LIGHTING THE WAY

Ten Years of National Centers for Systems Biology

Foreword

This booklet tells the story of an extraordinary community of scientists, educators and administrators brought together by a remarkable initiative on the part of the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH). From the outset, the National Centers for Systems Biology program tapped into the very heart of a movement that was rapidly sweeping through the biomedical research establishment. In retrospect, many may argue that the Systems Biology "revolution" was an inevitable consequence of the successes of the molecular biology revolution, which brought us (and continues to bring us) deep knowledge of biological mechanism, but provides only limited insight into the underlying principles of biological organization. Systems Biology seeks to remedy this deficiency, exploiting quantitative approaches and tools from Mathematics, Physics, Computer Science, and Engineering to unravel the complex relationships between molecular mechanism and organismal function.

What could not be seen as inevitable, however, was that one institute of the NIH would take it upon itself to "manage" the Systems Biology revolution, at least within the United States. At a time of deep confusion within the biological and biomedical research community about what Systems Biology is, and whether it was going to have any lasting impact, the NIGMS had the vision to support Centers that would lead by example, lighting the way for researchers everywhere. Even more remarkably, the NIGMS had the foresight to insist that Centers devote themselves not just to the task of producing exemplary Systems Biology research, but also in lighting the way in education, community outreach, and institutional transformation.

The NIGMS also demanded that Center leadership, along with a subset of each Center's membership, get together annually to share their accomplishments in science, education, and outreach. Out of these meetings grew a sense of common purpose and community that led to the establishment of a common web portal (at www.systemscenters.org) and a broad commitment to sharing resources and expertise for the benefit of the wider scientific community. Ultimately, the activities of the National Centers for Systems Biology galvanized a large group of scientific professionals into working together to make the Systems Biology revolution accessible to everyone.

One of the ways in which the Centers work together is that, if a task of importance to all of us needs to be done, one of the Center directors will always step forward to do it. In this case—on the occasion of the first Centers reaching their final (10^{th}) "sunset" year—my Center volunteered to organize the publication of this booklet, commemorating all of the National Centers for Systems Biology that have been designated to date. It has been a pleasure and an honor to bring together the stories and accomplishments of each current Center, and to see the common threads of excitement, innovation, and hope that run through all of them.

I hope you enjoy reading this.

Arthur D. Lander
Director, Center for Complex Biological Systems
University of California, Irvine

This book was printed by OC Printworks, Irvine California. The typeface is Adobe Caslon Pro.

The contents of these pages were assembled from summaries and photos generously provided by each of the 15 current National Centers for Systems Biology, as well as from information obtained from NIH program staff. The individual Centers retain copyright to their own pages.

The cover art was created by Yawei "Jenn" Ge, who just received her bachelor's degree in Applied Mathematics and Biology from Brown University, and perhaps someday will become a Systems Biologist.

The editorial team consisted of Arthur Lander, Felix Grün and Karen Martin, from the Center for Complex Biological Systems (UC Irvine), and Bodo Stern, from the Center for Modular Biology (Harvard).

Contents

How It All Began

By the late 1990s, biomedical researchers were producing a wealth of detailed information on the molecular components of biological systems, particularly of cellular systems. Rapid development of genomics, imaging, and molecular tagging technologies, and high-throughput approaches made it abundantly clear that the acquisition of new data would only accelerate. However, attempts to obtain quantitative understanding on how these myriad of components interact dynamically to produce life processes had only begun, and would be critical to any application to biomedical research.

In response, the National Institute of General Medical Sciences (NIGMS) convened a workshop of diverse researchers in 1997 (www.nigms.nih.gov/news/reports/complexbio.htm) to collect input on approaches for the study of complex biological processes. It was apparent that this study would require the expertise of diverse quantitative scientists, engineers and mathematicians. Based on the recommendations of this workshop, in 1998 the NIGMS Advisory Council approved several funding initiatives to provide supplements to existing awards (PA-98-024), to promote the development of new research projects (R01 and P01, PA-98-077) with the adoption of quantitative approaches to complex biological systems, and to develop courses that would provide training for quantitative biology.

The programs were intended to advertise NIGMS interest in stimulating what at that time was termed

Jerry Li, Program Director NCSB 2004-2008

James Anderson, Program Director NCSB 1997-2012

"Complex Biological Processes" research at a level more amenable to individual research labs. However, by early 2000, follow-up analysis of the response to these initiatives indicated that a much more sizeable program would be required to promote interdisciplinary collaboration and interdisciplinary training with strong commitment and support from the institutions.

In 2000, the NIGMS Advisory Council approved a P50 Center program in complex biological systems research. The first Request for Applications (RFA-GM-01-001) was issued in 2001 with the title "Centers of Excellence in Complex Biomedical Systems Research". The NIGMS awarded two P50 Centers under this program in 2002, two Centers in 2003 and one Center in 2004.

In 2004, NIGMS changed the name of the program to National Centers for Systems Biology (RFA-GM-05-010, most recent http://grants.nih.gov/grants/guide/pa-files/PAR-12-187.html), a reflection of the general acceptance of the concept of systems biology and the true mission of the program. The overarching goal is to establish national leaders in systems biology research and training that will stimulate further development of the field. As such, funded Centers would be provided sufficient resources to not only support coordinated research projects at the forefront of the field, but also to acquire the advanced infrastructure needed for these projects as well as resources adequate to develop new technologies, new curricula, and outreach programs to educate the next generation of quantitative investigators. Individual Centers would be funded for a maximum of two terms of five years each, with an

administrative review in year three of the first term and a competitive review for the second term.

Over the next few years, one to three new Centers were added each year to the program. And now a total of 15 Centers are supported by the NCSB program. The areas of the Centers' research emphasis reflect a broad swath of the NIGMS mission, from basic molecular cell biology to the physiome of the laboratory rat. The entire program meets yearly to communicate progress of individual Centers, to discuss inter-Center collaborations, and to coordinate efforts in placement and cross-training of young scientists. The program has developed a common portal that provides a wealth of information about the Centers, their accomplishments and resources at http://www.systemscenters.org/.

Systems Biology programs have developed in a number of institutions, some of which have cited the successes of the NIGMS NCSB program as a model, and some institutions' programs were developed around the core of their own NIGMS funded Centers. At NIH, other Institutes (e.g., National Cancer Institute; National Heart, Lung, and Blood Institute) have created their own programs, as the systems biology approach is being adopted by more and more research communities to study a wide range of human diseases.

In addition to broad scientific advances in systems biology, the NCSB program has been especially valuable in training and promoting the research careers of new scientists. Graduates of the individual Centers are in demand for their expertise in physics, engineering, computer science and mathematics.

Peter Lyster, Program Director NCSB 2008-Present

Paul Brazhnik, Program Director NCSB 2010-Present

Looking back over the last 12 years, the NIGMS NCSB program has served successfully as a pioneer and model in promoting the development of systems biology research and training both within the NIH and around the country. We look forward to the NCSB program at NIGMS continuing to play a significant role in advancing the field through research, training and outreach.

James Anderson (NIGMS/NIH)
Jerry Li (NCI/NIH)
Paul Brazhnik (NIGMS/NIH)
Peter Lyster (NIGMS/NIH)

Center for Cell Decision Processes

Massachusetts Institute of Technology **http://www.cdpcenter.org**

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Program Administrator:
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Key Personnel (cumulative): Gaudenz Danuser, Drew Endy, David Gifford, **Linda Griffith, Jeremy Gunawardena, Jongyoon Han, Khuloud Jaqaman**, Klavs Jensen, **Amy Keating, *Doug Lauffenburger, Gavin MacBeath, *Scott Manalis**, Leona Samson, Martin Schmidt, ***Elba Serrano**, Bruce Tidor, Forest White, ***Michael Yaffe** (current members in bold; executive committee starred)
)

Center History, Philosophy, and Environment:

The CDP Center at the Massachusetts Institute of Technology and Harvard Medical School is in its tenth and final year and is recognized for its work on modeling and measuring mammalian signal transduction and for developing novel microfluidic devices that facilitate mammalian systems biology. CDP had its origins in a series of collaborations on quantitative cell biology involving investigators in the Biology and Biological Engineering Departments at MIT funded by the Defense Advanced Research Projects Agency (DARPA). With CDP support this led to the creation of the MIT Computational and Systems Biology Initiative (CSBi) whose graduate program remains a centerpiece of systems biology at MIT.

CDP spans five departments and research units at MIT and two departments at Harvard Medical School with key collaborators at New Mexico State University (NMSU) and BioQuant in the University of Heidelberg, Germany. CDP emphasizes a combined computational and experimental approach and the majority of CDP trainees (particularly graduate students) have developed an interest and aptitude for both. CDP has always relied on students and postdocs to organize much of the agenda; one or more postdocs serve as "research coordinators" charged with ensuring that students and postdocs have a major say in determining who will speak at annual conferences, weekly group meetings and site visits. Over 20 CDP trainees run their own academic labs and more than a dozen hold leadership positions in industry.

Biological discovery is frequently driven by innovation in measurement and analytical methods and CDP therefore has a significant program in miniaturized instrumentation (microfluidics and micro engineered devices) and in novel computational algorithms.

Sabrina Spencer (ACS Senior Postdoctoral Fellow, Stanford; left), John Albeck (Assistant Professor, UC Davis; center) and Suzanne Gaudet (Assistant Professor, Harvard Medical School; right) during postdoctoral or graduate training in the CDP Center

CDP focuses on protein networks operating within and between cells and seeks to explain their cell-specific operation through models that incorporate detailed molecular mechanism. This approach was first articulated by Marvin Cassman, former Director of NIGMS and an early proponent of systems biology. Although all modern molecular biology relies on knowledge of the genome, our Center has deemphasized genomics in favor of biochemical and phenotypic analysis.

Scott Manalis (center) and colleagues testing a novel microfluidic device for measuring the mass of single cells

When planning our Center a decade ago, we thought it would be sufficient adapt existing algorithms and mathematical methods from other fields such as chemical engineering. When it became clear that this was not sufficient, CDP initiated a sustained effort to develop and implement a range of computational methods from networks of differential equations (which are highly specific and mechanistic) to logic-based modeling, Bayesian inference and various forms of multi-linear and partial least squares regression (which are data driven). The fusion of diverse biochemical, mass spectrometry, imaging and flow cytometry data using a such modeling methods has always been a hallmark of CDP research.

Research focus

On short time scales, the "decisions" that regulate cell fate are controlled by receptors that sense the extracellular environment and transduce signals via complex multi-component protein networks. Our Center primarily studies signaling by trans-membrane receptors responsive to growth factors, pro-apoptotic ligands and cytokines. These networks are frequently mutated in diseases such as cancer and chronic inflammation and are primary targets for many investigational and standard of care drugs. Three fundamental features of these networks guide our attempts to measure and model them.

The first is that signal transduction is a dynamic process with a significant spatial component; we therefore use methods that can detect and capture spatiotemporal variation. Much of our research relies on live and fixed-cell imaging, primarily of cultured cells but increasingly of living animals. We have also pioneered a variety of methods for analyzing cells and cell compartments using microfluidic devices or high density arrays capable rapid analysis of very small amounts of material. We also use modeling to fuse diverse data thereby exploiting the distinct strengths of different experimental methods.

A second feature is that the operational characteristics of even canonical signaling pathways depend strongly on cellular context. Determining the origins and phenotypic consequences of this variation (e.g. gene identity or catalytic activity) is essential for understanding tissue-specific cellular physiology and disease mechanisms. We have developed and verified a variety of models that reveal how proteins that are absolutely essential for correct execution of a fate decision (e.g. apoptosis) in one tumor type can be fully dispensable in another type simply because interacting molecules vary in concentration. We have also demonstrated that natural fluctuations in protein concentrations among genetically identical cells are sufficient to give rise to dramatically different phenotypic outcomes.

A third feature of signaling networks is that normal and disease physiology plays out on a wide range of time and spatial scales, and no single modeling or measurement approach can span mechanism on the time scale of seconds to minutes and cell fate changes on the time scale of days to weeks. As a corollary, it has been necessary to develop computational abstractions that make it possible to study cellular networks at different levels of detail. For example, recent work in the Center has focused on new domain-specific languages (in Python) for describing biochemical networks as programs that can be instantiated as in a variety of mathematical frameworks. It is our current belief that executable programs of this type - not models (and certainly not databases) - represent the optimal repository of computable biological knowledge.

CDP has enjoyed sustained success in its research programs, having published more than 150 primary papers to date with a Center-wide H-index in excess of 50. The 20+ former trainees now running independent laboratories at institutions such as Yale, Harvard, Georgia Tech., University of Virginia, U.C. Davis and the European Bioinformatics Institute (to name but a few) will sustain our vision of applying quantitative, multi-scale approaches to human physiology and disease even after CDP shuts down.

Education and outreach

The CDP Center maintains an active and multi-

faceted outreach and education program with elements that are Center-specific and others that strengthen ongoing programs in our community.

Faculty Sabbatical Program. We provide funding for a faculty member from a minority-serving institution to work in CDP for 3-6 months, typically with several students or postdocs. Our 2011 -2012 visitor, Dr. Kimberly Jackson of Spelman College, used her CDP sabbatical to advance study a potential therapeutic agent for prostate cancer.

The International Conference on the Systems Biology of Human Disease. CDP established the International Conference on the Systems Biology of Human Disease (SBHD) in 2008; the conference is now jointly managed by the German Cancer Research Center (DKFZ) based in Heidelberg, Germany and is held alternately in the US and Germany. Typical attendance is 200-250 people from industry and academe.

Women in Technology Program (WTP). Since 2002, the MIT-based WTP has brought ~40 female high school students per year to MIT for a 4-week residential program, aimed at increasing interest and skills in computer science and engineering (wtp.mit.edu). For ten years CDP has provided funding to WTP to provide 10-15 disadvantaged individuals with financial assistance.

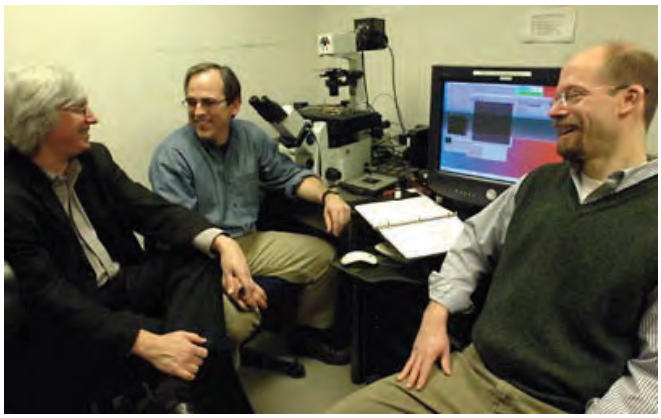
New England Science Symposium (NESS). CDP provides continuing support to NESS to enable college students from minority backgrounds to attend a symposium at HMS that serves as a primary vehicle for recruiting disadvantaged students to Harvard.

The Council for Systems Biology in Boston (CSB^2). CSB^2 is a joint effort of academic institutions and companies in Boston to coordinates local activities in the areas of quantitative biology and systematic analysis of human disease and therapy (www.csb2.org).

The National Centers for Systems Biology (NCSB) Portal. CDP developed the infrastructure for and hosts the primary website that communicates the NCSB mission to the general and scientific public. The site has ~8,000 unique visitors per year (www.systemscenters.org).

Institutional transformation

CDP was the first organized systems biology research program at MIT, although many groups already had quantitative biology programs. CDP provided a focus around which MIT's Computational and Systems Biology (CSBi) program was established. CSBi links Biology, Biological Engineering and Computer Science programs in joint research and education projects spanning engineering, computation and biomedicine. In its early days, CDP provided funding for six CSBi core facilities but over time we determined that our impact would be larger if we focused on research programs and technology development cores rather than general-purpose facilities. In this respect, CDP differs from other centers in which support for core facilities has been a key activity (illustrating the need for diversity in center organization).



The CDP Leadership team of Doug Lauffenburger, Peter Sorger and Mike Yaffe discussing newly identified links between inflammatory disease and cancer.

Over the past few years, the interests of many CDP faculty have grown to include quantitative analysis of therapeutic drugs. Sorger and Lauffenburger participated in a multi-year study culminating in preparation of an NIH White Paper ("*Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms*") that lays out a program for transforming pharmacology and drug discovery through the application of systems biology methods. Whereas CDP focused on bringing together engineers and biologists, a systems pharmacology program will require the active involvement of clinicians and clinical scientists. To explore how this might be done, the leaders for CDP recently founded the inter-institutional *Laboratory of Systems Pharmacology* (LSP) under the auspices of the Harvard Program in Therapeutic Science (http://hits.harvard.edu). LSP represents an attempt to transform not only the research culture of Harvard and MIT, but to change the ways in which physician scientists and industry discover and evaluate drugs.

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Center for Cell Decision Processes
National Center for Systems Biology since 2003

Research Achievements and Key Multi-Investigator Publications:
Key achievements of CDP investigators involve quantitative analysis of signal transduction, cell proliferation, apoptosis and innate immunity. This has revealed a general role for autocrine signaling in normal and tumor cells, dramatic variability in phenotype arising from stochastic fluctuation in protein levels among genetically identical cells and the importance of timing and order of addition in response to cancer chemotherapy.

- *Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks*. Lee et al (2012). Cell 149. PMID: 22579283.
- *Using buoyant mass to measure the growth of single cells*. Godin et al (2010). Nature Methods 7, 387. PMID: 20383132.
- *Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis*. Spencer et al. (2009). Nature. PMID: 19363473.
- *Modeling a snap-action, variable-delay switch controlling extrinsic cell death*. *Albeck* et al. (2008). PLoS Biol 6, 283. PMID: 19053173.
- *Common effector processing mediates cell-specific responses to stimuli*. Miller-Jensen et al. (2007). Nature 448, 604. PMID: 17637676.
- *The response of human epithelial cells to TNF involves an inducible autocrine cascade*. Janes, K. A et al. (2006). Cell 124, 1225. PMID: 16564013.

Resources and software:
- *Programmatic and rule-based modeling of biological networks using PySB software*. http://pysb.org/. Lopez et al (2013). Mol Syst Biol PMID: 23423320.
- *Bayesian calibration of non-identifiable kinetic models*. http://sorgerlab.github.io/bayessb. Eydgahi et al (2013). Mol Syst Bio. PMID: 23385484.
- *Semantic Data Cubes (XML-tagged HDF5 files) for managing complex multidimensional data*. http://www.semanticbiology.com Millard et al (2011). Nat Methods PMID: 21516115
- *Logic-based modeling of biological networks using Boolean and Fuzzy Logic* https://sites.google.com/site/saezrodriguez. Saez-Rodriguez et al (2009) Mol Syst Biol PMID: 19953085.
- Database and software for identifying peptide substrates for kinases. http://scansite.mit.edu/

Institutional transformation:
- Establishment of MIT's *Computational and Systems Biology Initiative;* http://csbi.mit.edu
- Establishment of the *Laboratory of Systems Pharmacology*, Harvard Therapeutics Program; http://hits.harvard.edu
- Establishment of the *Council for Systems Biology in Boston* (CSB^2) http://www.csb2.org.

Center for Modular Biology

Harvard University http://www.sysbio.harvard.edu/csb/research/center.html

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Key Personnel (cumulative): 19 Bauer Fellows: Aviv Regev, Kurt Thorn Michael Laub, Sharad Ramanathan, Oliver Rando, Hans Hofmann, Yaakov Benenson, Kevin Verstrepen, Christine Queitsch, Kevin Foster, Katharina Ribbeck, Irene Chen, Marcus Kronforst, Suckjoon Jun, Allan Drummond, Peter Turnbaugh, Rachel Dutton, Nicolas Chevrier, Lauren O'Connell; 7 faculty: Dan Fisher (Harvard), George Church, Johan Paulsson, Roy Kishony, Tim Mitchison (Harvard Medical School), Naama Barkai (Weizmann), Michael Elowitz (Caltech)

Center History, Philosophy, and Environment:

We believe that the future of new disciplines lies primarily in the hands of younger rather than older scientists, that the future of biology depends on closer interactions between theorists and experimentalists, that the search for organizing themes has been central to the advance of biological knowledge, and that truly successful groups change the outlook and philosophies of the scientists that pass through them.

At the core of the Harvard NIGMS Center are the Bauer Fellows, young scientists who have typically just finished a PhD. We give them funding ($275K/yr) and intense mentoring to run a small, independent research group for five years. The NIGMS Center directly supported 19 of 24 Bauer Fellows since 2003. We described the fellows program in our original NIGMS Center proposal as "an experiment in the conduct of research" because of two unique features: the Fellows form a tight community with joint lab and office space fostering a culture of peer support that keeps them from developing a dependency, intellectually or technologically, on nearby faculty groups. Secondly, we deliberately bring together scientists from different disciplines, exposing theory fellow to experimental biology approaches and experimental fellows to the modeling and analysis of more quantitative sciences. This commitment to building an interdisciplinary community among the fellows lies at the heart of the Bauer Fellows Program and distinguishes it from prestigious fellows programs at other institutions. The program is also committed to an unprecedented level of mentorship designed to support the fellows with a mixture of rigor and enthusiasm that is rarely found in modern academia.

The program director and PI of the NIGMS Center, Andrew Murray, meets weekly with fellows to advise them on research problems and lab management; a fulltime program administrator, first Laura Garwin, later Bodo Stern, supports the day-to-day research activities of the fellows including hiring, lab management and scientific communications; finally, the fellow groups present their research in weekly group meetings to get feedback from the larger research community at our center.

Bauer Fellow Reunion meeting 2012

Research focus

The Bauer Fellows have been outstandingly successful by any standard: 100% (all 19 who have moved on) have obtained faculty positions at a wide range of top institutions; the quality and quantity of what they've published (84 publications -12 in *Science, Nature,* and *Cell* - between 2003 and 2013 with the center grant as a critical funding source); the grants the NIGMS funded fellows received towards the end of or immediately after their Bauer Fellowship (nearly *twice* as much - $ 16 million – as the NIGMS Center grant invested in them - $ 9 million – with a third of supported fellows only recently departed or still in their fellow position). Much more importantly the Fellows program has transformed every young scientist who has passed through it: they expanded the frontiers of their research, begun collaborations with scientists (their fellow Fellows, Harvard faculty, and others) whose work lies well beyond their own disciplines, and become apostles for interdisciplinary science by developing the skills that will allow them to catalyze and lead similar efforts elsewhere.

In their own words:' Being a Bauer Fellow has transformed the way I do science, has made me the scientist that I am today, has let me make majors scientific discoveries, with important implications to human health, and has taught me how to build communities of scientists that do the same - a mission that I pursue today as a faculty member at MIT and the Broad Institute' (Aviv Regev, Broad Institute and MIT). 'Without the opportunity to be a Bauer Fellow, I would have never had a lab (no conventional academic department or funding agency would have ever supported my transition from Physics to Biology), and would probably be working on very different questions.' (Sharad Ramanathan, Harvard).

Education and outreach

The Bauer Fellows played a central role in the education and outreach activities of the NIGMS Center. They lectured to ~ 70 high school teachers in our annual fall outreach program and developed course material for the annual two-week summer workshop for high school teachers; Peter Turnbaugh, for example, helped to develop a microbiome outreach module together with teachers and our outreach coordinator Tara Bennett (http://outreach.mcb.harvard.edu/Microbiome/microbiome.html); the fellow and faculty group members participated as lecturers and teaching assistants in our one-day outreach laboratories that reach close to 100 high school students every spring. Finally, Bauer Fellows and faculty hosted many undergraduate summer interns in their labs.

Summer interns 2012

A serious research experience is often cited by undergrads as the transformative experience on the road to a career in a STEM field. The interns in the fellow groups particularly enjoyed their frequent direct interactions with the group leader, which is much less common in larger faculty groups, where graduate students and postdocs do most of the mentoring. 'In speaking with my friends who also work in labs, I've realized how truly remarkable an atmosphere the Center is and how lucky I was to become a part of it. It is my impression that most undergraduates involved in basic research do not have much contact with their principal investigators, nor do they have the opportunity to investigate what really excites them, at least not until they've been in a lab for awhile. I think what makes the internship program so unique is that students are hired not to simply be helpers in a lab, but to be taught what being a scientist really means.' (summer intern Lauren Herman).

Institutional transformation

Transformation at Harvard

The NIGMS Center grant and Bauer Fellows program has helped to erode intellectual and administrative barriers between departments by improving core facilities and engaging researchers from a broad variety of backgrounds and scientific departments in interdisciplinary research. Our genomics and proteomics core facility, which initially supported the interdisciplinary research efforts of the Bauer Fellows, now provides access to high-throughput laboratory equipment and experts in its use to hundreds of individual users across the university. The success of this shared infrastructure has also served as a model for the integration of other technologies and resources in the Harvard Life Sciences including IT, mass spectrometry and sequencing.

The Bauer Fellows program has transformed the Harvard life sciences community in several ways: the excitement generated by the program has helped to recruit and retain junior and senior faculty in surrounding departments. The regular turnover of Bauer Fellows guarantees that new technologies and exciting new research ideas reach our core facilities and life science communities to stimulate collaborations and to rejuvenate existing research projects. In times of shrinking research funding and fewer junior faculty hires the regular infusion of young, risk-taking group leaders is particularly critical to offset the reduced faculty turnover that a shrinking NIH budget implies. Finally, the program's strong mentoring record serves as a counterweight to the widespread impression that Harvard is unusually poor at supporting talented and independent young scientists. As a result the NIGMS supported Center has become a critical hub not only for interdisciplinary research but also for the shared interests in the Harvard Life Science community.

Transformation at NIH?

Our experience with the Bauer Fellows suggest that individual researchers who fully cross the divide between experiment and theory are likely going to make fundamental contributions to the biology of the 21st century. Although we hope that young Bauer Fellows will continue to apply their skills in mathematics, physics and computer science to fundamental questions in biology, the future of the program is uncertain. While the benefits for individual fellows and the biology community at large are tremendous, the benefits to institutions is counterweighed by the large annual costs of such programs, and the fact that we explicitly encourage our Fellows to look for jobs outside Harvard, rather than seeing the program as a device for producing the next generation of Harvard faculty. We suggest that programs like the Bauer Fellows Program are ideal targets for federal funding. The NIH Director's Early Independence (EI) Award, established in 2010, is an exciting program, which provides young scientists straight out of a PhD with full PI rights and similar level of funding as the Bauer Fellowship. We argue that the full benefits of giving talented young scientists full independence as early as possible will best be realized in the context of a *program with several fellows, shared infrastructure, a strong mentoring component, and an interdisciplinary environment*. Our experience has been that regular faculty mentoring, a full time program administrator, shared equipment and, probably most importantly, peer support from other fellows has been crucial to helping fellows adapt quickly to the various challenges, scientific, personnel, and political, of running a research group. In contrast, a lone fellow surrounded by established faculty groups will often drift intellectually towards a nearby faculty group with shared research interests (and useful equipment). Strong mentorship can still be established but it will be ad hoc and will often depend –like mentorship for postdocs - on an explicit interest of the faculty in the fellow's research program.

The success of the Bauer Fellows Program would not have been possible without the generous 10-year support from the NIGMS Center grant. We suggest that NIH ask whether our 'experiment in the conduct of research' has been successful enough to argue for an NIH funding mechanism that would be dedicated to creating other programs to support the early success of our brightest young scientists.

FACT SHEET
Center for Modular Biology
National Center for Systems Biology since 2003

Research Impact:
Center researchers asked initially whether networks of interacting components, or modules, are pervasive building blocks in biological systems, and explored in the second funding period how the existence of these building blocks restrains or enhances the generation of diversity.

- The center developed novel computational methods, for example to create an unprecedented gene ancestry catalogue for a large group of species by reliably distinguishing orthologs from paralogs on a genomic scale (a notoriously difficult problem). *Wapinski, I, .. Regev, A. Natural history and evolutionary principles of gene duplication in fungi. Nature, 2007*
- Center researchers used theory and experiment to demonstrate how evolutionary pressures lead to biofilms (medical relevance) and to multicellularity (which has evolved at least 20 times): *Xavier, J.B., and Foster, KR. Cooperation and conflict in microbial biofilms. PNAS, 2007; Smukalla S, … Foster KR, Verstrepen KJ. FLO1 is a variable green beard gene that drives biofilm-like cooperation in budding yeast. Cell. 2008*; *Koschwanez J, Foster KR, Murray AW. Improved use of a public good selects for the evolution of undifferentiated multicellularity. eLife, 2013.*
- The Center made critical contributions to the theory and functional relevance of stochastic events during gene expression. *Suel GM… Elowitz MB. Tunability and noise dependence in differentiation dynamics. Science. 2007; Hilfinger A and Paulsson J (2011) Separating intrinsic from extrinsic fluctuations in dynamic biological systems, PNAS. 2011; Hornung, G.. Barkai, N. Noise-mean relationship in mutated promoters. Genome Research 2012*
- Center researchers used theory to relate the rate of evolution to fundamental parameters like population size, mutation rate, interaction between mutations, and devised ways to measure these parameters in well-mixed and spatially structured populations. *Desai, MM, Fisher, DS, and Murray, AW. The Speed of Evolution and Maintenance of Variation in Asexual Populations. Curr. Biol. 2007*; *Korolev K, Murray AW.. Nelson DR, Selective sweeps in growing microbial colonies, Phys. Biol. 2012.*

A comprehensive publication list is at: http://sysbio.harvard.edu/csb/research/cmb_publications.html

Training and Outreach:
The Harvard NIGMS Center for Systems Biology has successfully disseminated its interdisciplinary and collaborative philosophy through training and outreach:

- Graduate students and postdoctoral trainees: the NIGMS Center directly supported the training of 19 Bauer Fellows, 57 postdoctoral fellows and 30 graduate students. All 15 Bauer Fellows and 22 of the 32 postdocs who left the NIGMS Center, are now in faculty position.
- Summer school: the center supported 61 graduate students and 6 postdocs with a quantitative science background to attend the MBL Physiology Course, a systems biology summer school in all but name.
- Undergraduate summer internship: the NIGMS Center directly supported half of 138 undergraduate summer interns (and 40 of the 51 underrepresented minority students). 51 (or 58%) of all graduated students (including 15 minority students) are now in graduate programs, 14 in systems biology programs.
- New England Science Symposium (NESS): since 2008 the center has supported and participated in NESS, the largest New England conference for underrepresented minority students in biomedical fields.
- High School Outreach: since 2008 the center has run spring, summer and fall high school programs: the spring program offers half-day laboratory classes for about 100 students; the intensive 2 week summer workshop provides curriculum development opportunities for teachers; lectures in the fall bring teachers up to date with current research topics.

Center for Quantitative Biology

Princeton University http://www.princeton.edu/quantbio/

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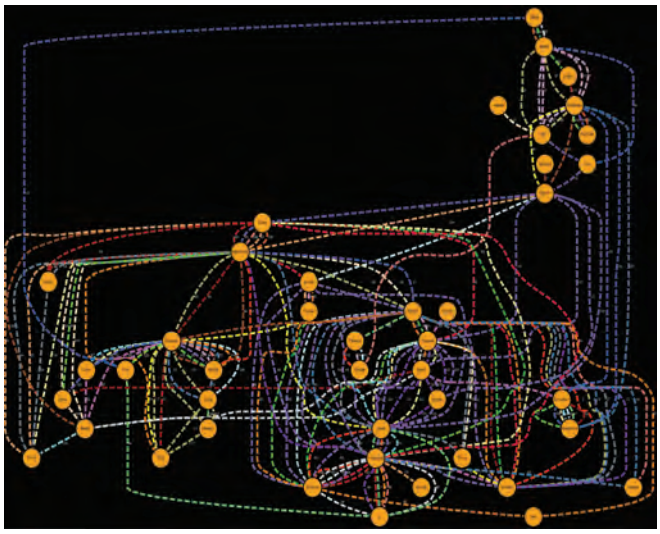
Key Personnel / Project Leaders (cumulative): David Botstein, James Broach, Joshua Rabinowitz, Thomas Shenk, Mona Singh, Olga Troyanskaya, Ned Wingreen

Center History, Philosophy, and Environment

In 1943, Salvador Luria and Max Delbrück wrote, "It may seem peculiar that this simple and important question should not have been settled long ago, but a close analysis of the problem in hand will show that a decision can only be reached by a more subtle quantitative study than has hitherto been applied…" The context was finding a way to understand Luria's difficulty in measuring the fraction of phage-resistant mutants in independent clones of the same bacterial strain, which he intuitively understood to be due at least in part to "jackpots" where a resistant variant arose early in the history of the clone. It took the collaboration with Delbrück to get full understanding of the problem, using mathematics well beyond what was taught then, or now, to biologists. This is one of the first instances of truly quantitative biology, and it resulted in the collaboration of a microbiologist and a theoretical physicist. In the current era, the number of "simple and important questions" requiring "more subtle quantitative study" has exploded. Today, we have achieved intuitive understanding of very many biological phenomena, but a real understanding, at the level of Luria and Delbrück, of remarkably few. At Princeton, we believe that achieving real understanding, in the future, will require the same process that Luria and Delbrück used: collaboration between scientists of different disciplines and ways of thinking, but who nevertheless understand enough of each other's language and mathematics to communicate effectively. This is why we named our NIGMS Center "The Center for Quantitative Biology;" our mission has been to instantiate at Princeton a research, teaching, and training environment that fully meets the challenge and opportunity to practice a useful quantitative biological science."

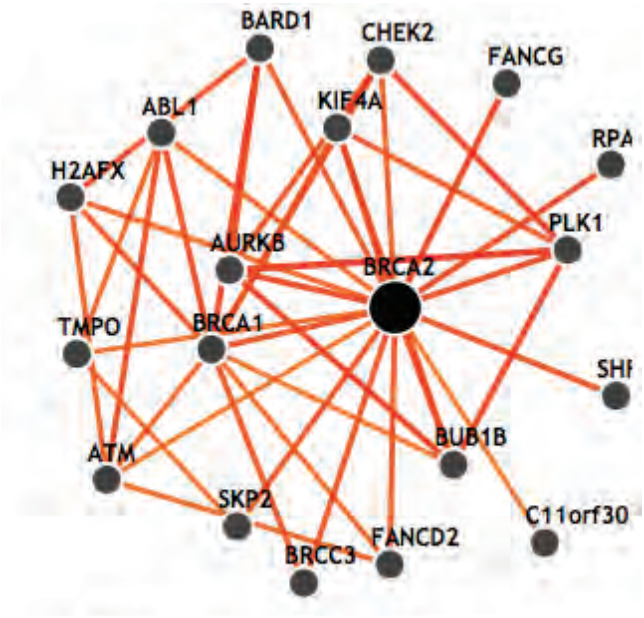
Because we are just now beginning to train the next generation of scientists who are truly fluent across disciplines, our Center has to be truly integrative and collaborative to succeed – we need Theorists, Experimentalists, and Computational Biologists to work together to gain more quantitative understanding of biological systems and processes. We have, by any measure, been successful in this regard. We have over twenty collaborative grants that have sprouted from Center seed funding, and, as is shown below, we continue to publish collaboratively, both within the Center and beyond Princeton's walls, at an impressive rate (130 such publications since the Center began).



Collaborative publications among the Center's P.I.'s since September, 2004. Nodes (circles) are P.I.'s and edges (dashed lines) are collaborative publications.

Research focus

Bioinformatics and Technology Development: A basic theme of the Princeton Center, from the beginning, has been the development and application of bioinformatic methods. On the analytic side, Princeton has led, through the development of integrative methods by Olga Troyanskaya, population genetic methodologies by Peter Andolfatto, analytic methods by Saeed Tavaozoie, Mona Singh and Stas Shvartsman as well as cutting-edge statistical technology by John Storey. Notably, it has often the case that major producers of data elsewhere have collaborated with our Center in analysis and annotation of their large data sets.

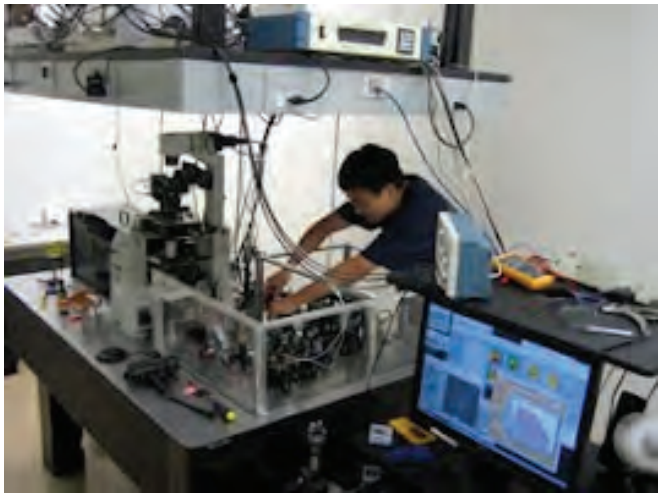


The functional gene network at BRCA2

The Princeton Center has also had notable successes in "wet-lab" technology development. Today, this kind of development often involves considerable computational input, and the collaborative nature of the Center facilitates this. For example, through Joshua Rabinowitz, Princeton has become pre-eminent in the development of fully quantitative methods for measuring dynamically the concentrations and fluxes of metabolites by a combination of chromatography and mass spectrometry. There have been several Center-supported publications that apply innovative methods in metabolomics to cancer biology, infectious disease (with Tom Shenk), and bacterial metabolism.

Genome Scale Data: The Center has also led in the production of very large data sets, by David Botstein, Leonid Kruglyak, Manuel Llinás and Coleen Murphy, that increase the "condition space" and have led to understanding regulatory networks in yeast, worms and the malaria parasite. The emphasis on computational biology and bioinformatics has an obvious symbiotic relationship with the generation of reliable and comprehensive datasets - it is one of the major features of the Princeton Center that this relationship is seamless at Princeton.

Biophysics and Imaging: Another theme running through the Princeton Center from the beginning is biophysics, especially as it intersects with the generation and transmission of biological information. Bill Bialek is a leading theorist in this area, and his long collaboration with David Tank (a world-leader in imaging) and Eric Wieschaus (a world-leader in Drosophila developmental genetics) was one of the pillars on which the Center was constructed. At our Center, the biological integrates with the physical sciences, providing quantitative models in areas that were traditionally the domain of qualitative, phenotypic observations. Thomas Gregor's quantitative models of Drosophila embryonic development, Josh Shaevitz and Zemer Gitai's collaboration on better understanding the internal structure of bacteria, and Ned Wingreen and Bonnie Bassler's collaboration on quorum sensing are excellent examples of this approach.



Education and outreach

The Center for Quantitative Biology has education and outreach programs from the secondary school to graduate school level. Our undergraduate Integrated Science Curriculum (ISC) is a series of courses taken in the freshman and sophomore years that provides students with first-rate preparation for a major in any of the core scientific disciplines in such a way that retains the connections to the other disciplines. The curriculum is founded on the expectation that much of

the most important science of the future, though based on the classical disciplines, will lie in areas that span two or more of them. Our ISC program is thriving, with those who have completed the curriculum moving on to the top graduate programs in the country.

The Center also supports our summer undergraduate research program and molecular biology/genomics boot camp for incoming graduate students. These programs are integrated with the diversity program, directed by Alison Gammie, at Princeton University. Due to Dr. Gammie's leadership and the support provided by Princeton University and our Center, our diversity program has made significant progress in addressing the challenging issue of recruiting and retaining under-represented minority graduate students. Dr. Gammie's efforts have recently been recognized by the American Society of Microbiology, who awarded her with the William A. Hinton Research Training Award this year.

The Center supports two successful outreach initiatives at the junior and senior high school level. Once a year, Princeton hosts ~1,000 middle school students at a campus-wide Science and Engineering Expo. For one day, these middle school students become Princeton students and attend lectures and demonstrations in our lecture halls, share hands-on activities in laboratories and even enjoy lunch in our student dining halls. This program has been very successful and continues to grow in popularity. At the high school level, we support satellite-training centers that provide up-to-date training for biology teachers. To date, the Center provided funds for nearly 200 such molecular biology training kits, which introduced molecular biology to over 4,000 students.

The Annual Junior High Science Expo at Princeton University.

Institutional transformation

Ten years ago, there was already significant interest in quantitative biology at Princeton; however, there was no undergraduate curriculum or graduate program, and interest was explored through a relatively small number of ad-hoc collaborations. Through the hub of the Lewis-Sigler Institute for Integrative Genomics, we have formalized quantitative biology as a discipline and are at the forefront of the field, both in research and in teaching. This was made possible in large part due to the abundant and stable funding provided by the NIGMS Centers for System Biology program. A key to our success was the availability of cutting edge infrastructure (both the equipment and the professional staff to run it) that was made readily accessible by the Center. In addition, the Center provided seed funding for collaborative projects across disciplines – by funding shared post-docs and graduate students, collaborative research got off the ground and, in many cases, led to several publications and successful collaborative grant applications.

The First Integrated Science Curriculum Class, Graduation Day, 2008. *Eleven of the fourteen students are in PhD programs at Stanford, Berkeley, Harvard, MIT, or University of Colorado, Boulder.*

FACT SHEET
Center for Quantitative Biology
National Center for Systems Biology since 2004

Collaborative Research: the Center for Quantitative Biology has fostered a unique collaborative research environment, both within Princeton and beyond. We believe that this is in no small part due to our investment in shared research infrastructure. Here, we list some of the most highly cited papers that were enabled by the infrastructure provided by Center for Quantitative Biology. The Center faculty from Princeton are bolded; the names in italic/underline are PIs at other institutions that collaborate with us, often because of our unique infrastructure.

- Costanzo, M., Baryshnikova, A., Bellay, J., Kim, Y., Spear, E. D., Sevier, C. S., Ding, H., Koh, J. L., Toufighi, K., Mostafavi, S., Prinz, J., St Onge, R. P., VanderSluis, B., Makhnevych, T., Vizeacoumar, F. J., Alizadeh, S., Bahr, S., Brost, R. L., Chen, Y., Cokol, M., Deshpande, R., Li, Z., Lin, Z. Y., Liang, W., Marback, M., Paw, J., San Luis, B. J., Shuteriqi, E., Tong, A. H., van Dyk, N., Wallace, I. M., Whitney, J. A., Weirauch, M. T., Zhong, G., Zhu, H., Houry, W. A., Brudno, M., Ragibizadeh, S., Papp, B., Pal, C., *Roth, F. P.*, Giaever, G., Nislow, C., **Troyanskaya, O. G.**, Bussey, H., Bader, G. D., Gingras, A. C., Morris, Q. D., Kim, P. M., Kaiser, C. A., Myers, C. L., Andrews, B. J. & Boone, C. The genetic landscape of a cell. Science. 2010;327(5964):425-431.
- Ward, P. S., Patel, J., Wise, D. R., Abdel-Wahab, O., Bennett, B. D., **Coller, H. A.**, Cross, J. R., Fantin, V. R., Hedvat, C. V., Perl, A. E., **Rabinowitz, J. D.**, Carroll, M., Su, S. M., Sharp, K. A., Levine, R. L. & *Thompson, C. B.* The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010;17(3):225-234. PMCID: 2849316.
- Gregor, T., **Tank, D. W., Wieschaus, E. F. & Bialek, W.** Probing the limits to positional information. Cell. 2007;130(1):153-164. PMCID: 2253670.
- Reguly, T., Breitkreutz, A., Boucher, L., Breitkreutz, B. J., Hon, G. C., Myers, C. L., Parsons, A., Friesen, H., Oughtred, R., Tong, A., Stark, C., Ho, Y., **Botstein, D.**, Andrews, B., Boone, C., **Troyanskya, O. G.**, *Ideker, T.*, **Dolinski, K.**, Batada, N. N. & *Tyers, M.* Comprehensive curation and analysis of global interaction networks in Saccharomyces cerevisiae. J Biol. 2006;5(4):11. PMCID: 1561585.
- Gresham, D., Ruderfer, D. M., Pratt, S. C., Schacherer, J., **Dunham, M. J., Botstein, D. & Kruglyak, L.** Genome-wide detection of polymorphisms at nucleotide resolution with a single DNA microarray. Science. 2006;311(5769):1932-1936.

Center for Genome Dynamics

The Jackson Laboratory http://www.genomedynamics.org

Program Director:
Gary Churchill, Ph.D. (Gary.Churchill@jax.org)

Program Administrator:
Imogen Hurley, Ph.D. (ihurley@jax.org)

Key Personnel (cumulative): Karl Broman, Gregory Carter, Elissa Chesler, Joel Graber, Matthew Hibbs, Ronny Korstanje, John Macauley, Susan McClatchy, Leonard McMillan, Beverly Paigen, Kenneth Paigen, Fernando Pardo-Manuel de Villena, Petko Petkov, Randy Smith, Karen Svenson, Wei Wang.

Center History, Philosophy, and Environment:

The Center for Genome Dynamics (CGD) at The Jackson Laboratory (Jackson) is an internationally recognized leader in mammalian systems genetics with collaborators at The University of North Carolina at Chapel Hill and The University of Wisconsin-Madison.

CGD originated as collaboration among a small group of investigators faced with a perplexing observation that the genomes of laboratory mouse strains harbored extensive networks of local and long-range linkage disequilibrium (LD). We hypothesized that LD networks reflect the outcome of selection during the derivation of these strains, originally as pets and later in the laboratory, in which divergent sub-species of wild mice were admixed followed by rapid inbreeding. We further hypothesized that LD patterns reflect a genome-wide organization of allelic loci that are co-adapted within subspecies and incompatible between subspecies. The idea was motivated by theory from the classical era of population genetics.

To address our hypothesis, we developed a detailed map of the origins of laboratory mice from multiple *M. musculus* subspecies, generated high-resolution maps of the recombination landscape, and investigated the functional organization of genes along mammalian chromosomes. Our efforts have profoundly altered the accepted view of the origins of laboratory mice. This has important implications for a model organism that is central to modern biomedical research.

During this same time period, major breakthroughs in human genetic mapping have yielded a flood of new loci but have also raised perplexing questions about the inheritance of complex genetic traits. Armed with a new understanding of the mouse genome and newly developed genetic resources, we are ideally positioned to address these questions.

Research focus

In our first grant period we laid the groundwork for a new generation of experimental approaches in systems genetics by developing novel genetic resources, high throughput measurement technologies, and new computational approaches to modeling biological systems. In the renewal period, we are capitalizing on these advances to launch an ambitious program to transform the way the laboratory mouse is used in biomedical research.

Our previous work provided a detailed molecular understanding of the evolutionary origins of the laboratory mouse, which in turn led to the adoption of two novel populations of mice with extensive genomic diversity. Derived from the same set of eight progenitor strains, and hence sharing the same allelic compositions, the Collaborative Cross recombinant inbred strains provide reproducible genomes optimal for multiple testing, while Diversity Outbred mice provide high genetic mapping resolution. To these we have added additional genetic crosses using the same progenitor strains. Collectively, these mouse populations provide an integrating backbone for

connecting multiple levels of genomic function, and for developing and validating predictive models of genetic and environmental effects.

The Center's research activities are built around a core set of experiments that were designed to yield data for analysis and systems-level modeling. The experiments all interrogate the same genetic material (a large, fixed universe of allelic variants) but use different strategies for combining alleles. The allelic variants derive from three different subspecies of mice that have evolved independently, with minimal admixture over the past 0.5 million years. This design allows us to address one of the most perplexing questions in genetics – how do novel phenotypes emerge when diverse genomes are interbred? This question has broad relevance for understanding the emergence of human diseases as well as addressing fundamental properties of genetic inheritance.

In order to lead the field, the Center must address questions about important biological processes that are bold and challenging, but not intractable. We are investigating four broad areas relating to dynamic functions that affect or involve whole genomes. These are epigenetic modification, recombination, gene expression, and metabolism. We are studying these areas to better understand how genetic variation on a genomic scale affects biological outcomes, which we call genome dynamics.

Education and outreach

CGD aims to provide national leadership in systems biology through the development of innovative training and outreach programs.

Since 2006 the Center has offered a yearlong course, Independent Studies in Computational Biology (ISCB), to high school students with exceptional science and math skills. The course was developed and taught by Center Director Dr. Gary Churchill and Center Outreach Coordinator Ms. Susan McClatchy. The course is divided into two 16-week semesters. The first semester covers research competencies such as writing and presentation skills. Students read current papers from the scientific literature and present their interpretation in journal club talks. Students write a review article and analyze data using R, and they learn to use bioinformatics tools, genome browsers and databases. The students then formulate a hypothesis and write an NIH style grant proposal, integrating the material they have assimilated in the first semester. Students learn concepts in genetics, statistics and computation.

In the second semester Center postdoctoral associates mentor teams of students as they carry out research projects. The mentoring experience is mutually beneficial as the high school students and postdoctoral associates work together to address their research questions using available data and computational resources, often those generated by the Center. At the end of the year, students present their findings in a presentation, a poster, and a written research report. ISCB brings the Center together with math and science magnet schools in Maine, North Carolina and Georgia. All three partners are public schools and none charge tuition to in-state residents.

In addition to developing its own innovative outreach programs, the Center is also building on existing outreach initiatives within Jackson. The nationally renowned Jackson Summer Student Program provides high school and college students with an opportunity to conduct independent research under the guidance of Jackson faculty.

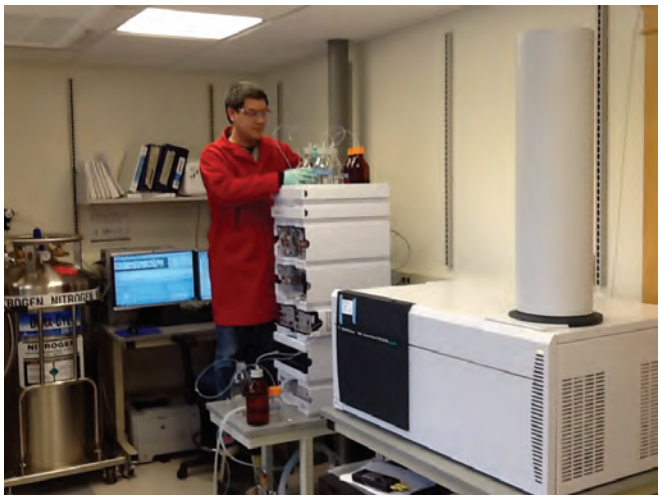
More than 2,000 students, including three Nobel laureates, have participated in the program since 1924. Several of the best students from the Center's high school course are admitted each year to the Program. The internships are designed to help students understand the nature of research science with an emphasis on methods of discovery and communication of knowledge, not just the mastery of established facts. They participate in active research groups, and conduct their work in a highly interactive and team oriented atmosphere under the guidance of their mentor. At the end of the summer the students present their work at the program's one-day symposium and prepare a written research report. Research conducted by previous Center students has resulted in two peer-reviewed publications. Examples of student projects include a web-based browser for viewing networks of linkage disequilibrium data, and a systems biology approach to identify candidate genes causing obesity in mice.

We continue to develop our education and outreach programs making them nationally available through online course modules. Systems Genetics Online delivers educational content integrating computer science and mathematics in the study of genetics. Content includes recorded lectures from the Center's ISCB course, and The Short Course on Systems Genetics (R25) led by Center investigators. Slides, lecture notes, R code, data, examples or exercises supplement recorded lectures. The first module to be launched was for Quantitative Trait Mapping and the Center was recently awarded the Science Prize for Inquiry-Based Instruction for this online program.

Institutional transformation

The Center has transformed systems biology research at Jackson, making it a major focus in recruiting and providing new resources to Jackson researchers.

The Center has succeeded beyond our expectations in the development of early stage investigators. During the initial grant period Drs. Pardo-Manuel and Graber were promoted to associate professor. Dr. Korstanje was promoted to Senior Research Scientist and took over the leadership of a Center project. He is currently under consideration for promotion to Assistant Professor. Dr. Svenson earned her Ph.D., was promoted to Research Scientist and initiated a new project within the Center. All of the Center's early stage investigators (Pardo-Manuel, Petkov, Graber, Korstanje, and Svenson) have been awarded research grants based in part on Center resources. The Center awarded projects to Drs. Wang and McMillan, in the University of North Carolina Department of Computer Science, that have helped to support their new focus on biological research. Three new investigators (Drs. Chesler, Hibbs, and Carter) have been recruited at Jackson and have each initiated or proposed new projects within the Center.



The Center has recently provided equipment to implement targeted metabolite profiling for the first time at Jackson, with institutional support for the infrastructure and staffing of this service. The acquisition of this technology will reduce costs, improve access for Jackson scientists, and provide an opportunity for the development of new assays and applications.

FACT SHEET
Center for Genome Dynamics
National Center for Systems Biology since 2006

Research impact

The Center has established a multidisciplinary research program that integrates experimental and computational approaches to investigate dynamic processes relating to whole-genome function and regulation, including DNA methylation, recombination, gene expression and alternative splicing, and metabolic regulation. In our first funding period, Center research highlights included developing a new understanding of the evolutionary origin of the laboratory mouse (Yang et al. Nat Genet 2007; Yang et al. Nat Genet 2011) and discovering the role of Prdm9 as the key regulator of recombination hot spot positioning (Parvanov et al. Science 2010; Paigen et al. PLoS Genet 2008; Petkov et al. Trends Genet 2007). In the initial renewal period we have characterized genetic diversity and demonstrated the power of the Collaborative Cross and Diversity Outbred mouse genetic resource populations (Aylor et al. Genome Res 2011; Svenson et al. 2012 Genetics), and developed analytical concepts and software for causal inference in genetics (Blair et al. 2012 PLoS Comp Biol.; Hageman et al. 2011, Genetics).

Community resources/software/collaborations

We are generating resources and infrastructure to support and stimulate new research activity. We have developed experimental designs for exploiting our novel genetic resources, new high throughput measurement technologies, including new applications of high throughput sequencing, and metabolite profiling. In doing so, we have developed open software, high performance computing approaches to multi-dimensional data analysis, and have shared our data resources, new analytic methods and integrative computational tools with the broader community. Our biological resources include the establishment of a DNA collection from over 2,000 samples of inbred strains, outbred populations, Collaborative Cross mice, wild caught mice and murine cell lines, and a repository of 24,000 DNA samples to map recombination hotspots. We have also developed and commercialized two genotyping platforms: Mouse Diversity Genotyping Array (MDA), and Mouse Universal Genotyping Array (MUGA). The Center website continues to provide the principal point of access to the public resources generated by Center researchers including 25 data collections from Center publications and 10 software tools which receive over 30,000 page views per month.

Training and outreach

Our education and outreach programs have helped to establish a diverse workforce of scientists who have the experimental and computational knowledge necessary to embrace a systems approach. We continue to develop our unique program of mentored research immersion for high school students, Independent Studies in Computational Biology, which has engaged over 60 elite students in real computational biology research projects since 2006, and already helped to produce 13 STEM undergraduate degrees and 5 STEM graduate students. To make this course nationally available, we are providing online educational content integrating computer science and mathematics in the study of genetics through Systems Genetics Online. Each summer the Center participates in the Jackson Summer Student Program, and has hosted 5 high school and 29 undergraduate students in Center research groups. At all levels of our training programs, we promote the recruitment and retention of groups traditionally underrepresented in biomedical science. Through a NIGMS Research Supplement to Promote Diversity in Health-Related Research, we have recently engaged two talented underrepresented youth, Jasmine Johnson and Gabriel Vela, in a two-year immersion in Center-initiated computational biology research for high school students under the guidance of the Center Director, Dr. Gary Churchill. The goal of this authentic research experience is to accelerate each student's scientific education and career at a very early age.

Center for Systems Biology

Institute for Systems Biology http://centerforsystemsbiology.org/

Program Director:
John Aitchison (jaitchison@systemsbiology.org)

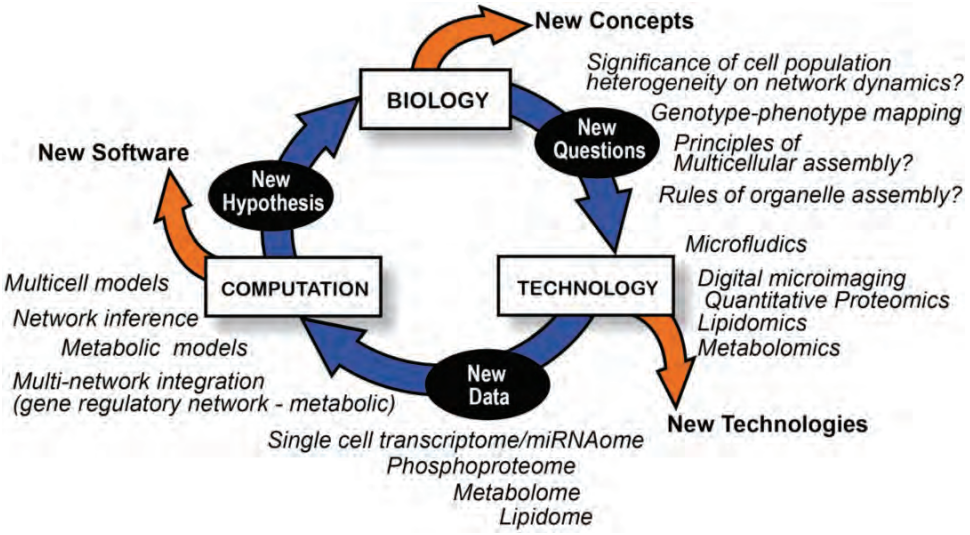
Program Administrator:
Jennifer Dougherty (jdougherty@systemsbiology.org)

Key Personnel (cumulative; faculty): John Aitchison, Nitin Baliga, Aimee Dudley, Lee Hood, Sui Huang, Rob Moritz, Adrian Ozinsky, Nathan Price, Jeff Ranish, and Ilya Shmulevich.

Center History, Philosophy, and Environment:

The Center for Systems Biology was established in March 2006 to enable the development of the field of systems biology, which is founded on the principle that cross-disciplinary research, involving teams of biologists, chemists, computer scientists, mathematicians, physicists and physicians will yield fundamentally new insights into biological complexity and disease. The basis of the research agenda for the Center is the vision that aggressively addressing complex systems-level biological problems inexorably drives the development of new systems-interrogation technologies, which, in turn, drive computational advances in data mining, integration and modeling. New insights continually lead to new systems-level biological questions, perpetuating an iterative progression of the systems biology cycle. Ultimately, technologies developed and improved understanding of biology will lead to new approaches to diagnostics, therapeutics and disease prevention, and a new kind of medicine that is predictive, preventive, personalized and participatory (P4 medicine). Thus, our Center drives innovation through iterative biology-driven advancements in technology and computation, has allowed us to establish a culture of collaboration that promotes the integration of scientists and disciplines, and has democratized data generation and analysis capabilities by allowing every scientist to participate in this new way of doing science in an integrative and multidisciplinary manner.

Interdisciplinary research has inherent challenges that demand sociological and institutional changes, the most fundamental of which is open communication across disciplines that engenders a general understanding and appreciation for the principles and approaches of different disciplines. The Center thus provides training, events, panels, programs, meetings, retreats, symposia and seminars to promote an intellectually stimulating and creative culture that fosters numerous training opportunities,



Our systems biology cycle. *Schematic of the iterative progression of systems biology, with a representation of Center-specific themes as they relate to the cycle.*

the free exchange of ideas, and an ongoing and *uninhibited* dialog among experimentalists, technologists and theoreticians.

Each year the Center *directly* supports the partial efforts of ~35 scientists from ~12 research labs and catalyzes systems approaches to diverse biological and technological problems, and leverages these results and insights to new funding opportunities and new collaborative partnerships. Since 2006, *our scientists have published 175 papers* acknowledging Center support.

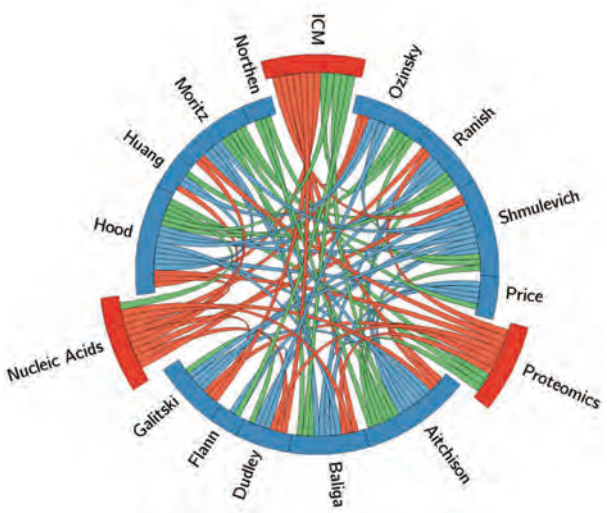
We believe teaching and training our junior scientists is inextricable from our roles as scientists. With Center support we have fostered the career development of >*100* high school and undergraduate *students*, *84 graduate students*, and *86 postdoctoral fellows*. We support these trainees through direct support, including providing new career development and training events, consumable and facility support, professional membership dues for career development, funding travel for our trainees for conferences and meetings, and providing resources for ad hoc requests as new training needs arise.

Research focus

We strive to develop data-driven descriptive, graphical and mathematical models for cellular mechanisms or processes that enable prediction of responses to intracellular and environmental stimuli. Predictability of cellular responses is the basis for applications as diverse as P4 medicine and the reengineering of microbes for biotechnology. The difficulty of this objective relates directly to the complexity of the organism in terms of numbers of genes and proteins, cell architecture, types of signaling mechanisms and number of cell types, and both genes, proteins, cells and cell types, as well as spatial and temporal dynamics. Carefully selected models provide relatively simple systems in which to understand the hierarchical organization of dynamic complex molecular networks that specify phenotypic traits of living systems.

Our Center focuses on what we consider to be central to the challenge of systems biology. Specifically: ***How do cells transition between states?*** Three projects are designed to attack three aspects of this key question:

1. How are environmental signals processed through molecular networks to transition cells between states?
2. How do cells establish and maintain spatiotemporal patterns of cell state transitions to form multicellular structures?



Collaborations and interactions established by the Center. *Research (blue), core use (red) and technology development (green).*

3. Are there defined quantized intermediate states during mammalian cell-type differentiation? If so, do these quantized states functionally interact in ways that are essential to proper differentiation?

Answers to these questions will *enable us to explain, predict and control cell state transitions. Such capabilities hold promise for ultimately understanding, and even reversing, transitions from health to disease.*

From a molecular level, we elucidate how genomic and environmental information acting through dynamical networks leads to physiological and developmental transitions. To do so, we study how network dynamics extend across a hierarchy of scales. In the context of cell populations, we also consider the contributions of stochastic and deterministic processes during state transitions. We address these challenges by using model systems with attributes specifically suited to address the conceptual, technical and computational challenges inherent to gaining new biological insights.

Education and outreach

Since 2006, the Center has devoted significant effort to promoting a cross-disciplinary "systems biology culture" that encourages *collaboration within and between research project teams.* Our goal has been to develop a common language shared by the diverse set of biologists, chemists, computer scientists, engineers, mathematicians, and physicists that comprise the Center's research community. To this end, the Center has supported six years of education and training including *courses, seminars, panel discussions, discussion forums, on-line discussion forums, research seminars, and invited speakers.*

Professional development. Our Center fosters professional development of our junior scientists through direct support provided to courses and workshops related to systems biology and new technologies. The goal is that once established courses will become self-sustaining. The Center also enables scientists to take risks on innovative development projects that have potential to be transformational to research programs and the advancement of systems biology. *For six years the Center has provided seed funding for high risk projects, support for the costs of facility runs, graduate students, postdoctoral fellows, and entry-level investigators to facilitate their science.*

Undergraduate intern program. The undergraduate intern program provides self-motivated young scientists effective education, training and mentoring in systems biology and the practice of research in a collaborative environment. The program includes underrepresented minorities and female undergraduate students who are pursuing a career in research, rather than medical school. The program is ten weeks long and mentors ~ 10 interns per summer. All interns are paid with Center support. Over six years, the program has become highly competitive, *in 2013 we had 107 applicants for nine, ten week summer research projects.*

Graduate students. In 2009, the Center formed a graduate student group to provide career development training with topics that are determined by the students. A monthly lunch for the student group is managed by a Center senior scientist, and topics have included 'op-ed' discussions relating to mentoring, current research, laboratory practice, and choosing a postdoctoral position.

Postdoctoral fellows. In 2008, a "Postdoc Association" was formed in response to a postdoc-initiated survey, which indicated that postdoctoral fellows needed additional career resources and a formal forum for broader peer networking. The Association formed its' own governing body and developed the annual "ISB Postdoc and Grad Student Retreat", an all-day workshop that includes agenda items such as: research topics, "Grant writing", "Postdoc issues forum", "All you need to know about IP", and a workshop "How to pitch to a biotech".

Outreach to underrepresented minorities. The Center took the lead to form two successful partnerships to engage individuals from underrepresented racial and ethnic populations, along with financially disadvantaged individuals, and persons with disabilities, as trainees and leaders to teach and learn interdisciplinary systems thinking, and systems biology. Through a partnership the Center formed in 2006 with a Physician Scientist Training (PSTP) program, a longitudinal training program first funded in 1985 with a Minority Access to Research Careers (MARC) award, the Center has *mentored and paid* ~24 minority *freshly graduated high school student* summer interns.

The second partnership engages entry level scientists and established investigators, and re-trains them in systems biology interdisciplinary thinking, and research. In 2007, we formalized a partnership with Virginia State University, also a historically black college/university, to develop a systems biology training program for undergraduate and graduate students, and to provide mentorship to VSU Faculty for the practice of interdisciplinary research.

Institutional transformation

The approach and philosophy of the Center lies at the heart of the Institute for Systems Biology. The Center has instantiated a culture of cross-disciplinary systems research that permeates all research at ISB and has been elaborated through collaborations and strategic partnerships established by ISB scientists, locally, nationally and internationally. Locally, we have established a partnership with Seattle Biomedical Research Institute to bring the advances of systems biology to infectious disease research. National strategic partners include Gladstone Research Institute, Caltech, Ohio State Medical School, and Mass General Hospital. But, the most significant partnership has been with The Grand Duchy of Luxembourg, which sought a partnership with us to establish a sister institute in Luxembourg that is modeled on the philosophy, structure, and successes of ISB catalyzed by the Center.

FACT SHEET

Center for Systems Biology

National Center for Systems Biology since 2006

Research Impact:
The Center is composed of cross-disciplinary teams of scientists dedicated to revealing biological complexity and using biology to drive advancements in technology and computation. In 2007, Center scientists published the first global, predictive transcriptional regulatory network model of a free living organism and provided a foundation for generating predictive network models in higher organisms, spanning different cellular processes from signaling to morphological responses to environmental stimuli. Collectively, these studies established that while data space is infinite, the number of responses an organism can mount is finite. This has profound implications for systems biology, specifically demonstrating that decoding these networks into predictive models is a tractable problem.

In parallel, Center scientists have developed mechanistic modeling approaches to understand the dynamics of the organizational and functional principles that underlie genome-wide network models. Integration of the two complementary approaches promises a comprehensive, contextual and rigorous mechanistic understanding of network structure and function. *Bonneau, R., et al., A predictive model for transcriptional control of physiology in a free living cell. Cell, 2007; Saleem, R.A., et al., Genome-wide analysis of signaling networks regulating fatty acid-induced gene expression and organelle biogenesis. J Cell Biol; Carter, G.W., et al., Prediction of phenotype and gene expression for combinations of mutations. Mol Syst Biol.; Ramsey, S.A., et al., Dual feedback loops in the GAL regulon suppress cellular heterogeneity in yeast. Nat Genet, 2006.*

A network view of biology led Center researchers to develop the concepts that disease emerges from disease-perturbed networks and that network analysis can predict disease prior to onset of clinical symptoms. This is foundational to P4 Medicine and powerful insights into the nature of disease can emerge from the correlation of histopathology, clinical signs, genetics and dynamical networks—revealing pathogenic mechanisms and potential strategies for therapeutic intervention. *Hwang, D., et al., A systems approach to prion disease. Mol Syst Biol, 2009; Hood, L., et al., Revolutionizing medicine in the 21st century through systems approaches. Biotechnology journal. 2012.*

Virtually all systems biology approaches developed through the Center are faced with the fundamental technical challenge of identifying proteins quantitatively and comprehensively in complex samples. Center personnel are actively developing and applying "selective reaction monitoring" as a mass-spectrometry based proteomics technology to meet this challenge. This targeted approach promises to revolutionize proteomics, enabling systems biology and comprehensive proteomes of model systems and humans. *Mirzaei, H., et al., Systematic measurement of transcription factor-DNA interactions by targeted mass spectrometry identifies candidate gene regulatory proteins. Proc Natl Acad Sci U S A, 2013; Farrah, T., et al., The state of the human proteome in 2012 as viewed through PeptideAtlas. J Proteome Res, 2013.*

A comprehensive Center publication list is at http://www.centerforsystemsbiology.org/publications/index.php.

Community Resources:
Below are a subset of Center resources, with supporting publications and scientist contact information. A list of *Institute for Systems Biology resources* can be found on the Institute website at www.systemsbiology.org.

A comprehensive list of *Center* resources is at http://www.centerforsystemsbiology.org/resource/index.php.

- *Gaggle* http://gaggle.systemsbiology.net/docs/ *Database and software integration framework* – The Gaggle is a framework for exchanging data between independently developed software tools and databases to enable interactive exploration of systems biology data. http://www.ncbi.nlm.nih.gov/pubmed/18021453.
- *Transproteomic Pipeline* http://tools.proteomecenter.org/software.php *Data analysis software* - a suite of software tools for the analysis of tandem mass spectrometry data sets. The tools encompass most of the steps in a proteomic data analysis workflow in a single integrated software system. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2373374/.
- *Cytoscape* http://www.cytoscape.org/ *Data analysis* - An open source bioinformatics software platform for visualizing molecular interaction networks and integrating these interactions with gene expression profiles and other state data. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2478690/.

Trainees:
Over 100 high school and undergraduate students; 84 graduate students; 86 post-doctoral fellows. Courses: Introduction to Systems Biology, Proteomics Informatics, Microfluidics and Imaging, Network Analysis; Nucleic Acids Technology; Graduate course at University of Washington Introduction to Systems Biology & Quantitative Approaches.

Duke Center for Systems Biology

Duke University http://www.genome.duke.edu/centers/systems-biology/

Program Director:
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Key Personnel (cumulative): L. Ryan Baugh, Nicholas Buchler, Blanche Capel, Herbert Edelsbrunner, Steve Haase, John Harer, Alexander Hartemink, Jack Keene, Paul Magwene, David McClay, Sayan Mukherjee, Uwe Ohler, David Schaeffer, Amy Schmid, Scott Schmidler, Joshua Socolar, Mike West, Gregory Wray, Lingchong You

Center History, Philosophy, and Environment:

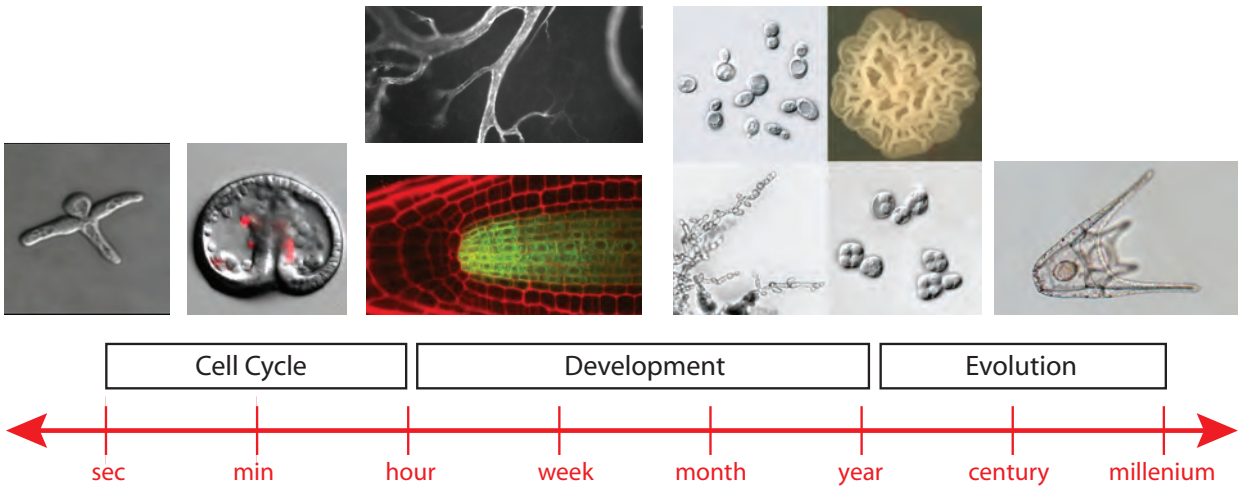
The Duke Center for Systems Biology (DCSB) began in 2004 as an informal discussion group of scientists from a wide range of departments and backgrounds who each had an interest in biological networks. By the end of the second year, computational scientists and experimentalists were equally involved in discussions; a welcoming environment had been created in which people from both cultures felt comfortable asking questions that might appear elementary to the other side. In 2006, we were granted designation as an official University Center, with the primary goal of nurturing interactions between experimental scientists and theorists with a common interest in biological systems. The Center has now evolved into a tightly integrated community sharing the common goal of understanding the dynamics of regulatory networks.

During our time as an NIGMS National Center for Systems Biology (7/1/2007 – 6/31/2013), we made substantial advances in research, education, and outreach. The interactive, interdisciplinary collaborative culture we developed fundamentally contributes to the success and vitality of DCSB research and education. Most importantly, highly productive collaborations have developed between experimental biologists and computational scientists. These links are dynamic and the structure of the Center encourages creation of new links based on new experimental and quantitative directions and methodologies. Over the past six years the group has nearly doubled and the enthusiasm for working at the systems level has increased dramatically. Our weekly research meetings generate lively discussions involving students and more senior researchers, which speaks to a high level of intellectual engagement and cross-disciplinary communication and interaction.

Beyond the research we have produced, we take great pride in the broad impact the DCSB has had, both locally and in the international systems biology community. Our outreach programs primarily fall into three areas: *outreach programs* that foster scientific exchange and collaboration between scientists in the local and international research communities; *education and training programs* that bring breadth and depth to systems biology education at Duke University; and *educational outreach programs* that engage students from disadvantaged and/or underrepresented backgrounds, to inspire interest in research and careers in science.

Research focus

The long-term research goal of the DCSB is to understand the dynamic properties of gene regulatory networks. Our major research successes were driven by strong collaborations between quantitative and experimental scientists and included the characterization of regulatory networks at three time scales — cell cycle, development, and evolutionary adaptation — and the development of analysis and modeling tools to address systems biology questions. With a wide range of experimental organisms, we benefit from insights gained through comparisons of different ways that nature has solved similar problems. In our efforts to analyze and model our data we bring to bear a broad range of quantitative expertise including Bayesian statistics, Boolean modeling, differential equations, algebraic topology, and image analysis.



Cell Cycle Networks: One of the major early accomplishments of the DCSB was the discovery that an oscillating transcriptional network underlies the yeast cell cycle. This insight grew out of collaborations between Haase, Hartemink, and Socolar. The results have been hailed as a seminal work in a mature field. A follow-up publication demonstrated that while cyclin-dependent kinase functions were not required for oscillations, they appear to function in positive feedback loops that support amplitude and period control. The manuscript also presented evidence that the transcriptional network is part of a time-keeping clock mechanism.

Work by You and West demonstrated that the Rb/E2F circuit acts as a bistable switch at the "restriction point" in the mammalian cell cycle. Statistical modeling innovations were used to infer network structure based on integration of experimental data into evolving dynamic stochastic network models. To integrate single-cell and population-level data, West has developed imaging methods and statistical tools for time course and interim or steady-state experimental data into discrete-time, dynamic stochastic mathematical models.

Developmental networks: In the *Arabidopsis* root, a direct connection was discovered between the developmental regulators SHR and SCR and a cell cycle factor, CyclinD6, which regulates the asymmetric division of a stem cell into the precursors of the endodermal and cortex lineages. To further characterize the patterning networks in the root, Benfey and Ohler performed RNA-seq and developed a novel Bayesian classifier to identify micro-RNAs that are specific to individual cell types. A second collaborative paper used cutting-edge proteomics techniques to identify cell-type specific proteins in the root. To monitor the dynamics of gene expression in real time at cell-type specific resolution, the RootArray, a microfluidics device and imaging platform capable of monitoring 64 seedlings, was developed.

To identify regulatory networks responsible for sex determination, the Capel and Magwene labs used a First Order Conditional Independence analysis to correlate expression values among F2 offspring from two inbred mouse strains. Consistent with genetic predictions, these data revealed the existence of both a male and female subnetwork operating antagonistically in the XY gonad during sex determination.

The gene regulatory network (GRN) of early embryogenesis in sea urchins is one of the best experimentally characterized GRNs in all of biology. With this as a starting point, McClay and Socolar have investigated how the embryo is able to rebuild itself after having cells removed from it. Evidence indicates that a process of trans-fating occurs and that it can cause a resetting of the regulatory networks. To better understand this process, a continuously updating three-dimensional model of the developing embryo has been constructed and Boolean models are being analyzed for their ability to predict cellular behaviors.

Network changes at evolutionary time scales: Sea urchins are also being used to address how regulatory networks evolve in the face of environmental stress. A genome-wide scan carried out by Wray revealed signatures of adaptation to distinct thermal environments in the wild. Exploiting natural genetic variation within populations, the Wray group followed up by

analyzing mRNA expression throughout the gene regulatory network and the resulting skeletal morphology under thermally stressed and unstressed conditions. Interestingly, gene interactions within the network contributed to buffering network function, beyond the role that chaperonins provide.

Magwene works on how genetic variation affects gene networks involved in developmental decision-making in yeast. The Magwene group identified signaling and regulatory networks that contribute to variation in pseudohyphal growth, sporulation, and biofilm formation in different yeast strains. A key network, with pleiotropic effects on all three of these phenotypes, is the cAMP-PKA signaling pathway.

Education and outreach

The DCSB's outreach programs are designed to promote collaborative exchange of knowledge and resources in the local Raleigh-Durham area of North Carolina as well as in the national and international systems biology communities, and translate systems biology approaches into commercial applications. Our scientific exchange program includes sabbatical visits, a seminar series with visiting lecturers, annual symposia, travel funding, and sharing of data and software online. To broaden our global reach, DCSB led the effort to create www.sysbionetwork.org, an international network of systems biology research entities to stimulate collaboration and outreach.

One of our primary educational goals is to inspire students in a variety of disciplines to pursue research and graduate training in systems biology. DCSB faculty members teach systems biology courses in a number of departments. Graduate training in systems biology is available primarily through the Computational Biology & Bioinformatics program, with which the DCSB faculty are highly involved.

The DCSB has formed an ongoing partnership with North Carolina Central University (NCCU), a local HBCU. Each year, DCSB scientists co-teach a course at NCCU titled "Complex Genetic Traits: Understanding Human Diseases and Plant Stress". In 2012 we developed and started teaching a new version of the Complex Genetic Traits course that incorporates team- and project-based learning approaches, with the goal of improving the students' critical thinking and communication skills. We also recruit NCCU students to participate in the DCSB/IGSP summer research fellowship program.

Since 2009, DCSB faculty Magwene and Schmid have been collaborating with teachers at the North Carolina School of Science and Mathematics (NCSSM) to offer systems biology "mini-term" courses. NCSSM is a statewide, public residential magnet high school for students with a strong aptitude and interest in math and science. In the eight-day courses, students learn current systems biology techniques, design and perform experiments in Center laboratories, learn to use computer-modeling approaches to analyze their data, and present a poster on their research. A few of the NCSSM students have continued their research projects at Duke over the summer.

Institutional transformation

The DCSB has become an intellectual nexus for systems biology research at Duke. For almost a decade the DCSB has played a critical role in fostering new and innovative research, has enabled collaborations across departments and schools, and has been a highly recruitive environment for faculty, postdocs, and graduate students for whom systems biology approaches are a critical component of their research and scholarship.

The Center has helped to nurture the careers of junior faculty members from Arts and Sciences, the Pratt School of Engineering, and the School of Medicine. All six of the junior faculty initially associated with DCSB have been promoted to Associate Professor with tenure. Center leadership was important for all of these promotions. The Center also played a key role in the recruitment of three faculty members who joined Duke after the DCSB was established as an official Center: Ryan Baugh (Biology), Nicholas Buchler (Biology and Physics) and Amy Schmid (Biology). Participation in DCSB activities and collaborations has been an important factor in the early success of each of these three.

FACT SHEET

Duke Center for Systems Biology

National Center for Systems Biology 2007-2013

PROGRAM	YEARS	IMPACT
RESEARCH		
Peer-Reviewed Publications	2007-	90 articles; 75% via collaborations within or outside of DCSB
Software Releases	2007-	15 software packages are publically available online
Spin-off Grants	2007-	Five research grants and two training grants were awarded
Commercial Applications	2007-	GrassRoots Biotechnology launched in 2009: now employs 21, awarded small business grants from NSF, NIH, and USDA
SCIENTIFIC EXCHANGE		
Seminars	2003-	Weekly 30-50 attendees; have led to numerous collaborations
Annual Symposium	2006-	Annually 150 attendees from all over the Research Triangle area
Annual Retreat	2008-	Annually 60 attendees including external advisory board
Lunch Forum	2008-	Weekly 30-40 attendees hear chalk-talks on research or presentations on career development topics
Systems Biology Network	2010-	www.sysbionetwork.org promotes exchange of ideas and resources between systems biology research organizations worldwide
DCSB Website	2007-	Annually 17,000 page views and 1500+ software downloads
EDUCATION & TRAINING AT DUKE		
Undergraduate Courses	2003-	Systems Biology courses have been offered through Biology, Biomedical Engineering, and Mathematics departments
Graduate Courses	2003-	Various courses and modules are offered through CBB, Biology, Genetics & Genomics Statistics, Math, and other programs
Computational Biology & Bioinformatics PhD Program	2001-	DCSB faculty serve leadership roles, teach 4+ courses relevant to systems biology, and have mentored 20 CBB students
Undergraduate Interns	2007-	76 undergraduate researchers have been mentored by DCSB faculty
Graduate Students	2007-	96 graduate students have been mentored by DCSB faculty
Postdoctoral Fellows	2007-	53 postdoctoral fellows mentored. Of the 27 alumni, 25 have positions in academia or industry and 2 are in other scientific careers
Faculty	2007-	Recruited three new tenure-track faculty members; six faculty were promoted to Assoc. Professor with tenure and one to Full Professor
Sabbatical Visitors	2007-	15 sabbatical researchers from 7 countries have trained at tbe DCSB
EDUCATIONAL OUTREACH		
NCCU Complex Genetics Course	2009-	Annually 15-20 students; 6-10 DCSB faculty and postdocs co-teach
Summer Research Fellowships	2009-	27 undergraduates mentored; 17 were NCCU students
NCCSM mini-term course	2009-	Uses inquiry-driven and project-based approaches to teach systems biology techniques to 20 high school students annually
Online course material	2011-	"Statistical Computing for Biologists" course workbook is available online
Woods Hole Short Course on Gene Regulatory Networks	2008-	24 students annually; DCSB faculty direct and co-teach the course

Systems Biology Center New York

Icahn School of Medicine at Mount Sinai http://www.sbcny.org

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Key Personnel (cumulative): Upi Bhalla (NCBS), Avrom Caplan (CUNY), Lakshmi Devi (ISMMS), Emilia Entcheva (Stony Brook), Jeanne Hirsch (ISMMS), Terry Krulwich (ISMMS), Avi Ma'ayan (ISMMS), David McQueen (Courant/NYU), Susana Neves (ISMMS), Charles Peskin (Courant/NYU), Suzanne Scarlata (Stony Brook), Eric Sobie (ISMMS), Gustavo Stolovitzky (IBM T.J. Watson)

Center History, Philosophy, and Environment

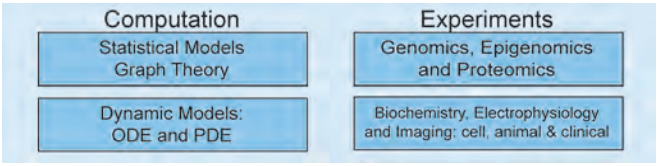
The Systems Biology Center New York originated as a collaborative effort between researchers and educators from Icahn School of Medicine at Mount Sinai, Courant Institute of Mathematical Sciences NYU, Stony Brook University (SUNY), City College of New York (CUNY), National Centre for Biological Sciences (India), and the IBM T.J. Watson Research Center. In the fall of 2013, the Center will expand to include faculty members from Colgate University and the University of Medicine and Dentistry - New Jersey.

SBCNY investigators study how molecular interactions are propagated across scales of organization from cells to tissues and organs giving rise to emergent physiology and pathophysiology. The dynamic organization of network motifs (regulatory loops) within multi-scale networks provides the basis for propagation of effects across scales from molecules to cells to tissues. Such propagation underlies physiology, pathophysiology and drug action. We focus on mechanisms of complex progressive diseases to enable the discovery of new drug targets and to understand and predict adverse events at the scale of the whole genome. These shared interests drive our contributions to the development of the new discipline of **Systems Pharmacology**.

Our education and research activities are seamlessly integrated for development of new approaches to undergraduate and graduate education in quantitative reasoning in systems biology focused on biomedicine and drug action. We are committed to making educational opportunities freely and universally available. We have published our systems biology modeling course through *Science Signaling* education forum and are offering three MOOCs (massively open online courses) through Coursera. To enhance diversity in the pipeline for producing quantitative biologists we run a summer undergraduate research program for students from the colleges of the CUNY system. Together these research and education efforts position us to make substantive contributions in developing new knowledge and a new and diverse workforce in systems biomedicine and pharmacology.

Research Focus

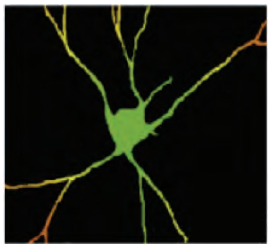
Our research integrates genomic/epigenomic and proteomic characteristics into mechanistic networks and dynamical models to predict and understand drug action in individuals. We utilize a multidimensional approach that implements a matrix integration within and between disciplines shown in the box. Within the computational



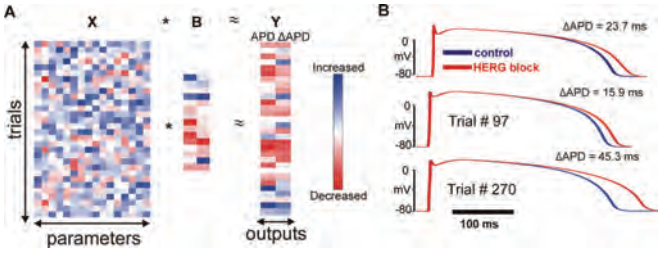
disciplines, we are developing methods to explicitly merge graph theory and dynamical models. Within the experimental disciplines, we are merging genomic/epigenomic and proteomic analyses with cell and organ-level electrophysiology, live cell imaging and cell signaling biochemistry experiments. Diagonal integration occurs in enhanced pharmacodynamic modeling (ePD) in which genomic/epigenomic and proteomic information is

incorporated into dynamical models of drug action and the biochemistry, physiology and imaging experiments enable the development of directed-sign-specified graphs for identification of regulatory motifs such as feedback and feedforward loops. Such a matrix integration approach needs a **team-science** format where researchers from different disciplines meld their expertise to produce new ways of thinking.

Collaborative research by the Center investigators has provided significant leaps in understanding. An important area of progress is how spatial organization in cells and tissues control emergent functions. Using new computational approaches, Peskin and co-workers, in a study in *Proceedings of the National Academy of Sciences* have found that spatial organization of chromatin may have been optimized for rapid access of transcription factors to their targets within genes. If structural organization is optimized for function, a key question is how such organizational information is transmitted. In a study published in *Cell,* Neves and colleagues showed that



a systems level mechanism that integrates cellular geometry, regulatory loops containing negative regulators in signaling pathways, and reaction rates together control information flow of spatial organization. This study led to a Transformative R01 obtained by Center investigators Iyengar and Neves with He (Mount Sinai) along with Loew (UConn) and Hone (Columbia). The integration of experimental and computational approaches continually enables new discoveries. In a study published in *Nature Medicine*, He and Ma'ayan identified HIPK2, a protein kinase that can serve as a new drug target to treat kidney fibrosis. Iyengar and Ma'ayan in a *Science Signaling* study show how graph theory models that combine clinical data from the FDA-Adverse Event Reporting System with cell regulatory networks enable predictions of drug-induced arrhythmias. Sobie and colleagues have published papers in *PLoS Computational Biology* and *Heart Rhythm* that combine large libraries of dynamical models and regression



analysis to determine the interplay between the different channels underlying the cardiac action potentials. From these analyses Sobie and colleagues are developing approaches to predict pro and anti-arrhythmic drug sensitivity in individuals.

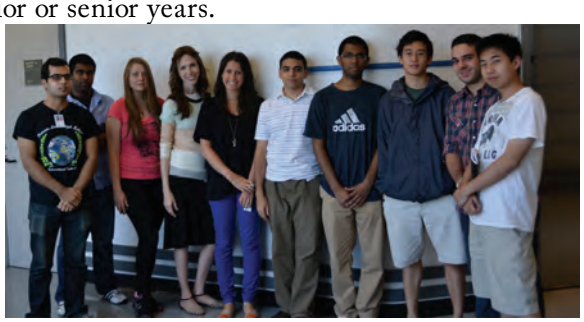
The Computational Core headed by Avi Ma'ayan has developed software tools such as **Lists2Networks**, **GATE** and **Expression2Kinases** that enable the construction and visualization of networks from high-throughput data and are widely used by Center investigators and others. These findings and tools set the stage for us to ask some difficult but feasible questions: Can we develop a blueprint for the application of systems approaches to yield mechanistic clarity to drug action that can be applied to several diseases? Will an integrated computational strategy enable us to incorporate genomic, epigenomic, translational and post-translational variations into network and dynamical models of molecules-to-physiology and thus predict a) new drug targets, b) drug efficacy and resistance, and c) the propensity for drug-induced adverse events in individuals? Will these approaches enable the integration of systems pharmacology and therapeutics and precision medicine into the practice of personalized medicine?

Education and Outreach

Education and outreach efforts of SBCNY have focused on the introduction of systems biology concepts and applications in diverse biomedical settings. The Center has supported the development of new graduate level courses: **Systems Biomedicine** focused on integration across biomedical disciplines and **Systems Biology-Biomedical Modeling** which we have published in *Science Signaling* and is freely available. The underlying philosophy of both courses is that quantitative reasoning serves as the glue to integrate across disciplines (e.g. biochemistry, cell and molecular biology, pharmacology and physiology) as well as across scales of biological organization. In the modeling course, we teach in an integrated manner statistical and network-based methods for analyzing large-scale data sets and dynamical modeling such as ODE and PDE models. Systems Biomedicine is a core course for PhD, MD/PhD and Master's students which uses a combination of experimental and computational approaches, including methodologies for handling large data sets and for generating different kinds of systems models. Avi Ma'ayan and his colleagues have run workshops at several universities in the US and in Brazil to introduce Center developed software tools for

network building and analysis. Ravi Iyengar, Avi Ma'ayan and Eric Sobie are offering three free systems biology massive open online courses (MOOCs) on Coursera. The courses, Introduction to Systems Biology (Iyengar), Network Analysis in Systems Biology (Ma'ayan), and Dynamical Modeling Methods in Systems Biology (Sobie) focus on training students to use computation to convert the information in large and small data sets in biomedicine into conceptual knowledge. The "Introduction to Systems Biology" course which runs from June 3 to July 15 2013 has over 26,000 enrolled students of whom over 14,000 are active students.

Undergraduate Training Program in Systems Biology: 50 undergraduates have been part of SBCNY research activities. 40 have participated in the summer research program and 10 have conducted yearlong research as scientific programmers, software specialists, database developers and experimental researchers. The SBCNY Summer Undergraduate Research Program offers training in quantitative reasoning and analysis for students entering their junior or senior years.

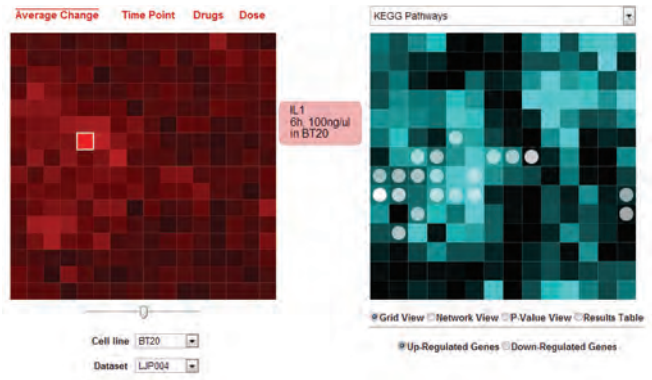


Most participants have been from the colleges of CUNY but we have also had students from Boston College, Carnegie Mellon, Colgate, Columbia, Fairleigh Dickinson, Rutgers, and Rochester. We have special interest in students who have plans to pursue PhD or MD/PhD degrees. We try to attract students who major in computer science, engineering, and mathematics and are interested in learning experimental systems biology as well as students who major in biological sciences and are interested in learning computational biology. We have a continued emphasis on attracting women and underrepresented minorities into computational biology. Half of our summer students have been women, several come from underrepresented minority ethnicities and almost all come from modest economic backgrounds and are the first in their families with a desire to pursue postgraduate education and research in emerging areas of biomedical sciences.

Institutional Transformation

The Educational Core of the Center has catalyzed the development of a rejuvenated graduate training program in Quantitative Systems Pharmacology and Biomedicine at Mount Sinai to prepare students to become experts in systems-level models of disease that identify therapeutic targets and predict adverse effects therapeutics. Multiple computational approaches are taught throughout the curriculum to integrate basic cell and molecular sciences with the physiology and pathophysiology of disease states.

The Computational Core headed by Avi Ma'ayan has made significant contributions to projects headed by non-SBCNY investigators. These studies have been published in excellent journals and clearly have had a strong impact on systems biology based studies in stem cell biology and complex diseases. Using the **Genes2Networks** software developed by the Computational Core, the Ma'ayan laboratory in collaboration with Gelb and colleagues identified a new disease gene, *SHOC2* which is causally associated with Noonan syndrome. This study was published in *Nature Genetics*. Lemischka, Ma'ayan and colleagues, in a paper in *Nature* used SBCNY's **GATE** software, to analyze time-series expression data from differentiating mouse embryonic stem cells to discover how single gene perturbations lead to progression of events from transcription to chromatin reconfiguration during stem cell differentiation. In a paper published in *Nature*, investigators from the Broad Institute at MIT, the Buxbaum laboratory at Mount Sinai and the SBCNY Computational Core, analyzed whole exome sequencing to identify connections between *de novo* mutations by using **Genes2Networks**.



Ma'ayan and his colleagues are currently collaborating with the LINCS Center at Harvard Medical School headed by Mitchison and Sorger to develop data analysis and visualization methods that integrate whole genome transcript measurements with kinase activity data using **Expression2Kinases** for mapping drug action to various cellular pathways.

FACT SHEET

Systems Biology Center New York

National Center for Systems Biology since 2007

Research Impact:
SBCNY has made significant contributions to multiple areas of Systems Biology including developing the new field of Quantitative and Systems Pharmacology. Key areas of research success and papers include:

- *Spatial organization and information flow*: Cell and Proceedings of the National Academy of Sciences.
- *Networks from high-throughput data to understand disease mechanisms*: Nature, Nature Genetics, Nature Immunology, and Nature Cell Biology.
- *Dynamical models for predicting disease in individuals*: PLoS Computational Biology, Heart Rhythm and Journal of Physiology.
- *Systems Pharma*cology: Nature Medicine, Science Translational Medicine, Science Signaling, Clinical Pharmacology and Therapeutics and Annual Review of Pharmacology.

Community Resources/Software/Collaborations:
SBCNY's Computational Core developed tools include: Genes2Networks, KEA, ChEA, Expression2Kinases, Lists2Networks, Enrichr, Sets2Networks, Genes2FANs, ESCAPE, DrugPairSeeker, and Network2Canvas.

All software tools are freely available and widely used. Overall these resources have been accessed by 1000-3000 unique visitors per month. Workshops have been conducted to train potential users on how to use these tools.

Training and Outreach:
SBCNY is strongly committed to efforts that foster increasing diversity in systems and computational biology.

- **Undergraduates (50)** SBCNY has trained 50 undergraduates in two tracks. 23 of the undergraduate trainees, who have graduated, are now in top graduate or medical school programs. *Summer Undergraduates:* This program has enabled us in enhancing diversity with 28% of our summer trainees being underrepresented minorities. Among the 40 undergraduates who participated in this research intensive computational systems biology training program, we had 20 women. Our trainees are largely from The City University of New York and most often the first members of their families with plans to pursue graduate education. *Research Support Personnel Undergraduates:* SBCNY has trained 10 undergraduates who conducted research in Center laboratories for 1 or 2 yrs. From these 9, trainees entered PhD (5), MD (2), DDS (1), or Master's (1) programs at schools that include MIT, Princeton, Cornell, Columbia and Icahn School of Medicine at Mount Sinai.
- **Graduate Students (9)** The Center has partially supported 9 graduate students, 2 are still in training, 3 have gone on to postdoctoral positions, 2 entered research residencies, and 2 have joined biotech companies.
- **Postdoctoral Fellows (15)** The Center has partially supported or indirectly (no salary but resource access) supported a diverse group of 15 postdoctoral fellows: 5 are still in training, 6 have tenure track faculty positions and 4 entered senior positions at leading biotech/pharmaceutical companies.

Center for Complex Biological Systems

University of California, Irvine http://ccbs.uci.edu

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Center History, Philosophy, and Environment:

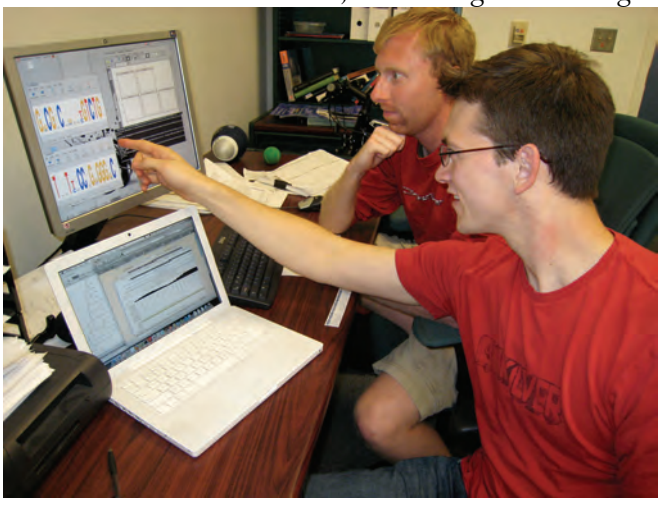
The Center for Complex Biological Systems (CCBS) was organized in 2001, in response to growing interest in collaboration among biologists, mathematicians, engineers, physicists and computer scientists at the University of California, Irvine. UCI is a young institution (founded 1967) that has expanded considerably over the past few decades (there are currently 22,000 undergraduates, 6,000 graduate and professional students, and 2,800 faculty). The campus has a very open feel—not just because of the mild Southern California weather, but because the faculty and administration have long worked to keep barriers to interdepartmental and interdisciplinary research very low.

Initial funding for CCBS came through a planning grant (P20) that was part of the initial National Centers for Systems Biology program. The theme of the grant, "Transport and Complexity," related to a group of emerging interdisciplinary collaborations focusing on how transport—diffusion of molecules, motor-based transport of cargoes, and transport of light—interacts with dynamical networks of cellular morphology, signaling and response.

An early goal of CCBS investigators was to solve some of the problems of interdisciplinary graduate training, and with the help of a three-year grant from the Howard Hughes Medical Institute, a new training program in Mathematical, Computational and Systems Biology was developed. A coming-out-party, of sorts, occurred in 2007, when CCBS joined with Caltech to sponsor the International Conference on Systems Biology in Long Beach, California. The year 2007 also marked formal entry of the center into the National Centers for Systems Biology program, through the award of a P50 grant entitled, "Systems Biology of Morphogenesis and Spatial Information Flow." This award extended the center's original focus on transport phenomenon to the more inclusive topic of "spatial dynamics", i.e. biological dynamics in space and time.

Since then, the center has grown well beyond the confines of its original group of investigators to a community of over 100 UCI faculty—representing the schools of biological sciences, medicine, engineering, physical sciences, and information and computer science. The influx of new members has broadened the center's focus to include all areas of systems biology, but those investigators directly supported by the P50 grant maintain a research focus on spatial dynamics.

The result of this arrangement is that, for the purpose of initiatives in education, outreach, and institutional transformation, the P50 grant leverages



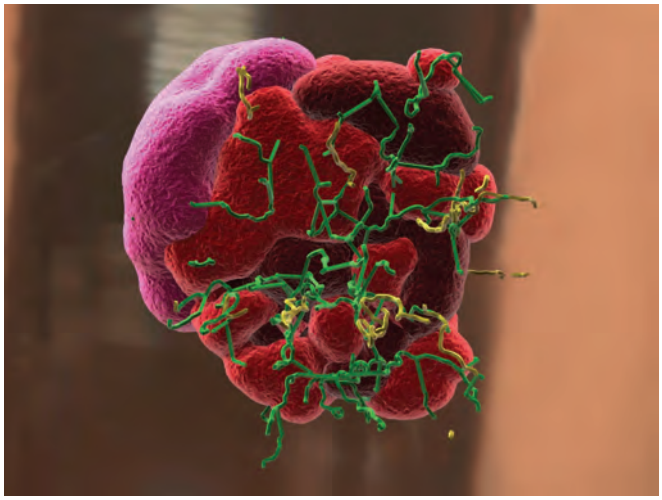
the activities of a larger group of individuals than those receiving direct research support. This has allowed the center to serve as an incubator for a variety of projects and initiatives, many of which have garnered external support. The philosophy of bringing people together across interdisciplinary lines to "spin off" new ideas permeates all of the center's activities. For example, all of the research activities specifically funded through the P50 itself involve groups of investigators from multiple disciplines.

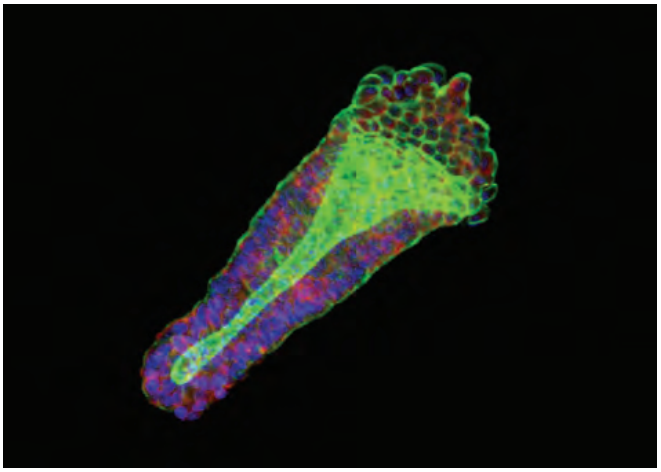
Research focus

A central tenet of Systems Biology is that biological processes cannot be understood apart from their dynamics. Most biology is dynamic not just in time, but also in space–i.e., where things occur within cells, tissues or organisms is just as important as when they occur, and just as changeable over time.

The behaviors of spatiotemporally dynamic systems are more difficult to analyze than those of merely time-varying dynamic systems, which is why many Systems Biologists have favored systems that can (at least initially) be treated as space-invariant (i.e. "well-stirred", as though the locations of things are not important). Yet many important phenomena are so fundamentally spatial in nature, that ignoring space is simply impossible. These include phenomena like morphogenesis, pattern formation, chemotaxis, cell migration, cell polarity, tumor growth and metastasis, and many aspects of ecology.

Even phenomena that are traditionally treated as well-stirred, such as gene expression, have spatial aspects yet to be understood (e.g. influences of nuclear organization). CCBS is committed to the application of Systems Biology approaches to all such systems. This viewpoint underlies three distinctive features of CCBS research.





First, the need for mathematical modeling tools that apply to the spatial domain creates opportunities for mathematicians to conduct research at the cutting edge of their own field. This includes development of rapid numerical algorithms for systems of partial differential equations; new methods for multidimensional stochastic simulation; improvement of discrete and hybrid modeling; and the development of improved methods for efficient exploration and representation of large parameter spaces. Such challenges have attracted mathematicians to become deeply involved in the center, and have made CCBS one of the most mathematics-oriented of the National Centers for Systems Biology.

Second, many of the most exciting problems in spatial dynamics lie in the field of Developmental Biology, where questions such as how patterns form robustly, how tissues self-organize, and how growth is controlled, are among the great unsolved mysteries. CCBS leverages UC Irvine's longstanding strength in experimental Developmental Biology to address such questions in organisms as diverse as flies, frogs, zebrafish, nematodes, mice and man.

Third, gathering time-series spatial data from living systems is a challenge intimately tied up with live-cell and tissue imaging, a field currently being propelled by rapid technological advances. A key link in CCBS's approach to data gathering is the UC Irvine Laboratory for Fluorescence Dynamics (LFD), which continually develops new approaches for extracting spatiotemporal data from the mathematical and statistical analysis of fluctuations in fluorescence images. Through such methods, processes such as diffusion, transport barriers, binding, reaction, and catalysis are now routinely measured in real time at multiple locations within cells and tissues.

These three areas—mathematics, development and morphogenesis, and fluorescence dynamic interrogation of living systems—are integrated into nearly every project that the center's P50 grant supports. Such work has led to novel insights into the strategies underlying robust pattern formation; the roles of scaffolds and compartments in signaling specificity, the underlying logic of controlled cell proliferation, the role of feedback in morphogenesis, and the tradeoffs inherent in filtering noise. CCBS research has also led to methodological advances in numerical simulation, multi-scale modeling, high-resolution microscopy, and real-time imaging of single molecule behaviors.

Education and outreach

Since starting the Mathematical, Computational and Systems Biology graduate program in 2007, CCBS has expanded its contributions to Systems Biology education greatly. For high school students, the center runs two modules of the California State Summer School for Mathematics and Science (COSMOS). At the college level, the center participates in an NSF-funded "Mathematical and Computational Biology for Undergraduates" program, which makes available special coursework and summer research for selected Mathematics and Biology majors. CCBS also helps expose local under-represented community college students to research through a two-week Undergraduate Student Initiative for Biomedical Research.

Since 2010, the center has annually run a three-week "Short Course" in Systems Biology. Course participants—who include students, postdocs, faculty and industry scientists from around the world—take part in intensive lectures and laboratory projects related to the theme of "Morphogenesis and Spatial Dynamics". The center also organizes periodic workshops and symposia, and together with the San Diego Center for Systems Biology, sponsors the annual Southern California Systems Biology Conference, in which participants from over a dozen universities and colleges participate.

Institutional transformation.

The intense degree of interdisciplinarity that the Systems Biology "revolution" is demanding of biological and biomedical research strains the academic structures under which research, teaching, and career advancement usually take place. Membership among the National Centers for Systems Biology has helped CCBS take a leadership role in confronting some of these issues locally.

The center uses a variety of strategies to educate faculty and researchers across disciplinary and departmental lines, and promote the development of interdisciplinary research projects. One such strategy employs "interest groups", which meet periodically and act as mini-think tanks to share expertise and develop new research ideas. Another strategy is a competitive seed grant program that challenges pairs or groups of students or postdocs to develop new, short-term, multi-investigator interdisciplinary research projects. Both strategies have been a good source of new long-term collaborations, publications, and funded research projects.

In addition, through its emphasis on interdisciplinary teaching, workshops and retreats, the center creates opportunities for faculty to co-teach and co-advise, which further foster interdisciplinarity. As a result of its success in these endeavors, CCBS was selected to manage the hiring of seven new faculty in Systems Biology, a task that was completed in 2013, with new hires in Mathematics, Developmental and Cell Biology, Biomedical Engineering, Ecology and Evolutionary Biology, and Physics.

FACT SHEET

Center for Complex Biological Systems

National Center for Systems Biology since 2007 (planning phase 2002-2007)

CCBS activities are supported by P50 and R25 grants from the NIGMS, as well as grants from other NIH institutes, the NSF, and the Howard Hughes Medical Institute. Initial center planning activities were supported by a NIGMS P20 grant for complex biological systems research.

Research: Work in the center has led, among other things, to major advances in understanding:

- How molecular gradients set up patterns in organs and tissues (*Zhou et al., 2012. Free extracellular diffusion creates the Dpp morphogen gradient of the Drosophila wing disc. Curr. Biol., 22, 668-675*).
- How feedback circuits tightly control cell proliferation to allow organs to grow to and maintain proper sizes (*Lander, et al,. 2009. Cell Lineages and the logic of proliferative control. PLoS Biol. 7: e1000015*).
- How scaffolds and compartments contribute to signaling specificity within cells (*Chan et al., 2012. Protein scaffolds can enhance the bistability of multisite phosphorylation systems. PLoS Comp. Biology 8: e1002551*).
- The positive role of gene expression noise in making tissue boundaries more precise (*Zhang, et al., 2012. Noise Drives Sharpening of Gene Expression Boundaries in Zebrafish Hindbrain. Molecular Sys. Biol., 8:613*).
- The mathematics behind the strategies that biological systems use to filter noise (*Wang et al., 2010. A Critical Quantity for Noise Attenuation in Feedback Systems. PLoS Comp. Biol., 6(4): e1000764*).

Resources/software/collaborations:

- The UC Irvine Laboratory for Fluorescence Dynamics (http://www.lfd.uci.edu) develops new approaches for extracting spatiotemporal data from the analysis of fluctuations in fluorescence microscopic images.
- New mathematical tools for modeling spatial dynamics, simulating stochastic processes, and analyzing networks are made freely available to the research community.

Training and outreach:

- The Mathematical, Computational and Systems Biology (MCSB) program provides interdisciplinary training for systems biology. Students (10-15/year) are recruited from diverse STEM backgrounds via a "gateway" program, and complete Ph.D. degrees in any of a large number of departments. Several mechanisms are used to encourage training for success in collaborative and team-science environments.
- An annual three-week short course in Systems Biology, exploring themes of "morphogenesis and spatial dynamics", serves graduate students, postdocs and faculty/industry researchers from around the world with little or no prior training in systems biology. The course consists of lectures, wet bench experimentation and hands-on modeling.
- Training for gifted high school students is provided through Center-run Systems Biology modules of the California Summer School for Mathematics and Science.
- Undergraduate training is provided within UCI, through the a Mathematics and Computational Biology program, and externally through a local community college initiative.
- The center hosts and co-sponsors the annual Southern California Regional Systems Biology meeting, involving over a dozen institutions from San Diego to Santa Barbara.
- The center manages pre-doctoral training grants in Mathematical, Computational and Systems Biology and Systems Biology of Development.

Institutional transformation: CCBS promotes interdisciplinary research through:

- "Interest groups" that promote development and sharing of new research ideas.
- Seed grant programs that challenge pairs or groups of students or postdocs to develop new, short term, multi-investigator interdisciplinary research projects.
- Opportunities for faculty to co-teach and co-advise through interdisciplinary courses, workshops and retreats. Over 100 faculty form 11 departments are affiliated with CCBS-sponsored activities.
- Leadership of interdisciplinary faculty recruitment initiatives.
- Administration of interdisciplinary grants.

Chicago Center for Systems Biology

The University of Chicago
and Northwestern University

http://www.chicago-center-for-systems-biology.org/

Program Director:
Kevin White (kpwhite@uchicago.edu)

Program Administrator:
Fabiola Rivas (frivas@bsd.uchicago.edu)

Key Personnel (cumulative): Barry Aprison, Aaron Dinner, Chuan He, John Reinitz, Marty Kreitman, Richard Morimoto, Ilya Ruvinksy, Luis Amaral, Ilaria Rebay, Richard Carthew, Harinder Singh, John Crispino, Lonnie Shea, Richard Jones, Michael Rust, Ravi Allada, Robert Grossman, Andrey Rzhetsky, Philip Cluzel, Rustam Ismagilov; Center Fellows: Aly Khan, Patricija van Oosten-Hawle

Center History, Philosophy, and Environment:

We believe that collaborative interactions between computational and experimental scientists are essential to building a better understanding of fundamental biological principles. We provide an environment for inter-disciplinary training for exceptional young researchers, with the dual goals of advancing the state of the field in quantitative modeling of complex biological systems and preparing a new generation of scientists for success in the fast-evolving field of Systems Biology.

Since its inception in 2008, the Chicago Center for Systems Biology has contributed to a new direction in the culture of biological science at the University of Chicago and Northwestern University, from individual labs working on selected molecules to interdisciplinary teams working on predictive models of complex systems. To foster new, interdisciplinary collaborations, the Center chose to organize its research program within a framework of multiple core research projects centered around a common theme – the study of robustness, a general property of biological systems that enables phenotypic resistance to environmental and genetic perturbation. Through this framework the Center directly involves more than 20 principal investigators from the University of Chicago and Northwestern, transforming research in these labs by introducing quantitative modeling approaches to biological problems that were previously only studied qualitatively. Scientific exchange by Center faculty, students and postdocs is further fostered by monthly research presentations and a yearly retreat, which are open to the broader scientific community. A seminar series organized in collaboration with the University of Chicago's Institute for Genomics and Systems Biology brings leaders in Systems Biology to Chicago.

Our Center has also been successful in implementing a multi-level education and outreach strategy that spans high school to post-graduate training. We have partnered with other educational institutions in Chicago and added a focus on quantitative and systems approaches to their programs. We have also led the way in implementing a new graduate program in Systems Biology at the University of Chicago. In this way we have built a vibrant and growing Systems Biology scientific community.

Research focus

Understanding biological robustness – phenotypic resistance to environmental and genetic perturbations –is central to understanding physiology, development, evolution, and disease. We founded the CCSB with the goal of advancing the mechanistic and molecular understanding of how robustness arises and evolves.

The projects at the core of the Center's research program examine robustness in different model systems and at different scales and levels of complexity with the overall aim of uncovering shared organizational principles that give rise to robustness in regulatory networks. Center projects examine robustness at unicellular, multicellular, organismal and population levels, and in physiological, developmental and evolutionary time scales. Each project incorporates a mathematical modeling

component that directs experiments by generating testable predictions; at the same time, experimental data shapes and refines the models. This integrated approach has led to key insights into the architecture of regulatory networks, and it has allowed the definition of motifs and molecules in the networks under study that enable robustness to perturbation.

We initially chose to focus our efforts on examining the structure and dynamics of transcriptional regulatory networks, and on the molecular mechanisms underlying robustness of gene expression. Research in the Center is now extending its scope to incorporate the signaling processes that feed into transcriptional inputs. With now established experimental systems and new tools in hand, we are ideally positioned to expand our research into this next level of complexity.

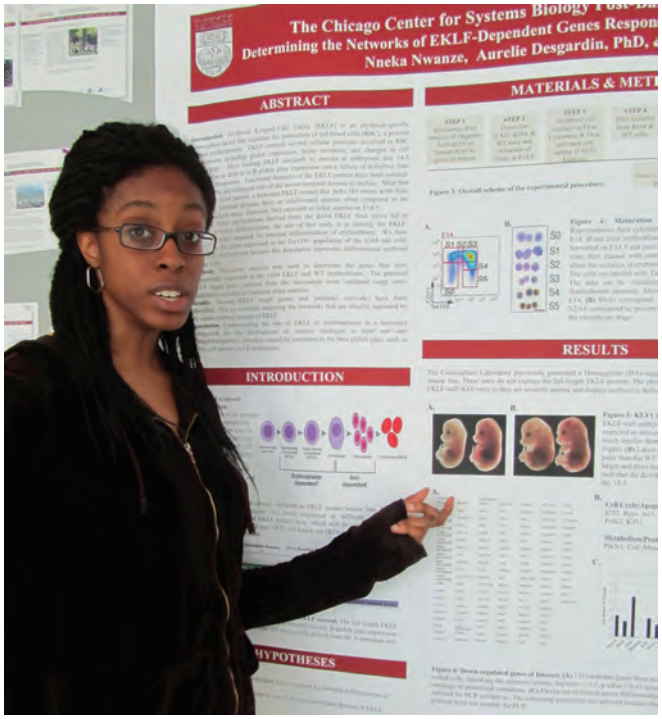
Education and outreach

The Center has taken a leadership role in designing and implementing education and outreach programs with the overall goal of promoting and anchoring research and education in Systems Biology in Chicago, and of providing resources and approaches for use beyond our Center.

The Center has developed innovative outreach programs that enrich the K-12 educational experience and bring Systems Biology concepts to high school scientific education. We initiated a partnership with The Field Museum of Chicago, with the goal of producing professional development programs for inner city teachers and new curricula and learning modules in both general Biology and Systems Biology. The learning modules produced through this collaboration include lesson plans, educational videos and materials that facilitate an interactive educational experience for high school students. These learning modules will be disseminated to teachers nationwide in the next phase of our Center.

The Center also offers 5-week summer research opportunities for Chicago Public Schools students grades 10-12 through the *Collegiate's Scholars Program* (CSP). Our investigators have worked the *Research in Biological Sciences* (RiBS) program at the University of Chicago over the last four years to produce systems biology learning modules based on projects in the Center. We have also partnered with the *Urban Teacher Education Program* (UTEP) to produce professional development workshops focused on systems biology. In the last four years our programs have directly impacted hundreds of high school teachers and students in the Chicago area.

The Center's education and outreach programs also extend to the undergraduate level in the form of a 10-week summer *Research Experience for Undergraduates* program and a year-long post-baccalaureate program aimed at preparing underrepresented minority students for graduate programs in the biomedical sciences. Over the last four years, 24 undergraduate students have participated in the Center's REU program. Of the students who have graduated college, 16 are now pursuing graduate degrees in STEM fields.



Post-baccalaureate student Nneka Nwanze presented her work at the Annual Medical Education Conference in Louisville, KY, March 27-31st.

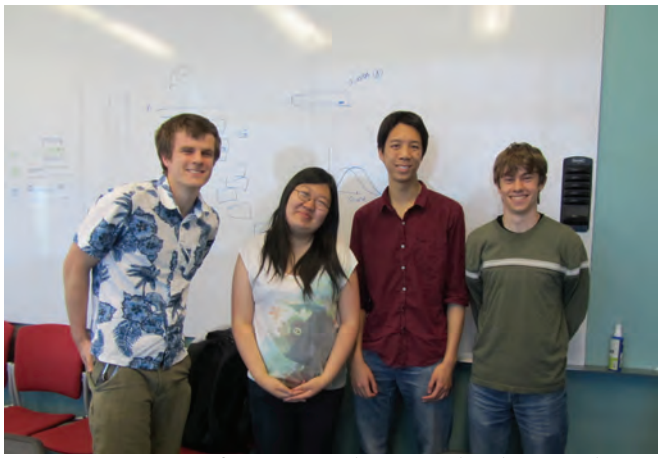
Institutional transformation

The Center has been transformative to the Chicago scientific community by making systems biology a focus of educational and research programs and by anchoring a vibrant, collaborative and interdisciplinary community.

Center investigators at the University of Chicago led the transformation of the 30-year old graduate program in Genetics into a new graduate program in *Genetics, Genomics and Systems Biology* (GGSB). This expansion involved the development of new

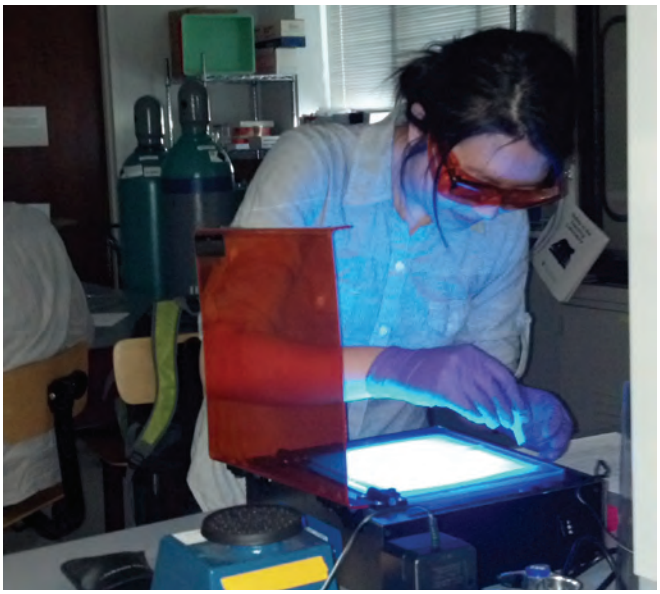
curriculum and the production of five graduate level courses on Systems Biology. To date, the GGSB program has matriculated 26 graduate students. In addition, Center investigators at the University of Chicago worked with the Medical Scientists Training Program to develop a special class focused on Systems Biology approaches to biomedical research for 1st and 2nd year MD/PhD students. In parallel, Center investigators have produced an undergraduate Systems Biology sequence consisting of four courses. The latest course in this sequence, *Systems Biology: Molecular Regulatory Logic of Networks*, is taught jointly by University of Chicago and Northwestern faculty who are investigators in the Chicago Center for Systems Biology, and presents a new model of cross-institutional collaboration. Furthermore, at Northwestern, Center investigators Richard Carthew and Lonnie Shea direct two recently organized graduate programs – *Developmental, Systems & Cell Biology* and *Systems & Synthetic Biology*, respectively.

The Center has also made a significant impact in interdisciplinary research training by fostering a co-mentoring approach that incorporates training in computational and experimental biology. Overall, twenty different Center faculty have, in different combinations, co-mentored more than 40 students and postdocs supported directly by the Center. Not included in this number are the even larger number of trainees who are not directly supported by the



Students of the class Systems Biology: Molecular Regulatory Logic of Networks.

Center but have been impacted by the change in training philosophy in the labs of Center investigators and their collaborators. The creation of new training programs that integrate systems biology and the implementation of successful co-teaching and co-mentoring approaches based on the collaborative research initiatives catalyzed by the Center have together had a transformative effect in the scientific training culture in Chicago.



Synthetic enhancers built by students in the Synthetic Biology and Regulation of Genes *class will be used by John Reinitz's group to test predictions made by their mathematical models of enhancer function.*

The Center has also taken a multi-level strategy for recruiting exceptional young researchers into the field of Systems Biology to the Chicago scientific community. Three new investigators joined the Center through our Pilot Grant program – Michael Rust, Richard Jones and Ravi Allada. These Pilot projects catalyzed new collaborations among these investigators and senior investigators in the center, and have matured to core projects in the Center.

In 2011 the CCSB launched a competitive Center Fellows program with additional support from the Searle Funds and the Chicago Biomedical Consortium. This program provides two years of funding for two independent postdoctoral level researchers working on projects related to robustness of biological systems. The two 2011 Fellows, Drs. Aly Azeem Khan and Patricija van Oosten-Hawle, are currently applying for competitive bridge grants as they prepare to pursue junior faculty positions.

FACT SHEET

Chicago Center for Systems Biology

National Center for Systems Biology since 2008

Research impact. Research at the Center focuses on the properties of complex networks that lead to biological robustness—the property of biological systems that enables phenotypic resistance to environmental or genetic perturbation. The research program is organized into five inter-related core projects that examine and compare both the structure and dynamics of a series of different regulatory networks in distinct model organisms. These networks were selected to represent different scales of biological organization and complexity, with the overall goal of providing, in combination, fundamental insights into the emergence of robustness in biological systems.

Center investigators defined mechanisms underlying molecular and phenotypic robustness including showing that the architecture of enhancers provides a strategy for robust gene expression, and that miRNAs function within regulatory networks to buffer developmental programs against variation. *Barriere A…Ruvinksky I, Distinct functional constraints partition sequence conservation in a cis-regulatory element. PLoS Genetics, 2011. Ludwig MZ …White KP, Kreitman M. Consequences of eukaryotic enhancer architecture for gene expression dynamics, development and fitness. PLoS Genetics, 2011. Li X…Carthew RW. A microRNA imparts robustness against environmental fluctuation during development. Cell, 2009.*

Center research combines experimental and computational approaches to delineate the architecture of signaling and transcriptional networks, and to define motifs that enable robustness in cell fate choices. *A recurrent network involving the transcription factors PU.1 and Gfi1 orchesrates innate and adaptive immune cell fates. Spooner CJ…Singh H. Immunity 2009. Modeling bi-stable cell fate choices in the Drosophila eye: qualitative and quantitative perspectives. Graham TG…Dinner AR, Rebay I, Development 2010. An incoherent regulatory network architecture that orchestrates B cell diversification in response to antigen signaling. Sciammas R …Dinner AR, Singh H. Molecular Systems Biology, 2011.*

Systems biology approaches developed by Center investigators have identified potential targets for cancer treatment. *Analysis of Drosophila segmentation network identifies a JNK pathway factor overexpressed in kidney cancer. Liu J…Rzhetsky A, White KP. Science 2009; Identification of regulators of polyploidization presents therapeutic targets for treatment of AMKL. Cell 2012; A comprehensive nuclear receptor network for breast cancer cells. Kittler R…White KP. Cell Reports 2013.*

The Center has also stimulated development of new technologies and core research infrastructure. *Systems analysis of EGF receptor signaling dynamics with microwestern arrays. Ciaccio MF …Jones RB. Nature Methods, 2010.*

A full list of Center publications can be found at: http://www.chicago-center-for-systems-biology.org/publications/

Training and outreach. The Center has successfully implemented a mutli-level strategy to build a systems biology community in Chicago. In collaboration with the Field Museum, the Center established professional development programs for inner city teachers and created innovative educational resources in systems biology that will be disseminated nationwide. The Center partnered with existing high school outreach programs, incorporating quantitative approaches and systems biology thinking into these training experiences. In this first cycle, 148 teachers and 579 students have participated in Center-associated programs. Center investigators have taken a leadership role in establishing an undergraduate sequence and a new graduate program in Genetics, Genomics and Systems Biology at the University of Chicago. The Center directly supported 24 students in its summer Research Experience for Undergraduates program over the last 4 years, and will welcome 7 new students into this summer's program. Of the REU students who have graduated college, 16 are currently pursuing graduate degrees in STEM disciplines.

The Center's collaborative research projects have extended into an interdisciplinary training framework based on co-mentoring by computational and experimental investigators. The Center has supported the training of 40 graduate students and postdocs as part of this framework. Career development programs encourage entry of young investigators into the field of systems biology. Three pilot projects have matured into core projects, bringing 3 new investigators fully into the Center. The two postdoctoral scientists selected into the Center's competitive Fellows program are currently applying for faculty positions and independent funding through the NIH Director's Early Independence Award.

NM Center for Spatiotemporal Modeling

University of New Mexico http://stmc.health.unm.edu/

Program Director:
Bridget S. Wilson, PhD (bwilson@salud.unm.edu)

Program Administrator:
Ryan Tanner

Key Personnel (cumulative): Diane Lidke, William Hlavacek, Keith Lidke, Jeremy Edwards, Anup Singh, Andrew Bradbury, Elaine Bearer, Janet Oliver, Stan Steinberg, Aaron Neumann, Jennifer Gillette, Judy Cannon

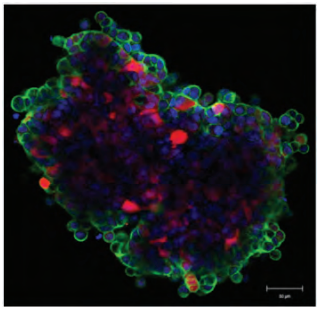
Affiliate Members: Lydia Tapia, Angela Wandinger-Ness, Vittorio Cristini, Tione Buranda, Alex Chigaev, Conrad James, Scott Ness, James Thomas, Melanie Moses Jerilyn Timlin, Jim Werner, Byron Goldstein, Chang-Shung Tung, Shivagaram Ghaanakaam

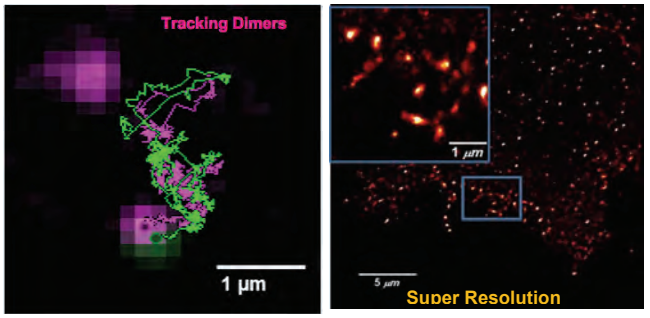
Center History, Philosophy, and Environment:

The New Mexico Center for the Spatiotemporal Modeling of Cell Signaling (STMC) is an interdisciplinary, inter-institutional program with two principal scientific goals: 1) to understand cell membrane spatial organization and dynamics; 2) to determine how the spatial proximity, dynamics, interactions and biochemical modifications of membrane receptors and signaling proteins together determine the outcome of complex, interacting cell signaling networks important in immune system diseases and cancer. Our research emphasizes the development of new single cell and single molecule technologies to generate improved quantitative data for modeling and the creation of new computational and mathematical tools for image analysis, hypothesis generation and prediction. We support training and outreach programs intended to recruit and equip a new generation of interdisciplinary researchers for successful careers focused on quantitative, systems level analyses of complex biomedical processes. Our infrastructure is designed to sustain systems biology research and training as a long-term area of scientific emphasis in New Mexico. In addition to UNM, we partner with the two major national labs, Los Alamos National Laboratory (LANL) and Sandia National Laboratories (SNL). A critical goal is to foster advancement of women and minorities within the discipline of systems biology.

Research focus

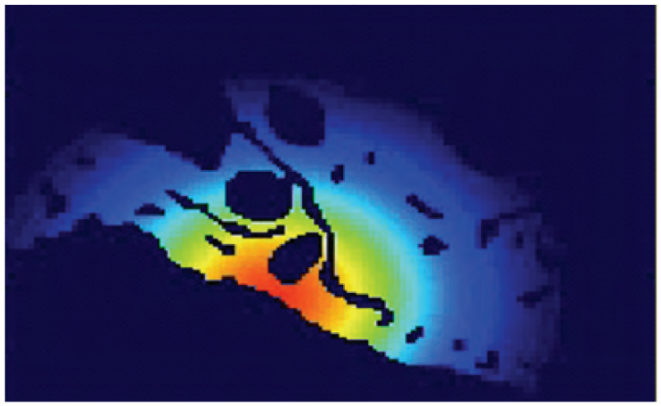
The STMC has a strong track record in maximizing quantitative imaging technologies to generate data for modeling. High resolution imaging technologies include correlated light & electron microscopy (Wilson), single particle tracking (Diane Lidke) and super-resolution technologies (Keith Lidke, Jennifer Gillette, Aaron Neumann). The STMC continues to push the boundaries of imaging through instrument development and image analysis, led by Keith Lidke (UNM), Jerilyn Timlin (Sandia National Labs) and Jim Werner (Los Alamos National Lab). Developments in microfluidics led by Anup Singh (Sandia) have enabled real-time imaging-based kinetics measurements of cellular responses to stimuli. The rich data sets enabled by these imaging modalities have supported the development of innovative mathematical modeling methods, including new platforms for spatial stochastic modeling (Jeremy Edwards). STMC modelers Bill Hlavacek and Byron Goldstein (Los Alamos National Labs) are leaders in the field of rule-based models, providing unique approaches to the combinatorial complexity associated with modeling receptors and their associated signaling pathways. Publications and other updates about research at the STMC may be viewed at: http://stmc.health.unm.edu/





Education and outreach

The first **q-bio conference** was launched in 2007 by



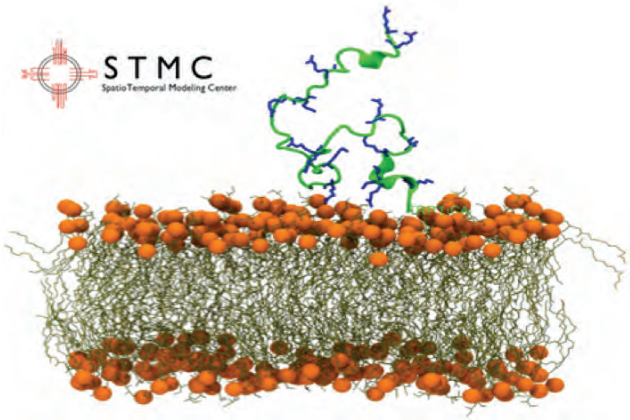
STMC's Hlavacek, along with LANL modeling specialists Jiang, Nemenman and Wall and Faeder at U. Pittsburgh. The goal was to highlight the revolutionary technological advances in modern biology and the trend for integration of biologists, physicists and engineers into teams that focus on quantitative aspects of cellular information processing. This international Systems Biology event is held at the St. John's campus in beautiful Santa Fe, NM. q-bio now ranks among the best in the world with its unique focus on all aspects of quantitative and computational biology. It is particularly known for the exceptional speakers, breadth of topics and lively discussions at shared meals and packed poster sessions. Partnering sponsors include the NM Consortium, the LANL Center for Nonlinear Studies and NIGMS.

The q-bio conference is preceded each summer by a 3 week **q-bio summer school** that attracts participants from all over the globe. The summer school's mission is to advance predictive modeling of cellular regulatory systems, by exposing participants to a broad survey of work in quantitative biology as well as by providing in depth instruction in relevant mathematical modeling techniques. The summer school is designed for graduate students, postdocs, or anyone with a quantitative background who is new to modeling cellular regulatory systems/networks. Five overlapping themes will be available to students at the 2013 session: *er, Cell Signaling, Stochastic Gene Regulation, Biomolecular Simulations, and Viral Dynamics.* There are 25-30 instructors and enrollment is limited to 30 students at the Santa Fe Campus. In 2012, the UCSD Center joined us though a shared summer school. For the upcoming summer, the UCSD campus will also host 20 students for themes in *Computational Neuroscience and Synthetic Biology.* Our own center's trainees may choose to enroll in either q-bio summer school program during their first year with the STMC.

The STMC also sponsors an annual **Systems Imaging Symposium** and **Workshop** (150 attendees, many from international locations). It is held each January on the UNM campus, with registration and details available on the STMC website. In addition, the STMC has a unique annual public outreach program entitled the **Art of Systems Biology**. Held in a Santa Fe art gallery, this popular and novel venue attracts over 500 people to attend a weekend of scientific art viewing, public lectures and learning experiences for children.

Institutional transformation

Through targeting recruiting in our P20 and P50 phases, the STMC has hugely strengthened the local interdisciplinary community needed for success at tackling the large challenges associated with systems-



level science. Key recruits during the planning phase were Jeremy Edwards (a specialist in spatial-stochastic modeling, with joint appointment in the UNM Depts. of Molecular Genetics and Chemical Engineering), biophysicist Diane Lidke (to the UNM Dept. of Pathology), physicist Keith Lidke (UNM Physics Dept.). Support from the P50 enabled us to recruit immunologist Aaron Neumann (Pathology), cell biologist Jennifer Gillette (Pathology), immunologist Judy Cannon, mathematical modeler Vittorio Cristini (Pathology) and computer scientist Lydia Tapia (CS). These new faculty have prospered in their own careers and are training a new generation of interdisciplinary fellows. In addition to our commitment to promoting women for computational careers, our trainees uniquely represent the minority populations of New Mexico (Hispanic, Native American). Institutional matches for training ensure that most STMC-aligned faculty have the opportunity to serve as funded mentors. Eight trainees have now moved to faculty positions and one to industry. In addition, recent PhD graduates have moved to postdoctoral positions at Yale and South Dakota University.

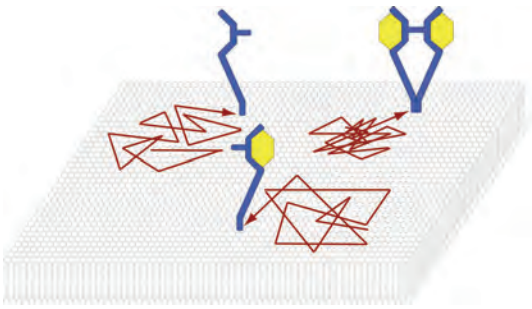
In addition to our core group of faculty members, the STMC supports the growth of our systems biology community through *Pilot Projects* and *Grand Challenge awards*. These initiatives are open to faculty on both the Health Sciences Center and the main campuses (Engineering, Physics, Chemistry, Mathematics, Computer Science).

q-bio summer school, 2012

A major training emphasis at the STMC is the composition of each graduate student's interdisciplinary dissertation or thesis committee. We recommend strong biology representation on the committees of physical sciences/engineering students and strong physical sciences/engineering representation on the committees of biomedical sciences students. Committee members are active members of research project teams and the multi-disciplinary approach assures that students emerge as credible systems biologists.

We also offer formal coursework reflecting scientific emphases at the STMC. Comments from students enrolled in a recent course on cancer modeling were:

- "Just the right depth of math description (perfect!)"
- "Really liked seeing how the basic physic & math theorems can explain phenomenon occurring at cell/or macro level"
- Course instructor's "passion is contagious"
- "Appreciated the cycle of experiments to models – back to impact on experiment"
- "Greatly enjoyed seeing math describing biology written out explicitly and step-by-step, so can see how the 2 join."



FACT SHEET

NM Center for Spatiotemporal Modeling (STMC)

National Center for Systems Biology since 2009 (planning phase 2002-2008)

Directors: Bridget S. Wilson (2013-present); Janet M. Oliver (2002-2012)

Representative publications:

Andrews et al. Actin restricts FceRI diffusion and facilitates antigen-induced receptor immunobilization. (2008) Nature Cell Biology 10(8):955-63; Andrews, et al. (2009) Small, mobile FcεRI receptor aggregates are signaling competent. Immunity 31:469–479.

These two papers use IgE-quantum dot probes track IgE receptors on the surface of live cells, showing that actin corrals restrict motion of receptors and linking aggregate state to IgE receptor immobilization.

Low-Nam et al. (2011) ErbB1 dimerization is promoted by domain co-confinement and stabilized by ligand. Nature Structural and Molecular Biology, 18:1244-9

Here, single particle tracking is used to capture ErbB1 dimerization in real time and calculate dimer dissociation rates.

Nieuwenhuizen, et al. (2013) "Measuring image resolution in optical nanoscopy," Nature Methods advance online publication; Smith, et al. (2012) Fast, single-molecule localization that achieves theoretically minimum uncertainly. Nature Methods 7(5):373-5.

These papers illustrate new microscopy methods being developed at the STMC super resolution core, led by physicist Keith Lidke.

Mazel, et al. (2009) Stochastic modeling of calcium in 3D geometry. Biophysical Journal. 96:1691-1706. PMC2996128.

Illustrates STMC initiatives to incorporate 3D information into mathematical models of calcium response in non-excitable cells.

Radhakrishnan, et al. (2012) Mathematical simulation of membrane protein clustering for efficient signal transduction. Annals of Biomedical Engineering 40(11):2307-18.

This review summarizes a major STMC emphasis on spatial Monte Carlo simulations to examine the effects of micrometer-scale cytoskeletal corrals and receptor concentration on EGFR receptor dimerization and clustering.

Barua D et al. (2012) A computational model for early events in B cell antigen receptor signaling: analysis of the roles of Lyn and Fyn. Journal of Immunology. 189, 646-658; Creamer et al. (2012) Specification, annotation, visualization and simulation of a large rule-based model for ErbB receptor signaling. BMC Systems Biology. 6:107.

Rule-based modeling provides a means to represent cell signaling systems in a way that captures site-specific details of molecular interactions. These papers apply rule-based modeling to the B cell receptor and to the EGFR family of receptors.

Steinkamp et al. (2013) Ovarian tumor attachment, invasion, and vascularization reflect unique microenvironments in the peritoneum: insights from xenograft and mathematical models. Frontiers in Oncology 3:97.

Illustrates how STMC investigators integrate data from imaging at the cell-tissue level into agent-based tumor models.

Community resources/software/collaborations: The STMC's *Cores in Super Resolution Imaging and Image Analysis* serve all members of the STMC community and play key roles in outreach to external collaborators seeking access as visitors and collaborators to novel imaging instruments and image analysis software. The *Measurement Core* and *Modeling Core* are also sites of scientific outreach. As well as providing cells and reagents to STMC members, the Measurement Core welcomes visitors to learn specific techniques, especially the preparation of membrane sheets and the conduct and analysis of SPT tracking experiments. It also shares cells and reagents externally. Similarly, the Modeling Cores welcome visitors and collaborators interested in applications of their simulation algorithms and protocols for visualizing and annotating rule-based models. For software resources go to: http://stmc.health.unm.edu/tools-and-data.html

Training and outreach:

The STMC takes pride in our female/minority faculty and trainees. Women comprise:

- 12 of 30 STMC leaders and members, including the PI
- 6 of 19 STMC postdocs
- 9 of 21 graduate students
- 7 of 14 STMC undergraduates

Minorities comprise:

- 5 of 30 STMC faculty (African American and Hispanic)
- 1 of 19 postdocs (Native American)
- 3 of 21 STMC graduate students (Hispanic and Native American)
- 7 of 14 STMC undergrads (Hispanic, Native American, African-American)

San Diego Center for Systems Biology

University of California, San Diego http://sdcsb.org

Program Director:
Alexander Hoffmann (ahoffmann@ucsd.edu)

Program Administrator:
Anna Lu (atlu@ucsd.edu)

Key Personnel (cumulative): Trey Ideker, Jeff Hasty, Sumit Chanda, Tracy Johnson, Amy Kiger, Lev Tsimring, Gentry Patrick, Roy Wollman, Bing Ren, Chris Glass, Jean Wang, Terry Hwa

Center History, Philosophy, and Environment:
Initiated by energetic young faculty intent on developing a collaborative community, the San Diego Consortium for Systems Biology (SDCSB) was founded in 2005 to bring together scientists across disciplines and institutions, to promote collaborative research and training, and to support the exchange of ideas and resources. Supported on these efforts, SDCSB became one of the National Centers for Systems Biology in 2010, funded by the National Institute of General Medical Sciences.

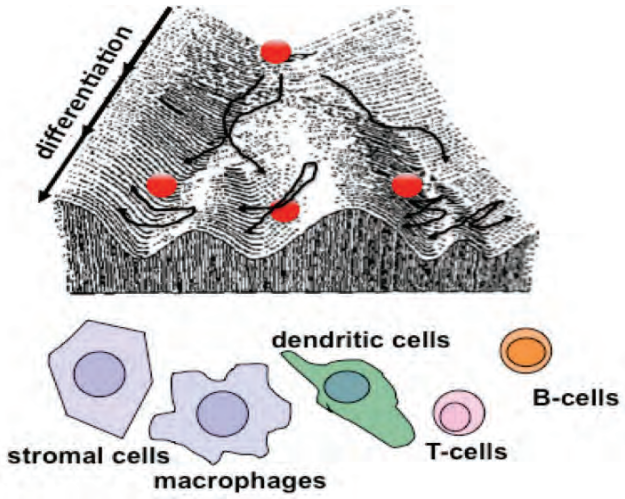
As measurement capabilities (sequencing, mass spectrometry, etc) continue to expand dramatically, the challenge for Systems Biology is less to discover the products of the genome but to understand how these products interact to produce systems emergent properties and thus biological function. A key goal is the linking of top-down and bottom-up Systems Biology approaches and the exploitation of resulting synergies.

The San Diego Center for Systems Biology aims to promote the Systems Biology approach by addressing the conceptual, technological, and cultural challenges associated with focusing on the emergent properties of the biological dynamical systems that control cellular stress responses. It thus serves the larger mission to transition Biology to a math-based science that should produce more reliable diagnosis, therapeutic options and environmentally sustainable solutions.

Research Programs constitute a dynamic network of investigators focused on understanding the control of cellular stress responses. These involve dynamic signaling events for coordinated repair steps that occur in the context of specific cellular steady states. Misregulation of cellular stress responses does not only impair the cell's ability to contain the damage, but may cause further damage, as manifested in chronic inflammatory diseases and cancer. A Seed Grant Program provides for funding for new research proposals that contribute to the overall mission of the Center.

Research Cores address conceptual, technological and cultural challenges as they pertain to (a) data analysis and network assembly, (b) mathematical modeling and image analysis, (c) dynamic data acquisition from living cells and light microscopy. The core portfolio is adapted in response to changing research challenges.

Outreach Cores aim to broaden SDCSB's impact to a larger scientific public, and the Systems Biology talent pool. The Scientific Outreach Core maintains a website, hosts seminar series, symposia, and an active best practices workshop series, as well as provides training opportunities for pre- and postdoctoral trainees. The Education Outreach Core aims to reach the undergraduate and pre-college pool of quantitative talent and develop a pipeline for future systems biologists.



Research focus

The SDCSB research focus is to understand the regulation of biological responses to stress (e.g. to DNA damage, pathogens, and metabolic perturbations) in terms molecular networks, molecular mechanisms, dynamic control, and other emergent systems properties; and the connections of these regulatory systems to other dynamic or homeostatic gene regulatory circuits that control key biological functions. Four Research Programs address different cellular stress responses utilizing different approaches whose common goal is to link top-down and bottom-up Systems Biology.

Program 1 focuses on the dynamic control of inflammatory signaling; how stimulus-responsive dynamics may represent a signaling code that specifies cellular responses, how such a code may be exploited for pharmacological targeting, and what the underlying mechanisms are that allow for dynamical encoding and decoding of signals.

Program 2 aims to develop a predictive understanding of pathogen-responsive gene expression, including the localization of signal-responsive transcription factors, the construction and function of enhancers, the interaction of enhancers and promoters via chromatin looping, and the interplay between transcription, histone modifications, and chromatin-associated splicing.

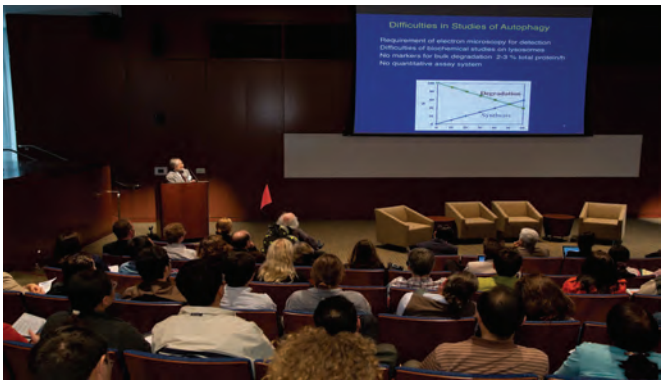
Program 3 addresses the regulatory network that controls cellular responses to genotoxic and metabolic stress including autophagy. Comparing mammalian and yeast networks, and connectivities in healthy and stressed conditions guides the development of predictive models.

Program 4 explores the roles of oscillatory biological circuits in technology and biology. Synthetic oscillators, when coupled, may form the basis for biopixels that may function as inexpensive biosensors. Natural oscillators form the basis for temporal phasing of metabolic circuits providing fitness advantages in changing environments.

Education and outreach

SDCSB is committed to promoting Systems Biology within the community via training, and sharing of resources and information. SDCSB's workshops and symposia have served as an effective means to connect with members of the diverse Torrey Pines Systems Biology Community. Connections forged during these events have enabled new research approaches, catalyzed collaborations, and connected reagent providers with scientists, or technical innovators and biologists, computational and experimental scientists. SDCSB has held major workshops and symposia on specific Systems Biology topics, such as Next Gen Gene Expression, Proteomics, RNAi Screening, miRNA, Drug Discovery, Cellular Imaging, and Discovery of Genetic Variation. These workshops attracted interest from industry, allowing us to use sponsorship to cover expenses, and to catalyze interactions between academic and private sector research. Thus, all of our events have been provided free of charge and usually reach maximum capacity at the venue – drawing over 200-300 participants for workshops/symposia and 45-75 participants for seminars. Our Annual

Systems-to-Synthesis Symposium routinely has over 300 participants and showcases no less than 35 posters each year.



SDCSB sponsors the Colloquium in Bioinformatics and Systems Biology organized by the students of the Bioinformatics and Systems Biology graduate program. In parallel, SDCSB sponsors the Quantitative Biology seminar series organized by the BioCircuits Institute. Both have played a vital role in the intellectual interdisciplinary exchange on our campus.

Institutional transformation

Graduate Education

Catalyzed by SDCSB activities, the inter-departmental Graduate Program in Bioinformatics (http://bioinformatics.ucsd.edu) transformed into an umbrella Graduate Program for Bioinformatics and Systems Biology. This Graduate Program is supported by five Schools/Divisions, namely the Jacobs School of Engineering, the Division of Biological Sciences, the Division of Physical Sciences, the School of Medicine, and the Skaggs School of Pharmacy and Pharmaceutical Sciences. Its 70 faculty are in more than 15 departments. A track structure was adopted, for Bioinformatics, Biomedical Informatics in 2012, and Systems Biology in 2013. In 2013, the Salk Institute will join the five Schools to provide further support of the Program. The size of the incoming class has increased from 4 students in Fall 2009, to 18 in Fall 2013. The T32 Training Grant in Bioinformatics was renewed and expanded from 7 to 10 slots, and a second T32 in Biomedical Informatics was obtained. A third Training Grant in Systems Biology is being prepared.

In addition, SDCSB has catalyzed graduate education initiatives in the Biological Sciences, the Biomedical Sciences, and the Chemistry/Biochemistry graduate programs. Each have added a training track in Systems Biology and developed a curriculum that addresses quantitative and computational training aspects.

qBIO Initiative

Catalyzed by SDCSB activities (as well as the NSF-funded Center for Theoretical and Biological Physics, CTBP), the qBio Initiative aims to catalyze the transformation of the biological and physical sciences and allow for an effective integration of them at UCSD (and beyond). Quantitative Biology involves quantitative measurement, mathematics and theory, akin to the approaches that revolutionized Physics in the 17th and 18th century. It applies to research, graduate research training, and undergraduate education.

A framework for interdepartmental faculty searches and hiring was developed where two simple programmatic criteria are applied: the research must focus on living things (cells, not only molecules in vitro) and involve mathematics (not merely the use of software). The Systems Biology community catalyzed by the P50 grant and SDCSB were significant factors in Junior Faculty recruitments. In addition, graduate education in qBio will be launched with qBio fellowships, and newly hired faculty is in the process of developing undergraduate curricula that will likely constitute a new major. The qBio Initiative is developing into a major fund raising focus for the campus. Mission, scope, leadership, and web presence will likely be announced in the summer of 2013.

FACT SHEET

San Diego Center for Systems Biology

National Center for Systems Biology since 2010

Research Impact. The biological focus of SDCSB is the cellular stress response. The Center has established four multidisciplinary programs that aim to bring both top-down and bottom-up Systems Biology approaches to bear in a synergistic manner, to develop a predictive understanding of four different aspects of cellular stress responses. These are assisted by three major and three minor Research Cores, which push technological development and the adoption of technology by the broader scientific public through collaboration and training. Since its inception, SDCSB researchers have made the following major contributions:

1- an unbiased, automated gene ontology links systems biology to gene function predictions (Dutkowski et al Nature Biotech 2013)

2– charting the stress-induced genetic interactome as the basis for whole-cell dynamic models of cellular stress responses (Bandyopadhyay et al Science 2010)

3- dynamical modeling explains how quantitative differences in epigenetic steady states may result in qualitatively different cell-type-specificity (Shih et al Nature Immu 2012, Loriaux et al Plos Comp 2013a and b)

4- signaling dynamics as a regulatory code, which specify stress-specific cellular responses and may be targeted pharmacologically (Behar & Hoffmann Current Opinion in G&D 2010, Wuerzburger-Davis et al Immunity 2011, Rao et al Nature 2012, Schrofelbauer et al Mol Cell 2012, Hirota et al Science 2012)

5- the pathogen-responsive transcriptome controlled by enhancer-mediated interactions of lineage-specific, signal-responsive TFs, and looping dynamics (Heinz et al Mol Cell 2010, Cheng et al Science Sig 2011, Escoubet-Lozach et al Plos Gen 2011, Dixon et al Nature 2012, Hossain et al MCB2013)

6- core cellular machineries for protein synthesis and degradation are key regulatory crosstalk mediators (Cookson et al MSB 2011, Baumgartner et al PNAS 2011, Djakovich et al J Neurosci 2012)

7- synchronized oscillators as "biopixels" harnessed for biosensors (Danino et al Nature 2010, Mondragon-Palomino et al, Science 2011, Prindle et al Nature 2011)

A complete list of publications may be found at the Center's website at: ***http://sdcsb.org.***

Community Resources/Software/Collaborations

SDCSB's Research Cores are drivers of community resources. Core A (Network Assembly) provides support to a large number of laboratories (funded or not funded by the P50 grant) in the analysis and visualization of genetic and physical networks, and the core's research has focused on efforts to integrate Gene Ontology (GO) terms in network analysis. Core B (Mathematical Modeling) has catakyzed the adoption of mathematical modeling approaches, as well as custom image analysis software vial collaborations, a summer school, workshops and hands-on training. Core C (Cell Dynamics) is developing affordable and easy-to-use microfluidic approaches that allow the probing of cells within dynamic environments. SDCSB has championed the development of key software tools, such as Cytoscape (for network visualization), Homer (for analysis of gene expression data), Pysub (for relating the steady state and dynamic response of mass action models), FlowMax (for the interpretation of CFSE data), and dynamical NFκB models (for identifying critical mechanisms).

Training and Outreach

Graduate and Research Training are hallmarks of SDCSB. Activities have given rise to Systems Biology tracks in four existing graduate programs catering to experimental biologists and computational bioinformaticists. SDCSB has pursued an active program of one-day workshops covering a range of topics pertinent to systems biology, such as siRNA screening, NextGen gene expression, live cell microscopy, etc. SDCSB organizes two tracks within the qBio summer workshop program. Educational outreach activities are focused on both local elementary/middle schools, as well as undergraduate transfer students coming from local colleges to UCSD.

Center for Systems and Synthetic Biology

University of California, San Francisco http://systemsbiology.ucsf.edu/

Program Director:
Wendell Lim, Ph.D. (wendell.lim@ucsf.edu)

Program Administrator/Associate Director:
Connie M. Lee, Ph.D. (connie.lee2@ucsf.edu)

Key Personnel (cumulative): Nevan Krogan (Deputy Director), Hana El-Samad (Deputy Director), Al Burlingame, Michael Fischbach, Zev Gartner, Hao Li, Wallace Marshall, Lei (Stanley) Qi, Jasper Rine, David Sivak, David Soloveichik, Chao Tang, Matthew Thomson, Chris Voigt, Leor Weinberger, Veronica Zepeda

Center History, Philosophy, and Environment:

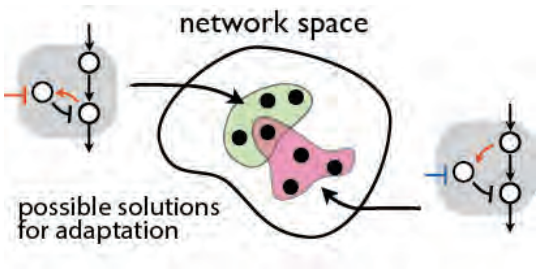
UCSF is a premiere medical school and basic biomedical research institution, promoting health worldwide through advanced research, graduate-level education in the life sciences and health professions, and high-quality patient care. However, UCSF lacks traditional quantitative science departments—such as physics, mathematics, engineering—and a deeper understanding and innovation in medicine and health will only come from approaching and understanding biology from a much broader perspective. Thus, a major goal in the creation of the center was to nucleate an interdisciplinary community at UCSF, and to mix the best talent from physics, mathematics and engineering within this health sciences institution. The UCSF Center for Systems and Synthetic Biology (CSSB) was funded in September 2010 as part of the NIGMS national centers for systems biology.

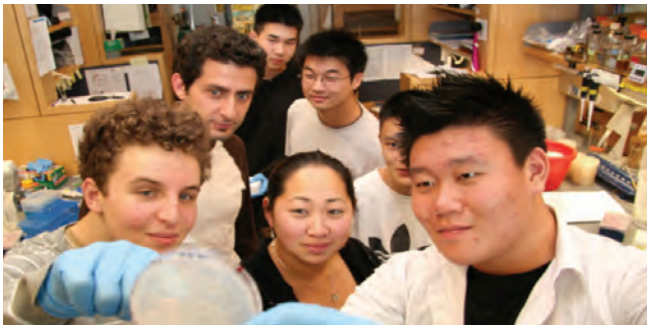
The center established a Systems Biology Fellow program as one of the mechanisms to bring in outstanding young scientists from non-traditional, non-biological backgrounds. Due to the collaborative UCSF environment and lack of traditional departmental silos, these Fellows are able to collaborate with any faculty of interest, which also serves to better integrate CSSB within the broader community. During the first two years, CSSB was fortunate to hire four outstanding and talented independent Fellows, with backgrounds in biophysics, computer science, and bioengineering. The Fellows have already made a tremendous impact at UCSF, including initiating a very popular theory group, teaching minicourses on new topics, and organizing a UCSF-wide Fellows discussion and peer group.

CSSB serves as a creative hub at UCSF for interdisciplinary and quantitative explorations into how biological systems function. Since CSSB started in 2010, it has grown well beyond the eight laboratories involved in the initial proposal. In the second year, the center solicited and awarded seed grants to four new investigators at UCSF, further strengthening and expanding upon our core strengths. The broader CSSB community now includes over 130 UCSF and Bay Area faculty, postdoctoral and independent Fellows, graduate and undergraduate students, and high school seniors, who regularly attend one or more of our monthly scientific meetings or focused discussion groups.

Research focus

The scientific focus of the center is to understand the design principles by which cells solve problems. We are interested in exploring whether, for a given type of biological function, there are a finite number of network solutions. If networks can be organized into a finite number of classes based on functional and structural properties (i.e., a dictionary of networks), then this understanding would greatly facilitate our ability to deconstruct complex biological networks into simpler modules, to





understand how networks functionally fail in disease, and to design synthetic networks for biotechnological and therapeutic purposes. In addition, we would like to use high-throughput approaches to map functional network structures in diverse species, and to identify evolutionary conservation of key network structures. A long-term goal is to achieve a deeper, unified understanding of network structure/function by combining our bottom-up approach of defining design principles with the top-down approach of high-throughput mapping of complex networks.

The initial grant period has focused around three central questions in understanding design principles of regulatory networks. First, we would like to theoretically define design rules of cellular circuits. In this regard, we have made significant progress the past three years in defining a dictionary of core molecular algorithms for executing common cellular decisions, including adaptation, memory, cell fate, and spatial self-organization.

A second goal is to experimentally test and learn to build potentially useful synthetic cellular systems, where precise modifications of cellular behavior have applications in biomedicine. We have successfully used synthetic biology approaches to show that we can construct minimal synthetic networks in live cells that are sufficient to execute complex behaviors such as robust self-organized cell polarization. A broad new direction that we have focused much attention on recently is building and understanding circuits involved in spatial organization of biological systems. This includes both organization of structure within individual cells, but also organization of cells in multicellular structures. In an exciting new translational direction, we have also begun applying synthetic biology approaches to engineer therapeutic immune cells targeted to specifically identify and kill tumor cells.

A foundation for our second aim has been the development of new tools and parts for synthetic engineering of cells. We have developed several cellular optogenetic tools that allow one to precisely control cellular behavior with light. With these, we have interrogated different cellular networks and dynamical systems within the cell (including Ras and PKA signaling), and created a light-inducible organelle targeting system for dynamically activating and inactivating proteins. We have also developed CRISPRi, a flexible new tool for achieving RNA-targeted DNA binding and transcriptional regulation in living cells. Finally, we have assembled and characterized an optimized set of fluorescent proteins for imaging in yeast in a center-supported collaboration with the Nikon Imaging Center core facility at UCSF.

Third, we would like to characterize natural cellular networks and their evolution. We have successfully developed methods to map genome-scale genetic interaction networks across evolution, in mammalian cells, and in different conditions, and harnessed these tools in a top-down approach to discover conserved network design principles. Additional projects include dissecting stress response pathways, noise and evolution of gene regulatory networks, and interspecies interaction networks.

Education and outreach

A hallmark of CSSB's outreach initiatives is the UCSF International Genetically Engineered Machine (iGEM) program. Promising young students from San Francisco Unified School District's Abraham Lincoln High School (ALHS) spend the summer working at UCSF on a team-based project. Two returning iGEM alumni (who are now undergraduate students) as well as a local community college student and an exchange student from Peking University, are also part of the annual team. They design a project in synthetic biology through innovative team challenges with which they compete at the iGEM competition in the fall. The program is a partnership between CSSB and ALHS, which has a two-year biotechnology program led by George Cachianes. The biotechnology program has expanded significantly since the advent of the UCSF iGEM program, and several other high schools in San Francisco have followed Mr. Cachinanes' curriculum. The UCSF iGEM program was

developed to offer talented young biologists a unique summer research experience while also providing graduate students and postdoctoral fellows at UCSF with valuable mentoring and teaching opportunities. CSSB's education coordinator, Veronica Zepeda, also teaches a two-week module on cloning at ALHS every spring in preparation for the summer research project.

CSSB has further contributed to and developed team-based challenge approaches to learning and innovation in other areas. UCSF has an umbrella graduate program (Integrative Program in Quantitative Biology or IPQB) that brings together three programs focused on applying physical, mathematical, and systems approaches to biological problems, which fits very well with the systems and quantitative biology themes of CSSB. The Systems Biology course for first year IPQB graduate students is co-taught by center deputy director and co-investigator Hana El-Samad using team-based approaches, and teaching assistance is provided by several CSSB-associated postdoctoral fellows and graduate students. CSSB also supported the salary of the new course coordinator hired for the fall 2012 semester. Furthermore, CSSB, together with Peking University, organized a 4-day team challenge workshop and exchange on innovative topics in quantitative biology in Beijing in July, 2012. The center was interested in breaking down some of the cultural barriers, and utilized joint brainstorming exercises to lay a roadmap for new cutting edge ideas in the life sciences. The workshop has acted as a springboard for joint projects and student exchange between UCSF and PKU. Lastly, several laboratories at UCSF, as well as at the institutional level, are incorporating these team-based brainstorming approaches for project generation and innovation.

Institutional transformation

There has been a substantive cultural and institutional change at UCSF since CSSB started in 2010. In the last few years, the center has become a catalyst for driving new initiatives. People with ideas and interest in exploring new directions have converged on CSSB, and because of this, the center has been the driving force behind several initiatives and interest groups on a variety of topics. The center supported discussion groups include the multicellularity systems biology discussion group (includes self-organization; brings together cell, developmental and cancer biologists, theorists and tool builders), the cell therapy club and cell-based therapeutics symposium (catalyzes those interested in applying systems and synthetic biology to new therapeutic platforms), the practical systems & synthetic biology discussion group (reaches out to local tech start-ups, and is a forum to discuss roadblocks and solutions in transitioning systems knowledge to actionable tools in everyday synthetic biology) and the Theorizza group (bringing together those interested in theory). All these initiatives have generated a lot of excitement in diverse parts of the UCSF community—including cancer biology, developmental biology, translational medicine, immunology—that extend beyond the systems and synthetic biology community we are building, and are already leaving a mark on the institution.

In addition to discussion groups, we've organized symposia and workshops on systems biology (Frontiers in Systems Biology; Mar. 2012), synthetic biology (Synthetic Biology Lablinks; Dec. 2011), Biology and Mathematics in the Bay Area (BaMBA 7; Nov. 2011), cell-based therapeutics and translational synthetic biology approaches (Cell-based Therapeutics: the Next Pillar of Medicine; Apr. 2013), and science and cooking ('Science & Cooking'; Apr. 2012). All these symposia and lectures were the first of their kind at UCSF, and therefore changing the perception of UCSF as a strictly health sciences campus. CSSB aims to change the way scientists approach and think about questions in biology, thus broadening the landscape of research at UCSF.

FACT SHEET

Center for Systems and Synthetic Biology

National Center for Systems Biology since 2010

Research Impact:
Major goals of the UCSF Center for Systems and Synthetic Biology (CSSB) are to expand the quantitative systems biology community at UCSF and, scientifically, to understand the design principles by which cells solve problems. CSSB currently has a core set of 10 faculty (plus one affiliate faculty member at Peking University) and four independent Systems Biology Fellows as primary investigators. The Fellows program was initiated to bring in outstanding young scientists from non-traditional, non-biological backgrounds into the strong biomedical research community of UCSF.

Some of the major research accomplishments in the first three years have been:

- design principles in biology: defined a dictionary of core molecular algorithms for executing common cellular decisions including memory, cell fate, and spatial self-organization (e.g., **WA Lim**, CM Lee, **C Tang**. Molecular Cell, 2013)
- used synthetic biology approaches to show that we could construct minimal synthetic networks in live cells that are sufficient to execute complex behaviors such as robust self-organized cell polarization (AH Chau, JM Walter, J Gerardin, **C Tang**, **WA Lim**. Cell, 2012)
- developed methods to map genome-scale genetic interaction networks across evolution and in different conditions, and harnessed these tools to discover conserved network design principles (e.g., CJ Ryan, **C Tang**…T Ideker, **NJ Krogan**. Molecular Cell, 2012; A Roguev…**NJ Krogan**. Nature Methods, 2013)
- reported that coregulated genes can exhibit a shared variability—or noise—in their expression levels, thus establishing noise as a quantitative tool to identify gene regulatory networks (J Stewart-Ornstein, J Weissman, **H El-Samad**. Molecular Cell, 2012)

Tools and Community Resources:

- developed cellular optogenetic tools that allow one to precisely control cellular behavior with light; developed approaches to interrogate dynamics of signaling in cells
- developed CRISPRi: a new, flexible tool to achieve RNA-targeted DNA binding and transcriptional regulation in living cells (**LS Qi**…JA Doudna, JS Weissman, AP Arkin, **WA Lim**. Cell, 2013)
- assembled an optimized set of fluorescent proteins for imaging in yeast in a center-supported collaboration with the Nikon Imaging Center core facility at UCSF (S Lee, **WA Lim**, KS Thorn. PLOS ONE, in press)

Training and Outreach:
In the first three years, CSSB has directly supported the training of 4 Systems Biology Fellows, 8 postdoctoral fellows, 8 graduate students, 8 undergraduate students, and 11 high school students. Of the direct trainee alumni from CSSB, 4 graduate students have gone on to do postdoctoral fellows, and 1 postdoctoral fellow has gone on to a faculty position.

CSSB has made an impact in the UCSF community. In addition to our directly participating faculty and directly funded trainees, the number of people participating in one or more of our regular scientific meetings (ie., monthly scientific meeting, theory group, multicellularity discussion group, practical systems & synthetic biology group, cell therapy club, UCSF fellows group) is growing rapidly. Currently we have 9 indirect participating faculty, 4 industry employees, 30 high school students, 2 undergraduate students, 59 graduate students, 46 postdoctoral fellows, and 9 independent Fellows.

Virtual Physiological Rat Project

Medical College of Wisconsin

http://www.virtualrat.org

Program Director:
Daniel A. Beard (beardda@gmail.com)

Program Administrator:
Stacy Romant (stromant@mcw.edu)

Key Personnel (cumulative): MCW: Allen Cowley, Julian Lombard, Aron Geurts, Brian Carlson, Ranjan Dash, Melinda Dwinell; University of Washington: James Bassingthwaighte, Maxwell Neal, Mike Bindschadler; North Carolina State University: Adam Mahdi, Mette Olufsen; University of Wisconsin: Tim Kamp; University of California San Diego: Andrew McCulloch, Jeff Omens; University of Auckland: Peter Hunter, David Nickerson, Edmund Crampin; King's College London: Nicolas Smith; Norwegian Life Sciences University: Stig Omholt.

Center History, Philosophy, and Environment:

Following the great successes in molecular genetics of the past decades, the challenge for integrative biology now is to "put Humpty Dumpty back together again" [Nobel, *The Music of Life: Biology Beyond Genes*, Oxford, 2008]. To meet that challenge, our National Center for Systems Biology is focused on the Virtual Physiological Rat (VPR) project—a title deliberately chosen to invoke comparisons to and collaborations with the European Commission's Virtual Physiological Human, or VPH. Both the VPR and VPH have common roots in the International Union for Physiological Sciences' "IUPS Physiome Project" which was initiated and organized by Peter Hunter, Jim Bassingthwaighte, and other leaders in integrative systems physiology. (Indeed we are lucky to have Peter and Jim helping to lead the VPR project.)

The VPR project broadly operates under three governing principles: (1.) Progress in physiology depends on application of computational modeling; (2.) Complex diseases manifest on the background of physiological control; and (3.) Computational physiology is a vehicle for genotype-to-phenotype mapping. Applying these principles we are putting Humpty Dumpty together using computational modeling as the engine to integrate knowledge of interacting systems (often operating at different time and space scales), to analyze systems-level data, to formulate and test quantitative hypotheses, and to explore how function may emerge from the integration of interacting components in biological systems.

Research Focus:

It is increasingly recognized that multi-factorial diseases arise from interaction between genetic and environmental factors and physiological systems. Examples of particular relevance to human health include the major health burdens that we face: cardiovascular disease and heart failure; metabolic syndrome and type 2 diabetes; and cancer. In all of these examples, acute and chronic (mal)adaptions of specific molecular mechanisms and pathways in disease states occur against a background of physiological regulation. Since processes involved in complex disease operate in the context of physiological regulatory mechanisms, an understanding of a disease process builds upon an understanding of the associated physiological systems.

The VPR project is addressing these challenges by developing the means to simulate the integrated cardiovascular function of the rat, and to build validated computer models that account for genetic variation across rat strains and physiological response to environment (i.e., diet). We have a particular emphasis on cardiovascular disease which represents a major world-wide health burden. Many of our efforts to date have focused on method development for acute and chronic physiological monitoring, and model/software development for simulating the long-term and short-term mechanisms controlling cardiovascular function, particularly with respect to interactions between the neurohumoral systems, the vasculature, the heart, and the kidneys.

One of our significant early findings is a determination (through a combination of data analysis and computational modeling) that arterial stiffening provides a sufficient explanation for the etiology of hypertension in the ageing population (arxiv.org/abs/1305.0727). This work, which directly contradicts the

major governing theories in the field, reveals how an emergent understanding of a physiological system can emerge from systems/computational analysis.

We have also developed a number of new tools that are necessary for this sort of large-scale integrative program: (1.) We have released version 0.1 of OpenCOR (http://opencor.ws/ download.php), an open source cross-platform modeling environment which can be used to organize, edit, simulate and analyze CellML files on Windows, Linux and OS X; (2.) We developed and distributed a Python package cgptoolbox for simulation studies of causally cohesive genotype-to-phenotype models which is now available on github (https://github.com/jonovik/cgptoolbox). We have used and are using the cgptoolbox in a number of simulation studies linking genetic and computational physiology; (3.) We have developed a parallel algorithm of reverse engineering biological networks that has unique properties in terms of numerical performance and scalability. We are applying this tool in a number of different contexts, including in uncovering genetic regulatory networks involved in cardio-genesis, and to predict the effects of gene copy number variation in infants born with congenital heart defects.

Education and Outreach:

The VPR Center has supported a number of initiatives in education and outreach, including developing new courses and workshops and supporting opportunities for undergraduate research.

One of these efforts has been support for the annual Cardiac Physiome Workshop. In 2012, Andrew McCulloch organized the fifth annual Cardiac Physiome Workshop, at which Dan Beard agreed to serve as meeting chair for the 2013 meeting. The 2013 meeting will be held 17-19 October in Bar Harbor, Maine, and the Jackson Lab Center is graciously providing logistical support (www.cardiacphysiome.org).

In addition, we have developed several online resources for teaching. The UW Seattle group has constructed a number of teaching resources, including a tutorial series of cardiovascular models based on Vincent Rideout's book "Mathematical and Computer Modeling in Physiological Systems" (there are now over 370 models at www.physiome.org; see particularly models 334-344 and 360). Dr. Beard has developed a set of online resources to compliment the Biosimulation textbook in the Cambridge Biomedical Engineering series. The electronic material, which so far includes data and codes for all examples from six of the nine chapters, can be obtained from www.cambridge.org/biosim. We have also established a YouTube channel associated with the VPR (http://www.you tube.com/user/VirtualRatProject). We have posted three tutorial videos to the channel and are currently exploring ways to improve the quality and impact of the content.

Finally, we have organized a number of workshops at international meetings. Dr. Beard has organized and will chair a session for the upcoming 2013 IUPS meeting on the topic of “Mechanistic Insights into Genotype-to-Phenotype Relationships”. Additionally, Drs. Olufsen and Beard have organized a Current Topics Workshop with the Mathematical Biosciences Institute at The Ohio State University, to be held in the spring of 2014. This workshop, entitled “From Molecular to Systems Physiology”, will bring approximately 50 researchers from around the world to discuss the mathematical machinery necessary for predictively mapping between variants identified by genome-wide association studies and complex traits.

Group photo from the 2012 VPR Annual Meeting

FACT SHEET
Virtual Physiological Rat Project
National Center for Systems Biology since 2011

Research Impact: We are contributing significant scientific advances in the areas of systems mechanics and energetics in heart failure, in the etiology of hypertension, and in genetic programming in cardiogenesis and congenital heart defects.

Systems identification on the genome scale is a major computational challenge. Center researchers have developed an efficient parallel algorithm for reverse-engineering of biological networks for application to uncover genome-scale dynamical systems models of genetic regulatory networks associated with cardiac development, and to predict the impact of copy number variations (CNV's) on gene expression profiles in tissue samples obtained from infants born with congenital heart defects. The algorithm was first reported in Integr Biol (2011) 3:1215-23.

The center brings together expertize in cardiac energy metabolism, mechanics, structure, electrophysiology, and calcium handling. Bringing this expertise together we have assembled computational models to represent morphological and metabolic changes that occur in heart failure, providing a vehicle to begin to tease apart causes and consequences linking mechanical and metabolic failure of the heart.

For decades, the major ruling theory of the etiology of hypertension has been that chronic change to arterial blood pressure must be linked in a primary way to renal dysfunction. Through a combination of data analysis and computational modeling, we have revealed an alternative theory that directly contradicts this view. Specifically, we have determined that arterial stiffening provides a sufficient explanation for the etiology of hypertension in the ageing population (http://arxiv.org/ abs/1305.0727). This finding has stimulated an emphasis on passive and active mechanical properties of the vasculature in the animal models that we are studying.

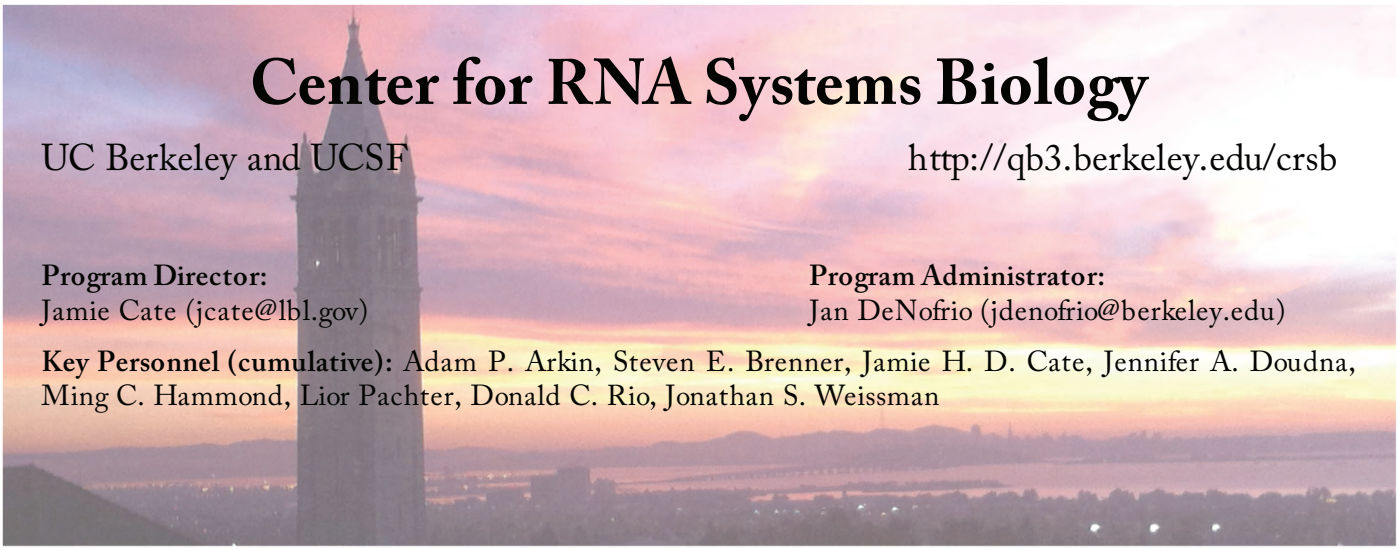
Resource Development and Dissemination: We have developed and distributed a number of software applications. Some highlights are:

- OpenCOR is a modeling environment used to organize, edit, simulate and analyze CellML files (http://www.cellml.org/). OpenCOR is an open source project (https://github.com/opencor/opencor) and binaries are currently available for Windows, Linux and OS X (http://www.opencor.ws/).
- SemPhysKB, developed by the UW Seattle team, is an OWL knowledge base that provides ontological terms for annotating and discovering models and simultaneously acts as a repository of reusable models and modeling components (http://bioportal.bioontology.org/ontologies/3198).
- We have developed the Python package cgptoolbox for simulation studies of causally cohesive genotype-phenotype (cGP) models which is now available on github (https://github.com/jonovik/cgptoolbox). We are using the cgptoolbox in a number of simulation studies linking genetic and computational physiology.

Training and Outreach: The UW Seattle group has constructed a number of teaching resources, including a tutorial series of cardiovascular models based on Vincent Rideout's book "Mathematical and Computer Modeling in Physiological Systems". See particularly Models 334-344 and 360 on www.physiome.org. (There are now over 370 models at www.physiome.org.)

We have established a YouTube channel associated with the VPR (http://www.youtube.com/user/VirtualRatProject). We have posted three tutorial videos to the channel and are currently exploring ways to improve the quality and impact of the content.

The VPR Center currently directly supports the training of 18 postdoctoral fellows and graduate students. Of previously supported trainees, one postdoctoral fellow has moved into a faculty position and continues to directly participate in the VPR project, and a former graduate student is currently a Cancer Prevention Fellow at the National Cancer Institute (NIH).



Center for RNA Systems Biology

UC Berkeley and UCSF http://qb3.berkeley.edu/crsb

Program Director:
Jamie Cate (jcate@lbl.gov)

Program Administrator:
Jan DeNofrio (jdenofrio@berkeley.edu)

Key Personnel (cumulative): Adam P. Arkin, Steven E. Brenner, Jamie H. D. Cate, Jennifer A. Doudna, Ming C. Hammond, Lior Pachter, Donald C. Rio, Jonathan S. Weissman

Center History, Philosophy, and Environment:

Established in 2012 and supported by the National Institutes of Health, the Center for RNA Systems Biology (CRSB) will use systems biology to establish a fundamental basis for understanding and predicting the control of mRNA fate due to RNA structure embedded in pre-mRNA and mRNA sequences. Leveraging the expertise of labs spanning mathematics, biology, chemistry and engineering, goal of the CRSB is to map the relationship between the placement of RNA structure in a pre-mRNA or mRNA sequence and mRNA fate.

Research focus

Project 1 will carry out a systems-level analysis of alternative pre-mRNA splicing. Alternative splicing provides a mechanism for cells to generate vast cellular proteomic diversity from a limited number of genes. Importantly, it has been found that many disease gene mutations in humans cause defects in RNA processing and surveillance pathways, including pre-mRNA splicing. The overall project goal is to systematically link cis-regulatory elements in pre-mRNAs to RNA structural features that control alternative pre-mRNA splicing in human cells. Project 2 will use systems approaches to map translation initiation control by mRNA structure. Protein levels in cells correlate only poorly with levels of mRNA transcripts and depend strongly on levels of translation. Regulation of translation initiation therefore serves as a key determinant of gene expression. The investigators in the CRSB seek to systematically define cis-regulatory elements in mRNAs that control translation initiation using RNA structural mapping and ribosome profiling in cells. Project 3 will map the influence of RNA structure on miRNA-mediated mRNA turnover. Gene silencing begins with the binding of messenger RNAs that are complementary to 21-nucleotide guide RNAs called short interfering RNAs (siRNAs) or microRNAs (miRNAs), ultimately leading to destruction of the targeted transcript. The importance of miRNA-mediated gene regulation in many human diseases underscores the need to develop tools for predicting miRNA targets accurately at a global level. The investigators at CRSB propose to determine structural properties of mRNAs that enhance or hinder miRNA-mediated regulation in human cells using ribosome profiling, RNA-structure detection, and SHAPE-based RNA chemical probing.

Education and outreach

Undergraduate: Through the Center's CRSB Undergraduate Fellowship Program, undergraduate students will carry out summer research in investigator labs in conjunction with activities sponsored by QB3, including the QB3 Lab Fundamentals Bootcamp. Graduate: Graduate students will have the option of choosing a Designated Emphasis (DE) in Computational and Genomic Biology. Postdoctoral: In addition to research, postdoctoral scholars in the Center will also pursue career development training in grant writing via QB3's Proposal Writing Workshop Series.

Institutional transformation

The CRSB expands the resources and collaborations of QB3—the California Institute for Quantitative Biosciences—while also providing a focal point for scientists at UC Berkeley in four Departments (Bioengineering, Chemistry, Mathematics, and Molecular and Cell Biology), and at UCSF, to address biological regulation mediated by RNA structure in human cells..

FACT SHEET

Center for RNA Systems Biology

National Center for Systems Biology since 2012

Three Projects explore mechanisms that control mRNA fate in humans

- Project 1. Systems Level Analysis of Alternative pre-mRNA Splicing
- Project 2. Systems-Wide Analysis of Translation Initiation Control by mRNA Structure
- Project 3. Influence of RNA Structure on miRNA-Mediated mRNA Turnover

Research Impact

CRISPR tools for interrogating the genome and the transcriptome: Cas9, CRISPRi and Csy4

Collaborations

Center for Systems and Synthetic Biology

Training and Outreach

CRSB Undergraduate Fellows program
Bay Area RNA Club sponsor

Microbial Ecology and Theory of Animals Center for Systems Biology

University of Oregon http://meta.uoregon.edu

Program Director:
Karen Guillemin (kguillem@uoregon.edu)

Program Coordinator:
Julie Hale (jhale@uoregon.edu)

Key staff : Brendan Bohannan, Research Area I Leader; Karen Guillemin, Research Area II Leader; William Cresko, Research Area III Leader; Judith Eisen, Gnotobiology Core Director; Raghuvheer Parthasarathy, Live Imaging Core Director; Eric Johnson, Genomics Core Director; John Conery, Bioinformatics Core Director; Peter O'Day, Diversity Director; Jessica Green, Outreach Director; Patrick Phillips, Education Director

Center Philosophy and Environment:

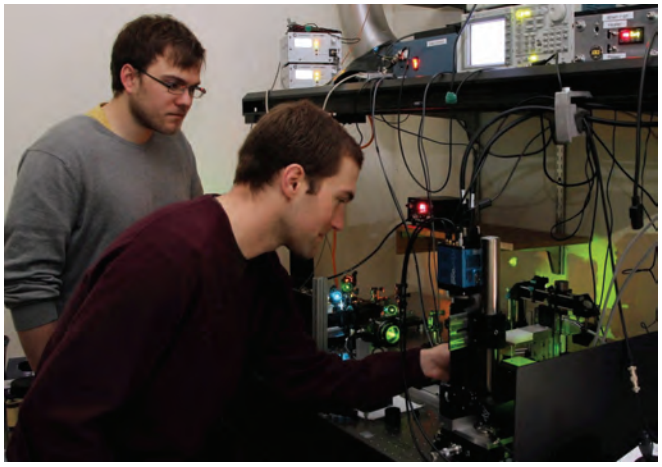
The Microbial Ecology and Theory of Animals (META) Center for Systems Biology is devoted to pioneering the field of host-microbe Systems Biology. Our Center is built on a longstanding tradition of interdisciplinary and collaborative research at the University of Oregon. Our research focus grew from an increasingly dense network of synergistic interactions between experimental biologists pioneering approaches to study animals with defined microbial associations, microscopists innovating new methods to image the dynamics of microbes inside animals, theoretical community ecologists developing new frameworks to describe host-associated microbial community assembly, and population geneticists addressing questions of host-microbe co-evolution. In many cases, these foundational collaborations were led by co-mentored graduate students and postdoctoral fellows who represent a new generation of bilingual scientists fluent in both experimental and theoretical approaches.

The philosophy of the META Center is to formalize and nurture the training of the next generation of systems biologists who will tackle the challenge of studying host-microbe systems. We are united in our fascination with the communities of microbes that inhabit all animals and so profoundly affect their development, physiology, and fitness, but our approaches to studying these systems are diverse. We are convinced that rapid progress will come from the melding of experimental and theoretical approaches to studying host-microbe systems and we have structured our research and training efforts to ensure that our postdoctoral fellows and students become proficient in

both. Our integration of experimental and theoretical approaches is enhanced by the fact that we work on systems of scalable complexity. On one hand, we embrace the natural diversity of host microbiota and harness this diversity to study system-level patterns in variation across individuals and populations to test ideas about community assembly. On the other hand, we use elegant experimental approaches to build simple, defined host-microbe systems that we can manipulate at the cellular and genetic levels and study with single cell resolution in space and time.

The META Center community draws from diverse groups at the University of Oregon who come together weekly for lively research talks and journal clubs and for regular planning meetings. We are infused with a spirit of congeniality from the longstanding tradition of community-building research at the University of Oregon, exemplified by the late George Streisinger who founded the field of zebrafish research that is a key part of the META Center endeavor. Our cross disciplinary research builds on a long history of

collaborative interactions, for example between evolutionary biologists and developmental geneticists, pioneering the field of evo-devo, and between molecular biologists and ecologists, leading to innovations in population genomics. During our first months of meetings we have embraced the diversity of our intellectual backgrounds and challenged ourselves to communicate our ideas in ways that span academic boundaries, that question conventions, and that critically evaluate the language, models, and metaphors of our individual disciplines.



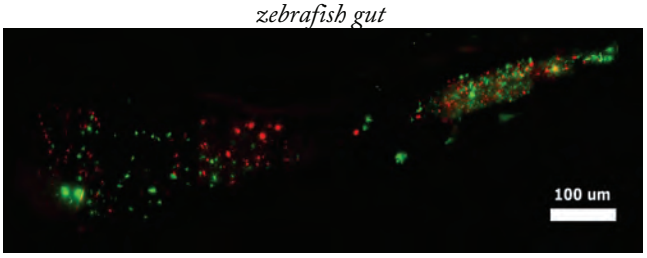
Research focus

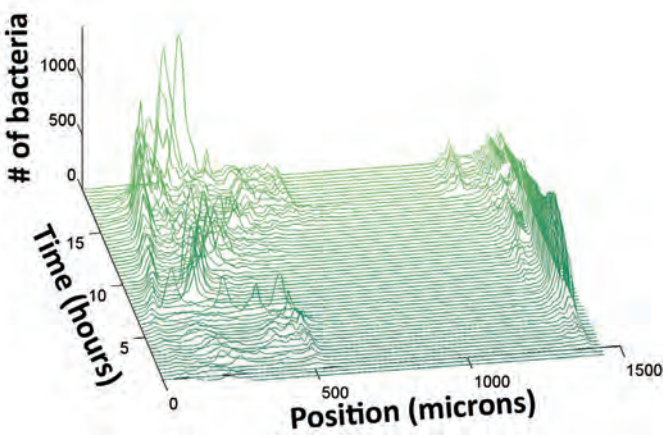
The META Center for Systems Biology has a focused research mission to understand the assembly, dynamics, and evolution of host-microbe systems. We meld the theoretical rigor of community ecology and population biology with the experimental elegance of our gnotobiotic fish models. We employ innovative live imaging and genomic approaches to create comprehensive large-scale datasets describing the membership and dynamics of host-associated microbial communities and corresponding host responses. We are developing new applications of sampling theory, spatial biodiversity theory, and probabilistic models to analyze our data and deduce system-level properties about host-microbe systems.

Assembly of Host-Microbe Systems: we are investigating the processes that govern the assembly of host-microbe systems by analyzing how ecological pressures such as bacterial competition and host immunity shape community phylogenetic structures. We are developing new phylogeny-based sampling theory to describe microbial community structures and we are using Bayesian networks to explore relationships between microbiota composition and host transcriptional responses in zebrafish models.

Dynamics of Host-Microbe Systems: we are using light sheet microscopy to investigate microbial dynamics in optically transparent fish, including bacterial colonization and growth and corresponding host innate immune responses. We are using computer simulations of bacterial adhesion and growth to explore parameters affecting microbial community structures across different spatiotemporal scales.

Light sheet micrograph of red and green fluorescent bacteria in a zebrafish gut





Topological representation of bacterial colonization of a zebrafish gut over space and time

Evolution of Host-Microbe Systems: we are using innovative population genomic approaches to study variation in networks of microbiota structures and corresponding host transcriptomes across genetically diverse populations to learn how host-microbe systems evolve. These studies focus on wild-caught and laboratory-reared populations of stickleback fish. We have been able to adopt many of our gnotobiotic and genetic methods developed in zebrafish to these genetically diverse fish populations.

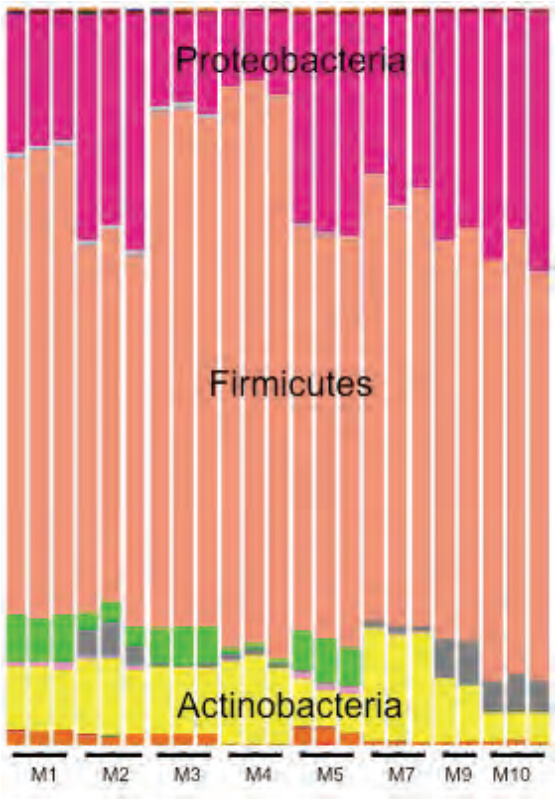
Education and outreach

Our META Center training and education vision is to nurture a new and diverse generation of scientists capable of working collaboratively across existing and emergent interdisciplinary domains of systems biology. Formal graduate education and training within the Center will take place primarily in our Graduate Education Modules (GEMs), which provide instruction in focused topics (e.g. whole genome sequence assembly, phylogenetic analysis of the microbiome, models of multi-trophic interactions, experimental design) in interactive, immersive and "cross-generational" workshop environments. Additional education and outreach occurs through our Center activities such as our weekly research meetings, journal club, and annual symposia.

To increase the diversity of scientists in systems biology, we have created the Alaska-Oregon Research Training Alliance (AORTA) as a pipeline for Alaska Native and Native American students to train at the META Center. This pipeline builds on our already extensive, ongoing research collaborations with University of Alaska labs and our close ties to the Alaska Native Science and Engineering Program (ANSEP). Our first cohort of four AORTA undergraduate interns arrived in Eugene in June and immediately were immersed in an innovative multi-disciplinary research program. During their summer, the interns will get to experience the joy of microbial discovery as they isolate new fish-associated bacteria and characterize their traits. They will learn molecular biology, genomics, and bioinformatics as they generate and analyze the genome sequences of their newly discovered microbes. In parallel, they will learn the power of gnotobiology and light sheet microscopy as they use their microbial isolates to inoculate germ-free transgenic zebrafish and monitor the responses of fluorescently labeled immune cells. In this program the interns will work as a cohort, mentored by expert graduate students and postdoctoral fellows, but they will have the freedom to pursue their individual projects and focus on the experimental and computational approaches that most captivate their individual interests. By the end of the summer they will have acquired an extensive research skill set and will have experienced the excitement of scientific discovery. We will foster long-term relationships with our interns and will encourage them to return for independent research projects and to enroll in our graduate program.

Institutional transformation.

The recent establishment of the META Center has already seen important institutional commitments to support for systems biology on campus. We are in the final stages of recruiting faculty for three new joint positions between the Mathematics and Biology Departments. If this search is successful, the new faculty will be transformative additions to the META Center and the University as a whole. The search process itself has catalyzed important new partnerships between the Mathematics and Biology Departments and will strengthen future planned hiring efforts in areas of bioinformatics and biostatistics.



Bacterial phyla in individual stickleback fish guts

FACT SHEET

Microbial Ecology and Theory of Animals Center for Systems Biology

National Center for Systems Biology since 2012

Research Focus:
The META Center for Systems Biology has three research areas devoted to advancing the field of host-microbe systems biology:

- Assembly of host-microbe systems
- Dynamics of host-microbe systems
- Evolution of host-microbe systems

Tools and Community Resources:
The META Center for Systems Biology has four innovation cores that will pioneer experimental approaches and best practices, develop analytical tools, and innovate novel theory for the field of host-microbe systems biology. These four cores are:

- Gnotobiology
- Live Imaging
- Genomics
- Bioinformatics

Training and Outreach:
The META Center for Systems Biology is dedicated to training the next generation of systems biologist in the area of host-microbe systems through our innovative training and outreach programs.

- Graduate Education Modules (GEMs)
- Alaska Oregon Research Training Alliance (AORTA)

Center for Cell Dynamics

University of Washington Friday Harbor Laboratories http:/celldynamics.org

Program Director: Garrett M. Odell, Ph.D.

National Center for Systems Biology from 2002-2007

Key Personnel (cumulative): Jonathan Alberts, Yvonne Beckham, Howard Clarke, Adriana Dawes, Victoria Foe, Kerry Kim, Kimberly Littlefield, Ryan Littlefield, Edwin Munro, Charles Paxton George von Dassow

The Center for Cell Dynamics is located at the University of Washington's Friday Harbor Laboratories. The Center sponsors research that combines experimental and computational approaches to basic questions in cell and developmental biology, including studies of cytokinesis, cell polarization, cell shape change and reorganization during morphogenesis, cytoskeletal mechanics and pattern formation by genetic networks. The Center hosts post-doctoral fellows, visiting scientists, and students, and provides a state-of-the-art laboratory including a distributed computing environment, confocal microscopes and other imaging systems, and a core molecular biology facility, at a premier marine research laboratory where investigators have unparalleled access to biological diversity.

Center for Modeling Integrated Metabolic Systems

Case Western Reserve University http://casemed.case.edu/mims/

Program Director: Gerald M. Saidel, Ph.D.

National Center for Systems Biology from 2002-2007

Key Personnel (cumulative): Joanne Belovich (Cleveland State University), Marco Cabrera, Daniela Calvetti, Jorge Gatica (Cleveland State University), Richard Hanson, Satish Kalhan, John Kirwan, Joseph LaManna, Michelle Puchowicz, William Stanley, Xin Yu

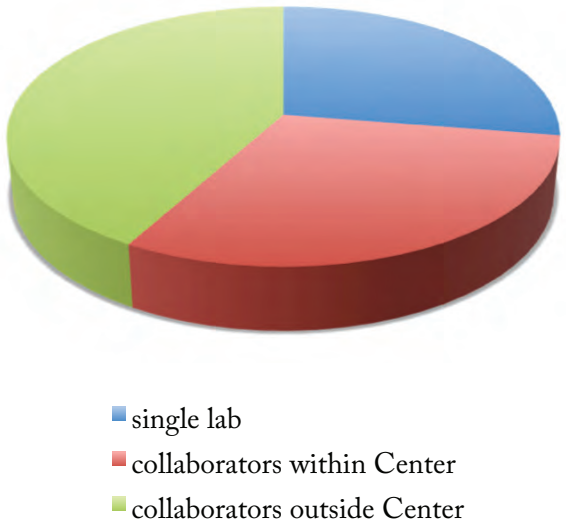
The MIMS Center develops mechanistic, mathematical models to simulate cellular metabolism in tissues and organs (i.e., skeletal muscle, heart, brain, and adipose tissue) and integrates these components in whole-body models. These biologically and physiologically based computational models incorporate cellular metabolic reactions and transport processes of a large number of chemical species. Model parameters characterize metabolic pathways and regulatory mechanisms under normal and abnormal conditions including obesity and hypoxia as well as in disease states including type-2 diabetes, cystic fibrosis, and chronic kidney disease. The large-scale, complex mathematical models are solved numerically using sophisticated computational algorithms to simulate and analyze experimental responses to physiological and metabolic changes. Model parameters are estimated using large-scale, nonlinear optimization algorithms. Experimentally validated models are used to predict effects of altering metabolic processes with disease states, pharmacological agents, diet, and physical training.

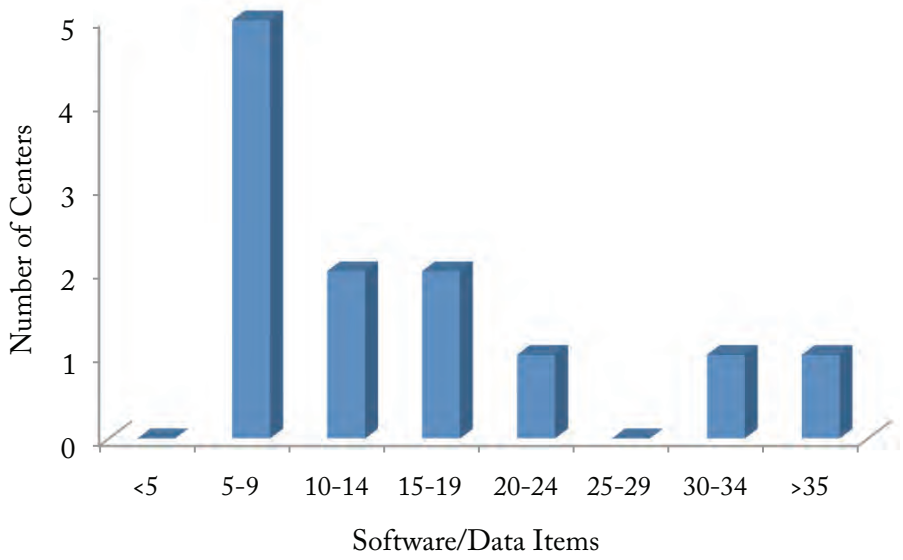
The Program in Numbers

The National Centers for Systems Biology have worked together to develop a common set of metrics for tracking research, education, and outreach activities. An aggregate analysis of these metrics provides a quantitative assessment of the output and, to some extent, the impact of the Centers program. Here we present the first such program-wide analysis. Among other things, it provides a snapshot of what the program has delivered, facilitating comparison with the expected outcomes of other sorts of research funding mechanisms (e.g. R01s).

Publications and Collaboration

Overall, the Centers have published 1761 articles since 2003, corresponding to a rate of 22 publications per year per center; 12 per year per center if one excludes publications for which Centers provided only non-essential or core facility support. Remarkably, 72% of all publications have reported collaborative research projects.



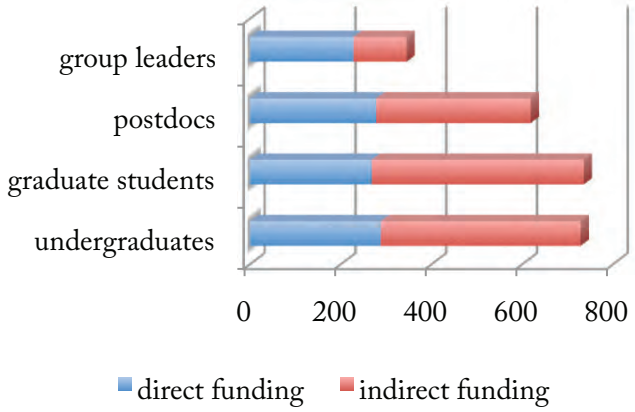


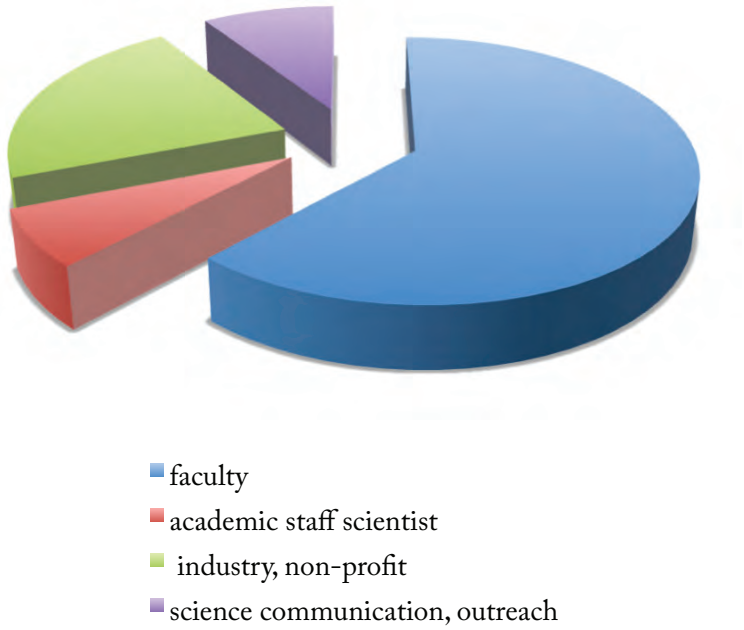
Resources: Software, Databases and Data Sets

The Centers developed 180 software packages and/or databases, more than 2 per funded year per center. These and other resources are made available to the scientific community through a common web portal, www.systemscenters.org

Group leaders and trainees

The program funded research of 228 group leaders, and directly supported 268 graduate students and 278 postdoctoral fellows; 467 graduate students and 340 postdocs benefited indirectly, by participating in grant-supported projects or center funded educational activities. The program trained on average 3.4 graduate students and 3.5 postdocs per center per funded year (ranging from 0.7 to 15 graduate students and 0.7 to 10 postdocs per year per center). The average number of graduate students and postdoctoral trainees increases to 9.1 and 8.5, respectively, if indirectly supported trainees are included.



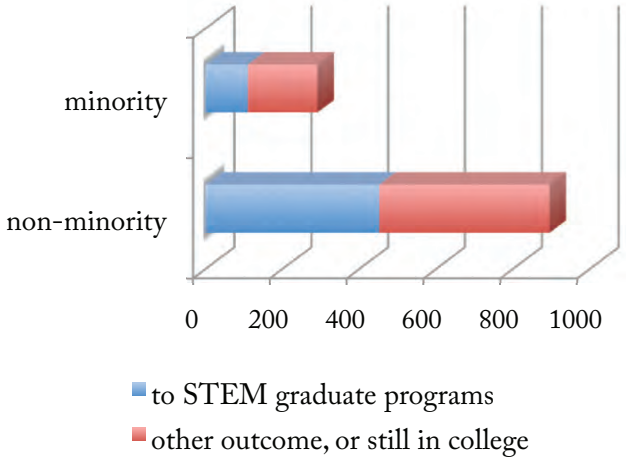


Career Outcomes

A large fraction of postdoctoral trainees leave the centers to start faculty positions. So far the Centers have produced 159 faculty, or 2 faculty per funded year per center.

Undergraduate Outreach and Diversity

The program supported 348 undergraduates directly (including 122 underrepresented minority [URM] students), and 1215 undergraduate students indirectly (including 220 URM students). For centers that have tracked the career choices of previous undergraduate trainees for several years, 50% of previous undergraduates (37% of URM students) are now enrolled in or heading to STEM graduate programs.



Acknowledgements

The National Centers for Systems Biology program owes its success to the tireless efforts of many dedicated people, both at the NIH and in the home institutions of the Centers. Some of those who have devoted large amounts of their time to activities that benefit the Centers program as a whole, are gratefully acknowledged below.

NIH Program Staff

Irene Eckstrand, Paula Flicker, James Anderson, Peter Preusch, Peter Lyster, Jerry Li, Shiva Singh, Paul Brazhnik, Sarah Dunsmore, Darren Sledjeski

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Connie Lee	Center for Systems and Synthetic Biology
Bill Collins	NM Center for Spatiotemporal Modeling of Cell Signaling
Jennifer Dougherty	Center for Systems Biology
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Anna Lu	San Diego Center for Systems Biology
Fabiola Rivas, Barry Aprison	Chicago Center for Systems Biology
Stacy Romant, Chris Thompson	Virtual Physiological Rat Project
Bodo Stern	Center for Modular Biology
Jana Stone	Duke Center for Systems Biology
Jamie Cate, Jan DeNofrio	Center for RNA Systems Biology
Kara Dolinski	Center for Quantitative Biology
Jeremy Muhlich, Leslie Ann Roldan	Center for Cell Decision Processes

Web masters

Jeremy Muhlich	Center for Cell Decision Processes
Chris Thompson	Virtual Physiological Rat Project

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Barry Aprison and Faby Rivas	Chicago Center for Systems Biology
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Kara Dolinski	Center for Quantitative Biology
Anna Lu	San Diego Center for Systems Biology
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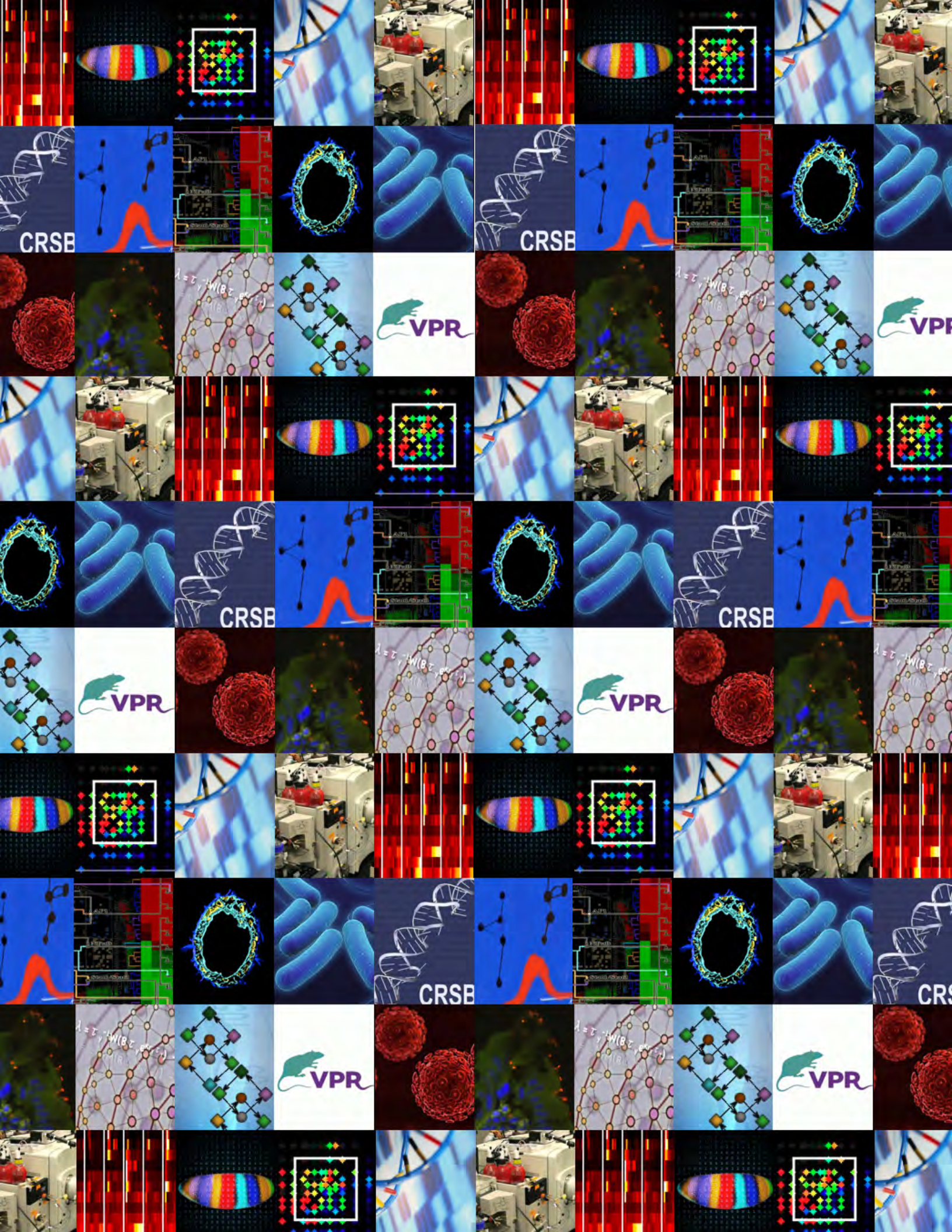
Julie Hale	META Center for Systems Biology
Jamie Cate	Center for RNA Systems Biology


CRSB
VPR