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

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Board on Life Sciences

Division on Earth and Life Studies

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October 19, 2012

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, Third 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 two years (October 1, 2010 – September 30, 2012), DESRES has made available to the non-commercial research community node-hours on an Anton system housed at the Pittsburgh Supercomputing Center (PSC), based on the advice of previous National Research Council committees convened in the fall of 2010 and 2011.

The success of the program has led DESRES to make the Anton machine housed at PSC available for an additional 3,700,000 node-hours over the 9 months following October 2012, 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 15 was chaired by Dr. L. Mario Amzel, Professor and Director, Department of Biophysics and Biophysical Chemistry, Johns Hopkins University, School of Medicine. The committee members were selected for their expertise in molecular dynamics simulations, as well as their experience in the subject areas represented in the 52 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 goal of the third 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 drew on these progress reports as supplemental material in 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 questions that arose.

The committee was asked to identify proposals that best met the selection criteria. As in the previous two rounds of time allocations for Anton, 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 try to allocate approximately 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 also 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 15 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 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 meeting in Washington, D.C. on September 7, 2012. 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. The committee then considered the slate of proposals as a whole, 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.

The committee concluded that the 45 proposals listed below best met the selection criteria set forth in the RFP for Biomolecular Simulation Time on Anton. Of these 45 proposals, 12 proposals were selected for a modified allocation (identified below with an *). Detailed comments for each of the 52 proposals considered by the committee are included in Appendix B.

In numerical order by proposal submission number, the proposals that the committee concluded best met the selection criteria are:

PSCA12004P **Structural and Dynamic Effects of Antifreeze Proteins on Water**; PI: Lin, Tufts University *[New user, identified for 65,000 node-hours]**

PSCA12005P **Dynamic coupling and fluctuations in protein-protein complexes**; PI: Buck, Case Western Reserve University *[Returning user, identified for 50,000 node-hours]*

PSCA12006P **Atomistic mechanism of the nucleotide-dependent kinesin conformational changes assisted by the microtubule**; PI: Hwang, Texas A&M University *[Returning user, identified for 100,000 node-hours]*

PSCA12008P **Watching a small chemical chaperone in action: a dynamical approach using the Anton supercomputer**; PI: Berne, Columbia University *[Returning user, identified for 100,000 node-hours]*

PSCA12010P **Dynamics of the Early Translational Machinery**; PI: Luthey-Schulten, University of Illinois *[Returning user, identified for 100,000 node-hours]*

PSCA12012P **Microsecond scale simulations to characterize mutations and phosphorylations in full length troponin**; PI: McCammon, University of California San Diego *[Returning user, identified for 100,000 node-hours]*

PSCA12013P **Hidden Intermediates and Salt-induced Refolding**; PI: Huo, Clark University *[Returning user, identified for 100,000 node-hours]*

PSCA12014P **Predicting experimental signatures of lateral phase separation in ternary bilayers: Anchored domains or floating rafts?**; PI: Lyman, University of Delaware *[Returning user, identified for 100,000 node-hours]*

PSCA12016P **Elucidating the mechanism of pH-gating, solute selectivity, and flux of UreI, the urea channel of Helicobacter pylori**; PI: Luecke, University of California Irvine *[Returning user, identified for 80,000 node-hours]*

PSCA12017P **20 microsecond simulation of charge-shift electron transfer reaction in bacterial photosynthesis**; PI: Matyushov, Arizona State University *[New user, identified for 45,000 node-hours]*

PSCA12018P **Exploring the Membrane Selectivity of Antimicrobial Peptides**; PI: Kim, University of California San Diego *[Returning user, identified for 59,000 node-hours]*

PSCA12021P **Molecular Dynamics Simulations of p53-DNA Complexes**; PI: Rohs, University of Southern California *[New user, identified for 65,000 node-hours]**

PSCA12023P **MD and NMR characterizations of psychrotrophic, mesophilic, and thermophilic enzymes**; PI: Palmer, Columbia University *[New user, identified for 100,000 node-hours]*

PSCA12024P **Dynamics and Ligand Binding by HSP40 and HSP104 Chaperones in Relation to Iron-Sulfur Cluster Biogenesis and Protein Disaggregation**; PI: Scheraga, Cornell University*[Returning user, identified for 65,000 node-hours]**

PSCA12025P **Starting transcription by bacterial RNA polymerase**; PI: Thirumalai, University of Maryland *[Returning user, identified for 100,000 node-hours]*

PSCA12026P **Altering the allosteric communication between an active-state receptor and its cognate G protein: Unconstrained molecular dynamics simulation studies of the metarhodopsin II-Gtα(GDP) mutant complexes**; PI: Beratan, Duke University *[Returning user, identified for 50,000 node-hours]*

PSCA12027P **Understanding the Dynamics of Human Histone Deacetylase 8: From Regulation to Substrate Binding**; PI: Coveney, Yale University *[Returning user, identified for 100,000 node-hours]*

PSCA12028P **Determining the mechanisms of protein folding in membranes**; PI: Gumbart, Argonne National Laboratory *[New user, identified for 100,000 node-hours]*

PSCA12029P **Mechanisms of transition from open to occluded state in the outward-facing structure of sodium-coupled leucine transporter**; PI: Bahar, University of Pittsburgh *[Returning user, identified for 100,000 node-hours]*

PSCA12030P **Anton Simulations to Show the Role of Environment and Co-factors in Conformational Change of the SERCA (Ca-ATPase) Pump**; PI: Woolf, Johns Hopkins University *[Returning user, identified for 100,000 node-hours]*

PSCA12031P **Understanding Kinase Regulation through Microsecond Timescale Simulations of Protein Kinase A**; PI: Amaro, University of California San Diego *[New user, identified for 100,000 node-hours]*

PSCA12032P **Mechanism of agonist/antagonist sensor in opioid receptors - role of water molecules;** PI: Palczewski, Case Western Reserve University *[New user, identified for 65,000 node-hours]**

PSCA12033P **The determinants of C-type inactivation and recovery in the KcsA channel**; PI: Roux, University of Chicago *[Returning user, identified for 100,000 node-hours]*

PSCA12034P **Activation of the G-protein coupled receptor squid rhodopsin on the microsecond timescale**; PI: Tobias, University of California Irvine *[Returning user, identified for 100,000 node-hours]*

PSCA12035P **Conformational changes in lactose permease of E. coli to understand spin label dynamics and helix movements**; PI: Klauda, University of Maryland *[Returning user, identified for 50,000 node-hours]*

PSCA12036P **Long Time Scale Molecular Dynamics Simulation of Protein Folding**; PI: Gruebele, University of Illinois *[Returning user, identified for 100,000 node-hours]*

PSCA12038P **Converging simulations of a DNA duplex and explorations of a DNA mini-circle on the microsecond timescale using MD on Anton**; PI: Cheatham, University of Utah *[Returning user, identified for 100,000 node-hours]*

PSCA12040P **Multi-microsecond simulations of two-domain proteins**; PI: Chong, University of Pittsburgh *[Returning user, identified for 50,000 node-hours]*

PSCA12041P **Atomistic modeling of ion conduction through voltage-sensing domains**; PI: Freites, University of California Irvine *[Returning user, identified for 100,000 node-hours]*

PSCA12043P **Nascent protein folding inside the ribosomal exit tunnel**; PI: Schulten, University of Illinois *[Returning user, identified for 100,000 node-hours]**

PSCA12044P **Sequencing DNA Using MspA**; PI: Aksimentiev, University of Illinois *[Returning user, identified for 100,000 node-hours]*

PSCA12045P **Exploration of the Human Adenovirus Protease Activation Pathway via Long Timescale Molecular Dynamics Simulations**; PI: Walker, University of California San Diego *[Returning user, identified for 65,000 node-hours]**

PSCA12047P **Characterizing Ion-coupled Structural Transitions in Secondary Membrane Transporters**; PI: Tajkhorshid, University of Illinois *[Returning user, identified for 100,000 node-hours]**

PSCA12048P **Examining the Role of Lipid-Protein Interactions in the Activation of Membrane Proteins Using Microsecond-scale Molecular Dynamics Simulation**; PI: Allen, University of California Davis *[Returning user, identified for 100,000 node-hours]*

PSCA12049P **Molecular Dynamics Simulations of PTEN in Solution and on the Lipid Membrane**; PI: Nanda, Carnegie Mellon University *[New user, identified for 65,000 node-hours]**

PSCA12050P **Using microsecond scale dynamics to assist the development of inhibitors of Ca2+-independent phospholipase A2 enzymes**; PI: Dennis, University of California San Diego *[New user, identified for 100,000 node-hours]*

PSCA12051P **How do slow motions regulate a kinase's activity at the atomistic level?**; PI: S. Taylor, University of California San Diego *[Returning user, identified for 50,000 node-hours]*

PSCA12052P **The substrate-binding induced conformational transitions in HepI: Structure, mechanism, and conformational dynamics of a GT-B enzyme**; PI: E. Taylor, Wesleyan University *[New user, identified for 50,000 node-hours]*

PSCA12053P **Detailed characterization of the gp120/CD4/Ibalizumab complex**; PI: Langmead, Carnegie Mellon University *[Returning user, identified for 50,000 node-hours]*

PSCA12054P **Recognition Mechanisms of Membrane-targeting Protein Domains**; PI: Voth, University of Chicago *[New user, identified for 86,000 node-hours]*

PSCA12055P **Entropy in Protein-Ligand Binding via Simulations at the Microsecond Time Scale: Exploring the Consequence of Protease Mutations**; PI: Gilson, University of California San Diego *[Returning user, identified for 100,000 node-hours]*

PSCA12056P **Simulating Gating Transitions in Glutamate Receptors**; PI: Kurnikova, Carnegie Mellon University *[New user, identified for 65,000 node-hours]**

PSCA12057P **Microsecond MD Studies of Allosteric Drugs in the Imidazole Glycerol Phosphate Synthase**; PI: Batista, Yale University *[Returning user, identified for 65,000 node-hours]**

PSCA12058P **Polycyclic Natural Products and Analogues through Computational Enzyme Engineering**; PI: Pande, Stanford University *[Returning user, identified for 65,000 node-hours]**

PSCA12059P **Structural basis for the Thermostability of mutant G-protein coupled receptors; PI: Vaidehi**, City of Hope Medical Center *[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 3,655,000 node-hours. Of these proposals, 26 were identified at the approximately 100,000 node-hour level and 19 at the approximately 50,000 node-hour level.[1] A total of 956,000 node-hours were allocated to 13 proposals whose principal investigator did not receive time on Anton during the past two years (identified as "new users"). The remaining 2,699,000 node-hours are allocated to 32 proposals from investigators who had received previous round time allocations (indentified 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 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 2012 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,

L. Mario Amzel
Chair

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

[1] 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:

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
2. 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, THIRD ROUND

L. MARIO AMZEL, (*Chair*), Professor and Director, Biophysics and Biophysical Chemistry, Johns Hopkins University School of Medicine
IOAN ANDRICIOAEI, Associate Professor, Chemistry, School of Physical Sciences, University of California, Irvine
NILESH BANAVALI, Research Scientist, Wadsworth Center, New York State Department of Health, and Assistant Professor, School of Public Health, State University of New York, Albany
RICCARDO BARON, Assistant Professor, Department of Medicinal Chemistry, College of Pharmacy, The University of Utah
ANGEL E. GARCIA, Professor of Physics and Senior Constellation Chaired Professor in Biocomputation and Bioinformatics, Rensselaer Polytechnic Institute
TOSHIKO ICHIYE, Professor and William G. McGowan Chair in Chemistry, Department of Chemistry, Georgetown University
TERRY P. LYBRAND, Professor, Department of Chemistry, Pharmacology, & Center for Structural Biology, Vanderbilt University
GLENN MARTYNA, Research Staff Member, Physical Sciences Division, IBM T. J. Watson Lab
DAVID L. MOBLEY, Assistant Professor, Department of Pharmaceutical Sciences, University of California, Irvine
RICHARD W. PASTOR, Chief, Membrane Biophysics Section, National Heart Lung Blood Institute, National Institutes of Health
LOUKAS PETRIDIS, Research Staff Scientist, Center for Molecular Biophysics, Oak Ridge National Laboratory
B. MONTGOMERY PETTITT, Robert A. Welch Distinguished Chair in Chemistry, Professor in the Departments of Pharmacology and Toxicology and of Biochemistry and Molecular Biology, and Director of the Sealy Center for Structural Biology and Molecular Biophysics, University of Texas Medical Branch.
SCOTT A. SHOWALTER, Assistant Professor, Department of Chemistry, Pennsylvania State University
FENG WANG, Associate Professor, Department of Chemistry and Biochemistry, University of Arkansas
ARIEH WARSHEL, Distinguished Professor of Chemistry, Department of Chemistry, University of Southern California

NATIONAL RESEARCH COUNCIL STAFF

KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
KATHRYN HUGHES, Senior Program Officer, Board on Chemical Sciences and Technology
ORIN LUKE, Senior Program Assistant, Board on Life Sciences
SAYYEDA AYESHA AHMED, Senior Program Assistant, Board on Life Sciences

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

CHAIR

L. Mario Amzel, Ph.D., is Professor and Director of the Department of Biophysics and Biophysical Chemistry at the Johns Hopkins University School of Medicine. Dr. Amzel's research interests include structural enzymology of redox and phosphoryl-transfer enzymes, particularly the enzymes MICAL, VP14, PI3K, and Nudix hydrolases, and selected areas of structural thermodynamics. He received his Ph.D. in Physical Chemistry in 1968 from the Universidad de Buenos Aires, Argentina and completed his postdoctoral research in the structure of proteins from 1969-1970 at the Johns Hopkins University School of Medicine.

MEMBERS

Ioan Andricioaei, Ph.D., is Associate Professor of Chemistry in the School of Physical Sciences at the University of California, Irvine. His research focuses on exploring theoretical and computational topics at the interface between molecular biophysics and physical chemistry, with the central themes of (1) developing novel theoretical techniques, and (2) applying computer and modeling methods to describe, in terms of dynamics and thermodynamics, biologically important molecular processes, with the aim to complement, enhance, or predict experimental findings. Research directions include enhanced sampling in trajectory space, computer simulations of DNA-binding machines, and dynamics-function relationships. Dr. Andricioaei received his Ph.D. from Boston University in 1999.

Nilesh Banavali, Ph.D., is a Research Scientist at the Wadsworth Center of the New York State Department of Public Health and an 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. He 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.

Riccardo Baron, Ph.D., is Assistant Professor of Medicinal Chemistry and Adjunct Assistant Professor of Bioengineering at the University of Utah. His research develops chemical theory and computational approaches to address problems of relevance for public health. Following his education at the Università degli Studi di Milano (Italy) and University of Cambridge (U.K.), he carried out his doctoral research at the Department of Chemistry and Applied Biosciences of the Swiss Federal Institute of Technology, ETH Zurich (Switzerland). During his Ph.D. with Prof. Wilfred F. van Gunsteren, he designed a wide range of methods for biomolecular simulation, including entropy and free energy calculation, force field and software development. His postdoctoral research with J. Andrew McCammon, Investigator, Howard Hughes Medical Institute at the University of California, San Diego, led to a paradigm shift on the understanding of the physicochemical forces driving molecular recognition, approaches to efficiently introduce protein dynamics ensemble models in drug discovery and design, and models to understand the reactants transport in biocatalysts. He has published more than forty publications in the field of biomolecular simulation and actively serves as a member of the American Chemical Society and as a reviewer for numerous international journals, scientific societies, and computational centers

in the areas of chemistry, biology, physics, medicine, and engineering. He was recently awarded the "Alfredo di Braccio" Prize for Chemistry from the Accademia Nazionale dei Lincei (Italy) and the Postdoctoral Research Award from the American Chemical Society (U.S.). His current research integrates computational approaches with experiments through collaborations with world leading groups in enzymology and drug discovery.

Angel E. García, Ph.D., is the Senior Constellation Professor of Biocomputation and Bioinformatics at Rensselaer Polytechnic University. His research focuses on the use of theoretical and computational methods to study biomolecular dynamics and statistical mechanics, with the objectives of understanding the folding, dynamics and stability of biomolecules. Particular interests include the hydrophobic effect, enzyme catalysis, nucleic acid structure and dynamics, RNA folding, electrostatics, protein hydration, and peptide interactions with membranes. Before joining Rensselaer he was Group Leader at the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory. Dr. García is a Fellow of the American Physical Society. He received the Edward Bouchet Award from the American Physical Society in 2006. Dr. García is the Associate Editor of Proteins, Structure, Function and Bioinformatics and belongs to the editorial board of Biophysical Journal and Molecular Simulations. He is a member of the American Physical Society, Biophysical Society, American Chemical Society, Protein Society and the American Association for the Advancement of Science.

Toshiko Ichiye, Ph.D., is Professor and William G. McGowan Chair in Chemistry at Georgetown University. She is a leader in the field of molecular dynamics simulations, an area of computational chemistry that enables pharmaceutical companies, biotechnology firms, and bioengineering firms to design and perfect their products. Dr. Ichiye's research interests include theoretical biophysical and physical chemistry, structure and function of proteins, statistical mechanics of macromolecules and liquids, and molecular dynamics simulations of biological macromolecules. She received her B.A. in Physics from Rice University in 1978 and her Ph.D. in Biophysics in 1985 from Harvard University.

Terry P. Lybrand, Ph.D., is a Professor in the Department of Chemistry at Vanderbilt University. Dr. Lybrand's research focuses on molecular modeling and bioinformatics techniques. His laboratory utilizes computational methods to study the properties and behavior of biomacromolecules and ligand-biomacromolecule complexes, and to aid in the design of small molecule ligands with desired binding properties for targeted receptors. Techniques used include quantum mechanical calculations, molecular dynamics and Monte Carlo simulation, and free energy perturbation methods. Dr. Lybrand received his Ph.D. in Pharmaceutical Chemistry from the University of California, San Francisco in 1984.

Glenn J Martyna, Ph.D., is a research scientist at IBM's T.J. Watson Research Lab in Yorktown Heights, NY. Dr. Martyna received his Ph.D. in chemical sciences from Columbia University in 1989 and was an NSF postdoctoral fellow in computational science and engineering at the University of Pennsylvania. Dr. Martyna was appointed to the faculty of Indiana University, Bloomington, in 1993 and was awarded tenure in 2000. In 2001, he joined IBM's TJ Watson Research Lab in Yorktown Heights, NY. Dr. Martyna was awarded an honorary Professorship of Physics at the University of Edinburgh, UK in 2008. His research focuses on the use of novel methodology, parallel algorithms, and computer simulation to probe biophysical, materials and chemical systems including studies of aqueous solutions, complex heterogeneous interfaces, phase change materials, and nanomaterials.

David L. Mobley, Ph.D., is an Assistant Professor in the Department of Pharmaceutical Sciences at the University of California, Irvine. 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 was previously an Assistant Professor in Chemistry at the University of New Orleans (2008 to 2012) and 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.

Richard W. Pastor, Ph.D., is Chief of the Membrane Biophysics Section at the National Heart Lung and Blood Institute of the National Institutes of Health. He received a B.A. in philosophy from Hamilton College (1973), a M.S. in chemistry from Syracuse University (1977), and Ph.D. in Biophysics from Harvard University (1984). He did research and review at the Food and Drug Administration from 1984 to 2007, and moved to the National Institutes of Health in 2007. His research focuses on computer simulations of membranes, including method development (all-atom and coarse grained lipid force fields); fundamental theory (treatment of diffusion in two dimensions, and spontaneous curvature in membranes); biological applications (conformations of peptides in bilayers; fencing of PIP2); and technological applications (polymer transport through ion channels). Dr. Pastor is also a CHARMM developer (algorithms involving pressure anisotropy and long range forces).

Loukas Petridis, Ph.D. is a Research Staff Scientist in the Center for Molecular Biophysics at Oak Ridge National Laboratory. His research focuses on high-performance computer simulation of biological macromolecules, neutron scattering in bioenergy research and polymer physics. In particular, he investigates the origins of biomass recalcitrance via the integration of computer simulation with neutron scattering experiments, undertakes computer simulations of lignocelluloses, and investigates molecular-scale mechanisms stabilizing soil organic carbon by application of molecular dynamics simulation and neutron reflectometry. He also studies scaling of molecular dynamics simulation on supercomputers and physics of biopolymers. He obtained his Ph.D. in theoretical physics from Cambridge University in 2006 and was a postdoctoral fellow at Oak Ridge National Laboratory from 2007 to 2009.

B. Montgomery Pettitt, Ph.D., is the Robert A. Welch Distinguished Chair in Chemistry and Professor in the Departments of Pharmacology and Toxicology and of Biochemistry and Molecular Biology at the University of Texas Medical Branch. He also directs the Sealy Center for Structural Biology and Molecular Biophysics, a research center serving the greater Houston-Galveston area with facilities for structural biology (x-ray, NMR and cryoEM) and scientific computing for use in the areas of simulation and modeling. His research focuses on understanding molecular recognition and folding of biopolymers in solution. His theoretical research interests have led to the development of novel methods for calculating the behavior of biopolymers in solution and near surfaces. He earned his B.S. and Ph.D. from the University of Houston, was a postdoctoral fellow at the University of Texas at Austin, and was an NIH Fellow at Harvard University.

Scott A. Showalter, Ph.D., is an Assistant Professor in the Department of Chemistry at the Pennsylvania State University. Dr. Showalter's research aims to understand structure-function relationships in biomolecular systems that display extensive conformational dynamics. His group has developed solution NMR spectroscopy methods based on direct carbon detection that enable high resolution structural and dynamic studies of intrinsically disordered proteins and the conformational changes they undergo in folding-upon-binding reaction mechanisms. Combining

NMR data with isothermal titration calorimetry assays and conformational modeling using ultra-long molecular mechanics calculations performed on the ANTON platform provides atomistic ensembles with high spatial and temporal resolution, as well as mechanistic insight into disordered protein function. The Showalter laboratory also applies similar biophysical techniques to study non-specific double-stranded RNA binding by double-stranded RNA binding proteins involved in microRNA maturation. Dr. Showalter received his Ph.D. from Washington University School of Medicine in St. Louis, MO, where he was an NSF predoctoral fellow. He was an NIH-NRSA postdoctoral fellow at the National High Magnetic Field Laboratory in Tallahassee, FL.

Feng Wang, Ph.D., is an Associate Professor in the Department of Chemistry and Biochemistry at the University of Arkansas. He was formerly an Assistant Professor in the Department of Chemistry at Boston University from 2005 to 2012. Dr. Wang's research focuses on developing high quality force fields, free energy calculations, and enhanced sampling. He received his B.S. in Chemistry from Peking University (1998) and Ph.D. in Theoretical Chemistry from the University of Pittsburgh (2003) with Prof. Kenneth D. Jordan. He did post-doctoral research in computational physical chemistry at the University of Utah with Professor Gregory A. Voth. While at the University of Pittsburgh, Dr. Wang received an IBM graduate student award in 2001 and a Mellon Fellowship in 2002. He received a NSF CAREER Award in 2007 and an HP outstanding Junior Faculty Award in 2010.

Arieh Warshel, Ph.D., is a Distinguished Professor of Chemistry and Biochemistry at the University of Southern California. Dr. Warshel is known for his work on computational biochemistry and biophysics, in particular for pioneering computer simulations of the functions of biological systems, and for developing what is known today as Computational Enzymology. Dr. Warshel made major contributions in introducing computational methods for structure function correlation of biological molecules, pioneering and co-pioneering programs, methods and key concepts for microscopic studies of functional properties of biological molecules including Cartezian based force field programs, the QM/MM method for simulating enzymatic reactions, the first molecular dynamic simulation of a biological process, microscopic electrostatic models for proteins, and free energy perturbation in proteins and other key advances. He 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. He is an elected member of the United States National Academy of Sciences (2009), a fellow of the Royal Society of Chemistry (2008), a fellow of the Biophysical Society (2000), and an Alfred P. Sloan fellow (1978). He has received awards including the Annual Award of the International Society of Quantum Biology and Pharmacology (1993); Tolman Medal (2003); President's award for computational biology from the ISQBP (2006); and RSC Soft Matter and Biophysical Chemistry Award (2012).

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 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:

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.