MILLER INSTITUTE NEWSLETTER

Winter 2012

Miller Fellow Focus: Matthew Good

Why is an elephant bigger than a mouse? Does the elephant have larger cells or does it contain a vastly greater number of cells? The simple answer is that although organisms contain a variety of cell types, cells with the same function in related species, with some exceptions, tend to be very similar in size. Therefore, to make a very large multicellular organism, biology increases the quantity of cells rather than the volume of a cell.

However, there are examples in which cell size varies widely within an individual organism. Since cells are biological replicators, all of the instructions and machinery required to build a new cell must be stored within the cellular compartment. If the volume of the compartment varies greatly, smaller cells must either have smaller intracellular structures or contain a more limited set of components. In fact, the former is true – biological structures can scale with cell size.

Matt Good, a second year Miller Fellow in the department of Molecular and Cellular Biology, is studying how protein complexes are assembled from their constituent subunits. In particular, he is focusing on how structures have evolved to fit within a changing cell volume. Motivated by Feynman's famous premise, "What I cannot create, I do not understand," Matt's research extends beyond a descriptive view of biology with the goal of reconstituting complex cell biological processes *in vitro*.

Spindle size regulation

The mitotic spindle is an important cellular structure that is regulated by cell size. In each cell cycle, the spindle is built from scratch and functions to organize and properly segregate duplicated chromosomes during cell division (mitosis, see Fig 1A). The spindle cannot make mistakes: cancer and developmental disorders occur when the apparatus malfunctions. The spindle is a large, highly complex and dynamic machine composed of growing and shrinking microtubule polymers, motors, and bundling proteins. It is the largest protein structure in the cell, composed of more than one thousand distinct polypeptides and can reach lengths of greater than fifty microns.

Cell size changes dramatically in the early stages of amphibian embryogenesis. During this process a fertilized egg undergoes a series

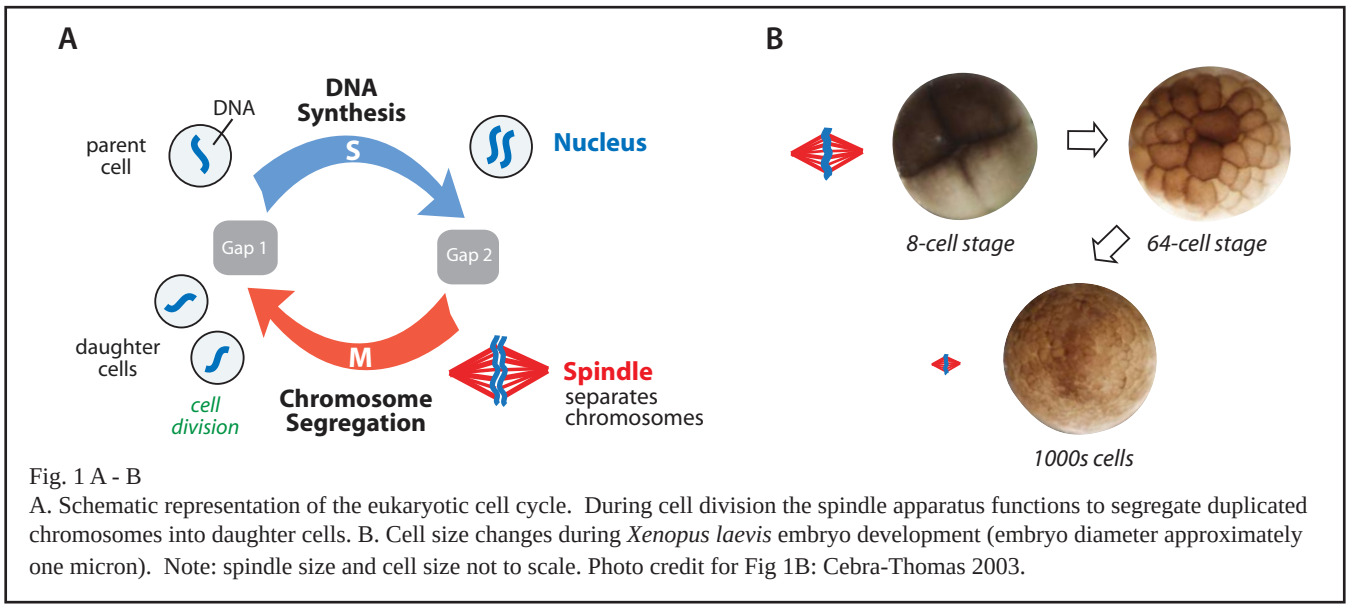


Fig. 1 A - B
A. Schematic representation of the eukaryotic cell cycle. During cell division the spindle apparatus functions to segregate duplicated chromosomes into daughter cells. B. Cell size changes during *Xenopus laevis* embryo development (embryo diameter approximately one micron). Note: spindle size and cell size not to scale. Photo credit for Fig 1B: Cebra-Thomas 2003.

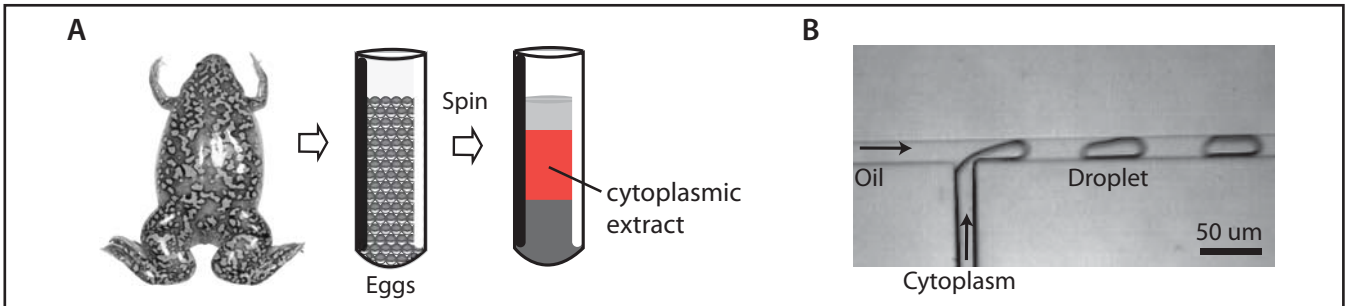


Fig. 2 A-D
A. *Xenopus* egg extract system. B. T-junction microfluidic device creates extract droplets (cell-like compartments) of specific size. C. Unpublished live image of a spindle assembled within a fifty micron droplet (M. Good and M. Vahey). Microtubules are labeled red, and DNA is stained blue. D. Models for spindle scaling in cell-like compartments *in vitro*.

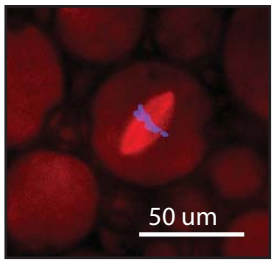
of rapid divisions, such that individual cells contract nearly one hundred-fold in diameter. Under these conditions, the mitotic spindle has been shown to scale with cell size, and can change more than one hundred-fold in volume (Fig. 1B). A fundamental question is whether spindle size is controlled by biological regulation, such as a specific stage of development or upon the activation of target genes. Alternatively, the size of the spindle may be controlled by simple physical confinement. Through research in the labs of Dr. Rebecca Heald and Dr. Dan Fletcher at UC Berkeley, Matt Good is testing the latter hypothesis, that during assembly, spindles can sense and respond to the size of their compartment.

A cell-free extract system to study the cell cycle *in vitro*

A major difficulty in the study of spindle scaling is that there is no natural cell culture system that can recapitulate the vast range of cell sizes found during amphibian embryogenesis (10 microns – 1 millimeter). Ideally, cell size could be tuned to a specific diameter and spindle length measured. These challenging experiments can now be carried out using a system Matt has pioneered for studying intracellular scaling *in vitro*. The two critical components are a cell-free extract system that can be used to build spindles and nuclei *in vitro* and the generation of cell-like compartments to encapsulate extract over a broad range of sizes. Egg extract from the African clawed frog, *Xenopus laevis*, has been shown to recapitulate many aspects of the eukaryotic cell cycle *in vitro*. The extract is prepared by collecting and centrifuging *Xenopus eggs* to isolate an active cytoplasmic fraction (Fig. 2A). By adding fluorescent protein components, such as rhodamine-labeled tubulin, meiotic spindle assembly can be imaged on a microscope slide. The power of this cell-free system is that organelle assembly can be monitored *in vitro*, and the concentrations of specific components can be controlled by depletion or by supplementing the extract with recombinant proteins. What makes this system so valuable for Matt's experiments is that spindles, formed around sperm chromosomes, reach a steady state size of thirty-five microns in extract, in the absence of any boundaries or developmental cues. If these extract spindles were forced to assemble inside of increasingly smaller compartments, would the spindles perceive the environment and change their size accordingly?

Building cell-like compartments for biology

In collaboration with the Fletcher lab in the department of Bioengineering, Matt has developed a microfluidic droplet system for encapsulating *Xenopus* egg extracts. A simple T-junction microfluidic device is shown in Figure 2B. Oil and cytoplasmic extract are pumped in through different channels, and extract is pinched off into droplets of varying size based on flow rates. Thousands of droplets can be made in minutes, and these droplets are kept stable by adding a surfactant, such as the lipid, phosphatidylcholine. After encapsulating the extract and incubating the droplets at room temperature, the spindle assembly reaction is initiated and spindles can be imaged in less than one hour (Fig. 2C).



A key prediction of the physical confinement model is that spindles will be shorter (or warped) in droplets that are smaller than the preferred size of unconfined spindles in extract (thirty-five microns, Fig. 2D). In this scenario, the spindle senses the size or stiffness of the compartment, or the amount of cytoplasm, and reaches a new steady state size to fit within the droplet boundary. In an alternative model, molecular factors are required to scale spindle length and, therefore, spindles will either not form in small droplets, or will try to maintain a larger, more energetically-favorable size, thus deforming the droplet.

Gifts to the Miller Institute

The Miller Institute gratefully acknowledges the following contributors to the Miller Institute programs during 2011. These generous donations help support both the Miller Fellowship program and the general programs of the Institute. Donations can be made by linking to the Miller Institute site at Give to CAL.

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The Judith K. and Gabor A. Somorjai endowment was established through a gift to the Institution in 2011 to create the Somorjai Visiting Miller Professorship Award. We are happy to acknowledge gifts in support of this fund.

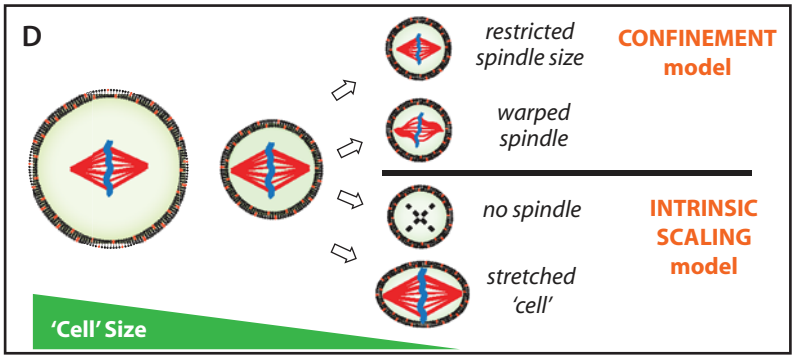
Somorjai Gifts

Lu & Georgina Sham

Miller Fellow Focus (continued)

Microfluidic droplets and vesicles are poised to become the new test tubes in biological reconstitution. Not only can droplets be made quickly and cheaply and with a much smaller volume of reagents, but they can also be tailored to mimic the chemical environment of a cell. Matt is planning future experiments to examine how spindle assembly and orientation are regulated through the localization of proteins to a cell-like cortex inside of droplets and vesicles. Additionally, by changing the stiffness of these cell-like compartments, Matt can begin to investigate the mechanisms of force generation within intracellular structures.

Matt received his B.A. in Biochemistry from UC Berkeley and completed a Ph.D. at the University of California San Francisco, in the lab of Dr. Wendell Lim. Matt's research centered on how to build protein kinase signaling networks from modular components using principles of evolution and engineering. When not in the Heald and Fletcher labs, you will find Matt reading about human origins and enjoying a beer from one of the many great Northern California breweries. Matt lives with his girlfriend and son in San Francisco.



The Advisory Board

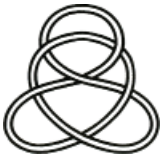
The Advisory Board of the Miller Institute met on December 5th to select next year's Miller Professors and Visiting Miller Professors. The Board is comprised of four advisors external to UCB: **Elizabeth Blackburn** (UCSF), **Claude Canizares** (MIT), **Harold Kroto** (Florida State University), and **Simon Levin** (Princeton 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, **Robert Birgeneau**.

Miller Professorship Awards

The Miller Institute is proud to announce the awards for Miller Research Professorship terms during the Academic Year 2012-2013. 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.

Ian Agol
Mathematics

Dmitry Budker
Physics



Edward Frenkel
Mathematics

Daniela Kaufer
Integrative Biology

Visiting Miller Professorship Awards

The Visiting Miller Professorship Awards for terms in the 2012-2013 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.

Ehud Altman
The Weizmann Institute of Science
Physics
Host: Dan Stamper-Kurn

Maria Elena Alvarez-Buylla Roces
Ecology Institute, UNAM
PMB
Host: Chelsea Specht

Robert Eisenberg
Rush Medical College
Chemistry
Host: Rich Saykally

Joseph Felsenstein
University of Washington, Seattle
Statistics
Host: Yun Song

Richard O'Connell
Harvard University
EPS
Host: Bruce Buffett

Feryal Ozel
University of Arizona
Astronomy
Host: Eliot Quataert

Svante Pääbo
Max Planck Institute for Evolutionary Anthropology
Integrative Biology
Host: Montgomery Slatkin

Bert Weckhuysen
Somorjai Visiting Miller Professor
Utrecht University
Chemistry
Host: Gabor Somorjai

Publications

The following Miller Institute members have recently published works resulting from research during their Miller Institute terms. For more information about these publications, please visit the Miller Institute's website at: millerinstitute.berkeley.edu/publications.htm.

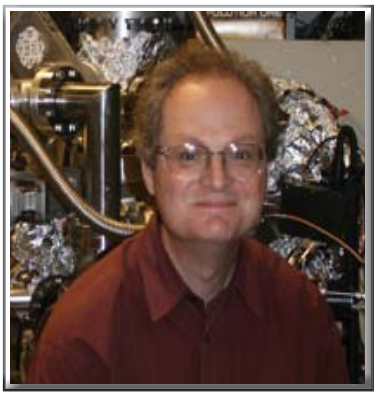
Gregory Crutsinger
(Miller Fellow 2009 - 2011)

Daniel Tataru
(Miller Professor Spring 2011)

Heather Knutson
(Miller Fellow 2009 - 2011)

Eric Agol
(VMP Spring 2011)

Awards & Honors



Paul Alivisatos (Miller Professor 2001 - 2002) was awarded the 2012 Wolf Prize in Chemistry. He has been a world leader in the synthesis of artificial nanostructures and quantum dot technology, and one of the principal scientific drivers behind the use of nanoscience technologies to create a new generation of solar photovoltaic cells. He is a Fellow of the National Academy of Sciences, American Physical Society and the American Association for the Advancement of Science, and is a co-editor of the scientific journal Nano Letters. For more information please visit Wolffund.org.il.

The Miller Institute would like to congratulate the following new members of the American Association for the Advancement of Science (AAAS).

Frederick Dahlquist
(Miller Fellow 1969 - 1971)

Chung-Pei Ma
(Miller Professor Fall 2010)

Stuart Russell
(Miller Professor Fall 1996)

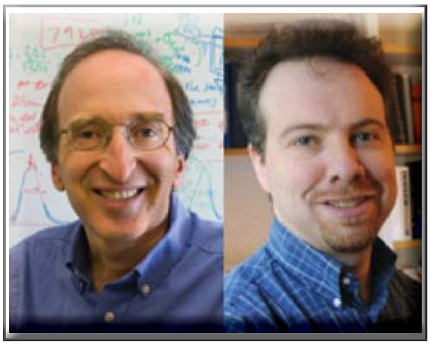
Michael Ryan
(Miller Fellow 1982 - 1984)

Lu Sham
(Visiting Miller Professor Fall 1998)

Alan Shusterman
(Miller Fellow 1980 - 1982)

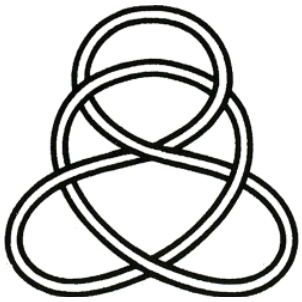
Congratulations to Professor **Marc Davis** (Miller Professor 1986 - 1987, Spring 2000) for winning the 2011 Gruber Cosmology Prize along with George Efstathious, Carlos Frenk, and Simon White. This award recognizes “a series of pioneering papers in the 1980s that relied on numerical simulations... to validate the ‘cold dark matter’ theory of cosmic growth.” To read more please visit Gruberprizes.org.

December 6, 2011: Nicholas McConnell, a University of California, Berkeley Astronomy graduate student and his professor **Chung-Pei Ma** (Miller Professor Fall 2010) discovered two enormous black holes: two objects in distant space whose center is more than 300 million light years away from Earth. The report of their discovery was published in the journal Nature. For more information concerning their discovery please visit Nature.com.



October 4, 2011: **Saul Perlmutter** (Miller Senior Fellow 2010 - 2015), a professor of physics at the University of California, Berkeley, and a faculty senior scientist at Lawrence Berkeley National Laboratory (LBNL), was awarded the Nobel Prize in Physics. He will share the prize with **Adam G. Riess** (Miller Fellow 1996-1998), and Brian Schmidt. To read more about the Supernova Cosmology Project please visit Nobelprize.org.

David Shelly (Miller Fellow 2007 - 2008) and **Feng Wang** (Miller Fellow 2005 - 2008) are among Early-Career Scientists awarded by White House. "President Obama today named 94 researchers as recipients of the Presidential Early Career Awards for Scientists and Engineers, the highest honor bestowed by the United States government on science and engineering professionals in the early stages of their independent research careers."



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Birth Announcements

Ed Feng (Miller Fellow 2005 - 2008) & Elizabeth welcomed their second child, Miles Feng on May 14th.

Erin Dueber (Miller Fellow 2004 - 2007) & John announced the birth of their baby girl, Daphne Laurel Dueber, born May 29th.

Dustin Rubenstein (Miller Fellow 2006 - 2009) & Katherine announced the birth of Ian Henry Rubenstein on August 17th.

Sheila Patek (Miller Fellow 2001 - 2004) & Charlie announced the birth of Jasper John Patek Nunn on August 19th.

Jiaxing Huang (Miller Fellow 2004 - 2007) & Shaorong announced the birth of their son Steven on November 6th.

Matthew Francis (Miller Fellow 1999 - 2001) & Catherine welcomed the arrival of their son, Ryan Robert Francis on December 24th.

Next Steps

Alexander Engström
(Miller Fellow 2009 - 2011)
Assistant Professor of Mathematics
Aalto University, Finland

Obituary

William Barnes Arveson
(Miller Professor 1985 - 1986, 1999 - 2000)

Howard Bern
(Miller Professor 1961 - 1962)

Online Newsletter

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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."