Report of the Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics: Second Round

ISBN
978-0-309-22019-4

22 pages
8 1/2 x 11
2011

Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics; National Research Council

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Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics, Second Round

Board on Life Sciences

Division on Earth and Life Studies

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Washington, D.C.
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In Memory of

Joel R. Stiles

Whose leadership helped established this program

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National Research Council

September 16, 2011

Jodi Swidzinski Hezky, Ph.D.
D. E. Shaw Research
120 West 45th Street, 39th Floor
New York, NY 10036

Dear Dr. Hezky:

This letter describes the work and transmits the final report of the Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics, Second Round.

The committee evaluated submissions received in response to a Request for Proposals (RFP) for Biomolecular Simulation Time on Anton, a supercomputer specially designed and built by D.E. Shaw Research (DESRES) that allows for dramatically increased molecular dynamics simulations compared to other currently available resources. Over the past year (October 1, 2010 – September 30, 2011), DESRES has made available to the non-commercial research community 3,000,000 node-hours on an Anton system housed at the Pittsburgh Supercomputing Center (PSC), based on the advice of a previous National Research Council committee convened in the fall of 2010.

The success of the program has led DESRES to make the Anton machine housed at PSC available for an additional 3,000,000 node-hours over the 9-months following October 1, 2011 and DESRES has asked the National Research Council to, once again, facilitate the allocation of time to the non-commercial research community. The work of the National Research Council committee to evaluate proposals for time allocations was supported by a contract between D.E. Shaw Research and the National Academy of Sciences and was performed under the auspices of the National Research Council's Board on Life Sciences.

To undertake this task, the National Research Council convened a committee of experts to evaluate the proposals submitted in response to the aforementioned RFP. The committee of 17 was chaired by Dr. Robert L. Jernigan, Director of the Baker Center for Bioinformatics and Biological Sciences and Professor of Biochemistry, Biophysics and Molecular Biology at Iowa State University. The committee members were selected for their expertise in molecular dynamics simulations, as well as their experience in the subject areas represented in the 81 proposals that were considered by the committee. They comprised a cross section of the biomolecular dynamics field in academia, industry and government including an array of both senior and junior investigators. The committee was assisted by two external reviewers,[1] who

[1] The two external reviewers were Dr. Douglas Tobias, University of California, Irvine and Dr. Gerhard Hummer, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Dr. Tobias submitted a proposal as a Principal Investigator for a time allocation on the Anton machine. Dr. Tobias provided the committee with an initial assessment of 8 proposals and provided his feedback to the committee only on those proposals. He took no part in other discussions or deliberations of the committee.

were selected to provide additional expertise in the areas of protein-lipid interactions and channel functions and who provided the committee with an initial assessment of a subset of the proposal submissions.

The goal of the second RFP for Biomolecular Simulation Time on Anton has been to continue to facilitate breakthrough research in the study of biomolecular systems by providing a massively parallel system specially designed for molecular dynamics simulations. These special capabilities allow multi-microsecond to millisecond simulation timescales, which previously had been unobtainable. The program seeks to continue to support research that addresses important and high impact questions demonstrating a clear need for Anton's special capabilities.

The Anton RFP described the three criteria against which the committee was asked to evaluate proposals:

- **Scientific Merit**, including the potential to advance understanding on an important problem or question in the field; potential for breakthrough science resulting in new discoveries and understanding; the impact that successful completion of the proposed research would have on knowledge, methods, and current barriers in the field; and a scientifically and technologically feasible project with clear, well-developed, and appropriate goals, objectives, and approach to proposed studies.

- **Justification for Requested Time Allocation**, including a clear and well-justified need for multi-microsecond simulation timescales and a clear and convincing justification that the length and number of proposed simulation runs and node-hours requested are necessary and sufficient to achieve the scientific objectives.

- **Investigator Qualifications and Past Accomplishments**, including the appropriate experience and training to successfully conduct the proposed studies, evidence of knowledge and prior experience in molecular simulations, and past publications.

Proposals from investigators who had previously received an allocation of time on Anton were required to include brief progress reports. Following guidance provided by DESRES and PSC, the committee did not use these progress reports as primary criteria but drew on them only to supplement its consideration of proposals. As explained in the RFP, staff at PSC conducted an initial assessment of all proposal submissions for completeness to determine whether they were technically feasible for simulation on Anton. A member of the PSC staff was also present as an observer throughout the review committee's discussions to address technical specification that arose.

In the second round of time allocations for Anton, DESRES and PSC will make time available at two levels. In the first level, approximately 15 proposals will receive an allocation of 100,000 node-hours each. The second level will include approximately 30 proposals to receive an allocation of 50,000 node-hours each. The committee was asked to identify proposals that best met the selection criteria defined above for allocations at each of the two levels. The committee was further asked to try to allocate approximately 50% of the time to investigators who did not receive an allocation in the first round. The judgments of the committee are based on which proposals adequately met or exceeded the selection criteria described above and on the estimates of required simulation time provided by the applicants. The committee was also permitted to

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Neither reviewer participated in the final committee discussion and assessment to achieve consensus on the list of proposals that best met the selection criteria.

consider a modified time allocation if it concluded that the proposed research required a greater or lesser number of node-hours than initially requested by an applicant.

Initial reviews of the proposals were provided by the 17 committee members and the two external reviewers. Each proposal was assigned a minimum of two primary reviewers who were asked to evaluate the proposal based on the RFP and guidelines described above. Review assignments were made so that no proposal was evaluated by a reviewer from the applicant's same institution or who had a collaborative relationship with an applicant.

The NRC committee held its 2-day meeting in Washington, D.C. on August 5-6, 2011. On the first day of the meeting, members undertook a detailed discussion of the proposals. The two primary reviewers were asked to summarize their review for the committee, which was followed by discussion of the proposed research. As described in detail above, committee members considered the scientific merit, justification of the requested time and the qualifications of the principal investigator (PI). The discussion aimed at reaching consensus on which proposals best met the selection criteria. The committee divided the proposals into three groups. Group 1 contained proposals that best met or exceeded the selection criteria, Group 2 contained proposals that adequately met the selection criteria, and Group 3 contained proposals that met the selection criteria less well than those in Groups 1 and 2. If consensus could not be reached on an individual proposal on day 1, an additional committee member was assigned to review the proposal in detail for discussion on the second day.

On the second day, committee members first discussed the proposals that were not easily categorized on day 1 and obtained further details from the additional reviewer, or a primary reviewer who had been unavailable on day 1. The committee then considered the slate of proposals as a whole, came to a consensus on the assignment of proposals into the three groups and, in some cases, decided to suggest a modified allocation of time on Anton.

The committee concluded that the proposals listed below best meet the selection criteria set forth in the RFP for Biomolecular Simulation Time on Anton. Detailed comments for each of the 81 proposals are included in Appendix B.

Group 1:
The committee has identified 23 proposals that best met or exceeded the selection criteria. Of these 23 proposals, 5 proposals were selected for a modified allocation (identified below with an *). In numerical order by proposal submission number, these are:

PSCA10006P **Investigating protein folding and dynamics with a highly optimized additive force field**; PI: Alexander MacKerell, University of Maryland, Baltimore *[New user, identified for 50,000 node-hours]**

PSCA10018P **What are the atomistic underpinnings of molecular allostery and signaling?**; PI: David Beratan, Duke University *[New user, identified for 50,000 node-hours]**

PSCA10030P **Recognition of kinesin by microtubule during the stepping process**; PI: Devarajan Thirumalai, University of Maryland, College Park *[New user, identified for 100,000 node-hours]*

PSCA10031P **Mapping slow dynamical regulation of a protein kinase by combining molecular dynamics with NMR data**; PI: Susan Taylor, University of California, San Diego *[New user, identified for 50,000 node-hours]*

PSCA10038P **Continued Exploration of the Human Adenovirus Protease Activation Pathway via Long Timescale Molecular Dynamics Simulations**; PI: Ross Walker, University of California, San Diego *[Returning user, identified for 100,000 node-hours]*

PSCA10039P **Determining the pathway of nascent-protein insertion through the protein-conducting channel and into the membrane**; PI: Klaus Schulten, University of Illinois, Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

PSCA10040P **Assessment of Multi-Microsecond Simulations of Intrinsically Disordered Proteins Using NMR: Applications to PDX1**; PI: Scott Showalter, The Pennsylvania State University *[Returning user, identified for 50,000 node-hours]*

PSCA10042P **Determining Effects of HIV-1 gp41 Membrane-Spanning Domain on the Local Composition of a Mixed Cholesterol/Lipid Bilayer using Microsecond MD Simulation**; PI: Cameron Abrams, Drexel University *[New user, identified for 70,000 node-hours]**

PSCA10043P **Unraveling anomalous subdiffusion in heterogeneous membranes**; PI: Edward Lyman, University of Delaware *[New user, identified for 50,000 node-hours]*

PSCA10061P **The determinants of C-type inactivation and recovery in the KcsA channel**; PI: Benoit Roux, University of Chicago *[Returning user, identified for 100,000 node-hours]*

PSCA10062P **Using microsecond scale dynamics to characterize different classes of allosteric interactions**; PI: J. Andrew McCammon, University of California, San Diego *[Returning user, identified for 100,000 node-hours]*

PSCA10066P **Molecular dynamics simulation of signal transduction in the squid rhodopsin G-protein coupled receptor**; PI: Douglas Tobias, University of California, Irvine *[Returning user, identified for 50,000 node-hours]*

PSCA10067P **Dynamic coupling and fluctuations in protein-protein complexes**; PI: Matthias Buck, Case Western Reserve University *[Returning user, identified for 50,000 node-hours]*

PSCA10074P **Chacterization of the structure and dynamics of a model two-domain protein using multi-microsecond simulations**; PI: Lillian Chong, University of Pittsburgh *[New user, identified for 50,000 node-hours]*

PSCA10076P **Long time MD simulations to study large scale conformational transitions in RNA enzymes**; PI: Darrin York, Rutgers University *[New user, identified for 50,000 node-hours]**

PSCA10081P **Exploring Lipid-Protein Interactions Using Microsecond-scale Molecular Dynamics Simulation**; PI: Toby Allen, University of California, Davis *[Returning user, identified for 100,000 node-hours]*

PSCA10085P **Propagation of conformational changes across a regulated catch-bond protein**; PI: Wendy Thomas, University of Washington *[New user, identified for 75,000 node-hours]*

PSCA10086P **Understanding the origin of high-fidelity co-translational protein targeting: Long-timescale simulations of the Signal Receptor Particle complex**; PI: Thomas Miller, California Institute of Technology *[Returning user, identified for 100,000 node-hours]*

PSCA10088P **Entropy and Allostery in Protein-Ligand Binding via Simulations at the Microsecond Time Scale**; PI: Michael Gilson, University of California San Diego *[New user, identified for 100,000 node-hours]*

PSCA10095P **Long Time Scale Molecular Dynamics Simulation of Protein Folding**; PI: Martin Gruebele, University of Illinois, Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

PSCA10096P **Computational Design and Evaluation of Novel Enzyme Catalysts**; PI: Kendell Houk, University of California, Los Angeles *[Returning user, identified for 50,000 node-hours]**

PSCA10097P **The effects of nonnucleoside inhibitors on the structure and dynamics of HIV wild type reverse transcriptase and drug resistant mutants**; PI: Michael Shirts, University of Virginia *[New user, identified for 50,000 node-hours]*

PSCA10099P **Folding of Ribosomal Signatures and Early tRNAs**; PI: Zaida Luthey-Schulten, University of Illinois, Urbana-Champaign *[New user, identified for 100,000 node-hours]*

Group 2:
The committee has identified 21 proposals that adequately met the selection criteria. Of these 21 proposals, 11 proposals were selected for a modified allocation and are identified below with an *. In numerical order by proposal submission number, these are:

PSCA10007P **Molecular dynamics simulation study of the diffusion fence for PIP2 (phosphotidylinositol 4,5-bisphosphate) in lipid membrane**; PI:Wonpil Im, The University of Kansas *[New user, identified for 50,000 node-hours]**

PSCA10008P **Simulation of the two-step mechanism for kinesin force generation in realistic time scale**: PI: Wonmuk Hwang, Texas A&M University *[Returning user, identified for 100,000 node-hours]*

PSCA10014P **Understanding the role of A-tracts in eukaryotic genome organization and their functions in transcriptional regulation**; PI: George Schatz, Northwestern University *[New user, identified for 45,000 node-hours]*

PSCA10017P **Investigate Hidden Intermediates in Protein Folding**; PI: Shuanghong Huo, Clark University *[New user, identified for 40,000 node-hours]**

PSCA10025P **Influence of ATP and ADP on conformation and dynamics of the nucleotide-binding domain of Hsp70 chaperones**; Harold Scheraga, Cornell University *[New user, identified for 50,000 node-hours]*

PSCA10029P **Exploring the Membrane Selectivity and Toxicity of Antimicrobial Peptides**; Judy Kim, University of California, San Diego *[New user, identified for 60,000 node-hours]*

PSCA10052P **Unraveling the Structure – Dynamics – Function Relationship of Human Histone Deacetylase 8**; Peter Coveney, Yale University *[Returning user, identified for 50,000 node-hours]**

PSCA10056P **Simulation and Analysis of Pressure Perturbation Dynamics of Proteins**; PI: Kim Sharp, University of Pennsylvania *[New user, identified for 50,000 node-hours]*

PSCA10059P **In-silico assembly of the Urel urea channel from H. pylori from helical fragments**; PI: Hartmut Luecke, University of California, Irvine *[New user, identified for 50,000 node-hours]*

PSCA10060P **Sequencing DNA Using MspA**; PI: Aleksei Aksimentiev, University of Illinois, Urbana-Champaign *[Returning user, identified for 50,000 node-hours]**

PSCA10063P **Continuous Long-Time Dynamics of RNA Molecules: Watching without Blinking for Microseconds through Anton's Microscope: Extension Request**; PI: Ioan Andricioaei, University of California, Irvine *[Returning user, identified for 50,000 node-hours]**

PSCA10065P **Exploring the Gating Motions of Connexin Channels on a Microsecond Timescale**; PI: Ivaylo Ivanov, Georgia State University *[New user, identified for 50,000 node-hours]*

PSCA10068P **Timescale of dynamics in unfolded/unstructured proteins: microseconds or nanoseconds?**; PI: Jeetain Mittal, Lehigh University *[New user, identified for 50,000 node-hours]**

PSCA10070P **Simple, Regulated Ion Channels: New Avenues for Synthetic Biology**; PI: Andrew Pohorille, University of California, San Francisco *[Returning user, identified for 50,000 node-hours]*

PSCA10071P **Molecular Dynamics Simulations of Conformational Dynamics in the p38α MAP Kinase: Effects of the Apo State's Flexibility on Inhibitor Binding Affinity**; PI: Adrian Elcock, University of Iowa *[Returning user, identified for 50,000 node-hours]**

PSCA10073P **Probing allosteric regulation in the Imidazole Glycerol Phosphate Synthase by microsecond MD simulations**; PI: Victor Batista, Yale University *[New user, identified for 50,000 node-hours]**

PSCA10080P **Anton Simulations of EPAC1 to illuminate the molecular details of cAMP based allosteric control of conformational change**; PI: Thomas Woolf, Johns Hopkins University *[New user, identified for 50,000 node-hours]**

PSCA10090P **Metabolite permeation and voltage-gating of the mitochondrial channel VDAC**; PI: Michael Grabe, University of Pittsburgh *[Returning user, identified for 50,000 node-hours]**

PSCA10093P **Atomistic modeling of the resting and activated states of a voltage-gated potassium channel voltage-sensing domain**; PI: J. Alfredo Freites, University of California, Irvine *[Returning user, identified for 50,000 node-hours]**

PSCA10100P **Dynamics of Calcium-Dependent Processes Essential for Cadherin Function in Hearing and Deafness**; PI: David Corey, HHMI & Harvard Medical School *[Returning user, identified for 100,000 node-hours]*

PSCA10102P **Capturing Large-Scale Structural Transitions in Membrane Transporters at Atomic Resolution**; PI: Emad Tajkhorshid, University of Illinois, Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

The time allocations for the 44 proposals identified by the committee as meeting or exceeding the selection criteria for time allocations total approximately 2,890,000 node-hours. Of the 44 proposals identified, 15 were identified at the 100,000 node-hour level and 29 at the 50,000 node-hour level.[2] A total of 1,340,000 node-hours were allocated to 23 proposals whose principal investigator did not receive time on Anton during the past year (identified as "new users"). The remaining 1,550,000 node-hours are allocated to 21 proposals from investigators who had received first round time allocations (indentified as "returning users").

After considerable deliberation, the committee has concluded that the most appropriate use of the remaining 110,000 node-hours would be for the Pittsburgh Supercomputing Center to use its discretion to allocate additional time to Group 1 proposals under the following guidelines:

1. No PI should be allocated more than a total of 100,000 node-hours
2. PIs may petition PSC for additional time after they have used their initial allocation
3. Preference should be given to PIs who did not receive allocations in the first round

In carrying out its task, the committee identified as many promising proposals as possible given the constraints on the total available simulation time. The committee also encourages D.E. Shaw Research and the Pittsburgh Supercomputing Center to establish a collective repository to share data generated, because the trajectories obtained may be of use to other investigators in the community.

The committee would like to thank D.E. Shaw Research, the Pittsburgh Supercomputing Center, and all of the 2011 Anton applicants for the opportunity to assist in identifying the proposals best meeting the selection criteria for time allocations on the Anton machine. The committee members were universally enthusiastic about the potential advances in the field that are facilitated by Anton and are looking forward to seeing the important new results from the Anton users.

Sincerely,

Robert L. Jernigan
Chair

cc: Dr. Markus Dittrich, Pittsburgh Supercomputing Center
Dr. Warren Muir, National Research Council
Dr. Frances Sharples, National Research Council

[2] The 100,000 node-hour level is defined as proposals that were identified for 70,000 node-hours or greater. The 50,000 node-hour level is defined as proposals that were identified for less than 70,000 node-hours.

Appendices:

A. Table 1: Proposals Reviewed by the Committee

B. Individual Proposal Summary Evaluations

C. Proposal Evaluation Criteria

D. Roster and Biographical Sketches of Committee Members and Reviewers

E. The Board on Life Sciences, the Board on Chemical Sciences and Technology, and the National Academies

F. Acknowledgment of Report Reviewer

APPENDIX A

TABLE 1: PROPOSALS REVIEWED BY THE COMMITTEE

This appendix is not available to the public.

APPENDIX B

INDIVIDUAL PROPOSAL SUMMARY EVALUATIONS

This appendix is not available to the public.

APPENDIX C

PROPOSAL REVIEW CRITERIA

The committee used the points below to help guide its review of the proposals. The reviewers were asked to comment on the strengths and weaknesses of the proposals by considering the following:

Level of scientific merit

1. Potential to advance understanding of an important problem or question in the field; potential for breakthrough science resulting in new discoveries and understanding
2. Impact that successful completion of the proposed research would have on the knowledge, methods, and current barriers in the field
3. Project is scientifically and technologically feasible with clear, well-developed, and appropriate goals, objectives, and approach to the proposed studies

Justification for requested time allocation

1. Clear and well-justified need for multi-microsecond simulation time
   Clear and convincing justification that the length and number of proposed simulation runs and node-hours requested are necessary and sufficient to achieve the scientific objectives

Investigator qualifications and past accomplishments

1. Appropriate experience and training to successfully conduct the proposed studies
2. Evidence of knowledge and prior experience with molecular simulations
3. Past publications

APPENDIX D

COMMITTEE ON PROPOSAL EVALUATION FOR ALLOCATION OF SUPERCOMPUTING TIME FOR THE STUDY OF MOLECULAR DYNAMICS, SECOND ROUND

ROBERT L. JERNIGAN (Chair), Director, Laurence H. Baker Center for Bioinformatics and Biological Statistics and Professor, Department of Biochemistry, Biophysics and Molecular Biology, Iowa State University
DAVID C. BAKER, Professor, Department of Chemistry**,** University of Tennessee
NILESH BANAVALI, Research Scientist, Wadsworth Center and Assistant Professor, School of Public Health, State University of New York, Albany
MICHAEL COLVIN, Interim Dean, Professor and Founding Faculty Member**,** School of Natural Sciences**,** University of California, Merced
RUXANDRA I. DIMA, Assistant Professor of Chemistry, University of Cincinnati
PHILLIP GEISSLER, Associate Professor, Department of Chemistry**,** University of California, Berkeley
WILLIAM A. GODDARD III, Ferkel Professor of Chemistry, Materials Science, and Applied Physics, California Institute of Technology
DAVID L. MOBLEY, Assistant Professor, Department of Chemistry**,** University of New Orleans
JOSE N. ONUCHIC, Professor of Physics and Co-Director Center for Theoretical Biological Physics, University of California, San Diego
CAROL PARISH, Professor, Department of Chemistry**,** University of Richmond
JERRY M. PARKS, Research Staff Scientist**,** Oak Ridge National Laboratory
STEVEN SCHWARTZ, Director, Seaver Foundation, Center for Bioinformatics and Professor of Physiology, Biophysics and Biochemistry, Albert Einstein College of Medicine
SADASIVAN SHANKAR, Senior Principal Engineer and Program Leader for Materials Design**,** Design and Technology Solutions, Technology and Manufacturing Group, Intel Corporation
TIMOTHY A. SPRINGER, Latham Family Professor of Pathology**,** Harvard Medical School
ROBERT STROUD, Professor, Biochemistry and Biophysics and Pharmaceutical Chemistry**,** University of California, San Francisco
ARIEH WARSHEL, Professor of Chemistry and Biochemistry, University of Southern California
HAREL WEINSTEIN, Chairman and Professor, Department of Physiology and Biophysics and Director, Institute for Computational Biomedicine**,** Weill Cornell Medical College of Cornell University

REVIEWERS

GERHARD HUMMER, Chief, Theoretical Biophysics Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
DOUGLAS J. TOBIAS, Professor of Chemistry**,** University of California, Irvine

NATIONAL RESEARCH COUNCIL STAFF

KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
DOUGLAS FRIEDMAN, Program Officer, Board on Chemical Sciences and Technology
KATHRYN HUGHES, Program Officer, Board on Chemical Sciences and Technology
ORIN LUKE, Senior Program Assistant, Board on Life Sciences

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS AND REVIEWERS

CHAIR

Robert L. Jernigan is the Director of the Laurence H. Baker Center for Bioinformatics and Biological Sciences as well as a Professor in the Department of Biochemistry, Biophysics, and Molecular Biology at Iowa State University. He received his B.S. in Chemistry from the California Institute of Technology in 1963 and completed his Ph.D. in 1968 at Stanford University. He has previously served as Deputy Chief of the Laboratory of Experimental and Computational Biology and Chief of the Section on Molecular Structure in the National Cancer Institute of the National Institutes of Health. He is also a former Chair of the NIH Advisory Committee on Computer Usage and has served on many committees on computing resources. Dr. Jernigan is currently on the editorial boards for the journals *Biochemistry* and *Bioinformatics and Biological Insights*. He is a Fellow of the Biophysical Society and a Fellow of the AAAS. His recent research focuses on mechanics of proteins and RNA and the role of mechanics in the mechanisms of molecular machines.

MEMBERS

David C. Baker is Professor of Organic Chemistry at the University of Tennessee. He is active in the Carbohydrate, Medicinal, and Organic Divisions of the American Chemical Society. Prior to his academic career he worked at the Parke-Davis Pharmaceutical Research, following a postdoctoral at Syntex Research. He is a frequent reviewer for the National Institutes of Health and serves as an editor of Carbohydrate Research, an international journal in the field. Dr. Baker received a Ph.D. in chemistry from The Ohio State University.

Nilesh Banavali received his Ph.D. from the University of Maryland in 2001 for studies on nucleic acid force fields and base flipping with Alexander MacKerell Jr. He pursued postdoctoral training at Weill Medical College of Cornell University and the University of Chicago with Benoît Roux on implicit and implicit/explicit solvent models and free energy characterization of conformational change and allostery in macromolecules. He currently serves as a Research Scientist at the Wadsworth Center and as Assistant Professor in the School of Public Health at the State University of New York, Albany. The primary goal of his research is to use computational calculations and refined analysis techniques to optimally extract free energy landscapes describing biologically relevant macromolecular conformational change. Dr. Banavali also develops techniques to facilitate validation of computational predictions with structural and biochemical data.

Michael Colvin is Interim Dean, Professor and Founding Faculty Member in the School of Natural Sciences at the University of California, Merced. Dr. Colvin's research uses a wide range of simulation methods to model biological systems at different levels. Much of his research uses molecular modeling to study biochemical problems, with a particular emphasis on modeling the activity of DNA-binding food mutagens and anticancer drugs. These methods involve computing the structures and energetics of biomolecules using either quantum or classical mechanics, and often require the use of supercomputers. Dr. Colvin received his Ph.D. from the University of California, Berkeley.

Ruxandra I. Dima has an interdisciplinary training in theoretical and computational physics and physical chemistry and her current research focuses on the area of computational biophysical chemistry with special emphasis on single molecule experiments and aggregation. After

receiving her undergraduate degree from the University of Bucharest, Romania in 1994, she studied at the Pennsylvania State University where she obtained her Ph.D. in 1999. Her thesis was concerned with the determination of mean field free-energy potentials between amino acids in proteins. She then took a postdoctoral appointment (2000-2005) at the Institute for Physical Science and Technology, University of Maryland where she worked on problems related to protein aggregation, allostery, RNA folding, and single-molecule biophysics. In 2005 she took a faculty position at the University of Massachusetts, Lowell. She joined the faculty at the University of Cincinnati in 2006. Dr. Dima's research focuses on the micromechanics of large protein assemblies from cytoskeletal filaments to fibrin fibers, using multi-scale models that are continuously developed in her group to access experimental length and timescales.

Phillip Geissler is an Associate Professor in the Department of Chemistry at the University of California, Berkeley. Dr. Geissler is also a faculty member of the Biophysics Graduate Group at the University of California, Berkeley, a faculty scientist in the Chemical Sciences, Physical Biosciences, and Materials Sciences Divisions of the Lawrence Berkeley National Laboratory, and a faculty affiliate at the California Institute for Quantitative Biosciences (QB3). His research focuses on the microscopic behavior of complex biological and material systems, particularly theories and simplified models for chemical phenomena in condensed phases, for biomolecular structure and dynamics, and for the role of fluctuations in nanoscale materials. Among his current interests are the polymeric framework of living cells and the dynamics of nanometer-sized solutes in a liquid undergoing phase change. In 2006, Dr. Geissler was named a Kavli Frontiers Fellow. He received his bachelor's degree in chemistry from Cornell University and Ph.D. in chemistry from the University of California, Berkeley.

William A. Goddard III is the Charles and Mary Ferkel Professor of Chemistry and Applied Physics, and Director, Materials and Process Simulation Center at the California Institute of Technology. He has made many contributions to theoretical chemistry, such as the generalized valence bond (GVB) method for ab initio electronic structure calculations and the ReaxFF force field for classical molecular dynamics simulations. He is a member of the International Academy of Quantum Molecular Science. His research interests include quantum mechanics for the electronic wave functions of large molecules and crystals, including the many-body effects needed to describe reactions, force fields to describe the dynamics of atomic motions, molecular dynamics of large molecules and solids to determine the structure, vibrations, and dynamical processes of materials and statistical mechanics to describe phase diagrams (mixtures of molecules and polymers; metallic alloys). Dr. Goddard received his Ph.D. from the California Institute of Technology. He is an elected member of the National Academy of Sciences.

David L. Mobley is an Assistant Professor in the Department of Chemistry at the University of New Orleans. His research focuses on applying computational and theoretical methods to understand and quantitatively predict fundamental biological processes such as protein-ligand binding, solvation, and solubility. His research interests include the binding of small-molecule ligands to proteins and the interactions of small molecules with water and other solvents. Current computational methods have limited accuracy for pharmaceutical drug discovery applications, and his laboratory seeks to develop and apply more accurate methods for computing and even predicting binding affinities. Recent work has also examined solute geometry and the role of entropy in small molecule solvation. Dr. Mobley received the Hewlett-Packard Outstanding Junior Faculty Award in Computational Chemistry from the American Chemical Society (2009). He received his B.S. and Ph.D. degrees in physics from the University of California, Davis.

Jose N. Onuchic is the co-Director of the Center for Theoretical Biological Physics and Professor of Physics at the University of California, San Diego. His research group introduced the concept of protein-folding funnels to show the types of amino acid sequences that can fold into a

unique protein structure. Dr. Onuchic and his collaborators also created the concept of tunneling pathways and the methodology for reducing proteins into a combination of relevant tubes of pathways that provides a new way of designing electron transfer proteins. His research interests include exploring theoretical and computational methods for molecular biophysics, chemical reactions in condensed matter and gene networks. Dr. Onuchic received his Ph.D. in chemistry from the California Institute of Technology and M.S. degree in applied physics from the University of California, San Diego. He is an elected member of the National Academy of Sciences.

Carol Parish is Professor of Chemistry, Computational and Theoretical Physical Chemistry at the University of Richmond. Her research focuses on understanding the dynamical behavior of molecular systems using the tools of quantum mechanics, conformational searching and free energy simulation to answer questions about the structure, energy and dynamics of HIV-1 protease inhibitor drugs, Bergman cyclization in enediyne anti-cancer warhead drugs, homology modeling of membrane-bound desaturase enzymes, investigations of the flexibility of polyoligomeric silsesquioxane cages (POSS), the role of O-to-N acyl migration in insect defense secretions, and oligomeric models for synthetic enzymes that display enzyme-like acyltransferase activity. Dr. Parish is a member of the American Chemical Society. She received her Ph.D. in physical chemistry from Purdue University.

Jerry M. Parks is a Research Staff Scientist for the Center for Molecular Biophysics in the Biosciences Division at Oak Ridge National Laboratory. His research involves molecular simulations and free energy calculations to solve chemical problems. Dr. Parks received his Ph.D. in Chemistry from Duke University and his M.S. in Chemistry from Southern Methodist University.

Steven Schwartz is Director of the Seaver Foundation, Center for Bioinformatics and Professor of Physiology, Biophysics and Biochemistry at the Albert Einstein College of Medicine. He was elected as a Fellow of the American Physical Society and a Fellow of the American Association for the Advancement of Science. Dr. Schwartz's selection recognizes his development of the theory of the coupling of protein vibrations to catalytic function in enzymes. Dr. Schwartz is the executive editor of the Journal of Theoretical and Computational Chemistry. He also serves on the editorial boards of the Biophysical Journal and Progress in Theoretical Chemistry. His research interests include theoretical studies of biophysical systems and theoretical condensed phase chemistry. Dr. Schwartz received his Ph.D. in theoretical chemical physics from the University of California, Berkeley.

Timothy A. Springer majored in Biochemistry at the University of California, and graduated Phi Beta Kappa with Distinction and the Departmental Citation. He received his Ph.D. in biochemistry working with Jack Strominger on the isolation, protein chemistry, and organization in the membrane of major histocompatibility complex antigens. Realizing the power of monoclonal antibodies for the characterization of proteins on the cell surface, Springer did postdoctoral work with César Milstein. He started as an Assistant Professor at Harvard Medical School in 1977 where he has been ever since, moving a few blocks down the street to the Dana-Farber Cancer Institute in 1981 and to the CBR Institute for Biomedical Research in 1988. He is an elected member of the National Academy of Sciences.

Robert Stroud is Professor of Biochemistry and Biophysics and Pharmaceutical Chemistry and Principal Investigator of the Stroud laboratory at the University of California, San Francisco. At the Stroud laboratory, scientists seek to understand molecular mechanisms of certain key biological processes, as well as signal transduction between processes at the level of protein structure, dynamics, and mechanism. Three-dimensional molecular structures are defined

primarily by x-ray crystallography and are often used to facilitate structure-based drug design, providing a quintessential test of our understanding of the relationship between structure and recognition. Currently the integration enzyme from HIV is subject to molecular biological, biochemical, and structural approaches. The molecular mechanisms of thymidylate synthase are derived from numerous structural studies in the laboratory. An important cancer target, these mechanisms pertain directly to our structure and mechanism based design of anticancer drugs. Dr. Stroud received his PhD in Biological Crystallography from Birkbeck College, London University, U.K. He is an elected member of the National Academy of Sciences.

Arieh Warshel received his BS degree in Chemistry, Summa Cum Laude, from Technion Israel in 1966, and his M.S. and Ph.D. degrees in Chemical Physics in 1967 and 1969, respectively, from the Weizmann Institute of Science, Israel. After his PhD, he did postdoctoral work at Harvard University. From 1972 to 1976, he was at the Weizmann Institute and at the MRC Laboratory for Molecular Biology in Cambridge, England. In 1976 he joined the faculty of the Department of Chemistry at USC, where he now is Professor of Chemistry and Biochemistry and a Full Member of the USC Norris Cancer Center. Dr. Warshel has authored over 350 peer-reviewed research articles (H index 92) and book chapters, two books, and several key computer programs. Dr. Warshel's research focuses on simulations of the functions of biological system and other challenging problems in modern computational biophysics and chemistry. He and his coworkers have pioneered the key approaches for simulating the functions of biological molecules, including introducing molecular dynamics (MD) in Biology, developing the quantum mechanical/molecular-mechanical (QM/MM) approach, introducing simulations of enzymatic reactions, developing simulations of electron transfer and proton transfer processes in proteins, pioneering microscopic modeling of electrostatic effects in macromolecules and introducing simulation of protein folding. Dr. Warshel received the Tolman Medal in 2003, has been elected a Fellow of the Biophysical Society in 2000, a Fellow of the Royal Society of Chemistry in 2008, and a Member of the National Academy of Sciences in 2009.

Harel Weinstein is the Maxwell Upson Professor of Physiology and Biophysics and Chairman of the Department of Physiology and Biophysics, and the Director of the Institute for Computational Biomedicine at Weill Cornell Medical College (WCMC) of Cornell University in New York City. As a Tri-Institutional Professor, he holds professorial appointments at Rockefeller University, Sloan-Kettering Institute and Cornell University. He is the founding director of the Institute for Computational Biomedicine (ICB), which he developed it into an academic and research unit responsible for a novel approach to biomedicine that involves the mathematical, physical and computational sciences in combination with engineering and medical informatics. The ICB aims at fundamental study and practical use of the basic, quantitative understanding of physiological function and disease, in an integrative, multi-scale approach based on gene structure and defects responsible for properties and behaviors at all levels–from protein, to cell, tissue and organ. He has received numerous honors and awards, he was elected to the Executive Board of the International Society for Computational Biology in 2006, and President of the Biophysical Society in 2008. He has also served as President of the Association of Chairmen of Departments of Physiology, President of the International Society for Quantum Biology and Pharmacology, Chair of the Biophysics Section of the New York Academy of Sciences and Councilor of the Biophysical Society and of the New York Academy of Medicine. His research interests include studies in molecular and computational biophysics that address complex systems in physiology, and to the development and application of bioinformatics and engineering approaches to systems biology.

REVIEWERS

Gerhard Hummer received a doctoral degree in physics for work done jointly at the Max-Planck Institute for Biophysical Chemistry in Göttingen and the University of Vienna (1992). In 1996, he started his independent career in the Theoretical Division of Los Alamos National Laboratory after his postdoctoral work there. In 1999, Dr. Hummer joined the Laboratory of Chemical Physics in the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health where he is a Senior Investigator. His research focuses on areas including theory of single-molecule experiments; channel function; peptide and protein folding; complex formation and ligand binding; proton pumping and bioenergetics; reaction-rate calculations; and the development of new methods for biomolecular simulation and electrostatics.

Douglas J. Tobias is a Professor in the Department of Chemistry at the University of California, Irvine. His research involves the use of atomic-scale computer simulation techniques to study the structure and dynamics of biological molecules and biomimetic materials and aqueous interfaces with air. A substantial portion of his work is devoted to the development, implementation, and optimization of novel simulation methodology and analysis tools. Current projects include interactions of peptides and proteins with lipids, molecular mechanisms of ion channel gating, and the dynamics of native and denatured proteins and their hydration water, among others. Dr. Tobias is an elected Fellow of the American Association for the Advancement of Science. He received his bachelors and masters degrees in chemistry from the University of California, Riverside and his Ph.D. in Chemistry and Biophysics from Carnegie Mellon University.

APPENDIX E

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The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

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The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

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APPENDIX F

ACKNOWLEDGMENT OF REPORT REVIEWER

This report has been reviewed in draft form by an individual chosen for his perspective and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individual for his review of this report:

Sean Eddy, Howard Hughes Medical Institute, Janelia Farm Research Campus

Although the reviewer listed above has provided many constructive comments and suggestions, he was not asked to endorse the conclusions. In addition, he was asked to ensure that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.