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

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Board on Life Sciences

Division on Earth and Life Studies

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September 19, 2014

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, Fifth Round.

The committee evaluated submissions received in response to a Request for Proposals (RFP) for Biomolecular Simulation Time on Anton, a supercomputer designed and built by D. E. Shaw Research (DESRES). Over the past four years (October 1, 2010 – September 30, 2014), DESRES has made an Anton system housed at the Pittsburgh Supercomputing Center (PSC) available to the non-commercial research community, based on the advice of previous National Research Council committees convened in 2010 – 2013. As in prior rounds, the goal of the fifth RFP for simulation time on Anton is 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 capabilities allow multi-microsecond 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 success of the program has led DESRES to make the Anton machine housed at PSC available for an additional 3,300,000 node-hours over the period following October 2014, 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 RFP. The committee of 16 was chaired by Dr. Angel Garcia, Department Head and Professor of Physics, and Senior Constellation Chaired Professor in Biocomputation and Bioinformatics at Rensselaer Polytechnic Institute. The committee members were selected for their expertise in molecular dynamics simulations and their experience in the subject areas represented in the 55 proposals that were considered by the committee. They comprised a cross section of the biomolecular dynamics field in academia, industry, and government including both senior and junior investigators.

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 the 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 progress reports. Following guidance provided by DESRES and PSC, the committee drew on these progress reports as supplemental material in its consideration of proposals. The committee also received information from PSC on the number of node-hours of simulation time remaining on 2013 Anton allocations.[1] As explained in the RFP, staff at PSC conducted an initial assessment of all proposal submissions for completeness and to determine whether they were technically feasible for simulation on Anton. A member of the PSC staff was present as an observer throughout the review committee's discussions to address any additional questions that arose on Anton's technical capabilities or on how the computer will be made available to researchers during the period of the project.

The committee was asked to identify proposals that best met the selection criteria defined above. As in the previous rounds of Anton time allocations, 100,000 node-hours was the maximum amount of time available to a proposal. Principal investigators could also request a lesser time allocation. The committee was further asked to allocate at least 25% of the time to principal investigators who had not previously received an Anton allocation. The judgments of the committee are based on which proposals best met the selection criteria described above and on the estimates of required simulation time provided by the applicants. The committee was permitted to 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 16 committee members. 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 proposals were not evaluated by reviewers from the applicant's same institution or who had close collaborative relationships with an applicant.

[1] This information was provided as of August 12, 2014. The committee was advised that approximately two months of simulation time remained on the 2013 round of allocations, and thus investigators who had not yet used their full allocation of simulation time may still be able to do so.

The committee held its meeting in Washington, D.C. on August 15, 2014. At 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 and key personnel. The committee then considered the slate of proposals, came to a consensus on which proposals it judged best met the selection criteria, and, in some cases, decided to suggest a modified allocation of time on Anton. Detailed comments for each of the 55 proposals are included in Appendix B. The committee has often included constructive suggestions for improvements in the research plans, which is of significant benefit to the broader community.

The committee concluded that the proposals listed below best met the selection criteria set forth in the RFP for Biomolecular Simulation Time on Anton. Of these 45 proposals, 18 proposals were selected for a modified allocation (identified below with an *).

In numerical order by proposal submission number, the proposals judged by the committee as best meeting the selection criteria of the RFP are:

PSCA14002P **Mechanical Control of Kinesin's ATPase Machinery**; PI: Wonmuk Hwang, Texas A&M University *[Returning user, identified for 50,000 node-hours]**

PSCA14003P **Multi-Microsecond Simulations of A Model Two-Domain Protein**; PI: Lillian Chong, University of Pittsburgh *[Returning user, identified for 50,000 node-hours]*

PSCA14004P **The Roles of Protein Conformational Dynamics and Lipid Membrane Properties in the Function of B-Barrel Assembly Machinery**; PI: Karen Fleming, Johns Hopkins University *[New user, identified for 100,000 node-hours]*

PSCA14005P **Roles of N-linked Glycans and GPI Anchor in Human Prion Protein Misfolding**; PI: Wonpil Im, University of Kansas *[Returning user, identified for 100,000 node-hours]*

PSCA14006P **Molecular Basis of G Protein-Biased Agonism at the Mu-Opioid Receptor**; PI: Marta Filizola, Icahn School of Medicine at Mount Sinai *[Returning user, identified for 100,000 node-hours]*

PSCA14007P **Investigation into the Coupling between Helix 6 Opening, RNA Binding and the Oligomeric State of the Lassa Virus Nucleoprotein**; PI: Eric May, University of Connecticut *[New user, identified for 50,000 node-hours]**

PSCA14008P **Microsecond Simulations to Study Microbial Infection Mechanisms**; PI: Jianing Li, University of Vermont *[New user, identified for 50,000 node-hours]**

PSCA14010P **Molecular Machinery Controlling Synaptic Vesicle Fusion**; PI: Maria Bykhovskaia, Universidad Central del Caribe *[Returning user, identified for 50,000 node-hours]**

PSCA14011P **Dynamics of the Translational Machinery**; PI: Zaida Luthey-Schulten, University of Illinois *[Returning user, identified for 50,000 node-hours]*

PSCA14012P **The Molecular Determinants of Selective Ion Binding in the Sodium-Potassium Pump ATPase**; PI: Benoît Roux, University of Chicago *[Returning user, identified for 100,000 node-hours]*

PSCA14013P **The Structure of Peptide and Protein-induced Pores in Lipid Membranes**; PI: Themis Lazaridis, City College of New York *[Returning user, identified for 50,000 node-hours]**

PSCA14014P **Sensing and Binding Mechanisms of Membrane Proteins**; PI: Gregory Voth, University of Chicago *[Returning user, identified for 84,000 node-hours]*

PSCA14015P **Self-assembly of Transmembrane Signaling Proteins**; PI: Klaus Schulten, University of Illinois at Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

PSCA14016P **Charting the Microscopic Pathway of DNA Branch Migration**; PI: Aleksei Aksimentiev, University of Illinois at Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

PSCA14023P **Mechanism of Allosteric Coupling in the Voltage-Sensing Phosphatase Ci-VSP**; PI: Eduardo Perozo, University of Chicago *[Returning user, identified for 50,000 node-hours]**

PSCA14025P **MD Simulations of Interactions and Misfolding of Amyloid Beta (Aß) Proteins**; PI: Yuri Lyubchenko, University of Nebraska Medical Center *[New user, identified for 50,000 node-hours]**

PSCA14026P **Substrate-Specific Allosteric Behavior in the Leucine Transporter from Analysis of Microsecond-Scale Molecular Dynamics Simulations**; PI: Harel Weinstein, Weill Cornell Medical College of Cornell University *[Returning user, identified for 91,000 node-hours]*

PSCA14027P **Molecular Determinants in Folding of Voltage-Gated Potassium Channel Kv1.3 Pore Helix**; PI: Tobin Sosnick, University of Chicago *[New user, identified for 50,000 node-hours]**

PSCA14030P **Yeast Membrane Simulations with Inositol Phosphoceramide with Applications to Lateral Organization and binding of a Peripheral Membrane Protein**; PI: Jeffery Klauda, University of Maryland *[Returning user, identified for 100,000 node-hours]*

PSCA14031P **Characterizing the Disordered FG Repeat Domains of Nuclear Pore Complexes by Simulation and Experiment**; PI: David Cowburn, Albert Einstein College of Medicine *[Returning user, identified for 50,000 node-hours]**

PSCA14032P **Glutamate Receptor Ligand Binding and Desensitization**; PI: Albert Lau, Johns Hopkins University School of Medicine *[Returning user, identified for 100,000 node-hours]*

PSCA14033P **Large-Scale Exploration of Sodium Channel Interactions with Small Molecules and Peptide Toxins**; PI: Vladimir Yarov-Yarovoy, University of California, Davis *[New user, identified for 100,000 node-hours]*

PSCA14034P **Formation and Breakdown of Peptide-Lipid Pores by the Antimicrobial Peptide Piscidin 1 in POPC/POPG Bilayers**; PI: Richard Pastor, National Institutes of Health *[New user, identified for 100,000 node-hours]*

PSCA14035P **Exploring Protein Core Plasticity and Rapid Ligand Access to Buried Binding Sites**; PI: Rommie Amaro, University of California, San Diego *[Returning user, identified for 100,000 node-hours]*

PSCA14036P **Revealing the Structural Basis of Functional Selectivity in GPCRs**; PI: Ron Dror, Stanford University *[New user, identified for 100,000 node-hours]*

PSCA14037P **The Conformational Rearrangement of Influenza Hemaggluinin: Molecular Details of the Initial Order-Disorder Transition**; PI: Jose Onuchic, Rice University *[Returning user, identified for 50,000 node-hours]**

PSCA14038P **The Electron Transfer Rate in Ferredoxins**; PI: Toshiko Ichiye, Georgetown University *[New user, identified for 50,000 node-hours]*

PSCA14039P **Atomistic Modeling of the Resting and Activated States of the Human Hv1 Voltage-Gated Proton Channel**; PI: Douglas Tobias, University of California, Irvine *[Returning user, identified for 75,000 node-hours]**

PSCA14040P **Structure, Conductance and Mechanism of Action of Calcium Channels Involved In Human Diseases**; PI: Andrew Pohorille, University of California, San Francisco *[Returning user, identified for 50,000 node-hours]*

PSCA14041P **Long Time Scale Molecular Dynamics Simulation of Protein Folding**; PI: Martin Gruebele, University of Illinois at Urbana-Champaign *[Returning user, identified for 100,000 node-hours]**

PSCA14042P **Characterizing Conformational Dynamics of Sugar Transporters GLUT1 and XylE**; PI: Emad Tajkhorshid, University of Illinois at Urbana-Champaign *[Returning user, identified for 100,000 node-hours]*

PSCA14043P **Simulations of Protein Association and Transmembrane Peptides**; PI: Matthias Buck, Case Western Reserve University [Returning user, identified for 50,000 node-hours]

PSCA14044P **Determining the Mechanisms of Protein Folding in Membranes**; PI: James Gumbart, Georgia Institute of Technology *[Returning user, identified for 100,000 node-hours]*

PSCA14045P **Ligand-Specific Conformational Changes in CCR7 Coupled to Signaling Pathway Selection**; PI: Dimitrios Morikis, University of California, Riverside *[New user, identified for 100,000 node-hours]*

PSCA14047P **Functional Mechanism of a Bile Acid Transporter**; PI: Fatemeh Khalili-Araghi, University of Illinois at Chicago *[New user, identified for 43,000 node-hours]*

PSCA14048P **Real Time Exploration of Photosynthetic Light Harvesting Complex 2 (LH2) and Their Membrane Environments**; PI: Seogjoo Jang, Queens College of the City University of New York *[New user, identified for 60,000 node-hours]*

PSCA14051P **Beyond Active Site Catalysis: Determining the Role of Remote Mutations and Solvent in Substrate Recognition by Microsecond Molecular Dynamics**; PI: Kendall Houk, University of California, Los Angeles *[Returning user, identified for 100,000 node-hours]*

PSCA14052P **Microsecond Dynamics of HIV-1 Stem Loop1 RNA and A-Tract DNA for Computation of NMR Order Parameters and Comparison**; PI: Ioan Andricioaei, University of California, Irvine *[Returning user, identified for 50,000 node-hours]*

PSCA14053P **Evolution of Allosteric Signatures in GPCR**; PI: Brian Dominy, Clemson University *[New user, identified for 50,000 node-hours]**

PSCA14054P **Receptor-Specific Distinction of Functional Mechanisms in G Protein Coupled Receptors**; PI: Nagarajan Vaidehi, Beckman Research Institute at City of Hope Medical Center *[Returning user, identified for 100,000 node-hours]*

PSCA14057P **Bacterial Membrane Selectivity in Antimicrobial Peptides**; PI: Jeffrey Comer, Kansas State University *[New user, identified for 50,000 node-hours]**

PSCA14058P **Molecular Modeling Studies of Drug Binding to Human P-glycoprotein**; PI: Alfredo Freites, University of California, Irvine *[Returning user, identified for 75,000 node-hours]**

PSCA14059P **The Role of Nascent Chain Tension in Modulating Codon Translation Rates**; PI: Edward O'Brien, Pennsylvania State University *[New user, identified for 75,000 node-hours]**

PSCA14062P **The Role of Long-Range Interaction Formation in Determining Protein Topology at the Onset of Folding**; PI: Jennifer Poutsma, Old Dominion University *[New user, identified for 50,000 node-hours]**

PSCA14063P **How Do Small-Molecule Interactions Alter the Conformational Landscape of Intrinsically Disordered P27?**; PI: Chakra Chennubhotla, University of Pittsburgh *[New user, identified for 50,000 node-hours]**

The time allocations for the 45 proposals identified by the committee as best meeting the selection criteria for time allocations total approximately 3,303,000 node-hours. Of the 45 proposals identified, 23 were identified at the approximately 100,000 node-hour level and 22 at the 50,000 node-hour level.[2] A total of approximately 1,128,000 node-hours were allocated to 17 proposals whose principal investigator did not receive time on Anton during the past four years (identified as "new users"). Approximately 34% of the available simulation time thus was allocated to new users of Anton. The remaining 2,175,000 node-hours are allocated to 28 proposals from investigators who had received allocations of time on Anton in previous rounds (identified as "returning users").

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 wishes to raise two questions that arose during the proposal discussions. The first involves the restriction stated in the RFP that "each investigator can serve as a PI for only a single application for computer time on Anton." It is common for proposals to include co-PIs and other key personnel in addition to the stated PI. The committee observed that it was also common for experts in molecular dynamics simulations to be associated with multiple proposals.[3] The committee encourages D. E. Shaw Research and the Pittsburgh Supercomputing Center to consider whether additional guidance on the maximum number of proposals with which a senior investigator may be affiliated would add clarity to any future rounds of proposal solicitations.

[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.

[3] With the intention solely of pointing to an example from among the current round of proposals, Professor Benoît Roux was listed as PI on one proposal and co-PI on two additional proposals. This type of situation was not unique to Professor Roux.

Finally, the committee encountered a request for simulation time awarded in the fourth round (2013-2014) to carry over into the fifth round of allocations (2014-2015). In this instance, the committee declined to recommend a time extension. However, the committee would like to note this request so that D. E. Shaw Research and the Pittsburgh Supercomputing Center can consider whether a policy on time extensions should be made.

The committee would like to thank D. E. Shaw Research, the Pittsburgh Supercomputing Center, and all of the 2014 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,

Angel Garcia
Chair

cc: Dr. Markus Dittrich, Pittsburgh Supercomputing Center
Dr. Gregory Symmes, National Research Council
Dr. Frances Sharples, National Research Council

Appendices:

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, FIFTH ROUND

Members

ANGEL GARCIA *(Chair)*, Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, Troy, New York
ORLANDO ACEVEDO, Department of Chemistry and Biochemistry, Auburn University, Alabama
IVET BAHAR, Department of Computational and Systems Biology, University of Pittsburgh, Pennsylvania
DAVID BERATAN, Department of Chemistry, Duke University, North Carolina
BERNARD BROOKS, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland
THOMAS CHEATHAM III, Department of Medicinal Chemistry, University of Utah, Salt Lake City
DONALD HAMELBERG, Department of Chemistry, Georgia State University
ANDRZEJ KLOCZKOWSKI, Battelle Center for Mathematical Medicine, Nationwide Children's Hospital, Columbus, Ohio
MARIA KURNIKOVA, Department Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania
EDWARD LYMAN, Department of Physics and Astronomy, University of Delaware, Newark
ALEXANDER MACKERELL, School of Pharmacy, University of Maryland, Baltimore
SERGEI NOSKOV, Department of Biological Sciences, University of Calgary, Alberta, Canada
JED PITERA, IBM Almaden Research Center, San Jose, California
SCOTT SHOWALTER, Department of Chemistry, Pennsylvania State University, University Park
CHUNG WONG, Department of Chemistry and Biochemistry, University of Missouri-St. Louis
TROY WYMORE, Center for Molecular Biophysics, University of Tennessee-Knoxville and Oak Ridge National Laboratory

National Research Council Staff

KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
CAMLY TRAN, Postdoctoral Fellow, Board on Chemical Sciences and Technology
LAUREN SONI, Senior Program Assistant, Board on Life Sciences

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

Chair

Angel Garcia, Ph.D., is Department Head of the Physics, Applied Physics and Astronomy Department at Rensselaer Polytechnic Institute. He is also Professor of Physics and Senior Constellation Chaired Professor of Biocomputation and Bioinformatics. The Garcia Research Group focuses on the use of theoretical and computational methods to study aspects related to biomolecular dynamics and statistical mechanics. Their main research objectives are to understand the folding, dynamics and stability of biomolecules. Research interests include the hydrophobic effect, enzyme catalysis, nucleic acid structure and dynamics, RNA folding, electrostatics, protein hydration, and peptide interactions with membranes. Dr. García received a Ph.D. in Theoretical Physics from Cornell University. He is a fellow of the American Physical Society and a member of the Biophysical Society, The Protein Society, the AAAS, and the American Chemical Society. He received the Edward Bouchard prize of the American Physical Society in 2006. Dr. García is an Associate Editor of Proteins, Structure, Function and Bioinformatics, a member of the editorial board of the Biophysical Journal, Molecular Simulations, and a member of the Faculty of 1000 for BioMed Central.

Members

Orlando Acevedo, Ph.D., is an S. D. and Karen H. Worley Associate Professor of Chemistry and Biochemistry at Auburn University. Dr. Acevedo's research program focuses upon the application and development of new computational tools that target organic and enzymatic catalyst design, alternative environmentally friendly solvent design, and drug discovery. Fundamental problems in organic and medicinal chemistry are probed, such as elucidation of enzymatic reactions, controlling enantioselectivity for chiral compounds, transition structure prediction, de novo design of high-affinity inhibitors, and origins of drug resistance. Obtaining quantitative success with large-scale quantum and molecular mechanical calculations involves the development of improved force fields, software, and methodology. Dr. Acevedo received his B.S. from Florida International University, his Ph.D. from Duquesne University and completed postdoctoral work at Yale University.

Ivet Bahar, Ph.D., is Distinguished Professor and JK Vries Chair in the Department of Computational and Systems Biology at the University of Pittsburgh School Of Medicine. She is also Associate Director of the University of Pittsburgh Drug Discovery Institute and Co-Director of the Molecular and Systems Modeling Core of the Clinical and Translational Science Institute. Dr. Bahar was the Founding Chair of the University of Pittsburgh School of Medicine's Department of Computational Biology and Founding Director of the joint University of Pittsburgh and Carnegie Mellon University Ph.D. program in computational biology. Her research focuses on biomolecular systems dynamics at multiple scales, the evolution of protein sequence, structure, dynamics and function, computer-aided drug discovery and polypharmacology, network models for protein-protein interactions, modeling and simulation of membrane proteins dynamics, and mechanisms of membrane protein interactions. Dr. Bahar has served on the Council and the Executive Board of the Biophysical Society and as member and chair of NIH study sections including Modeling and Analysis of Biological Systems, National Technology Centers for Networks and Pathways, and Computational Biology, Image Processing, and Data Mining. She received her Ph.D. in Chemistry from Istanbul Technical University, Turkey.

David Beratan, Ph.D., is the R. J. Reynolds Professor of Chemistry, Biochemistry, and Physics at Duke University. Through his research, Dr. Beratan has established a molecular-level theory that

describes the rate of charge tunneling reactions in biomolecules, thus establishing the theoretical underpinnings for biological energy capture and conversion processes. He has also developed theoretical methods to assign the absolute chirality of complex natural products and is developing theoretical methods to navigate molecular space in order to discover promising new structures of use in biomedical, energy, and materials science. Dr. Beratan was a National Research Council Resident Research Associate at NASA's Jet Propulsion Laboratory and later a member of the technical staff. In 1992, he moved to the University of Pittsburgh as Associate Professor of Chemistry; he was promoted to the rank of Professor in 1997. Dr. Beratan became the R. J. Reynolds Professor at Duke in 2001, where he served as Chair of Chemistry from 2004 to 2007. He has been a visiting Professor at All Souls College—University of Oxford, Conrad E. Ronneberg Visiting Scholar—University of Chicago, and Ralph and Lucy Hirschmann Visiting Professor—University of Pennsylvania. He has received the National Science Foundation National Young Investigator award, is a Fellow of the American Physical Society, and is a Fellow of the American Association for the Advancement of Science. He received a bachelor of science from Duke University and Ph.D. in chemistry from California Institute of Technology.

Bernard Brooks, Ph.D., is Chief of the Laboratory of Computational Biology at the National Heart, Lung, and Blood Institute of the National Institutes of Health. He also directs the Computational Biophysics Section of the Laboratory, which develops simulation and modeling techniques and applies them to the study of problems of biological significance. Techniques employed include molecular dynamics, quantum and molecular mechanics, ab initio analysis of small molecule structures, molecular modeling, and electron microscopy image analysis.

Thomas E. Cheatham III, Ph.D., is an Associate Professor in the Department of Medicinal Chemistry and an Adjunct Associate Professor in the Department of Bioengineering at the University of Utah. He is also a member of the Henry Eyring Center for Theoretical Chemistry, a senior fellow of the Center for High Performance Computing, a member of the NSF Teragrid Scientific Advisory Board, and a member of the University of Utah Information Technology Council and the University of Utah Cyberinfrastructure Council. He serves as a member of the board of editors of the *Journal of Biomolecular Structure & Dynamics*. Dr. Cheatham's research focuses on the development of molecular dynamics, free energy simulation, and trajectory analysis methodologies in applications aimed at better understanding biomolecular structure, dynamics and interactions including the representation of nucleic acid systems in solution. He received his Ph.D. in pharmaceutical chemistry from the University of California, San Francisco, and B.A. degrees in chemistry and in mathematics and computer science from Middlebury College. He was subsequently an NRC postdoctoral fellow in the Computational Biophysics Section of the Laboratory of Biophysical Chemistry at the National Heart, Lung and Blood Institute, National Institutes of Health.

Donald Hamelberg, Ph.D., is Associate Professor of Computational Biophysical Chemistry and Associate Graduate Director of Computational Chemistry and Biophysical Chemistry at Georgia State University. His research focuses on the application and development of theoretical and computational methods for understanding biological functions. Many interactions in cell signaling pathways are mediated by networks of interacting proteins and RNA molecules. Deregulation of these pathways could trigger cellular transformation, oncogenesis, and other diseases. The research in Dr. Hamelberg's laboratory seeks to decipher the underlying principles governing cell signaling mechanisms and biomolecular interactions involving proteins and RNA. In these endeavors, he uses simulation based approaches, statistical mechanics, and classical and quantum mechanical methods as a complementary tool to experiments. Dr. Hamelberg received his Ph.D. from Georgia State University. He was a Postdoctoral Research Fellow at the University of Illinois, Chicago (2001-2003) and at Howard Hughes Medical Institute and the University of California, San Diego (2003-2005).

Andrzej Kloczkowski, M.D., is a Principal Investigator in the Battelle Center for Mathematical Medicine of The Research Institute at Nationwide Children's Hospital. He is also a Professor of Pediatrics at The Ohio State University College of Medicine. Dr. Kloczkowski completed his graduate education at Warsaw University, received his MD from the Institute of Physical Chemistry of the Polish Academy of Sciences, and completed his postdoctoral work at Stanford University and Warsaw University. Dr. Kloczkowski's NIH-funded research program focuses on computational structural biology and bioinformatics, including protein structure prediction from the amino acid sequence, prediction of biomacromolecular dynamics using elastic network models, development of coarse grained models and potentials for proteins and nucleic acids, and studies of protein-protein and protein-nucleic acid integrations. He is also interested in application of machine learning methods to various biomedical and clinical problems, and has ongoing collaboration with several experimental and clinical centers.

Maria Kurnikova, Ph.D., is an Associate Professor of Chemistry at Carnegie Mellon University. Her research focuses on the area of computational chemistry and biophysics. She is interested in understanding the work of membrane proteins, such as receptors, signal transduction proteins, toxins and ion channels. The goal is to model and predict structure-function relationships in these proteins associated with ligand binding, gating of channels and mechanisms of selectivity and mobility in the confined environment of the channel. The systems she is interested specifically include Glutamate Receptors (AMPA and NMDA types), alpha-Hemolysin, Diphteria Toxin t-domain, Gramicidin A, PDZ-domain — ligand interaction of the NHERF1 protein. The approach her research group is taking includes a combination of physics-based computational methodologies, such as molecular dynamics simulations, continuum electrostatics and quantum chemistry. Dr. Kurnikova received her Ph.D. in Theoretical Chemistry from the University of Pittsburgh.

Edward Lyman, Ph.D., is an Assistant Professor within the Department of Physics and Astronomy at the University of Delaware. He received his Ph.D. in physics from Virginia Tech, where he studied nonequilibrium critical phenomena with Beate Schmittmann. He then did postdoctoral research in the Department of Computational Biology at the University of Pittsburgh with Dan Zuckerman. While in Pittsburgh he focused on methods development for biomolecular simulation, with an emphasis on statistically rigorous approaches for sampling protein conformation space. He then moved to Salt Lake City, Utah, where he joined the lab of Greg Voth. In Utah he worked on membrane protein simulation and multiscale simulation methods development.

Alexander MacKerell, Ph.D., is the Grollman-Glick Professor of Pharmaceutical Sciences at the University of Maryland School of Pharmacy. Research in Dr. MacKerell's lab involves the development and application of computational methods to investigate the relationships of structure and dynamics to function in a range of biological and chemical systems. These efforts range from empirical force field development, implementation of novel sampling methodologies, understanding the physical forces driving the structure and dynamics of proteins, nucleic acids and carbohydrates and computer-aided drug design (CADD) studies. Dr. MacKerell received his B.S. in Chemistry from the University of Hawaii, Honolulu and completed his Ph.D. in Biochemistry at Rutgers University.

Sergei Noskov, Ph.D., is an Associate Professor at the Institute of Biocomplexity and Informatics at the University of Calgary. His research interests include molecular modeling, membrane proteins (ion channels and ion-coupled transporters), quantum chemistry of biologically relevant molecules, free energy profiles, and protein structure/function prediction. Dr. Noskov's lab is comprised of a group of theoretical biologists and chemists interested in the understanding of molecular determinants of ligand transport across cellular membranes. Projects in his lab focus on studies of the family of fundamentally important ion-coupled neurotransmitter transporters implicated in diverse mechanisms of signal transduction in the brain. Their studies resulted in series of methods and software developed

in close collaboration with other theoretical groups across the world. Dr. Noskov received his Ph.D. from the Russian Academy of Sciences and completed his postdoctoral studies within the Department of Biochemistry and Structural Biology at Weill Medical College of Cornell University. Dr. Noskov is a recipient of AHFMR Scholar, CIHR New Investigator; and AIF New Faculty Awards (Canada); INTAS Young Scientist Award (European Union); and the Academia Sinica Research Fellowship and the American Epilepsy Foundation Post-Doctoral Fellowship (USA).

Jed Pitera, Ph.D., is a Research Staff Member in Science and Technology at the IBM Almaden Research Center. His research focuses on the use of computer simulation to address questions in biology and chemistry, particularly in the areas of protein folding, molecular recognition, self-assembly, and computer-aided materials design. His current research projects include simulations of polymeric materials for lithography, desalination, and drug delivery applications. Dr. Pitera received undergraduate training in Biology and Chemistry at the California Institute of Technology, where he worked in Prof. Pamela Bjorkman's protein crystallography group. Subsequently, he pursued graduate studies in Biophysics at the University of California, San Francisco (UCSF) in the laboratory of Prof. Peter Kollman. In Dr. Kollman's group, he developed an interest in the use of biomolecular simulation and free energy calculations in the rational design of proteins and pharmaceuticals. He pursued similar work in a postdoctoral position with Prof. Dr. Wilfred van Gunsteren at the ETH in Zurich, Switzerland, where his research focused on novel methods to calculate free energies for ligand design. Dr. Pitera is also an adjunct assistant professor in the UCSF Department of Pharmaceutical Chemistry, and maintains active collaborations with groups at UCSF and Stanford.

Scott Showalter, Ph.D., is an Associate Professor of Chemistry at Pennsylvania State University. He received his B.S. from Cornell University, his Ph.D. from Washington University School of Medicine, and completed his postdoctoral research at The National High Magnetic Field Laboratory in Tallahassee, Florida. Dr. Showalter's lab applies biophysical chemistry techniques to understand the function of partially disordered proteins and work to define the features of protein-RNA interactions.

Chung Wong, Ph.D., is an Associate Professor in the Department of Chemistry and Biochemistry at the University of Missouri-Saint Louis. He received his B.Sc. (Hons.) degree from the Chinese University of Hong Kong and his Ph.D. degree from the University of Chicago. He completed his postdoctoral work at the University of Houston. He has held academic and industrial positions at the University of Houston, Mount Sinai School of Medicine, SUGEN, Inc., University of California-San Diego, and the Howard Hughes Medical Institute before joining the faculty of University of Missouri, St. Louis in 2004. His research involves the development and applications of computational methods to study biomolecular structure, dynamics, and function and to aid the design of bioactive compounds. He has served on multiple grant review panels for the National Institutes of Health and the European Union and as a mentor for students in the Student Teacher as Research Scientist (STARS) program, a joint venture among University of Missouri-Saint Louis, Washington University, Saint Louis University, and several non-profit and for-profit institutions in Saint Louis to provide research opportunities to high-school students and teachers.

Troy Wymore, Ph.D., is a Research Assistant Professor in the Department of Biochemistry, Cellular and Molecular Biology at the University of Tennessee-Knoxville. He completed his B.S. and Ph.D. in Chemistry at the University of Missouri-Columbia. His research focuses on applying hybrid QC/MM simulations to investigate the enzymatic mechanisms of DFPase, Xylose Isomerase, and 5-epi-aristolocholene synthase. The results of these studies provide insight into strategies for redesigning these enzymes to more effectively degrade nerve agents (DFPase) and improve the process of biofuel and pharmaceutical agent production.

APPENDIX E

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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 National Research Council'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:

Robert Jernigan, Iowa State University

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.