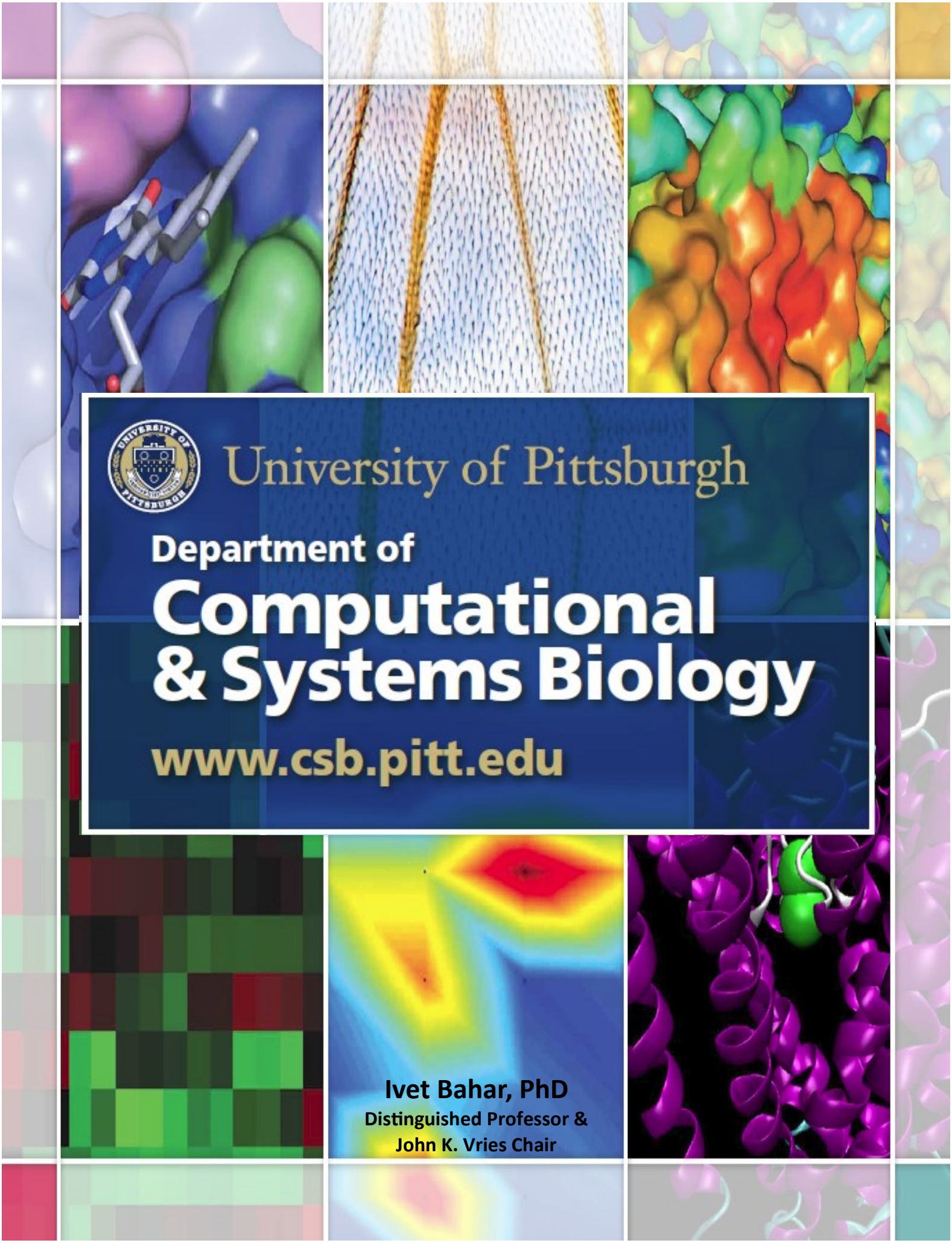
University of Pittsburgh
Department of
Computational
& Systems Biology
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Department of

COMPUTATIONAL & SYSTEMS BIOLOGY

School of Medicine
University of Pittsburgh

IVET BAHAR, PH.D.
DISTINGUISHED PROFESSOR AND
JOHN K. VRIES CHAIR

FISCAL YEAR 2014
ANNUAL REPORT

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(2001-2014)

Section I

General Description

Computational and Systems Biology – Who We Are

As we anticipate the celebration in October of 10 years as a department, the Department of Computational and Systems Biology (CSB) has continued to be a leader in the field. Our increasing focus on multi-scale interactions in biological systems, and enabled us to tackle more research at an integrated, *Systems* level. The post-genomic and big data eras have brought a new excitement to science. With this excitement also come new challenges that require new and innovative approaches with which to tackle them. CSB continues to play a leading role in driving discovery through continued interdisciplinary efforts to answer the research challenges of today, and define the new approaches to address the questions of tomorrow. Concomitant, with our research foci, we also make concerted efforts in educating the next generation of scientists, who will continue this work. The unique, hands-on research opportunities that we provide to students at the graduate, undergraduate, and even high school levels provide these students with the necessary interdisciplinary and hands-on training to prepare them for careers in these fields. At the same time, these efforts provide numerous opportunities for our postdoctoral fellows and junior faculty to serve as mentors for our scientists-in-training, especially those at the undergraduate and high school level. These early experiences in mentoring are valuable opportunities that allow these scientists to hone their mentoring skills, while working together with some of the best and brightest in the next generation.

In 2014, the contributions of our Faculty were highlighted by various awards and articles. Dr. Ivet Bahar received the 2014 Chancellor's Distinguished Research Award, was featured in International Innovation, and the MMBioS Resource was featured in the 2013/14 winter edition of EMBO encounters and at the Biophysical Society Meeting. Dr. Chennubhotla was received the Medical Student Research Mentoring Merit Awards and appeared in PLoS One for his studies on odor, which received substantial press (NBC News, LA Times, BBC, etc). Jeremy Berg, the Director of Personalized Medicine, published "How the NIH can help you get funded: An insider's Guide to Grant Strategy". Dr. Berg and Dr. Taylor, Director of the Drug Discovery Institute, organized a Workshop on Quantitative Systems Pharmacology (QSP) in Personalized Medicine (PM). In addition, Dr. Benos, along with Dr. Schwartz of CMU, were the Conference Chairs and hosted RECOMB 2014: the 18th International Conference on Research in Computational Molecular Biology in Pittsburgh. Our educational programs received recognition with our CPCB program being featured in "The Scientist" and TECBio REU's article, "Of lab rats and computer mice", in the NSF highlights. We are committed to providing a home that welcomes highly interdisciplinary faculty, and that firmly establishes the University of Pittsburgh in nationally recognized leadership roles in rapidly growing and evolving fields that are driving the next wave of scientific discovery.

In keeping with the interdisciplinary nature of the field, the department has recruited two additional tenure-track faculty with diverse academic training. Robin Lee, starts with the Department in August 2014 and Jianhua Xing will join us in January of 2015. To assist all of our faculty, CSB is committed to providing the highest level of support from our staff.

CSB Research – Leading the Field with Cutting-edge Science

Increasingly complex biological problems and extremely large biological data sets have necessitated new approaches to answer many of today's current research challenges. As one of the fields in what are now being called the "New Biologies", Computational and Systems Biology encompasses an interdisciplinary approach to harness the power of computation to tackle the emerging big data challenges and to answer

questions in biology not amenable to traditional approaches. Thus, to rise to these challenges and to continue to be a leader in this newly emerging field, CSB has set our research mission to:

Advance the scientific understanding of biological systems through computational tools and theoretical approaches based on the fundamental principles of physical sciences

Design new computational/mathematical models and methods for simulating complex biological processes and for extracting useful information from accumulating data

CSB investigators pursue this mission by investigating leading questions in biology and medicine in four major areas of specialization/growth in the field:

1. Bioinformatics and Computational Genomics and Proteomics
2. Cell and Systems Biology
3. Molecular Structural Biology
4. Pharmacology and Drug Discovery

Bioinformatics and Computational Genomics and Proteomics

The genomics and proteomics fields are primarily based on computer science and statistics, and aim to digest the daunting quantity of "-omics" data now available by systematic development and application of probability and statistics theories, information technologies and data mining techniques. Within *Genomics* there are three main categories: functional genomics, structural genomics, and comparative genomics. Functional genomics generally refers to the high throughput determination of gene functions. Structural genomics is the systematic effort to gain a complete structural description of a defined set of molecules, ultimately for an organism's entire proteome. Comparative genomics uses evolutionary relationships between various organisms to understand the structure and function of the genome. *Proteomics* aims at quantifying the expression levels of the complete protein complement (the proteome) in a cell at any given time. While proteomics research was initially focused on two-dimensional gel electrophoresis for protein separation and identification, proteomics now refers to any procedure that characterizes the function of large sets of proteins. Proteomics may be considered as a subset of functional genomics.

Cell and Systems Biology

Systems biology seeks to integrate different levels of information to understand how biological systems function at multiple scales, with the goal of developing an understandable model of a whole system. This is accomplished by studying the relationships and interactions between various parts of the particular system of interest, which could range over orders of magnitude, from molecular assemblies to subcellular-, multicellular-, and tissue-level systems.

Molecular Structural Biology

Studying the architecture, shape, and dynamics of biological macromolecules is paramount to understanding the basic mechanisms that drive the essential processes of all life. Macromolecules such as proteins and nucleic acids carry out most of the functions of a cell, and are able to perform these functions by adopting ensembles of structures under native state conditions. Structural biology is concerned with the driving forces and interactions that determine the three-dimensional shapes and dynamics of biomolecules. Moreover, by applying the fundamental principles of the physical sciences, we are beginning to establish sequence-structure-dynamics-function relationships that enable deeper levels of discoveries, and summon the possibility of *de novo* structural and functional predictions at the proteome level.

Pharmacology and *Drug Discovery*
Computational and theoretical approaches are revolutionizing Pharmacology and Drug Discovery. Predicting, modeling, and simulating potential therapeutic agents and their interactions with target molecules is a powerful new first step in the drug discovery process. This *in silico* approach streamlines the often laborious, expensive, and slow process of identifying and testing lead compounds for use as treatments. Combining these advances with high-throughput and high-content cellular- and systems-level pharmacological and poly-pharmacological approaches is profoundly impacting medical science. The UPDDI is committing major efforts in "Quantitative Systems Pharmacology" (QSP) alongside "Chemistry and Molecular Biophysics", while all technical areas of drug discovery and development will continue to be employed and extended in our programs.

While the four areas may appear distinct, there is considerable overlap, and they all share a common goal: *quantitative evaluation/prediction of biological data/processes*. Traditionally, these areas have been advanced by researchers specialized in one of the specific disciplines. However, it is now widely recognized that they can advantageously complement/guide each other, and their combined use can induce synergistic effects. Thus, multidisciplinary expertise is essential for efficient development and use of computational biology tools.

CSB Educational Endeavors – Training the Next Generation of Scientists
As one of the first departments in computational and systems biology in the nation, the faculty and staff of the department strive to establish a successful model for inter-disciplinary research by collaborating with experimentalists and theoreticians alike and training a new generation of researchers capable of meeting the next wave of scientific challenges and thereby propagating scientific advances and breakthroughs. To this end, we have also set forth the educational goals of offering first-class programs at the graduate, undergraduate, and high school levels in computational biology, all of which serve multiple purposes: (i) to introduce computational biology problems and methods to students from chemistry, physics, engineering, mathematics, and computer sciences, (ii) to teach fundamental concepts of the quantitative and physical sciences to biology and biomedical sciences students, (iii) to prepare and encourage students at all levels for a career in computational biology research, and (iv) to reach out to and recruit students from backgrounds that are underrepresented in the sciences. In all cases, the aim is to train students and postdoctoral researchers to identify and tackle **complex biological problems** on a computer—managing and integrating databases, simulating biological phenomena at different levels.

Joint CMU-Pitt Ph.D. Program in Computational Biology
To support this educational mission, the Joint CMU-Pitt Ph.D. Program in Computational Biology (CPCB) was developed as a collaborative effort between the University of Pittsburgh and Carnegie Mellon University. This program was conceived as a cross-institutional (Pitt and CMU) and cross-campus (Pitt SOM and SAS) Ph.D. program that would exploit the complementing strengths of the different universities or schools. (For additional details about this program please refer to the *Teaching Activities* section of the department's Annual Report.

The CPCB is supported through the Graduate Studies Office of the School of Medicine. In the first year of the program, students' stipends and tuition expenses are covered by their respective universities. Beginning in their second year, students' stipend costs are supported by their respective mentors through research dollars and/or other funding sources. Tuition costs for those students enrolled in the University of Pittsburgh are allocated to their respective departments via the university's annual step down cost model. In its first year, the CPCB enrolled six students (4 at Pitt and 2 at CMU). Including the 7 students who joined the program in Fall 2012, the program has a total of 56 students, of which 34 are domestic. About 25% of our students are female. Through aggressive recruiting efforts and wide dissemination of program information, CPCB expects to steadily increase enrollment each year. In FY14, the following activities are planned: Creation and distribution of a program flyer; direct mail approach to attendees of ABRCMS conferences to reach out to students underrepresented in the sciences; increased recruitment at research

conferences and workshops. In FY 14, we anticipate that 3-5 students will apply for graduation to complete their thesis requirements.

In November 2005, Carnegie Mellon University, in partnership with the University of Pittsburgh, was selected to receive a $1 million grant from the Howard Hughes Medical Institute (HHMI) to support the development of the CPCB. In FY09, our program was awarded an NIBIB T32 Training Grant: Integrated, Interdisciplinary, Inter-University Ph.D. Program in Computational Biology (PIs: Ivet Bahar and Robert Murphy). This training grant supports 8 students each year. In FY14, CPCB will continue to pursue additional funding opportunities to support our graduate training.

Other Graduate Programs

Besides their role in CPCB, CSB faculty play an active role in mentoring and teaching students enrolled in several other graduate programs at the University of Pittsburgh. These include the Interdisciplinary Biomedical Graduate Program, Molecular Biophysics + Structural Biology Graduate Program, Program in Integrative Molecular Biology (PIMB), Biomedical Informatics Training Program, Human Genetics Ph.D. Program, and Physics Ph.D. Program. In FY14 and beyond, CSB faculty will continue to make themselves available as advisors/co-advisors in these programs.

Undergraduate Summer Programs

In 2003, The University of Pittsburgh was one of only 11 institutions funded for a summer training initiative in computational biology. This NIH-NSF-funded program, "BBSI @ Pitt: Simulation and Computer Visualization of Biological Systems at Multiple Scales" was a multi-institutional program between the University of Pittsburgh (lead institution), Duquesne University, the Pittsburgh Supercomputing Center, and Carnegie Mellon University. This program was conducted from Summers 2003 to 2009. In order to continue our commitment to providing graduate-level research experiences to undergraduate students, we applied for and received an NSF award for a Research Experiences for Undergraduates (REU) program that we began hosting in summer 2010, maintaining the continuity of our undergraduate mentoring efforts from the BBSI program. For this new REU summer program entitled Training and Experimentation in Computational Biology (TECBio), we have built off of the success of our BBSI program, and have kept many of the components that made the previous program a success. In our first summer we had 150 applicants for our 10-week program, which yielded a group of high quality students for inaugural program. In our second and third summers, our average applicant pool was over 200 and for our 2013 and 2014 programs our application pool sky-rocketed to over 300 applicants. Our applicants were a very diverse group who came from many academic and ethnic backgrounds, including many students from groups underrepresented in the sciences and those that are at universities that have limited research opportunities. We recently submitted and obtained a 4-year renewal of our TECBio program. Since the program received one of the top scores in the review process, the Department of Defense is now a co-sponsor of our program. With the TECBio REU program, we look forward to continuing our traditions of undergraduate mentoring and training to inspire the next great generation of scientists.

High School Summer Program

The summer of 2011 saw the start of a new initiative in the CSB that reached out to high school students in the Pittsburgh area. In collaboration with the Department of Biomedical Informatics, we started a new component of the University of Pittsburgh Cancer Institute's (UPCI) High School Summer Academy, which we called the Computational and Systems Biology and Biomedical Informatics (CoSBBI) Academy. In the first two summers of this initiative, we accepted 13 students in our program and matched them up with a research mentor for an 8-week summer research experience. In the summer of 2013, the CoSBBI program expanded into 2 separate and larger programs, one still housed in Biomedical Informatics and one hosted by CSB in partnership with the UPDDI. This new program, which is called the Drug Discovery, Systems and Computational Biology (DiSCoBio) Academy, offers computational and experimental training opportunities to our cohort. The mentored research component was complemented by numerous other enrichment activities, including didactic training in the major disciplines in drug discovery and computational and systems biology, hands-on and demonstration sessions, research and career seminars, tours of labs and

research facilities on campus, educational and social field trips, and a number of opportunities for the students to present their work and hone their communication skills. Many of our faculty, postdoctoral fellows, graduate students, and summer undergraduate students were involved in this program through their efforts as research advisors, mentors, lecturers, information session panelists, and/or hosts of students on various tours and other events. Students in the DiSCoBio program were also specifically integrated in the tiered-mentoring framework with the graduate and undergraduate students in the CSB to provide them with important sources of information on how to conduct their research, and what it is like to be an undergraduate/graduate student and how to prepare oneself to go about the application processes for both.

Research Associates

Research associates form an integral part of every research environment, as they are capable of mostly independent research, and are also in a position to assist students during their dissertation work. New faculty recruited to the CSB received three years of support for research associates. In addition, research associates in the CSB are encouraged by their faculty mentors to seek out fellowships, awards, and other sources of funding.

Computational Biology Classroom

For effective teaching of computational biology to students and/or other individuals, it is important to have an infrastructure capable of such education. Unlike other disciplines, computational biology is best taught "hands-on," where the instructor has the option of demonstrating concepts using the appropriate audio-visual technology/equipment, and students can simultaneously participate. The CSB classroom (3073 BST3) has been designed to meet this necessity. In the classroom, there are 22 17" Intel Core i5 Dell laptops at each desk, plus an additional one at the presentation podium, which are all set up for wireless access and configured with specific software to assist and complement the teaching of computational biology courses. Four Linux workstations featuring quad-core AMD phenom cpu, 8Gb ram, 750 Gb hard drive, nVidia video card, and dual 22" monitors are also available. These are intended for use by students for more graphic-intensive applications, such as PyMol and VMD. A mobile 46" LCD-flat-panel-based Smart Board can be used in the classroom and conference room for interactive whiteboard, presentations, and video conferencing.

The classroom has served as a major hub for many of our educational programs and other departmental activities. Throughout the academic year, the classroom houses lectures for the courses in our graduate program, a host of special seminars, many lab meetings, and various other events. In the summers, this classroom is utilized by the REU program for courses, seminars, journal clubs, research projects, and other activities. The CoSBBI program also uses the classroom for their didactic activities, and also as a place for the students to work on their research projects. Throughout FY14, CSB will continue to both seek out state-of-the-art equipment and software to optimize this classroom for teaching of computational biology courses and workshops and also provide high-level, cutting-edge research, and didactic training experiences to students at all levels.

Section II

Research and Other Scholarly Activities

Ivet Bahar, Ph.D.

Distinguished Professor and John K. Vries Chair

My research interests are: (i) **Computational Structural Biology**, i.e., modeling and simulations of biomolecular systems structure and dynamics, and developing new theories and computational tools for analyzing the structure-based dynamics of large complexes and assemblies toward understanding their mechanisms of biological function, (ii) **Molecular Biophysics**, i.e., understanding the basic principles of macromolecular systems dynamics, the physical basis of observed events such as allosteric signal transduction, protein-protein and protein/ligand interactions, toward a molecular level description of cellular events, with focus on the interactions involved in cell cycle regulation and signaling; (iii) **Bioinformatics**, i.e. structure-function relationship of proteins and developing novel statistical natural language models for predicting structure, folding/misfolding, and function; establishing the relationship between sequence evolution and functional dynamics; (iv) **Computer-aided drug discovery**, i.e. development of novel models and methods for efficient characterization of protein-ligand interaction geometry and energetic, and interpretation of *in vivo* data from a **Systems Biology** perspective, integrating pharmacology and systems biology methods with focus on the pathways and networks of interactions that may be affected upon targeting particular proteins.

My lab has worked on research pertaining to the following grants throughout the past year:

1) **HIGH PERFORMANCE COMPUTING FOR MULTISCALE MODELING OF BIOLOGICAL SYSTEMS:** The National Center for Multiscale Modeling of Biological Systems (MMBioS) develops tools to advance and facilitate cutting-edge research at the interface between high performance computing and the life sciences. Our overarching goal is the predictive multi-scale modeling of the spatiotemporal organization and evolution of neurosignaling systems and events. The advances made here will impact the research activities of a broad group of scientists, from molecular and structural biologists to cell and systems biologists. These advances will also facilitate the translation of basic tools to biomedical and clinical research by establishing and then disseminating a computational framework which integrates theory with experiment and models with methods originating from different disciplines.

We are building on the state-of-the-art technology and methods at the forefront of molecular and cellular modeling that have been developed at our partner sites. Rapid advances in experimental technologies which enable the study of events ranging from single molecule dynamics to tissue level organization also create multi-scale modeling challenges. We are addressing these emerging challenges, including high performance computing, data storage and networking needs.

This work continues to be conducted within the scope of the NIGMS-funded P41 (PI: Bahar), in collaboration with Carnegie Mellon University and the Salk Institute.

2) **STRUCTURAL DYNAMICS OF BIOMOLECULAR SYSTEMS:** An increasing number of computational studies have adopted network models for investigating biomolecular systems dynamics and interactions in recent years. In particular, elastic network models have proven useful in elucidating the dynamics and allosteric signaling mechanisms of proteins and their complexes. This work presents an overview of the two most widely used elastic network models, the Gaussian Network Model (GNM) and Anisotropic Network Model (ANM). We illustrate their use in (i) explaining the anisotropic response of proteins observed in external pulling experiments, (ii) identifying residues that possess high allosteric potentials, and demonstrating in this context the propensity of catalytic sites and metal-binding sites for enabling efficient signal transduction, and (iii) assisting in structure refinement, molecular replacement and comparative modeling of ligand-bound forms via efficient sampling of energetically favored conformers.

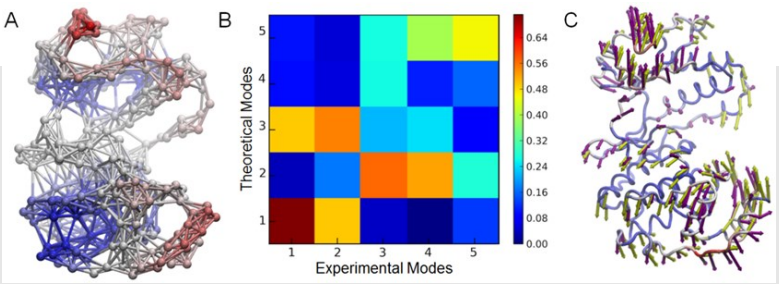


Fig. 1. ANM analysis of p38 and comparison with experimental data. **A.** Network model representation of p38 is shown. **B.** ANM modes are compared to experimental (PCA) modes. **C.** ANM mode 1 (green) and PC1 (purple) are depicted using arrows. Panels A and B are prepared using NMWiz and VMD.

This work continues to be conducted within the scope of the NIGMS-funded R01 (PI: Bahar) on the structural dynamics of biomolecular systems, in collaboration with the SIMBIOS lab at Stanford University.

3) **CONTINUED DEVELOPMENT OF PROTEIN DYNAMICS SOFTWARE PRODY:** Global Dynamics of Proteins: Bridging Between Structure and Function. In recent years, elastic network models used in conjunction with normal mode analyses have proven to be useful for elucidating the collective dynamics intrinsically accessible under native state conditions, including in particular the global modes of motions that are robustly defined by the overall architecture. With increasing availability of structural data for well-studied proteins in different forms, there is increasing evidence in support of the correspondence between the functional changes in structures observed in experiments and the global motions predicted by these coarse-grained analyses. These observed correlations suggest that computational methods may be advantageously employed for assessing functional changes in structure and allosteric mechanisms intrinsically favored by the native fold.

This research continues to be supported by NIGMS-funded R01 (PI: Bahar) (See Fig 1 above)

4) **COMPUTATIONAL PHARMACOLOGY**: The Bahar lab is leading the Computational Pharmacology Core of the NIDDK funded Program Project (P50) "New Therapies for liver fibrosis and hyperproliferation in alpha1-antitrypsin deficiency" led by Dr. Perlmutter (PI). This program project aims at discovering and testing novel compounds as potential therapeutic agents, as well as test and discover signaling pathways as potential modifiers, of liver disease due to alpha1-antitrypsin deficiency (ATD), one of the most common genetic causes of liver disease and a frequent indication for liver transplantation. The Bahar lab will provide expertise in developing and applying computational tools for modeling protein-inhibitor interactions, and analyze high throughput and high content screening (HTS/HCS) data for assessing target proteins, identifying relevant pathways and networks, evaluate systems (poly)pharmacological effects of therapeutic strategies.

The Core resources for high-throughput virtual screening of molecular libraries as well as modeling protein-ligand interactions and mining databases are extensively used to serve the research goals of the Center. The specific aims focus on two areas: (i) quantitative and systems pharmacology (OSP) analyses and (ii) ligand- and target-based discovery approaches. QSP delivers new therapeutical targets with small-molecule modulators and polypharmacology strategies for experimental tests in Project 1. We identify new potential targets by analyzing RNAi and small-molecule screening data from Project 2 using machine learning techniques. We also assess the polypharmacological effect of simultaneously targeting more than one protein. In particular, we investigate the effects of combining modulators of autophagy and proteasome pathways, newly identified targets, and/or other specific targets investigated in Project 1 towards designing polypharmacological strategies. Target- and ligand based approaches, on the other hand, are used for repurposing existing drugs, computational assessment of identified targets, and identifying new compounds. We mine drug-target association databases such as DrugBank, and protein structural databases using sequence- and binding site shape similarity metrics. Targets with known structural data are examined for availability of alternative more selective inhibition mechanisms by identifying potential allosteric sites. To this aim, we use the structural ensemble analysis software and elastic network models developed in the Bahar lab. Finally, we identify new chemical scaffolds by pharmacophore-based screening of purchasable compound libraries. Structure-based models of Project 1 targets, experimental HTS hits from Project 2, compounds from literature (e.g. autophagy inducers), and chemical mitogens investigated in Project 3 are used in pharmacophore model building. Compounds that we identify and prioritize are tested in cell lines, mouse and worm models of ATD. Results are used to refine pharmacophore models and to iteratively search for new compounds.

5) **CHEMOINFORMATICS**: The Bahar lab is leading the Chemoinformatics Core of the Center Grant "Mitochondrial targeted small molecule radiation mitigators" led by Dr. Greenberger, funded by NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES.

The specific aims ofthe Chemoinformatics core are the following: A.I. Contribute computational expertise to the hit-to-lead activities, library design, lead optimization and identification of potential mitigators of radiation damage at the CMCR A.2. Provide computer-aided predictions of drug toxicity and metabolism A.3. Identify target-mitigator interaction pathways and networks to correlate molecular functions to physiological processes that will help in designing safe and efficient mitigators of radiation damage. The Computational Chemistry and Computational Biology resources from the Department of Computational Biology (DCB) will be used to integrate workflow and dataflow for optimum effectiveness in achieving the goals ofthe CMCR projects. At the same time we are thoroughly examining the dynamics and druggability of certain molecules, such as VDAC (Figure 2) toward controlling apoptotic response prompted by cytochrome c release from the mitochondria.

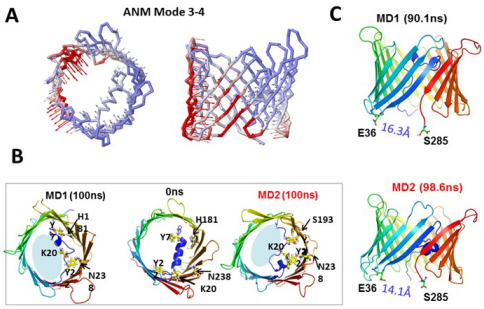


Figure 2. Examination of the structure and dynamics of VDAC as a target for controlling mitochondria-mediated apoptosis. (A) Collective movements accessible to VDAC. The amplitude (*color-coded*) and directions (*arrows*) of the most probable two (2-fold degenerate) modes predicted by the ANM degenerate modes 3 and 4 are mapped onto the VDAC1 backbone structure. *Blue* indicates less mobility whereas *red* indicates higher mobility. The lengths of the arrows scale with the amplitude of the motion. **(B) Dynamics and interactions of the N-terminal -helix and surrounding coiled segments.** hVDAC conformations at the end of 100 ns runs (*left* and *right*), compared to the original structure (*middle*). Y7, originally facing the pore (*middle*), reorient to interact with H181 (*left*) or S193 (*right*); Y22 also undergoes a significant conformational change to interact with N238 on barrel in both MD1 and MD2. **(C) Weakening of 1-19 interactions and unraveling of the -barrel.** The top panel shows conformations at t = 90.1ns (MD1) and bottom panel at t = 98.6 nm (MD2), highlighting the separation between 1 and 19. (Shrivastava et al, 2014; in preparation).

In addition, my lab will start research pertaining to the following grant throughout the coming year:

1) NIDA Center of Excellence OF Computational Drug Abuse Research (CDAR): The overarching aim of the Cores is to develop, implement and enable broad usage of computational technology (algorithms, methods, software and tools) for enhancing the effectiveness of DA research, both on a local level (by supporting ongoing funded projects at Pitt/CMU) and at the national level (via close cooperation with other labs including the NIDA Centers Consortium members).

This research is funded through our collaboration between Sean Xie (Pitt) and Eric Xing (CMU). The Bahar lab is leading the project as one of the three PIs (together with Xie and Xing).

Panayiotis (Takis) Benos, Ph.D.

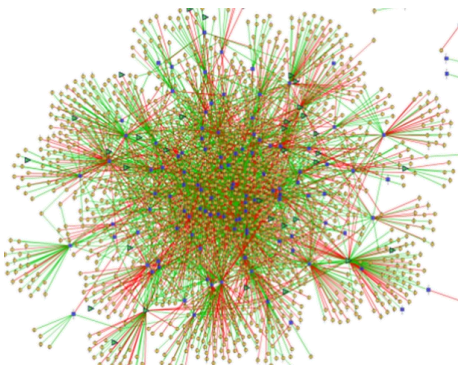
Associate Professor

Current Research Interests: Modeling transcriptional and post-transcriptional gene regulation; modeling of gene networks; statistical analysis of heterogeneous biomedical, genetic and clinical data.

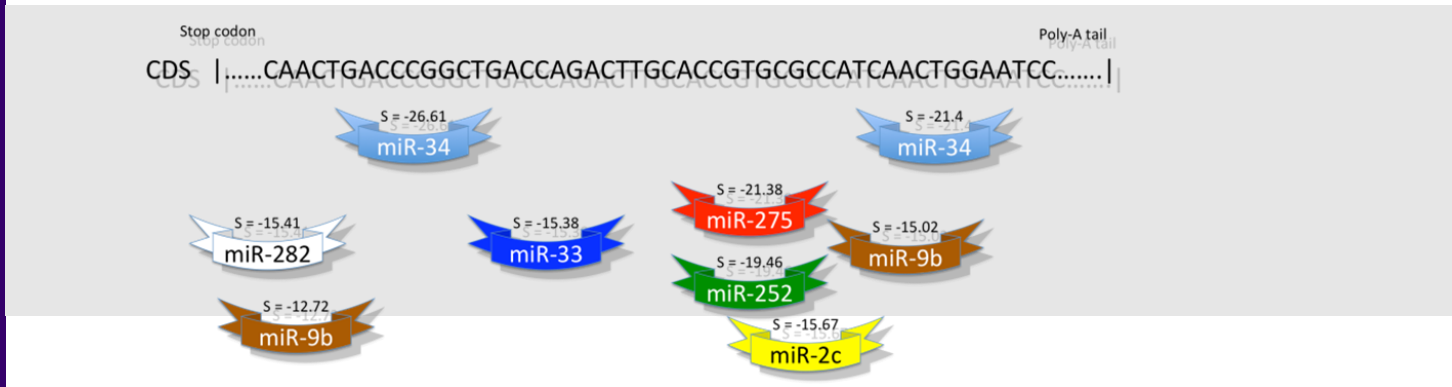
Gene expression regulation is a fundamental process in the life of the cell. It determines, in a unique way, its response to changing environment, communication with other cells, and its developmental fate. Mis-regulation of genes' expression has been linked to a plethora of abnormal conditions from cancer to autoimmune diseases.

Our group is mainly interested in understanding gene regulation, its dynamics, the mechanistic characteristics of the protein-DNA interactions and the evolution of DNA and RNA "signals." We develop mathematical models and computational algorithms to study the gene-DNA and gene-gene interactions from heterogeneous high-throughput data. We are particularly interested on the interactions between transcription factors and microRNA (miRNA) genes in the context of terminal diseases. miRNA genes are short (20-22 nt long) non-coding RNAs that are shown to play a very important role in developmental processes as well as in many diseases and abnormal phenotypes in humans. More recently, our group started developing machine learning algorithms that can analyze efficiently multi-modal datasets consisting of heterogeneous data streams.

DNA motifs. Among the laboratory's early findings is the development of computational algorithms for the identification of DNA *cis*-regulatory elements, like FOOTER (Corcoran, *et al.*, *Genome Res* (2005), **15**:840-847) and an improved version of SOMBRERO (Mahony, *et al.*, *Bioinformatics* (2005) **21 Suppl:** i283-i291.) Our group also studied the co-evolution of transcription factors and their DNA binding motifs (Mahony, *et al.*, *PLoS Comput Biol* (2007), **3:**e61) and developed the first web server that can perform pairwise and multiple DNA motif alignments, phylogenetic tree constructions and comparisons and clustering of DNA patterns (the equivalent of BLAST and CLUSTALW for DNA motifs.) We also participated in the analysis and annotation of the opossum genome, the first non-eutherian mammal sequenced (Mikkelsen, *et al.*, *Nature* (2007) **447:**167-



177; Mahony, *et al.*, *Genome Biol* (2007) **8:**R84.) More recently, the laboratory published algorithm DiSCo. DiSCo identifies transcription factor sub-motifs that recognize DNA targets only in the presence of certain co-factors (Bais, Kaminski, Benos, *Nucl Acids Res* (2011) **39:**e76.) We are continue to extend these algorithms to analyze high-throughput DNA-binding data, such as ChIP-seq and ChIP-exo.



miRNA genes and gene networks. Benos' laboratory developed a new algorithm (HHMMiR) for *de novo* identification of microRNA genes without using evolutionary information (Kadri, *et al.*, *BMC Bioinformatics*, (2009) **10**(Supl 1)**:**S35.) This algorithm is based on the hierarchical hidden Markov model framework and was proven to be very efficient in correctly predicting the miRNA-containing stemloops even for distantly related species. In addition, we used a support vector machine algorithm to identify core *RNA polymerase II* promoters with application to miRNA promoters (Corcoran, Pandit, *et al.*, *PLoS One* (2009) **4:**e5279.) The information we gained from the miRNA promoters was used to identify network modules that were associated with *idiopathic pulmonary fibrosis* (IPF). In particular, we found that *let-7d* participated in a feed-forward-loop which is crucial for the epithelial to mesenchymal transition (EMT) and to IPF (Pandit, Corcoran, *et al.*, *Am J Resp Crit Care Med*, (2010) **182:**220-229). These findings are expected to enhance our understanding of the role of miRNAs play in the context of gene regulatory networks in IPF and other diseases. Last year, the laboratory published a new algorithm (mirConnX) and web server (http://www.benoslab.pitt.edu/mirconnx/) that predicts regulatory networks from mRNA and miRNA gene expression data and prior (static) information (Huang, Athanassiou, Benos, *Nucl Acids Res* (2011) **39:**W416-423.) This year we developed a new algorithm for predicting how a set of miRNA genes is expected to influence the expression of given mRNAs. The new algorithm, ComiR, is based on a comprehensive thermodynamic binding model, which we have shown that improves overlap between existing target prediction algorithms. The effectiveness of ComiR in predicting the effect that certain SNPs have in miRNA binding was demonstrated by the discovery of a SNP that is associated with osteoporosis through the perturbation in the ER pathway (Coronnello, *et al.*, *PLoS Comput Biol* (2012) **8:**e1002830.) Later, we developed ComiR web server to make our algorithm broadly available (Coronnello, Benos, *Nucl Acids Res* (2013) **41:** W159-W164.)

Machine learning method development to analyze multi-modal data. In the last few years, Dr. Benos' laboratory became interested in developing algorithms that can specifically analyze heterogeneous datasets (such as omics and clinical data) under a unifying framework. Towards that goal they are using graphical models to represent biomedical information and they develop fast methods to infer network structure, which is indicative of *causal relationships* between clinical and other variables.

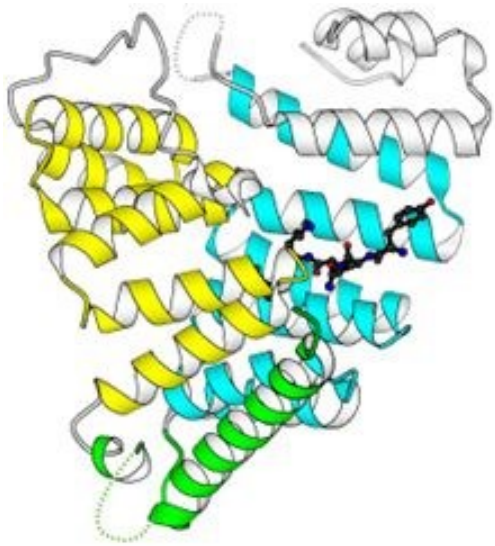
Jeremy Berg, Ph.D.

Associate Vice Chancellor for Science Strategy and Planning in the Health Sciences
Director, Institute for Personalized Medicine
Professor, Computational & Systems Biology

Jeremy M. Berg is Pittsburgh Foundation Chair and Director of the Institute of Personalized Medicine, Associate Vice Chancellor for Science Strategy and Planning in the Health Sciences, and Professor of Computational and Systems Biology at the University of Pittsburgh. Prior to coming to Pittsburgh in August 2011, Dr. Berg served as the director of the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH), where he oversaw a $2 billion budget that funded basic research in the areas of cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics and computational biology as well as research in anesthesiology, wound healing, and critical care related to burn and trauma.

Prior to his appointment as NIGMS director, Dr. Berg directed the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine in Baltimore, MD, where he also served as professor and director of the department of biophysics and biophysical chemistry. Among Dr. Berg's numerous awards and honors are the American Chemical Society Award in Pure Chemistry, election to the Institute of Medicine of the National Academies, and a public service awards from the Biophysical Society, the American Society for Biochemistry and Molecular Biology, the American Chemical Society, and the American Society for Cell Biology.

His major research activities have focused on computational studies on the complex between the human peroxisomal targeting receptor Pex5p and peptide containing targeting sequences. He and his research group had previously performed extensive experimental studies examining the ability of Pex5p to bind peptides containing a range of variants of the type 1 peroxisome targeting sequence -X-X-X-Ser-Lys-Leu-COO^-. He has been using free energy perturbation methods to determine if the observed differences in binding free energy can be reproduced computationally and studies with variations in place of the Ser and Leu have been encouraging.



Carlos Camacho, Ph.D.

Associate Professor

My main research interests are molecular interactions, from the biophysics of molecular recognition to the prediction and validation of physical interactions.

Specific research projects include:

1. Understanding Protein-DNA and RNA interactions, including the development of accurate free energy estimates and the analysis of the specificity of DNA binding proteins. The PI is developing a structural understanding of the molecular basis of non-specific and specific protein-DNA and RNA binding interaction. Currently, the most common methods used for target prediction are based on sequence information obtained from known binding sequences, which in combination with consensus patterns or weight matrices are used to scan the DNA. However, due to the short length of binding sites and intrinsically degenerate nature of DNA, the number of false positives is quite high. Based on mechanistic insights of protein-DNA and RNA recognition, we are developing new tools to dock and score single stranded DNA and RNA chains. Using modern optimization techniques, we are currently devoted to delineate the binding specificity of important families of transcription factors, RNA and miRNA targets.

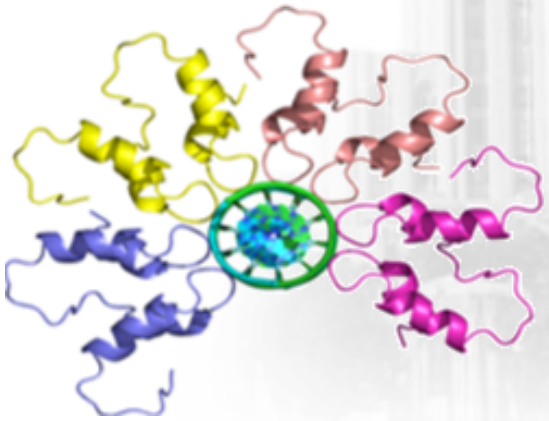
2. Developing technologies to understand and predict the interaction of disordered proteins and peptides with their substrates. Special emphasis is in understanding "adapter proteins" such as PDZ, SH2/3, WW domains that bind disordered peptides, mediating protein-protein interactions, as well structural rearrangements due to post-translational modifications. Adapters are highly promiscuous, and characterizing their binding specificity is critical to reveal their multiple roles in cell regulation. Using insights from crystallographic studies, the PI has developed the first semi-flexible docking method to model the bound structure of peptide-adapter complexes and estimate their absolute binding affinities. Besides using this technology to predict novel protein-protein interactions, we are using insights resulting from the quantitative analysis of interactions with disordered molecules to answer questions such as: How and why does Nature regulate signal transduction through these disordered motifs? These efforts have also led to the development of the first quantitative theory to understand molecular interaction, including signal transduction and promiscuous interactions.

3. In-silico high throughput discovery of ant (agonists) of protein-protein interactions. Funded by NIH, the PI in collaboration with Dr. Doemling are developing a radically new open access technology to facilitate the true collaboration amongst biologists, say, experts on specific protein-protein interactions (PPIs) and chemists who are interested in the rational development of protein interaction small molecular weight (ant)agonists. Specifically, we seek to benefit from the growing structural information on protein-protein interactions (PPIs), exemplified in the Protein Data Bank (PDB), to develop a PDB wide – *sic* system biology – approach that combine biophysical insights with multiple component reaction (MCR) chemistry to develop and screen million-size *virtual* libraries of chemically accessible novel compounds. This platform builds on the role anchor side chains, i.e., those that bury large surface area in the acceptor protein, have on PPIs, which at the onset of the recognition process target well defined "druggable" pockets, and the use of chemical mimicry of these functional groups to redesign these entry points into small molecules using MCR chemistry. In this area, we have obtained first in class inhibitors for several targets: DNA repair (in collaboration with Dr. Sobol); Transcription (Dr. Roninson, USC); cancer invasion (Dr. Finn);

Hypertension (Dr. Straub), while working as well in several other collaborations.

4. Assembly and Disassembly of macromolecular complexes. Recently, a major interest in the lab has been the understanding of regulatory networks in the context of cell signaling via intrinsically disordered proteins and post-translation modifications. In collaboration with Dr. Wells, we are trying to understand the actin cytoskeleton network, which is important for several fundamental biological processes, from muscle contraction to cell motility and surface remodeling. Speicfically, alpha-actinin-4 (ACTN4) is a calcium sensitive member of the spectrin-family of actin crosslinking proteins specific to non-muscle cells. We are studying how crosslinking is regulated by three phosphorylation states, ions and lipids. Collectively, our studies aim to provide insight pertinent to the molecular basis of actin crosslinking by ACTN4, while revealing a quantitative framework for understanding how post-translational modifications can result in robust signals by assembling and disassembling multi-domain complexes of the actin-binding protein.

5. Develop novel structural insights into antigenicity, and the development of autoimmune diseases. Specifically in the context of citrullinated Hsp90 isoforms as autoantigens in rhermatoid arthritis. In the conventional paradigm of humoral immunity, B cells recognize their cognate antigen target in its native form. However, it is well known that relatively unstable peptides bearing only partial structural resemblance to native protein can trigger antibodies recognizing higher order structures found in native protein. Recently, we have shown that structural criteria rather than sequence *per se* play an important role in both antigen recognition and affinity maturation. Moreover, examples exist where sera from individuals with autoimmune disease cross-react with peptides extracted from antigens and/or microbes, even in the absence of common linear amino acid sequences. These observations have led to the hypothesis that autoimmunity could result from cross-reactive antimicrobial or cleaved peptide immune responses targeting limited structural motifs. In collaboration with Dr. Ascherman, the PI is developing a more precise mapping of B cell responses over time to help define the sequence of molecular recognition events leading to epitope spreading and antigen cross-reactivity, thereby elucidating the structural component of this process. A major application is the study of the Hsp90 citrullination as a biomarker for rheumatoid arthritis. The ultimate goal of this study is to provide insight regarding processes of molecular mimicry that generate multiple autoantigens and ultimately lead to autoimmunity.



Chakra Chennubhotla, Ph.D.

Assistant Professor

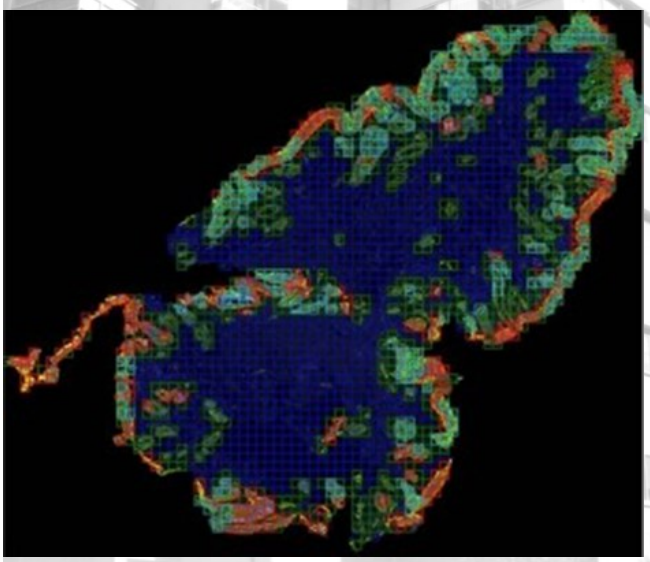
The research focus of my group is in translation science and big-data analysis in the form of computational bioimaging and statistical inference. My group tackles big data challenges emerging in the domains of digital pathology, molecular diagnostic imaging, genotype-phenotype correlative studies, molecular biophysics and more recently public health dynamics. A few of the on-going projects in the lab are summarized below:

I. *Computational Pathology*

We are developing image analysis and machine learning algorithms to (i) detect early signs of dysplasia in esophageal biopsies and (ii) study the progression of Barrett's esophagus to cancer. Barrett's esophagus is a benign condition that afflicts 10% of heartburn sufferers. However, in the small group of Barrett's patients who develop dysplasia, there is a 10% risk of progression to cancer each year. In order to treat cancer proactively, medical doctors perform regular biopsies of Barrett's patients, looking for first signs of dysplasia. For medical researchers, this longitudinal data provides insight into the development of cancer. We are analyzing multiplexed tissues images from large time-series patient data to stratify risk of cancer in Barrett's patients. We are applying whole slide segmentation techniques to optical biomarker images to quantify the spread of cancer into non-cancerous tissue.

II. *Computational Bioimaging*

Primary ciliary dyskinesia (PCD) is a rare disorder associated with severe sinopulmonary disease due to dyskinetic ciliary motion in the respiratory epithelia. The current diagnostic standard relies on manual inspection of nasal biopsies using high-speed videomicroscopy to identify abnormal ciliary motion. This approach is error prone and highly subjective. We are developing novel computational approaches for visual recognition and quantitative identification of abnormal ciliary motion phenotypes. Using a series of clustering steps on image velocity invariants, we are establishing canonical ciliary motion patterns for PCD diagnosis. This computational algorithm can be deployed for automated clinical diagnosis of PCD.



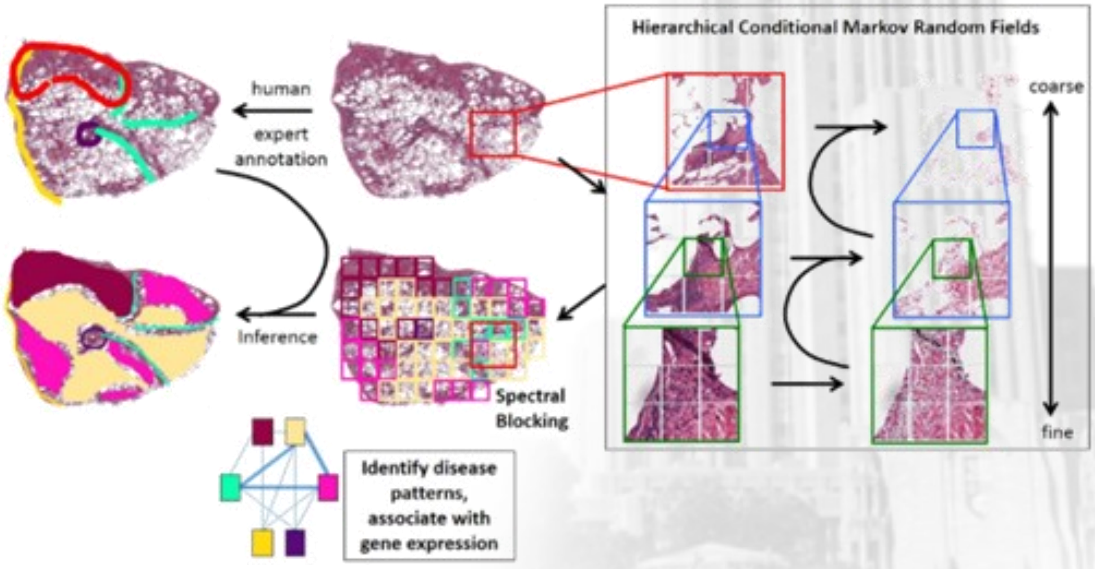
III. *Computational Olfaction*

A key challenge in olfactory research is to describe the relationship between chemical structure and odor percept. Despite many decades invested in this problem by basic science and industry, there is still no means for systematically and accurately assigning descriptive odor labels – "minty", "oily", "woody," etc – to arbitrary odorants. We are developing new graph theoretic and semi-

supervised learning (SSL) methods to accomplish this. In contrast to traditional approaches, which have sought a structure-percept mapping through experiments involving small and idiosyncratic subsets of odorant space, we aim to densely characterize odor space using computational techniques applied to a publically available database (PubChem) of ~3×10^7 chemical compounds. A critical piece of our project will be the use of human judgments of odor quality to test these hypotheses.

IV. *Computational Biophysics*

A key challenge in molecular biophysics is to discern short-lived, rare intermediate conformations that proteins access in order to natively fold, bind signaling partners, and perform inhibition or catalysis. To this end, we are developing higher-order statistical trajectory analysis toolbox, named anharmonic conformational analysis in combination with network-based approaches, to integrate experimental observations from nuclear magnetic resonance (NMR) relaxation dispersion, small angle neutron scattering (SANS) and single molecule Forster resonance energy transfer (smFRET) techniques with long timescale molecular dynamics simulation trajectories. We are applying these techniques to characterize conformational sub-states and discern the intermediate conformations that are relevant to protein function, including enzyme catalysis, molecular recognition and signaling.

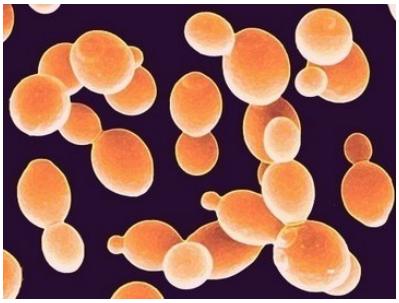


Nathan Clark, Ph.D.

Assistant Professor

Our overarching goal is to understand how the functions of proteins change over time. We are particularly focused on the process of co-evolution within genetic networks and the ways by which proteins influence each other during evolution. We study a variety of organisms ranging from yeast to primates and use both computational and experimental approaches. We are particularly interested in the evolution of sexual reproduction and cellular transport proteins.

Specific Research Topics:

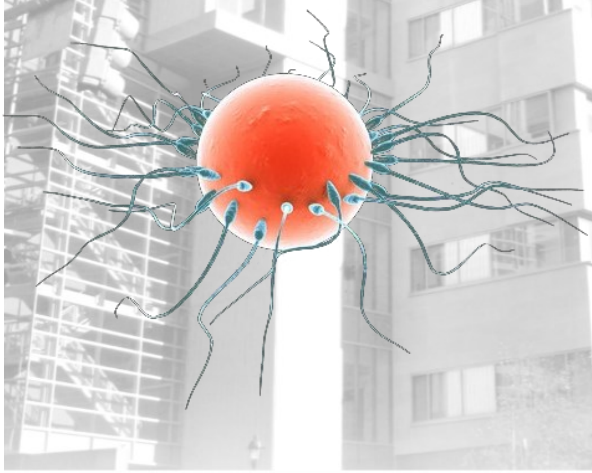


· **Evolutionary Rate Covariation (ERC):**
ERC is a phylogenetic signature that reflects co-functionality between genes. We develop genome-wide datasets of ERC to provide co-evolutionary predictions and to interpret major functional shifts during evolution.

· **Co-evolution within the Nuclear Pore:**
Yeast genetics shows that molecular incompatibilities arise quickly between nuclear pore proteins. How does the process of compensatory co-evolution maintain these crucial protein-protein interactions?

· **Yeast Mating: Reproductive Isolation and Co-evolution :**
What is driving the evolution of gamete recognition proteins in yeast? What are the implications of this divergence for reproductive isolation and speciation?

· **Evolution of Female-Male Interactions in the Cabbage White Butterfly:**
Post-copulatory interactions between males and females have been shaped by a complex set of competitive and conflictive forces, resulting in specialized male and female traits.



"In the near future, a researcher studying a particular disease or pathway will be able to plug a couple of known genes into a database of evolutionary rate covariation to find other genes with parallel histories. This will provide insight into the workings of biological pathways."

James R. Faeder, Ph.D.

Associate Professor

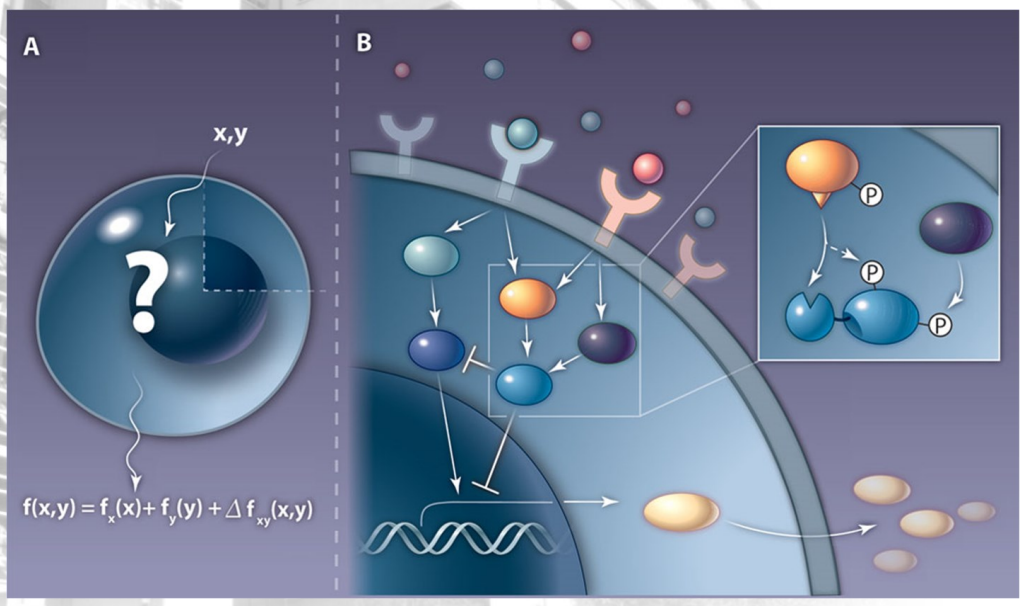
My research involves the development of new methods for representing and simulating molecular biochemistry by formulating models in the form of rules that describe basic biochemical interactions and applying these methods to gain greater understanding of cell decision processes. Using this approach allows us to construct detailed models of intracellular signaling pathways based on available knowledge and data, and to avoid the ad hoc assumptions required when such models are formulated using standard chemical kinetics approaches. The basic issue with the latter is that in the absence of grossly simplifying assumptions, the number of feasible chemical species and reactions in the system undergoes a combinatorial explosion, making simulation with current methods impossible (see below). Rules serve as generating functions for such networks, and provide a tractable and concise representation of signaling systems. In collaboration with a group at Los Alamos National Laboratory we have developed the software package BioNetGen to enable development and simulation of rule-based models, and to make this approach accessible to a wide range of scientists, including those with limited mathematical training.

We have also collaborated with Dr. Thierry Emonet in the Molecular and Cell Biology Department at Yale University to develop a powerful simulator for BioNetGen models called NFsim that is capable is simulating virtually any model that can be specified in the language, regardless of the implied number of possible states. A report describing the simulator, the underlying algorithms, and several applications to biological problems was published in Nature Methods at the beginning of 2011. The development of this technology opens the door to the development of large scale, comprehensive models of cell signaling networks. We have recently extended the simulation capabilities of NFsim by developing a hybrid algorithm that allows the mixing of particles and population variables in the same simulation. Our implementation was shown to greatly reduce memory costs without affecting either computational time or accuracy, and it opens the door for the implementation of accelerated stochastic simulation algorithms that could greatly reduce simulation times. This method was recently described in PLOS Computational Biology. Other areas of active research within the group are the development of improved model visualization capabilities for rule-based models, the integration of rule-based and spatial simulation algorithms and tools, automatic inference of biochemical rules from reaction network models, and using visualization to perform comparative analysis of models.

Besides efficient formulation and simulation of rule-based models, another major issue is the estimation of model parameters. In our view, parameter estimation is best approached in combination with the closely-related problem of predicting model behavior. In developing models of biological systems we are less concerned with quantitative accuracy than in qualitative insights that can be used to guide experiments and ultimately therapeutic discoveries. Toward this end, we are collaborating with several computer scientists at

Carnegie Mellon University to apply algorithms for statistical model checking, which is the rigorous determination of whether a model satisfies a specified property, to rule-based models. Using these methods, we aim to provide a full characterization of model behavior over its set of feasible parameters, and use this to determine the likelihood that a given model is consistent with available observations. This rigorous approach allows us also to place a likelihood estimate on any model prediction and to assess the potential value of any proposed experiment in refining the predictive capability of a model.

Our efforts in method development are tightly coupled to applications of the methods to specific biological systems of interest and driven by data from experimental collaborations. We have recently collaborated with Dr. Penelope Morel in the Department of Immunology at the University of Pittsburgh to develop a coarse-grained model of the biochemical signaling pathways involved in T cell differentiation, a process that is dysregulated in opposite ways in cancer (suppressed immune response) and autoimmune disorders (hyperactive immune response). The model demonstrated how the structure of the signaling network could lead to differential responses depending on the duration of T cell stimulation through its antigen receptor. Experiments confirmed the model prediction that varying the duration of stimulation with antigen determined the types and proportion of differentiated immune cells produced. This work was recently published in Science Signaling. The model also predicted that a critical regulator of this process was a lipid phosphatase called PTEN, and subsequent experiments have confirmed the model predictions for the kinetics of PTEN activity and demonstrated multiple modes of regulation of this protein. Other systems that we are actively exploring include signaling through innate immune receptors, heterogeneity in germination of bacterial spores, and multivalent receptor aggregation in T cell activation.



Elodie Ghedin, Ph.D.

Associate Professor

My lab's research focus is on the study of microbial pathogens using comparative genomics, bioinformatics analyses, and functional assays. The questions we try to address are: What is the intra-host diversity of a microbial population? How are microbes adapting to their hosts? What effect do they exert on their host? How are microbes functionally interacting? Details of presently active projects are listed below.

Influenza intra-host diversity & evolutionary dynamics

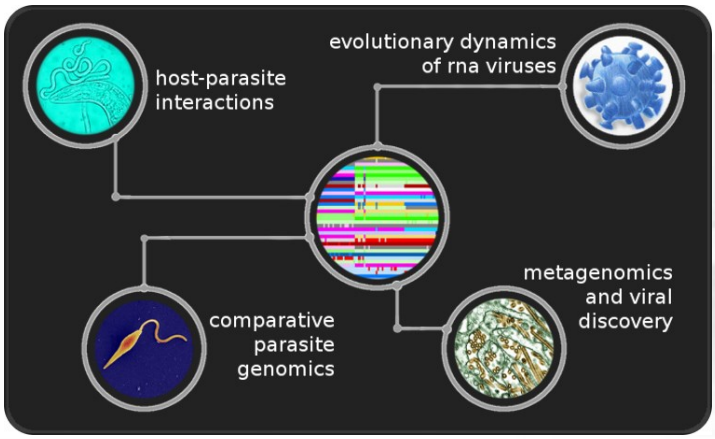
The principle objective of this project is to determine, using ultra-deep sequencing, the extent, structure and underlying mechanisms of genetic variation in populations of influenza A virus sampled from within individual hosts. We set out to characterize the fitness distribution of all variants transmitted and the extent of the population bottleneck at intra-host transmission. Data collected would be essential to understand the process of viral emergence.

The Lung Microbiome in HIV Infection

This project is in collaboration with Dr. Alison Morris (Departments of Medicine and Immunology). The overall goals of this project are to examine the respiratory microbiome before and after HAART initiation and in subjects with chronic obstructive pulmonary disease (COPD), to determine how changes in the microbial flora present relate to airway obstruction and emphysema.

Predictive modeling of clinical outcome of flu infectionss

This project integrates many aspects of my research, bringing together virus evolution work, microbiome studies, host transcriptomics components, and host-pathogen interactions. In this program, we take a systems biology approach to understand pathogenesis in influenza A virus infections. Host response to influenza infection is a complex trait that involves entire host-pathogen interaction networks of RNA transcripts, proteins, and metabolites that have an impact on cellular, tissue, and whole-organism behaviors, which ultimately define both the risk and severity of infection. The focus of this program is to integrate multiscale data collected over the course of influenza infections to identify risk-stratifying prognostic biomarkers. The ultimate goal is to develop point-of-care testing that can easily be applied to clinically relevant respiratory samples, such as nasal swabs, to identify patients at risk for severe influenza disease.



Molecular mechanisms of filarial endosymbiosis

The goal of this project is to define the mechanisms that determine the interdependencies between the parasitic nematode Brugia malayi – one of the agents responsible for lymphatic filarisis – and its bacterial endosymbiont, Wolbachia.

D. Lansing Taylor, Ph.D.

Professor

Since joining the University of Pittsburgh in November 2010, I have organized the Drug Discovery Institute while developing my personal research strategy. We have made some key hires and now have an outstanding team of core UPDDI scientists. I am creating novel protein-based fluorescence biosensors coupled to the application of advanced, high throughput microscope-based imaging of cells and experimental animals to form the field of "cellular systems biology" (CSB). CSB investigates the integrated and interacting networks of genes, proteins and metabolites that bring about normal and abnormal cellular processes at the level of the cell. CSB requires the harnessing and continual advancement of multiple technologies to evolve an increasingly powerful platform, useful in drug discovery and early safety assessment. A CSB platform must combine increased throughput of image-based cellular measurements with an increase in the number and molecular significance of the measured cellular parameters. I will be working to build more physiologically relevant 3-D cell-based models of cancer (head and neck and breast) and early safety assessment. The 3-D models will entail the use of tissue engineering using both primary cells and stem cell-based cells where applicable. Fluorescence-based biosensors of biochemical and molecular processes will continue to be a critical research direction in order to maximize the molecular specificity of measurements made in the cellular models. Our past development of High Content Screening (HCS) has allowed light microscope imaging to become a sophisticated tool in drug discovery and early safety assessment, but further advances in 3-D imaging and computational and systems biology of complex data sets are required to fully harness the platform in both drug discovery and basic biomedical research.

The major research objectives in cancer biology are to: 1) assemble the most advanced HCS platform; 2) develop 3D tumor microenvironment (TME) models of head and neck, as well as breast cancers including cancer cells, stromal cells and migratory immune cells; 3) assemble panels of multicolor, fluorescence-based biomarkers (protein-based biosensors and antibodies) to characterize the pathway responses to drug treatments; and 4) develop computational and systems biology tools to analyze the complex data sets including heterogeneity of cancer cell responses to drug treatments. We have begun testing heterogeneity of response of Cal33 head and neck cancer cells to IL-6 stimulation that activates STAT3 as a point of reference using the Cellomics VTI, HCS platform. We are currently leasing the GE InCell 6000 platform as the most advanced HCS platform and have submitted a shared instrumentation grant to fund it.

The major research objectives in early safety assessment are to: 1) implement a microfluidic device that combines primary human hepatocytes (or stem-cell derived hepatocytes) with other key cell types to create a more physiological model for early safety assessment; 2) create a panel of multicolor, fluorescence -based biosensors or key cellular toxic responses including formation of reactive oxygen species, stress kinase activation, oxidative stress and mitochondrial functions; 3) harness the advanced HCS platform to acquire correlative data sets from the multiple cell types; and 4) create a classifier that will link the cell data with published toxicity data on a library of known drugs to make a predictive tool that will be human relevant, faster and more cost-effective than rodent safety testing. I was awarded an NIH grant *"A 3D biomimetic liver sinusoid construct for predicting physiology and toxicity"* jointly with Maish Yarmoush from the Massachusetts General Hospital (MGH) in late July, 2012.

John K. Vries, M.D.

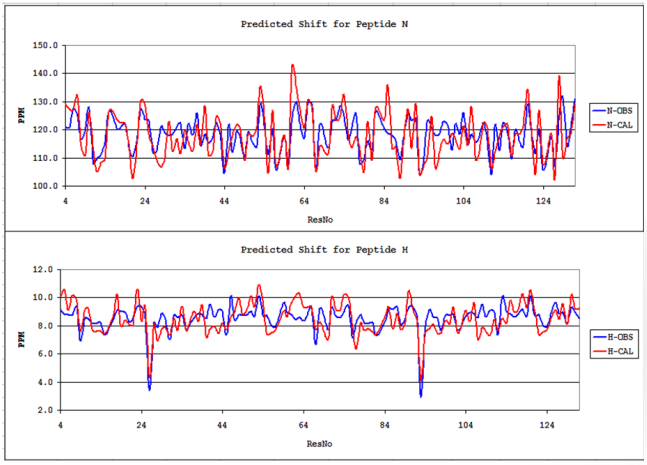
Associate Professor

I developed a quantum mechanical (QM) approach for studying isolated regions of interest (ROIs) in proteins. Recently, this approach has been extended to calculate the chemical shifts associated with the atoms in peptide bonds.

The process begins with an energy determination for the ROIs surrounding each peptide bond in a protein. The ROI conformations are obtained by drawing random samples from the trajectories of molecular dynamics (MD) simulations. Several hundred ROI samples are obtained for each peptide bond. The chemical shifts for the nitrogen, hydrogen and alpha carbon atoms in each peptide bond are determined for each conformation from the magnetic resonance shielding tensors associated with these atoms. The shielding tensors are calculated using the GIAO method at the density functional level of QM theory (B3LYP) with a 6-311+(G(2d,p) basis set.

A pilot study was carried out in collaboration with Dr. Angela Gronenborn from the Department of Structural Biology to see if the chemical shifts from the ROI samples could be used to predict the chemical shifts obtained from NMR spectroscopy. An MD simulation of a protein with potent anti-HIV activity (OAA) was carried out and the ROI conformations for each peptide bond in each frame of the MD trajectory were extracted. Chemical shifts were assigned to each peptide in each frame by matching geometric parameters with the sample set of ROIs with calculated chemical shifts. The chemical shifts were calculated from ensemble averages. Initial results showed errors in the 10% range with respect to the chemical shifts observed from NMR spectroscopy. The sampling and conformational matching routines were then refined and applied to the protein ubiquitin. A new ROI library containing 28,000 ROI samples with calculated chemical shifts has been constructed. The new library and the new conformational matching routines have yielded error rates in the 2-4% range with respect to observed chemical shifts. In theory, this approach can be applied to all proteins if the library of ROI samples is expanded sufficiently. It also should be noted that the ROI conformations associated with alpha helices, beta sheets and coils have few conformational variants suggesting that a relatively small library could be applicable to the common regions in a wide range of proteins.

Chemical shifts predicted from MD simulations could have several important applications: (1) They could be helpful in conformational selection in NMR structure determination; (2) They might reveal subtle changes associated with mutations or drug binding events; (3) They might provide an objective means for comparing different force fields in MD simulations; and (4) They might reveal allosteric effects associated with local structural perturbations that could point to new drug binding targets. In the coming year we will attempt to identify new targets for study in consultation with Dr. Gronenborn. We will continue to expand the library of ROI samples to cover a wider range of protein conformations. New grant proposals will be developed to support this work.



Chemical Shift Prediction for OAA

Dan Zuckerman, Ph.D.

Associate Professor

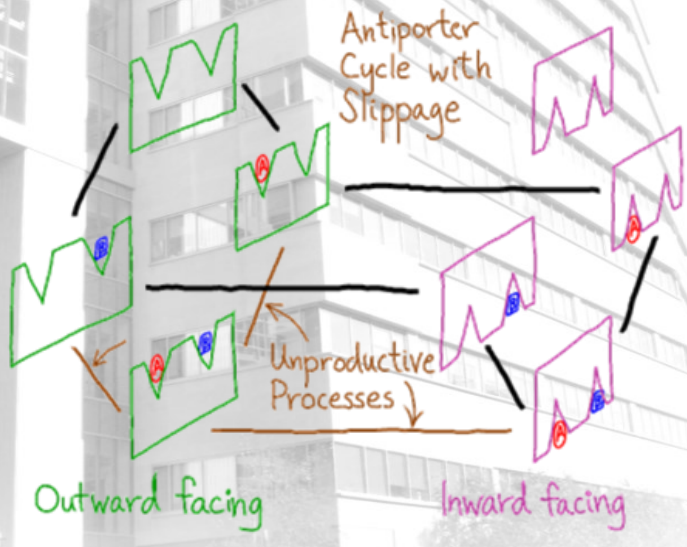
Research Interests: Computational Study of Protein Binding, Allostery, and Molecular Machines

Molecular-level biology is inherently dynamic. No signal can pass, no ligand can bind, no motor can walk, no enzyme can catalyze—without motion. Beautiful but static experimental structures—which indeed explain substantial biochemistry—are only the beginning of the story. We therefore pursue ensembles of protein structures and pathways of conformational change that play a key role in binding, allostery and molecular machines.

The group has been active in developing scale-free "weighted ensemble" (WE) software, which is now in use around the world. Zuckerman and colleagues developed WE methods for sampling steady-state and equilibrium conditions that have been applied to all-atom protein binding and to highly complex systems biology models of cell signaling.

Another focus is the development of mixed-resolution models of proteins for application to small-molecule binding and drug design. Methodologically, the binding site is modeled in atomistic detail, with the remainder of the protein represented in a simplified form to save resources while preserving flexibility. The approach is being applied to designing drugs suitable for metastatically enriched mutations that occur in the ligand-binding domain of the estrogen receptor.

Pedagogically, Professor Zuckerman is the author of a textbook, *Statistical Physics of Biomolecules: An Introduction,* and is currently developing on online book, *PhysicalLensOnTheCell.org,* explaining the physics of cellular processes, for advanced undergraduates.



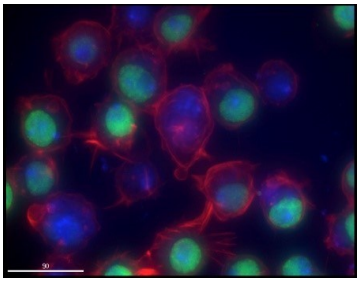
Joesph C. Ayoob, Ph.D.

Assistant Professor

Research – As we develop, we make too many cells. These extraneous cells are eliminated by an orderly processes of cell death (apoptosis) and cell engulfment (efferocytosis) to ensure proper development. These processes are also important in adults for maintaining a proper homeostatic balance in the body. Errors in these signaling pathways can result in the progression of cancer and auto-immune diseases. My research investigates the molecular mechanisms that ensure the proper elimination of effete and dying cells. In particular, we are interested in the link between apoptosis and efferocytosis – how do cells that are triggered to die signal that they need to be eliminated by phagocytosis? While some of these cues have been discovered, our full grasp of this process if far from complete. To this end we are using a novel, genetically-encoded, cell engulfment reporter to identify the genes required for the proper phagocytosis of apoptotic cells. We use the fruitfly Drosophila melanogaster as our model system for these studies on account of its high degree of conservation of gene function with humans, the large array of molecular-genetic, biochemical, and imaging tools available in vivo and in vitro, and the ability to easily observe developmental phenomenon in the living, intact animal.

In a related project, we have also been investigating the molecular mechanisms of Hsp27, which is a ubiquitous small heat shock protein that is conserved across species. Hsp27 can function in an anti-apoptotic capacity that spares doomed cells from being eliminated and thus contributing to the disease state, though its precise mechanism of action is muddied by its complex regulation via changes in expression, localization, phosphorylation, and oligomerization. We are using computational and experimental approaches to better understand how this key, multifunctional protein is regulated in response to stress and other cellular insults.

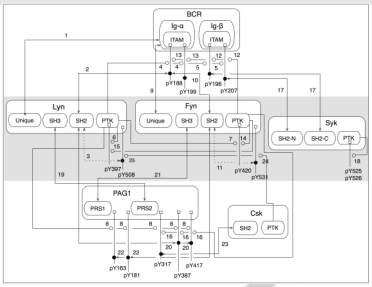
Teaching/Mentoring/Outreach – Reaching out to and training the next generation of scientists is an important responsibility of the scientific community, and is a necessity if we are to continue to make progress and reach our research goals. My efforts along these lines have primarily focused on my roles as the Co-director of the Laboratory Methods for Computational Biologists Course (a core course in the joint CMU-Pitt Computational Biology (CPCB) graduate program), and as the PI and Program Director of the NSF-funded Training and Experimentation in Computational Biology (TECBio) Research Experiences for Undergraduates (REU) program. The TECBio REU at Pitt program has the focus of "Simulation and Visualization of Biological Systems at Multiple Scales" and is a 10-week NSF- and DOD-funded REU program that provides a challenging graduate-level experience in computational biology to students from a host of different backgrounds.



In addition to my efforts at the graduate and undergraduate level, I have founded and directed two summer research programs for high school students in collaboration with the University of Pittsburgh Cancer Institute, the Department of Biomedical Informatics, and the University of Pittsburgh Drug Discovery Institute. These programs, the Computational and Systems Biology and Biomedical Informatics (CoSBBI; 2011-2012) and the Drug Discovery, Systems and Computational Biology (DiSCoBio; 2013-present) Academies provide students with a primary, mentored research experience plus didactic training and additional enrichment activities.

Dipak Barua, Ph.D.

Research Assistant Professor



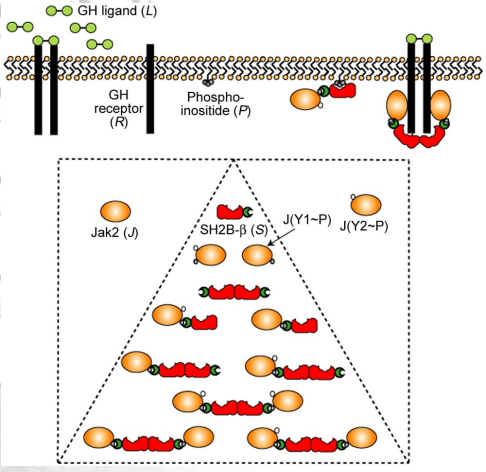
My current research is focused on development of systems biology approaches and their applications to complex biological systems. I am particularly interested in extending the rule-based modeling approach, a powerful method for modeling of complex reaction network systems, with capabilities for spatial modeling. Such extension is aimed at modeling and simulation of large-scale reaction-diffusion systems with arbitrarily complex geometries associated with mammalian cell, tissue, or organ. My ultimate goal is to apply the integrated methods to study the function of immune systems.

Integration of BioNetGen and MCell

I am working on integration of rule-based modeling software BioNetGen with spatial modeling software MCell. BioNetGen is an efficient tool for automated generation of complex reaction network models. BioNetGen can create reaction networks of thousands of chemical species from a small set of user-defined reaction rules describing the biochemical transformations of functional domains and motifs of signaling proteins. MCell is a powerful tool for simulation of particle reaction and diffusion in complex geometries. Integration of BioNetGen and MCell will provide a unique ability to model and simulate large reaction network systems in the spatial context of a cell, tissue or organ, which are typically associated with complex 2D and 3D geometries. As a preliminary step, I have created a translator to convert the BioNetGen-generated reaction network models into model description language (MDL) recognized by MCell. The translated models can be integrated with externally created geometries and simulated in MCell. As an alternative, I have created a BioNetGen model importer in CellBlender, a Blender plug in that provides an interface for interactive creation of MCell geometries and models. The importer in CellBlender allows a more direct conversion of BioNetGen-generated reaction network models into spatial MCell models.

Spatial rule-based modeling of cell of immune recognition systems

I am interested in applying the integrated spatial rule-based modeling approaches to study cell signal transduction associated with immune systems. A collaborative project is underway with experimental scientists at the New Mexico Center for Spatiotemporal Modeling of Cell Signaling (STMC). The goal of the project is to investigate how spatial geometries of the plasma membrane and intracellular organelles regulate signal activation when antigens are recognized via cell-surface receptor protein. One particular focus of the project is to interrogate the effect of distribution of signaling proteins and lipids in the plasma membrane. In a recent work, I have studied the roles of lipid heterogeneity in the cell membrane in spatial segregation of signal activating proteins and inhibitory protein tyrosine phosphatases. An integrated spatial and rule-based modeling approach is aimed at broadening the scope of the study and interrogating properties in further details in a more realistic approach.



Robert Boltz, Ph.D.

Research Associate Professor

I received a BS in Zoology from Penn State in 1967. I switched fields to Biophysics and in 1978 received my PhD specializing in the electrophoretic separation of mammalian cells. This was my first exposure to the emerging field of Analytical Cytology. By graduation, I was considered an expert in electrophoretic separations. After graduation, I accepted a visiting scientist position with Universities Research Space Association to work on the development of electrophoretic separation of mammalian cells in microgravity. In 1978, I accepted the position of Senior Research Immunologist with Merck/Rahway working in the Cell Separation and Analysis Facility. In 1982, I became Director of the Flow Cytometry/Cell sorter on the Rahway site. I would build this laboratory into a world class center of excellence of fluorescence cytometry with cutting edge, innovative development and instrumentation modifications over the next 23 years. Much of the evolution of the Facility was through collaborations, formal and informal, with various instrumentation companies. I had the first 8 parameter B-D Cell sorter which further evolved into the B-D LSR flow cytometer. I acquired and modified a Fluorescence Imaging Plate Reader I (FLIPR I) to do 2 additional membrane potential and calcium kinetics. This was used to develop a screen on immobilized primary human T cells. I modified our Fluorescent Digital Imaging Microscope (FDIM) to allow T cell activation kinetics. Through collaborations with Lans Taylor at Carnegie Mellon University, I have been involved in the High Content Imaging (HCI) field since its inception. This resulted in the development of the first HCI screen of NF-kB translocation. Since then, I have been responsible for many of the advances in the HCI technology as a key collaborator with industry. I am considered a sophisticated cytometry scientist with experience in combining the biology, reagent chemistry, cytometer and data management and analysis tools to solve problems in drug discovery.

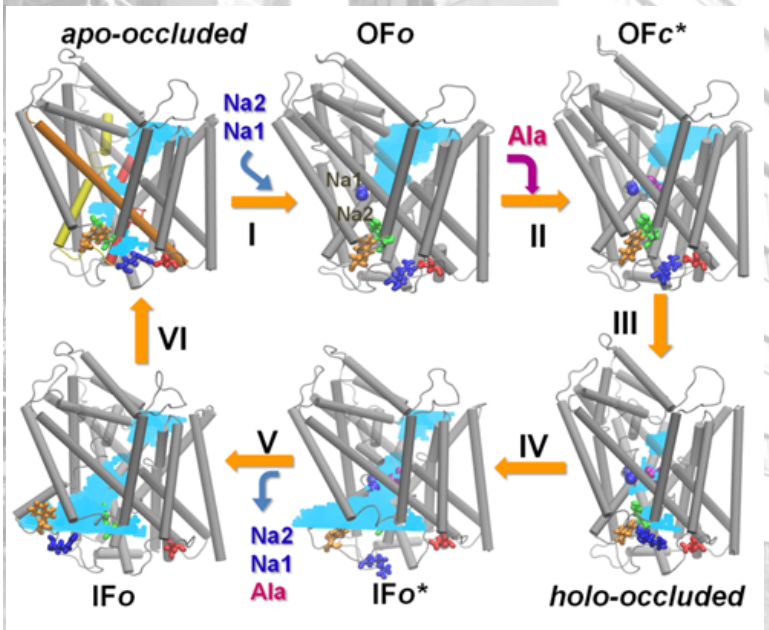
I joined the University of Pittsburgh Drug Discovery Institute as a Research Associate Faculty appointment in the Department of Computational and Systems Biology in November 2011. My research interests lie in further developing High Content Analysis (HCA) and flow cytometry instrumentation and techniques toward systems pharmacology approach through “hyperplexed” multiple readouts of signaling pathways, cellular functions, and cell morphology to establish signatures that characterize the response of cells to stimulation by agonists and antagonists. The cellular systems “fingerprint” which includes the integrated functional responses of the cell, would be the basis for the development of screening assays to identify novel chemical entities. I am involved in extending High Content Analysis to 3-D multi cell type liver organoid cultures for drug discovery.

Mary Hongying Cheng, Ph.D.

Research Assistant Professor

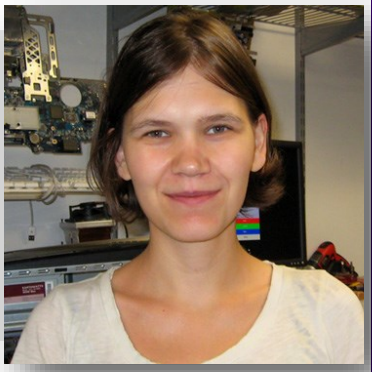
I have modeling experience in a wide range of ion channels/transporters, including several types of sodium coupled neurotransmitter transporters, neurotransmitter-gated ion channels, CLC channels/transporters, and gap junction Claudin-2. My research interest and expertise lie in protein modeling and medicinal chemistry, focusing on molecular mechanisms of i) transporter functions, i.e., transporter cycle; ii) ion transport through membrane protein channels, i.e. channel conductance and charge selectivity; iii) drug modulation of protein receptors, i.e. ligand binding sites and binding affinity; and iv) protein-lipid and lipid-lipid interactions. I am particularly interested in development/implement of multi-scale modeling technology to investigate biological systems at both molecular and cellular levels. I developed a hybrid molecular dynamics/Brownian dynamics methodology that can be applied to investigate ion permeation through membrane protein channels.

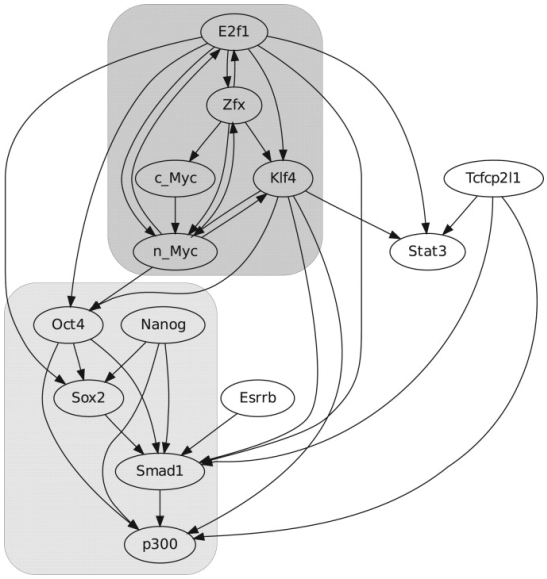
My current research focuses on the functional mechanism of neurotransmitter:sodium symporter (NSS) family and its interactions with drugs and substrate proteins. Unraveling the molecular mechanism of function of NSS family members has been a challenge due to the involvement of both local (extracellular or intracellular gate opening/closure) and global (between outward- and inward-facing) changes in structure. These events usually occur at different time scales (e.g. tens of nanoseconds for local, microseconds or slower for global). Their examination thus necessitates to adoption of multiscale methods. We have implemented a multiscale approach that combines conventional molecular dynamics (MD), targeted MD and accelerated MD (aMD), to investigate the complete transport cycle of a NSS ortholog LeuT. Our simulations reveal at atomic resolution all successive stages from substrate recognition in the outward-facing open (OFo) state, to closure of the extracellular gate leading to the outward -facing closed state (OFc*), along with accompanying rearrangements of TM helices to proceed to a holo-occluded state, release of substrate and ions in the inward-facing open (IFo*/IFo) state, closure of intracellular gate, and transition back to a temporarily stabilized apo-occluded conformer predisposed to substrate-uptake.



Maria Chikina, Ph.D.

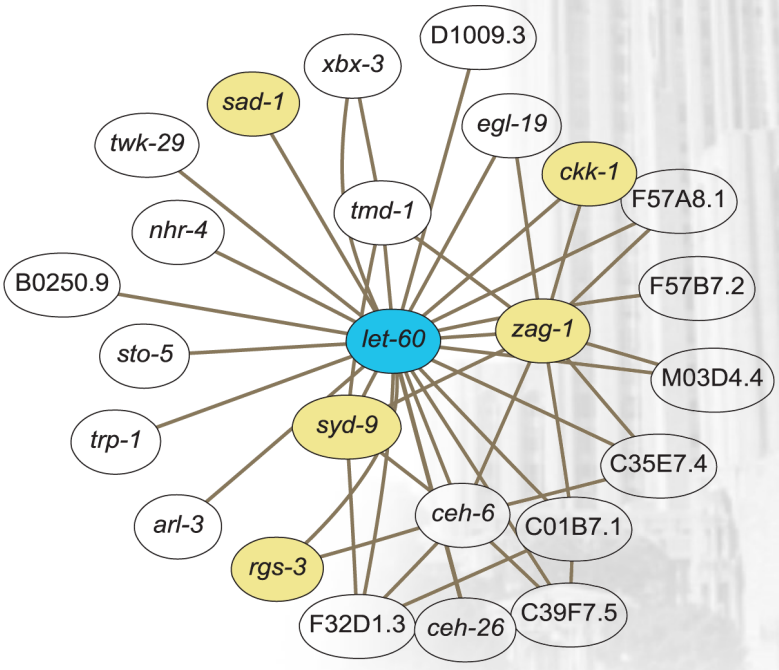
Assistant Professor





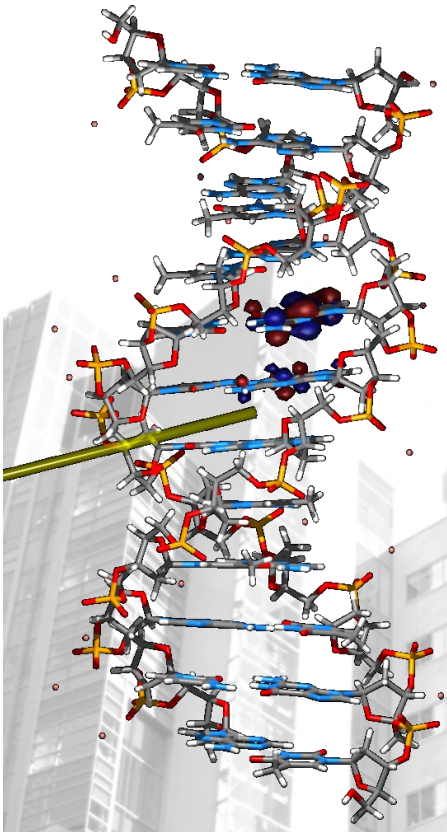
The goal of my research is to use genome scale data to advance our understanding of how genes contribute to the function of a complex organism, in health and disease. I develop computational methods that use large datasets to build gene networks, predict gene function, and understand the molecular basis of disease.

One important challenge in predicting gene function in a multicellular organism is that genes may have several different functions that are context dependent. In my research I develop new machine learning techniques that can fully utilize all existing data to predict nuanced, context-dependent gene function. Inferring context-dependent gene function is particularly difficult in studies of human diseases, and the other focus of my research is the development of new statistical methods for analyzing targeted clinical datasets which are capable of elucidating subtle relationships between molecular perturbations and disease states.



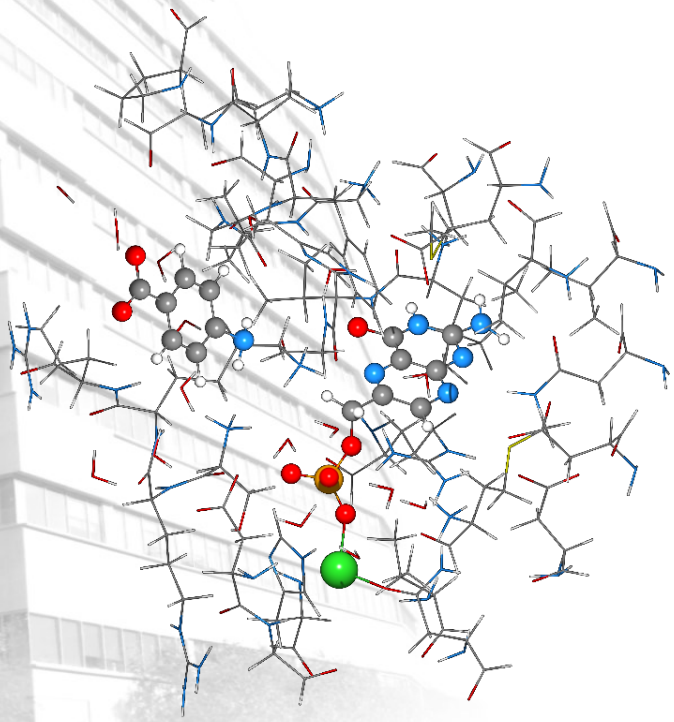
Antonio Ferreira, Ph.D.

Visiting Research Associate Professor
Acting Executive Director of the
Center for Simulation and Modeling



Molecular biophysics seeks to develop a rigorous understanding of the fundamental forces driving biological systems. Dr. Ferreira's research focuses on applying the insights of quantum mechanics to the understanding of how biomolecular systems function and interact. Working at the interface of physics and biology, he applies a variety of quantum chemical methods in combination with more traditional force field-based methods to model biochemical systems important in cancer biology, membrane transport, and *in silico* drug development.

Prior to coming to the University of Pittsburgh, Dr. Ferreira was a staff scientist in Structural Biology at St. Jude Children's Research Hospital in Memphis, TN. He is a co-inventor on three patents for glioma and neuroblastoma drug development and has broad experience in biophysical chemistry, methods development, and computational drug design.



Albert Gough, Ph.D.

Research Associate Professor

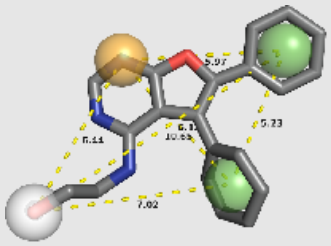
High Content Screening (HCS) was developed as a method for high throughput cell biology. HCS sparked a revolution in image-based cell analysis, going from a few measurements on a few hand-picked cells to multiplexed measurements on large populations of cells, providing statistically significant data on objectively chosen populations of cells. Although HCS platforms measure and record data for each cell, the vast majority of applications only make use of the population average results. My research is focused on mining the individual cell data to identify pathway interactions and cell microenvironment effects that will provide insights into disease progression and new therapeutic or diagnostic approaches. Genomics and proteomics profiling methods have resulted in inference maps of many interconnected signaling pathways. In both cases, the principle focus has been on understanding the activity of populations of cells. However, it has long been known that cellular activity is heterogeneous, and therefore the average activity, while certainly important, is not the whole story with regards to cellular function. The differential response of a minority of cells has important implications in cell biology, cancer, and drug discovery. An understanding of these differences at the level of the cellular pathways will be important in understanding polypharmacology, and developing combination therapies to target the heterogeneity of the population, not just the average.

To optimally assess heterogeneity at the cellular level, across a wide range of cellular function, I am developing methods for optimizing the reproducibility of imaging cytometry systems, methods to enhance the multiplexing of cellular measurements, 'hyperplexing,' and improved methods for the segmentation of subpopulations of cells using highly multiplexed data. The goal is to use profiles of cellular function on a cell-by-cell basis to segment large populations of cells into subpopulations with similar phenotypes to identify the variable pathway activation in the underlying signaling networks. We have developed and published a set of Heterogeneity Indices that can be used to identify heterogeneity in large scale screens, and are now applying that approach to a screen for inhibitors of STAT3 activation in Head and Neck cancer cells. A better understanding of the heterogeneity in cellular signaling and response is expected to result in improved in vitro models to guide treatment and especially the use of combinations of therapeutics with complementary or synergistic activity.

A second component of my research is the development of computational models that predict drug effects in humans using cell-based assays in 2D and 3D models. We have shown that HCS data from simple 2D liver models can be used to predict some modes of human liver injury, and are now developing a 3D human liver model that is expected to provide improved predictivity. Furthermore, this liver model will be integrated with kidney and gut models to address mechanisms that result from organ interactions. To support this project we are developing a Microphysiology Database that will be used to relate measurements in the model to human clinical findings, to make this liver model truly predictive of the effects of chemical exposure on human liver physiology.

David Koes, Ph.D.

Research Assistant Professor



The goal of my research is to remove barriers to computational drug discovery. I create novel computational methods for accelerating the pace of discovery and enhancing the accuracy virtual screening. Specific projects include:

Ligand-Protein Scoring Affinity prediction and hit identification of small-molecule inhibitors. We are designing an empirical scoring function for energy minimization and affinity estimation of small-molecules posed in a binding site. We have participated in the CSAR blind docking exercise and the Teach-Discover-Treat challenge. We have developed a general, high-performance, framework for empirical scoring forked from AutoDock Vina called smina. The goal is to support the inclusion of expert knowledge while being broadly applicable in the default case. (http://smina.sf.net)

ShapeDB Fast, efficient search of molecular shapes. We have developed a computational method for searching for specific molecular shapes using novel indexing scheme. The user sculpts a precise definition of the desired molecular shape and millions of molecular shapes can be screened for matches in a matter of seconds. (https://github.com/dkoes/shapedb)

PocketQuery Rapid identification of small-molecule starting points in protein-protein interactions. Protein -protein interactions (PPIs) are a promising, but challenging target for pharmaceutical intervention. One approach for addressing these difficult targets is the rational design of small-molecule inhibitors that mimic the chemical and physical properties of small clusters of key residues at the protein-protein interface. PocketQuery is a web service for interactively exploring and identifying these key clusters of residues. A consensus score derived using machine learning immediately and effectively identifies the most promising small-molecule starting points. PocketQuery is integrated with AnchorQuery and ZINCPharmer (see below). (http://pocketquery.csb.pitt.edu)

AnchorQuery Specialized pharmacophore search of an easy to synthesize virtual chemical space that is biased to target protein-protein interactions. The AnchorQuery concept leverages anchors, amino acid residues that bury a large amount of solvent accessible surface area at the protein-protein interface. Every compound in our multi-component reaction (MCR) accessible virtual library contains an anchor analog, a functional group that is a chemical mimic of a specific amino acid. AnchorQuery pharmacophore queries always include an anchor feature in addition to the standard hydrophobic, ionic, and hydrogen bond donors. All non-anchor features are stored relative to a coordinate system defined by the anchor in an efficient spatial index. Pharmacophore searches scale relative to the breadth and complexity of the query, not the size of the database. As a result, full 3D pharmacophore searches can be executed over hundreds of millions of explicit conformations in a matter of seconds. (http://anchorquery.csb.pitt.edu)

ZINCPharmer Online interactive pharmacophore search of the ZINC database. ZINCPharmer is an online interface for searching the ZINC database of purchasable compounds with a general 3D pharmacophore model (a spatial arrangement of essential interaction features, such as hydrophobes and hydrogen bonds). ZINCPharmer uses the Pharmer search technology (below).
http://zincpharmer.csb.pitt.edu

Pharmer Open-source pharmacophore search software. Pharmer is a pharmacophore search technology that uses a custom spatial index data structure to search millions of chemical structures in seconds. Unlike other technologies, the performance of Pharmer scales with the complexity of the query, not the size of the library being searched. (http://pharmer.sf.net)

NucleoQuery Specialized pharmacophore search of an easy to synthesize virtual chemical space that is biased to target protein-nucleic acid interactions. NucleoQuery applies the principles of AnchorQuery to target protein-nucleic acid interactions with the goal of discovering small-molecule inhibitors that contain a nucleic acid analog. (http://nucleoquery.csb.pitt.edu/)

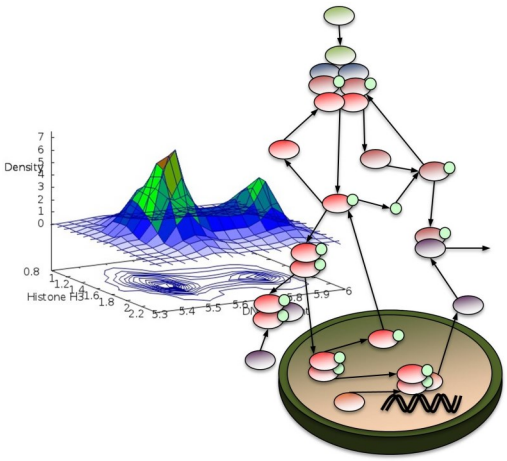
Timothy Lezon, Ph.D.

Assistant Professor

My research focuses on developing models for investigating global protein dynamics and the analysis of high content screening data in systems biology.

As the number of solved protein structures increases, it is becoming increasingly clear that many proteins do not simply fluctuate about a single stable native state conformation, but that proteins under physiological conditions populate conformational ensembles and are capable of experiencing fluctuations of several Angstroms. These global conformational changes frequently facilitate functional activity such as protein-protein binding, molecular transport and allosteric regulation. In order to properly understand the behavior of proteins, we require the ability to accurately model their motions on multiple levels. Although all-atom molecular dynamics simulations have enjoyed great success in predicting local motions or those that occur in much less than one microsecond, their high computational cost limits their effectiveness in studies of large-scale protein dynamics. Instead, coarse-grained models that use simplified protein structures and interactions are of great use in studying global protein dynamics. We are interested in learning how these models should be parameterized to best reproduce experimentally obtained conformational ensembles. We are also studying how external factors, such as viscous damping, the presence of lipid bilayer, or interactions with external protein complexes influence the dynamics predicted by these models. Further, we are investigating the accuracy of conventional statistical measures of elastic network model performance. From these studies we hope to learn which factors are most influential in determining protein conformational ensembles and to produce models that can accurately predict ensembles.

Cellular behavior emerges from the complex network of interactions between chemicals in the cell, the details of which remain largely unknown. Many regulatory pathways are redundant and interdependent, hindering our ability to accurately model their *in vivo* behavior. Further complicating matters are slight differences between cells within a population, as well as the interplay between individual cells and their environment. Thus, seemingly identical cells may respond differently to the same environmental perturbation. As part of the quantitative systems pharmacology team at the University of Pittsburgh Drug Discovery Institute, I am developing new techniques for analyzing patterns of cellular heterogeneity from high content screening (HCS) data. By analyzing fluorescent microscopy images of thousands of cells under a variety of environmental conditions, we hope to identify cellular phenotypes that indicate effective cancer therapies, and to identify putative drug combinations for treating tumors.

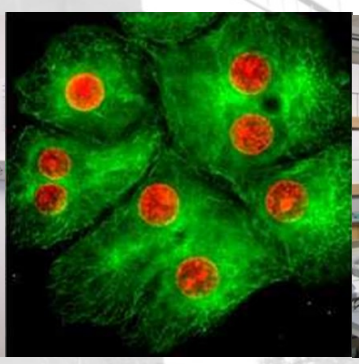


Mark Schurdak, Ph.D.

Visiting Research Associate Professor

I received a BS degree in Biology from the University of Miami in 1982, and my PhD degree in Pharmacology from Baylor College of Medicine in 1987. My postdoctoral training was at Hoffman-La Roche, Inc., in the department of Oncology and Virology after which I accepted a senior scientist position at PharmaGenics, Inc. (PGI), as the third employee of that start-up biotech company. There I was instrumental in establishing the company and building the department of Molecular and Cell Biology and in developing novel technologies for the discovery of oligonucleotide-based therapeutics. After five years at PGI, I was recruited to Abbott Laboratories' Department of Combinatorial Chemistry to develop methodologies to screen large combinatorial libraries. My research there was instrumental in the development and patenting of the µARCS technology, and in establishing affinity selection mass spectrometry screening technology. Subsequently, I moved into the high-throughput screening (HTS) department where I assumed the role of a group leader. Here I instituted and led the early high-throughput ADME group, enabled HTS siRNA screening, spearheaded the adoption of High Content Screening (HCS) and directed the HCS group. In 2007, I moved to the Target and Lead Discovery department where I was responsible for leading the hit-to-lead biology efforts for various therapeutic area projects. In 2009, I took on the role of lead biologist in the Early Pain Discovery Group within the department of Neuroscience where I advanced new molecular targets for the treatment of pain from target identification through hit-to-lead.

I joined the University of Pittsburgh Drug Discovery Institute as the Director of Operations and Screening in 2011 and have a Research Associate Faculty appointment in the Department of Computational and Systems Biology. My research interests lie in applying a systems pharmacology approach to develop more effective drug discovery strategies that utilize integrated phenotype/function-based analysis including HCS to "hyperplex" multiple readouts for signaling pathways, cellular functions, and cell morphology and establish signatures that characterize the response of cells to stimulation by drugs and toxins. The signatures, which are the integrated functional responses (encompassing all affected pathways and systems) of the cell, would be the basis for the development of screening assays to identify novel chemical (and biological) entities predicted to produce desired functional effects.



Indira Shrivastava, Ph.D.

Research Assistant Professor

I am interested in exploring the structure-function paradigm which equates the function of the protein to its three-dimensional structure by employing multiple computational modeling approaches. At one end of the computational approach spectrum, lies the structure-based coarse-grained network models, such as Gaussian Network Model (GNM) and Anisotropic Network Model (ANM) used to analyze the global dynamics. Fully atomistic molecular dynamics (MD) simulations is used to analyze the structural dynamics at the residue/atomic level interactions. Thus a combination of ANM and MD provide a more or less 'complete' picture of protein dynamics, which aids in understanding its functional mechanism.

Mitochondrial Membrane Proteins

VDAC is a major Mitochondrial Outer Membrane (MOM) channel, primarily responsible for flux of mitochondrial metabolites from the mitochondria, to the cytosol. The permeability of the metabolites is regulated by the Bcl-2 family of proteins, which are both pro- and anti- apoptopic. In addition, cardiolipin, a lipid present in high concentration at the MOM/inter-membrane space (IMS) interface, is also suggested to contribute towards regulation of cytochrome release. Understanding the role structural dynamics of VDAC in the interaction with cardiolipin within the membrane environment, is the main purpose of these project. The dynamics of VDAC will be assessed using elastic network models and interactions with cardiolipin will be studied via molecular-dynamics simulations and docking studies.

Cell Free Plasma Hemoglobin

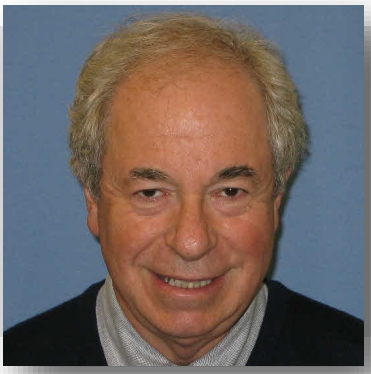
Primary goal of this project is to inhibit the reaction of NO with plasma Hb by developing small molecules which bind to and shield the heme group from subsequent reactions with NO. We will use a combination of computational and experimental methods for the identification of high-affinity binding sites, also known as 'hot-spots' in hemoglobin. We will use a novel automated computational algorithm in collaboration with GSK (Bakan et al, 2012) to identify high-affinity 'hot-spots' which will be further extended and applied to Hb.

Snake Venom Toxins

Snake venom toxins are responsible for causing toxicity following envenomation including necrosis, apoptosis, neurotoxicity, mytotoxicity, cardiotoxicity, etc. Thus, snake venoms represent a significant hazard to snakebite victims, which underscores the need to develop efficient anti-venom drugs. However, some snake venoms also have great potential for drugs for treating human diseases. We plan to characterize interaction of venom toxins with membrane bilayers using molecular modeling and molecular dynamics simulations.

PINK1/ATP_ADP carrier interactions

PTEN-induced putative kinase 1 (PINK1) is a mitochondrially targeted serine/threonine kinase whose loss of function mutations leads to striking changes in mitochondrial structure and function. The recessively inherited Parkinson's disease, a neurodegenerative disorder, is linked to mitochondrial dysfunction. There have been numerous studies supporting the role of neuroprotective roles for PINK1, since it protects cells from damage-mediated mitochondrial dysfunction and cell apoptosis. The kinase domain of PINK1 is known to associate with mitochondrial ATP/ADP carriers. We will build homology models of PINK1 and dock these on ATP/ADP carriers, in order to determine PINK1/carrier interactions at the residue level. These modeled interactions will be experimentally tested to determine the validity of the docked poses.



Andrew Stern, Ph.D.

Visiting Research Associate Professor

The overarching goal of our research is to identify mechanisms involved in complex human disease progression and use this knowledge to develop novel therapies for individual patients. We apply a holistic clinically relevant quantitative systems biology and pharmacology approach. This involves the development, implementation, and integration of several high throughput and high content molecular and cell-based technologies and models to comprehensively define fundamental biological processes that are perturbed in particular diseases. Although this approach is modular and has general applicability, we have thus far focused primarily on cancer. For example, we recently (*Cell*, 2012) implemented an integrated target identification platform involving proteomic, shRNA, and small-molecule screening that identified AURKA as a negative regulator of megakaryocyte differentiation in the rare disease acute megakaryocyte leukemia (AMKL). Based upon additional cellular and in vivo model studies, the clinical candidate Alisertib is being repurposed for this specific indication with trials scheduled to begin later this year. In another study (*Cell*, 2013), we developed the Cancer Therapeutics Response Portal (http:/www.broadinstitute.org/ctrp) that can be used to develop novel therapeutic hypotheses and to accelerate discovery of drugs matched to patients by their cancer genotype and lineage. As one example, we identified a candidate dependency associating activating mutations in the oncogene b-catenin with sensitivity to the Bcl2 family antagonist navitoclax. These results form the basis for a patient stratification strategy that will be tested through a collaboration between Abbott Laboratories and the Broad Institute. In another study (*Nature Chemical Biology* in press), our goal was to discover more effect therapies for acute leukemia by developing high throughput screening systems that reflect the complex physiology of this disease, including leukemia stem cells and supportive interactions with the bone-marrow microenvironment. One clinically relevant result that has emerged from this project is that leukemia stem cells have been shown to exquisitely sensitive to HMGCoA inhibition in contrast to normal hematopoietic stem and progenitor cells. These results suggest that statins should be re-evaluated as anti-leukemia agents and further pre-clinical validation is ongoing.

In collaboration with Professor Adrian Lee at the University of Pittsburgh Cancer Institute (UPCI) we are using our prospective and retrospective tissue collection to compare and contrast the cellular and molecular heterogeneity of primary breast cancer to patient-matched early and late metastatic disease. Our goal is to identify pathways in recurrent disease that represent specific metastatic events with dependencies targetable by systems biology-based rationally-designed combinations of known drugs. In another UPCI collaboration, we are working with Professor Robert Ferris to probe pathways specific to HPV-associated head and neck cancers and translate this knowledge into effective novel therapies.

Lawrence Vernetti, Ph.D.

Research Associate Professor

My research is focused on developing *in vitro/in vivo* models and analysis methods to evaluate human risk to small molecules. The driving force is a desire on the part of researchers, regulators and the drug industry to reduce the number of animals used in drug safety testing with the eventual goal to replace animal trials using 3D human cell based model systems. Since 2011, I have implemented several early drug safety cell based assays for hepatotoxicity, a rapid microsomal screen for drug metabolism and an *in vivo* cardiotoxicity assay in Zebrafish. These assays not only provide immediate and possible crucial information to de-risk compounds prior to pre-clinical candidate selection for ongoing projects, but will also provide some of the experimental data needed to populate a database for building the predictive bioinformatics tool.

At the present, a valuable component to predictive hepatotoxicity is the identification of compounds that induce the same toxic mechanism of actions (MOA) which are found in preclinical and clinical toxicity. The liver is the primary organ responsible for drug metabolism which can lead to the generation of toxic metabolites. These metabolites can produce mitochondrial dysfunction and oxidative stress which are common pathways leading to hepatotoxicity. These two functional processes can be efficiently captured using High Content Screening to read out mitochondrial sand oxidative stress responsive fluorescent probes. This approach has proven beneficial to the Acute Kidney Injury project and HIV Nef inhibitor program by identifying structural based toxicology 'hot spots' on the molecules in these two large SAR drug series.

Cardiotoxicity is often caused by drug interactions against key ion channels in the heart which can result in arrhythmia and a reduction in cardiac efficiency. These rapid acting responses are best measured in an intact functioning whole organ. For example, the zERG potassium rectifier channel in the Zebrafish embryo heart has high similarity to hERG potassium rectifier channel in the human heart so this small vertebrate organism has been employed as a 'fit for purpose' model to evaluate potassium rectifier channel-linked cardiotoxicity. The Zebrafish cardiotoxicity model was co-developed, along with Chakra Chennubhotla, as a low cost, non-invasive, moderate throughput assay. We now have validated and are starting to use an automated, image-based computation algorithm to assess beat rate and beat periodicity method from short video clips of drug treated Zebrafish embryos. An automated video capture method was developed for High Content Screening instruments to produce a moderate throughtput screen with the capability to screen 200-400 compounds per week for cardiotoxicity.

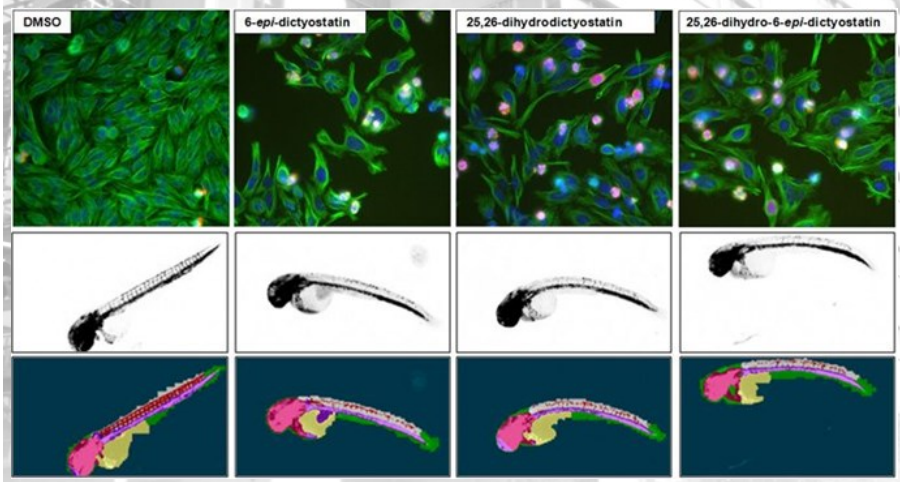
As part of the long term goal to improve human safety assessment and decrease the numbers of animals used in toxicology, I have been an active participate since 2012 to develop, validate and deploy a physiologically relevant 3D, 4 cell type human liver organoid model for toxicity and efficacy testing. The funding for this research has been extended for 3 additional years. The model is a re-construction of the sinusoid, the smallest function unit of the liver. The concept is to arrange the 4 key liver cell types into the same organization as found in the sinusoidal hepatic cords in a media flow-through device. This arrangement generates an approximation of the oxygen and metabolic gradient believed to be responsible for much of the toxicity found in the in vivo liver. Furthermore, subsets of the integrated cells are genetically encoded with functional protein based 'biosensors' which provide real-time and quantitative readouts of cell health and molecular mechanisms of toxicity. The 3D liver organoid have progress beyond the design concept and into the final validation and optimization stage before they can be used with unknown compounds. In parallel with the construction of the artificial liver is the development of a searchable database and the tools needed to relate the experimental results from the construct to literature based chemical, bioactivity, pre-clinical and clinical data to predict the safety of new compounds.

Andreas Vogt, Ph.D.

Associate Professor

My research interests center around the discovery of small molecules affecting proliferative diseases using functional cellular and whole organism models. My major targets of interest are the mitogen-activated protein kinase phosphatases or MKPs. MKPs play important roles regulating the activities of mitogen-activated kinases, and have been implicated in cancer, immune response, and myocardial infarction. The search for small molecule inhibitors of MKPs has been challenging due to a lack of structural guidance for inhibitor design, the abundant use of uninformative in vitro assays for phosphatase activity, and the absence of definitive assays to probe MKP inhibition in the context of the living cell or a whole organism. With the help of collaborators in the Departments of Developmental Biology, Computational and Systems Biology, and Pharmaceutical Sciences, I am currently using a combination of high-content analysis, transgenic zebrafish, and computational modeling to engineer novel approaches to MKP inhibition.

My second focus is the continued development of novel drug discovery tools that enhance the information content of biological assays. Over the past six years, I have been involved in the establishment of the University of Pittsburgh Drug Discovery Institute (UPDDI) as a nationally respected academic center with high-content analysis (HCA) capabilities. Collaborative drug discovery projects using HCA include kidney regeneration, FGF signaling, microtubule perturbation, HIV-Nef dimerization, activation of p53 upregulated modulators of apoptosis (PUMA), and breast cancer metastasis. A natural extension of my work is the expansion of image-based analysis from cell culture to zebrafish. The zebrafish embryo is a particularly attractive candidate for contemporary drug discovery because it is small, easily kept and obtained, and optically transparent. The NIH, AHA, and the University of Pittsburgh Institute of Aging are currently supporting collaborations with Neil Hukriede and Michael Tsang (Department of Developmental Biology), Beth Roman (Biology), and Edward Burton (Neurology) aimed at developing novel image-based methods to analyze fluorescent transgenic zebrafish embryos. Of particular interest is an artificial intelligence-based method termed Cognition Network Technology (CNT) that emulates human cognitive processes. Using this approach, we are currently performing automated chemical genetics screens for activators of Fibroblast growth factor (FGF) and Nodal/TGF-beta signaling as potential regenerative therapies.



Peer Review Activities (p.41)
Collaborative Research Activities (p.46)
Presentations at National and International Meetings (p.57)

Peer Review Activities

Ivet Bahar

Editorial Board Membership
Proteins: Structure, Function and Bioinformatics, June 2008 – present
Protein Science, 2011 – present

Reviewer:
Science
Nature
Cell
Molecular Systems Biology
PLoS Computational Biology
Proteins: Structure, Function, Bioinformatics
Protein Science
Journal of Chemical Physics
Journal of Molecular Biology
Biophysical Journal; Biochemistry: Polymer
Bioinformatics
Structure
Journal of Structural Biology
Phys Review Letters
Physical Reviews E
Proceedings of the National Academy of Sciences
Macromolecules
and others

NIH Review Panels

2013 NIH Study Section Member, Special Emphasis Panel for Director's New Innovator Award (DP2) Program (Phase I, Mail Review)
July 1-3, 2013: NIH-Interdisciplinary Molecular Science and Training (IMST) Program Review Panel-Site Visit for P41 Application. University of Wisconsin, Madison. Review Panel.
December 9-10, 2013: NIH R15 Area Review, Washington, DC. Review Panel (Study Section) Member.
January 20-22, 2014: The International Human Frontier Science Program Research Grant Review Committee.Strasbourg, France. Review Committee Member.
March 5-7, 2014: NIH Review Panel for National Biomedical Computation Resource (P41-BTRC) Program.UCSD, San Diego, CA. Review Panel Member.
April 7, 2014: NIH U54 Area Review. Washington, DC. Review Panel Chair.

Grant Reviews
NIH MABS Study Section, Reviewer (at Bethesda, MD), Regular-quarterly meetings

October 20-22. 2013: NIH Advisory Board Meeting. University of Illinois Urbana-Champaign, IL. Advisory Board Member.

Panagiotis Benos

1.A. Grants
National Institutes of Health (NIH) (11/2013), ZRG1 F08-B (20) L, GGG panel member
National Institutes of Health (NIH) (02/2014), ZRG1 F08-B (20) L, GGG panel member
National Institutes of Health (NIH) (06/2014), ZRG1 F08-B (20) L, GGG panel member
(**) Due to substantial service to peer review at the National Institutes of Health I became eligible for Continuous Submission from August 2014 to September 2015.

1.B Papers
Applied Bioinformatics (2004-), Bioinformatics (1998-), BMC Bioinformatics (2003-), BMC Genomics (2009-), Genome Research (2007-), Genomics (2007-), Molecular Systems Biology (2007-), Nucleic Acids Research (2005-), PLoS Computational Biology (2005-), PLoS One (2011-) Proceedings of the National Academy of Sciences (USA) (2003-), OncoTarget (2014-) and

Acta Pharmacologica Sinica (2003-), Biochemistry (2003-), Cancer Letters (2012-), Compar Biochem Physiol (2007-), FEBS Letters (2004-), Gene (2008-), J Theor Biol (2009-), Molecular Biology and Evolution (2007-), RNA (2009-).

1.C Conference papers
RECOMB 2014
ISMB 2014
ECCB 2014

Jeremy Berg

Manuscript reviewer for: Cell, Journal of the American Chemical Society, Proceedings of the National Academy of Sciences

Carlos Camacho

Biology Editorial Board member, *International Journal of Molecular Science* (2009-Present)
Regular Reviewer:
Proteins, 1992-To present
Biophysical Journal, 1992-To present
Bioinformatics, 1992-To present
PNAS, 2000-To present
JMB, 2000-To present
And sporadic reviewer for several other journals.
Reviewer for grants of
NSF, 2008-2011. Panel Member
NIH, 2009-Present Study Section Permanent Member

Chakra Chennubhotla

Reviewer:
Biophysical Journal;
Bioinformatics;
PLoS One

Nathan Clark

Manuscript Reviewer for:
Genome Biology and Evolution
Molecular Biology and Evolution

James Faeder

Editorial board member
Mathematical Biology section of *Biology Direct*, 2007-*present*.
Board of Reviewing Editors, *Science Signaling*, May, 2010-present.
Reviewer for journals
Bioessays, Bioinformatics, Biology Direct, Biophysical Journal, BMC Bioinformatics, BMC Systems Biology, Complexity, Computational Methods in Systems Biology Conference, Genes and Development, IET Systems Biology, Interface Focus, Journal of Cellular Physiology, Journal of Chemical Physics, Journal of Molecular Biology, Journal of Physical Chemistry, Journal of Theoretical Biology, Mathematical Bioscience, Molecular and Cellular Biology, Nature, Nature Reviews Immunology, Physical Biology, Physical Review E, PLoS Computational Biology, PLoS One, Proceedings of the National Academy of Science (USA), Science Signaling, Theoretical Biology and Medical Modeling
Conference and workshop organization
Chair of Program Committee. 7th International q-bio Conference on Cellular Information Processing, Santa Fe, NM, August, 2013.
Chair of Program Committee. 8th International q-bio Conference on Cellular Information Processing, Santa Fe, NM, August, 2014.
Conference reviewing
Program Committee, BioVis 2014 Papers (the 4th IEEE Symposium on Biological Data Visualization), July 11-12, 2014 in Boston, MA, US.

Elodie Ghedin

Ad hoc reviewer for the following Journals:
American Journal of Tropical Medicine and Hygiene; BMC Bioinformatics; BMC Genomics; Bioinformatics; Clinical Infectious Diseases; Emerging Infectious Diseases; Genomics; Infection, Genetics and Evolution; International Journal for Parasitology; ISME Journal; Journal of Biological Chemistry; Journal of Clinical Investigations; Journal of Eukaryotic Microbiology; Journal of Molecular Biology; Journal of Molecular Diagnostics; Journal of Pathology; Journal of Virology; Mbio; Molecular & Biochemical Parasitology; Microbiome; Molecular Ecology; Molecular Microbiology; Nature; Nature Biotechnology; Nature Genetics; Nature protocols; Philosophical Transactions of the Royal Society (Biological Sciences); PLoS Computational Biology; PLoS ONE; PLoS Pathogens; PLoS Neglected Tropical Diseases; Proceedings of the National Academy of Sciences USA; Trends in Parasitology.

Grant review:
2013 European Science Foundation Research Conference Scheme
2013 Discovery Grant Applications, Z-N-EVOLUTION-ECOLOGY, Natural Sciences and Engineering

Research Council of Canada (NSERC)
2014 Alfred P. Sloan Foundation

Editorial duties:
2013 – 2018 Member, External Advisory Board for the University of Michigan Host/Microbiome Initiative
2013 – *present* Guest Editor, *PLoS Pathogens*
2012 – *present* Editorial board member, *Microbiome*
2008 – *present* Deputy Editor (2011-present), Associated Editor (2008-2011), *PLoS Neglected Tropical Diseases*
2009 – *present* Editorial board member, *Genes*

D. Lansing Taylor

Editor for Experimental Biology and Medicine
Reviewer for European Pharmaceutical Review
Member/Reviewer, NCI Working group on biomarkers

Daniel Zuckerman

Reviewer - journals
J Chem Phys
J Phys Chem
Biophys J
J. Comp. Chem.
J. Chem. Theory Comp.
J. Stat. Phys.

Associate Editor – BMC Biophysics: 2011 – 2013

Reviewer - grants
NSF proposals

—-

Joseph C. Ayoob

Review Panelist, NSF Graduate Research Fellowship Program (GRFP) (January 28/30, 2014).
Review Panelist, NSF FY14 Postdoctoral Fellowships in Biology (PRFB) Panel 1 (December 9-10, 2013).

Dipak Barua

Reviewer:
PLoS Computational Biology
Physical Biology
Mathematical Biosciences

Maria Chikina

PlosOne
Bioinformatics
PeerJ
ECCB Conferece proceedings

Antonio Ferreira

Reviewer for XSEDE14 Technical Program Committee

Albert Gough

Reviewer for PlOS ONE

David Koes

Reviewer:
Algorithms

Timothy Lezon

Reviewer:
Journal of Molecular Graphics and Modelling
Proteins
Chemical Physics Letters
Biophysical Journal
ACS Chemical Biology

Indira Shrivastava

Reviewer
Biomedical Central Structural Biology
Biophysical Journal
European Biophysics Journal
Journal American Chemical Society
Journal of Molecular Recognition
Journal of Physical Chemistry
PLoS Computational Biology
Proteins: Structure, Function and Bioinformatics
PLoS One

Lawrence Vernetti

Identifying and Quantifying Heterogeneity in High Content Analysis: Application of Heterogeneity Indices to Drug Discovery. Gough AH, Chen N, Shun TY, Lezon TR, Boltz RC, Reese CE, Wagner J, **Vernetti LA**, Grandis JR, Lee AV, Stern AM, Schurdak ME, Taylor DL. PLoS One. 2014 Jul 18; 9(7) PMID:25036749

In vitro platforms for evaluating liver toxicity.
Bale SS[1], Vernetti L, Senutovitch N, Jindal R, Hegde M, Gough A, McCarty WJ, Bakan A, Bhushan A, Shun TY, Golberg I, Debiasio R, Usta BO, Taylor DL, Yarmush ML. Exp Biol Med (Maywood). 2014 Apr 24. [Epub ahead of print] PMID:24764241

Towards a three-dimensional microfluidic liver platform for predicting drug efficacy and toxicity in humans. Bhushan A, Senutovitch N, Bale SS, McCarty WJ, Hegde M, Jindal R, Golberg I, Berk Usta O, Yarmush ML, **Vernetti L**, Gough A, Bakan A, Shun TY, DeBiasio R, Lansing Taylor D. Stem Cell Res Ther. 2013;4 Suppl 1:S16. Epub 2013 Dec 20. PMID:24565476

Andreas Vogt

Study Section member

Small Business: Cancer Drug Development & Therapeutics, NIH
ZRG1 OTC-T (10) B, (2012- 2013)

Small Business: Chemistry, Biochemistry, Biophysics & Drug Discovery, NIH
ZRG1 IMST-G (10) B (2014)

Small Business: Cancer Drug Developments & Therapeutics, NIH
ZRG1 OTC-T (12) B (2014)

Invited Journal Referee: Science, Journal of Medicinal Chemistry, Molecular Pharmacology, Molecular Cancer Therapeutics, Biochemical Pharmacology, Toxicology in vitro, ChemMedChem, PloS One

Collaborative Research Activities

Ivet Bahar

University-wide Collaboration with
1. Dr. Susan Amara on the molecular mechanism of functioning of glutamate transporters
2. Dr. Bard Ermentrout (Mathematics) and Yoram Vodovotz (Surgery) on modeling apoptotic pathways
3 Dr. Joel Greenberger, UPMC, on the development of PUMA inhibitors
4. Dr. A. Gronenborn on comparing the fluctuation dynamics of proteins structurally determined by NMR and X-ray
5. Dr. Valerian Kagan on the inhibition of the peroxidase activity of cytochrome c.
6. H. Karimi (Information Science and Telecommunications, School of Information Sciences) in the development of an online database of molecular motions, available to the scientific community
7. Dr. Oltvai (Pathology) on elucidating transcription/regulation pathways
8. Dr. Ed Prochownik, UPMC, on the development of c-Myc-Max inhibitors
9. Drs. Steve Shapiro and Murat Kaynar on modeling the activation and deactivation mechanisms of matrix metalloprotein 8.
10. Dr. Lans Taylor and coworkers at the Drug Discovery Institute

11. Dr. Michael Tsang (Biochemistry and Molecular Genetics) on developing inhibitors for MAP kinase phosphatases
12. Dr. Ben van Houten, at UPCI, Molecular Biology on the mechanism of function of UvrA and UvrB
13. Dr. Andreas Vogt
14. Dr. Alan Wells (Pathology) on ligand binding affinities of epidermal growth factor Receptors
15. Dr. Peter Wipf

External
1. Drs. Russ Altman and Jeanette Schmidt at Stanford U on the development of molecular models and methods for examining supramolecular systems
2. Prof. R. Elber (UT Austin), on a R33 project on the Computational Prediction of Biomolecular Dynamics (PI: Bahar).
3. Collaboration with Lila Gierasch (U Mass) on elucidating the allosteric mechanisms underlying the activity of chaperones
4. Dr. Ingo Greger (Cambridge, UK) on the examination of the allosteric dynamics of glutamate receptors.
5. Collaboration with Dr. Pietrokovski (Weizmann) on the identification of correlated mutations from sequence information
6. Dr. David Perlmutter (UPMC) on mitochondrial targeting against radiation damage.
7. Gary Silverman (U Pitt) on preclinical drug discovery for the prevention of neonatal necrotizing enterocolitis.
8. Drs. Eduardo Perozo and Benoit Roux at the University of Chicago, and Harel Weinstein at Cornell Weill Medical School on The Membrane Protein Structural Dynamics Consortium
9. Collaboration with Klaus Schulten and Emad Tajkhorshid (University of Illinois, Urbana Champaign) on developing an efficient molecular dynamics simulation method that combines elastic network models with full atomic models.

Panagiotis Benos

2.A. Intra-departmental
1. Ivet Bahar (Computational and Systems Biology).
Project title: **Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data.** Dr. Benos laboratory collaborated with Dr. Bahar (Comput & Systems Biol), in aU54 grant proposal for the establishment of a Center that will develop and apply causal modeling algorithms to Big Biomedical Data. This grant was reviewed favorably and we are waiting for the final funding decision.
2. Chakra Chennubhotla (Computational and Systems Biology)
Project title: **Efficient spectral clustering methods for disease feature identification.** In collaboration with Dr. Chenubhotla (Comput & Systems Biol), we continue developing various methods to surpass the problem of disease heterogeneity.

2.B. University-wide
1. Steffi Oesterreich (Magee Womens Research Institute, School of Medicine):
Project title: Understanding the role of estrogen receptor in breast cancer. In collaboration with Dr. Oesterreich we analyze DNA binding data (ChIP-seq) for estrogen receptor and other factors to identify mutations that are affecting transcription in breast cancer. We are currently finalizing the results of this analysis to prepare the manuscript
2. Richard Duerr (Gastroenterology):
Project tile: Investigating molecular mechanisms involved in inflammatory bowel disease (IBD). In collaboration with Dr. Duerr we have analyzed data from Th17-enriched cell populations stimulated with

different compounds in order to identify mechanisms and SNPs that might be relevant to IBD. We are now preparing the results of this work for publication. Drs Benos and Duerr have one NIH grant funded together.
3. Robert Friedlander (Neurosurgery):
Project title: Investigating the role of coding and non-coding RNAs in atherosclerosis. We recently established a collaboration with Dr. Friedlander to investigate the possible role of mRNAs and miRNAs in plaque formation. We are now preparing the results of this work for publication.
2.C. External
1. Naftali Kaminski (Yale University, School of Medicine):
Project title: Analysis of high-throughput data associated with terminal diseases. In collaboration with Dr. Naftali Kaminski (Dept of Medicine, SOM) we develop computational methods to analyze gene expression and protein-DNA binding data aiming to uncover the underlying structure of the involved gene regulatory networks. The methodology we develop is general and can be applied to practically any phenotype, including cancer. Drs Benos and Kaminski have two NIH grants funded together.

Jeremy Berg

Intra-departmental

1. Professors Ivet Bahar and Dan Zuckerman on free-energy perturbation calculations

Carlos Camacho

"Ongoing collaborations with Dr. Dana Ascherman (Medicine, University of Miami) in peptide immunogenicity; Dr. Alex Doemling (Drug Design, University of Groningen) in inhibitors of protein interactions; Dr. Igor Roninson (Cancer biology, University of South Carolina) in developing novel inhibitors of cancer targets; Dr. Alan Wells (Pathology) regulatory mechanisms of ACTN4; Dr. Yohei Doi (Infectious diseases) developing metallo-beta-lactomase inhibitors; Adam Straub (Pharmacology) developing cytochrome B5 reductase 3 inhibitors; DNA repair (in collaboration with Dr. Sobol); cancer invasion (Dr. Finn);

Intra-departmental
Chair Admission Committee
Member Executive Committee

University-wide
Member Tenure committee

Chakra Chennubhotla

Intra-departmental
1. Computational Pathology: Ongoing collaboration with Dr. Takis Benos (DCB) on interstitial lung diseases

University-wide
2. Computational Pathology: Ongoing collaboration with Dr. Lans Taylor (DCB) and Drug Discovery Institute, Dr. Adrian Lee, Magee Women's Research Institute, and General Electric Research Center team on breast cancer
3. Computational Pathology: Ongoing collaboration with Dr. Yang Liu (Medicine) on nano-architectures based markers for cervical cancer and emerging microscopy platform for cancer risk detection
4. Computational Bioimaging: Ongoing collaboration with Dr. Cecilia Lo (Developmental Biology) on the role of ciliary dysfunction in congenital heart disease

External
5. Computational Olfaction: Ongoing collaboration with Dr. Jason Castro, Bates College, on computational olfaction
6. Computational Biophysics: Ongoing Collaboration with Drs. Pratul Agarwal, Arvind Ramanathan, Christopher Stanley, Oak Ridge National Laboratory and Dr. Nicolas Doucet, INRS, Quebec on computational identification of functionally relevant biomolecular intermediates – bridging experimental timescales with atomistic details
7. Computational Pathology: Ongoing Collaboration with Dr. Rebecca Critchley-Thorne, Bruce Campbell, Cernostics Inc. on digital pathology

Nathan Clark

Intra-deparmental:
1. Work with Joe Ayoob to predict novel regulators of cellular engulfment in *Drosophila.*

University-wide
2. Dr. Hong Nguyen and Dr. Neil Clancy (Division of Infectious Disease) on gene regulation in *Candida albicans* infections samples from human infection sites.
3. Kara Bernstein - Describing the evolution of the Shu complex involved in DNA repair and recombination.
4. Dr. Allyson O'Donnell - Matching alpha-arrestin trafficking proteins with their cargoes in yeast and human renal proteins.

James Faeder

1. NIH R01 project "Systems Biology Approach to MAPK Regulation of Malaria Infection in Stephansi." Role: co-I. In collaboration with the project PI Shirley Sluckhart and University of California at Davis and Yoram Vodovotz in the Department of Surgery are developing species-specific mathematical models of MAPK signaling downstream multiple signaling inputs.

2. DoD Multidisciplinary University Research Initiative (MURI) project "Mechanisms of Bacterial Spore Germination and its Heterogeneity." Role: Institutional PI. In collaboration with Peter Setlow at the University of Connecticut Health Center and researchers at Oregon State and East Carolina Universities are building mathematical and computational models of bacterial spore germination.

3. NSF Expeditions in Computing Program "Computational Modeling and Analysis of Complex Systems." Role: Institutional PI. In collaboration with lead PI Edmund Clarke at CMU this project will involve the analysis of large-scale rule-based models of signaling pathways that are dysregulated in pancreatic cancer. The goal of the project is to apply revolutionary modeling and analysis techniques and algorithms to complex biological problems.

4. Ongoing collaboration with Penelope Morel and Lawrence Kane in the Department of Immunology to model peripheral T cell differentiation in response to antigen stimulation. Funded in part through the CTSI Molecular and Systems Modeling Core in the Department of Computational and Systems Biology. Additional support for this project may be provided by a pending R01 application.

5. Ongoing collaboration with Liz Marai in the Pitt Department of Computer Science to develop new approaches and tools for the visualization of rule-based models and associated simulation data. This collaboration has resulted in two journal papers and two conference papers, one of which won a Best Paper award at the 2011 BioVis Conference. Additional support for the project may be provided by a pending NSF grant application.

Elodie Ghedin

1. E. Ghedin/B. Zhang/E. Schadt (MPI) Omics-Based Predictive Modeling of Age-Dependent Outcome to Influenza Infection
2. E. Ghedin/S. Lustigman/ T. Unnasch (MPI) Molecular mechanisms of filarial endosymbiosis
3. E. Ghedin/A. Morris (MPI) Pathogenesis of Obstruction/Emphysema and the Microbiome (POEM) in HIV
4. N. Kaminski (PI) Sarcoidosis and AAT genomics and informatics center
5. Y. Kawaoka (PI) High Throughput Identification of Influenza Virus Amino Acids Responsible for Human to Human Transmission
6. E.C. Holmes (PI) Genomic analysis of the canonical case of virulence evolution: Myxomatosis in Australia
7. D. Burke (PI) Computational Models of Infectious Disease Threats – Models of Infectious Disease Agent Study (MIDAS)
   Major Goals: developing models of intra-host influenza virus evolution, which can be incorporated as subsystems into larger models and simulations of influenza epidemiology.
8. K. Nelson (PI) Influenza Genome Project
9. G. Clermont/T. Ross (co-PIs) Predictive biosignatures of complicated Influenza A infection
10. P. E. Ghedin Stock/H.Goodrich-Blair/D. Bird (co-PIs) Nematode-Bacteria Symbioses Research Coordination Network

D. Lansing Taylor

Continued research on heterogeneity in cellular responses to cytokines and drug candidates in head and neck and breast cancer models. Major collaboration within the UPDDI with Bert Gough, Dutch Boltz, Andy Stern, Tim Lezon and Mark Schurdak. One publication. Grants being planned to apply the new analyses to breast cancer.

Continued research program to build human tissue engineered liver model that contain fluorescence-based biosensors to create a platform for better in vitro efficacy and safety testing of new chemical entities. NIH Microphysiology grant extended for 3 more years. Collaborations within Pitt (Bert Gough, Dutch Boltz and Larry Vernetti) and Massachusetts General Hospital. Two publications.

Developed a strategy for a new vision in drug discovery for the UPDDI based on quantitative systems pharmacology. Three disease areas serve as the biomedical drivers where the UPDDI has a leadership role: a) metastatic breast cancer-with Adrian Lee; b) Huntington's disease-with Robert Friedlander and Ivet Bahar; and c) Non-alcoholic fatty liver disease-with Jai Behari. The groundwork led to the submission of a Center for Systems Biology grant: Quantitative Systems Pharmacology with Ivet Bahar, Jeremy Berg and Bob Murphy (CMU) as executive committee-this was not funded, but an R01 is planned for metastatic breast cancer.

Collaboration with Tim Lezon and co-mentoring of Cemal Erdem, a C&SB graduate student, on developing a combined experimental and cellular model of IGF signal transduction in breast cancer. Progress made and publication planned.

Collaboration with Ivet Bahar and Robert Friedlander with some support from Peter Strick and the Brain Institute to combine experimental profiling and computational biology to identify compounds that will provide neural protection in Huntington's Disease. Ivet and I co-mentor Murat Can Cobanoglu, a C&SB graduate student with input from Andy Stern.

Collaboration with Adrian Lee and Andy Stern on Breast Cancer sub-types. Co-mentoring Luong Nguyen, a C&SB graduate student with Chakra Chennubhotla with strong support from Andy, Adrian and Dutch Boltz. Combining genomics data analyses with image data sets.

Collaboration with Don Burke and Mark Schurdak in the development of a diagnostic test for HIV that can be applied in the field. Supported by the Gates Foundation. Mark Schurdak leads this project.

Collaboration with GE Global research on the application of the MultiOmyx platform to cancer research and diagnostics with a starting point in breast cancer. Collaborators from Pitt include Chakra Chennubhotla, Bert Gough, Adrian Lee and Dutch Boltz. I co-mentor Dan Spagnolo, a C&SB granduate student, with Chakra with strong input from Bert Gough and Dutch Boltz. We are working on a pilot study from GE now and have submitted 2 separate grant proposals.

Collaboration with GE Molecular Diagnostics developed over three years. Complete failure of Pitt and UPMC to agree on a deal and GE walked away.

STAT3 project in head and neck cancer that has been funded for 2 1/5 years by the NCI. Collaboration with Jennifer Grandis and Donna Huryn. Mark Schurdak is the lead from the UPDDI with database and imaging input from Bert Gough. This project was completed in February 2014.

John Vries

Departmental: David Koes

University Wide: Angela Gronenborn

Daniel Zuckerman

1. Chemistry Dept, U. Pittsburgh, collaborations with Lillian Chong and Sunil Saxena
2. Computational & Systems Biology, collaboration with James Faeder
3. Drug Discovery Institute, collaboration with Andy Stern
4. Magee Women's Research Institute, collaboration with Steffi Oesterreich
5. Structural Biology, collaboration with Rieko Ishima

—-

Joseph C. Ayoob

1. Collaboration with Elane Fishilevich in Developmental Biology; funded by NIH-NIAID-R21AI101593: “Eat-Me Signaling Cascade in the Apoptotic Cell Engulfment”. This project studies the molecular basis of cellular elimination by identifying and characterizing novel signals from dying cells that triggers their engulfment.

2. Collaboration with Dan Zuckerman, Carlos Camacho, Nathaniel Clark, Bino John, and Timothy Lezon in Computational and Systems Biology; funded by Commonwealth of PA Department of Health CURE funds: “Dissecting the Molecular Mechanisms of Stress-Response Proteins in Cancer”. This project focuses on establishing and characterizing both the molecular interaction networks of two stress-response proteins, YB -1 and Hsp27, and their structural properties in macromolecular complexes.

3. Collaboration with Jonathan Minden in Biological Sciences at CMU to examine the possible mechanisms of action that the small heat shock protein, Hsp27, plays in developmentally regulated cell death and other stress-related processes.

Dipak Barua

External

1. Dr. Markus Dittrich (Director, National Resource for Biomedical Supercomputing) (with Prof. Faeder) Development of MCell, CellBlender, BioNetGen-MCell integration.

2. Dr. Thomas M. Bartol (Senior Scientist, Computational Neurobiology Laboratory, The Salk Institute for Biological Studies) (with Prof. Faeder) Development of MCell, CellBlender, BioNetGen-MCell integration.

3. Prof. Briget S. Wilson (Director, New Mexico Center for Spatiotemporal Modeling of Cell Signaling) Effect of eterogeneity in cell plasma membrane on immune recognition systems.

Hongying (Mary) Cheng

(1) Dr. Sorkin lab, I) PIP2 lipids binding sites in the dopamine transporter; (2) mutations of C-terminus of the dopamine transporter;

(2) Dr. Torres lab, i) investigation of the G-protein binding sites in the dopamine transporter and its regulatory effects

Maria Chikina

Intra-departmental: Collaboration with Nathan Clarks's group: understanding patterns of evolutionary conservations.
University Wide: Mark Schlomichik's group: data analysis for a project investigating B cell sub-types
External: Ichan School of Medicine at Mount Sinai: investigating biomarkers for neurological disease.

Antonio Ferreira

Intra-departmental: John Vries – Ab initio chemical shift prediction applied to protein conformational studies.

University-Wide: Peter Friedman (Pharmacology) – Modeling NHERF1 self-interactions for novel therapeutic development.

External: None

Albert Gough

1. Continued research on heterogeneity in cellular responses to cytokines and drug candidates in head and neck and breast cancer models. Major collaboration within the UPDDI with Lans Taylor, Dutch Boltz, Andy Stern, Tim Lezon and Mark Schurdak. One publication. Grants being planned to apply the new analyses to breast cancer.
2. Collaboration with GE Global research on the application of the MultiOmyx platform to cancer research and diagnostics with a starting point in breast cancer. Collaborators from Pitt include Chakra Chennubhotla, Lans Taylor, Adrian Lee and Dutch Boltz. I also give strong input in Lans

Taylor's co-mentoring (co-mentor, Chakra Chennubhotla) of Dan Spagnolo, a C&SB graduate student.

3. Collaboration with Martin Yarmush at Mass General Hospital on the development of a Microphysiology Liver Platform including development of an internet database for modeling the relationships between microphysiology and human clinical results. Collaborators from Pitt include Lans Taylor, Lawrence Vernetti and Ahmet Bakan.
4. Gave imaging input for STAT3 project in head and neck cancer that has been funded for 2 1/5 years by the NCI. This project was completed in February 2014.

David Koes

University-wide research collaborations (unfunded):

1. Carlos Camacho—Wide assortment of projects.

2. Lee McDermott—Computational identification of potential serine hydroxymethyltransferase inhibitors; Computational prioritization of glutaminase inhibitors.
3. Partha Roy, Andy Stern, Lee McDermott-Computational modeling of profiling

External research collaborations (unfunded):

1. Chang-Deng Hu-Computational identification and modeling of PRTM5:MEP50 protein-protein interaction.

2. Alessandro Paiardini, Roberto Contestabile, Francesca Cutruzzola - SHMT inhibitors

Timothy Lezon

Internal collaborations with

1. Ivet Bahar, on coarse-grained protein dynamics
2. Lans Taylor, Bert Gough, Dutch Boltz and Larry Vernetti, on the analysis of HCS data for drug development

External collaborations with

1. Jean-Pierre Vilardaga, Department of Pharmacology, on GPCR pathway kinetics
2. Adrian Lee, Magee-Womens Research Institute, on IGF signaling in breast cancer
3. GE GRC, along with UPDDI, on developing novel technologies for imaging

Mark Schurdak

1. Discovery of STAT3 inhibitors. Collaborators: Lans Taylor, Jennifer Grandis, University of Pittsburgh Chemical Diversity Center (Donna Huryn and Peter Wipf), and Pittsburgh Specialized Application Center (Paul Johnston). Funded by NExT Program of NCI.
2. Detection of Recent HIV-1 Infections based on Naturally Inspired Synthetic Oligomers. Collaborators: Donald Burke, Lans Taylor. Funded by the Bill and Malinda Gates Foundation.

3. The orphan receptor NRA41 – novel target for ovarian cancer therapy? Collaborators: Steffi Oesterreich and Robert Edwards. Funded by CTSI.

4. Understudied Orphan Receptors – Novel Treatment Targets in Ovarian Cancer. Collaborators: Steffi Oesterreich. Funding approved by the Department of Defense.

Indira Shrivastava

Internal
1. *Prof. V. Kagan* (Dept. of Environmental Sciences and Occupational Health) Structure and functional dynamics of mitochondrial membrane proteins.
2. *Hulya Bayir, MD* (Dept. of Critical Care Medicine). Structure and functional dynamics of mitochondrial membrane proteins.
3. *Mark E. Gladwin, MD* (Vascular Medicine Institute) Identifying ligands for cell free Hemoglobin using druggability simulations.
4. Prof. Charleen T. Chu (Dept. of Pathology) Modeling PINK1 interactions with mitochondiral transporter proteins.

External
4. *Prof. Ingo Greger* (Cambridge, UK)Structural and functional Dynamics of Glutamate receptors. A combination of network models and molecular dynamics simulations is applied to gain insights on structural stabilities of the receptors.
5. *Prof Ruben K Dagda* (University of Nevada, Reno) Modeling and simulating interactions of snake venom toxins with membrane bilayers.

Andrew Stern

1. Translational tumor microenvironment and virus oncology center developmental research project; Role:
Principal Investigator
University of Pittsburgh Cancer Institute
06/01/2013 – 05/31/2014
$78,492 ADC
The major goal of this program is to identify and characterize small molecules using high throughput screening that selectively kill HPV-dependent tumors
2. Determine the clinical relevance of estrogen receptor mutations engendering resistance to estrogen deprivation therapy and identify novel therapeutic strategies to address this resistance; co-Principle Investigator with Drs. Adrian Lee and Steffi Oesterreich, Magee Womens Research Institute, University of Pittsburgh Cancer Institute; funded through the Breast Cancer Research Foundation and donor support from Fashion Footwear Association of New York
3. Apply Quantitative Systems Pharmacology (QSP) to Huntington's disease to determine mechanisms of disease progression and identify novel therapeutic strategies to treat this fatal disease; Principle Investigator working with Drs. Mark Schurdak, Diane Carlisle, Robert Freidlander, Peter Strick, and Lans Taylor from the Drug Discovery Institute, Brain Institute, and Department of Neurosurgery, University of Pittsburgh; grant from the University of Pittsburgh Brain Institute; $250,000 (01/2014-12/2014)

Lawrence Vernetti

Active Collaborations

1. *Neil Hukriede, Department of Developmental Biology, University of Pittsburgh.* Developing Zebrafish cardiotoxicity models and moving forward with AKI compounds for PK and animal toxicity studies. This project was supported through the State of PA-Tobacco Funds until end of 2013. The project is active and supported through Hukriede funding.

2. *Chakra Chennubhotla, Department of Computational and Systems Biology, University of Pittsburgh*. We are developing image based analysis of Zebrafish and human cardiomyocyte beating rate, force of contraction, and 3-D cell culture volume measurements. This project was supported through the State of PA-Tobacco Funds until end of 2013. The project is still active pending new funding source.
3. *Maish Yarmush, Center for Engineering in Medicine (CEM) at Massachusetts General Hospital.* We are co-developing a human cell based, in vitro liver organoid for toxicology and pharmacology testing use as part of the human on a chip program. This project is funded by NIH # 1UH2TR000503-01 and has been extended until 2017.
4. *Samuel Poloyak and Margaret Minnigh, Department of Pharmaceutical Sciences, University of Pittsburgh.* We have previously developed and deployed a metabolic stability screen using Mass Spec analysis. The project has been re-deployed for the liver MPS project and will be supported by NIH # 1UH2TR000503-01 until 2017.
5. *Jonathan Himmelfarb, Department of Nephrology, University of Washington*-implementation of UW-Nortis kidney model, supply of biosensors for kidney, use of the MPS database and integration of Kidney module for NIH # 1UH2TR000503-01. The collaboration is active until 2017.
6. *Mark Donowitz,* Hopkins Center for Epithelial Disorders and Mary Estes, Department of Molecular Virology & Microbiology, Baylor University, supply of biosensors for gut, use of MPS database and integration of Nortis-gut module for NIH # 1UH2TR000503-01. The collaboration is active until 2017.
7. *John Wikswo Department of Biomedical Engineering, Molecular Physiology & Biophysics*, *Vanderbilt University*-use of MPS database, pumps and electronic sensors for O_2 and pH and DMPK modeling for NIH #1UH2TR000503-01 with funding through 2017. In addition I am active collaboration with John Wikswo as part of the EPA as the VPROMPT Center grant R835736 to incorporate the liver organoid into a four tissue integrated device for environmental toxin testing. This collaboration is active until 2018.
8. *Shane Hutson, Department of Physics, Vanderbilt University.* We are modifying our human cell based, in vitro liver organoid for toxicology and pharmacology testing as one of 4 organs for environmental toxin testing. This is funded through the EPA as the VPROMPT Center grant R835736. The collaboration is active until 2018.
9. *Alex Soto, Department of Pathology, University of Pittsburgh*. We are evaluating the use of the Soto iPSC differentiated hepatocytes in the liver organoid device. This project is funded by NIH # 1UH2TR000503-01 and will extended into 2017

Other Collaborations

1. Lei Yang, Department of Developmental Biology, University of Pittsburgh. We initiated a project to co-develop toxicology and pharmacology assays using human adult stem cell derived cardiomyocytes. The project is currently inactive.
2. *Thomas Smithgall, Department of Microbiology and Molecular Genetics, University of Pittsburgh.* Exploiting the Nef dimerization interface for HIV drug discovery. The goal of this project is to explore the Nef dimerization interface as a novel target in HIV infection. We have developed a high-throughput assay for Nef dimerization based on bimolecular fluorescence complementation and will perform a large scale compound screen for disruptors of Nef dimerization. This project was supported through the State of PA-Tobacco Funds until end of 2013. The project is currently inactive

Andreas Vogt

1. Neil Hukriede, Michael Tsang, Department of Developmental Biology, University of Pittsburgh. Small molecule mediated augmentation of heart and kidney regeneration. The goal of this collaboration is to develop methodology for automated, quantitative analysis of zebrafish phenotypes and to discover novel

small molecules affecting heart and kidney repair and regeneration using zebrafish. This project is supported by NIH grants R01HD053287 and will result in an R01 application this fall.

2. Beth Roman, Department of Biology, University of Pittsburgh. Enhancing ALK1 expression as an approach to hereditary hemorrhagic telangiectasia (HHT) therapeutics. HHT is a haploinsufficiency disease lading to arteriovenous malfomations. The goal is to develop image-based analysis to analyze Alk1 expression in the vasculature of transgenic zebrafish harboring an Alk1 mutation. This project is supported by American Heart Association grant 13GRNT16830049.

3. Ed Burton, Departmant of Neurology, University of Pittsburgh. Zebrafish Parkinson's disease models for drug discovery and evaluation of the role of aging in pathogenesis. The goal is to develop zebrafish models of synucleopathies for drug discovery. This project was supported by an Institute of aging seed grant.

4. Platypus Technologies, LLC, Madison, Wisconsin. Development and HTS validation of high-throughput cell migration and invasion assays. This project aims to implement and HTS validate a multiparameter, HCS compatible cell invasion assay that does not require cell wounding. This project was supported by NIH grant R44GM090386.

5. Ivet Bahar, Ahmet Bakan, Billy Day, Department of Computational and Systems Biology and Pharmaceutical Sciences, University of Pittsburgh. Mitogen-activated protein kinase (MAPK) phosphatases as pharmacologic targets in cancer and myocardial infarction. The goal is to discover novel, potent, selective, and non-redox active inhibitors of MAPK phosphatases as potential anticancer and cardioprotective agents. We are using a combination of high-content analysis, automated cell migration assays, transgenic zebrafish, and computational modeling to explore novel allosteric binding sites on mitogen activated protein kinase phosphatases. This project is supported by NIH grant R01HD053287 and an R01 application is pending (1R01CA172030-01A1) .

6. Partha Roy (Department of Bioengineering), Steffi Oesterreich, Adrian Lee (Women's Cancer Research Center), Andrew Stern, Dutch Boltz, Lans Taylor (UPDDI). Targeting Profilin-1 and Estrogen Receptor alpha in breast cancer metastasis. Profilin-1 is a proof-of-concept molecule that has been found underexpressed in metastatic breast cancer; we are currently developing methodology to exploit profilin-1 expression to modulate breast cancer aggressiveness. This is a new, exploratory project that supports the new paradigm of Drug Discovery at the UPDDI, namely discovery of novel therapeutics based on genetic validation of novel drug targets and pathways identified from clinical samples. The nascent project is a new research direction emanating from and supported by my NIH grants R44GM090386, R21CA147985, and R01HD05328. A Department of Defense Breakthrough Award level 2 and two NIH grant applications (R21CA195239 and R01HL124123) are pending. The second project aims to anticipate and address resistance to target cancer therapy based on recent findings that estrogen receptor alpha was found mutated specifically in metastatic breast cancer samples, and I am part of a large multidisciplinary team to exploit these findings to discover and develop novel antimetastatic therapies. The ultimate goal is an interdisciplinary program aimed at personalized medicines for breast cancer metastasis.

7. Thomas Smithgall, Department of Microbiology and Molecular Genetics, University of Pittsburgh. Exploiting the Nef dimerization interface for HIV drug discovery. The goal of this project is to explore the Nef dimerization interface as a novel target in HIV infection. We have developed a high-throughput assay for Nef dimerization based on bimolecular fluorescence complementation and will perform a large scale compound screen for disruptors of Nef dimerization. This project is supported by NIH grant R01 AI057083.

Presentations at National or International Meetings

Ivet Bahar

June 3-6, 2013: "In-silico Drug Design and In-silico Screening" track in Drug Discovery & Therapy World Congress 2013 International Conference. Boston, MA, Invited Speaker.
June 10-14, 2013: Theoretical and Computational Biophysics Group Computational Biophysics Workshop, Pittsburgh, PA, Invited Speaker.
July 21-26, 2013: 7th International Discussion Meeting on Relaxations in Complex Systems (7th IDMRCS). Session: Amorphous pharmaceuticals and biopharmaceuticals - physical and chemical stability. Barcelona Spain. Invited Speaker.
October 1-2, 2013: MMBioS National Center for Multiscale Modeling of Biological Systems External Advisory Board Meeting. Pittsburgh, PA. Principal Investigator.
October 2-3, 2013: MMBioS National Center for Multiscale Modeling of Biological Systems Workshop: Critical Challenges for Spatially temporally-realistic Cell Modeling Packages. Pittsburgh, PA. Workshop participant.
October 4, 2013: Science 2013 Meeting. Pittsburgh, PA. Invited Speaker.
October 25, 2013: Publications Committee Meeting. Rockville, MD. Committee Member.
January 14, 2014: Laufer Center Seminar Series. Stony Brook University, New York. Invited Seminar Speaker.
February 15-19, 2014: Biophysical Society 58th Annual Meeting on "Bridging the Sciences to Explore Biology".Moscone Center in San Francisco, California. Invited Speaker at the Mid-Career Luncheon.
February 19, 2014: Biophysical Society Publications Committee Meeting. San Francisco, California. Publications Committee Member.
March 24-45, 2014: National Institute of Biomedical Imaging and Bioengineering (NIBB) and National Institute for General Medicine Sciences (NIGMS) Biomedical Technology Research (P41) Centers Principal Investigator Meeting. Rockville, Maryland. P41 Principal Investigator.
April 4, 2014: Saint Francis University Seminar Series. Invited Seminar Speaker.
May 7-9, 2014: Membrane Protein Structural Dynamics Consortium Frontiers in Membrane Protein Structural Dynamics. Chicago, IL. Invited Speaker.
May 11-19, 2014: Collaborative book writing meeting at Stony Brook University. Stony Brook, New York.
May 19-23, 2014: Hands-on Workshop on Computational Biophysics. Pittsburgh Supercomputing Center, Pennsylvania. Instructor.
June 2-6, 2014: Gordon Research Conference (GRC) on Biopolymers. Salve Regina, Rhode Island. Chair (elected at the GRC on Biopolymers in 2010).
June 15-19, 2014: Coarse-graining as a Frontier of Statistical Mechanics Conference. Santa Fe, New Mexico, Invited Speaker.
July 16-19, 2014: Zing Conference on Protein Folding. Punta Cana, Dominican Republic, Invited Speaker.

Panagiotis Benos

During the above period Dr. Benos did not present in national or international meetings. However, together with Dr. Russell Schwartz from CMU, they organized the RECOMB 2014 in Pittsburgh. RECOMB is one of the three largest international computational biology conferences.

Jeremy Berg

1. “Experimental and Computation Studies of Peroxisome Protein Targeting", Experimental Biology Meeting (American Society for Biochemistry and Molecular Biology), San Diego, CA, 2014

Carlos Camacho

Invited Speaker: *Protein Non-folding as a Regulatory Phenomenon*, NIH-RISE, San Juan, PR March 2014.

Invited Speaker: *New Chemistry and Powerful Interactive Technologies to Discover PPI Antagonists*. ACS National Meeting, Dallas, March 2014

Invited Speaker: *Protein folding and the origin of disordered proteins and their function*. Biomedical Engineering, Boston University, Boston, March 2014.

Speaker: *Pharming: A Crowdsourcing Approach to Teach and Discover Protein-Ligand Interactions*. RECOMB 2014, CMU, April 2014.

Invited Speaker: *Google-like technologies as alternative to fragment based drug discovery*. Cambridge Healthtech Institute's Fourteenth Annual Structure-Based Drug Design conference. Boston May 2014

Invited Speaker: *Modeling the assembly and disassembly of multi-domain proteins can explain the regulation of function by external cues*. Gordon Research Conference on Biopolymers, Newport June 2014.

Keynote Invited Speaker: *Applying chemical tools to study biology*, Universiteit Gent, Antwerp June 2014.

Invited Speaker: *Specificity of Transcription Factors: Where are the Waters?* ACS National Meeting, San Francisco, August 2014.

Invited Speaker: Assembly of macromolecular complexes, MPI 2014, Modeling Protein Interactions, University of Kansas, Oct 2014

Organizer: 2014 EU-US Frontiers of Engineering, National Academy of Engineering, Seattle November 2014.

Invited Speaker: *Targeting Disorder with Small Molecules*, ASBMB, Boston March 2015.

Chakra Chennubhotla

Oct 16, 2013: Computational Pathology: Strategies for Early Disease Detection, **Graduate Seminar Series**, Department of Electrical and Computer Engineering, University of Pittsburgh.

May 19-23, 2014: Hands-on Workshop on Computational Biophysics, **Instructor**, http://www.mmbios.org/index.php/hands-on-workshop-on-computational-biophysics-2014-agenda

July 14-18, 2014: Intrinsically Disordered Proteins Workshop, Telluride Science Research Center http://www.telluridescience.org/meetings/workshop-details?wid=466

Nathan Clark

1. Poster presentation at Society for Molecular Biology and Evolution 2014 on Butterfly reproductive protein evolution
2. Poster presentation at Yeast Genetics Meeting on Evolutionary Rate Covariation as a predictor of gene function.

James Faeder

Invited lecture, "Methods for Simulating Rule-Based Models", *The Sixth q-bio Summer School on Cellular Information Processing*, Los Alamos National Laboratory, July 30, 2013.

Invited talk, "Rule-Based Modeling of Cell Signaling and Decision-Making in the Immune System," 2013 NIAID Future of Computational Immunology Workshop, Bethesda, Maryland, August 5, 2013.

Contributed tutorial, "Rule-Based Modeling of Biochemical Systems with BioNetGen," *Sixth International q-bio Conference on Cellular Information Processing*, Santa Fe, NM, August 7, 2013.

Invited talk and session chair, "Energy Lasso: Combining Rule-Based Modeling and Bayesian Parameter Estimation to Infer Biochemical Mechanisms" in session "Physiology based modeling of disease states" at the International Conference on Systems Biology 2013, Copenhagen, Denmark, August 30 -September 3, 2013.

Keynote address, Annual Retreat of the University of Pittsburgh Immunology Department, Twentieth Century Club, Pittsburgh, Pennsylvania, November 22, 2013.

Session co-chair, "Systems & Synthetic Biology Session," Northeast Biomedical Engineering Conference (NEBEC), Northeastern University, Boston, Massachusetts, April 25-27, 2014.

Elodie Ghedin

The Society for Analytical Chemists of Pittsburgh (SACP), 13 January 2014, Pittsburgh, PA

"Science Girls Gone Wild", Board Meeting, Rosalind Franklin Society, 19-20 December 2013, Washington, DC

"*Influenza Transmission Networks*", Pittsburgh International Lung Conference, 18 October 2013, Pittsburgh, PA

"*Tracking viral evolution & transmission by high-resolution mapping of genomic variants*", Novartis Institutes for Biomedical Research, 23 September 2013, Emeryville, CA

"*Tracking viral evolution & transmission by high-resolution mapping of genomic variants*". The Pennsylvania State University, 30 September 2013, State College, PA

D. Lansing Taylor

- 7/23 – NIH Microphysiology meeting, Arlington, VA
- 9/7 -- Fundraising event and lecture at the home of the Dr. and Mrs. Gromis in Los Angeles
- 9/17 – Sanofi lecture and meeting
- 9/19 – Merck lecture and meeting
- 9/25 – Visit and lecture at University of Washington, Seattle, WA
- 10/28 – Lecture at CHI's Inaugural Phenotypic Drug Discovery meeting in Cambridge, MA
- 11/4 – Bay City Capital meeting, New York, NY
- 11/15 – Lecture at 3rd Annual WCRC Scientific Retreat at Nemacolin
- 11/19 – Lecture at Quantitative Systems Pharmacology Workshop at PITT
- 1/27 – NIH Microphysiology meeting, Bethesda, MD
- 2/18 – CHI's High-Content Analysis meeting, La Jolla, CA
- 4/7 – China Symposium, Beijing, China
- 5/7 – Chemical Biology consortium Steering Committee meeting, Bethesda, MD
- 5/22 – Lecture at Curie Institute, Paris, France
- 5/23 – Lecture at Institut de Recherches en Technologies et Sciences pour le Vivant, Grenoble, France
- 6/27 – USA-India BioPharma Summit, Cambridge, MA

Daniel Zuckerman

1. Five posters, February 2013 Annual Meeting of the Biophysical Society, Corresponding contributor
2. The weighted ensemble paradigm for parallel sampling of equilibrium and non-equilibrium processes. Presented at "Free energy calculations: Three decades of adventure in chemistry and biophysics" workshop in Snowmass, CO; Organizers: J. Andrew McCammon, Benoit Roux, and Wei Yang (July, 2013).
3. Two lectures at University of Sao Paolo Workshop on pDynamo and Molecular Simulation (November, 2013): From the physics of trajectories to simulation methods for slow events at multiple scales; Tunable, mixed-resolution modeling with Library-based Monte Carlo.
4. Progress and Challenges in Weighted Ensemble Simulation. American Chemical Society Annual Meeting, Dallas (March, 2014).
5. Exploring non-Markovian analysis for the weighted ensemble and beyond. Telluride workshop on Searching for Reaction Coordinates and Order Parameters; Organizers: Ron Elber Graeme Henkelman (July, 2014).

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Joseph C. Ayoob

1. Accepted Abstract and Poster Presentation, RECOMB-BE 2014 Bioinformatics Education Satellite Conference, "Training Computer Mice to be Lab Rats: Teaching Experimental Design and Laboratory Techniques to Computational Biology Graduate Students" Karen R. Thickman and Joseph C. Ayoob. (April 1, 2014).

2. Poster Presentation, REU PI Meeting, "Tiered Mentoring and Training Tiered Mentoring and Training in a Medical School-housed Computational Biology REU" Joseph C. Ayoob, Kelly Gentille, Leah Russell, and Chakra Chennubhotla. (April 10-12, 2014).

3. Invited Speaker, "The Importance of Finding Mentors and Getting Involved" – Find your path to a career in the health professions: The Path to Walk Symposium, University of Pittsburgh School of Medicine, Pittsburgh, PA. (July 9, 2013).

Dipak Barua

Contributed talk: 6th q-bio conference, Santa Fe, NM, 2012
Computational Model for Autophagic Vesicle Dynamics in Single Cells
Invited talk: Second Workshop on Rule-based Modeling of Biochemical Systems, Santa Fe, NM, 2011
A Computational Model for Early Events in B Cell Antigen Receptor Signaling: Analysis of the Roles of Lyn and Fyn
Poster: 5th q-bio conference, Santa Fe, NM, 2011
A mechanistic model of early FcεRI signaling: lipid rafts and the question of protection from dephosphorylation

Hongying (Mary) Cheng

Poster presentation on the GRC 2014 Biopolymer
Mary H. Cheng and Ivet Bahar, "Molecular mechanism of the dopamine transporter"

Albert Gough

Characterizing Heterogeneity in Cancer Cell Activation and Inhibition: Establishing a "Heterogeneity Index" at Physiologically-Relevant Cellular Models for Drug Discovery; La Jolla, CA: Cambridge Healthtech Institute; February, 2014.

Timothy Lezon

1. Lecture on *Introduction to ProDy and its Applications*, MMBios Workshop on Biological Physics, Pittsburgh Supercomputing Center, June 2014

Indira Shrivastava

Talk: Ion Channel meeting, Bordeau, France 2013.
Poster: Society of Toxicology, San Antonio, Texas, 2013
Interaction of cardiolipin and acrolein with cytochrome c and implications: A molecular dynamics study.
Poster: Structural Biology Related to HIV/AIDS, NIH, Bethesda, 2012.
HIV-1 glycoprotein, gp120: Molecular Dynamics simulations of spontaneous bridging-sheet rearrangement
Poster: Biophysical Society, Baltimore, Maryland, 2011.
Insights into the Mechanism of Release of Transport in the Inward facing Glutamate transporter from molecular dynamics simulations.
Poster: Biophysical Society, San Francisco, California, 2010
Transport of Substrate in Glutamate Transporters: A molecular Dynamics Simulation Perspective.

Lawrence Vernetti

1. L. Vernetti, N. Senutovitch, A. Bakan, R. DeBiasio, A. Gough, T. Shun, **L. Vernetti**, O. B. Usta, A. Bhushan, S. S. Bale, W. J. McCarty, M. Hegde, R. Jindal, I. Golberg, M. L. Yarmush and D. L. Taylor. Development of a Human 3D Biomimetic Liver Construct for Predicting Physiology and Toxicology. Poster at Society of Toxicology, March 2014.

2. DL Taylor, A Gough, N Senutovitch, B Usta, **L Vernetti**, R DeBiasio, A Bakan, T Shun, and M Yarmush. A 3D Biomimetic Liver Platform for Predicting Physiology and Toxicity. Presentation at Joint DARPA/NCATS Microphysiology Bi-Annual Meeting, January 2014.

Andreas Vogt

CNT as an enabling technology for zebrafish drug discovery. 4th international Definiens symposium, Boston, MA (2013)
High-content screening for small molecule inhibitors of HIV Nef. Cambridge Healthtech Institute high-content analysis conference, San Francisco, CA (2013)

GRANTS AWARDED

Last Name	Agency Abbr	Project title	Annual DC	Annual IDC	Annual TC
Ayoob	NIAID	Eat-Me Signaling Cascade in the Apoptotic Cell Engulfment	$115,401	$59,811	$175,212
Ayoob	NSF	REU-TECBio	$89,378	$7,486	$96,864
Subtotal			**$204,779**	**$67,297**	**$272,076**
Non-Federal:					
Ayoob	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	$38,302	$7,660	$45,962
Total Ayoob (Federal and non-federal agencies)			**$243,081**	**$74,957**	**$318,038**
Bahar	NLM	Bridging Sequence Patterns and Structural Dynamics	$22,448	$11,131	$33,579
Bahar	NIGMS	Continued Development of Protein Dynamics Software ProDy	$181,170	$84,844	$266,014
Bahar	NIGMS	High Performance Computing for Multiscale Modeling of Biological Systems	$1,317,118	$80,563	$1,397,681
Bahar	NIGMS	High Performance Computing for Multiscale Modeling of Biological Systems-Supplement	$1,195,334	$52,214	$1,247,548
Bahar	NIAID	Mitochondrial Targeting Against Radiation Damage - CMCR renewal	$94,409	$46,985	$141,394
Bahar	NIDDK	New Therapies for Liver Fibrosis and Hyperproliferation in Alpha 1-AT Deficiency	$95,946	$48,624	$144,570
Bahar	NIGMS	Structural Dynamics of Biomolecular Systems (SIMBIOS)	$63,847	$32,881	$96,728
Bahar	NCI	Structure-Based Design of Novel Low Molecular Weight c-Myc Inhibitors	$16,698	$8,599	$25,297

Subtotal			**$2,986,970**	**$365,841**	**$3,352,811**
Non-Federal					
Bahar	PA Dept Health	Cellular Systems Biology in Cancer Drug Discovery	$14,730	$7,587	$22,317
Total Bahar (Federal and non-federal agencies)			**$3,001,700**	**$373,428**	**$3,375,128**
Benos	NCI	Cell-Specific Transcription in Cancer Microenvironment in vitro and in vivo	$29,886	$12,219	$42,105
Benos	NCRR	CTSI-Molecular Systems Modeling Core	$1,598	$823	$2,421
Benos	NHLBI	Gene networks beyond organ boundaries: heart, lung and pulmonary vascular disease	$41,204	$16,255	$57,459
Benos	NIBIB	Integrated Interdisciplinary, inter-university PhD Program Computational Biology (T32)	$330,933	$8,346	$339,279
Benos	NLM	Modeling in vivo Protein-DNA Interactions from High-Throughput Data MP1/1	$25,034	$12,914	$37,948
Benos	NIDDK	NIDDK IBD Genetics Consortium Genetic Research Center	$28,194	$11,528	$39,722
Benos	NIH	Sarcoidosis and A1AT Genomics & Informatics Center	$5,717	$2,944	$8,661
Benos	NHLBI	The Emphesematous Microenvironment Promotes Lung Tumorigenesis and Progression	$31,721	$14,341	$46,062
Benos	NSF	The role of microRNA regulation in the evolution of development	$8,946	$4,607	$13,553
Total Benos			**$503,233**	**$83,977**	**$587,210**

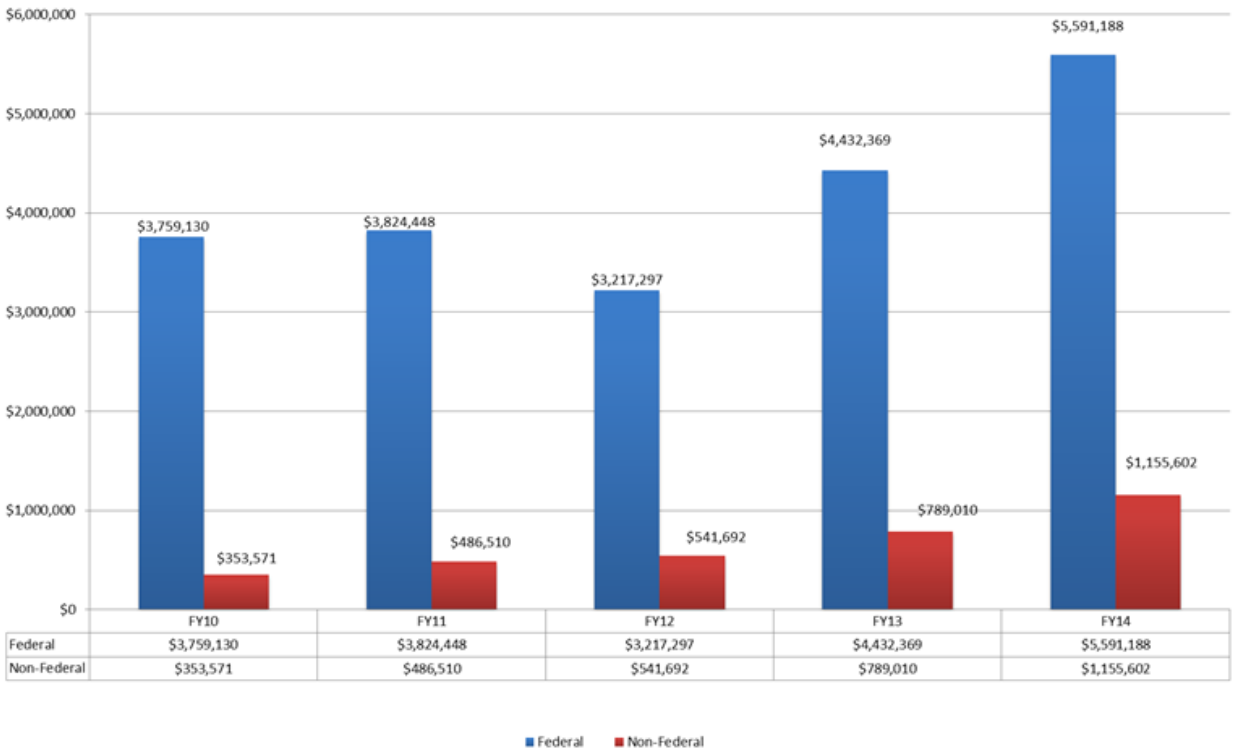
Berg	PA Dept Health	Thermodynamic Studies of Protein-Peptide Interactions	$101,068	$0	$101,068
Total Berg			**$101,068**	**$0**	**$101,068**
Camacho	NIGMS	ANCHOR: A PDB-Wide Real time Discovery resource of Novel PPI (Ant)-agonists	$248,170	$53,773	$301,943
Camacho	Mathers Foundation	Genomics and evolution of novel polyneucleotide-tailed RNAs using single molecule RNA sequencing	$146,041	$14,604	$160,645
Camacho	NIGMS	Spatial Segregation of Cell Functioning during Motility	$34,253	$12,850	$47,103
Subtotal			**$428,464**	**$81,227**	**$509,691**
Non-Federal:					
Camacho	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	$75,720	$15,144	$90,864
Total Camacho (Federal and non-federal agencies)			**$504,184**	**$96,371**	**$600,555**
Chennubhotla	NIGMS	Conformational sub-states in enzyme catalysis: Applications to the ribonuclease family	$28,602	$12,740	$41,342
Chennubhotla	Geisinger Health	Diagnostic Prognostic Testing in Patients at High Risk for Esophogeal Cancer	$6,245	$1,249	$7,494
Chennubhotla	NCI	Nano-architecture based biomarkers for cervical cancer screening	$12,649	$5,901	$18,550
Chennubhotla	DOE	Investigate use of Big Data Architecture	$9,754	$3,414	$13,168
Chennubhotla	DOE	Research Support to CMS Project	$6,316	$2,463	$8,779
Chennubhotla	DOE	Research Support to CMS Project	$19,357	$7,886	$27,243
Total Chennubhotla			**$82,923**	**$33,653**	**$116,576**

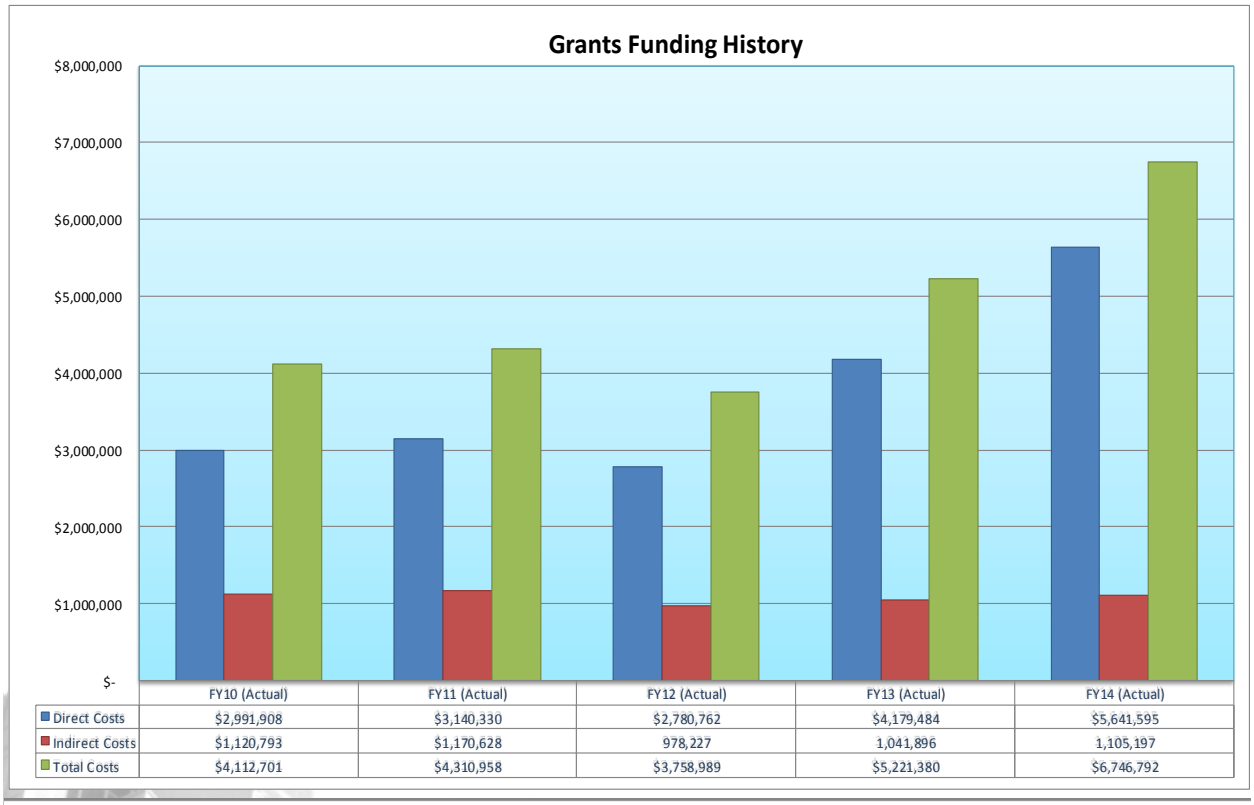
Chikina	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	**$77,074**	**$15,415**	$92,489
Total Chikina			**$77,074**	**$15,415**	**$92,489**
Clark	BCRF	Impact of intra-tumor hetogeneity (ITH) on breast cancer prognosis and response to therapy	$4,758	$952	$5,710
Clark	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	$240,746	$48,149	$288,895
Total Clark			**$245,504**	**$49,101**	**$294,605**
Faeder	NHLBI	Cardiolipin as a Novel Mediator of Acute Lung Injury	$10,073	$5,289	$15,362
Faeder	NIH	High Performance Computing for Multiscale Modeling of Biological Systems	$81,676	$36,171	$117,847
Faeder	Army	Mechanisms of bacterial spore germination and its heterogeneity	$111,430	$51,098	$162,528
Faeder	NIGMS	Molecular Biology of Hemorrhagic Shock-Project #V	$14,644	$7,541	$22,185
Faeder	NIAID	Negative Control of IL-17R Signaling: Implications for Fungal Immunity	$9,278	$4,871	$14,149
Faeder	NSF	Next Generation model checking and abstract interpretation with a focus on embedded control and systems biology	$11,876	$6,353	$18,229
Faeder	NIAID	Systems Biology Approach to MAPK Regulation of Malaria Infection in A. Stephansi	$65,269	$33,433	$98,702
Total Faeder			**$304,246**	**$144,756**	**$449,002**

Koes	NIGMS	BIGDATA: Small: DA: ESCE: Interactive and Collaborative On-line Virtual Screening	$100,244	$29,476	$129,720
Total Koes			**$100,244**	**$29,476**	**$129,720**
Lezon	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	$40,268	$8,054	$48,322
Total Lezon			**$40,268**	**$8,054**	**$48,322**
Pullara	RiMED	Rimed Foundation Fellowship	$118,793	$62,366	$181,159
Total Pullara			**$118,793**	**$62,366**	**$181,159**
Sedgewick	JMNMF	Finding Biomarkers in Melanoma by Integrated Analysis of Genomic Data	$10,000	$0	$10,000
Total Sedgewick			**$10,000**	**$0**	**$10,000**
Zuckerman	NSF-MCB	Complementary methods for equilibrium sampling of biomolecules	$146,083	$75,233	$221,316
Zuckerman	NIH	High Performance Computing for Multiscale Modeling of Biological Systems	$79,297	$41,631	$120,928
Subtotal			**$225,380**	**$116,864**	**$342,244**
Zuckerman	PA Dept Health	Dissecting the molecular mechanisms of stress-response proteins in cancer	$83,897	$16,779	$100,676
Total Zuckerman (Federal and non-federal agencies)			**$309,277**	**$133,643**	**$442,920**
TOTAL DEPARTMENT FUNDING			**$5,641,595**	**$1,105,197**	**$6,746,792**

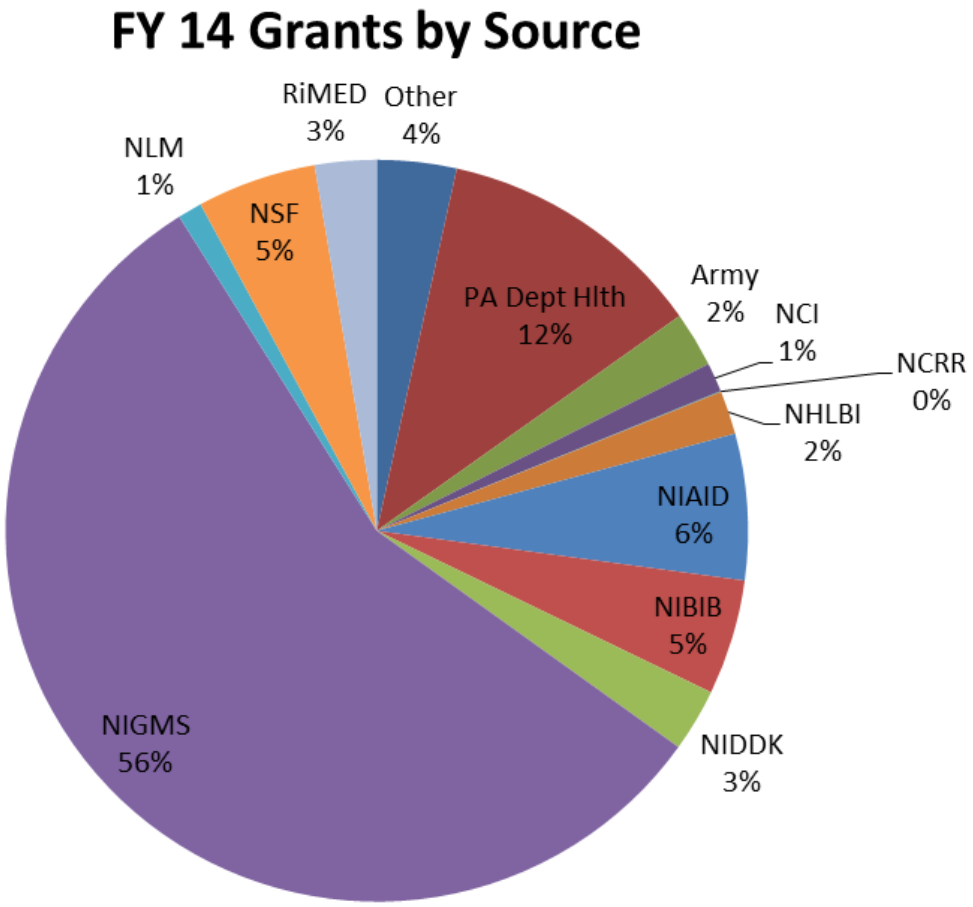
Computational Biology	
Percentage Grant Effort-FY14	
Joseph Ayoob	77.30%
Ivet Bahar	91.00%
Dipak Barua	17.00%
Panagiotis Benos	41.00%
Jeremy Berg	40.00%
Carlos J. Camacho	63.00%
Mary H. Cheng	98%
Chakra Chennubhotla	52.00%
Maria Chikina	98%
Nathan Clark	66.00%
James R. Faeder	63.00%
Antonio Ferreira	0%
David Koes	98.00%
Indira Shrivastava	98.00%
John K. Vries	0%
Daniel M. Zuckerman	63.00%

Research Funding by Sponsor Type



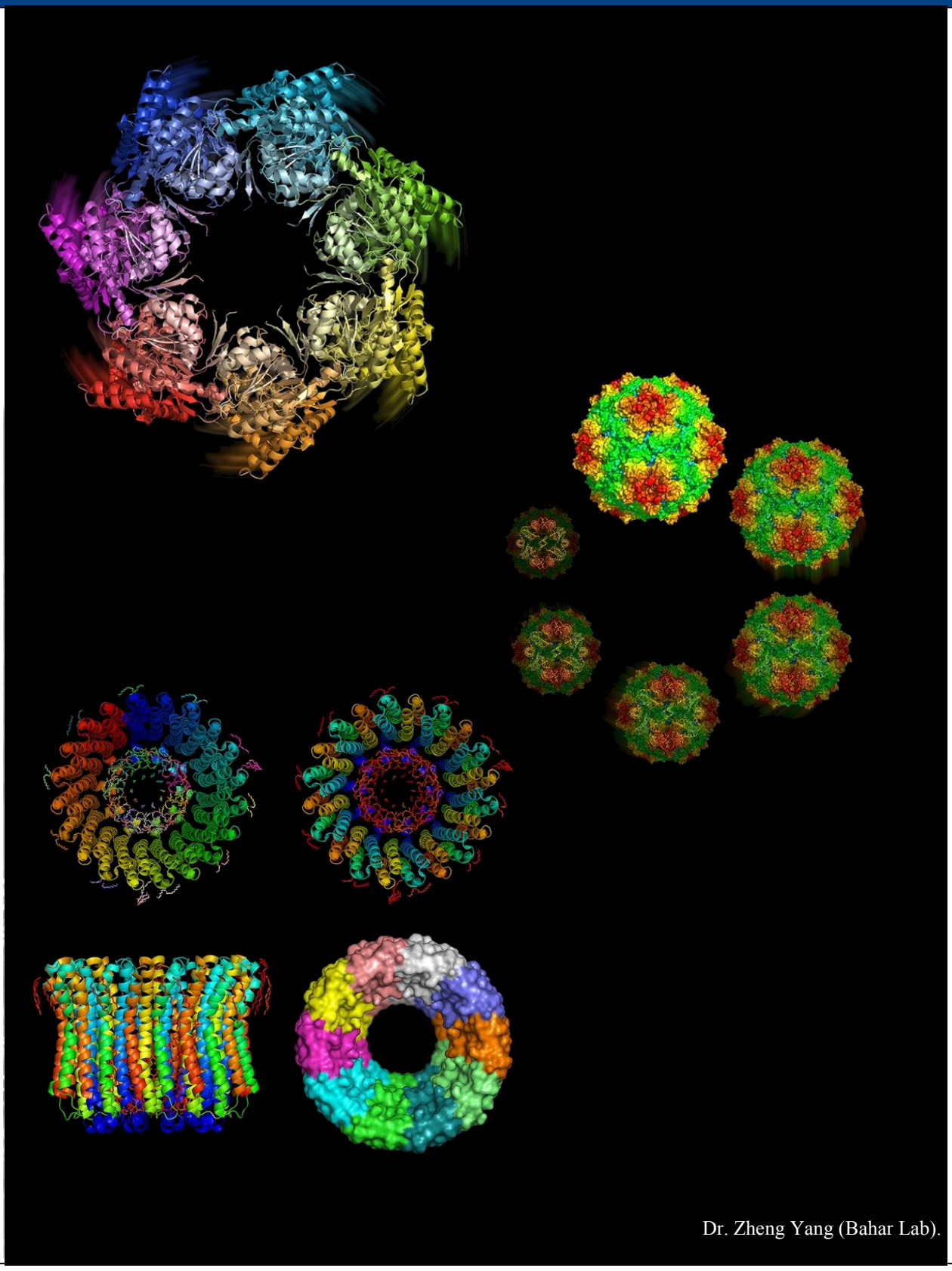


	FY10 (Actual)	FY11 (Actual)	FY12 (Actual)	FY13 (Actual)	FY14 (Actual)
Direct Costs	$2,991,908	$3,140,330	$2,780,762	$4,179,484	$5,641,595
Indirect Costs	$1,120,793	$1,170,628	978,227	1,041,896	1,105,197
Total Costs	$4,112,701	$4,310,958	$3,758,989	$5,221,380	$6,746,792



Recently Awarded Grants since 7/1/14

PI	Project title	Agency	Total Award
Ayoob	NIDA Center of Excellence for Computational Drug Abuse Research (CDAR)	NIDA	$74,599
Ayoob	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$53,662
Bahar	NIDA Center of Excellence for Computational Drug Abuse Research (CDAR)	NIDA	$1,575,716
Bahar	Integrated Interdisciplinary, inter-university PhD Program Computational Biology (T32)	NIBIB	$259,559
Bahar	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$525,478
Benos	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$770,452
Benos	Integrated Interdisciplinary, inter-university PhD Program Computational Biology (T32)	NIBIB	$259,559
Benos	Methods for Analysis of Hetergeneous Biomedical and Clinical Data Using the PARADIGM Software and Pathways	Five3Genomics, LLC	$72,325
Berg	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$247,271
Chennubhotla	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$570,223
Chennubhotla	Eat-Me Signaling Cascade in the Apoptotic Cell Engulfment	NIAID	$11,655
Chennubhotla	Assaying Heterotaxy Patient Genes in Cilia Motility and Left-Right Patterning	NIH	$257,617
Chikina	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$102,112
Clark	Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data	NIH	$106,612
Clark	Co-evolutionary Signatures as a Novel Approach to Gene Discovery	Kaufman Fdn	$150,000
Clark	Pittsburgh Center for Kidney Research	NIDDK	$60,000
Koes	Identification of serine hydroxymethyltransferase inhibitors	Samuel & Emma Winters Fdn	$1,300
	Department Total		**$5,098,140**



Dr. Zheng Yang (Bahar Lab).

Section III

Teaching Activities

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TEACHING ACTIVITIES

The educational mission of the CSB is to offer first-class research and training programs in computational biology at the graduate, undergraduate, and high school levels, all of which serve multiple purposes: (i) to introduce computational biology problems and methods to students from chemistry, physics, engineering, mathematics, and computer sciences, (ii) to teach fundamental concepts of the quantitative and physical sciences to biology and biomedical sciences students, and (iii) to prepare and encourage students at all levels for a career in computational biology research. In all cases, the aim is to train students and postdoctoral researchers to identify and tackle **complex biological problems** on a computer—managing and integrating databases, simulating biological phenomena at multiple scales, and other related research problems.

These objectives are in concert with those of the School of Medicine, which aims to integrate the diverse research and educational activities being supported at the University, and to further develop our expertise in using computational and quantitative approaches to elucidate biological phenomena.

Graduate Training Programs

1. Joint CMU-Pitt Ph.D. Program in Computational Biology (CPCB)

The Joint CMU-Pitt Ph.D. Program in Computational Biology (CPCB) is offered jointly by the University of Pittsburgh and Carnegie Mellon University. (The program admitted the first class of students in Fall 2005, and has to date 29 graduates.) The development of this Ph.D. program in computational biology was a natural consequence of the foreseen educational goals and research progress of the erstwhile Center for Computational Biology and Bioinformatics (CCBB), and the subsequent creation of the new Department of Computational Biology.

In this program, students, who come from a wide variety of academic backgrounds (see chart below), receive their doctoral degree from the university in which their thesis advisor holds their primary appointment. Within the University of Pittsburgh, the degree-granting schools are the School of Medicine and the School of Arts & Sciences. The Program institutes a curriculum that is designed to train students who will shape the next generation of discovery in computational biology in academia and industry, and offers students the opportunity to participate in research studies in one of four areas of specialization: Computational Genomics, Computational Structural Biology, Cellular and Systems Modeling, and Bioimage Informatics. Students have access to a community of faculty mentors from both institutions thereby providing a breadth of research areas for investigation.

The Program enhances the use of faculty resources and promotes scientific interactions between the two universities. It serves as a catalyst to generate more advanced topics courses that exploit the research and teaching talents of faculty associated with the School of Arts & Sciences and the School of Medicine at the University of Pittsburgh, and the Mellon College of Sciences and the School of Computer Science at Carnegie Mellon University. Creating new courses benefits all graduate students, regardless of program association. An additional positive consequence is the enhanced interaction of faculty members between the participating Schools. Documented evidence of cross-campus interaction among faculty and students via the new program, coupled with its tight thematic focus, provides a strong foundation for training grant applications.

In terms of applications to the CPCB program, in FY2012. There were a total of **113 applications received during the 2014-2015 recruiting season.** Following extensive review and discussion, 23 offers were extended to students; of which 8 **students accepted the offer**; 7 students will join the program in 2014.

Our new cohort has an average GPA of 3.74 and averaged scores in the 95rd and 84th percentiles on the GRE quantitative and verbal sections, respectively. The following is a listing of the new CPCB students on both sides (Pitt and CMU) of the program.

(Pitt)

Student, University (Student Degrees)

Sanjana Gupta, **Indian Institute of Technology, Guwahati (B.Tech Biotechnology)**
Weiguang (Wayne) Mao, **Tsinghua University (B.A.Sc. Pure and Applied Mathematics)**
Ravhavendran Partha, **Indian Institute of Technology, Madras (B.Tech Biotechnology)**
Jocelyn Sunseri, **Carnegie Mellon University (B.A. English)**
Tim Wall, **Massachusetts Institute of Technology (B.S. Computer Science & Biology)**

(CMU)

Student, University (Student Degrees)

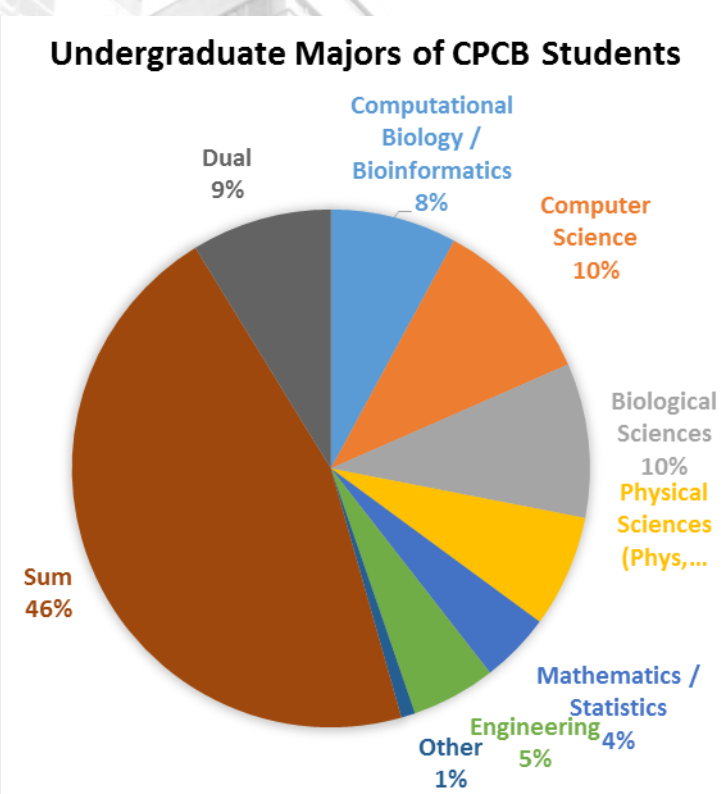
Sabrina Rashid, **Bangladesh University of Engineering and Technology (**Electrical and Electronic Engineering)
Xiongtao Ruan, **University of Science and Technology of China, Hefe** (Biological Science)

Some additional undertakings in the program during FY2014 were:

A new group of trainees was selected to be supported by the renewal of the NIBIB T32 Training Grant: Integrated, Interdisciplinary, Inter-University Ph.D. Program in Computational Biology, PIs Panayiotis Benos and Russell Schwartz. The new trainees are: Nicolas Pabon, Dan Spagnolo and Marta Wells from the University of Pittsburgh; David Farrow, Greg Johnson and Theodore Roman from CMU..

The graduate program directors conducted the annual Directors and Students meeting to solicit comments and evaluations on the program from the students.

A new group of students was recruited for 2014-2015 school year.



2. Molecular Biophysics + Structural Biology (MB+SB) Graduate Program

The campus-wide Ph.D. pro-gram in Molecular Biophysics and Structural Biology is inherently interdisciplinary, re-quiring the viewpoints of fac-ulty from divergent backgrounds. However, unlike the CPCB, the program emphasis experimental techniques and methodologies (such as X-ray diffraction, NMR, optical spectroscopy) and basic physical principles to elucidate molecular form and function of fundamental biological processes. Since Computational biology is one of the important research areas under molecular biophysics, faculty from this department contribute in this program in two ways: (i) Actively teach the core courses in molecular biophysics (Molecular Biophysics I and I); and (ii) Serve as Training Faculty for the program wherein students admitted to the program can choose to complete their dissertation under the mentorship of faculty in the Department of Computational Biology.

3. Interdisciplinary Biomedical Graduate Program

This program introduces students to a variety of fields through interdisciplinary courses and experimental techniques that convey knowledge of the molecular mechanisms controlling cell and tissue function in one of nine degree granting programs at the School of Medicine.

4. Summer Training Programs for Undergraduates and High School Students

Training and Experimentation in Computational Biology (TECBio)

Our National Science Foundation (NSF)-funded Research Experiences for Undergraduates (REU) program has taken its fourth cohort of students, and continues to build on the solid foundation that our previous Bioengineering and Bioinformatics Summer Institute (BBSI) initiative started. In our fourth year of the TECBio REU at Pitt, we have continued on the great success of our previous summer programs by continuing to provide a challenging graduate-level research experience in computational biology. In addition to performing cutting-edge research, TECBio students also participate in other academic activities, such as classes, seminars, and discussions, while experiencing the various social and cultural activities available in Pittsburgh. Once again our applicant pool comprised well over 300 (an increase of over 100 applications) students from across the 50 states and Puerto Rico. Again, our applicants were a very diverse group who came from many academic and ethnic backgrounds, including many students from groups underrepresented in the sciences and those that are at universities that have limited research opportunities. Our 2014 cohort consisted of 12 students in total – 10 supported by our NSF award (90%) of whom are from underrepresented backgrounds and/or from small non-PhD granting institutions), and 2 students (from Pitt) supported by departmental funds granted by the Deans of the medical school. With the renewal of the supporting TECBio REU program grant, we look forward to continuing our traditions of undergraduate mentoring and training to inspire the next great generation of scientists.

High School Summer Program

This past summer saw the continuation of last year's inaugural initiative in the CSB that reached out to high school students in the Pittsburgh area. In collaboration with the Department of Biomedical Informatics, we are a component of the University of Pittsburgh Cancer Institute's (UPCI) High School Summer Academy, which we call Drug Discovery, Systems and Computational Biology (DiSCoBio). In our third summer, we accepted 9 students in our program and matched them up with a research mentor for an 8-week summer research experience. The mentored research component was complemented by didactic training in the major disciplines, hands-on and demonstration sessions, tours of labs and research facilities on campus, educational and social field trips, and a number of opportunities for the students to present their work and hone their communication skills. Many of our faculty were involved in this program through their efforts as mentors, lecturers, and/or hosts of students on various tours and other events. Students in the DiSCoBio program were also integrated with the graduate and undergraduate students in the CSB to provide them with important sources of information on how to conduct their research, and what it is like to be an undergraduate/graduate student and how to prepare oneself to go about the application processes for both.

2013-2014 Seminar Series | Fridays at 11am

Carnegie Mellon - University of Pittsburgh
Ph.D. Program in Computational Biology

Date/Location	Speaker
Aug. 30, 2013 6115 GHC Host: Ziv Bar-Joseph	Pierre Baldi *University of California, Irvine* Deep Learning: Theory, Algorithms, and Biological Applications
Sep. 6, 2013 3073 BST3	Hanna Salman *University of Pittsburgh* Mechanisms of bacterial migration in temperature gradients
Sep. 13, 2013 6014 BST3	Carlos Camacho *University of Pittsburgh* Modeling the assembly and disassembly of multi-domain structures of alpha-actinin-4 explains how external cues regulate actin binding
Sep. 20, 2013 6014 BST3 Host: James Faeder	Eric Deeds *University of Kansas* The evolution of crosstalk in signaling networks
Sep. 27, 2013 6014 BST3 Host: Indira Shrivastava	Judith LaLonde *Bryn Mawr College* Antagonism of HIV-1 Entry: Targeting Hotspots at the CD4-gp120 Protein-Protein Interface
Oct. 4, 2013 6115 GHC Host: Robert F. Murphy	Wing Wong *Stanford University* Characterization of hESC transcriptome by hybrid sequencing

Oct. 11, 2013 8102 GHC Host: Seyoung Kim	Matthew Stephens *University of Chicago* Assessing association between genetic variants and multiple phenotypes
Oct. 25, 2013 6014 BST3 Host: Nathan Clark	Antony M. Dean *University of Minnesota* Evolution of Catalytic Mechanisms
Nov. 8, 2013 6115 GHC	Ziv Bar-Joseph *Carnegie Mellon University* Reconstructing dynamic regulatory networks in development and disease
Nov. 15, 2013 6115 GHC	Kathryn Roeder *Carnegie Mellon University* Statistics and Genetics Open a Window into Autism
Nov. 22, 2013 6014 BST3 Host: Elodie Ghedin	Raul Rabadan *Columbia University* The Topology of Evolution
Dec. 6, 2013 6014 BST3 Host: Hanna Salman	Ido Golding *Baylor College of Medicine* Quantitative Adventures in Gene Regulation
Jan. 24, 2014 6014 BST3 Host: Dennis Kostka	Kaspar Hansen *Johns Hopkins University* Statistical analysis of epigenomewide data
Jan. 31, 2014 8102 GHC Host: Karen Thickman	Arijit Chakravarty *Takeda Pharmaceuticals* An evolving view of cancer: how mathematical modeling helps effective drug development in the face of tumor evolution

Feb. 7, 2014 6115 GHC Host: Veronica Hinman	Julia Zeitlinger *Stowers Institute for Medical Research* Genome-wide approaches to understand gene regulation during development
Feb. 21, 2014 6115 GHC	Ge Yang *Carnegie Mellon University* Image-based computational analysis of regulatory mechanisms of axonal transport
Feb. 28, 2014 6014 BST3 Host: Dan Zuckerman	Ilya Shmulevich *Institute for Systems Biology* Integrative Analysis and Interactive Exploration of Data from The Cancer Genome Atlas
Mar. 21, 2014 6115 GHC Host: Seyoung Kim	Su-In Lee *University of Washington* Learning network features reveals novel biomarkers for survival, chemosensitivity and surgical resectability phenotypes in cancer
Mar. 28, 2014 6014 BST3 Host: Carlos Camacho	Nathan A. Baker *Pacific Northwest National Laboratory* Geometric flow for biomolecular solvation
Apr. 18, 2014 6115 GHC Host: Russell Schwartz	Hector Corrada Bravo *University of Maryland* Exploring tumor epigenetic heterogeneity by cell-specific methylation pattern reconstruction
Apr. 25, 2014 6014 BST3 Host: Dan Zuckerman	David H. Matthews *University of Rochester Medical Center* RNA Molecular Mechanics: Estimating Free Energy Changes Facilitates Comparison with Experiments

ADMINISTRATIVE DUTIES RELATED TO EDUCATION

Ivet Bahar, Ph.D.

Distinguished Professor, and John K. Vries Chair, Department of Computational and Systems Biology (2013 – present)
Dickson Prize Committee Member (2013 - present)
Director/PI, NIGMS Biomedical Technology & Research Center (2012 - present)
Associate Director, University of Pittsburgh Drug Discovery Institute (2010-present)
Director, ChemoInformatics Core, Center for Medical Countermeasures Against Radiation Pitt & UPCI (2010-present)
Professor, Department of Computational and Systems Biology (2010-2013)
Member, Center for Simulations and Modeling (SAM) (2008 -present)
Faculty and Executive Committee Member, Carnegie Mellon University/Pitt PhD Program in Computational Biology (2005-present)
Faculty, Program in Integrative Molecular Biology (PIMB) (2005 - present)
Faculty, PhD Program in Structural Biology and Molecular Biophysics (CMU-Pitt) (2005-present)
Faculty, Peterson Institute of Nanoscience and Nanotechnology (2005 - present)
Professor, Department of Computational Biology (2005-2010)
Founding Director, Carnegie Mellon University and U of Pittsburgh, Joint PhD Program in Computational Biology (2005-2009)
Faculty, Interdisciplinary Biomedical Graduate Program, School of Medicine (2002-present)
Member, McGowan Institute for Regenerative Medicine (2002-present)
Member, Molecular Medicine Institute, University of Pittsburgh (2002-present)
Member, Center for Molecular & Materials Simulations (CMMS), (2002 -present)
Faculty; Pittsburgh Medical Informatics Training Program (2001-present)

Joseph C. Ayoob, Ph.D.

Course Co-Director, Lecturer, and Laboratory Head, Laboratory Methods for Computational Biologists course (MSCBIO/CMPBIO 2050). This is a core course in the joint CMU-Pitt Computational Biology Graduate Program that uses experiential teaching approaches to educate computational scientists on how to perform experiments and better understand the data that are generated. Spring 2010-present.

Founding Program Director and Principal Investigator, Training and Experimentation in Computational Biology (TECBio) Research Experiences for Undergraduates (REU) summer program. This project was funded during the first three years by NSF grant: DBI-1004555 and was recently renewed for 4 additional years of support by the NSF and the Department of Defense (NSF DBI-1263020). The TECBio REU @ Pitt supports an immersive, 10-week, graduate-level, summer research experience for 12 students each summer. Summer 2010-present.

Founding Program Director and Instructor, Drug Discovery, Systems and Computational Biology (DiSCoBio) Summer Academy. The DiSCoBio summer academy is an 8-week summer research and training program that is one of the six University of Pittsburgh Cancer Institute (UPCI) Summer Academies. This program, which highlights a mix of experimental and computational research projects, didactic training, and enrichment activities, reaches out to 6-9 high school scholars each summer from schools both locally and

nationwide. Summer 2011-present; Summers 2011-2012 as the Computational and Systems Biology and Biomedical Informatics (CoSBBI) Academy.

Training Coordinator, Center for Multiscale Modeling of Biological Systems (MMBioS). The P41 Biomedical Technology Research Center headed by PI, Ivet Bahar has a substantial education and outreach component to help train scientists in the tools, methodologies and expertise housed in and generated by the MMBioS investigators. September 2012-present.

Panayiotis (Takis) V. Benos, Ph.D.

Member of the Executive Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology
DBI Bioinformatics (Concentration) Training Program Core, Member, June 2003–now
Course Lecturer, TECBio Program, Summer 2013
CPCB Curriculum Committeee Member
CPCB Student Advising Committee Member
CPCB Journal Club Committee Member

Carlos J. Camacho, Ph.D.

Co-organizer, Seminar Series, Joint CMU-Pitt Ph.D. Program in Computational Biology
Course Lecturer, Introduction to Computational Structural Biology (MSCBIO 2030)/Molecular Biophysics II (MSMBPH 2002)
Supervisor of one REU student, Summer 2014
CPCB Executive Committee Member
CPCB Curriculum committee Member
CPCB Admissions Committee Member

Chakra Chennubhotla, Ph.D.

Continuing Member, Curriculum Committee, Joint CMU-PITT PhD Program in Computational Biology
Co-Investigator and Co-Program Director for NSF-funded REU program: Training and Experimentation in Computational Biology (TECBio): Simulation and Visualization of Biological Systems at Multiple Scales (PI: Dr. Ayoob) 2010-2014

Nathan Clark, Ph.D.

Member of Joint Carnegie Mellon – University of Pittsburgh Ph.D. program in Computational Biology including the following active roles:
CPCB Admissions Committee member
CPCB Instructor of 3-credit graduate program course “Molecular Evolution” (MSCBIO 2075).
-Mentor for rotation students
-Mentor TECBio student

James R. Faeder, Ph.D.

Fall, 2013. Co-director with Christopher Langmead (CMU) of the course Cellular and Systems Modeling (CMPBIO2040), a core course in the joint CMU-Pitt PhD (CPCB) program in computational biology. Responsibilities include 50% of the weekly lectures and an additional two-hour lab session per week.

Spring, 2014. Co-director with Christopher Langmead (CMU) of the course Cellular and Systems Modeling (CMPBIO2040), a core course in the joint CMU-Pitt PhD (CPCB) program in computational biology. Responsibilities include 50% of the weekly lectures and an additional two-hour lab session per week.

Fall, 2013. Co-director with Christopher Langmead (CMU) of the course Cellular and Systems Modeling (CMPBIO2040), a core course in the joint CMU-Pitt PhD (CPCB) program in computational biology. Responsibilities include 50% of the weekly lectures and an additional two-hour lab session per week.

CPCB Curriculum Committee Member

David Koes

Co-Director, Drug Discovery, Computational and Systems Biology
(DiSCoBio) Academy, Summer 2013,2014
Course Lecturer, TECBio, Summer 2013,2014 Course Lecturer, DiSCOBio, Summer 2013,2014 Guest Lecturer, MSCBIO/CMPBIO 2030: Introduction to Computational Structural Biology, Fall 2012

Mentored Students: Christine Grassi: TECBio (Summer 2014), Rafael Bergerman: DiscoBio Scholar, Summer 2014, James Castiglione: TECBio (Summer 2013) and Pitt Bioinformatics Undergraduate (Spring 2013), Charles Yuan: DiSCoBio Scholar, Summer 2013 Rieck Hairston, Matthew Pierce, Andrew

Timothy R. Lezon, Ph.D.

Co-Director, Drug Discovery, Computational and Systems Biology (DiSCoBio) Academy, Summer 2013
Course Co-Instructor, MSCBIO/CMPBIO 2030: Introduction to Computational Structural Biology, Fall 2013

Course Lecturer, TECBio, Summer 2013
Mentored Students:
Cemal Erdem, CPCB Graduate Student
Ariel Gewirtz, TECBio Student, Summer 2013
Morgan Essex, TECBio Student, Summer 2013
Ashok Biju, DiSCoBio Scholar, Summer 2013

Daniel M. Zuckerman, Ph.D.

Director, Joint CMU-Pitt Ph.D. Program in Computational Biology
Course Head, Intro to Computational Structural Biology (MSCBIO 2030)/Mol. Biophysics II (MSMBPH 2002)
Co-organizer, Pittsburgh Biophysical Theory Club, a monthly seminar series
Co-Chair, Student Advising Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology
Member, Curriculum Committee, Molecular Biophysics and Structural Biology Graduate Program
Member Executive Committee

POSTDOCTORAL ASSOCIATES

Ivet Bahar, Ph.D.
Ahmet Bakan, Ph.D. in Computational Biology, University of Pittsburgh, 2009
Ignacio General, Ph.D. in Physics (minor in Mathematics), North Carolina State University, 2006
Mert Gur, Ph.D. in Computational Science & Engineering, Koc University, Turkey, 2010
Bing Liu, Ph.D. Computer Science, National University of Singapore, 2011
Filippo Pullara, Ph.D. in Physics, University of Palermo, Italy, 2013
Elia Zumot, Ph.D. in Biology, Hebrew University, Jerusalem, Israel, 2009

Nathan Clark, Ph.D.
Camille Meslin, Ph.D. in Life Science and Health, University of Tours, France, 2011
Zelia Ferreria, Ph.D. Biodiversity, Genetics, and Evolution, University of Porto, Portugal, 2013

James R. Faeder, Ph.D.
Leonard Harris, Ph.D. Chemical Engineering, Cornell University, 2008
Natasa Miskov-Zivanov, Ph.D. Electrical and Computer Engineering, Carnegie Mellon University, 2009

Elodie Ghedin, Ph.D.
Matthew Rogers, Ph.D. Botany, University of British Columbia, 2006
Kazima Saira, Ph.D. Biomedical Science, University of Nebraska-Lincoln, 2008

Bino John, Ph.D.
Sang Woo Kim, Ph.D, Biotechnology, Daegu University, 2008

Mark Schurdak, Ph.D.
Evan Delgado, Ph.D. Cellular and Molecular Pathology, University of Pittsburgh, 2014

D. Lansing Taylor, Ph.D.
Ning Chen, Ph.D. Cellular, Molecular and Biophysical Studies, Columbia University, 2004
Nina Senutovitch, Ph.D. Biological Sciences, Carnegie Mellon University, 2011

Daniel M. Zuckerman, Ph.D.
Ernesto Suarez Alvarez, Ph.D. Theoretical and Computational Chemistry, University of Oviedo, Spain, 2011
Justin Spiriti, Ph.D. Chemistry, Arizona State University, 2011
Sundar Subramanian, Ph.D. Biophysics, Chemical Laboratory, CLRI, India, 2010

GRADUATE STUDENTS

Ivet Bahar, Ph.D.
Murat Can Cobanaglu, CMU-Pitt Ph.D. Program in Computational Biology
Chang Liu, PIMB
Wenzhi Mao, University of Tsinghua
Feizhuo Hu, University of Tsinghua

Panagiotis Benos, Ph.D.
Kristina Buschur, CMU-Pitt Ph.D. Program in Computational Biology
Andrew J. Sedgewick, CMU-Pitt Ph.D. Program in Computational Biology
Lucas Santana dos Santos, MSc student, DBMI

Carlos Camacho, Ph.D.
Timothy Travers, CMU-Pitt Ph.D. Program in Computational Biology
Matthew Baumgartner, CMU-Pitt Ph.D. Program in Computational Biology
Nicolas Pabon, CMU-Pitt Ph.D. Program in Computational Biology
Zhiyu Xu, University of Tsinghua

Chakra Chennubhotla, Ph.D.
Andrej Savol, CMU-Pitt Ph.D. Program in Computational Biology
Shannon Quinn, CMU-Pitt Ph.D. Program in Computational Biology

James Faeder, Ph.D.
John Sekar, CMU-Pitt Ph.D. Program in Computational Biology
Jose-Juan Tapia-Valenzuela, CMU-Pitt Ph.D. Program in Computational Biology
Robert Sheehan, CMU-Pitt Ph.D. Program in Computational Biology
Cihan Kaya, CMU-Pitt Ph.D. Program in Computational Biology

Elodie Ghedin, Ph.D.
Timothy Song, CMU-Pitt Ph.D. Program in Computational Biology
Laura Tipton, CMU-Pitt Ph.D. Program in Computational Biology

D. Lansing Taylor, Ph.D.
Dan Spagnolo, CMU-Pitt Ph.D. Program in Computational Biology
Luong Nguyen, CMU-Pitt Ph.D. Program in Computational Biology
Cemel Erdem, CMU-Pitt Ph.D. Program in Computational Biology

Daniel Zuckerman, Ph.D.
Rory Donovan, CMU-Pitt Ph.D. Program in Computational Biology
Zining Zhang, University of Tsinghua

TRAINING GRANT PUBLICATIONS 2013-2014:

SC, Rabizadeh S, Soon-Shiong P, Vaske CJ. Learning Subgroup-Specific Regulatory Interactions and Regulator Independence with PARADIGM. *Bioinformatics* 29: i62-i70. (Proceedings Issue for International Conference on Intelligent Systems for Molecular Biology (*ISMB 2013*)) PMCID: PMC3694636

Tsai MC, Blelloch G, **Schwartz R, Ravi R**. (2013) Coalescent-based method for learning parameters of admixture events from large-scale genetic variation data. *IEEE/ACM Trans Comput Biol Bioinform.*10(5):1137-49. PMCID: PMC4019315

Donovan RM, Sedgewick AJ, Faeder JF, and **Zuckerman DM**. (2013) Efficient stochastic simulation of chemical kinetics networks using a weighted ensemble of trajectories. *J Chem Physics* 139(11) PMCID: PMC3790806

Taylor DP, Wells JZ, **Savol A, C. Chennubhotla C**, and Wells A. (2013) Modeling boundary conditions for balanced proliferation in metastatic latency. *Clin. Cancer Res.*, vol. 19, no. 5, pp. 1063.1070, Mar. 2013. PMCID: PMC3594128

Mowrey D, Chen Q, Liang Y, Liang J, **Xu Y and Tang P**. (2013) Signal transduction pathways in the pentameric ligand-gated ion channels. *PLoS ONE* 8(5): e64326. doi:10.1371/journal.pone.0064326 PMCID: PMC3648548

Mowrey D, Cheng MH, Liu LT, Willenbring D, Wymore T, **Xu Y, Tang P**. (2013). Asymmetric ligand binding facilitates conformational transitions in pentameric ligand-gated ion channels. *J Am Chem Soc*. 35(6): 2172-2180. PMCID: PMC3582375

Shao H, **Travers T, Camacho CJ**, Wells A. (2013) The carboxyl tail of alpha-actinin-4 regulates its susceptibility to m-calpain and thus functions in cell migration and spreading. *Int J Biochem Cell Biol*. 45(6):1051-63. PMCID: PMC3633689

Travers T, Shao H, Wells A, **Camacho CJ**. (2013) Modeling the assembly of the multiple domains of α-actinin-4 and its role in actin cross-linking. *Biophys J.* 104(3):705-15. PMCID PMC3566466

Koes, DR, **Baumgartner, MP, & Camacho, CJ** (2013). Lessons Learned in Empirical Scoring with smina from the CSAR 2011 Benchmarking Exercise. *J. Chem Info and Modeling* 2013 Feb 12. PMID: 23379370

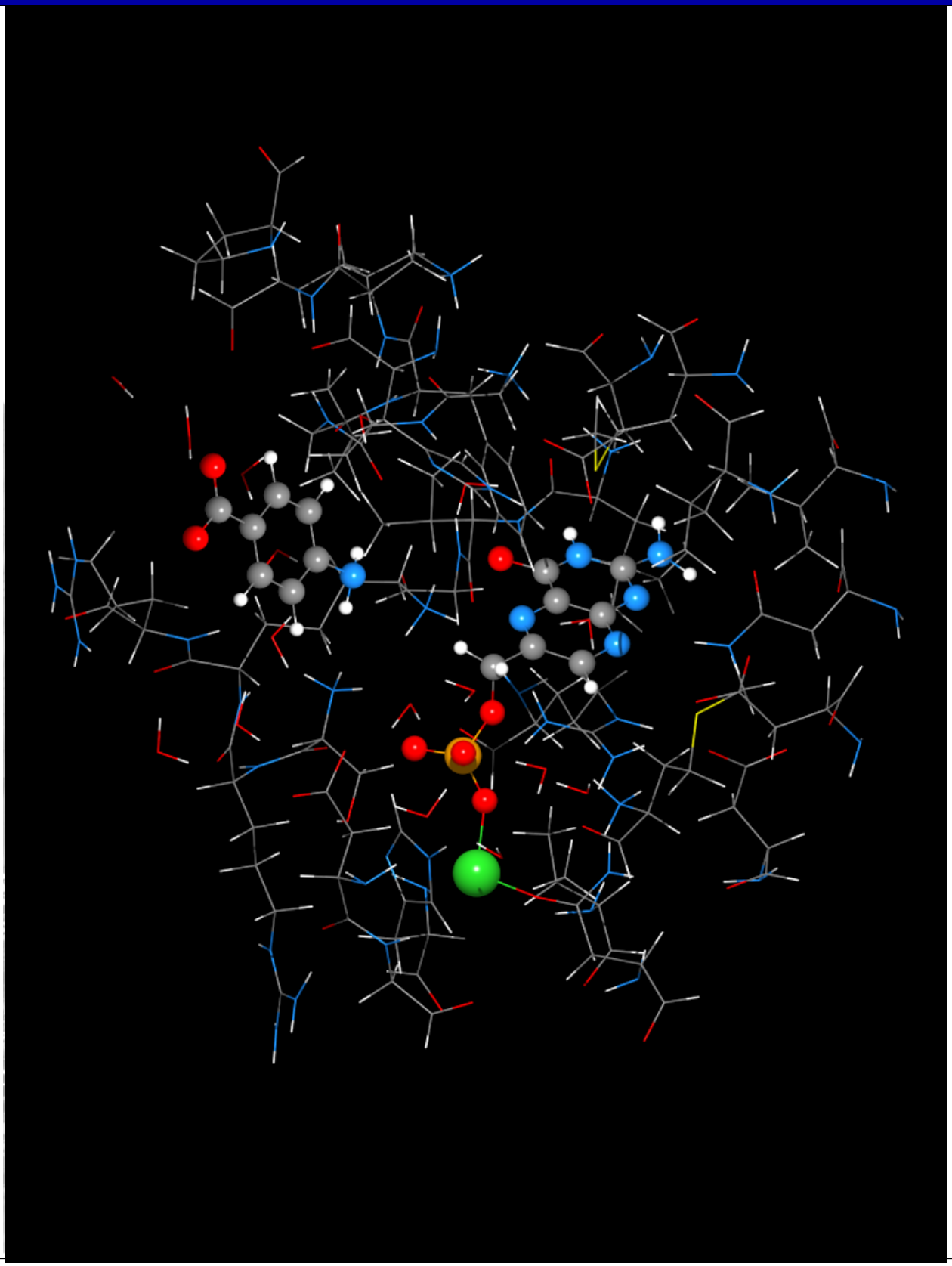
DEPARTMENT SEMINAR SERIES

Speaker	Affiliation	Title	Date
Eran Eyal, PhD	Sheba Medical Center, Israel	Global Regulation of Alternative Splicing by Adenosine Deaminase Acting on RNA (ADAR)	July 30, 2013
Pierre Baldi, PhD	University of California, Irvine	Deep Learning: Theory, Algorithms, and Biological Applications	August 30, 2013±
Hanna Salman, PhD	University of Pittsburgh	Mechanisms of Bacterial Migration in Temperature Gradients	September 6, 2013±
Carlos Camacho, PhD	University of Pittsburgh	Modeling the Assembly and Disassembly of Multi-domain Structures of Alpha-actinin-4 Explains how External Cues Regulate Actin Binding	September 13, 2013±
Eric Deeds, PhD	University of Kansas	The Evolution of Crosstalk in Signaling Networks	September 20, 2013±
Judith Lalonde, PhD	Bryn Mawr College	Antagonism of HIV-1 Entry: Targeting Hotspots at the CD4-gp120 Protein-Protein Interface	September 27, 2013±
Wing Wong, PhD	Stanford University	Characterization of hESC transcriptome by Hybrid Sequencing	October 4, 2013
Karl Debiec	University of Pittsburgh	Are Salt Bridges Overstablized? A Comparison of Current Biomolecular Force Fields	October 9, 2013. *
David Koes, PhD	University of Pittsburgh	Algorithms and Systems for Interactive Online Drug Discovery	October 9, 2013. *
Matthew Stevens, PhD	University of Chicago	Assessing Association Between Genetic Variants and Multiple Phenotypes	October 11, 2013±
Canan Atiligan, PhD	Sabanci University	On Detecting and Achieving Conformational Selection in Proteins by Computational Approaches	October 18, 2013
Antony M. Dean, PhD	University of Minnesota	Evolution of Catalytic Mechanisms	October 25, 2013±
Steven Heinikoff, PhD	Fred Hutchinson Cancer Research Center	Histone Variants, Nucleosome Dynamics and Epigenetics	October 29, 2012
Jianmin Sun, PhD	University of Pittsburgh	Cooperativity can Enhance Signal Detection	November 6, 2013*

Deborah Evans, PhD	University of Mexico	Molecular-level Simulations of Ferritin Properties	November 6, 2013*
Ziv Bar Joseph, PhD	Carnegie Mellon University	Reconstructing Dynamic Regulatory Networks in Development and Disease	November 8, 2013±
Olga Boudker, PhD	Weil Cornell Medical College	Dance Lessons for Proteins: Structural Dynamics of a Glutamate Transporter Homologue	November 12, 2013
Kathryn Roeder	Carnegie Mellon University	Statistics and Genetics Open a Window into Autism	November 15, 2013±
Brian Shoichet, PhD	University of California San Francisco	The Metabolic Code	November 20, 2013
Raul Rabadan, PhD	Columbia University	The Topology of Evolution	November 22, 2013±
David Swigon, PhD	University of Pittsburgh	Modeling the Dynamics of DNA Supercoiling and Compaction?	December 4, 2013*
Bard Ermentrout, PhD	University of Pittsburgh	Synchronization in a Slowly Changing Environment: How Slow Coupling Becomes Fast Weak Coupling	December 4, 2013*
Ido Golding, PhD	Baylor College of Medicine	Quantitative Adventures in Gene Regulation	December 6, 2013±
Markus Dittrich, PhD	Pittsburgh Supercomputing Center	Structure and Function of Synapses: Novel Insights from Spatially Realistic Cell Simulations	January 15, 2014*
Rozita Laghaei, PhD	University of Pittsburgh	Computational Studies of the Paracellular Claudin-2 Channel	January 15, 2014*
Kaspar Hansen, PhD	Johns Hopkins University	Statistical Analysis of Epigenomonewide Data	January 24, 2014±
Arijit Chakravarty, PhD	Takeda Pharmaceuticals	An Evolving View of Cancer: How mathematical Modeling Helps Effective Drug Development in the Face of Tumor Evolution	January 31, 2014±
Antonio M. Ferreira, PhD	University of Pittsburgh	Applications of Quantum Chemistry in Molecular Biophysics	February 4, 2014
Christopher Langmead, PhD	Carnegie Mellon University	Probabilistic Graphical Models of Fitness	February 5, 2014*
John Wenskovitch	University of Pittsburgh	Fixing TIM: Identifying Functional Mutations in Protein Families through the Interactive Exploration of Sequence and Structural Data	February 5, 2014*
Julia Zeitlinger, PhD	Stowers Institute for Medical Research	Genome-wide Approaches to Understand Gene Regulation During Development	February 7, 2014±
Zeba Wunderlich, PhD	Harvard Medical School	Interrogating Gene Regulatory Circuit Function Using Natural Variation in Animals	February 11, 2014

Ge Yang, PhD	Carnegie Mellon University	Imaged-based Computational Analysis of Regulatory Mechanisms of Axonal Transport	February 21, 2014[±]
Tomi Sawyer, PhD	Merck Research Laboratories	Stapled Peptide Drugs: Nature'α-Helix to Breakthrough Medicines	February 25, 2014
Robin EC Lee, PhD	Dana-Farber Institute	Leveraging Cell-to-Cell Variability to Dissect TNF-Induced Signal Transduction Circuits	February 26, 2014
Ilya Shmulevich, PhD	Institute for Systems Biology	Integrative Analysis and Interactive Exploration of Data from the Cancer Genome Atlas	February 28, 2014[±]
Christopher Guerriero	University of Pittsburgh	How do Membrane-Spanning Domains Move out of a Lipid Bilayer?	March 5, 2014*
Dariush Mohammedyami	University of Pittsburgh	Oxidized Triacylglycerols in Lipid Droplets: Coarse-Grained Molecular Dynamics	March 5, 2014*
Jun Huang, PhD	Stanford University	A Single Peptide-MHC Triggers Digital Cytokine Secretion in $CD4^+$ T Cells	March 10, 2014
Michael White, PhD	Washington University St. Louis	How Regulatory DNA Encodes Function in Genomes and Gradients	March 12, 2014
Jianhu Xing, PhD	Virginia Polytechnic Institute and State University	Quantitative Biology of Cell Phenotypic Transitions	March 17, 2014
Megan N. Mclean, PhD	Princeton University	Elucidating Principles of Biological Signal Processing Using Microfluidic and Optogenetic Tools	March 20, 2014
Su-In Lee, PhD	University of Washington	Learning Network Features Reveals Novel Biomakers for Survival, Chemosensitivity and Surgical Resectability phenotypes in Cancer	March 21, 2014[±]
Nathan A. Baker, PhD	Pacific Northwest National Laboratory	Geometric Flow for Biomolecular Solvation	March 28, 2014[±]
Timothy Lezon, PhD	University of Pittsburgh	Strategies for Systems-based Drug Discovery	April 9, 2014*
Eric Berequist	University of Pittsburgh	Ab Initio Electron Paramagenetic Resonance and Metalloprotein Applications	April 9, 2014*
Hector Corrada Bravo, PhD	University of Maryland	Exploring Tumor Epigenetic Heterogeneity by Cell-specific Methylation Pattern Reconstruction	April 18, 2014[±]
David H. Matthews, PhD	University of Rochester Medical School	RNA Molecular Mechanics: Free Energy Changes Facilitates Comparison with Experiments	April 25, 2014[±]

[±] Carnegie Mellon – University of Pittsburgh Ph.D. Program in Computational Biology
*The Pittsburgh Biophysical Theory Club
[≠] CSB^2 – Department of Computational & Systems Biology, Casual Science Briefings



Section IV

Faculty Data

Faculty Data
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Primary Faculty

Professor

Ivet Bahar, Ph.D., Distinguished Professor and John K. Vries Chair, Istanbul Technical University, Turkey, 1986
Jeremy Berg, Ph.D., Professor, Harvard University, Cambridge, 1985
Hagai Meirovitch, Ph.D., Emeritus, The Weizmann Institute of Science, Rehobot, Israel, 1974
D. Lansing Taylor, Ph.D, Professor, State University of New York at Albany, 1973

Associate Professor

Pangiotis V. Benos, Ph.D., University of Crete, Greece, 1997
Carlos J. Camacho, Ph.D., University of Maryland, College Park, 1991
James R. Faeder., Ph.D., University of Colorado at Boulder, 1998
Elodie Ghedin, Ph.D., John Hopkins University, Maryland, 2006
Andreas Vogt, Ph.D., University of Hamburg, Germany, 1990
John K. Vries, M.D., University of California at San Francisco, 1966
Daniel M. Zuckerman, Ph.D., University of Maryland, College Park, 1998

Research Associate Professor

Robert Boltz, Ph.D., Pennsylvania State University, University Park, 1978
Albert Gough, Ph.D., Carnegie Mellon, Pittsburgh, 1992
Lawrence Vernetti, Ph.D., University of Arizona, 1991

Visiting Research Associate Professor

Antonio Ferreira, Ph.D., University of Memphis, 2000
Mark Schurdak, Ph.D., Baylor College of Medicine, Houston, 1987
Andrew Stern, Ph.D., University of California at Los Angeles, 1977

Assistant Professor

Joseph Ayoob, Ph.D., John Hopkins University, Maryland, 2006
Chakra S. Chennubholta, Ph.D., University of Toronto, 2004
Nathan Clark, Ph.D., University of Washington, Seattle, 2007
David Koes, Ph.D. Carnegie Mellon University, 2009
Timothy R. Lezon, Ph.D., The Pennsylvania State University, University Park, 2007

Visiting Assistant Professor

Maria Chikina, Ph.D., Princeton University, 2010

Research Assistant Professor

Dipak Barua, Ph.D., North Carolina State University, 2008
Indira Shrivastava, Ph.D., University of Pune, 1993

Joint Appointments

Professor

Rob D. Coalson, Ph.D., Harvard University, 1984
Gregory Cooper, M.D., Ph.D., Stanford University, 1985 (Ph.D.) and 1986 (M.D)
G. Bard Ermentrout, Ph.D., University of Chicago, 1979
Graham Hatfull, Ph.D., Edinburgh University, UK, 1981
Naftali Kaminski, M.D., Medical School of Hadassah and the Hebrew University in Jerusalem, 1989
John Rosenberg, Ph.D., MIT, 1973
Jonathan Rubin, Ph.D., Brown University, 1996
Alexander Sorkin, Ph.D., Institute of Cytology, Academy of Sciences of the USSR, 1986
Pei Tang, Ph.D., SUNY at Stony Brook, 1990
Bennett Van Houten, Ph.D., University of Tennessee, 1984
Yoram Vodovotz, Ph.D., Cornell University, 1993
Alan Wells, M.D., Brown University, 1988 D.M.Sc., Karolinska Institute, Sweden, 1982
Xiang-Qun (Sean) Xie, MBA, University of Connecticut, 1990 (Ph.D.) and 2003 (E.M.B.A.)

Associate Professor

Lillian Chong, Ph.D., University of California at San Francisco, 2002
Alexander Doemling, Ph.D., Technical University of Munich, 1994
Vanathi Gopalakrishnani, Ph.D., University of Pittsburgh, 1999
Zoltan Oltvai, M.D., Semmelweiss Medical University, Budapest, Hungary, 1984
Chien-ChengTseng, Ph.D., University of California at San Francisco, 2002
Lance Davidson, Ph.D., Biophysics, University of California at Berkeley, Berkeley, CA, 1995

Assistant Professor

David Earl, Ph.D., University of Durham, UK, 2003
Michael Grabe, Ph.D., University of California, Berkeley, 2002
Dennis Kostka, Ph.D. Free University, Berlin, Germany, 2006
Judith Klein-Seetharaman, Ph.D., MIT, 2000
Elisabeta (Liz) Marai, Ph.D., Brown University, 2007
Hanna Salman, Ph.D., Weizmann Institute of Science, 2002
David Swigon, Ph.D., Rutgers University, 1999

Adjunct Professor

Jeffry Madura, Ph.D., Purdue University, 1985
Robert Swendsen, Ph.D., University of Pennsylvania, 1971
Michael Widom, Ph.D., University of Chicago, 1983

Visiting Adjunct Professor

Jaime Carbonell, Ph.D., Yale University, 1979
Ronald Rosenfeld, Ph.D., Carnegie Mellon University, 1994
Gordon Rule, Ph.D., Ph.D., Carnegie Mellon University, 1986
Mahadev Satyanarayanan, Ph.D., Carnegie Mellon University 1983

Adjunct Associate Professor

Maria Kurnikova, Ph.D., University of Pittsburgh, 1998
Eric Poe Xing, Ph.D., University of California, Berkeley, 2004
Bino John, Ph.D., The Rockefeller University, New York, 2003

Adjunct Assistant Professor

Ziv Bar-Joseph, Ph.D., MIT, 2003
Markus Dittrich, Ph.D., Carnegie Mellon University, 2009
Christopher Langmead, Ph.D., Dartmouth, Christopher, 2003

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
COMMITTEE SERVICE

Ivet Bahar, Ph.D.
Distinguished Chairperson, (John K. Vries)
Member, Health Sciences Research Advisory Committee, 2001-present
Molecular Biophysics and Structural Biology Ph.D. Program Steering Committee, Member, 2005-present
Search Committee for Faculty in Computational Biology, Chair, 2002-present
Member, University of Pittsburgh Graduate Faculty, School of Medicine
Member, Executive Committee, University of Pittsburgh School of Medicine
Member, RiMed Scientific Committee
Member, Program Development Committee, Ph.D. Program in Molecular Biophysics
Founding the cross-institutional (between Pitt and CMU) PhD program in Computational Biology
Member of Program in Integrative Molecular Biology (PIMB)
Member of Center for Molecular & Materials Simulations
October 1-2, 2013: MMBioS National Center for Multiscale Modeling of Biological Systems External Advisory Board Meeting. Pittsburgh, PA. Principal Investigator.
Member of Personalized Medicine Task Force

Panayiotis (Takis) V. Benos, Ph.D.
Member of the Admissions Committee of the PhD program in Biomedical Informatics, Department of Biomedical Informatics, School of Medicine
Bioinformatics (Concentration) Training Program Core, member, June 2003 – present
Member, Training Program Faculty, Department of Biomedical Informatics (DBMI), 2003-, meetings as needed
Director, CMU-Pitt Joint PhD Program in Computational Biology (University of Pittsburgh) 2009-2013
Member, Advising Committee, CMU-Pitt Joint PhD Program in Computational Biology, 2008 - present)
Member, University of Pittsburgh Graduate Faculty, School of Medicine
Member, Department of Computational Biology Promotion Committee, 2009 - present
Member**,** Department of Computational Biology Faculty Selection Committee, 2009 – present
Student Dissertation Committees
Secondary Appointment, Associate Professor, Department of Biomedical Informatics, 2008 – present.
Secondary Appointment, Associate Professor, Clinical and Translational Science Institute (CTSI), 2010 – present.
Member (elected), Committee for Tenured Faculty Promotions and Appointments (TFPA), elected in 2013 to serve Jan 2014-Dec 2016 Member, Task Force, Institute for Personalized Medicine, 2012-, meetings as needed. Contact PI and responsible for all the reports for the T32 NIBIB grant that funds the CPCB program (2010-now).
Co-director of the Center for Translational Bioinformatics.

Jeremy Berg, Ph.D.
Founding Director of the Institute for Personalized Medicine.
Scientific Director of the University of Pittsburgh-Tsinghua University scholars program.
Review Committee Chair, RIMed Fellows
Distinguished Faculty committee member

Carlos J. Camacho, Ph.D.
Tenure Committee SOM
Member, Executive Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology, 2006-present
Member, Curriculum Committee (2004-2005; 2008-Present) Ph.D. program in Computational Biology.
Member, Executive Committee (2005-present) Ph.D program in Computational Biology

Member, University of Pittsburgh Graduate Faculty, School of Medicine
Member Faculty Search Committee
Seminar Series Director DC&SB

Chakra Chennubhotla, Ph.D.
Joint CMU-Pitt Ph.D. Program in Computational Biology Curriculum Committee, Member, 2007 – present
Joint CMU-Pitt Ph.D. Program in Computational Biology Admissions Committee, Member, 2008 - present
Membership, University of Pittsburgh Graduate Faculty, Dec 2009 - present
Chair, Journal Club Committee

Nathan Clark, Ph.D.
Member, University of Pittsburgh Graduate Faculty, School of Medicine
Admissions Committee member (2013 – present) for Joint CMU-Pitt PhD Program in Computational Biology
Seminars Committee Chair (2013 – present) for Department of Computational and Systems Biology and Joint CMU-Pitt PhD Program in Computational Biology
Faculty Position Search Committee member (2013 – 2014) for Department of Computational and Systems Biology
Hosted seminar speakers:
Joint Carnegie Mellon - Pitt PhD Program Seminar Series
Josh Akey (University of Washington) 2013
Anthony M. Dean (University of Minnesota) 2013
Department of Computational and Systems Biology Distinguished Lecture Series
Steve Henikoff (Fred Hutchinson Cancer Research Center) 2013
I continue to serve the School of Medicine in administering and conducting research for a CURE Funds grant for which I receive no compensation beyond that already provided in my start-up package. All funding direct in my name went to the School of Medicine.

James R. Faeder, Ph.D.
Chair, Faculty Search Committee of the Department of Computational and Systems Biology, 2013-2014.
Member, Admissions Committee of the Joint CMU-Pitt PhD Program in computational Biology, Fall, 2012-2013.
Chair, Admissions Committee of the Joint CMU-Pitt PhD Program in computational Biology, 2013-present.
Member, Departmental Seminar Committee, Fall, 2012- present.
Chair, Curriculum Committee of the Joint CMU-Pitt PhD Program in computational Biology, 2012-present.
Committee member, Curriculum Committee of the Joint CMU-Pitt PhD Program in Computational Biology, 2008-present
Member, University of Pittsburgh Graduate Faculty, School of Medicine, 2010 – present

Elodie Ghedin, Ph.D.
Member, University of Pittsburgh Graduate Faculty, School of Medicine
CVR: Regional Biocontainment Laboratory Utilization Committee
Center for Vaccine Research IT committee, 2011 – *present*
Competitive Medical Research Fund (CMRF) review committee, 2011 - present
Institutional Biosafety Committee
Chancellor's Distinguished Research Awards Committee
Facilitator in "Methods and Logic in Biomedicine" for visiting scholars from Tsinghua University.

D. Lansing Taylor, Ph.D.
Led the development of a new course in Drug Discovery scheduled for the Fall 2012 (Course leader) Co-directors: Lans Taylor, Ivet Bahar, Barry Gold, Peter Wipf, Bruce Freeman, Ed Chu and Jeremy Berg. The course is designed for graduate students and advanced undergraduates from all sciences, computer science and engineering with a limit of 30 students. 3-credit course meeting 2/week

Co-mentored a CMU graduate student in the CMU/Pitt computational biology program with Bob Murphy
Invited Lectures:
2/8/2014 Gastroenterology Research Conference at PUH
4/9/2014 Basic and Translational Research in Lung Disease Conference, University of Pittsburgh
6/25/2014 TecBio REU Program

John Vries, M.D.
Member, Faculty Promotion Committees and Faculty recruitment committee**s**
Member, University of Pittsburgh Graduate Faculty, School of Medicine
Member of the tenure promotion committee
CSB Computer Committee

Daniel M. Zuckerman, Ph.D.
Chair, Curriculum Committee, Molecular Biophysics and Structural Biology Graduate Program
Member and Co-head of Computational Structural Biology Section, Curriculum Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology
Student Advising Committee, Co-Chair, Joint CMU-Pitt Ph.D. Program in Computational Biology
Search Committee Chair, Department of Computational and Systems Biology
Member, University of Pittsburgh Graduate Faculty, School of Medicine
School of Medicine Tenure and Promotion Committee, January 2010 – present

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Joseph Ayoob, Ph.D.
Coordinator, Clinical and Translational Science Institute (CTSI) Molecular and Systems Modeling (MSM)
Advisory Committee Member, Office of Science Education Outreach, University of Pittsburgh School of Medicine.
Scientific Administrator, Department of Computational and Systems Biology
Program Director, TECBio REU@ Pitt and CoSSBI UPCI Summer Academy for High School Students
Program Manager/Student Outreach and Recruiting Coordinator, Joint CMU-Pitt Computational Biology Graduate Program
Organizer, Computational and Systems Biology Casual Science Briefings $(CSB)^2$ (2012-present)
Executive Committee Member, Computational and Systems Biology Casual Science Briefings $(CSB)^2$ (2010-present).
Invited Speaker, "The Importance of Finding Mentors and Getting Involved" – Find your path to a career in the health professions: The Path to Walk Symposium, University of Pittsburgh School of Medicine, Pittsburgh, PA. (July 9, 2013)
Judge, Biomedical Graduate Student Association (BGSA) 17th Annual Research Symposium Poster Session. (October 23, 2013)
Coordinator and other administrative roles for Training, Education, and Outreach components of 3 proposed Center Grants (P50 Systems Biology, U54 Big Data to Knowledge, and NIDA P30 Center of Excellence)
Internship Coordinator, NIH-funded P41 BTRC – High Performance Computing for Multi-Scale Modeling of Biological Systems
(MSM) Internship Coordinator, NIH-funded P41 BTRC - High Performance Computing for Multi-Scale Modeling of Biological Systems

Robert Boltz, Ph.D.
Serve on UPDDI management committee.
Group Leader, Flow and Imaging Cytometry
Directed the Cellular Systems Biology Program in the DDI.

Albert Gough, Ph.D.
Served as a member of the Faculty committee for the UPDDI
Provided project management support to projects in the Drug Discovery Institute
Played a major role in the design and implementation of the new website for the Drug Discovery Institute
Serving on the Seminar Speaker Selection Committee for the Department of Computational & Systems Biology
Project Manager, Chemical Biology Consortium (CBC) for the UPDDI.
Manager, IT and Informatics for the UPDDI.

David Koes, Ph.D
Member, CSB Departmental Computing Committee

Timothy R. Lezon, Ph.D.
Chair, Department of Computational and Systems Biology Retreat Committee, 2012
Course Lecturer – Computational and Systems Biology and Bioinformatics (CoSBBI) Academy, summer 2012

Mark Schurdak, Ph.D.
Coordinated and Developed the Drug Discovery Course
Participant, AMSA PharmFree program for second year medical students
Took the lead role in assisting potential collaborators in understanding what is involved in drug discovery and in establishing critical paths for implementing drug discovery projects in DDI.
Assumed leader role for the DDI portion of DiSCoBio program coordinating efforts of the DDI faculty.
Initiated evaluation of a natural products library and a newly available small molecule library from Roche for inclusion in the DDI collection.
Reviewer for the CTSI pilot grant program.
Co-organizer of the DISCoBio Program, a part of the UPCI Summer Academy program.

Andrew Stern, Ph.D.
Director of Novel Therapeutics, UPDDI Core Management Team
Associate Director, Center for Quantitative Pharmacology
Thesis Advisory Committee

Lawrence Vernetti, Ph.D.
Joined the Mitochondria, Metabolism and Disease Working Group (M & Ms), a group of University of Pittsburgh scientists interested in mitochondria in regards to basic research and drug discovery. 5 meetings per year and 1 weekend seminar.

Andreas Vogt, Ph.D.
Reviewer, Clinical and Translational Science Institute (CTSI) Basic to Clinical Collaborative
Representative, School of Medicine, Chemical Hygiene Officers Committee, University of Pittsburgh, 2004-present
Member, School of Medicine Ambassador's program, 2009 - present
Member, UPDDI Core management team
Member, UPDDI New Projects Subgroup
MED5133 – Neuroscience, MSII medical students (2007 – present)
Facilitator, Adrenergic Pharmacology Workshop
MED5224 – Medical Pharmacology MSII, first year medical students (2008 – present)
Facilitator, Cell Signaling/Pharmacology Workshop
MSMPHL 3360 – Molecular Pharmacology, graduate students (2010 - present)
Lecture Topics: Antibacterial and Antifungal Drugs
MSMPHL 2370 – Drug Discovery Course

UNIVERSITY OF PITTSBURGH COMMITTEE SERVICE

Ivet Bahar, Ph.D.
CATER (Cellular Approaches to Tissue Engineering and Regeneration) pre-doctoral program, McGowan Institute for Regenerative Medicine
Member of Petersen Institute of NanoScience and Engineering Member, Curriculum Committee, 2002-present

Takis Benos, Ph.D.
Member, Advising Committee, Joint CMU-Pitt PhD Program in Computational Biology (CPCB), 2008-, two meetings a year plus preparation time
Member, Training Program Faculty, Department of Biomedical Informatics (DBMI), 2003-, meetings as needed.
Member, GPCL Advisory Board, 2013 - present

Carlos Camacho, Ph.D.
Member, Thesis Committee for Engineering School
Search Committee School of Pharmacy

Elodie Ghedin, Ph.D.
Member, Chancellor's Distinguished Research Awards Committee, 2011 – 2014
Member, University: Genomics Core Advisory Committee – 4 meetings per year
Member, Institutional Biosafety Committee – monthly meetings and review of forms submitted.
Competitive Medical Research Fund (CMRF) review committee
Facilitator in "Methods and Logic in Biomedicine" for visiting scholars from Tsinghua University.

D. Lansing Taylor, Ph.D.
Delivered seminars on the plans of the UPDDI and how to collaborate to Cancer Institute Department of Computational & Systems Biology and Department of Infectious Diseases,
Developmental Biology, and Women's Cancer Research Center.
Served as a mentor to John Maier, MD, PhD, a young faculty member in Family Medicine
Served on Thesis Committees for Joint CMU/Pitt Ph.D. Program in Computational and Systems Biology's Graduate Program
Invited Speaker:
6/3/2014 Scientific Ethics and the Responsible Conduct of Research at Pitt
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Anthony Ferreria, Ph.D.
HPC Consultant within SaM.

Albert Gough, Ph.D.
Served as a member of the Faculty committee for the UPDDI.
Provided project management support to projects in the Drug Discovery Institute.
Played a major role in the implementation of the new website for the Drug Discovery Institute.
Serving on the Seminar Speaker Selection Committee for the Department of Computational & Systems Biology.

Lawerence Vernetti, Ph.D.
Serves a university wide function of having experience as a Study Director in the Pharmaceutical Industry.

Andreas Vogt, Ph.D.
Member**,** UPCI Cytometry Committee 2011 – present
Member, University of Pittsburgh Cancer Institute, molecular therapeutics/drug discovery program. 2008 – present

OTHER SERVICES OUTSIDE OF UNIVERSITY OF PITTSBURGH

Ivet Bahar, Ph.D.

Editorial Board Member for *Proteins*
Quarterly meetings of the Biophysical Society Executive Committee (attended 3 in the past year)
Biophysical Society Council meetings (attended 4 in the past year)
Acted as referee for several journal papers, including *Science, Nature Structural and Molecular Biology, PNAS, PLoS Computational Biology, Molecular Systems Biology, Biophysical Journal, Proteins* and others
Several invited talks (including plenary lectures) in national and international meetings
Serving as referee for EMBO fellowships, Israel Sciences Foundation (ISF) projects, European Research Council (ERC) proposals, TUBA (Turkish Academy of Sciences) fellowships.
The International Human Frontier Science Program Organization (Member of Review Committee for Research Grants in the 2013 Round of Awards)
July 1-3, 2013: NIH-Interdisciplinary Molecular Science and Training (IMST) Program Review Panel-Site Visit for P41 Application. University of Wisconsin, Madison. Review Panel.
July 21-26, 2013: 7th International Discussion Meeting on Relaxations in Complex Systems (7th IDMRCS). Session: Amorphous pharmaceuticals and biopharmaceuticals - physical and chemical stability. Barcelona Spain. Invited Speaker.
October 1-2, 2013: MMBioS National Center for Multiscale Modeling of Biological Systems External Advisory Board Meeting. Pittsburgh, PA. Principal Investigator.
October 2-3, 2013: MMBioS National Center for Multiscale Modeling of Biological Systems Workshop: Critical Challenges for Spatially temporally-realistic Cell Modeling Packages. Pittsburgh, PA. Workshop participant.
October 4, 2013: Science 2013 Convergence Meeting. Pittsburgh, PA. Invited Speaker: Computational Approaches in Molecular and Systems Pharmacology.
October 20-22. 2013: NIH Advisory Board Meeting. University of Illinois Urbana-Champaign, IL. Advisory Board Member.
October 25, 2013: Biophysical Society Publications Committee Meeting. Rockville, MD. Committee Member.
October 30-November 1, 2013: Beckman Institute for Advanced Science and Technology at the University of Illinois External Advisory Committee Member.
December 9-10, 2013: NIH R15 Area Review. Washington, DC. Review Panel (Study Section) Member.
2013 NIH Director's New Innovator Award Program - Reviewer
2013 - Present, Dickson Prize Committee Member
Member of the Hiring and Promotion Committee of the International School for Advanced Studies of Trieste (SISSA), chaired by Professor Guido
Reviewer for promotions of faculty members from outside institutions (e.g the Hebrew University of Jerusalem, most recently)
Selected Organizer for national (e.g Gordon Research Conference at Salve Regina, RI) and international (e.g. Biophysical Society Thematic Meeting in Istanbul) meetings.

Takis Benos, Ph.D.

Associate Editor, *PLoS One*
Member, *International Society for Computational Biology* (ISCB) Education Committee.
Student Dissertation Committee
(advisor/program)Panagiotis Papasaikas (Lopez/Biological Sciences, CMU)
Ad hoc reviewer for nearly 20 peer-reviewed journals, including *Molecular Systems Biology*, *PNAS*, *Genome Research*, *PLoS Computational Biology*, *Bioinformatics*, *Nucl Acids Res*, *RNA*,
Member, *International Society for Computational Biology* (ISCB) Education Committee.
Member, *Faculty of 1000 for Biology*
Ad hoc reviewer for nearly 20 per-reviewed journals, including *BMC Systems Biology*, *Molecular Systems Biology*, *PNAS*, *Genome Research*, *PLoS Computational Biology*, *Bioinformatics*, *Genomics*, *Nucl Acids Res*, *RNA*, etc.

Four NIH grant review panels and *ad hoc* reviewer for the Israel Science Foundation (ISF). Member, Editorial Board, Biology Direct Conference co-chair (together with Dr. Russell Scwartz, CMU) of the RECOMB 2014 to be hosted in Pittsburgh in April 2014. RECOMB is one of the top three conferences in our field (Computational Biology).

Jeremy Berg, Ph.D.
President, American Society for Biochemistry and Molecular Biology (ASBMB)
Member, National Research Council Committee on Women in Science, Engineering and Medicine (NRC CMSEM)
Participant, Science 2013 Career planning sessions
Dickson Prize committee co-chair
Book with Michelle Kienholz "How the NIH Can Help You Get Funded" has been published by Oxford University Press.

Carlos Camacho, Ph.D.
Permanent member of MSFD NIH Study Section.
Ad-hoc reviewer for NSF
Reviewer for multiple journals and ISMB.
Panel Member, NSF
Reviewer, NSF Panel in Molecular Biophysics Panel 2007-present
Review about 1.5 papers a month.
Editorial Board, International Journal of Molecular Sciences 2009-present
Referee, *Nature, PNAS, Biophysical Journal, Proteins, Protein Science, J. Mol. Biol., Bioinformatics, Physical Biology, Nanotechnology, Physical Review Letters, Physical Review, European Physical Journal*
Consultant for Carmolex
June: Protein-DNA workshop, Banff, Canada
Invited Speaker: September 2013; Department of Computational Medicine and Bioinformatics *University of Michigan Medical School, Ann Arbor, MI*
October: Protein-Protein Interaction Conference (October 23-25, 2013 in San Diego, CA)

S. Chakra Chennubhotla, Ph.D.
Co-Organizing a workshop at the Telluride Science Research Center (TSRC) on Intrinsically Disordered Proteins: Sequence, Structure, Dynamics and Function
07/14/2014 – 07/18/2014
http://www.telluridescience.org/meetings/workshop-details?wid=466
Reviewer in 2012-2013 for: PLoS One, Bioinformatics, and Journal of Pathology Informatics

Nathan Clark, Ph.D.
Manuscript Reviewer for:
PNAS *Molecular Biology and Evolution*
Genome Research *Evolution*
PLoS Genetics *Molecular Ecology*
Biological Reviews *Gene*
Journal of Molecular Evolution *PLoS ONE*
BMC Evolutionary Biology *Journal of Proteomics*
International Journal of Evolutionary Biology *Journal of Insect Science*
Genome Biology and Evolution *Molecular Biology and Evolution (2 separate times)* *Proceedings of the Royal Society: Biological Sciences* *Biology Letters*
Frontiers in Evolutionary and Population Genetics *Radiation Research*
Carnegie Science Center "Sci-Tech Days" 2013
Provided and facilitated an interactive and evolution-themed activity for area high school students.

Reviewed a grant application for the Leaky Foundation.
In January, serve as the University as a member of the Institutional Biosafety Committee for the University of Pittsburgh (2014 – present)

James Faeder, Ph.D.
Editorial board member
Mathematical Biology section of *Biology Direct*, 2007-*present*.
Board of Reviewing Editors, *Science Signaling*, May, 2010-present.
Chair of Program Committee. *7th International q-bio Conference on Cellular Information Processing*, Santa Fe, NM, August, 2013.
Chair of Program Committee. *8th International q-bio Conference on Cellular Information Processing*, Santa Fe, NM, August, 2014.
Reviewer for approximately 30 journal articles for many important journals in my field including *Science Signaling*, *Nature Reviews Immunology, PLoS Computational Biology*, *PLos One, Bioinformatics, Biophysical Journal, BMC Bioinformatics, BMC Systems Biology*, *IET Systems Biology*, *Interface Focus* and *Journal of Chemical Physics. Bioessays, Biology Direct, Complexity, Computational Methods in Systems Biology Conference, Genes and Development, IET Systems Biology, Journal of Cellular Physiology, Journal of Chemical Physics, Journal of Molecular Biology, Journal of Physical Chemistry, Journal of Theoretical Biology, Physical Biology, Physical Review E, Proceedings of the National Academy of Science (USA), Mathematical Bioscience, Nature, Theoretical Biology and Medical Modeling* Organizing committee.

Elodie Ghedin, Ph.D.
Peer Review Activities:
- PLoS NTDs, PNAS, mBio, JVI, PLoS_ONE, ISMEJ, Microbiome, Nature Genetics.Ad hoc reviewer for PLoS ONE, International Journal of Parasitology, Journal of Clinical Virology, Journal of Pathology, Trends in Parasitology, PLoS Computational Biology,
PLoS Pathogens, PLoS Neglectde Tropical Diseases, Nature Biotechnology, Nature Genetics, BMC Genomics, MEEGID, Molecular and Biochemical Parasitology, NAR, Phil Trans Proc, and iConcept.

Editorial Board Memberships Associate Editor, PLoS Neglected Tropical Diseases; Associate Editor, and Genes.

Industry Consulting
Consultant for SAGE Analytica, consulting company specializing in infectious diseases
Deputy Editor, *PLoS Neglected Tropical Diseases,* 2011 – present
Microbiome, 2012 – present

Grant Reviewer:
1. Special panel NIAID/NIH study section for "Understanding the Functions of Uncharacterized Genes in Infectious Disease Pathogens"
2. European Science Foundation Research Conference Scheme

Editorial work:
- Deputy Editor, PLoS Neglected Tropical Diseases
- Associate Editor, Genes
- Editorial board member, Microbiome
- Guest Editor, PLoS Pathogens

Speaker invitations:
Board Meeting, Rosalind Franklin Society, 19-20 December 2013, Washington, DC
"Influenza Transmission Networks", Pittsburgh International Lung Conference, 18 October 2013, Pittsburgh, PA

"Tracking viral evolution & transmission by high-resolution mapping of genomic variants", Novartis Institutes for Biomedical Research, 23 September 2013, Emeryville, CA
"Tracking viral evolution & transmission by high-resolution mapping of genomic variants". The Pennsylvania State University, 30 September 2013, State College, PA
"Virus emergence and transmission", Institute for Advanced Study, 15 April 2013, Princeton, NJ
"Tracking influenza virus emergence and transmission", American Society for Microbiology, 18-21 May 2013, Denver, CO
"Design of high-throughput pipelines for virus discovery and characterization", Pittsburgh – Philippines Joint Workshop on Emerging Diseases and New Pathogen Discovery, 18-19 April 2013, Pittsburgh, PA
"Deep sequencing in tracking viral emergence and transmission", University of Missouri, Informatics Institute, 7 March 2013, Columbia, MO
"Brugia malayi Genomics", Gordon Research Conference: Tropical Infectious Diseases, 12-15 February 2013 (co-chair of Filaria session), Galveston, TX

Conference organization:
1. Great Lakes Bioinformatics Conference 2012 (GLBIO2012), May 2012, Ann Arbor, Michigan
2. Nematode Symbiosis (NemaSym), "Ecology of Nematode-Bacteria Associations", 11-16 August 2013, Pittsburgh, PA
3. Kavli Frontiers of Science Korea-US Symposium, 12-14 August 2013 in Irvine (Member of the Organizing committee)
4. Pittsburgh International Lung Conference, 17-18 October 2103, Pittsburgh, PA (Member of the Organizing committee)
5. EMBO Workshop on Integrating omic approaches to host pathogen interactions, 25-27 June 2013, Liverpool, UK. Co-organizer with Julian Hiscox and Jonathan Wastling (U. Liverpool) and David Matthews (U. Bristol)

Lans Taylor, PhD
Created pharmaceutical company collaboration committee to recruit pharma industry to Pitt for collaborations; working on all pharma companies for collaborations, secured collaboration with J&J
Worked on several life sciences company interactions for Pitt and UPMC
-General Electric – multiplexed fluorescence pathology project; early negotiation stage
-General Electric – cellular systems biology collaboration; early negotiation stage
-Omnyx – reviewed company plans and recommended strategy for patent issue with GE
-Thar Pharmaceutical-reviewed technology and plans
Life Technologies - genomics project with UPMC-initial steps taken by UPMC
Delivered symposium talk at the annual RiMED meeting in Sicily
Served on special NIH review committee for technologies
Reviewed candidates for election as a fellow of the American Insitute of Medical and Biological Engineering
Served on the NCI NeXT program advisory committee for the chemical biology consortium-ongoing
Served as a mentor to John S. Maier, MD, PhD, a young faculty member in Family Medicine.
Corporation Member, Marine Biological Laboratory, Woods Hole, MA,
Consultant for Light Optical Methods for NIH and NSF grants
Chairman of the Board, Pittsburgh Life Sciences Greenhouse, Pittsburgh,
PA Scientific Advisory Board, Reaction Biology Inc., Pittsburgh,
PA Board of Directors, Celsense, Inc., Pittsburgh,
PA Board of Directors,
PA BIOBoard of Directors, Cernostics, Inc.
Advisor, Cernostics, Inc, a cancer diagnostics company

Invited Speaker:
5/13/2014 Gulf Coast Consortia's CPRIT Screening program at Texas A&M Health Science Center

Daniel M. Zuckerman, Ph.D.
Referee for numerous journals
Co-coordinator: Pittsburgh Biophysical Theory Club
Grant reviewing for NSF and NIH (ad hoc)

Joseph Ayoob, Ph.D.
Judge, Sigma Xi Honor Society Poster Competition at the Meeting of the Minds: Undergraduate
Review Panelist, NSF Research Experiences for Undergraduates (REU) Programs, 2010-present
Review Panelist, NSF Postdoctoral Research Fellowship in Biology – Broadening Participation
Mentor, MentorNet. Heather Andrews – protégé (January 2013 – present).

Robert Boltz, Ph.D.
Member of the Society for the Advancement of Cytometry
Member of the Society for Laboratory Automation and Screening
Manuscript review boards: Cytometry, Biotechniques, The Analyst

Maria Chikina, Ph.D.
Completed data analysis for an industry-academia partnership project involving animal models of depression. A manuscript describing the results is currently being prepared.
Reviewer for PLoSOne and Bioinformatics.

Albert Gough, Ph.D.
Provided consulting support to local Biotech Community.
Provided consulting to the U.S. Army Medcom on automating safety analysis.
Reviewer the Journal of Biomolecular Screening.

David Koes, Ph.D.
ACM/IEEE Member
ACS Member
Mentor for SciTech Executive Experience
Science Fair Judge
Consultant for Carmolex

Timothy R. Lezon, Ph.D.
Reviewer:
PLoS Computational Biology
Biophysical Journal
Bioinformatics
Chemical Physics Letters
Proteins
Journal of Molecular Graphics and Modeling
Journal of Structural Biology
Journal of Chemical Information and Modeling
Journal of Chemical Theory and Comp.

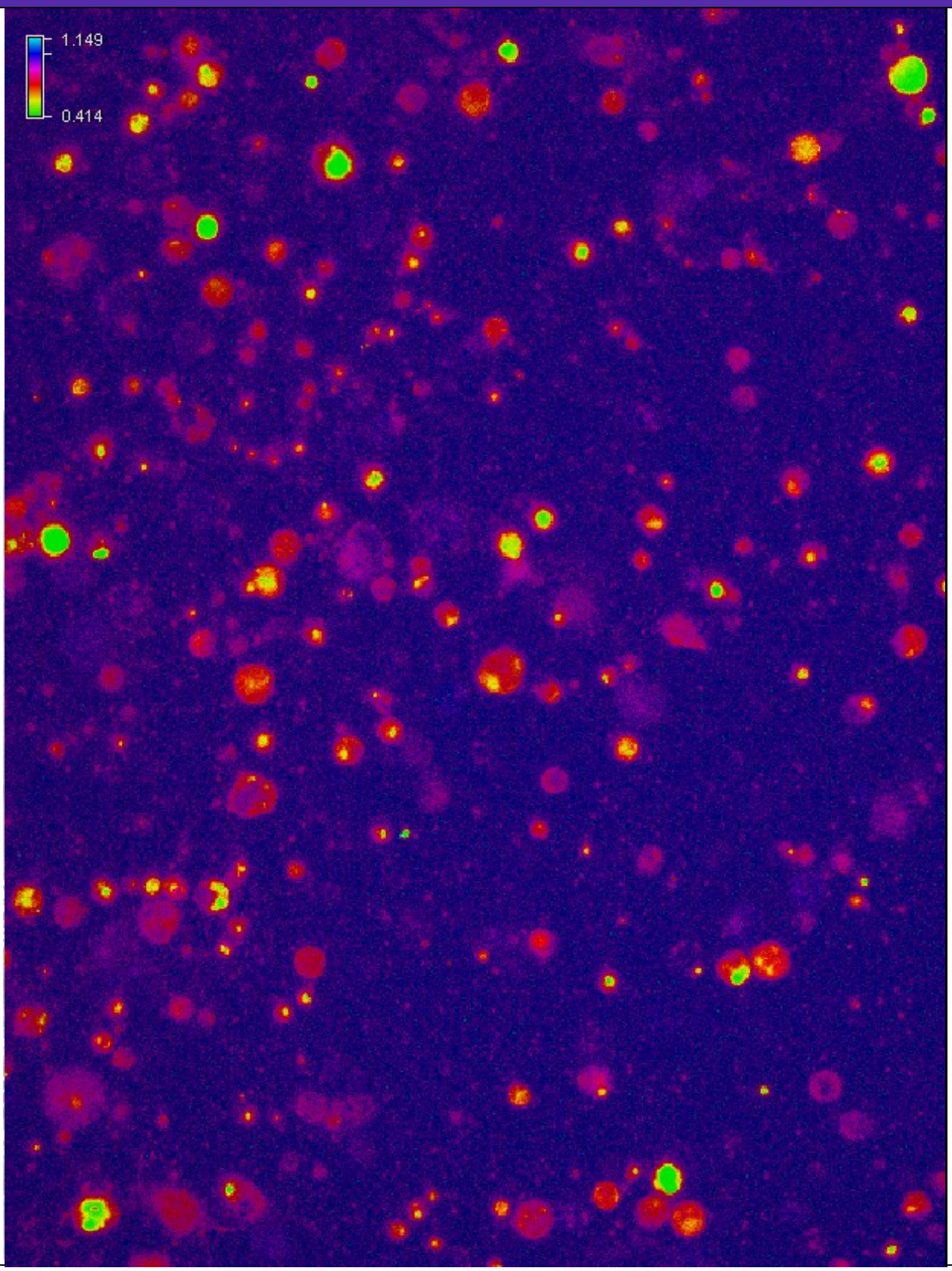
Mark Schurdak, Ph.D.
Member of the NCI Chemical Biology consortium steering committee. Participated in quarterly meetings and discussion regarding CBC projects and activities.
Member of the NCI Chemical Biology Consortium HTS/HCS Assay Validation Working Group to draft standard guidelines for assay validation for CBC projects.
Reviewer for PLoS One.

Member, AACR, American Chemical Society, AAAS, and Society for Laboratory Automation and Screening (SLAS).

Andrew Stern, Ph.D.
Reviewer for Nature and Plos One

Lawrence Vernetti, Ph.D.
Associate membership in Society of Toxicology. Acceptance into SOT is by sponsorship only after establishing a record of research and publication in the area of toxicology.
Organized a workshop for the 2013 SOT meeting on the use of zebrafish as an alternative organism model for toxicology studies.
Nominated as an 2013 Society of Toxicology (SOT) counselor to the Drug Discovery Toxicology sub-section.
Reviewer for Vitro Toxicolgoy Journal, PLoS One, and the Journal of Biomolecular Screening.
Attended DARPA and NIH Joint Bi-Annual Meetings.

Andreas Vogt, Ph.D.
Ad hoc journal referee for Cancer Research, Clinical Cancer Research, Current Molecular Pharmacology, Oncogene, Molecular Pharmacology, Journal of Medicinal Chemistry, Journal of Pharmacology and Experimental Therapeutics, Molecular Cancer Therapeutics, Biochemical Pharmacology, Chem Med Chem, and Science.
Study Section Member:
Special Emphasis Panel/Scientific Review Group ZRG1 OTC-T10) B, Small Business: Cancer Drug Development and Therapeutics Meeting, NCI Developmental Therapeutics Program, 2013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Section V

Tenure Track Faculty.....101
Non-Tenure Track Faculty.....113

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TENURE-TRACK FACULTY

Ivet Bahar, Ph.D.

2014

Bahar I (2014) Coupling between Neurotransmitter Translocation and Protonation State of a Titratable Residue during Na(+)-Coupled Transport *Biophys J* **106**: 2547-8 [JIF=3.832]

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LaRusch J, Jung J, General I, Lewis MD, Woo Park H, Brand RE, Gelrud A, Anderson MA, Banks PA, Conwell D, Lawrence C, Romagnuolo J, Baillie J, Alkaade S, Cote' G, Gardner TB, Amann ST, Slivka A, Sandhu B, Aloe A, Kienholz ML, Yadav D, Barmada MM, **Bahar I**, Lee MG, Whitcomb DC, North American Pancreatitis Study Group (2014) Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis *PLoS Genetics* **10**: (7):e1004376 [JIF=8.167]

General IJ, Liu Y, Blackburn M, Mao W, Gierasch L, **Bahar I** (2014) ATPase subdomain IA is a mediator of interdomain allostery in Hsp70 molecular chaperones *PLoS Comp Bio* **10**: e1003624 [JIF=4.829]

Korotchenko VN, Saydmohammed M, Vollmer LL, Bakan A, Sheetz K, Debiec KT, Greene KA, Agliori CS, **Bahar I**, Day BW, Vogt A, Tsang M (2014) In Vivo Structure-Activity Relationship Studies Support Allosteric Targeting of a Dual Specificity Phosphatase *ChemBioChem* **15:** 1436-1445 [JIF=3.060]

Das A, Gur M,* Cheng MH,* Jo S, **Bahar I**, Roux B (2014) Exploring the conformational transitions of biomolecular systems using a simple two-state anisotropic network model *PLoS Comput Biol* **10(4)**: e1003521 [JIF=4.829]

Jiang J, Bakan A, Kapralov AA, Ishara Silva K, Huang Z, Amoscato AA, Peterson J, Krishna Garapati V, Saxena S, Bayir H, Atkinson J, **Bahar I**, Kagan VE (2014) Designing inhibitors of cytochrome c/cardiolipin peroxidase complexes: mitochondria-targeted imidazole-substituted fatty acids *Free Radic Biol Med* **71C:** 221-230 [JIF=5.710]

Lui VW, Peyser ND, Ng PK, Hritz J, Zeng Y, Lu Y, Li H, Wang L, Gilbert BR, General IJ, **Bahar I**, Ju Z, Wang Z, Pendleton KP, Xiao X, Du Y, Vries JK, Hammerman PS, Garraway LA, Mills GB, Johnson DE, Grandis JR (2014) Frequent mutation of receptor protein tyrosine phosphatases provides a mechanism for STAT3 hyperactivation in head and neck cancer *Proc Natl Acad Sci USA 111(3): 1114-9 [JIF=9.809]*

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2012

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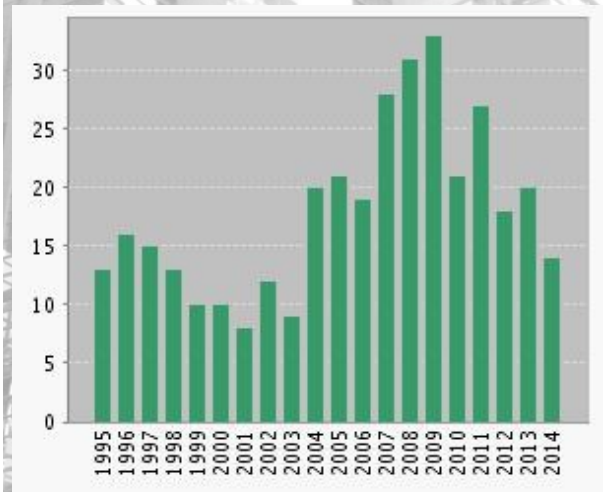

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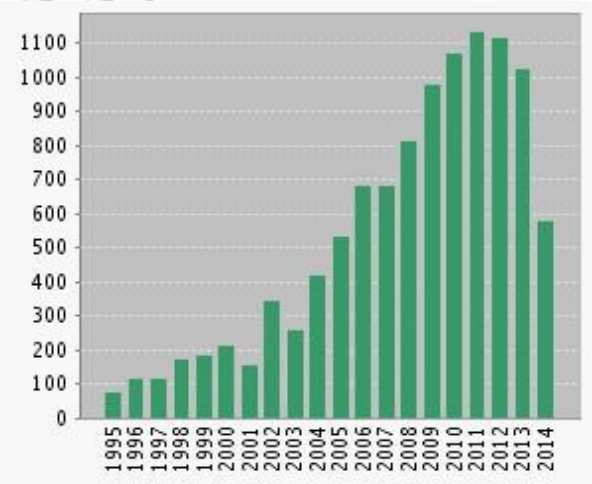

Sum of The Times Cited: 11004

h-index: 50

Panagiotis (Takis) V. Benos, Ph.D.

2014

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2013

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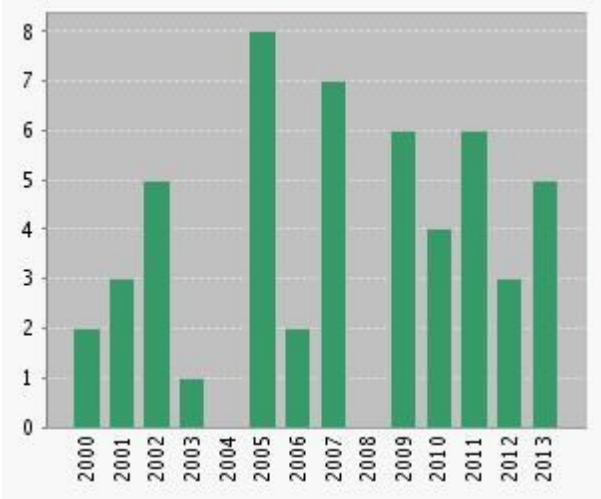

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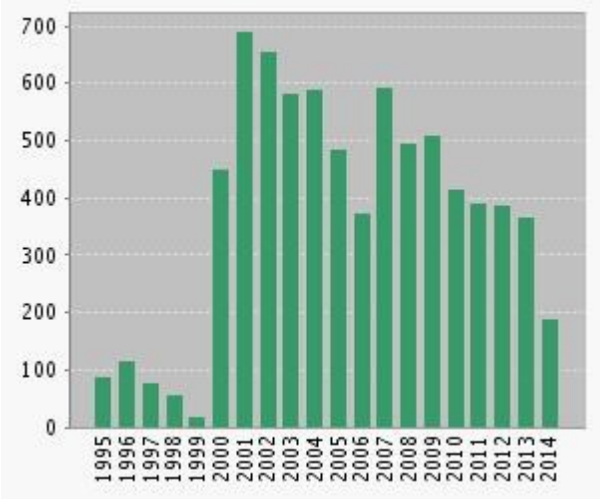

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Jeremy M. Berg, Ph.D.

2013

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2012

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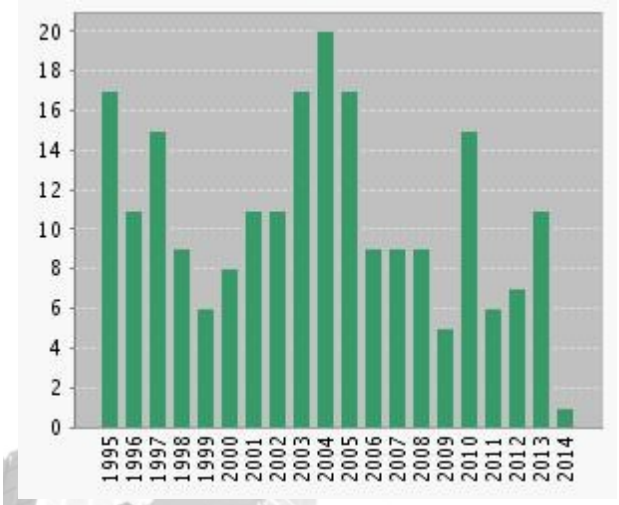

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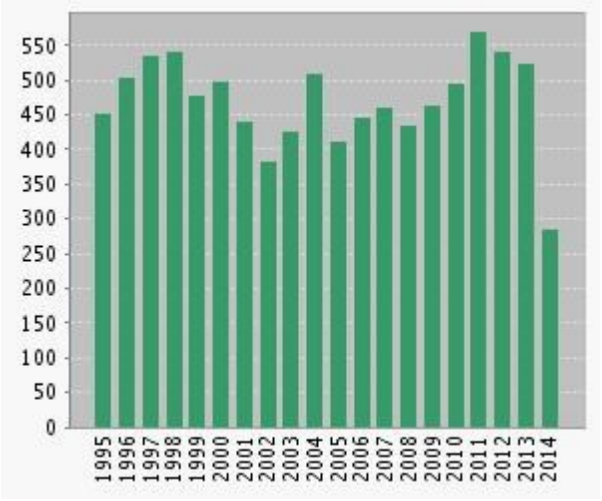

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Carlos J. Camacho, Ph.D.

2014

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2013

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2012

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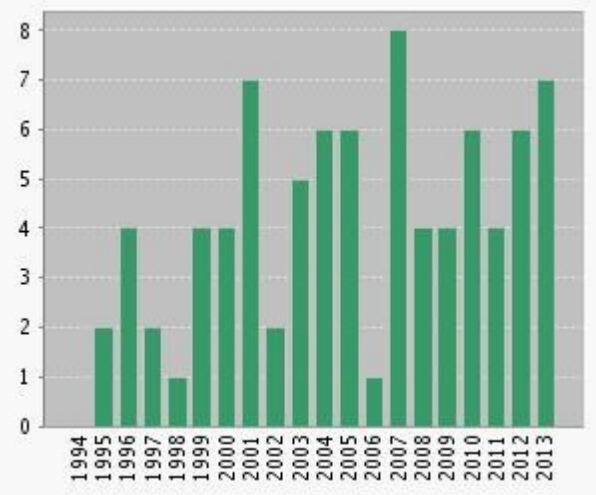
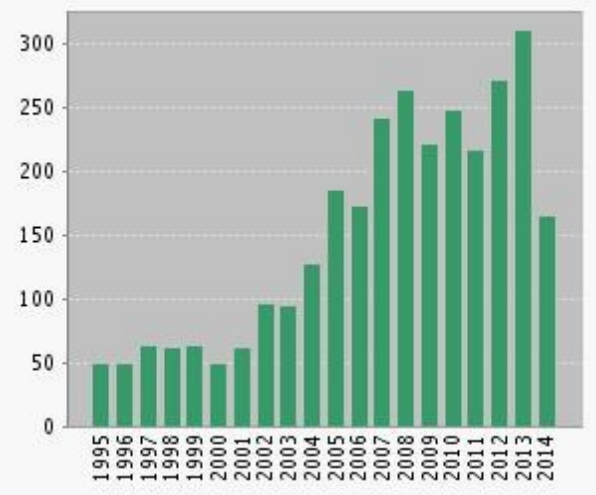


Citation in Each Year



Sum of the Times Cited: 3097

h-index: 30

Chakra Chennubhotla, Ph.D.

2014

Bakan A, Dutta A, Mao W, Liu Y, **Chennubhotla C**, Lezon TR, Bahar I. (2014) Evol and ProDy for bridging protein sequence evolution and structural dynamics. Bioinformatics. **2014** May 21. pii: btu336. [Epub ahead of print] [JIF=4.621]

Ramanathan A, Savol A, Burger V, **Chennubhotla CS**, Agarwal PK (2014) Protein conformational populations and functionally relevant substates. Acc Chem Res. Jan 21;47(1):149-56. doi: 10.1021/ar400084s. Epub 2013 Aug 29. Review. [JIF=24.348]

2013

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2012

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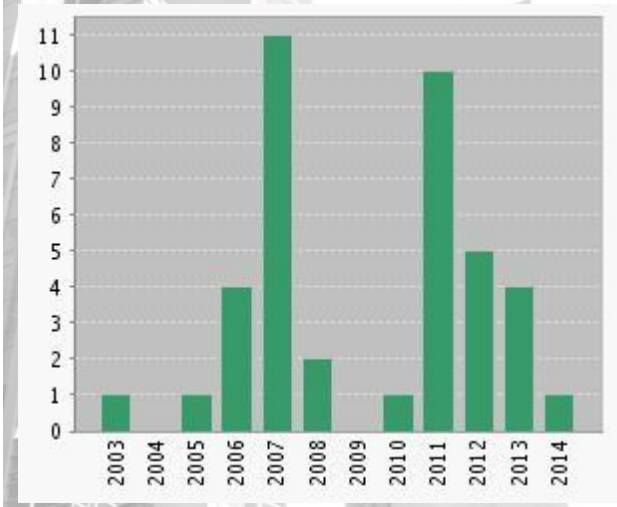

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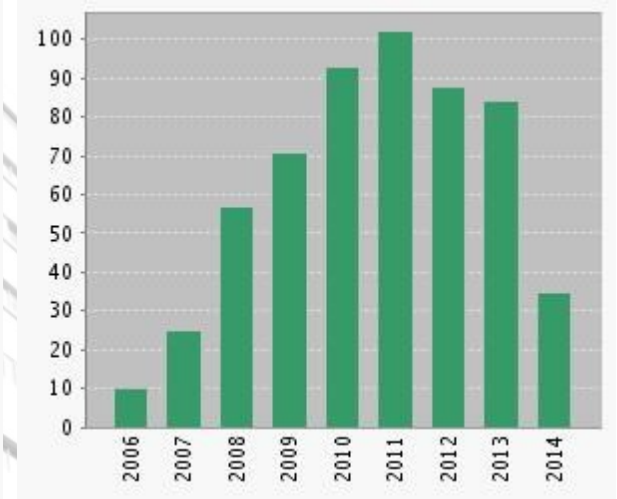

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Nathan Clark, Ph.D.

2014

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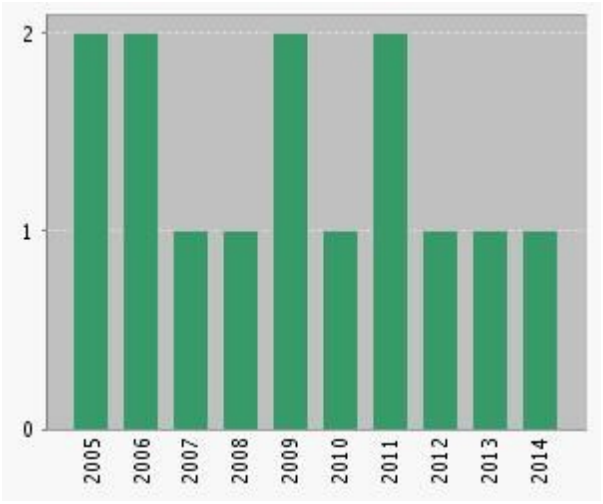

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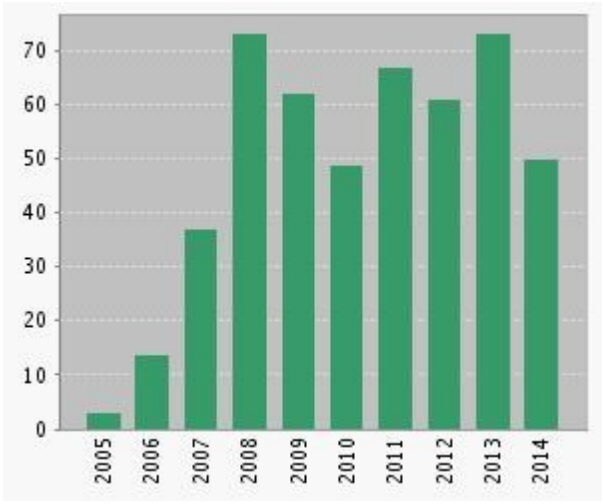

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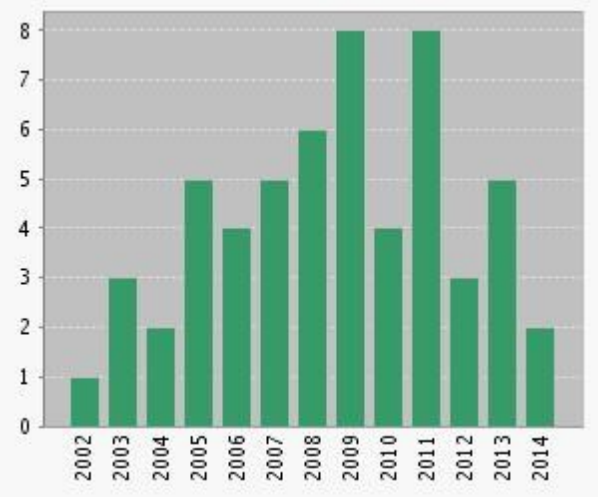

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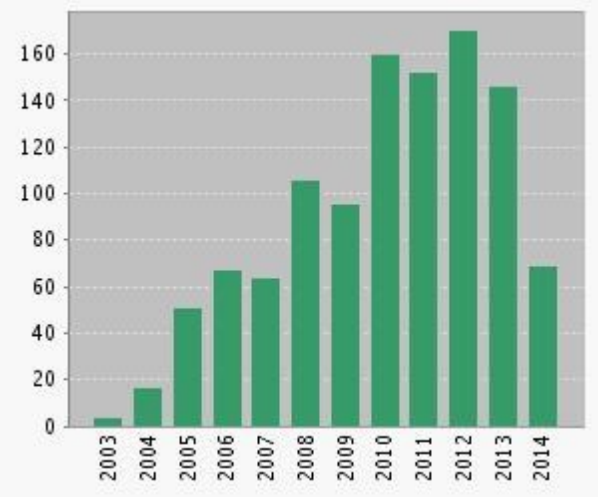

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Elodie Ghedin, Ph.D.

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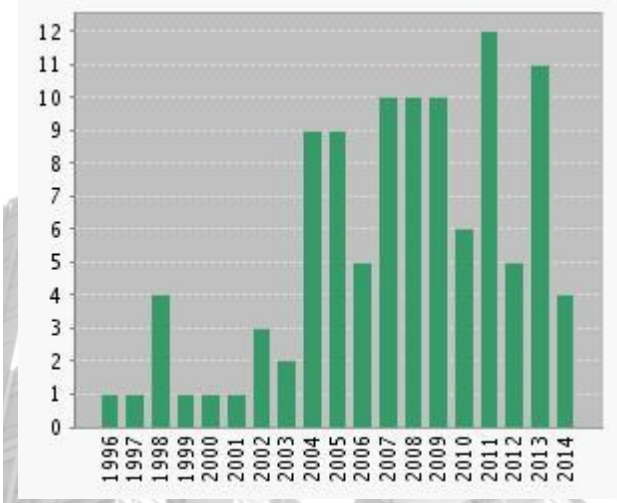

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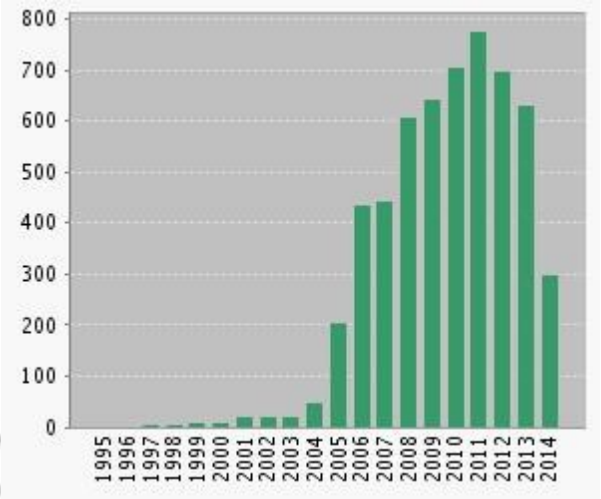

Sum of the Times Cited: 5588

h-index: 30

D. Lansing Taylor, Ph.D.

2014

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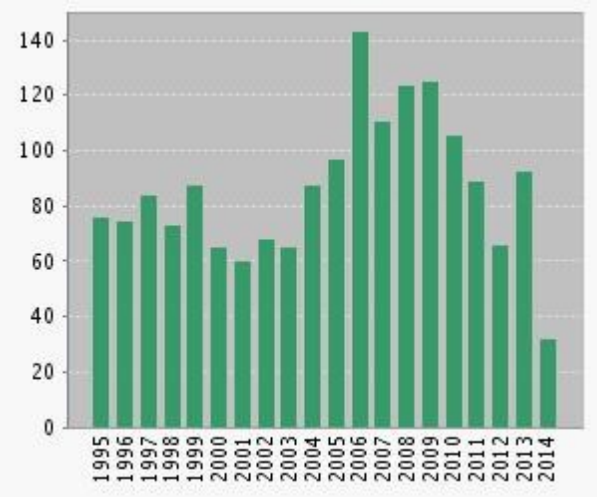

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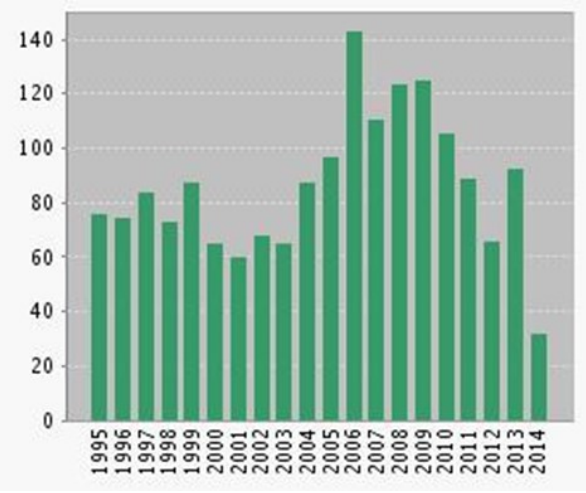

Sum of the Times Cited: 1800

h-index: 22

John K. Vries, M.D.

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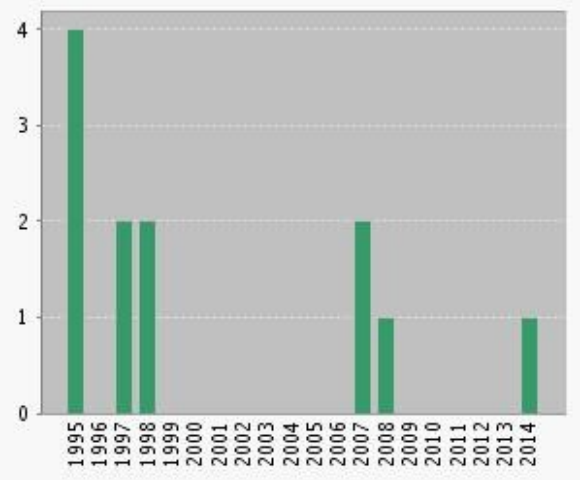

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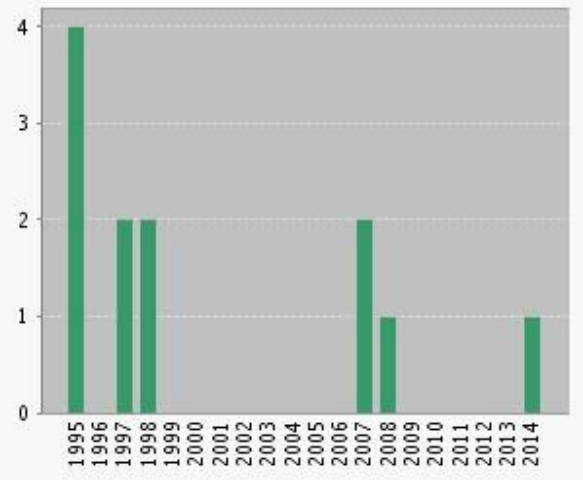

Sum of the Times Cited: 942

h-index: 16

Dan Zuckerman, Ph.D.

2014

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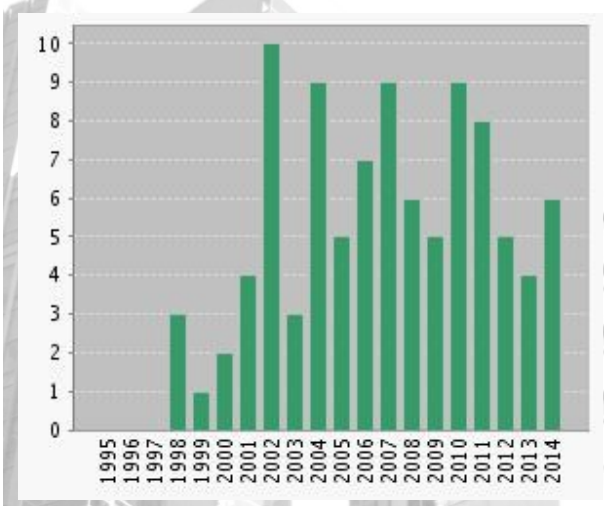

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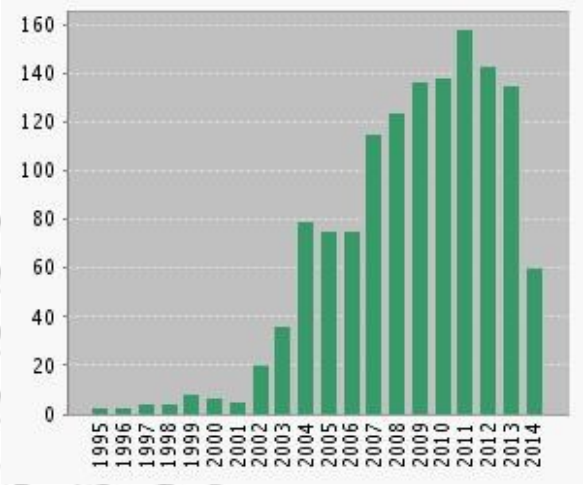

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NON-TENURE TRACK FACULTY AND STAFF SCIENTISTS

Joseph C. Ayoob, Ph.D.

2012

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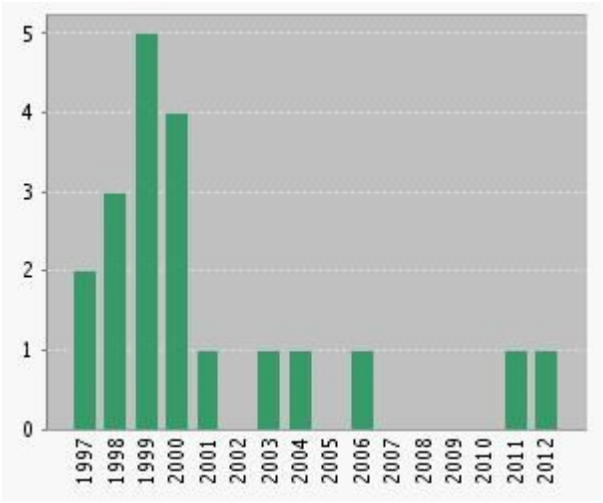

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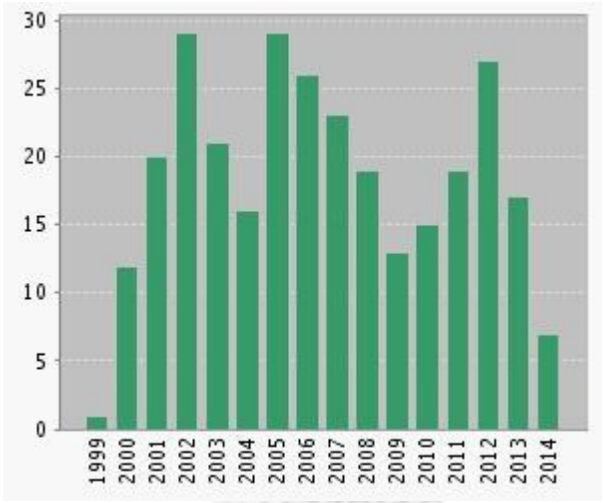

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Dipak Barua, Ph.D.

2014

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□ equally contributed authors

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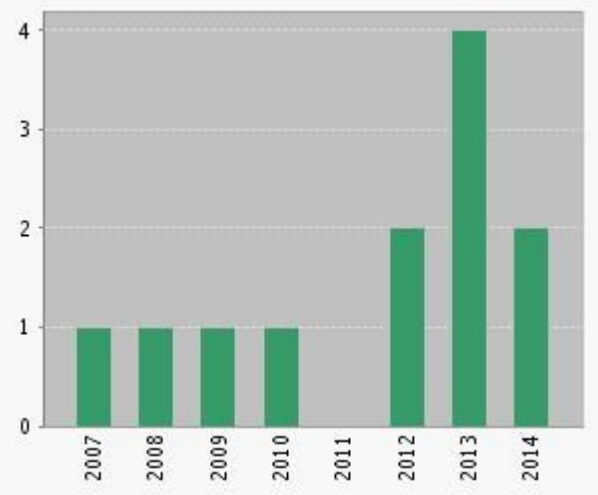

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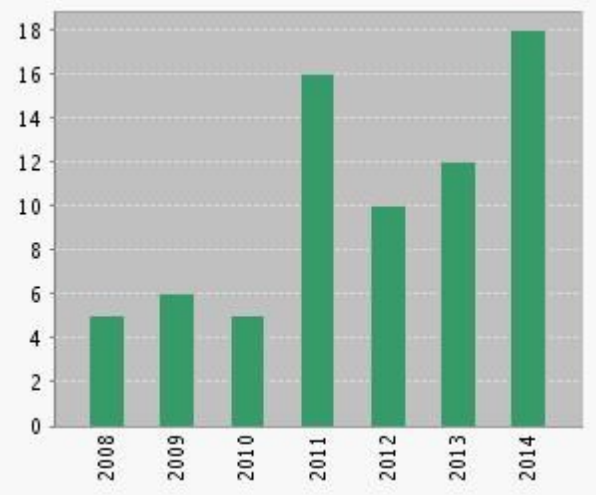

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h-index: 5

Robert Boltz, Ph.D.

2014

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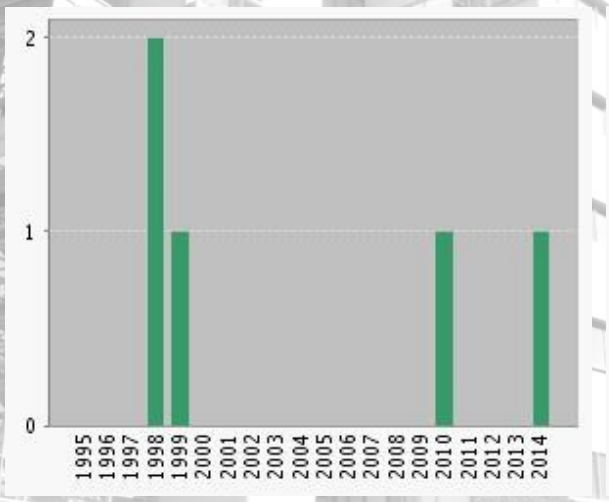

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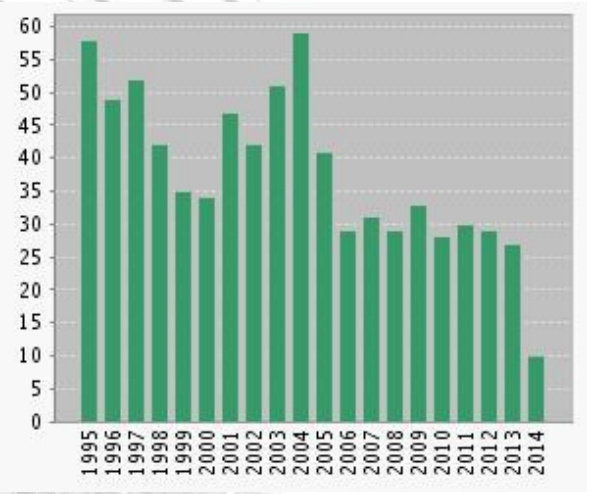

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h-index: **15**

Hongying (Mary) Cheng, Ph.D.

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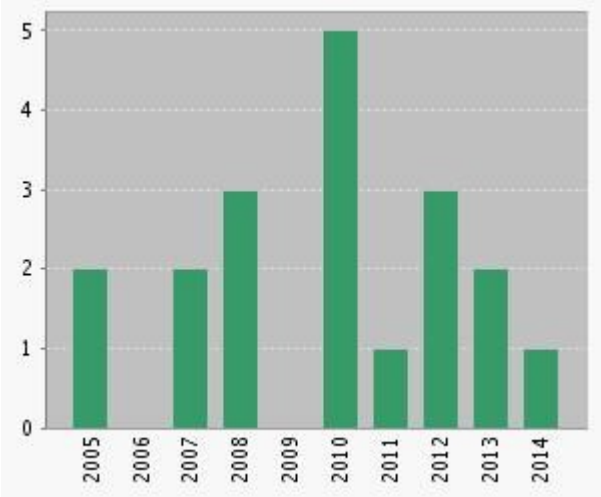

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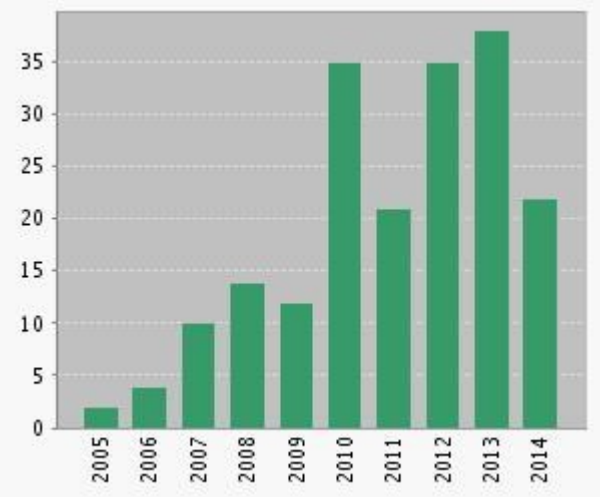

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h-index=9

Maria Chikina, Ph.D.

2014

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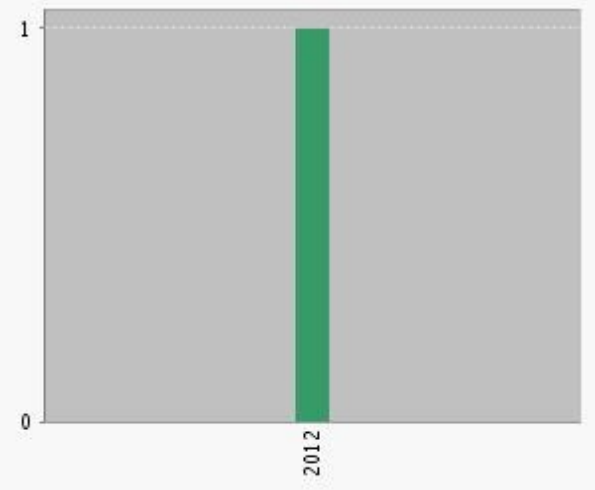

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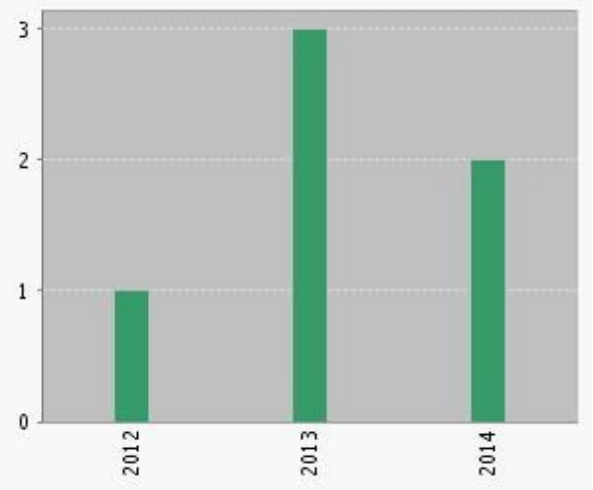

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Antonio M. Ferreira, Ph.D.

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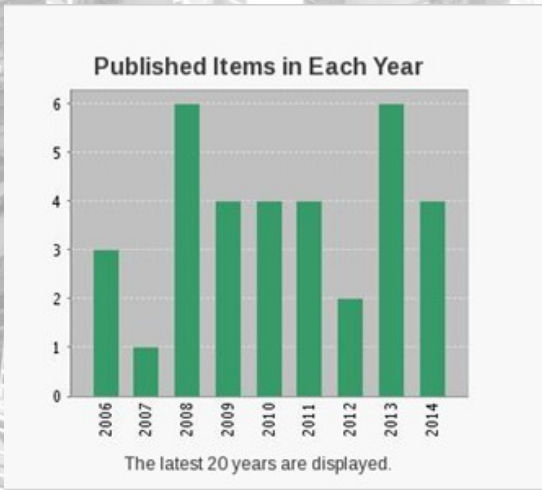

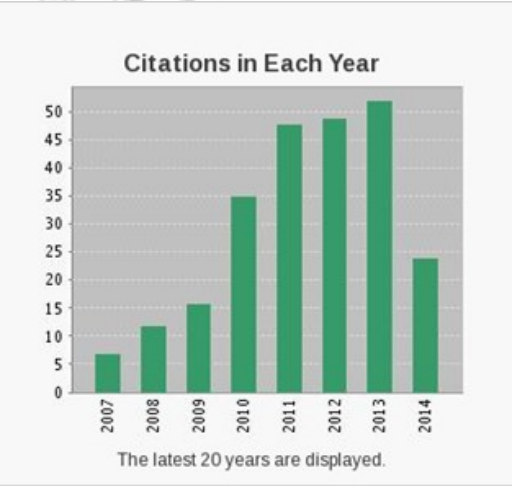

Sum of The Times Cited: 243

h-index: 10

Albert Gough, Ph.D.

2013

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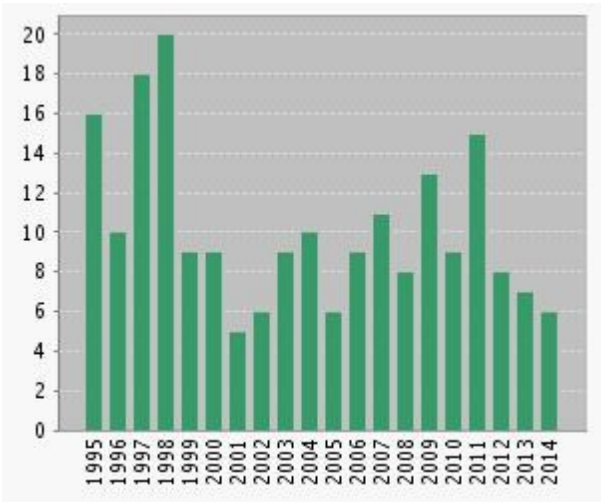

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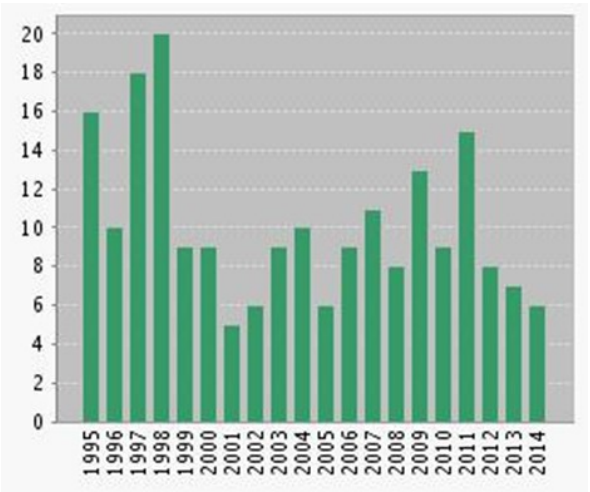

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David Koes, Ph.D.

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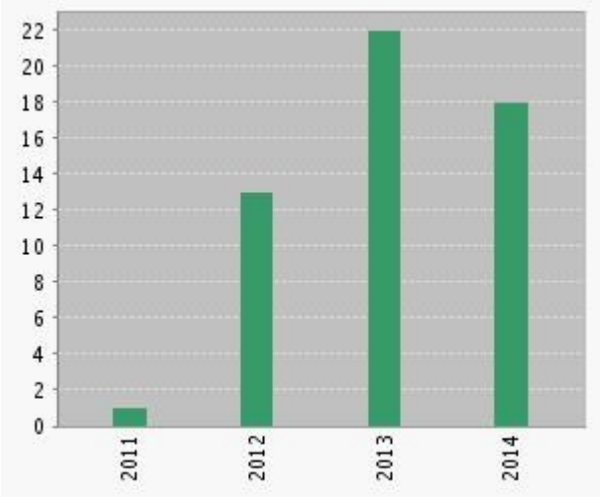

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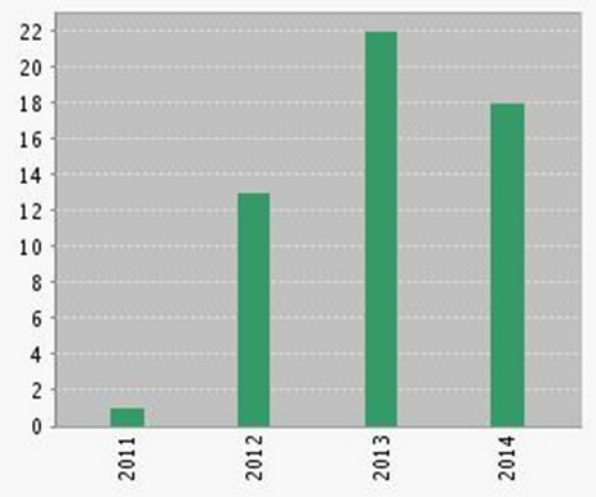

Sum of The Times Cited: 54

h-index: 4

Timothy Lezon, Ph.D.

2014

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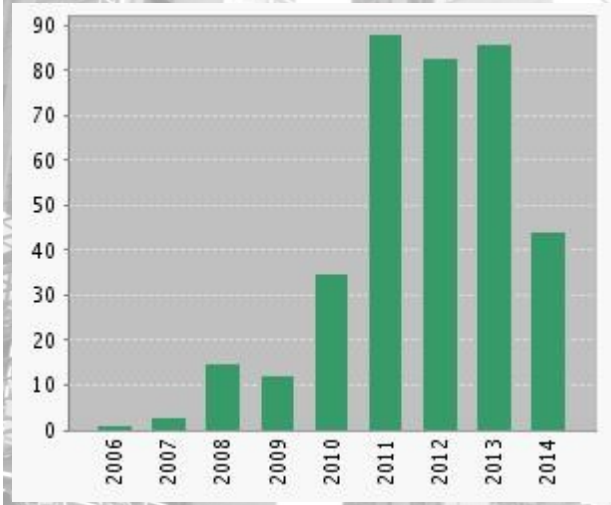

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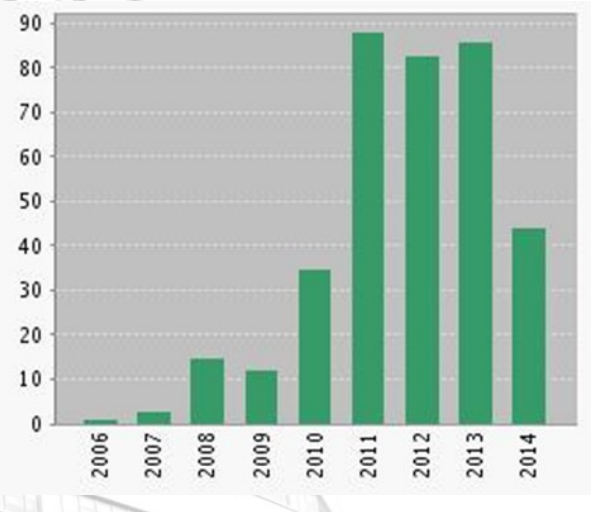

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h-index: 7

Mark Schurdak, Ph.D.

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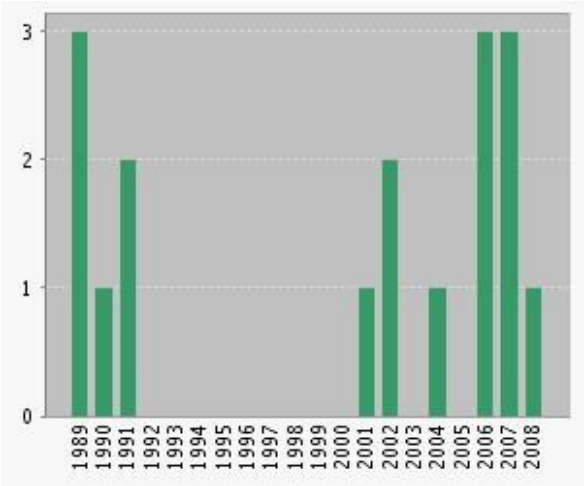

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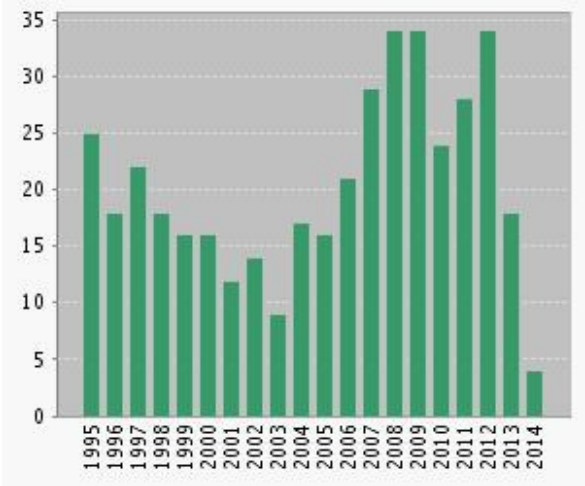

Sum of the Times Cited: 658

h-index: 15

Indira Shrivastava, Ph.D.

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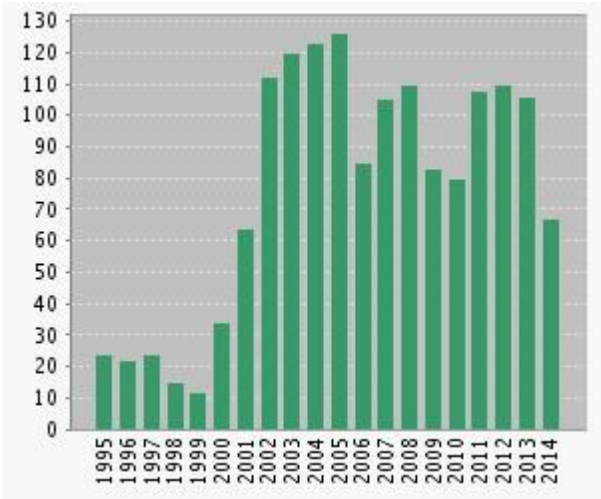

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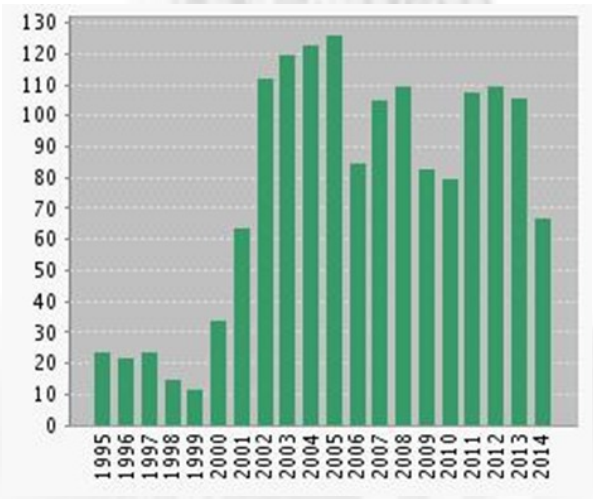

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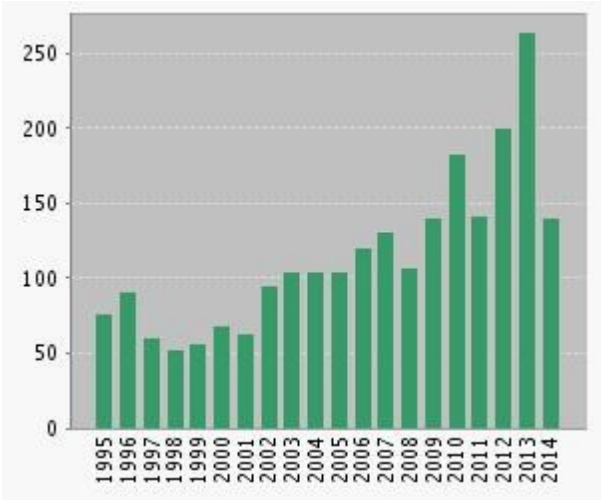

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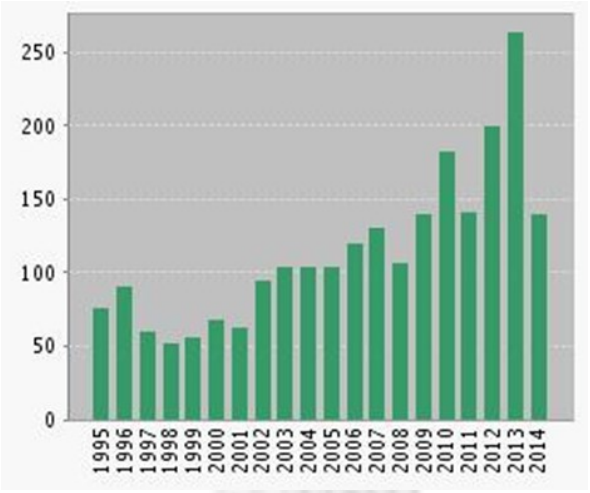

Sum of the Times Cited: 2572

h-index: 29

Lawrence Vernetti, Ph.D.

2014

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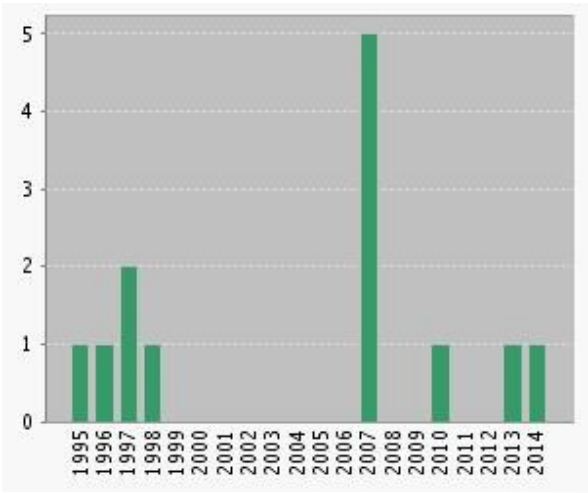

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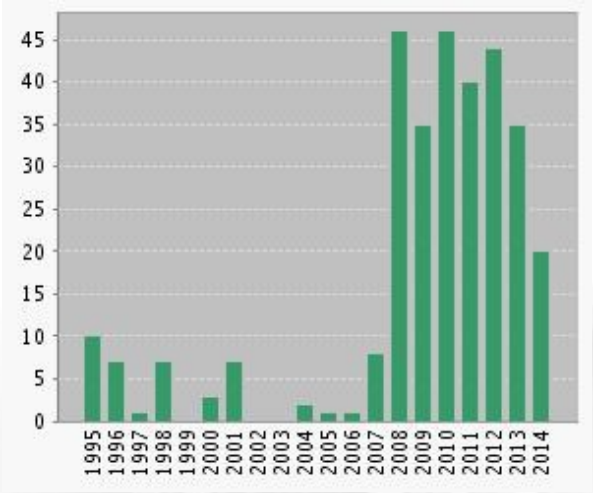

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h-index: 6

Andreas Vogt, Ph.D.

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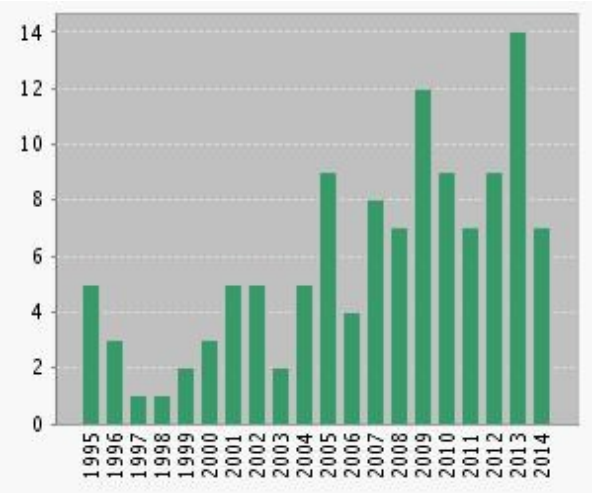

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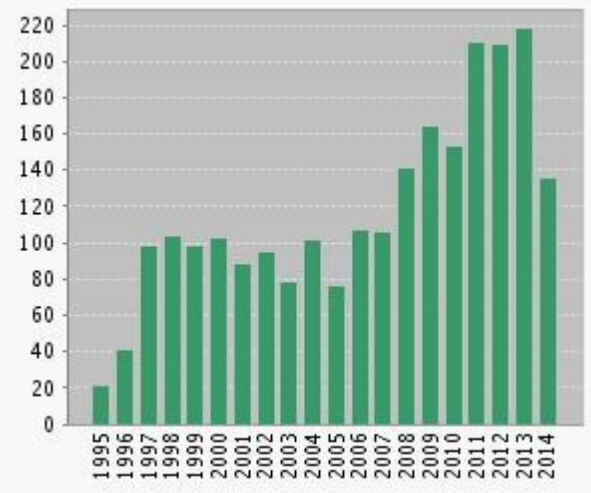

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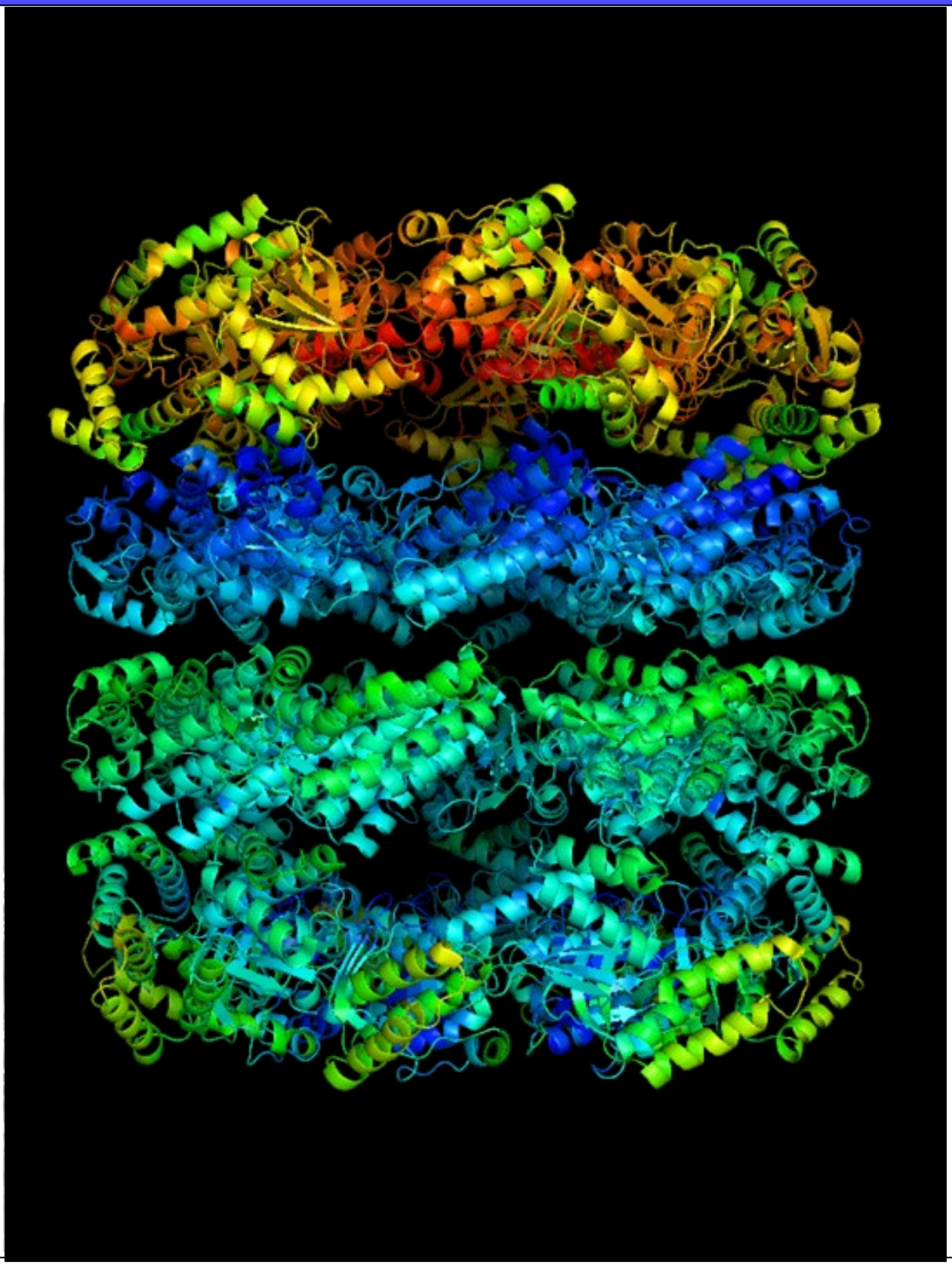

Section VI

Financial Plan for Fiscal Year 2014

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EXECUTIVE SUMMARY

The Department of Computational & Systems Biology (CSB) financial plan for Fiscal Year 2015 largely reflects the goals as outlined in the proposal for creation of the department. Our current goals fall into three categories: 1. Recruiting additional faculty members, 2. Increasing the amount of funding for research and educational programs, and 3. Continuing our strong tradition of training postdoctoral fellows as well as graduate, undergraduate, and high school students in a tiered mentoring framework. These goals are driven by the department's educational mission to train the next generation of computational and systems biology researchers, as well as our two-fold research mission to (i) advance the scientific understanding of biological systems through computational tools and theoretical approaches based on the fundamental principles of physical sciences and (ii) design new computational/mathematical models and methods for simulating complex biological processes and for extracting useful information from accumulating data.

The CSB research mission is supported by recruitment of faculty with balanced interests and experience to broaden the department's expertise in four key areas of specialization/growth: 1. Bioinformatics and Computational Genomics and Proteomics, 2. Cellular and Systems Biology; 3. Molecular Structural Biology, and 4. Pharmacology and Drug Discovery. We also strive to continue our current research collaborations while reaching out to establish new collaborations within the University of Pittsburgh and beyond through aggressively pursuing extramural grant support, external funding, additional interdisciplinary projects as well as by providing administrative support as necessary to ensure smooth operation of the department and attainment of departmental goals.

Our educational efforts are being achieved by our faculty's involvement in the Joint Carnegie Mellon-University of Pittsburgh Computational Biology (CPCB) Graduate Program, other graduate programs at the University, the Training and Experimentation in Computational Biology (TECBio) Research Experiences for Undergraduates (REU) summer program, and the Drug Discovery, Systems and Computational Biology (DiSCoBio) Summer Academy for High Students, which is a partnership with the Drug Discovery Institute under the umbrella of the University of Pittsburgh Cancer Institute's International Summer Academy. These endeavors have been and are supported by funds from the NIH, NSF, Department of Defense, Howard Hughes Medical Institute, and the Doris Duke Foundation, as well as our infrastructure which includes a state-of-the-art computational biology classroom, a department compute cluster with over 2,300 CPU cores and 64 GPUs for intensive computations and simulations, and the additional involvement of CSB graduate students and postdoctoral fellows.

Introduction

Under the direction of Dr. Ivet Bahar, Distinguished University Professor and John K. Vries Chair, the Department of Computational Biology (DCB) was created in October 2004 and was renamed in February 2010 to The Department of Computational and Systems Biology (CSB) to reflect our present and future research and education efforts and signal our increasing focus on multi-scale interactions in biological systems, enabling us to tackle more research at an integrated, Systems level. Moreover, our close association with the University of Pittsburgh Drug Discovery Institute facilitates an important effort combining computational, systems, and experimental approaches to improve the design, screening, and testing of new therapeutics for a host of diseases. Lastly, our extensive collaborations have built the infrastructure that support nationwide, large-scale, center grants for the investigation of new therapies for liver fibrosis and hyperproliferation and for multiscale (molecular, cellular, and systems level) modeling of biological systems to study the structural basis of glutamate transporters, the mechanisms of synaptic and T -cell signaling, and the architecture of neuronal pathways.

The FY15 plan of the CSB largely reflects a continuation of the goals as outlined in the proposal for creation of the department. These goals fall into three categories:

Recruiting new faculty members
Increasing the amount of funding for research and educational programs
Training graduate, undergraduate, and high school students and Postdoctoral fellows

As stated in the proposal:

Our intent is for the Department of Computational Biology to become a fully functioning and nationally acclaimed department. We continue to recruit the most promising faculty candidates, to obtain substantial extramural funding from a variety of public and private agencies, and to train top graduate students and postdoctoral fellows.

While our success will be quantifiable in terms of grant funding, we believe it is of equal importance to establish the future Department of CSB as a top-tier department for computational biology, and Pittsburgh as a pre-eminent city. Today, Pittsburgh is being characterized as among the top places to live, work and visit in the United States. CSB contributes to Pittsburgh by recruiting faculty at both the junior and senior levels, by creating a unique research and development environment, and by offering a first-class graduate program. Pittsburgh's growing reputation makes it easier to recruit these Top Tier scientists.

Our aim was that within ten years, trainees from the CSB Department will be faculty members at top universities nationwide, or scientists working on cutting-edge technology in pharmaceutical industry or biomedical research institutions. We are accomplishing this objective with a roughly 50/50 split of graduates going to Industry and Academia in the STEM (Science, Technology, Engineering, and Mathematics) disciplines.

CSB continues to more fully pursue the integration of Systems research into the department. This is being realized by the recent addition of Jianhua Xing, joining us from Virginia Tech as Associate Professor, (January 2015) and Robin Lee of Harvard. Our expectation is that Dr. Xing will conduct independent and collaborative research in Epithelial-to-Mesenchymal Transition (EMT) characterized by loss of cell-cell adhesion and increased cell motility, and Dr. Lee's research will combine principles of systems and synthetic biology to understand how information flows through a cell's complex network of molecular circuits and fine-tunes cellular responses.

Financial Plan Initiatives and Implementation Strategy

The mission of the Department of Computational & Systems Biology has two components: research and education.

Research

The research mission of the department is: (i) to advance the scientific understanding of biological systems through computational tools and theoretical approaches based on the fundamental principles of physical sciences; (ii) to design new computational/mathematical models and methods for simulating complex biological processes and for extracting useful information from accumulating data, in close cooperation with experimental groups doing research in these fields, and (iii) efficiently publicizing and disseminating the tools and generated data to the scientific community. In terms of research topics, the department pursues four areas of specialization/growth: 1. Bioinformatics and Computational Genomics and Proteomics, 2. Cellular and Systems Biology, 3. Molecular Structural Biology, and 4. Pharmacology and Drug Discovery.
In recent years, a new generation of researchers with computational modeling expertise has emerged. Computational modeling expertise is necessary in order to address the new dimensions and challenges in life science research. These researchers develop sophisticated algorithms using theories and methods derived from computer science, physical sciences and engineering, and test them on existing datasets. The mere application of these technologies alone adds little to the knowledge of the underlying biology if they

lack the necessary focus to, or impetus driven by, a problem of biological or biomedical interest. Thus, there is a need for creating an environment that will bring together scientists from both communities to enhance interactions by helping the exchange of ideas, methods, and expertise on biologically motivated complex problems of today's era.

The Department of Computational and Systems Biology has taken a leading role in spearheading new research initiatives with collaborators here at the university and across the nation that will undoubtedly generate novel and groundbreaking research. Our BTRC P41 that established a Center for Multiscale Modeling of Biological Systems (MMBioS) is a partnership with leading researchers from the Salk Institute, Cal Tech, Harvard, Carnegie Mellon, and the Pittsburgh Supercomputing Center, and is led by our chair, Dr. Bahar. An additional Center Grant, NIDA Center of Excellence for Computational Drug Abuse Research (CDAR), has just recently been awarded that is a collaborative with Professor Xiang-Qun Xie of the University of Pittsburgh School of Pharmacy and Professor Eric Xing of Carnegie Mellon University, Computer Science Department. These efforts and our partnership with the Drug Discovery Institute, in addition to adding Systems Biology to our departmental focus, will allow us to reach a broader and larger group of potential students, post-doctoral fellows, and faculty doing both experiments and computations, who will be critical for the further growth and advancement of our department and the School of Medicine. We are making progress in several research areas such as the molecular mechanisms of chronic diseases and acute responses; systems modeling for polypharmacology; systems modeling of vaccine acquired immunity; molecular mechanisms of DNA damage recognition and repair; small RNAs function and dynamics; and microbial network modeling.

The members of CSB will work together to generate new ideas, methods, tools, biological information, and potential therapeutics that will jointly address tomorrow's problems, by using holistic approaches in a systems biology framework.

To expand on these efforts, the CSB will also build on existing collaborations with those in Medicine, Pathology, Critical Care Medicine, the Center for Vaccine Research, the Drug Discovery Institute, and the Institute for Personalized Medicine. These research activities focus on the molecular mechanisms determining the onset and progression of chronic diseases and acute responses in humans. Our systems biology-focused approaches will be applied in several of these areas (e.g., the modeling of vaccine acquired immunity and drug discovery). Moreover, the CSB will be pursuing opportunities to apply our computational expertise to the Big Data analysis efforts, especially in how large sets of genomic, imaging, and other types of data can be incorporated into our emerging Personalized Medicine efforts. We anticipate that a large number of researchers from various Schools and Departments in the University of Pittsburgh and the Carnegie Mellon University will participate in this effort.

Faculty Recruitment

To broaden the department's expertise in the above mentioned four principal areas of focus, attention would be given to recruiting individuals with balanced interests and experience.

The main reason for seeking to increase the number of faculty was to increase the number of opportunities for collaborative projects. As stated in the proposal for the creation of the Department:
From the large number and diversity of active projects, it is evident that
(i) there is a huge demand in the life and physical sciences community at Pitt for computational biology expertise, and for coordinating experimental and computational studies, and
(ii) such interactions provide the foundations for pending or future grant proposals.
(ii) the CSB would have responded much more effectively to the needs and requests of the scientific community at Pitt, if there were a larger number of Faculty at the CSB - a fact that became clear over the last ten years.
(iv) the higher number of Faculty will permit the Department to respond to a larger number of grant opportunities in biological/biomedical computing currently being announced by NIH and other agencies.

The CSB currently has 25 full-time faculty members. There are 8 Tenured faculty in the Department. With two new faculty starting in FY 15, we don't anticipate a concerted search effort, however, promotion of current Research Associates is not out of the question. The CSB currently has 38joint/adjunct faculty from other departments at the University of Pittsburgh, as well as Carnegie Mellon University, Yale, New York University, University of Groningen and Duquesne University.

Collaborations

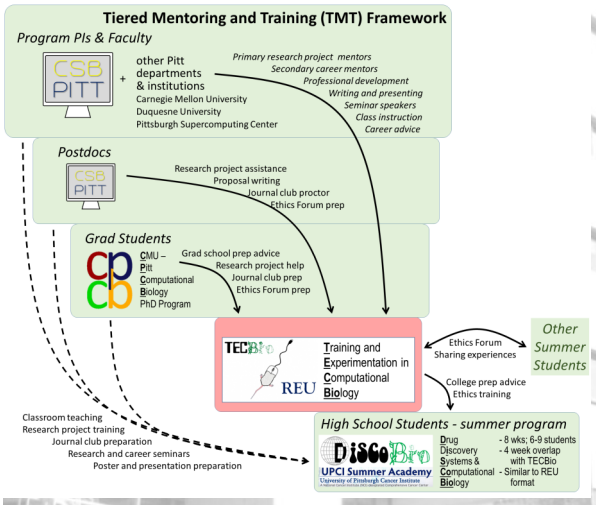
In addition to faculty recruitment, the CSB is continuing to tap into the extensive basic and clinical research programs that exist at the University of Pittsburgh. We are also strengthening our efforts at external consortium building, as is evidenced by successful research collaborations between members of the CSB and faculty from the University of Pittsburgh Cancer Institute, Children's Hospital of Pittsburgh of UPMC, Carnegie Mellon University, Duquesne University, University of Connecticut, UC Davis, The Salk Institute, Yale University, Oak Ridge National Laboratory, Massachusetts General Hospital, the University of Groningen, Harvard University, University of Tennessee, Insitut National de la Recherche Scientifique and the Pittsburgh Supercomputing Center.

Grant Funding

CSB Faculty served as Principal Investigators or Co-Investigators on a cumulative total of $54.4 million in funded research projects since 2001. CSB faculty served as Principal Investigator or Co-investigator on 41 active funded research projects in FY14 totaling $ $32 mil; $6.7mil of which was expensed in 2014. The portfolio of funding continued to grow with 8 new grants awarded.

Our junior faculty members understand the importance of obtaining extramural grant support, and are encouraged to make every effort in securing external funding and pursuing interdisciplinary projects. Given the current funding climate and the projected decline in the number of NIH-funded research projects (R01s), our projected goals for salary support for all tenure stream faculty, although attainable, will likely require more ambitious efforts on our part to obtain adequate research funding. Along these lines, 39 Applications for funding were submitted in FY14 and entering FY 2015, we have 19 applications for funding pending and continue to diversify funding applications to National Science Foundation, the Breast Cancer Foundation, The Edward Mallinckrodt, Jr. Foundation, The Kaufman Foundation, The Samuel & Emma Winters Foundation, Five3Genomics LLC, The Burroughs Wellcome Fund, Leidos Biomedical Research Inc, Department of Defense, Department of Energy and General Electric Corporation. Of the 19 applications pending 7 will be or have been awarded. These new grants amount to $3.9 million in Total Cost.

Education



The CSB is committed to providing first-class programs at the graduate, undergraduate, and high school level in computational biology, all of which serve multiple purposes: (i) to introduce computational biology problems and methods to students from biology, chemistry, physics, engineering, mathematics, and computer sciences, (ii) to teach fundamental concepts of the quantitative and physical sciences to biology and biomedical sciences students, (iii) to prepare and encourage students at all levels for a career in computational biology research, and (iv) to reach out to and recruit students from backgrounds that are underrepresented in the sciences. In all cases, the aim is to train students and postdoctoral researchers to identify and tackle complex biological problems on a computer—, simulating biological phenomena at multiple scales, modeling signal transduction pathways, and many other efforts. We have incorporated these efforts into a tiered-mentoring framework that

maximizes interactions between students and trainees at similar experience levels, while providing important mentoring experience for emerging scientists. We are also constantly striving to improve our existing programs, reaching out to a larger group of students, and pursuing funding opportunities to support our programs. For instance, under the umbrella of the University of Pittsburgh Cancer Institute International Summer Academy, and in collaboration with the Drug Discovery Institute, we started a new initiative to reach out to students at the high school level, and provide them a mentored research experience and didactic training in experimental and computational approaches to study cancer biology and drug discovery. This new endeavor mirrors and has been built on the success of our existing training programs for graduate students – the joint Carnegie Mellon-University of Pittsburgh Computational Biology (CPCB) graduate program – and for undergraduate students – the Training and Experimentation in Computational Biology (TECBio) Research Experiences for Undergraduates (REU) program. The programs have benefited greatly from each other and with the addition of the new cohort of high school students. Additionally, CPCB and TECBio are funded by grants from the NIH and the NSF, respectively; the CPCB T32 training grant is renewed for 5 years of additional support and the TECBio REU was renewed for 4 additional years in 2013 and is also being co-funded by the Department of Defense.

Administration

The CSB moved into its facility, a 10,000 sq ft office suite located in the BST3, in September 2005. Configured roughly as a rectangle, the suite has offices for faculty, staff, and postdoctoral research associates. Twenty-eight cubicles are available for Joint-Program graduate students. Additional space houses the classroom, server room, copying and printing equipment, and additional staff offices. The central core is made up of an informal conference/meeting area, a cubicle area houses 28 workstations for students, an enclosed conference room, a reception area, and additional staff offices. A kitchenette/lounge area is located outside of the main office suite.

In 2012, we acquired approximately 3,600 sq. ft of space on the 10th floor of BST3 to house the wet labs: currently , Nathan Clark and Joseph Ayoob, are utilizing this lab space with Robin Lee and Jianhua Xing locating their laboratories within this space in the next few months.

Resources

The Department of Computational Biology uses a large number of computers to conduct its research in an efficient and effective manner. These computers include high-end workstations in the offices and a number of rack-mounted Linux clusters in the server room. The clusters are for running complex simulations, models, and computations that take a long time to complete or can run in parallel across nodes. The server room itself has 2 chilled-water based InRow Air Conditioners and a traditional CRAC. It also has a 225kVA Uninterruptible Power Supply, and a FM200 fire suppression system. The building (BST3) provides backup power generator as well as chilled water plant.

The two In-Row air conditioners were installed in early 2010 as part of the 2nd phase of an air conditioning upgrade project. We now have double the previous cooling capacity plus redundancy. The room has maintained consistent cool temperature through a summer with several 90ºF+ weeks. The pipes were sized and routed such that one more unit could be added in the future if necessary.

There are two clusters total. The first cluster is shared by the department and the second is reserved for exclusive use by one research group.

Cluster	Nodes *	CPU cores total	Mem total (GB)	Storage total (TB)	Infiniband **
1	134	2256	5553	177.8	63 DDR / 21 QDR
2	7	104	120	20.6	no
Totals	*141*	*2250*	*5673*	*198.4*	*84 nodes*

*Nodes include compute nodes only. The (2) Login and (11) Storage servers are extra.
**All clusters have Gigabit Ethernet. Infiniband speeds are 20 Gbps (DDR) and 40 Gbps (QDR)

GPU Computing:

In addition to the CPU cluster nodes, we are adding rackmount servers to house several Graphics Processing Units "GPUs", which can be used for speeding up scientific computations. Currently available GPUs consist of two nVidia Geforce GTX 680 cards, eight nVidia Geforce GTX 690 cards, two GTX Titan cards, 32 nVidia GTX 780Ti cards, six nVidia GTX Titan Black cards, three nVidia Tesla M2090 cards and three Tesla K20 cards. There are also 7 GPU workstations with cards varying between GTX 480 and 780Ti. Six are Linux and one is Windows, all use nVidia CUDA software development kit (SDK). Software such as NAMD and Amber already support running on GPU hardware.

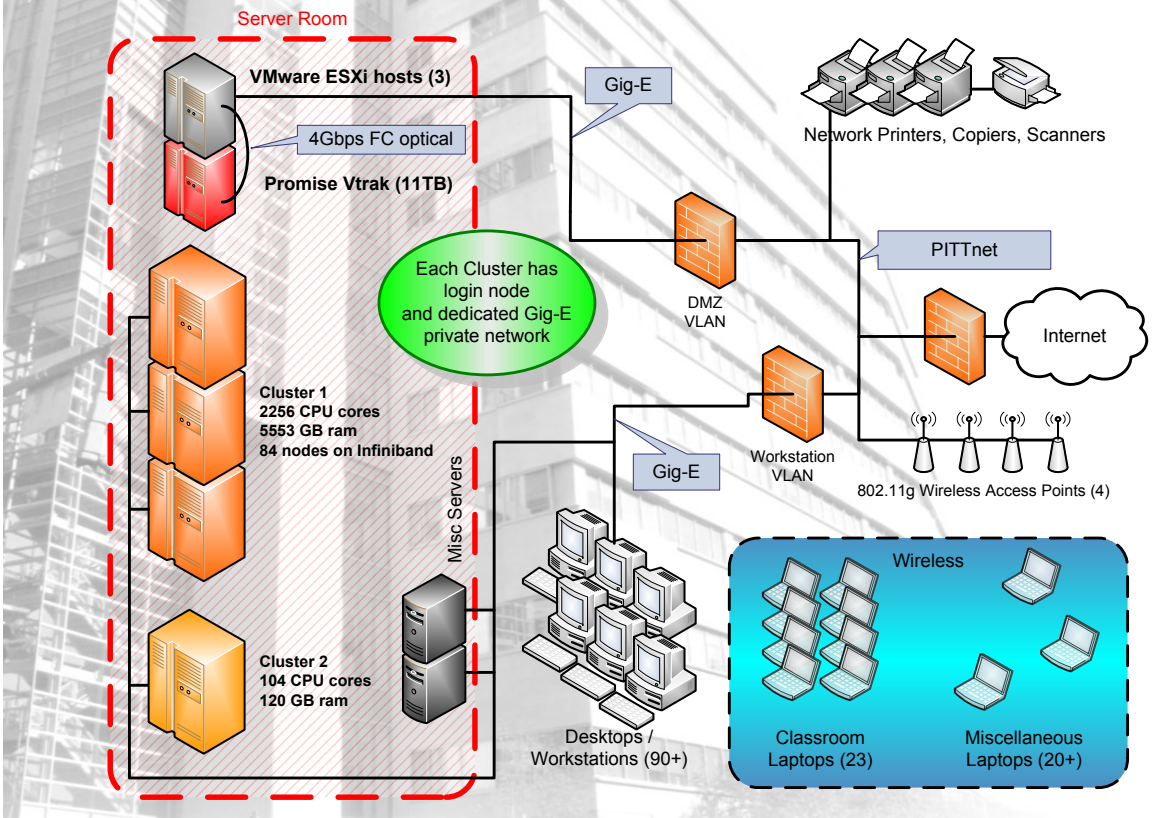
Application Servers:

The department has a VMware vSphere 5 cluster for running multiple application servers on 3 ESXi hosts configured for N+1 High-Availability with a vCenter server managing all three. The ESXi hosts each consist of dual 6-core Opterons with 32GB of ram. The Virtual Machines are stored on a fully redundant fibre-channel attached Promise vTrak enterprise storage array configured with both SATA and SAS drives for reliability and increased performance when needed. The virtualized environment provides for high-availability with no single point of failure.

The department also uses a number of Windows and Linux servers for sharing files, printers, and other domain functions. These servers also host several research software tools including Midas, VMD, GNM, ANM, and several network accessible databases of biological research data.

Storage:

88+TB full-redundant network attached storage (NAS). 11TB redundant Fibre-Channel (FC) array for Vmware servers. 3TB of FC-attached storage for Windows servers. Linux NAS, 17.3TB, for backing up linux workstations over the network. 18TB Network backup server for cluster data.



University of Pittsburgh School of Medicine - FY 2015 Budget

Computational & Systems Biology	School of Medicine Accounts
Revenue:	
School of Medicine ECU Allocation	$ 165,774
School of Medicine Other Support	$ 4,591,824
SVC Support	$ 269,000
Grant Revenues	$ 6,305,421
Interest Income	$ 1,988
Endowment Income	$ 84,948
Other University Support	$ 20,939
Total Revenue	$ 11,439,894
Expenses:	
Medical School Faculty Salaries	$ 2,023,796
Staff	$ 590,866
Research Associates	$ 833,583
GSA/GSR/TA/TF	$ 508,118
Fellows, Students (taxable)	$ 36,663
Fellows, Students (non-taxable)	$ 663
Fringe Benefits	$ 1,281,999
Subtotal Compensation	$ 5,275,688
Supplies and Minor Equipment	$ 504,523
Capital Equip. & Renovations	$ 1,376,967
Travel and Business	$ 193,850
Professional Services	$ 70,333
Rent (if **not** incl. in stepdown)	$ 19,388
Financial Aid	$ -
Other Expenses	$ 1,605,882
Overhead (incl.stepdown)	$ 1,899,333
Transfers (Pitt sub 8260 only)	$ 476,185
Subtotal Other Expenses	$ 6,146,461
Total Expenses	$ 11,422,149
Surplus/(Deficit)	$ 17,745
Restricted Balance as of 6/30/14	$ 186,829
University Endowment as of 6/30/14	$ 2,137,893