Evolutionary Biophysics of Cell Membranes

**Miller Fellow Focus: Itay Budin**

Structural organization is central to biology: organisms are composed of self-compartmentalized units (cells), which in turn can feature a myriad of internal compartments (organelles) that carry out distinct tasks. Cell membranes, made of a sheet of lipids only two molecules (~5 nanometers) thick, define the boundaries of these structures. Membranes also serve as the microenvironments for a host of the cell’s protein-based molecular machinery. As a second year Miller Fellow in the Department of Chemical Engineering, I investigate how the lipid composition and resulting physical properties of these membranes regulate cellular function and behavior. The goal of this work is to understand the evolution and diversity of lipid composition in biology, which varies greatly between different tissues, cells, and organelles.

**Lipids, Membranes, and Cells**

The central role of lipid molecules in the chemical composition of cells has been known since the mid 19th century, long before the structure and function of membranes was elucidated. Unlike their droplet-forming cousins, fats and oils, membrane lipids are amphiphilic, containing both non-polar, hydrocarbon tails and a polar or charged head group (Figure 1A). Amphiphiles can self-assemble into a variety of ordered structures in aqueous solution, with cellular lipids preferring bilayers in which two lipid layers are oriented tail to tail. These structures, which form the basis for all biological membranes, fold up into membrane compartments (vesicles) reminiscent of cells when suspended in water. Counterintuitively, the spontaneous assembly of membranes is driven by intermolecular affinities between water molecules, not the lipids themselves. Because non-polar moieties do not feature dipoles with which to hydrogen bond, the hydrocarbon tails of lipids are effectively excluded from the hydrogen-bonding network in liquid water, a phenomenon known as the hydrophobic effect. The lack of strong inter-lipid affinities allows for a fluid-like structure within which both lipids and embedded proteins can freely diffuse. In contrast, the polar nature of metabolites and macromolecules makes the bilayer a formidable diffusion barrier for them, allowing membranes to effectively organize cells into chemically distinct compartments.
The first cellular lipids identified were phospholipids, which are now known as major membrane components in almost all cells. During my graduate work, I proposed a model for how these lipids could have arisen in the very earliest cells from abiotically generated precursors (Budin and Szostak, PNAS 2011). In the subsequent 4 billion years of evolution, cells have evolved the ability to synthesize thousands of chemically distinct membrane components through a combinatorial diversity of lipid backbones and modifications. Lipid composition is tightly regulated within cells, but varies tremendously between different membranes (Figure 1B). Prokaryotes have evolved a wide variety of exotic lipid structures that often correspond to metabolic or environmental niches, such as the membrane spanning tetraether lipids characteristic of extremophilic archaee. Membranes of Eukaryotes, in addition to phospholipids, contain large amount of sterols and sphingolipids, and each eukaryotic organelle features a characteristic stoichiometry of these distinct lipid classes. Multicellular organisms show striking tissue-specific lipid compositions, such as the high enrichment of polyunsaturated lipids in mammalian photoreceptor cells and other neurons. Even disease states in humans, including cancer and liver disease, have been associated with changes in the lipid composition of infected tissues.

Membranes as physical regulators of cell function

Modern mass spectrometry techniques, which underlie the emerging field of lipidomics, are providing ever increasingly detailed chemical descriptions of membranes. However, the functional basis for the complexity and diversity of these compositions remains poorly understood. Like any other material, the composition of membranes determines their physical properties in a given environment. Membrane biophysics has contributed significantly to the understanding of how various lipid structures influence the physical properties of bilayers. For example, the incorporation of cis double bonds (unsaturations) or branching into phospholipid chains decreases the viscosity of the bilayer by disrupting van der Waals interactions between neighboring lipids. Sterols and other planar polycyclic lipids have the opposite effect, stiffening membranes by intercalating between the acyl chains of phospholipids. Using spectroscopic probes, I have measured apparent viscosities that span a ~100 fold range in reconstituted membranes with varying phospholipid unsaturations and cholesterol levels. Sterols have also been shown to nucleate phase separation of lipids into domains within the bilayer, known as lipid rafts, which has been proposed to spatially organize cell membranes. Despite our detailed understanding of the biophysics of lipid membranes, relating these properties to in vivo behaviors continues to be challenging.

My hypothesis is that the diversity of lipid composition in biology represents a set of optimized material properties for evolved membrane-hosted or membrane-associated cellular processes in varying physical environments. Many, if not all, cells adapt their membrane composition to counteract changes in their environment, such as a drop in temperature, suggesting the importance of the physical state of the membrane, as opposed to its exact chemical composition. In what ways can physical regulation influence function? Because diffusion rates...
and biophysical characterization. I am currently applying this approach to understanding the membrane compositions of the bacterium *E. coli* and yeast *S. cerevisae*, which are widely used model systems with well-characterized synthesis pathways and promoters. Future development of genetic tools should allow for membrane manipulations in increasingly complex, multicellular hosts. I am also exploring non-native lipid species by introducing whole synthetic pathways into these systems in order to address evolutionary questions in lipid composition, such as the basis for the relative scarcity of sterol-like molecules in prokaryotes. Finally, with colleagues at the Joint Bioenergy Institute, where I am based, I am assessing the potential of membrane modifications for biotechnology applications, such as increasing the tolerance of production strains against the toxic effects of biofuels. These efforts have convinced me that combining an engineering approach with a biophysical perspective represents a promising avenue to understanding membrane biology.

Figure 2: Genetic engineering of cell membrane composition. (A) Schematic: compositional effects are studied by genetically modulating the stoichiometry of both native (blue) and novel (red) membrane components in model cell lines. (B) An *E. coli* strain in which the fraction of unsaturated lipids, which natively regulate the physical state of the membrane, is modulated as a function of inducer concentrations (left). This strain then allows for characterizing the fitness landscape for this membrane component (right). Fitness was quantified by measuring specific growth rates of cultures grown under different inducer concentrations, whose membrane composition was then assayed by mass spectrometry.
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The Advisory Board
The Advisory Board of the Miller Institute met on December 6 to select next year’s Miller Professors and Visiting Miller Professors. The Board is comprised of four advisors external to UCB: David Botstein (Princeton University), Claude Canizares (MIT), Vaughan Jones (Vanderbilt University) and Harold Kroto (Florida State University); and four internal Executive Committee members: Executive Director Michael Manga (Earth & Planetary Science), Craig Evans (Mathematics), Jasper Rine (Molecular & Cell Biology), and Rich Saykally (Chemistry). The Board is chaired by Chancellor Nicholas Dirks.

Miller Professorship Awards
The Miller Institute is proud to announce the awards for Miller Research Professorship terms during the Academic Year 2014-2015. These outstanding scientists are released from teaching and administrative duties during their Miller appointments, allowing them to pursue their research, full-time, following promising leads as they develop.

Britt Glaunsinger
Plant & Microbial Biology

Yun Song
Electrical Engineering & Computer Science / Statistics

Constantin Teleman
Mathematics

Visiting Miller Professorship Awards
The Visiting Miller Professorship Awards for terms in the 2014-2015 Academic year have been selected from an outstanding pool of nominees. These eminent scientists will join faculty hosts on the Berkeley campus for collaborative research interactions.

Lynne Boddy
Plant & Microbial Biology
Host: John Taylor

Angel Rubio
Physics
Host: Steve Louie

Martina Havenith-Newen
Chemistry
Host: Teresa Head-Gordon

Sjors Scheres
Molecular & Cell Biology
Host: Eva Nogales

Benjamin Paul Weiss
Earth & Planetary Science
Host: David Shuster

Patrick Huerre
Mechanical Engineering
Host: Phil Marcus

Eske Willerslev
Integrative Biology
Host: Rasmus Nielsen

Elon Lindenstrauss
Mathematics
Host: Maciej Zworski

Karen Winey
Chemical & Biomolecular Engineering
Host: Nitash Balsara

Scott Ransom
Astronomy
Host: Aaron Parsons

Miller Fellow Focus
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Itay Budin (Miller Fellow 2012-2015) received his B.S. from Cornell University in Bioengineering and his Ph.D. from Harvard University in Biochemistry. His Ph.D. research, in the lab of Prof. Jack Szostak, focused on physical models for the origin of cell membranes. Outside the lab, Itay enjoys traveling, hiking, cooking, and attending the occasional Miller happy hour.

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In the News

Randy Schekman (Miller Senior Fellow 2008-2013) has been awarded the 2013 Nobel Prize in Physiology or Medicine for his role in revealing the machinery that regulates the transport and secretion of proteins in our cells. Schekman is UC Berkeley’s 22nd Nobel Laureate, and the first to receive the prize in the area of physiology or medicine.

Adrian Bejan (Miller Fellow 1976-1978) was selected to become a member of the Academia Europaea, the Academy of Europe.

Linyou Cao (Miller Fellow 2010-2013) is the recipient of ARO YIP Award: The Young Investigator from the Army Research Office. The results from Cao’s research have the potential to lead to next generation lasers, light emission diodes, and photo detectors that are important for defense needs.

Roland Bürgmann (Miller Professor Spring 2014) was honored as a member of the 2013 class of fellows of the American Geophysical Union (AGU). This honor is bestowed upon members of the union who have made exceptional scientific contributions and attained acknowledged eminence in the fields of Earth and space science. Bürgmann’s citation was awarded “for elucidating the role of the micromechanical properties of the ductile lithosphere to understand the earthquake deformation cycle.”

Robert Bergman (Miller Professor 1982-1983, Fall 1993, Spring 2000) will be honored at the 2014 Reactions Mechanism Conference for his “achievements and contributions to organic chemistry”.

Geoff Marcy (Miller Professor 2011-2012) was highlighted in a November 4, 2013 UC Berkeley News Center article entitled, “Astronomers answer key question: How common are habitable planets?” Their analysis and findings were published in the online edition of the journal Proceedings of the National Academy of Sciences.

Edward Frenkel (Miller Professor Spring 2013) Edward Frenkel’s new book, Love and Math: The Heart of Hidden Reality, aims to show the beauty of mathematics, inspire awe at its power, and challenge his colleagues to wield it for good. Three printings have sold out on Amazon.

Terence Speed (Miller Professor Spring 2005) has been awarded the Australian 2013 Prime Minister’s Prize for Science for fighting cancer with statistics.

Nicholas Jewell (Miller Professor Fall 1994 & Fall 2004) has been awarded the Berkeley Faculty Service Award. The Berkeley Division of the Academic Senate awarded him for outstanding and dedicated service to the Berkeley campus.

Julius Lucks (Miller Fellow 2007-2010) was awarded the NIH New Innovators Award. The award is accompanied by a five-year, $1.5 million research grant under the NIH’s “High Risk High Reward” grant program.

Jeremy Thorner (Miller Professor 1984-1985, 1999-2000) has been chosen to receive the Lifetime Achievement Award at the Genetics Society of America sponsored Yeast Genetics and Molecular Biology Meeting that will be held in the Summer of 2014. Professor Thorner was selected in recognition of his many scientific contributions and outstanding community service.


Ray Jayawardhana (Miller Fellow 2000-2002) was awarded The Rutherford Memorial Medal in Physics. He is a recognized leader in the study of extra-solar planets, brown dwarfs and young stars. His pivotal and wide-ranging contributions include several high-profile discoveries related to sub-stellar astrophysics and planet formation.

Paul Alivisatos (Miller Professor 2001-2002) has been appointed to the Samsung Distinguished Chair in Nanoscience and Nanotechnology at UC Berkeley in recognition of his many scientific achievements. The endowed chair will help cement the campus’s leadership in research and innovation in an area that has great implications for many fields ranging from biology to energy. Alivisatos is known for his research into quantum dot semiconductor nanocrystals, clusters of hundreds to thousands of atoms with novel properties that can be applied to electronic devices and solar cells as well as light-emitting diodes (LEDs).

Philip Chang (Miller Fellow 2005-2008) was awarded an NSF Career award for his work on blazars.

David Jenkins (Miller Fellow 2005-2008) was awarded an NSF Career grant for work on catalytic aziridination.

Eric Agol (Visiting Miller Professor Spring 2011) has discovered one of two exoplanets that Geoffrey Marcy (Miller Professor 2011-2012) regards as "tantalizingly similar to Earth". These two "are the best candidates yet for the possibility of life".

Daniela Kaufer (Miller Professor Fall 2012) Her research on stress was funded by a BRAINS (Biobehavioral Research Awards for Innovative New Scientists) award from the National Institute of Mental Health of the NIH and the National Alliance for Research on Schizophrenia and Depression.

Grigori Perelman (Miller Fellow 1993-1995)
The Poincaré Chair: launched in January 2013 by the Institut Henri Poincaré aims to allow young mathematicians to focus on their research projects, just in the same way as Grigori Perelman benefited from the support of the Miller Institute in Berkeley (California, USA) at the beginning of his career.
Fall Dinner

Miller Senior Fellow Saul Perlmutter

Executive Committee member Jasper Rine

Miller Professor Roland Bürgmann

Miller Fellow Rebekah Dawson, Erica Martin, Miller Fellows Chris Martin & Justin Kim

Advisory Board member Harold Kroto, Miller Fellow Adam Retchless and Margaret Kroto

Miller Fellow Greg Bowman, Angela Bowman and Visiting Miller Professor Scott Tremaine

Miller Senior Fellow Barbara Meyer presents a talk entitled, "Sex and Death".
Birth Announcements


August Johansson (Miller Fellow 2010-2013) & Miriam Kjellgren announced the birth of their son, Sixten Werner August Kjellgren, born August 10, 2013.

David Shelly (Miller Fellow 2007-2008) & Elizabeth announced the birth of their daughter, Hazel Martha, born September 12, 2013.

Stephane Bodin (Miller Fellow 2002-2005) & Lisa announced the birth of their son, Rafael, born September 18, 2013.

Philip Starks (Miller Fellow 1999-2002) & Caroline Blackie announced the birth of their son, Matthew Craig, born November 7, 2013.

Linyou Cao (Miller Fellow 2010-2013) & Yu Zheng announced the birth of their son, Larry Pingde, born November 10, 2013.

Daniel Rabosky (Miller Fellow 2009-2012) & Alison announced the birth of their daughter, Maya Lorelei, born December 19, 2013.


Qian Chen (Miller Fellow 2012-2015) & Yingjie Zhang announced the birth of their daughter, Angelina Shuyao, born December 29, 2013.

Saurabh Jha (Miller Fellow 2002-2005) & Frances announced the birth of their son, Kiran Altair, born December 31, 2013.

Next Steps

The Miller Institute congratulates these Miller Fellows on their next endeavors:

Mikhail Shapiro (Assistant Professor @ Caltech)

Justin Brown (AMO Physicist @ Charles Stark Draper Laboratory)

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The Miller Institute is “dedicated to the encouragement of creative thought and the conduct of research and investigation in the field of pure science and investigation in the field of applied science in so far as such research and investigation are deemed by the Advisory Board to offer a promising approach to fundamental problems.”

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