

# 2014 - 2015 Scientific Strategic Plan

Institute for Systems Biology

## VISION:

Facilitate wellness, predict and prevent disease and enable environmental sustainability.

## STRATEGY:

Develop a powerful approach to predict and engineer state transitions in biological systems.

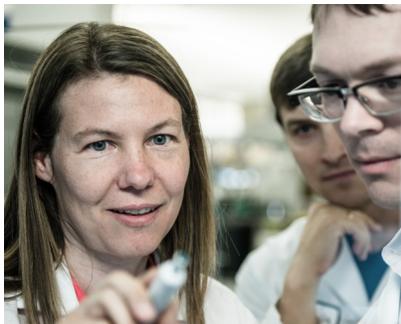
## TACTICS:

We will execute this strategy through four tactics:

1. Develop a **theoretical framework** to define states and state transitions in biological systems.
2. Use **experimental systems** to quantitatively characterize states and state transitions.
3. Invent **technologies** to measure and manipulate biological systems.
4. Invent **computational methods** to identify states and model dynamics of underlying networks.

## APPLICATIONS:

We will drive tactics with applications to enable **predictive, preventive, personalized, and participatory (P4) medicine** and a **sustainable environment**.



## MISSION

We will revolutionize science with a powerful systems approach to predict and prevent disease, and enable a sustainable environment.

## STRATEGY

ISB will develop a systems approach to characterize, predict, and manipulate state transitions in biological systems. This strategy is the common denominator to accomplish the two vision goals. By studying similar phenomena across diverse biological systems (microbes to humans) we will leverage varying expertise, ideas, resources, and opportunities to develop a unified systems biology framework.

# ISB IS A UNIQUE ORGANIZATION

ISB is neither a classical definition of an academic organization nor is it a biotechnology company. We are unique. Unlike in traditional academic departments, our faculty are cross-disciplinary and work collaboratively toward a common vision. This cross-disciplinary approach enables us to take on big, complex problems. While we are vision-driven, ISB is also deeply committed to transferring knowledge to society. We participate in the formation of companies, and strategically partner with industry to transfer technologies, products and new concepts generated by our ambitious projects. We also transfer knowledge by training students and postdocs, offering advanced courses, developing new curricula for high schools, training K-12 educators as well as community college faculty, and influencing education policy at the state and national levels.



**WE ARE NOT AN ACADEMIC  
INSTITUTION**



**WE ARE A NON-PROFIT SCIENTIFIC  
RESEARCH ORGANIZATION**



**WE ARE NOT A BIOTECH  
COMPANY**

## CORE VALUES:

**We understand that effective systems biology requires constant attention to a very complex, very human social experiment** –the success of systems biology is entirely dependent on creating and nurturing the kind of financial, social and psychological environment that assures the world’s best scientists, technologists, engineers and mathematicians can do their best work together.

**We cherish intellectual freedom** –not because it offers us the ability to explore wherever our hearts, minds and interests take us, but because it is essential to breakthrough science. In addition to driving scientific advancement across multiple arenas, we must devote a significant portion of our work to the kind of research that does not require an “answer.”

**We value collaboration** –we are committed to breaking down the natural barriers and silos that exist between different disciplines and various schools of thought so that we assure the most comprehensive understanding possible.

**We have a responsibility to share what we learn** –we seek opportunities to share everything we learn— not just to advance science across all disciplines of human health, but to encourage and educate the next generation of scientists, technologists, engineers and mathematicians who will create breakthroughs that we cannot even imagine today.

**We do not seek roadmaps, we create them** –we work hard to resist the all-too-human temptation to find “safe harbors” for our exploration, or bend our science so that it better fits funding conventions. Our work almost always assures that we will be ahead of the conventions of the time, so we must create new conventions.

**We expect to invent the future of human health and environmental sustainability** –everything we do creates the possibility for breakthroughs in how the entire array of human health issues are understood, prevented and treated. Our systems approach demands that we incorporate best-in-class thinking on the critical role the environment plays in human health and well-being.

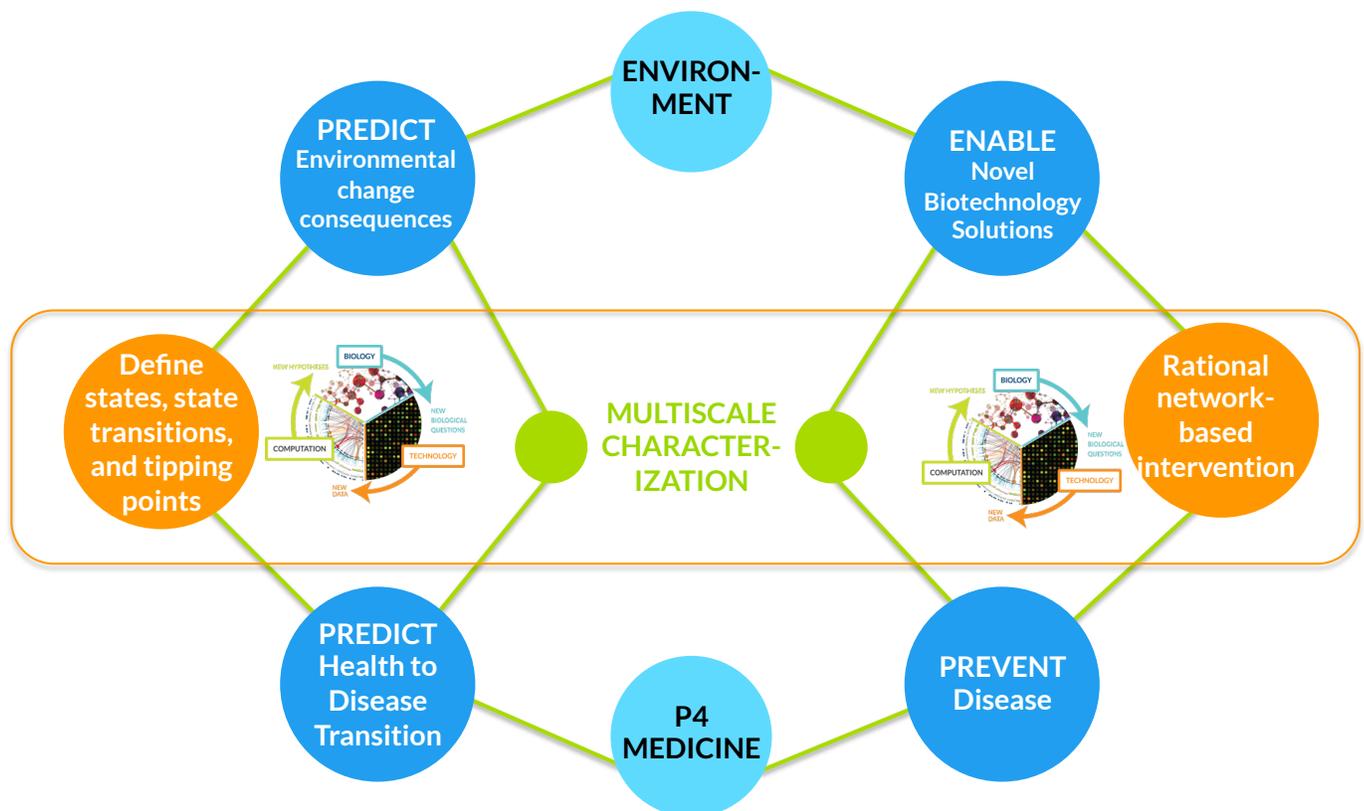
# VISION TO STRATEGY

## PHILOSOPHY AND RATIONALE

Biological systems exist in a quasi-stable state that can evolve and adapt to environmental change, yet they are sufficiently robust to withstand stressful conditions and antagonistic interactions. Critical transitions across states and tipping points lay at the heart of most complex problems in modern biology – including reversible physiological adaptation to environmental change, evolution of interactions in the microbial loop, development of an adult body plan from an embryo, differentiation of a stem cell, and transition from health to disease. Characterizing warning signals before a tipping point is encountered is essential to develop early presymptomatic diagnostics for complex diseases. Finding the causal molecular mechanisms responsible for such transitions in turn will provide the strategies for prevention, intervention, and reversal of disease. These concepts of diagnosis and intervention are also relevant for environmental issues as they will provide tools for better ecosystem monitoring, remediation, and sustainable biotechnological solutions.

Efforts at ISB are geared toward generating a predictive understanding of robustness, resilience, and evolvability of complex systems that underlie transitions across states, and from stability to instability, i.e. **state transitions and tipping points**. We seek to elucidate the mechanistic underpinnings of these phenomena through **multiscale characterization** of networks within model systems (organisms and communities). We will test and apply our understanding by steering these networks with precise genetic and environmental perturbations to **rationally reengineer** system properties.

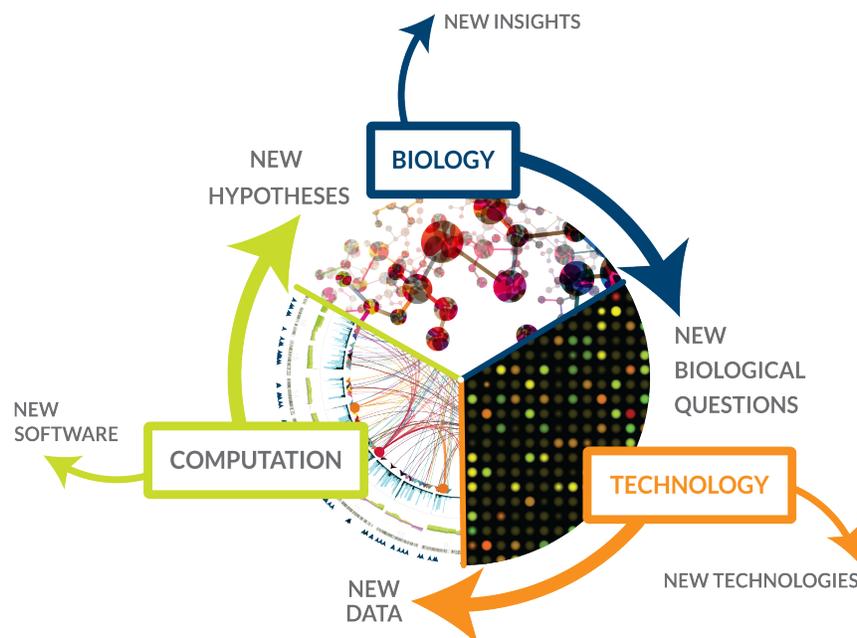
## ONE APPROACH TO TWO PROBLEMS



## WHAT MAJOR IMPACT CAN ISB MAKE IN THESE AREAS?

ISB can make ground-breaking contributions by developing a theoretical framework and a systems biology approach to characterize states, state transitions and tipping points in biological systems. We will leverage our cross-disciplinary expertise and collaborative culture to investigate health- and environmentally relevant diverse model systems – from microbes to human – to unify and generalize principles underlying these phenomena, and define warning signatures (e.g. slow recovery time – “critical slowing down” and “saw-tooth oscillatory dynamics”), and specific parameters (e.g. species diversity, biomarkers, gene interactions) that are **predictive and actionable**. The detailed multiscale understanding of nested networks in a biological system further presents an opportunity to go beyond theory and diagnostics to develop rational network-based strategies to modify, block and even reverse undesired states with chemical or genetic perturbations – i.e. rational reengineering.

### ISB'S INNOVATION ENGINE: BIOLOGY DRIVES TECHNOLOGY DRIVES COMPUTATION



# STRATEGY

There are two major drivers of the ISB approach - **discovery and hypotheses**. Depending on the specific hypothesis or discovery-based biological question, we will measure global molecular changes during normal or perturbation-induced changes in behaviors of model organisms, microbial communities, cell lines, or patient cohorts. If necessary, we will develop **technologies** for new types of measurements. We will invent new **computational methods** to integrate data for the purpose of reverse-engineering and modeling the dynamics of interactions across multiple scales. The models will be tested using **experimental systems** for mechanistic and predictive accuracy, by analyzing performance with targeted environmental and genetic perturbations. **Integration of discovery and hypotheses-driven approaches is accomplished by this iterative strategy wherein biological questions drive technological advancements, which in turn drive the development of innovative computational tools.** Each turn of this cycle will generate new biological information.

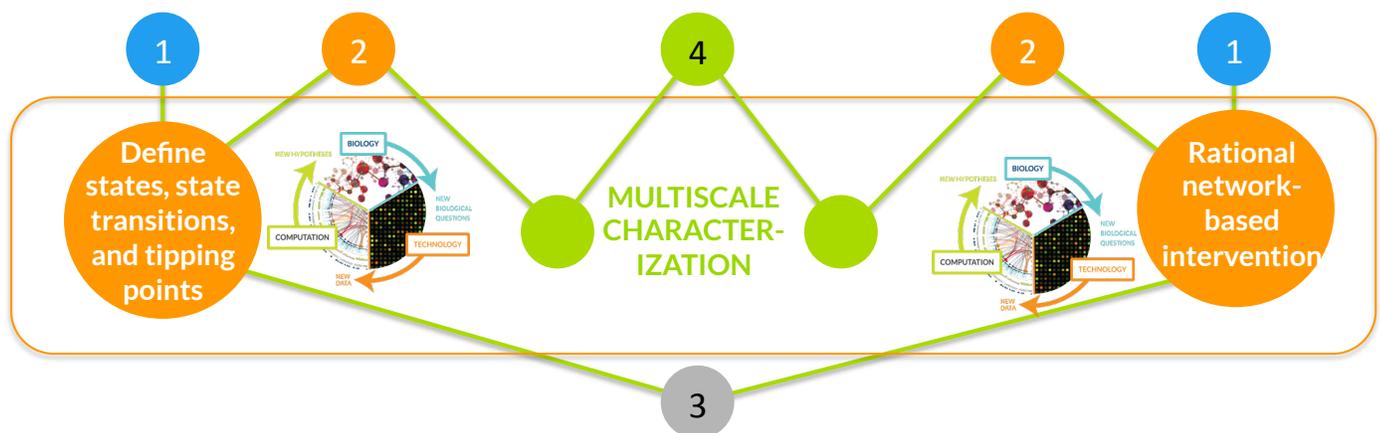
The iterative strategy, technologies, and computational methods will unify all projects at ISB to simultaneously reveal deep mechanistic insights into specific problems, and develop generalized theory, principles, and signatures of states, state transitions and tipping points in biological systems. Moreover, the rational reengineering strategies will generate novel approaches to drug discovery, drug repositioning, combinatorial therapeutics, environmental monitoring, environmental cleanup, and sustainable production of high value commodity chemicals.

ISB will focus on the basic science challenges, recruiting faculty and scientists with cross-disciplinary expertise in key subject areas and by striking collaborations with academic, environmental, medical and commercial institutions in areas of complementary expertise. ISB will also translate basic science discoveries through strategic partnerships with industry and by spinning out companies.

# TACTICS OVERVIEW

- 1 Develop a theoretical framework for characterizing states and state transitions
- 2 Use experimental systems to quantitatively characterize states and state transition

- 3 Invent technologies to measure and manipulate biological networks
- 4 Invent computational methods to define system states and model network dynamics of state transitions



# MANY SCHOOLS OF THOUGHT. One mind.



Here both individuality and collaboration are as vital as the air we breathe. We remain steadfast in breaking down the barriers and silos that exist between different disciplines and various schools of thought. When walls no longer exist between minds, a more comprehensive understanding is possible; true collaboration is possible.

**VALUES**



# THEORETICAL FRAMEWORK

## BACKGROUND

The central challenge in defining the theoretical basis for ISB's envisioned "unified systems biology framework" to solve complex problems of human and environmental health is to balance and integrate burgeoning "big data" with thorough theory. The next leaders in systems biology will be those who can successfully marry fundamental theory with the deluge of data generated by advances in the omics technologies and unite hypothesis-driven with discovery-driven approaches.

With ISB's overarching focus on **states and state transitions in human and environmental health**, we can build on an existing, rich, well-grounded but still developing framework of theories of complex dynamical systems. The theory that deals with the dynamics of system states and their "phase transitions" in complex systems has enjoyed steady ascendance in the past decades, attracting increasing numbers of physicists and mathematicians. However, the integration of theory with big data from experimental research in life sciences, let alone its translation to practical applications lags behind. ISB is well-poised to take the lead in incorporating theory in big data and to move beyond finding statistical patterns in order to make sense of big data.

## GRAND CHALLENGE (1)

***Balance between data-driven and theory-driven approaches by integrating existing theory in data generation and analysis to maximize gain from big-data projects***

### WHAT WE NEED TO DO:

- Evaluate each big data project on formal theory and the conceptual biological framework that complements the big data analysis.
- Teach ISB computational biologists about theory of complex dynamical systems and the key concepts of biology (to avoid default to statistical data analysis)
  - » Hire new faculty in the pertinent domains with motivation to teach ISB scientists

- » Partner with new long-term academic collaborators that reach beyond opportunistic sharing of complementary expertise and tools.
- » Provide courses and self-organized reading clubs on theory.
- Adapt specific, existing theories of **critical state transitions** to high-dimensional data analyses on temporal evolution, such as those from burgeoning personalized medicine and environmental projects.
- Focus analyses on higher-level networks, e.g. cell-cell or tissue-tissue networks.
- Adapt multiscale analysis to systems biology data that transcend molecular, cellular, tissue and organismal levels.
- Identify mechanisms (RFIs, perspective pieces, etc.) to influence how funding agencies view the need for integration of theory and big data.

### WHAT WE HAVE ACCOMPLISHED:

- Established a developmental biology textbook reading club and completed reading of first book.
- Demonstrated criticality in gene networks; Theory of probabilistic networks (Shmulevich).
- Demonstrated high-dimensional attractors in GRN; bifurcations in cell fate decision. Construction of quasi-potential landscape from system equations of GRN; formalism for non-genetic phenotype change. (Huang)
- Formulation of dynamical system models with an optimal complexity; generalized hill functions; exploration of biological systems with multiple feedback and feed-forward loops. (Aitchison)
- Developed a computational framework (Biocellion) for multiscale modeling and simulation of multicellular biological systems. (Shmulevich)
- Developed approaches to predict single-cell growth distributions in *E. coli* and yeast strains. (Price)
- Advanced methods for metabolic network and gene regulatory network integration, linking mechanistic and data-driven modeling. (Price)
- Identified "network" restructuring during disease progression in prion disease. (Hood)
- Achieved prediction of disease probability based on family genome analysis. (Hood)

## GRAND CHALLENGE (2)

*Identify the inherent limits of brute-force statistical approaches to analysis of big data*

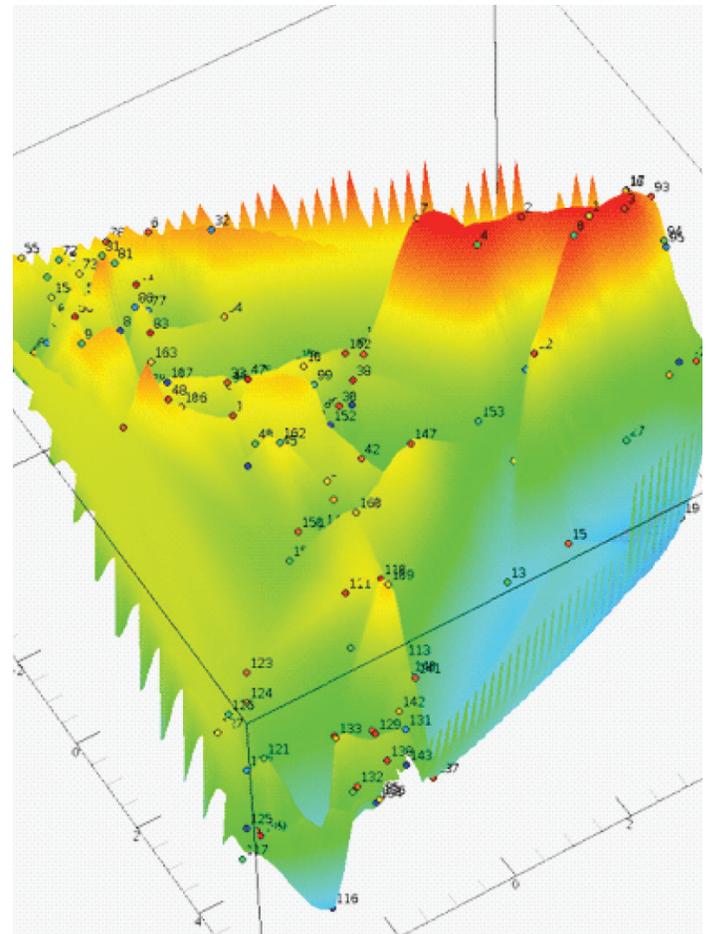
### WHAT WE NEED TO DO:

- Develop a formal procedure, an epistemic framework or an informal intuition to determine when “theory-free” modeling based solely on finding statistical patterns (machine learning, brute-force associations, etc.) is meaningful and useful for a given problem; such a capacity is paramount to better design large collaborative projects.
- Develop a formal theory of complex, non-linear, high-dimensional, stochastic systems to predict and quantitate the inherent limits of prediction of system behavior in order to optimize resource investment in big projects.
- Apply the above to domains where an inherent limitation of brute-force association appears to have been reached. For example:
  - » GWAS of complex diseases, missing-heredity problem.
  - » gene expression signature in cancer prognosis, etc.
  - » somatic mutations and cancer phenotype (TCGA).
- Establish long-term partnerships with experts in theoretical fields to enable the development of new theories of complex systems – if continuing accumulation of big data exposes the limit of the theory-free, brute-force statistical approaches for a given problem – with, for example:
  - » Santa Fe Institute
  - » Karolinska/KTH (Sweden’s Royal Institute of Technology)
  - » UC Santa Barbara/KITP (Kavli Institute for Theoretical Physics) on multiscale, robustness, and climate.

### WHAT WE HAVE ACCOMPLISHED:

This would be the next big challenge and we have not yet embarked on a project in this direction.

However, ISB’s activities at many fronts of big data (GWAS of psychiatric diseases, 100K, etc.) place us in a pole position to be the first to move into this uncharted terrain of the future of biological big data.



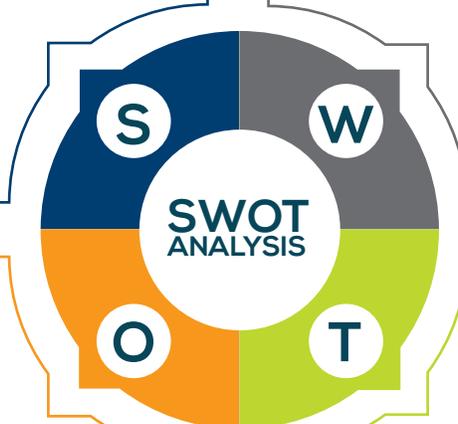
Screen capture from [trel.systemsbio.net](http://trel.systemsbio.net), an online tool for mapping the differentiation of cell types.

**EXPERTISE:**

- Non-linear dynamical systems reaches cutting edge global dynamics (landscapes)
- Continuous (ODE) and discrete networks (Boolean networks): elementary theory and application to modeling biological systems
- Theory of metabolic flux balance
- Not only application (modeling) but also active front in theory development
- Unique experimental observation informed by fundamental theory of complex living organism
- Spectrum of theoretical analysis spans wide range from abstract to concrete modeling: from toy systems to bioinformatics of genome sequence analysis to cells as dynamical systems
- Research on variety of organisms - opportunity for comparative analysis (microorganisms to mammals)
- Experimentalists in same research environment within reach - reality check for the theory
- Critical mass of researchers knowledgeable and interested in theory of complex systems

**EXPERTISE:**

- Expertise in complex systems theory with background statistical physics/nonlinear dynamics (branch of physics most relevant for complex systems)
- Communication between theoreticians and experimentalists to drive optimal experimental design
- Lack of expertise in classical, epidemiological/population and evolutionary genetics



**EXPERTISE:**

- Integration of various levels of analysis (molecular, cellular, tissue) offers opportunity for vertical integration in the future (including multiscale models) - basis for reaching out to clinical domain
- Data available for building network of networks, a signature concept at ISB, not yet explicitly explored
- Opportunity to enhance dialogue and awareness of concepts to guide experimental design and data interpretation
- Unique access to latest technologies could be better integrated to evaluate testability of theories to drive new technologies

**PARTNERSHIPS AND COLLABORATIONS:**

- Leverage ISB's unique expertise and resources in state-of-the-art technology and experiment and biological knowledge to establish long-term collaborations with renowned, prestigious partners from leading institutes of theoretical research

**FUNDING/COMPETITION:**

- Limited funding opportunities for collaboration between theoreticians and experimentalists
- No strong reputation in theoretical research may compromise funding opportunity in theory-focused programs (see partnerships)
- Competition with math and physics departments ("inexpensive") at universities for same resources
- Theoreticians are much faster in moving across fields and into new interesting problems (inertia of experimentalists!)

# EXPERIMENTAL SYSTEMS

## BACKGROUND

The reality of biological systems is that there is a dynamic interplay between molecular networks that leads to complex phenotypes. Central to the systems approach is the fundamental question of how cells read, interpret and respond to complex stimuli. Response to stimuli or changes within systems lead to transitions between states, which are mediated by molecular as well as higher order networks. We consider transitions between two otherwise stable states as state transitions. Stable systems resist perturbation until a tipping point is reached and thereafter transition to a new state. Understanding these transitions and being able to use modeling to predict the outcome of perturbations is central to systems biology. Ultimately we seek an understanding of systems to enable intervention with predictable outcomes.

Multiscale characterization of complex biological phenomena requires tractable model systems that can be manipulated and interrogated across scales to test wide-ranging hypotheses. Model systems have been central to key advances in biology. At ISB, there is a diverse array of model systems that we can use depending on the specific objective. While *Saccharomyces cerevisiae* and *Halobacterium salinarum* are most commonly used to develop technologies and computational methods, they are also powerful systems for addressing important questions regarding fundamentally important biological processes such as genetic information processing and evolution. We also feel that it is essential to employ new model systems that are most appropriate to study specific biological phenomena, such as how diatoms and algae are used to study sustainable environment-related issues, while mouse models are used to study mechanisms of human disease. Often this requires collaborations with domain experts as illustrated by the Hood Lab collaboration with Terry van Dyke at NCI to conduct studies on a mouse that is genetically engineered to replicate the pathology of glioblastoma. The following four grand challenges capture the range of new and established model organisms, as well as associated activities that are necessary to advance systems biology toward furthering our understanding of complex human diseases and strategies for enabling a sustainable environment.

## GRAND CHALLENGE (1)

***Develop and combine different tractable model systems to characterize complex biological phenomena across multiple scales***

### WHAT WE NEED TO DO:

- Develop and deploy appropriate model systems to study important fundamental questions regarding conserved biological phenomena and processes (see applications to P4 medicine and sustainable environment)
- Use tractable model systems to advance technologies and computational methods for single cell analysis
- Generalize and apply technologies developed using model microbes to more complex systems
- Elucidate principles and test these hypotheses across experimental systems

### WHAT WE HAVE ACCOMPLISHED:

- Established extensive expertise and a track record in using yeast and Halobacterium as model systems for developing data driven approaches to:
  - » infer topology and dynamics of multiscale networks (Baliga, Aitchison, Ranish)
  - » track evolution of biological networks during long term directed selection (Baliga, Aitchison)
  - » advance technologies to map protein interactions (Ranish, Aitchison)
  - » advance technologies for high-throughput phenotyping (Aitchison)
- Demonstrated extensive expertise and a track record in microbial systems (e.g. *E. coli*, *H. salinarum*, *S. cerevisiae*, etc.) and mammalian cell lines (immune cells, cancer cells, iPS cells) for advancing single-cell technologies (Huang, Aitchison, Baliga, Hood)

## GRAND CHALLENGE (2)

*Design simple and experimentally accessible model systems that accurately recapitulate complex diseases*

### WHAT WE NEED TO DO:

- Explore the utility of model organisms to study human disease
- Develop methodology to use insights from analysis of clinical data to drive experimentation in appropriate cell lines and animal models of human disease

### WHAT WE HAVE ACCOMPLISHED:

- Established yeast models for peroxisomal-disorders (Aitchison)
- Utilized mouse models for immune response, infection and injury (Subramanian, Aitchison, Hood, Price), neurodegenerative disease (Price, Baliga, Hood), cancer (Price, Baliga, Hood)
- Discovered biomarkers for correlation and prediction of disease states, and monitoring progression and treatment (Price, Hood, Baliga, Moritz)
- Established deep collaborations with domain experts on pathogens including prokaryotes such as *Francisella*, *Salmonella*, *Mycobacterium*, *Pseudomonas* (Baliga, Aitchison, Moritz, Price), eukaryotes such as *Plasmodium falciparum*, trypanosomes (Aitchison), and viruses like dengue and influenza (Aitchison) for study of host-pathogen interactions



Human



Mouse



Yeast



Halobacterium

## GRAND CHALLENGE (3)

*Elevate new environment/biotechnology-relevant organisms to model system status*

### WHAT WE NEED TO DO:

- Establish synthetic microbial communities to investigate microbial ecology within communities
- Customize framework to perform comprehensive systems biology analysis with new organisms and communities
  - » Develop and customize tools for high throughput genomics, transcriptomics, and proteomics (e.g. by developing SRM atlas for proteomic analysis)
- Simulate complex changes in the natural environment within photobioreactors and mesocosms

### WHAT WE HAVE ACCOMPLISHED:

- Performed studies on evolution of syntrophy using a synthetic microbial community of two organisms: *Desulfovibrio vulgaris*, a sulfate-reducing bacterium (SRB), and *Methanococcus maripaludis*, a hydrogenotrophic methanogen (Baliga in collaboration with Stahl at UW)
- Investigated ocean acidification consequences on diatoms using *Thalassiosira pseudonana*, using an array of photobioreactors and mesocosm (Baliga with Armbrust at UW, mesocosm studies in collaboration with Friday Harbor Labs)
- Performed studies on inter-species interactions in the microbial loop with *Dunaliella salina*, a eukaryotic chlorophyte, and *H. salinarum*, an archaeon (Baliga)
- Investigated enhancing TAG production using *Chlamydomonas reinhardtii* as a model organism (Baliga, Price, collaboration with Sapphire Energy, Inc.)
- Developed curated genome-scale metabolic model and genetic system for knockouts in *Clostridium beijerinckii* (Price)

**EXPERTISE:**

- ISB's approach – involves innovation at all levels – biology, technology, computation, etc.
- ISB's deep domain expertise in model systems
- Multiple collaborations on experimental models have broadened the scope of projects and enabled broader insight to principles
- Modeling – combined with experimental interrogation, prediction and testing

**MODEL SYSTEMS:**

- In-house capabilities to work with diverse microbial and eukaryotic model systems
- Access to a diverse array of other model systems through collaborations

**TECHNOLOGY AND CAPABILITIES:**

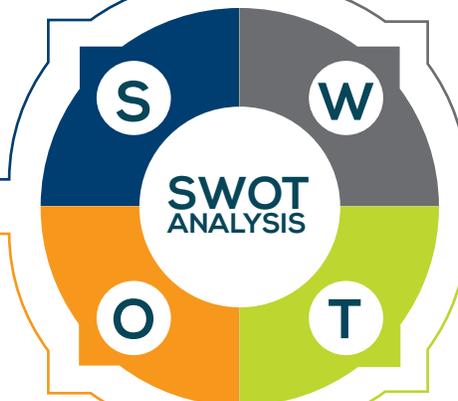
- Technologies – proteomics, single cell biology, anaerobic culturing, high throughput screening and phenotypic characterization

**EXPERTISE:**

- Critical mass of expertise on the biology of systems
- Limited existence of in-house experimental systems in neurology, cancer, or infectious disease
- No clinical expertise
- Lack of epidemiology expertise
- Lack of microbial ecology expertise
- Lack of microbiome expertise as it relates to disease states

**MODEL SYSTEMS:**

- Limited capacity in animal models of disease
- Need better and more relevant models for human disease



**EXPERTISE:**

- New collaborations:
  - » Domain experts in novel disease/environmental models
  - » Clinical expertise on new diseases
  - » Clinicians for access to patients
- Redefine how biology needs to be done
  - » Team based science
  - » Multi-institutional collaborations to bring greater resources

**FUNDING/COMPETITION:**

- Other domain expert institutes (cancer, infectious disease, brain) are quickly adopting systems approaches
- Maintaining distinguishing status in technology
- Resources are limited

# TECHNOLOGIES

## BACKGROUND

ISB is a leader in the development of scalable technologies to make accurate, high-throughput measurements of biological properties and generate new comprehensive and quantitative omic datasets. A major strength at ISB is the focused and integrated development of new and matured technologies coupled with the required computational methods to process large volumes of raw data into biologically meaningful information. The cross-disciplinary culture at ISB uniquely enables biological question-driven technology development and parallel advancement of the computational tools required to analyze and interpret the new data. Moreover, our integrated approach to study complex biological problems drives simultaneous and complementary advances across multiple technologies.

We also recognize the importance of adopting technologies developed by others. At ISB, we have implemented a model where technologies that are used across multiple labs are centralized into core facilities that offer services at competitive rates. The core facilities evolve with the changing needs and status of specific technologies. For instance, when commoditized we have sometimes found it to be more efficient to outsource the service. We will continue this model to advance technologies that are crucial and necessary to do our science. From a strategic standpoint, we have identified four grand challenges that cut across the areas of genomics, proteomics, cell biology and automation.

Characterizing heterogeneity and organization of cell populations is critical for understanding complex phenomena across all biological systems – from microbes to human. This will require the development of sensitive technologies to make high-throughput, system-wide measurements of molecular changes across the hierarchies of cellular organization (genome, transcriptome, proteome, metabolome). In addition, to truly appreciate biological complexity, we also need to map and model the 3D spatial organization of all key cellular components including the genome, transcriptome, proteome and metabolome. ISB has played a major role in the development and application of imaging, microfluidics and other capabilities toward characterizing 3D organization of sub-cellular (molecular and organellar)

and cellular structures. While much of these activities, especially integration, will happen in-house at ISB, we will also leverage our academic and industry partnerships to broaden our capabilities in technology development.

## GRAND CHALLENGE (1)

***Advance technologies for high-throughput sensitive quantitative measurement of proteins, protein modifications and metabolites from complex samples***

### WHAT WE NEED TO DO:

- Create new user-friendly proteomics data pipelines for quantitative proteomics with new statistical validation tools and visualizations developed in-house and in conjunction with collaborators
- Continued development of technologies for global and systematic protein identification and quantification, i.e. SWATH and SRM-based methods
- Establish greater access to collaborative efforts with NIH-funded centers in metabolomics (e.g. Northwest Metabolomics Research Center)

### WHAT WE HAVE ACCOMPLISHED:

- Advanced methods for comprehensive quantitative proteomics (Moritz, Price, Ranish, Hood)
- Developed methods for targeted proteomics and systematic measurements of proteins and protein-DNA interactions (Moritz, Ranish)
- Created whole proteome spectral libraries for many organisms (Moritz)
- Advanced extensive computational tools with statistical validation (Moritz, Hood)
- Established ourselves as world leaders in proteomics technology development (Moritz, Ranish)
- Developed extensive high mass accuracy lipidomics expertise (Moritz)
- Developed assays for global phosphoproteomic analysis and network integration (Aitchison, Moritz)

## GRAND CHALLENGE (2)

*Develop technologies for high-throughput, multiscale characterization of protein-protein interactions (PPIs) and protein complexes*

### WHAT WE NEED TO DO:

- Continue development of MS-based technologies to study the dynamic composition and architecture of protein complexes and identify protein-protein interactions on a global scale
- Develop methods to collect MS data to readily interpret crosslinked regions of multi-protein assemblies
- Develop algorithms to generate interaction maps from raw data generated by MS of cross-linked complexes
- Develop pipeline for high-throughput isolation of protein complexes and analysis by MS

### WHAT WE HAVE ACCOMPLISHED:

- Developed novel cross-linking reagents (Ranish)
- Determined the architecture of multi-protein assemblies (Ranish)
- Determined the architecture of the nuclear pore complex (Aitchison)
- Analyzed kinetochore biorientation in *Saccharomyces cerevisiae* (Moritz Lab)
- Developed pipeline for chemical crosslinking/mass spectrometry (CXMS) analysis of protein complexes (Ranish)
- Developed MS-based computational tools for identification of cross-linked peptides from complex samples (Ranish and Moritz)
- Developed approaches to study dynamics of protein interactions during cellular responses (Aitchison)

## GRAND CHALLENGE (3)

*Develop and integrate technologies for high-throughput multi-parameter analysis at single-cell resolution*

### WHAT WE NEED TO DO:

- Develop new and integrate mature technologies for ultrasensitive single-cell genomics and proteomics
- Develop high-throughput technologies to perform whole genome sequencing on individual FACS-sorted cells

- Develop microfluidics and imaging technologies for high-throughput phenotyping at single-cell resolution
- Integrate new third- and fourth-generation sequencing technologies for de novo assembly of DNA and RNA sequences from individual cells

### WHAT WE HAVE ACCOMPLISHED:

- Advancement for multiparameter single-cell transcriptomics and proteomics (Hood)
- Advancement of FACS technology to sort live anaerobic microbial cells from anoxic environments, such as the human gut, to perform single-cell phenotyping and whole genome sequencing (Baliga)
- Developed high-throughput single-cell growth assay to analyze mixed microbial populations (ODELAY) (Aitchison)

## GRAND CHALLENGE (4)

*Acquire and develop new technologies to enable multiscale systems cell biology*

### WHAT WE NEED TO DO:

- Acquire capabilities for specialized imaging, spatial sampling of cells
- Develop technologies for spatial sampling and micromanipulation of cells
- Advance microfluidics technology for cell culture and single-cell analysis
- Multicellular imaging analysis through sophisticated computational tools
- Upgrades to imaging facility, including expanded capabilities for HTP liquid handling, to support large-scale high-resolution 3D imaging capabilities

### WHAT WE HAVE ACCOMPLISHED:

- Applied technology for differentiating iPS cells into cardiomyocytes and neurons (Hood)
- Developed image analysis and computational methods for multiscale modeling of multi-cellular systems (Shmulevich, Price, Hood)
- Translated bioengineering technology into products (e.g. Nanostring, Plexera SPR) (Hood)
- Developed a method for high-throughput single-cell growth analysis of mixed microbial populations (ODELAY) (Aitchison)

**EXPERTISE:**

- Chemistry and computational expertise for interactomics

**MODEL SYSTEMS:**

- Yeast
- *Halobacterium*

**TECHNOLOGY AND CAPABILITIES:**

- Imaging, processing and other software licenses
- MS-based metabolomics & lipidomics capabilities in-house
- High-quality proteomics facility with cutting-edge MS-based technology available for discovery and targeted efforts

**EXPERTISE:**

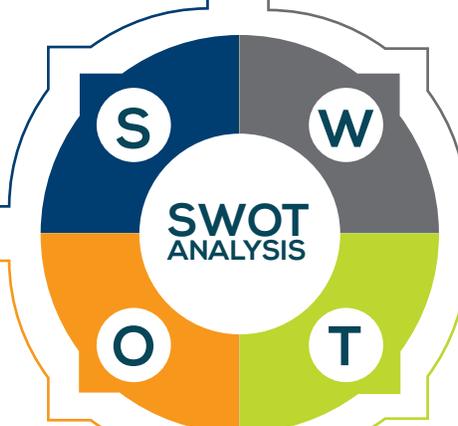
- Interactomics – ISB lacks organic chemist expertise

**MODEL SYSTEMS:**

- Lack of a model organism of intermediate complexity (e.g. *C. elegans*, *Drosophila*)

**TECHNOLOGY AND CAPABILITIES:**

- Challenges in incorporating rapid advances in nucleic acids analysis technologies (e.g. sequencing) as a core service
- Limited imaging capabilities
- Access to affordable high-end (cloud) computing resources to support development work



**EXPERTISE:**

- Faculty hires in the areas of cell biology and organic chemistry with focus on technology development in organism of intermediate complexity

**TECHNOLOGY AND CAPABILITIES:**

- Expand live cell imaging capabilities
- Provide SRM-based targeted quantitation with metabolite panels
- Drug screens with UW SLU
- Development of computational core to support cross-lab common data processing pipelines (e.g. RNAseq analysis).
- Mature common research-grade tools to provide stable software packages
- Co-develop scientific computational cloud efforts with Amazon
- Expand proteomics capabilities
- Develop automation of CRISPR for HTP studies

**PARTNERSHIPS AND COLLABORATIONS:**

- Potential partnerships with MIT, Stanford, PNNL, Bioengineering groups
- Collaborations for high-dimensional imaging (e.g. Oregon Health Sciences University)
- Collaborations for HTP small molecule and drug screening
- Collaborations with chemistry groups interested in cross-linking applications

**FUNDING/COMPETITION:**

- Offering state-of-art core services at competitive rates: e.g. competition with local NIH-funded metabolomics & lipidomics core facility
- Metabolomics and lipidomics not matched by experimentalists in these fields
- Proteomics equipment hardware is limited and aging
- Competition from local proteomics groups who are developing similar technologies for protein quantification and interactomics

# COMPUTATIONAL METHODS

## BACKGROUND

Computational methods in systems biology are foundational in multiple respects. Computers today are essential not only for processing, integrating and analyzing very large biological datasets, but also for constructing and applying models of biological systems, with applications in health, energy and the environment. As these areas are central to ISB's strategy, we have an opportunity to be a leader in the development of computational methods and pipelines for processing large-scale biological data and developing models of biological systems that can be used to predict tipping points in organisms or ecosystems. Such models can also be used to develop appropriate intervention strategies. Computation has historically been a major strength of ISB, which has developed a multitude of pipelines for genomics, proteomics and image analysis, as well as multiple modeling and visualization frameworks for studying biological networks in model organisms and human. This experience coupled with an integrated multidisciplinary environment puts ISB in a strong position to partner with industry and academia, as well as to recruit world experts in the required areas, such as machine learning and image analysis. The following challenges are central to ISB's research goals.

## GRAND CHALLENGE (1)

***To develop computational methods and pipelines to extract biologically meaningful information from complex raw data generated by new technologies***

### WHAT WE NEED TO DO:

- Develop pipelines that can scale to very large datasets and sample sizes
- Incorporate appropriate quality control metrics and corrections where needed
- Develop methods for filtering out uninformative or noisy features of genomes, transcriptomes or proteomes

### WHAT WE HAVE ACCOMPLISHED:

- Developed the Trans-Proteomic Pipeline (TPP) (Moritz)
- Developed ChIPseq analysis pipelines (Shmulevich, Baliga)
- Developed RNAseq analysis pipeline (Price, Baliga)
- Developed approaches for whole genome sequence analysis (Hood, Shmulevich)
- Developed computational methods for biological image analysis (Shmulevich)

## GRAND CHALLENGE (2)

***Formalizing a systematic and generalizable methodology for creating mechanistic models from statistical associations in measurement data***

### WHAT WE NEED TO DO:

- Develop methods to infer statistical associations (networks) by integrating multiple heterogeneous datasets
- Develop computational methods to infer actionable patterns in heterogeneous multidimensional data

### WHAT WE HAVE ACCOMPLISHED:

- Developed methods for probabilistic boolean networks (Shmulevich)
- Developed methods for gene regulatory network inference: cMonkey, Inferelator, miRvestigator, FIRM (Baliga)
- Developed methods for automated metabolic network inference: PROM, EGRIN-PROM (Baliga, Price)
- Developed methods for signaling-gene regulatory network inference (Aitchison)
- Developed approaches for inference of signaling networks: Phosphochain (Aitchison)
- Developed methods for inference of associations from heterogeneous data: Random Forest (Shmulevich)

## GRAND CHALLENGE (3)

*To delineate algorithmic foundations of biological states, state transitions and tipping points*

### WHAT WE NEED TO DO:

- Establish quantitative definitions for biological states, state transitions and tipping points
- Generate computational methods to analyze longitudinal time course data for detecting characteristic patterns of molecular changes that are predictive of states, state transitions and tipping points

### WHAT WE HAVE ACCOMPLISHED:

- Developed approaches to identify two-gene classifiers of cell states (Shmulevich, Huang, Price)
- Identified quantized cell states (Hood, Huang)
- Measured information dynamics and phase transitions in dynamical systems (Shmulevich)

## GRAND CHALLENGE (4)

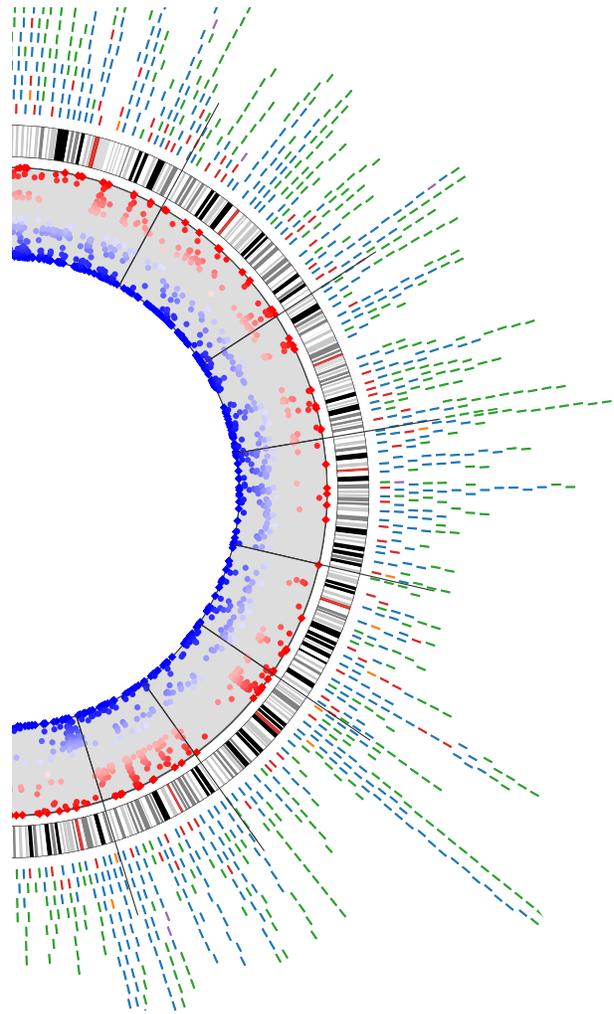
*Integrating software and computing infrastructure into a framework for multiscale modeling for visualization and simulation of complex biological systems*

### WHAT WE NEED TO DO:

- Build hardware and software infrastructure
- Develop formalisms and methods for hybrid modeling
- Develop modeling methodology
- Construct modules and libraries that can be reused to build new models
- Develop visualization methods and tools to explore heterogeneous large datasets and spatiotemporal dynamics of biological systems
- Develop multiscale modeling framework to scale to billions or trillions of cells
- Integrate across multiple intracellular information processing networks
- Model and simulate multicellular biological systems

### WHAT WE HAVE ACCOMPLISHED:

- Developed computational tools for genome visualization: Gaggle Genome Browser, iGBweb, Gestalt (Hood, Baliga)
- Developed computational tools for network visualization: Cytoscape, Biotapestry, Regulome Explorer (Hood, Shmulevich)
- Improved software interoperability: Gaggle, Firegoose, ChromeGoose (Baliga)
- Advanced multiscale modeling capabilities: Biocellion (Shmulevich)
- Developed systems for Biological Content Management: Network Portal, Addama (Baliga, Shmulevich)
- Developed the Protein/Peptide/SRM Atlas (Moritz)



Screen capture from ISB's *Cancer Regulome Explorer*, an online tool for visualizing cancer genomics data.



# ENABLING P4 MEDICINE

## BACKGROUND

Systems approaches offer tremendous potential to drive forward medical discovery and ultimately revolutionize medicine. High-throughput technologies coupled with computational analysis make it possible to harness vastly more information about our bodies than ever before – and harnessing this information to drive forward the unmet challenges of medicine is a central mission of ISB. Led by the pioneering vision of its founder, ISB pushes toward a new kind of medicine that is personalized, predictive, preventive and participatory (P4). ISB seeks to play a catalytic role in the medicine of the future by bringing systems approaches to four major focus areas: diagnostics; network analysis and disease mechanisms; therapeutic strategies; and P4 medicine.

## GRAND CHALLENGE (1)

*Develop next-generation diagnostics for differential and pre-symptomatic diagnosis of diseases*

### WHAT WE NEED TO DO:

- Create a robust analysis platform that can be leveraged with clinical and pharmaceutical partners and is versatile to permit adjustments to emerging challenges
- Build partnerships with clinical institutions, and diagnostic and pharmaceutical companies to translate promising markers for clinical use
- Leverage the 100K project and other longitudinal studies as a test bed to develop pre-symptomatic diagnostics
- Develop approaches for unsupervised diagnosis of multiple diseases simultaneously (e.g. create a panel of organ-specific and other blood proteins to monitor major human diseases)

### WHAT WE HAVE ACCOMPLISHED:

- Developed a clinically used blood test that can distinguish benign from malignant lung nodules (Hood and Price labs, in collaboration with ISB spinout company InDi)

- Performed integrative cancer analysis for TCGA (Shmulevich)
- Developed an SRM Atlas for all human proteins (Moritz)
- Developed a proteomics biomarker discovery platform (Moritz, Hood)
- Developed organ-specific blood protein panels for brain, liver and heart (Hood)
- Established cell-based assays for detecting circulating biomolecules (Aitchison)
- Identified quantized cell populations in human cancer for understanding tumor heterogeneity (Hood)
- Identified pre-symptomatic markers of sepsis in surgery patients (Hood)
- Discovered multi-gene markers for multi-class classification (Shmulevich, Price, Hood)
- Discovered candidate blood biomarker panel for glioblastoma diagnosis (Hood, Price)
- Developed network-based strategies for simultaneously sub-typing disease and stratifying cancer patients

## GRAND CHALLENGE (2)

*Identify the mechanisms underlying the initiation and progression of disease*

### WHAT WE NEED TO DO:

- Develop systematic approach to identifying disease-perturbed networks that expose the distributed mechanism of pathogenesis, therefore allowing the prediction and design of multi-pronged intervention
- Leverage longitudinal studies (such as the 100K and in animal model systems) to establish theories and build predictive models for progression of disease
- Develop new or advance existing animal models to study the multivariate longitudinal dynamics of diseases and extract characteristics that can be mapped to clinical data where de novo discoveries of such dynamic states are not feasible.

## WHAT WE HAVE ACCOMPLISHED:

- Discovered prion disease dynamics in mouse (Hood)
- Advanced our understanding of host-virus interactions (Aitchison)
- Mapped molecular mechanisms of Parkinson's networks in yeast platform (Aitchison)
- Demonstrated network stochastic behaviors of cells that drive malignancy (Huang)
- Identified dynamics of molecular patterns during progression of Huntington disease (Price and Hood)
- Established mouse models to elucidate inflammasome-driven disease processes (Subramanian)
- Developed data-driven approaches to reverse engineer and mechanistically characterize cancer perturbs networks directly from patient data (Baliga, Shmulevich)

## GRAND CHALLENGE (3)

*Rationally steer biological systems away from disease and back to health*

### WHAT WE NEED TO DO:

- Develop integrated approaches to analyze multi-omics data for drug target identification by leveraging existing capabilities in theory of network dynamics and predictive modeling
- Develop and expand existing partnerships with drug companies to help develop systems approaches to discover multi-target drugs

## WHAT WE HAVE ACCOMPLISHED:

- Developed new approaches for identifying network drivers of disease (Baliga)
- Applied state transition theory and experiments with single cancer cells (Huang)
- Identified transcriptional regulatory switches driving disease (Shmulevich)
- Advanced efforts to improve immune therapeutic approaches for Alzheimer's disease (Price)

## GRAND CHALLENGE (4)

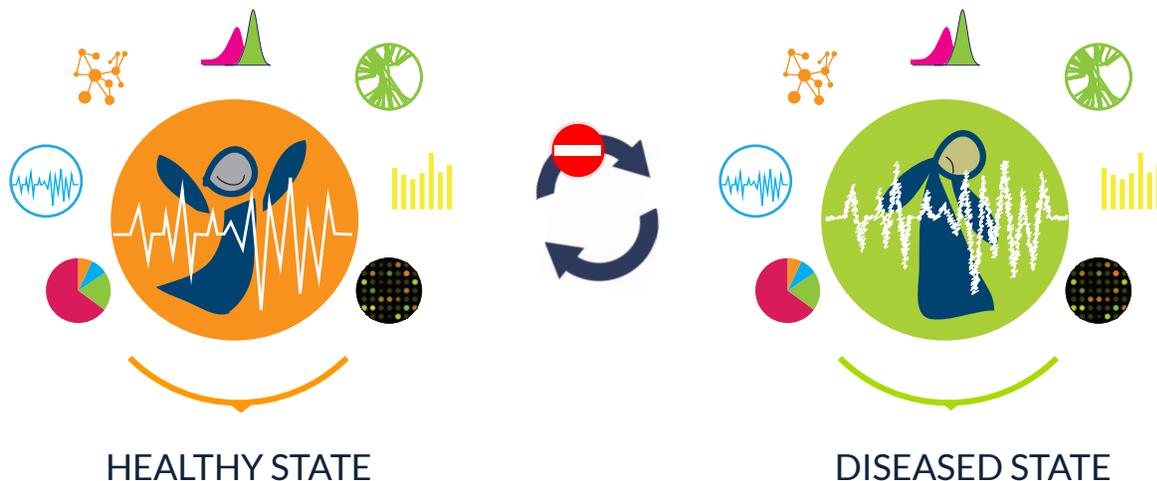
*Catalyze translation of our vision for P4 medicine to a working reality in society*

### WHAT WE NEED TO DO:

- Successful execution of the 100K project, which embodies the P4 vision
- Demonstrate the ability to predict and prevent disease in a cost-effective manner
- Learn to assemble theories, analyses and technologies to guide individual recommendations/actions

### WHAT WE HAVE ACCOMPLISHED:

- Initiated the 100 Person Wellness Project (Hood and Price labs) – this is the pilot study for the 100K project, that will generate the data for predicting and preventing disease, in a personalized and participatory framework
- Integrated genomic and single-cell analysis strategies for patient stratification in clinical trials (Hood)



**EXPERTISE:**

- Recognition as leader in systems biology and P4 medicine

**TECHNOLOGY AND CAPABILITIES:**

- Ability to analyze complex high-dimensional data
- Track record in diagnostics, family genome sequencing, model organisms
- Large in-house genomic/proteomic datasets
- Ability to “close the loop” – i.e. InDi example and others

**PARTNERSHIPS AND COLLABORATIONS:**

- Ability to partner well – by being flexible and adding value
- Several examples of synergistic high-impact research collaborations (e.g. Seattle Biomed, Fred Hutchinson Cancer Research Center, University of Washington, Gates Foundation, etc.)

**EXPERTISE:**

- Not a clinical institution and no built-in ties to such, hindering easy access to clinical samples and data

**MODEL SYSTEMS:**

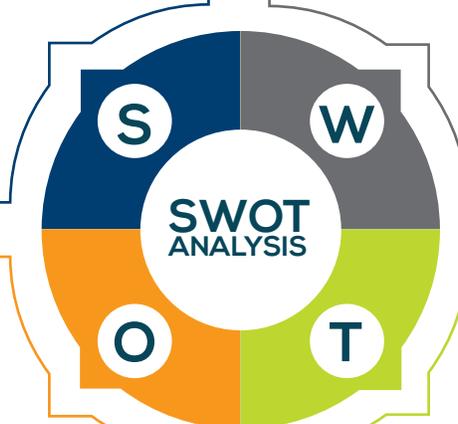
- Limited capabilities in animal model systems

**TECHNOLOGY AND CAPABILITIES:**

- High-throughput data generation capability currently limited

**PARTNERSHIPS AND COLLABORATIONS:**

- No major institute-level clinical partner



**PARTNERSHIPS AND COLLABORATIONS:**

- Increase access to data through new relationships, including leveraging the 100K project
- Identify key partners (academic and pharma) to accelerate translational efforts
- One large pharma partner on systems medicine – increase the impact of our efforts on clinical relevance
- Become the go-to institute for bioinformatic analysis and integration of omics data
- High-impact collaborations with local institutions, including FHRC, Seattle Biomed, Allen Brain Institute
- Wellness pitch to congress – a multi-billion dollar project to deliver on the genome’s promise for P4 medicine

**FUNDING/COMPETITION:**

- Competitors with 100K project (e.g. Human Longevity, Inc., Google’s Baseline Health Study, Personal Genomes Project, UK’s 100K genomes project)
- Potential societal backlash in climate of privacy concerns, anti-big projects
- Other big computational efforts in health with low entry barriers (IBM, Google, Microsoft)
- Contractual partnerships interfere with experimental programs
- “First-mover” advantage in systems biology fading

# ENABLING A SUSTAINABLE ENVIRONMENT

## BACKGROUND

Fifty percent of C-sequestration on Earth occurs in the oceans. Each year, 30 gigatons or one-half of this sequestered C in the oceans is processed through a network of interactions among microorganisms. Inarguably, this microbial loop is essential for life on earth, yet we know little about the organisms and their system of interactions within the loop, or how they would respond to complex changes in the speciation of C that is resulting from rapid ocean acidification. We have an opportunity at ISB to develop a scalable, data-driven systems approach to understand and predict climate change consequences on microbial systems, and simultaneously unlock enormous untapped biotechnology potential within the vast numbers of understudied organisms. ISB has significant strengths across diverse disciplines and partnerships with key organizations (e.g. University of Washington, Berkeley Labs, etc.) that together make it possible to take on this challenge.

The following four grand challenges encapsulate fundamental questions regarding understanding and manipulating biological responses to complex environmental changes. The challenges and the specific tactics required to address them have many parallels to the previous section on Enabling P4 Medicine. The advancements in network biology enabled by analysis of microbial responses to the environment can be (and have been) applied toward understanding disease biology.

## GRAND CHALLENGE (1)

***Identify units of selection across the hierarchies of complex microbial communities, and determine how they interrelate***

### WHAT WE NEED TO DO:

- Develop data-driven approach(es) to infer the topology and dynamics of multiscale biological networks
  - » Elucidate how information propagates across signaling, transcriptional, post-transcriptional, translational, post-translational, metabolic, and inter-cellular interactions
  - » Elucidate how variation within an individual

organism confer fitness advantage to a community of organisms

- Elucidate principles and evolutionary units of selection across hierarchies of biological systems:
  - » Genes
  - » Modules, pathways and networks
  - » Interacting cells of the same or different species - group selection

### WHAT WE HAVE ACCOMPLISHED:

- Developed methods for signaling network inference and modeling (Aitchison)
- Developed methods for dynamic network modeling (Aitchison)
- Developed methods for Gene Regulatory Network (GRN) inference – EGRIN (Baliga)
- Developed approaches for metabolic network modeling and integration – PROM, GEMINI (Price)
- Integrated across all levels of information-processing networks (Baliga, Aitchison, Price)
- Established single and multispecies model systems to discover and track evolution of molecular and cellular networks (Baliga, Aitchison, Ranish)

## GRAND CHALLENGE (2)

***Identify properties and characteristics of a biological system that are indicative and predictive of an impending state transition or tipping point***

### WHAT WE NEED TO DO:

- Characterize reversible vs. irreversible transitions within and across states
  - » Establish bounds and key determinants for dynamic, reversible physiological transitions within a state – define distinct states (e.g. single celled vs. filamentous yeast)
  - » Discover and characterize switches for normal transitions across states
  - » Define resilience and robustness for normal reversible and irreversible state transitions
  - » Discover and characterize signatures associated with abnormal, irreversible state transitions – tipping points

- Elucidate how biological systems anticipate and respond to environmental change
  - » Discover what mechanisms exist for encoding memory of environmental history
  - » Study how new patterns of environmental change internalized
  - » Understand how microbial community structures evolve

### WHAT WE HAVE ACCOMPLISHED:

- Studied the evolution of a two-organism synthetic community (ENIGMA) (Baliga)
- Measured response of diatoms to ocean acidification (Baliga)
- Advanced our understanding of peroxisome biogenesis (Aitchison)
- Observed the evolution of anticipatory behavior (Baliga and Aitchison)
- Identified spatial and morphological mechanisms for encoding memory (Aitchison)

## GRAND CHALLENGE (3)

*Apply signatures of tipping point and states of keystone biological systems to monitor natural and engineered biological systems (e.g. bioreactors, ecosystems)*

### WHAT WE NEED TO DO:

- Translate signatures into biomarkers for desired and undesired states and design assays and biosensors
- Develop and deploy technologies for monitoring closed (bioreactors, wastewater treatment) and open (open ponds, ocean) systems

### WHAT WE HAVE ACCOMPLISHED:

- Measured response of diatoms to ocean acidification (Baliga)
- Monitored live cell-based dynamics (Aitchison)
- Performed mesocosm and synthetic community studies to test utility of novel biomarkers of environmental health (Baliga)

## GRAND CHALLENGE (4)

*Rationally steer environmentally and genetically a biological system to a desired state*

### WHAT WE NEED TO DO:

- Develop methodology to rationally reprogram biological systems with novel capabilities
  - » Elucidate biological design principles from systems-scale models
  - » Invent genome engineering and synthetic biology capabilities for redesigning an entire biological system
- Develop methodology to rationally steer and engineer microbes and microbial communities with novel capabilities
  - » Develop methodology for target selection, experimental design, and formulate reengineering strategies
- Demonstrate how systems biology can drive better (faster, more robust) reengineering capabilities

### WHAT WE HAVE ACCOMPLISHED:

- Engineered yeast for PHA production in the peroxisome (Center for Systems Biology grant) (Baliga, Aitchison, Price)
- Developed models to optimize biomass production and lipid accumulation in algae (Baliga, Price with Sapphire, Inc.)



**EXPERTISE:**

- Microbiology, cell biology, molecular biology, data mining and integration, network inference and modeling (signaling, metabolic, transcriptional, etc.) systems biology, technology development

**MODEL SYSTEMS:**

- Yeast, *Halobacterium*, other microbial systems (phytoplankton, diatoms, microalgae), methanogens, SRBs

**TECHNOLOGIES AND CAPABILITIES:**

- SN, GRN and MN inference, modeling and integration
- HTP phenotyping
- HTP omics analysis: genomics, transcriptomics, proteomics
- Cell culturing

**PARTNERSHIPS AND COLLABORATIONS:**

- Virginia Armbrust (University of Washington) – diatom biology
- Sapphire – algal biology, scale up, techno-economic analysis
- ENIGMA (LBNL + 10 other institutions): environmental microbiology, microbial communities
- BD/Cytopeia: anaerobic FACS
- NCDIR (structural proteomics)
- David Stahl (SRBs, synthetic microbial communities)

**EXPERTISE:**

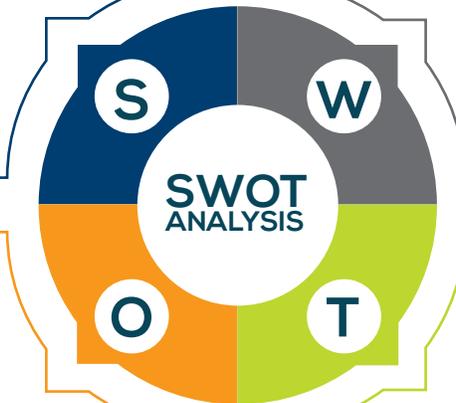
- Microbial ecology
- Synthetic biology
- Microbiome analysis
- Evolutionary biology
- Environmental microbiology
- Industrial biotechnology
- Biophysics

**MODEL SYSTEMS:**

- Model systems of intermediate complexity
- Tractable microbial communities

**TECHNOLOGIES AND CAPABILITIES**

- Live cell imaging
- Genome engineering
- Single cell analysis



**EXPERTISE**

Faculty hires in the areas of:

- Microbial ecology
- Synthetic biology
- Microbiome analysis
- Environmental microbiology
- Model systems

**TECHNOLOGIES AND CAPABILITIES:**

- Develop technology in HTP cell culturing and (cell by cell) parameter measurement of model, non-model and human systems
- Opportunity to learn foundational and widely applicable biological principles
- Opportunity to extensively characterize a model system for demonstration/proof-of-concept project (e.g. engineering yeast for PHA production)

**PARTNERSHIPS AND COLLABORATIONS:**

- Biotechnology companies that can make use of predictive signatures for assessing health of bioreactors and for rational engineering (e.g. Genomatica)
- Opportunity to access resources from DOE, DOD, DARPA, NSF, and foundations such as Moore Foundation
- Opportunity to drive community science projects

- Directed selection or some other approach provides faster route to engineering goal
  - » Clearly define nature of problem we are trying to address
- Competitors: JBEI, JCVI, NRL, EBI,
- Balancing breadth vs. depth at the laboratory level and the institute level
- Reconciling our success with traditional metrics of success
- Long term investment in biological systems analysis without immediate milestones

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