29th ALTENBERG WORKSHOP IN THEORETICAL BIOLOGY

Evolutionary Systems Biology

organized by

Maureen O´Malley, Sabina Leonelli, Orkun Soyer

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Konrad Lorenz Institute

for Evolution and Cognition Research

Altenberg, Austria

Welcome

to the 29th Altenberg Workshop in Theoretical Biology. The Altenberg Workshops are interdisciplinary meetings organized by the Konrad Lorenz Institute for Evolution and Cognition Research in Altenberg, Austria. The workshop themes are selected for their potential impact on the advancement of biological theory, and leading experts in their fields are asked to invite a group of internationally recognized scientists, philosophers, and historians of science for three days of open discussion in the relaxed atmosphere of the Lorenz mansion. By this procedure the KLI intends to generate conceptual advances and research initiatives in the biosciences. We are delighted that you are able to participate in this workshop, and wish you a productive and enjoyable stay.

Gerd B. Müller
Chairman

The topic

Evolutionary theory is one of the great scientific achievements of the last century. In the biological domain, evolutionary theory is central to several closely related fields, including population genetics, molecular evolution, phylogeny, and comparative genomics. Despite its multiple facets, evolutionary research is still seldom implemented in many biological and biomedical fields. Evolutionary systems biology (ESB) may change this situation quite drastically.

ESB is an emerging field of evolutionary investigation. It combines systems biology, which is focused on dynamic cellular processes, with evolutionary analyses of populations and organisms. There are several motivations for synthesizing evolutionary and systems-biological perspectives. One is that network properties need to be understood in a variety of organisms, and network models can effectively be generalized through evolutionary analyses. Another is to explain network-level properties such as robustness. A third is to gain a mechanistic understanding of mutational effects, and a fourth is to extend systems-biology – currently focused on intracellular networks – to intercellular networks that have emerged in coevolutionary relationships.

To gain insight into these issues, researchers in evolutionary systems biology draw on and combine diverse approaches, including the construction of mechanistic models and *in silico* evolutionary simulations, the application of comparative analysis of omic data to predict the evolution of network structure, and the use of synthetic constructs to analyse potential evolutionary trajectories in specific systems. The field is highly integrative and interdisciplinary. In addition to evolutionary biology, molecular and systems biology, ESB draws on engineering and computer science, and sometimes ecosystem science.

The KLI ESB meeting will take this integration further by engaging in philosophical and historical discussion of ESB. Scientists, philosophers, and historians will examine the different strands of ESB, discuss challenges, and anticipate future developments of the field. Arguments against ESB will also be very much on the agenda. A particular topic of interest will be the implications of

ESB for evolutionary and systems biology considered separately. Workshop discussions will be developed as papers for publication after the workshop, some of them on the basis of collaborations between scientists and philosophers and historians.

Aims

The meeting has three objectives: to discuss ESB in a broad multidisciplinary context in order to initiate a dialogue between scientists, philosophers, and historians of science on the different ways in which ESB is done; to identify core themes, both practical and theoretical, that arise from a broader overview of ESB's trajectory; to identify central challenges in the main strands of ESB, and investigate ways in which these challenges may be addressed in the future development of diverse ESB research programs.

The format

The workshop will be run in a seminar/discussion format. There are 19 presentations, with 40-45 minutes allotted for each—roughly 25-30 minutes for each talk, followed by up to 15 minutes for specific questions and broader discussion of each talk. After the final talk on Sunday, there will be an extended general discussion session.

Publication of workshop proceedings

The Altenberg Workshops in Theoretical Biology are fully sponsored by the KLI. Following standard practice at the KLI, the organizers are expected to publish an edited volume or a journal issue on the workshop topic. The book or the thematic issue will not consist of conference proceedings; rather, it will further develop the novel ideas and concepts generated at the meeting. The contributions are not

necessarily limited to those of the original participants; they may be complemented by expert papers on topics that emerged as important for the respective issues. Contributions may be in the form of brief notes, opinion pieces, and commentaries on other full papers. Details will be discussed in the final session of the workshop. Because of the explicitly interdisciplinary nature of ESB, the meeting, and the publication, the outcome should be valuable to a wide range of philosophers and scientists from various fields of biology and neighboring disciplines.

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Evolutionary Systems Biology

Thursday 5 September	Evening		
6.00 pm		Welcome reception, introductions, and dinner at the KLI	
Friday 6 September	**Morning**	**ESB: Introduction, Scope, Significance**	**Chair: Leonelli**
9.00 am – 9.30 am	Callebaut	Welcome; Reflections on ESB	
9.30 am – 10.00 am	Soyer	Scope and Significance	
10.00 am – 10.30 am	O´Malley	ESB: Pros and Cons	
10.30 am – 11.00 am	Coffee		
Friday 6 September	**Morning**	**Evolution and Multilevel Systems**	**Chair: Calcott**
11.00 am – 11.40 am	Hogeweg	Evolution Is a Multilevel Process and Should Be Studied as Such	
11.40 am – 12:20 pm	Cornish-Bowden	The Evolution of Metabolic Systems	
12.20 pm – 1:00 pm	Wolkenhauer	Does the Notion of Evolvability Apply to a Society of Cells?	
1:00 pm – 2.30 pm	Lunch	at the KLI	

Friday 6 September	Afternoon	Robustness and Evolved Systems	Chair: Laubichler
2.30 pm – 3.15 pm	Levy	Causal Order and Kinds of Robustness	
3.15 pm – 4.00 pm	Siegal	Two Empirical Challenges to Robustness	
4.00 pm – 4.30 pm	Coffee		
Friday 6 September	Afternoon	Prediction and Integration in ESB	Chair: Fagan
4.30 pm – 5.15 pm	Pal	Is Evolution Predictable?	
5.15 pm – 6.00 pm	Krohs	Prospects of Overcoming Massive Under-determination by Combining Data and Models from Different Fields of Research	
6.20 pm		Departure for Dinner at a Viennese Heurigen	
Saturday 7 September	Morning	Adaptive and Non-Adaptive Processes in Evolving Systems	Chair: Levy
9.00 am – 9.40 am	Lynch	Mutation, Drift, and the Origin of Subcellular Features	
9.40 am – 10.20 am	Wagner	The Origins of Evolutionary Adaptations and Innovations	
10.20 am – 11.00 am	Braillard	How Can Functional and Evolutionary Approaches be Integrated in Order to Avoid the Adaptationist Pitfalls in the Study of Biological Networks?	

11.00 am – 11.30 am	Coffee		
Saturday 7 September	Morning	Engineering and Design in ESB	Chair: Krohs
11.30 am – 12.10 pm	Green	Reverse Tinkering the Evolution of Organisms	
12.10 pm – 12.50 pm	Calcott	Evolutionary Change as an Engineering Puzzle	
12.50 pm – 13.30 pm	Soyer	Evolution of Response Dynamics in Cellular Networks	
13:30 pm – 3.00 pm	Lunch	at the KLI	
Saturday 7 September	Afternoon	The Evolution of Developmental Regulatory Systems	Chair: Braillard
3.00 pm – 3.45 pm	Jaeger	Life's Attractors: Reverse-Engineering the Evolution of Developmental Systems	
3.45 pm – 4.30 pm	Laubichler	The Regulatory Genome in Development and Evolution	
4.30 pm – 5.30 pm	Coffee		
5.30 pm		Departure to the hotel and open evening for exploration of Vienna	

Sunday 8 September	Morning	Challenges for ESB	Chair: Soyer
9.00 am – 9.45 am	Fagan	Concerns About Evolutionary Systems Biology	
9.45 am – 10.30 am		General Discussion	
10.30 am – 11.00 am	Coffee		
Sunday 8 September	Morning	Summary and Reflections on ESB	Chair: Leonelli
11.00 am – 1.00 pm	Facilitated by Leonelli	General Discussion	
1.00 pm – 2.30 pm	Lunch	at the KLI	
2.40 pm		Departure for a Boat Trip on the Danube with Dinner in Dürnstein	
9.30 pm		Return to the hotel	

Abstracts

MAUREEN O´MALLEY
The University of Sydney

Evolutionary Systems Biology: Pros and Cons

As new fields and approaches develop, advocates and critics often propose the merits and demerits of such developments. Evolutionary systems biology (ESB) attracts these sorts of discussions, and they are worth examining in order to gain a clearer picture of ESB claims and challenges. Reasons for ESB are often advanced as greater integration, more predictive power, and increased generalizability. Reasons against ESB are given more sparsely and informally (i.e., not in published papers, but in blogs, personal comments, and referee reports). Two connected reasons against ESB are that it is not a unified field, and that it covers too broad an area to be covered by a single label. More substantive criticisms focus on the non-predictiveness of evolution, and the problems of modeling evolutionary processes in ways that go beyond existing approaches. After an examination of these two sets of reasons (for and against), I will suggest some responses that may weaken the force of the critical appraisals but at the same time indicate some important hurdles for ESB's future.

PAULINE HOGEWEG
Utrecht University

Evolution Is a Multilevel Process and Should Be Studied as Such

Despite the apparent simplicity of the processes of Darwinian evolution, mutation, and selection, leading to drift and/or adaptation, and despite a large body of theory (population genetics), as well as the vast amount of empirical data, the full potential of these processes is as yet only partially understood. Using non-supervised modeling strategies, novel generic properties of Darwinian evolution studied as a multilevel process are being uncovered. I will discuss results of studying several ‘paradigm’ systems in which interaction over multiple space and time scales emerge. In particular, I will discuss the evolution of coding structures, and the specific moulding of the ‘mutational landscape,’ which not only increases or decreases robustness and evolvability, but can lead to a variety of ‘functional roles’ of mutants, i.e., can lead to an 'ecosystem' or 'society' of mutants.

ATHEL CORNISH-BOWDEN
CNRS Marseille

The Evolution of Metabolic Systems

So far as metabolism is concerned, many enzymologists have been extremely slow to incorporate systemic ideas in their thinking. Enzymes continue to be studied mainly one at a time, and proposals about their regulatory functions are made with almost no consideration of the system as a whole. Even researchers who describe their field as systems biology often fail to think systemically, and systems biology often seems to be little different from traditional quantitative biology done on a huge scale. Nonetheless, systemic thinking is necessary. To understand how, for example, the tricarboxylate cycle could evolve step by step, without eight enzymes appearing simultaneously, one needs to think both about the pathway as a whole and how it could operate both today and in the primitive reducing atmosphere. Using examples such as this, I will show how understanding the evolution of metabolic systems has a bearing on what is called ESB, with lessons that can be drawn for its development.

OLAF WOLKENHAUER
University of Rostock

Does the Notion of Evolvability Apply to a Society of Cells?

The principle of evolution describes competing individuals and the consequences of their fitness for changes in the population over successive generations. This principle has also been used to describe the malfunctioning of human tissues in neoplasms and tumors.

Here I question the application of evolutionary ideas to describe cells in healthy tissues, which form a highly coordinated and cooperative society characterized by multiple levels of structural and functional organization. In tissues, every cell owes its presence to the behavior of all the remaining cells, and also functions for the sake of the others. The whole (tissue) and its parts (cells) reciprocally produce each other; determine the functioning of each other. In this special bi-directional whole-part relationship, higher-level structures (organs) and their function (physiology) emerge from the interactions at the cell level (in particular cell growth, proliferation, differentiation, and apoptosis).

On the other hand, the cells in a tissue also create the environment that coordinates the behavior of its cells: tissues are self-referential systems. A remarkable property of this self-organization is robustness: the structural and functional organization at higher levels is maintained despite and because of changes in the structural and functional organization at the lower level. To the observer, complex biological systems change in unpredictable ways while paradoxically remaining essentially the same. A hallmark of these systems is multi-levelness, and a key aspect of their organization is that levels are interdependent but also autonomous: cross-level determination is not by instruction. The cells of a tissue sense and interpret their environment, and then select an appropriate response in what may also be described as a form of 'cognition.'

I believe that conventional mechanistic modeling approaches, used in systems biology to describe cell functions, and mathematical formalisms, used to realize an evolutionary perspective, are not appropriate to investigate cross-level determination in tissue organization. In response to this challenge, I propose a combination of mathematical general systems theory and category theory as a novel approach to discover the principles of tissue (self-)organization.

ARNON LEVY
The Van Leer Jerusalem Institute

Causal Order and Kinds of Robustness

This talk is part of a project that centers on the notion of *causal order*. I use this term to mark a distinction between two kinds of parts-whole dependence. Orderly systems display a rich internal structure in that they have parts with differential roles, which interact locally. Speaking generally, orderliness matters for epistemic purposes, since such systems are typically amenable to decomposition, in both explanatory and empirical respects. My focus here will be on the connection between order and robustness. Many biological systems are robust in the sense that their level of performance remains stable in the face of internal or environmental perturbations. Understanding robustness is, needless to say, of central important in the study of biological systems, both in a proximate context and from an evolutionary perspective.

Relying on the notion of causal order, I will distinguish three types of robustness. *Ordered robustness* consists in a system's having a specific organizational pattern that ensures stability in the face of perturbations. Feedback loops and other forms of internal monitoring are key examples of this class. These occur, for instance, in genetic regulatory networks. *Messy robustness*, on the other hand, occurs when a system's resilience stems from the aggregate outcome of a multiplicity of indistinguishable parts. Some simple diffusion-based phenomena exhibit this mode of robustness, but it remains to be seen whether they have importance in more central biological contexts. In between these two categories, we find *semi-ordered robustness*, which involves a messy ensemble of elements upon which is superimposed a selection or stabilization mechanism. Enervation of muscles via synapse elimination is an example in this vein.

After outlining the three forms of robustness and looking at an example for each, I will discuss some connections between them. In particular, I will discuss whether there is reason to expect the different forms of robustness to play differ-

ent roles depending on developmental stage (e.g., whether messy robustness is more common in early development) and/or evolutionary context.

MARK SIEGAL
New York University

Two Empirical Challenges to Robustness

Biological systems appear to produce phenotypes that are robust to perturbations from the environment and from mutations. A central goal of ESB has been to understand the causes and consequences of this robustness. I will present two examples from our recent research that challenge this focus on robustness. Both involve highly parallel measurements of single-cell phenotypes in the budding yeast, *Saccharomyces cerevisiae*. In the first example, involving measurement of the growth rates and stress susceptibilities of individual cells, I will present evidence that natural selection appears to have favored heterogeneity, rather than uniformity, of cell behavior. In the second example, involving measurement of the morphologies of individual cells, I will present the first rigorous test that a gene product confers robustness to the effects of naturally occurring mutations. Despite strong evidence that this gene product confers robustness to environmental fluctuations, I will show equally strong evidence that it does not confer robustness to mutations. Both examples suggest that robustness should not be taken as a given, and highlight the importance in ESB of testing theoretical predictions with data-rich, high-throughput experiments.

CSABA PÁL
University of Szeged

Is Evolution Predictable?

Understanding this question requires an understanding of the mutational effects that govern the complex relationship between genotype and phenotype. In practice, it involves integrating systems-biology modeling, microbial laboratory evolution experiments and large-scale mutational analyses—a feat that is made possible by the recent availability of the necessary computational tools and experimental techniques. We will investigate recent progresses in mapping evolutionary trajectories and discusses the degree to which these predictions are realistic.

ULRICH KROHS
University of Münster

Prospects of Overcoming Massive Underdetermination by Combining Data and Models from Different Fields of Research

Systems-biological models are based on enormously rich data sets. Unfortunately, each data set or combination of data sets, and hence the underlying biochemical and genetic structures and processes, can be modeled in different ways, the result depending on the data mining techniques applied and on the modeling strategies. In short: the model is not fully determined by data, various models are equally adequate. Such an ambiguous relation between data and models is, of course, not restricted to systems biology. It is a ubiquitous feature of empirical science, known as *underdetermination*. Underdetermination leads, among others, to the following problem: if two equally adequate models make different predictions, which one should be trusted? My presentation will show that several branches of ESB can be understood as aiming at restricting the underdetermination of systems biological models by feeding in additional data from other fields, namely data from population and/or quantitative genetics. One may also look at this from the opposite perspective: the field aims at restricting the underdetermination of quantitative genetic models, which is in part responsible for the problems in establishing genotype-phenotype maps, by feeding in systems biological data.

The results obtained so far in ESB are highly promising. This may be true for various reasons: (a) Strategies of combining fields that tackle related or overlapping topics might in general help reducing underdetermination of models from the isolated fields. (b) The particular combination of systems biology with (quantitative) genetics might be successful in reducing underdetermination for some special reason (possible reasons including that both of its sub-fields might represent incomplete, 'deprived' research programs only, or that ESB provides a unifying theory which overarches both fields). (c) Each single problem tackled so far by ESB might have been chosen carefully for explanatory or predictive suc-

cess, without success being generalizable. So reduction of underdetermination in ESB might be due (a) to a general feature of field-overarching modeling in science, (b) to some particular reason valid for ESB only, or (c) to the choice of particular cases. I will show that each of the three aspects plays a certain role. Discussion of those roles will lead to a better understanding of which kind of research program certain branches of ESB are, and in which respect the integration of evolutionary and systems biological approaches may serve as a model for other integrative approaches.

MICHAEL LYNCH
Indiana University Bloomington

Mutation, Drift, and the Origin of Subcellular Features

Understanding the mechanisms of evolution and the degree to which phylogenetic generalities exist requires information on the rate at which mutations arise and their effects at the molecular and phenotypic levels. Although procuring such data has been technically challenging, high-throughput genomic sequencing is rapidly expanding our knowledge in this area. Most notably, information on spontaneous mutations, now available in a wide variety of organisms, implies an inverse scaling of the mutation rate (per nucleotide site) with the effective population size of a lineage. The argument will be made that this pattern naturally arises as natural selection pushes the mutation rate down to a lower limit set by the power of random genetic drift rather than by intrinsic molecular limitations on repair mechanisms. This drift-barrier hypothesis has general implications for all aspects of evolution, including the performance of enzymes and the stability of proteins. The fundamental assumption is that as molecular adaptations become more and more refined, the room for subsequent improvement becomes diminishingly small. If this hypothesis is correct, the population-genetic environment imposes a fundamental constraint on the level of perfection that can be achieved by any molecular adaptation. Additional examples consistent with this hypothesis will be drawn from recent observations on the transcription error rate and on the evolutionary of the oligomeric states of proteins. Finally, I will discuss the evolution of layers of surveillance mechanisms within cells, demonstrating that the emergence of what might seem like robust cellular features endow the organism with no long-term selective advantage, while also increasing the cost of maintaining overly complex features.

ANDREAS WAGNER
University of Zürich

The Origins of Evolutionary Adaptations and Innovations

Life can be viewed as a four billion year-long history of innovations. These range from dramatic macroscopic innovations like the evolution of wings or eyes, to a myriad molecular changes that form the basis of macroscopic innovations. We know many examples of such innovations—qualitatively new phenotypes that provide an advantage to their bearer—but we have no systematic understanding of the principles that allow organisms to innovate. Most phenotypic innovations result from changes in three classes of systems: metabolic networks, regulatory circuits, and protein or RNA molecules. I will discuss evidence that these classes of systems share two important features that are essential for their ability to innovate.

PIERRE-ALAIN BRAILLARD
Université Lille 1

How Can Functional and Evolutionary Approaches be Integrated in Order to Avoid the Adaptationist Pitfalls in the Study of Biological Networks?

An important part of systems biology is based on the analysis of molecular networks with models and concepts inspired by engineering, with the goal of uncovering these networks' design principles. These approaches are very useful and fruitful in decomposing and analyzing these complex systems and explaining how biological functions emerge from the dynamics of interacting components. Although engineering approaches are fundamentally functional, many studies have drawn evolutionary conclusions by arguing that these systems' general design principles are the result of convergent evolution and hence adaptations. However, such conclusions have been criticized because they apply too straightforwardly analogies with artificial systems, and they describe too many systems properties in terms of purpose and design. The problem is that what appears as good design might for a large part be the result of non-adaptive processes.

The solution to overcome these limits is to integrate in some ways these engineering approaches and other kinds of models that recognize a plurality of evolutionary processes, both adaptive and non-adaptive. Such integrative and pluralistic approaches are now emerging in ESB, but they raise many questions.

The issue I will explore is how such integration can proceed in order to escape adaptationist pitfalls in the study of molecular networks. How network explanations based on design analyses can integrate models and data from other domains (population genetics, comparative approaches, theoretical works on network evolution, etc.)? To what extent can we expect that these approaches will converge? It might turn out that they are partly incompatible. It is indeed arguable that the very framework used by this engineering- minded tradition in systems biology is ill suited for addressing evolutionary questions and is more misleading than illuminating, because of its almost exclusive focus on design

(this might also put into question these explanatory models from a functional point of view). In short, my goal is to explore and clarify how functional adaptationist approaches can be integrated with more pluralistic evolutionary methods and explanatory strategies.

SARA GREEN
Aarhus University

Reverse Tinkering the Evolution of Organisms

In this paper I reflect on the philosophical implications of the notion of evolutionary design principles. I first highlight the difference in the epistemic scope of biological mechanisms and design/organizing principles. Then I discuss whether and how evolutionary design principles differ from (non-evolutionary) design principles in systems biology and from 'traditional' evolutionary explanations. I suggest that design principles are conceptualizations of schemes of biological organization of a higher level of abstraction than mechanistic explanations. This feature enables the methods to investigate these and the knowledge of these to be applicable across a variety of different systems. Evolutionary design principles signify general *evolutionary* processes that underpin the emergence of network features across different biological systems. Rather than the narrow focus on design by natural selection, 'design recovery' in ESB aims at an integrated picture of different evolutionary processes. Computational modeling is here a central investigative tool to understand the possible trajectories of change leading to the network features we can observe in living systems today. Based on examples of such research, I propose that the methodology of ESB may be conceptualized as *reverse tinkering* of possible routes to innovation within the constraints of previous and existing evolvable systems.

BRETT CALCOTT
Australian National University

Evolutionary Change as an Engineering Puzzle

Both philosophers and biologists have argued that engineering is a poor analogy for evolution. Despite this, many biologists in ESB continue to draw comparisons between the two. Approaching this issue as an engineer, rather than a biologist, can clarify on the debate. The abilities of organisms to do such things as fly, stick, and navigate, have always provided inspiration and ideas for engineers. And our understanding of biology has often benefited from this interaction too, as the failures and successes of engineers to emulate evolved mechanisms have provided insights into how these mechanisms work. These interactions look like they are limited to proximate biology—to learning from how biological mechanisms work *at a time*. But what has been made abundantly clear in recent years (in software engineering, for example) is that the way complex systems are built not only affects how they work *at a time*, but also how they *change over time*. In these disciplines, engineers must build systems that work now, but structure them so they can be modified or extended when demands change. By examining what engineers might learn (and what they won't) about evolutionary change in complex systems under changing demands, we can get a clearer picture of both the extent and limits of comparisons between evolution and engineering.

ORKUN SOYER
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Evolution of Response Dynamics in Cellular Networks

Systems biology increasingly provides detailed information on the structure and dynamics of cellular networks. This information reveals intricate structures (e.g., feedback loops) and dynamics (e.g., transient responses), which poses the question of how such features of cellular networks—seemingly perfectly suited for the physiological response they mediate—could have evolved in a stepwise manner. I will use several examples to show that changes in selective pressures as well as system structure can underpin stepwise evolution of more complex systems. Understanding these intermediary steps in the evolution of biological systems provide us with testable hypotheses about evolutionary dynamics and with design suggestions for synthetic biology.

JOHANNES JAEGER
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Life's Attractors: Reverse-Engineering the Evolution of Developmental Systems

Adaptation is the product of phenotypic variability and natural selection. While we know a lot about the latter, we do not yet truly understand the sources and nature of the former. An understanding of phenotypic variability in multi-cellular organisms requires a systematic and quantitative study of the principles underlying development. The structure of developmental regulatory networks determines not only their function, but also influences the ways in which they can (or cannot) change during evolution. I present an approach that allows us to reverse-engineer the structure and dynamics of developmental regulatory networks, and to simulate their evolutionary transitions. In this approach, information on gene regulatory interactions is extracted from quantitative expression data through mathematical models called gene circuits. These models enable us to characterize regulatory changes during evolution in terms of changes in the attractor states of the system. I illustrate this approach with a case study, the gap gene system involved in patterning the early embryo of *Drosophila* and other flies (Diptera). Gap gene circuit models in *Drosophila* reproduce observed gene expression with high accuracy and temporal resolution, and reveal a dynamic mechanism for the control of positional information through shifts of gap gene expression domains. My group is extending this approach to a comparative study of the gap gene network between different species of dipterans. Our approach yields precise, quantitative predictions of how changes of gene regulatory feedback affect the timing and positioning of expression domains, and supplies us with an explanation of these evolutionary transitions in terms of changes (bifurcations) in the attractors of the system.

MANFRED LAUBICHLER
Arizona State University

The Regulatory Genome in Development and Evolution

With the rise of a molecular understanding of genomic regulatory systems evolutionary biology has been transformed and is now rapidly becoming a mechanistic science in the context of such developments as developmental evolution and ESB. The basis of these conceptual and empirical transformations is the concept of the genome as a four-dimensional sequence of regulatory states (as opposed to a sequence). Based on the regulatory logic of the genome we can expand this perspective in a hierarchical way to include concrete mechanistic causes of relevant cellular, environmental and behavioral contexts. Furthermore, the regulatory logic can be turned into a computational model to test empirical findings as well as explore possible evolutionary scenarios in the context of *in silico* synthetic experimental evolution. This talk will present findings from research with social insects (the developmental evolution of the superorganism) and sea urchins to sketch some conceptual and theoretical contours of ESB.

MELINDA FAGAN
Rice University, Houston

Concerns About Evolutionary Systems Biology

I discuss several concerns about the new field of ESB. These are offered in a spirit of friendly criticism, rather than presented as devastating objections. First, is it productive to identify a new field, rather than pursue evolutionary questions as part of Systems Biology more generally? Many systems biologists appeal to evolutionary ideas, notably when proposing design principles for living things. Often, their assumptions are adaptationist and reveal limited understanding of evolutionary biology. Proponents of ESB could improve these accounts. But the most efficient way to do would seem to be 'from within,' not as part of a distinct sub-field with its own moniker and agenda. The interdisciplinary nature of Systems Biology, and its commitment to integration of data, methods, and models, lowers barriers to such collaboration. Would a program of ESB impose unnecessary boundaries? Other concerns to be discussed include: tensions arising from different epistemic goals and standards, upsetting the 'balance' of theory and experiment, and commitment to general evolutionary principles as necessary for 'real science.'