The Center for Biology and Society at Arizona State University
and the Institute for Systems Biology present:

“What’s New about Systems Biology?”

An ISHPSSB off-year workshop
August 16th & August 17th, 2012

All sessions will be held in the Discovery Room of the Seattle Biomedical Research Institute
307 Westlake Ave North, Suite 500, Seattle, WA 98109 (206) 256-7200

PROGRAM with SCHEDULE

THURSDAY, AUGUST 16, 2012
8:00am    Arrive at the DISCOVERY ROOM for registration
8:15-8:45am    Opening Comments from Manfred Laubichler

Session 1: What’s New about Systems Biology?

PRESENTATIONS (20 MINUTES + 5 MINUTES Q&A)
Presenters will please set-up during the preceding Q&A

8:45-9:10am    “Regulation of TGF-β Signal Transduction by Mono- and Deubiquitylation of Smads”
Stuart Newfeld, Arizona State University

Members of the highly conserved TGF-β family of proteins are signaling molecules involved in many biological processes. Mirroring their multiple roles, defects in TGF-β signaling are associated with numerous syndromes such as birth defects, tissue fibrosis and cancer. The posttranslational mechanism of polyubiquitylation leading to proteasomal degradation is a well-studied system for turning off TGF-β signal transducers known as Smads. Recently, an equally important role was discovered for monoubiquitylation of Smads that dampens their activity without protein degradation. Monoubiquitylation of Smads was discovered in tandem with the identification of Smad deubiquitylases. Taken together, these discoveries suggest that systematic episodes of Smad mono- and deubiquitylation are required for proper TGF-β signal transduction. Here we summarize our work on this system of Smad post-translational regulation.

9:10-9:35am    “The Sum of the Parts: Molecular Biology and Systems Biology as Heuristic Research Strategies”
Fridolin Gross, European School for Molecular Medicine
I want to address the question whether and to what extent systems biology provides strategies of discovery and explanation that differ significantly from those of traditional molecular biology. My starting point is that any such strategy is always linked to assumptions about the architecture and organization of living systems. I argue that molecular biology implicitly relies on a particular idea of biological complexity that allows it to frame its research in a particular way. I conclude that approaches in systems biology are different in philosophically interesting ways when they propose different ideas of dealing with biological complexity.

My focus is not only on the different kinds of understanding that can be gained by adopting such different perspectives, but also on the trade-offs that are involved in leaving the framework of molecular biology. The guiding idea is that, in order to be successful, any conceptual approach in the life sciences must offer efficient heuristics, that is, ways to manage complexity. Therefore, any approach introduces biases by making simplifying assumptions about the system under study, without itself providing the tools to justify these assumptions. Framing the analysis in terms of heuristics avoids drawing an overly simplistic picture of the epistemic approaches involved. The strength of alternative perspectives mainly lies in the potential to detect biases in the mechanistic framework of molecular biology. The idea of systems biology as providing an alternative scientific paradigm that replaces the epistemic approach of molecular biology is, therefore, mistaken. Different approaches have to be integrated because they depend on each other. The success of integration crucially depends on an awareness of the limits of different approaches.

9:35-10:00am  **“Systems Biology before Systems Biology: The Case of Gene Regulatory Networks”**  
Manfred Laubichler, Arizona State University

While the term Systems Biology is of relatively recent origin, the question of its intellectual predecessors has identified a number of “systems theories” and ideas that could qualify as intellectual antecedents. In this talk I will take a different approach. Rather than discussing theories and ideas that could be linked to Systems Biology I ask the question of what the main properties of a systems approach are and then discuss an example—the case of gene regulatory networks—that incorporates all the central elements of today’s systems biology. Analyzing the historical origins of the concept of gene regulatory networks then sheds some light on the multiple origins of systems biology.

10:00-10:15am  **Coffee Break**

10:15-11:30am  **DISCUSSION (Led off by two 5 minute syntheses by session commentators)**
Andy Yang, School of the Art Institute of Chicago & Karl Matlin, University of Chicago

11:30-12:45pm  **LUNCH with Continuing Discussion**

1:00-2:00pm  **Tour of the Institute for Systems Biology**
Meet at the Institute for Systems Biology  
401 Terry Avenue North  
Seattle, WA 98109  
(206) 732-1200  
Tour ends at 1:45pm
Session 2: What are the Methodological and Conceptual Foundations of Systems Biology?

PRESENTATIONS (20 MINUTES + 5 MINUTES Q&A)

Presenters will please set-up during the preceding Q&A

2:00-2:25pm  “Explaining Robustness”
Veli-Pekka Parkkinen, University of Oslo

Robustness is a central object of study for systems biology. Robustness is a system property that emerges from the organization of many multifunctional components, therefore robust phenomena are expected to resist reductionistic explanation. In the presentation I consider if explanations of robust functions have characteristics that essentially differ from the mechanistic explanations of molecular biology.

Mechanistic explanation involves analyzing a complex system-behavior into simpler subfunctions, and showing how each subfunction is carried out by some distinct components of the system. Mechanistic explanations allow piecemeal understanding of system-level phenomena – they give answers to what-if questions concerning how aspects of the system would change if individual components were changed or manipulated. Mechanistic explanation assumes that the functioning of individual components is determined by their internal structure and not strongly dependent on interactions with other components, so that one can conceive changes in individual components such that these changes do not simultaneously affect the functioning of other components or connections between them.

Distributed forms of robustness arise when two (or more) structurally heterogeneous components can perform the same function in some circumstances, but distinct functions in others. This belies simple localization of functions to components, because component functions are largely determined by their relations to each other. Accordingly, perfectly local changes or manipulations of components are not conceivable, because a change in a single component might prompt compensatory changes in other components and their relations. This ramifies the inferences about the outcomes of local manipulations of components, undermining the power of mechanistic explanation to make complex phenomena intuitively tractable. This necessitates the use of inferential tools such as mathematical modeling and simulation to obtain proper understanding of the phenomenon under scrutiny. I consider whether robustness as explanandum requires investigative strategies that break off from the mechanistic mode of explanation, or if these explanations are merely more advanced mechanistic explanations with the help of modeling and simulation.

Marta Bertolaso, University Campus Bio-Medico of Rome

Systems Biology is often viewed as an advanced method, which, by both integrating a multiplicity of data and assuming multiple representations, is eventually able to grasp the complexity of biological processes. It has also been seen as a reaction to reductionist approaches in biology. Both accounts of Systems Biology, however, have a common root in the challenge of explaining how biological processes are regulated at different levels of biological organisation and how their coherence is maintained.

Collective behaviours of cells in the organism are paradigmatic among phenomena for which a systemic explanation is required. In this paper, I thus focus on one kind of regulation that is involved in collective behaviours and their hierarchical control, and I will analyse the explanatory role that the notion of ‘functional field’ has within it. What emerges from this analysis is also a clarification of the epistemological status of the systemic perspective that holds Systems Biology and of the heuristic power...
of this systemic perspective in identifying ‘mesoscopic levels’.

The contribution of Systems Biology in contemporary science is thus mainly related to its epistemological assumptions, although often implicit, that have interesting impacts on methodological aspects as well. These epistemological assumptions depend on the organizational principles that Systems Biology seeks to explain. A clarification of this relationship might help us to overcome some aspects of the reductionism-anti-reductionism debate and to move forward in developing epistemological tools that are still needed to explain the hierarchical control of biological systems.

2:50-3:10pm  **Coffee Break**

3:10-4:30pm  **DISCUSSION** *(Led off by two 5 minute syntheses by session commentators)*

Rick Creath, *Arizona State University* & Stuart Newfeld, *Arizona State University*

4:30-5:30pm  **“Network Fever” - Considering Unity and Uniformity in the Visualization of Biological Systems**

Andy Yang, *School of the Art Institute of Chicago*

The visualization of networks now extends from cellular systems to social ones, food webs to world wide webs. The apparent similarities in network structure across this diverse range of phenomena may suggest a deep and underlying unity among complex systems. At the same time, it has been argued that these congruences may also result from the standardized models and tools by which we uniformly analyze such systems. What kinds of inferences and explanations do network approaches justify? Does the recent explosion of network understanding represent the birth of new paradigm in the biological sciences, or might it reflect a trend that claims to supercede the constraints of “reductionism” by means of its own surprisingly reductive strategy? This talk addresses the broad philosophical concerns the current “network fever” raises for the study of complex systems and the issues of interdisciplinary work across the biological and the computational communities.

6:00pm  **Appetizers at The Brave Horse Tavern**

310 Terry Ave North
Seattle WA, 98109
(206) 971-0717
FRIDAY, AUGUST 17, 2012

Session 3: Investigating the Historical Foundations of an Emerging Field

PRESENTATIONS (20 MINUTES + 5 MINUTES Q&A)

Presenters will please set-up during the preceding Q&A

8:30-8:55am “Systems Biology, Between Mechanical Models and Historical Constraints”
Michel Morange, Ecole Normale Supérieure

There is a long tradition of mechanical models in biology, and molecular biology has been its last avatar. Does the rise of systems biology mean the end of this dominant position of mechanical models? I will explore two ways in which systems biology might challenge it: by the methods used to acquire information on the systems, and by the type of explanations that are produced. The selection of the systems under study is also a crucial issue. A recurrent difficulty for mechanical explanations has always been to account for the natural formation of the machines present within organisms. Does systems biology sufficiently take into account the complex historical process that generated these systems? Is this historical dimension susceptible to contribute to explain the behaviour of the systems understudy?

8:55-9:20am “Selective Integration between Compatible Data and Mathematical Models”
Josephine Donaghy, University of Exeter

Systems biology involving -omics data happens when this data can be integrated into appropriate mathematical models. Mathematical models of metabolism began to be established in the 1960's, mostly requiring stoichiometric and kinetic data about metabolic systems. Whole genome sequence data became available in the mid 1990's, and annotated sequences could provide compositional data about the reactions in metabolic networks. Metabolic flux balance analysis (FBA) was developed in the mid 1980's as a tool for teaching undergraduate biochemistry. FBA requires a minimal stoichiometric data set about metabolic systems, yet can analyse this to say something about a dynamic systemic property of metabolism, the distribution of metabolic flux. The compositional data supplied by genomics was rapidly combined with existing data from biochemistry to provide the stoichiometric data required to carry out this analysis. This modelling strategy has generated a highly diverse range of research related to phenomics, robustness, evolution, and ecology. Despite ongoing improvements to the model building procedure questions still remain about the strength of metabolic analysis based only on stoichiometric, rather than stoichiometric and kinetic data.

In this paper I will argue that initial discrepancies in the availability of different data types produced by high throughput approaches affected the types of mathematical models this data could be integrated into. This selective integration between -omics data and mathematical models of metabolism has shaped the epistemic trajectory of work on metabolism. Additionally I will argue that modelling approaches can become entrenched, as they accumulate bodies of research, and due to the complex and work intensive infrastructure required to support the integration of -omics data sets into mathematical models. Even as the data types supplied by high throughput approaches diversify established modelling strategies provide an important framework for their contextualisation.

9:20-9:45am “Modeling in the Age of Arabidopsis: The Emergence of Brachypodium distachyon as a Model Monocotyledonous Grass for Systems Biology Research”
Christopher Lyons, Texas A&M
Individual and institution perspectives towards plant biology research have changed dramatically in the past century. It was not until late in the 20th century that Arabidopsis thaliana was chosen as the model for plant biology research, nearly 40 years after its infancy. This decision of the early plant biology community—composed of not only individuals with inherent interests within the field—to support research on a single organism, fit well with a reductionistic, basic-science platform. However, this “narrow but deep” tactic was not without its costs. Translational research from Arabidopsis to agricultural production is still lacking. In the late 1990s, Brachypodium distachyon was proposed as a new model system to meet perceived gaps in basic and applied research for cereal, bioenergy, and forage grasses. It can be argued that scientists now have an epistemological foundation of the principles of plant biology. That is—the Arabidopsis Community, as a component of the larger plant biology field, has, in the words of Sabina Leonelli, reached its goal of “integration” of the Arabidopsis model. However, for example, there exist many instances within the studies of plant-microbe interactions where the Arabidopsis community has failed to achieve its goal of “representativeness”. The plant biology community now has the ability to rapidly incorporate Brachypodium, an emerging model, with Arabidopsis, using modern systems biology approaches—a spectrum of methodology from bioinformatics to molecular biology to host-pathogen interactions. The goal of this research is to explore the establishment of Brachypodium as it has emerged with inherent systems biology applications in mind and how this contextually differs from the humble beginnings of basic Arabidopsis research.

9:45-10:10am “The Dialectics between Parts and Wholes: Valuable Antecedents to Systems Approaches in 20th Century Biology”
Karl Matlin, University of Chicago

It is an unfortunate tendency of histories of science to focus more on dominant theories and perspectives of any given era and pay less attention to the concurrent alternatives. As a consequence, we are often presented with a linear succession of “paradigms” that somehow “shift.” Systems biology, which is about to/has already replaced the reductionist perspective of molecular biology, may be one such paradigm shift. Closer inspection of historical developments, however, reveals that even during periods considered to be molecular biology’s most successful, an epistemic strategy that depended on a dialectic between parts-based and holistic explanations not only thrived but may also have provided more insight into biological phenomena than the purely reductionist approach. We will introduce a few examples of this “contextual” strategy and suggest that systems approaches that look to this antecedent rather than traditional molecular biology are likely to be more productive.

10:10-10:25am Coffee Break

10:25-11:45am DISCUSSION (Led off by two 5 minute syntheses by session commentators)
Michel Morange, Ecole Normale Supérieure & Jane Maienschein, Arizona State University

11:30-1:00pm LUNCH with Continuing Discussion
Session 4: What are the Implications of Systems Biology for Investigating Complex Systems?

PRESENTATIONS (20 MINUTES + 5 MINUTES Q&A)

Presenters will please set-up during the preceding Q&A

1:00-1:25pm  "Engineering Approaches in Systems Biology"
Sara Green, Aarhus University

A large part of scientific research in systems biology regards reverse engineering of networks in search for so-called organizing principles. These are thought to be general principles that apply to a wide variety of biological systems regardless of evolutionary contingencies. Even though living systems are overwhelmingly complex, organizing principles give some hope that living systems can be understood. This optimism comes from the belief that not all details are necessary for understanding living systems. The challenge is, however, to find out which of the details are important for understanding how the system is organized to bring about the functioning of its cells.

Engineering approaches provide an increasingly important methodological and conceptual framework for investigating functional organization, drawing on mathematical tools and concepts from control theory. An influential but also problematic assumption is that artificial and biological systems share similar functional constraints and therefore have common design principles. Analogies proposing similarities between these two types of systems have led to new insights in how complex systems function. However, these tendencies have also met with critique. Some have argued that the attempt to integrate methodologies and conceptual frameworks from engineering with biology neglects the importance of evolutionary biology, and that these approaches rest on a misleading and simplistic view of living systems.

The talk draws on a case study of network modeling in systems biology to reflect on the implications of engineering approaches for understanding biological complexity. I argue that the integrative efforts are indeed productive in spite of - but also because of - the differences between artificial and living systems.

1:25-1:50pm  "Finding a Niche in Systems Biology"
Lynn Chiu, University of Missouri-Columbia

Systems Biology aims to explain how internal genetic components and external inter- and intra-system relations together contribute to system-level biological properties. While many have drawn conceptual tools from non-biological fields such as information theory and physics, few, with the exception of research in human-microbial systems, have considered another field in biology also concerned with internal biological and external interactive properties—ecology. I argue from example how ecological tools can offer important insights for Systems Biology. The “ecological niche” is used as an organizing concept to study how community systems evolve in the ecological short and evolutionary long run after internal or external shocks to population-environment relations. Historically, the “ecological niche” underwent three conceptual phases: the “environmental niche,” or the “Grinnellian niche,” refers to the environmental conditions suitable for population growth, the “functional niche,” or the “Eltonian niche,” refers to the causal-functional relations between participants within the community, and the “population niche,” or the “Hutchinsonian niche,” refers to the idealistic environmental requirements for a specific species based on its internal makeup (Colwell, 1992, Griesemer, 1992, Schoener, 1989). I take a pluralistic approach and argue that these three conceptions are not mutually exclusive. Each conception of the “niche” represents a set of rules that determine whether a population thrives within its environment: rules that govern environmental dynamics, determine community structure and assembly, and cause changes in internal properties, with the first two determining equilibrium states. These rules are upset by new attributes of the participants or environment. I argue that it is appropriate to parse molecular, cellular,
and organismic systems into “individual” and “environment” components (example: the cell-extracellular matrix relation). Individual-environment relations, analyzed through these three conceptual lenses, can explain system equilibrium/disequilibrium, consequences of foreign invasion, and regular emigration/migration of system components.

1:50-2:15pm  "System-Driven Research: A Different Way to Produce New Scientific Knowledge"
Eve Roberts, Dalhousie University

Biomedical research is going through an exciting period of rapid change, due to the explosion of knowledge about cellular and structural biology plus our ever-expanding capability to store and manipulate very large data sets through computer-based technologies. Thus we can now investigate biological organisms in detail as highly complex systems. Systems biology, developed mainly in the past 10-15 years, addresses the complexity of biological systems directly. Instead of being organized around a hypothesis, the research project is organized around a system. Instead of being hypothesis-driven, the research project is system-driven. Such experiments entertain no predictions about what patterns will emerge, and yet the patterns revealed in the emerging data constitute new knowledge. I call this strategy of interrogating a system directly, which is characteristic of system-driven research, the ‘systems biology experimental strategy’ (SBES). The established, time-honoured approach to experimental science involves articulating a hypothesis and examining it by well-designed experiments focused on that hypothesis. Within philosophy, this standard strategy is known as the hypothetico-deductive method (HDM), and it derives its cogency from the certainty of deductive inference and the plausibility of abductive inference. SBES appears diametrically opposed to the HDM, precisely because since no data or general patterns of data are predicted and no hypotheses are being tested.

The resulting situation is highly problematic for scientists and philosophers. The advent of systems biology challenges the current hegemony of hypothesis in experimental design in biological/biomedical research. In effect, it proposes a new way of doing science. Having performed scientific investigation by HDM and by SBES, I will compare these two experimental strategies in relation to the metabolism of copper in parenchymal liver cells. Relinquishing preconceptions and utilizing a broad-based analytical methodology, SBES identifies relevant intracellular entities, otherwise not envisioned by HDM; new dimensions of how the system may function become apparent. SBES establishes its epistemic strength from revealing the coherence of the system. A hypothesis is not a defining feature of a scientific enterprise but rather one instrument that can be used to support a scientific enterprise. Moreover, system-driven research is not hypothesis-driven research in disguise.

2:15-2:30pm  Coffee Break

2:30-4:00  DISCUSSION (Led off by two 5 minute syntheses by session commentators)
Marta Bertolaso, University Campus Bio-Medico of Rome & Manfred Laubichler, Arizona State University

4:00-4:15pm  Break

4:15-5:30pm  Wrap-up Discussion (Led off by Manfred Laubichler)

Special thanks to the institutions and people that made this workshop possible: Arizona State University, Center for Biology and Society, the Institute for Systems Biology, the International Society for the History, Philosophy, and Social Studies of Biology, Jennifer Dougherty, Daniel Rodriguez, and our ISB committee (Nicola Pinel, Aaron Brooks, Alexey Kolodkin, and Evangelos Simeonidis), our ASU committee (Manfred Laubichler, Kate MacCord, Lijing Jiang, Nathan Crowe, Guido Caniglia, Valerie Racine, and Erick Peirson), and all of our speakers and presenters.
LOGISTICS

1. **Hotel**  
   *Holiday Inn Express (Seattle-City Center)*  
   226 Aurora Ave  
   Seattle, WA 98109  
   Front Desk: (206) 441-7222  

2. **Workshop Venue**  
   *Seattle Biomedical Research Institute*  
   307 Westlake Ave North  
   Suite 500  
   Seattle, WA 98109  
   (206) 256-7200

3. **Appetizers**  
   *Brave Horse Tavern*  
   310 Terry Ave North  
   Seattle, WA 98109  
   www.bravehorsetavern.com

4. **Institute for Systems Biology**  
   401 Terry Ave North  
   Seattle, WA 98109  
   (206) 732-1200

In case of emergency, please contact event hosts: Manfred Laubichler (480) 241-5481 OR Kate MacCord (480) 734-1004
**ENJOY SEATTLE**

These selections, compiled thanks to our committee member, Erick Peirson, are intended to get you headed in the right direction, and are not a comprehensive inventory of the closest/easiest places to eat. All distances are from the *Seattle Biomedical Research Institute*.

**Things to See and Do**

**Space Needle** - 0.8 miles - 400 Broad St - **Seattle Center** - Every workshop needs a panopticon. You can take the elevator to the top of this World's Fair spectacle.

**Seattle Pacific Science Center** - 0.9 miles - 200 2nd Ave N - **Seattle Center** -  
[http://www.pacificsciencecenter.org/](http://www.pacificsciencecenter.org/) - While you're there, you might venture up the Space Needle...

**Pike Place Market** - 1.0 miles - 85 Pike St - **Downtown** - Meet at the pig, and walk through this open-air market with views of Elliott Bay. Try the baclava and Turkish coffee at **Turkish Delight**.

**Seattle Art Museum** - 1.1 miles - 1300 First Ave - **Downtown** -  

**Seattle Asian Art Museum** - 1.7 miles - 1400 E Prospect St - **Capitol Hill** -  
[http://www.seattleartmuseum.org/visit/visitSAAM.asp](http://www.seattleartmuseum.org/visit/visitSAAM.asp) - While you're there, check out the conservatory at Volunteer Park.

**Burke Museum of Natural History** - 3.6 miles - 17 Ave NE & NE 45th St -  

**Coffee**

**Uptown Espresso** - 0.2 miles - 500 Westlake Ave N

**Inner Chapters Bookstore and Cafe** - 0.3 miles - 419 Fairview Ave N

**Moka's Cafe & Coffee Bar** - 0.3 miles - 329 Fairview Ave N

**Espresso Vivace, Alley 24** - 0.4 miles - 227 Yale Ave N - Represents all that is sublime about the Seattle coffee experience.

**Stumptown** - You MUST NOT LEAVE THE NORTHWEST without trying Stumptown coffee.

1.0 miles - 616 E Pine St - **Capitol Hill** - Smaller cafe; go here if you just want the coffee.

1.5 miles - 1115 12th Ave - **Capitol Hill** - Stumptown is now roasting on-site at this café near the Seattle University campus. Take your coffee downstairs to see where the magic happens! Public coffee tasting daily at 3pm.
**Breakfast/Lunch**

- **Serious Biscuit** - 364 ft - 401 Westlake Ave N.
- **Portage Bay Café** - 0.1 miles - 391 Terry Ave N.
- **Nollie's Cafe** - 0.3 miles - 1165 Harrison St - Bakery.
- **Citizen Coffee** - 0.7 miles - 706 Talor Ave N - **Queen Anne** - Crepes and sandwiches.

**Restaurants**

- **Taylor Shellfish Farms** - 0.8 miles - 1521 Melrose Ave - **Capitol Hill** - Oysters.
- **La Bête** - 0.8 miles - 1802 Bellevue Ave - **Capitol Hill** - On the more expensive side.
- **Pike Place Chowder** - 0.9 miles - 1530 Post Alley - **Downtown**
- **Wedgwood II Vegetarian Thai** - 1.2 miles - 420 Broadway E - **Capitol Hill**
- **Marination Station (Korean)** - 1.2 miles - 1412 Harvard Ave - **First Hill**
- **Panevino (Italian)** - 1.2 miles - 416 Broadway E - **Capitol Hill** - Restaurant and wine bar.
- **Pho Than Brothers** - 1.3 miles - 516 Broadway E - **Capitol Hill** - Rated best Pho in Seattle by Seattle Magazine.

**Pubs, Microbreweries, Tasting Rooms**

- **Feierabend** - 0.5 miles - 422 Yale Ave N - German bar, with outdoor seating.
- **The Pine Box** - 0.8 miles - 1600 Melrose Ave - **Capitol Hill** - Great selection of craft beers, happy hour, outdoor seating. Food.
- **Stumbling Monk** - 0.9 miles - 1635 E Olive Way - **Capitol Hill** - Another great spot for craft beer. And only beer.
- **The Tasting Room** - 0.9 miles - 1924 Post Alley - **Downtown** - A great wine bar, featuring Washington state wines. Open late on Friday and Saturday, 8pm Mon - Thurs.
- **Sun Liquor Distillery** - 1.0 miles - 514 E. Pike St. - **Capitol Hill** - Distillery, bar, and restaurant.