THE JOURNAL OF PHYSICAL CHEMISTRY B
A JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

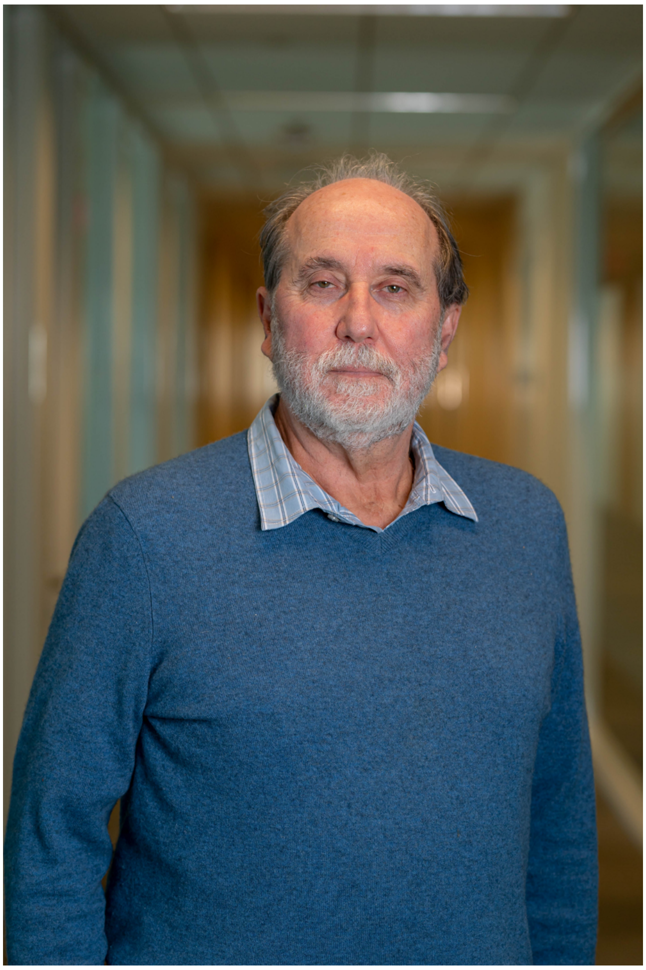
pubs.acs.org/JPCB

Special Issue Preface

Tribute to José N. Onuchic

Published as part of The Journal of Physical Chemistry virtual special issue "José N. Onuchic Festschrift".

Cite This: *J. Phys. Chem. B* 2023, 127, 7553−7555



This Festschrift Virtual Special Issue in *The Journal of Physical Chemistry B* is dedicated to the scientific contributions of Prof. José Nelson Onuchic and serves as a celebration of his years of service, mentorship, and leadership to the biological physics, theoretical chemistry, and computational biology communities. This collection of 62 articles has been compiled from an extensive network of scientists that have, in distinct ways, been impacted by the scientific legacy of Prof. Onuchic. It is a written testament to how his work has influenced many areas related to the physics and chemistry of biological systems. This Festschrift provides a good sample of the areas in which Professor Onuchic has had a direct impact via collaboration, mentorship, and scientific dissemination of his research.

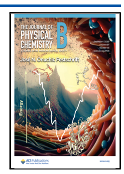
Prof. Onuchic has made seminal contributions that have shaped the study of biological physics at all scales, ranging from the dynamics of individual electrons to genomes and systems of organisms. To lead in a range of areas, he has repeatedly redefined himself as a scientist, and through this process, has established fundamental theoretical concepts that have guided each field.

A SCIENTIFIC JOURNEY THROUGH ENERGY LANDSCAPES

Prof. Onuchic is a native of São Carlos, a municipality in the state of São Paulo in Brazil. In São Carlos, as a student at the University of São Paulo, he already started to work in biological physics and received a master's degree under the direction of Prof. Sérgio Mascarenhas. In the mid-1980s, Prof. Onuchic moved to the United States to work under the direction of Prof. John Hopfield at Caltech. His first major success arose when, as a Ph.D. student, he began developing a theoretical framework for studying the kinetics of biological electron transfer reactions. During his training and in the early stages of his independent career, he developed the concept of tunneling pathways, a methodology for describing a protein as a combination of relevant "tubes" that provides ways to design electron transfer proteins.[1−3] The effectiveness of the theoretical framework is illustrated by the broad range of experimental groups that have adopted this perspective, as well as ongoing theoretical efforts that continue to build upon these early achievements.

As a young independent investigator at the University of California at San Diego, he helped revolutionize our understanding of protein folding dynamics by introducing a physical framework explaining why only a small number of amino acid sequences can rapidly fold to unique native structures. He was one of the pioneers in the field of protein folding energy landscape theory among others in the field like Prof. Peter Wolynes.[4−6] He proposed the folding funnel concept as a quantitative tool for understanding the dynamics

Published: September 7, 2023



https://doi.org/10.1021/acs.jpcb.3c05234
J. Phys. Chem. B 2023, 127, 7553−7555

of proteins.[7] According to the funnel paradigm, convergent kinetic pathways, or folding funnels, guide the protein to a low-energy native conformation. Energy landscape theory and the funnel concept provided a much needed and robust theoretical framework, allowing the field to methodically dissect the energetics of protein folding and functional dynamics. Analogous to his efforts to study electron transfer, these theoretical advances have guided much of the experimental research in protein folding over the last three decades. His pursuit and development of the funnel landscape perspective highlights his outlook as a scientist, in that he profoundly believes in the power of statistical physics techniques to understand complex biological processes. Through rigorous physical analysis, he has repeatedly demonstrated how fundamental concepts can help shape next-generation experimental approaches.

In addition to his seminal contribution to understanding protein folding, his scientific reach expands to other relevant aspects of protein function. Cells contain an extensive range of molecular machines that control and maintain cellular functions with exquisite precision. One key feature of biological machines is that conformational changes are often triggered by external noise. By adopting statistical approaches for describing diffusion of biomolecules on energy landscapes, he has shown how fluctuations in kinesin lead to versatile adaptation of the molecular structure, allosteric communication, and large amplitude stepping motion.[8]

His efforts to understand protein folding also led to the study of evolutionary energetic signatures in the ever-increasing set of known protein sequences. In particular, he co-developed Direct Coupling Analysis,[9] a widely used method for identifying co-evolving residues in proteins. This technique has been used as a basis for understanding how constraints imposed by evolution affect protein amino acid composition and how these statistical signatures can be used to predict protein structures, formation of complex assemblies, molecular specificity, and the effect of mutations on protein energetics and function.

More recently, he has further expanded his ideas from the energy landscapes of protein folding to tackle the complex problem of chromatin folding dynamics and function. He has shown how chromatin architecture can be predicted *de novo* using only epigenetic data derived from chromatin immuno-precipitation-sequencing (ChIP-Seq).[10,11] A particularly exciting advance has been the ability of these approaches to reveal how the genome reorganizes during different stages of the cell cycle.

Despite Prof. Onuchic's success, he is relentlessly searching for new areas of biology for which novel physical concepts are required to understand dynamics. For example, he broadened his interests from individual molecules to study stochastic effects in genetic networks, particularly those associated with bacteria and cancer. In nature, bacteria form colonies, where large-scale collective dynamics control the community's survival. His research in this area has focused on how, under stressful conditions, bacteria communicate via chemical messages. These messages allow bacteria to synthesize external stimuli and perform a sophisticated decision process that involves a specialized network of genes and proteins. Since the cell only possesses small numbers of some specific components (proteins and mRNA), his work using stochastic methods has been critical to establishing a quantitative understanding of these systems. Recently, he has continued to generalize these ideas to mammalian cells, which holds promise for understanding the mechanisms that govern cancer.[12−14] Another example of his visionary intuition to attack new scientific problems is his work during the COVID-19 pandemic. He worked, among other collaborators on an aerosol-based vaccination methodology that elicits immune responses in mice. This methodology has the advantages of being robust and easy to engineer with mass production cost benefits and importantly can be manipulated at room temperature.[15] This example is one of many where Dr. Onuchic established a physics-based approach to understand and solve problems in biology and biomedicine.

■ AN EXCEPTIONAL MENTOR AND LEADER IN THEORETICAL BIOLOGICAL PHYSICS

In concert with his outstanding scientific achievements, Prof. Onuchic has exhibited exceptional professional leadership among his peers and mentees. In 2002, Dr. Onuchic made two important and everlasting contributions to his field. First, he was the founding co-organizer of the Gordon Research Conference in Protein Folding Dynamics, which has been held for more than 20 years and has grown into one of the most vibrant and enriching conferences in the field of protein dynamics. Every two years, theorists and experimentalists come together to exchange scientific advances that have led to many new avenues of research. Prof. Onuchic has been instrumental to the success of this important scientific meeting. Second, in 2002, he was one of the founders of the Center for Theoretical Biological Physics (CTBP) and has since been its co-Director. CTBP is the longest-running NSF-funded Physics Frontiers Center, and it encompasses a broad spectrum of research and training activities at the forefront of the biology−physics interface. Research topics include molecular and computational biophysics, statistical biophysics, and biological dynamics at the cellular/multicellular scale. CTBP has proven to be a unique place where interdisciplinary problems are carried out jointly by physicists, chemists, mathematicians, computer scientists, and biologists.

The scientific contributions of CTBP have provided a deeper understanding of the mechanisms that govern complex systems and infused physicists with an appreciation of the complexity found in biology. Under the leadership of Prof. Onuchic, CTBP became synonymous with innovation and excellence in theoretical biological physics. Many of CTBP's more than 100 trainees have gone on to build successful independent research careers as faculty members and research scientists. Just to name a few examples, members of his group have rapidly become world leaders in their domains, including Cecilia Clementi (protein folding), Joanna Sulkowska (knotted proteins), and Koby Levy (biomolecular association). The three coauthors of this tribute were also once under his aegis at UCSD and Rice University.

■ A CHARISMATIC TEACHER AND EDUCATOR

During his career as a scientist and leader in his field, Prof. Onuchic has also maintained a career in education. His courses in introductory physics have influenced the lives of many students at the University of California San Diego and Rice University. Importantly, he has shown a clear enthusiasm to train young undergraduates, and his charismatic style has become a staple of undergraduate physics education at these institutions. His commitment to undergraduate education does

https://doi.org/10.1021/acs.jpcb.3c05234
J. Phys. Chem. B 2023, 127, 7553−7555

not stop in the classroom. As Magister of the Lovett College at Rice University, Prof. Onuchic and his wife, Mayra, lived in the student residences, where they opened the doors for out-of-classroom interactions with undergraduate students. Through CTBP and its outreach activities, Prof. Onuchic has spearheaded efforts to provide research opportunities to many students from community colleges in California and Texas, expanding his reach in education and increasing opportunities for scientific enrichment to undergraduates. Finally, he has also had a role in educational efforts for internationalization, establishing institutional alliances with countries like Brazil, which has promoted scientific cooperation and exchange of human and intellectual capital.

We cannot conclude this tribute without highlighting Prof. Onuchic's personal attributes. Everyone who knows José will attest to his energy and excitement about science and his approach to human interactions. His legacy goes beyond publications and awards. He has become a unifying figure for a generation of scientists who not only have learned from him but also aspire to promote the field of biological physics, uniting individuals academically and personally. His legacy permeates among his colleagues, mentees, and friends in a very unique and special way that only those who know him would understand. We believe this Festschrift collection serves as evidence of the profound respect and appreciation of the field for his exceptional contributions to physics, chemistry, and biology.

Faruck Morcos orcid.org/0000-0001-6208-1561
Paul C. Whitford orcid.org/0000-0001-7104-2265
Margaret S. Cheung orcid.org/0000-0001-9235-7661

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcb.3c05234.

Table of contents for the José N. Onuchic Festschrift (PDF)

AUTHOR INFORMATION

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jpcb.3c05234

Notes

Views expressed in this preface are those of the author and not necessarily the views of the ACS.

REFERENCES

(1) Onuchic, J. N.; Beratan, D. N.; Winkler, J. R.; Gray, H. B. Pathway analysis of protein electron-transfer reactions. *Annu. Rev. Biophys. Biomol. Struct.* **1992**, *21*, 349−377.

(2) Betts, J. N.; Beratan, D. N.; Onuchic, J. N. Mapping electron tunneling pathways: an algorithm that finds the ″minimum length″/maximum coupling pathway between electron donors and acceptors in proteins. *J. Am. Chem. Soc.* **1992**, *114*, 4043−4046.

(3) Garg, A.; Onuchic, J. N.; Ambegaokar, V. Effect of Friction on Electron-Transfer in Biomolecules. *J. Chem. Phys.* **1985**, *83*, 4491−4503.

(4) Bryngelson, J. D.; Onuchic, J. N.; Socci, N. D.; Wolynes, P. G. Funnels, pathways, and the energy landscape of protein folding: a synthesis. *Proteins* **1995**, *21*, 167−195.

(5) Onuchic, J. N.; Luthey-Schulten, Z.; Wolynes, P. G. Theory of protein folding: the energy landscape perspective. *Annu. Rev. Phys. Chem.* **1997**, *48*, 545−600.

(6) Onuchic, J. N.; Wolynes, P. G. Theory of protein folding. *Curr. Opin Struct Biol.* **2004**, *14*, 70−75.

(7) Leopold, P. E.; Montal, M.; Onuchic, J. N. Protein folding funnels: a kinetic approach to the sequence-structure relationship. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 8721−8725.

(8) Hyeon, C.; Onuchic, J. N. Internal strain regulates the nucleotide binding site of the kinesin leading head. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 2175−2180.

(9) Morcos, F.; Pagnani, A.; Lunta, B.; Bertolino, A.; Marks, D. S.; Sander, C.; Zecchina, R.; Onuchic, J. N.; Hwa, T.; Weigt, M. Direct-coupling analysis of residue coevolution captures native contacts across many protein families. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, E1293−E1301.

(10) Di Pierro, M.; Zhang, B.; Aiden, E. L.; Wolynes, P. G.; Onuchic, J. N. Transferable model for chromosome architecture. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 12168−12173.

(11) Di Pierro, M.; Cheng, R. R.; Lieberman Aiden, E.; Wolynes, P. G.; Onuchic, J. N. De novo prediction of human chromosome structures: Epigenetic marking patterns encode genome architecture. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 12126−12131.

(12) Vilchez Mercedes, S. A.; Bocci, F.; Levine, H.; Onuchic, J. N.; Jolly, M. K.; Wong, P. K. Decoding leader cells in collective cancer invasion. *Nat. Rev. Cancer* **2021**, *21*, 592−604.

(13) Lu, M.; Jolly, M. K.; Levine, H.; Onuchic, J. N.; Ben-Jacob, E. MicroRNA-based regulation of epithelial-hybrid-mesenchymal fate determination. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 18144−18149.

(14) Bocci, F.; Gearhart-Serna, L.; Boareto, M.; Ribeiro, M.; Ben-Jacob, E.; Devi, G. R.; Levine, H.; Onuchic, J. N.; Jolly, M. K. Toward understanding cancer stem cell heterogeneity in the tumor microenvironment. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116*, 148−157.

(15) Staquicini, D. I.; Tang, F. H. F.; Markosian, C.; Yao, V.J.; Staquicini, F. I.; Dodero-Rojas, E.; Contessoto, V. G.; Davis, D.; O'Brien, P.; Habib, N.; et al. Design and proof of concept for targeted phage-based COVID-19 vaccination strategies with a streamlined cold-free supply chain. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2105739118.

https://doi.org/10.1021/acs.jpcb.3c05234
J. Phys. Chem. B 2023, 127, 7553−7555