BIOGRAPHICAL SKETCH

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NAME: Rama Ranganathan

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

POSITION TITLE: Professor

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)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Berkeley	B.S.	1985	Bioengineering
University of California, San Diego	Ph.D.	1992	Biology
University of California, San Diego	M.D.	1994	Medicine

A. Personal Statement

Biological systems self-assemble under physiological conditions and can display functional properties that rival or exceed the performance of many man-made systems. For example, proteins fold spontaneously into well-ordered three-dimensional structures that exhibit the capacity for specific molecular recognition, catalysis of complex chemical reactions, signal transmission, and allosteric regulation. At a larger spatial scale, networks of proteins assemble in cells to form well-ordered signaling systems that provide for complex, non-linear signal processing capabilities. Because we assume that such properties require great precision in the design of systems, one view is to regard proteins and cells as finely tuned machines that are somehow exactly arranged for mediating their selected function. However, other aspects seem less consistent with this view. For example, biological systems are thought to be robust to random perturbation; that is, they display tolerance to removal or alteration of many system components. In addition, they are plastic; that is, they maintain the ability to adapt to changing selection pressures by allowing specific variation of a few system components to alter function profoundly. This curious mixture of robustness to random perturbation and yet sensitivity to specific perturbation suggests that despite the appearance of precise construction throughout, strong functional heterogeneity exists in the design of evolved systems. That is, some parts and connections are much more important than others. Inspired by these ideas, our main goals are (1) to systematically map the pattern of interactions between the components that make up biological systems, (2) to mechanistically understand the physics of these systems, and (3) to define the evolutionary principles that generate these (and not other) architectures. In other words, we wish to understand what nature has built, how it works, and why it is built the way it is. In principle, such understanding would provide powerful rules for the rational engineering and control of biological systems, and would begin to explain how they are even possible through the random algorithmic process that we call evolution.

B. Positions and Honors

PROFESSIONAL TRAINING AND APPOINTMENTS

1984-1985 Research, Biochemistry/Biophysics, University of California, San Francisco, CA

1988-1992	Graduate Student, Biology, University of California, San Diego, CA
1994-1995	Postdoctoral Fellow, Neurobiology, Harvard Medical School, Boston, MA
1995-1997	Postdoctoral Fellow, Structural Biology Laboratory, The Salk Institute, La Jolla, CA
1997-2002	Assistant Professor, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX
2002- 2006	Associate Professor, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX
2004-2017	Founding Director of the Cecil H. and Ida Green Center for Systems Biology, University of Texas Southwestern Medical Center, Dallas, TX
2006-2017	Professor, Departments of Pharmacology and Biophysics, University of Texas Southwestern Medical Center, Dallas, TX
2012-2017	Professor, Green Center for Systems Biology, University of Texas Southwestern Medical Center, Dallas, TX
2017-present	Professor, Biochemistry/Molecular Biology and the Institute for Molecular Engineering, The University of Chicago, Chicago, IL.
2017-present	Director, BioCARS, Advanced Photon Source, Argonne National Laboratory.
2017-present	Founding Director, Center for the Physics of Evolving Systems, The University of Chicago.

HONORS AND MEMBERSHIPS

	Member, Tau Beta Pi, Engineering Honor Society
1995-1997	Burroughs-Wellcome Fellow of the Life Sciences Research Foundation
2001-2004	Edward Mallinckrodt, Jr. Foundation Scholar
2004-2005	Participant, The National Academies, *Keck Futures Initiative*
2005-present	Editorial Board, Nature Molecular Systems Biology
2005-present	Advisory Board, Green Center for systems Biology Science, UT Dallas
2005	University Lecture, UT Southwestern Medical Center
2006-2010	Scientific Review board, Damon-Runyan Cancer Research Foundation
2006-present	Cecil H. and Ida Green Chair in Biomedical Science
2006	William H. Stein Lecture, Rockefeller University
2007	Koshland Memorial Lecture, UC Berkeley
2007-2010	Editorial Board, PIOS Computational Biology
2007	Woodward Lecture in Chemistry, Harvard University
2008	Edith and Peter O'Donnell Award for Basic Science
2009-present	Editorial Board, Cell
2010	Tay Hayashi Lecture in Physiology, Marine Biological Laboratory
2010-present	Editorial Board, Science Signaling
2011-2015	Scientific Review Board, Searle Scholars Program
2015	Inaugural Pearl Seiden Symposium, Technion Institute
2015	Outstanding Teacher Award, UT Southwestern Academy of Teachers
2016	NIH Director's Transformative Research Award

ADVISORY BOARDS AND COMMITTEES

Editorial Board, Cell Systems, 2014-**present**.
Editorial Board, Cell, 2009-**present**.
Editorial Board, Nature Molecular Systems Biology, 2005-**present**
Board Member, Protein Modules Consortium, 2005- **present**.
Scientific Review Board, Searle Scholars Program, 2011-2015.
Scientific Review Board, Damon-Runyan Cancer Research Foundation, 2006-2010.
Board of Reviewing Editors, eLife, 2012-2015.
Editorial Board, Science Signaling, 2010-2012.
Editorial Board, PLoS Computational Biology, 2007-2012.
UTSW Dean's 6-year Planning Committee for Research, 2005, 2009, 2009, 2011, 2013, 2015.
UTSW President's Information Technology Council, 2009
Review Committee, NIH New Innovator Award, 2007, 2015.

Steering Committee, Shared Bioengineering Department, UTSW/UT Dallas, 2007-2013.
Advisory Board, Green Center for Systems Biology Science, UT Dallas, 2005-2017.
Admissions Committee, UTSW Medical Scientist Training Program, 1999-2012.
Host Institution Advisory Committee for the Alliance for Cellular Signaling, 1999- 2005.
UTSW Basic Science Information Resources Advisory Committee, 1999-2003.

C. Contribution to Science

(1) **An evolutionarily consistent model for proteins**. Proteins display the capacity to spontaneously fold and to carry out complex biochemical activities, properties that require great precision in the positioning and coupling of amino acids. However, proteins also display great tolerance to perturbation (robustness) and the capacity for adaptive variation (evolvability). We have taken a fundamentally new approach to this problem that has led to a model for the evolutionary "design" of proteins that may explain the basis for all of these properties. This work has fueled experiments in many laboratories throughout the world to test the generality of the basic assertions.

a. Lockless SW, **Ranganathan R**. Evolutionarily conserved pathways of energetic connectivity in protein families. Science 1999; 286:295-299.
b. Suel GS, Lockless SW, Wall MA, **Ranganathan R**. Evolutionarily conserved networks of residues mediate allosteric communication in proteins. Nature Structural Biology 2003, 10:59-69.
c. Halabi NM, Rivoire O, Leibler S, and **Ranganathan R**. Protein sectors: evolutionary units of three dimensional structure. Cell 2009, 138: 774-786.
d. Rivoire O, Reynolds KA, **Ranganathan R**. Evolution-based functional decomposition of proteins. PLoS Computational Biology 2016, 12: e1004817.

(2) **Evolution-inspired design of synthetic proteins.** Understanding the rules behind the folding and function of proteins is a major goal in protein biochemistry, and a definitive test of such understanding is the design of artificial proteins that recapitulate the properties their natural counterparts. We have developed new computational methods that have achieved this goal in two different model systems. This work opens up many new avenues for understanding and rationally engineering protein structure and function.

a. Socolich, M, Lockless SW, Russ WP, Lee H, Gardner KH, **Ranganathan R**. Evolutionary information for specifying a protein fold. Nature 2005, 437:512-518.
b. Russ WP, Lowery DM, Mishra P, Yaffe MB, **Ranganathan R**. Natural-like function in artificial WW domains. Nature 2005, 437:579-583.
c. Lee, J, Natarajan M, Nashine VC, Socolich M, Vo T, Russ WP, Benkovic SJ, **Ranganathan R.** Surface sites for engineering allosteric control in proteins. Science 2008, 322: 438-442.
d. Reynolds KA, Russ WP, Socolich M, **Ranganathan R**. Evolution-based design of proteins. Methods in Enzymology 2013, 523: 213-35.

(3) **The physics of protein function**. The internal mechanics of proteins – the coordinated motions of amino acids and the forces constraining these motions – links structure to function, but remains poorly defined in general. We have advanced new approaches to address this fundamental problem. Most recently, we have described a method combining the application of strong electric-field pulses to protein crystals with fast time-resolved X-ray crystallography to visualize these motions with high spatial and temporal accuracy. This work lays the foundation for a comprehensive experimental study of the mechanical basis for protein function, a major future goal of our laboratory.

a. Jain R, **Ranganathan R**. Local complexity of amino acid interactions in a protein core. Proc Natl Acad Sci USA 2003, 101: 111-116.
b. Hekstra DH, White KI, Socolich MA, Henning R, Srajer VS, **Ranganathan R**. Electric field-stimulated protein mechanics. Nature 2016, 540: 400-405.

(4) **Evolvability in biological systems**. A fundamental property of biological systems is their capacity to adapt to fluctuating conditions of fitness imposed by a constantly changing external environment. What structural and dynamic properties of these systems enable adaptation and how are systems built through the process of

evolution to be adaptive? How can complex activities emerge through a process consistent with stepwise variation and selection? We have explored these questions in several powerful model systems using both theory and experiment.

a. Reynolds KA, and **Ranganathan R**. Hotspots for the emergence of allosteric control in proteins, Cell 2011, 147: 1564-1575.
b. McLaughlin RN, Poelwijk FJ, Raman A, Gosal WS, and **Ranganathan R**. The spatial architecture of protein function and adaptation. Nature 2012, 491:138-42.
c. Stiffler MA, Hekstra DR, **Ranganathan R**. Evolvability as a function of purifying selection in TEM-1 b-lactamase. Cell 2015, 160: 882-92.
d. Raman AR, White KI, **Ranganathan R**. Origins of allostery and evolvability in proteins: a case study. Cell 2016, 166: 468-480.
e. Bandaru P, Shah, NH,…, **Ranganathan R***, Kuriyan J*. Deconstruction of the Ras switching cycle through saturation mutagenesis. eLife 2017, 6: e27810. *corresponding authors

(5) **Information processing in cellular signaling systems**. Cellular signaling systems operate to convert a variety of external signals into changes in protein activities and intracellular messenger concentrations. The spatial and temporal dynamics of these fluctuations are the language of the intracellular compartment, and are read out by the cellular machinery to produce the correct response to a given stimulus. A central objective in our work is to understand how the protein networks that comprise the membrane-signaling systems encode such properties, and to define the basic principles of signal flow through such networks. In this regard, we have worked on two main model systems: the primary sensory neurons of the *Drosophila* eye, and mammalian immune cells.

a. Kiselev A, **Ranganathan R**. A Molecular Pathway for Light Dependent Photoreceptor Apoptosis in Drosophilia. Neuron 2000; 28:139-152.
b. Natarajan, M, Sternweis PC, Lin KM, Hsueh RC, and **Ranganathan R**. A global analysis of cross-talk in a mammalian cellular signaling network. Nature Cell Biology 2006, 8, 571:580.
c. Mishra PM, Wall MA, Socolich M, Graves J, Wang ZF, and **Ranganathan R**. Dynamic scaffolding in a G protein coupled signaling system. Cell 2007, 131: 80-92.
d. Pumir, A, Graves J, **Ranganathan R**, and Shraiman BI. Nonlinear dynamics underlying signal transduction in *Drosophila* photoreceptors. Proc Natl Acad Sci USA 2008, 105: 10354-9.

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