BIOGRAPHICAL SKETCH

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NAME: Levy, Ronald M

eRA COMMONS USER NAME (agency login): ronlevy

POSITION TITLE: Laura H. Carnell Professor of Biophysics & Computational Biology

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Reed College, Portland, OR	AB	06/1970	Biology/Math
Harvard University, Cambridge, MA	PHD	06/1976	Biophysics
Harvard University, Cambridge, MA	OTH	06/1980	Biophysical Chemistry

A. PERSONAL STATEMENT

My research interests are focused on the development and application of computational methods for studying the structure, function, and dynamics of proteins. I have worked for more than thirty years on problems involving the interplay between computational models in structural biology and experiments at different levels of resolution and different time scales. Using a statistical mechanics framework, we are mapping conformational free energy landscapes that determine the statistical thermodynamic basis for protein-ligand binding and allostery. We are surveying corresponding fitness landscapes in sequence space, and developing new statistical methods to analyze how correlated mutations evolve under drug selection pressure, leading to resistance. I have authored over two hundred publications, H index 67.

B. POSITIONS AND HONORS

Positions and Employment

1980 - 1984	Assistant Professor, Chemistry, Rutgers University, New Brunswick, NJ
1984 - 1987	Associate Professor, Chemistry, Rutgers University, New Brunswick, NJ
1986	Visiting Professor, Crystallography Laboratory, CNRS, Strasbourg
1987 - 1991	Professor, Chemistry, Rutgers University, New Brunswick, NJ
1991 - 2002	Professor II, Chemistry, Rutgers University, New Brunswick, NJ
2002 - 2004	Co-Director, BioMaPS Institute for Quantitative Biology, Rutgers University, NJ
2002 - 2014	Board of Governors Professor of Chemistry and Chemical Biology, Rutgers University, New Brunswick, NJ
2004 - 2013	Adjunct Professor of Biochemistry, Robert Wood Johnson Medical School, UMDNJ, New Brunswick, NJ
2005 - 2012	Director, BioMaPS Institute for Quantitative Biology, Rutgers University, New Brunswick, NJ
2005 - 2012	Co-Director, Graduate Program in Computational Biology & Molecular Biophysics
2014 -	Laura H. Carnell Professor of Biophysics & Computational Biology, Temple University, Philadelphia, PA
2014 -	Director, Center for Biophysics and Computational Biology, Temple University, Philadelphia, PA
2014 -	Professor of Chemistry (primary appointment), Physics and Biology, Temple University, Philadelphia, PA

Other Experience and Professional Memberships

1998	Co-Editor, *Current Opinion in Structural Biology*, Vol. 8, No. 2, 1998
2000	Co-Editor, *Current Opinion in Structural Biology*; Vol. 10, Number 2, 2000
2017	Co-Editor, *Current Opinion in Structural Biology*; Vol. 43, Number 1, 2017
2004 - 2014	Editorial Board, *Journal of Chemical Theory and Computation* (ACS)
2011 - 2020	Associate Editor, *Protein Science*
2001, 2002	NIH Biomedical Information Science and Technology Initiative (BISTI) Panel
1991 - 1995	NIH Study Sections BBCA, standing member (and ad hoc member, 2002; 2004)
2005	NIH Study Sections BCMB-Q
2008	NIH Study Section MSFD
2015 – 2021	NIH Study Section MSFD, standing member
2010	National Academy of Sciences, Committee to Evaluate Proposals for the Study of Molecular Dynamics on Anton, a special purpose computer
2000	NSF Information Technology Research (ITR) Panel
1997 -2000	Executive Committee, American Chemical Society, Physical Chemistry Division
2007 - 2010	American Physical Society, Division of Computational Physics

Spring 2004	Organizer, American Chemical Society National Meeting, Symposium on "Interplay between Computer Modeling and Experiments on Complex Biological Systems", Anaheim, CA
August 2004	Organizer, American Chemical Society National Meeting, Symposium on "Frontiers in Biophysical Chemistry", Washington, DC
March 2001	Co-Organizer, DIMACS Symposium on "Protein Structure and Structural Genomics: Prediction, Determination, Technology and Algorithms", Piscataway, NJ
	Advisory Boards: Schrödinger Inc. (1995-present); NIH Research Resource--Biological Magnetic Resonance Databank (University of Wisconsin, Madison) (1997-2003); Center for Biological Modeling, Michigan State University (2001-2005); University of Pittsburgh School of Medicine Center for Computational Biology and Bioinformatics (2003-2005); Japan Ministry of Science & Technology Priority Research Area "Physical Forces Affecting Protein Folding and Misfolding" (2004-2008).
March 2014	Co-Organizer, ACS Symposium “Tracing Pathways in Biomolecular Simulations”, Dallas TX
March 2016	Co-Organizer, ACS Symposium “Computer Simulations of Thermodynamics and Long Time Kinetics of Molecular Events”, San Diego CA

Honors

1982-1984	Alfred P. Sloan Foundation Fellow
1982-1987	NIH Research Career Development Award
1986	NIH Fogarty International Center Senior Fellowship
1987	Johnson and Johnson Discovery Research Award
1995-1996	John Simon Guggenheim Foundation Fellowship
1996	Rutgers University Board of Trustees Award for Excellence in Research
1996	Japan Society for the Promotion of Science Fellowship
1998	AAAS Fellow
2016	Festschrift Special Issue of Protein Science in Honor of Ronald Levy, Vol. 25, no. 1, January 2016

C. CONTRIBUTIONS TO SCIENCE

Ronald Levy is one of the founding members of the group of scientists who developed molecular dynamics simulations of proteins into the powerful technique used in biophysics and structural biology that it is today. He was the first to connect molecular simulations of proteins with Nuclear Magnetic Resonance relaxation experiments, and the first to carry out a simulation of a protein under high pressure. Using computational statistical mechanics as a framework, he has been a leader in studying solvation effects in chemistry and biophysics, and in developing methods and effective potentials for simulating these systems. Levy has pioneered the construction of multiscale models for studying protein kinetics on very long time scales based on Markov State Models built from Replica Exchange simulations. His studies of protein-ligand binding have emphasized the importance of entropic effects, as exemplified by the binding of ligands to Cytochrome P450s and to HIV Protease and Integrase. His group came in first among the computational groups in the 2013 SAMPL4 challenge virtual screening of inhibitors to HIV Integrase. He is a leader in an emerging field which uses maximum entropy Potts statistical models of sequence variation to map the fitness landscapes of proteins and viruses.

1. Protein Dynamics, Folding, and Misfolding In recent work we have coupled replica exchange simulations with kinetic network models to elucidate the heterogeneity of the pathways by which small proteins fold. In 2015 we explained why relaxation within the protein unfolded basin can be very fast even though state to state first passage times within that basin can be very slow, thus resolving a paradox the field was grappling with. Our work also explains why many small proteins fold with single exponential kinetics even though the folding pathways are diverse with different barriers.

1. Levy, R.M.,M. Karplus and P.G.Wolynes (1981). NMR Relaxation Parameters in Molecules with Internal Motion: Exact Langevin Trajectory Results Compared with Simplified Relaxation Models. J. Am. Chem. Soc., 103, 5998-6011
2. Andrec, M., A.K. Felts, E. Gallicchio, and R.M. Levy (2005). Protein Folding Pathways from Replica Exchange Simulations and a Kinetic Network Model. Proc. Natl. Acad. Sci. USA, 102, 6801-6806.
3. Wu, K., D. S. Weinstock, C. Narayanan, R. M. Levy, and J. Baum (2009). Structural Reorganization of α-Synuclein at Low pH Observed by NMR and REMD Simulations. J. Mol. Biol., 391, 784-796. DOI: 10.1016/j.jmb.2009.06.063. PMCID: PMC2766395.
4. Dai, W., A. M. Sengupta, and R. M. Levy (2015). First Passage Times, Lifetimes, and Relaxation Times of Unfolded Proteins. Phys. Rev. Lett., 115 (4), 048101. DOI: 10.1103/PhysRevLett.115.048101. PMCID: PMC4531052.

2. Solvation Thermodynamics in Biophysics and Structural Biology We were among the first to develop multipole and ewald sum methods for treating protein electrostatics in simulations with explicit solvent and to build linear response models from fully atomic simulations. We have developed physics based implicit solvent models which are widely cited.

We are developing a new statistical thermodynamic framework for analyzing the role of interfacial water in protein-ligand binding, and for inhibitor design.

1. Levy, R.M., and E. Gallicchio (1998). Computer Simulations with Explicit Solvent: Recent Progress in the Thermodynamic Decomposition of Free Energies, and in Modeling Electrostatic Effects. Annual Review of Physical Chemistry, 49, 531-567.
2. Levy, R.M., L.Y. Zhang, E. Gallicchio, and A.K. Felts (2003). On the Non-Polar Hydration Free Energy of Proteins: Surface Area and Continuum Solvent Models for the Solute-Solvent Interaction Energy. J. Am. Chem. Soc., 125, 9523-9530.
3. Levy, Ronald M., Di Cui, Bin W. Zhang, and Nobuyuki Matubayasi (2017). The Relationship Between Solvation Thermodynamics from IST and DFT Perspectives. The Journal of Physical Chemistry B, . DOI: 10.1021/acs.jpcb.6b12889.
4. Cui, Di, Bin W. Zhang, Nobuyuki Matubayasi, and Ronald M. Levy (2018). The Role of Interfacial Water in Protein–Ligand Binding: Insights from the Indirect Solvent Mediated Potential of Mean Force. Journal of Chemical Theory and Computation, Web publication. DOI: 10.1021/acs.jctc.7b0107

3. Mapping Free Energy Landscapes for Protein-Ligand Binding and Allostery We carried out some of the earliest simulations of allosteric transitions in a protein by umbrella sampling with free energy analysis. Our binding energy distribution analysis method (BEDAM) is a high throughput protein-ligand free energy simulation method which occupies a place between docking and high resolution free energy perturbation methods. It has been shown to substantially improve the enrichment of actives in large ligand libraries when used to refine the docked libraries. We have developed novel replica exchange algorithms for carrying out molecular simulations and new reweighting schemes to estimate free energies.

1. Ravindranathan, K.P., E. Gallicchio, and R.M. Levy (2005). Conformational Equilibria and Free Energy Profiles for the Allosteric Transition of the Ribose Binding Protein, J. Mol. Biol., 353, 196-210.
2. Gallicchio, E., and R.M. Levy (2011). Advances in all atom sampling methods for modeling protein-ligand binding affinities. Current Opinion in Structural Biology, 21, 161-166, PMCID: PMC3070828. Doi.10.1016/j.sbi.2011.01.010
3. Tan, Zhiqiang, Emilio Gallicchio, Mauro Lapelosa, and Ronald M. Levy (2012). Theory of binless multi-state free energy estimation with applications to protein-ligand binding. J. Chem. Phys., 136, 144102. DOI: 10.1063/1.3701175. PMCID: PMC3339880.
4. Zhang, Bin W., Nanjie Deng, Zhiqiang Tan, and Ronald M. Levy (2017). Stratified UWHAM and Its Stochastic Approximation for Multicanonical Simulations Which are Far from Equilibrium. *Journal of Chemical Theory and Computation*, 13, 4660-4674 PMCID: PMC5897113. DOI: 10.1021/acs.jctc.7b00651.

4. Design of inhibitors of HIV Reverse Transcriptase (RT) and Integrase (IN), and the Mechanism by which ALLINIS Promote the Multimerization of IN We have long standing strong collaborations with structural biologists, biochemists and virologists, working on the design of inhibitors of HIV proteins. Our model of the structure of the ALLINI induced IN multimer, was validated by the first reported crystal structure published in December 2016.

1. Paris, K.A., O. Haq, A.K. Felts, K. Das, E. Arnold, and R.M. Levy (2009). Conformational Landscape of the HIV-1 RT NNIBP: Lessons for Inhibitor Design from a Cluster Analysis of Many Crystal Structures. J. Med. Chem., 52, 6413-6420, PMCID: PMC 3182518. Doi.10.1021/jm900854h
2. Gallicchio, E., N. Deng, P. He, L. Wickstrom, A.L. Perryman, D.N. Santiago, S. Forli, A.J. Olson, and R.M. Levy (2014). Virtual screening of integrase inhibitors by large scale binding free energy calculations: the SAMPL4 challenge. Journal of Computer-Aided Molecular Design, 28, 475-490. PMCID: PMC4137862. doi: 10.1007/s10822-014-9711-9.
3. Slaughter, A., K.A. Jurado, N. Deng, L. Feng, J.J. Kessl, N. Shkriabai, R.C. Larue, H.J. Fadel, P.A. Patel, N. Jena, J.R. Fuchs, E. Poeschla, R.M. Levy, A. Engelman, and M. Kvaratskhelia (2014). The mechanism of H171T resistance reveals the importance of Nδ-protonated His171 for the binding of allosteric inhibitor BI-D to HIV-1 integrase. Retrovirology, 11. (2014) PMCID: PMC4251946. doi: 10.1186/s12977-014-0100-1.
4. Deng, Nanjie, Hoyte, Ashley, Mansour, Yara E., Mohamed, Mosaad S. Fuchs, James R., Engelman, Alan N., Kvaratskhelia, Mamuka, and Ronald M. Levy (2016). Allosteric HIV-1 Integrase Inhibitors Promote Aberrant Protein Multimerization by Directly Mediating Inter-Subunit Interactions: Structural and Thermodynamic Modeling Studies. Protein Science Accelerated Communications

5. Mapping the Fitness Landscapes of Proteins and the Evolution of Drug Resistance We are pioneering new sequence based statistical inference methods to analyze correlated mutations and the fitness landscape of kinase family proteins and of HIV-1 evolving under drug selection pressure. We have constructed Potts Hamiltonian models based on

multiple sequence alignments of HIV-1 Protease and Integrase, and used these models to study the entrenchment of primary mutations through epistatic interactions with the sequence background.

1. Haldane, A., W. F. William, P. He, R. Vijayan, and R. M. Levy (2016). Structural propensities of kinase family proteins from a Potts model of residue co-variation. Protein Science, 25, 1378-1384. DOI: 10.1002/pro.2954
2. Levy, R., A.Haldane, and W. F. Flynn (2017). Potts Hamiltonian models of protein co-variation, free energy landscapes, and evolutionary fitness. Current Opinion in Structural Biology, 43, 55-62. DOI: 10.1016/j.sbi.2016.11.004.
3. Flynn, William F., Allan Haldane, Bruce E. Torbett, and Ronald M. Levy (2017). Inference of epistatic effects leading to entrenchment and drug resistance in HIV-1 protease. Molecular Biology and Evolution, TBD. DOI: 10.1093/molbev/msx095.
4. Haldane, Allan, William Flynn, Peng He, and Ronald M. Levy (2018). Co-Evolutionary Landscape of Kinase Family Proteins, Subsequence Probabilities, and Functional Motifs. Biophysical Journal, 114(1),21-31. DOI: 10.1016/j.bpj.2017.10.028.

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