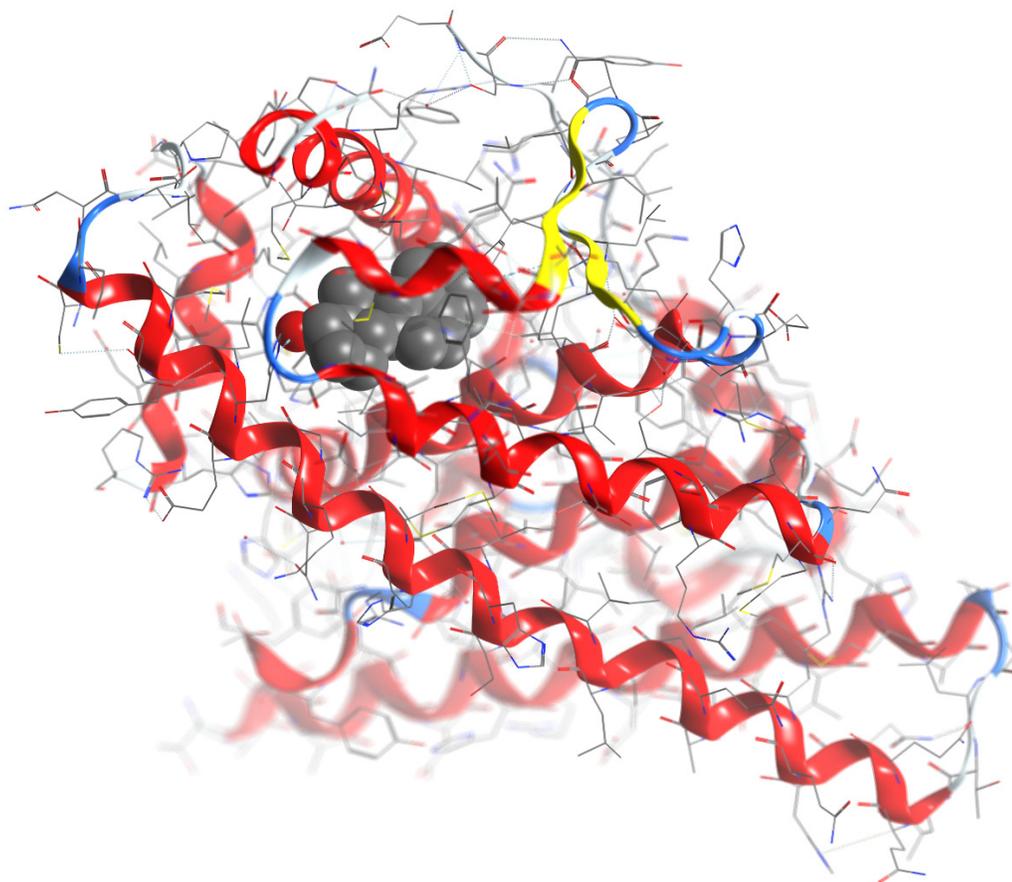
The findings can be found in the article, “Molecular Origin of Gerstmann–Sträussler–Scheinker Syndrome: Insight from Computer Simulation of an Amyloidogenic Prion Peptide” in this month's edition of the *Biophysical Journal*.

The research was funded in part by a Marie Curie grant from the European Union.

# Supercomputing Research Opens Doors for Drug Discovery

Source: <http://www.sciencedaily.com/releases/2010/12/101209164146.htm>

*A quicker and cheaper technique to scan molecular databases developed at the Department of Energy's Oak Ridge National Laboratory could put scientists on the fast track to developing new drug treatments.*



*Supercomputers could help speed up the drug discovery process by identifying suitable chemicals (seen as gray spheres) that can dock onto a designated target in the body, such as a protein (seen as red ribbons). (Credit: Image courtesy of DOE/Oak Ridge National Laboratory)*

A team led by Jerome Baudry of the University of Tennessee-ORNL Center for Molecular Biophysics adapted a widely used existing software to allow supercomputers such as ORNL's Jaguar to sift through immense molecular databases and pinpoint chemical compounds as potential drug candidates.

The research was published in the *Journal of Computational Chemistry* as "Task-parallel MPI implementation of Autodock4 for docking of very large databases of compounds using High Performance Super-Computers."

"Our research is the missing link between supercomputers and the huge data available in molecular databases like the Human Genome Project," Baudry said. "We have an avalanche of data available to us, and now we need to translate that data into knowledge."

Such translation is critical for the first stages of drug development, in which researchers look for appropriate chemicals that interact with a target in the body, typically a protein. If the chemical is suitable, it attaches onto the protein and produces a desirable effect in the cell.

But with thousands of known proteins and millions of chemicals as potential drugs, the number of possible combinations is astronomical.

"It is very expensive and time-consuming to measure these interactions experimentally," Baudry said. "But with supercomputers, we can process millions of molecules a day."

The quick and efficient processing of molecules offers scientists an opportunity to take risks on previously unexamined drug candidates, which could lead to diverse and innovative classes of drugs.

"Before, we threw away a lot of information because molecules did not have a preferred profile," Baudry said. "Now, every molecule can be examined

without worrying about wasting resources."

The researchers have already started work to launch the research into reality through a new collaboration supported by the National Institutes of Health. The project team plans to put the computational development to work on ORNL supercomputers to look for chemicals that could treat prostate cancer. The research is funded by a NIH Clinical Translational Science Award, which was awarded to Georgetown and Howard Universities and includes ORNL, Med/Star Health and the Washington D.C. Veterans Affairs Medical Center as key partners.

"Our development work is the computational equivalent of building the Saturn V rocket," Baudry said. "Now we want to fly it to the moon."

Funding for the initial development work was provided by ORNL's Laboratory Directed Research and Development program. The University of Tennessee and the Joint UT/ORNL Genome Sciences and Technology graduate program also supported the work. The research team included Barbara Collignon, Roland Schulz and Jeremy Smith of the UT-ORNL Center for Molecular Biophysics. The three researchers as well as Baudry are also affiliated with the University of Tennessee's Department of Biochemistry and Cellular and Molecular Biology.

# Enzyme Catalysis

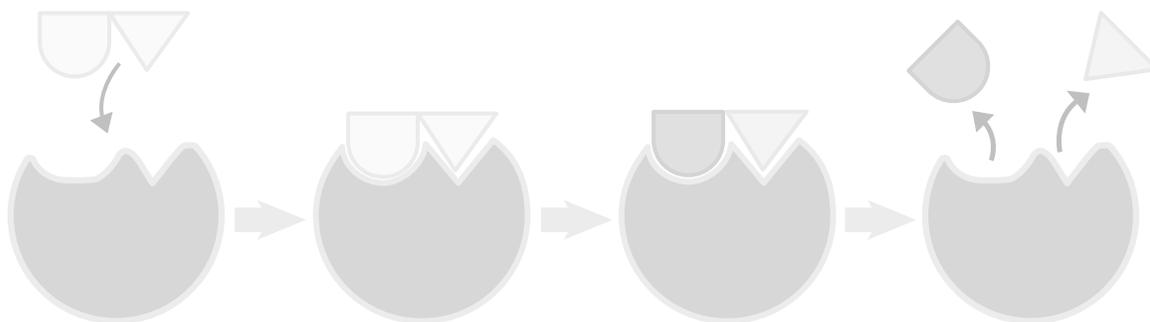
## FASTER PLEASE

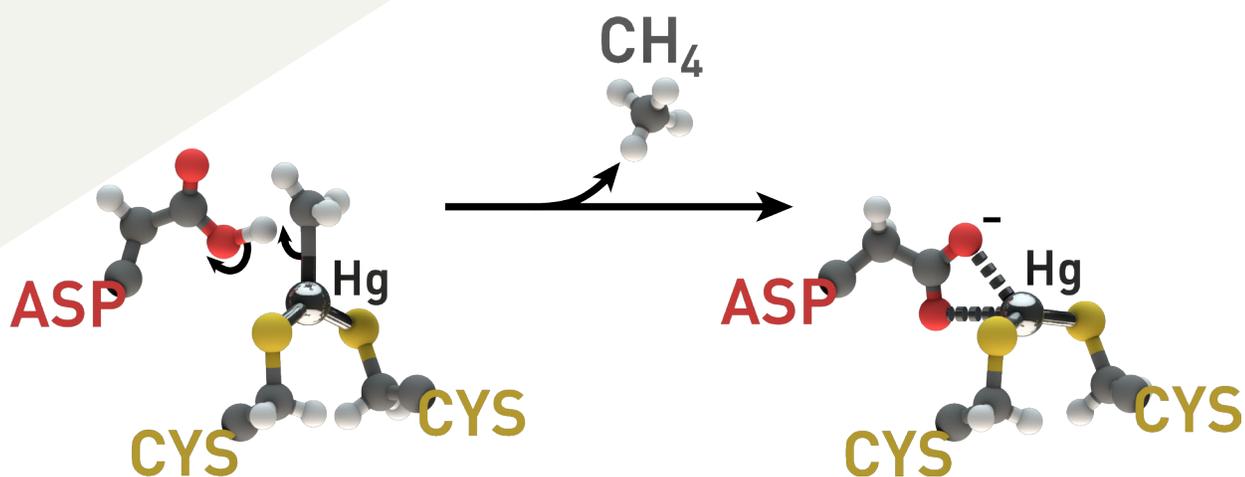
*Understanding enzyme catalysis is an important part of our work, with two principal investigators, Hong Guo and Jerry Parks specializing in this field. Enzymes accelerate chemical reactions that are of critical importance in bioenergy, such as the hydrolysis of cellulose, and subsurface biogeochemistry, such as mercury detoxification. Although enzymologists can find out much useful information experimentally, only computer simulation, and, in particular quantum chemistry, can determine complete reaction mechanisms, producing 'molecular movies' of reactions happening with the corresponding energetics.*

**Hong Guo** has a general interest in understanding the origin of the high catalytic efficiency and selectivity of enzymes. In addition to being of fundamental scientific importance, these studies also improve the basis for designing inhibitors, efficient drugs and enzyme mimics. He normally studies several systems at once, including recent work on protein lysine methyltransferases, RNA polymerases, serine-carboxyl peptidases, chorismate mutase, cytidine deaminase, and adenosine deaminase.

He has also participated in DOE work understanding the mechanism of action of a mercuric reductase and cellulases.

**Jerry Parks** came to CMB from the renowned group of Weitao Yang at Duke University, and is now spearheading research into catalysis involving mercury. Here, he discusses recent achievements and methodological roadblocks facing mixed quantum mechanical/molecular mechanical (QM/MM) methods.





Quantum mechanical description of organomercurial protonolysis. Two cysteine side chains in the active site of MerB coordinate with methylmercury, weakening the Hg-C bond. An aspartic acid side chain then protonates the  $-\text{CH}_3$  leaving group, breaking the bond and forming Hg(II) and methane.

### What is the challenge of QM/MM calculations? Is it the accuracy? Is it the many possible reactions that need to be considered?

**Parks:** The issue is that there's not just one challenge — there are several. For example, there's always a trade-off between accuracy and affordability of the calculations. A given method needs to be assessed carefully to make sure it's accurate enough for the questions you're trying to address. There are often many potential reaction pathways that need to be considered, and it is important not to introduce bias when selecting reaction coordinates. Describing the electrostatic effects correctly right can be a challenge, and achieving converged statistical sampling isn't easy either. The simulations are not simple. It's really a bit of an art to do things correctly, and we're definitely still learning. Also, you don't

always need to use QM/MM calculations. You can greatly simplify your life sometimes by just using a QM-only approach.

### What characteristics of mercury catalysis have you learned from your calculations?

**Parks:** Using a QM-only active site model of the enzyme MerB, we learned how the enzyme breaks mercury-carbon bonds in methylmercury. Two cysteine side chains coordinate very strongly with methylmercury, which makes the mercury-carbon bond a bit longer and weaker. Then, a nearby aspartic acid side chain delivers a proton to the carbon atom. The result is that the enzyme produces inorganic Hg(II) and methane, and gets rid of methylmercury.

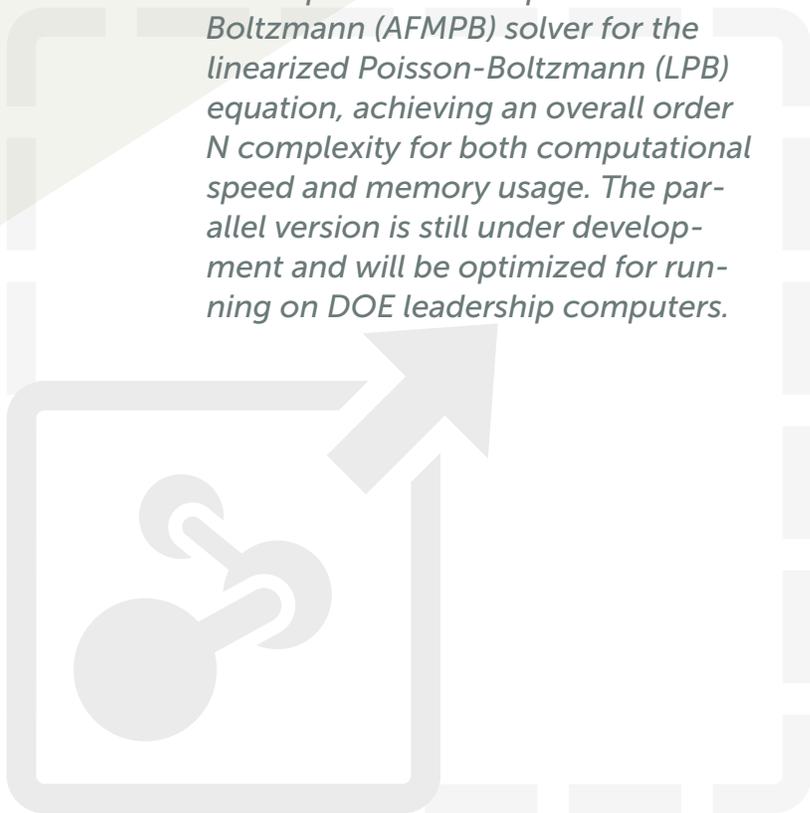
# Multiscale Methods

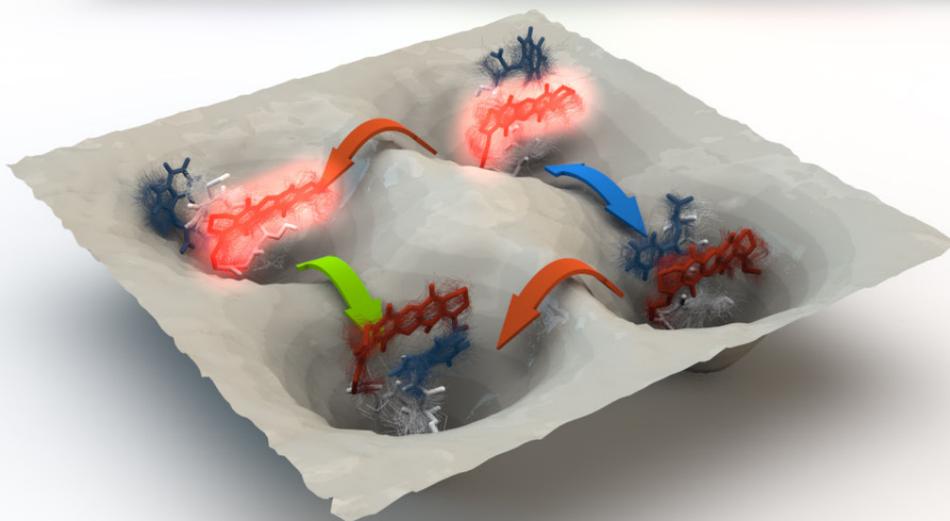
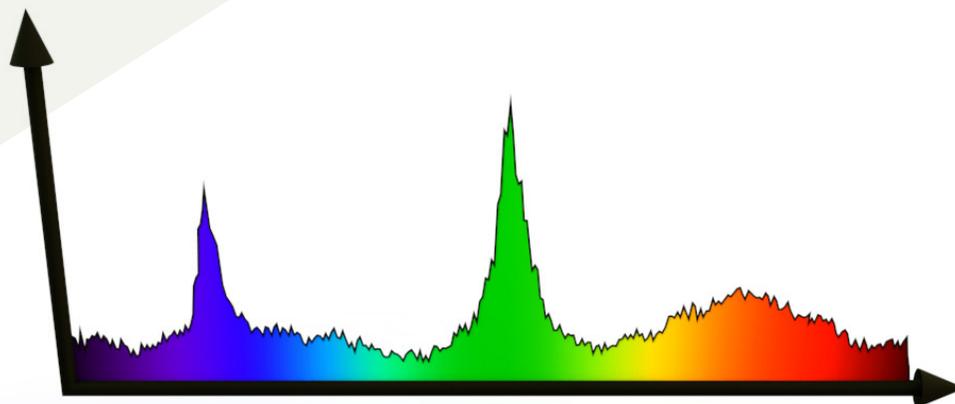
## SCALING FROM ATOMS UPWARDS

*The simultaneous representation of biological processes at different length- and time-scales is a fervent area of research at present, and comes from the realization that coarse-graining of atomistic interactions is necessary to allow the simulation of processes at the cellular, and eventually organismal level. We are particularly interested in developing multiscale concepts that will be able to be used on petascale and exascale capability supercomputers. Work in this area spearheaded by Xiaolin Cheng has involved finding ways to treat solvent implicitly, rather than explicitly, using "treecode" electrostatics. Cheng, together with graduate student Xiaohu Hu has developed an Adaptive Fast Multipole Poisson-Boltzmann (AFMPB) solver for the linearized Poisson-Boltzmann (LPB) equation, achieving an overall order  $N$  complexity for both computational speed and memory usage. The parallel version is still under development and will be optimized for running on DOE leadership computers.*

*Coarse graining work performed by postdoctoral fellow Goundla Srinivas and graduate student Dennis Glass, in collaboration with the Ames National Laboratory in Iowa, involves the development and application of Boltzmann inversion techniques and of the "REACH" (Realistic Extension Algorithm via Covariance Hessian) methodology developed by Kei Moritsugu of the RIKEN National Laboratory in Tokyo with Jeremy Smith, which maps results obtained from atomistic MD simulations onto models for larger-scale, coarse-grained MD.*

*Applications of CMB multiscale methodology have been directed toward understanding plant cell-wall deconstruction. Hydrolysis of cell-wall cellulose is the critical, rate-limiting step in cellulosic biofuel production. The physical properties of lignocellulosic biomass thus derived serve as a basis for interpreting an array of biophysical experiments, and, in particular, the simulation models derived will be used to calculate and interpret a variety of neutron-scattering properties. This combination of simulation and experiment will eventually lead to a description of the physicochemical mechanisms of biomass recalcitrance to hydrolysis, and thus will aid in developing a strategy as to how rationally to overcome the resistance.*





Dynamical fingerprints, calculated from discrete states obtained from high-performance simulation, permit spectra to be calculated that can be directly compared with equivalent experimentally derived quantities.

## Dynamical Fingerprints

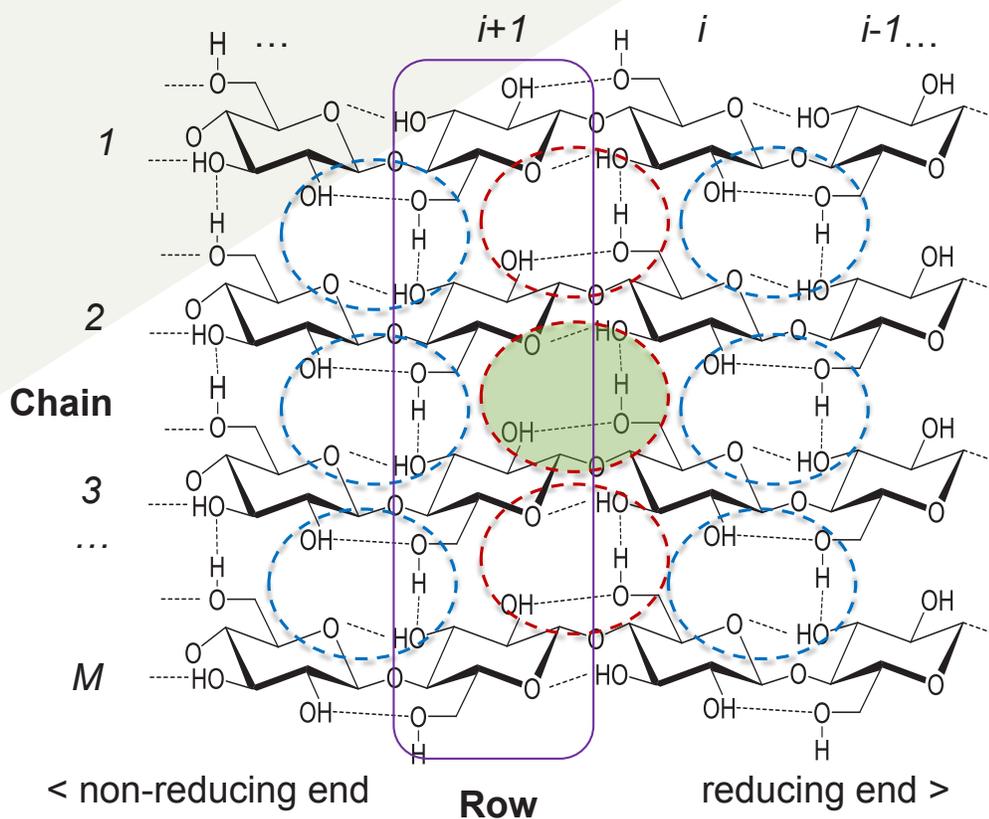
There is a gap between kinetic experiments and simulations in their views of the dynamics of complex biomolecular systems. CMB in collaboration with Frank Noé of the Freie Universität Berlin, have presented a theoretical framework that reconciles these two approaches. “Dynamical fingerprints” contain peaks at the time scales of the dynamical processes that are involved with amplitudes determined by the

experimental observable. Fingerprints can be generated from both experimental and simulation data, and their comparison by matching peaks permits assignment of structural changes present in the simulation to experimentally observed relaxation processes. This approach allows simulations to add a layer of complexity and realism to the interpretation of experiments such as neutron scattering.

# Hydrogen Bond Networks in Cellulose

A major cause of biomass recalcitrance to deconstruction is the high structural ordering of natural cellulose fibrils, which arises largely from an extensive hydrogen-bond network between and within the cellulose polymers. Tongye Shen, Xiaolin Cheng and Jeremy Smith have worked with Heinrich Klein, an undergraduate student at the University of Heidelberg, to derive a lattice-based model of hydrogen bonding in cellulose I $\alpha$ . The plasticity of the hydrogen bond network as evidenced

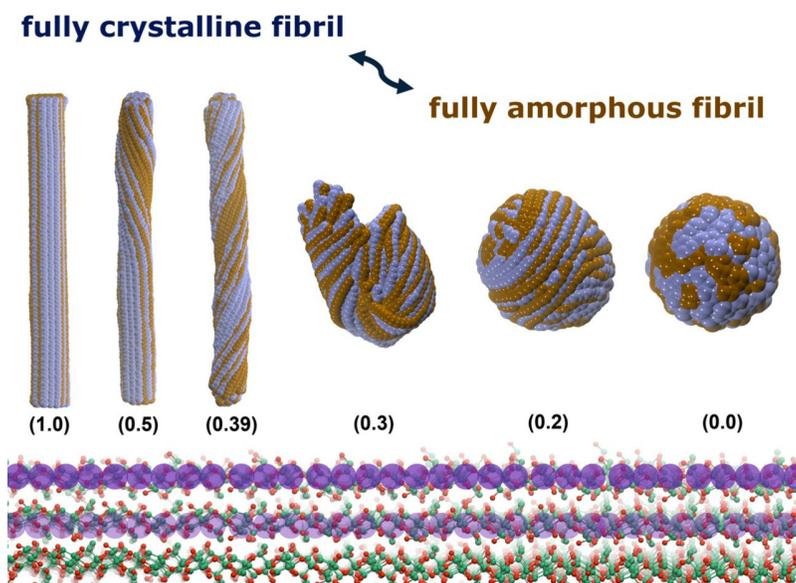
by two competing hydrogen bond patterns leads to an entropic contribution stabilizing the crystalline fibril at intermediate temperatures. At these temperatures, an enhanced probability of hydrogen bonding causes increased resistance of the entire fibril to deconstruction, before the final disassembly temperature is reached. The results thus provide a microscopic explanation for the physical origin of recalcitrance arising from the frustration of the hydrogen bond network.



An illustration of the sheet structure of cellulose I $\alpha$  and the hydrogen bond network.

## Coarse-Graining Cellulose

A systematic method has been developed by postdoctoral researcher Goundla Srinivas for generating and representing both crystalline and amorphous cellulose states. The developed CG models allow the exploration of cellulose fibril structures for length- and time-scales beyond the reach of atomistic simulations. Srinivas has also been developing a CG force-field for cellulose fibrils in explicit water.



Transition of cellulose fibril from crystalline to amorphous structures.

*Poplar: a potential biofuel feedstock investigated at ORNL.*



# How does a Physicist Survive in a Biology Department?

*Tongye Shen is an Assistant Professor in the UT Department of Biochemistry, Cellular and Molecular Biology. However, he looks at biological phenomena from a very physical standpoint, and his training differs substantially from that of most other faculty in the department.*



## How does a physicist survive in a biology department?

**Shen:** That is a tough question, and I am still figuring it out. You need so many things to be just right, such as luck and curiosity, and to ask the correct type of question that a physicist can answer. Physics always focuses on pure, ideal, and neat problems, while biological systems are much more complex. You can ask a lot of questions in biology and get a thousand different answers, but you don't know which one is correct.

## How does one overcome the inevitable communications problems that must exist between biologists and physicists?

**Shen:** I don't see this as a huge problem. You just have to be open-minded, patient, and find common ground by using simple terms to explain what you mean. It is very rewarding to learn from researchers from other fields and everybody is intrinsically curious.

## Many experts think that the most innovative research is that which crosses disciplines. Why do you think this is so?

**Shen:** Not sure. But, assuming that each field has 10 good and trendy ideas, three fields may have 20 good ideas. If you cross several fields, you may be familiar with a lot more ideas than if you only know what is going on in your field alone. And of course 20 ideas can be a lot better than 10 ideas in solving a particular problem.

## Tell us about your research on cellulose.

**Shen:** We are currently focused on understanding the structural stability of different phases of cellulose. I am surprised that not a lot more physical science researchers study this – it is really a very interesting problem. Just like ice having multiple phases due to extensive hydrogen bonding possibilities, polysaccharides also have a lot of bonding opportunities intramolecu-

larly and with their neighbors. Cellulose has many polymorphs as a result. To figure out how cellulose can transform from one form to another is very interesting. Postdoctoral researcher Xianghong “Hanna” Qi, a physicist and self-proclaimed expert on everything (Editorial note: said with a big grin), uses statistical physics to study this problem. We also examine the stochastic dynamics of the cellulose degradation by enzymes. This system is an excellent bridge to many other biological problems.

### **Why are lectins interesting and what have you discovered about them?**

**Shen:** My early work was 100% on proteins, and then I moved on to study polysaccharides such as cellulose. So lectins are kind of a natural follow-up. Lectins have a bit of both, how proteins interact with sugar. With postdoctoral fellow Ricky Nellas, who is a chemist, and expert on nucleation theory, we are starting to look at how proteins effectively recognize sugars. This work is of importance in biology. In particular, we look at the cooperativity of protein-sugar recognition. That is, often lectins have multiple binding sites. This common feature indicates a certain enhancement of signaling. Cooperative binding will give an amplification effect on recognition.

### **You are adept at analytical physical theory. Are you working on applying analytical techniques to understanding biological systems at the moment?**

**Shen:** I like analytical models, probably because my first study area was the quantum mechanics of the excitation of heavy elements. For biological systems, analytical models can be tough for many reasons and I don’t particularly want to force it. I focus on the physical results and often have to settle for numerical results. Right now, we do have some very small analytical models: one for active assembly of swimming cells, another for the degradation of biopolymer chains. More often one cannot find many analytically solvable problems in biology, but more likely there is a specific condition of a system preventing solution. But analysis can nevertheless be useful in several ways. For example, say we use simulation/numerical methods to study  $F(x)$ , with  $x$  in  $[0, 1]$ . Now we cannot solve it generally, but if we use an independent analytical method to get the solution at the end points, of  $F(0)$  and  $F(1)$ , at least we get a sense of whether our numerical results are correct, and at those limiting cases, of what is happening.

# ORNL over the Decades

*CMB functions smoothly due in large part to Julia Cooper, our Administrative Assistant. Julia has been at ORNL for quite a while, and we found it interesting to hear her thoughts on life at the lab in earlier times.*

Past years at ORNL were very different from the present. Union Carbide had the contract from the late 1940s until 1984. Other contractors before UT-Battelle were Lockheed Martin and Martin Marietta.

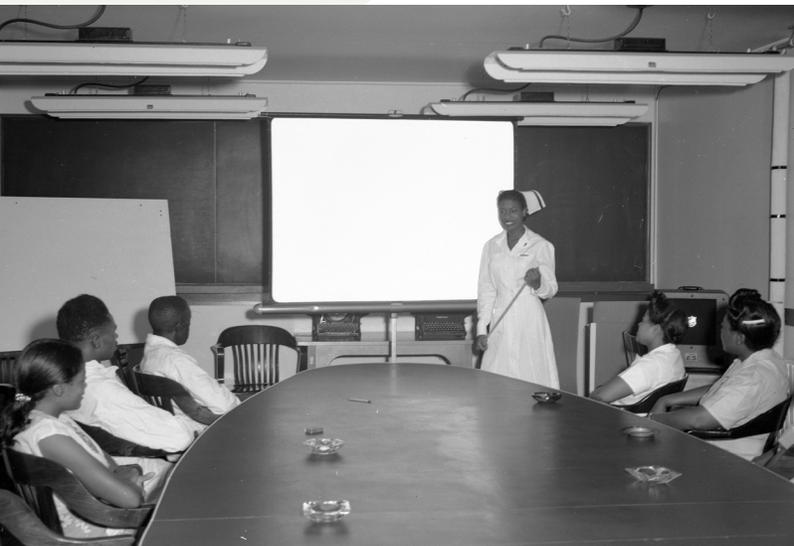
Before September 2001, Bethel Valley Road was open to all cars without restriction and there were no guard gates at either end as there are now. There was an approximately 10-foot fence with barbed wire on the top around the entire perimeter of the laboratory and guards were at each main entrance only for certain hours of the day, usually during regular working hours. Cars were required



*Julia Cooper*

to be backed into the angled parking space – no pulling forward into it.

The management structure was much different. There were Group Leaders, Section Heads and Division Directors for each division. Section heads did general supervision while division directors got the programs from DOE. There were more big programs in those days like Coal Conversion, and the Biology Division was internationally known for their genetics work. The big programs drew together a cross-section of expertise from across the whole lab. We had more immediate presence of the craft people, but also more support for the experimental scientists in the form of technicians. There are probably fewer technicians now since bench-type science has been replaced with more computer-based research. People with seniority were generally



*Nurses sitting around a table with starched white uniforms*

left alone to do their work, but there also was perhaps less openness. Safety has always been emphasized, but was not as micro-managed in years past. The complexity of lab regulations has grown considerably, which in some ways made things easier administratively. We didn't use computers in the same ways we do now.

Women were regarded very differently in those days – there was less equality. The lab even had a "Miss ORNL" at some point – possibly in the early 60s! I'm not sure how she was chosen or the years this took place. Also, life in general was more formal. Both men



*The old ORNL visitors center, with cars parked, presciently, "en battelle".*

and women wore more "dress" clothes to work – women often wore heels and men typically wore coats and ties. Very few wore jeans or casual attire. The nurses in medical wore starched white uniforms – all provided by ORNL!



*Bethel valley before ORNL*

# Five Germans in Tennessee

*When Jeremy Smith left Heidelberg to come to Tennessee in 2006 he managed to persuade five German students to follow him and register for a Ph.D. at UT. All five have now spent several years in East Tennessee and feel they even have a slight Southern accent to their English. We asked them to compare life in Knoxville to that in the rarified academia of Germany's oldest university.*



*Coming from far far away (left to right):  
Barmak Mostofian, Benjamin Lindner, Dennis Glass, Roland Schulz, Xiaohu Hu*

## How's life in Tennessee?

**Barmak:** Pretty laid-back. I have to say my time here has helped me to become much more relaxed about many things in life.

**Benjamin:** I like it. Being able to go shopping at 3 a.m. really fits the life

of a scientist. Cars are essential – something you have to get used to – especially if you come from Europe, where public transit is very popular.

**Dennis:** It's different in many small aspects, for example, the status of university sports, which are fun to discover.

**Roland:** I like it. The nature is beautiful and the people are very nice. The main thing I don't like is the urban sprawl.

**Xiaohu:** Nice warm weather – life is less hectic in general, nice people... and great BBQ! Oh my God is that good!

### **How would you compare the atmosphere at UT compared to the University of Heidelberg?**

**Dennis:** I think undergraduate students in Heidelberg need to be more autonomous in planning their degree and workload, as the German system is quite flexible and formally wants students to get a broad education. Here, students benefit from well-designed degree paths and thus can give science a larger focus.

**Benjamin:** The differences are very subtle. Both are gigantic institutes where the quality of the classes can vary significantly. A main difference is the timing of the semesters. UT allows you to enjoy Christmas because the fall semester ends before Christmas takes place.

**Barmak:** There are cultural differences as well. I think the University of Heidelberg has one of the largest medical centers in Germany while Knoxville has one of the largest football stadiums in the U.S. They name their department buildings after famous scientists in Heidelberg, while in Tennessee they are named after famous football players.

**Xiaohu:** In Heidelberg, we didn't care much about University sports events,

but here everybody is crazy about UT's football team. It was quite an amazing phenomenon for me at the beginning.

**Roland:** In Heidelberg the learning process is less structured, e.g. attendance is often not required and for a PhD few classes are mandatory. UT offers more help with non-subject skill development such as grant writing.

### **Are the students the same?**

**Benjamin:** At UT you see more international students. The students themselves are not that different.

**Roland:** The German school system causes Heidelberg students to be on average a bit older but better prepared in Math.

**Xiaohu:** I'd say yes. People are working hard to get their degrees similar to Heidelberg.

### **Has Jeremy become a little less snobbish since leaving the German "Herr Professor" establishment?**

**Benjamin:** I never had the feeling that Jeremy was snobbish. Otherwise I wouldn't be here.

**Dennis:** I think Jeremy was always "Jeremy" and never "Herr Professor", and he still is "Jeremy" in Tennessee.

**Roland:** I think that the majority of professors in Germany are not snobbish. This included Jeremy when he was still there.



*Liang Hong expresses an opinion to a hard-working visiting student from Heidelberg – Mai Zahran.*

**Xiaohu:** “Herr Professor”? I don’t think these words have ever been in Jeremy’s vocabulary. Besides, these words would make our young and dynamic Jeremy sounds he was 75+ and driving a motorized wheelchair to work rather than a BMW M3 convertible (*Editorial note: it’s actually a 3-series convertible, not an M3*), which is envied by all of us poor graduate students, but at the same time, also motivates us to work hard to become like Jeremy in the future. No, we have never called him anything else but Jeremy... Wait, what is his last name again? Jeremy Schmidt? :)

## What’s the verdict on outdoor activities in Tennessee?

**Barmak:** Hiking, biking, climbing, rafting, canoeing, boating, camping – you name it! If it wasn’t for the Smokies, I’ve heard, we all would have been much more productive at work.

**Benjamin:** Not good for skiing though – also the climate can be tough sometimes.

**Dennis:** You can go hiking and actually see wildlife, unlike in Germany where the only “wildlife” that will cross your way is mostly other hikers. Be aware if they just left a “Hütte” that served alcoholic beverages, they might literally cross your way.

**Roland:** The large number of trails, both for hiking and mountain-biking, is very nice. In Heidelberg mountain-bikers have to share trails with hikers and are hated by most of them. The Smokies are very beautiful. Particularly amazing are the synchronized fireflies.

**Xiaohu:** Well, there are some similarities between Heidelberg and Knoxville in this aspect: near Knoxville, there is the Great Smoky Mountains and near Heidelberg, there is the Odenwald (Oden-forest). Both are good for hiking, but I think there is clearly more wildlife in the Smokies. I don’t think anyone has seen wild bears in the Odenwald before.

## What’s the difference between science in Germany and the USA?

**Benjamin:** The leadership feeling. Great science takes place in both

locations, but it's like comparing the NBA with the German basketball league. Incidentally, a current NBA superstar is German: Dirk Nowitzki.

**Dennis:** I can just speak for the graduate student part of science – Here I prefer the German system where you start graduate school on a level similar to the Master's degree, have no obligatory coursework, and can focus right on your research (instead of course-work).

**Roland:** The three difference I find most striking are: 1) Scientific Computing receives more attention and funding than in Germany. E.g. 51% of the TOP500 and 50% of the TOP10 of supercomputers are in the US versus 6% of TOP500 and 0% of TOP10 for Germany. The current plans in the US for Exascale computing are far ahead of plans in Germany. 2) The funding of research groups is much more reliant on external funding by research grants than it is in Germany; thus the importance of grant writing is much higher in the US. 3) For science education a striking difference is the acceptance of some scientific theories. Having volunteered for the UTK Darwin Day I have experienced some of the challenges evolution education faces in the US. Also climate science is much more political than it is in Germany whereas the opposite is true for food biotechnology and nuclear research.

**Xiaohu:** In principle, not really different, working hard and producing good publications.

## **Will Juergen Klinsmann succeed as coach of Soccer Team USA?**

**Barmak:** Haha, I guess he will be just fine. In fact, I would say if there is one team that would not lose against Germany in the 2014 World Cup, it will be Team USA.

## **Benjamin - You were a top-class wrestler back in Germany, and even competed for the national team. Does the US pull its weight in international wrestling?**

**Benjamin:** As a matter of fact I don't know. Even though I was a successful wrestler I never really cared about the who's who in wrestling. I wrestled because that is what I loved to do. Now it's computational science.

## **Which is the liveliest: the Cumberland Strip or the Heidelberg Hauptstraße?**

**Dennis:** Heidelberg what? I've been here for a while and hardly remember a previous life...

## **Jeremy infinitely prefers bluegrass music to German "Volksmusik". Do you agree?**

**Xiaohu:** Oh yes, definitely! Compared to other music, Volksmusik is not nearly as enjoyable as is a Volkswagen compared to other automobiles.

The article below was posted on the energy blog of the Department of Energy.

## 10 Questions for a Biophysicist: Jeremy Smith

Source: <http://energy.gov/articles/10-questions-biophysicist-jeremy-smith>

*In 2006, Dr. Smith came to Oak Ridge National Laboratory (ORNL). Since then, he has led a wide-ranging spectrum of projects focusing on everything from biofuels to drug discovery. He recently gave us the download on his many projects.*

**Question: What sparked your interest to pursue a career in science?**

**Jeremy Smith:** In England in the 1970s one had to specialize early, very early -- at 16. For me it could have gone either way, arts or sciences. To be honest I wasn't very interested in science at that time. I was never a geeky, gadget-type kid, although scientific concepts did interest me. My high school teachers advised science as having safer career prospects than arts subjects, so from 17 on that's all I did. Later in high school I became interested in protein structures and how atoms interact. I sometimes wonder what would have happened if I'd chosen the other way at 16...

**Q: As the Director of the Center for Molecular Biophysics, your work spans across a multitude of fields. Can you tell us a little about your research background -- what led you to this unique position?**

**JS:** My first degree was in biophysics at Leeds, England. After that, I did a Ph.D. in neutron scattering in France, a post doc in chemistry at Harvard, and then ran my first group at the French National Lab in Saclay. Before coming to Tennessee I held the Chair of Computational Molecular Biophysics at the University of Heidelberg in Germany. Yes, our work involves theoretical physics, quantum chemistry, statistical mechan-



*Dr Jeremy Smith | Photo Courtesy of ORNL*

ics, computer science, supercomputing, catalytic chemistry, polymer science, biochemistry, molecular biology -- you name it!

I find it difficult to not get enthusiastic about a crisp new idea in molecular science and how we might help develop it.

**Q: What projects are you working on right now? What do you hope they will lead to?**

**JS:** We're working on many different projects. Some of these include: cellulosic biofuels, which we hope will lead to cheap alternative energy, drug discovery towards curing prostate cancer and mercury biogeochemistry to understand the fate of mercury in the environment. We're also working on describing the structure and dynamics of biological materials through neutron scattering. With regards to supercomputing, those

cheeky hardware guys keep building more and more powerful machines and challenging us to perform cutting-edge simulations that efficiently use their full capability.

**Q: You are also a professor at University of Tennessee -- do you have any advice for students interested in science?**

**JS:** Yes. Learn to write well -- too many youngsters can do science but not precisely express their thoughts and findings. Furthermore, don't forget to lead a balanced, active, fun life -- it will help the scientific part.

**Q: What classes do you teach? What have your students taught you?**

**JS:** I teach an introduction to molecular biophysics, a journal club and our group meetings. My co-workers and students come up with all the crazy ideas and then do all the work -- they're sickeningly bright and inexhaustibly hard-working.

**Q: What can you never start a day at the lab without?**

**JS:** I like to start the day finding a new research manuscript on my desk that a co-worker has left for me, preferably with a cookie on top.

**Q: Do you have a favorite fictional scientist?**

**JS:** Yes, Gromit. He remembered to take the handbrake off his rocket.

**Q: We heard that you are an avid soccer fan and player -- having lived in England, France, Germany and now the United States, do you have a favorite for the next World Cup?**

**JS:** Concerning playing soccer -- my 79-year-old father still plays ninety minute games so I can't possibly give up playing until he does, can I?

I'm the equivalent of a Cubs fan. I support Norwich City, a team in England apparently consigned to perennial failure, except of course, maybe, this year (hope springs eternal)! As for the World Cup, supporting England is too painful so I'll just say anyone but Germany, please.

**Q: What is it like to work in ORNL's Spallation Neutron Source (SNS) facility?**

**JS:** Well, the SNS brings together scientists from many different fields. It's sometimes difficult for me to understand what someone from, for example, magnetism is working on but the diversity of backgrounds leads to fertile discussion. It will take a while before SNS achieves full science productivity and then a couple more years until the results obtained have their full effects on the scientific community but we're getting there.

**Q: Last question -- why is neutron scattering research important?**

**JS:** Neutrons give direct, simultaneous information on molecular structure and dynamics and no other probe of matter does this. This should help us design new materials in the energy sciences, and understand important topics in bio-energy and biology. For example, we recently demonstrated with neutrons how a cancer drug, methotrexate, softens the target it binds to -- that's fundamental understanding of how drugs work.

# CMB Publications

## 2006 (October onwards)

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Visiting Researcher,  
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4/2007 to 4/2008

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Postdoctoral Fellow,  
4/2007 to 4/2010

**Saharay Moumita**  
Postdoctoral Fellow,  
4/2007 to 4/2010

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Postdoctoral Fellow,  
11/2008 to 9/2011

**Christopher Topham**  
Visiting Researcher,  
2006

**Jiancong Xu**  
Postdoctoral Fellow,  
9/2007 to 8/2009

## Short-term Students and the China Connection:

A large number of graduate and undergraduates have passed through CMB over the last five years, doing rotations or more extended research. Jerome Baudry, in particular, has typically hosted five to seven rotation students each summer. Most of the students have come from UT, but we have also hosted students from Cambridge and Heidelberg Universities. Also, we have a developing relationship with Shanghai Jiao-Tong University, which Xiaolin Cheng, Hong Guo and Jeremy Smith visited in March 2011. Two Jiao-Tong graduate students are currently on extended research stays at CMB.

# CMB External Funding

## DOE - Office of Biological and Environmental Science (OBER)



Title: ORNL Scientific Focus Area  
"Biofuels"

Funding period: 10/1/2010-10/1/2013

Jeremy C. Smith: Co-PI

## DOE - OBER Science Focus Area



Title: Biogeochemical and Molecular Mechanisms Controlling Contaminant Transformation in the Environment

Funding Period: 10/2009-10/2014

Jeremy C. Smith: Co-PI and Task leader

## DOE - OBER



Title: Bioenergy Science Center

Funding Period: 2007-2012

Jeremy C. Smith: Task Leader

## NIH - PEER



Title: Program for Excellence and Equity in Research

Funding Period: 01/01/2009-01/01/2014

Jeremy C. Smith: Senior Personnel

## NSF - IGERT



Title: SCALE-IT  
(Scalable Computing and Leading Edge Innovative Technologies) for Biology

Funding Period: 10/2008-10/2013

Jeremy C. Smith: Co-PI

## DOE - Advanced Scientific Computing Research (ASCR)



Title: LAB 08-19 Software Development Tools for Improved Ease-of-Use of Petascale Systems ERKPE92 Scalable Development Environment for Petascale Computing

Funding Period: 09/2009-09/2012

Jeremy C. Smith: Co-PI

## DOE - EpsCOR Implementation Award



Title: DE-FG02-08ER46528 Neutron Scattering Research Network for EPSCoR States

Funding Period: 10/1/2008-10/1/2011

Jeremy C. Smith: Co-PI

## DOE - Laboratory Directed Research and Development Fund



Title: Neutron scattering methodologies for the study of protein dynamics

Funding Period: 10/1/2009-10/1/2012

Jeremy C. Smith: PI

## NSF 07-597 EF - BIO CENTERS



Title: Nimbios -  
Center for Synthesis of  
Mathematics and Biology

Funding Period: 10/1/2008-10/1/2012

Jeremy C. Smith: Senior Personnel

**DOE – Laboratory Directed Research and Development Fund**



**Title:** A Systems Biology Approach to Study Metabolic and Energetic Interdependencies in the *Ignicoccus-Nanoarchaeum* System

**Funding Period:** 10/1/2009-10/01/2011

**Jeremy C. Smith:** Co-PI

**Deutsche Forschungsgemeinschaft: Excellence Initiative Dritte Säule: Internationale Zusammenarbeit**



**Title:** International cooperation  
**Funding Period:** 01/2009-01/2013  
**Jeremy C. Smith:** PI

**DOE- OBER/ASCR**



**Title:** ERKJE84 and ERKPE84 Multiscale Mathematics for the Simulation of Complex Biological Systems  
**Funding Period:** 09/2009-09/2012  
**Jeremy C. Smith:** PI

**NSF Award Biosystems Cluster No. MCB-0842871**



**Title:** Integration of Computer Simulation and Neutron Scattering in the Characterization of Protein Dynamics  
**Funding Period:** 8/1/2009-7/31/2012  
**Jeremy C. Smith:** PI  
**Hong Guo:** Co-PI

**DOE Subsurface Biogeochemical Research**



**Title:** Molecular Mechanisms of Bacterial

**Mercury Transformation**  
**Funding Period:** 08/2010-08/2013  
**Jeremy C. Smith:** PI

**DOE - OBER**



**Title:** Program Announcement LAB 07-12 New Analytical and Imaging Technologies for Lignocellulosic Material Degradation, and for Multiplexed Screening for Plant Phenotypes ERKP704 "Dynamic Visualization of Lignocellulose Degradation by Integration of Neutron Scattering Imaging and Computer Simulation"

**Funding Period:** 10/1/2007-10/1/2010

**Jeremy C. Smith:** Co-PI

**DOE – Laboratory Directed Research and Development Fund: Systems Biology**



**Title:** Computational Methods for Molecular Biophysics  
**Funding Period:** 10/1/2006-10/1/2009  
**Jeremy C. Smith:** PI

**NIH – U54: No. UL1RR031975-01**



**Title:** Novel Translational Methodologies (NTM)  
**Funding Period:** 07/01/2010-03/31/2012  
**Jerome Baudry & Jeremy C. Smith:** Task Leader

**NIH-R01 – GM072285-06**



**Title:** Computational Genomics of Signal Transduction  
**Funding Period:** 04/01/2010 – 03/31/2014  
**Jerome Baudry:** Co-PI

# Supercomputer Allocations

## Cellulosic Ethanol: Simulation of Multicomponent Biomass System

Organization: INCITE

Allocation: 30 million CPU hours

Platform: Jaguar, Lens (NCCS)

PI: Jeremy C. Smith



## Molecular Dynamics Simulations of Protein Dynamics and Virtual High-Throughput Screening of Estrogenic Compounds

Organization: NERSC

Allocation: 5 million CPU hours

Platform: Hopper, Franklin, Carver (NERSC)

Co-PIs: Jeremy C. Smith, Jerome Baudry



## Docking and Molecular Dynamics Simulation of Biomolecules

Organization: TeraGrid

Allocation: 4.7 million CPU hours

Platform: Kraken, Nautilus (NICS)

PI: Jerome Baudry



## QM/MM Study of Sedolisins

Organization: TeraGrid

Allocation: 200 thousand CPU hours

Platform: Ranger (TACC)

PI: Hong Guo



**Amazon Cloud Computing Award:  
Virtual High-Throughput Docking using Cloud Infrastructure**

Organization: Amazon

Allocation: 7500 CPU hours

Platform: EC2

PI: Jerome Baudry



**ANTON Computing Award: Investigation of Chemotaxis Initiation**

Organization: DESRES

Allocation: 50 thousand CPU hours

Platform: ANTON

PI: Jerome Baudry



**High Performance Computing for Rational Drug Discovery and Design  
Supercomputing molecular discovery of prostate cancer molecular effectors**

Organization: NCCS

Allocation: 5.8 million CPU hours

Platform: Jaguar

Task Leader: Jerome Baudry





# Awards

## Jerome Baudry

Outstanding Teaching Award for Junior Faculty 2011

Jerome Baudry received the Outstanding Teaching Award for Junior Faculty 2011 at the University of Tennessee Knoxville. Through this award, the BCMB faculty acknowledges faculty members who demonstrate a commitment and excellence in teaching at the undergraduate level.



## Julia Cooper

ORNL divisional award

Julia Cooper received the ORNL Biosciences Divisional Administrative Award in 2009 for her role in the establishment and continued operation of CMB.



## Sally Ellingson

NSF funded Broader Engagement Grant 2011

NSF funded Scholarship / ACM student research competition GHC 2011

Sally Ellingson received an NSF funded Broader Engagement grant to attend Supercomputing 11 in Seattle, WA, and a NSF funded scholarship to attend the Grace Hopper Celebration 11 in Portland, OR to present her work in the Baudry lab on developing Cloud strategies for virtual docking.





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