OAK RIDGE National Laboratory
Managed by UT-Battelle for the Department of Energy

University of Tennessee

Center for Molecular Biophysics

http://cmb.ornl.gov

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 the University of Tennessee, and we thank these organizations for putting up with us and our griping. Everything we have accomplished, was enabled by our systems administrators, Michael Galloway, Steve Moulton (2013 – 2015), Nathan Grodowitz and David Hester, and also our administrative assistants: Julia Cooper (2006 – 2013), Anita Alton (2014 – 2015) and Lora Davis.

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, the center has now established 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 a drug discovery program. 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 Associate Professors: Jerome Baudry, who specializes in ligand binding and computational biochemistry, and Tongye Shen, who is more physics-oriented. Hong Guo, a Full Professor who I first met in 1982 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 were subsequently 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 many successful grant proposals and over 300 peer-reviewed publications. 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 booklet a stimulating read!

Jeremy C. Smith, Director, CMB.

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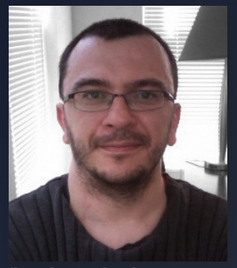
Principal Investigators

OF THE CENTER FOR MOLECULAR BIOPHYSICS



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Jerome Baudry

Associate 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 and he was tenured in 2014. 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, membranes, gating mechanisms in ion channels and drug resistance of HIV integrase.

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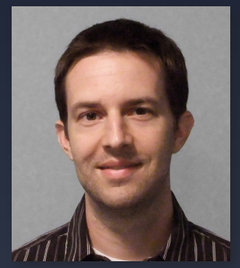
Hong Guo

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

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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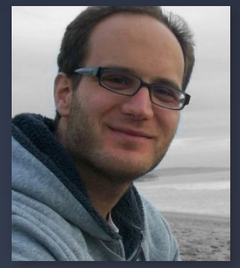
Jerry M. Parks

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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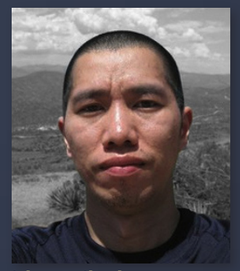
Loukas Petridis

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

Associate 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 UCS D, 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.

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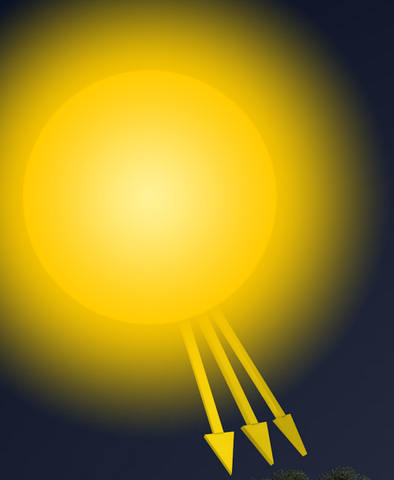
Jeremy C. Smith

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 2016 Smith had published close to 400 peer-reviewed scientific articles.

Research Highlights



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Lignin/cellulose interactions

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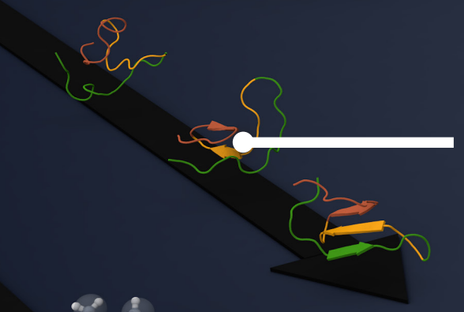

Folding, Dynamics & Function

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Sugar recognition by ricin-like domains

Single proteins: nonequilibrium fractal time dynamics

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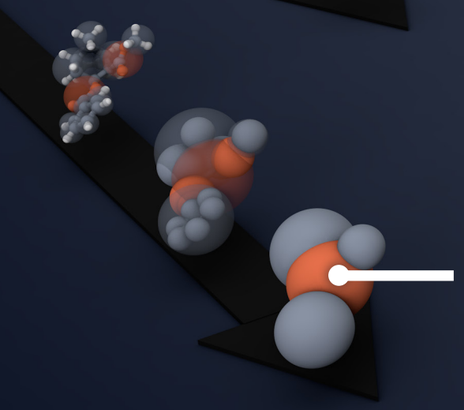

Multiscale

Coarse-graining biomolecular dynamics

Transition networks, metastable states and dynamical fingerprints of proteins

Treecode fast electrostatics

Multiscale in adaptive biosystems imaging

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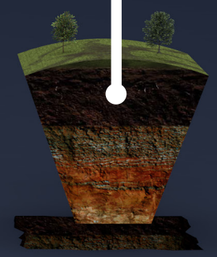

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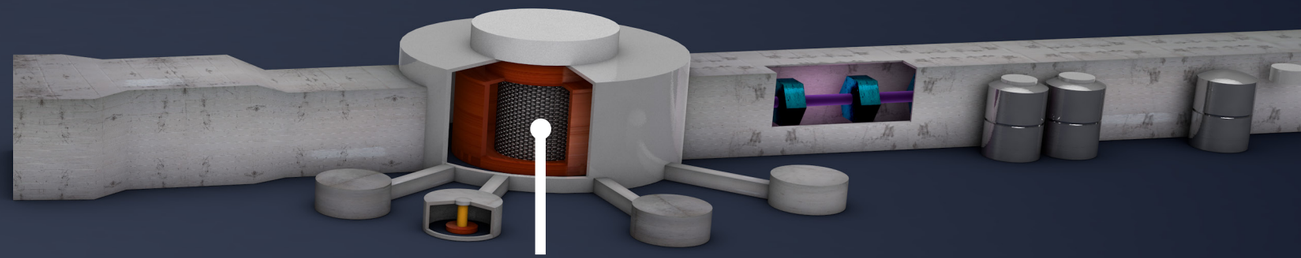

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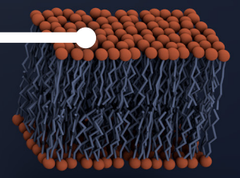
Rapid docking of ligands on supercomputers and cloud architectures

- 100% success in hit identification in drug design for protein targets

Molecular origin of Gerstmann-Sträussler-Scheinker syndrome

Bio-membranes



Lateral organization and diffusion dynamics of lipids

Cross-layer coupling in biomembranes

Adaptive Biosystems Imaging (ABI)

Cell and cell-compartment simulations

Bioenergy

THE RECALCITRANCE OF PLANTS

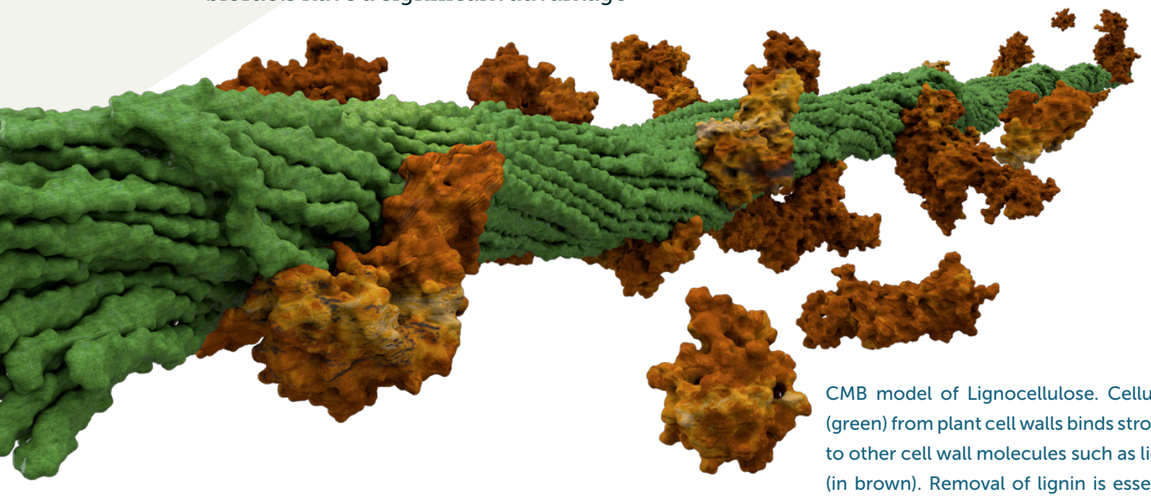
Bioenergy is of critical national importance as we strive to develop viable alternatives to fossil fuels. Our efforts in computer simulation and neutron scattering are aimed at understanding "biomass recalcitrance".

Cellulose as a fuel source

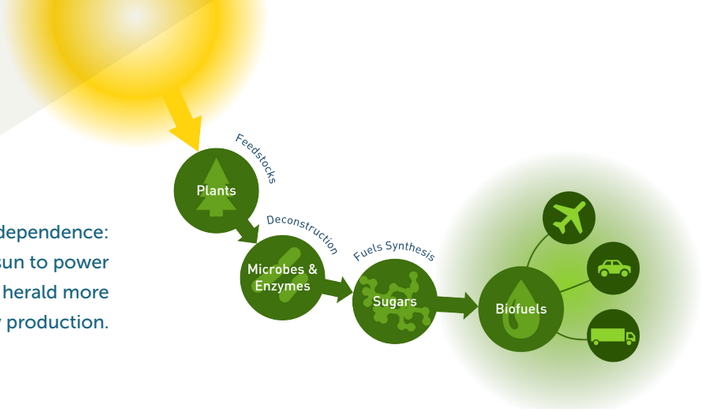
"Biofuels serve as a substitute for a very important part of our current technology: combustion driven engines", says Benjamin Lindner, who obtained his PhD at CMB and performed simulations of biomass with the ORNL Jaguar supercomputer. "This work is also relevant when you consider national security, 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."



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.

According to Barmak Mostofian, who also graduated with a PhD with us, one of the main issues, 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".

Micholas Dean Smith, a post-doc researcher at the Center of Molecular Biophysics further explained, "As we move away from a petroleum based source of carbon for our chemical/fuel industries, it is imperative that we find an abundant feedstock for our ever growing industrial demands. As lignocellulosic biomass is perhaps the most abundant source of carbon (as well as environmentally neutral) it is a logical replacement for petroleum; however, the use of this raw material is limited by our limited understanding of its resistance to chemical breakdown. As such, it is necessary for us to apply a variety of techniques to elucidate the physical and chemical properties of lignocellulose. Armed with an enhanced understanding of lignocellulose, we can then begin to design chemical processes to take full advantage of its abundance."

ORNL Biofuels Science Focus Area and the Bioenergy Science Center

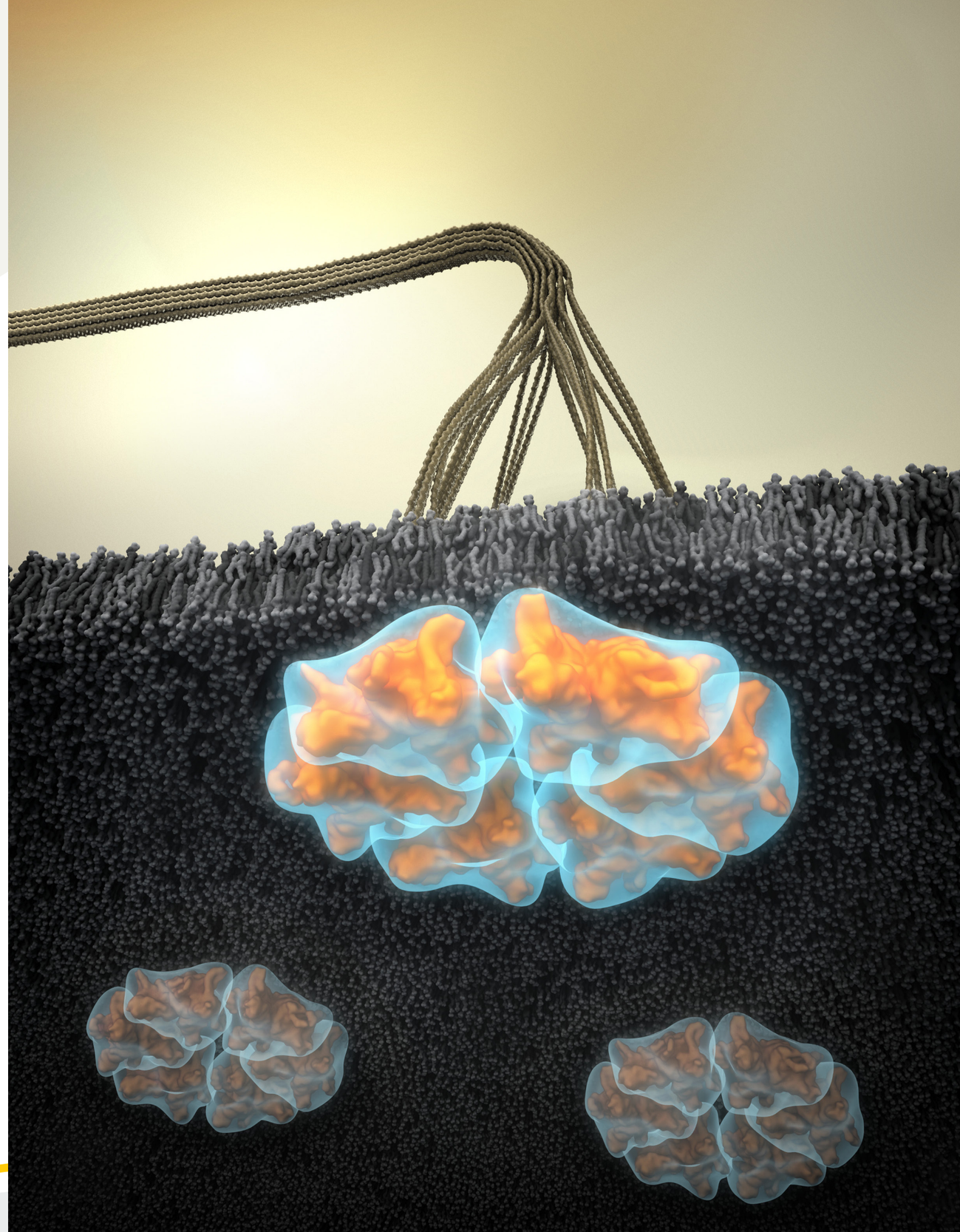
CMB participates in the Bioenergy Science Center (BESC), which integrates experts from a wide range of scientific disciplines to understand biomass recalcitrance. According to Loukas Petridis, "Most of the chemical data used to construct our lignocellulose (biomass) models are derived from experiments performed at BESC. Also, many fruitful ideas have arisen from interactions with experimentalists at BESC. For example, 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 at 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 been achieved. CMB has participated in high-profile studies, commented on by former Secretary of Energy Steven Chu, identifying and characterizing a single microbial gene linked to increased ethanol tolerance. Former postdoctoral fellow Amandeep Sangha and Jerry Parks carried out quantum chemical calculations aimed at understanding lignin polymerization,

and CMB has also performed calculations to understand cellulase catalysis and cellulosome function. According to Loukas Petridis, "We have leveraged unique capabilities in neutron scattering and HPC simulation to address key fundamental issues in the thermochemical pretreatment of plant biomass for biofuels production. The anticipated findings will provide fundamental scientific insight critical in underpinning the rational design of next-generation plant biomass and the formulation of pretreatment protocols tailored to achieve desired outcomes."

Plant cellulose synthesis

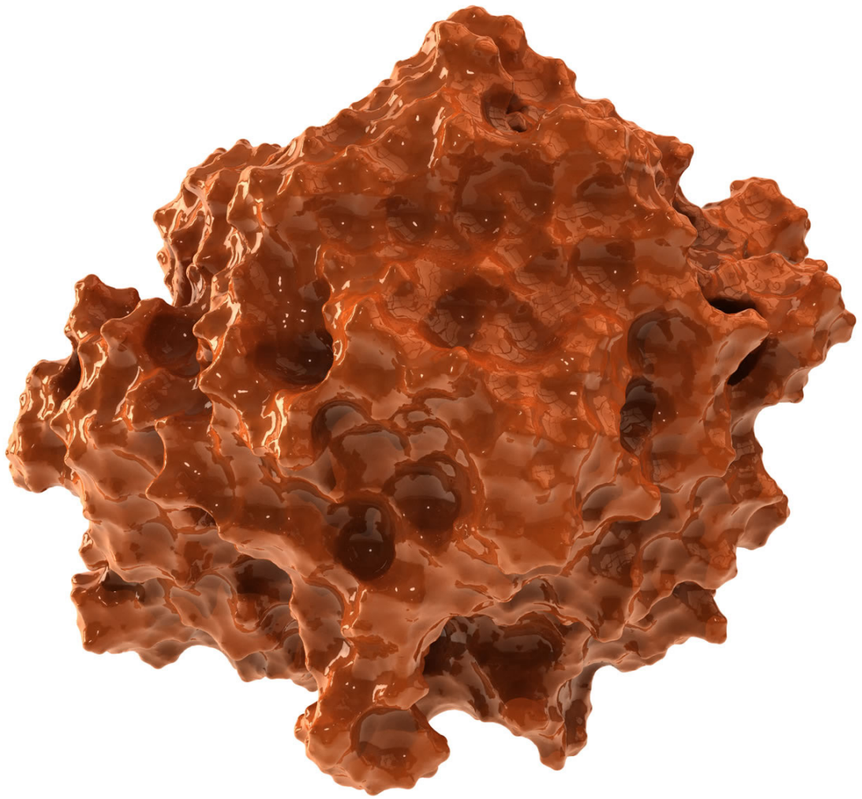
Cellulose is the major structural component of plant cell walls and because of its abundancy it has great potential as a renewable source of energy. The plant cellulose synthesis complex (CSC), also called a 'rosette' because of its hexameric appearance in transmission electron microscope (TEM) images, is a large multi-subunit transmembrane protein complex responsible for synthesis of cellulose chains and their assembly into microfibrils. Despite the importance of cellulose, fundamental properties of the CSC remain unclear. The number of cellulose synthase (CESA) proteins in the CSC and the number of cellulose chains in a microfibril have been debated for years. We have recently worked with scientists from the ORNL Center for Structural Molecular Biology to derive a solution structure of the catalytic domain of CESA1 from Arabidopsis thaliana, determined by small-angle neutron scattering, that provides the first experimental evidence for the self-assembly of CESA into a stable trimer. This study strongly supports the 'hexamer of trimers' model for the rosette CSC that synthesizes an 18-chain cellulose microfibril as its fundamental product.



The cover shows ab initio structures of CESA trimers calculated from small-angle scattering data represented by semi-transparent grey surface envelopes, superposed with the computational atomic models in orange. The trimer models are arranged in a hexameric configuration consistent with the rosette shape observed in TEM images. The presented view is from the cytosolic side of the membrane. Cellulose microfibrils are visible in the apoplastic space.

ORNL neutrons, simulations reveal details of bioenergy barrier

Source: www.ornl.gov/news/ornl-neutrons-simulations-reveal-details-bioenergy-barrier



New molecular models of lignin aggregates are helping scientists understand a limiting factor in the production of ethanol. (Image courtesy of 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.

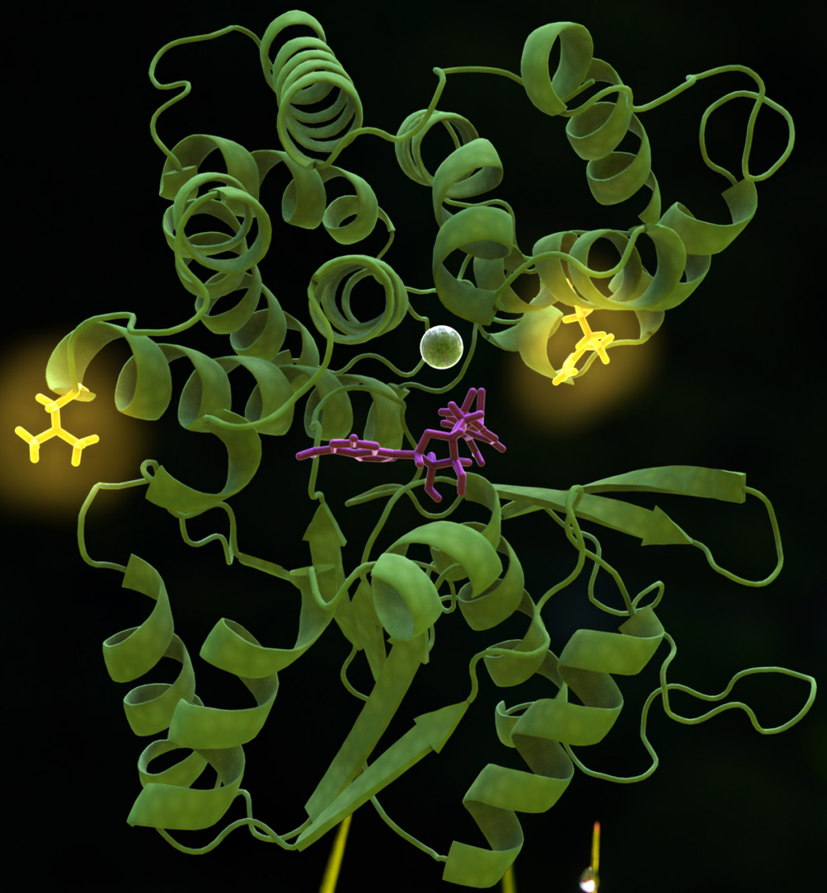
Lignin's highly folded surface creates more opportunities to capture the passing enzymes than a smooth surface would. An improved understanding of the lignin aggregates will aid scientists in efforts to design a more effective pretreatment process, which in turn could lower the cost of biofuels.

"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 and since then. Also, UT 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 postdoctoral fellow, and Roland Schulz and Sally Ellingson, both of whom graduated with PhDs here, about their experiences with petaflop supercomputers and prospects as we move towards the exascale. Roland and John have also worked on porting the molecular dynamics engine "GROMACS" to INTEL machines.

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. Also, using VinaMPI, a high-throughput virtual screening program developed to utilize a large number of cores on Supercomputers, I ran a virtual screen that performed over 15 million docking calculations. We were investigating the use of protein conformations obtained from simulations to improve the enrichment (increase the number of high scoring true positive compounds) for protein targets known to perform poorly in virtual screenings.

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 TITAN 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. Titan allows us to run more flexible codes and is more suitable for our very large simulations.

Eblen: Shaw's Anton supercomputer is quite impressive, being built from scratch for MD simulations. Both the instruction pipeline inside the custom processor and the communication patterns between all of the custom processors are designed to optimize particle force calculations. Thus Anton can run simulations about 100 times faster than a general-purpose supercomputer. To take advantage of this capability, of course, you have to use Anton! Simulation codes developed for TITAN, on the other hand, will be able to run on future HPC machines and take advantage of hardware and software advances being developed by researchers all over the world. This includes ideas and techniques learned from Anton.

Incidentally, I am not clear on the range of operations optimized by Anton. GROMACS, for example, applies

With a peak speed of over 20 petaflops (over 20,000 trillion calculations per second), Titan is a supercomputer composed of 299,008 AMD Opteron cores supported by additionally 18,688 Nvidia Tesla K20 GPU accelerators 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.

multiple algorithms to improve the accuracy of simulations. I'm not sure how many of those algorithms are or could be optimized by Anton.

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 development. 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.

Roland, you are a GROMACS core developer. How does GROMACS make sure that all the additions and improvements to the code are self-consistent and accurate?

Schulz: We use Gerrit for code review. Every change submitted to our server has to get two positive reviews from other developers. The code review helps us improve the software design and lets us find correctness issues before they ever make it into the development version. Besides the manual code review, we have unit and regression tests. These automated tests get run for every change as soon as it is uploaded to the central server. Before we release a version for production usage, a beta version is made available to the community to help in finding any remaining bugs.

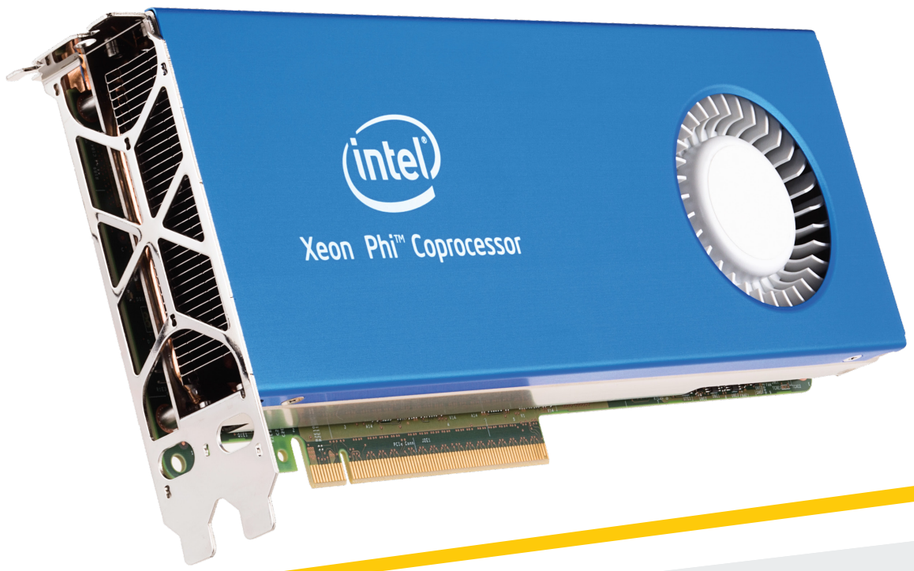
With funding from INTEL, you are now working on getting GROMACS working well on the Xeon Phi processors. What has this mighty struggle taught us?

Schulz: We learned how to make efficient use of large number of threads and wide vector instructions. Moore's law, which predicts a doubling of the number of transistors every two years, is still going strong. But single CPU cores are not getting faster anymore, partly because of the energy cost of very high frequency cores. Thus the majority of performance we can expect in the next decade from the extra transistors will be in form of extra parallelism. The Xeon Phi with its 240 threads and 16 wide vector register has this large parallelism which will be common in the future. Thus the performance optimizations we made for Xeon Phi will be required for most future hardware.

Eblen: In my opinion, the most valuable lesson is the importance of good code design. GROMACS has a nice abstraction layer for SIMD operations, and as a result, adding Xeon Phi-specific SIMD instructions was something we were able to finish fairly early. Also, GROMACS neatly organizes the different high-level operations, allowing them to be profiled and optimized separately. This has been a great help in optimizing different sections of the code. GROMACS is not perfect, of course. We have struggled quite a bit with our offload implementation, where GROMACS begins running on a host computer and offloads data and computations to the Xeon Phi. GROMACS uses rather large and complex data structures, which are passed around all over the code, making it hard to know what data is actually read or written by any specific section. Additionally, some data may only be used in certain modes of operation, because GROMACS is highly configurable. This problem is again a design problem. Ideally, we would have narrowly-defined interfaces between different parts of the code, rather than passing around these monstrous data structures. Developing code this way, though, requires a great deal of discipline, because data structures always start out small and grow incrementally. I suspect that large, catch-all data structures are quite common in scientific programs built for supercomputers. Unfortunately, once you have such structures, they become like global data, with all of the well-known problems associated with global data.

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 take quite some time...



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 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. Work performed principally by former 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 by former graduate student graduate student Thomas Neusius demonstrated that the subdiffusive behavior of peptide dynamics has a fractal origin. Later work provided a clear demonstration of the propagation of solvent frictional effects into a protein core, and showed how protein inter-domain motion can be described in terms of "De Gennes Narrowing".
Also, former postdoctoral fellows Yi Zheng and Yinglong Miao worked 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 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 former postdoctoral fellow Nikolai Smolin concentrated on, and the second is the application of neutrons to the energy biosciences, and, in particular, the structure and dynamics of lignocellulosic biomass. In the latter respect our collaboration with experimental neutron scattering researchers here at ORNL provided a physical mechanism behind steam-explosion biomass pretreatment has had considerable impact.
Finally, Jeremy would like to realize a vision of unifying exascale supercomputing with high-performance neutron scattering, in which molecular simulations, performed using the full power of the exascale supercomputer, 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 was taken by the former graduate student and postdoctoral fellow Benjamin Lindner, who has efficiently parallelized software for scattering calculations. Given the resources and further developments in both computational and experimental techniques, this unification can be realized in the foreseeable future.

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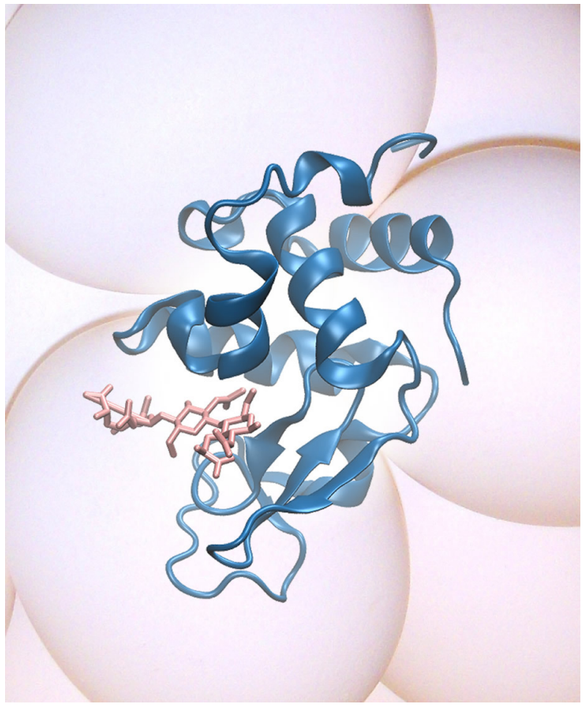
High-performance simulation, neutrons uncover three classes of protein motion

Source: www.ornl.gov/news/high-performance-simulation-neutrons-uncover-three-classes-protein-motion

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.

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Deciphering Distinct Atomic Motions in Proteins with Dynamic Neutron Scattering

COMBINING COMPUTER SIMULATIONS WITH LABORATORY MEASUREMENTS PROVIDES INSIGHTS ON MOLECULAR-LEVEL FLEXIBILITY

Source: science.energy.gov/bes/highlights/2015/bes-2015-02-i

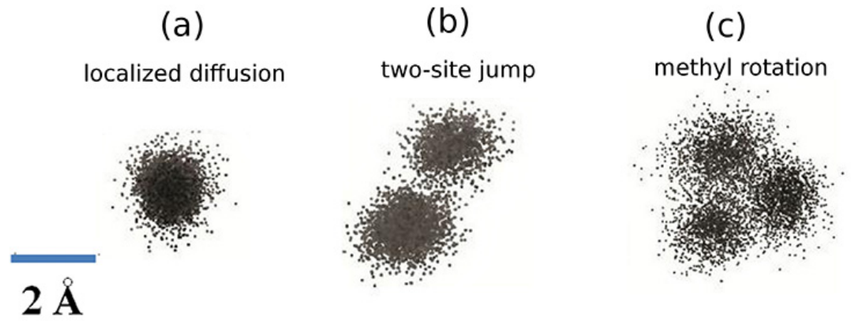
OAK RIDGE, Tenn., Feb, 2015 — Whether inside algae converting biomass to fuels or human cells responding to radiation exposure, proteins change their shape via atomic motions to perform a specific function. Today these shape-changing processes are still difficult to measure and understand. Scientists recently determined three classes of atomic motion using neutron scattering coupled with computational simulations.

The Impact

Providing a viable approach to quantify specific types of atomic motion that can be linked to proteins' biological functions could enable a detailed understanding necessary for designing biobased or bio-inspired materials for energy production, energy storage, and other uses.

Summary

Flexibility or "softness" is required for proteins to carry out their catalytic and other biological activities. This flexibility conferred by the motion of atoms includes components from spring-like atomic vibrations, rotation of atoms about chemical bonds, random jumps, and diffusive motion. In this research, scientists obtained a comprehensive description of these components in a protein by combining dynamic neutron scattering experiments with molecular dynamics computer simulations to interpret the scattering data. Extracted data from this approach clearly show that each of these components is associated with a characteristic signal, in terms of length and time. The signature of elastic vibrations of isolated atoms within a single energy well, was designated as localized diffusion and separated from true conformational changes, such as two-site jumps and methyl rotations which are between energy wells. The new approach of coupling advanced neutron scattering with high-performance computing could enable a better understanding of how proteins function and inform the design of protein-based biomaterials for various functions.



The schematic shows the molecular structure of a protein. In this research, protein atoms were found to undergo motion that can be placed into three distinct classes: localized diffusion (a), jumps between sites (b), and rotation (c) of hydrogen atoms in the methyl (-CH_3) groups.

Funding

DOE Office of Science, Basic Energy Sciences and the Experimental Program to Stimulate Competitive Research (EPSCoR) Program. The work utilized the National Institute of Standards and Technology Center for Neutron Research; the Spallation Neutron Source, a DOE Office of Science Basic Energy Sciences user facility; and facilities supported in part by the National Science Foundation.

Publications

L. Hong, B. Lindner, N. Smolin, A. Sokolov, J.C. Smith, "Three classes of motion in the dynamic neutron-scattering susceptibility of a globular protein," *Physical Review Letters 107*, 148102, **2011**. [DOI: 10.1103/PhyRevLett.107.148102]

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Neutrons help understand enzymes that could produce improvements in biomass processing

Source: www.ornl.gov/news/neutrons-help-understand-enzymes-could-produce-improvements-biomass-processing

OAK RIDGE, Tenn., Oct 7, 2015 — Plants and other biomass can be converted into a variety of renewable high-value products including carbon fibers, plastics, and liquid fuels such as ethanol and biodiesel that are beneficial for reducing petroleum use and vehicle emissions. Breaking down plants in order to release energy can require many steps and harsh chemicals, so researchers are seeking efficient natural catalysts, specifically enzymes, to deconstruct plant material.

Scientists at the U.S. Department of Energy's Oak Ridge National Laboratory are using neutron crystallography to understand enzymes and learn how to bioengineer those enzymes for large-scale improvements in the efficiency of biomass processing. Using the MaNDi instrument at ORNL's Spallation Neutron Source (a DOE Office of Science User Facility), the LANSCE Protein Crystallography Station in Los Alamos, N.M., and the FRMII BioDiff instrument in Munich, Germany, they determined the structure of xylanase, an enzyme used to digest hemicellulose during biofuel production, at unprecedented detail.

When processing plant-based biomass, hemicellulose—an abundant polysaccharide in plant cell walls—must first be degraded to monomeric sugars that can be converted to high-value products such as biofuels. Current non-harsh methods to pretreat biomass result in very basic (high pH) conditions. Native enzymes are not very efficient in such conditions, however, preferring an acidic (low pH) environment for maximum activity. By re-engineering hemicellulose-hydrolyzing enzymes to increase their activity at high pH, researchers can improve the process, but that requires researchers to understand the intricate details of how the enzymes work.

"We need to look deeper into their structures than what X-rays usually can provide," said ORNL's Andrey Kovalevsky, the senior author of the study. "That is, we have to know where all of the hydrogen atoms are before, during and after a chemical reaction has occurred in an enzyme's active site. Neutrons can give us this information."

In fact, using neutrons, the team directly and unequivocally visualized hydrogen atoms and hydrogen bonding in xylanase at different stages of the catalytic reaction.

"No one has ever observed hydrogen atoms in a glycoside hydrolase enzyme, and until now we did not know how the catalytic glutamic acid residue is protonated," said Kovalevsky.

Kovalevsky and his colleagues are interested in protonation because they need to know how protons move during catalysis. For example, to start the hemicellulose hydrolysis reaction, the catalytic glutamic acid must be protonated and the catalytic base must be deprotonated. Understanding the acid/base chemistry of enzymatic biomass hydrolysis is key to rationally engineering enzymes that improve biomass processing.

Kovalevsky and his colleagues determined five neutron structures of xylanase at various pH values and in complex with a ligand. The structures showed how hydrogen atoms are arranged in the active site of xylanase, where they move and how hydrogen bonding is altered due to pH changes and ligand binding. The low-pH structure, obtained from data collected on MaNDi, helped them understand how the enzyme functions.

"This enzyme, used in biofuels production, is a target for enzyme design to improve its performance in an industrial setting," said Kovalevsky. "Exact knowledge of its mechanism will improve protein engineering efforts."

The team has discovered that the catalytic glutamic acid can orient itself in two different conformations that have very different affinities for a proton. When the glutamate side chain rotates down and away from a substrate, it is a weaker acid than when it adopts an upward orientation. As a result, the catalytic group obtains a proton from water only when it faces downward, but can be an efficient proton donor to the substrate to initiate the hydrolysis reaction when it is in the upward conformation.

"This is a big revelation for glycoside hydrolases, and specifically for xylanases, because we now know where to make amino acid substitutions in order to improve the enzyme," said Kovalevsky.

The combination of neutron diffraction experiments with high-performance computing is a powerful approach for understanding how enzymes function. The researchers were curious to know how easily the glutamate side chain switches conformations. To answer that question, they turned to computer simulations.

"Using neutron structures as a starting point for molecular dynamics simulations, we showed that the glutamate can readily cycle between the two conformations," said Jerry Parks, an ORNL researcher and co-author of the study. "With another computational approach, we also found that the acidity of the glutamate changes significantly based on how it is oriented, which agrees nicely with the neutron structures."

This research was published in the Proceedings of the National Academy of Sciences (www.pnas.org/content/112/40/12384.abstract), and is the first user publication of the MaNDi instrument, which was commissioned at SNS in 2014. The research was supported by DOE's Office of Science.

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Non-equilibrium, fractal and self-similar dynamics in proteins

Proteins are the molecular level machines carry out virtually all vital biological functions in the cells. They are dynamical entities that are jiggling and wiggling at all time. In fact, this unique flexibility within a yet well-defined, folded structure is what enables proteins to perform all sorts of important functions, such as catalyzing biochemical reactions, opening and closing ion channels, etc.

For a long time, a common assumption has been that the structural fluctuations of the globular proteins (i.e. the jiggling and wiggling) driven by the thermal energy are Brownian motions, which are completely random and uncorrelated. More importantly, these motions were assumed to be in thermodynamic equilibrium. In other words, over a sufficiently long observation time, the structural fluctuation of individual proteins behave on average the same as the average behavior of a large ensemble of proteins. Therefore, one could draw conclusions about the behavior of single proteins by measuring the behavior of a sample containing a large number of proteins, as in typical experiments in laboratories.

However, the results from a series of massive computer simulations carried out by graduate student Xiaohu Hu at CMB on various supercomputers, including DOE's TITAN and HOPPER, as well as the ANTON supercomputer provided by D. E. Shaw research at the Pittsburgh Supercomputing Center, revealed that the thermal structural dynamics of proteins are not equilibrium Brownian motions, but rather out of equilibrium and non-ergodic, contrary to the traditional assumptions. This means that there is not a characteristic "average time" of the motion, but rather, the observed timescale of the motion increases with the length of the observation itself. In other words, the longer one watches, the slower the motion becomes, and this may go on beyond the typical lifespan of proteins. This is often referred to as an "aging effect". Furthermore, the motion appears self-similar in time, meaning if a stochastic trajectory from the protein motion is displayed without time units, one will not be able to distinguish, for example, whether the trajectory has the length of 1 nano-second or maybe 1 micro-second.

One important consequence of such non-equilibrium behavior is that two proteins with identical primary amino acid sequences and same folded structure will not exhibit the same dynamical behavior, and, in fact, they can deviate substantially from each other. The average behavior of a group of a protein no longer reflects the behavior of each individual proteins. This potential for different behavior within the group raises many interesting questions that call for more future studies: such as, what is the biological implication of this non-ergodic behavior? Or how does the cell cope with a group of largely differently efficient enzymes carrying out a vital biological function? The answers to these questions will further advance our understanding of the complexity of biological systems from a single cell to entire organisms.

New supercomputer simulations enhance understanding of protein motion and function

Source: www.ornl.gov/news/new-supercomputer-simulations-enhance-understanding-protein-motion-and-function

OAK RIDGE, Tenn., Nov. 23, 2015—Supercomputing simulations at the Department of Energy's Oak Ridge National Laboratory could change how researchers understand the internal motions of proteins that play functional, structural and regulatory roles in all living organisms. The team's results are featured in *Nature Physics*.

"Proteins have never been seen this way before," said coauthor Jeremy Smith, director of ORNL's Center for Molecular Biophysics and a Governor's Chair at the University of Tennessee (UT). "We used considerable computer power to provide a unified conceptual picture of the motions in proteins over a huge range of timescales, from the very shortest lengths of time at which atoms move (picoseconds) right up to the lifetimes of proteins in cells (roughly 1000 seconds). It changes what we think a protein fundamentally is."

Studying proteins—their structure and function—is essential to advancing understanding of biological systems relevant to different energy and medical sciences, from bioenergy research and subsurface biogeochemistry to drug design.

Results obtained by Smith's UT graduate student, Xiaohu Hu, revealed that the dynamics of single protein molecules are "self-similar" and out of equilibrium over an enormous range of timescales.

With the help of Titan— the fastest supercomputer in the U.S., located at the DOE Office of Science's Oak Ridge Leadership Computing Facility—Smith's team developed a complete picture of protein dynamics, revealing that the structural fluctuations within any two identical protein molecules, even if coded from the same gene, turn out to be different.

"A gene is a code for a protein, producing different copies of the protein that should be the same, but the internal fluctuations of these individual protein molecules may never reach equilibrium, or converge," Smith said. "This is because the fluctuations themselves are continually aging and don't have enough time to settle down before the protein molecules are eaten up in the cell and replaced."

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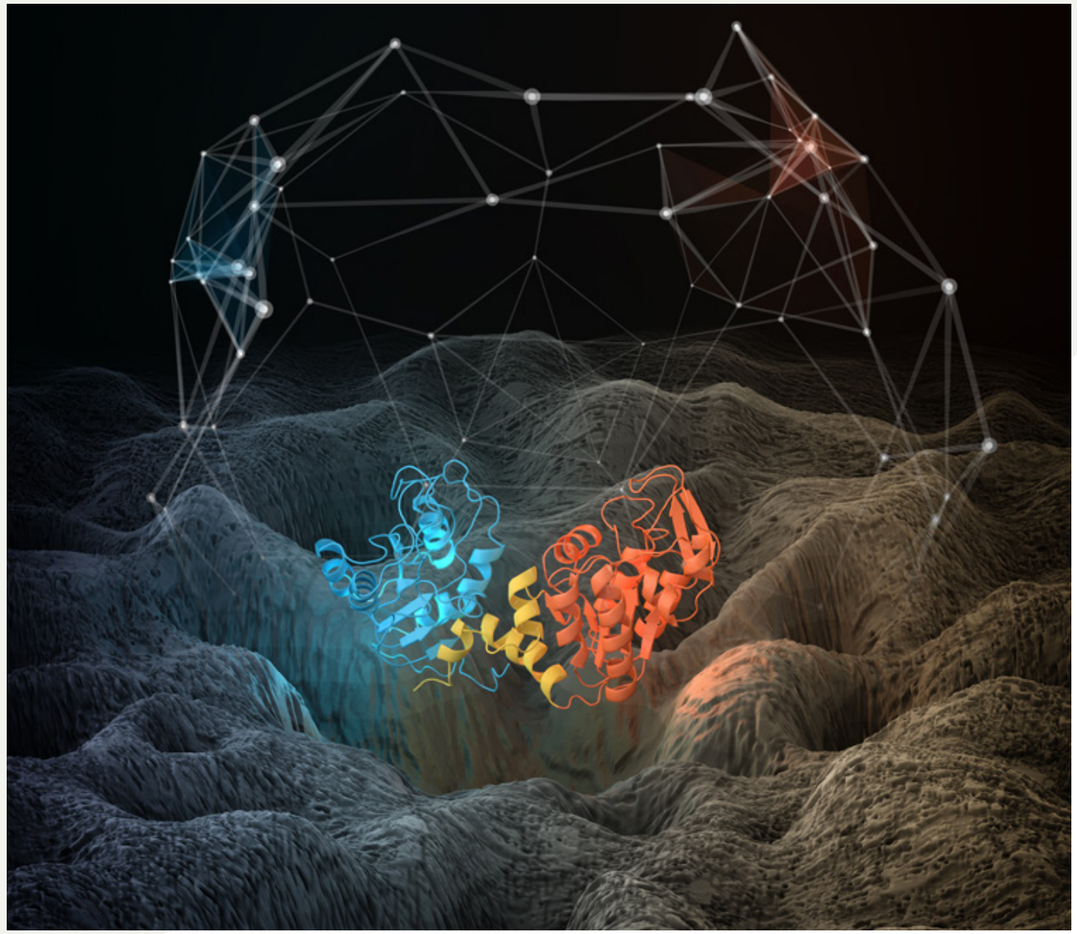

Illustration of the structure of a phosphoglycerate kinase protein that was subjected to molecular dynamics simulations. The relative motions of the red and blue domains of the proteins are highly complex, and can be described in terms of motion of a configurational point on a rough energy landscape (illustrated). The transitions of the structure between energy minima on the landscape can be described in terms of a network (illustrated), which is found to be fractal (self-similar) on every timescale. Image credit: Thomas Splettstoesser; www.scistyle.com

Understanding the out-of-equilibrium phenomenon has biological implications because the function of a protein depends on its motions. Two individual protein molecules, even though they come from the same gene, will not function precisely the same way within the cell.

"You may have, for example, two identical enzyme molecules that catalyze the same reaction," said Smith. "But due to the absence of equilibrium, the rate at which the catalysis happens will be slightly different for the two proteins. This affects the biological function of the protein."

The team also discovered that the dynamics of single protein molecules are self-similar, or fractal over the whole range of timescales. In other words, the motions in a single protein molecule look the same however long you look at them for, from picoseconds to hundreds of seconds.

"The motions in a protein, how the bits of the protein wiggle and jiggle relative to each other, resemble one another on all these timescales," Smith said. "We represent the shape of a protein as a point. If it changes its shape due to motions, it goes to a different point, and so on. We joined these points, drawing pictures, and we found that these pictures are the same when you look at them on whatever timescale, whether it's nanoseconds, microseconds, or milliseconds."

By building a more complete picture of protein dynamics, the team's research reveals that motions of a single protein molecule on very fast timescales resemble those that govern the protein's function.

To complete all of the simulations, the team combined the power of Titan with two other supercomputers—Anton, a specialty parallel computer built by D.E. Shaw Research, and Hopper, the National Energy Research Scientific Computing Center's Cray XE6 supercomputer located at Lawrence Berkeley National Laboratory.

"Titan was especially useful for us to get accurate statistics," Smith said. "It allowed us to do a lot of simulations in order to reduce the errors and get more confident results."

The title of the *Nature Physics* paper is "The Dynamics of Single Protein Molecules is Non-Equilibrium and Self-Similar Over Thirteen Decades in Time."

This research was supported by the DOE Office of Science through an Advanced Scientific Computing Research (ASCR) Leadership Computing Challenge (ALCC) allocation and funded in part by a DOE Experimental Program to Stimulate Competitive Research (EPSCoR) award. The Oak Ridge Leadership Computing Facility and National Energy Research Scientific Computing Center are DOE Office of Science User Facilities.

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—By Miki Nolin

Subsurface Biogeochemistry

TRANSPORT AND TRANSFORMATION OF MERCURY

The fate of mercury as a subsurface contaminant is of particular interest at ORNL because of legacy contamination from cold war activities at the nearby Y-12 plant in Oak Ridge 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 and particulates in the streams and sediments. Anaerobic bacteria are able to methylate inorganic mercury, rendering it more toxic, but aerobic bacteria can demethylate methylmercury. Biotic and abiotic transport and transformation of mercury in stream systems is a subject of intense interest for CMB in the framework of a DOE-funded Science Focus Area (SFA) project.

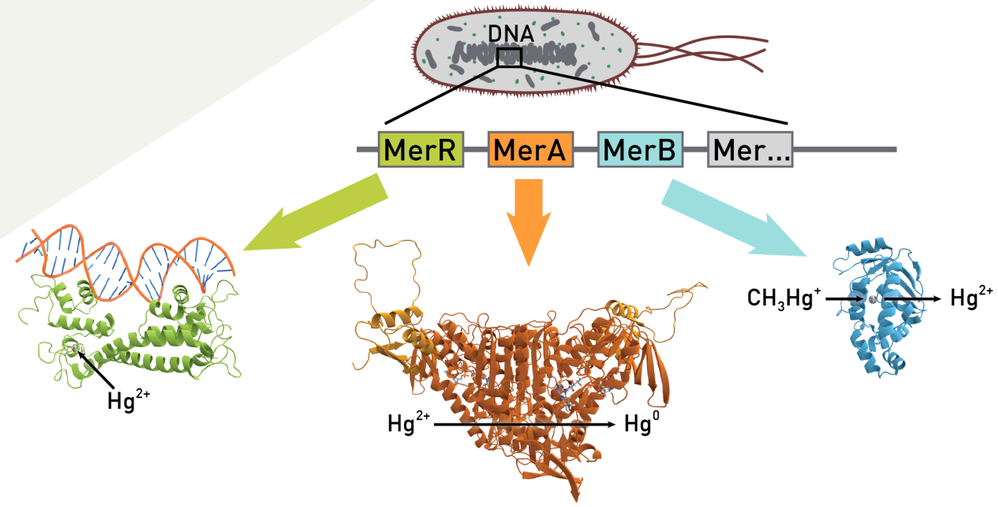
Among the methods applied are semi-empirical quantum mechanical/molecular mechanical (QM/MM) calculations, which the former postdoctoral fellow Demian Riccardi was working at streamlining, MD simulations and subsequent structural analysis, which Jerry Parks and former postdoctoral Work done in the ORNL mercury SFA project led to a major discovery in 2013: solving the decades old question of how bacteria methylate mercury.

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

Why is mercury research important?

Mercury (Hg) — the liquid quicksilver at the bottom of old thermometers — is a curious heavy metal that readily binds to many other elements. The elemental form of mercury is not readily absorbed by humans, so its toxicity is relatively low. Unfortunately, mercury can exist in more toxic forms. Oxidized mercury, Hg^{2+}, is toxic because it binds very tightly to sulfur-containing compounds, which are essential to life, thereby disrupting cellular processes. The methylated form, methylmercury, is a potent neurotoxin that readily crosses the blood-brain barrier, causing debilitating and often fatal neurological diseases.

All organisms consume trace amounts of Hg over the course of their lives with negligible ill effect. However, because mercury binds so strongly to biological compounds it is rarely excreted. In this way, prey exact revenge on their predators by passing on the mercury in their tissue. As a result, mercury climbs up the food web through the process of biomagnification. Because significant mercury concentrations can be found in apex predators such as swordfish and tuna, limited consumption of these species is recommended for humans.



Binding of Hg^{2+} 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^{2+}, and the mercuric reductase, MerA, which reduces Hg to Hg(0).

Why is mercury a global concern?

Mercury constantly cycles from the earth below, evaporating into the sky to be transported globally by atmospheric currents and later returning to the surface in rainwater. Water again finds it back into the earth, but not before transporting mercury throughout earth's vast, interconnected waterways. Over the course of its journey, mercury can undergo a countless series of oxidation, methylation, demethylation and reduction events. Mercury also enters the global cycle naturally by weathering of minerals into the groundwater or by volatilization during volcanic eruptions, which are collectively responsible for half of all atmospheric mercury. Humans are responsible for the other half. The onset of elevated mercury levels globally coincides with the dawn of the Industrial Revolution and has continued onward because of our use of coal for fuel. The little mercury that is not vaporized during combustion leaches into ground water from coal ash piles. Its "stickiness" toward other metals has led to its prevalent use in gold mining as a way to separate the wheat from the chaff in refining processes. Leaching from legacy chemical disposal sites is another significant source of mercury contamination.

Mercury Speciation. Mercury strongly binds to ligands when traveling through natural and contaminated waterways. The chemical composition of the water system and the oxidation state of mercury determines which ligands it will bind. For example, mercury prefers to bind to decomposing plant matter in freshwater streams but to chloride in the ocean. Former postdoc Demian Riccardi developed an accurate quantum mechanical (QM) approach to calculate the strength of mercury-ligand binding. Current postdoc Ryne Johnston is actively extending that approach to account for pH-depended redox processes and to investigate how different binding partners compete for mercury under a broader set of environmentally relevant conditions. These calculations will help to understand and

map aquatic mercury transport from local to global scales.

Bacterial Mercury Resistance. Some bacteria are adapted to survive in environments with high mercury concentrations. These organisms owe their mercury resistance to mer genes, which encode a set of "Mer" proteins and enzymes responsible for detoxifying the cell of mercury. We have combined neutron and X-ray scattering experiments with molecular dynamics (MD) simulations to study the structures and functions of some of the Mer proteins and enzymes. We applied these methods to understand how the MerR sentry protein flips the switch to produce the rest of the mer machinery when it encounters mercury. MerR looks like a sort of hinge that clasps onto and holds the mer operator DNA strand taut with the two DNA-binding domains at each end. Mercury binding induces a conformational change in MerR, which then induces the DNA strand to underwind and balloon out. This regulator protein initiates transcription of the mer proteins and enzymes only when they are needed. Understanding how one of these enzymes, MerB, breaks down methylmercury to its inorganic form was an early success story from the SFA project. Two cysteine amino acids coordinate methylmercury through their sulfur atoms, and these interactions lengthen and therefore weaken the mercury-carbon bond. A third amino acid, aspartic acid, delivers a proton to the carbon atom in methylmercury, which cleaves the bond We have recently embarked on a study to identify the factors that control passive diffusion of mercury compounds through the lipid bilayers of bacterial cell membranes.

The Great Methylation Discovery

Whereas some bacteria detoxify mercury-containing compounds, others do the opposite. Certain anaerobic microorganisms convert inorganic mercury to methylmercury. The genetic and biochemical basis for the reaction, however, remained elusive for more than four decades.

In the early to mid-1990s, mercury methylation was shown to be an enzyme-catalyzed process involving cofactor B12 and biochemical reaction pathways. However, these pathways are shared by numerous bacteria but only a small fraction of which were known to be Hg methylators, and there was no obvious phylogenetic pattern to suggest which organisms could and could not perform the reaction. Therefore, it was unclear which specific protein or proteins were needed to methylate mercury.

Jerry tackled this problem by using an unconventional approach to identify the genes and corresponding proteins responsible for Hg methylation by considering the chemical aspects and structural elements in proteins that would be required for the methylation reaction. The project

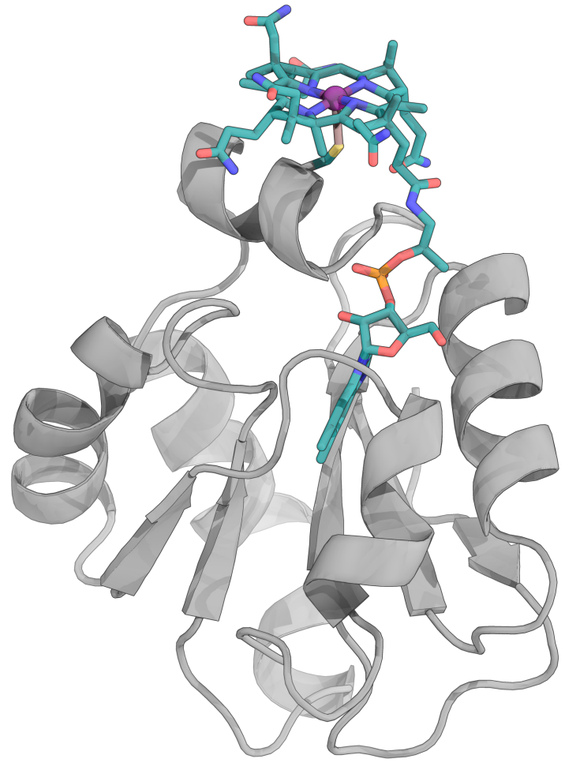


Fig 1: Model of HgcA showing the predicted bond between cobalt (purple sphere) and sulfur (yellow).

led to the discovery of two genes, *hgcA* and *hgcB*, that are required for methylmercury production by bacteria and archaea. The proteins encoded by these two genes are a cobalamin-dependent methyltransferase and an electron-donating ferredoxin. He predicted that a unique cobalt-sulfur bond in HgcA enables the transfer of a methyl anion ($H_3C:^-$) to mercury, rather than methyl radical ($H_3C^•$) or methyl cation (H_3C^+) transfer, which are ubiquitous across all life. Such a reaction is unprecedented in biology, as neither this unique bonding pattern nor methyl anion transfer has ever been observed for any cobalamin-containing protein.

A major implication stemming from this research is the prediction that any microorganism encoding *hgcA* and *hgcB* genes in its genome sequence will be able to produce methylmercury. To date, all of the bacteria and archaea that have been tested have methylated mercury, confirming this prediction. With this major discovery in environmental science, we can now start to understand and detect bacterial methylmercury production worldwide, which hopefully will lead to strategies to limit potential harm that can be caused by the methylmercury produced by these microbes.

Bioinorganic Chemistry of HgcA Methylation. Cobalamin (vitamin B12) and its chemical relatives are biological workhorses that can use their central, redox-active cobalt atom to transfer methyl groups. The electronic properties of the lower ligand affect the chemistry of the upper ligand; on this basis was Jerry's prediction founded. Jing Zhou sought to quantify and compare the energies of methyl radical and methyl anion transfer to mercury with different lower ligands and model corrinoids. She found that anionic sulfur coordination promotes methyl anion transfer, whereas the typical neutral nitrogen coordination promotes methyl radical transfer. Subsequent mutagenesis experiments by collaborators bolster Jing's simulations and Jerry's prediction. Jing and Ryne are extending the simulations a step further to investigate exactly how different lower ligands affect the electrochemistry of cobalt. Understanding the electrochemistry in HgcA provides insights into its biophysical mechanisms and cellular functions. Their robust methodology to tackle large, inorganic complexes is widely extensible to other systems and can also help develop accurate geochemical speciation models.

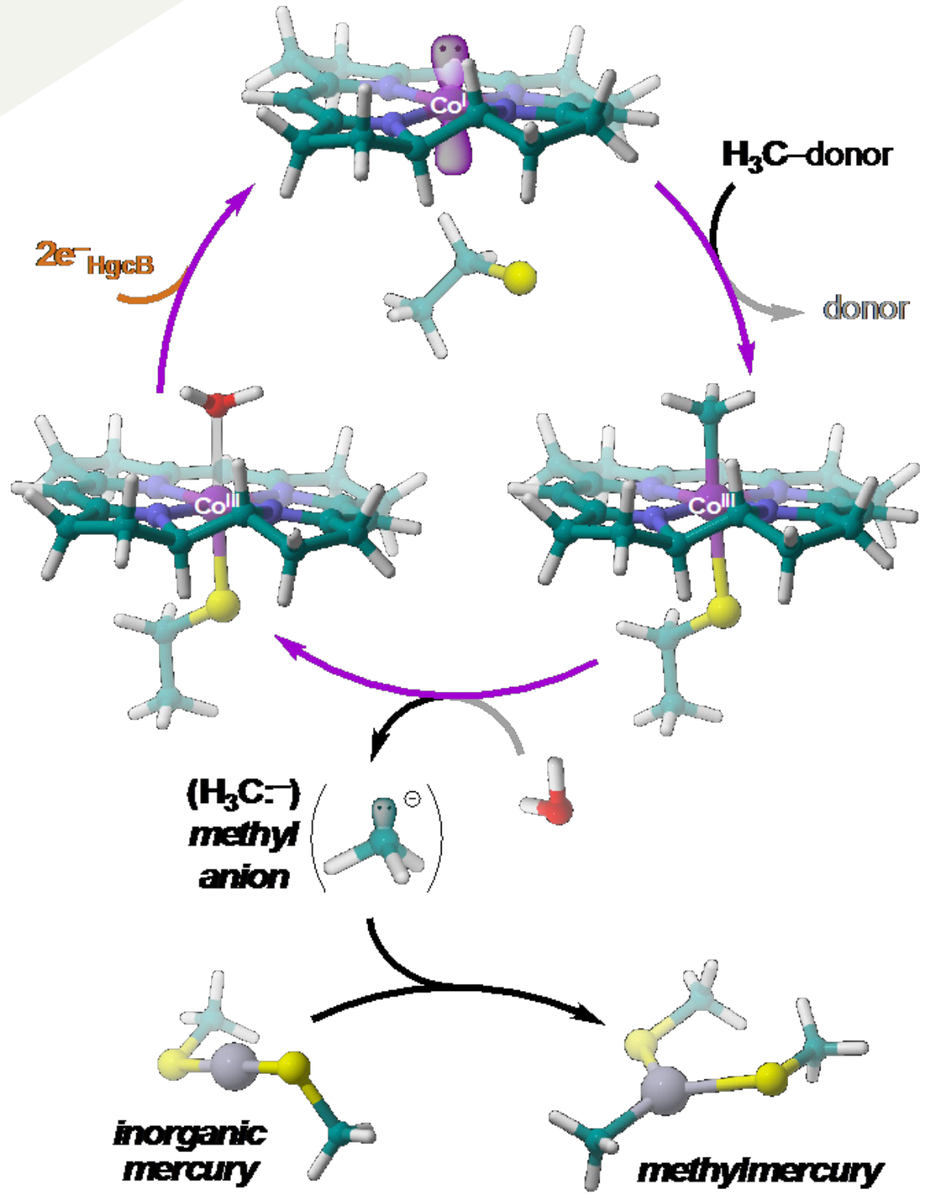


Fig 2: Concept of the redox-mediated HgcA methylation mechanism. The bond between cobalt (purple) and sulfur (yellow) promotes methyl anion (H3C:–) transfer to inorganic mercury (grey), producing methyl mercury. Reduction of cobalt by HgcB starts a new cycle.

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ORNL scientists solve mercury mystery

Source: www.ornl.gov/content/ornl-scientists-solve-mercury-mystery

OAK RIDGE, Tenn., Feb. 7, 2013 — By identifying two genes required for transforming inorganic into organic mercury, which is far more toxic, scientists today have taken a significant step toward protecting human health.

The question of how methylmercury, an organic form of mercury, is produced by natural processes in the environment has stumped scientists for decades, but a team led by researchers at Oak Ridge National Laboratory has solved the puzzle. Results of the study, published in the journal Science, provide the genetic basis for this process, known as microbial mercury methylation, and have far-reaching implications.

"Until now, we did not know how the bacteria convert mercury from natural and industrial processes into methylmercury," said ORNL's Liyuan Liang, a co-author and leader of a large Department of Energy-funded mercury research program that includes researchers from the University of Missouri-Columbia and University of Tennessee.

"This newly gained knowledge will allow scientists to study proteins responsible for the conversion process and learn what controls the activity," said Liang, adding that it may lead to ways of limiting methylmercury production in the environment.

For some 40 years scientists have known that when mercury is released into the environment certain bacteria can transform it into highly toxic methylmercury. Exactly how bacteria make this happen has eluded scientists. The challenge was to find proteins that can transfer a certain type of methyl group and to identify the genes responsible for their production.

Ultimately, by combining chemical principles and genome sequences, the team identified two genes, which they named hgcA and hgcB. Researchers experimentally deleted these genes one at a time from two strains of bacteria, which caused the resulting mutants to lose the ability to produce methylmercury. Reinserting these genes restored that capability, thus verifying the discovery.

The researchers found that this two-gene cluster is present in all known mercury-methylating bacteria, and they predicted that more than 50 other microorganisms may methylate mercury because they have a pair of similar genes.

Another key to the development was the collection of talent assembled to work on this problem.

"This discovery was made possible by our diverse team, which includes scientists with expertise in chemistry, computational biology, microbiology, neutron science, biochemistry, and bacterial genetics," said Liang, who rated this paper as one of the most satisfying of her career.

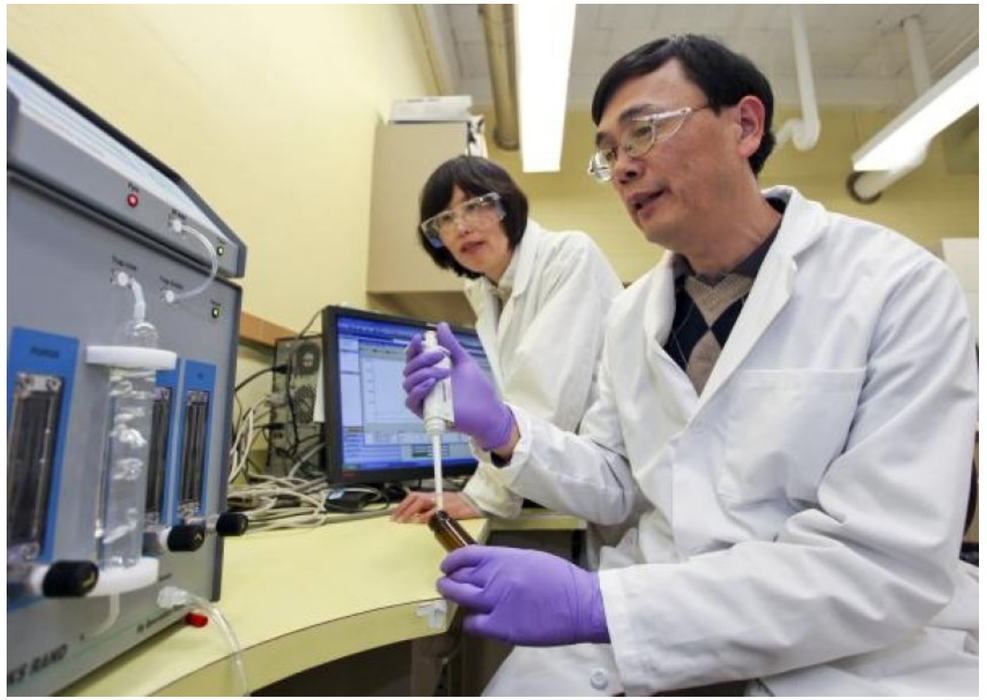


Photo credit: Jason Richards

Oak Ridge National Laboratory scientist Liyuan Liang, left, and a team of researchers have identified two genes required for bacteria to transform inorganic mercury in the environment into methylmercury, an organic and far more toxic form. Pictured with Liang is ORNL researcher Baohua Gu.

Mercury is a toxin that spreads around the globe mainly through the burning of coal, industrial use, and through natural processes such as volcanic eruptions. The chemical element bioaccumulates in aquatic food chains, especially in large fish. Various forms of mercury are widely found in sediments and water.

In a report just released by the United Nations Environmental Programme, Achiim Steiner, UN under-secretary general and executive director of UNEP, notes that "mercury remains a major global, regional, and national challenge in terms of threats to human health and the environment."

This research was funded by DOE's Office of Science. Other ORNL co-authors are Jerry Parks, Alexander Johs, Mircea Podar, Richard Hurt, Stephen Tomanicek, Yun Qian, Steven Brown, Craig Brandt, Anthony Palumbo, Jeremy Smith, and Dwayne Elias. Podar, Brown, Smith, and Elias hold joint appointments at the University of Tennessee. Authors from the University of Missouri are Romain Bridou, Steven Smith, and Judy Wall.

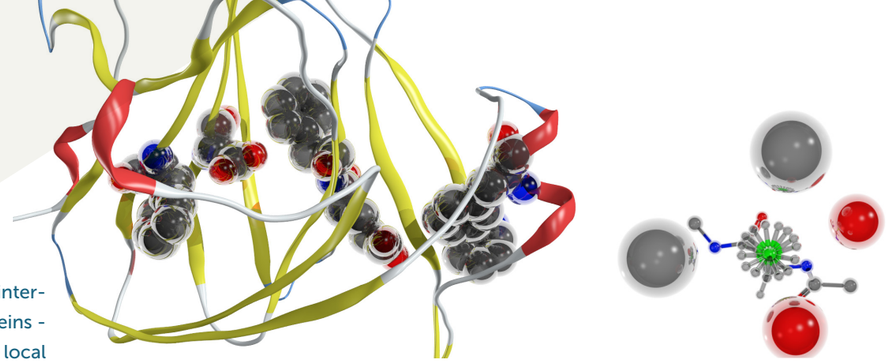
Reference: Parks, J. M., et al. **2013**. "The Genetic Basis for Bacterial Mercury Methylation," *Science* 339(6125), 1332–35. DOI: 10.1126/science.

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 Discovery and Drug Design

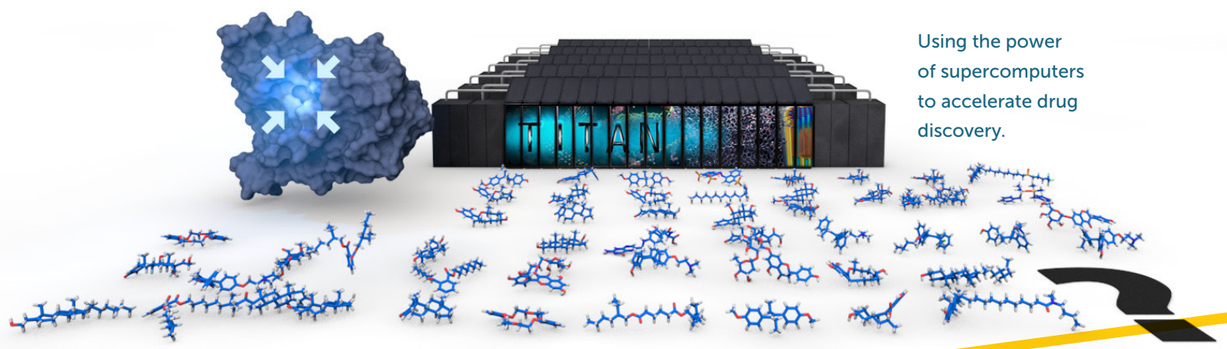
The drug discovery and drug design projects in the Center for Molecular Biophysics integrate technological, fundamental advances in many aspects of computational biology and apply these advances to contemporary, industrial-scale projects. The Center's expertise in supercomputing and the dynamics of biomolecules has led us to develop extremely powerful computational approaches to drug discovery on supercomputers. This success allows us to investigate biomedical problems that are quite complex in nature, beyond protein-drug interactions, such as modulating protein-protein interactions, or characterizing the effect of small molecules on biochemical pathways. The Center addresses fundamental questions relevant to the mechanisms of conformational selection, to the characterization of interactome structures and dynamics, relevant to fundamental chemical biology perspectives of biological control. In addition, the Center is fully engaged in collaborative research with academic and industrial groups on specific drug discovery endeavors that have all led to novel molecular entities being discovered against diverse targets. The following descriptions detail these successes for selected projects. The Center's groups are now developing a fully integrated, supercomputer-based technological approach that predicts the specificity and toxicity of drug candidates, resulting in a virtual platform for structure-based pre-clinical and clinical essays, cutting the time and cost of molecular discovery and changing the shape of the drug discovery field.



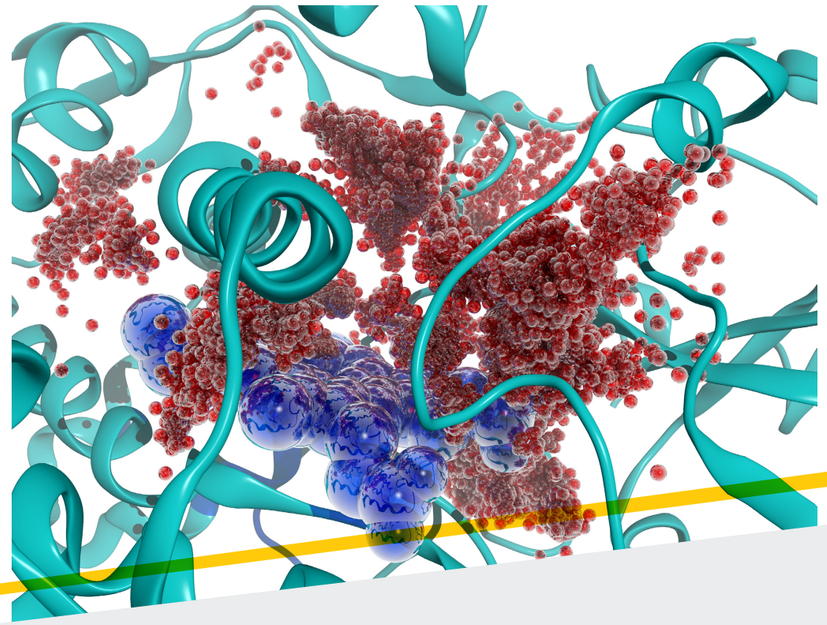
Detailed analysis of interactions within proteins - methyl groups probe local environments.

Supercomuputer Assisted Drug Discovery

A traditional view of protein-ligand or protein-drug binding can be understood conceptually as a lock-and-key model. The protein is the lock or a static structure that provides a complementary shape for a ligand (the key) to fit into and result in a biological function. However, this model is not an accurate description of reality. Proteins are dynamic molecules that can exist in an abundance of different conformational states representing an ensemble. Ligand binding can then be understoand through the lens of a new model known as conformational selection. In this new model, a given ligand or drug may select for a certain conformation of a protein that precedes binding. This presents a challenge for traditional computational drug discovery methods which typically only use one structure, such as a crystal structure or homology model, to screen or dock many different potential drugs. As a result, our group has developed

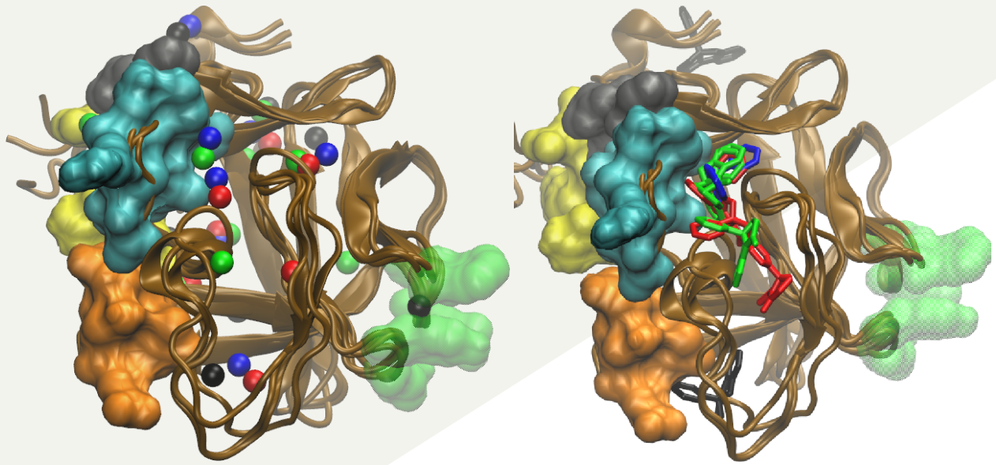


Using the power of supercomputers to accelerate drug discovery.



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

an open-source software known as VinaMPI that allows for thousands of potential drugs to be docked onto many different conformations of proteins in parallel using leadership-class supercomputing facilities such as the Titan supercomputer. The software and the ensemble docking method discovered using the ensemble docking approach could help to tackle the problem of multidrug resistance in bacteria. The final application completed, thus far, in our group involved the fibroblast growth factor 23(FGF23), which is discussed below.



Superimposed conformers of FGF23 identify new binding sites used in ensemble docking(left). Binding sites are indicated by blue, red, and green balls. Docking shows that many small molecules can bind to these identified binding sites(right). In the image on the right, small molecules are shown in red, green, and blue.

have demonstrated an improved enrichment, ability to identify known ligands, over docking to only the crystal structure for a number of different proteins. In addition, our group has recently applied VinaMPI and/or the ensemble docking method to a number of different projects that have all led to the discovery of novel inhibitors. First, docking of 80 compounds to three conformations of the Z variant of alpha-1-antitrypsin led to the discovery of a novel inhibitor for the polymerization of the protein, which is associated with fatal symptoms. Second, we have used VinaMPI and ensemble docking to identify 11 inhibitors of the efflux pump in *E.coli*, a tripartite protein complex that ejects numerous antibiotics out of the cell contributing to resistance. Our new inhibitors

The binary complex forms a receptor that interacts with a hormone known as FGF23 (fibroblast growth factor 23). FGF23 is responsible for keeping blood phosphate levels within a normal range. The binary complex composed of the alpha-klotho and fibroblast growth factor receptor exists as an ensemble of representative structures. FGF23 can exist as two cleaved fragments known as the N-terminal and C-terminal fragments or as the full-length hormone. When the C-terminal fragment binds the binary receptor, a specific conformation of that complex is selected for to bind the C-terminal fragment. This conformation becomes known as an active state leading to an increase in blood phosphate levels. On the other hand, when the full-length FGF23 hormone binds the receptor complex, a different conformation is selected for that leads to a decrease in phosphate levels. Diseases such as hypophosphatemia (low blood phosphate) and hyperphosphatemia (high blood phosphate) result from different genetic mutations that disrupt the function of FGF23 and the binary receptor to regulate phosphate. As a result, new small molecules are needed to restore phosphate levels to within a normal range during these diseased states. Our group is able to use computer simulations to generate and identify different conformations of the FGFR/alpha-klotho complex and then screen thousands of small molecules to each conformation in order to discover new inhibitors and binding sites. If a small molecule is able to bind to a given conformation of the receptor complex, it would stabilize that conformation leading to an increase or decrease in blood phosphate levels restoring them to a normal range.

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 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/π-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.

Design of smart anticoagulant drugs using ensemble-based high-throughput virtual screening

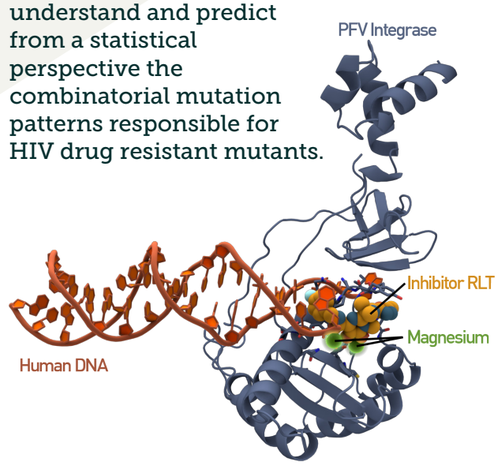
Karan Kapoor (who is now a post-doc researcher after graduating from Jerome Baudry's lab at University of Tennessee) has developed and applied computational approaches in aiding the drug-discovery efforts. He was working on a project in collaboration with Shifa Biomedical Corporation (Shifa), a structure-based drug discovery company located in Malvern, Pennsylvania. The project was funded by the NIH Small Business Innovation Research (SBIR) program, that supports early-stage small businesses engaged in research and development (R&D) with a strong potential for commercialization.

The prothrombinase (PTase) enzymatic complex, consisting of the enzyme factor Xa (FXa) and a protein cofactor factor Va (FVa), catalyzes the cleavage of prothrombin (PT) leading to the formation of thrombin and clot-formation. The risk of serious bleeding, particularly at high dosage, is a major liability of anticoagulant drugs that are active-site competitive inhibitors targeting the FXa-PT binding site. The goal of this project was to target FXa within the PTase complex, but instead of seeking another active-site directed inhibitor, a novel computational approach utilizing MD simulations and ensemble-based high-throughput virtual screening was used to identify compounds that can potentially alter the interaction between FXa and FVa. This lead to the successful identification of ten compounds, represented by three small-molecule families of inhibitors, that achieve dose-independent partial inhibition of PTase activity in a non-active site dependent and self-limiting mechanism.

Identification of successful leads is only the first step in the drug-discovery pipeline, which usually takes 12–15 years. A major challenge facing the pharmaceutical industry today is finding innovative ways of reducing the high-attrition rates associated with the drugs, especially in the clinical trials stage. 'Phase 0' clinical trials have been suggested by the Food and Drug Administration (FDA) that seeks metabolism, toxicology, and other data from micro-doses administered to very small (10-15) groups of patients. Innovative computational techniques can be developed that will complement this data by predicting the metabolic pathways and off-target effects of the potential drug candidates. This will need to be complemented by policy changes that makes it profitable for companies to develop naturally occurring compounds like curcumins and catechins that have been shown to target different cancers. At the end of the day, the goal of this research is to provide safe and sustainable treatments for the major diseases to everyone in a cost-effective manner.

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 HIV/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.

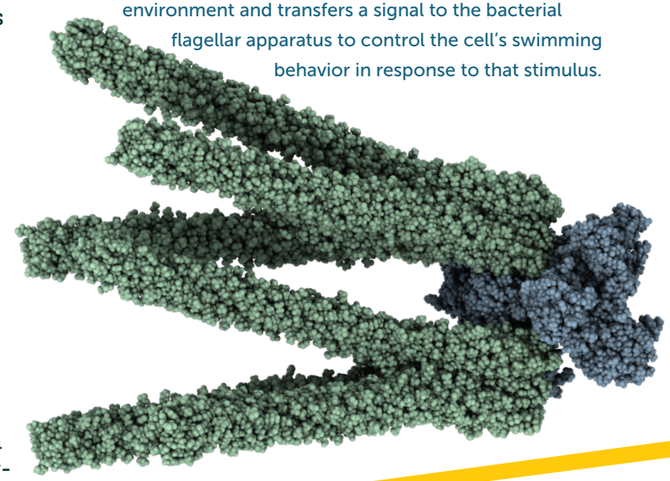
Interactions in Proteins

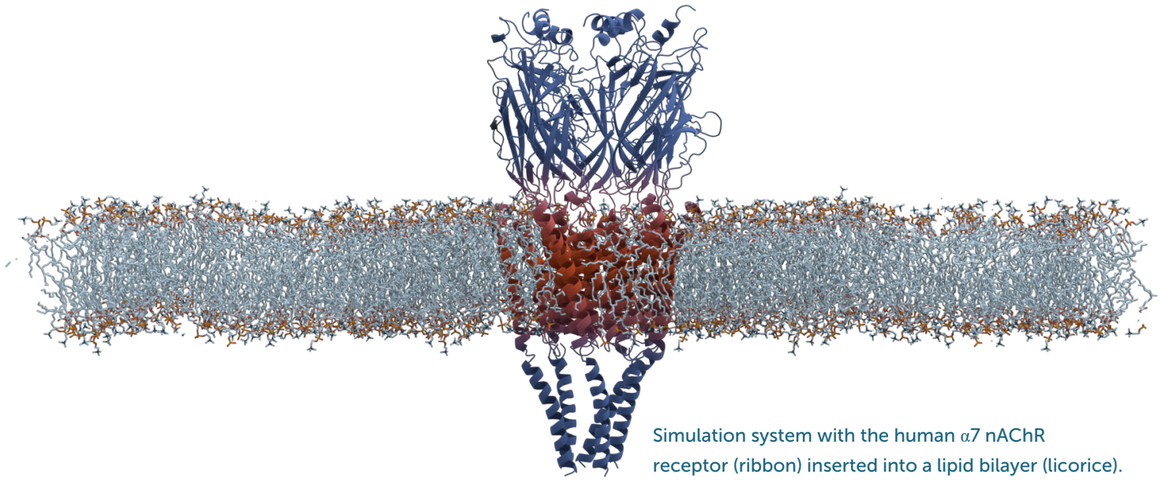
The Baudry group is also interested in the effect of nonbonded interactions in protein-protein and protein-ligand complexes. Undergraduate student William Hembree used quantum chemistry to investigate how the rotational dynamics of methyl groups, an important marker in chemistry, is affected by their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

Chemotaxis - Ligand based signaling pathways

Postdoctoral researcher Derek Cashman worked on a 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 was 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 were then 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 α7 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 molecules 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

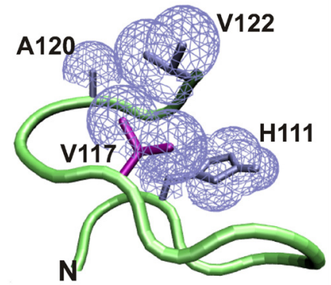
Source: www.utk.edu/tntoday/2011/06/22/jeremy-smith-gss-protein

June 22, 2011 - 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 structures 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.

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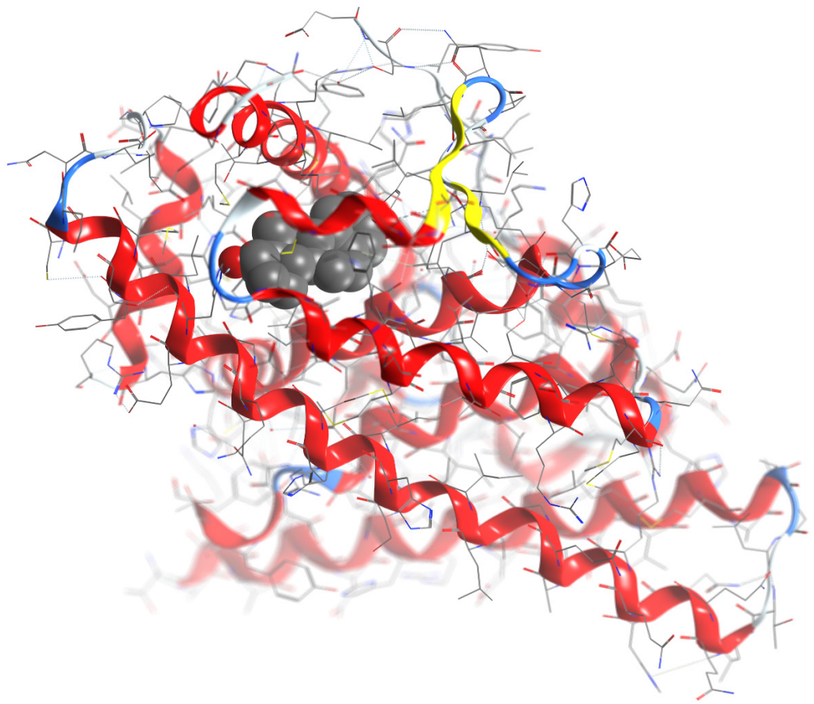
Supercomputing Research Opens Doors for Drug Discovery

Source: 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.

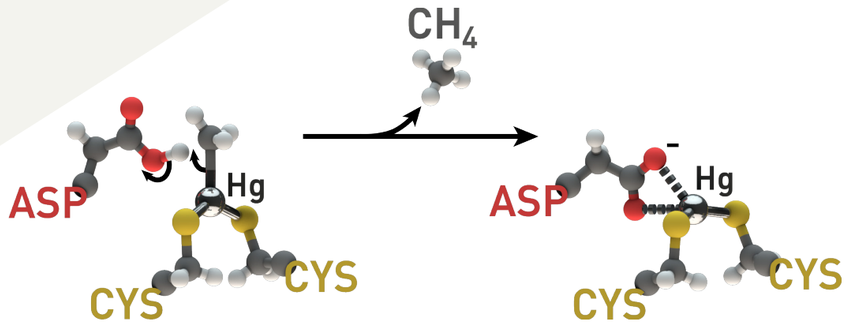
Hong Guo has a general interest in understanding the origin of the high catalytic efficiency and selectivity of enzymes. In addition to being of fundamental scientific importance, these studies also improve the basis for designing inhibitors, efficient drugs and enzyme mimics. He normally studies several 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.

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.



Quantum mechanical description of organomerucrial 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 -CH_3 leaving group, breaking the bond and forming Hg(II) and methane.

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.

What's the chemistry behind the microbial methylation of mercury?

Binding of Hg^{2+} by two Cys thiolates is thermodynamically extremely favorable. Hg^{2+} and its associated species have extremely high affinities for thiols and form very tightly bound complexes. However, these complexes can undergo rapid exchange between thiols, that is, one of the thiolates can readily dissociate, provided that a third thiolate first coordinates to Hg. Thus, a transient, trigonal complex species of mercury ion and three thiol groups is expected to be important in Hg^{2+} transfer reactions. Also, acid-base chemistry in which thiols are deprotonated to generate nucleophilic thiolates, or coordinated thiolates are protonated to generate neutral leaving groups, can enhance the rates of Hg^{2+} transfer among pairs of thiols. QM/MM calculations were used to identify a possible mechanism for the intramolecular Hg^{2+} transfer in MerA, which can be considered a prototype for Hg transfer. Specifically, an X-ray crystal structure of the catalytic core of MerA with Hg^{2+} was used as a starting point for simulating Hg^{2+} transfer from the surface of the protein to the buried, inner pair of Cys residues in the active site.
From the computed Hg^{2+} transfer pathway, we note that Hg^{2+} is always paired with two or more thiolates. As Hg^{2+} is transferred from the solvent-exposed protein surface to the buried catalytic site, a proton is transferred in the opposite direction. The key mechanistic insight from the simulations is that Hg^{2+} transfer is facilitated by coupling the competitive binding of pairs of Cys residues with the proton affinities of the thiolates. These principles are expected to be general to other proteins and enzymes of the mer operon and metal ion trafficking in biological systems.

Multiscale Methods

SCALING FROM ATOMS UPWARDS

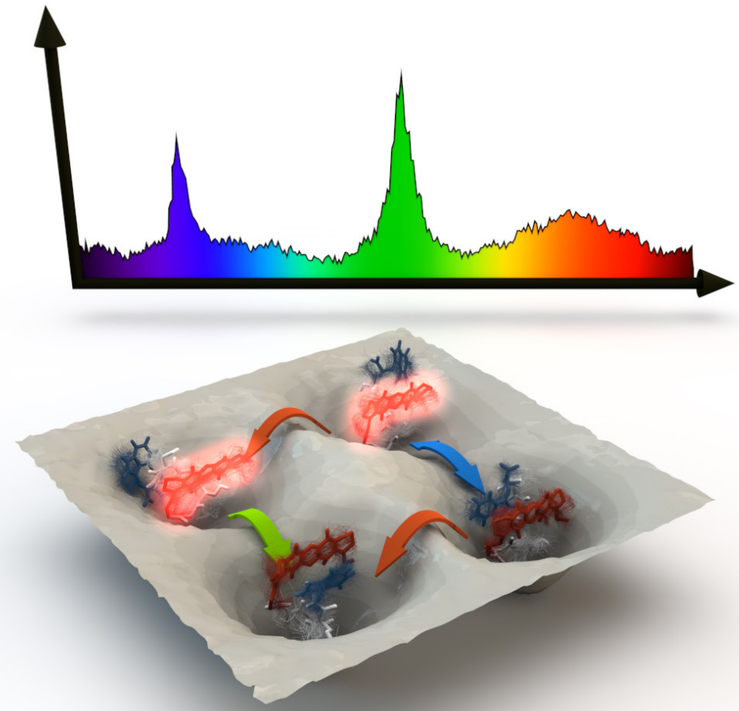
The simultaneous representation of biological processes at different length- and time-scales is a fervent area of research at present, and comes from the realization that coarse-graining of atomistic interactions is necessary to allow the simulation of processes at the cellular, and eventually organismal level. We are particularly interested in developing multiscale concepts that will be able to be used on 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

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.



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.

'Fingerprints' match molecular simulations with reality

Source: www.ornl.gov/news/fingerprints-match-molecular-simulations-reality

February 22, 2011 - A theoretical technique developed at the Department of Energy's Oak Ridge National Laboratory is bringing supercomputer simulations and experimental results closer together by identifying common "fingerprints."

ORNL's Jeremy Smith collaborated on devising a method -- dynamical fingerprints --that reconciles the different signals between experiments and computer simulations to strengthen analyses of molecules in motion. The research will be published in the Proceedings of the National Academy of Sciences.

"Experiments tend to produce relatively simple and smooth-looking signals, as they only 'see' a molecule's motions at low resolution," said Smith, who directs ORNL's Center for Molecular Biophysics and holds a Governor's Chair at the University of Tennessee. "In contrast, data from a supercomputer simulation are complex and difficult to analyze, as the atoms move around in the simulation in a multitude of jumps, wiggles and jiggles. How to reconcile these different views of the same phenomenon has been a long-standing problem."

The new method solves the problem by calculating peaks within the simulated and experimental data, creating distinct "dynamical fingerprints." The technique, conceived by Smith's former graduate student Frank Noe, now at the Free University of Berlin, can then link the two datasets.

Supercomputer simulations and modeling capabilities can add a layer of complexity missing from many types of molecular experiments.

"When we started the research, we had hoped to find a way to use computer simulation to tell us which molecular motions the experiment actually sees," Smith said. "When we were finished we got much more - a method that could also tell us which other experiments should be done to see all the other motions present in the simulation. This method should allow major facilities like the ORNL's Spallation Neutron Source to be used more efficiently."

Combining the power of simulations and experiments will help researchers tackle scientific challenges in areas like biofuels, drug development, materials design and fundamental biological processes, which require a thorough understanding of how molecules move and interact.

"Many important things in science depend on atoms and molecules moving," Smith said. "We want to create movies of molecules in motion and check experimentally if these motions are actually happening."

View a supercomputer simulation of a protein in motion here:http://www.ornl.gov/ornlhome/hg_mer.htm

"The aim is to seamlessly integrate supercomputing with the Spallation Neutron Source so as to make full use of the major facilities we have here at ORNL for bioenergy and materials science development," Smith said.

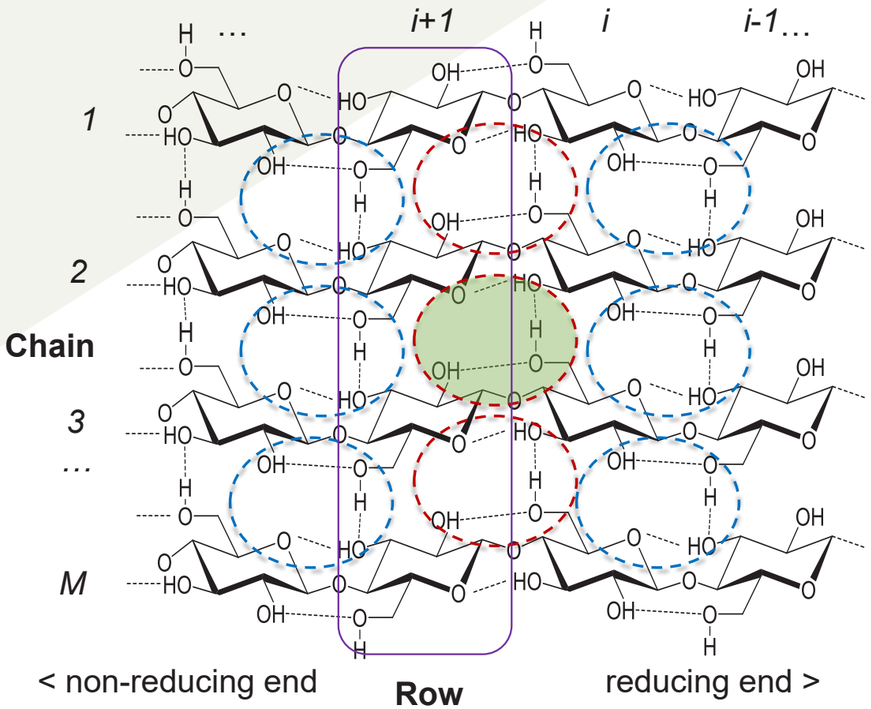
The collaborative work included researchers from L'Aquila, Italy, Wuerzburg and Bielefeld, Germany, and the University of California at Berkeley. The research was funded in part by a Scientific Discovery through Advanced Computing grant from the DOE Office of Science.

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

Poplar: a potential biofuel feedstock investigated at ORNL.

Hydrogen Bond Networks in Cellulose

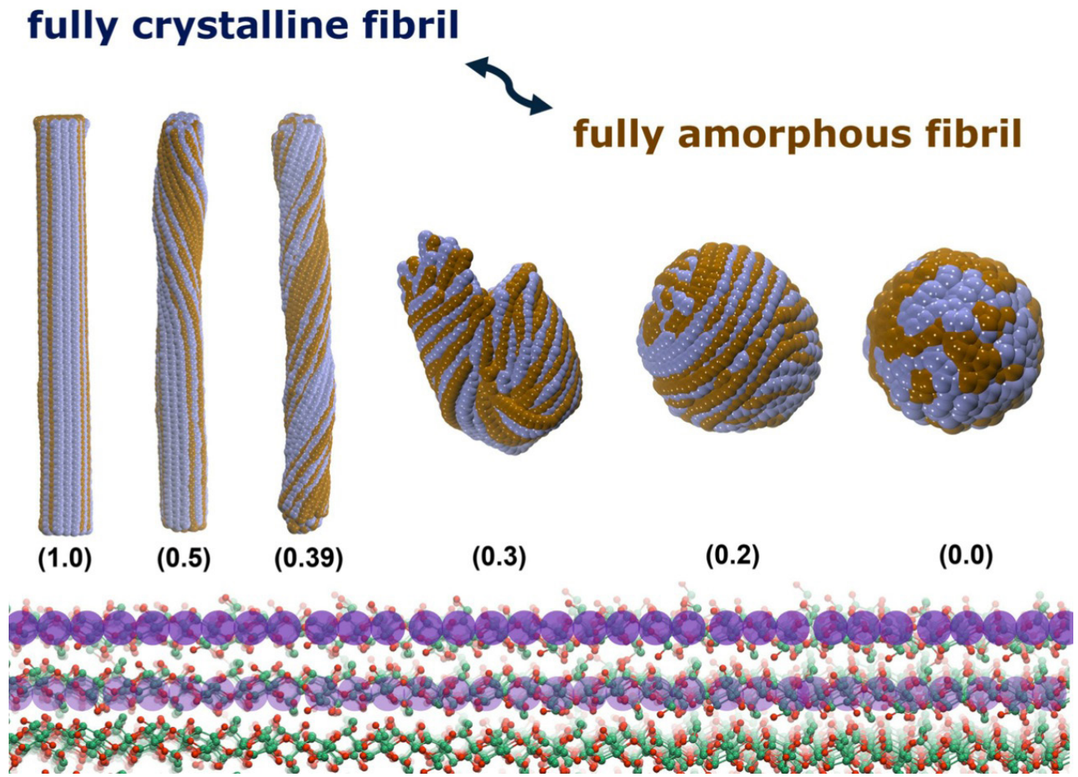
A major cause of biomass recalcitrance to deconstruction is the high structural ordering of natural cellulose fibrils, which arises largely from an extensive hydrogen-bond network between and within the cellulose polymers. Tongye Shen, Xiaolin Cheng and Jeremy Smith have worked with Heinrich Klein, an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

Coarse-Graining Cellulose

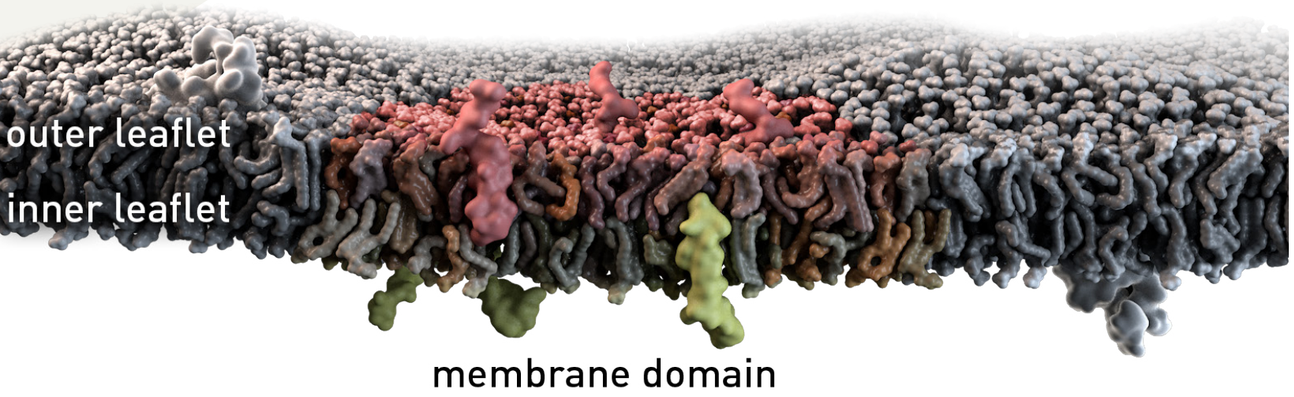
A systematic method has been developed by postdoctoral researcher Goundla Srinivas for generating and representing both crystalline and amorphous cellulose states. The developed CG models allow the exploration of cellulose fibril structures for length- and time-scales beyond the reach of atomistic simulations.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



Transition of cellulose fibril from crystalline to amorphous structures.

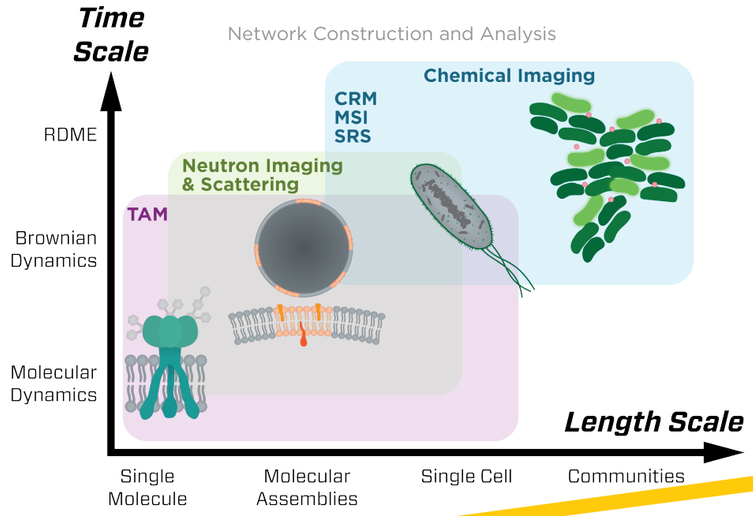
Biomembrane research at CMB

Cell membranes display remarkable organization. In the transverse dimension, they are compositionally asymmetric, while in the lateral dimension, they are believed to contain nanoscopic domains ("lipid rafts") critical to their function. In this regard, questions arise about the interplay between lipid rafts and compositional asymmetry, including how asymmetry is maintained, whether rafts bridge the two halves (leaflets) of asymmetric bilayers, and if so, how. To resolve these questions, Xiaolin Cheng and Jianhui Tian, a post-doc researcher at CMB are combining high-performance computer simulations, bottom-up assembly of asymmetric model membrane systems and neutron scattering experiments. Neutron scattering is used to study the effects of compositional asymmetry, while atomistic molecular dynamics simulations of the experimental systems have been performed on ORNL's TITAN supercomputer using innovative, scalable enhanced sampling algorithms. The system will comprise ~60 million atoms, and span time scales ≥10 μs, making it among largest atomistic biological simulations to date. These efforts will culminate in the development of a synthetic protocell displaying key hallmarks of a living cell - active membrane transport; dynamic, asymmetric membrane structure; and respiratory energy metabolism. In this way, it is planned to address long-standing questions in membrane biology regarding asymmetry and the transverse coupling of lipid domains.



Adaptive Biosystems Imaging (ABI)

Although diverse tools are available to image biological systems, each provides only narrow windows of spatial, temporal and chemical data and, by itself, no systems-level knowledge. Therefore, the overarching problem is how to assemble intracellular, extracellular and phenotypic data, collected across multiple platforms and over many orders of magnitude of length and time, into a coherent understanding of coupled and interdependent biological processes. Xiaolin Cheng and his collaborators at various other research institutions are developing and implementing an Adaptive Biosystems Imaging (ABI) capability that integrates new ways of acquiring chemical image data with a hierarchical computational framework in order to realize correlated measurements and interpretations of biological processes at extended spatial and temporal scales. By adaptive, we mean an imaging approach that involves the coordinated, mutual evolution of observation and systems models. Observations, derived from multiple imaging techniques, structural biology and omics-based measurements, are animated and explained through multiscale simulations. On the computational front, effort is focused on developing and coupling multiscale computational techniques and algorithms (e.g., molecular dynamics, Brownian dynamics and whole-cell simulations) to bridge resolution gaps, to integrate structural and functional data from multiple sources and to embed complex structures into their biological context.



Eppur Si Muove!
The 2013 Nobel Prize in Chemistry

Source: www.cell.com/structure/abstract/S0969-2126(13)00439-5

By Jeremy C. Smith and Benoît Roux

The 2013 Nobel Prize in Chemistry has been awarded to Martin Karplus, Michael Levitt, and Arieh Warshel for their work on developing computational methods to study complex chemical systems. Their work has led to mechanistic critical insights into chemical systems both large and small and has enabled progress in a number of different fields, including structural biology.

Structure determines function! For decades, this has been the mantra of biologists worldwide. For molecular biologists, since the solving of the quintessential double helix, the serial revelations of awe-inspiring atomic-detail architectures have done little to dissipate this structure-function frenzy. And yet, even from the epoch of the first protein structures from X-ray crystallography in the 1960s, experimentalists have always known that their static structures are not enough. Structure can only ever serve as a starting point to understanding biology. It has long been obvious to all that biomolecules must move to perform their functions (“Eppur si muove!” [And yet it does move! (Galileo Galilei)]). Energies and forces are what form structure and drive the thermodynamics and dynamical motions that underlie biological function. Thus, to understand and comprehend how macromolecules work, one must ultimately be able to “visualize” the manner in which these complex nanoscale “molecular machines” move and change their shape atom-by-atom as a function of time as they perform their activities. The problem, however, is that the three-dimensional architectures provided by the major atomic-resolution structural techniques tell us nothing about the energies and forces involved. In order to quantify dynamics, some way to associate energies and forces with molecular geometry was urgently needed. The solution to this problem, largely built around the pioneering work of the three 2013 Nobel Laureates in Chemistry, has been to reconstruct a virtual reality in the computer to simulate molecular dynamics.

Transformative research can best be appreciated with long hindsight, and although this luxury is not often afforded at the time of the Nobel award, this year’s prize gives us this pleasure. The “origins” of the field are, of course, arbitrary to define, but might pragmatically be placed in the 1940s–1950s, with the first computational molecular dynamics simulations and the development of spectroscopic force fields to interpret infrared and Raman spectra. Also progressing was the field of the previous chemistry “theory” Nobel prize, awarded in 1998, of quantum chemistry. Although not always yielding quantitatively correct results, quantum chemistry does provide a relatively consistent framework for looking at molecules, and, in contrast to biomolecular simulation, the associated computer programs, with their limited functionality, are, in the main, arguably hard to use incorrectly. However, accurate quantum chemistry scales atrociously with the number of electrons involved, a challenge that may never be overcome without discovering an alternative, computationally-tractable, theoretical route for electronic structure calculations. Hence, to tackle large interesting biomolecular systems, a large helping of empiricism was needed, and “molecular mechanics” was born.

The middle and late 1960s found all three future Nobelists influenced by Schneior Lifson at the Weizmann Institute, who was developing ideas for using molecular mechanics empirical functions to calculate the energies of large molecules. The novel idea was to use a functional form that could serve not only for calculating vibrational frequencies, as did the spectroscopic force fields using expansions of the potential about a minimum-energy structure, but also for determining that structure. The so-called “consistent force field” (CFF) of Lifson and his coworkers, particularly Warshel, included nonbonded interaction terms so that the minimum-energy structure could be found after the energy terms had been appropriately calibrated. The possibility of using such energy functions for larger systems was becoming apparent at that time, and Levitt and Lifson pioneered the calculation of the energy of a protein from atomic coordinates (Levitt and Lifson, 1969).

The 2013 Nobel citation specifically focused on a form of multiscale modeling in which calculation of the energy of a real system, such as an enzyme, is performed by combining molecular mechanics modeling of the environment with quantum chemical modeling of the core region (such as the active site) in which the chemically interesting action takes place. An important step was taken when Warshel visited Karplus at Harvard in the beginning of the 1970s. They constructed a computer program that used a hybrid method combining classical and quantum mechanics to describe the p-electron and vibrational spectra of a number of planar molecules (Warshel 2102 Structure 21, December 3, 2013 ª2013 Elsevier Ltd All rights reserved and Karplus, 1972). Later, in 1976, Warshel and Levitt constructed a more general scheme for a partitioning between electrons that are included in the classical modeling and those that are explicitly described by a quantum chemical model. They reported this in their study of the “Dielectric, Electrostatic and Steric Stabilisation of the Carbonium Ion in the Reaction of Lysozyme” (Warshel and Levitt, 1976). These techniques initiated what, today, is known as the “QM/MM” approach, which combines quantum mechanics with molecular mechanical modeling and is widely used to understand enzyme reactions. The original work at Harvard involved calculating the vibronic spectra of retinal and related molecules. Retinal, of course, is the chromophore in the light-driven proton pump protein, bacteriorhodopsin, and this work illustrates nicely the convergence of broad goals in structural biology and computational chemistry. At around the same time as the pioneering QM/MM polyene calculations, efforts were being made to obtain the first high-resolution structure of a

Photo credit: Bengt Nyman

Martin Karplus, the former post-doc mentor of Jeremy C. Smith and Ph.D. advisor of Hong Guo

membrane protein, using none other than bacteriorhodopsin itself.
QM/MM was one of many creative ideas in biomolecular modeling, and simulation from the three laureates in the 1960s and 1970s seeded much of what is possible today. However, although important, QM/MM is only one area of activity of the three winners, and the 2013 Nobel prize is therefore seen by many also as recognition of the numerous other critical contributions of the three as well as recognition of the field of biomolecular simulation as a whole. In large part, the conceptual contribution of biomolecular simulation relates to dynamics. In a CECAM workshop at Orsay in 1976, calculations were performed by Andrew McCammon, leading to the first publication with Bruce Gelin and Martin Karplus of a molecular dynamics (MD) simulation of a protein (McCammon et al., 1977). These CECAM workshops were opportunities for very fertile discussion and exchange among scientists, and it is clear that a number of people at the time contributed to the ideas that led to ''molecular dynamics'' simulations of biological macromolecules. One name that particularly comes to mind is Aneesur Rahman, who had been the first to carry out MD simulations of liquids using realistic models (Rahman, 1964). The subject of the 1976 calculation was the small protein BPTI (Figure 1A), simulated in vacuum for a fleeting 9 ps. Although crude and short by modern standards, this simulation arguably changed mindsets, ushering in the era of the dynamic protein. One of the major conclusions was that the internal motion of the protein is fluid-like at room temperature, and much subsequent research has concentrated on the comparison between this fluid-like physiological state and the glass-like state of proteins at low temperatures. Even to this day, the mere suggestion that proteins might display any fluid- or liquidlike dynamics on such a short timescale and lengthscale provokes the ire of some crystallographers.
However, MD suffers from statistical convergence problems and force field errors, and, in years ensuing from the first simulation, its use in structure prediction was found to be equivocal. Levitt himself referred to the use of molecular mechanics in structure refinement of homology models as ''the central embarrassment of molecular mechanics, namely that energy minimization or molecular dynamics generally leads to a model that is less like the experimental structure'' (Koehl and Levitt, 1999). Many of the calculations performed were, and often are, wrong, inconsistent, and biased and disagree with experiment. Such shortcomings were assailed by solid, dependable structuralists. ''It's all rubbish!'' was the opinion of biomolecular modeling and simulation expressed in the 1990s to one of the present authors by the director of a prestigious experimental structural biology laboratory. Although clearly rather a generalization, this opinion was perhaps forgivable, given that modeling papers had just been published on the critic's own favorite system in which the active site structure had been completely massacred. To this day, harsh opinions about the field are still encountered, although perhaps to a lesser extent. And certainly, all three of the winners have had to endure their share of heavy professional criticism from different segments of the scientific community over the years.
One problem is that a lot can go wrong in an MD simulation of a biomolecular system, and authors publishing the results can end up looking like chumps. For a start, the ''model system,'' i.e., the atoms included in the calculation, can be incomplete; the experimental structures from which simulations started can be too inaccurate, or can be missing bits. Moreover, the environment, i.e., the solvent, including the water molecules and counterions must be represented reasonably well, even if some of this information is not known from experiments. Furthermore, the interaction potential (or ''force field'') used in most simulations is an empirical compromise that is subject to several approximations. Finally, there is often not enough computing power to exhaustively sample what one is trying to look at, and simulators have been all too often tempted to read significance into isolated anecdotal events.
Even this year's winners have not been immune to simulation gremlins. The Warshel and Levitt study folding BPTI (Levitt and Warshel, 1975), was later found to use overly-permissive criteria for success; a structure superficially resembling that of native BPTI was found from a sequence containing only alanines and glycines (Hagler and Honig, 1978). Levitt's early papers did not Figure 1. Biomolecular Simulation Systems in the 1970s and Now (A) Bovine pancreatic trypsin inhibitor: the subject of the first published MD simulation of a protein (McCammon et al., 1977). (B) Modern-day multimillion-atom simulation model of lignocellulosic biomass with cellulose (green), lignin (brown), and hemicellulose (green strands). Structure explicitly include electrostatic interactions, because they were too expensive to compute. His paper on the simplicity of the prediction of stability and activity of a protein core (Lee and Levitt, 1991) was later criticized; comparable, if not better, agreement with the experimental data was reached using much simpler models based on straightforward structural considerations, which do not even require calculations on a computer (van Gunsteren and Mark, 1992). Exacerbating this type of problem was, and is, the public in-fighting between experts about which approach is best and the 1970s opinions of some theoretical chemistry purists that simulation is a cop-out, because we're not bright enough to figure out an appropriate analytical theory. The field of biomolecular simulations has been, and continues to be, animated by numerous debates and controversies regarding the relative value of different approximations and the significance of various approaches. Computations are an ''artifact'' in the true sense of the term—they are the product of human craft—so there is an unavoidable element of subjectivity in judging them. Getting the ''right'' answer is nice, but it's not enough; one must get it for the right reason, most theoreticians would argue (and argue they sure do!). Perhaps, then, we can understand why it took the Nobel committee 40 years to recognize the field!
The 2013 prize recognizes the sustained, profound effect that computational modeling and simulation has had on structural biology. Harnessing statistical mechanics to connect with macroscopic experiments, simulations have gone much further than simply describing internal motions. Indeed, these models provide a formal link between microscopic interactions and thermodynamics. Using computer ''alchemy'' has made it possible to calculate differences in free energies, entropies, and enthalpies on changing a ligand binding to a protein or on mutating an active site; these methods—pioneered by Arieh Warshel, Andrew McCammon, and William Jorgensen in the early 1980s—have been used in the initial stages of the design of drugs currently on the market. There is real promise—with improved force fields and increased computational power—that free energy calculations will play an increasingly important role in the design of drugs in the long term. Simulations can be used to suggest

novel mechanisms or hypotheses about complex processes. Another of the wonderful features of MD is that one can calculate so many different things from a single simulation. For example, because of the weak coupling between experimental radiation probes (X-rays, neutrons, microwaves, etc.) and molecular systems, one doesn't have to explicitly include the probes in the simulation itself. That means that one can calculate, using correlation functions, many different scattering and spectroscopic quantities from a single simulation. Simulations therefore play a role in unifying different experimental observations in a single self-consistent physical model. Methodologies improving simulation accuracy and speed have proliferated. Conformational sampling, the difficulty of which increases exponentially with chain length, provides grist for the theoretician's mill. Techniques such as simulated annealing (in the 1980s) and parallel tempering and adaptive biasing (nowadays) were adopted. Furthermore, the massive increase in computer power since the 1970s and the development of a new generation of highly performing simulation programs such as NAMD (Phillips et al., 2005) have enabled the useful atomic-detail simulation of large proteins and protein complexes, protein: DNA interactions, membranes, receptors, and ion channels. The outer MD limits, which were a few picoseconds for ~100 atoms in 1975, are now about one microsecond for 100 million atoms on a highlyparallel supercomputer (Figure 1B), and when the exascale of computing power is reached, we will, in principle, have the capacity to simulate a whole living cell at atomic detail. Work will also be performed sitting on the Cloud. The special purposebuilt Anton supercomputer (Shaw et al., 2009) has extended MD capabilities to a millisecond, and thus a further raft of atomic detail biological phenomena moves into view. In another form of multiscale, coarse-graining potentials allow further spatiotemporal extension, and feelers are being extended to systems biology tools such as metabolic network and cell-compartment simulations.

A profound mechanistic understanding of biomolecular systems will be recognized by our ability to make quantitatively accurate and reliable predictions of structure, dynamics, and function from computational models. While simplified "toy" models and back-of-the-envelope theories have played and continue to play an important role in formulating new concepts or elaborating new strategies, there is an increasing need for the "virtual reality" provided by simulations to quantitatively match, with some reasonable accuracy, what can happen in the real world. Thus, even if the simulations are not perfect, we would like to be sure that the "correct" answer falls reliably and predictably within some interval around the computational result. Achieving such reliability is critically important for consolidating the usefulness of molecular simulation in the biomedical sciences. Confidence that simulations provide true, genuine information about the system under study has important implications. For example, when the result of a computation does not match some experimental measurement, then one should be able to conclude that it is not the calculation but some underlying hypothesis about the system that is wrong. This situation is similar to the case in which two types of experiments, e.g., solution NMR and X-ray crystallography, appear to disagree with each other. In this case, one does not immediately conclude that one of them is "wrong," but rather that the structure in solution must be different than that in the crystalline form. This becomes possible when one knows that the computation, while not perfect, has systematic reliability in accomplishing a specific task. Confidence in the general correctness of simulations does exist for some types of calculations for which there have been extensive previous experience and validation. In those cases, the results of computer simulations can already be used to unequivocally confirm or refute specific hypotheses that resist other modes of investigation.

But the field of simulations is still rough around the edges, a work in progress. Simulation inaccuracies have dogged for decades the relationship between simulation and experiment in structural biology. As a result, the field has been plagued by a distrust of predictions. Whereas an elegantly constructed theory in physics often triggers interest prior to experimental testing, wariness of theory is prevalent in biology. Evolution away from this situation has been a very slow process. As noted by Karplus in his autobiographical review (Karplus, 2006), if a theory agrees with experiment, it is not interesting because the result is already known, whereas if one is making a prediction, then it is not publishable because there is no experimental evidence that the prediction is correct. The mindset that must be adopted to achieve systematic reliability, so that prediction can stand on its own two feet, is akin to sculpture or engineering, requiring systematic efforts at chipping away, cleaning, and polishing. We must improve force fields, establish standardized best practices in simulation methodology and free energy computations, develop effective sampling strategies, etc. Perhaps, though, the singular ability of numerical simulation to furnish a firm energetic and thermodynamic foundation for the formation and functional use of three-dimensional structure meant that it was inevitable that this field would slowly but surely take a hold in molecular biophysics. At any rate, there's no turning back. Computations are at the forefront of modern-day scientific planning, and simulation is now firmly established as the third pillar of science, linking experiment to theory for complex systems resisting the back of an envelope calculations. For all their infuriating aspects, maybe accurate computer simulations are indeed the only way to unlock a deep understanding of how a biological system works.

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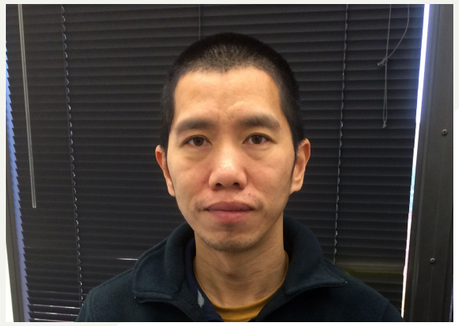
How does a Physicist Survive in a Biology Department?

Tongye Shen is an Associate 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 for 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 intramolecularly 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?

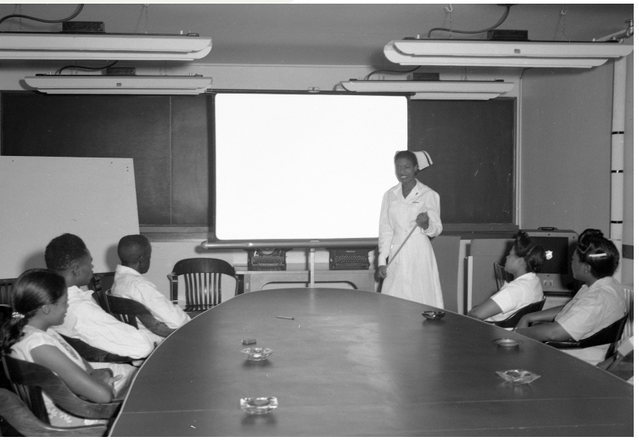
Shen: I like analytical models, probably because my first study area was the quantum mechanics of the excitation of heavy elements. For biological systems, analytical models can be tough for many reasons and I don't particularly want to force it. I focus on the physical results and often have to settle 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 our Administrative Assistants. Julia Cooper was CMB's first admin from 2006 to 2013. She worked at ORNL for nearly four decades since the 1960s and we found it interesting to hear her thoughts on life at the lab in earlier times.

Julia Cooper

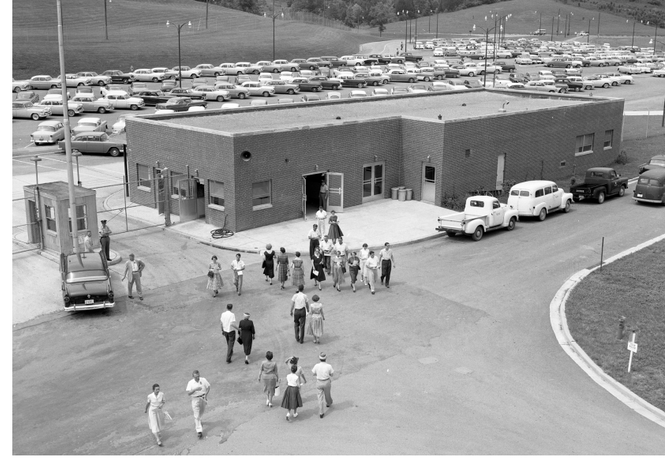
Past years at ORNL were very different from the present. Union Carbide had the contract from the late 1940s until 1984. Other contractors before UT-Battelle were Lockheed Martin and Martin Marietta.
Before September 2001, Bethel Valley Road was open to all cars without restriction and there were no guard 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 to be backed into the angled parking space – no pulling forward into it.



Nurses sitting around a table with starched white uniforms

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 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 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!



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

Bethel valley before ORNL

Welcome to the Real World

UNDERGRADS IN CMB

CMB has had dozens of more-or-less ephemeral undergraduate researchers working together with the graduated researchers. Some seem to visit us for a few hours then go AWOL, whereas other form working relationships with us that last years. We asked them for their views on working in research.

Why do you like science?

Kate: Science is amazing! It's the study of the world and how things work, put simply. How could that not be interesting? Plus, I really like to wear lab goggles. I chose a scientific career path so I don't have to explain that to people.

Brian: My entire life I've wondered how and why things are the way they are. Science either provides the answers for these questions or enables me to find the answers myself.

Madison: I find comfort in the objectivity of science and its perpetual relevance in the evolution of literally everything.

Jordan: I love how science ties into the real world and the challenge it presents when trying to understand the unknowns. Additionally, I like how it relates to bodily functions and how it can create cures for diseases.

Megan: Through science I can learn about the principles underlying everyday phenomena and uncovering those principles is always fascinating.

After all those years of study-study-study, what does it feel like to be doing real research?

Kate: It's really fun! Except sometimes it makes me cry.

Brian: It feels like the light at the end of the tunnel. It's completely refreshing to be applying some of the knowledge I spent so much time and effort gaining.

Madison: There's more pressure to become independent, along with the daunting realization that you have to rely on everything you've ever learned ever.

Jordan: It feels like all those years of studying finally are paying off. It is rewarding to be able to apply my knowledge to certain problems presented in science and having the potential to help solve some of those problems.

Megan: It's nice to be able to apply the concepts I've been studying in my classes. Using those concepts also makes it easier to better understand them.

Do taking exams and writing essays etc really prepare you for research?

Kate: Exam preparation helps you understand what you don't know. The skills for pursuing a better understanding of coursework are essential to doing research well. But caffeine prepares you better.

Brian: I wouldn't say exams prepare you for research because all of the information you need is at your fingertips. Some papers have helped because they included analytical and explanatory sections. They also help acclimate you to documenting your progress, which I consider important to any research process.

Caption placeholder

Madison: Research allows creative license to learn more about and explore a desired field, but the knowledge gained from extensive exam preparation and papers become necessary for a successful foundation in the pursuance of any science.

Jordan: I do not believe that taking exams truly helped me in preparing me for research because exams are so much pressure and stress. I do think that some of my scientific essays assisted me in my preparation for research.

Megan: Taking exams and writing essays are both necessary for forming a foundational knowledge of the principles underlying research. Additionally, they help develop necessary problem solving and communication skills. They provide a good foundation to start research put they don't completely prepare you.

CMB is computational. What's your view of the usefulness of computational science?

Kate: The usefulness of computational science correlates directly to its use in computational science and, strangely, donuts in the breakroom.

Brian: It's completely necessary for scientific analysis and research. Unless you'd like to do all of that math by hand.

Madison: Computational science is an unparalleled method of research because the complexity of mathematical algorithms running simulations are not limited by the less efficient analytical approaches of man.

Jordan: I cannot believe that a computer is capable of such scientific analysis. Computational science makes research more enjoyable and easier to understand because most of the leg work is done for you.

Megan: Computational science is incredibly useful for processing and understanding large amounts of data. It can overcome some of the limitations of in vitro or in vivo methods and can cut the costs associated with some areas of research like the drug design process.

What are your plans for the future? Will they include research?

Kate: Plan A: I'll probably pursue my master's degree and then specialize in medicine or pharmaceuticals. Ideally, I'll try going the route of MD-PhD, though those programs are very competitive. Plan B: Vacationing in Switzerland indefinitely (I'm still working out the logistics...)

Brian: I'm applying to medical schools soon so I hope to attend one next year. I'm sure at some point in my future I'll do research whether it's medical in nature or otherwise.

Madison: After watching the TV show Scrubs, I was 100% reaching toward medical school. However, research has given me a new perspective on different paths I could take, so I am currently at 87%.

Jordan: My plans for the future are to apply to medical school. I'm sure one day I will be able to apply some of the knowledge I have gained during undergraduate research to my future medical research or any other scientific career path I decide to take.

Megan: I hope to attend medical school after I complete my undergraduate degree. I do plan on continuing research in some form as a doctor whether it be clinical research or pursuing a dual MD/PhD program.

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 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.

Former CMB post-doc Liang Hong in a discussion with the then visiting Ph.D. student Mai Zahran from Jeremy's lab in the University Heidelberg, 2011. Liang is now a professor at Shanghai Jiaotong University and Mai a professor at New York City College of Technology.

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 was 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 . (Ed. note: Actually, they did play and Germany won with 1:0)

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.

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

10 Questions for a Biophysicist: Jeremy Smith

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

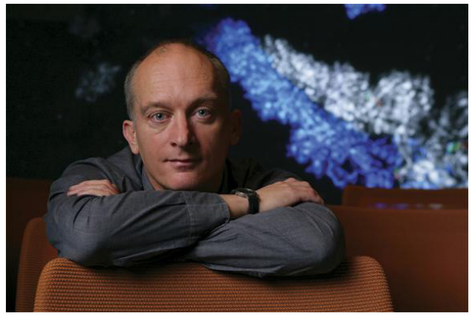
In 2006, Dr. Smith came to Oak Ridge National Laboratory (ORNL). Since then, he has led a wide-ranging spectrum of projects focusing on everything from biofuels to drug discovery. He recently gave us the download on his many projects.

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



Dr Jeremy Smith | Photo Courtesy of ORNL

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 bioenergy 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.

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Jordan Finley
Undergraduate Research Assistant since 2016

Megan Landon
Undergraduate Research Assistant since 2015

Madison Leonard
Undergraduate Research Assistant since 2016

Brian Simon
Summer Intern 2016

Graduate Students

Rupesh Agarwal
Graduate Student since 2014

Sarah Cooper
Graduate Student since 2015

Willy Evangelista Falcon
Graduate Student since 2011

Adam Green
Graduate Student since 2014

John Ossyra
Graduate Student since 2013

Jing Zhou
Graduate Student since 2011

Postdoctoral Fellows

Mayank Aggarwal
Postdoctoral Fellow since 2014

John Eblen
Postdoctoral Fellow since 2011

Mikolai Fajer
Postdoctoral Fellow since 2015

Xiaohu Hu
Postdoctoral Fellow since 2016

Quentin Johnson
Postdoctoral Fellow since 2015

Ryan C. Johnston
Postdoctoral Fellow since 2015

Hector Velazquez
Postdoctoral Fellow since 2014

Administration

Lora Davis
Administrative Assistant since 2015

System Administration

Michael D. Galloway
System Administrator since 8/2006

Nathan T. Grodowitz
System Administrator since 2014

David G. Hester
System Administrator since 2015

Alumni

Anita Alton
Administrative Assistant
2013 – 2015

Derek Cashman
Postdoctoral Fellow
2011 – 2013

Janamejaya Chowdhary
Postdoctoral Fellow
2013 – 2016

Barbara Collignon
Postdoctoral Fellow
2008 – 2011

Julia Cooper
Administrative Assistant
2006 – 2013

Sally Ellingson
Graduate Student
2009 – 2014

Pavan Ghatty
Postdoctoral Fellow
2007 – 2013

Dennis C. Glass
Graduate Student
2009 – 2012

Hao-Bo Guo
Postdoctoral Fellow
2007 – 2014

Jason Harris
Graduate Student
2009 – 2014

Liang Hong
Postdoctoral Fellow
2010 – 2014

Benjamin Lindner
Graduate Student
2007 – 2012
Postdoctoral Fellow
2012 – 2014

Krishnan Marimuthu
Postdoctoral Fellow
2007 – 2010

Sylvia E. McLain
SNS Clifford G. Shull Research Fellow and Group Leader
2006 – 2008

Yinglong Miao
Postdoctoral Fellow
2009 – 2012

Dan Mihailescu
Visiting Researcher in 2006

Kei Moritsugu
Postdoctoral Fellow
2007 – 2008

Saharay Moumita
Postdoctoral Fellow
2007 – 2010

Ricky Nellas
Postdoctoral Fellow
2010 – 2013

Xianghong Qi
Postdoctoral Fellow
2011 – 2014

Demian Riccardi
Postdoctoral Fellow
2011 – 2014

Amandeep Sangha
Postdoctoral Fellow
2010 – 2014

Nikolai Smolin
Postdoctoral Fellow
2008 – 2011

Goundla Srinivas
Postdoctoral Fellow
2009 – 2011

Jianhui Tian
Postdoctoral Fellow
2013 – 2016

Christopher Topham
Visiting Researcher in 2006

Derya Vural
Postdoctoral Fellow
2014 – 2016

Jiancong Xu
Postdoctoral Fellow
2007 – 2009

Quin Xu
Postdoctoral Fellow
2010 – 2012

Zheng Yi
Postdoctoral Fellow
2009 – 2012

Past and Current Funding

Starting 2006

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Computational Methods for Molecular Biophysics
Funding Period: 2006 – 2009
Jeremy C. Smith: PI

Starting 2007

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: Bioenergy Science Center
Funding Period: 2007 – 2012
Jeremy C. Smith: Task Leader

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: LAB 07-12 Dynamic Visualization of Lignocellulose Degradation by Integration of Neutron Scattering Imaging and Computer Simulation
Funding Period: 2007 – 2010
Jeremy C. Smith: Co-PI

Starting 2008

U.S. Department of Energy (DOE) – EpsCOR Implementation Award (+ 50% Univ. Tennessee matching)
Title: DE-FG02-08ER46528 Neutron Scattering Research Network for EPSCoR States
Funding Period: 2008 – 2011
Jeremy C. Smith: Co-PI

National Science Foundation (NSF)
Title: NIMBioS – Center for Synthesis of Mathematics and Biology
Funding Period: 2008 – 2012
Jeremy C. Smith: Co-PI

National Science Foundation (NSF) – Integrative Graduate Education and Research Traineeship Program (IGERT)
Title: SCALE-IT (Scalable Computing and Leading Edge Innovative Technologies) for Biology
Funding Period: 2008 – 2013
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: ORNL Scientific Focus Area Program: Biogeochemical and Molecular Mechanisms Controlling Contaminant Transformation in the Environment
Funding Period: 2008 – 2012
Jerry Parks: Co-PI

Starting 2009

Deutsche Forschungegemeinschaft (DFG) – Excellence Initiative Dritte Säule: Internationale Zusammenarbeit
Title: International cooperation
Funding Period: 2009 – 2013
Jeremy C. Smith: PI

National Institute of Health (NIH)– PEER
Title: Program for Excellence and Equity in Research
Funding Period: 01/2009 – 01/2014
Jeremy C. Smith: Senior Personnel

National Science Foundation (NSF)
Title: Integration of Computer Simulation and Neutron Scattering in the Characterization of Protein Dynamics
Funding Period: 08/2009 – 07/2012
Jeremy C. Smith: PI
Hong Guo: Co-PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: Computer Purchase Grant
Funding Period: 09/2009
Jeremy C. Smith: PI

U.S. Department of Energy (DOE) – Advanced Scientific Computing Research (ASCR)
Title: LAB 08-19 Software Development Tools for Improved Ease-of-Use of Petascale Systems
Funding Period: 2009 – 2012
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – OBER/ ASCR
Title: Multiscale Mathematics for the Simulation of Complex Biological Systems
Funding Period: 2009 – 2013
Jeremy C. Smith: PI

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: A Systems Biology Approach to Study Metabolic and Energetic Interdependencies in the *Ignicoccus-Nanoarchaeum* System
Funding Period: 2009 – 2011
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Catalytic Conversion of Lignin Feedstocks for Bioenergy Applications
Funding Period: 2009 – 2011
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Neutron scattering methodologies for the study of protein dynamics
Funding Period: 2009 – 2012
Jeremy C. Smith: PI

U.S. Department of Energy (DOE) – Scientific Discovery through Advanced Computing (SciDAC)/Biological and Environmental Research (BER) Award
Title: Multiscale Mathematics for the Simulation of Complex Biological Systems and Application to Lignocellulosic Biomass
Funding Period: 2009 – 2012
Jeremy C. Smith: PI
Xiaolin Cheng: Co-PI

Starting 2010

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: ORNL Science Focus Area "Biofuels"
Funding Period: 2010 – 2013
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER) Science Focus Area (Renewal)
Title: Biogeochemical and Molecular Mechanisms Controlling Contaminant Transformation in the Environment
Funding Period: 2010 – 2015
Jeremy C. Smith: Co-PI and Task leader

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Photocatalytic Approach to the Degradation of pf Renewable Lignin-Cellulose Feedstock for Hydrogen Production
Funding Period: 2010 – 2011
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE)

National Institute of Health (NIH)
Title: Georgetown-Howard Universities Center for Clinical and Translational Science
Funding Period: 2010 – 2015
Jeremy C. Smith: Senior Personnel

National Institute of Health (NIH) – U54
Title: Novel Translational Methodologies (NTM)
Funding Period: 2010 – 2012
Jerome Baudry: Task Leader
Jeremy C. Smith: Task Leader

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: Molecular Mechanisms of Bacterial Mercury Transformation
Funding Period: 2010 – 2013
Jeremy C. Smith: PI
Hong Guo: Co-PI

U.S. Department of Energy (DOE) – Director's Research and Development (R&D) Fund
Title: Incorporating molecular-scale mechanisms stabilizing soil organic carbon into terrestrial carbon cycle models
Funding Period: 2011 – 2013
Loukas Petridis: Co-PI

Starting 2012

U.S. Department of Energy (DOE) – EpsCOR Implementation Award + 50% Univ. Tennessee matching
Title: DE-FG02-08ER46528 Neutron Scattering Research Network for EPSCoR States (Renewal)
Funding Period: 2012 – 2015
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Office of Science
U.S. Department of Energy (DOE) – Genomics Biological and Environmental Research
Title: Dynamic Visualization of Lignocellulose Degradation by Integration of Neutron Scattering Imaging and Computer Simulation
Funding Period: 03/2012 – 03/2015
Loukas Petridis: Senior Personnel

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Joining Neutron Scattering and Simulations towards Improved Lipid Modelling
Funding Period: 2012 – 2013
Xiaolin Cheng: PI
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: High-Performace Computer Simulation Study of the Mechanism of Nerve Agent Degradation by an Enzymatic Bioscavenger
Funding Period: 2012 – 2013
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: Combining neutrons with high-performance computing to produce value-added products from lignocellulosic biomass
Funding Period: 2012 – 2013
Jerry Parks: Co-PI

ORNL – Laboratory Directed Research & Development (LDRD)
Title: High-performance computer simulation of nerve agent degradation by a catalytic bioscavenger
Funding Period: 2012 – 2014
Jerry Parks: PI

American Chemical Society Petroleum Research Fund (ACS-PRF)
Title: Organic Solvent-Specific Gating Motions of an Extremophilic Lipase.
Funding Period: 2012 – 2014
Tongye Shen: PI

Starting 2013

National Science Foundation (NSF)
Title: NIMBioS – Center for Sythesis of Mathematics and Biology (Renewal)
Funding Period: 10/2013 – 10/2018
Jeremy C. Smith: Senior Personnel

National Science Foundation (NSF)
Title: SI2-SSI: A Productive and Accessible Development Workbench for HPC Applications Using the Elcipse Parallel Tools Platform
Funding Period: 2013 – 2014
Jeremy C. Smith: Subcontractee from Univ. Illinois

INTEL Corporation
Title: Porting and Optimization of the General-Purpose Molecular Dynamics Code GROMACS on Next-Generation Intel-Based Computers
Funding Period: 2013 – 2014
Jeremy C. Smith: PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: ORNL Science Focus Area "Biofuels" (Renewal)
Funding Period: 2013 – 2017
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: Bioenergy Science Center (Renewal)
Funding Period: 2013 – 2017
Jeremy C. Smith: Task Leader

U.S. Department of Energy (DOE) National Nuclear Security Administration (NNSA)
Title: Toward rational design of nerve agent bioscavengers using QM/MM simulations
Funding Period: 2013 – 2014
Jerry Parks: PI

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: ORNL Scientific Focus Area Program: Biogeochemical and Molecular Mechanisms Controlling Contaminant Transformation in the Environment
Funding Period: 2013 – 2015
Jerry Parks: Co-PI

U.S. Department of Energy (DOE) – Director's Research and Development (R&D) Fund
Title: Probing the Structure-Function Relationship of Protein Kinase A
Funding Period: 2013 – 2015
Loukas Petridis: Co-PI

U.S. Department of Energy (DOE) – Director's Research and Development (R&D) Fund
Title: Structural Biology of Metabolic and Signaling Pathways in Plants
Funding Period: 2013 – 2015
Loukas Petridis: Co-PI
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: Bioenergy Science Center
Funding Period: 2013 – 2015
Jerry Parks: Co-PI

ORNL-UT Joint Directed Research and Development (JDRD)
Title: Coarse-Grained Modeling of the Conformational Dynamics of Signaling Protein Complex.
Funding Period: 2013 – 2014
Tongye Shen: PI

Starting 2014

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Understanding the principles of small peptide binding and inhibition of amyloid fibril growth in Alzheimer's, amyloid kidney disease and other amyloidosis using high-performance computational docking and molecular dynamics
Funding Period: 01/2014 – 12/2014
Xiaolin Cheng: Co-PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: Active Biosystem Imaging
Funding Period: 2014 – 2017
Jeremy C. Smith: Co-PI

National Institute of Health (NIH) – National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Title: Regulation and Function of FGF23
Funding Period: 2014 – 2015
Jeremy C. Smith: Co-PI

National Institute of Health (NIH) – National Institute of Allergy and Infectious Diseases (NIAID)
Title: Design of Accelerated Acetylcholinesterase Reactivators through Mechanistic Neutron Diffraction Studies
Funding Period: 07/2014 – 06/2019
Xiaolin Cheng: Co-Investigator

U.S. Department of Energy (DOE) – Laboratory Directed Research & Development (LDRD)
Title: Functional domains in model membranes and protocells probed with high performance simulation and neutron scattering
Funding Period: 2014 – 2017
Xiaolin Cheng: PI
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Biological and Environmental Research (BER)
Title: Adaptive Biosystems Imaging
Funding Period: 2014 – 2016
Jeremy C. Smith: Co-PI
Xiaolin Cheng: Co-Investigator

U.S. Department of Energy (DOE) – Basic Energy Sciences (BES)
Title: Center for Lignocellulose Structure and Formation
Funding Period: 2014 – 2018
Loukas Petridis: Senior Personnel

National Institute of Health (NIH) – National Institute of Allergy and Infectious Diseases (NIAID)
Title: Transport across two membranes by AcrAB-TolC
Funding Period: 2014 – 2019
Jerry Parks: Co-PI
Jeremy C. Smith: Co-PI

National Institute of Health (NIH)
Title: Transport Across Two Membranes by ArcAB-TolC
Funding Period: 2014 – 2019
Jeremy C. Smith: Co-PI
Jerome Baudry: Co-PI
Jerry Parks: Co-PI

INTEL Corporation
Title: Porting and Optimization of the General-Purpose Molecular Dynamics Code GROMACS on Next-Generation Intel-Based Computers (Renewal)
Funding Period: 2014 – 2015
Jeremy C. Smith: PI

Starting 2015

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: ORNL Science Focus Area "Biofuels" (Renewal)
Funding Period: 2015 – 2017
Jeremy C. Smith: Co-PI

U.S. Department of Energy (DOE) – Office of Biological and Environmental Science (OBER)
Title: Biogeochemical and Molecular Mechanisms Controlling Contaminant Transformation in the Environment (Renewal)
Funding Period: 2015 – 2018
Jerry Parks: Task Leader
Jeremy C. Smith: Co-PI and Task Leader

U.S. Department of Agriculture (USDA)
Title: Zinkicide A Nanotherapeutic for HLB
Funding Period: 2015 – present
Loukas Petridis: Co-PI

U.S. Department of Energy – Laboratory Directed Research & Development (LDRD)
Title: Overcoming Antibiotic Resistance: Neutron Crystallographic and Quantum Chemical Studies of a Beta-Lactamase Enzyme
Funding Period: 2015 – 2017
Jerry Parks: Co-PI

Starting 2016

INTEL Corporation
Title: Porting and Optimization of the General-Purpose Molecular Dynamics Code GROMACS on Next-Generation Intel-Based Computers (Renewal)
Funding Period: 2016 – 2017
Jeremy C. Smith: PI

U.S. Department of Energy (DOE) – Subsurface Biogeochemical Research (SBR)
Title: ORNL Scientific Focus Area Program: Biogeochemical Transformations at Critical Interfaces
Funding Period: 2016 – 2018
Jerry Parks: Task Leader

Supercomputer Allocations

2011 NCCS Director Discretionary Application: High Performance Computing for Rational Drug Discovery and Design, Supercomputing molecular discovery of prostate cancer molecular effectors

Organization: National Center for Computational Sciences (NCCS)
Allocation: 5.8 million CPU-hours
Platform: Jaguar supercomputer
PI: Jerome Baudry

2011 INCITE Award: Cellulosic Ethanol: Simulation of Multicomponent Biomass System

Organization: ORNL Leadership Computing Facility (OLCF)
Allocation: 30 million core-hours
Platform: Jaguar supercomputer
PI: Jeremy C. Smith

2012 NCCS Director Discretionary Application: Dynamics of the Chemotaxis Receptor

Organization: National Center for Computational Sciences (NCCS)
Allocation: 5 million core-hours
Platform: Titan supercomputer
PI: Jerome Baudry

2012 NRBSC/PSC award for ANTON supercomputer: Multi-microseconds molecular dynamics simulations of the signaling domain of the bacterial chemotaxis receptor

Organization: National Resource for Biomedical Supercomputing (NRBSC)/Pittsburgh Supercomputing Center (PSC)
Allocation: 50 thousand node-hours
Platform: ANTON
PI: Jerome Baudry

2012 Amazon Cloud Computing Award: Virtual High-Throughput Docking using Cloud Infrastructure

Organization: Amazon.com, Inc.
Allocation: 7500 CPU-hours
Platform: EC2 cloud computers
PI: Jerome Baudry

2012 INCITE Award: Cellulosic Ethanol: Simulation of Multicomponent Biomass Systems

Organization: ORNL Leadership Computing Facility (OLCF)
Allocation: 23 million core-hours
Platform: Jaguar supercomputer
PI: Jeremy C. Smith

2012 XSEDE award: Atomistic Simulations on Nuclear Receptor Complex and on the Organic Solvent-Dependent Motions of an Extremophilic Lipase

Organization: National Science Foundation (NSF) XSEDE Program
Allocation: 2 million core-hours
Platform: Kraken supercomputer
PI: Tongye Shen

2013 NICS award: High-throughput Docking in Undergraduate Curriculum

Organization: National Institute for Supercomputing Sciences (NICS)
Allocation: 70 thousand CPU-hours
Platform: Kraken supercomputer
Task Leader: Jerome Baudry

2013 NCCS Director Discretionary Application: Massive screening for drug discovery and toxicity prediction

Organization: National Center for Computational Sciences (NCCS)
Allocation: 5 million core-hours
Platform: Titan supercomputer
PI: Jerome Baudry

2013 INCITE Award: Cellulosic Ethanol: Simulation of Multicomponent Biomass Systems

Organization: ORNL Leadership Computing Facility (OLCF)
Allocation: 78 million core-hours
Platform: Titan supercomputer
PI: Jeremy C. Smith

2013 ASCR Leadership Computing Challenge (ALCC) award: Simulating the Structure and Dynamics of Protein Kinase A

Organization: Advanced Scientific Computing Research (ASCR), DOE
Allocation: 4 million processor-hours
Platform: NERSC supercomputer
Task Leader: Loukas Petrides

2014 ASCR Leadership Computing Challenge (ALCC) award: Molecular Simulation in Bioenergy

Organization: Advanced Scientific Computing Research (ASCR), DOE
Allocation: 59 million core-hours
Platform: Titan supercomputer
Task Leader: Jeremy C. Smith

2014 ANTON Computing Award: Investigation of long time protein dynamics under physiological conditions

Organization: Pittsburgh Supercomputing Center and D. E. Shaw Research
Allocation: 100 thousand node-hours
Platform: ANTON supercomputer
PI: Xiaolin Cheng
Co-PI: Jeremy C. Smith

2014 NCCS Director Discretionary Application: Drugging the undrugable

Organization: National Center for Computational Sciences (NCCS)
Allocation: 10 million core-hours
Platform: Titan supercomputer
PI: Jerome Baudry

2014 XSEDE award: Atomistic Simulations of Proteins on a Lipid Droplet Surface

Organization: National Science Foundation (NSF) XSEDE Program
Allocation: 322,215 core-hours
Platform: Texas Advanced Computing Center's STAMPEDE
PI: Tongye Shen

2016 INCITE award: A generic plant cell wall and its deconstruction for bioenergy

Organization: ORNL Leadership Computing Facility (OLCF)
Allocation: 100 million core-hours
Platform: Titan supercomputer
PI: Jeremy C. Smith

2016 Computing Award: Molecular Dynamics Simulations of Protein Dynamics and Lignocellulosic Biomass

Organization: National Energy Research Scientific Computing Center (NERSC)
Allocation: 12 million core-hours
Platform: Edison/Cori supercomputers at NERSC
PI: Jeremy C. Smith

2016 XSEDE award: A High-Throughput Computational Method to Detect Allostery in Biomolecular Complexes

Organization: National Science Foundation (NSF) XSEDE Program
Allocation: 243,484 core-hours
Platform: Texas Advanced Computing Center's STAMPEDE
PI: Tongye Shen

Awards

2009

Julia Cooper

Award title: ORNL Biosciences Divisional Administrative Award
Description: Julia received the ORNL Biosciences Divisional Administrative Award in for her role in the establishment and continued operation of CMB.

2011

Jerome Baudry

Award title: Outstanding Teaching Award for Junior Faculty
Description: 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.

Sally Ellingson

Award title: NSF funded Broader Engagement Grant
Award title: NSF funded Scholarship / ACM student research competition Grace Hopper Celebration
Description: 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.

2012

Chelsea Knotts

Award title: The Torchbearer Award by the University of Tennessee
Description: Chelsea, a former BCMB major and long-term undergrad research student in the Baudry lab, who was also a Haslam Scholar and Lady Vols student athlete, was awarded with the highest student honor conferred by the University of Tennessee: The Torchbearer Award. This award was presented to Chelsea particularly for her outstanding social work in the Knoxville community. She led hundreds of UT students in an effort to end chronic homelessness, particularly in the Fort Sanders neighborhood. She began a running group for homeless men and women, organized a 5K benefit run, and regularly befriends people who are without shelter and social stability.

2013

Jerry Parks and Jeremy C. Smith

Award title: UT/Battelle Award for Scientific Achievement
Award title: ORNL Director's Award for Outstanding Team Achievement
Description: Jerry Parks and Jeremy Smith of CMB are part of the Mercury SFA Team that won both the 2013 UT/Battelle Award for Scientific Achievement and the 2013 ORNL Director's Award for Outstanding Team Achievement.

Jerry and Jeremy in the group photo with ORNL director Tom Mason during the award ceremony for ORNL Director's Award for Outstanding Team Achievement

Sally Ellingson

Award title: The Chemical Computing Group (CCG) Excellence Award for Graduate Students by the American Chemical Society (ACS)
Description: Sally has been awarded for her work in the Baudry lab with the American Chemical Society CCG award by the Computers in Chemistry division of the ACS. The CCG award is given to no more than 10 graduate students nationwide every year to recognize the quality and significance of their research in the general field of computational (bio) chemistry.

Sally Ellingson

Award title: The University of Tennessee Science Alliance Award for Graduate Students
Description: Sally has been awarded for her work in CMB with the Science Alliance Award. The Science Alliance has a mission to expand cooperative ventures in research with the Oak Ridge National Laboratory and recognizes achievements of UTK graduate students.

2014

Xiaohu Hu and Jason Harris

Award title: The University of Tennessee Science Alliance Award for Graduate Students
Description: Xiaohu and Jason were awarded for their research works in CMB with the Science Alliance Award. The Science Alliance has a mission to expand cooperative ventures in research with the Oak Ridge National Laboratory and recognizes achievements of UTK graduate students.

Xiaolin Cheng

Award title: Superb Performance Award by the ORNL Computer Science and Mathematics Division
Description: Xiaolin was presented with this award for his outstanding research work carried out at CMB and ORNL.

Designed and edited by:
Thomas Splettstößer
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Composed and edited by:
Xiaohu Hu, Jeremy C. Smith

Contact

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