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

DETAILS

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Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics, Sixth Round; Board on Life Sciences; Board on Chemical Sciences and Technology; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

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Board on Life Sciences

Board on Chemical Sciences and Technology

Division on Earth and Life Studies

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September 28, 2015

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, Sixth 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 five years, 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. As in prior rounds, the goal of the sixth 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. 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 2015, and DESRES asked the National Academies of Sciences, Engineering, and Medicine to once again facilitate the allocation of time to the non-commercial community. The work of the 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 Academies' Board on Life Sciences.

To undertake this task, the National Academies convened a committee of experts to evaluate the proposals submitted in response to the RFP. The committee of 22 was chaired by Dr. Robert Eisenberg, Bard Endowed Professor and Chairman Emeritus of the Department of Molecular Biophysics and Physiology at Rush University. The committee members were selected for their expertise in molecular dynamics simulations and experience in the subject areas represented in the 70 proposals that were considered. The members 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, which the committee drew on 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 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 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 22 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.

The committee held its meeting in Washington, D.C. on August 4, 2015. At the meeting, the two primary reviewers were asked to summarize their reviews 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 considered the slate of proposals under consideration, 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 70 proposals are included in Appendix B.

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 48 proposals, 30 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:

PSCA15002 McCammon, University of California, San Diego; **MD simulation to elucidate activation pathway of TLR8** *[Returning user, identified for 50,000 node-hours]**

PSCA15003 Weinstein, Weill Cornell Medical College; **Mechanistic differences in LeuT-fold transporter family proteins** *[Returning user, identified for 50,000 node-hours]**

PSCA15005 Axelsen, University of Pennsylvania; **Amyloid beta protein misfolding in reverse micelles** *[New user, identified for 25,000 node-hours]**

PSCA15007 Tobias, University of California, Irvine; **Modeling diffusion of membrane–bound signaling proteins on the microsecond timescale** *[Returning user, identified for 100,000 node-hours]*

PSCA15008 Li, University of Vermont; **Mechanistic Study to Reveal How a Class B GPCR Responds to Hormone Signals** *[Returning user, identified for 50,000 node-hours]**

PSCA15009 Im, University of Kansas; **Influence of Glycosphingolipid Composition and Concentration on Lipid Clustering and Membrane Properties and Curvature** *[Returning user, identified for 100,000 node-hours]*

PSCA15018 Beratan, Duke University; **Simulating the Electron Transfer Mechanisms of Extremophiles** *[Returning user, identified for 50,000 node-hours]**

PSCA15020 Matyushov, Arizona State University; **Anton Allocation: microsecond simulation of rate-limiting electron transfer in bacterial photosynthesis** *[Returning user, identified for 63,000 node-hours]*

PSCA15021 Lazaridis, City College of New York; **The structure of peptide-induced pores in lipid membranes: Effects of lipid composition, molecularity, and peptide charge** *[Returning user, identified for 100,000 node-hours]*

PSCA15022 Scheraga, Cornell University; **The effect of L- to D-amino acid racemization on the stability and protein dynamics of a beta-crystallin tetramer from the mammalian lens** *[Returning user, identified for 50,000 node-hours]*

PSCA15023 Loesche, Carnegie Mellon University; **PTEN Signaling: Membrane Association as a Function of Protein Status** *[Returning user, identified for 100,000 node-hours]*

PSCA15025 Thirumalai, University of Maryland; **Gateway for Phosphate Release from Myosin VI Nucleotide Binding Site** *[Returning user, identified for 75,000 node-hours]*

PSCA15026 Polenova, University of Delaware; **Dynamic Characterization of the Spacer Peptide 1 in HIV-1 Capsid Protein Assemblies** *[New user, identified for 100,000 node-hours]*

PSCA15027 Weng, Whitehead Institute for Biomedical Research; **Structural basis for enzyme catalytic promiscuity in plant specialized metabolism** *[New user, identified for 50,000 node-hours]*

PSCA15028 Gruebele, University of Illinois at Urbana-Champaign; **Testing the mechanistic convergence of protein folding experiments and simulations** *[Returning user, identified for 75,000 node-hours]**

PSCA15029 van der Vliet, University of Vermont; **Structure/Function Relationships of the Redox-Regulation of the Src Kinase** *[New user, identified for 50,000 node-hours]**

PSCA15030 Pohorille, University of California San Francisco; **Toward rational design of antiviral drugs: linking structure and electrophysiology of viral ion channels** *[Returning user, identified for 50,000 node-hours]*

PSCA15032 O'Brien, Pennsylvania State University; **Co-translational protein folding on the ribosome: Pathways, interactions and translation rates** *[Returning user, identified for 50,000 node-hours]**

PSCA15034 Ulmschneider, Johns Hopkins University; **Membrane assembly and the equilibrium configurational ensemble of antimicrobial peptide channels** *[New user, identified for 75,000 node-hours]**

PSCA15035 Ackad, Southern Illinois University, Edwardsville; **Determining the Motion of a Molecular Nano Bio-Switch** *[New user, identified for 50,000 node-hours]**

PSCA15036 Aksimentiev, University of Illinois at Urbana-Champaign; **Molecular basis of epigenetic regulation** *[Returning user, identified for 100,000 node-hours]*

PSCA15038 Cisneros, Wayne State University; **Molecular dynamics investigation of hen egg white lysozyme folding/unfolding for enabling mass spectrometry interpretation** *[New user, identified for 50,000 node-hours]*

PSCA15039 Roux, University of Chicago; **Proton traffic in the sodium-potassium pump ATPase** *[Returning user, identified for 60,000 node-hours]**

PSCA15041 Garcia, Rensselaer Polytechnic Institute; **Comparing the Role of Arginine and Lysine Sidechains in Antimicrobial Peptide Activity** *[Returning user, identified for 100,000 node-hours]*

PSCA15043 Klauda, University of Maryland; **Phase Separation of Long-chained Inositol Phosphoceramide in Model Yeast Membranes** *[Returning user, identified for 100,000 node-hours]*

PSCA15044 Pastor, NHLBI, National Institutes of Health; **A 25 µs Trajectory of Alamethicin in a DOPC Bilayer** *[Returning user, identified for 100,000 node-hours]**

PSCA15046 Bahar, University of Pittsburgh; **Microsecond molecular dynamics guided by elastic network model: Application to AMPA receptor druggability** *[Returning user, identified for 75,000 node-hours]**

PSCA15047 Cowburn, Albert Einstein College of Medicine; **Characterizing the disordered FG repeat domains of Nuclear Pore Complexes by simulation and experiment** *[Returning user, identified for 50,000 node-hours]**

PSCA15050 Lyman, University of Delaware; **Compositional Complexity: Packing, Lateral Structure, and Nanoscale Dynamics in Plasma Membrane Mixtures** *[Returning user, identified for 100,000 node-hours]*

PSCA15051 Buck, Case Western Reserve University; **Simulations of TM helix dimers and GTPase lipid interactions** *[Returning user, identified for 50,000 node-hours]*

PSCA15052 Luthey-Schulten, University of Illinois at Urbana-Champaign; **Dynamics of the Translational Machinery** *[Returning user, identified for 50,000 node-hours]*

PSCA15053 Dror, Stanford University; **Structural basis for protein-ligand-mediated, constitutive, and biased signaling in chemokine GPCRs** *[Returning user, identified for 100,000 node-hours]*

PSCA15056 Shukla, University of Illinois at Urbana-Champaign; **Ligand-Binding Pathways in a Glutamate Receptor** *[New user, identified for 100,000 node-hours]*

PSCA15057 Sosnick, University of Chicago; **Molecular Determinants of Folding of Potassium Channel** *[Returning user, identified for 60,000 node-hours]**

PSCA15058 Post, Purdue University; **The Effect of Tyr130 Phosphorylation on the Structure, Dynamics and Binding Energetics of the SYK tandem SH2 Protein** *[Returning user, identified for 50,000 node-hours]**

PSCA15059 Haddadian, University of Chicago; **Modeling the Amyloid-β fibril formation on 2D surfaces using self-assembled-monolayers (SAM)** *[New user, identified for 50,000 node-hours]**

PSCA15060 Palczewski, Case Western Reserve University; **Mechanism of biased signaling in serotonin receptors** *[Returning user, identified for 100,000 node-hours]*

PSCA15061 Onuchic, Rice University; **The Conformational Rearrangement of Influenza Hemagglutinin: Molecular Details of the Transition** *[Returning user, identified for 100,000 node-hours]*

PSCA15066 Schulten, University of Illinois at Urbana-Champaign; **A Computational Study for Understanding Structure and Dynamics in Circular Proteins** *[Returning user, identified for 75,000 node-hours]**

PSCA15071 Freites, University of California, Irvine; **Molecular modeling studies of eye lens proteins at physiological concentrations** *[Returning user, identified for 50,000 node-hours]**

PSCA15072 Grant, University of Michigan; **G protein activation mechanisms** *[New user, identified for 50,000 node-hours]*

PSCA15073 Perozo, University of Chicago; **Coupled movements between the voltage-sensing and the phosphatase domains of Ci-VSP** *[Returning user, identified for 60,000 node-hours]**

PSCA15074 Tombola, University of California, Irvine; **Atomistic modeling of the human Hv1 voltage-gated proton channel** *[New user, identified for 50,000 node-hours]**

PSCA15075 Sotomayor, Ohio State University; **Bending and Refolding of an Atypical Cadherin Fragment Involved in Inner Ear Mechanotransduction** *[New user, identified for 100,000 node-hours]*

PSCA15077 Yarov-Yarovoi, University of California, Davis; **Large-scale exploration of sodium channel interactions with small molecules and peptide toxins** *[Returning user, identified for 70,000 node-hours]**

PSCA15078 Agard, University of California San Francisco; **Conformational Dynamics of the Molecular Chaperone Heat Shock Protein 90 (HSP90)** *[New user, identified for 74,000 node-hours]**

PSCA15079 Jang, Queens College of the City University of New York; **Exploration of stability and quasistatic disorder of in silico models for mutant and synthetic analogues of photosynthetic light harvesting 2 (LH2) complex through microsecond molecular dynamics simulation** *[Returning user, identified for 20,000 node-hours]**

PSCA15080 Kurnikova, Carnegie Mellon University; **Simulating Gating in Glutamate Receptors** *[Returning user, identified for 100,000 node-hours]*

The time allocations for the 48 proposals identified by the committee as best meeting the selection criteria for time allocations total approximately 3,357,000 node-hours. Of the 48 proposals identified, 24 were identified at the approximately 100,000 node-hour level and 24 at the 50,000 node-hour level or below.[1] A total of approximately 824,000 node-hours were allocated to proposals whose principal investigator did not receive time on Anton during the past five years (identified as "new users"). Approximately 25% of the available simulation time thus was allocated to new users of Anton. The remaining 2,533,000 node-hours are allocated to 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 total simulation time requested by the submitted proposals was over 6 million node hours. As a result, a number of interesting proposals were not able to be recommended in this round, entailing difficult decisions.

The committee would like to thank D. E. Shaw Research, the Pittsburgh Supercomputing Center, and all of the 2015 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 Eisenberg
Chair

cc: Dr. Markus Dittrich, Pittsburgh Supercomputing Center
Dr. Gregory Symmes, National Academies of Sciences, Engineering, and Medicine
Dr. Frances Sharples, National Academies of Sciences, Engineering, and Medicine

[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
   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

ROBERT EISENBERG *(Chair)*, Department of Molecular Biophysics and Physiology, Rush University, Chicago, Illinois
L. MARIO AMZEL, Department of Biophysics and Biophysical Chemistry, Johns Hopkins University School of Medicine, Baltimore, Maryland
NILESH BANAVALI, Wadsworth Center, New York State Department of Health, Albany
JAMES BRIGGS, Department of Biology and Biochemistry, University of Houston, Texas
CHARLES L. BROOKS III, Department of Chemistry and Biophysics, University of Michigan, Ann Arbor
CHIA-EN ANGELINA CHANG, Department of Chemistry, University of California, Riverside
JIANHAN CHEN, Department of Biochemistry and Molecular Biophysics, Kansas State University, Manhattan
ALEMAYEHU GORFE, Department of Integrative Biology and Pharmacology, University of Texas Medical School, Houston
FATEMEH KHALILI-ARAGHI, Department of Physics, University of Illinois at Chicago
ANDRZEJ KLOCZKOWSKI, Battelle Center for Mathematical Medicine, Nationwide Children's Hospital, Columbus, Ohio
JEFFRY D. MADURA, Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania
SILVINA MATYSIAK, Fischell Department of Bioengineering, University of Maryland, College Park
JEETAIN MITTAL, Department of Chemical Engineering, Lehigh University, Bethlehem, Pennsylvania
SERGEI NOSKOV, Department of Biological Sciences, University of Calgary, Alberta, Canada
ROMAN OSMAN, Icahn Medical Institute, Mount Sinai School of Medicine, New York, New York
PATRICIA REGGIO, Department of Chemistry and Biochemistry, University of North Carolina at Greensboro
DAVID SEPT, Biomedical Engineering, University of Michigan, Ann Arbor
SADASIVAN SHANKAR, John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts
LEI SHI, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland
NADEEM VELLORE, Huntsman Cancer Institute, University of Utah, Salt Lake City
CHUNG WONG, Department of Chemistry and Biochemistry, University of Missouri-St. Louis
RUHONG ZHOU, Soft Matter Science Group, IBM Research, Armonk, New York

National Research Council Staff

KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
KATHRYN HUGHES, Senior Program Officer, Board on Chemical Sciences and Technology
COTILYA BROWN, Senior Program Assistant, Board on Chemical Sciences and Technology

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

Chair

Robert Eisenberg, Ph.D., is the Bard Endowed Professor and Chairman emeritus in the Department of Molecular Biophysics and Physiology at Rush University. Dr. Eisenberg has been working at the interface of physics, physiology, and computation since he used Green's functions to solve and compute the linear electrical properties of nerve cells, and has worked on multiple scales, from inside ion channels, to cell membranes, cells, and tissues. All of this work has used computation to allow theories to confront real experimental data taken on physiological scales. Dr. Eisenberg's recent work has concentrated on understanding the selectivity of calcium (e.g., L-type cardiac) and sodium channels, an area in which he has done extensive Monte Carlo simulations and a wide variety of multi-scale models. Dr. Eisenberg has a Ph.D. in Biophysics from the University of London.

Members

L. Mario Amzel, Ph.D., is Professor and Director at Johns Hopkins University School of Medicine, Department of Biophysics and Biophysical Chemistry. Dr. Amzel received his Ph.D. in Physical Chemistry in 1968 at the Universidad de Buenos Aires, Argentina. During his 1969-1970 postdoctoral fellowship at Johns Hopkins University School of Medicine, he studied protein structure. Dr. Amzel's research interests include the structural enzymology of redox and phosphoryl-transfer enzymes: MICAL, VP14, PI3K, and Nudix hydrolases as well as structural thermodynamics.

Nilesh Banavali, Ph.D, is a Research Scientist at the Wadsworth Center of the New York State Department of 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.

James Briggs, Ph.D., is an Associate Professor within the Biology and Biochemistry Department at the University of Houston. Dr. Briggs received his Ph.D. in Chemistry from Purdue University. His research focuses on computational studies of protein structure and function, inhibitor design, investigations of possible inhibitor resistance pathways, and development of methods for the above project areas. Targets for these studies include those important in the treatment of AIDS, cancer, bacterial infections, and other disease states. In addition, Dr. Briggs is currently working on inhibitors for cancer, addition control and heart disease targets.

Charles L. Brooks III, Ph.D., serves as the Warner-Lambert/Parke-Davis Professor of Chemistry and a Professor of Biophysics in the Department of Chemistry at the University of Michigan. Professor Brooks serves as the Member of Technology Advisory Board at EPIX Pharmaceuticals, Inc. Since August 2008, Professor Brooks has authored or co-authored more than 240 journal articles and book chapters. Professor Brooks' research interests focus on the application of statistical mechanics, quantum chemistry and computational methods to chemically- and physically-oriented problems in biology. His current research interests include free energy based methods for screening and optimization lambda-dynamics, ligand docking, protein stability and continuum based free energy

approximations, the development of new polarizable force fields for proteins, lipids and small molecules, protein folding, and protein structure prediction, ab initio folding, and homology modeling. He holds a Ph.D. in Physical Chemistry from Purdue University.

Chia-en Angelina Chang, Ph.D., is Associate Professor of Chemistry and Bioinformatics at the University of California, Riverside. The central goal of her research is to understand the fundamental mechanism of biomolecular recognition and binding kinetics using theory and classical mechanical models. Her research involves the development and application of computational methods and theoretical models to address medically and chemically important problems. These methods are of practical importance in studying biomolecular function, and in the design of new molecules that bind strongly to their receptors. Systems of particular interest include existing or potential drug targets, cell signaling complexes and chemical host-guest systems. Dr. Chang has a Ph.D. from the University of Maryland, College Park.

Jianhan Chen, Ph.D., is an Associate Professor in the Department of Biochemistry and Molecular Biophysics at Kansas State University. The general focus of his research is on theoretical and computational studies of biomolecular structure, dynamics and function. He and his team are particularly interested in modeling weakly stable peptides and proteins and understanding their roles in important biological processes including regulation of transcription and translation, signal transduction and disease-related protein misfolding. Further, Dr. Chen's research team applies computer modeling to determine the selectivity, transport and gating mechanisms of designed anion selective channels. Dr. Chen has a Ph.D. in Chemical and Material Physics from the University of California, Irvine.

Alemayehu (Alex) Gorfe, Ph.D., is an Associate Professor in the Department of Integrative Biology and Pharmacology at the University of Texas Medical School at Houston. He has a Ph.D. in Biochemistry from the University of Zurich in Switzerland. Dr. Gorfe and his research team use computer simulations to study the organization of cell signaling components, interfacial interactions and allostery to aid in the development of treatments for unsolved health challenges. Their special focus is on the Ras family of lipid-modified enzymes that regulate a variety of cell signaling pathways and whose malfunction leads to many forms of cancer. There is an urgent need for an ongoing effort to find drugs that abrogate signaling through defective Ras. Aiming at contributing to this effort, Dr. Gorfe and his team study Ras at the atomic, molecular and supramolecular levels of detail using multi-scale simulations and collaborative cell-biological and biophysical experiments. They are particularly interested in understanding how dynamics and lateral distribution of Ras and related G-proteins on membrane surfaces may affect their ability to functionally interact with other proteins. Other interests of the group include modeling transient signaling complexes and interaction between specific drugs and phospholipids.

Fatemeh Khalili-Araghi, Ph.D., is an Assistant Professor of Physics at the University of Illinois at Chicago. She was born in Santa Barbara, California on April 25, 1979. She lived in Iran for most of her childhood, and entered Sharif University of Technology in Tehran to pursue her B.Sc. degree in Physics (1996-2001). Upon graduation, she joined the Physics Department at the University of Illinois at Urbana-Champaign, where she performed her Ph.D research under the supervision of Klaus Schulten. Dr. Khalili-Araghi received her Ph.D. in Physics from the University of Illinois at Urbana-Champaign in 2010 and completed her postdoctoral studies at the University of Chicago under the supervision of Benoit Roux in 2012.

Andrzej Kloczkowski, Ph.D., is Principal Investigator at the Battelle Center for Mathematical Medicine of The Research Institute at Nationwide Children's Hospital and a Professor of Pediatrics at The Ohio State University College of Medicine. 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.

Jeffry D. Madura, Ph.D. is Professor and the Lambert F. Minucci Endowed Chair in Computational Sciences and Engineering in the Department of Chemistry and Biochemistry at Duquesne University located in Pittsburgh, PA. He earned a B.A. from Thiel College in 1980 and a Ph.D. in Physical Chemistry from Purdue University in 1985 under the direction of Professor William L. Jorgensen. The Ph.D. was followed by a postdoctoral fellowship in computational biophysics with Professor J. Andrew McCammon at the University of Houston. Dr. Madura's research interests are in computational chemistry and biophysics. He has published more than 100 peer-reviewed papers in physical chemistry and chemical physics. Dr. Madura has taught chemistry to undergraduate and graduate students for 24 years and was the recipient of a Dreyfus Teacher-Scholar Award. Dr. Madura was the recipient of the 2014 American Chemical Society Pittsburgh Section Award and received the Bayer School of Natural and Environmental Sciences and the Duquesne University Presidential Award for Excellence in Scholarship in 2007. He is an ACS Fellow and a Fellow of the Royal Society of Chemistry. He is currently working with high school students and teachers as part of the ACS Science Coaches program.

Silvina Matysiak, Ph.D., is an Assistant Professor in the Fischell Department of Bioengineering at the University of Maryland, College Park. Dr. Matysiak was awarded a diploma in chemical engineering from the Instituto Tecnologico de Buenos Aires, Argentina in 2001, and received her Ph.D. in Chemistry from Rice University in 2007. Before joining the University of Maryland, she was a postdoctoral fellow at the University of Texas at Austin in the department of Chemistry and Biochemistry and at the Institute of Computational Sciences and Engineering. She was a fellow at the Institute for Pure and Applied Mathematics at UCLA, and has been a visiting scientist at the Max-Planck Institute for Polymer Research and the Manufacturing Research Center at the Georgia Institute of Technology. Dr. Matysiak's primary area of interest is in the characterization of protein dynamics and function at the molecular level. Her work includes using computer simulations to study the mechanisms of protein folding and misfolding associated with Alzheimer's and Parkinson's diseases, protein assembly in biomedically relevant systems, protein-membrane interactions, and how solvent organization affects cooperative transitions in bio-molecular systems. Dr. Matysiak received the ACS-PRF award (2013) and the NSF CAREER Award (2015).

Jeetain Mittal, Ph.D., is an Associate Professor of Chemical and Biomolecular Engineering at Lehigh University. He holds a Ph.D. in Chemical Engineering from The University of Texas at Austin, an M.Tech in Chemical Engineering from the Indian Institute of Technology, and a B.Tech in Chemical Engineering from Beant College of Engineering and Technology. Research interests include the simulation and theory of protein stability and dynamics, hydrophobic transport, and molecular thermodynamics. In 2013, Dr. Mittal received the Allan P. Colburn Award from the American Institute of Chemical Engineers (AICHE), and in 2014, he was named an Alfred P. Sloan Research Fellow in Chemistry.

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. The studies of Dr. Noskov and his team resulted in a 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. In Canada, Dr. Noskov is a recipient of the AHFMR Scholar, CIHR New Investigator, and AIF New Faculty awards. In the European Union, he is the recipient of the INTAS Young Scientist Award. Finally, in the U.S., he is the recipient of the Academia Sinica Research Fellowship and the American Epilepsy Foundation Post-Doctoral Fellowship awards.

Roman Osman, Ph.D. is Professor of Structural and Chemical Biology and Professor of Pharmacology and Systems Therapeutics in the Icahn School of Medicine at Mount Sinai Hospital. Dr. Osman's research focuses on theoretical and computational approaches to evaluating the energetics and dynamics of waters trapped inside G-protein coupled receptors (GPCRs). His group is applying these approaches to study the role of waters in GPCR activation, protein-protein interaction and protein-small molecule complexes. His group also studies the interaction of peptide antigens with immune system MHC proteins responsible for autoimmune thyroid diseases and type I diabetes and the protein interactions of melanoma antigen (MAGE) family proteins associated with induction of cellular apoptosis. He received his M.S. from Hebrew University and his Ph.D. from Tel-Aviv University.

Patricia Reggio, Ph.D. is Marie Foscue Rourk Professor and Head of the Department of Chemistry and Biochemistry at the University of North Carolina, Greensboro. Dr. Reggio has a Ph.D. in Physical Chemistry from the University of New Orleans, where she also completed her postdoctoral fellowship. The major focus of her research group is on the G protein-coupled cannabinoid receptors, including the well-known cannabinoid CB1 and CB2 receptors, as well as new orphan receptors that appear to be cannabinoid receptors, GPR55 and GPR18. Additionally, her research also focuses on designing drugs for a specific target using computational chemistry and optimizing them for use as a medication. Dr. Reggio was previously a professor at Kennesaw State University and is also a past President of the International Cannabinoid Research Society.

David Sept, Ph.D., is a Professor of Biomedical Engineering at the University of Michigan in Ann Arbor. Research in the Sept lab covers four primary areas. The first focuses on the molecular interactions underlying cell migration, a process central to many aspects of development, differentiation and the cellular response to diseases such as cancer. Related to this is work characterizing and developing drugs that target sub-cellular filaments to treat parasitic diseases like toxoplasmosis, leishmaniasis and malaria. The third area of research concerns channels that regulate the flow of ions in and out of the cell, how these channels are activated and how they malfunction in diseases such as epilepsy. The final research area is on nanoparticle based drug delivery and how these particle drug combinations are metabolized and distributed within the body.

Sadasivan (Sadas) Shankar, Ph.D. is the first Margaret and Will Hearst Visiting Lecturer in Computational Science and Engineering at Harvard School of Engineering and Applied Sciences. In fall 2013, as the first Distinguished Scientist in Residence at the Institute of Applied Computational Sciences in Harvard, along with Dr. Tim Kaxiras, he developed and co-instructed with Dr. Brad Malone, a graduate-level class on Computational Materials Design, which covered fundamental atomic and quantum techniques and practical applications for new materials by design. Dr. Shankar earned his Ph.D. in Chemical Engineering and Materials Science from University of Minnesota, Minneapolis. Dr. Shankar has initiated and led multiple efforts in Intel, most recently the Materials Design Program. Over his tenure in research and development in the semiconductor industry, he and

his team have worked on several new initiatives – using modeling to optimize semiconductor processing and equipment for several technology generations, advanced process control using physics-based models, thermo-mechanical reliability of microprocessors, thermal modeling of 3D die stacking, and using thermodynamic principles to estimate energy efficiency of ideal computing architectures.

Lei Shi, Ph.D., is an Investigator and Chief of the Computational Chemistry and Molecular Biophysics Unit, Intramural Research Program, National Institute on Drug Abuse, NIH. He had graduate and postdoctoral training from Columbia University Medical Center, and was an Assistant Professor at Weill Medical College of Cornell University before being recruited by NIH. Dr. Shi's research is focused on the structure-function understanding of membrane proteins, many of which play critical roles in signal transduction and transport processes.

Nadeem Vellore, Ph.D. is a Research Scientist at the Huntsman Cancer Institute of the University of Utah. Dr. Vellore received his Bachelors in Biotechnology from Bharathidasan University, India in 2003. After completion of his postgraduate program in 2004, he spent two years working on computational drug discovery at AstraZeneca Pharmaceuticals. He obtained his PhD from Clemson University in 2011, studying protein-surface interactions using molecular simulation and developing advanced sampling methods. His postdoctoral work at The University of Utah focused on understanding epigenetic regulation using computational simulation in the direction of pharmaceutical relevance. He joined the Huntsman Cancer Institute at The University of Utah as a Research Scientist in 2014. His current research focuses on understanding the molecular roots of drug resistance due to mutations and rational inhibitor design to target these mutant proteins.

Chung Wong, Ph.D. is a Professor within the Department of Chemistry and Biochemistry at the University of Missouri-St. Louis. He received his B.Sc. (Honors) 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. His laboratory's research involves the development and applications of computational methods to study biomolecular structure, dynamics, and function and to aid the design of bioactive compounds. Dr. Wong 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.

Ruhong Zhou, Ph.D. is a Distinguished Research Staff Scientist (DRSM) and Manager of the Soft Matter Science Group at IBM Research, as well as an Adjunct Professor at the Department of Chemistry, Columbia University. He received his Ph.D. in Chemistry from Columbia University (with Prof. Bruce Berne) in 1997. His current research interests include development of novel algorithms for computational biology and bioinformatics, protein folding dynamics, protein-protein interaction, confined water and hydrophobicity, as well as protein-nanoparticle interactions (nanotoxicity/nanomedicine). He has published 150+ peer-reviewed papers and 22 patents, and delivered 150+ invited talks worldwide. He was part of the IBM Blue Gene team which won the 2009 National Medal on Technology. He also won the IBM Outstanding Technical Achievement Award (OTAA), the highest IBM technical award, in 2005, 2008 and 2014, and IBM Outstanding Innovation Award (OIA) in 2012, and the DEC Award from American Chemical Society (ACS). He serves as Editor-in-Chief of Current Physical Chemistry, Editor of (Nature) Scientific Reports, Guest Editor for Nanoscale (2011), and Editorial Board Member of 5 other international journals. He sits on the Board of Directors of Telluride Science and Research Center (TSRC), and the Scientific Advisory Board of Center for Multiscale Theory and Simulation, University of Chicago. He was elected an AAAS Fellow and APS Fellow in 2011, and IBM Distinguished RSM in 2014.

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 her perspective and technical expertise, in accordance with procedures approved by the Academies' 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 her review of this report:

Kathleen Hall, Washington University in St. Louis

Although the reviewer listed above has provided many constructive comments and suggestions, she was not asked to endorse the conclusions. In addition, she 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.