The Adolph C. and Mary Sprague

Miller Institute

for Basic Research in Science

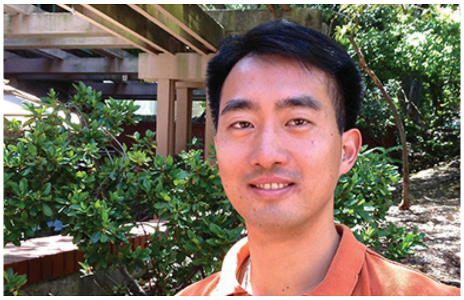
Newsletter
Fall 2013

Physical Limits of Biology

Miller Fellow Focus: Milo M. Lin

The notion that biology is subject to physical limits is very intuitive at the macroscale. For example, the differential scaling in volume (heat production) and surface area (heat transport) limits how big a land mammal can get without overheating. Although generic physical constraints exist at all length scales, their direct role in shaping the morphology and capabilities of biology can be more obscure at the cellular and sub-cellular levels. This is due not only to the increased difficulty of visualizing such scales, but to the prominence of effects that don't have a direct macroscopic analog. Depending on the length scale, different physical quantities, such as viscosity, thermal fluctuations, and entropy, become either dominant or insignificant players.

Beginning at the organism level and magnifying to the scale of the macromolecular building blocks of life, 9 orders of magnitude, from nanometer to meter, are traversed. In conjunction, the time scale of the relevant dynamics ranges over 22 orders of magnitude, from femtoseconds to years. Amazingly, life maintains both complexity and robustness, i.e. structural and functional reproducibility, over these vast length and time domains. The root of this complex robustness can be traced, at the nano-scale, to proteins, which largely



constitute the cleaners, builders, motors, messengers and infrastructure that make life possible at the cellular level. Proteins are molecular chains composed of twenty types of amino acids, and the particular amino acid sequence of every protein is encoded by a corresponding segment of DNA, a gene. When a particular protein is needed, its DNA blueprint is copied and the code translated into the matching amino acid sequence. The linear chain is then folded into a complicated three-dimensional conformation; it is in this *native* folded state that the protein is capable of carrying out its designated function. Two physical constraints that dominate at the scale of proteins are the hydrophobic effect and dissipation. These two constraints have been a major focus of my research due to their influence on the two defining stages of a protein's existence: folding and function.

Protein Folding and the Hydrophobic Force

The folded protein is stabilized by chemical forces both within the

Inside this edition:

Call for Nominations:

Miller Research Fellowship Nominations
Deadline: Thursday, September 12, 2013

Miller Research Professorship Applications
Deadline: Thursday, September 19, 2013

Visiting Miller Professorship Departmental Nominations
Deadline: Friday, September 20, 2013

See page 5 for more details.
For complete information on all our programs, visit: MillerInstitute.berkeley.edu

"The Miller Institute adds hugely to the collective intellectual life of UC Berkeley. It is a jewel."

Lord Robert M May of Oxford OM AC Kt FRS
Theoretical Physicist & Biologist
Former President of the Royal Society
Former Chief Scientific Advisor to the PM & UK Government

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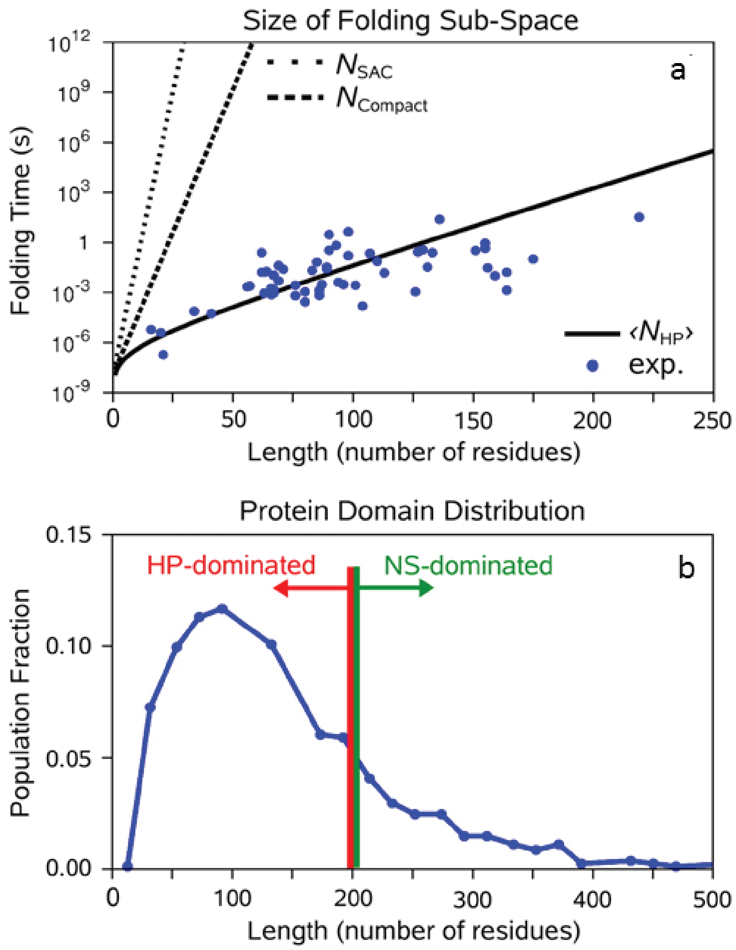
protein and between the protein and its surrounding environment (mostly water). These forces collectively shape a protein into one of roughly 1,300 topologically distinct folding classes.

Proteins need to be functionally reliable, so the native fold must be more stable than all other possible folds combined. This is made all the more amazing by the fact that many proteins can fold by themselves without the aid of cellular machinery. In contrast to self-organization in periodic systems (freezing of water), and heterogeneous structures that non-reliably self-organize (the weather), proteins are unique because they are heterogeneous structures that *reliably* self-fold. Because each of the individual interactions that stabilize the native fold are no more favorable than the myriad non-native interactions available to the protein, many promising "leads" during the folding process turn out to be dead-ends or non-native structural intermediates. This gives rise to the Levinthal "paradox": the number of possible folds grows exponentially with the length of the protein such that it would require more than the age of the universe to stochastically arrive upon the native fold even for the smallest proteins; on the other hand, proteins typically fold within seconds.

A widespread evolution-centric explanation of this puzzle is the concept of the folding funnel, whereby natural selection has biased the protein toward sampling the miniscule region of the folding space that contains the native fold. This suggested that evolution is responsible for fast protein folding and that if one were to design a totally new protein with a thermodynamically stable fold, it would most likely never find the stable fold in a biologically relevant time.

In contrast to this paradigm, a second viewpoint posits that fundamental physical forces generic to protein folding can sufficiently reduce the size of the conformational space to allow the protein to find the native fold without any evolutionarily encoded folding pathways or biases; this is not to say that such biases don't exist, merely that they are not required. The prime candidate for this mechanism is the *hydrophobic force*, which collapses the chain into a compact shape and segregates the hydrophobic amino acids in the protein sequence into the protein interior, away from the solvent.

Figure 1. Hydrophobic Collapse and the Protein Length Limit. Number of folds on a cubic lattice is plotted as a function of chain length (a). Conformational degeneracies of self-avoiding chain (SAC), self-avoiding compact chain, and the sequence-averaged lowest energy HP chain are shown with dotted, dashed, and solid lines, respectively. The degeneracies are multiplied by the 10 nanosecond residue reorganization time to obtain the folding times. The experimental domain length distribution of a representative set of 1236 proteins shows that most protein domains fall within the predicted length limit (b). Modified from Lin and Zewail, PNAS 109, 9851 (2012).



Validating the second view, we recently showed analytically that the hydrophobic force is *sufficient* to account for the kinetics of fast folding. Namely, the number of folds fulfilling the hydrophobic constraint, averaged over all possible protein sequences, is:

$$\langle N_{HP} \rangle \approx L \left(\frac{3}{e} \right)^{L}$$

where e is Euler's number. The protein length L is the only parameter of the solution.

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The folding time for random search is then given by:

$$\tau_{\text{folding}} = \langle N_{\text{HP}} \rangle \cdot \tau_{\text{sampling}}$$

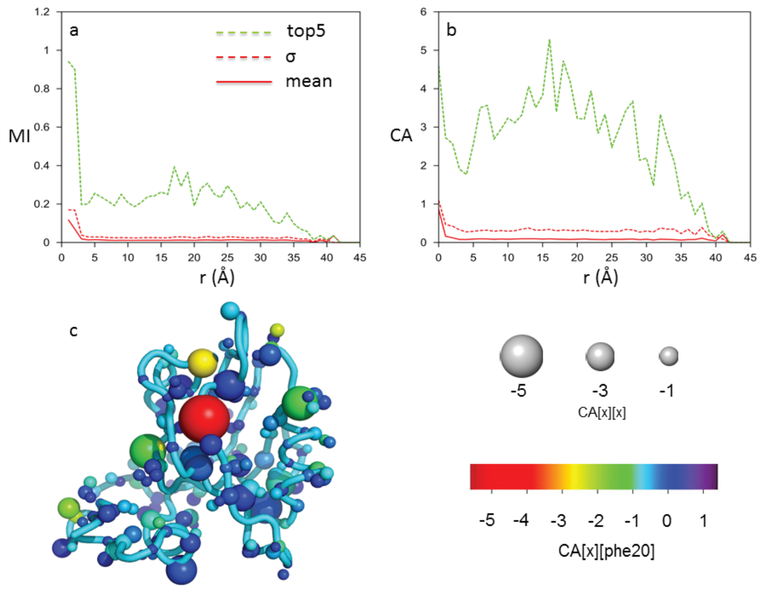
where τ_{sampling} (~ 10 nanoseconds) is the relevant timescale to translate real atomic motion in proteins to the lattice representation of the theory. As shown in Figure 1(a), in accordance with Levinthal, the number of all possible folds becomes astronomically large for very short chains. Nevertheless, if confined to $\langle N_{\text{HP}} \rangle$ by the hydrophobic force, exhaustive search of this subspace can be accomplished in biological time (nanoseconds to minutes) for $L < 200$. The predicted length limit of 200 is also consistent with the empirical evidence (Figure 1(b)): although proteins often consist of more than 1000 amino acids, they are typically composed of domains of independently folding subparts. The majority of these domains are shorter than 200 amino acids. The tail of the distribution representing violations of the length limit may arise from sequence selection or molecular chaperones to achieve folding of longer domains.

Protein Function and Dissipation

Besides protein folding, I'm also currently investigating, with the help of Prof. David Chandler, protein allostery, which is defined as information transfer within and between proteins. In many proteins, this is manifest by a significant increase or decrease in the functionality of a protein's active site following a perturbation such as ligand binding at a site far away from the active site. Allostery may link opposite sides of a single protein or two proteins that are docked together.

Ligand binding may shift the thermodynamic equilibrium in such a way that the overall fold of the protein undergoes a discernable rearrangement, with the consequence that the shape of the active site also changes. In such cases, the allosteric mechanism is relatively clear. In contrast, sometimes the protein undergoes no measureable structural change upon binding of the ligand, yet the activity of the active site is profoundly affected. Energy transfer is ruled out as a potential mechanism; an exothermic reaction at the ligand site would immediately dissipate the excess energy to the many adjacent atomic degrees of freedom and could never be channeled to the active site. Similarly, thermodynamic propagation of structural correlations decays rapidly with distance because the energy scale of the correlations is comparable to the thermal noise. This is shown in the decay of the mutual information (a measure of the thermodynamic correlation) between all pairwise degrees of freedom in a protein (Figure 2 (a)).

Figure 2. Information Transfer within Proteins in a Dissipative Environment. Although the mutual information between any two degrees of freedom in a protein decay rapidly with distance (a), the conditional activity (CA) is robust for a sparse network of dynamically correlated degrees of freedom (b). The sparse correlation network in the protein PDZ3 extends from the active site (encompassing the red sphere) to a proposed ligand binding site (encompassing yellow sphere) (c). The diagonals of the CA matrix are a measure of the non-Markovianness, and is shown proportional to sphere size, whereas the colors denote the CA of all the other degrees of freedom relative to the degree of freedom shown as a red sphere.



In contrast to the mutual information, the purely dynamical portion of the correlation between two degrees of freedom seems to persist over long distances within a protein (Figure 2 (b)). Extending ideas from the theory of glasses, an area of physics dealing with densely packed amorphous systems, we've defined a new measure of the dynamical correlation, which we call the conditional activity (CA). As a purely dynamical analog of the mutual information, the CA can be interpreted as the change in the mobility of one degree of freedom after another degree of freedom becomes mobile. By keeping only the dynamical portion of the information (active or inactive) the highly jammed interior of the protein facilitates long-distance transport of such information for a sparse set of degrees of freedom, which may serve as allosteric pathways (Figure 2 (c)). Faced with the constraint of a highly dissipative environment at the nanoscale, biology has apparently found a way to communicate over long distances.

General physical constraints can have profound effects on the size, morphology, and functionality of biological processes.

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From the Executive Director

It is a great pleasure to return to the Executive Committee after a brief sabbatical in Paris. The opportunity to work in a new setting with new collaborators is special, and a personal reminder of the importance of the Miller Professorships and Fellowships. Immersing oneself in a different setting leads to new ideas and research directions, both for the visitor and the hosts, often through serendipity and unanticipated interactions. This is the objective of the current Miller programs, lunches, dinners, receptions, happy hours, the symposium, and field excursions. Compared with a typical sabbatical, it is these interdisciplinary community events that make the Miller Institute special; they are not only fun, but they foster scientific interactions and an exchange of ideas. I welcome all ideas for new and more effective ways to enhance the experience of members of the Miller Institute and their ability to make new scientific advances and discoveries.

During the past year, the most significant change at the Miller Institute was a remodeling of the Miller Professorship program. Owing to a flat nominal budget for a decade, the budget cuts have largely been accommodated by reducing the number of Miller Professors, from about a dozen to a couple per year. The new financial model will allow the number of professorships to increase several-fold, but will still provide the same opportunities to pursue new research directions and participate in the full range of Miller Institute activities.

Another change during this past year, initiated by the previous Executive Director Jasper Rine, is to arrange coaching by non-specialists in preparation for the weekly lunchtime talks. The results have been dramatic -- talks are much more accessible and informative. This is a nice example of the value of interdisciplinary mentoring.

Members of the Miller Institute continue to receive so many recognitions for their work that they cannot be acknowledged here (though we do endeavor to track awards on our website). Take the Miller Fellow class of 2011, as an example. Mikhail Shapiro and Greg Bowman won Borroughs Welcomme CASI awards. Alex Hayes received the Greeley award in recognition for significant early career contributions in planetary science and the NASA Early Career Fellow.

I would like to extend my sincere appreciation to several people for their contributions and service to the Miller Institute, and also welcome new members. Randy Schekman, the very first Miller Senior Fellow, completed his 5 year term, though he has agreed to continue to participate in Miller Institute activities. Joining the other Senior Fellows is biologist Barbara Meyer. Elizabeth Blackburn of UCSF stepped down from the Advisory Board. She will be replaced by Vaughan Jones from Vanderbilt University. Vaughan knows the Miller Institute well, having served on the Executive Committee while on the faculty in the math department. He also regularly attends the annual Miller symposium. Chancellor Birgeneau, always a passionate and involved member of the Advisory Board, will be replaced by the incoming Chancellor, Nicholas Dirks. Eliot Quataert from Astronomy and Bob Bergman from Chemistry finished their appointments on the Executive Committee. Their enthusiasm and insights will be difficult to replace, but I am sure returning committee member Rich Saykally from Chemistry will do his best.

In closing, the Miller Institute's 60th birthday is approaching – stay tuned for details about the celebration.

Sincerely, Michael Manga
Executive Director of the Miller Institute &
Professor of Earth and Planetary Science

Call For Nominations: Miller Research Competitions

Miller Research Fellowship 2014-2017

Online Nomination Deadline: Thursday, Sept. 12, 2013

The Miller Institute for Basic Research in Science invites department chairs, faculty advisors, professors and research scientists at institutions around the world to submit nominations for Miller Research Fellowships in the basic sciences. The Miller Institute seeks to discover and encourage individuals of outstanding talent, and to provide them with the opportunity to pursue their research on the Berkeley campus. Fellows are selected on the basis of their academic achievement and the promise of their scientific research. The Miller Institute is the sponsor and the administrative home department for each Miller Fellow who is hosted by an academic department on the Berkeley campus. All research is performed in the facilities provided by the host UC Berkeley academic department. A list of current and former Miller Research Fellows is available on our website.

Qualifications:
Miller Research Fellowships are intended for exceptional young scientists of great promise who have recently been awarded, or who are about to be awarded, the doctoral degree. Normally, Miller Fellows are expected to begin their Fellowship shortly after being awarded their Ph.D. A short period as a post-doctoral fellow elsewhere does not exclude eligibility. However, candidates who have already completed substantial postdoctoral training or other work are unlikely to be successful except in unusual circumstances. A nominee cannot hold a paid or unpaid position on the Berkeley campus at the time of nomination or throughout the competition and award cycle, which can run into February. Nominees who are non-US citizens must show eligibility for obtaining J-1 Scholar visa status for the duration of the Miller Fellowship. The Miller Institute does not support H1B visa status. Eligible nominees will be invited by the Institute to apply for the fellowship. Direct applications and self-nominations are not accepted.

Abbreviated Terms of Appointment:
+ Miller Fellowships are granted for a period of three years. Starting dates are negotiable but must commence between July 1 & October 1.
+ The Institute provides a stipend of $61,000 with annual increases.
+ Miller Fellows are entitled to all normal holidays observed by the University; are granted an annual bank of 24 days of personal time off and twelve days of sick leave annually.
+ Miller Fellows receive a research fund of $12,000 per annum.
+ There is provision for travel to (but not away from) Berkeley for Miller Fellows and their immediate families and an additional allowance of $3,000 for the transport of personal belongings.
+ Benefits including medical, dental, vision, short term disability and life insurance are provided, with Miller Fellows making a small contribution towards the premium. Long term disability is voluntary.
+ All University of California postdocs are exclusively represented by the UAW and are subject to the terms of the contract including payment of membership dues or agency fees.
+ Approximately eight to ten Fellowships are awarded each year.
+ Candidates will be notified of the results of the competition between mid-December and mid-February, and a general announcement of the awards will be made in the spring.

Nomination & Application details: MillerInstitute.berkeley.edu
Questions? Kathryn Day: 510-642-4088 | millerinstitute@berkeley.edu

Miller Research Professorship 2014-2015

Online Application Deadline: Thursday, Sept. 19, 2013

The Advisory Board of the Miller Institute for Basic Research in Science welcomes faculty from the University of California Berkeley to submit an application for a Miller Professorship term in the 2014-2015 academic year. The purpose of the Miller Professorship is to release members of the Berkeley faculty from teaching and administrative duties and allow them to pursue research on the Berkeley campus. Appointees are encouraged to follow promising leads that may develop in the course of their research effort whether or not they fall within the original research outline. Applications are judged competitively. Between five to eight awards are made annually.

Applicants who are not members of the Berkeley faculty should seek affiliation with and a nomination through an academic department at Berkeley for the Visiting Miller Professorship Program.

Miller Professors will retain their academic appointment in their home department, but will be placed on a modified status relieving recipients of teaching obligations during the appointment term. Awardees are expected to devote full time and effort to basic research.

Additional terms are posted on the Miller Professorship webpage.
Candidates will be notified of the results in December.

Visiting Miller Research Professorship AY14-15

Online Nomination Deadline: Friday, Sept. 20, 2013

The Advisory Board of the Miller Institute for Basic Research in Science invites Berkeley faculty to submit online nominations for Visiting Miller Research Professorships and the Gabor A. and Judith K. Somorjai Visiting Miller Professorship Award. The purpose of these is to bring promising or eminent scientists to the Berkeley campus on a short-term basis for collaborative research interactions. The Somorjai Award supports an early-career visiting scientist within the broad field of chemical sciences for a one-month term. Both programs require that awardees are in residence at Berkeley during their appointment term, and it is the department host faculty member's responsibility to ensure their presence on campus. It is stipulated that the appointee do no formal teaching, however public talks and department colloquia are encouraged. All absences away from the Berkeley campus during the award term must be coordinated with the Miller Institute office in advance and payments will be adjusted accordingly.

Terms of appointment may range from a minimum of thirty days to a maximum of one semester (120 days). Full semester appointments are encouraged and nominations should include justification, within the research proposal for this long-term collaboration. Each appointment starting date will be negotiated separately, with the restriction that appointments must take place during either Fall 2014 or Spring 2015 of the regular academic year. Faculty members or research scientists from any place in the world are eligible to be considered for sponsorship. Non-US citizens must be eligible for J-1 Scholar visa status. Visitors cannot be supported on H1B or B visas. Announcements of the awards will be made in December.

In the News

Saul Perlmutter (Miller Senior Fellow 2010-2015) was profiled in the July 6 issue of the England's The Guardian - part of a series on "rational heroes."

Mikhail Shapiro (Miller Fellow 2011-2014) & **Greg Bowman** (Miller Fellow 2011-2014) won **Borroughs Welcomme CASI** awards.

Alexander Hayes (Miller Fellow 2011-2014) received the **Ronald Greeley Early Career Award, American Geophysical Union** in recognition for significant early career contributions in planetary science. He also received the **NASA Early Career Fellow.**

Daniela Kaufer (Miller Professor Fall 2012) & **Feng Wang** (Miller Fellow 2005-2008) have been awarded **Bakar Fellowships**. The Bakar Fellows Program is a unique UC Berkeley initiative to support innovative research by early career faculty, in particular those who want to focus on a project that has real-world applications in areas ranging from health care and agriculture to high-tech and biotech.

Steven Balbus (Visiting Miller Professor Spring 2012) received the 2013 **Shaw Prize in Astronomy**... "for their discovery and study of the magnetorotational instability, and for demonstrating that this instability leads to turbulence and is a viable mechanism for angular momentum transport in astrophysical accretion disks."

National Academy of Sciences (NAS) announced the election of new members and foreign associates in recognition of their distinguished and continuing achievements in original research. The honorees include five former Miller Institute members:

+ **Kenneth A. Farley** (Visiting Miller Professor Sp03)
+ **Sarah P. Otto** (Miller Fellow 1992-94)
+ **James A. Sethian** (Miller Professor Sp11)
+ **Eva Tardos** (Visiting Miller Professor Fa99)
+ **John B. Pendry** (Visiting Miller Professor Fa91)

American Academy of Arts and Sciences (AAAS)
Seven former Miller Institute members have been named members of the American Academy of Arts and Sciences, a prestigious 233-year-old national honorary society of leaders from academia, business, public affairs and the humanities. The 2013 members include:

+ **Jitendra Malik** (Miller Professor Fa01)
+ **Hitoshi Murayama** (Miller Professor Sp06)
+ **T. Don Tilley** (Miller Professor 2004-05)
+ **Bin Yu** (Miller Professor Sp04)
+ **Shaul Mukamel** (Visiting Miller Professor Sp96)
+ **Marc Kamionkowski** (Visiting Miller Professor Fa10)
+ **Arunava Majumdar** (Miller Professor 2003-04)

Randy Schekman (Miller Senior Fellow 2008-2013) &
Terence Speed (Miller Professor Spring 2005) were elected to the Fellowship of the **Royal Society**. The backbone of the Society is its Fellowship, which is made up of the most eminent scientists, engineers and technologists from the UK and the Commonwealth. Fellows and Foreign Members are elected for life through a peer review process on the basis of excellence in science.

Alexander Levitzki (Visiting Miller Professor Spring 2008) received the **(AACR) American Association for Cancer Research's 2013 Award** for Outstanding Achievement in Chemistry in Cancer Research for his contributions to signal transduction therapy and his work on the development of tyrosine kinase inhibitors as effective agents against cancer. Last year, Alexander Levitzki received the **2012 Nauta Award** for outstanding achievements in the field of Medicinal Chemistry by the European Federation for Medicinal Chemistry (EFMC).

John Lott (Visiting Miller Professor Spring 2005) was awarded the **NAS Award** for Scientific Reviewing for the explication of Grigori Perelman's (Miller Fellow 1993-1995) celebrated solution of the Poincare Conjecture.

Tamas Hausel (Miller Fellow 1999-2002) was awarded one of the **2012 European Research Council's Advanced Grant** (worth 1.3 million euros).

Gabor Somorjai (Miller Professor 1977-1978 & Miller Senior Fellow 2009-2014) was awarded the **2013 National Academy of Sciences Award** in Chemical Sciences. This award, which honors innovative research in the chemical sciences, was awarded for the "groundbreaking experimental and conceptual contributions to the understanding of surface chemistry and catalysis at a microscopic and molecular level."

Sandra Faber (Visiting Miller Professor Spring 2005) was awarded the **National Medal of Science**. This award is considered the U.S. government's highest award for scientists. She was awarded for "work charting the properties of galaxies."

Jesse Thaler (Miller Fellow 2006-2009) & **Julius Lucks** (Miller Fellow 2007-2010) were awarded the prestigious **Sloan Foundation Fellowships**. These fellowships are awarded in recognition of distinguished performance and a unique potential to make substantial contributions to their field.

Ian Agol (Miller Professor Fall 2012) won the **2013 AMS Oswald Veblen Prize**. The Veblen Prize is given every three years for an outstanding publication in geometry or topology that has appeared in the preceding six years.

Alexander Engstroem (Miller Fellow 2009-2012) was awarded 25000 EUR for research expenses through "**The Ruth and Nils-Erik Stenback Prize**" awarded by the **Finnish Society of Science and Letters**.

Juan Ignacio Cirac (Visiting Miller Professor Spring 2014) was awarded the **Wolf Prize in Physics**... often considered the most prestigious award in those fields after the Nobel Prize. He was awarded for groundbreaking theoretical contributions to quantum information processing, quantum optics and the physics of quantum gases.

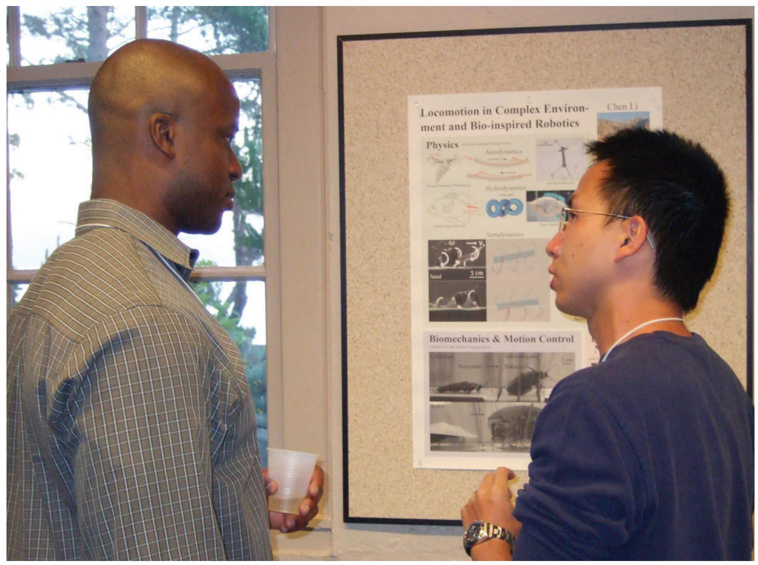
17th Annual Interdisciplinary Symposium

Miller Senior Fellow Saul Perlmutter listens to Speaker Kevin Laland.

Melissa Wilson Sayres outlines her research for Speaker Pamela Ronald.

Speaker Edward Burger chats with current Miller Fellow Francesco D'Eramo.

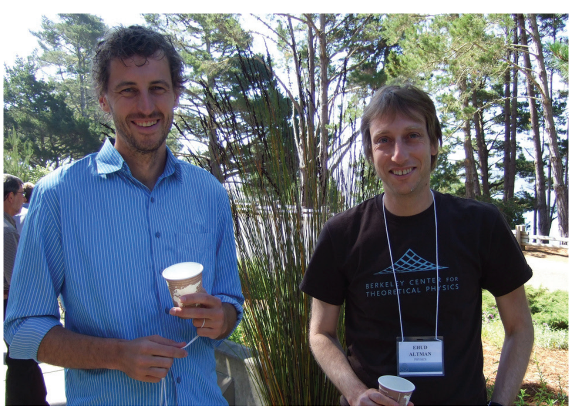
Speaker Julie Theriot and Miller Fellow Adam Retchless listen to Miller Fellow Mark Laidre explaining his work.



Miller Fellow Chen Li describes his research to Speaker John Dabiri.

Miller Fellow Eric Neuscamman describes his research to Advisory Board member, Vaughan Jones.

Speaker Scott Ransom makes a point to Miller Fellow Eric King and Eliot Quataert.



Former Miller Fellow Scott Morrison and Visiting Miller Professor Ehud Altman enjoy a break.

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The nature of the constraints, as well as their effects, vary greatly depending on the length scale. At the level of proteins, which inhabit the nanometer scale, the hydrophobic effect and dissipation shape how proteins can fold, how big they can get, and what types of information can be robustly transferred, respectively. The profound influence of these constraints on proteins means that they directly shape the type of limitations and functionalities inherited by biological processes on larger scales.

Next Steps

The Miller Institute congratulates the Miller Fellows on their next endeavors:
Franziska Bleichert (James Berger Lab @ Johns Hopkins)
Adam Day (Lecturer @ Victoria University of Wellington, New Zealand)
Alexander Hayes (Assistant Professor @ Cornell University)
Meredith Hughes (Assistant Professor @ Wesleyan University)
Kirk Lohmueller (Assistant Professor @ UCLA)
Yogesh Surendranath (Assistant Professor @ MIT)
Jun Zhao (Professor @ Fudan University, China)

Birth Announcements

Julius Lucks (Miller Fellow 2005-2008)
& Sera Young announced the birth of their daughter,
Aurora Penelope Lucks, born June 21, 2013.

Matt Reidenbach (Miller Fellow 2004-2007)
& Jennie Chiu announced the birth of their daughter,
Leia Reidenbach, born April 9, 2013.

Jason Stajich (Miller Fellow 1999-2002)
& Amy Steelman announced the birth of their son,
Emerson Wesley Stajich, born May 14, 2013.

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."