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

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

Board on Life Sciences

Division on Earth and Life Studies

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

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September 2, 2010

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

Dear Dr. Hezky:

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

The committee evaluated submissions in response to a Request for Proposals (RFP) for Biomolecular Simulation Time on Anton, a specialized supercomputer designed and constructed by D.E. Shaw Research that allows for dramatically accelerated molecular dynamics simulations. D.E. Shaw is making time on a 512 node Anton machine available to the non-commercial research community without cost. During this time, the Anton machine will be housed at the Pittsburgh Supercomputing Center (PSC)'s National Resource for Biomedical Supercomputing; the related support work to enable Anton to be used by the community is supported by a grant from the National Institute of General Medical Sciences to the PSC. The work of the National Research Council (NRC) committee to evaluate proposals requesting allocations of time on Anton 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 consider the proposals submitted in response to the Anton allocation RFP. The committee of 16 was chaired by Dr. Robert L. Jernigan, Director of the Baker Center for Bioinformatics and Biological Statistics and Professor of Biochemistry, Biophysics, and Molecular Biology at Iowa State University. The committee members were chosen for their expertise in molecular dynamics simulations, as well as in the subject areas represented in the 67 proposals that were considered by the committee for simulation time. The committee comprised a cross section of the biomolecular MD field, including both senior members and more junior investigators. The biographies of all of the committee members can be found in Appendix D.

The goal of the RFP for Biomolecular Simulation Time on Anton is to facilitate breakthrough science in the study of biomolecular systems by providing access to a dedicated, massively parallel supercomputer that allows significantly faster simulations of biomolecular systems using periodic boundary conditions and explicit solvent models. Anton's capabilities allow questions to be addressed on multi-microsecond simulation timescales, so the program seeks to support

projects addressing important and potentially high impact questions that would be most advanced by receiving time on this specialized machine.

The Anton RFP and a review guidance document listed criteria against which the committee was requested to evaluate proposals, including:

- **Scientific Merit**, including potential to advance understanding of an important problem or question in the field; potential for breakthrough science resulting in new discoveries and understanding; impact that successful completion of the proposed research would have on the 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 time 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**, including appropriate experience and training to successfully conduct the proposed studies, evidence of knowledge and prior experience with molecular simulations, and past publications.

As described in the RFP, staff at PSC provided an initial review of proposal submissions for completeness and to determine whether they met technical requirements for simulation on Anton. A PSC staff member was also present as an observer during the review committee discussions in the event that additional technical specification questions arose.

D.E. Shaw Research and Pittsburgh Supercomputing Center will make time on Anton available in two phases. During the first six months, 15 proposals will receive allocations of 100,000 node-hours each and during the second six months, approximately 30 proposals will receive allocations of 50,000 node-hours each. The committee was asked to identify the proposals which best met the selection criteria to receive simulation time on Anton for each of these two phases. The committee's judgments are based on a determination of which proposals best met or exceeded the selection criteria described above and on the estimates of required simulation time provided by the applicants.

In assembling the committee and conducting the review, the National Research Council sought to balance the need to include committee members with specialized expertise in the subfields of biomolecular MD (in order to evaluate the technical details of proposals), the desire of D.E. Shaw Research and the National Resource for Biomedical Supercomputing at the Pittsburgh Supercomputing Center (PSC) to allow members of the review committee to take advantage of the specialized opportunity provided by Anton and to submit proposals if they chose, and the need for a review process that was fair and credible. The following process was used to address these sometimes conflicting goals:

- Committee members were allowed to submit proposals[1];

[1] Three members of the committee submitted proposals as either Principal Investigators or affiliated faculty: Carol Post was the PI for proposal PSCA00077P, Klaus Schulten was the PI for proposal PSCA00024P, and David Beveridge was a member of the ABC Consortium that submitted proposal PSCA00033P (PI: Thomas Cheatham).

- Prior to the committee meeting, each proposal was read by two primary reviewers and evaluated based on the criteria in the RFP. These criteria are described in Appendix C;
- The proposals were divided into two subgroups and any committee member who was either a Principal Investigator (PI) or affiliated faculty on a proposal was only involved in reviewing the subgroup of proposals that did not include their own[2];
- All other committee members participated in the review and discussion of all proposals in both subgroups, except for those proposals submitted by PIs or affiliated faculty from their own institution or for which they either had a current academic or collaborative relationship, or with whom they had some past academic or personal relationship that led the committee member to voluntarily recuse him/herself and leave the room during the discussion of that specific proposal; and
- All committee members, except for those who were a PI or affiliated faculty on the proposals under consideration, participated in a final session on the second day to combine the results of the subgroup discussions and agree on proposals to be identified for allocations of time on Anton.

Table 1 (Appendix A) lists the subgroups to which all proposals were assigned and the names of the committee members who were not involved in the review or discussion of each proposal.

The NRC committee held its 2-day meeting in Washington, D.C. on July 26-27, 2010. On the first day of the meeting, members of the committee first discussed proposals from subgroup A and then proposals from subgroup B, following the general procedures described above. For each subgroup of proposals, the committee members who served as primary reviewers were asked to summarize their reviews of the proposals for which they were responsible, and these summaries were followed by discussion among the group. Committee members considered the relative strengths of the proposals and worked toward reaching consensus on which ones best met the Anton selection criteria. If a decision could not be made during this round of discussion, an additional committee member was assigned to review the proposal in detail. Committee members then returned to the discussion at a later time.

On the second day, all committee members, except for those who were either a PI or affiliated faculty on the proposals, participated in a final session to combine the results of the subgroup discussions and agree on proposals to be identified for allocations of time on Anton. Although the committee was motivated by its desire to enable as many members of the community as possible to have the opportunity to receive time, it particularly sought to identify those proposals which it judged were most likely to lead to high impact or breakthrough science, even if these entailed some risk of failure.

The proposals listed below addressed important biological questions and were those which the committee judged took best advantage of Anton's specialized capabilities to address questions over multi-microsecond simulation timescales. The committee debated the relative advantages of using Anton to address kinetic versus equilibrium questions. In many cases, the proposals identified by the committee as best meeting the selection criteria dealt with kinetic questions and incorporated Anton's ability to generate dynamic trajectories; they frequently involved informative comparisons between experimental and computational results. In other cases, the committee judged that proposals addressing important thermodynamic issues or aspects of methods and force-field validation would be of significant practical value to the community and would also be greatly advanced by receiving time on Anton. Conversely, some of the proposals which were evaluated as meeting the Anton selection criteria less well were judged by the

[2] Dr. Post reviewed proposals in subgroup A; Drs. Beveridge and Schulten reviewed proposals in subgroup B.

committee to lack focus, to pose questions that needed additional preliminary research and development, or that might be alternatively met using other computational resources or analysis methods.

The committee has concluded that the proposals listed below best meet the objectives of the RFP for Biomolecular Simulation Time on Anton. More detailed comments for all 67 proposals are included in Appendix B.

Phase 1 (initial six months):
The committee was asked to identify 15 proposals that best met the criteria of the RFP to receive approximately 100,000 node-hours each of simulation time on Anton, for a total time allocation of approximately 1,500,000 node-hours.

The 44 proposals that initially requested approximately 60,000-100,000 node-hours of time were evaluated by the committee for Phase 1. Of these, the proposals listed below were judged by the committee as being the 15 that exceeded the Anton selection criteria and would most benefit from receiving full allocations of requested time. In numerical order by proposal submission number, these are:

PSCA00007 **Capturing Large-Scale Structural Transitions in Membrane Transporters at Atomic Resolution**; PI: Emad Tajkhorshid, University of Illinois at Urbana-Champaign

PSCA00010 **Structural Determinants of Flickering in K+ Channels**; PI: Benoit Roux, University of Chicago

PSCA00013 **The Atomistic Scale Kinesin Mechanism Elucidated on the Experimental Time Scale**; PI: Wonmuk Hwang, Texas A&M University

PSCA00023 **Visualizing the Pathway of Integrin Headpiece Opening Induced by Ligand Binding**; PI: Timothy Springer, Harvard University

PSCA00024 **Determining the Pathway of Nascent-Protein Insertion through the Protein-Conducting Channel and into the Membrane**; PI: Klaus Schulten[3], University of Illinois at Urbana-Champaign

PSCA00028 **Long Time Simulations of Protein Folding: a Synergistic Approach**; PI: Vijay Pande, Stanford University

PSCA00046 **Toward gaining insights into the mechanism of substrate transport by the aspartate transporter GltPh**; PI: Ivet Bahar, University of Pittsburgh

PSCA00047 **Long Timescale Molecular Dynamics Simulation of Protein Folding**; PI: Martin Gruebele, University of Illinois at Urbana-Champaign

PSCA00048 **Computational Design and Evaluation of Novel Enzyme Catalysts**; PI: Kendall Houk, University of California-Los Angeles

[3] Dr. Schulten is a member of the Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics.

PSCA00052 **Sequencing DNA using MspA**; PI: Aleksei Aksimentiev, University of Illinois at Urbana-Champaign

PSCA00059 **Study of microsecond time scale protein dynamics crucial for phosphorylation-mediated signaling**; PI: Michael Hagan, Brandeis University

PSCA00065 **Atomistic modeling of the resting and activated states of a voltage-gated potassium channel voltage-sensing domain**; PI: Alfredo Freites, University of California-Irvine

PSCA00072 **Understanding Sec-facilitate protein translocation and membrane integration: New mechanistic insights from microsecond-timescale trajectories on Anton**; PI: Thomas Miller, California Institute of Technology

PSCA00074 **Resolving the Molecular Mechanisms of Calcium Binding to Cadherins Involved in Hearing and Deafness**; PI: David Corey, Harvard Medical School

PSCA00077 **Investigation of conformational properties of residues near 5-fold symmetry axis during uncoating of rhinovirus capsid by long time scale molecular dynamics simulation using Anton at NRBSC**; PI: Carol Post[4], Purdue University

Phase 2 (second six months):
The committee also was asked to identify approximately 30 proposals that best met the criteria of the RFP to receive approximately 50,000 node-hours each of simulation time on Anton, for a total time allocation of approximately 1,500,000 node-hours.

The proposals identified by the committee for inclusion under this phase of the project fell into three categories:

A. Proposals that *initially requested approximately 50,000 or fewer* node-hours of simulation time and that the committee judged would most benefit from a full allocation of requested time.

B. Proposals that *initially requested more than 50,000* node-hours of simulation time. The committee concluded that these proposals well met the criteria of the RFP and addressed questions that would benefit from receiving simulation time on Anton. However, these proposals were evaluated by the committee as meeting the goals of the RFP for Biomolecular Simulation Time on Anton slightly less well that the proposals selected for inclusion in Phase 1. The committee concluded that valuable progress could still be made in addressing the goals of these proposals with a reduced allocation of time of 50,000 node-hours each.

C. Additional proposals that the committee concluded would also benefit from receiving simulation time on Anton, ranging from 15,000 to 50,000 node-hours, to complete the available allocation of simulation time.

[4] Dr. Post is a member of the Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics.

A. Proposals initially requesting approximately 50,000 node-hours of time

The committee judged that these proposals also exceeded the Anton selection criteria and should be considered for a full allocation of requested simulation time of 50,000 node-hours. In numerical order by proposal submission number, these are:

PSCA00014 **Dynamic coupling and binding in a GTPase-effector complex**; PI: Matthias Buck, Case Western Reserve University

PSCA00015 **Understanding the mechanics of energy conversion in Na+-dependent co-transporters**; PI: Michael Grabe, University of Pittsburgh

PSCA00029 **Linking Structure and Conductance of Ion Channels**; PI: Andrew Pohorille, University of California-San Francisco

PSCA00034 **Molecular Dynamics Simulation of Signal Transduction in the Squid Rhodopsin G-Protein Coupled Receptor**; PI: Douglas James Tobias, University of California-Irvine

PSCA00037 **Dynamics and functional motions of the GlpG intramembrane protease**; PI: Ana Nicoleta Bondar, University of California-Irvine

PSCA00057 **Lipid-mediated assembly of membrane proteins**; PI: Stephen White, University of California-Irvine

PSCA00058 **Application of New Tools for Characterizing Protein Dynamics to Microsecond-Scale, Explicitly-Solvated MD Simulations of Intrinsically Disordered and Natively Folding Proteins**; PI: Michael Colvin, University of California-Merced

PSCA00061 **Exploring Lipid-Protein Interactions Using Microsecond-scale Molecular Dynamics Simulation**; PI: Toby Allen, University of California-Davis

PSCA00062 **To knot or not to knot: slipknotting in the smallest knotted protein**; PI: Jose Onuchic, University of California-San Diego

PSCA00067 **Development and testing of improved fixed-charge force fields for proteins**; PI: David Case, Rutgers University

B. Proposals initially requesting more than 50,000 node-hours of simulation time, to be considered for a modified allocation of 50,000 node-hours.

The committee judged that these proposals well met the Anton selection criteria. However, because only 15 proposals could receive the maximum allocation of simulation time, the committee has included them among those proposals to be considered for a modified allocation of 50,000 node-hours. In numerical order by proposal submission number, these are:

PSCA00001 **Detailed Characterization of the Equilibrium Fluctuations of the Engrailed Homeodomain**; PI: Christopher Langmead, Carnegie Mellon University

PSCA00026 **Characterization of Dynamics Control of Chemotaxis Initiation**; PI: Jerome Baudry, University of Tennessee at Knoxville

PSCA00027 **Molecular Flexibility in Drug Design Using Microsecond Molecular Dynamics**; PI: James Andrew McCammon, University of California-San Diego

PSCA00033 **Molecular Dynamics of DNA and Protein DNA Complexes: A Proposal for Obtaining Micro-second Trajectories using Anton**; PI: Thomas E. Cheatham[5], University of Utah

PSCA00068 **Mechanistic insights into the "inside-out" signaling of integrins**; PI: Marta Filizola, Mount Sinai Medical Center

C. Additional proposals that would benefit from receiving time allocations on Anton, some with modified allocations, to complete the available allocation of simulation time

The committee judged that these proposals met the Anton selection criteria and would benefit from receiving simulation time on Anton ranging from 15,000 to 50,000 node hours. In numerical order by proposal submission number, these are:

PSCA00005 **Exploration of the Human Adenovirus Protease Activation Pathway via Long Timescale Molecular Dynamics Simulations**; PI: Ross Walker, University of California-San Diego *[identified for 50,000 node-hours]*

PSCA00006 **Continuous Long-Time Dynamics of RNA Molecules: Watching without Blink-ing for Microseconds through Anton's Microscope**; PI: Ioan Andricioaei, University of California-Irvine *[identified for 50,000 node-hours]*

PSCA00009 **Simulations of a Sterol Transport Protein (Osh4) that Tethers Membranes of the Endoplasmic Reticulum and Plasma Membrane**; PI: Jeffery B. Klauda, University of Maryland at College Park *[identified for 25,000 node-hours]*

PSCA00012 **Using ANTON to probe the conformational space of poly-glutamine and its aggregation to understand its role in Huntington's disease, a protein aggregation disease**; PI: Bruce J. Berne, Columbia University *[identified for 50,000 node-hours]*

PSCA00017 **Understanding the Transcriptional Regulation of MerR**; PI: Jerry M. Parks, Oak Ridge National Laboratory *[identified for 50,000 node-hours]*

PSCA00020 **Aβ Peptides Interactions with Lipid Bilayers: Implications for Aggregation and Neurotoxicity**; PI: Jie Zheng, University of Akron *[identified for 50,000 node-hours]*

PSCA00036 **Uncovering the mechanism of Protein Tyrosine Phosphatase 1B induced insulin resistance in Type 2 Diabetes Mellitus through MD simulations of the PTP1B-IRK complex**; PI: Thanh Truong, University of Utah *[identified for 15,000 node-hours]*

PSCA00039 **Micro-Second Molecular Dynamics Simulation of the Folding Pathways of Tetratricopeptide Repeat Units in the Cargo Binding Domain of Kinesin Motor Proteins**; PI: Carol Parish, University of Richmond *[identified for 50,000 node-hours]*

[5] Dr. Beveridge, a member of the Committee on Proposal Evaluation for Allocation of Supercomputing Time for the Study of Molecular Dynamics, is a member of the Consortium that submitted this proposal.

PSCA00040 **Molecular Dynamics Simulations of Conformational Dynamics in the p38a MAP Kinase: Differential Dynamics in the Crystal and Solution Environments and the Effects of Binding a Small Molecule Inhibitor**; PI: Adrian H. Elcock, University of Iowa *[identified for 50,000 node-hours]*

PSCA00041 **Growth mechanisms of amyloid fibrils**; PI: Jian-Min Yuan, Drexel University *[identified for 50,000 node-hours]*

PSCA00042 **Characterizing changes in the conformation and dynamics of epidermal growth factor receptor induced by mutations associated with anti-cancer drug treatment**; PI: Peter Coveney, Yale University *[identified for 50,000 node-hours]*

PSCA00043 **Structural and Functional Water Dynamics in Rhodopsin Activation from Picoseconds to Microseconds**; PI: Mark R. Chance, Case Western Reserve University *[identified for 50,000 node-hours]*

PSCA00045 **All Atom Molecular Dynamics Simulation of Connexin Hemichannel Voltage Gating**; PI: Thaddeus A. Bargiello, Albert Einstein School of Medicine *[identified for 24,000 node-hours]*

PSCA00049 **Assessment of Multi-Microsecond Simulations of Intrinsically Disordered Proteins Using NMR: Applications to FCP1 in the Unbound State**; PI: Scott A. Showalter, Pennsylvania State University *[identified for 50,000 node-hours]*

PSCA00063 **All-Atom Molecular Dynamics Simulations of S-Adenosyl Methionine (SAM) Assisted SAM-I Riboswitch (Un)Folding Pathways: A Small Molecule with a Strong Arm**; PI: Shantenu Jha, Louisiana State University *[identified for 50,000 node-hours]*

PSCA00064 **Structural mechanism of integrin activation induced by talin**; PI: Cheng Zhu, Georgia Institute of Technology *[identified for 50,000 node-hours]*

PSCA00073 **The Effect of α-Synuclein on Membrane Structure**; PI: Jonathan Sachs, University of Minnesota *[identified for 50,000 node-hours]*

The time allocations for the 47 proposals judged by the committee as best meeting the Anton selection criteria total approximately 3,000,000 node-hours. In carrying out its charge, the committee identified as many promising proposals as feasible given the overall constraints on simulation time, to allow the maximum number of users possible the opportunity to take advantage of this special resource. If additional node-hours of simulation time become available during the course of the project, the committee encourages D.E. Shaw Research and Pittsburgh Supercomputing Center to allocate these hours to the research groups showing the most promising results and which would benefit most greatly from the additional time. The committee also encourages D.E. Shaw and PSC to provide a collective repository and to encourage investigators to share the data generated, since the trajectories obtained may be of use to other investigators in the community.

The committee wishes to thank D.E. Shaw Research, Pittsburgh Supercomputing Center, and all of the 2010 Anton applicants for the opportunity to review these proposals and to identify which of the proposals best met the requirements set forth in the RFP. The committee members were vocal in their enthusiasm for the computational opportunities provided by Anton and pleased to be a part of helping determine how to allocate time on this important resource.

Sincerely,

Robert L. Jernigan
Chair

cc: Dr. Joel Stiles, Pittsburgh Supercomputing Center
Dr. Warren Muir, National Research Council
Dr. Frances Sharples, National Research Council

Appendixes:

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

ROBERT L. JERNIGAN (Chair), Director, Laurence H. Baker Center for Bioinformatics and Biological Statistics and Professor, Department of Biochemistry, Biophysics and Molecular Biology, Iowa State University
NILESH BANAVALI, Research Scientist, Wadsworth Center and Assistant Professor, School of Public Health, State University of New York, Albany
DAVID L. BEVERIDGE, Professor of Theoretical Chemistry and Molecular Biophysics, Wesleyan University
CHARLES L. BROOKS III, Warner-Lambert/Parke-Davis Professor of Chemistry and Professor of Biophysics, University of Michigan
XIAOLIN CHENG, Staff Scientist, Oak Ridge National Laboratory and Adjunct Professor, University of Tennessee, Knoxville
RUXANDRA DIMA, Assistant Professor of Chemistry, University of Cincinnati
BARRY H. HONIG, Director, Center for Computational Biology and Bioinformatics and Professor of Biochemistry and Molecular Biophysics, Columbia University
GERHARD HUMMER, Chief, Theoretical Biophysics Section, The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
RONALD M. LEVY, Board of Governors Professor of Chemistry & Chemical Biology and Director, BioMaPS Institute for Quantitative Biology, Rutgers University
GLENN J. MARTYNA, Researcher, IBM
GREGORY PETSKO, Gyula and Katica Tauber Professor of Biochemistry and Chemistry, Brandeis University
CAROL B. POST, Professor of Medicinal Chemistry and Molecular Pharmacology, Purdue University
KLAUS J. SCHULTEN, Swanlund Professor of Physics, University of Illinois, Urbana-Champaign
JEFFREY SKOLNICK, Professor and Director of the Center for the Study of Systems Biology, Georgia Research Alliance Eminent Scholar in Computation Systems Biology, Georgia Institute of Technology
FENG WANG, Assistant Professor, Department of Chemistry, Boston University
ARIEH WARSHEL, Professor of Chemistry and Biochemistry, University of Southern California

STAFF

KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
KATHRYN HUGHES, Program Officer, Board on Chemical Sciences and Technology
CARL-GUSTAV ANDERSON, Senior Program Assistant, Board on Life Sciences
JAMES MULLER, Intern, Board on Life Sciences

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

CHAIR

Robert L. Jernigan is the Director of the Laurence H. Baker Center for Bioinformatics and Biological Sciences as well as a Professor in the Department of Biochemistry, Biophysics, and Molecular Biology at Iowa State University. He received his B.S. in Chemistry from the California Institute of Technology in 1963 and completed his Ph.D. in 1968 at Stanford University. He has previously served as Deputy Chief of the Laboratory of Experimental and Computational Biology and Chief of the Section on Molecular Structure in the National Cancer Institute of the National Institutes of Health. He is also a former Chair of the NIH Advisory Committee on Computer Usage and has served on multiple committees on computing resources. Dr. Jernigan is currently on the editorial boards for the journals *Biochemistry*, the *Journal of Data Mining in Genomics and Proteomics*, and *Bioinformatics and Biological Insights*.

MEMBERS

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

David L. Beveridge attended the College of Wooster, Wooster Ohio graduating in 1959, with a major in chemistry. After two years at Monsanto Research Laboratory, he went for graduate studies at the University of Cincinnati. Based on his studies and research under the mentorship of the eminent physical chemist, Hans H. Jaffe, he was awarded a Ph.D. in Physical Chemistry in 1965. He was granted an NIH Postdoctoral Fellowship to study molecular quantum mechanics at the Centre de Mecanique Ondulatoire Appliquee in Paris, France with Dr. Odilon Chalvet. Dr. Beveridge continued his postdoctoral studies at Carnegie Mellon University with Prof. J.A. Pople, where he worked on the development of INDO molecular orbital theory. In 1968, Dr. Beveridge joined faculty of the City University of New York, at first in a joint appointment with Hunter College Chemistry Department and The Mount Sinai School of Medicine and subsequently full time at Hunter College. In 1986, Dr. Beveridge moved from New York City to become Professor of Chemistry at Wesleyan University. In 1988, he was granted a Merit Award by the NIH and named University Professor of the Natural Sciences and Mathematics. His current research involves theoretical and computational modeling studies of the structure, motions, salvation, and ligand binding properties of DNA and RNA using molecular dynamics simulation. He served as Dean of Natural Sciences and Mathematics (1992-1999) and has authored or co-authored over 200 papers in the scientific literature. In addition to research and teaching, he now serves Wesleyan as Director of the NIH supported Program in Molecular Biophysics and Biological Chemistry.

Charles L. Brooks received a B.S. from Alma College in 1978. Dr. Brooks pursued graduate studies at Purdue University under the direction of Professor Stephen A. Adelman. His graduate

work focused on the development of non-equilibrium statistical mechanical theories for reactions on surfaces, in solids and in liquids using molecular timescale generalized Langevin (MTGLE) theory. In 1982, he received his Ph.D. in Physical Chemistry from Purdue University. Dr. Brooks was engaged in postgraduate work at Harvard University with Professor Martin Karplus between the years of 1982 and 1985, focusing on theoretical and computational biophysics. Dr Brooks was also the recipient of an NIH Postdoctoral Fellowship between 1983 and 1985. In 1985, Professor Brooks joined the Chemistry Faculty of Carnegie Mellon University and was promoted to Professor of Chemistry in 1992. He received an Alfred P. Sloan Research Fellowship in 1992 and during this period, 1992-1993, spent a sabbatical year working at the Karolinska Institute in Stockholm Sweden and The Scripps Research Institute in La Jolla California. Dr. Brooks has recently moved to the University of Michigan, where he holds the positions of Warner-Lambert/Parke-Davis Professor of Chemistry and Professor of Biophysics. Dr. Brooks' research includes multi-scale modeling of the dynamics and assembly of complex biological assemblies, protein folding, unfolding and aggregation, and free energy approximations.

Xiaolin Cheng is a staff scientist at the Center for Molecular Biophysics of the Oak Ridge National Laboratory. He is also an adjunct professor in the Department of Biochemistry and Cellular and Molecular Biology at the University of Tennessee, Knoxville. Dr. Cheng received his B.S. from Nanjing University, China, and his Ph.D. in Computational Chemistry from the State University of New York at Stony Brook, where he worked with Professor Carlos Simmerling on application of enhanced sampling approaches to biomolecular simulations. He subsequently joined Professor Andy McCammon's group at University of California, San Diego as a postdoctoral research associate, mainly working on nicotinic acetylcholine receptor simulation, and methodological development for fast and scalable continuum electrostatic calculation. Dr. Cheng moved to Oak Ridge National Laboratory in early 2008.

Ruxandra I. Dima has an interdisciplinary training in theoretical and computational physics and physical chemistry and her current research focuses on the area of computational biophysical chemistry with special emphasis on single molecule experiments and aggregation. After receiving her undergraduate degree from the University of Bucharest, Romania in 1994, she studied at the Pennsylvania State University where she obtained her PhD in 1999. Her thesis was concerned with the determination of mean field free-energy potentials between amino acids in proteins. She then took a postdoctoral appointment (2000-2005) at the Institute for Physical Science and Technology, University of Maryland where she worked on problems related to protein aggregation, allostery, RNA folding, and single-molecule biophysics. In 2005 she took a faculty position at the University of Massachusetts, Lowell. She joined the faculty at the University of Cincinnati in 2006.

Barry H. Honig is a biophysicist who specializes in bioinformatics and in developing theoretical methods for analyzing the physical chemical properties of macromolecules. He received a B.A. from the Polytechnic Institute of Brooklyn in 1963, an M.A. from Johns Hopkins University in 1964, and completed a Ph.D. in chemistry at the Weismann Institute of Sciences. He is particularly noted for innovating methods to compute and display the electrostatic potentials of macromolecules based on their 3D structures. The computer programs DelPhi and GRASP were developed in his laboratory and are widely used by the academic and industrial communities. Since 1981, Dr. Honig has been a Professor of Biochemistry and Molecular Biophysics at Columbia University. In 1990, Dr. Honig was elected President of the Biophysical Society, he received an NIH Merit Award in 1995, and he is a recipient of the 2002 Founders Award of the Biophysical Society. Dr. Honig is a Howard Hughes Medical Institute (HHMI) Investigator. He serves on the editorial boards of several journals and has published over 190 scientific papers

throughout his distinguished career. He was elected to membership in the National Academy of Sciences in 2004.

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

Ronald M. Levy is a Board of Governors Professor of Chemistry at Rutgers University. He received his B.A. from Reed College in 1970 and completed his Ph.D. in 1976 at Harvard University. His research is primarily in the areas of protein simulation and modeling and molecular solvation. He has been awarded a Sloan Foundation Fellowship, a Johnson and Johnson Discovery Research Award, an NIH Research Career Development Award, and a Guggenheim Fellowship. Over the past two decades he has developed the IMPACT molecular modeling code. Current interests include the exploration of energy landscapes for protein binding and folding, new molecular simulation methods and multi-scale models, and the determination of solvation free energies.

Glenn J Martyna received a Ph.D. in chemical from Columbia University in 1989. He was then a NSF postdoctoral fellow in computational science and engineering at the University of Pennsylvania. Dr. Martyna was appointed to 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.

Gregory A. Petsko is the Gyula and Katica Tauber Professor of Biochemistry and Molecular Pharmacodynamics and the director of the Rosenstiel Basic Medical Sciences Research Center at Brandeis University. He was elected to membership in the National Academy of Sciences in 1995 and to the Institute of Medicine in 2001. He has developed low-temperature methods in protein crystallography and their use to study enzymatic mechanisms and has pioneered the study of protein dynamics in enzymatic reactions. For over 25 years, he has worked to understand how enzymes achieve their extraordinary catalytic power, developing crystallographic methods for direct observation of productive enzyme-substrate and enzyme-intermediate complexes that led to techniques for studying protein crystal structures at very low temperatures. Dr. Petsko is also a founding scientist of the combinatorial-chemistry company ArQule, Inc.

Carol Post received her B.S. from the University of Arizona in 1975, and received a Ph.D. from the University of California, San Diego in 1981. She pursued post-graduate research between 1982 and 1985 at Harvard University. She is currently a Professor of Medicinal Chemistry and Molecular Pharmacology at Purdue University, where she operates the Post Lab (Computational and Structural Biology Research Group). The research focus of the Post Lab is broadly described as investigations to understand the regulation and function of protein-protein interactions associated with cell signaling and viruses. Multi-dimensional, multinuclear NMR methods are used to determine 3-dimensional structure of protein complexes. Computational methods are

used to study the mechanism of action of antiviral compounds, and the molecular mechanism for phosphotyrosine control of protein function in signal transduction.

Klaus Schulten received his Ph.D. from Harvard University in 1974. He is Swanlund Professor of Physics and is also affiliated with the Department of Chemistry as well as with the Center for Biophysics and Computational Biology at the University of Illinois, Urbana-Champaign. Professor Schulten is a full-time faculty member in the Beckman Institute and directs the Theoretical and Computational Biophysics Group. His professional interests are theoretical physics and theoretical biology. His current research focuses on the structure and function of supramolecular systems in the living cell, and on the development of non-equilibrium statistical mechanical descriptions and efficient computing tools for structural biology.

Jeffrey Skolnick received his B.A. in Chemistry, Summa Cum Laude, from Washington University, St. Louis in 1975. He received his M. Phil. in Chemistry from Yale University in 1977 and his Ph.D. in Chemistry from Yale University in 1978, with Professor Marshall Fixman. Dr. Skolnick is a Professor at Georgia Technical University and Director of the Center for the Study of Systems Biology. Dr. Skolnick has recently completed a very promising study in cancer metabolomics where he and his research group validated a predictive algorithm that can identify novel metabolites with anticancer properties. They have also developed a new, powerful algorithm that can predict protein function and binding sites, and which can be used for rapid screening ligand libraries. In addition, Dr. Skolnick has developed physics based, atomic potentials for protein structure refinement. He and his team demonstrated that the library of all protein folds is above the percolation threshhold, i.e., any protein structure can be related to any other by no more than eight intermediate structures.

Feng Wang received his B.S. in Chemistry from Peking University (1998) and Ph.D. in Theoretical Chemistry from the University of Pittsburgh (2003). He did post-doctoral research in computational physical chemistry at the University of Utah with Professor Gregory A. Voth. Since 2005, he has been an Assistant Professor in the Department of Chemistry at Boston University. Dr. Wang received a Mellon Fellowship at the University of Pittsburgh in 2002, an NSF CAREER Award in 2007, and an HP Outstanding Junior Faculty award in 2010. His research focuses on systematic development of high quality force fields, free energy determinations, and enhanced sampling.

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

APPENDIX E

THE BOARD ON LIFE SCIENCES AND THE NATIONAL ACADEMIES

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

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

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

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

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APPENDIX F

ACKNOWLEDGEMENT OF REPORT REVIEWER

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

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

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