## BIOGRAPHICAL SKETCH

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NAME: Ravi Radhakrishnan

eRA COMMONS USER NAME (credential, e.g., agency login): rradhak

POSITION TITLE: Professor of Bioengineering, Professor of Chemical and Biomolecular Engineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Start Date MM/YYYY | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| Indian Institute of Technology, Madras, India | B. Tech. | 08/1991 | 05/1995 | Chemical Engineering |
| Cornell University, Ithaca, NY | Ph.D. | 09/1995 | 01/2001 | Chemical Engineering Minor in Physics |
| Massachusetts Institute of Technology | Postdoctoral | 09/2000 | 08/2002 | Chemical Engineering |
| New York University and HHMI | Postdoctoral | 09/2002 | 07/2004 | Molecular Biophysics |

### A. Personal Statement

Ravi Radhakrishnan Ph.D. holds the title of Professor of Bioengineering and Professor of Chemical and Biomolecular Engineering. He is also a member of the graduate groups of Genomics and Computational Biology and Biochemistry and Molecular Biology. He is currently the Chairman of Bioengineering. He is a founding member and the former Director of the Penn Institute of Computational Sciences and a project leader of the NCI funded Penn Physical Sciences in Oncology Center.

Radhakrishnan directs a computational research laboratory with research interests at the interface of biophysics, chemical physics, and biomedical engineering with applications to cellular engineering in cancer and immunology. The goal of his computational molecular systems biology laboratory is to establish digital twin simulation platforms enabled by a combination of multiscale modeling and AI. The digital twin simulators enable multiscale and mechanistic characterization of complex systems and formulate accurate and predictive models for precision oncology and nanomedicine applications. His lab specializes in several computational algorithms spanning the molecular and cellular scales, in conjunction with the theoretical formalisms of statistical mechanics, and applications of high-performance scientific computing in parallel architectures. He has successful and funded collaborations with pharmacologists, cell biologists, biophysical chemists, anesthesiologists, and oncologists primarily through grants from US National Science Foundation, US National Institutes of Health, and the European Research Council.

Radhakrishnan has authored over 170 articles in leading peer reviewed Journals, serves as a referee for over 45 leading journals, publishers, and federal funding agencies, and serve on the editorial board of five journals. He is a Fellow of the American Institute of Medical and Biological Engineers, Overseas Fellow of the Royal Society of Medicine, and a Fellow of the Biomedical Engineering Society and serves as the Working Group Leader for High Performance Computing for an Inter-Governmental Panel involving NIH, NSF, NASA, DOE, DOD, and DARPA.

In the 17 years of experience as a PI, he has mentored 25 doctoral and 18 post-doctoral scholars. Radhakrishnan has trained and graduated 11 Doctoral students of whom all 11 have gone on to research related carriers. He has graduated 17 postdoctoral researchers in which all 17 have gone on to research related careers. He currently mentors 8 doctoral and 2 postdoctoral scholars. In addition, his lab has mentored over 20 undergraduate researchers and 12 Masters researchers. Trainees receive high level computational modeling training in his lab that often complements experimental mechanisms studied. Radhakrishnan runs the bridge-to-masters and bridge-to-phd programs in Bioengineering in partnership with two minority serving

institutions (Coastal Carolina Univercity and LaSalle University) and one HBCU (Lincoln University). He also coordinates the certificate program on high-performance computing in PICS and runs an undergraduate focussed research outreach program for students in Western Africa in partnership with the NGO Afrisnet.

**Ongoing Projects to highlight include:**
NIH U01 CA250044, R. Radhakrishnan (MPI), W. Guo (MPI), V. M. Weaver (MPI) 9/1/2021-8/31/2026
Physical Science Approach to Investigating the Role of Exosomes in Metastatic Cancers
Goals: To develop cellular, in vivo, and insilico biophysical models for investigating the mechanosensitivity of exosomes and their role in metastatic progression and immune response; Role: PI

NIH 1R01CA244660-01 M. A. Lemmon (MPI), R. Radhakrishnan (MPI) 02/01/20 – 01/31/25
Multiscale Modeling to Optimize Inhibition of Oncogenic ERK Pathway Signaling
Goals: The goal is to develop computational models of signaling pathways relevant to Erk signaling by incorporating information on molecular states of kinase conformations under drug treatment; Role: MPI

NIH 1R35GM136259-01 P. A. Janmey (PI) 01/01/20 – 12/31/24
Regulation of cell function by mechanical properties of biopolymer networks and lipid bilayers
Goals: This MIRA application combines studies of the 3-D networks formed by protein filaments and the 2D surfaces formed by phospholipids to determine how the physical-chemical properties of these structures help determine their biological function; Role: Senior Project Personnel

NIH U01 CA227550 A. Raj (MPI), R. Radhakrishnan (MPI), A. Weeraratna (MPI) 7/1/2018-6/31/2023
A plasticity and reprogramming paradigm for therapy resistance at the single cell level
Goals: Quantitative analysis of single cell mechanisms of drug resistance in melanoma; Role: MPI

**Recently completed projects to highlight include:**
NIH U54 CA193417 Discher (Center PI), Radhakrishnan (Lead PI, Project 2) 08/1/16-07/31/22
Penn Physical Sciences in Oncology Center
Goals: To establish pathways of oncogenic signals triggered by liver fibrosis; Role: Project Leader

NIH R01 GM111942 Janmey (PI) 9/1/15-8/31/20
Phosphoinositide Clustering, Interactions and Protein Recruitment
Goals: To establish molecular mechanisms of phosphoinositide clustering for actin assembly; Role: co-I

Selected Citations on New Algorithms and Methods for Multiscale Modeling
Our laboratory has developed new methods for biophysical and transport processes (nanoscale mechanics and hydrodynamics), network dynamics, stochastic and fluctuation analysis in cellular dynamics through the development of numerical techniques inspired by foundational principles in equilibrium and non-equilibrium statistical mechanics, high-performance computing, and data science and machine learning. We have spearheaded the development of new algorithms and methods for multiscale modeling emphasizing the subcellular and cellular length scales.

R. Radhakrishnan, A survey of multiscale modeling: foundations, historical milestones, current status, and future prospects, 2021, AIChE Journal, e17026: pp1-21. DOI: 10.1002/aic.17026. PMCID PMC7988612
E. Jordan, K. Patil, K. Suresh, J. Park, Y. Mosse, M. A. Lemmon, R. Radhakrishnan, Computational Algorithms for In Silico Profiling of Activating Mutations in Cancer, Cellular and Molecular Life Sciences, 2019, 76(14):2663-2679; DOI: 10.1007/s00018-019-03097-2. PMID: 30982079. PMCID: PMC6589134.
R. Radhakrishnan, H.-Y. Yu, D. M. Eckmann, P. S. Ayyaswamy, Computational models for nanoscale fluid dynamics inspired by non-equilibrium thermodynamics, Journal of Heat Transfer, 2017, 139, 033001:1-9. PMID: 28035168 PMCID: PMC5125320 DOI: 10.1115/1.4035006.
N. Ramakrishnan, P. B. Sunil Kumar, R. Radhakrishnan, Mesoscale computational methods for membrane remodeling by curvature inducing proteins, Physics Reports, 2014, 543, 1-60. PMID: 25484487 PMCID: PMC4251917. DOI: 10.1016/j.physrep.2014.05.001.

**B. Positions, Scientific Appointments, and Honors**

**Employment**
University of Pennsylvania, Philadelphia, PA
2020-Present Chair, Department of Bioengineering
2018-2020 Director of Penn Institute of Computational Sciences

2017-2019 Graduate Group Chair, Bioengineering, University of Pennsylvania
2015-2018 Professor of Biochemistry and Biophysics
2015- Professor of Bioengineering, Professor of Chemical and Biomolecular Engineering
2013-2014 Visiting Associate Professor, Department of Bioengineering, University of California Berkeley
2013 Founding Member of Penn Institute of Computational Sciences
2010- Member of Graduate Group, Biochemistry and Molecular Biology, School of Medicine
2010-2015 Associate Professor of Bioengineering, Associate Professor of Chemical and Biomolecular Engineering, Associate Professor of Biochemistry and Biophysics
2006- Member, Institute of Targeted Medicine and Therapeutics
2004- Member of Graduate Group, Genomics and Computational Biology, School of Medicine
2006-2010 Assistant Professor of Biochemistry and Biophysics, School of Medicine
2004-2010 Assistant Professor of Bioengineering, Assistant Professor of Chemical and Biomolecular Engineering, School of Engineering and Applied Sciences

**Other Experience and Professional Service (last 5 years)**

2021 Founding Member, Penn Anti-Cancer Engineering Center
2019 Adhoc member for Gene and Drug Delivery Study Section; SRA: Dr. Leslie Itsara
2018-Present Adhoc Member for Review of NIH Innovator Award Proposals, SRA: Dr. Srikanth Ranganathan
2017-Present Graduate Group Chair, Bioengineering Graduate Group, University of Pennsylvania
2016-Present Adhoc Member for NIH/NCI's Center for Cancer Systems Biology Program, SRA: Dr. Adriana Stoica, November 2016, 2017
2018-2020 Director, Penn Institute for Computational Science
2016, 2021 Adhoc Member for NIH/NIGMS special emphasis panel for P01; SRA: Dr. Nitsa Rosenzweig, September 2016; James Li 2021
2016-Present Editorial Board Member, Scientific Reports
2015-2021 Project Leader, Penn/NCI Physical Sciences in Oncology Center
2014, 2016 Panelist, National Science Foundation, Proposal Review Panel for CDS&E (Cyber-enabled discovery in science and engineering), Program Managers: Dr. Thanasis Sambanis and Dr. Carol Lucas
2014-2015 Adhoc Member for NIH/NCI, U01 applications for NCI PAR13-184 "Collaborative Research in Integrative Cancer Biology", October 2014. Program Manager: Zhiqiang Zou.
2014 Guest Editor, Plos Computational Biology
2014-Present Working Group Leader, High-performance computing working group, Multiscale Modeling Consortium, Interagency Modeling Group (NIH, NSF, NASA, DOD, DOE)
2012-Present Editorial Board Member, Nanocarriers
2011-Present Editorial Board Member, Frontiers in Computational Physiology and Medicine
2008-Present Referee for 45 peer-reviewed journals, 8 publishers, 6 funding agencies

**Honors (Selected)**

2022 Review Board Member, Department of Bioengineering, Stanford University
2021 Invited Speaker, Systems Biology Meeting, Aiche Conference, Boston, MA
2020 Invited Speaker, The International Symposium on Cell Surface Macromolecules, Pune, India
2019 Invited Speaker, Thematic meeting of the Biophysical Society: Quantitative aspects of membrane fusion and fission, Padova, Italy
2018 Invited Speaker, Virtual Physiological Human 2018 Conference VPH for In Silico Medicine, Zaragoza, Spain
2012-17 Investigator, Computational Horizons in Cancer (CHIC); Insilico Oncology Consortium, Virtual Physiological Human, European Commission
2017 Invited Speaker, Telluride Science Research Center (TSRC) Workshop on Molecular engineering of soft matter: Spanning small molecules to macromolecules, Telluride CO, 2017
2017 Invited Speaker, Physical Sciences in Oncology Network, National Cancer Institute and the Koch Institute of Integrative Genomics, Cambridge, MA
2016 Invited Speaker, Pediatric Oncology Meeting, Toronto, Canada
2015 Fellow of the American Institute of Medical and Biological Engineering
2015- Member of the Physical Sciences in Oncology Network and Cancer Systems Biology Network (PSON/CSBN) of the National Cancer Institute (NCI)

2014- Group Leader of the High Performance Computing Working Group, Multiscale Modeling Consortium and the Interagency Modeling Group, NIBIB
2014 Invited Speaker, Insilico Oncology Session, Tumor Models, Boston, MA
2021 Fellow, Royal Society of Medicine
2013 Invited Speaker, International Conference in Bioengineering and Nanotechnology, Ft. Lauder., FL.
2012 Member of Organizing Committee: 5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation - The TUMOR Project Workshop, Athens, Greece, 2012.
2011 Invited Keynote Speaker, First International Workshop on Insilico Oncology, Crete, Greece, 2011
2011 Invited Speaker, Multiscale Modeling Consortium Meeting, Inter Agency Modeling Group, NIH, Bethesda MD, 2011
2010 Invited Speaker, Molecular Biophysics Subgroup Symposium, Biophysical Society Annual Meeting
2008 Invited Speaker, NSF US-Poland Workshop on Nanoscience, Sponsored by NSF/CBET, Gdansk
2008 Invited Speaker, 1st Transatlantic Workshop on Multiscale Cancer Modeling, Sponsored by NCI and European Commission, Brussels, Belgium.
2008 Hewlett-Packard Outstanding Junior Faculty Award, American Chemical Society
2003 Computational Associate of the Howard Hughes Medical Institute
1999 Certificate in Parallel Computing, Cornell Theory Center
1991-95 Undergraduate Fellowship from the Council of Scientific and Industrial Research

**C. Contributions to Science**

Computational Structural Biology and Network Models in Cancer

Applications of our work on studying the mutational landscape of kinases have widespread impact the field of oncology, where our predictive models of how kinase-domain mutations alter function, have been integrated with clinical investigations and patient trials in various cancers.

K. Patil, E. J. Jordan, J. Park, K. Suresh, C. M Smith, A. A Lemmon, Y. P. Mosse, M. A. Lemmon, R. Radhakrishnan, Computational Studies of Anaplastic Lymphoma Kinase Mutations Reveal Common Mechanisms of Activation Amidst a Varied Mutational Landscape in Neuroblastoma Patients, 2021, Proceedings of the National Academy of Sciences, 118(10) e2019132118; DOI: 10.1073/pnas.2019132118. PMID: 33674381; PMCID: PMC7958353;

A. Ghosh, R. Radhakrishnan, Time-dependent antagonist-agonist switching in receptor tyrosine kinase mediated signaling, 2019, BMC Bioinformatics, 20, 242. PMID: 31092187; PMCID: 6521356; DOI: 10.1186/s12859-019-2816-3.

D. M. Freed, J. H. Park, R. Radhakrishnan, M. A. Lemmon, Deletion mutations keep kinase inhibitors in the loop, Cancer Cell, 2016, 29(4):423-425; PMID: 27070691 PMCID: PMC5028821 DOI: 10.1016/j.ccell.2016.03.017.

S. Bressler, D. Weiser, P. J. Huwe, R. Radhakrishnan, M. A. Lemmon, Y. Mosse, Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma, Cancer Cell, 2014, 26, 682-694. PMID: 25517749 PMCID: PMC4269829 DOI: 10.1016/j.ccell.2014.09.019.

Multiscale Models in Intracellular Cellular Trafficking

Intracellular trafficking represents a fundamental aspect of cell physiology that has ramifications in the basic cell function but also in technological aspects of drug delivery. We have built the necessary theoretical foundations as well as established a computational platform to investigate curvature contributions for single proteins and small protein assemblies from molecular simulations and then utilized this curvature field in coarse-grained models, where we directly compute the driving forces for intracellular transport. Our methods enable predictions as functions of physical variables such as membrane tension, and matrix stiffness.

K. K. Sreeja, P. A. Janmey, R. Radhakrishnan, Membrane signalosome: where biophysics meets systems biology, 2021, Current Opinion in Systems Biology, 25, 34-41 DOI: 10.1016/j.coisb.2021.02.001; PMID: 33997528; PMCID: PMC8117111

S. K. Kandy, R. Radhakrishnan, Emergent membrane morphologies in relaxed and tense membranes in presence of reversible adhesive pinning interactions, Physical Biology, 2019, 16, 066011 (pp1-10). PMCID: PMC6830734. DOI: 10.1088/1478-3975/ab48d5.

N. Ramakrishnan, R. P. Bradley, R. W. Tourdot, R. Radhakrishnan, Biophysics of membrane curvature remodeling at molecular and mesoscopic lengthscales, J Phys Condens Matter, 2018, 11, 30(27), 273001. PMID: 29786613 PMCID: PMC6066392 DOI: 10.1088/1361-648X/aac702.

R. W. Tourdot, R. P. Bradley, N. Ramakrishnan, R. Radhakrishnan, Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking, IET Systems Biology, 2014, 8(5), 198-213. PMID: 25257021 PMCID: PMC4336166 DOI: 10.1049/iet-syb.2013.0057.

‘Algorithms from for Biological Adhesion at the Nanoscale

Our work on biological adhesion has led to the formulation of quantitative expressions for absolute free energy of binding of multivalent interactions where there is significant enthalpy-entropy compensation. Our results have led to paradigm-shifting conclusions and implications for nanoparticle design: specifically, entropic forces are delicately traded through modulation of multivalency, shape, and flexibility of the nanoparticle, substrate.

S. Farokhirad, S. Kutti Kandy, A. Tsourkas , P. Ayyaswamy, D. M. Eckmann, R. Radhakrishnan, Biophysical Considerations in the Rational Design and Cellular Targeting of Flexible Polymeric Nanoparticles, , 2021, Advanced Materials Interfaces, 8, 2101290. DOI: https://doi.org/10.1002/admi.202101290; NIHMSID: 1764219

M. McKenzie, S. M. Ha, A. Rammohan, R. Radhakrishnan, and N. Ramakrishnan, Multivalent binding of a ligand coated particle: Role of shape, size and ligand heterogeneity, 2018, Biophysical Journal, 114(8):1830-1846. PMID: 29694862 PMCID: PMC5937168 DOI: 10.1016/j.bpj.2018.03.007.

N. Ramakrishnan, D. M. Eckmann, V. M. Muzykantov, P. S. Ayyaswamy, and R. Radhakrishnan, Biophysically inspired model for functionalized nanocarrier adhesion to cell surface: roles of protein expression and mechanical factors, , 2016, Royal Society Open Science, 2016, 3, 160260. PMID: 27429783 PMCID: PMC4929918 DOI: 10.1098/rsos.160260; supplementary information DOI: doi:10.5061/dryad.4h76d

J. Liu, G. E. R. Weller, B. Zern, P.S. Ayyaswamy, D. M. Eckmann, V. Muzykantov, R. Radhakrishnan, A Computational Model for Nanocarrier Binding to Endothelium Validated Using In Vivo, In Vitro, and Atomic Force Microscopy Experiments, Proceedings of the National Academy of Sciences, 107: 16530-16535, 2010. PMID: 20823256 PMCID: PMC2944711 DOI: 10.1073/pnas.1006611107.

Multiscale Models in Pharmacology and Targeted Drug Delivery

We have shown how the various multiscale models and methods can be translated to next-generation pharmacokinetic models for targeted drug delivery by realizing successful applications of nanocarrier targeting. Our unique vision is to develop a quantitative multiscale platform for in silico pharmacology, where through multiscale modeling, we can conduct in silico trials.

D. M. Eckmann, R. P. Bradley, S. K. Kandy, K. Patil, P. A. Janmey, R. Radhakrishnan, Multiscale Modeling of Protein Membrane Interactions for Nanoparticle Targeting in Drug Delivery, Current Opinion in Structural Biology, 2020, 64, 104-110. PMID 32731155 PMCID: PMC7666034; DOI: 10.1016/j.sbi.2020.06.023.

S. Farokhirad, A. Ranganathan, J. Myerson, V. M. Muzykantov, D. M. Eckmann, P. S. Ayyaswamy, and R. Radhakrishnan, Stiffness can mediate balance between hydrodynamic forces and avidity to impact the targeting of flexible polymeric nanoparticles in flow, Nanoscale, 2019, 11, 6916-6928, PMCID: PMC7376444. DOI: 10.1039/c8nr09594a

J. S. Brenner, K. Bhamidipati, N. Ramakrishnan, Z. Jabeen, D. Jiang, A. J. Paris, E. Hood, C. Villa, R. Kisleva, J. Myerson, D. Pan, V. Shuvaev, C. Greineder, G. S. Worthen, R. Radhakrishnan, V. Muzykantov, The spatial heterogeneity of acute lung injury selectively shunts different drug classes either towards or away from flooded alveoli, Nanomedicine: Nanotechnology, Biology, and Medicine, 2017, 13(4), 1495–1506. PMID: 28065731 PMCID: PMC5518469 DOI: 10.1016/j.nano.2016.12.019.

B. J. Zern, A-M. Chacko, J. Liu, C. F. Greineder, E. R. Blankemeyer, R. Radhakrishnan, V. R. Muzykantov, Reduction of nanoparticle avidity enhances the selectivity of vascular targeting and PET detection of pulmonary inflammation, ACS Nano, 2013, 7(3):2461-2469. PMID: 23383962 PMCID: PMC3609928 DOI: 10.1021/nn305773f.