Report of a Workshop that addressed the Grand Challenge: How Organisms Walk the Tightrope Between Stability and Change

Report of a Workshop held at The Banbury Center,
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Summary

Living systems are complex systems, made of multiple interconnected elements with the capacity to change and respond to environmental conditions through experience, have many non-linearities in responses, and have emergent properties. Understanding the mechanisms that underlie animal function, development and interactions with the environment is a major challenge for biology. This knowledge is essential because there is an urgent demand for scientists to accurately predict the response of organisms to short and long term changes in their environments. Animals around the world face unprecedented pressures from expanding human populations, habitat destruction and fragmentation, ocean acidification, and climate change. The viability of wild animal populations and our ability to manage and utilize both domesticated and wild animal populations for human benefit (e.g., to supply dietary protein, pollination of crops, stability of ecological communities, and sources of medicines) will depend on an improved understanding of how animals function and how they respond to environmental change. Our ability to predict what features of complex integrated systems will or will not allow organisms to respond to changing environments and maintain function is poorly developed. Predictive organismal biology will require a more

quantitative approach, including complex systems modeling approaches common to engineering. Such approaches will help us identify common patterns and strategies that organisms use to maintain function under changing conditions, and respond or adapt to changing environments.

After decades of research, we still lack understanding of what characteristics of complex living systems allow them to change in response to either internal or external environments, and what characteristics create inflexibility. Addressing the grand challenge of how metazoans walk the tightrope between stability and change will require a transformation of the way animal biologists approach their discipline. To comprehend the dynamics of complex living systems, we must move beyond the traditional approaches of organismal biology, and incorporate methodological tools of other disciplines that also study complex systems, particularly mathematics, engineering, and physics. Not only will we gain a deeper, mechanism-based understanding of how organisms will face future environmental challenges, but in pursuing this research endeavor, we will also reveal nature-inspired solutions to stability and agility of exceedingly complex systems.

This workshop brought together engineers and mathematicians with a broad range of biologists to build bridges and initiate a common dialog. Together, we identified key areas where new research and tools could make significant inroads on this grand challenge.

Workshop Goals

1. To develop a research agenda to address the organismal biology grand challenge question, "*How do animals walk the tightrope between stability and change?*"
2. To identify research needs and the collaborations necessary to make progress and, if possible, to articulate or identify specific systems, questions or approaches that will best accommodate our needs.
3. To develop strategies that can be followed in the short and long term to coordinate research efforts of individuals and collaborative groups working on this grand challenge and to build capacity for addressing important questions in the future.
4. To identify societal benefits and deliverables from investment in this effort.

Introduction

This document is the result of an NSF-funded workshop on one of the grand challenges of organismal biology articulated by Schwenk, Padilla, Bakken and Full (2009); "How organisms walk the tightrope between stability and change". This workshop was preceded by a smaller workshop in November of 2012 that included members of the steering committee (Appendix I). The full workshop was held at the Banbury Center, which is run by the Cold Spring Harbor Laboratory, Lloyd Harbor, New York (Appendix II). We focused on metazoan animals, rather than considering all organisms, as metazoans have a common evolutionary history distinct from unicellular and plant life, and share many characteristics including being predominantly macroscopic, motile (during some stage of life), and heterotrophic. These and other commonalities provide general and unifying themes for our community of organismal biologists.

Why now?
After decades of developing molecular biology tools and continually increasing computing capacity, we now see a range of tools available to organismal biologists, including ubiquitous sensing, genomic tools, and high throughput measurement methods such as machine vision. These advances provide an opportunity to develop new, interdisciplinary approaches and advancement through integrated approaches to organismal biology. They make what was once impossible, a possibility. Biologists, engineers and mathematicians are now addressing similar questions about the integration and functioning of complex systems with the use of control theory and other dynamic systems modeling tools; moreover, they are often using biological design and function to inspire new approaches and solutions to long-standing problems. The combination of these advances not only provides an opportunity for new, integrated approaches, but also a rejuvenated and redirected organismal biology, which can infuse new insight into developing models and methods to predict how organisms respond to changes in internal and external environments.

Making Progress
A central paradox in biology is that organisms must maintain the integration of complex developmental, morphological and physiological systems while simultaneously responding and adapting to continuously changing internal and external environments. Understanding how organisms maintain the balance between integrated stability and adaptive flexibility (both short term accommodation and long term evolutionary adaptation) is of growing importance. However, we do not understand the functional and system-level attributes of organisms that make them resilient or robust, or conversely, sensitive or fragile, to internal or external environmental perturbations. In particular, we need to identify mechanisms that mediate both genetic and phenotypic responses to environmental inputs across different temporal and spatial scales.

It is clear that this Grand Challenge question is beyond the scope of any single scientific community. It has also been shown that collective intelligence far exceeds individual intelligence (Woolley et al. 2010). It is also broadly acknowledged that collaborative, interdisciplinary research that integrates knowledge across fields and levels of biological organization is needed (Schwenk, Padilla, Bakken and Full 2009). Through a series of previous workshops and collaborations, scientists from a wide range of biological disciplines and related fields have articulated the need for integration and collaboration to tackle these big questions (e.g., Denny and Helmuth 2009, Mykles et al. 2010, Tsukimura et al. 2010, Stillman et al. 2011). This has included a call for greater inter-disciplinary teaming with applied mathematicians and engineers (e.g., Csete and Doyle 2002; Cohen 2004). For example, dynamical systems and control theoretic approaches may facilitate this endeavor, especially for our understanding of organisms as modular, hierarchical and networked systems. However, such disparate groups do not presently share a common scientific framework or language, and generally do not work together, making any sort of progress hard to attain.

This workshop brought together engineers and mathematicians who deal with complex systems with a wide range of animal biologists. Participating fields included developmental biology, evolution, cellular and organismal physiology, environmental physiology, functional ecology, neurophysiology, behavior, functional morphology, biomechanics, and control and dynamical systems engineering and mathematical modeling. We included senior, mid-career and junior researchers, as well as a postdoctoral fellow, from a range of public and private universities, colleges and research institutions to increase the diversity of thought and background of the participants (Appendix II). The focus of the workshop was to initiate dialogue, determine overlapping areas of research, identify critical areas and questions that require new information or approaches, and define new research agendas to address this grand challenge.

1. Challenge: Living organisms are multiscale systems in both time and space

Animals operate by the integration of systems (e.g., nervous systems, circulatory systems, skeletal and muscular systems), and modules (compartmentalized components that function as a unit) that are organized and function at multiple temporal and spatial scales. Genomes of animals hold the information needed for all life functions, but the interactions of genes and metabolites (including various signaling molecules), operate in the context of complex networks and control everything from cell differentiation and division, to morphogenesis of whole structures and organisms. Modules within networks can cross scales of levels of organization or can be nested within levels of organization. For example, there are modules associated with genes that control gene expression, several genes can be organized into a modular genetic network, or the signaling pathways associated with differentiation of a tissue can also function as a module.

Although some processes in organisms, such as many biochemical interactions and transmission of information within the nervous system, can operate in milliseconds, other processes, such as development and ontogeny to the adult form, operate on much longer time scales, up to decades for some long-lived animals. Evolutionary responses occur over time scales from a single generation to eons.

We lack a firm understanding of how stability of function is maintained at each level of biological organization (e.g., gene network, endocrine regulatory network, whole-animal behavioral repertoire), and how stability of whole-animal function is maintained through integration of lower levels of organization or component modules. Nor have we identified general principles about how some or all lower level modules must change functionally, and in an integrated way, in response to internal or external environmental changes that are within the limits of organismal performance (i.e., in a way that maintains overall organismal function instead of failure or death). Changes at different levels or organization, different scales or within different modules can translate into whole organism changes as well. There is a complex interplay of biological and physical factors that together determine the maintenance of function and stability versus failure and decline, or the ability of a system in one state to controllably change and move to a new state. Continued work and new, interdisciplinary approaches are needed to identify the fundamental design principles of animals, the importance and presence of stability or change over time in systems within organisms and among species, both during the lifetime of an organism, and through its ontogeny within an environment, and through evolutionary time as the genome, organismal systems, and networks evolve.

Organismal biologists are uniquely positioned at the interface of: 1) integrative approaches to studying animal function, 2) quantitative approaches to modeling aspects of animal function, 3) an ability to connect genetic information to organisms and link organismal traits to performance and response to natural environments, and 4) a comparative/evolutionary/phylogenetic framework. With the integration of control theory and systems modeling into organismal biology, these interfaces will provide launch points for advances in understanding biological response to changing environments.

Important questions for the multiscale nature of organisms

1. Are there recurrent themes or design principles across or within scales of organization or across types of response to environmental change that govern stability or change, either flexible change to a new functional state, or failure and loss of function, whose characterization will provide new paradigms for the field?
2. Are organisms mostly constructed of modules rather than levels of organization, or are levels functioning as modules? If they are modular, do the same principles apply across temporal and spatial scales of organization or integration?
3. Are systems and modules organized similarly across taxa, and do the same factors govern their integration and control?
4. Are there emergent properties at different levels of organization of organisms? Can emergent properties be revealed by understanding how different levels of organization are integrated in functional or structural modules? If so, how can we identify them, and once identified, what is the most efficient way to determine if they apply broadly?

2. Challenge: Using mathematical and engineering modeling approaches to provide insights into stability and change in animal systems

Modeling approaches, such as dynamical systems modeling and control theory, can make exploration of complex systems more tractable, can be used to both test and generate hypotheses, and can rigorously identify principles that apply across disciplines and systems. Dynamical systems models from engineering can be used to describe, explain, and predict many of the same multiscale challenges that are found in biological systems, varying both across space and through time. At present, properties of complex systems including robustness, stability, controllability, and observability are most commonly modeled with linear control theory. However, as is well known, biological systems often operate with significant non-linearity, which will require development of tools and models to satisfactorily describe and analyze this essential feature of life. Herein lies a dual challenge to the domains of both biology and engineering.

Organismal biology offers true synergy with the various fields of mathematics and engineering. Mathematical tools and models applied to biological systems have the potential to identify the critical features that are important determinants of stability, and the dynamics of systems as they change from one stable state to another, or lose function. Organismal systems pose new challenges for mathematics and engineering due to their complexity and diversity of solutions to complex problems of structure and function as displayed through evolutionary time. Therefore, major theoretical advances will generally involve contributions from both mathematics and biology. As nicely summarized by Avner Friedman (2010), "… mathematics is the future frontier of biology and biology is the future frontier of mathematics."

Because biological phenomena are frequently much more complex -- chemically, physically and organizationally -- than inorganic phenomena, a cause-and-effect understanding of system dynamics will inevitably foster innovative analytic, computational and technological advances. Some key examples emerging today include genetic (or evolutionary) algorithms that search massive parameter spaces for optimal solutions that underlie some complex physical or biological problem. For engineering and mathematics, learning algorithms, robotic control designs modeled after complex nervous systems, and DNA or synapses as models for information science all present new horizons. A significant synergism therefore exists between the life sciences and engineering and mathematical sciences: the combination of massive data sets, complex interactions, and uncertainty underlying many of the fundamental open problems in biology is spurring the development of advanced computational, analytic and technological innovations. These tools enable organismal biologists and engineers to push the envelope further in ways that will bootstrap even greater innovations.

A number of concepts from control theory are already an integral part of understanding the function of organismal systems, including feedback, robustness (no change in system properties under some range of different conditions), stability (system maintains function within some bounds, though various definitions abound), controllability (ability to force the system to a particular state by some control signal), and observability (use of output measures to determine the internal state of the system), all of which can provide a framework for modeling and understanding how organismal systems function (Kalman 1961) and can be applied to any level of biological organization. To date, control theory has already been used to successfully study a range of biological phenomena, from the activity of gene networks, to whole organism functions such as locomotion, including flight and swimming (Cowan and Fortune 2007). These applications only hint at the potential for insights in organismal biology that are possible with these approaches. For example, compared to the intuitive but somewhat fuzzy use of terms like stability in biology, control theory offers formal definitions from which explicit, quantifiable definitions of dynamic stability around a central mean, the type of stability, and the range of conditions under which organismal systems are stable versus fragile, or uncontrollable or "broken". Until now, concerted efforts have been lacking to bring biologists and mathematicians and engineers together to advance the field of organismal biology as a whole.

Biological research challenges mathematicians and engineers to broaden their analytical approaches in important ways, including the non-linear characteristics inherent in many biological systems. In control theory models, fragility or any move from stability is often considered "bad", and to be avoided. However, in biological systems, there are many cases when stability may be favored or needed over some range of inputs, but transitions to new states are advantageous or necessary for other inputs. Examples include environmental triggering of phenotypic plasticity, altering or modulating neural transmissions, and long-term evolutionary transformations.

Important questions for the use of engineering and mathematical models to address stability/fragility/flexibility and change in organisms

1. What solutions can be found in nature to solve questions about how complex control systems can operate?
2. Mathematical systems biologists have discovered modularity, which developmental biologists have been studying for a long time. Can new lessons be learned by translating knowledge from development into mathematical systems biology?
3. Are there general control characteristics for biological systems that are stable, versus those that have the flexibility to transition to another stable state or are fragile and cannot rebound? How do we discover those rules?
4. Do all animal biological systems have feedback loops? Under what conditions do these feedbacks provide (or fail to provide) robustness to disturbances and constraints?
5. Are there general properties, such as tradeoffs and feedbacks, of multi-scale systems that can be identified and applied to understanding the stable/fragile properties of biological systems?

3. Challenge: Networks, modularity, and interactions among components of complex organismal systems

Networks are inherent in many different biological systems, and are important components of organisms, from gene regulatory networks that are part of physiological responses or developmental controls, to neural networks, to interaction networks among species.

Modularity is a common feature of complex networks, and has been found across all levels of biological organization, from genes to development to populations, and this modularity provides a potential reservoir of evolutionary flexibility and resilience. Animals have genetic, physiological and developmental mechanisms that provide both homeostatic regulation in the face of environmental variability, and the ability to change a phenotype in response to external or internal change. One example is the large fraction (25-50%) of animal genes that contain alternatively spliced exons, often organized in cassettes that are conserved across species. Networks of alternatively spliced genes have been shown to affect phenotypes such as pleuripotency of stem cells, muscle responses to changing body weight, longevity in humans, and the metabolic sensitivity of caste regulation in honeybees (Lyko et al. 2010; Salomonis et al. 2010; Schilder et al. 2011). Other types of modularity and network topology, such as microRNA regulation and DNA methylation are likely to show similar features. Such modularity and network regulation may enable many of the plastic responses organisms make to environmental variation and involve feedback regulation amenable to control theory approaches.

The nervous system provides another example of networks and modularity. Neurons are organized into networks that serve a variety of functions for animals. Function within a network and the interactions between multiple networks that control related functions influence both the stability and change in the systems they control. Motor networks, for example, can produce rhythmic outputs that are remarkably stable in the face of clear differences in the detailed makeup of the neurons that comprise them. Both the levels of mRNA encoding specific ion channels and the density of those channels can vary substantially between the same neurons in different animals, yet the activity pattern of those neurons and their participation in a network are often virtually indistinguishable (e.g., Prinz et al. 2004; Schulz et al. 2006). At the same time, external inputs can change the functioning of both individual neurons and the networks as a whole. On a more global level, it is clear that different neural networks must interact with one another to enable appropriate coordination of multiple aspects of motor functioning, and that the extent of these interactions is variable. Thus, although a single pattern or type of interaction between networks can be relatively stable, and can be maintained for long periods of time, that coordination can then change to another stable state relatively rapidly. Perhaps the best-known example of this is in the coordination between breathing and locomotion, which changes as rate of locomotion increases. Additionally, neural networks interact not only with one another, but also with the systems they are controlling: feedback from a variety of target organs is common (e.g., Cooke 2002). While some work has been done examining the details of such network interactions in relatively simple systems, they are far from being understood, and, while a variety of modeling approaches have been used to address questions related to neural network functioning, the application of control theory to examine the switch between different stable states or between stable and non-stable states could provide new insights.

Important questions for understanding networks and interactions among components of complex organismal systems

1. Are there regulators of large effect (a.k.a. ‘hot knobs’), within complex systems? If there are, what are the most efficient ways to find them?
2. Are there rules about how many hot knobs are likely to be in a given system, or limits to how complicated are they? Do these features differ for relatively simple regulation (few nodes or within a single module) versus complex regulation (regulation among interacting modules, or across different, large networks or systems).
3. Can we identify regulators that have large effects in complex systems without individually measuring every potential regulatory factor or node in a network?

4. Challenge: Phenotypic plasticity and sensitivity to changing environments

A recurrent theme across biology is the need to understand the link between genotypes and phenotypes, especially in the context of understanding the evolution and regulation of phenotypic plasticity (A New Biology for the 21st Century, NRC Report 2009; Schwenk, Padilla, Bakken and Full 2009; Evolution and Climate Change in the Ocean workshop report, NSF 2010)

Virtually all aspects of organismal structure and function, including morphology, physiology, neurobiology and development, have the potential to display phenotypic plasticity and are amenable for studying how a genome can give rise to different phenotypes in different environments. Phenotypic plasticity can arise from modification of a default (ancestral) state to a new state when cues associated with new conditions or perturbations are present, which result in movement away from a stable realm to a new state until the cue is removed, after which the system returns to an original, stable state. There can also be switching among alternative phenotypes, each triggered by particular cues (alternative states with drivers needed to switch from one to another). Or animals may produce continually varying phenotypes that move in response to varying environmental conditions, with no set stable state or states (e.g., many physiological traits that vary along a continuum). Each of these types of plasticity will have different controlling mechanisms, and will demand a different type of model to describe or predict system behavior and its consequences.

Modeling the dynamics between developmental and physiological stability, while still allowing phenotypic plasticity and trait evolution in response to particular environmental inputs, is of particular importance as organisms face ever increasing rates of environmental and climatic change. Thus, there is a critical need to understand these dynamics and identify the underlying mechanisms. Questions about how stability is maintained in the face of certain disturbances (homeostasis) and how these balancing acts may generate greater sensitivity or change to other perturbations are not unique to organismal biology. For example, engineers that study control systems are interested in similar phenomena. In engineering, and perhaps also biology, there are tradeoffs between the stability (tendency to remain near some value) of closed-loop control systems or their insensitivity to perturbations (resistance, or maintaining a state when faced with some disturbance), and fragility, where perturbations break the system, or the system loses functionality. While it may seem clear that biologists and engineers have overlapping conceptual interests, cross talk and transfer of ideas and approaches is inhibited because scientists in these disparate disciplines use different vocabularies and definitions.

The importance of developing common vocabularies and perspectives between biologists and engineers can be further demonstrated. Consider that the close ties between structural and functional responses to different environments and organismal performance and fitness, questions regarding the favorable match of controlling mechanisms and evolutionarily adaptation, maximizing fitness under different conditions are essential for understanding the adaptive value of phenotypic plasticity, how it may arise, and conditions that will or will not favor plasticity. Understanding the system level properties and differences between a highly regulated (and likely evolutionarily selected) plastic response to environmental change, and a non-regulated response to change (e.g., the product of physical and chemical properties, such as thermal sensitivity), or environmental insensitivity or no response to environmental change is critical. Determining when insensitivity (no response) to environmental change should be selected for is as important as understanding different types of phenotypically plastic responses. The underlying regulatory and developmental systems that produced a “regulated” response may due to the networks or modules that are selected because they have that very property of insensitivity. Control systems theory and dynamic systems models in general provide an opportunity to address these issues. Such approaches will require the vertical integration of systems within organisms (e.g., gene networks controlling development or physiological responses) with whole organism phenotypes and interactions with both the temporal and spatial scales of environmental change, both for internal environments as well as external environments, including interactions with other species. Such approaches will allow determinations of when plasticity would be predicted to evolve or be maintained because of a lack of a regulated response, or the ability of an organism or organismal system to maintain stability, and the consequences of a lack of a single state of stability. Determining the role of internal feedbacks and tradeoffs, and whether animals that possess different types of plasticity are either resistant to becoming fixed adaptations (constraint between stability and change) or are more evolvable, and whether taxa that have more plasticity are more or less likely to diversify or whether they are more or less likely to persist through evolutionary time would also be approachable. Control Theory can be a means to blend these disparate fields into a predictive mechanism. In addition, these models may identify biological areas where greater information is necessary to polish models of phenotypic plasticity.

Important questions for understanding phenotypic plasticity and sensitivity to changing environments

1. What are the roles of and limits to phenotypic plasticity, environmental sensitivity and variability among organisms and their responses to varying environments?
2. To what extent do systems with different modes of phenotypic plasticity share general properties regarding the control of the plasticity, and what are the integrated linkages among developmental, physiological and structural systems?
3. Are there common characteristics among traits that have tightly regulated and controlled plasticity versus those that are due to a lack of regulation, or loose regulation?
4. Do rates or magnitude of environmental change limit or provide opportunity for plastic phenotypic responses for different types of plasticity or for plasticity in different organismal systems?
5. Does regulatory modularity enhance or limit the plasticity of traits, and is this different for morphological, physiological, life history or behavioral traits?

5. New opportunities

New technologies and conceptual advances have resulted in an explosion of data. The 'omics' revolution has resulted not only in producing genome sequences for an array of taxa, but also in allowing us to use functional genomics to examine responses of organisms to different environments (e.g., proteomics, metabolomics, transcriptomics). At present, biologists are working to determine organismal function and response from such data. In addition, biologists are gathering data that enable elucidation of organismal physiology, design and performance across taxa at unprecedented rates.

The pendulum of biological progress is swinging back toward the recognition that the next big challenge is to integrate across biological levels to understand broadly the workings of whole animals in their natural environments. This assimilation requires novel approaches that extend beyond the level of protein interactions (the present definition of systems biology used by biochemists and cellular biologists). A new, grander systems biology that extends from genes through development, organismal phenotypes and function in natural settings, demands that we approach our discipline using a much broader set of tools, including modeling, and engineering approaches. Parallel to the efforts of organismal biologists, engineers and mathematicians are addressing similar questions with the use of control theory and other dynamic systems modeling tools; moreover, they are often using biological design and function to inspire new approaches and solutions to long-standing problems. With increasing availability of data across biological taxa and systems, syntheses will be possible. The discovery of guiding and generalizable principles will rely on the development of robust modeling approaches and tools.

6. Addressing challenges and taking advantage of opportunities

From this workshop, several common challenges emerged across disciplines, including the need for a common language and mechanisms for facilitating interactions and collaboration among organismal biologists and engineers and mathematicians.

1. There is a need to identify trans-disciplinary principles, approaches and frameworks that are "robust to context". These are principles that are important and applicable not only in biology, but also in engineering and control theory – and likely in other fields as well. Examples include feedback and trade-offs. The organization of systems into "modules" or nodes, which then interact, is another example. For theoretical advances to be made in mathematics, engineering and biology, it is important that we have common models that will work across disciplines.

2. A major challenge is defining and articulating the limits of biological questions so that appropriate modeling techniques can be applied. Linking quantitative biology to mechanisms in a meaningful way will allow the development of predictive models and methods necessary to identify generalizations and overarching principles.

3. Facilitating and ensuring productive communications between engineers, mathematical modelers and biologists is important to build bridges and develop the

cross-talk needed for progress. Biologists and control theorists both use terms that have explicit definitions within their disciplines, but are used with quite different meanings in common language or in other disciplines. For example, a controlled system is a “plant” to control theorists, but has a different meaning in biology. “Adaptation” has an explicit definition in evolutionary biology, but is used more loosely in other contexts, even by other biologists. To effectively work together on common problems, biologists and engineers must agree on a shared lexicon, a common set of definitions for all important terms. Additionally, it is important that biologists are trained in quantitative and modeling methods, on the one hand, and that engineers gain a greater appreciation of the biological problems that are being addressed, on the other. This will benefit both disciplines, providing biologists with increased rigor, predictability and quantitative approaches, and providing engineers with bountiful questions inspired by nature and the possibility of developing new solutions to old problems.

4. Scientists must work together to coordinate research so that comparative studies addressing the same issue in different species are conducted rigorously and in such a way that the results can be compared in a meaningful manner. Additionally, we need to standardize the ways in which data are compiled and archived such that they can be used in comparative studies, or synthesis, especially synthesis with statistical methodology such as meta-analyses. A final related challenge is replication. To infer general principles we must determine not only the range different taxa that should be investigated, but also the number of species (or higher taxa) and the number of individuals within each taxon, especially to address interindividual variability, need to be sampled. This is particularly important as studies focused on a few model species are unlikely to address the range of important questions, or solutions found, among the diversity of animal life. We also need best practices to reliably estimate the number of experiments/studies or species that are needed to answer a given question (i.e., scope of sampling). In addition, there is a challenge in obtaining replicates among species or systems for specific questions, which is important for prioritizing research questions and systems. Prioritization is relevant also to funding agencies as they weigh support for replicated studies in different species versus projects on entirely new questions.

5. The nature of the biological questions we are interested in is a challenge in itself for existing engineering and mathematical approaches. Successfully answering many questions will require the development of new techniques. Biological systems are inherently non-linear; many are characterized by thresholds, or ‘tipping points', which lead to sudden changes in the characteristics of that system. However, the mathematical and engineering theory that is well established, such as most control theory, is based on linear systems. There is also a need for ‘vertical integration’ and the ability to model across scales that include very different types of systems. For example, systems at the lowest levels of biological organization (molecules) are characterized by stochasticity, requiring stochastic models. At higher levels, more deterministic models are likely more appropriate. The challenge will be developing the theory to simultaneously examine both types of processes, and how they interact and influence one another.

Solutions and important capacity building

Answering these complex questions will require comparative studies across greater taxonomic and disciplinary divides than scientists normally tackle. This effort will entail community buy-in, cooperation, collaboration among organismal biologists, and mechanisms for interfacing with engineers, mathematicians and modelers addressing similar systems-level questions. Thus, we need mechanisms for developing and integrating knowledge across systems, for using mathematical and engineering approaches to solve similar problems, and for training the next generation of scientists to be adept at these new approaches for organismal studies. As part of this effort, we need ways for scientists in different disciplines to find commonalties and to collaborate, as well as mechanisms for broadening the training of young scientists. Here, we propose a multi-pronged approach to achieve such goals.

Organismal Biology Synthesis Center

Participants in the workshop overwhelmingly agreed that a synthesis center would be the most effective means of promoting this research agenda and training the next generation of scientists to participate in it. Organismal biologists face challenges similar to those faced by ecologists a number of years ago: they were faced with large amounts of data across systems, space and time, but were unable to use those data to the fullest. The National Center for Ecological Analysis and Synthesis (NCEAS) enabled theorists, empiricists, and modelers to work together to address important questions in their field, ultimately developing new statistical methodologies and approaches to accomplish the synthesis that was needed. It allowed the field to grow and develop by training researchers at all stages of their careers, by using existing data to their fullest, and by identifying important research and data needs. NCEAS impacted the nature of ecological studies in general, and developed novel research areas, such as ecoinformatics. NCEAS has supported over 500 projects, engaging over 5000 researchers in developing synthetic means of ecological data analysis. The strength of their approach was in developing and disseminating technical tools that facilitate analysis and synthesis of ecological data. NCEAS accomplished this without a permanent scientific staff, but rather relied upon resident postdoctoral fellows and visiting scientists to develop tools and train the next generation of researchers. In many ways, NCEAS transformed the field of ecology.

Integrating engineering and mathematics approaches and organismal biology is similarly well suited for development and training through a synthesis center. A synthesis center in organismal biology, involving both biologists and quantitative scientists (engineers, mathematicians, and modelers), would facilitate talking across the disciplines and working together on problems. It would also be critical in training new researchers across disciplines, and in re-training more advanced researchers, so that they can work (or at least talk) across disciplines. This synthesis center could develop novel frames of reference of organismal biology to discover emergent properties.

Science Boot Camps and Beyond

Clearly, capacity building through training the next generation of organismal biologists to have the quantitative and integrative skills is needed to address big questions. Several possibilities exist to increase cross-disciplinary training. Opportunities for short term exchanges or sabbatical funding for early and mid-career scientists would facilitate incorporation of new approaches into organismal biology. Similarly, cross disciplinary postdoctoral training opportunities would provide in-depth training in multiple fields for recent PhDs, allowing biologists to gain quantitative and modeling skills, and engineers or mathematicians to develop the knowledge of biological systems needed to address complex questions.

For graduate students, intensive summer courses or "boot camps" that bring together scientists, engineers and mathematicians with different expertise to address a similar question can be an effective means of training. This type of approach has been very effective in a number of disciplines, and includes courses at field stations such as the Marine Biological Laboratory, Woods Hole MA, and Friday Harbor Laboratories, Friday Harbor WA. These courses have been fundamental in training biologists in many fields including molecular biology, neurobiology and development. They have also been important in the development of new fields such as evolution and development (EvoDevo) and biomechanics. A notably successful series of courses has been the NSF-funded International Graduate Training Program in Integrative Biology and Adaptation of Antarctic Organisms. This program has provided intensive, cross-disciplinary training opportunities for graduate students, postdoctoral fellows, and early-career scientists in biochemistry, biomechanics, physiology, ecology, and organismal biology in extreme environments. The development of courses that embed researchers together with students (graduate students through mid-career faculty) could be used to address single questions from multiple approaches, such as from biomechanics to physiological stress, and to incorporate engineering and modeling approaches into investigations of biological phenomena at the organismal level.

Scientists engaged in addressing similar questions could develop Research Coordination Networks (RCN) to bring together organismal biologists and engineers to facilitate cross training of graduate students, post-docs and undergraduates. In cases where RCN's have had great success, such as the Evo-Devo-Eco-Network (EDEN), the main focus has been undergraduate training through internships and the development of shared protocols. Such networks may be important for developing the common language and definitions needed for the new transdisciplinary approaches proposed.

In the short term there are a variety of ways to push a new research agenda forward and to develop community awareness and enthusiasm for combining organismal biology and engineering, control theory, and mathematical systems modeling approaches. These include:

(1) "Perspectives" papers in a number of different journals, including those that address broad audiences as well as those that focus on specific sub-disciplines.

(2) Symposia at national and international meetings that present and discuss the potential benefits and new frontiers that can be addressed by these new approaches; such symposia would involve engineers and mathematicians as well as biologists. Publication of symposium papers would enable the information to be broadly available. Such symposia have been important for launching certain

subdisciplines, such as biomechanics of organismal systems.

(3) Workshops that introduce biologists and engineers to these ideas could include narrowly focused workshops (e.g., on a specific type of biology) or broader ones. In addition to introducing the ideas (e.g., a tutorial on control theory for biologists), they could include opportunities for individual scientists to talk to others about their research, and potentially to set up collaborations between theorists and biologists.

(4) "Matchmaking" services could provide biologists and engineers mechanisms to meet one another, talk about their research and find the appropriate collaborations. Workshops at national meetings could accomplish this to some extent, but ongoing initiatives are needed to initiate the dialogs needed between different communities.

7. Practical applications and broader impacts

The impacts of the proposed research agenda extend beyond advances in our understanding of organismal biology and beyond the impacts of individual research projects that fall into its purview. They can be divided into two major categories: (1) opportunities to advance the development of mathematics and engineering, and (2) benefits to society beyond scientific advances.

Benefits to scientific knowledge and understanding.

Developing a deep quantitative understanding of the complex functions and interactions of many aspects of organismal biology will require the development of new mathematical and engineering tools, particularly new types of applied mathematics. At present, we do not have the ability to model across scales that are characterized by fundamentally different types of systems. Our ability to model non-linear systems is also very limited. By having engineers, mathematicians and biologists working together on the complex problems that organismal systems provide, advances will be made in each of these fields. Because this work involves engineers and applied mathematicians, these advances may in turn lead to the development of new devices, materials, and applications as described in the next section.

Another benefit to science lies in the development of "people infrastructure"; the effort to apply tools of mathematics and engineering to organismal biology will inevitably lead to the development of new collaborations. Given the nature of the scientific problems that will be addressed, and the need for deep understanding of the problems and solutions, it is likely that many of these collaborations will be long lasting, with the potential to lead not only to deeper scientific development, but also to training more students in cross- and trans-disciplinary approaches, to the development of other applications, and to unforeseen scientific advances.

Benefits to society

TECHNOLOGY DEVELOPMENT

A deep understanding of organismal biology, at an engineering level, can lead to the development of "translational principles" that can be used in engineering. This in turn can lead to a wide range of technological advances. The potential for bio-inspired design of materials and engineered products is enormous. Organisms have evolved a myriad of solutions to life's challenges. Evolutionary innovations are excellent starting points for developing novel materials, designing robots, low drag vehicles, or using plant hairs to deter bed bugs. An example is spider silk. Over the past ~400 million years, diverse web-building behaviors and silk spinning physiologies have evolved. The result is that extant spiders possess a vast catalog of protein motifs that can be the starting points for new biomaterials. Many spiders, such as orb-weavers, spin multiple types of silk fibers, with each silk type having a unique biochemical composition and functional role (dragline, frame, capture spiral, egg case, etc.). Extensive research on silk biomechanics, coupled with molecular characterization of silk proteins and genes, is being harnessed to mass produce spider silk for human applications. Deeper integration of engineering and organismal biology will make this strategy considerably more effective.

Organisms often have the capacity to be resilient in the face of a variety of insults. Understanding how they do so and when/why they sometimes do not may reveal general principles that can be used in engineering applications, such as the design of manufacturing plants. For example, models of the control systems and regulatory networks that make animals robust may be of use in the design of components and how they are integrated in a variety of infrastructure that society relies on, including manufacturing plants, transportation networks and power grids. Studies of what determines lifespan of organisms and key regulators of metabolic networks are also going to be important. Knowing more about how organisms manage energy storage and metabolism, and fundamental biochemical processes will inform our understanding of obesity, diabetes and metabolic syndrome. Knowledge of such endocrine controlled systems may facilitate understanding and treating human endocrine diseases.

Another aspect of technological development involves sensors and other instrumentation that would likely be developed to enable examination of the physiological responses of animals in their natural environment in real time. Such sensors would almost certainly have other uses. Avenues for the development of such tools are also needed.

Resource Management

Information on many aspects of animal function, including responses to environmental changes in a natural environment, can be used to inform practical decision making in a number of areas, including fisheries management, land use policy, and the management of other animal resources. This information will be important for animal breeding and the development of new domesticated varieties of animals used for food. It can be used for the development of new species that should (or should not) be targeted for aquaculture. Research that integrates from genomes and physiological systems to animal cultures may allow us to answer urgent questions, such as how recombinant growth hormone in salmon affects the biology of escapees from aquaculture.

Invasive species and pests will expand their ranges as climate change occurs. Models that address physiological and functional flexibility, as well as the factors that limit species in new environments, can facilitate development of management plans that account for species expansion or contraction in response to increasing environmental extremes. Such models may also assist in predicting responses of organisms to habitat fragmentation and climate change for endangered species or other species of special concern.

RESPONSES TO CLIMATE CHANGE

A new research agenda can capitalize on natural solutions to environmental problems. Examples include using taxonomic diversity to understand if there are recurring themes among taxa in response to environmental challenges. Many of the insights from this kind of research will also be informative for human health; for example, understanding general principles underlying how organisms deal with hypoxia may inform our ability to treat recovery from heart attack or stroke.

Determining why some organisms have survived for millennia with seemingly little change whereas others have changed quickly or diversified in response to environmental changes may also be informative as we face increasing rates of climate change in the near future. Such comparative studies in this context can also address whether long term adaptive responses of organisms are the same as short term acclimation to environmental change.

HUMAN HEALTH

The broad principles of animal design and function equally apply to humans. Studies of fundamental mechanisms that govern development and reproduction, as well as regeneration in many species, will yield principles that can provide a starting point for further examinations of issues associated with human disease, injury, healing, and recovery. A greater understanding of gene networks will be important for treating important diseases, such as cancers, as well as the impacts of aging. Tumors grow, metastasize and transform neighboring cells via mechanisms very similar to the workings and development of simple multicellular organisms. There are environmental triggers for many important diseases that are linked to physiological function, such as diabetes, one of the major health issues facing our nation. Understanding the functioning of physiological systems across scales and in response to different environments will be critical to understanding and treating important metabolic and physiological diseases of humans.

Greater understanding of the complexity of tight mutualistic systems and the physiological interplay between hosts and symbionts will also be important for human health issues. Knowing the links between interactions of hosts with microbes, such as those in the digestive system or other organs, will be informative to our understanding of how immune systems work and the importance of these microbiomes for human health.

Advances in neurobiology and neural systems will be important for finding treatments for behavioral disorders such as autism, which will require complex systems level studies including the environment and genetics. In addition, work in this area will facilitate the development of new model systems to study issues such as regeneration and to apply those principles to human systems and regenerative medicine. For example, the lamprey spinal cord exhibits full functional regeneration after spinal cord injury; understanding the mechanisms of this regeneration may shed light on problems in human spinal cord injury.

Conclusions

Biology is rapidly becoming more quantitative. Biologists must deal regularly with massive data sets and the functioning of complex systems at scales from single genes, to whole genomes, as well as the entirety of complex organismal systems such as the nervous systems to mapping the human brain. Addressing the grand challenge of how animals walk the tightrope between stability and change requires transforming the field of organismal biology. Similarly, predicting and understanding whether and how organisms can respond to short and long term changes in environments are pressing needs given current rates of climate change. Better knowledge of system-level attributes of organisms that make them resilient or robust, or conversely, sensitive or fragile, to internal or external environmental perturbations is needed to understand the dynamics and evolution of complex living systems. Accomplishing these goals will require new approaches that extend beyond our traditional disciplinary comfort zone, especially the degree to which we collaborate with mathematicians, engineers, and physicists. Pursuing this research endeavor will not only give us deeper understanding of how organisms will face future environmental challenges, but it will also reveal nature-inspired solutions to stability and agility in complex engineered systems that will benefit science and society.

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Appendix I.
Steering Committee

Prior to the workshop, the steering committee convened November 8-11 at the Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, to formulate how best to tackle this complex biological research question. The steering committee also dealt with questions of capacity building and the need for training the next generation of organismal biologists such that they are able to tackle big questions.

The steering committee proposed the participant list, and produced an agenda for the workshop that was sent to all participants in advance of the meeting. The participants came to the workshop prepared to maximize productive interactions.

Steering Committee Members:
Dianna K Padilla, Professor, Department of Ecology and Evolution, SUNY Stony Brook - Organizer
Other Steering Committee Members
Brian Tsukimura, Professor, Department of Biology, California State University, Fresno - Co-Organizer
Billie J. Swalla, Professor, Biology Department, University of Washington - Co-Organizer
Tom Daniel, Professor, Department of Biology, University of Washington
Patsy Dickinson, Josiah Little Professor of Natural Sciences, Bowdoin College
Daniel Grünbaum, Associate Professor, School of Oceanography, University of Washington
Cheryl Hayashi, Professor of Biology, University of California Riverside
Donal Manahan, Professor, Department of Biological Sciences, and Vice Dean for Students, University of Southern California
James Marden, Professor, Department of Biology, Pennsylvania State University

Dr. William Zamer, NSF Program Director, was also in attendance.

Appendix II
Attendees for the Grand Challenges Workshop

The workshop was held at the Banbury Center of the Cold Spring Harbor Laboratory, Lloyds Harbor, NY. Participants arrived Thursday pm Feb 28, and departed Sunday am March 3. Of the 30 participants, we had an equal gender ratio, 4 underrepresented minority scientists, 4 from small colleges, and scientists from 15 different states and Puerto Rico. There were 10 Full Professors, 10 Associate Professors, 9 Assistant Professors, and one Postdoctoral Fellow.

Dianna K. Padilla organized the workshop.

Attendees:

Neda Bagheri, Assistant Professor, Northwestern University, Control Theory, Systems Engineering, Computational Systems Biology

Alexa Bely, Associate Professor, University of Maryland, Developmental Biology and Evolution

Zac Cheviron, Assistant Professor, University of Illinois @ Urbana-Champaign, Physiological and Functional Genomics

Noah Cowan, Associate Professor, Johns Hopkins University, Mechanical Engineering, Electrical and Computer Engineering and Computer Science, Control Theory, Computational Sensing and Robotics

Elizabeth Dahlhoff, Professor, Santa Clara College, Physiological Ecology, Biochemical Adaptation

Tom Daniel, Professor, Department of Biology, University of Washington, Biomechanics, Flight Control, Dynamics and Neural Processing

Xinyan Deng, Assistant Professor, Purdue University, Mechanical Engineering, Biologically-Inspired Design and Robotics

Manuel Diaz-Rios, Assistant Professor, University of Puerto Rico, Neural Control of Locomotion, Neuronal Networks, Mammalian Motor Systems

Patsy Dickinson, Josiah Little Professor of Natural Sciences, Bowdoin College, Neural Systems Control of Behavior

Colleen Farmer, Assistant Professor, University of Utah, Comparative Physiology, Functional Morphology and Evolutionary Innovation in Vertebrates

Kendra Greenlee, Assistant Professor, North Dakota State University, Scaling of Physiological Processes, Development of Physiological Traits

Daniel Grünbaum, Associate Professor, School of Oceanography, University of Washington, Biomechanics, Mathematical Theory, Quantitative Relationships Between Short-Term, Small-Scale Processes Of Individuals And Long-Term, Large-Scale Population Level Effects

Melina Hale, Associate Professor, University of Chicago, Biomechanics and Neurobiology of Movement and Behavior

Cheryl Hayashi, Professor of Biology, University of California Riverside, Evolutionary Biology, Biomechanics, and Multiscale Integration from Genomics to Functional Ecology of Silks

Laura Corley Lavine, Associate Professor, Washington State University, Development and Evolution of Adaptive Phenotypic Plasticity, Sexual Selection

Donal Manahan, Professor, Department of Biological Sciences, and Vice Dean for Students, University of Southern California, Comparative and Environmental Physiology, Development and Adaptation in Marine Animals

James Marden, Professor, Department of Biology, Pennsylvania State University, Physiological Ecology, Functional Genomics, Evolutionary Ecology, Biomechanics, and Behavior

Kristi Montooth, Assistant Professor, Indiana University, Evolutionary Genetics of Physiological Traits, Physiological Adaptation to Complex Environments

Amy Moran, Associate Professor, Clemson University, Physiological and Morphological Adaptations of Early Life History Stages

Fred Nijhout, Professor, Duke University, Developmental Physiology, Development and Evolution of Complex Traits

Dianna K Padilla, Professor, Department of Ecology and Evolution, SUNY Stony Brook, Phenotypic Plasticity, Functional and Evolutionary Ecology and Invasion Biology

David Plachetsky, Howard Hughes Postdoctoral Fellow, UC Davis, Evolution and Development of Sensory Systems, Evolution and Integration of Complex Traits

Matt Reidenbach, Assistant Professor, University of Virginia, Biomechanics and Sensory Systems, Environmental Fluid Dynamics and Hydrology, and Physical-Biological Interactions

Scott Santos, Associate Professor, Auburn University, Population Genetics, Genomic Evolution and Symbiosis in Microbes and Multi-cellular Organisms

Joel Smith, Assistant Scientist, Marine Biological Laboratory, Woods Hole, Evolution of Gene Regulatory Networks, Developmental Biology

Eduardo Sontag, Professor, Rutgers University, Systems Molecular Biology, Mathematical Control and Dynamical Systems Theory and Computational Biology

Billie J. Swalla, Professor, Biology Department, University of Washington, Developmental Biology, Molecular Analysis of the Evolution and Development of the Chordates, Phylogenetics and Diversification, and Evolution of Coloniality in Deuterostome Animals,

Lars Tomanek, Associate Professor, California Polytechnic State University at San Luis Obispo, ◦Ecological Physiology of Marine Organisms, Biochemical Temperature Adaptation, and Global Climate Change

Brian Tsukimura, Professor, Department of Biology, California State University, Fresno, Reproductive Physiology and Endocrinology in Crustaceans

William G Wright, Associate Professor, Chapman University, Neurobiology and Invertebrate Behavior

Dr. William Zamer, NSF Program Director, was also in attendance.