The Adolph C. and Mary Sprague

Miller Institute

for Basic Research in Science

Newsletter
Winter 2014

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.

CONTINUED ON PAGE 2 >

Inside this edition:

In the News

Randy Schekman (Miller Senior Fellow 2008-2013) receiving his **Nobel Prize** in Physiology or Medicine from His Majesty King Carl XVI Gustaf on Dec. 10, 2013.

Credit: Nobelprize.org Live Streaming - Image Capture

MORE ON PAGE 6 >

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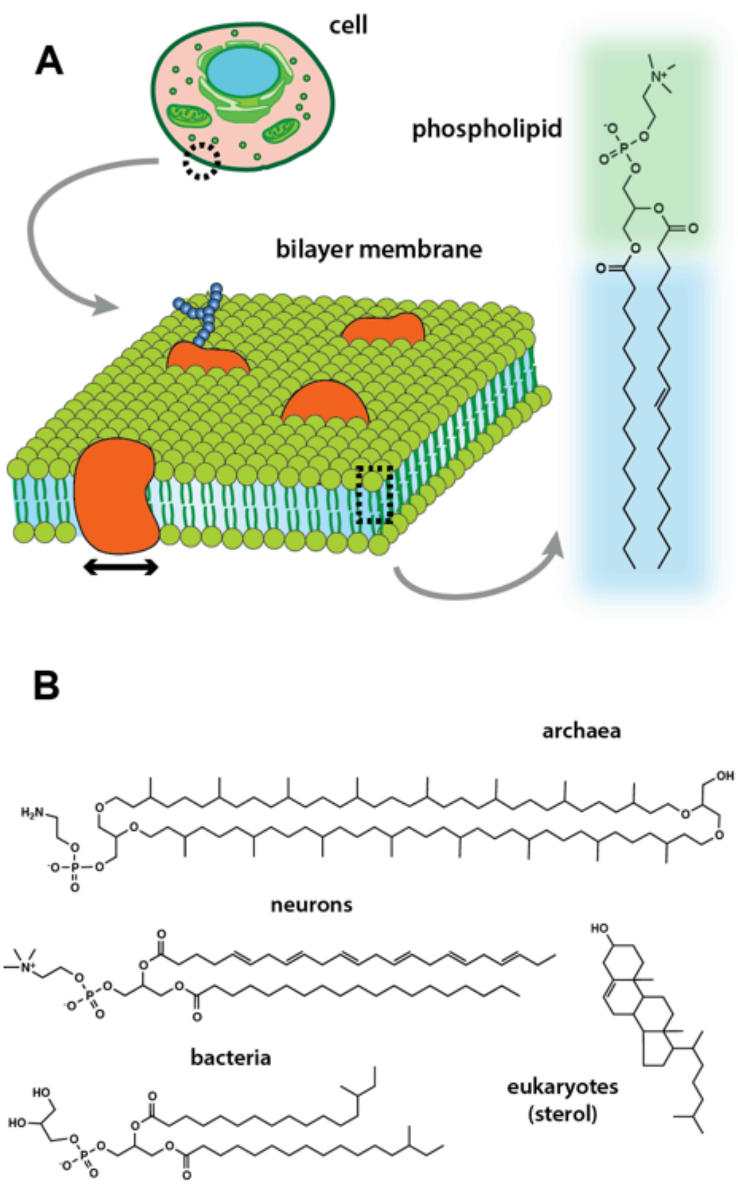
"The Miller Fellowship provided the best combination of freedom and support I could imagine."

Adam Riess, *Thomas J. Barber Professor of Physics and Astronomy*
Johns Hopkins University & Space Telescope Science Institute
Miller Research Fellow 1996-1999
Nobel Prize in Physics 2011

> CONTINUED FROM PAGE 1 [Miller Fellow Focus]

Figure 1: Membrane organization and lipid diversity in cells. (A) Cell membranes are bilayer structures containing lipids (green) and embedded proteins (orange). Diffusion of these components occurs along the plane of the membrane (black arrows). Lipids assemble into bilayers due to their chemical structure, which contains both polar (green) and non-polar (blue) moieties. (B) A few examples of the diversity of membrane lipids found in biology and mentioned in the text. Included is an archaeal tetraether lipid, a polyunsaturated lipid enriched in neurons, an example of branched-chain lipids common in bacteria, and a sterol (cholesterol), which are ubiquitous in eukaryotes.



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 extremophillic archaea. 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.

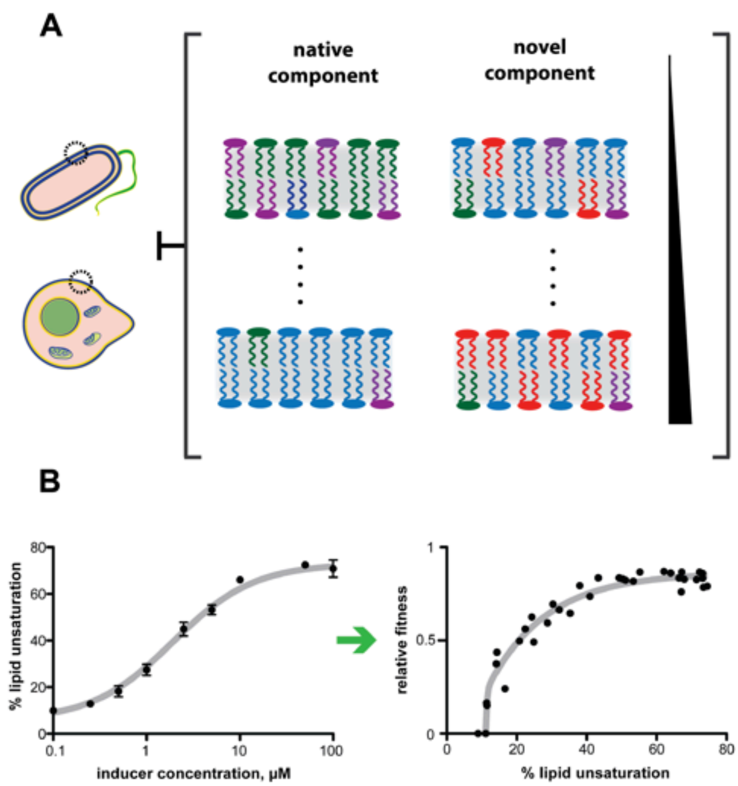
My hypothesis is that the diversity of lipid composition in biology represents a set of optimized material properties for evolved membrane-hosted or membrane-associated cellular processes in varying physical environments. Many, if not all, cells adapt their membrane composition to counteract changes 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 generally scale inversely with solvent viscosities, molecular processes that are diffusion-limited are potentially regulated by fluidizing aspects of lipid composition. Diffusion-coupled reactions between membrane-associated components are a common motif in signal transduction networks and are central to the electron transport chains utilized by both respiration and photosynthesis. Intriguingly, both these processes are prominently associated with highly unsaturated, low viscosity membranes. Regulation of the physical properties of membranes could also be important for post-translational folding of polypeptides into functional membrane proteins, which occurs within the lipid solvent of the bilayer. A host of functions require the budding and fusion of membranes, including intracellular transport, secretion, and uptake of proteins and other cargo, as well as the assembly and release of viral particles. These related processes all depend on the recruitment of accessory proteins and the subsequent remodeling of the local membrane structure and thus are likely to be dependent on a tightly regulated physical environment.

Engineering membrane composition in cells

The major hurdle for the systematic investigation of membrane function is the paucity of tools for manipulating lipid composition in vivo. The study of membrane biophysics has largely depended on in vitro work in synthetic vesicles (liposomes). While ideal for studying bilayer properties or isolated proteins, these systems struggle to mimic the complexity of cellular interactions and provide no information on the resulting cellular phenotypes. Chemical manipulation of membrane composition in vivo is commonly used to deduce compositional effects on cells, but is difficult to control and induces unpredictable homeostatic responses in native lipid synthesis. Traditional genetic approaches, which disrupt or reintroduce genes involved in lipid synthesis, are powerful for mapping out the biosynthetic routes and their regulation but do not allow for fine-tuning of component stoichiometry.

During my Miller Fellowship, I am working with Prof. Jay Keasling to apply the principles and tools developed by metabolic engineering to modulate membrane composition in model cell lines. Key to this approach is the use of titratable promoters, which allow for the expression of neighboring genes in a variable manner as function of the concentration of an inducer molecule added to a culture. By removing key genes involved in lipid synthesis pathways and then reintroducing them under titratable expression, I am building cell lines in which the stoichiometry of lipid components can be arbitrarily modulated in vivo (Figure 2). These strains then allow me to directly assess the effects of composition on cellular fitness and physiology as well as test specific hypotheses on individual membrane-associated molecular processes. Phenotypic effects can then be followed up with traditional reconstitution approaches for mechanistic 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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Gifts to the Miller Institute

The Miller Institute gratefully acknowledges the following contributors to the Miller Institute programs in 2013. These generous donations help support both the Miller Research Fellowship program and the general programs of the Institute.

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Miller Research Competitions: Awards

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

Martina Havenith-Newen

Chemistry

Host: Teresa Head-Gordon

Patrick Huerre

Mechanical Engineering

Host: Phil Marcus

Elon Lindenstrauss

Mathematics

Host: Maciej Zworski

Scott Ransom

Astronomy

Host: Aaron Parsons

Angel Rubio

Physics

Host: Steve Louie

Sjors Scheres

Molecular & Cell Biology

Host: Eva Nogales

Benjamin Paul Weiss

Earth & Planetary Science

Host: David Shuster

Eske Willerslev

Integrative Biology

Host: Rasmus Nielsen

Karen Winey

Chemical & Biomolecular Engineering

Host: Nitash Balsara

Miller Fellow Focus

> CONTINUED FROM PAGE 3 [Miller Fellow Focus]

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.

Alexei Filippenko (Miller Fellow 1984-86, Miller Professor Spring 1996, 2005)
presented a talk at the **49th Annual Nobel Conference** - "The Universe at its Limits" - at Gustavus Adolphus College in St. Peter, Minnesota.

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

Executive Director Michael Manga, Advisory Board member Vaughan Jones & Executive Committee member Rich Saykally

Visiting Miller Professor Douglas Black & Miller Fellow Shayan Oveis Gharan

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

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

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

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Birth Announcements

Thomas Bodin (Miller Fellow 2012-2015)
& Shinta Bonnefoy announced the birth of their daughter,
Kali, born July 27, 2013.

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,
Rafaël, 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.

Philip Chang (Miller Fellow 2005-2008)
& Morgan Jones announced the birth of their twin sons,
Liam and Gregory, born December 28, 2013.

Qian Chen (Miller Fellow 2012-2015)
& Yingjie Zhang announced the birth of their daughter,
Angeline 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 Labratory)

Miller Institute

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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