Computational and Systems Biology – Who We Are

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 enabled us to tackle more research at an integrated, Systems level. The post-genomic and big data era has brought a new excitement to science. With this excitement also comes 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. Concomitantly, 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.

A Brief History

Computational biology was established as a research discipline at the University of Pittsburgh with the vision of the Senior Vice Chancellor, Dr. Arthur S. Levine, who recruited Dr. Bahar to create a new Center for Computational Biology and Bioinformatics in March 2001, which soon became a highly visible center. The creation of the Department of Computational Biology within the School of Medicine followed in October 2004. Built on the premise of the founding Center for Computational Biology and Bioinformatics, the department was created with Dr. Ivet Bahar as the Founding Chair, to establish a home uniquely welcoming to highly interdisciplinary faculty, and to firmly establish the University of Pittsburgh in a nationally recognized leadership role in a field of tremendous growth and excitement. The department name was changed to Department of Computational and Systems Biology in 2009, to reflect the expansion in research and educational goals and activities of the department.

In 2019, the contributions of our Faculty were highlighted by various awards and promotions. Within our department: Dr. Ivet Bahar received the Kadir Has Outstanding Achievement award in Turkey; Dr. Nathan Clark was promoted to Associate Professor with Tenure and received the 2019 Chancellor’s Distinguished Research Award; Anne-Ruxandra Carvunis was awarded 2018 Searle Scholar award; received the 2018 Trailblazer Award from the Ladies Hospital Aid Society and was selected for the Senior Vice Chancellor’s Research Seminar, presenting “Proto-genes and De Novo Gene Birth”; Dr. S. Chakra Chenubhotla and Dr. Lans Taylor launch a Healthcare startup “SpIntellx”, a Computational Pathology company; Dr. John K. Vries retired from the University and has Emeritus Status; Nicole Munne, Discobio Alumna was selected Regeneron Science Talent Search Scholar; DISCOBio Alumna Isha Das wins the 2019 NCWIT Award; Jocelyn Sunseri, Graduate Student Researcher received Phase-I MolSSI Software Fellowship as well as the NVIDIA GPU Award; Dr. Jacob Stewart-Ornstein from Harvard Medical School joined the department as an Assistant Professor in the Tenure Stream. As a member of the Genome Stability Program at the Hillman Cancer Center, Dr. Stewart-Ornstein will pursue his elegant work on p53 regulation, stress signaling and network biology. Additionally, Dr. Harinder Singh of Cincinnati Children’s Hospital Medical Center joined the Department of immunology as the Director of the Systems Immunology Institute (CSI). The leadership of CSB has been actively involved in developing the ideas as well as recruiting Dr. Singh and they will play key statutory roles in leading and governing the CSI, the specifics of which will be developed in collaboration...
upon Dr. Singh’s arrival. 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.

**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 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 that are beyond the reach of traditional approaches.

**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 21 students who joined the program in Fall 2019, the program has a total of 77 students, of which 34 are domestic. About 36% of our students are female. Through aggressive recruiting efforts and wide dissemination of program information, CPCB expects to steadily increase enrollment each year. In FY20, the following activities are planned: Creation and distribution of a more dynamic 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; further updates and improvements to program website; social networking. In FY 20, we anticipate that 5-6 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 was renewed in August 2019 (PIs: James Faeder, Russell Schwartz, Ivet Bahar and Ziv Bar-Joseph) and supports 6 students each year.

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. Panayiotis Benos is acting as Associate Director of a new interdisciplinary program, Integrated Systems Biology (ISB), led by the Developmental Biology Department. Other programs include the Interdisciplinary Biomedical Graduate Program, Molecular Biophysics + Structural Biology Graduate Program, Biomedical Informatics Training Program, Human Genetics Ph.D. Program, and Physics Ph.D. Program. In FY19 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. Today our application pool has sky-rocketed to over 300 applicants per year. Our applicants are always a very diverse group who come 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 (together these groups compose over 85% of our participants). In 2012 and 2016, we submitted and obtained 4-year renewals of our TECBio program. The first renewal received one of the top scores in the review process and thus the Department of Defense co-sponsored that period of our program. With the TECBio REU program, we look forward to continuing our traditions of undergraduate mentoring and training to inspire and prepare 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 (UPCI) High School Academy (now called the UPMC Hillman 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 latter new program, which is now called the Computational Biology (CompBio) Research 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, “bootcamps” for computational and experimental research, 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
are 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 CompBio program are 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.

**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.

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 CompBio Academy program also uses the classroom for their didactic activities and also as a place for the students to work on their research projects. Throughout FY19, 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.
The Four Distinct Research Areas in Computational and Systems Biology

**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.
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.

**CELL AND SYSTEMS BIOLOGY**

**BIOINFORMATICS AND COMPUTATIONAL GENOMICS AND PROTEOMICS**

**MOLECULAR STRUCTURAL BIOLOGY**

**PHARMACOLOGY AND DRUG DISCOVERY**

*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 polypharmacological 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.
The Bahar lab 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. Our lab major focus is to bridge between structure and function, by modeling and establishing molecular systems dynamics.

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; An extremely interesting observation made in our studies of structural dynamics in the last decade is the close correlation between the conformational fluctuations that are predicted to be most easily accessible under native state conditions and the structural changes experimentally observed in different functional forms of a given protein.

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. In the post-genomic era, it has become increasingly important to develop efficient analytical techniques to assess structure and function from sequence information. We developed several sequence-based methods and servers to this aim. Yet, it is widely recognized that we need information beyond sequence and even structure to gain insights into the machinery of biomolecules. Our goal is to systematically explore and establish the link between sequence patterns and covariance, as well as structural and functional dynamics.

IV. **Computer-aided drug discovery at both molecular and systems levels**, i.e. development of novel models and methods for efficient characterization of protein-ligand interaction geometry and energetics, for identifying new protein-drug associations and for drug repurposing. Our lab utilizes quantitative systems pharmacology (QSP) and computational modeling methods, structure-based docking analyses, druggability simulations, pharmacophore modeling, and virtual screening to elucidate the mechanisms of protein-drug interactions at the molecular and cellular systems level and help discover new drugs.

V. **Systems Biology methods and applications**, 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, simulations of microphysiological events using images from cryo-electron microscopy and tomography that are reconstructed in silico to mimic the cellular environment, with applications to neurobiological systems, and to complex events like cell signaling, autophagy, or programmed cell death.

The Bahar lab has worked on research pertaining to the following NIH-funded grants throughout the past year:

1) **High Performance Computing for Multiscale Modeling of Biological Systems (MMBioS)** (Project #1 P41 GM103712-07) (NIH-National Institute of General Medical Sciences) (2012-2019; PI: Bahar): MMBioS is Biomedical Technology and Research Resource (BTRR) organized as a joint effort between the University of Pittsburgh (Pitt; lead institution), Carnegie Mellon University (CMU), the Pittsburgh Supercomputing Center (PSC), and the Salk Institute for Biological Studies (Salk). We continue to develop computational methods and usable software tools to advance research and training at the interface between computing technology and life sciences. Our biological theme remains: realistic and efficient modeling, analysis and simulations of molecular and cellular structure and dynamics toward understanding and predicting the origin and mechanism of biological function/dysfunction at multiple scales, with focus on synaptic signaling and regulation events, thus facilitating the discovery of new treatments against nervous and immune systems’ disorders. We are expanding our efforts in structural biology, cellular microphysiology and largescale bioimage analysis toward developing more powerful tools and an integrated platform for efficient implementation and use of our technology. We have increased the scope and number of our
Technology Research and Development Projects from 3 to 4, to advance and enable the adaptation of molecular modeling (TR&D1), cell modeling (TR&D2), (cellular) network modeling (TR&D3), and image-derived modeling (TR&D4) methods and software to new challenges using structural data at multiple scale. These are driven by seven Driving Biomedical Projects (DBPs) on: the dynamics of neurotransmitter transporters at both molecular and cellular levels (DBP1; NIH and U of Florida); regulation and binding to PSD-95 and its relation to CAMKII signaling and AMPAR trafficking (DBP2; Caltech), multiscale modeling of dopamine transporter function (DBP3; Pitt); spatiotemporal modeling of T cell signaling (DBP4; Bristol, UK); constructing a dynamic, spatial map of transcription and chromatin structure (DBP6; NIH); structure and function of synapses (DBP7; UT Austin); and scalable approaches to modeling using large sets of rules and images (DBP8; Harvard). Previous DBP5 (Allen Brain Institute) on functional connectomics has been successfully completed. We continue our vigorous training and dissemination programs, and a broad range of Collaboration of Service Projects (C&SPs), taking advantage of the unique experience and capabilities of the PSC, the strengths of the Departments of Computational and Systems Biology (Pitt) and Computational Biology (CMU), and cutting-edge research at the Computational Neurobiology Laboratory at Salk.

Recent studies have drawn attention to the evolution of protein dynamics, in addition to sequence and structure, based on the premise structure-encodes-dynamics-encodes-function. We therefore introduced, **SignDy**, an integrated pipeline for evaluating the signature dynamics of families based on elastic network models (Fig 1), which allows for dynamics-based categorization as a new layer of information relevant to distinctive mechanisms of action of subfamilies, beyond sequence or structural classifications.

![SignDy workflow](image.png)

**Fig 1: SignDy workflow.** The workflow is separated into two main parts: dataset preparation (left; steps 1-3) and SignDy operations and outputs (right; steps 4-7). Cylinders and light grey rectangular boxes represent databases and corresponding query inputs, respectively. Details see Zhang et al *Mol Biol & Evol* (2019).

2) **Computational Systems Pharmacology Core (Project # U19 AI068021-13, 5086) (NIH National Institute of Allergy and Infectious Diseases) (2005-2018; PI: Greenberger; Bahar):** The University of Pittsburgh CMCR proposes a “paradigm-shifting” approach to administer a series of new highly effective small molecule radiation mitigators, each with a different mechanism of action, and each delivered by novel topical biodegradable microneedle arrays. The Bahar lab leads the Computational Systems Pharmacology Core of the Center Grant “Mitochondrial targeted small molecule radiation mitigators” led by Dr. Greenberger, funded by National Institute of Allergy and Infectious Diseases, and determines efficient sequenced times of delivery of radiation mitigators based on each mechanistic step in the total body irradiation response. The Computational Systems Pharmacology Core will support the activities of the CMCR with the help of computational pharmacology and systems modeling tools applied to the cellular systems and molecular targets that are being investigated by the four Projects. The specific aims of the Core are the following: (1) Constructing and analyzing computational models for quantitative assessment...
of the time evolution of the protein-protein interactions that underlie radiation-induced apoptosis, necroptosis, and inflammatory responses; (2) Predicting and optimizing small molecules that can serve as radiomitigators, including repurposable drugs, for selected targets, using a combination of machine learning and chemoinformatics approaches; and (3) Designing polypharmacological strategies and/or combination therapies and identifying the optimal timings for effective intervention protocols. We will also continue to utilize advantageously the methods and software that have been developed and used in the previous funding term, including in particular our server for estimating repurposable drugs and side effects. The Core will take advantage of the computational resources at the Department of Computational & Systems Biology at the University of Pittsburgh, School of Medicine to provide an integrative framework that will help build or prioritize new strategies and assist in accelerating the research activities of the four Projects.

In a recent work (Wenzel et al, Cell 2017), we discovered that the PEBP1-15LOX complex represents a new drug target for ferroptosis-related diseases. In collaboration with Kagan and Bayir labs, we have continued to extend the computational studies on LOX superfamily members. Using multiple computational tools, developed in Bahar Lab, we showed how structural, sequence and dynamical differences in the LOX superfamily members, manifests as substrate specificity and/or plays a major role in allosterry. Comparative analysis of sequences (Fig 2) distinguished two clusters among human LOXs (i) LOX15 and LOX12 (ii) LOX15B and LOX5. Surprisingly, although LOX15 and LOX15B have similar 3D structures, cross-correlation and effectors, they differ in perturbation response scanning, forming a separate cluster (Fig 2D).

Fig 2. Comparison of different features for LOX family members. Features include comparison of: (A) sequence, (B) structure (RMSD), (C) cross-correlation, (D) perturbation response scanning (PRS), (E) sensitivity, (F) effectiveness; which are displayed as a matrix and tree of life. Colors of bars on the top of the matrices and colors of the branches corresponds to following members of LOX family: green - Manganese lipoxygenase (F2QXM5, MNLOX), violet - Arachidonate 15-lipoxygenase (LOX15, 15LO1) and Arachidonate 12-lipoxygenase (LOX12), cyan - Arachidonate 5-lipoxygenase (LOX5) and Arachidonate 15-lipoxygenase B (LX15B/15LO2, pointed by blue arrow), black - Allene oxide synthase-lipoxygenase protein (AOSL) and 11R-lipoxygenase (Q2N410), red - Seed linoleate 13S-lipoxygenase-1 (LOX1) and Seed linoleate 9S-lipoxygenase-3 (LOX3), blue - Linoleate 9/13-lipoxygenase (LOX), Arachidonate 15-lipoxygenase (LOXA) and Arachidonate 15-lipoxygenase (B7JX99). Details see Mikulska-Ruminska et al. J Chem Inf Model (2019).

3) Data Science Research (Project #3 U54 HG008540-05, 6985) (NIH-National Human Genome Research Institute) (2018-2019; PI: Cooper, Bahar, Berg): A partnership of the University of Pittsburgh (Pitt), Carnegie Mellon University (CMU), Pittsburgh Supercomputing Center (PSC), and Yale University, the Center for Causal Discovery (CCD) is working to develop, implement, and evaluate an integrated set of tools that support causal modeling and discovery (CMD) of biomedical knowledge from very large and complex biomedical data. CCMD Goal 1, is to develop and provide algorithms and easy-to-apply tools for CMD that will significantly advance progress in biomedical science. Our goal is to make CMD computational approaches accessible and useful to a wide variety of biomedical researchers, data analysts, and data scientists, who might not otherwise take advantage of them. We are using large, complex data from 3 driving biomedical problems (DBPs) to drive the development of our tools and methods. Our domain scientists working on these DBPs are working closely with the data scientists working to improve the analytic methods, both individually and as part of monthly all-hands meetings. In addition, new discoveries
made in each of these research domains, the larger and longer-term impact will result from the development of the methods, which will generalize to the full spectrum of biomedical research. Our goal 2, is to train target constituencies about the concept, development, and application of CMD methods and tools. Our training goal is to advance the development and use of CMD in accordance with the target constituency. For data scientists, our goal is to teach them to contribute to the development of new algorithms and software using CMD to answer biomedical questions with Big Data. For biomedical investigators, our goal is to train them to plan and conduct CMD analyses of large complex datasets and to collaborate effectively with data scientists, thus enabling the use of CMD approaches and the further advancement of these methods. For software users (who may be data scientists or biomedical investigators, from academia or industry), our goal is to train them to efficiently master use of Center products and quickly apply CMD tools to Big Data problems. We are customizing our education and outreach according to career stage (graduate student, postdoctoral trainee, early-stage investigator, established investigator) and context (academia, industry, government) as well as training location (Pittsburgh, conferences, online). We will use qualitative and quantitative evaluation methods to improve and extend our educational programs to meet the specific needs of each constituency.

We have introduced a new machine learning method that demonstrated for the first time the significance of protein dynamics in determining the pathogenicity of missense variants (Ponzoni and Bahar, *PNAS* 2018). We recently presented a significant extension that integrates coevolutionary data from Pfam database and we also introduced a new interface (Rhapsody) that enables fully automated assessment of pathogenicity. Benchmarked against a dataset of about 20,000 annotated variants, the methodology is shown to outperform well-established and/or advanced prediction tools. The tool is now made available both as a new webtool (rhapsody.csb.pitt.edu) and an open source Python package.

**Fig 3. In silico saturation mutagenesis results for human H-Ras.** (A) The predicted pathogenicity probabilities for all possible SAVs in H-Ras computed by Rhapsody are shown as a heatmap with a color code ranging from red (deleterious) to blue (neutral). The corresponding residue-averaged pathogenicity profile is shown in red in the bottom panel, compared to analogous profiles from PolyPhen-2 (blue) and EVmutation (green) and from experimental fitness measures (grey). The two strips along the upper abscissa of the heatmaps display the secondary structure and solvent accessibility (SASA) along the sequence. (B) Residue pathogenicities displayed by color-coded ribbon diagrams for active (top panel) and inactive (middle panel) H-Ras. Red and blue colors indicate the regions with high and low propensities for pathogenicity, respectively. Details see Ponzoni et al. bioRxiv 2019.

4) Computational Pharmacology Core (Project #4 P01 DK096990-06A1, 7264) (NIH- National Institute of Diabetes and Digestive and Kidney Diseases) (2013-2019; PI: Perlmutter, Bahar): The Bahar lab is leading the Computational Systems Pharmacology Core of the NIDDK funded Program Project (P01) “New
Therapies for Liver Fibrosis and Hyperproliferation in Alpha1-AT Deficiency led by Dr. Perlmutter (PI). This program project will discover and test novel compounds as potential therapeutic agents, as well as test and discover signaling pathways as potential modifiers, of liver disease due to α1-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 computational biology and quantitative systems pharmacology (QSP) support and contribute to the research goals of the P01 in three major ways: identification of targets (proteins, pathways or networks) implicated in ATZ accumulation (Specific Aim 1); quantitative modeling and analysis of the cellular networks identified to be associated with ATZ elimination, and systematic interrogation of these networks to generate plausible hypotheses for (poly)pharmacological strategies (Specific Aim 2); and refinement of drug candidates discovered in the first term (e.g. glibenclamide and its analog G2, cyclodextrin family members, and selected agonists of mucolipins) and identification of new testable candidates (both repurposable drugs and new compounds) to assist in the design and development of mechanism-based ATD therapeutics (Specific Aim 3). In line with the progress and contributions made in the first term, we will analyze high-throughput/content (RNAi, EMS chemical mutagenesis, and small-molecule library screening) data collected by Project 2 and gene expression profile data of ATZ-expressing iPS cells (Project 3). Quantitative model construction and analyses will support Project 1 team to assess (i) the cell signaling and regulation mechanisms that predominantly determine the cell fate in response to the proteotoxic effect of ATZ accumulation, with focus on autophagic, proteostasis and calcium signaling pathways; (ii) the pathophysiological effects of sequence variants detected in cohort exome sequencing studies (in coordination with Project 3); (iii) optimal modifications of drug candidates to increase their potency, and particular combination therapies (e.g. prochlorperazine and amiodipine) that may act synergistically. In collaboration with Perlmutter and Silverman labs, we identified an analog of glibenclamide that can selectively enhance autophagic degradation of misfolded α1-antitrypsin Z protein using our computational systems pharmacology pipeline (Fig. 4).

Fig 4. Computational systems pharmacology pipeline identifies GLB as a potential repurposing candidate. Computational workflow of eight steps (1–8) customized to assess repurposable drugs against ATD using RNAi screening data (step 1). Specifically, we trained a discriminative logistic regression classifier to distinguish the modulators of ATZ accumulation (step 2–4). We compared the sequence of these genes to those of the known targets and identified three human orthologues that had significant sequence similarity to the known drug orthologues that had significant sequence similarity to the known drug targets (steps 5–7). Of these, we picked the highest confidence gene (step 8) and identified the drug that interacts with the least promiscuous human targets based on available data, leading to GLB. Details see Wang et al. PLoS ONE (2019).

5) NIDA Center of Excellence of Computational Drug Abuse Research (CDAR) (Project #5 P30 DS035778-05) (NIH-National Institute on Drug Abuse) (2014-2019; PI: Xie, Bahar, Xing): Recent years have seen a significant increase in the number of structurally characterized membrane proteins, including those implicated in drug abuse and addiction. CDAR has been established as a joint initiative between U of Pittsburgh and Carnegie Mellon University, to assist in accelerating DA research with the help of computational resources and tools. Bahar lab is leading the CB4DA (Core B), among the three Cores. Core B takes advantage of the rapidly accumulating structural data as well as advances in biocomputing technology to generate data, and develop, implement and disseminate software that will facilitate the discovery and development of structure-based computer-aided strategies against DA. Figure 7 illustrates...
the application to g-secretase. Core B enables easy access to computing resources and data, including tools for initiating and visualizing druggability or docking simulations. Access to software and tools maintained and updated by Core B benefit both DA researchers and the computer-aided drug discovery community.

In collaboration with Greger lab, we performed a systematic analysis of the druggability of two major iGluR subfamilies, using molecular dynamics simulations in the presence of drug-like molecules. We provided novel insights into iGluR NTD dynamics and identified druggable sites and permits the determination of pharmacophoric features towards novel iGluR modulators (Fig 5).

![Fig 5. Druggability Simulations, X-Ray Crystallography, and Pharmacophore model for AMPA receptor](image)

**Fig 5.** Druggability Simulations, X-Ray Crystallography, and Pharmacophore model for AMPA receptor (A) Druggability MD detecting a known ligand binding site of GluA2 LBD: Large balls are hot spots by probe molecules and their colors are different probes. They closely overlap with the experimentally observed positions of the allosteric modulators cyclothiazide (cyan balls/stick; from PDB ID: 1LBC) and (R, R)-2b (magenta balls/sticks; PDB ID: 4U5B). (B) Novel ligand binding site in GluA3 NTD. (top) Druggability MD probes are shown as spheres near the LL interfaces of the GluA3 NTD dimer. (middle) New crystal structure of the GluA3 NTD reveal new dimeric state, which is similar to the open dimer. (bottom) Number of contacts between probe molecules and residues at the LL interface are observed in the MD simulations. (C) Pharmacophore model in GluA3 NTD LL interface. Details see Lee et al *Structure* (2019).

6) Integrated, Interdisciplinary, Inter-University PhD Program Computational Biology (Project #6 T32 EB009403-10) (NIH-National Institute of Biomedical Imaging and Bioengineering) (2009-2019; PI: Schwartz, Bahar, Benos, Murphy): The practice of biomedical research has undergone dramatic changes in recent years, largely driven by new biotechnology for high-throughput data generation. These technologies include high-throughput methods for imaging, genetic sequencing, proteomics, structure determination, and numerous other tasks that now make it possible to finely characterize numerous aspects of living systems from the molecular to the organismal levels. These advances in biotechnology and the vast amounts of data they are producing have revolutionized biomedical research. They have also, however, created a pressing need for scientists capable of working in a field that is increasingly data-driven and dependent on advanced computational methods. In particular, modern biomedical research depends on a new breed of computationally and mathematically sophisticated researchers who can understand new biotechnologies, develop innovative mathematical models and computer algorithms needed to make sense of their data, and apply this knowledge to drive biological and medical advances. To do so, these researchers require a strong command of computational science, the biomedical applications on which they work, and the biological and physical sciences that inform them. The Carnegie Mellon University/University of Pittsburgh Ph.D. Program in Computational Biology (CPCB) was created to meet this need for training experts in computational biology. The program aims to prepare the future leaders of computational biology: research scientists with deep knowledge of computational theory, biological and physical sciences, and a
A growing body of specialized interdisciplinary knowledge at the intersection of these areas. To accomplish this, the program leverages the shared strengths of its two hosts institutions, collectively world leaders in computer science, engineering, and medical research with long track records of innovation in computational biology research and educational. The training program includes an innovative curriculum covering fundamentals of computational biology, broadly defined, and a large body of advanced elective coursework spanning four broad domains of computational biology research: bioimage informatics, cellular and systems modeling, computational genomics, and computational structural biology. Program students perform thesis research in any of numerous laboratories at the cutting edge of computational biology research. These primary components of coursework and thesis research are supplemented by numerous mechanisms to facilitate student success, promote professional development, encourage responsible conduct of research, and aid in recruiting and retaining underrepresented groups. The proposed program seeks to renew training support for a select subset of students in the broader CPCB graduate program. It will provide the most promising students with two years of research support, providing them added resources and flexibility to pursue the most innovative research directions and to aid in their development into future leaders of computational biology and biomedical research as a whole. Biomedical research has become a data-intensive field that depends on researchers with sophisticated knowledge of both computational and biomedical sciences. By training a core of exceptionally talented students in these skills, the proposed work will help advance numerous directions in improving medical treatment that now critically depend on computational innovation, such as medical image analysis, personalized and genomic medicine, and modern drug design.

**Awards**

- **The 2019 Kadir Has Outstanding Achievement Award**, Kadir Has University. Istanbul, Turkey. Award Recipient.

**Science**
- BMC Bioinformatics
- PLoS Computational Biology
- Current Opinion in Structural Biology
- Scientific Reports
- BBSRC
- PNAS
- Nature Methods
- Molecular Systems Biology.

**Peer-Review Activities**

Reviewer for:

**Review Boards**

1. NIH-NLM Biomedical Informatics, Library, and Data Sciences Review Committee (BILDS) Chartered Member of the Review Panel
2. European Research Council (ERC) Starting Grant Review PE5 Panel Member
3. The NIH Biotechnology Center for Macromolecular Modeling and Bioinformatics at The Beckman Institute
Institute, University of Illinois Urbana-Champaign External Advisory Board Member

4. External Advisory Board Member for NIH funded Biomedical Technology and Research Resource (BTRR) Center for Biomolecular NMR Data Processing and Analysis, 1P41-GM111135-01A1 (PI: Jeffrey C. Hoch, UConn). (2016-present)

5. The Biophysical Society Awards Committee Judge

Grant Reviews
National Institute of Health
1. November 15-16, 2018: Biomedical Informatics, Library, and Data Sciences (BILDS) Study Section, Bethesda, MD.
2. March 2019: BILDS Study Section
3. June 2019: BILDS Study Section
4. NIH NLM Biomedical Informatics, Library and Data Sciences Review Committee (BILDS) Chartered Member of Review Panel (2016-2020)

Committees
1. University of Pittsburgh Chancellor’s Distinguished Research Awards Selection Committee
2. 2019 Chair of the University of Pittsburgh Distinguished Faculty Committee
3. 2019 The University of Pittsburgh/Carnegie Mellon University Pittsburgh Supercomputing Center (PSC) Director Search Committee
4. 2018-2019 University of Pittsburgh, School of Medicine, Center for Systems Immunology Director and Faculty Search Committee
5. 2019 University of Pittsburgh Senior Vice Chancellor for the Health Sciences and John & Gertrude Petersen Dean of the School of Medicine Search Committee Member
6. 2018 17th European Conference on Computational Biology (ECCB) Program Committee and Symposium Chair
7. 2018-2019 University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center Co-director of the Faculty Search Committee

Editorial Boards
1. Associate Editor, Proteins: Structure, Function, and Bioinformatics (Wiley)
2. Editorial Board, Structure (Cell Press)
3. Editorial Board, Scientific Reports (Nature Publishing Group)
4. Editorial Board, Protein Science (Wiley-Blackwell)

Presentations at National or International Meetings

National Meetings

- **July 31-August 2, 2018**
  6th Annual iGluRetreat, jointly held with the Department of Chemistry of Carnegie Mellon University and the Department of Neuroscience of the University of Pittsburgh. Pittsburgh, PA. Invited Speaker.

- **October 6-8, 2018**

- **October 10, 2018**

- **November 8-10, 2018**
  Conference on Modeling of Protein Interactions (MPI). Lawrence, Kansas. Invited Speaker

- **November 15-16, 2018**

- **March 2-4, 2019**
  63rd Annual Meeting of the Biophysical Society, Symposium on Glutamate Receptors.
Baltimore, MD. Invited Speaker.

- **May 14, 2019**

- **May 13-17, 2019**
  Hands-on Workshop on Computational Biophysics Pittsburgh Supercomputing Center. Pittsburgh, PA. Instructor.

- **June 13-14, 2019**

**International Meetings**

- **September 8-12, 2018**
  17th European Conference in Computational Biology (ECCB) 2018. Athens, Greece. Symposium Chair, Session Organizer, and Invited Speaker.

- **September 12-14, 2018**

- **September 18-21, 2018**
  Inaugural International Transmembrane Transporter Society (ITTS) Symposium. Vienna, Austria. Session Organizer and Speaker.

- **October 15-17, 2018**

- **March 5-8, 2019**
  European Research Council (ERC) Starting Grant Panel Meeting. Brussels, Belgium. Panel Member.

- **March 20-26, 2019**
  The 2019 Kadir Has Outstanding Achievement Award, Kadir Has University. Istanbul, Turkey. Award Recipient.

- **March 31-April 5, 2019**

- **May 20-24, 2019**
  Jacques Monod Conference, Sciences biologiques Ecologie et Environnement, Ligand-gated ion channels from atomic structure to synaptic transmission. Roscoff, France. Invited Speaker.

- **June 3-7, 2019**
  European Research Council (ERC) Starting Grant Panel Meeting. Brussels, Belgium. Panel Member.

- **June 27-29, 2019**
  Izmir Statistical Physics Days Conference, Izmir University of Technology, Izmir, Turkey. Keynote Speaker.
### Collaborative Research Activities

**University-wide**

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| Valerian Kagan | Environmental and Occupational Health; Center for Free and Radical Antioxidant Health (CFRAH); Chemistry; Pharmacology; Chemical Biology; Radiation and Oncology; IM Sechenov Moscow State Medical University: Moscow, Russia | *Pseudomonas Aeruginosa* Utilizes Host Polysaturated Phosphatidylethanolamines to Trigger Theft-Ferroptosis in Bronchial Epithelium  
Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE PE to Ferroptotic Death Signals, HpETE-PE  
Iron Catalysts of Lipid Peroxidation in Ferroptosis: Regulated Enzymatic or Random Free Radical Reaction?  
Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE PE to Ferroptotic Death Signals, HpETE-PE |
| Hulya Bayir | Critical Care Medicine; Environmental and Occupational Health; Center for Free and Radical Antioxidant Health (CFRAH); Children’s Hospital of Pittsburgh, UPMC | *Pseudomonas Aeruginosa* Utilizes Host Polysaturated Phosphatidylethanolamines to Trigger Theft-Ferroptosis in Bronchial Epithelium  
Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE PE to Ferroptotic Death Signals, HpETE-PE  
Iron Catalysts of Lipid Peroxidation in Ferroptosis: Regulated Enzymatic or Random Free Radical Reaction? |
| Peng Yang; Dong Hu; Mert Gur | Pharmaceutical Sciences and Computational Genomics Screening Center; Pathology and Pediatrics; Computational and Systems Biology; Istanbul Technical Univ., Turkey | A Novel Small-molecule Antagonizes PRMT5-mediated KLF4 Methylation for Targeted Therapy |
| Joel S. Greenberger | Biostatistics; Radiation and Oncology; UPMC Hillman Cancer Center | *Pseudomonas Aeruginosa* Utilizes Host Polysaturated Phosphatidylethanolamines to Trigger Theft-Ferroptosis in Bronchial Epithelium  
CMCR  
Radioresistance of Serpinb3a-/- Mice and Derived Hematopoietic and Marrow Stromal Cell Lines |
| Yylia Y. Tyurina; Vladimir A. Tyurin | Environmental and Occupational Health; Center for Free Radical and Antioxidant Health (CFRAH) | *Pseudomonas Aeruginosa* Utilizes Host Polysaturated Phosphatidylethanolamines to Trigger Theft-Ferroptosis in Bronchial Epithelium  
Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE PE to Ferroptotic Death Signals, HpETE-PE  
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<td>Critical Care Medicine; Safar Center for Resuscitation Research/Center for Critical Care Nephrology; Children’s Neuroscience Institute; Center for Free Radical and Antioxidant Health (CFRAH); Environmental and Occupational Health; IM Sechenov Moscow State Medical Univ.; Biological Sciences</td>
<td>Empowerment of 15-Lipoxygenase Catalytic Competence in Selective Oxidation of Membrane ETE_PE to Ferroptotic Death Signals, HpETE-PE</td>
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<td>Jinning Zhao; Tamil S. Anthonymuthu; Alexander Kapralov</td>
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<td>Hong Wang; Simon Watkins; Joseph M. Pilewski; Rama K. Mallampalli; Claudette Marie St. Croix; Erkin Bayir; Catherine R. Armbruster; Hsiu-Chi Ting; Matthew R. Parsek; Yohei Doi; Janet S. Lee; Becca A. Filter; Jordan R. Gaston; Abiola F. Ogunsoila; Jennifer M. Bomberger</td>
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<td>Gaowei Mao; Haider H. Dar</td>
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<td>Sally E. Wenzel</td>
<td>Medicine-Allergy; Critical Care Medicine; Pulmonary Critical Care Medicine; Asthma Institute</td>
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<td>Panagiotis (Takis) V Benos; James R. Faeder; Ziv Bar-Joseph</td>
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| Hongying “Mary” Cheng and Bing Liu | Computational and Systems Biology                         | Quantitative Systems Pharmacological Analysis of Drugs of Abuse Reveals the Pleiotropy of Their Targets and the Effector Role of mTORC1  
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| Pemra Doruker                      | Computational and Systems Biology                         | NIDA Center of Excellence of Computational Drug Abuse Research (CDAR), NIH  
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<p>| Ramon Bataller, Argemi Ballbe, and Josepmaria Argemi | Gastroenterology, Hepatology, and Nutrition               | HNF4A                                                              |
| Jean-Pierre Vilardaga; Ieva Sutkeviciute | Pharmacology and Chemical Biology; Endocrine Unit at Massachusetts General Hospital &amp; Harvard Medical School | PTHR Receptor Complex                                                |
| Stephanie Thermozier; Xichen Zhang; Wen Hou; Renee Fisher; Michael W. Epperly; Hong Wang | Radiation Oncology, UPMC Hillman Cancer Center            | Radioresistance of Serpinb3a/-/- Mice and Derived Hemtopoietic and Marrow Stromal Cell Lines |</p>
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<td>Lei Shi</td>
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<td>Universidade de ABC, Brazil; Academia Sinica Institute of Molecular Biology, Taiwan</td>
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<td>Moshe Arditi</td>
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<td>Shoshana J. Wodak; Emanuele Paci; Nikolay V. Dokholyan; Igor N. Berezovsky; Amnon Horovitz; Jing Li; Vincent J. Hilser; John Karanicolas; Gerhard Stock; Peter Hamm; Roland H. Stote; Jerome Eberhardt; Yassmine Chebaro; Annick P. Dejaegere; Marco Cecchini; Jean-Pierre Changeux; Peter G. Bolhuis; Johelynne Vreeed; Pietro Facciol; Simone Orioli; Riccardo Ravasio; Matthieu Wyart; Le Yan; Carolina Brito; Paraskevi Gkeka; Ivan Rivalta; Giulia Palermo; J. Andrew McCammon; Joanna Paneck-Hofman; Rebecca C. Wade; Antonella Di Pizio; Masha Y. Niv; Ruth Nussinov; Chungjong Tsai; Hyunbum Jang; Dzmitry Padhorny; Dima Kozakov; Tom McLeish</td>
<td>VIB-VUB Centre for Struct. Biology, Belgium; University of Leeds; Univ. of North Carolina at Chapel Hill; Penn State Medical Center; National Univ. of Singapore; Weizmann Inst. of Science, Israel; Johns Hopkins; Fox Chase Cancer Center, Philadelphia; Inst. of Physics, Albert Ludwigs Univ., Germany; Univ. of Zurich, Switzerland; Institut de Genetique et de Biologie Moleculaire et Cellulaire (IGMBC), France; Institut de Chimie de Strasbourg, France; Insitit Pasteur &amp; College de France; van ‘t Hoff Institute for Molecular Sciences (HIMS), Univ. of Amsterdam; Universita di Trento and INFN-TIFPA, Italy; Ecole Polytechnique Federale de Lausanne, Switzerland; Univ. of California at Santa Barbara; Universidade Federal do Rio Grande do Sul, Brazil; Structure Design &amp; Informatics, Sanofi R&amp;D, France; Ecole Normale Superieure de Lyon, Univ. de Lyon, CNRS, France; University of California at San Diego and Riverside; Univ. of Warsaw, Poland; Heidelberg Univ., Germany; Univ. of Munich, Germany; The Hebrew Univ., Israel; National Cancer Institute; Tel Aviv Univ., Israel; Stony Brook Univ; Univ. of York, UK</td>
<td>Allostery in Its Many Disguises: from Theory to Applications</td>
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Dr. Ivet Bahar receives Kadir Has Outstanding Achievement Award in Turkey

The 15th Annual Kadir Has Awards were held on Friday, March 22nd in Istanbul, Turkey. Member of the Science Academy, Dr. Ivet Bahar, received the Kadir Has “Outstanding Achievement Award” for her contributions to the development of theoretical and computational models for explaining the functional dynamics of biomolecular systems as well as mentoring and teaching a new wave of scientists. She was presented with the award by the Chairman of the Board of Trustees of Kadir Has University, Mr. Nuri Has, the Kadir Has Foundation President, Mr. Can Has, and the President of Kadir Has University, Dr. Sondan Durukanoglu Feyiz.

The Kadir Has Awards seek to recognize the outstanding accomplishments that Turkish scientists have made at the national and international level and to promote people and institutions that have contributed to the development of society.

Drs. Mary Cheng and Ivet Bahar published in Nature Structural & Molecular Biology

Monoamine transporters: structure, intrinsic dynamics and allosteric regulation

Elucidation of the structural dynamics of monoamine transporters and their conformational landscape and transitions, as well as allosteric regulation mechanisms.

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 autoimmune 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 is 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 fruit fly 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.

Peeth: Mentoring/Outreach – Reaching out to and training the next generation of scientists is an important responsibility of the scientific community and a necessity if we are to continue to make progress towards our research goals. My efforts along these lines have focused on the graduate, undergraduate, and even high school level. In the joint CMU-Pitt Computational Biology (CPCB) graduate program, I am the Co-director of the Laboratory Methods for Computational Biologists Course (a core course in the program), the Co-Chair of the Professional Development Committee, and Co-Director of the CPCB MetaSchool, which is a professional development series that helps prepare our graduate students for success in graduate school and their future careers. Our department also hosts an NSF-funded Research Experiences for Undergraduates (REU) program called Training and Experimentation in Computational Biology (TECBio). The TECBio REU at Pitt program, for which I serve as PI and Program Director, provides a challenging graduate-level experience in computational biology to students from a host of different academic, geographic, and racial backgrounds. Lastly, at the high school level, I have founded and direct a summer research program in collaboration with the Hillman Cancer Center and the University of Pittsburgh Drug Discovery Institute called the Comp Bio Research Academy. This program provides students with a primary, mentored research experience plus didactic training and additional enrichment activities to prepare them for successful careers in science and medicine.

Peer-Review Activities

Committees
1. University of Pittsburgh Seed Project: Chancellor’s Seed Funding Awards 2019, Reviewer

Panels
1. National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP), Review Panelist
2. Research Experiences for Undergraduates (REU), Panel 3, Review Panelist.
Collaborative Research Activities

Intra-departmental

1. Chakra Chennubhotla, Ph.D. TECBio REU at the University of Pittsburgh; Univ. of Pittsburgh Masters Program on Computational Biomedicine and Biotechnology Co-Founding Director

2. David Koes, Ph.D.; Tim Lezon, Ph.D.; Mark Schurdak, Ph.D. University of Pittsburgh and Hillman Cancer Center Comp Bio Research Academy

3. Ivet Bahar, Ph.D.; James R. Faeder, Ph.D. National Center for Multiscale Modeling of Biological Systems (MMBioS); Univ. of Pittsburgh Masters Program on Computational Biomedicine and Biotechnology Co-Founding Director

4. Tim Lezon, Ph.D. Univ. of Pittsburgh Masters Program on Computational Biomedicine and Biotechnology Founding Program Director

External

1. Josh Kangas, Ph.D. (Carnegie Mellon University) CPCB MetaSchool and Laboratory Methods for Computational Biologists Course

2. Vera Procaccia, Ph.D. (Carnegie Mellon University) Laboratory Methods for Computational Biologists Course

3. Phillip Compeau, Ph.D. and Alex Ropelewski (Carnegie Mellon University and Pittsburgh Supercomputing Center) National Center for Multiscale Modeling of Biological Systems (MMBioS)

Presentations at National or International Meetings

National Meetings

1. April 2019

“Committee Service for REU Students” Poster Presentation, REU Principal Investigator Meeting. Arlington, VA.
Understanding the risk factors and molecular mechanisms that drive the onset or progression of a disease or phenotype is the key to begin developing personalized medicine strategies. The availability of complex, multi-modal, biomedical datasets can help towards this goal, but to do so we need algorithms that can efficiently integrate data collected from multiple sources and scales.

Our group is interested in investigating the effect of gene regulatory networks and genotype in chronic lung disease and cancer in combination with demographics, patient’s history, or clinical imaging data. We develop mathematical models and machine learning algorithms to perform integrative analyses of multiple, heterogeneous datasets, including -omics and clinical data.

**Disease mechanisms.** The Benos’ lab has developed innovative methods and tools to integrate various “omics” data with clinical information; and use them to identify risk factors and disease-specific networks. We were the first identify a microRNA (let-7d), whose silencing drives epithelial-to-mesenchymal transition (EMT), an important pathway for the development of cancer or pulmonary fibrosis (Pandit, Corcoran, et al., Am J Resp Crit Care Med, (2010) 182:220-229). We also identified an important SNP that affects microRNA-mediated regulation of the estrogen receptor pathway, which leads to increased risk of osteoporosis in women (Coronnello, et al., PLoS Comput Biol (2012) 8:e1002830). More recently, we used probabilistic graphical models (PGMs) to identify molecular microRNA expression signatures associated to melanoma progression (Villaruz, Huang, et al, Clin Epigenet, (2015) 7:58) and gene expression signatures associated to sensitivity to statins (cholesterol reducing drugs that reduce proliferation of tumor cells) (Raghu, et al, BBRC, (2018) 495: 659-665) and identify drugs that can be used in combination therapy against cancer (Abecassis, Sedgewick et al, Sci Rep (2019) 9:3309.) Dr. Benos’ laboratory has now expanded these methodologies to the analysis of single cell RNA-seq data. Their recent collaborative paper identified gene-gene interactions between and within cell types in idiopathic pulmonary fibrosis (Morse et al, Eur Respir J, (2019) in print.)

Machine learning methods for causal discovery and precision medicine. 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 we are using graphical models to represent biomedical information and we develop fast methods to infer network structure, which is indicative of causal relationships between clinical and other variables. An important aspect of the methodologies we develop is that they can learn causal inference graphs over mixed data types (continuous and discrete), which is a significant advance over previous methods and critical for integration of multi-modal biomedical and clinical data. Over the past few years, we developed graph modeling methods for mixed data (Sedgewick, et al, BMC Bioinf, (2016) 17(Suppl 5):175; Sedgewick et al, Bioinformatics, (2019) 35:1204-1212) and extended them to include latent confounders (Raghu, et al, Int J of Data Sci and Analytics, (2018) 6:33-45) and to incorporate prior information in the graph learning (Manatakis, Raghu, Benos, Bioinformatics, (2018) 34:i848-i856.) We have applied these methodologies to various clinical problems involving multi-modal data. In patients in the Intensive Care Unit (ICU), we identified microbiome taxa and blood biomarkers that are predictive of developing pneumonia (Kitsios, et al, Front Microbiol, (2018) 9:1413). In clinical and blood biomarker data from COPD patients, we identified risk factors for longitudinal lung function decline (Sedgewick et al, Bioinformatics, (2019) 35:1204-1212.) More importantly, we recently developed a lung
cancer scoring function that based on a clinical and two radiographic (low dose CT scan) variables can screen off 28% of people with benign nodules without risking cancer misdiagnosis (Raghu et al, Thorax, (2019) 74:643-649.) Given that 96% of the identified nodules found in high-risk population are benign, this finding has the potential of significantly reducing unnecessary follow up screenings for a significant number of benign cases.

**Peer-Review Activities**

**Grant Reviews**
1. National Institutes of Health (NIH) (01/2018), ZRG1 BCMB-N (50), NIH Director’s Pioneer Award Program, Stage 1 mail-in reviewer
2. National Institutes of Health (NIH) (02/2018), Biomedical Computing and Health Informatics (BCHI), panel member
3. National Institutes of Health (NIH) (03/2018), ZHD1 DSR-L (50) 1, panel member
4. National Institutes of Health (NIH) (04/2018), ZRG1 BST-H (02) M, Bioengineering sciences (teleconference), panel member
5. National Institutes of Health (NIH) (06/2018), Biomedical Computing and Health Informatics (BCHI), panel member
6. National Institutes of Health (NIH) (11/2018), ZHD1 DSR-L (55), Gyn-omics, panel member
7. National Institutes of Health (NIH) (12/2018), ZRG1 MOSS-R (70) R, NIH Director’s New Innovator Award Program, Stage 1 mail-in reviewer
8. National Institutes of Health (NIH) (2/2019), ZRG1 BCMB-N (50) R, NIH Director’s Pioneer Award Program, Stage 1 mail-in reviewer
9. National Institutes of Health (NIH) (2/2019), Modeling and Analysis of Biological Systems, (MABS), panel member
11. National Institutes of Health (NIH) (6/2019), ZDK1 GRB-S O4 R, Human Pancreas Analysis Program for Type -2 Diabetes (HPAP-T2D), panel member

**Collaborative Research Activities**
1. Systems Biology of Diffusion Impairment in HIV (with A. Morris, S. Chan)
2. Genomic Analysis of Tissue and Cellular Heterogeneity in IPF (with N. Kaminski/Yale)
3. Integrative Graphical Models For Large Multi-Modal Biomedical Data (with C. Glymour/CMU)
4. Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data (with D. Guhatkurta)

**Presentations at National or International Meetings**
Jeremy M. Berg, PhD, is associate senior vice chancellor for science strategy and planning, health sciences, and professor of computational and systems biology in Pitt’s School of Medicine. Berg works to advance the University’s position as a biomedical research leader. In July 2016, he was named editor-in-chief of Science magazine and the Science family of journals.

Berg was the founding director of Pitt’s Institute for Precision Medicine, which he oversaw from 2013–16. Launched by Pitt and UPMC, the institute applies genetics, genomics, and research in other areas to advance evidence-based medicine and treatments tailored to individual patients, often through genetics and DNA analysis.

Prior to his appointment at Pitt in 2011, Berg served as director of the National Institute of General Medical Sciences (NIGMS), one of the National Institutes of Health (NIH), where he oversaw a $2 billion budget supporting basic research across a wide range of areas, including cell biology, genetics, biological chemistry, bioinformatics, anesthesiology, wound healing, and critical care medicine. Before serving as NIGMS director, Berg directed the Institute for Basic Biomedical Sciences at Johns Hopkins University School of Medicine, where he was professor and director of the Department of Biophysics and Biophysical Chemistry.

Berg’s research into the structures and functions of biological molecules has elucidated how zinc-containing proteins bind to DNA or RNA and regulate gene activity. As a bioinorganic chemist, Berg investigates biomolecule interaction inside cells using experimental and computational methods.

Berg’s awards and honors include the American Chemical Society’s Public Service Award, the Distinguished Service Award from the Biophysical Society, and election to the National Academy of Medicine. He is a fellow of the American Association for the Advancement of Science and past president of the American Society for Biochemistry and Molecular Biology. Berg earned his BS and MS in chemistry at Stanford University, received his PhD in chemistry from Harvard University, and was a postdoctoral fellow in biophysics at Johns Hopkins.

**Peer-Review Activities**

I oversee peer review at six journals in my role as Editor-in-Chief of the Science family of journals:

- *Science*
- *Science Signaling*
- *Science Translational Medicine*
- *Science Advances*
- *Science Immunology*
- *Science Robotics*

**Collaborative Research Activities**

I collaborated with Wendie Berg, M.D., Ph.D. in the Department of Radiology at the University of Pittsburgh and Cindy Lee, M.D. from the NYU Langone Medical Center on analysis of data from the National Mammography Database.
Presentations and National and International Meetings

Presentation on "Open Access Publishing" at the Annual Meeting of the American Association for the Advancement of Science in Washington, D.C. in April, 2019

BERG NAMED EDITOR-IN-CHIEF OF SCIENCE

Starting July 1, 2016, Dr. Jeremy Berg will be the Editor-in-Chief of the Science family of journals.

He will be the 20th Editor-in-chief since the journal’s inception in 1880 and will serve a 5-year term.

He will continue to hold his roles at the University as associate senior vice chancellor for science strategy and planning, health sciences, and professor of computational and systems biology in Pitt’s School of Medicine.

Congratulations, Jeremy!
Dr. Camacho’s research continues to have a significant impact in several areas related to the biophysics of proteins and their interactions, as well as in the development of original computational solutions to complex biological problems. He has published more than 85 peer-reviewed articles, with a h-index of 40. Of note, Dr. Camacho is first, last or corresponding author of his 19 most cited papers, and in 34 out of the 40 publications included in his h-index. Moreover, the number of citations to his papers is at a record high and growing, testifying to the fact that he is at the peak of his career. Key ongoing projects are itemized below.

Specific research projects include:
Over the last five years, Dr. Camacho’s lab has developed cutting edge virtual screening technologies for drug discovery. The highly cited technologies incorporate key concepts of molecular recognition, like anchor residues, and novel computational algorithms to enable the interactive discovery and design of compounds for difficult pharmaceutical targets. The approach has been described as google-like searches of chemical space, since they allow for the screening of billions of compound conformations in just a few seconds. Concurrently, Camacho’s lab has developed the largest libraries of readily synthetizable bioactives small molecules to identify new chemical probes of protein function and potential early-stage novel therapies. These unique resources are widely available to the world in the form of open access webservers or open source code hosted by Dr. Camacho’s server. These efforts have led to the successful discovery of a significant number of first-in-class compounds in different therapeutic areas. Some of these efforts include: NO pathway (Patent; Dr. Straub); cystic fibrosis (Dr. Brodsky); neuron protection (Patent; Dr. Aizenman); inflammation (Patent; Dr. Lee); cancer invasion and metastasis (Dr. Finn); glioblastoma (Dr. Sobol); Ovarian/AML/Lung cancer (Dr. Gartel); Pain (Dr. Khanna).

The lab is also working towards new ways to understand how small molecules perturb gene expression in normal and disease cells as one of the most important goals of systems biology. To advance towards this goal, we developed a novel method that integrates gene expression profiles from gene knockdown and drug treatment experiments and an orthogonal structure-based screen to detect correlations that signal physical drug-target interactions. We delineate the role of small molecules in perturbing protein networks by capturing direct correlations between drug- and target knockdown-induced expression profiles as well as indirect correlations with knockdowns of genes up/downstream of the actual target. Our findings could accelerate drug discovery by assessing the impact of promising bioactive chemistries in modulating gene expression for novel therapeutic targets.

Protein dynamics is also a subject that the lab devotes significant efforts. Many eukaryotic regulatory proteins adopt distinct bound and unbound conformations, and use this structural flexibility to bind specifically to multiple partners. However, we lack an understanding of how an interface can select some ligands, but not others. The lab is working in developing new methodologies to understand this phenomenon. Recently, we presented a molecular dynamics approach to identify and quantitatively evaluate the interactions responsible for this selective promiscuity. We apply this approach to the anticancer target PD-1 and its ligands PD-L1 and PD-L2. We discover that while unbound PD-1 exhibits a hard-to -drug hydrophilic interface, conserved specific triggers encoded in the cognate ligands activate a promiscuous binding pathway that reveals a flexible hydrophobic binding cavity. Specificity is then established by additional contacts that stabilize the PD-1 cavity into distinct bound-like modes. Collectively, our studies provide insight into the structural basis and evolution of multiple binding partners, and also suggest a biophysical approach to exploit innate binding pathways to drug seemingly undruggable targets. We are extending these efforts to other proteins of interest in Schizophrenia, in which the Lab has been recently funded for a collaboration with Dr. Sweet.
Peer-Review Activities


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

Collaborative Research Activities

*University-wide*

- Ongoing collaborations: Dr. Sweet (Psychiatry); Dr. Brodsky (Biological Sciences); Dr. Nicotra (SOM); Dr. Finn (SOM); Dr. Aizenman (Neuro degenerative program); Dr. Lee (CSB); Dr. Wells (SOM).
What makes each species unique? Research in The Carvunis Lab aims at understanding the molecular mechanisms of evolutionary change and innovation. Our approach is to examine systems biology in the light of evolution and evolution in the light of systems biology.

**Systems biology** is the study of biological networks. The information contained in the genome of every living cell encodes a specific set of biomolecules (e.g. transcripts, proteins). These biomolecules interact with each other, with the genome and with the environment, forming intricate and dynamic networks that underlie all cellular processes. Biological networks define how organisms look and behave, whether they will die or thrive in different environments. Ultimately, biological networks influence the probability that genomic information will be propagated to the next generation. Thus studying networks will transform how we think about evolution.

**Evolution** is the process through which populations and species change over successive generations. We know a lot about how natural selection and random drift together govern the inheritance of genetic material. However, the mechanisms underpinning evolutionary innovation remain obscure. How do new genes appear? How do organisms adapt to changing environments? If biological networks performed their functions in the manner of predictable machines, they could not evolve. There must be organizational principles that make biological networks plastic and robust for evolutionary innovation to take place. We seek to discover what these principles are. Through this quest we hope to expand knowledge of how cells work and of how evolution works.

The research tools we rely on most are bioinformatics, yeast genetics and genomics. Generally though, we strive to foster an interdisciplinary and collaborative research environment where researchers can develop creative approaches to describe, engineer and predict the genetic and network-level determinants of species-specificity.

**Peer-Review Activities**

**Reviewer for:**
1. PloS One
2. PNAS
3. Nature Methods
4. Genome Research
5. Bioinformatics
6. Philosophical Transaction B

**Guest Editor:**
1. PloS Genetics

**Collaborative Research Activities**

**Inter-departmental**
1. Carlos Camacho, PhD.

**University-wide**
1. Joel Greenberger, MD (Radiology)
2. Allyson O'Donnell, PhD (Biology)
External

1. Aoife McLysaght, PhD (Smurfit Institute of Genetics, University of Dublin)
2. Trey Ideker, PhD (University of California at San Diego, USCD)
3. Nikolaos Vakirlis, PhD (Benaki Phytopathological Institute, Greece)
4. Ralph Keeling, PhD (University of California at San Diego, USCD)
5. Charisse (Crenshaw) Nartey, PhD (University of Texas at Dallas)

Presentations at National or International Meetings

International Meetings

- September 2018—Evolutionary Biology Meeting “Predicting the Evolution of Novel Genes”, Invited Speaker. Marseilles, France.
- July 2019—Society for Molecular Biology and Evolution Conference, “De novo Emergence of Adaptive Membrane Proteins from Thymine-rich Intergenic Regions”. Invited Speaker. Manchester, UK.

National Meetings

- June 2018—University of Pittsburgh School of Medicine Senior Vice Chancellor for the Health Sciences Research Seminar, “Proto-genes and de novo Gene Birth”, Invited Lecturer. Pittsburgh, PA.
- September 2018—The Ladies Hospital Aid Society Fire and Ice Gala, 2019 Trailblazer Award Recipient
- November 2018—Dupont Experimental Station Special Seminar, “The Adaptive Potential of Proto-genes”, Invited Lecturer. Wilmington, DE.
- November 2018—University of Pittsburgh Department of Biomedical Informatics Seminar Series, “Where Do Genes Come From?”, Speaker. Pittsburgh, PA.
I have a broad background in computational modeling, with expertise in atomic molecular dynamics, coarse-grained dynamics, elastic network modeling, kinetic modeling, and implementation of multiscale molecular modeling for biological applications. My research interest focuses on 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; iv) protein-lipid and lipid-lipid interactions; v) assembly/clustering of protein complex and their collective dynamics; and vi) phosphorylation of protein by kinase.

My current research focuses on the functional mechanism of sodium coupled neurotransmitter transporters, voltage-gated sodium and calcium channels, ATP-driven chaperone proteins, and PTEN-induced kinase 1 (PINK1). Sodium coupled neurotransmitter transporters are transmembrane proteins that are essential regulators of neurotransmission in the brain, and their malfunction is implicated in several neurological disorders. We have now made significant progress in understanding the complex machinery of these secondary transporters, the way they undergo cooperative structural changes between outward-facing and inward-facing states for transporting their substrate and sodium ions, while they also permit for chloride channeling (Cheng et al, eLife 6: e25850. 2017). Unraveling the molecular mechanism of the transporter function 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 (Cheng and Bahar, Biophys J 2013). 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 multiscale approaches that combine conventional molecular dynamics (MD), targeted MD, accelerated MD, and anisotropic network model (ANM) to investigate the binding properties and transport cycle of neurotransmitter:sodium symporter (NSS) family members LeuT (Cheng and Bahar, PLoS Comput Biol 2014) and human dopamine transporter (hDAT) (Cheng and Bahar, Structure 2015), permitting us to generate for the first time a first estimate of the energy landscape of hDAT (Cheng et al JPCB 2018). 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 (Cheng and Bahar, Nat Struct Mol Biol 2019). We adopt the kinetic scheme assessed from molecular modeling as input in cellular-based MCell simulations, together with fluorescence images of dopaminergic neurons, to study the effect of DAT spatial distributions and structural heterogeneities on the efficiency of DA reuptake (Kaya et al, eNeuro 2018). Our study highlights that realistic spatial descriptions are required to accurately assess the mechanism of DAT function.

Elucidation of the structural dynamics of monoamine transporters and their conformational landscape and transitions, as well as allosteric regulation mechanisms.

Peer-Review Activities

Scientific Reviewer for:
- The Journal of Chemical Theory and Computation
- Journal of Chemical Physics

Collaborative Research Activities

Intra-departmental
- Structures, intrinsic dynamics and allosteric regulations of monoamine transporters. Monoamine transporters (MATs) regulate neurotransmission by reuptake of dopamine, serotonin, and norepinephrine from extra-neuronal regions, thus maintaining neurotransmitter homeostasis. As targets of a wide range of compounds, including antidepressants, substances of abuse, and drugs for neuropsychiatric and neurodegenerative disorders, their mechanism of action and their modulation by small molecules have long been of broad interest. Recent advances in the structural characterization of dopamine and serotonin transporters have opened new way to structure-based modeling and simulations, which, together with experimental data, now provide a mechanistic understanding of their transport function and interactions. We are elucidating the structural dynamics of MATs, their conformational landscape as well as allosteric regulation mechanisms.


Ivet Bahar, Ph.D. (Chair and Distinguished Professor)

University-wide
- Oligomerization of dopamine transporter triggered by small molecules. We explored the trimerization of dopamine transporter (DAT) triggered by a furopyrimidine, AIM-100, using a combination of computational and biochemical methods, and single-molecule live-cell imaging assays. The study suggests the possibility of controlling dopamine transport upon altering the oligomerization state of DAT by small molecular binding, as a possible intervention strategy to modulate dopaminergic signaling. We continue to study the oligomerization of DAT by other small molecules.


Alexander Sorkin, Ph.D. (Cell Biology)
Molecular basis of the regulation of PINK1 neuroprotective activity by substrate proteins. We found that PINK1 binds and phosphorylates the catalytic subunit of PKA at T197 [PKA cat(pT197)], a site known to activate the PKA holoenzyme. PKA in turn phosphorylates p47 at a novel site (S176) to regulate dendritic complexity. Given that PINK1 physically interacts with both the PKA holoenzyme and the VCP-p47 complex to promote dendritic arborization, we propose that PINK1 scaffolds a novel PINK1-VCP-PKA-p47 signaling pathway to orchestrate dendritogenesis in neurons. These findings highlight an important mechanism by which proteins genetically implicated in Parkinson’s disease (PD; PINK1) and frontotemporal dementia (FTD; VCP) interact to support the health and maintenance of neuronal arbors. We continue to investigate the association network of PINK1-VCP-p47.

PINK1 interacts with VCP/p97 and activates PKA to promote NSFL1C/p47 phosphorylation and dendritic arborization in neurons. For details see the following reference:


Charleen Chu, Ph.D. (Neuropathology)

We are using a novel combination of strategic chemical synthesis (Wipf lab, Chemistry, U Pitt), VGCC mutagenesis and biophysical measurements of VGCC function (Meriney lab, neurology, U Pitt) and computational modeling (Bahar lab), to develop a model of Cav2 VGCC gating.

Stephen Meriney, Ph.D. (Neuroscience)
Peter Wipf, Ph.D. (Chemistry)

External

Susan Amara, Ph.D. (National Institute of Mental Health, Chief of Laboratory of Molecular and Cellular Neurobiology (LMCNI)) Molecular insights into the function of excitatory amino acid transporters (EAATs) and EAAT-associated anion channel gating mechanism.


Amy Newman, Ph.D. (National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) Acting Scientific Director) Molecular Insights into the atypical dopamine transporter inhibitors.
• Min Goo Lee, Ph.D. (Yonsei University College of Medicine, Korea) and David Whitcomb, M.D. Ph.D. (University of Pittsburgh Cell Biology, Molecular Physiology, and Human Genetics, UPMC)
  Molecular mechanisms of how [Cl\(^-\)]-sensitive kinases regulate CFTR anion selectivity, which will provide new insights into the regulation of the ion selectivity of CFTR and the pathogenesis of CFTR-related disorders.

• Daniel Khananshvili, Ph.D.; Liat van Dijk, Ph.D.; Moshe Giladi, Ph.D.; Bosmat Refaeli, Ph.D.; Reuben Hiller, Ph.D. (Tel-Aviv University, Sackler School of Medicine, Physiology and Pharmacology, Israel)
  Using ion exchange assay, H/D exchange data and molecular modeling, we identify key residues controlling bidirectional ion-movements in the sodium-calcium exchanger.
The research interests in my group span the areas of computational systems pathology, spatial tumor biology and molecular biophysics. My group tackles big data challenges emerging in the domains of digital pathology, molecular diagnostic imaging, genotype-phenotype correlative studies, and molecular biophysics. Here are some project descriptions:

### Computational Pathology: How does the appearance of a breast lesion evolve from benign to atypia to ductal carcinoma in situ to invasive?

~1.6 million breast biopsies are performed each year in the US, typically in response to suspicious radiographic findings. Histopathological review of these biopsies is used to identify ~600,000 of these biopsies as malignant. Benign lesions such as atypical ductal hyperplasia (ADH) when properly diagnosed are also treated like malignant lesions, which includes surgery. For example, ADH is found in 10% of the 1M+ benign biopsies and exemplifies diagnostic dilemmas faced by pathologists. Interestingly, benign breast lesions are an important source of disagreement and uncertainty (52% discordance on ADH diagnoses) for pathologists when evaluating breast core biopsies as part of multidisciplinary breast cancer screening programs. Diagnostic accuracy can decrease if the pathologist is not a breast pathology subspecialist. More importantly, inaccuracies in pathological assessments of breast core biopsies can lead to unnecessary surgical resections, missed diagnosis of malignancy and increased probability of medical malpractice litigation. ADH diagnosis must be reliable, as it confers significant consequences to the patient and an economic burden to healthcare delivery systems because of the potential of unnecessary surgeries and the required frequent screening of these patients. Thus, there is a significant need for methods to more accurately and efficiently identify the specific breast pathology in a patient. We are building appearance models of breast lesions from transmitted light images to understand the disease progression from benign to atypia to ductal carcinoma in situ to invasive.

### Spatial Tumor Biology: How is spatial intratumor heterogeneity correlated with disease progression?

The tumor microenvironment (TME) is a dynamic multidimensional ecosystem of spatially interacting cancer and non-cancer cells and is marked by genomic, epigenomic, transcriptomic, proteomic and cellular heterogeneity and intercellular communication. The prevalence of spatial intratumoral heterogeneity (ITH) and its correlation with clinical outcomes have defined an unmet need to deconvolve and exploit the complexity of the TME to determine the underpinnings of metastasis, the major cause of cancer mortality, and other landmarks of disease progression (i.e., tumorigenesis, immune evasion and resistance to therapy).

The recent explosion of next-generation, high-content, high-throughput spatial imaging technologies for intact tissues measuring protein expressions, DNA and RNA probes has attracted the interest of NIH and other international agencies in funding precision medicine efforts, including HTAN, IOTN, HuBMAP, Human Cell Atlas and Human Protein Atlas. To help propel translational discoveries and lay
foundations for precision medicine, we are building a comprehensive computational systems pathology (CSP) platform capable of integrating, visualizing and modeling high dimensional in situ imaging data, collected through HxIF, imaging mass spectrometry and other imaging methods that allow for a large array of cellular and subcellular probes. This platform will be capable of deciphering diverse molecular and cellular signaling networks supporting the reciprocal coevolution of malignant cells and their specific TME. http://ith.csb.pitt.edu

Computational Biophysics: Discerning Conformational Sub-states

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 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.
Peer-Review Activities

Scientific Reviewer for:
- Nature Communications
- PloS One; Bioinformatics
- Proteins
- Journal of Pathology Informatics
- RECOMB
- American Association for Artificial Intelligence (AAAI)
- International Conference on Image Processing (ICIP)

Study-section Activities:
- **June 2018**
  Member, NIH-NIGMS SCORE Study Section Review Meeting 2018/10 ZGM1 RCB-Y (SC)

- **November 1, 2018**
  Member, NIH-NCI Study Section Review Meeting ZCA1 SRB-C (J1) Cancer Systems Biology

- **November 7, 2018**
  Member, NIH-NCI Study Section Review Meeting ZCA1 SRB-5 (J1)

- **2018-2019**
  Emory University Tenure Faculty Application Review

Collaborative Research Activities

Intra-departmental
1. **Takis Benos, Ph.D.** (Vice-Chair) Co-analysis of Imaging Phenotypes and Genomic Signatures in the Lung DBP for the BD2K grant.
2. **D. Lansing Taylor, Ph.D.** (Director, UPDDI) Computational Pathology.

University-wide
1. **Jeffrey Fine, M.D.** (Pathology and UPMC Magee Women’s Research Institute) Computational Pathology.

External
1. **Naftali Kaminski, M.D.** (Yale) Co-analysis of Imaging Phenotypes and Genomic Signatures in the Lung DBP for the BD2K grant.
2. **Fiona Ginty, Ph.D.** (GE Global Research Center)
3. **Pratul Agarwal, Ph.D.** (Univ. of Tennessee); **Arvind Ramanathan, Ph.D.** (Argonne National Laboratory); **Christopher Stanley, Ph.D.** (Oak Ridge National Laboratory); **Nicolas Doucet, Ph.D.** (INRS-Quebec) Computational identification of functionally relevant biomolecular intermediates-bridging experimental timescales with atomistic details.

Presentations at National or International Meetings

National Meetings:
• **March 30, 2018**  
  Case Western University Image Computing Seminar Series, Invited Speaker. Cleveland, OH.  
  “**Spatial Statistics from Multiplexed Immunofluorescence Images: to Elucidate Tumor Microenvironment, to Characterize Intratumor Heterogeneity, and to Predict Metastatic Potential**”.

• **May 21, 2018**  
  “**Platform for Quantitative Evaluation of Spatial Intratumor Heterogeneity in Multiplexed Fluorescence Images**”.

• **May 23-24, 2018**  
  Informatics Tools for Cancer Research (ITCR) Annual PI Meeting, NIH, Speaker. Bethesda, MD.  
  “**THRIVE: Tumor Heterogeneity Research Interactive Visualization**”.

• **June 1, 2018**  
  Society for Imaging Informatics in Medicine (SIIM), Panel Member. Washington, DC.  
  “**Innovations in Pathology Informatics**”.

**International Meetings:**

• **September 2018**  
  “**Computational Systems Pathology and Machine Learning for Mechanistic Understanding of Cancer Metastasis**.”
My group works on variety of problems in computational genomics and our broad goal is to develop algorithms that take large and noisy data and transform them into meaningful representations that can be used for infer biological mechanisms. We particularly focus on two areas: functional genomic data and comparative genomics. In the realm of functional genomic data we develop algorithms that model the underlying data structure and maximize the utility of datasets by revealing hidden global patterns which are not apparent in the individual measurements. In comparative genomics we work on understanding how animal phenotypes influence the evolutionary pressure on specific sequence elements. Our analyses give insight into evolutionary-scale genotype-phenotype relationships, which are difficult to address experimentally.

**Peer-Review Activities**
- PlosOne
- Hepatology

**Collaborative Research Activities**

**Intra-departmental**
- Collaboration with Nathan Clarks’s group: correlating physical traits and molecular evolution in mammals

**University Wide**
- Mark Shlomchik’s group: data analysis for a project investigating B cell sub-types and germinal center dynamics.
- Dario Vignali’s group: data analysis for various projects investigating the role of T regulatory cells in cancer and autoimmunity.

**External**
- Ichran School of Medicine at Mount Sinai: investigating biomarkers for neurological disease.
Dr. Maria Chikina Receives DARPA Grant for WMD ECHO Detector

The Epigenetic CHaracterization and Observation (ECHO) program aims to diminish the threat posed by weapons of mass destruction (WMD). To do this, the program is building a man-portable device that analyzes an individual's epigenetic “fingerprint” to potentially reveal a detailed history of that individual’s exposure to WMD or their precursors. DARPA envisions that the same technology could provide rapid diagnostics for troops who may have been exposed to threat agents or who may be suffering from infections, providing a timely signal to apply effective medical countermeasures.

Dr. Maria Chikina

Dr. Stuart Sealfon
Juhn School of Medicine at Mount Sinai

Weiguang Mao and Dr. Maria Chikina Publish in Nature Methods

Pathway-level information extractor (PLIER): a new tool to quantify pathway level effects in gene expression data.

A major challenge in gene expression analysis is to accurately infer relevant biological insights, such as variation in cell-type proportion or pathway activity, from global gene expression studies. We present pathway-level information extractor (PLIER), a broadly applicable solution for this problem that outperforms available cell proportion inference algorithms and can automatically identify specific pathways that regulate gene expression. Our method improves interstudy replicability and reveals biological insights when applied to trans-eQTL (expression quantitative trait loci) identification.

Weiguang Mao
Dr. Maria Chikina

Currently my research studies focus on CRISPR-based gene knock-in for studying the dynamics of EMT, developing CRISPR based in vivo chromosome labeling techniques, and chromosome dynamics and conformational change during cell phenotypic conversion. They contain two parts:

(1) The epithelial-to-mesenchymal transition (EMT) is an important process and has attracted much attention recently. Time lapse live cell measurements of expression changes of EMT related proteins, such as E-cadherin, Vimentin, and Snail1, can provide mechanistic understanding on this process. Therefore, fusing the fluorescence protein (FP) with these EMT related proteins are very helpful to track their dynamics during EMT. CRISPR-based gene knock-in at endogenous sites is desirable in multiple fields such as quantitative studies of signal transduction pathways and gene regulation, synthetic biology, and disease modeling. Contrasting the knock-out procedure, a key step of CRISPR knock-in procedure relies on the homology-directed repair (HDR) process that requires a donor construct as a repair template. Thus, it is desirable to generate a series of donor DNA constructs efficiently and cost-effectively. In this project, we developed a general Gibson assembly procedure that combines strengths of the Modular Overlap-Directed Assembly with Linkers (MODAL) strategy and a restriction enzyme based hierarchical framework. This procedure also allows for fusing single guide RNAs (sgRNAs) to the constructs for enhanced homology-directed repair efficiency. The modularized procedure is simple, fast and cost-effective while making multiple constructs, and a computer package is provided for customized design.

(2) The CRISPRRainbow is a system to label chromosomes in live cells through combination of dCas9 (nuclease-dead Cas9) and sgRNA (single guide RNA) scaffolds which associated sets of fluorescent proteins. It has been shown that this system could be used in imaging six chromosomes and tracking their dynamics in cells. However, there are some potential problems in it. Currently we are working on improving and enhancing the image quality of DNA labeling. Next, we will apply this technique in labeling different players in the EMT regulatory network and chromosome mis-segregation in cells.
Collaborative Research Activities

(1) NIH R01 funding (obtained through Dr. Jianhua Xing, 2018-2023)
• Collaborators: Dr. Jianhua Xing (Department of Computational and Systems Biology), Dr. Shilpa Sant (Department of Pharmaceutical Sciences)

I developed the technique of CRISPR knock-in system and generated the several knock-in cell lines for investigating breast cancer progression in Dr. Sant’s lab. It helped Dr. Sant and Dr. Xing to obtain a NIH R01 funding.

(2) Charles E Kaufman Foundation (obtained through Dr. Jianhua Xing, 2018-2020)
• Collaborators: Dr. Jianhua Xing (Department of Computational and Systems Biology), Dr. Yang Liu (Department of Biomedical Informatics)

This project is about characterization of dynamic nanoscale chromatin reorganization during induced cell reprogramming and aims to use CRISPR-dCas9 based live cell imaging and super-resolution imaging to study how chromosome structures changeover time during cell reprogramming. Therefore, I developed a CRISPR labeling technique. This technique helped Dr. Xing to obtain the Kauffman foundation granting collaboration with Dr. Yang Liu.

(3) NIDDK R01 grant (obtained through Dr. Jianhua Xing, 2018-2023)
• Collaborators: Dr. Jianhua Xing (Department of Computational and Systems Biology), Dr. Simon Watkins (Department of Cell Biology)

This project is about the role of the Snail1-Twist-p21 axis on cell cycle arrest and renal fibrosis development and aims to use quantitative single cell imaging and mathematical modeling to study how cell cycle and epithelial-to-mesenchymal transition are coupled and regulated by the Snail1-Twist-p21 axis after acute kidney injury. Through the CRISPR labeling technique that I developed, it helped Dr. Xing and Dr. Watkins to obtain NIDDK R01 grant.

(4) Cancer Research collaboration
• Collaborators: Dr. Luhua Lai (College of Chemistry and Molecular Engineering, Peking University)

Protein Rel A is one of key regulators of immune, inflammatory and acute phase responses and are also implicated in the control of cell proliferation and apoptosis. However, the real regulating function and dynamics of Rel A in cell proliferation is unclear. I developed the technique of CRISPR knock-in system and generated the several knock-in constructs to help Dr. Lai’s lab to study RelA function during cell proliferation.

Presentations at National or International Meetings

National Meetings

Local Seminars:

Local Conferences:
1. CSI Research Forum, May, 2019
3. PGH Fly Meeting, University of Pittsburgh, Feb. 2013

International Conference
1. International Conference on Systems Biology (ICSB), Blacksburg, VA, Aug. 2017
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 to achieve adaptive phenotypes. We study a variety of organisms ranging from yeast to primates and use both computational and experimental approaches. A major theme in the Clark lab is to connect basic evolutionary biology to discoveries of broader impact in species conservation and medicine.

Specific Research Topics:

· Convergent evolution of mammals in novel environments, such as for aquatic and subterranean species:

When multiple independent species undergo the same evolutionary transition, it allows us to identify the genetic underpinnings of their newly evolved phenotypes. We develop software to identify the genes and regulatory regions that change, and then follow them up with functional validation in model organisms.

Our work in subterranean mammals was featured in eLife and has led to translational collaborations with Dr. Ken Nischal, a clinical scientist in the Eye and Ear Institute. This year we selected a pool of patients in which we will examine gene regulatory regions brought to our attention by studies of blind mammal species. The goal is to identify specific mutations causing human eye abnormalities.

· 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. This year we produced the most powerful ERC dataset to date by integrating the results from 5 different sets of species: mammals, vertebrates, insects, nematodes, and fungi. Using these ERC datasets we discovered new genes in 2 different genetic pathways controlling DNA repair and cellular adhesion. Those studies were just published in PLOS Genetics and PNAS.

“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.”

Peer-Review Activities

Dr. Clark has reviewed 13 manuscripts over the academic year, in journals such as PNAS, Genome Research, PLOS Genetics, and Molecular Biology and Evolution, Genome Biology and Evolution.

Collaborative Research Activities

1. The Clark lab has a close collaboration with Dr. Maria
Chikina’s lab, also in Computational and Systems Biology.

2. We also work with Dr. Ken Nischal, a clinical and research ophthalmologist at Children’s Hospital of Pittsburgh.

3. Drs. Clark and Nischal have published together in *eLife* and have received a grant to study the genetics of eye disease. We have also submitted multiple grant applications together that bridge between basic genomics research and clinical diagnosis of congenital eye diseases.

4. Dr. Clark also works with a large number of researchers through his ERC methods, which predict new genes in certain biological functions using patterns of gene evolution between species. Those collaborators can be found at Cornell University, Holy Cross, New York University, Duquesne and the University of Pittsburgh. At Pitt those collaborators are Allyson O’Donnell, Adam Kwaitkowski, Kiril Kiselyov, Jacob Durrant, and Kara Bernstein.

**Presentations at National or International Meetings**

**National Meetings**

1. Plenary address at the Biology of Spermatozoa. (Nynäshamn, Sweden)
2. Oral presentation for the Departments of Human Genetics and Biology at the University of Utah (Salt Lake City, Utah).
My research is focused on uncovering the structure-dynamics-function relationship in biomolecular systems with varying degrees of complexity, from relatively small enzymes all the way up to the supramolecular machinery like the ribosome. Coarse-grained models and simulation techniques become a necessity to handle such large-scale systems effectively. I am involved in the development of hybrid simulation techniques by integrating elastic network models (ENM), knowledge-based Monte Carlo simulations and/or molecular dynamics (MD) simulations (Kurkcuoglu et al., J Chem Theory Comput, 2016). Such techniques have enabled the simulation of conformational transitions and sampling for highly flexible proteins and large complexes, and also proven useful for protein-ligand docking applications (Kurkcuoglu and Doruker, PLOS One, 2016).

ENMs have served as essential tools in my research on functional dynamics of various biological systems, such as the enzyme triosephosphate isomerase (TIM) and the supramolecule ribosome (Kurkcuoglu et al, Biophys J, 2009, Can et al., PLOS One, 2017). We have previously shown that the vibrational dynamics based on collective, functional modes from ENMs are in conformity with the essential dynamics from MD simulations. Another important finding is that ENMs at high levels of coarse-graining can still provide consistent collective modes, which has indicated their utility for coarse-grained structural input from cryo-EM experiments. Recently, we developed a residue-based ENM, called RESPEC (Kaynak et al., J Phys Chem B, 2018), which can realistically model protein complexes in presence of atomistic ligands/inhibitors. As such, RESPEC can also form the link between ligand binding, vibrational dynamics and allostery in proteins (Kaynak and Doruker, J Chem Inf Model 2019).
Peer-Review Activities

Journals
1. Bioinformatics
2. PloS One
3. Journal of Structural Biology
4. Proteins
5. Journal of Chemical Information and Modeling

Collaborative Research Activities

Intra-departmental
1. **Ivet Bahar, Ph.D.** (Chair) Hybrid simulation techniques including ENMs are our focus for understanding the conformational dynamics and transitions of important biological systems, such as toroidal proteins and CamKII. We introduced the ClustENM (Kurkcuoglu et al., J Chem Theory Comput, 2016) algorithm to perform efficient ENM-based conformation sampling of proteins and supramolecules. We are currently assessing ClustENM in comparison with other available atomistic sampling techniques.

University-wide
1. **Jean-Pierre Vilardaga, Ph.D.** (Pharmacology) G-protein coupled receptors are one of the key receptors for drug design. We perform structure-based virtual screening of the parathyroid hormone (PTH) type 1 receptor (PTHR), which is a GPCR regulating blood levels of vitamin D, calcium and phosphate ions, and bone turnover.

External
1. **Guang Hu, Ph.D.** (Soochow University, China) We focus on the functional dynamics of toroidal systems, such as DNA-clamps using ENMs.
2. **Ana Ligia Scott, Ph.D.** (Universidade Federal do ABC, Brazil) We perform assessment of conformational sampling methods including hybrid approaches with classical normal mode analysis, ENM and MD simulations.
3. **Demet Akten, Ph.D.** (Kadir Has University, Turkey) We have previously studied the allosteric coupling between the extracellular and intracellular regions in β2- adrenergic receptor- a GPCR-using atomistic simulations. We were also interested in the possible implications of this allosteric mechanism for drug design (Dilcan et al., Chem Biol Drug Des, 2019).
Dr. Faeder’s 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. This approach allows construction of detailed models of intracellular signaling pathways based on available knowledge and data without making ad hoc assumptions required to limit the combinatorial explosion of species when such models are formulated using standard chemical kinetics approaches. Rules serve as generating functions for such networks and provide a tractable and concise representation of signaling systems. Dr. Faeder’s lab maintains and develops the software package BioNetGen, which is geared at making the rule-based modeling approach accessible to a wide range of scientists, including those with limited mathematical training.

Methods under development include improved model visualization capabilities for rule-based models, integration of rule-based and spatial simulation algorithms and tools, automatic inference of biochemical rules from reaction network models, and parameter estimation for models using Bayesian approaches to distinguish essential and non-essential model features. As part of the Center Multiscale Modeling of Biological Systems (MMBioS), the group is also working to integrate rule-based modeling with tools for performing spatially resolved simulations in order to develop accurate models of how the complex geometries of cells affect signaling dynamics. Novel visualization and simulation capabilities will be used in collaboration with researchers at Harvard Medical School to develop comprehensive network models of signal transduction that will be calibrated with high-throughput imaging data obtained through the LINCS project.

The lab’s 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. One collaboration involves developing models 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. Development of a detailed model of the network led to the identification of PTEN, a lipid phosphatase, as a critical regulator of the differentiation process, which led to the discovery of a novel mechanism for regulation of PTEN in T cells. The model also demonstrated that a positive feedback loop involving PTEN sets a threshold for the signaling strength and duration required for differentiation to form T helper cells, and experiments have confirmed the operation of this mechanism. Other systems being actively investigated include cytokine signaling in the immune system, multivalent receptor aggregation in T cell activation, inhibitory receptors in T cell signaling, and dopamine transport and signaling in the nervous system.

Finally, the lab has recently developed several collaborations directed toward the modeling and development of cancer therapies based on selective boosting of the immune response by targeting negative regulators. In collaboration with the Vignali lab in the Department of Immunology, the lab has developed a mechanistic model of
inhibition of T cell activation by LAG3, a protein expressed on the surface of T cells that have undergone prolonged stimulation. Although LAG3-based therapies are currently in clinical trials, the precise mechanism by which LAG3 inhibits immune responses remains unknown and could be critical to developing successful therapeutic strategies. The lab has also been part of a collaboration between the University of Pittsburgh Drug Discovery Institute and the pharmaceutical company Sanofi to develop a predictive model of immunotherapy targeted at Acute Myeloid Leukemia, which has a poor prognosis in part because tumors induce a high degree of immune suppression. As with all immunotherapies, effective therapy requires maintenance of an optimal degree of activation, because too much can be equally detrimental to the patient. Therefore, development of quantitative models to determine optimal dosing may be critical to the development of effective therapies.

Peer-Review Activities

Journals
1. Bioinformatics
2. Biology Direct
3. Biophysical Journal
4. BMC Informatics
5. JCO Clinical Cancer Informatics
6. Journal of Chemical Physics
7. Journal of the Royal Society Interface
8. Nature Communications
9. PLoS Computational Biology
10. Proceedings of the National Academy of Science (USA)
11. Science Advances
12. Science Signaling

Conference Reviewing
1. American Association of Immunologists (AAI) Intersect Postdoctoral Fellowship Review Panel. Rockville, MD. November 2018
2. National Science Centre Poland, OPUS funding scheme, Panel ST7. Headquarters of the National Science Centre, Krakow, Poland. May 2019.

Editorial Board
1. Named Associate Editor of PLoS Computational Biology, August 2019.

Committee Member

Collaborative Research Activities
1. Multiscale Modeling of Biological Systems (MMBioS) – An NIH P41-funded center to develop novel methods and software for simulation of biological systems. Dr. Faeder is leader of Project 3, Network Modeling, which develops software for simulation and analysis of dynamical cellular networks. This project involves close collaboration with researchers at the University of Pittsburgh, Pittsburgh Supercomputing Center, Carnegie Mellon University, and the Salk Institute and external collaborations with researchers at Harvard Medical School, Los Alamos National Laboratory, and the Icahn School of Medicine.
   • University of Pittsburgh: Ivet Bahar, Ph.D. (Chair Computational and Systems Biology, Lead PI, and Project 1 Co-leader); Joseph Ayoob, Ph.D. (Computational and Systems Biology/Training and Dissemination); Penelope Morel, Ph.D. (Immunology)
   • Carnegie Mellon University: Robert Murphy, Ph.D. (Chair, Computational and Systems Biology, Lead PI)
2. Modeling of T cell differentiation. This is an ongoing collaboration with Dr. Morel to model peripheral T cell differentiation in response to antigen stimulation. This project was led to joint publications that have been published in *Science Signaling* and *The Journal of Immunology* (Cutting Edge).
   - *University of Pittsburgh*: Penelope Morel, Ph.D. (Immunology)

3. High-performance weighted ensemble software for simulation of complex bio-events. This collaboration with Dr. Zuckerman and Dr. Chong develops open-source software to enhance the power of simulations at any scale (e.g. molecular, cellular) using rare-event sampling methods.
   - *University of Pittsburgh*: Lillian Chong, Ph.D. (Chemistry)
   - *Oregon Health Sciences University*: Dan Zuckerman, Ph.D. (Biomedical Engineering)

4. Modeling negative regulation of T cell activation. The aim of this collaboration with Drs. Vignali and Workman is to identify mechanisms by which cell surface proteins such as LAG3 act to negatively regulate T cell activation, an effect that plays a key role in cancer cells’ ability to suppress immune responses. Understanding such mechanisms is important for the development of novel immunotherapies.
   - *University of Pittsburgh*: Dario Vignali, Ph.D. (Chair of Cancer Immunology/Vice-Chair Immunology) and Creg Workman, Ph.D. (Immunology)

5. Modeling targeted cancer immunotherapy. This collaboration with the University of Pittsburgh Drug Discovery Institute and Sanofi aims to develop a predictive model of cancer immunotherapy using bi-specific targeted antibodies for the treatment of acute myelogenous leukemia.
   - *University of Pittsburgh Drug Discovery Institute (UPDDI)*

6. Modeling cellular heterogeneity in immune responses. In collaboration with Dr. Lee, we are developing models to provide mechanistic understanding of the factors that drive diversity in the responses of individual cells to external stimuli. The project involves development of new experimental and computational tools for measuring and modeling single-cell responses.
   - *University of Pittsburgh*: Robin E.C. Lee, Ph.D. (Computational and Systems Biology)

**Presentations at National or International Meetings**

**International Meetings**
- **June 4-7, 2018**

- **July 22-26, 2019**

National Meetings
- March 7-9, 2018
- September 6-7, 2018
- November 1, 2018
  Oregon Health Sciences University (OHSU) Special Seminar. Invited Speaker: “Cell Individuality: Identifying the Factors that Give Rise to Heterogeneity in Cellular Responses”. Portland, OR.
- April 9-12, 2019
- May 8-10, 2019
  MMBioS Cell Modeling Workshop, Pittsburgh Supercomputing Center. Organizer and presenter. Pittsburgh, PA.
- July 2019
- September 16-17, 2019
Prior to coming to the University of Pittsburgh, my focus was on the development High Content Screening (HCS) technologies for high throughput cell biology. HCS sparked a revolution in image-based cell analysis, allowing multiplexed measurements on objectively chosen populations of cells, providing statistically significant results. HCS is an important component of our quantitative systems pharmacology (QSP) approach to drug discovery.

Traditionally, HCS was focused on the use of 2D cellular models in microplates for high throughput compound testing. However, recent data has demonstrated significant differences in cellular functions in 2D models when compared with 3D models. We have now developed a more relevant 3D cellular model of the liver comprising 4-5 human cell types in a microphysiology system (MPS), which is expected to have a major impact on development of drugs and testing compounds for human effects in our QSP paradigm. Presently I am co-investigator on three projects using our microfluidic human liver module as a model of non-alcoholic fatty liver disease (NAFLD), in combination with a pancreatic islet MPS as a model of type 2 diabetes, and as a metastatic niche for melanoma. Each of these liver models is constructed in a single microfluidic device that allows sampling of media for analysis of the secretome, as well as high content imaging for cell-by-cell analyses. To enhance the throughput of these models, I am working with Mimetas (Gaithersburg, MD) funded by an SBIR grant to implement the 3D microfluidic liver model in a microplate format with 96 models per plate. We have recently demonstrated the ability to automate the construction of these models using standard liquid handlers and are preparing to run our first screen in this format.

The complexity of MPS models with multiple cell types, sometimes complicated experimental protocols and a wide array of model readouts requires a different approach to data management and analysis. To address this need we are developing the Microphysiology Systems Database (MPS-Db), an open source, internet hosted database for associating data generated by MPS models with human safety and efficacy data from a variety of sources. The database is currently available at https://mps.csb.pitt.edu, and contains experimental data from 58 models covering 11 organs developed at 14 centers across the US. We have developed online tools for reproducibility analysis, power analysis and are currently working on a pharmacokinetics (PK) module. The combined data is being used to construct computational models to predict human safety and efficacy.

It has long been known that cellular activity is heterogeneous, and therefore the average activity, while certainly important, is not the whole story concerning cellular function. The differential response of a minority of cells has important implications in cell biology, disease, 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 whole system. To address heterogeneity in our QSP approach to drug discovery, I have developed heterogeneity indices to characterize heterogeneity at the cellular level, across a wide range of cellular functions, which continues to be an important component of our assay development and screening projects.
**Collaborative Research Activities**


2. Development of an MPS model of non-alcoholic fatty liver disease (NAFLD) with Lans Taylor, Lawrence Vernetti, Andrew Stern.

3. Collaboration with Vanderbilt and Wisconsin on development of liver and brain niche models of metastatic melanoma using the Pitt liver microphysiology system (MPS), the Vanderbilt brain MPS, and the Wisconsin liver and brain organoid models. Pitt collaborators are Mark Miedel, John Kirkwood and Lans Taylor. Vanderbilt collaborators are Jacquelyn Brown, and John Wikswo. Wisconsin collaborator is William Murphy.


5. Collaboration with Vanderbilt on an EPA project to develop a broad tox panel for drug and environmental compounds, using microphysiology organ models. Pitt collaborators are Lans Taylor, Rocky Tuan, and Lawrence Vernetti. External collaborators at Vanderbilt are Shane Hutson, Lisa McCawley, Kevin Osteen and John Wikswo, resulting in 1 publication.

6. Development of a breast cancer niche using the microfluidic liver model, to evaluate the influence of the liver microenvironment on the proliferation of cancer cells. Collaboration with Mark Miedel, Lans Taylor and Lawrence Vernetti, resulting in 1 publication.


**Presentations at National or International Meetings**

1. Sept 20, 2018 - Presentation on the Microphysiology Database at NCATS project meeting

2. March 11, 2019 - Presentation on the Microphysiology Database developments at NCATS project meeting

**Honors, Recognitions, Invited Lectures, Editorships, and Professional Affiliations**

1. Invited Journal Referee: Lab on a Chip
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 of virtual screening. Specific projects include:

**gnina** Deep learning for structure-based drug design. State-of-the-art algorithms are used to learn 3D neural networks for predicting the affinity and pose of potential ligands. We are the first to apply 3D deep learning to energy minimization and pose generation. ([https://github.com/gnina](https://github.com/gnina))

**qsar-tools** A python software package for constructing, validating, and visualizing 2D quantitative structure-activity relationship (QSAR) models that predict chemical properties from chemical 2D structure. ([https://github.com/dkoes/qsar-tools](https://github.com/dkoes/qsar-tools))

**leadit** Structure-based lead optimization through efficient fragment-based search. An existing hit is deconstructed and alternative leads are reconstructed using predefined chemical reactions to match specified shape and pharmacophore criteria. ([https://github.com/dkoes/leadit](https://github.com/dkoes/leadit))

**MD2NMR** Calculation of NMR chemical shifts from molecular dynamics simulations. This *ab initio* method provides a way to validate and suggest improvements for molecular dynamics forcefields. ([https://github.com/dkoes/MD2NMR](https://github.com/dkoes/MD2NMR))

**Pharmit** Online interactive exploration of chemical space. Pharmit is a web interface for exploiting our ShapeDB, Pharmer, 3Dmol.js, and smina technologies to create and screen libraries of chemical compounds. ([http://pharmit.csb.pitt.edu](http://pharmit.csb.pitt.edu))

**3Dmol.js** Modern molecular visualization for the web. 3Dmol.js is a JavaScript library for viewing 3D molecular data using hardware accelerated 3D graphics in a web browser. 3Dmol.js is an essential component for supporting online collaboration and workflows. ([http://3dmol.csb.pitt.edu](http://3dmol.csb.pitt.edu))

**smina** We have developed a general, high-performance, framework for empirical scoring forked from AutoDock Vina called smina. ([http://smina.sf.net](http://smina.sf.net))

**ShapeDB** Fast, efficient search of molecular shapes. We have developed a computational method for searching for specific molecular shapes using a 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](https://github.com/dkoes/shapedb))

**PocketQuery** Rapid identification of small-molecule starting points in protein-protein interactions. PocketQuery is a web service for interactively exploring and identifying key clusters of residues at a protein-protein interface. 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. ([http://pocketquery.csb.pitt.edu](http://pocketquery.csb.pitt.edu))

**AnchorQuery/NucleoQuery** Specialized pharmacophore search of an easy to synthesize virtual chemical space that is biased to target protein-protein and protein-nucleic acid interactions. All compounds in an MCR chemistry database are designed to include an anchor fragment that is a mimic of an amino or nucleic acid.
acid. This chemistry is exploited by a novel pharmacophore search engine and lead optimizer. (http://anchorquery.csb.pitt.edu and http://nucleoquery.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.

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)

**Drug Discovery** We are applying our methods in a number of ongoing collaborative drug discovery projects, including those targeting the metabolism of cancer (glutaminase, NNMT, DUSP6, SHMT), immunotherapy (TIGIT) and stroke (CYP4F2).

*Joint work with Carlos Camacho.

**Peer-Review Activities**
1. Nature Methods
2. Nature Communications
3. Journal of Chemical Information and Modeling
4. Journal of Cheminformatics
5. Scientific Reports
6. Biophysical Journal
7. Journal of Molecular Graphics and Modeling
8. Journal of Medicinal Chemistry
9. Bioinformatics
10. Proteins: Structure, Function and Bioinformatics
11. Chemical Biology
12. Drug Design

**Collaborative Research Activities**

**External Collaborators**
1. Partha Roy, Ph.D. (Dept. of Bioengineering and Pathology, UPMC) – Computational modeling of profilin
2. Sameer Agnihotri, Ph.D. (Dept. of Neurological Surgery, UPMC Children’s Hospital) – Computational modeling of NNMT inhibition

**University-wide**
1. Samuel M. Poloyac, Ph.D. (Dept. of Pharmaceutical Sciences)- Computational modeling of CYP4F2 inhibition.
2. Lee McDermott (Dept. of Pharmaceutical Sciences) – Computational modeling support for various projects
3. Andreas Vogt, Ph.D. (Drug Discovery Institute) – Computational modeling of DUSP6 inhibition
4. Imad al Ghouleh, Ph.D. (Division of Cardiology, Vascular Medicine Institute) – Computational modeling of EBP50
5. Geoff Hutchison, Ph.D. (Dept. of Chemistry) - Machine learning driven conformer generation

Presentations at any National or International Meetings

International Meetings:

December 2, 2018

June 7, 2019
Deep Learning for Drug Discovery. Canadian Chemistry Conference. Quebec City, Quebec, Canada.

National Meetings:

- August 2018
- October 2, 2018
- October 15, 2018
  Deep Learning for Computational Drug Discovery, Michigan State University. East Lansing, MI.
- January 15, 2019
  Deep Learning for Drug Discovery: The Hype and the Hope. Eli Lilly. Indianapolis, IN.
- February 15, 2019
- March 8, 2019
- March 20, 2019
  Deep Generative Models for Computational Drug Discovery. GPU Technology Conference. San Jose, CA.
- March 31, 2019
- March 31, 2019
- May 19, 2019
• July 14, 2019


NSF has awarded the following project:

CSDE: D3SC: Conformer Toolkit: Generating Accurate Small Molecule Conformer Ensemble

The proposed work will greatly expand the use of conformer ensembles in computational chemistry by providing efficient generation of Boltzmann-weighted geometries. Accurate recurrent neural-network thermochemical models will be produced for molecules of different sizes with a wide range of chemicals.

David Koes Awarded R21 as Co-I to Identify Novel Inhibitors of 20-HETE Formation to Treat Cardiac Arrest Induced Brain Injury

20-hydroxyeicosatetraenoic acid (20-HETE) is a regulator of brain blood flow that has been implicated as a mediator of brain damage after cardiac arrest and stroke. 20-HETE levels in the spinal fluid are associated with poor outcomes in patients and inhibition of 20-HETE formation has been shown to protect the brain after injury in animal models. We have identified a novel series of compounds that can inhibit 20-HETE formation. This project aims to optimize our series, identify a lead compound, and then further evaluate its efficacy in the pediatric rat model of cardiac arrest.
How do cells make decisions? To survive environmental challenges, each cell engages molecular signal transduction circuits that process information about the type or intensity of stimulus, and then mounts an adaptive response. By this, cells effectively use a language of interacting molecules to compute their response to drugs, or environmental ‘cues’, and make decisions such as whether to differentiate, proliferate, or die. Although we have only begun to scratch the surface, an emerging principle is that dynamic behaviors of molecules within signal transduction circuits, such as changes in protein abundance or localization, provide a temporal code that is critical to each cell’s response. Dynamics of signaling molecules are therefore a semantic component of the molecular language that cells use, and must be tracked within single cells to gain a predictive understanding of how cell fate decisions are made.

Dr. Lee’s research combines principles of systems and synthetic biology with physics and engineering to understand how information flows through molecular circuits, with emphasis on cellular responses to inflammatory cytokines. By observing input-output relationships in the same cell using live-cell and single-molecule microscopy with microfluidics, the Lee lab aims to decode the meaning of dynamic molecular signals and develop mathematical models of the decision process with single-cell resolution. The ultimate goal is to understand how responses of cell populations emerge from single-cell heterogeneity, and develop strategies to rationally manipulate cell fate decisions in disease. Specific projects in the lab include:

**Dynamics of signal transduction.** In response to inflammatory cues, proteins rapidly reorganize to distinct subcellular localizations within each cell to transmit signals. We use microfluidic systems and fluorescent biosensors to monitor dynamics of protein localization and abundance in living cells exposed to time-varying concentrations of inflammatory cues, and then observe in the same cell how dynamic signals correlate with 1) other dynamic signals, and 2) cell fate. These relationships inform models of how molecular circuits transmit and process information in single cells, with the goal of predicting cellular responses to stimuli.

**Transcriptional diversity through competition.** Proteins bound to DNA promoters can either activate or repress transcription of nearby genes, and different genes can respond distinctly to the same signal even though they are regulated by the same molecules. Our work with NF-kB suggests that cells use an incoherent type-1 feed forward (I1-FFL) network motif consisting of competing activator and repressor proteins to decode dynamic signals and mediate gene-specific responses. We use single-cell assays to determine how features of different promoter sequences fine-tune diverse transcriptional responses.

**Information flow in signaling systems.** Sources of noise make biological systems appear unpredictable at the level of single cells, but that does not mean they are unreliable. Despite cell-to-cell heterogeneity we find that single cells can grade multiple levels of responses to cytokines over a range of doses. Through accounting for heterogeneity in cell states, the information transmission capacity of a single cell can be measured and we are exploring how variability between cells in their capacity to transmit information affect cell fate decisions, either cell autonomous or through cell-cell communication.

**Signal transduction in dynamic microenvironments.** The Greek philosopher Heraclitus asserted “Panta rhei”, that everything is continuously changing. This is especially true for the microenvironment of cells in vivo, yet most studies of biological systems in the lab are surprisingly static – exposing monoclonal cells to a single unchanging stimulus over an experiment’s duration. The capabilities and limitations of cells are underestimated in the ‘static view’ of biology, leaving hidden a dimension of therapeutic opportunities that can only be revealed in
time-varying microenvironments. To address this challenge, we have developed a robot-controlled dynamic cell culture system to generate and investigate cellular responses to user-defined dynamic microenvironments. We are particularly interested in understanding/modeling how different cell types share dynamic information in co-cultures.

Peer-Review Activities
Scientific Reviewer for:
1. Trends in Cell Biology
2. Cell Systems
3. Cell Reports
4. PloS Computational Biology
5. Nature Communications
6. IEEE Nanobiosciences
7. BMC Systems Biology
8. Oncotarget.

Collaborative Research Activities
Intra-departmental:
1. James R. Faeder, Ph.D. Reduction, parameterization, and investigation of the capabilities for Systems Biology models (Numerous publications; co-mentored student).
2. Carlos Camacho, Ph.D. Network-centric approaches to drug dynamic signal transduction systems (Publication and ongoing collaboration).

University-wide:
1. Yuan Chang, M.D. (Pathology; Graduate Program in Microbiology and Immunology (PMI) and Cellular & Molecular Pathology Graduate Program; UPCI) Regulation of mitotic protein translation mediated by oncogenic viruses (Funded R01; PI: Chang).
2. Patrick Moore, M.D. (Microbiology & Molecular Genetics) Regulation of mitotic protein translation mediated by oncogenic viruses (Funded R01; PI: Chang).
3. Rachel Gottschalk, Ph.D. (Immunology; Center for Systems Immunology) The impact of dynamic microenvironments on M1/M2 macrophage polarization (R01 under consideration; PI: Lee)
4. Bokai Zhu, Ph.D. (Integrative Systems Biology (ISB); Medicine; Endocrinology & Metabolism, Aging Institute of UPMC) The impact of cyclic environments on non-circadian rhythms in obesity (R01 under consideration; PI: Zhu)

Presentations at National or International Meetings
National Meetings
- July 2018
- October 2018
- March 2019
  Cold Spring Harbor Laboratory (CSHL) Networks Meeting, Huntington, NY. Speaker.
- April 2019
- August 2019
Dr. Lezon’s lab focuses on using mathematical models to understand cellular behavior in response to therapeutic intervention.

Inferring disease-associated pathways from phenotypic screens – Many complex diseases can only be successfully treated with multi-drug therapeutic strategies. Identifying the proper drugs, doses and scheduling for an effective combination therapy is a daunting task, hindered by the sheer number of permissible combinations. Working with other researchers at the University of Pittsburgh Drug Discovery Institute, Dr. Lezon has developed a combined experimental and computational methodology for streamlining the discovery of combination therapeutics. The team has applied a novel chemogenomics approach to uncover pathways that modulate cell death in Huntington’s Disease, and are creating methodology for predicting which drug targets will generate synergistic effects when co-targeted.

Modeling Cancer Immunotherapy – An important part of drug discovery is determining safe dose regimens for a heterogeneous patient population. Increasingly, this means personalizing medications and doses to provide optimal effects in individual patients. Working with industry collaborators, Dr. Lezon’s lab is developing mathematical models of the immune response to a novel bispecific antibody that attaches cytotoxic T cells to leukemic cells. Our goal is to quantitatively predict how individual patients will react to a variety of dosing regimens, in order to optimize the efficacy and minimize the side effects of cancer therapy.

Peer Review Activities:
Reviewer:
1. Scientific Reports
2. Cancer Research
3. Journal of Molecular Graphics and Modeling

Major Collaborations:
Intra-departmental
1. D. Lansing Taylor, Ph.D. (Director of UPDDI); Andy Stern, Ph.D.; James R. Faeder, Ph.D.: Developing a QSP model of bispecific antibody.
3. Ivet Bahar, Ph.D. (Chair); Chakra Chennubhotla, Ph.D.; James R. Faeder, Ph.D.; Joseph C. Ayoob, Ph.D.: Co-founding directors of the Masters Program for Computational Biomedicine & Biotechnology (COBB), of which I am the Program Director.

University-wide
2. Lisa Borghesi, Ph.D. (Immunology) B cell phenotype identification.
External
1. Spyros Stamatelos, Ph.D. (Sanofi SSA) Developing a QSP model of a bispecific antibody.
2. James Kozloski, Ph.D. (IBM) Modeling aberrant neuronal function in Huntington’s disease.
The central theme of my research is on the development of computational modeling, simulation and analysis techniques for the study of biological systems. My work builds mathematical models to describe the dynamics of biological processes and uses techniques from machine learning, formal methods, and control theory to analyze their quantitative behaviors. I use probabilistic models to address stochasticity in biological systems and develop advanced algorithms to construct model structures, estimate unknown rate constants, discover new biology as well as design personalized therapeutic strategies. I also leverage high-performance computing techniques to enable the analysis of large-scale multicellular systems. As an integral part of my research, I collaborate closely with biologists and clinicians to study various biological systems and tackle real-world problems that are crucial to medicine and healthcare. Specific directions of my research include:

Probabilistic and verification techniques for systems biology. I have developed a suite of computational methods for the study of signaling pathways. The key idea is to probabilistically approximate the dynamics of a systems of ordinary differential equations (ODEs) as a dynamics Bayesian network. Consequently, tasks such as parameter estimation, sensitivity analysis and probabilistic verification can be carried out efficiently using advanced Bayesian inference techniques. To handle large-scale models, we implemented our approach as a GPU-enabled tool. I have also developed model checking based techniques for pathway analysis. Model checking is a Turing Award winning technique for analyzing computer systems automatically. I have developed a suite of model checking based methods for analyzing stochastic and hybrid systems in biology. Our statistical model checking based method can utilize both quantitative data and qualitative knowledge for calibrating large stochastic models with hundreds of unknown parameters. Our delta-reachability based method enabled us to perform parameter synthesis for hybrid models. Our recent case studies on radiation diseases, cardiac disorders, pancreatic cancer and prostate cancer have demonstrated the wide applicability of our methods by carrying out crucial tasks including patient-specific therapy optimization and disease related parameter ranges identification.

Integrative study of biological systems. I am working closely with various teams of biologists to utilize mathematical models to study the mechanism of diseases, identify drug targets and predict therapeutic strategies. I am applying the algorithms I developed to combat with radiation diseases, children liver diseases, asthma, drug abuse, breast cancer, etc. I have modeled various biological systems ranging from immune system to cell fate decision. Our combined experimental and computational study revealed that TLR3-TLR7 crosstalk may confer immune cells the innate immune memory and homeostasis. The stochastic model of p53 induced apoptosis we built offered new insights into novel polypharmacological strategies for both mitigating radiation damage and alleviating the side effects of anti-cancer radiotherapy. In resent works, I built several kinetic models and assist our collaborators in discovering the metabolic pathways regulating ferroptosis, a newly discovered form of cell death, which is promising for killing cancer cells that are resistant to current therapies. Our findings were published in high-impact journals such as Science Signaling and Nature Chemical Biology.
Peer-Review Activities

Journals
1. Bioinformatics
2. Integrative Biology
3. Nature Scientific Reports
4. PLoS One
5. BMC Systems Biology
6. Chaos: An Interdisciplinary Journal of Nonlinear Science
7. Journal of Theoretical Biology, BioSystems
8. Mathematical Biosciences
9. Computers in Biology and Medicine
10. Journal of Bioinformatics and Computational Biology
11. Theoretical Computer Science
12. International Journal of Biomedical Science
13. Theoretical Biology and Medical Modelling

Editorial Board Member
1. Computers in Biology and Medicine
2. Journal of Bioinformatics, Computational and Systems Biology
3. Austin Journal of Lung Cancer Research

Grand Reviewer
1. Medical Research Council (UK)
2. Swiss National Science Foundation (SNSF)

Conference Program Committee Member
International Conference on Genome Informatics (GIW) and Australian Bioinformatics and Computational Biology Society (ABACBS) joint conference (GIW/ABACBS’19), Sydney, Australia, 2019.

Collaborative Research Activities

Intra-Departmental
1. Ivet Bahar, Ph.D. (Chair) Multiscale modeling, computational drug-abuse research, and drug discovery for anti-trypsin deficiency and radiation diseases.
2. James Faeder, Ph.D. (Vice-Chair): Parameter estimation for rule-based models
3. P.S. Thiagarajan, Ph.D. (Research Assistant Professor) De-compositional approaches for model calibration and analysis.
4. Hongying “Mary” Cheng, Ph.D. (Research Assistant Professor) Spatiotemporal modeling of dopamine transporter on lipid rafts.

University-wide
1. Joel Greenberger, M.D. (Radiation & Oncology; UPMC) Optimizing therapeutic strategies that target distinct cell death pathways for improving total body irradiation survival.
3. Sally Wenzel, M.D. (Chair, Environmental & Occupational Health; GSPH) Analyzing implications of PEBP-15LO1-LC3 interaction with Hi-2 asthma.
4. Xiang-Qun “Sean” Xie, Ph.D. (Research Innovation and Pharmaceutical Sciences) Studying the endocytosis and trafficking of CB2 receptor.

External
1. David Perlmutter, M.D. (Washington University in St. Louis) Drug discovery against anti-trypsin deficiency induced liver disease.
3. Jintao Liu, Ph.D. (Tsinghua University, China) Understanding biofilm antibiotic resistance.
5. Wei Wu, Ph.D. (Carnegie Mellon University) Studying the endocytosis and trafficking of CB2 receptor.
Malignant phenotypes that drive metastatic disease progression co-evolve with stromal and immune cells within the heterogeneous tumor microenvironment. The overall goal of my research is to define the unique interactions within tumor microenvironment (TME) that support distinct phenotypes for various cancer types in the liver metastatic niche. We are using liver microphysiology systems (MPS) to investigate metastatic mechanisms associated with both breast cancer and melanoma. Our recent work [Jia, S. et al., Oncology (2018) and Miedel et al., Scientific Reports (2019)] using liver MPS in breast cancer models demonstrates that the metastatic liver microenvironment can indeed impart unique phenotypes on cancer cells. We are taking two primary avenues to address these issues:

**The effect of the human liver microenvironment on the growth of ER+ breast cancer cells in a human liver microphysiological system.** Given the importance of non-cell-autonomous interactions within the tumor microenvironment that support metastatic phenotypes, we have initiated studies in liver microphysiological systems that recapitulate critical aspects of the breast cancer metastatic niche aimed at identifying emergent ER-dependent heterotypic signaling networks that may represent targetable metastatic dependencies for mutant ER-expressing clones. In addition to their hallmark constitutive (but ER-dependent) growth phenotype, different ESR1 missense mutations, prominently observed during estrogen deprivation therapy, confer distinct estrogen-enhanced growth and drug resistant phenotypes not evident under cell autonomous conditions. Under low molecular oxygen within the physiological range (~5-20%) of the normal liver acinus, the estrogen-enhanced growth phenotypes are lost, a dependency not observed in monoculture. In contrast, the constitutive growth phenotypes are invariant within this range of molecular oxygen suggesting that ESR1 mutations confer a growth advantage not only during estrogen deprivation but also at lower oxygen levels. These results highlight the overall importance of the metastatic microenvironment during tumor cell growth and the further characterization of distinct phenotypes among ER LBD mutants will allow us to define key metastatic dependencies in the liver microenvironment that support metastatic disease and enhance our ability to design/implement therapeutic strategies to more effectively treat MBC. In addition to modeling aspects of breast cancer progression, we are also implementing liver MPS platforms to gain mechanistic insight into progression of metastatic melanoma. In this multi-institutional study, we are using both liver and brain MPS model systems to identify targetable dependencies in these metastatic microenvironments.

**Development and Evaluation of the HepaPlate iPS: a high-throughput organ-on-a-chip iPS Hepatotoxicity Screening Platform.** Liver toxicity is among the most common reasons leading to the discontinuation of drugs in clinical trials and the withdrawal of drugs from the market. Traditional toxicology studies rely heavily on the identification of organ selective adverse drug reactions in animal models, which may not be predictive of human safety due to the well-documented species differences. Furthermore, drug induced liver injury is often idiosyncratic, suggesting that patient specific models are needed. Thus, human iPS cell-based in vitro models that closely mimic the human liver environment in vivo are urgently needed. The established collaborative effort has demonstrated the feasibility of a 3D liver-on-a-chip platform (the HepaPlate iPS) for high-throughput hepatotoxicity prediction. MIMETAS is one of the leading companies developing microfluidic high throughput Organ-on-a-Chip tissue models for drug discovery and toxicity testing. This collaborative effort is being developed to facilitate screening platforms that can be used in both liver toxicology and metastatic cancer models.
Collaborative Research Activities

Intra-departmental

1. D. Lansing Taylor, Ph.D. (Director, University of Pittsburgh Drug Discovery Institute, Distinguished Professor and Allegheny Foundation Professor of Computational and Systems Biology) My research is a collaborative effort with the Liver Microphysiology Program at the UPDDI where we are focused on identifying unique phenotypes conferred by ER LBD mutations within the liver metastatic niche for both breast cancer and melanoma. We are focused on developing novel technology to achieve the important translational research objective of defining the heterocellular signaling networks within the liver TME to identify 1) biomarkers mechanistically linked to ER+ metastatic disease and 2) targetable tumor dependencies that can inform novel therapeutic strategies.

External

1. MIMETAS, Inc. In a collaborative effort, we are working with MIMETAS to implement their OrganoPlate liver MPS platform to develop model systems useful for both liver toxicology studies as well as liver disease models.

Presentations at National or International Meetings

- June 2019 31st Annual UPMC Hillman Cancer Center Scientific Retreat and Satellite Conference, Soldiers and Sailors Memorial Hall, University of Pittsburgh, Pittsburgh, PA. “Modeling the Effect of the Metastatic Microenvironment on Phenotypes Conferred by Clinically Relevant Estrogen Receptor Alpha Mutations Using a Human Liver Microphysiological System.”
My overall research interest is on using system biology approaches to understand biological principles and disease pathologies and develop improved diagnostic and therapeutic approaches for them. Currently active research projects are described below.

**Design principles of bacterial cell communication**
Communication and coordination play a major role in the ability of bacterial cells to adapt to changing environments. Recent work has shown that such coordination underlies several aspects of bacterial responses including their ability to form biofilms and develop antibiotic resistance. In this project we combine modeling with experiments to identify basic principles by which bacterial cells communicate with each other. We create physically and chemically defined environments using microfluidic platforms and test the behavior of *E. coli* cells in the presence of various signaling molecules and drug gradients or when interacting with chemically coupled but spatially separated bacterial swarms. This project is in collaboration with Ziv Bar-Joseph and Hanna Salman.


Review on our work on bacterial chemotaxis:

**Cancer metastasis inhibition with statins**
Metabolic reprogramming is essential for tumor growth and the formation of metastases. Most primary tumor cells undergo epithelial-to-mesenchymal transition during initiation of the metastatic cascade. We previously observed that statins, widely used cholesterol-lowering agents, selectively inhibit the growth of slowly dividing cancer cell lines with mesenchymal cell-like transcriptome profiles and abundant cyto-solic vimentin and absent cell surface E-cadherin expression, a signature that is characteristic of metastatic cancer cells. We study the mechanistic basis of statin’s antitumor effect and aim to identify FDA-approved drugs and other compounds that enhance the cancer inhibitory effect of statins on statin-sensitive cancer cell lines. This goal will be achieved by using computational-, high content screening- and metabolic enzyme targeted approaches. This project is in collaboration with Katsuhiro Warita and Alan Wells.


**Pathogenicity predictions of single nucleotide variants**
The biological effects of human missense gene variants have been studied for decades both in cell culture and animal models but predicting their effects in clinical molecular diagnostics remains...
challenging. To address this problem, several in silico prediction tools have been developed, based on the analysis of various attributes such as sequence conservation and structural properties of the encoded mutant protein. I am collaborating with Dr. Ivet Bahar on a project that aims to improve the fidelity of calls on single nucleotide variants in clinically relevant genes, with a focus on assessing the clinical utility of algorithms developed by her group.


Peer Review Activities

Journals
1. Scientific Reports

Editorial Board Member
1. BMC Biology
2. Scientific Reports

Collaborative Research Activities

Inter-Departmental
1. Dr. Ivet Bahar on modeling the effects of single nucleotide variants on human proteins

University-wide
1. Dr. Hanna Salman (Physics & Astronomy) on the biologic principles of bacterial chemotaxis
2. Dr. Alan Wells (Pathology) on statin therapy of metastatic breast cancer

External
1. Dr. Ziv Bar-Joseph (Carnegie Mellon University) on the biologic principles of bacterial chemotaxis
2. Dr. Katsuhiko Warita (Tottori University, Japan) on statin co-therapy development
Machine learning for biophysics: Predicting Structures of Flexible Loops in Proteins with generative adversarial networks

The notion that proteins in their functional native state have a specific, well-ordered three-dimensional structure has been recently challenged by growing evidence that many functional proteins are either fully disordered or contain long stretches of disordered regions. It is known that protein interactions occur also via very flexible and unstructured parts of the protein. These flexible regions are called Intrinsically Disordered Loops (IDL) or natively disordered peptides. As a matter of fact, it is very challenging to investigate the dynamics and energetics of such systems both from experimental and computational points of view. In recent years a strong effort in the scientific community has been made for improving accuracy of computational study of IDL with the design of ad hoc force fields. As a result of experimental difficulties in capturing structures of IDLs, deposited protein structures are in many cases incomplete and missing several residues. This means that structural and dynamical information is often incomplete even for those proteins with available structures. Usually, those missing regions of the proteins are crucial regions which correspond to flexible loops frequently involved in the interaction between proteins and other objects like other proteins, membranes, small molecules and drugs. It is of fundamental importance to be able to model those missing loops and, ideally to find a strategy to analyze their conformation and energetics. The critical challenge is to actually predict structures and interaction properties of IDL in otherwise structured proteins. Here we propose to apply ML techniques to explore the conformational space of proteins presenting IDL with the aim of predicting structures for those loops and the possible interactions with other proteins or possible drugs.

The approach we will use is a novel generative adversarial probing applied to structural biology.

Computational Systems Pathology for cancer metastasis

Determining the mechanistic underpinnings of progression in metastatic disease is a major unmet need. The majority of cancer deaths are caused by metastases, a process involving the local migration and dissemination of cancer cells from the primary tumor and their survival, albeit with high attrition rates, leading to lethal secondary tumors at distant sites in vital organs. Comprehensive genetic profiling has revealed intrinsic molecular variability, or intratumor heterogeneity (ITH), in multiple cancers. Additionally, multiple lines of evidence across several tumor types indicate that spatial, functional, and genomic intratumor heterogeneity (ITH) among malignant cells, non-malignant cells (e.g., immune cells, cancer associated fibroblasts (CAFs), endothelial cells), and their localized interactions within the tumor microenvironment (TME) is a critical determinant of disease progression landmarks that include metastasis, immune evasion, therapeutic response, and drug resistance.

Metastatic potential evolves from coevolution of heterotypic signaling networks and manifests as spatial intratumor heterogeneity that is strongly correlated with clinical outcomes. With the goal of understanding the transition from locally invasive to metastatic cancer, I am employing in situ immunofluorescence (IF) labeling and imaging technology and novel machine learning tools to build a comprehensive iterative computational systems pathology platform. This platform will be capable of deciphering diverse molecular and cellular signaling networks conferring malignant (metastatic) phenotypes within distinct sub-regions. Systems analysis of these interactions will provide a network model predicting additional (emergent) interactions which can then be tested iteratively on the same tissue sample. Corroboration of the predictive model will generate causal hypotheses that could inform novel therapeutic strategies to remodel the primary tumor TME to be less permissive for metastasis.

How oxidative stress modulates CaMKII/Calmodulin interactions in neurodegenerative diseases?

Altered Ca\(^{2+}\) homeostasis is one of the critical pathogenic events in Parkinson’s disease (PD)-related nigro-striatal degeneration. Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII) is abundantly expressed in nigro-striatal neurons, where it is implicated in neuronal mechanisms including learning, memory and motor behavior. CaMKII has been extensively studied in the central nervous system (CNS)
and, most recently, CaMKII dysfunction has been implicated in PD, but, how its function is modulated under pathogenic conditions remains unexplored. Reductive-oxidative (redox) imbalance is a common feature in neurodegeneration, including in PD. Using an integrated computational and experimental approach, we hypothesize the formation of a disulphide bridge in CamKII complex under oxidative stress conditions. We support this hypothesis with experimental results from neuronal primary cultures and animal models in both physiological conditions and in rotenone-induced Parkinson’s like disease. Additionally, we provide mutagenesis experimental results, confirming the disulphide bridge formation.

**Peer-Review Activities**

2. Editorial Board member for the BioMed Research International
3. Reviewer for PROTEINS: Structure, Function, and Bioinformatics

**Collaborative Research Activities**

**University-wide**

1. *Multiplex immunofluorescent analysis on human tissue aimed to relate on psoriasis patients the immunoresponse with tissue spatial heterogeneity.*
   - **Daniel Kaplan**, MD, PhD, Department of Immunology and Department of Dermatology
   - **Jonhan Ho**, MD, Director of the Dermatopathology Unit. Department of Pathology

2. *Effect of oxidative stress on CamKII/CAM interaction in neurodegenerative diseases*
   - **J. Timothy Greenamyre**, MD, PhD, PIND
   - **Roberto Di Maio**, PhD, PIND

3. *Immuno-response on Melanoma primary tumor and metastasis*
   - **Hassan Zarour**, MD, Hillman Cancer Center Research Pavilion, University of Pittsburgh Cancer Institute
   - **Diwakar Davar**, MD, Hillman Cancer Center Research Pavilion, University of Pittsburgh Cancer Institute

**External**

1. *Effect of treatment with kinase inhibitors on prostate cancer evolution in mice tibias: a multiplex immunofluorescent analysis*
   - **Eleonora Dondossola**, PhD, Department of Genitourinary Medical Oncology, Division of Cancer Medicine MD Anderson Cancer center
   - **Taran Gujral**, PhD, Division of Human Biology, Fred Hutchinson Cancer Research Center

2. *Atopic Dermatitis treatments: assessment and comparison of the efficacy of the thermal therapeutic treatment vs traditional cortisone treatments*
   - **Ermanno Baldo**, MD, Health Director of the Comano Terme center for Atopic Dermatitis.

3. *Phosphorylations in CamKII: study of the effects on activity using Molecular Dynamics Simulations approaches*
   - **Ignacio J. General**, PhD, Professor, Universidad Nacional de San Martin, Argentina
   - **Eliana Asciutto**, PhD, Professor, Universidad Nacional de San Martin, Argentina

**Presentations at any National or International Meetings**


2. F. Pullara, “Synergy between experiments and computer simulations: Newly observed intra-complex interactions on CaMKII with effect on brain function”, CMCC- Centro de Matemática, Computação e Cognição, University Federal of ABC, Sao Paulo, Brazil, Invited talk
My research focus is in the application of Quantitative Systems Pharmacology (QSP) to develop more effective drug discovery strategies that utilize integrated computational and phenotype/function-based analysis. I am leading the Huntington’s Disease QSP program where we are aligning transcriptomic data with chemogenomic data to infer critical molecular pathways involved in the disease progression and in the protection of neurotoxicity by small molecule drugs. I am the PI for the NCATS TCTC project to extend the Microphysiological systems (MPS) database to include data from a variety of MPS organ modes. In addition, I am also involved in several other projects to support investigators across the University of Pittsburgh. Finally, my research efforts extend to developing approaches to detect and quantify heterogeneity in cell based model systems.

MARK E. SCHURDAK
Research Associate Professor
**Peer-Review Activities**

1. Reviewer for PLOS One journal.
2. Reviewer on the Research Review Committee for the Department of Psychiatry.
3. Reviewer for CTSI Biomedical Modeling Pilot Awards
4. Reviewer for SLAS Discovery
5. Reviewer for the American Association of Pharmaceutical Scientists Journal (AAPSJ)

**Major Collaborations**

3. Development of HT screening assays for ID of small molecule inhibitors of the Mcm2-7 replicative tissue. Collaborators: Tony Schwacha, Andreas Vogt. Funded by NIH.
4. Acute pancreatitis as a model to predict transition of systemic inflammation to organ failure in trauma and critical illness. Collaborator: David Whitcomb. Funded by DOD.
The overarching goal of our research is to identify mechanisms involved in complex human disease progression and use this knowledge to develop novel optimized therapies for individual patients. All too often, even amidst the growth of genomic medicine, drug candidates with no limiting toxicity and exhibiting well-defined pharmacokinetic and pharmacodynamics profiles fail to demonstrate proof-of-concept in Phase II and III trials. To address this challenge, we have developed a comprehensive, unbiased, pathway-centric, quantitative systems pharmacology (QSP) drug discovery and development platform (Handb Exp Pharmacology, 2019; Journal of Biomolecular Screening, 2016).

Intrinsic to QSP is its integrated use of multi-scale experimental and computational models to identify mechanisms of disease progression and to test predicted therapeutic strategies likely to achieve clinical validation for appropriate sub-populations of patients. A key feature of the QSP platform is its ability to embrace heterogeneity (SLAS Discovery, 2017) and to anticipate the evolution of resistance mechanisms, both major challenges in drug discovery and development programs. The full implementation of this platform involves multidisciplinary, multi-institutional, highly cooperative efforts dedicated to gaining a holistic understanding of disease biology. Accordingly, we have built QSP-driven programs for metastatic breast cancer, Huntington’s disease (J Neurotrauma, 2019; Scientific Reports, 2017), and several diseases of the liver. The first two programs are supported by a PADOH CURE grant. The platform is helping to drive these development programs creating both novel therapies and opportunities to repurpose existing drugs. For example, in a study that helped inspire the QSP platform (Cell, 2012) we 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 these mechanistic studies and additional cellular, computational, and in vivo model studies, the clinical candidate Alisertib is being repurposed as a novel differentiation therapy for this specific indication. As a result of the demonstration of mechanism-based clinical benefit, Alisertib has advanced to Phase II in collaboration with Takada Pharm and Professor John D Crispino, Northwestern University.
Comprehensive Cancer Center. Our metastatic breast cancer program involving the Lee, Oesterreich, and Puhalla laboratories in collaboration with AstraZeneca is focused upon determining the clinical relevance of estrogen receptor mutations acquired during estrogen deprivation therapy to enable the identification of targetable metastatic disease dependencies (Scientific Reports, 2019; Oncology, 2018; Clinical Cancer Research, 2016; Breast Cancer Research, 2017). Similarly, our multidisciplinary Huntington’s Disease program in collaboration with the Friedlander laboratory, the Brain Institute, and the National Center for Advancing Translational Sciences (NCATS) is using mammalian isogenic cell-based and patient-derived iPSC-based models in conjunction with chemogenomic and systems biology approaches to identify optimal therapeutic strategies that address the pleiotropic consequences of the disease-causing mutation (Scientific Reports, 2017). In focusing on the patient as the starting and the end point, the QSP platform will help promote the paradigm shift from reactive population-based medicine to proactive personalized medicine. Furthermore, by analogy to our recent studies (Nature Chemical Biology, 2013; Cell Reports, 2015) we have taken a QSP approach to model the tumor microenvironment in metastatic breast cancer (Cancer Research, 2017; Journal of Pathology Informatics, 2016) and colon cancer in collaboration with Chakra Chennubhotla and GE Global Research and in head and neck cancer in collaboration with Dr. Robert Ferris and the Tumor Virus and Microenvironment Center. Most recently we have applied QSP to understand drug resistance mechanisms in glioblastoma collaborating with Professor Ian Pollack and his clinical laboratory at Children’s Hospital. We also have a collaboration with Professor Stuart Schreiber and the Broad Institute developing mutant specific targeted therapies for several oncology indications (ACS Medicinal Chemistry Letters, 2016).

**Peer-Review Activities**
1. The Shire-University of Pittsburgh Joint Steering Committee for rare disease programs
2. The Pharmaceutical Companies Collaboration Committee
3. Mentor for the Tsinghua University Scholar program

**Presentations at any National or International Meetings**
1. QSP Congress, San Francisco, December 6-7 2016; Harnessing QSP for Drug Discovery and the Advancement of Personalized Medicine
Dr. Jacob Stewart-Ornstein’s research is focusing on understanding how DNA damage is measured and interpreted by cells of different types. He uses panels of cell lines which can be characterized genomically using next-generation sequencing (NGS) and at the single cell level using timelapse microscopy. Computational models of cell signaling, both stochastic and deterministic, link these two different types of information together. This approach allows for a single cell based interpretation of bulk clinical data and specifically for prediction of the potential for relapse.

Cell biologically, Jacob’s group is focused on understanding how the tumor suppressing transcription factor p53 is tuned across cell types. This includes extensive use of NGS approaches to probe the structure of a cell’s genome and correlate that with it’s signaling. We measure gene expression, p53 DNA binding, and genomic accessibility across time after treating cells with DNA damaging perturbations. Our current work is focused on determining how p53 binding is regulated in the genome, we have shown that at many loci p53 can bind and activate transcription without pre-existing chromatin opening. However, at other binding sites p53 is dependent on the chromatin state of that locus as a permissive signal for DNA binding. In particular, we find this arrangement around cytokine genes in melanoma cell lines, and also in cells induced to undergo an epithelial-to-mesenchymal transition. The regulation of cytokine and other pro-survival signals by p53 suggests that in some contexts this tumor suppressor may promote tumor formation.

Though bulk approaches have significant power for studying well synchronized responses in homogenous cell systems, many cellular events are heterogenous across the population. To understand how cellular heterogeneity in cell state relates to DNA damage signaling and response we use live cell imaging to watch cells as they respond to DNA damage and complement this live cell data with highly multiplexed in situ tools that we are developing. To image live cells with reporters of cellular processes we use endogenous tagging approaches that Jacob developed to study key proteins such as p53, p21, and ki67. Our multiplex approach allows ~10 plex imaging of RNA species combined with >20 proteins. Together these tools let us identify epigenetic states that are particularly sensitive or resistant to DNA damage.

The live and fixed cell data Jacob’s lab collects naturally fits into modeling approaches. The group uses small conceptual (or phenomenological) models of cell death and growth and attempts to parameterize them from cell biological data. For example, DNA repair rates and cell growth and death data is being used to construct simple qualitatively predictive models of how a population of cells responds to DNA damage of different intensities. An orthogonal input for our model building is data from cas9 screens of cells exposed to DNA damage, this approach allows for high throughput assessment of how cells with different DNA repair or signaling defects respond to DNA damage of different durations and intensities.
**Peer-Review Activities**

**Reviewer**
1. BMC Systems Biology; Cell Systems; iScience.

**Collaborative Research Activities**

**Intra-departmental**
1. Yi-nan Gong, Ph.D. (Immunology) Identifying the role of membrane damage in death signaling. A continuing collaboration, we aim to understand the signaling events that take place upon membrane rupture.

**External**
1. Galit Lahav, Ph.D. (Harvard Medical School, Chair of Systems Biology) Tissue dynamic responses to radiation. This is an ongoing collaboration which focuses on determining the dynamics of p53 and DNA damage signaling in living tissues when exposed to DNA damage from ionizing radiation.
2. Adrian Ranada, Ph.D. (Humboldt-Universität zu Berlin, IRI Life Sciences) Cellular rhythms and survival at the single cell level. An ongoing collaboration between myself and Dr. Granada, we use live cell imaging and deterministic models to identify the nature of interactions between oscillatory cellular properties (cell cycle, circadian rhythm, p53 signaling) and survival after DNA damage.
3. Hana El-Samad, Ph.D. (University of California at San Francisco, Vice-Chair of Biochemistry and Biophysics) Optogenetic tools for control of cellular signaling. This is a collaboration on developing optogenetic tools to control cellular signaling in budding yeast and mammalian cells. This work resulted in a manuscript that is currently in review.

**Presentations at National or International Meetings**

**National Meetings**

- **May 8, 2018**
  UPMC Hillman Cancer Center and the University of Pittsburgh Special Seminar on Molecular and Cellular Cancer Biology, “What Determines Radiosensitivity? Non-genetic Regulation of DNA Damage Signaling”. Invited Speaker. Pittsburgh, PA.

- **December 6, 2018**
  American Society of Cell Biology “p53 DNA Binding is Tuned by Chromatin Accessibility”, poster presentation. San Diego, CA.

- **December 13, 2018**
  The University of Pittsburgh Chromatin Club Mini-Symposium “Transcriptional Linearity and Dynamic Feedback are Hallmarks of Stress Responses from Budding Yeast to Cancer”, **Keynote Speaker**. Pittsburgh, PA.

- **February 15, 2019**

- **June 19-20, 2019**
  University of Pittsburgh and UPMC Hillman Cancer Center 31st Annual Scientific Retreat. Poster judge. Pittsburgh, PA.
I continue to develop both my personal research program as part of the overall UPDDI research and development plans applying quantitative systems pharmacology (QSP) to drug discovery, development and personalized medicine. I have major efforts in applying our 4 cell-type human, 3-D, microfluidic, liver model on chips with funding from the NIH. As part of the liver microfluidic model system, we are developing fluorescence-based biosensors for real-time monitoring of the physiological state over a one-month time period. In addition, we continue to extend our a “Microphysiological Database” (MPDb) that is used to capture multiplexed data sets from the models, analyze and computationally model the data for PK and PD studies. The MPS-Db has been selected by the NIH to analyze all of the data from a range of organs on chips in the “Tissue Chip Testing Centers” and is currently being evaluated by the IQ Consortium (group of 23 pharmaceutical and biotechnology companies) for licensing. With NIH funding, the liver on a chip system is being used to perform toxicology studies, as well as to create models of human disease for drug discovery, including non-alcoholic fatty liver disease (NAFLD), Type 2 Diabetes (with connected human pancreatic islets) and a metastatic site for breast and melanoma cancers. A combination of grants, pharmaceutical company collaborations and philanthropy is driving the programs. These programs involve multiple faculty, post-docs and students working across multiple laboratories.

I am also involved in the development and application of “hyperplexed fluorescence” pathology (>9 biomarkers) to characterize the spatial relationships between cell types and tumor microdomains in primary tumors. The goal is to create prognostic and diagnostic tests, as well as to develop therapeutic strategies for individual patients.

Collaborative Research Activities
1. Continued research program to build human tissue engineered liver models on chips that contain fluorescence-based biosensors to create a platform for better in vitro efficacy and safety testing of new chemical entities. We received funding from NCATS to study the use of the liver on a chip to model metastasis of melanoma, from NIDDK to use our liver models and QSP to identify novel therapeutics for non-alcoholic fatty liver disease (NAFLD) and from a joint program from NCATS and NIDDK to develop therapeutics for Type 2 Diabetes. We have collaborations with 5 companies in these grants. Collaborations within Pitt include Bert Gough, Alex Soto-Gutierrez, Larry Vernetti, Paul Monga, Ivet Bahar, Ramon Bataller, Ipsita Banerjee, Vijay Yechoor, Erin Kershaw and Andy Stern. Three research assistant professors (Mark Miedel, Vineet Mahajan and Xiang Li), two research scientists, and two graduate students are involved in the programs. Ten papers were published in the last year.

2. Quantitative systems pharmacology (QSP) continues to be the driving force of the UPDDI. Three disease areas serve as the biomedical drivers where the UPDDI has a leadership role: a) metastatic melanoma with John Kirkwood, Bert Gough and Andy Stern; b) Huntington’s Disease with Robert Friedlander, Andy Stern, Mark Schurdak, Tim Lezon and Ivet Bahar; Traumatic Brain injury with David Okonkwo, Patrick Kochanek, Andy Stern, Tim Lezon, Andy Stern and Mark Schurdak (IFunded with a CURE grant) and c) two liver-focused diseases, Type 2 Diabetes and alcoholic and non-alcoholic fatty liver disease with Paul Monga and Ramon Bataller and others listed above. We (Chakra Chennubhotla-PI) are submitting a UO1 grant on colon cancer in the Fall of 2019 based on a computational pathology/systems pathology paper that is in review. We established a funded collaboration with Sanofi to apply our computational modeling capabilities to one of their cancer projects to predict the mechanism of action of one of their drug candidates. This is an interdisciplinary project between the computational biologists at Sanofi, Tim Lezon,
3. Collaboration with Ivet Bahar, Andy Stern, Mark Schurdak 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 (HD). A publication in Science Reports summarizing the first phase of the work has been published. Ivet and I co-mentor Fen Pei, a C&SB graduate student with input from Tim Lezon, Andy Stern and other members of the UPDDI. A research collaboration with NCATS at NIH has progressed and extended to include the development of iPSCs for HD experimental models. We have recently extended our QSP approach to Alzheimer’s Disease and will be submitting a grant in the Fall, 2019.

4. Collaboration with Chakra Chennubhotla, Adrian Lee, Jeffrey Fine and Andy Stern on Breast Cancer sub-types. Combining genomics data analyses with image data sets generated our initial computational pathology project that was supported by UPMC to extend the software to function as a computational guide to pathologists. A company based on computational pathology, SplIntellx, was spun-off from Pitt.

5. Collaboration with GE Global research on the application of the MultiOmyx platform to cancer research and diagnostics with a starting point in breast cancer and colon cancer. Collaborators from Pitt include Chakra Chennubhotla, Bert Gough. I co-mentored Dan Spagnolo, a C&SB graduate student, with Chakra until Dan graduated in 2018.

6. Collaboration initiated with DILIsym Services with a submission of an SBIR to integrate our liver chip, microphysiology database with the DILIsym computational model to create a platform to better predict drug-induced liver injury (DILI) for drugs in development. The Pitt technology will be licensed to DILIsym Services.

**Study Sections and Advisory Committees**

1. Invited and accepted to join an SBIR study section in the Fall of 2019
2. Chairman of the Board, SplIntellx

**University of Pittsburgh Committee Service**

1. Chemical Biology Facility Advisory Committee meeting
2. PA Cure Advisory Committee
3. Member of the Coulter review committee in the school of engineering
4. Drug Discovery Institute Executive Committee

**Other Services Outside Of the University Of Pittsburgh**

1. Invited to review articles for Biosensors, European Research Council, and Nature Biomedical Engineering
2. Member of the EPA VPROMPT Steering Committee
3. TCTC Executive Committee
4. NCI Chemical Biology Consortium Steering Committee
5. Foundation for the NIH-Biomarkers Consortium-High Content Data Integration Group

**Presentations and National or International Meetings**


• Taylor, DL, BMS, “Application of quantitative systems pharmacology (QSP) and human microphysiology systems (MPS) to develop therapeutic strategies for liver diseases,” Lawrenceville, New Jersey. October 26, 2018.


My research vision is to employ a quantitative approach that integrates computational pathology, systems biology, and the human visual and cognitive aspects to investigate and improve cancer research. Through my postdoctoral training with Dr. S. Chakra Chennubhotla at the University of Pittsburgh School of Medicine and my Ph.D. training in computer science and engineering, I have gained expertise in machine learning, medical imaging, computer vision, computer assisted diagnosis, human-computer interactions, pattern recognition, and computational modeling.

**Causal understanding of disease progression:** My current research, funded by the National Institute of Health BD2K effort: Center for Causal Discovery, with a focus on understanding heterogeneity in lung diseases (idiopathic pulmonary fibrosis and chronic obstructive pulmonary diseases), involves defining context aware features to accurately represent the heterogeneity in the lung tissue architecture and detect structural patterns to help diagnose lung tissues from digital whole slide images. This is achieved by modeling lung tissue architecture with spatial analysis to understand the nature of normal and diseased tissue structures and by harnessing machine learning tools to integrate imaging, genomics and clinical data and to improve decision-making process. I have applied these tools successfully to model heterogeneity in tissue architectures from other organs (e.g., breast, brain, and colon).

**Computational pathology versus manual microscopy:** I worked on computer assisted diagnosis systems and cognitive studies on pathologists’ assessments through human-computer interfaces to design next generation workflow for future pathology laboratories, funded by Pittsburgh Health Data Alliance. We built computational pathology tools that minimizes diagnostic discordance by providing quantitative measurements. Together with Dr. Chakra Chennubhotla and Dr. Jeffrey Fine, MD, we have built a computational pathology pipeline (Fig. 1) for histological diagnosis of breast lesions from whole slide images (WSIs) to guide the pathologist to examine the slide on screen by showing regions of interest in importance-ranked order and increase effectiveness of breast pathologists through their daily routine by 56%. In these studies, we developed algorithms to detect structural patterns in WSIs using context-aware features extracted from representative tissue component. We also conducted visual psychophysics experiments on expert pathologists to elicit their subjective preferences for various color palettes and defined a stain color normalization method as a key step: standardization of histopathological images.

**Computational aids for pathology:** As part of my future research priorities, I plan to design new computational pathology tools for expanding my studies to hyperplexed tissue image analysis for personalized tumor identification and therapy optimization and discover the reasoning behind diagnostic decisions with the help of human-computer interaction tools such as eye-tracking devices and brain-computer interfaces. It is important to develop next-generation pathology laboratories that enhance the power of intelligent computational tools, which can observe, train and assist pathologists.
and oncologists, and minimize errors due to human factors. These data-driven approaches will uncover the potential of human experts (e.g., pathologists) while providing novel insights into cancer progression, and will lead to the development of new diagnostic, prognostic, and treatment strategies that will ultimately improve patient outcomes.

**Peer-Review Activities:**

**Associate Editor:**


**Reviewer**

1. Nature Scientific Reports;
2. IEEE Transactions on Medical Imaging journal;
4. Journal of Imaging;
5. IEEE Journal of Biomedical and Health Informatics;
6. IEEE Transactions on Biomedical Engineering journal;
7. MICCAI 2017 conference;
8. Artificial Intelligence Review journal.

**Collaborative Research Activities:**

**Intra-departmental**

1. Co-analysis of Imaging Phenotypes and Genomic Signatures in the Lung DBP for the BD2K grant with Dr. Takis Benos (DCB) and Dr. Naftali Kaminski (Yale).

**University-wide**

1. Multiplexed immunofluorescence image analysis: 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
2. Detection of atypia in breast lesion from digital whole slide images: Ongoing collaboration with Dr. Jeffrey Fine, Department of Pathology
3. Informatics for cancer research: Ongoing collaboration with Dr. Michael Becich (DBMI)

**Presentations and National or International Meetings**

My research leverages interconnections between signals and systems, optics, and machine learning to develop (i) new optical and computational imaging approaches, (ii) mathematical models for image formation and analysis of tumorigenesis, and (iii) analytical methods in cancer systems biology.

Spatial systems biology of colon cancer recurrence: Cancer is a heterogenous disease that exhibits inter- and intra-tumor heterogeneity, both at the genetic and cellular levels. Indeed, tissues and organs, where cancer originates, are multi-cellular systems, which interact within and amongst themselves, to define emergent hetero-cellular phenotypes. My research in spatial systems biology of cancer utilizes hyperplexed immunofluorescence imaging of in situ markers – of epithelial, immune and stromal cells, oncogenes, tumor suppressors, and posttranslational modifications – to sample the network biology of primary tumors of colorectal cancer (CRC) patients and develop a spatial model of CRC recurrence phenotype that (a) provides improved prediction of CRC recurrence in Stage I-III patients over state-of-the-art assays such as immunoscore; and (b) identify recurrence-driven epithelial and stromal spatial-domain networks that reveal connections of CRC recurrence with consensus molecular subtypes (CMS) of CRC progression. I am interested in using these networks to methodologically express the malignant CRC phenotype in individual patients as an emergent property of the TME ecosystem.

Clinically relevant mapping of the evolution of early stage colorectal cancer: In April 2019, Dr. Yang Liu (Dept. of Medicine) and I were awarded R01 grant from NCI whose goal is to utilize 3D nanoscale nuclear architecture mapping (nanoNAM) of epithelial cell nuclei to track the evolution of early stage carcinogenesis using a taxonomy of nanoNAM markers progressing on a cancer-risk manifold (Fig. 1). nanoNAM is a Fourier-domain optical coherence tomography (FD-OCT) derived imaging approach that I developed. It extends the principle of FD-OCT to quantify, with nanoscale sensitivity, the depthresolved alterations in aberrant 3D intrinsic architecture of cell nuclei. The grant focuses on first quantifying progression (sensitivity) and regression (specificity) of nanoNAM markers respectively to acceleration and inhibition of colorectal cancer (CRC) in well-established mouse models of CRC and use them to develop risk-based taxonomy of markers. It then aims at translating them to the patient population. The grant will address the clinically unmet need of characterizing pre-cancerous and pre-cursor lesions in colorectal cancer and predicting its risk of development. An important focus of the grant is on developing new computational and data science methods, with potential of use in other fields.

Computational biophysics: Critical to the diverse biological functionality of proteins is their structural flexibility that allows them to achieve conformations that make the biological functions possible. These conformations are not static, but instead are part of an equilibrium dynamics over a complex energy landscape. Perturbations, such as mutations and protein-ligand bindings, change the energy landscape through complex interactions that are not necessarily limited to the perturbation site, and can be difficult to describe analytically. We are developing a generative information-theoretic framework to learn and compare protein dynamics between different macromolecules (or same molecule before and after perturbation) at the level of both single and groups of residues. These comparisons can also be extended temporally and could have important consequences for drug discovery and drug resistance to mutations.

Peer-Review Activities
Reviewer for the following journals:
1. Optics Express (Optical Society of America (OSA)
2. Applied Optics (OSA)
3. Optics Letters (OSA)
4. Biomedical Optics Express (OSA)
5. IEEE Transactions on Geoscience and Remote Sensing
7. Nature Communications (Nature Publishing Group)
8. Scientific Reports (Nature Publishing Group)

Collaborative Research Activities

Intra-departmental
1. Chakra Chennubhotla, PhD: Diverse areas in computational biophysics and computational bioimaging.
2. D. Lansing Taylor, PhD (Director, Drug Discovery Institute (UPDDI)); Andrew Stern, Ph.D. (UPDDI) Spatial proteomics and intratumor heterogeneity.

University-Wide
1. Yang Liu, Ph.D. (Medicine) Nanoscale nuclear architecture mapping and chromatin remodeling

1. Patricia L. Opresko, Ph.D. (Environmental and Occupational Health) Role of chronic oxidative stress in telomere shortening.

External
1. Cernostics: Incorporating spatial heterogeneity analytics to impact the ability to predict the progression of Barretts Esophagus.
2. GE Global Research: Hyperplexed immunofluorescence imaging for predicting colon cancer risk recurrence.
3. Rebecca C. Burgess, PhD (Stevenson University): Modeling the impact of chromatin modifications on the DNA Damage Response in Yeast.

Presentations at National or International Meetings

National
- March 29-April 3, 2019
  American Association for Cancer Research Annual Meeting 2019. Invited paper. Atlanta, GA.

International
- June 23-27, 2019
My career has focused on development of in vitro animal and human liver models for pharmacokinetics, toxicology and disease research. The laboratory in the Drug discovery Institute at University of Pittsburgh has built and validated a multi-cell, 3D, microfluidic, microphysiology human liver model (MPS liver) that is designed to augment and then replace animal models used for human liver drug safety, pharmacokinetics and complex human disease research. The MPS liver is a re-construction of the sinusoidal -acinus, the smallest function unit of the liver. The model has proven capable to identify human hepatotoxic drugs that were found safe in animal pre-clinical drug development but manifested as human specific liver toxins during clinical trials. The second advantage of the MPS liver over a traditional 2D monolayer in vitro approach is the dense cellular, 3D organization which allows the cells to interact in the manner similar to the in vivo tissue. This has already been shown to be an important step toward re-creating complex liver diseases such as non-alcoholic liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and alcoholic liver diseases (ALD) which result from multifactorial pathological mechanisms. For example, fibrosis can be induced by the drug methotrexate in the 4-cell MPS liver but not in simpler cultures. Liver fibrosis is an important component of liver diseases such as NAFLD, NASH and cirrhosis. The eventual goal of the MPS liver is to gain better understanding of genes, proteins and cellular interactions driving toxicity, disease initiation and progression to improve therapeutics for various human hepatic diseases.

**Peer-Review Activities**
1. PloS One
2. In Vitro Toxicology
3. Experimental Biology and Medicine
4. Nanobiomedicine
5. Molecules

**Collaborative Research Activities**

**Intra-departmental**
1. **Ivet Bahar, Ph.D.** (Chair) Multiscale modeling, computational drug-abuse research, and drug discovery for anti-trypsin deficiency and radiation diseases.
2. **James Faeder, Ph.D.** (Vice-Chair): Parameter estimation for rule-based models
3. **P.S. Thiagarajan, Ph.D.** (Research Assistant Professor) De-compositional approaches for model calibration and analysis.
4. **Hongying “Mary” Cheng, Ph.D.** (Research Assistant Professor) Spatiotemporal modeling of dopamine transporter on lipid rafts.

**University-wide**
1. **Ramon Bataller, M.D., Ph.D.** (Medicine; UPMC) The liver MPS team at the Drug Discovery Institute is entering a collaboration with Dr. Bataller to evaluate the use of our platform technology to study alcoholic liver diseases. The effort will additional be supported by a no cost extension of the NIH # 1UH2TR000503-01 award and the recently awarded R01 NAFLD grant.
2. **Alex Soto-Gutierrez, M.D., Ph.D.** (Pathology; UPMC) Dr. Soto-Gutierrez is developing iPSC-derived mature human hepatocytes. We have an active collaboration to study the level of metabolism in these cells and will continue to be support through the recently awarded RO1 NAFLD grant.

3. **Samuel Poloyak, PharmD, Ph.D., FCCM and Margaret Minnigh, Ph.D.** (Pharmaceutical Sciences) We have previously developed metabolic stability and metabolite identification screen using Mass Spec analysis. A recent small grant from the Alternatives Research and Development Foundation was awarded. The money will support the collaboration from August 2018 to August 2019 to add the intrahepatic bile duct in the existing liver MPS platform.

**External**

1. **John Wikswo, Ph.D.** (Vanderbilt University, Director of The Vanderbilt Institute for Integrative Biosystems Research and Education) Collaboration EPA V PROMPT Center grant to incorporate the liver organoid as part of the four-tissue integrated device for environmental toxin testing of developmental tissues. We are also collaborating on the newly funded Clinical and Translational Science Awards (U01 # TR002383-01) to use human brain and liver microphysiological systems for testing therapeutics for metastatic melanoma.
My research interests center around the discovery of small molecules affecting proliferative and degenerative diseases using functional cellular and whole organism models in connection with biochemical and biophysical methods. 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, Pharmaceutical Sciences, and Structural Biology I am currently using a combination of high-content analysis, transgenic zebrafish, computational modeling, and biophysical interaction assays 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 fifteen 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. Ongoing collaborative drug discovery projects using HCA include kidney and heart regeneration, lamin B1-mediated nuclear morphology changes in ADLD, a rare demyelinating disease (with Quasar Padiath, Human Genetics), and a new project (with Michael Palladino, Pittsburgh Institute for Neurodegenerative Diseases) for correctors of triose phosphate isomerase deficiency (TPI-Df), a devastating genetic childhood disorder for which no cure exists.

A natural extension of my work in HCA 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. For more than ten years, the NIH has been supporting a collaboration with Neil Hukriede and Michael Tsang (Developmental Biology) 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 have performed automated chemical genetics screens for activators of Fibroblast growth factor (FGF) and are currently screening for compounds that augment kidney regeneration after injury. These efforts have yielded a number of promising candidates that have activity in multiple mouse models of acute kidney injury.

Peer-Review Activities
Editorial Board Member
Society for Laboratory Automation and Screening (SLAS) Discovery (2017-present)

Invited Journal Reviewer

Professional affiliations
1. Member, American Association for Cancer Research, 1994 - current
2. Member, American Chemical Society, 1992 - current
3. Deutsche Pharmazeutische Gesellschaft, 1995 - current
4. Society of Laboratory Automation and Screening (SLAS), 2002 – current

**Collaborative Research Activities**

1. **Neil Hukriede, Department of Developmental Biology, University of Pittsburgh.** Small molecule mediated augmentation of 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 kidney repair and regeneration using zebrafish. This project is supported by NIH grant R01 DK107210.

2. **Quasar Padiath (Human Genetics), Albert Gough (UPDDI).** High-content screening for modulators of lamin B1 as a therapeutic target in autosomal dominant leukodystrophy (ADLD). ADLD is a rare fatal, adult-onset demyelinating disorder that presents in the 4th or 5th decade of life. ADLD patients experience significant disability during the course of the disease and usually survive for only ~10-15 years after the onset of symptoms. No treatment exists for this fatal disease, representing an urgent and unmet clinical need. ADLD is caused by a duplication of the lamin B1 gene, resulting in increased LMNB1 protein expression and the appearance of nuclear abnormalities. We have developed methodology to quantify those abnormalities and are currently performing a high-throughput screen for modifiers of Lamin B1 expression and associated changes in nuclear structure. This project is supported by an NIH IGNITE grant NS106087.

3. **Michael Tsang (Department of Developmental Biology), Andrew Hinck (Department of Structural Biology), David Koes (Computational and Systems Biology), Lee McDermott (Pharmaceutical Sciences).** 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 agents. We are using a combination of high-content analysis, automated cell migration assays, transgenic zebrafish, biophysical interaction studies, and computational modeling to explore novel allosteric binding sites on mitogen activated protein kinase phosphatases. Most recently we found that MKP inhibitors sensitize cancer cells to lymphokine activated killer cell activity, identifying an intriguing intersection of MKP activity and immune cell killing that we are currently exploring as a dual-specific pharmacological approach to antineoplastic therapy. An R01 application (CA172030) is pending resubmission.

4. **Anthony Schwacha (Biological Sciences), Mark Schurdak (UPDDI).** Development of High-Throughput screening assays for identification of small molecule inhibitors of the Mcm2-7 replicative helicase. Aberrant DNA replication is a hallmark of cancer, however disease-specific inhibitors for this process are largely unavailable. Many chemotherapeutic agents target DNA replication but have deleterious side effects. As blocking of DNA replication during elongation may itself cause genome instability, developing inhibitors to specifically block replication before it starts (during initiation) is an attractive approach. The Schwacha laboratory has identified the Mcm2-7 replicative helicase as a novel cancer-specific potential target in DNA replication initiation. The project is funded by NIH grant R01GM114336.

5. **Michael Palladino (Pittsburgh Institute for Neurodegenerative Diseases).** Triosephosphate isomerase (TPI) deficiency is a rare genetic multisystem disorder. It is characterized by lack or reduced activity of the enzyme triosephosphate isomerase, an enzyme necessary for the breakdown (metabolism) of certain sugars in the body. Affected individuals experience low levels of circulating red blood cells due to premature destruction of red blood cells (hemolytic anemia) and severe, progressive neurological symptoms. Affected individuals usually develop life-threatening complications early during childhood. The Palladino lab has discovered that pathogenic mutations are those that retain isomerase function but increase protein turnover. Using genetically modified cells that express fluorescently tagged mutant TPI we are developing a multiplexed high-content screening assay for compounds that stabilize mutant TPI.

6. **David Koes (Computational and Systems Biology), Gary Kohanbash (Neurological Surgery), Lee McDermott (Pharmaceutical Sciences), Andrew Hinck (Department of Structural Biology).** Small
Molecule Immunotherapy Targeting TIGIT. Antibodies against immune checkpoint inhibitors have become one of the most successful developments in anticancer therapy. The best established target is the PD1/PD-L1 receptor/ligand pair. However, a large proportion of patients does not respond to PD-1/PD-L1 therapy, and inhibition of alternative immune checkpoints or combinatorial inhibition of multiple inhibitory receptors has become a field of intense study. One such alternative target is TIGIT. We have discovered the first small-molecule inhibitor of TIGIT and shown that it disrupts the TIGIT-PVR interaction in vitro. The team is now developing a comprehensive platform for TIGIT inhibitor discovery.

7. Sandra Cascio (Department of Immunology), Daniel Altschuler (Pharmacology and Chemical Biology), Andrew Hinck (Department of Structural Biology). Exploiting the Muc1-CIN85 interaction as a novel cancer metastasis target. MUC1 is a transmembrane glycoprotein abnormally expressed in human adenocarcinomas. The extracellular domain of MUC1 contains a variable number of tandem repeats (VNTR) region that is extensively O-glycosylated in normal epithelia and underglycosylated in tumor cells. This change in posttranslational modification of MUC1 exposes, among others, a region of Muc1 that interacts with CIN85, an adaptor protein involved in signal transduction, cytoskeletal remodeling and cancer cell invasion. In vivo, mice injected with CIN85-depleted melanoma cells exhibited few or no lung metastasis and overexpression of MUC1 recovered the shCIN85-reduced metastatic process. This new, exploratory collaborative project aims to discover small molecules of the Muc1-CIN85 interaction.

8. Partha Roy (Department of Bioengineering), David Koes, D. Lansing Taylor (UPDDI). Targeting Profilin-1 as a mediator of 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 an ongoing 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 project is a new research direction emanating from my prior NIH grants R44GM090386 and R21CA147985 (with Platypus Technologies).

Study Sections and Advisory Committees

NIH Study Sections
2. NIH Small Business: Cancer Drug Developments & Therapeutics ZRG1 OTC-T (12) B (2014), Co-Chair
5. NIH S10 Shared Instrumentation 2016/01 ZRG1 IMST-B (30) I (Co-Chair)

Outside expert reviewer
1. North Carolina Biotechnology Center Research Grant Program, 2009
2. Medical Research Council, UK, Research Grant Program, 2009
3. National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), UK, 2010
4. Clinical and Translational Science Institute (CTSI), University of Pittsburgh, Basic to Clinical Collaborative Research Pilot Program (BaCCoR), 2011
5. Netherlands Organization for Health Research and Development, Medium Investment Subsidy Programme (ZonMw), 2011
7. National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), UK (2016)
9. Representative, School of Medicine, Chemical Hygiene Officers Committee, University of Pittsburgh, 2004-present
10. Member, School of Medicine Ambassador’s program, 2009 - present
11. Member, UPMC Hillman Cancer Center, Cancer Therapeutics Program (CTP), 2008 – present
12. Member, UPCI Cytometry Committee (2011 – present)

**Teaching Activities**

1. MSMPHL 2370 – Drug Discovery Course  
2. Lecturer, TECBio joint Pitt/CMU program (2014-2017)
3. Mentor and Lecturer, Drug Discovery and Computational Biology (DisCoBio) program (now CoBRA; 2014-2019)
4. Lecturer, ISB 2035 Systems Biology II (2018 - 2019)  
   Lecture topic: Automated screening and imaging in zebrafish
5. Undergraduate mentoring, Aaron Zheng (Honors College Health Sciences Fellow 2018), Exploring allosteric binding sites on dual specificity phosphatases
The non-covalent interactions responsible for protein-ligand binding are accompanied by alterations in the electron density profiles of the participating protein, ligand and solvent atoms. These density alterations are ultimately related to the thermodynamic changes associated with the binding process. We developed a method for quantifying these alterations using Mulliken population analysis (MPA). We confirmed that MPA carried out with a properly selected basis set can produce results that are comparable to the analysis of molecular interactions in real space using the reduced density gradient (RDG) approach. These methods were validated on a series of molecular models containing non-covalent interactions. We focused on the relationship between electron density and electronic energy as interacting molecular pairs are separated. We showed that the electronic energy necessary to break non-covalent bonds is tightly correlated with electron density alterations. We combined MPA with protein fragmentation to assess the strength of the interaction between each unique pair of protein and ligand atoms. Pairwise interactions involving the same atom were summed to construct binding profiles for protein and ligand atoms and protein residues. We applied this approach to a series of inhibitors bound to wild-type and mutated HIV-1 proteases. We measured and compared the strength of hydrogen bonds, induced dipoles, aromatic interactions and steric hindrances. We believe this approach could be important for in-silico engineering of ligands with stronger binding affinities. The current work has been submitted to Proteins, Structure, Functions and Bioinformatics for publication. At the present time this work is being extended to interactions between unbound proteins and ligands and water molecules. If successful, this will permit quantification of the favorable enthalpy associated within binding and the unfavorable enthalpy associated with desolvation. We are also working on approaches for estimating the entropy of binding based on the electron density profiles of interacting water molecules.

The following slide from our paper demonstrates the effect of the V82F/I84V mutation in HIV-1 protease on binding at the mutation site for the KNI-577 protease inhibitor. A favorable interaction between one of the aromatic rings in KNI-577 and the protease becomes unfavorable suggesting steric hindrance.

**Collaborative Research Activities**

*Intra-departmental*
- David Koes

*External*
- Angela Gronenborn
Figure 14. Effect of the V82F/I84V mutation at the H17 ligand site. The position of the aromatic ring containing H17 is shifted resulting in new interactions that are predominantly unfavorable with a net e-MPA loss of 0.038. The total e-MPA loss for all interacting ligand sites is 0.138. The electron density isosurface (r) is set to the level of a weak hydrogen bond.
Physical biology of cell phenotypic transitions

We are interested in the following fundamental questions. How do thousands of molecules species orchestrate temporally and spatially to determine a cell phenotype? How can one regulate and direct cell phenotype? Specifically, the lab currently focuses on Epithelial-to-Mesenchymal Transition (EMT), characterized by loss of cell-cell adhesion and increased cell motility. EMT plays important roles in embryonic development, tissue regeneration, wound healing and pathological processes such as fibrosis in lung, liver, and kidney, and cancer metastasis. The lab uses integrated experimental and computational approaches to study the coupled gene expression and epigenetic dynamics of EMT. In a 2013 Biophysical Journal article, we proposed a mathematical model to explain different cell phenotypes appeared during EMT. In a subsequent Science Signaling (2014) paper, we experimentally confirmed several model predictions. Currently we are working on the following projects:

1. Cells live under ever-changing environment, thus it is important for them to sense the external environment and transmit the information to downstream elements faithfully. Using quantitative single cell measurements and mathematical modeling we worked out a mechanism how cells decipher TGFβ strength and duration and respond accordingly (NPJ Sys Biol Appl 2018). We are performing live cell imaging on the process.

2. How does a phenotypic conversion process take place step-by-step? We are using live cell imaging and deep-learning based image analysis tools to examine the EMT process. For imaging we use both fluorescence-based labeling (see cells with E-cadherin-GFP) aided with the CRISPR-Cas9 technique, and cell morphology-based bright-field imaging.

3. During EMT cells undergo global change of transcriptome, epigenome and chromosome structures. By analyzing different types of high-throughput data we aim at unraveling some basic principles of cell phenotype regulation (PLoS Comp Biol., 2019). In parallel, we are developing CRISPR-based techniques to tag and track selected genomic loci in live cells, and compare with polymer physics based model studies.

4. After acute kidney injury (AKI) a kidney repair system is activated. By combining mathematical modeling and mouse model studies (in collaboration with Dr Youhua Liu at Pathology Department), we unraveled some basic design principles of the repair system, and resolved puzzling roles of Wnt and EMT on the recovery process and progression to chronic kidney diseases (CKD).

5. Cell phenotypic transition (CPT) is ubiquitous in biology and EMT is an example. Advances of single cell techniques catalyze a new field of studying how a CPT proceeds step-by-step. In collaboration with the Jonathan Weissman lab at UCSF, we are developing an experimental/computational procedure that can map out the governing vector field of a CPT process, and applying it to study cell differentiation.

“We aim at developing cell phenotypic transition studies as a field of physical sciences.”
**Peer-Review Activities**

**Reviewer**
1. *PloS Computational Biology*
2. *Interface*
3. *iScience*
4. *Journal of Cancer Metastasis and Treatment*
5. *Nature Communications*
6. *Journal of Cell Biology*
7. *Nucleic Acid Research*
8. Scientific Reports

**Associate Editor**
1. BMC Systems Biology

**Guest Editor**
1. Physical Biology

**Tenure Package Reviewer**
1. University of California at Los Angeles (UCLA)

**Funding Foundation Reviewer**
1. Qiushi (China)
2. Breast Cancer Grant (UK)

**Committees**
1. International Member of the Faculty Recruitment Committee: PKU-Tsinghua University Life Science Center

**Collaborative Research Activities**

**Intra-departmental**
1. Ivet Bahar, Ph.D. (Chair)
   - Studying protein dynamics from cryo-EM data.
   - Mapping single cell regulatory network vector field from single cell RNA-Seq data.

**University-wide**
2. Simon Watkins, Ph.D. (Cell Biology)
   - The coupling between cell cycle and EMT.
   - Studying chromosome structure and dynamics.
External

1. Jonathan Weissman, Ph.D. (Cellular Molecular Pharmacology, University of California at San Francisco, UCSF) Mapping single cell regulatory network vector field from single cell RNA-Seq data.

2. Fan Bai, Ph.D. (China Rehabilitation Research Center, China) and Guang Yao, Ph.D. (Cancer Systems Biology, University of Arizona) Regulation mechanism of cell quiescence.


Presentations at National or International Meetings

National Meetings

- January 2019

International Meetings

- June 2019

- June 2019
  Peking University "Study Cell Phenotypic Conversion Dynamics with Live Cell Imaging". Invited Seminar. Peking, China.

- June 2019
  Tsinghua University "Chromosome Structure and Gene Regulation". Invited Seminar.

- June 2019
  Beijing Institute of Technology "Study Cell Phenotypic Conversion Dynamics with Live Cell Imaging" Invited Seminar.

- June 2019
  Renmin University of China "Extending the Horizon of Physical Chemistry to Biology" Invited Seminar.

- July 2019
Learn to segment single cells with deep distance estimator and deep cell detector

Single cell segmentation is a critical and challenging step in cell imaging analysis. Traditional processing methods require time and labor to manually fine-tune parameters and lack parameter transferability between different situations. Recently, deep convolutional neural networks (CNN) treat segmentation as a pixel-wise classification problem and become a general and efficient method for image segmentation. However, cell imaging data often possesses characteristics that adversely affect segmentation accuracy: absence of established training datasets, few pixels on cell boundaries, and ubiquitous blurry features. We developed a strategy that combines strengths of CNN and traditional watershed algorithm.

A collaboration between the labs of Drs. Xing and Sant (Pharmacy) leads to publication in Cancer Research

Targeting the temporal dynamics of hypoxia-induced tumor-secreted factors halts tumor migration

Computational and experimental studies showed that inhibition of tumor-secreted factors effectively halts microtumor migration despite tumor-to-tumor variation in migration kinetics, while inhibition of hypoxia is effective only within a time window and is compromised by tumor-to-tumor variation, supporting our notion that hypoxia initiates migratory phenotypes but does not sustain it. In summary, we show that targeting temporal dynamics of evolving microenvironments, especially tumor-secreted factors during tumor progression, can halt tumor migration.

Dr. Shilpa Sant
Dr. Jianhua Xing

# Grants Awarded

## Recently Awarded Grants since 7/1/19

<table>
<thead>
<tr>
<th>PI</th>
<th>Project title</th>
<th>Agency</th>
<th>Total Award</th>
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<td>Immunosuppression in Acute Lung Injury</td>
<td>NHLBI</td>
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<td>New Therapies for Liver Fibrosis and Hyperproliferation in Alpha 1-AT Deficiency</td>
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<td>From non-coding to coding: uncovering the hidden coding potential of non-coding sequences and its role in de novo gene evolution</td>
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<td>WMD ECHO Detector</td>
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<td>High-performance weighted ensemble software for simulation of complex bio-events</td>
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<td><strong>$163,250</strong></td>
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<td>Clark</td>
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<td>CAREER: Regulation of Cargo Selection and Ubiquitination by Protein Trafficking Adaptors</td>
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<td>Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data</td>
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<td>Functional Annotation of Genomes via Phenotypic Convergence</td>
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<tr>
<td>Last Name</td>
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<td>Faeder</td>
<td>NHLBI</td>
<td>Cardiolipin as a Novel Mediator of Acute Lung Injury</td>
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<td>High Performance Computing for Multiscale Modeling of Biological Systems</td>
<td>$141,781</td>
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<td>High-performance Weighted Ensemble Software for Simulation of Complex Bio-events</td>
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<td>Nature’s Rotary Molecular Dynamos: A systematic Modeling Framework</td>
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<td>20-HETE Formation Inhibitors in Cardiac Arrest</td>
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<td>CSDE: D3SC: Conformer Toolkit: Generating Accurate Small Molecule Conformer Ensembles</td>
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<td>Methods, Tools and Resources for Interactive Online Virtual Screening and Lead Optimization</td>
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<td>Relay Therapeutic Virtual Screening with Generated Pseudoligands</td>
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<td>Deciphering dynamic signals in control of cell fate decisions</td>
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<td>Role of Novel Mitotic 4E-BP1 Protein Isoform in Cellular Transformation</td>
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<td>Last Name</td>
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<td>Pullara</td>
<td>Spintellx</td>
<td>Optimizing, scaling, and evaluating the University Technology for digital whole side hematoxylin and eosin stained breast tissue images</td>
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<td>Uttam</td>
<td>NCI</td>
<td>Three dimensional nanoscale nuclear architecture mapping based taxonomy of precursor lesions for predicting colorectal cancer</td>
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<td>NIGMS</td>
<td>Investigating Mechanisms of de Novo Gene Birth in Saccharomyces Cerevisiae</td>
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<td>Collaborative Research: Modeling the coupling of epigenetic and transcriptional regulation</td>
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<td>Role of the Snail1-Twist-p21 axis on Cell Cycle Arrest and Renal Fibrosis Development</td>
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### Research Funding by Sponsor Type

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### Grant Spending History

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<td>FY19</td>
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</table>
FY 19 GRANTS BY SOURCE

- NIGMS 47%
- Private/Corp. 7%
- NSF 7%
- NIAID 4%
- NIDA 5%
- NHGRI 10%
- NCI 6%
- NHLBI 4%
- NIDDK 2%
- NLM 4%
- Other NIH/DOD 4%
Dr. Xing (PI) and Dr. Simon Watkins (co-I) received a R01 award from NIDDK

“Role of the Snail1-Twist-p21 axis on cell cycle arrest and renal fibrosis development”

Takis Benos Group Receives UPMC ITTC Funding

Takis Benos group participates in a research team that received UPMC ITTC funding to develop a new technology that will determine the health functional status in the elderly.
NIH NATIONAL CANCER INSTITUTE

Dr. Robin Lee to receive collaborative R01 grant with Dr. Yuan Chang

**Title**
Rule of a Novel Mitotic 4E-BP1 Protein Isoform in Cellular Transformation

**PI**
Yuan Chang

**Co-I**
Robin Lee and Patrick Moore

**Brief description**
Our aims will use quantitative approaches and models to advance our fundamental understanding of how a mitosis-specific, hyperphosphorylated form of 4E-BP1 functions in normally cycling cells and how its deregulation in cancer cells may contribute to human malignancies.

Dr. Yuan Chang
Dr. Patrick Moore  Dr. Robin Lee

Figure 4. New pathway for control of cap-dependent translation during mitosis

Dr. Yuan Chang

Cell cycle specific maintenance of cap translation

Dr. Maria Chikina Receives DARPA Grant for WMD ECHO Detector

The Epigenetic Characterization and Observation (ECHO) program aims to diminish the threat posed by weapons of mass destruction (WMD). To do this, the program is building a man-portable device that analyzes an individual’s epigenetic “fingerprint” to potentially reveal a detailed history of that individual’s exposure to WMD or their precursors. DARPA envisions that the same technology could provide rapid diagnostics for troops who may have been exposed to threat agents or who may be suffering from infections, providing a timely signal to apply effective medical countermeasures.

Dr. Maria Chikina

Dr. Stuart Sealfon

Institute of Medicine at Mount Sinai
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 70 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, there were 243 applications received during the 2019-2020 recruiting season. Following extensive review and discussion, 45 offers were extended to students; of which 23 students accepted the offer; twenty-two students will join the program in 2019, including one student who deferred from the last recruitment cycle. Our new cohort has an average GPA of 3.60 and averaged scores in the 87th and 94th percentiles on the GRE quantitative and verbal sections, respectively.

The following is a listing of the new CPCB students on both sides (Pitt and...
Some additional undertakings in the program during FY2019 were:

- We were awarded a continuing renewal of our T32 grant.
- 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 23 students was recruited for 2019-2020 school year.
- The CPCB Directors, with support from the training faculty, eliminated the GRE application requirement beginning with the 2020 recruitment cycle.

**University of Pittsburgh**
Roshni Bhatt, Case Western Reserve
Marissa Di, University of Southern California
Mark Ebeid, University of Maryland, Baltimore County
Gabriella Gerlach, Skidmore
Andrew McNutt, Purdue
Daniel Penaherrera, Arizona State University
Dante Poe, Michigan State
April Rich, Fordham
Steven Smeal, Colorado State University - Daniel Yuan, B.S., Johns Hopkins University

**Carnegie Mellon University**
Abhinav Adduri, University of California, Berkeley
Haoran Chen, South China University of Technology
Xiaoyue Cui, Tsinghua University / CMU
Monica Dayao, University of Cambridge
Mustafa Guler, University of California, San Diego
Caroline Larkin, University of Maryland, Baltimore County
Ke Ni, University of California, Santa Barbara
Hannah Schriefer, University of Georgia
Jingjing Tang, Nanjing University
Donghui Yan, University of Wisconsin
Muyu (Wendy) Yang, Carnegie Mellon University
Haotian Teng, Peking University
2. Computational Biomedicine and Biotechnology Masters Program
The new Computational Biomedicine and Biotechnology (CoBB) master's program generates leaders who can translate cutting-edge computational technologies into real-world advances in biomedicine and biotechnology. The program focuses on the interface between computer science and applied biology and is appropriate for students with backgrounds in quantitative disciplines, such as computer science and engineering, or biological sciences who want to make an impact in the rapidly evolving field of computational biotechnology.

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

The campus-wide Ph.D. program in Molecular Biophysics and Structural Biology is inherently interdisciplinary, requiring the viewpoints of faculty 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.

4. 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.

5. 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 tenth cohort of students (2010-2019) and continues to build on the solid foundation that our previous Bioengineering and Bioinformatics Summer Institute (BBSI) initiative started. In our eighth 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 students from across the 50 states and Puerto Rico. Again, our applicants were a very diverse group who came from many academic, geographic, and racial/ethnic backgrounds, including many students from groups underrepresented in the sciences and those that are at universities that have limited research opportunities. Our 2019 cohort consisted of 12 students in total – 10 supported by our NSF award (100% of whom are from underrepresented backgrounds and/or from small non-PhD granting institutions) and 2 students from Pitt (2 supported by departmental funds granted by the Deans of the medical school). We look forward to continuing our traditions of undergraduate mentoring and training to inspire the next great generation of scientists. Our students have gone on to enjoy many successes including selections for research presentations at national conferences and securing awards such as the NIH and NSF pre-doctoral fellowships.

   High School Summer Program This past summer saw the continuation of the CSB initiative that reached out to high school students in the Pittsburgh area. We are a component of the UPMC Hillman Academy (formerly the University of Pittsburgh Cancer Institute’s (UPCI) High School Summer Academy), which we call Computational Biology Research Academy (CoBRA). In our ninth summer, we accepted 10 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 and postdoctoral fellows 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 CoBRA 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. Most of our students enroll in top undergraduate programs across the country return with many of them returning to Pitt for their college education.
## 2018-2019 CPCB Seminar Series | Fridays at 11am

### Carnegie Mellon - University of Pittsburgh

**Ph.D. Program in Computational Biology**

<table>
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<th>Date</th>
<th>Speaker</th>
<th>Host</th>
<th>Title</th>
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<tbody>
<tr>
<td>September 14, 2018</td>
<td>Warren Ruder</td>
<td>Russell Schwartz (CMU)</td>
<td>Modeling Emergent Behavior in Synthetic Biological Systems</td>
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<td>September 21, 2018</td>
<td>Bokai Zhu</td>
<td>Robin Lee (Pitt)</td>
<td>Unveiling “Musica universalis” of the Cell: A Brief History of Biological 12h Rhythms</td>
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<td>October 5, 2018</td>
<td>Chad Myers</td>
<td>Anne-Ruxandra Carvunis (Pitt)</td>
<td>Translating insights from yeast to discover genetic interactions in humans</td>
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<td>October 12, 2018</td>
<td>Ryan Suderman</td>
<td>James Faeder (Pitt)</td>
<td>Understanding the limits of information transmission in cellular signaling networks</td>
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<tr>
<td>November 2, 2018</td>
<td>Robert Jernigan</td>
<td>Ivet Bahar (Pitt)</td>
<td>Improving Protein Sequence Matching to Aid Genome-Based Medicine</td>
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<td>November 9, 2018</td>
<td>Guo-Cheng Yuan</td>
<td>Jian Ma (CMU)</td>
<td>Systematic Mapping of Cellular States and Regulatory Circuits</td>
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<td>November 30, 2018</td>
<td>Aaron Wise</td>
<td>MetaSchool Event (Pitt)</td>
<td>Oh the places you can go: A bioinformatics odyssey</td>
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<td>December 7, 2018</td>
<td>Peter Kekenes-Huskey</td>
<td>Jacob Durrant (Pitt)</td>
<td>Understanding cardiac calcium signaling through computation: The Calcium, Calmodulin, Calcineurin signaling ‘triad”</td>
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<td>January 18, 2019</td>
<td>Rachel Gottschalk</td>
<td>Robin Lee (Pitt)</td>
<td>Quantitative control of macrophage signaling and inflammatory thresholds</td>
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<td>January 25, 2019</td>
<td>Iman Hajirasouliha, Ph.D.</td>
<td>Hosein Mohimani (CMU)</td>
<td>Novel algorithms and applications of Linked-Read genomics and metagenomics</td>
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<tr>
<td>Date</td>
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<td>Speaker 2</td>
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<td>February 1, 2019</td>
<td>Will Fairbrother</td>
<td>Joel McManus</td>
<td>Pathogenic variations often disrupt splicing – implications for clinical genetics and evolutionary models of regulatory signals</td>
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<td>James Taylor</td>
<td>Jian Ma (CMU)</td>
<td>Making large-scale genomic analysis accessible, transparent, and reproducible</td>
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<td>Johns Hopkins University</td>
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<td></td>
<td>Jacob Stewart-Ornstein</td>
<td>Hosein Mohimani</td>
<td>Conservation and divergence in p53 and DNA damage signaling dynamics</td>
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<td>University of Pittsburgh</td>
<td>(CMU)</td>
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<td>Hillman Cancer Center</td>
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<td>February 15, 2019</td>
<td>Alberto Bartesaghi</td>
<td>Robert F. Murphy</td>
<td>Workflows for high-resolution structure determination by single particle Cryo-EM</td>
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<td></td>
<td>Duke University</td>
<td>(CMU)</td>
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<td>March 22, 2019</td>
<td>Dennis Vitkup</td>
<td>Robin Lee (Pitt)</td>
<td>Phenotypic evolution of bacteria and ecological dynamics of microbiomes</td>
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<td>Columbia University</td>
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<td>March 29, 2019</td>
<td>Paul Medvedev</td>
<td>Hosein Mohimani</td>
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<td>Penn State University</td>
<td>(CMU)</td>
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<td>April 5, 2019</td>
<td>We Chen</td>
<td>Jianhua Xing (Pitt)</td>
<td>Clustering Single-Cell Sequencing Data from Population Studies</td>
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<td>University of Pittsburgh</td>
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<td>April 19, 2019</td>
<td>Bo Huang</td>
<td>Jianhua Xing (Pitt)</td>
<td>Mapping the inner world of cells</td>
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TRAINING GRANT PUBLICATIONS

10. X. Ruan, C. Wülfing, and R. F. Murphy (2017) Image-based Spatiotemporal Causality Inference for Protein Signaling Networks. Bioinformatics 33:i217-i224

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

Administrative Duties related to Education

Joseph Ayoob, Ph.D.
Course Director and Instructor: Laboratory Methods for Computational Biologists (LMCB) Course (2010-present)
Course Director: Communication, Presentation, and Career Building (CPCB) Course (2017-present)
PI and Program Director: Training and Experimentation in Computational Biology (TECBio) Research Experiences for Undergraduates (REU) Program (2010-present)
Program Director: Computational Biology Research Academy (CoBRA) Hillman Academy Program (2011-present)

Ivet Bahar, Ph.D.
Joint PI with Drs. Xiang-Qun and Xing, NIH-NIDA - P30, NIDA Center of Excellence for Computational Drug Abuse Research (CDAR) (2014-present)
Joint PI, with Drs. Cooper & Berg, NIH-NHGRl - U54, Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data (CCD) (2014-present)
Distinguished Professor, and John K. Vries Chair, Department of Computational and Systems Biology (2012 – present)
Dickson Prize Committee Member (2013 - present)
Joint Center between Pitt, Carnegie Mellon, PSC & Salk Inst, 2012-present
Director/PI, NIGMS Biomedical Technology & Research Center (2012 - present)
Director/PI, NIH-NIGMS - R01, Continued Development of Protein Dynamics Software ProDy (2012-2016)
Director, NIH-NIDDK – P01, Computational Pharmacology Core, New Therapies for Liver Fibrosis and Hyperproliferation in α1-AT Deficiency (2012-present)
Associate Director, University of Pittsburgh Drug Discovery Institute (2010-present)
John K. Vries Chair, Department of Comp & Systems Biology, SOM, Pitt, 2005-present
Director, ChemInformatics Core, Center for Medical Countermeasures Against Radiation Pitt & UPCI (2010-present)
Professor, Department of Computational and Systems Biology (2013 - present)
Joint PI with Drs. Murphy, Russell & Benos, NIH-NIBIB - T32, Integrated, Interdisciplinary, Inter-University PhD Program in Comp Biology (CPCB) (2009-present)
Member, Pitt Center for Simulations and Modeling (SAM) (2008 -present)
Training Faculty and Executive Committee Member, Carnegie Mellon University/Pitt PhD Program in Computational Biology (2005-present)
Faculty, Program in Integrative Molecular Biology (PIMB) (2005 - 2014)
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 (2004-2009)
Founding Director, Carnegie Mellon University and University 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)

Panayiotis (Takis) V. Benos, Ph.D.
DBMI Bioinformatics (Concentration) Training Program Core, Member, June 2003–present
Course Lecturer, TECBio Program
CPCB Curriculum Committee Chair
Associate Director of the Integrative Systems Biology Program
Chair of Integrative Systems Biology Curriculum Committee
Member of CPCB Admissions Committee
Member of Integrative Systems Biology Admissions Committee
Core Course director, Integrative Systems Biology program
Member of Executive Committee of the Biomedical Informatics Training Program
Carlos J. Camacho, Ph.D.
Member, Executive Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology, 2005-present.
Member, University of Pittsburgh Graduate Faculty, School of Medicine.
Course Director of 4-credit graduate program course “Introduction to Computational Structural Biology” (MSCBIO 2030)

Anne-Ruxandra Carvunis
Recruiting committee, ISB program
Thesis committee: She Zhang, CPCB program
Thesis committee: Natalie Sauwerwald, CPCB program
Thesis committee: Sarah Munyoki, ISB program
Teaching: Genomics and Evolutionary Biology, TECBio program
Teaching: Genomics and Evolutionary Biology, CoBRA program
Graduate student mentor: Omer Acar, CPCB program
Graduate student mentor: Saurin Parikh, BioEngineering
Rotation student mentor: BaDoi Phan, MSTP program
Rotation student mentor: Trevor Frisby, CPCB program
Rotation student mentor: Feng Shan, ISB program
Undergraduate research mentor: Selin Sevgi, Biology, Koc University (Turkey)
Undergraduate research mentor: John Iannota, Molecular Biology, Pitt
Undergraduate research mentor: Dominique Cantave, TecBio program, Mathematics, Harvard University
Undergraduate research mentor: Thomas Dougherty, TecBio program, Mathematics, Harvey Mudd College

Maria Chikina, Ph.D.
Admissions Committee Member 2017 – Present
Chair of the CPCB Admissions Committee, 2018
Mentor CPCB Graduate Student Weiguang Mao
Member CPCB Course Committee

Chennubhotla, Ph.D.
Member, Organizing Committee for a Masters Program in Computational and Systems Biology.
Member, Curriculum Committee, Integrative Systems Biology Program http://www.pimb.pitt.edu/.
Course Co-Director of 3-credit graduate program course, Scalable Machine Learning for Big Data Biology (MSCBIO 2065)

Nathan Clark, Ph.D.
Member of Joint Carnegie Mellon – University of Pittsburgh Ph.D. program in Computational Biology including the following active roles:
Associate Director of the PhD program
Course Instructor of 3-credit graduate program course “Molecular Evolution” (MSCBIO 2075)
Mentor for Graduate Students, Raghav Partha and Amanda Kowalczyk
Mentor TECBio student, Gabrielle Coffing
Member, Executive Committee
Member of Integrative Systems Biology PhD program

James R. Faeder, Ph.D.
Vice Chair of Educational Activities, CSB, 2016-present.
Co-Program Director, Joint CMU-Pitt PhD program, 2016-present.
Member, Departmental Seminar Committee, Fall, 2012 – present.
Course Director, MSCBIO 2040 Cellular and Systems Modeling, 2010 – present.
Member of the Graduate Faculty of the University of Pittsburgh School of Medicine, 2010 – present.
Member, Executive Committee, Joint CMU-Pitt Ph.D. Program in Computational Biology

David Koes, Ph.D.
Co-Director, Computational Biology Research Academy (CoBRA), Summer 2019
Course Lecturer, TECBio, Summer 2019
Course Lecturer, CoBRA, Summer 2019
Guest Lecturer, MSCBIO/CMPBIO 2030: Introduction to Computational Structural Biology
Course Director, MSCBIO 2025: Introduction to Bioinformatics Programming in Python
Course Co-Director, Scalable Machine Learning for Big Data Biology MSCBIO 2065
CPCB Curriculum Committee Chair

Robin Lee, Ph.D.
Evaluator, MSTP.
Member, ISB admissions committee.
Member, CPCB Seminar series Committee.

Timothy Lezon, Ph.D.
Course Director, MSCBIO/CMPBIO 2030: Introduction to Computational Structural Biology, Fall 2017
Facilitator, MS-2: Investigation and Discovery, Fall 2017
Facilitator, MS-1: Evidence-Based Medicine – Applied, Spring 2018
Co-Director, Drug Discovery, Computational and Systems Biology (CoBRA) Academy, Summer 2018
Students Mentored:
Cemal Erdem, CPCB graduate student
Feng Guo, Tsinghua research scholar
Derek Alton, mathematics undergraduate
Glenn Mersky, mathematics undergraduate
Stephen Provencher, chemical and petroleum engineering undergraduate
Michelle Situ, bioinformatics undergraduate

Mark Schurdak, Ph.D.
Co-organizer, CoBRA program.
John Vries, M.D.
Member, University of Pittsburgh Graduate Faculty, School of Medicine.

Jianhua Xing
Supervisor of one “First experience in Research” students, Spring, 2018
Supervisor of three undergraduate students (taking research credits)
Supervisor of one REU student, Summer 2018
Member of the CPCB Curriculum Committee

POSTDOCTORAL ASSOCIATES

Joseph Ayoob, Ph.D.
Emily Furbee, Ph.D. in Biology, Carnegie Mellon University, 2014

Ivet Bahar, Ph.D.
James Krieger Ph.D. in Computational Biology, University of Cambridge, UK, 2016
Hongchun Li, Ph.D. in Chemical Biology, Xiamen University, China 2014
Karolina Mikul ska-Ruminska, Ph.D. in Biophysics, Nicolaus Copernicus University, Torun Poland, 2014
Luca Ponzoni, Ph. D. in Physics and Chemistry of Biological Systems, SISSA, Italy, 2016

Panagiotis Benos, Ph.D.
Hyokyeong Lee, Ph.D. in Computer Science, University of Southern California, 2010
Dimitrios Manatakis, Ph.D. in Computer Science, University of Athens, 2014

Carlos Camacho, Ph.D.
Dhilon Sureshshbai Patel, Ph.D. in Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, India, 2011

Anne-Ruxandra Carvunis, Ph.D.
Stephen Branden Van Oss, Ph.D. in Molecular Biology, University of Pittsburgh, 2017
Aaron Wacholder, Ph.D. in Evolutionary Biology, University of Colorado Boulder, 2017

Nathan Clark, Ph.D.
Wynn K. Meyer, Ph.D. in Human Genetics, University of Chicago, 2013

James Faeder, Ph.D.
Ernesto Suarez Alvarez, Ph.D. in Theoretical and Computational Chemistry, University of Oviedo, Spain, 2011
Ali Sinan Saglam, Ph.D. in Chemistry, University of Pittsburgh, 2018

Robin Lee, Ph.D.
Juan Agustin Cruz-Vasquez, Ph.D. in Immunology, University of Pittsburgh, 2018

D. Lansing Taylor, Ph.D.
Xiang Li, Ph.D. in Electrical Engineering, West Virginia University, 2014
Jianhua Xing, Ph.D.
Xiaojun Tian, Ph.D. in Biophysics, Nanjing University, China, 2012
Weikang Wang, Ph.D. in Physics, Peking University, 2015

RESEARCH ASSOCIATE
S. Chakra Chennubhotla, Ph.D.
Filippo Pullara, Ph.D. in Physics, University of Palermo, Italy, 2006

RESEARCH SCIENTISTS
Ivet Bahar, Ph.D.
JiYoung Lee, Ph.D. in Physics, Pohang University of Science and Technology, Korea, 2008
Burak Kayak, Ph.D. in Physics, Bogazici University, Turkey, 2009

S. Chakra Chennubhotla, Ph.D.
Om Prakash Choudhary, Ph.D. in Computational Biology, University of Pittsburgh, 2013

GRADUATE STUDENTS
Ivet Bahar, Ph.D.
Fen Pei, CMU-Pitt Ph.D. Program in Computational Biology
Yan Zhang, CMU-Pitt Ph.D. Program in Computational Biology
She Zhang, CMU-Pitt Ph.D. Program in Computational Biology

Panagiotis Benos, Ph.D.
Minxue Jia, CMU-Pitt Ph.D. Program in Computational Biology
Tyler Lovelace, CMU-Pitt Ph.D. Program in Computational Biology
Daniel Yuan, CMU-Pitt Ph.D. Program in Computational Biology

Carlos Camacho, Ph.D.
Bentley Wingert, CMU-Pitt Ph.D. Program in Computational Biology
Samir el Abdouni, University of Groningen
Rick Oerlemans, University of Groningen

Anne Ruxandra Carvunis, PhD
Omer Acar, CMU-Pitt Ph.D. Program in Computational Biology
Carly Houghton, CMU-Pitt Ph.D. Program in Computational Biology
Saurin Parikh, Integrative Systems Biology Program

Nathan Clark, Ph.D.
Raghavendran Partha, CMU-Pitt Ph.D. Program in Computational Biology

ANNUAL REPORT FY 2019
Amanda Kowalcyzk, CMU-Pitt Ph.D. Program in Computational Biology

**Chakra Chennubhotla, Ph.D.**
Samantha Furman, CMU-Pitt Ph.D. Program in Computational Biology
Weiguang Mao, CMU-Pitt Ph.D. Program in Computational Biology
Akash Parvarticar, CMU-Pitt Ph.D. Program in Computational Biology

**James Faeder, Ph.D.**
Kunal Aggarwal, CMU-Pitt Ph.D. Program in Computational Biology
Neha Cheemalavagu, CMU-Pitt Ph.D. Program in Computational Biology
Sanjana Gupta, CMU-Pitt Ph.D. Program in Computational Biology

**David Koes, Ph.D.**
Paul Francoeur, CMU-Pitt Ph.D. Program in Computational Biology
Jonathan King, CMU-Pitt Ph.D. Program in Computational Biology
Jocelyn Sunseri, CMU-Pitt Ph.D. Program in Computational Biology

**Robin E.C. Lee, Ph.D.**
Sanjana Gupta, CMU-Pitt Ph.D. Program in Computational Biology
Yue Guo, Physics
Chaitanya Mokashi, CMU-Pitt Ph.D. Program in Computational Biology

**D. Lansing Taylor**
Fen Pei, CMU-Pitt Ph.D. Program in Computational Biology

**Jianhua Xing, Ph.D.**
Yan Zhang, CMU-Pitt Ph.D. Program in Computational Biology
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<td>Edward Marcotte</td>
<td>University of Texas</td>
<td>Evolution and the Proteome: Insights into Human Disease From Deeply Conserved</td>
<td>October 23, 2018</td>
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<tr>
<td>Luca Ponzoni &amp; James Kreiger</td>
<td>University of Pittsburgh</td>
<td>Integrated Approach for Pathogenicity Prediction of Missense Variants Normal Mode Sampling Simulations and</td>
<td>October 30, 2018</td>
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<td>Robert Jernigan</td>
<td>Iowa State University</td>
<td>Improving Protein Sequence Matching to Aid Genome-Based Medicine</td>
<td>November 2, 2018</td>
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<td>Agustin Cruz &amp; Hongchun Li</td>
<td>University of Pittsburgh</td>
<td>Uncovering Properties of Dynamic Signal Propagation in Single Cells Quantitative Systems Pharmacological Analysis of Drugs of Abuse Reveals the Pleiotropy of Targets</td>
<td>November 13, 2018</td>
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<td>Aaron Wacholder</td>
<td>University of Pittsburgh</td>
<td>Evolution and Function of Proto-genes</td>
<td>November 27, 2018</td>
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<td>Jeffrey Gross</td>
<td>University of Pittsburgh</td>
<td>Genetic and Epigenetic Regulation of Retinal Development</td>
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<td>Yang Liu</td>
<td>University of Pittsburgh</td>
<td>Super-resolution Imaging of Higher-Order Chromatin Organization</td>
<td>December 11, 2018</td>
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<td>Oliver Lichtarge</td>
<td>Baylor College of Medicine</td>
<td>Making Personal Sense of Disease: Machine Learning and Mutational</td>
<td>December 18, 2018</td>
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<td>Sarah Hainer</td>
<td>University of Pittsburgh</td>
<td>Profiling Pluripotent Factors in Single Cells and Early Embryos</td>
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<td>Branden Van Oss</td>
<td>University of Pittsburgh</td>
<td>Methionine Starvation in Budding Yeast: Investigation of Strange Phenotypes in a</td>
<td>February 5, 2019</td>
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<td>Weikang Wang</td>
<td>University of Pittsburgh</td>
<td>Single cell morphology trajectory analysis on cell cycle and Epithelial-to-</td>
<td>February 12, 2019</td>
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<td>Ipsita Banerjee</td>
<td>University of Pittsburgh</td>
<td>Bioengineering and Systems Biology of Human Pluripotent Stem Cells</td>
<td>February 19, 2019</td>
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<td>Yuanyuan Chen</td>
<td>University of Pittsburgh</td>
<td>The Roles of Rhodopsin Homeostasis and Signaling in Retinal Diseases</td>
<td>February 26, 2019</td>
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<td>Wynn Meyer</td>
<td>University of Pittsburgh</td>
<td>Fantastic Yeasts and What to Feed Them: A genome-wide analysis of metabolic trait evolution across 274 yeasts</td>
<td>March 5, 2019</td>
</tr>
</tbody>
</table>
Primary Faculty

Emeritus
Hagai Meirovitch, Ph.D., Emeritus, The Weizmann Institute of Science, Rehobot, Israel, 1974

Professor
Ivet Bahar, Ph.D., Distinguished Professor and John K. Vries Chair, Istanbul Technical University, Turkey, 1986
Panayiotis V. Benos, Ph.D., University of Crete, Greece, 1997
Jeremy Berg, Ph.D., Professor, Harvard University, Cambridge, 1985
D. Lansing Taylor, Ph.D., Professor, State University of New York at Albany, 1973

Associate Professor
Joseph Ayoob, Ph.D., John Hopkins University, Maryland, 2006
Carlos Camacho, Ph.D., University of Maryland, College Park, 1991
S. Chakra Chennubhotla, Ph.D., University of Toronto, 2004
Nathan Clark, Ph.D., University of Washington, Seattle, 2007
James Faeder, Ph.D., University of Colorado at Boulder, 1998
Andreas Vogt, Ph.D., University of Hamburg, Germany, 1990
John Vries, M.D., University of California at San Francisco, 1966
Jianhua Xing, Ph.D., University of California, Berkeley, 2002

Research Associate Professor
Albert Gough, Ph.D., Carnegie Mellon University, Pittsburgh, 1992
Mark Schurak, Ph.D., Baylor College of Medicine, Houston, 1987
Andrew Stern, Ph.D., University of California at Los Angeles, 1977
Lawrence Vernetti, Ph.D., University of Arizona, 1991

Assistant Professor
Anne-Ruxandra Carvunis Ph.D., Université Joseph Fourier, 2011
Maria Chikina, Ph.D., Princeton University, 2011
David Koes, Ph.D., Carnegie Mellon University, 2009
Robin Lee, Ph.D., University of Ottawa, 2010
Timothy Lezon, Ph.D., The Pennsylvania State University, University Park, 2007
Jacob Stewart-Ornstein, Ph.D., University of California, San Francisco, 2012

Research Assistant Professor
Hongying (Mary) Cheng, Ph.D., Polytechnic Institute, 2002
Bing Liu, Ph.D., National University of Singapore, 2011
Mark Miedel, Ph.D., University of Pittsburgh, 2008
Indira Shrivastava, Ph.D., University of Pune, 1993
Shikhar Uttam, Ph.D., University of Arizona, 2010

Research Instructor
Joint and Adjunct Appointments

Professor
Gregory Cooper, M.D., Ph.D., Stanford University, 1985 (Ph.D.) and 1986 (M.D)
Alexander Doemling, Ph.D., Technical University of Munich, 1994
G. Bard Ermentrout, Ph.D., University of Chicago, 1979
Graham Hatfull, Ph.D., Edinburgh University, UK, 1981
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 Vodovoz, 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
Vaughn Cooper, Ph.D., Michigan State University, 2000
Lance Davidson, Ph.D., Biophysics, University of California at Berkeley, Berkeley, CA, 1995
Vanathi Gopalakrishnan, Ph.D., University of Pittsburgh, 1999
Zoltan Oltvai, M.D., Semmelweiss Medical University, Budapest, Hungary, 1984
Chien-Cheng (George) Tseng, Ph.D., University of California at San Francisco, 2002

Assistant Professor
Jacob Durrant, Ph.D., University of California San Diego, 2010
Ossama Kashlan, Ph.D., University of Pennsylvania, 2002
Dennis Kostka, Ph.D., Free University, Berlin, Germany, 2006
Miler Lee, Ph.D., University of Pennsylvania, 2009
Hanna Salman, Ph.D., Weizmann Institute of Science, 2002
Jason Shoemaker, Ph.D., University of California, 2009
David Swigon, Ph.D., Rutgers University, 1999
Erik Wright, Ph.D., University of Wisconsin-Madison, 2016
Da Yang, Ph.D., Harbin Medical University, China, 2009
Natasa Miskov-Zivanov, Ph.D., Carnegie Mellon University, 2009

Adjunct Professor
Naftali Kaminski, M.D., The Hebrew University-Hadassah Medical School, Jerusalem, 1989
Robert Swendsen, Ph.D., University of Pennsylvania, 1971
Daniel M. Zuckerman, Ph.D., University of Maryland, College Park, 1998

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

Visiting Adjunct Associate Professor
Eric Poe Xing, Ph.D., University of California, Berkeley, 2004

Adjunct Assistant Professor
Ziv Bar-Joseph, Ph.D., MIT, 2003
Christopher Langmead, Ph.D., Dartmouth, 2003

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
COMMITTEE SERVICE

Joseph Ayoob, Ph.D.
Co-Chair, Journal Club Committee, CPCB Program

Ivet Bahar, Ph.D.
Distinguished Professor and John K. Vries Chair
Faculty; Pittsburgh Medical Informatics Training Program, 2001 - present.
Faculty, Interdisciplinary Biomedical Graduate Program, School of Medicine 2002 – present.
Search Committee for Faculty in Computational Biology, Chair, 2002 – present.
Member, McGowan Institute for Regenerative Medicine, 2002 – present.
Member, Center for Molecular & Materials Simulations (CMMS), 2002 – present.
Member, Molecular Biophysics and Structural Biology Ph.D. Program Steering Committee, 2005 – present.
Faculty, Ph.D. Program in Structural Biology and Molecular Biophysics (CMU-Pitt), 2005 – present.
Faculty, Program in Integrative Molecular Biology (PIMB), 2005 – present.
Faculty, Peterson Institute of Nanoscience and Nanotechnology, 2005 – present.
Executive Committee Member, Carnegie Mellon/University of Pittsburgh Ph.D. Program in Computational Biology, 2005 – present.
Executive Committee Member, Integrative Systems Biology (ISB-Pitt)
Member, Molecular & Cellular Cancer Biology Program, UPMC Hillman Cancer Center
Co-Director Clinical & Translational Science Institute (CTSI) Molecular and Systems Modeling Core (2010-2012)
Member, University of Pittsburgh Graduate Faculty, School of Medicine.
Member, Executive Committee, University of Pittsburgh School of Medicine.
Member, Program Development Committee, Ph.D. Program in Molecular Biophysics.
Co-founded the cross-institutional (between Pitt and CMU) Ph.D. program in Computational Biology.
Member, University of Pittsburgh Center for Protein Conformational Diseases. 2016-present.
Member, Program in Integrative Molecular Biology (PIMB)
Member, Personalized Medicine Task Force.
Member, Center for Molecular & Materials Simulations
Member, Pitt Center for Simulations and Modeling (SAM), 2008 – present.
Associate Director, University of Pittsburgh Drug Discovery Institute (UPDDI) 2010 – present.
Director, Chemo Informatics Core, Center for Medical Countermeasures Against Radiation Pitt & University of Pittsburgh Cancer Institute (UPCI), 2010 – present.
Director/PI, NIGMS Biomedical Technology & Research Resource (BTRR) on Multiscale Modeling of Biological Systems (MMBioS) (Joint between the University of Pittsburgh (Pitt) (lead), Carnegie Mellon University, Pittsburgh Supercomputing Center, and the Salk Institute for Biological Studies). 2012-present
Co-PI (with Xiang-Qun Xie, Eric Xing, and Wei Wu) NIDA Center for Computational Drug Abuse Research (CDAR) (Joint between University of Pittsburgh and Carnegie Mellon University) 2014-present

Panayiotis (Takis) V. Benos, Ph.D.
Vice Chair of Faculty Affairs, Department of Computational and Systems Biology
DBMI Bioinformatics (Concentration) Training Program Core, Member, June 2003 – present.
Member and Chair, Curriculum Committee, Integrative Systems Biology (ISB) PhD Program, 2014 - present,
one meeting a month plus preparation time as the program is built up.
Jeremy Berg, Ph.D.
Advisor, the Institute for Precision Medicine.
Steering Committee, University of Pittsburgh-Tsinghua University scholars program.
Member, Dickson Prize Committee.

Carlos J. Camacho, Ph.D.
Member, University of Pittsburgh Graduate Faculty, School of Medicine.

Anne-Ruxandra Carvunis, Ph.D.
Pittsburgh Center for Evolutionary Biology and Medicine executive committee (co-founder)
Thesis committee: She Zhang, CPCB program
Thesis committee: Natalie Sauerwald, CPCB program
Thesis committee: Sarah Munyoki, ISB program
Thesis committee: Yang Yang, CPCB program
CPCB retreat, poster judge
CPCB program T32 selection committee, member
Admissions committee, ISB graduate program, member
DCSB move, space committee member
LCME accreditation, new faculty committee
Joint DCSB/Immunology Center for Systems Immunology retreat, discussion leader
SPRINGBOARD program, advising lunch table leader

Srinivas Chakra Chennubhotla, Ph.D.
Member, Committee for Tenured Faculty Promotions and Appointments (TFPA) 2017-2020
Co-Founding Directors, Masters Program in Computational and Systems Biology
Member, Curriculum Committee, Integrative Systems Biology Program http://www.pimb.pitt.edu/

Maria Chikina, Ph.D.
Admissions Committee CSB

Nathan Clark, Ph.D.
Member, University of Pittsburgh Graduate Faculty, School of Medicine.
Associate Director of the Joint CMU-Pitt PhD Program in Computational Biology.
TEC-BIO student advisor - 10-week summer program targeting students from underrepresented groups and non-research universities.

James R. Faeder, Ph.D.
Chair, Executive Committee of the Joint CMU-Pitt PhD Program in Computational Biology, 2016-present.
Vice Chair of Educational Activities, CSB, 2016-present.
Director, Joint CMU-Pitt PhD Program in Computational Biology, 2016-present.
Committee member, Departmental Seminar Committee, Fall, 2012 – present.
Committee Member, Curriculum Committee of the Integrative Systems Biology Program, 2014-present.
Member, Departmental Seminar Committee, Fall, 2012-present.
Member of the Graduate Faculty of the University of Pittsburgh School of Medicine, 2010 – present.
Member, Competitive Medical Research Fund (CMRF) Review Committee, 2018.
Co-chair, Faculty Search Committee of the Department of Computational and Systems Biology, 2019.
Albert Gough, Ph.D.
Served as a member of the Faculty committee for the UPDDI.
Provided project management support for Drug Discovery Institute collaborations.

David Koes, Ph.D.
Chair, CSB Departmental Computing Committee.
Co-Chair, Curriculum Committee.
Member, Admissions Committee

Robin Lee, Ph.D.
Evaluator, MSTP.
Member, ISB admissions committee, 2017-2019
Member, CPCB Seminar series Committee.

Timothy Lezon, Ph.D.
Executive Director, CoBB Master’s of Science Program
Director, CTSI Biomedical Modeling Core
Co-Chair, Joint DCSB/Immunology retreat committee
Member, Modeling Social Dynamics & Health Behavior Conference planning committee
Member, Center for Systems Immunology planning committee
Co-Director, UPMC Hillman Academy ComBio site

Mark Schurdak, Ph.D.
Co-organizer, CompBio Academy program
Assist potential collaborators in understanding what is involved in drug discovery and in establishing critical paths for implementing drug discovery projects and programs in DDI, and in preparing grant applications.

Indira Shrivastava, Ph.D.
Poster Judge at Data & Dine Symposium

Andrew Stern, Ph.D.
Mentor, Tsinghua University Scholar Program

Shikhar Uttam, Ph.D.
Grant Review: Institution: Clinical and Translational Science Institute (CTSI)

Lawrence Vernetti, Ph.D.
Member, Liver Research Center Forum, weekly seminars.
Re-acquire the yearly IRB necessary to continue with lentiviral transductions.
Maintain the departmental DEA license needed to use controlled substances.

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

Jianhua Xing, Ph.D.
Department seminar coordinator.
CPCB admission committee member.
CPCB curriculum development committee member.
CPCB Graduate Faculty Member, SOM.
Poster Judge for UPMC Hillman Cancer Center retreat.
UNIVERSITY OF PITTSBURGH COMMITTEE SERVICE

**Joseph Ayoob, Ph.D.**
Faculty Fellow, University of Pittsburgh Center for Mentoring
Co-Director, University of Pittsburgh Mentoring Academy

**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 Nanotechnology Engineering Member, Curriculum Committee, 2002-present.
Dickson Prize Committee member at the University of Pittsburgh (2013 - present).
Member, The International Human Frontier Science Program Research Grant Review Committee, 2016 – present.
Member, RiMed Scientific Committee.
Chair of the University of Pittsburgh Distinguished Faculty Committee. 2019
University of Pittsburgh/Carnegie Mellon Pittsburgh Supercomputing Director Search Committee Member
University of Pittsburgh Center for Systems Immunology Director and Faculty Search Committee Member
University of Pittsburgh Senior Vice Chancellor for the Health Sciences & John and Gertrude Petersen Dean of the School of Medicine Search Committee Member
University of Pittsburgh Chancellor's Distinguished Research Award Committee. 2016-present.

**Takis Benos, Ph.D.**
Member, Training program faculty, department of biomedical informatics (DBMI), 2003 – present, meetings as needed.
Secondary Appointments:
Professor, Department of Biomedical Informatics, 2015 - present.
Professor, Department of Computer Science, 2016 - present.

**Anne-Ruxandra Carvunis, Ph.D.**
Thesis committee: Yunye Zhu, Biology program
Dickson Prize committee, member
WISE women group, member

**Nathan Clark, Ph.D.**
Secondary Appointment, Biological Sciences
Primary advisor for a graduate student in Biological Sciences
Program leader of Molecular Evolution Lab Discussion (MELD), a cross-university research discussion seminar series.
Serve on 3 graduate student committees in Biological Sciences

**D. Lansing Taylor, Ph.D.**
Chemical Biology Facility Advisory Committee meeting
Member of the EPA VPROMPT Steering Committee
TCTC Executive Committee
PA Cure Advisory Committee
Member of the Coulter review committee in the school of engineering

**Andrew Stern, Ph.D.**
The Shire-University of Pittsburgh Joint Steering Committee for rare disease programs.
The Pharmaceutical Companies Collaboration Committee
Andreas Vogt, Ph.D.
Member, University of Pittsburgh Cancer Institute, molecular therapeutics/drug discovery program. 2008 – present.

OTHER SERVICES OUTSIDE OF UNIVERSITY OF PITTSBURGH

Joseph Ayoob, Ph.D.
Member, BIO Research Experiences for Undergraduates (REU) Leadership Council
Associate Member, American Society for Cell Biology Education Committee
Review Panelist, NIH K99 Panel
Review Panelist, NIH Youth Enjoy Science (YES) Program
Review Panelist, NSF Graduate Research Fellowship Program (GRFP)
Review Panelist, NSF Research Experiences for Undergraduates (REU) Program
Reviewer, PLoS One
Reviewer, CourseSource, an online open-access journal of peer-reviewed teaching resources
Mentor, MentorNet and National Research Mentoring Network
CV Reviewer, American Society for Cell Biology
Abstract Reviewer, Annual Biomedical Research Conference for Minority Students
Judge, Pittsburgh Regional Science and Engineering Fair (PRSEF); Biology – Senior Division
Grand Awards Judge, Intel International Science and Engineering Fair (ISEF)

Ivet Bahar, Ph.D.
American Chemical Society (ACS), 1987-97, 2002- present.
American Association for the Advancement of Science (AAAS), 1995 – present.
Member, The Protein Society, 1999-present.
Member, The Biophysical Society, 2001 – present.
Member, International Society for Computational Biology (ISCB) 2001-present
Member, The Society for Neuroscience. 2008-present.
Member, The American Society for Biochemistry and Molecular Biology (ASBMB) 2008-present.
Member, The International Society of Quantum Biology and Pharmacology (ISQB) 2008-present.
Member, The International Transmembrane Transporter Society (ITTS) 2017-present.
The Biophysical Society Awards Committee 2016-present.
Associate Editor, Proteins: Structure, Function and Bioinformatics (Wiley) 2017-present.
Quarterly meetings of the Biophysical Society Executive Committee.
Biophysical Society Council meetings.
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.
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).
NIH Study Section Chair/Reviewer, Special Emphasis Panel for *Library of Integrated Network-Based Cellular Signatures (LINCS)*.
*Elected Member of EMBO (European Molecular Biology Organization)* [http://www.embo.org/](http://www.embo.org/)
Chair and/or Reviewer in several NIH Study Sections, including MABS (Modeling and Analysis of Biological Systems), EUREKA, IMST, DP2.
Member, The International Human Frontier Science Program Research Grant Review Committee, 2016 – present.
Review of several national and international projects/awards, including NSF and DoD grants; proposal submitted to international funding agencies such as EMBO research grants and fellowships; TWAS Fellowships, NATO projects, Israel Science Foundation grants, Science Foundation of Ireland projects.
Biophysical Society Thematic Meeting "Modeling of Biomolecular Systems Dynamics, Allostery and Regulation: Bridging Experiments and Computations." Istanbul, Turkey. Organizing Committee Member.
August 31-September 2, 2016: 9th SFB35 Symposium, “Transmembrane Transporters in Health and Disease,” Vienna, Austria. Invited Chairperson.
September 20, 2016: Academia Sinica, Seminar Series. Taiwan. Taiwan International Graduate Program Distinguished Lecturer.
September 22, 2016: Institute of Bioinformatics and Structural Biology, National Tsing Hua University. Taiwan. Invited Lecturer.
External Advisory Board Member for the NIH-funded Biomedical Technology and Research Resource (BTRR) Center for Biomolecular NMR Data Process and Analysis, 1P41-GM111135-01A1 (PI: Jeffrey C. Hoch, UConn).

**Takis Benos, Ph.D.**
Member, Organizing Committee, 17th European Conference in Computational Biology (ECCB) 2018.
Member, International Society for Computational Biology (ISCB) Education Committee.
Member, Faculty of 1000 for Biology.
Member, Editorial Board, PLoS One.
Member, Editorial Board, Frontiers in Bioengineering and Biotechnology and Genetics.

**Jeremy Berg, Ph.D.**

**Carlos Camacho, Ph.D.**
Reviewer for multiple journals and ISMB.

**Anne-Ruxandra Carvunis, Ph.D.**
Organizing committee: Cold Spring Harbor Laboratories international conference on Network Biology
Organizing committee: Women in Network Science session at above conference
Center for Interdisciplinary Research, advisory board member

**Mary Cheng, Ph.D.**
S. Chakra Chennubhotla, Ph.D.
June 26, 2018 – Member, NIH-NIGMS SCORE Study Section Review Meeting 2018/10 ZGM1 RCB-Y (SC)
Nov 1, 2018 – Member, NIH-NCI Study Section Review Meeting ZCA1 SRB-C (J1) Cancer Systems Biology
Nov 7, 2018 – Member, NIH-NCI Study Section Review Meeting ZCA1 SRB-5 (J1)
External Reviewer, Tenure Committee, Emory University

Ad-hoc Reviewer for
PLoS One
Bioinformatics
Journal of Pathology Informatics
RECOMB
AAAI: American Association for Artificial Intelligence

Maria Chikina, Ph.D.
Reviewer for journals:
Nature Medicine
Nature Genetics
Nature Methods
PNAS
Bioinformatics
MBE
ISMB Proceedings
NIH (GVE) study section

Nathan Clark, Ph.D.
Conceived and Organized symposium for annual SMBE conference in Austin, Texas. Leader of “Molecular Evolution Lab Discussion (MELD)” meetings.
Manuscript Reviewer for:
Molecular Biology and Evolution
Axios Review
PLoS Genetics
Journal of Molecular Evolution
BMC Evolutionary Biology
Journal of Proteomics
Genome Biology and Evolution
Radiation Research
Genes Genomes Genetics (G3)
Journal of Insect Physiology
Frontiers in Plant Science
Scientific Reports

James Faeder, Ph.D.
Member, American Association of Immunologists, 2003-present.
Mathematical Biology section of Biology Direct, 2007-present.
Associate Editor, PLOS Computational Biology, 2019-.
Reviews extensively for NIH study panels including Special Emphasis Panels for NIAID, NCI, and
NIBIB.

Albert Gough, Ph.D.
Reviewer for PLoS ONE and Lab on a Chip.

David Koes, Ph.D.
Journal of Chemical Information and Modeling
Bioinformatics
Journal of Computer-Aided Molecular Design
Journal of Molecular Graphics and Modelling.
Proteins: Structure, Function, and Bioinformatics
Chemical Science
Chemical Biology & Drug Design
Nature Communications

Robin Lee, Ph.D.
Member, Program Committee, qbio conference
Member, Program Committee, PDP 2018 Parallel distributed computing conference
Grant reviewer, Swiss Cancer League
Grant Reviewer NIH MABS study section

Mark Miedel, Ph.D.
Member, American Society for Cell Biology.

Mark Schurdak, Ph.D.
Member, American Chemical Society, (AAAS).
Reviewer for PLOS One Journal.
Member, American Chemical Society, (ACS).
Member, American Association for Cancer Research (AACR).
Member, American Association for the Advancement of Science.
Member, Society for Laboratory Automation and Screening (SLAS).
Member of a special emphasis panel for ZAG1 ZIJ-1 (A1): Alzheimer Center for Discovery of New Medicines

Indira Shrivastava, Ph.D.
Reviewer for ACS Omega
Reviewer for Chemistry and Physics of Lipids
Reviewer for PLoS Computational Biology
Reviewer for PROTEINS: Structure, Function and Bioinformatics
Reviewer for PROTEOMES

Andrew Stern, Ph.D.
Advisor, Protagenic Therapeutics, Inc.

Lans Taylor, Ph.D.
Invited to review articles for Communications Biology, Journal of Cancer Treatment and Diagnosis and the Journal of Cardiology and Cardiovascular Sciences

Shikhar Uttam, Ph.D.
Journal Reviewer:
Optics Express (Optical Society of America)
Applied Optics ((Optical Society of America)
Optics Letters (Optical Society of America)
Biomedical Optics Express (Optical Society of America)
IEEE Transactions on Geoscience and Remote Sensing
IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing
Nature Communications (Nature Publication Group)
Scientific Reports (Nature Publication Group)
Cancer Research (American Association for Cancer Research)
Cancer Prevention Research (American Association for Cancer Research)
Clinical Cancer Research (American Association for Cancer Research)
Cancer Epidemiology, Biomarkers & Prevention (American Association for Cancer Research)
Grant Reviewer:
Biomedical Modeling Pilot Awards

Lawrence Vernetti, Ph.D.
Reviewer for In Vitro Toxicology, Applied In Vitro Toxicology, PLoS One, Experimental Biology and Medicine, Nanobiomedicine, Molecules, Lab on a Chip, Drug Design, Development and Therapy, Toxicology Sciences
Full Member, Society of Toxicology (1993-present).

Andreas Vogt, Ph.D.
NIH Special Emphasis Panel “Member Conflict: Molecular Probes and Tools for Studying the Nervous System” ZRG1 MDNC-G (05) (2017)
Editorial Board Member, SLAS Discovery (formerly Journal of Biomolecular Screening)
American Chemical Society 1992 - current
American Association for Cancer Research 1994- current
Deutsche Pharmazeutische Gesellschaft 1995 - current
Licensing Executives Society 1999-2003
Society for Laboratory Automation and Screening (SLAS, formerly Society of Biomolecular Sciences) 2002-current
Society for Biomolecular Imaging and Informatics 2017 - current

Jianhua Xing, Ph.D.
Executive committee member of the EMT International Association (TEMTIA).
Member of International Advisory Committee, the 9th EMT International Association Conference, Kumamoto, Japan
International advisory committee member for the joint Tshinghua-Peking University Life Science Center.
Associate Editor, BMC Systems Biology
Guest editor, Physical Biology Theme issue on EMT
Session Chair, the 2019 American Physical Society March Meeting
Ad hoc grant reviewer for NSF, Army Research Office, Qiushi Foundation in China,
Ad hoc grant reviewer for the Research Foundation – Flanders (FWO), Belgium, Breast Cancer Now (UK’s largest breast cancer charity)
Ad hoc reviewer for faculty tenure promotion at UCLA.


2017


2019


2018


2017


JEREMY M. BERG, PH.D.

Published Items By Year

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<td>2016</td>
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Sum of Times Cited :25,133

h-index: 69

2018


2016


CARLOS CAMACHO, PH.D.

Published Items in Each Year

Citations in Each Year

Sum of the Times Cited : 4,287

h-index : 34

2019


2018


Pabon NA, Camacho CJ. (2017) Probing protein flexibility reveals a mechanism for selective promiscuity. Elife. 22; 6 [JIF=7.725]


ANNE-RUXANDRA CARVUNIS, PH.D.

Published Items in Each Year

Citations in Each Year

Sum of the Times Cited: 3,933
h-index: 16


CHAKRA CHENNUBHOTLA, PH.D.

Published Items in Each Year

Citations in Each Year

Sum of the Times Cited: 2,320  h-index: 22


PUBLICATIONS


Narayanan C, Bernard DN, Bafna K, Choudhary OP, Chennubhotla CS, Agarwal PK, Doucet N (2017) Conformational Motions Impacting Function in an Enzyme Superfamily The FASEB Journal 31 (1 Supplement), 762.6-762.6


NATHAN CLARK, PH.D.

Published Items In Each Year

Citations in Each Year

Sum of the Times Cited: 1,311

h-index: 16

2019


2018


A Kowalczyk, WK Meyer, R Partha, W Mao, NL Clark, M Chikina (2018) RERconverge: an R package for associating evolutionary rates with convergent traits bioRxiv, 451138


2017


Namboodiri H, Clark N, Kashlan OB, Subramanya AR. (2017) WNK1 is an Ancient Cell Volume Regulator that was Repurposed for Terrestrial Evolution. The FASEB Journal 31 (1 Supplement), 856.7-856.7.
Published Items in Each Year

Sum of the Times Cited: 6,369

Citations in Each Year

h-index: 42

2019

2018


2017


Morel PA, Lee REC, Faeder JR. (2017) Demystifying the cytokine network: Mathematical models point the way. Cytokine 98, 115-123.


Published Items in Each Year

Citations in Each Year

Sum of times cited: 45,254

h-index: 41

2019

2018


2017
Published Items in Each Year

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Citations in Each Year

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<td>2019</td>
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Sum of times cited: 7,823

h-index: 52

2019


2018


2017


JOHN K. VRIES, M.D.

Published Items in Each Year

Citations in Each Year

Sum of times cited: 7,823

h-index: 52


JIANHUA XING, PH.D.

Published Items in Each Year

Citations in Each Year

Sum of times cited: 1,909

h-index: 22
**2019**


Jianhua Xing, Xiao-Jun Tian (2019) Investigating epithelial-to-mesenchymal transition with integrated computational and experimental approaches Physical biology 16 (3), 031001


**2018**


**2017**


**NON-TENURE TRACK FACULTY AND STAFF SCIENTISTS**

JOSEPH C. AYOOB, PH.D.

**2015**


HONGYING (MARY) CHENG, PH.D.

**2019**


MARIA CHIKINA, PH.D.


Deepali V. Sawant, Hiroshi Yano, Maria Chikina, Qianxia Zhang, Mengting Liao, Chang Liu, Derrick J. Callahan, Zhe Sun, Tao Sun, Tracy Tabib, Arjun Pennathur, David B. Corry, James D. Luketich, Robert Lafyatis, Wei Chen, Amanda C. Poholek, Tullia C. Bruno, Creg J. Workman & Dario A. A. Vignali (2019) Adaptive plasticity of IL-10+ and IL-35+ Treg cells cooperatively promotes tumor T cell exhaustion Nature Immunology 20, 724–735

Qanber Raza, Jae Young Choi, Yang Li, Roisin M O'Dowd, Simon C Watkins, Maria Chikina, Yang Hong, Nathan L Clark, Adam V Kwiatkowski (2019) Evolutionary rate covariation analysis of E-cadherin identifies Raskol as a regulator of cell adhesion and actin dynamics in Drosophila PLOS Genetics doi: 10.1371/journal.pgen.1007720

Kristina L Buschur, Maria Chikina, Panayiotis V Benos (2019) Causal network perturbations for instance-specific analysis of single cell and disease samples bioRxiv 637710; doi: https://doi.org/10.1101/637710

Amanda Kowalczyk, Raghavendran Partha, Nathan Clark, Maria Chikina (2019) Cancer control is a key functionality underlying evolution of extended lifespan in mammals bioRxiv 615914; doi: https://doi.org/10.1101/615914


2018


2017


PEMRA DORUKER, PH.D.

2019

Kaynak Burak, Doruker Pemra (2019) Protein-Ligand Complexes as Constrained Dynamical Systems Journal of Chemical Information and Modeling DOI: 10.1021/acs.jcim.8b00946

Dilcan, Gonca; Doruker, Pemra; Akten, Ebru Demet (2019) Ligand-binding affinity of alternative conformers of human beta(2)-adrenergic receptor in the presence of intracellular loop 3 (ICL3) and their potential use in virtual screening studies. Chemical Biology & Drug Design DOI: 10.1111/cbdd.13478

2018


2017


ALBERT GOUGH, PH.D.

2019


2018


2017


DAVID R. KOES, PH.D.

2019

Y Li, E Cifuentes-Pagano, ER DeValliance, DS de Jesus, S Sahoo, DN Meijles, D Koes, CJ Camacho, M Ross, C St Croix, PJ Pagano (2019) NADPH oxidase 2 inhibitors CPP11G and CPP11H attenuate endothelial cell inflammation & vessel dysfunction and restore mouse hind-limb flow Redox Biology Vol 22, April 2019, 101143 https://doi.org/10.1016/j.redox.2019.101143


2018


**2017**


**TIMOTHY R. LEZON, PH.D.**

**2018**


**2017**


Suofu Y, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J, Baranov SV, Leronn D, Mihalik AC, He Y,


BING LIU, PH.D.

2019


2018

2017


MARK MIEDEL, PH.D.

2019


2018


MARK E. SCHURDAK, PH.D.

2019


2018


2017


ANDREW M. STERN, PH.D.

2019


2018


JACOB STEWART-ORNSTEIN


J Stewart-Ornstein, G Lahav (2017) p53 dynamics in response to DNA damage vary across cell lines and are shaped by efficiency of DNA repair and activity of the kinase ATM Sci. Signal. 10 (476), eaa6671

J Stewart-Ornstein, G Lahav (2017) Integrating genomic information and signaling dynamics for efficient...
cancer therapy Current opinion in systems biology 1, 38-43


SHIKHAR UTTAM, PH.D.

2019


2018


2017

LAWRENCE VERNETTI, PH.D.

2019

**2018**


**2017**


**ANDREAS VOGT, PH.D.**

**2019**


**2018**


**2017**


EXECUTIVE SUMMARY

The Department of Computational & Systems Biology (CSB) financial plan for Fiscal Year 2020 reflects the continued growth in 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 Computational Biology Research Adacemy (CoBRA) Summer Academy for High School Students, which is a partnership with the Drug Discovery Institute under the umbrella of the University of Pittsburgh Cancer Institute 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 computer cluster with over 3,396 CPU cores and 102 GPUs for intensive computations and simulations, and the additional involvement of CSB graduate students and postdoctoral

Introduction

Under the direction of Dr. Ivet Bahar, Distinguished 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 FY20 plan of the CSB largely reflects three main goals:
1. Recruiting new faculty members
2. Increasing the amount of funding for research and educational programs
3. 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. In early FY2020 the department is recruiting for a new faculty member in the area of Structural and System Biology and later in 2020 a recruitment of a faculty member to address current challenges in computational neurobiology research, including aging, Alzheimer’s disease or other neurodegenerative diseases and neurological disorders research, and to facilitate the translation of basic research into clinical applications. The collaborations between Immunology and CSB will be fostered by a joint workshop to be held in January of 2020. Computational & Systems Biology will select a faculty member to key statutory roles in leading and governing the CSI.

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 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. Towards this goal, our promising young scientists are entering the workforce equally selecting Industry and Academia in the STEM (Science, Technology, Engineering, and Mathematics) disciplines. Present examples of accomplishments include four graduates who have been appointed to faculty positions, at Penn State University, The University of Georgia, Carnegie Mellon, and the most recent is now faculty at Pitt School of Medicine, in the department of Pathology; as well as program graduates who currently hold positions at premier establishments Goldman-Sachs, Oak Ridge National Laboratory, Amazon, Pinterest, and Apple.

**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. Collaborations currently exist with Yale University, University
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 28 full-time faculty members. There are 9 Tenured faculty in the Department. CSB currently has 37 joint/adjunct faculty from other departments at the University of Pittsburgh, as well as Carnegie Mellon University, Yale, University of Utah, 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, The Salk Institute, Yale University, Oak Ridge National Laboratory, Massachusetts General Hospital, the University of Groningen, Harvard University, Mt. Sinai, University of Tennessee, University of Miami, University of Georgia, Oregon Health & Science University, MD Anderson, Institut National de la Recherche Scientifique, University of Illinois at Chicago, General Electric Research and the Pittsburgh Supercomputing Center.

Grant Funding

As of June 30, 2019 CSB Faculty served as Principal Investigators or Co-Investigators on a cumulative total of $83 million in funded research projects since 2001. CSB faculty served as Principal Investigator or Co-investigator on 44 active funded research projects in FY19 totaling $45 mil; $6.6 mil of which was expensed in 2019. The portfolio of funding continued to grow with 19 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 (R01’s), 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, 83 Applications for funding were submitted in FY19 and entering FY 2020, we have 41 applications for funding pending and continue to diversify funding applications to National Science Foundation, The Searle Scholars Program, Melanoma Research Alliance, Human Frontier Science program, SONOFI, The American Heart Association, The Kaufman Foundation, Department of Defense, Packard Foundation, The Cystic Fibrosis Foundation, and SpIntellx. Of the 41 applications pending 12 will be or have been awarded. These new grants amount to $7.5 million in Total Cost.

**Education**

The CSB is committed to providing 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 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. Our programs train students and postdoctoral researchers, for example, to identify and tackle complex biological problems on a computer, simulate biological phenomena at multiple scales, model signal transduction pathways. Students often work with collaborators doing wet-lab experiments and many perform these experiments themselves. We have incorporated these efforts into a tiered-mentoring framework that maximizes interactions between students and trainees at near-peer experience levels, while providing important mentoring experience for emerging scientists. We also constantly strive 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 Medical Center (UPMC) Hillman Academy, and in collaboration with the Drug Discovery Institute, we have an ongoing 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 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 in FY 2019 and the TECBio REU was renewed for 4 additional years both in 2013, with co-funding by the Department of Defense, and also in 2016.

Additionally, CSB is introducing an intensive Master of Science (MS) degree program in Computational Biomedicine and Biotechnology (COBB) to enable and accelerate the training and development of highly qualified, motivated, and passionate students who are eager to translate the cutting edge computational technologies learned from our program into meaningful contributions in biomedicine and biotechnology. We will accomplish this vision by offering a comprehensive, interdisciplinary and quantitative MS degree-granting training program that can respond to current and future needs in computational modeling and data analyses emerging in the postgenomic, big data, and precision medicine era.

**Administration**

The CSB currently occupies, a 10,000 sq ft office suite located in the BST3 3rd Floor and 4,200 Sq. Ft. on the 10th Floor composed of Wet Lab space.. 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. Currently the faculty occupying Wet Lab space on the 10th Floor are Nathan Clark, Jianhua Xing, Robin Lee, Joseph Ayoob and Anne-Ruxandra Carvunis.

In 2020, the department will move part of its operations to the Murdoch building on Forbes Avenue, 2 blocks from the BST3. We will acquire an additional 3,300 sq. ft. of space on the 10th floor of the BST3 to house the computational personnel of the wet labs. The remaining computational personnel and staff of the
CSB will move in February 2020. This space will be composed of 10,367 sq ft of office and classroom space over the space of 7th and 8th floors of the building. A classroom with capacity for 64 students and a conference room for 24 will be constructed. The classroom will be able to be split in two. A cubicle area housing 31 Graduate Students and 17 work study student stations will be provided. A kitchenette/lounge area will be on each floor.

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 for cpu jobs and the second is for gpu jobs.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Nodes *</th>
<th>CPU cores total</th>
<th>Mem total (GB)</th>
<th>Storage total (TB)**</th>
<th>GPU cards</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPU</td>
<td>114</td>
<td>2,560</td>
<td>8,998</td>
<td>236</td>
<td>NA</td>
</tr>
<tr>
<td>GPU</td>
<td>30</td>
<td>580</td>
<td>3,647</td>
<td>142</td>
<td>127</td>
</tr>
<tr>
<td>Totals</td>
<td>144</td>
<td>3,140</td>
<td>12,645</td>
<td>378</td>
<td>127</td>
</tr>
</tbody>
</table>

*Nodes include compute nodes only. The (3) Login and (13) Storage servers are extra.
** Storage includes only available local workspace (scratch).

GPU Computing:
In addition to the CPU cluster nodes, we added rackmount servers to house several Graphics Processing Units “GPUs”, which can be used for speeding up scientific computations. In our GPU cluster are 127 various GPUs. Currently available GPUs consist of six GTX Titan Black cards, 32 nVidia Titan X cards, 8 nVidia GTX 780Ti cards, 8 nVidia GTX 980 cards, 16 nVidia GTX 1080 cards, 22 nVidia GTX 1080ti cards, 11 nVidia Titan X (Pascal) cards, 4 Titan V cards, two nVidia Tesla M2090 cards, 7 Tesla K40 cards, three Tesla K20 cards and 4 Tesla V100 cards. There are also 14 GPU workstations with cards varying between GTX 480 and GTX 2080Ti. Each workstation runs Linux and 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 6.5 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 10-core Xeon Gold with 96GB of ram. The Virtual Machines are stored on a fully redundant vSAN storage array configured with both SSD 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 VMD, GNM, ANM, and several network accessible databases of biological research data.

Storage:
400+TB full-redundant network attached storage (NAS). 34TB redundant vSAN storage for VMware servers. Linux NAS, 100TB, for backing up linux workstations over the network. 270TB Network backup server for cluster data.

### University of Pittsburgh School of Medicine - FY 2020 Budget

<table>
<thead>
<tr>
<th>Revenue:</th>
<th>School of Medicine Accounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>School of Medicine ECU Allocation</td>
<td>$ 299,455</td>
</tr>
<tr>
<td>School of Medicine Other Support</td>
<td>$ 2,361,069</td>
</tr>
<tr>
<td>SVC Support</td>
<td>$ 2,288,602</td>
</tr>
<tr>
<td>Grant Revenues</td>
<td>$ 6,834,675</td>
</tr>
<tr>
<td>Other Revenue</td>
<td>$ 221,143</td>
</tr>
<tr>
<td><strong>Total Revenue</strong></td>
<td><strong>$ 12,004,944</strong></td>
</tr>
</tbody>
</table>

| Expenses:                                     |                             |
| Medical School Faculty Salaries               | $ 2,676,458                 |
| Staff                                         | $ 1,628,751                 |
| GSA/GSR/TA/TF                                 | $ 781,750                   |
| Fellows, Students (taxable)                   | $ 50,500                    |
| Fellows, Students (non-taxable)               | $(10,000)                   |
| Fringe Benefits                               | $ 1,760,206                 |
| **Subtotal Compensation**                     | **$ 7,001,581**             |
| Supplies and Minor Equipment                  | $ 384,637                   |
| Capital Equip. & Renovations                  | $ 725,000                   |
| Travel and Business                           | $ 167,000                   |
| Professional Services                         | $ 1,094,900                 |
| Rent (if not incl. in stepdown)               | $ 183,600                   |
| Financial Aid                                 | $ 48,000                    |
| **Other Expenses**                            | **$ 2,449,668**             |
| Overhead (incl.stepdown)                      |                             |
| Transfers (Pitt sub 8260 only)                | $ 1,000                     |
| **Subtotal Other Expenses**                   | **$ 5,150,829**             |
| **Total Expenses**                            | **$ 12,152,829**            |
| **Surplus/(Deficit)**                         | **$(147,466)**              |

Restricted Balance as of 6/30/19
$ 4,696,188

University Endowment as of 6/30/19
$ 2,531,456