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Special Issue Preface

A Tribute to Gregory A. Voth

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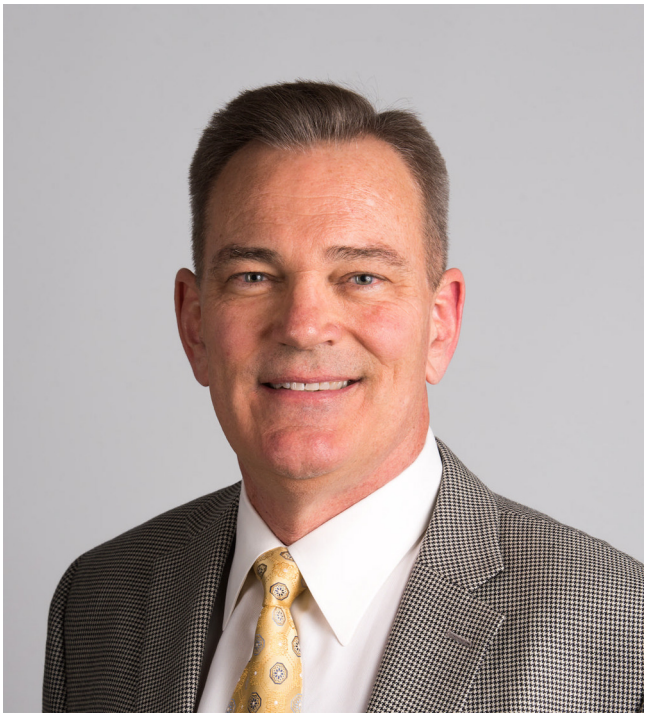

This Virtual Special Issue honors Professor Gregory A. Voth and his pioneering contributions to the field of physical chemistry. Over the past 35 years, Greg has made a remarkable number of groundbreaking contributions that have dramatically advanced our understanding of the structure and dynamics of complex condensed phase systems, ranging from ionic liquids to viral capsids, while addressing both classical and quantal aspects of these phenomena. To attack these problems, Greg and his co-workers have developed theories and simulation methodologies that are now widely adopted by the scientific community to gain deep mechanistic insights and accurately model the behavior of strongly interacting condensed phase systems over a wide range of length and time scales. In the following, we highlight some of these important breakthroughs.

Greg's thesis work at Caltech with Rudy Marcus started him along the path to thinking about problems from a semiclassical perspective. The fact that his first published paper was written with two Nobel laureates (Marcus and Zewail)[1] portended the future success he would have in this area. After graduating from Caltech (and receiving the Herbert Newby McCoy Award for best thesis), he moved upstate to UC Berkeley as an IBM Postdoctoral Fellow, working jointly with David Chandler and William Miller. This period of Greg's career was transformational as it gave him a perspective on how to think about condensed phase problems using the tools of statistical mechanics as well as rigorous methods to compute reaction rates. Inspired by Gillan's work on the importance of the path-integral centroid variable in estimating quantum reaction rates in condensed phases,[2] Voth, Chandler, and Miller greatly widened its scope, transforming it into a quantum transition state theory which could be used in complex systems while also forming a rigorous theoretical basis for many quantum rate theories that followed.[3] This work set the stage for Greg's first major independent scientific breakthrough, as described below.

Greg started his independent career at the University of Pennsylvania in 1989. He immediately built a thriving group focusing on a variety of condensed phase problems such as barrier crossing dynamics, charge transfer, water models, and path integral simulations. During this period, Greg and his postdoc Jianshu Cao recognized a much broader and deeper connection between the centroid variable and the quantum behavior of condensed phase systems.[4−8] Importantly, they demonstrated a powerful link between the dynamics of the centroid variable and the approximate time evolution of quantum systems. This connection led to the development of "centroid molecular dynamics" (CMD), an accurate and computationally efficient approach to include nuclear quantum effects in molecular dynamics simulations.[5] Over the 30 years since its discovery, CMD has been used by many researchers, stimulated the community to extend the method (e.g., to electronically non-adiabatic problems), and inspired new approaches to calculate quantum reaction rates and time correlation functions in condensed phases. Following the success of CMD, Greg continued his leading role in the development of original quantum dynamics simulation methods and rate theories, including non-adiabatic instanton approaches, various sampling methods, and new electron transfer theories. Many of these methods have inspired further

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progress that later developed into mature methodologies and theories.

Greg's efforts in developing computational methods have always been strongly motivated by his desire to gain physical insight into fundamental questions in chemistry, materials, and biology. Thus, Greg created CMD with specific systems in mind. In particular, since CMD accurately describes the essential quantum mechanical aspects of proton mobility, Greg was interested in discovering the mechanism of proton transport in complex aqueous environments. As someone who had been involved in the development of *ab initio* molecular dynamics for decades, Greg well understood that, in the pre-AI, primitive DFT days, these techniques would be too limited in terms of time scale, accuracy, and system size to treat the complex systems he ambitiously targeted. With postdoc Udo Schmitt, Greg took the important step of developing a flexible and accurate multi-state empirical valence bond (MS-EVB) model which, when combined with CMD, opened the door to the detailed and accurate quantum mechanical description of proton transfer in a variety of contexts.[9,10] This model has been continuously improved and extended to correctly capture aqueous proton solvation and transport.[11−13] Indeed, over the last 25 years, Greg, along with his group and collaborators, has made significant contributions to elucidating the mechanisms of proton transfer in systems that range from liquid water to large-scale energy storage materials and complex biomolecular settings.[14−19]

Greg's pioneering and impactful work on proton transfer dovetails with other important contributions he and his group have made to understand liquid-state phenomena more broadly. Among these contributions, Wu, Tepper, and Voth developed a flexible simple point charge force field for liquid water, known as the SPC/Fw model, which offers distinct advantages over other simple rigid water models.[20] A major motivation for this work was to introduce a flexible and accurate water model for MS-EVB simulations, as conventional SPC and TIP models are rigid and thus not suitable for modeling chemical reactions. While still providing the computational efficiency of classical water models, the SPC/Fw model reproduces the diffusion and dielectric constants of water much more accurately than the existing rigid simple point charge models. In later work, Paesani et al. reparametrized this model (q-SPC/Fw) for treating quantum mechanical effects via path integral and CMD computations.[21] Another distinct example arises in the investigation of increasingly complex fluids. Over the last two decades, Greg and co-workers have written several important and highly cited papers on the structure and dynamics of ionic liquids.[22−26] These works were among the first to accurately model these systems and to reveal the origins of their structural heterogeneity and slow dynamical relaxation motifs.

Since 2005, the Voth group has developed and explored a multi-faceted approach for describing large, heterogeneous systems that are found in biology, such as membranes, vesicles, and the cellular interior. Because of their massive size and overwhelming complexity, such systems cannot be reliably studied by brute force atomistic modeling. Consequently, it is necessary to aggressively and systematically excise superfluous information from atomically detailed models, while incisively and accurately retaining the essential physics that govern meso- and macro-scale phenomena. This bottom-up approach allows one to quantitatively model exceedingly complex systems on very large length- and time-scales. Greg's initial steps in this "coarse-graining" program drew inspiration from earlier *ab initio* work by Ercolessi and Adams, who parametrized molecular mechanics force fields from *ab initio* data.[27] Izvekov and Voth significantly advanced their work by extending and generalizing the force matching approach to infer the effective interactions between (pseudo) atoms for coarse-grained models of liquid-state and lipid bilayer systems.[28,29] In collaboration with Hans Andersen, Noid, Voth, and colleagues demonstrated that force matching provides a rigorous and computationally efficient variational principle for approximating the effective "renormalized" potential that results from formally integrating atomic details out of an underlying microscopic model.[30,31] This foundational work has paved the way for developing a rigorous theory of bottom-up coarse-graining, as well as a powerful "multi-scale coarse-graining" (MS-CG) method for simulating length- and time-scales that cannot be effectively addressed with conventional atomic models. In particular, Greg and his co-workers have employed this MS-CG method to accurately model the structure and dynamics of systems ranging from simple liquids to complex liquids, interfaces, ionic liquids, lipid bilayers, and peptides.[32] Perhaps most impressively, by leveraging the latest developments in this MS-CG framework, Greg and his co-workers have investigated the membrane remodeling processes on a molecular level[33−36] and elucidated critical stages in the assembly of viral capsids, including influenza A M2 virus[37] and HIV-1 virus,[38−40] and, notably, created the first coarse-grained model of the COVID virion (SARS-CoV-2).[41]

While advancing coarse-graining theory and simulations to describe long length- and time-scale processes, Greg recognized the potential of combining this approach with enhanced sampling techniques to accelerate the efficient exploration of complex chemical space, enabling free energy estimation and the calculation of barrier crossing dynamics. This timing of the growth of coarse-graining methodology in the Voth group coincided with the development of the metadynamics approach pioneered by Parrinello and colleagues.[42] With Parrinello, Greg showed that conventional well-tempered metadynamics asymptotically converges to the exact free energy of the system, affirming its correctness and exactness.[43] The numerical implementation of metadynamics in complex molecular systems often requires additional refinement, and this limitation has led to the development of several improved metadynamics methods.[44,45] Presently, these novel methods are used to elucidate the complex free energy profiles of biomolecules in a wide range of chemical environments at both the atomistic and coarse-grained levels, e.g., ATP hydrolysis in microtubules.[46,47]

Greg Voth has dramatically altered the landscape of physical chemistry and biophysics. He has invented and developed a vast array of powerful computational methods for effectively modeling complex phenomena that once seemed intractable. By leveraging these methods Greg has profoundly advanced our understanding of many outstanding questions in biological, chemical, and material science. The citations to his work provide obvious and unequivocal evidence of Greg's impact. However, the many independent scientists who have passed through Greg's group perhaps provide an even more clear testimony to Greg's impact. Indeed, it is easy to see the influence of Greg's crystal-clear thinking, his creativity, his physical insights, and his big-picture vision in the work of his former students and postdocs. For his leadership in the

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community as both a scientist and a mentor, we are very proud to dedicate this special issue to Greg Voth.

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Notes

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REFERENCES

(1) Voth, G. A.; Marcus, R.; Zewail, A. The Highly Excited C-H Stretching States of CHD_3, CHT_3, and CH_3D. *J. Chem. Phys.* **1984**, *81*, 5494−5507.
(2) Gillan, M. Quantum-Classical Crossover of the Transition Rate in the Damped Double Well. *J. Phys. C: Solid State Phys.* **1987**, *20*, 3621.
(3) Voth, G. A.; Chandler, D.; Miller, W. H. Rigorous Formulation of Quantum Transition State Theory and Its Dynamical Corrections. *J. Chem. Phys.* **1989**, *91*, 7749−7760.
(4) Cao, J.; Voth, G. A. The Formulation of Quantum Statistical Mechanics Based on the Feynman Path Centroid Density. I. Equilibrium Properties. *J. Chem. Phys.* **1994**, *100*, 5093−5105.
(5) Cao, J.; Voth, G. A. The Formulation of Quantum Statistical Mechanics Based on the Feynman Path Centroid Density. II. Dynamical Properties. *J. Chem. Phys.* **1994**, *100*, 5106−5117.
(6) Cao, J.; Voth, G. A. The Formulation of Quantum Statistical Mechanics Based on the Feynman Path Centroid Density. III. Phase Space Formalism and Analysis of Centroid Molecular Dynamics. *J. Chem. Phys.* **1994**, *101*, 6157−6167.
(7) Cao, J.; Voth, G. A. The Formulation of Quantum Statistical Mechanics Based on the Feynman Path Centroid Density. IV. Algorithms for Centroid Molecular Dynamics. *J. Chem. Phys.* **1994**, *101*, 6168−6183.
(8) Cao, J.; Voth, G. A. The Formulation of Quantum Statistical Mechanics Based on the Feynman Path Centroid Density. V. Quantum Instantaneous Normal Mode Theory of Liquids. *J. Chem. Phys.* **1994**, *101*, 6184−6192.
(9) Schmitt, U. W.; Voth, G. A. The Computer Simulation of Proton Transport in Water. *J. Chem. Phys.* **1999**, *111*, 9361−9381.
(10) Schmitt, U. W.; Voth, G. A. Multistate Empirical Valence Bond Model for Proton Transport in Water. *J. Phys. Chem. B* **1998**, *102*, 5547−5551.
(11) Day, T. J.; Soudackov, A. V.; Čuma, M.; Schmitt, U. W.; Voth, G. A. A Second Generation Multistate Empirical Valence Bond Model for Proton Transport in Aqueous Systems. *J. Chem. Phys.* **2002**, *117*, 5839−5849.
(12) Wu, Y.; Chen, H.; Wang, F.; Paesani, F.; Voth, G. A. An Improved Multistate Empirical Valence Bond Model for Aqueous Proton Solvation and Transport. *J. Phys. Chem. B* **2008**, *112*, 467−482.
(13) Biswas, R.; Tse, Y.-L. S.; Tokmakoff, A.; Voth, G. A. Role of Presolvation and Anharmonicity in Aqueous Phase Hydrated Proton Solvation and Transport. *J. Phys. Chem. B* **2016**, *120*, 1793−1804.
(14) Day, T. J.; Schmitt, U. W.; Voth, G. A. The Mechanism of Hydrated Proton Transport in Water. *J. Am. Chem. Soc.* **2000**, *122*, 12027−12028.
(15) Brewer, M. L.; Schmitt, U. W.; Voth, G. A. The Formation and Dynamics of Proton Wires in Channel Environments. *Biophys. J.* **2001**, *80*, 1691−1702.
(16) Petersen, M. K.; Iyengar, S. S.; Day, T. J.; Voth, G. A. The Hydrated Proton at the Water Liquid/Vapor Interface. *J. Phys. Chem. B* **2004**, *108*, 14804−14806.
(17) Petersen, M. K.; Voth, G. A. Characterization of the Solvation and Transport of the Hydrated Proton in the Perfluorosulfonic Acid Membrane Nafion. *J. Phys. Chem. B* **2006**, *110*, 18594−18600.
(18) Swanson, J. M.; Maupin, C. M.; Chen, H.; Petersen, M. K.; Xu, J.; Wu, Y.; Voth, G. A. Proton Solvation and Transport in Aqueous and Biomolecular Systems: Insights from Computer Simulations. *J. Phys. Chem. B* **2007**, *111*, 4300−4314.
(19) Liang, R.; Swanson, J. M.; Madsen, J. J.; Hong, M.; DeGrado, W. F.; Voth, G. A. Acid Activation Mechanism of the Influenza a M2 Proton Channel. *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113*, E6955−E6964.
(20) Wu, Y.; Tepper, H. L.; Voth, G. A. Flexible Simple Point-Charge Water Model with Improved Liquid-State Properties. *J. Chem. Phys.* **2006**, *124*, 024503.
(21) Paesani, F.; Zhang, W.; Case, D. A.; Cheatham, T. E.; Voth, G. A. An Accurate and Simple Quantum Model for Liquid Water. *J. Chem. Phys.* **2006**, *125*, 184507.
(22) Del Pópolo, M. G.; Voth, G. A. On the Structure and Dynamics of Ionic Liquids. *J. Phys. Chem. B* **2004**, *108*, 1744−1752.
(23) Yan, T.; Burnham, C. J.; Del Pópolo, M. G.; Voth, G. A. Molecular Dynamics Simulation of Ionic Liquids: The Effect of Electronic Polarizability. *J. Phys. Chem. B* **2004**, *108*, 11877−11881.
(24) Wang, Y.; Voth, G. A. Unique Spatial Heterogeneity in Ionic Liquids. *J. Am. Chem. Soc.* **2005**, *127*, 12192−12193.
(25) Wang, Y.; Voth, G. A. Tail Aggregation and Domain Diffusion in Ionic Liquids. *J. Phys. Chem. B* **2006**, *110*, 18601−18608.
(26) Jiang, W.; Wang, Y.; Voth, G. A. Molecular Dynamics Simulation of Nanostructural Organization in Ionic Liquid/Water Mixtures. *J. Phys. Chem. B* **2007**, *111*, 4812−4818.
(27) Izvekov, S.; Parrinello, M.; Burnham, C. J.; Voth, G. A. Effective Force Fields for Condensed Phase Systems from Ab Initio Molecular Dynamics Simulation: A New Method for Force-Matching. *J. Chem. Phys.* **2004**, *120*, 10896−10913.
(28) Izvekov, S.; Voth, G. A. Multiscale Coarse Graining of Liquid-State Systems. *J. Chem. Phys.* **2005**, *123*, 134105.
(29) Izvekov, S.; Voth, G. A. A Multiscale Coarse-Graining Method for Biomolecular Systems. *J. Phys. Chem. B* **2005**, *109*, 2469−2473.
(30) Noid, W. G.; Chu, J.-W.; Ayton, G. S.; Krishna, V.; Izvekov, S.; Voth, G. A.; Das, A.; Andersen, H. C. The Multiscale Coarse-Graining Method. I. A Rigorous Bridge between Atomistic and Coarse-Grained Models. *J. Chem. Phys.* **2008**, *128*, 244114.
(31) Noid, W. G.; Liu, P.; Wang, Y.; Chu, J.-W.; Ayton, G. S.; Izvekov, S.; Andersen, H. C.; Voth, G. A. The Multiscale Coarse-Graining Method. II. Numerical Implementation for Coarse-Grained Molecular Models. *J. Chem. Phys.* **2008**, *128*, 244115.
(32) Jin, J.; Pak, A. J.; Durumeric, A. E.; Loose, T. D.; Voth, G. A. Bottom-up Coarse-Graining: Principles and Perspectives. *J. Chem. Theory Comput.* **2022**, *18*, 5759−5791.
(33) Ayton, G. S.; Lyman, E.; Krishna, V.; Swenson, R. D.; Mim, C.; Unger, V. M.; Voth, G. A. New Insights into Bar Domain-Induced Membrane Remodeling. *Biophys. J.* **2009**, *97*, 1616−1625.
(34) Simunovic, M.; Voth, G. A.; Callan-Jones, A.; Bassereau, P. When Physics Takes Over: Bar Proteins and Membrane Curvature. *Trends Cell Biol.* **2015**, *25*, 780−792.
(35) Simunovic, M.; Evergren, E.; Golushko, I.; Prévost, C.; Renard, H.-F.; Johannes, L.; McMahon, H. T.; Lorman, V.; Voth, G. A.; Bassereau, P. How Curvature-Generating Proteins Build Scaffolds on Membrane Nanotubes. *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113*, 11226−11231.
(36) Simunovic, M.; Manneville, J.-B.; Renard, H.-F.; Evergren, E.; Raghunathan, K.; Bhatia, D.; Kenworthy, A. K.; Voth, G. A.; Prost, J.; McMahon, H. T. Friction Mediates Scission of Tubular Membranes Scaffolded by Bar Proteins. *Cell* **2017**, *170*, 172−184.

(37) Madsen, J. J.; Grime, J. M.; Rossman, J. S.; Voth, G. A. Entropic Forces Drive Clustering and Spatial Localization of Influenza a M2 During Viral Budding. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, E8595−E8603.
(38) Ayton, G. S.; Voth, G. A. Multiscale Computer Simulation of the Immature HIV-1 Virion. *Biophys. J.* **2010**, *99*, 2757−2765.
(39) Grime, J. M.; Dama, J. F.; Ganser-Pornillos, B. K.; Woodward, C. L.; Jensen, G. J.; Yeager, M.; Voth, G. A. Coarse-Grained Simulation Reveals Key Features of HIV-1 Capsid Self-Assembly. *Nat. Commun.* **2016**, *7*, 11568.
(40) Pak, A. J.; Grime, J. M.; Sengupta, P.; Chen, A. K.; Durumeric, A. E.; Srivastava, A.; Yeager, M.; Briggs, J. A.; Lippincott-Schwartz, J.; Voth, G. A. Immature Hiv-1 Lattice Assembly Dynamics Are Regulated by Scaffolding from Nucleic Acid and the Plasma Membrane. *Proc. Natl. Acad. Sci. U.S.A.* **2017**, *114*, E10056−E10065.
(41) Yu, A.; Pak, A. J.; He, P.; Monje-Galvan, V.; Casalino, L.; Gaieb, Z.; Dommer, A. C.; Amaro, R. E.; Voth, G. A. A Multiscale Coarse-Grained Model of the SARS-CoV-2 Virion. *Biophys. J.* **2021**, *120*, 1097−1104.
(42) Laio, A.; Parrinello, M. Escaping free-energy minima. *Proc. Natl. Acad. Sci. U.S.A* **2002**, *99*, 12562−12566.
(43) Dama, J. F.; Parrinello, M.; Voth, G. A. Well-Tempered Metadynamics Converges Asymptotically. *Phys. Rev. Lett.* **2014**, *112*, 240602.
(44) Dama, J. F.; Rotskoff, G.; Parrinello, M.; Voth, G. A. Transition-Tempered Metadynamics: Robust, Convergent Metadynamics Via on-the-Fly Transition Barrier Estimation. *J. Chem. Theory Comput.* **2014**, *10*, 3626−3633.
(45) Dama, J. F.; Hocky, G. M.; Sun, R.; Voth, G. A. Exploring Valleys without Climbing Every Peak: More Efficient and Forgiving Metabasin Metadynamics Via Robust on-the-Fly Bias Domain Restriction. *J. Chem. Theory Comput.* **2015**, *11*, 5638−5650.
(46) McCullagh, M.; Saunders, M. G.; Voth, G. A. Unraveling the Mystery of Atp Hydrolysis in Actin Filaments. *J. Am. Chem. Soc.* **2014**, *136*, 13053−13058.
(47) Sun, R.; Sode, O.; Dama, J. F.; Voth, G. A. Simulating Protein Mediated Hydrolysis of ATP and Other Nucleoside Triphosphates by Combining QM/MM Molecular Dynamics with Advances in Metadynamics. *J. Chem. Theory Comput.* **2017**, *13*, 2332−2341.

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