Addressing Grand Challenges In Organismal Biology: The Need For Synthesis

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Animals are complex systems operating at multiple spatial and temporal scales, facing the challenge of how to change in appropriate ways, degrees, and times, in response to the diverse internal and external influences to which they are exposed. Discovering the system-level attributes of organisms that make them resilient or robust—or sensitive or fragile—to change presents a grand challenge for biology. Knowledge of these attributes and the underlying mechanisms controlling them is crucially needed to predict how organisms will respond to short- and long-term changes in internal and external environments, including those driven by climate change. Organismal biologists require novel approaches that extend beyond traditional disciplinary boundaries, especially when they partner with mathematicians and engineers. Pursuing this research enterprise will not only give us a deeper understanding of how organisms will face future challenges, but it will also reveal nature-inspired solutions in complex engineered systems, both of which will benefit science and society.

Keywords: organismal biology, grand challenges, integrative biology, systems engineering, predictive modeling

Animals are inherently complex and are composed of multiple interconnected elements. They and their component elements must have the capacity to maintain stability and to simultaneously change in response to internal and external stimuli. For example, young animals must be able to process neurosensory inputs as they move through the environment while their brains and nervous systems continue to develop. As they grow and develop, structures used for locomotion may simultaneously change in their function and control because of changes in size and morphology (Hale 2014). Those same animals must maintain the internal physiological function of all of their systems throughout ontogeny and as they experience shifting internal and external environments. In addition, animals and animal systems exhibit many nonlinear and time-dependent characteristics. They also have suites of properties with dynamics that cannot be easily deduced from the behavior of individual elements (emergent properties), such as homeostatic physiological responses or phenotypes that can be relatively stable, even when they are controlled by gene networks with considerable genetic variation (e.g., Nijhout and Reed 2014). For multicelluar animals (our focus here, although much of the same applies to plants and microbes), understanding the mechanisms that underlie the function, development, and interaction with biotic or abiotic environments has long been a major challenge. Gaining insight into these mechanisms is essential with the increasingly urgent demand for accurate predictive models of the responses of organisms to short- and long-term environmental change. Animals face unprecedented pressures globally from expanding human populations, habitat destruction and fragmentation, ocean acidification, and climate change. The viability of wild populations and our ability to manage and use 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. After decades of research, we still lack fundamental insight into which characteristics of complex living systems allow them to change in response to either internal or external environments and which characteristics create stability or resistance to change, both being essential for maintaining functioning systems.

Scientists have been identifying grand challenge questions for a wide range of fields over the past decade. These are long-standing, important research questions that have yet to be answered, as well as questions that address the pressing needs of society, such as human health and the impacts of global climate change (Padilla and Tsukimura 2014). Accordingly, organismal biologists have begun articulating

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a range of grand challenge questions (e.g., Denny and Helmuth 2009, Schwenk et al. 2009, Mykles et al. 2010, Kültz et al. 2013). Here, we focus on one of these questions, how animals walk the tightrope between stability and change, and argue that addressing this question will require a transformation in the way we approach our discipline. We argue that in order to comprehend the dynamics of complex living systems, we must move beyond solely traditional approaches of organismal biology to incorporate the methodological tools of other disciplines that also involve complex systems—particularly, mathematics, engineering, and physics. Predictive organismal biology will require more quantitative approaches, including the complex system modeling that is used in engineering and applied mathematics. Such approaches will help us identify shared patterns and strategies that organisms use to maintain function under changing conditions and to respond or adapt to changing environments or complex tasks. In pursuing this research endeavor, not only will we gain a deeper, mechanism-based understanding of how organisms will respond to future environmental challenges, but we will also spur the development of new quantitative methods and reveal nature-inspired solutions to the stability and agility of exceedingly complex systems. Few, if any, synthetic systems operate with the level of complexity and adaptability seen in living organisms. Biology has already inspired the development of new mathematics, including algebraic statistics (Drton et al. 2009), conformal geometry (Lipman and Daubechies 2011), probability theory (Earnshaw and Keener 2010) and probability theory on non-Euclidean spaces (Hotz et al. 2013), queuing theory (Mather et al. 2011), and new questions in dynamical systems (Rinzel 1987, Golubitsky and Stewart 2006, Anderson 2011, Veliz-Cuba 2012).

We brought together engineers and mathematicians with a broad range of biologists to build bridges and to seek synergy. We initiated a common dialog to identify key areas in which new research and tools could make significant inroads on the grand challenge question of how organisms walk the tightrope between stability and change. Our goals were to develop a research agenda to address this question, to identify research needs and the collaborations necessary to make progress, to devise strategies that can be implemented in the near and distant future, to coordinate the research efforts of individuals and collaborative groups working on this grand challenge, to build capacity for addressing important questions in the future, and to identify societal benefits from investment in these efforts. We focus on multicellular animals because they are diverse but share a single common evolutionary history (monophyletic lineage) that is distinct from unicellular and plant life and because they share characteristics such as being predominantly macroscopic, motile (during some stage of life), and heterotrophic. These commonalities provide unifying themes for our community of animal organismal biologists, although we expect progress here to be transferable to the study of other life forms.

After decades of developments in molecular biology techniques and a continual increase in computing capacity and complexity, there is now a vastly expanded range of research approaches available to organismal biologists. These include powerful sensing and genomic tools; data-driven methodology; and high-throughput measurement methods, such as machine learning and vision. These burgeoning technologies provide new opportunities to develop interdisciplinary approaches in organismal biology—in particular, investigating how both model and nonmodel organisms maintain the balance between integrated stability and adaptive flexibility (both short-term accommodation and long-term evolutionary adaptation).

Organismal biology is uniquely positioned at the interface of integrative approaches to studying animal function; quantitative approaches to modeling aspects of animal function; connections between genetic and molecular information and organismal traits, performance, and responses to natural environments; and a comparative evolutionary or phylogenetic framework. At present, we do not fully understand the functional and system-level attributes of organisms that make them resilient or robust or, conversely, sensitive or fragile with respect 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 spatial and temporal scales.

This grand challenge question is clearly beyond the scope of any single scientific community. It has been shown that collective intelligence can far exceed 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 et al. 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 expansive, ambitious questions (e.g., Denny and Helmuth 2009, Mykles et al. 2010, Tsukimura et al. 2010, Stillman et al. 2011), including calls for greater interdisciplinary collaboration with applied mathematicians, computer scientists, and engineers (e.g., Ceste 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 (e.g., West-Eberhard 2003, Moczek 2010). However, such disparate groups as organismal biologists and engineers do not presently share a common scientific framework—or even a mutual scientific language—and generally do not work together, which makes any sort of cross-disciplinary collaborative progress hard to attain. As we describe more fully below, the integration of control theory and systems modeling into organismal biology will provide launch points for advances in the understanding of biological response to changing environments. To address our grand challenge, we identified four major subchallenges, with each leading to avenues of investigation to understand how organisms walk the tightrope between stability and change.

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Challenge 1: Understanding living organisms as multiscale systems in time and space

Animals operate through the integration of systems (e.g., nervous systems, circulatory systems, skeletal and muscular systems) and modules (compartmentalized components that function as a unit; e.g., eyes) that are organized and function at multiple scales. Just as living systems encompass a vast range of spatial scales, they also operate across a similarly vast range of temporal scales. Therefore, some processes in organisms, such as many biochemical interactions and the transmission of information within the nervous system, can operate in milliseconds, whereas other processes, such as ontogeny and development to the adult form, operate on much longer time scales—up to decades for some long-lived animals. Evolutionary and ecological processes occur over time scales from a single generation to eons.

We lack a firm understanding of how the stability of function is maintained at each level of biological organization (e.g., gene network, endocrine regulatory network, whole-animal behavioral repertoire) and how the stability of whole-animal function is maintained through the integration of lower levels of organization or component modules. Nor have we identified general principles explaining how some or all lower level modules change function, while maintaining integration, in response to nonlethal internal or external changes. Changes at different levels of organization, over different scales, or within different modules or systems can translate into whole-organism changes as well. A complex interplay of biological and physical factors determines 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. Collaborations between biologists and engineers have the potential to move our understanding of these interactions of biological and physical factors forward effectively. Such collaborations have, for example, led to the discovery of two independent mechanisms that animals can use to overcome the trade-off between stability and maneuverability in locomotion. Fish use mutually opposing forces (Sefati et al. 2013), whereas insects accomplish the same ends using flexible airframes (Dyhr et al. 2012, 2013). These collaborations also led to advances in engineering. The collaboration on fish locomotion led to a biology-inspired robot. The insect strategy was used in designing a novel controller for a robotic flyer. More new, interdisciplinary approaches are needed to identify the design principles of animals. Achieving this goal depends on understanding the importance and presence of stability (or change) over time in different systems within an organism during its lifetime within a well-characterized environment. The great diversity of animal species affords an opportunity to infer common design principles and to gain insights about the constraints on the evolution of organismal component systems (e.g., gene, metabolic, physiological networks) imposed by requirements for stable but flexible integration.

Important questions for the multiscale nature of organisms include whether there are recurrent themes or design principles across and within scales of organization or across types of responses to environmental change associated with the failure and loss of function. Are systems and modules organized similarly across taxa, and do the same factors govern their integration and control? Are there commonalities among properties at different levels of organization of organisms, and can they be revealed by understanding functional or structural modules?

Challenge 2: 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 the exploration of complex systems more tractable, can be used both to test and to generate hypotheses, and can rigorously identify principles that apply across disciplines and systems. Models can be used to describe, explain, and predict many of the same types of multiscale phenomena that are found in biological systems, which vary across both space and time. For the mathematical and engineering communities, the properties of complex systems (including robustness, stability, controllability, and observability) are, at present, most commonly modeled with linear approaches. However, as is well known, biological systems often operate with significant nonlinearity; modeling them will require the development of tools and methods to satisfactorily describe and analyze this essential feature of life. Therein lie a dual challenge and mutually reciprocal benefits for the domains of biology and engineering.

Organismal biology allies synergistically with the various fields of mathematics and engineering. Mathematical tools and models applied to biological systems could 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 (Cowan et al. 2014). Organismal systems pose new challenges for mathematics and engineering both because of their complexity and because of the diversity of solutions to complex problems of structure and function that are displayed through evolutionary time. Therefore, major theoretical advances will generally involve contributions from both mathematics and biology. As was aptly summarized by Friedman (2010, p. 857), "mathematics is the future frontier of biology, and biology is the future frontier of mathematics." Now is the time to bring biologists and mathematicians and engineers together to advance the field of organismal biology as a whole and to amplify the collaborations that are beginning to form among those domains.

Because biological phenomena are frequently much more variable and complex—chemically, physically and organizationally—than inorganic phenomena, cause-and-effect understanding of organismal 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

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complex physical or biological problems. To engineers and mathematicians, learning algorithms, robotic control designs modeled after complex nervous systems, and DNA or synapses as models for information science all present new horizons. In addition, data sets describing biological phenomena (e.g., phenotypic plasticity) should be analyzed and developed into models that provide predictive power of phenotypic behavior under different conditions. A significant synergism therefore exists between the life sciences and the 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 drive even greater innovations.

A number of concepts from control theory are already an integral part of understanding the function of organismal systems. These include feedback, robustness (little or no change in system properties over some range of different conditions), stability (the maintenance of system function within some bounds), controllability (the ability to force the system to a particular state by some control signal), and observability (the 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). To date, control theory has been used successfully to study a range of biological phenomena, from the activity of gene networks to whole-organism functions (e.g., Cowan and Fortune 2007). These applications only hint at the potential for insight in organismal biology that is possible with these approaches. However, to successfully integrate biological and engineering or mathematical approaches, we need to develop common terms and definitions for the phenomena that are being studied. For example, control theory has formal definitions for stability and types of stability that are not yet recognized by biologists but that may have different implications for organism function. By developing a common lexicon and definitions appropriate for the biological phenomenon under study, it will be possible to identify the range of conditions under which organismal systems are stable versus fragile, controllable versus uncontrollable, or functional versus broken.

Biological research challenges mathematicians and engineers to broaden their analytical approaches in important ways, including the nonlinear 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 in which stability may be favored or necessary over a range of inputs, but transitions to new states are advantageous or required for other inputs. Examples include environmental triggering of phenotypic plasticity, altering or modulating neural activity patterns, stability versus maneuverability in locomotion, and long-term evolutionary transformations.

Important questions for which engineering and mathematical models can be used to address stability, fragility, and flexibility and change in organisms include what solutions can be found in nature to answer questions about how complex control systems can operate. Can new lessons be learned by translating knowledge from studies of modularity in development into mathematical systems biology (e.g. Nijhout and Reed 2014), in which engineers have discovered similar systems? Are there general control characteristics for biological systems that are stable or those that have the flexibility to transition to another stable state or that are fragile and cannot rebound; if so, how would we discover the rules for that flexibility? Are there general properties, such as trade-offs and feedbacks, of multiscale systems that can be identified and applied to understanding the stable or fragile properties of biological systems?

Challenge 3: Deciphering network dynamics among the components of modular 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 and social behaviors and 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 and populations. This modularity provides a potential reservoir of evolutionary flexibility and resilience (Levine and Davidson 2005). 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. Modularity and network regulation may be amenable to control theory approaches to examine the plastic responses that organisms display in response to environmental variation, as well as concomitant feedback regulation (West-Eberhard 2003, Moczek 2010, Nijhout and Reed 2014). In some cases, feedbacks in complex gene networks regulate the development of organismal functional modules, such as wings or eyes. For example, the heat shock protein Hsp 90 can buffer genetic variance and plays a role in invertebrate metamorphosis (Rutherford et al. 2007). Recently, Hsp 90 been shown to play a role in controlling the development of eyes in blind cavefish (Rohner et al. 2013) and in the fruit fly (Rutherford et al. 2007).

All animal nervous systems are organized into networks that serve a variety of functions. Some neuronal 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 compose them (Schulz et al. 2006, Marder 2011). At the same time, external inputs can change the functioning of both individual neurons and the networks as a whole (Nusbaum and Blitz 2012). 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

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of these interactions is variable (Viala 1986, Dickinson et al. 1990, Mentel et al. 2008). Therefore, although a single pattern or type of interaction between networks can be relatively stable and can be maintained for long periods of time, coordinated function can cause rapid change to another stable state. Engineers and mathematicians are now addressing similar questions about the integration and functioning of complex systems with the use of control theory and other dynamical systems modeling tools. The analysis of biological design and function has often inspired new approaches and solutions to long-standing challenges in the analysis of complex dynamical systems (e.g., Nishikawa et al. 2007).

Important questions for understanding networks and interactions among the components of complex organismal systems include whether there are regulators of large effect within complex systems and, if so, how we might identify them. Are there rules about how many such large impact regulators are likely to be in a given system or limits to how complicated they are? Can we identify regulators of large effects in complex systems without individually measuring every potential regulatory factor or node in a network?

Challenge 4: Interpreting the causes and effects of 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 (NRC 2009, Schwenk et al. 2009, 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 be inducible, emerging from the modification of a default (ancestral) phenotype to a new phenotype when cues associated with new conditions or perturbations are present. These cues result in movement away from a stable realm to a new state until the cue is removed, after which the system returns to the 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). Alternatively, animals may produce continually varying phenotypes that change in response to varying environmental conditions, with no set stable state (e.g., traits such as body size or size-specific mass that vary along a continuum). Each type of plasticity likely has different controlling mechanisms and will require a different type of model to describe or predict the system's behavior and the consequences of that behavior.

Understanding the developmental and physiological dynamics balancing requirements for stability or for phenotypic plasticity with trait evolution in response to environmental inputs is of particular importance because organisms face ever-increasing rates of environmental and climatic change. Therefore, there is a crucial need to understand these dynamics and to 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 in response to potentially novel perturbations are not unique to organismal biology. For example, in engineering, there are trade-offs between the stability (the tendency to remain near some value) of closed-loop control systems (in which the output feeds back to regulate control) or their insensitivity to perturbations (resistance or maintenance of a state when faced with some disturbance) and fragility, in which perturbations break the system or in which the system loses functionality. It is tantalizing to consider the extent to which biological trade-offs with analogous attributes could be better understood through engineering approaches.

The importance of developing common vocabularies and perspectives between biologists and engineers can be further demonstrated through the need for understanding the system-level properties and differences between highly regulated (and likely evolutionarily selected) plastic responses to environmental change, unregulated responses to change (e.g., the consequence of physical and chemical properties, such as thermal sensitivity), and insensitivity to environmental change. Determining when insensitivity (i.e., a lack of response) to environmental change should be advantageous is as important as understanding the benefits of phenotypically plastic responses. The underlying regulatory and developmental systems that produced a "regulated" response may be due to the networks or modules that are selected because they have the property of insensitivity (Nijhout and Reed 2014). Control systems theory and dynamic systems models in general provide an opportunity to address these issues. Such approaches will yield greater information about the vertical integration of systems within organisms (e.g., gene networks controlling development or physiological responses). They also facilitate whole-organism responses to the temporal and spatial scales of internal and external environmental change, including interactions with other species. These avenues of study will allow predictions of when plasticity will evolve and when it might be maintained through a lack of a regulated response. They would also assess the conditions that allow an organism or organismal system to maintain stability and the consequences of multiple stable states. It should also be possible to examine the role of internal feedbacks and trade-offs, particularly considering the extent to which animals that possess different types of plasticity are able to evolve and the extent to which taxa that exhibit different levels of plasticity are likely to diversify and to persist through evolutionary time (Woods 2014).

Important questions for understanding phenotypic plasticity and sensitivity to changing environments include the roles of and limits to phenotypic plasticity, environmental sensitivity, and variability among organisms and their responses to varying environments. To what extent do systems with different modes of phenotypic plasticity share

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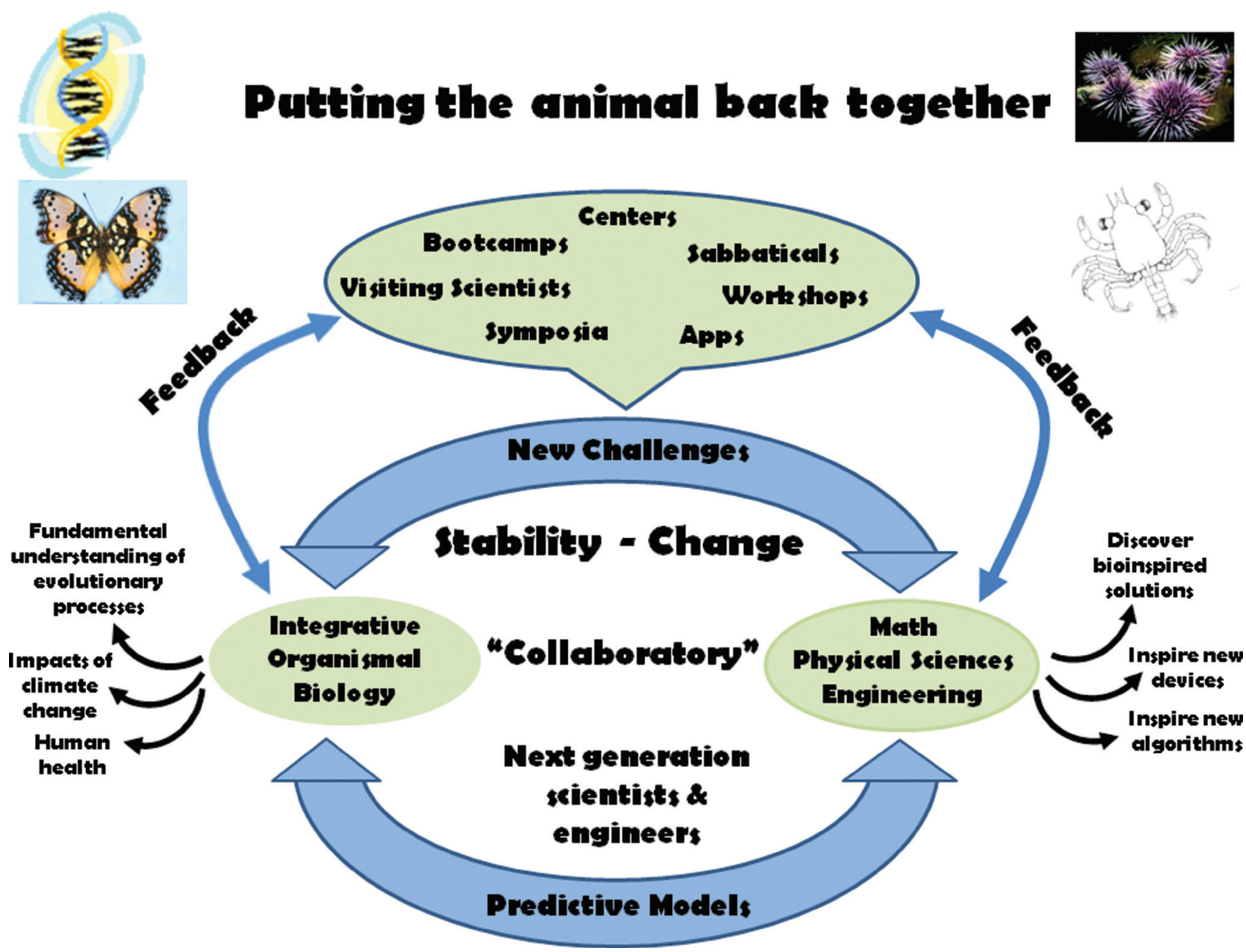

Figure 1. A new organismal systems biology. Partnerships between organismal biologists and applied mathematicians, engineers, and other physical scientists who address questions about complex systems will provide mutual benefits. These collaborations will provide organismal biologists with the power of predictive models, and both groups will reap benefits from insights in each other's fields. Changes in our field will require training new scientists and retraining senior scientists in new approaches. Possible mechanisms for fostering education and enabling collaboration are depicted at the top of the figure. Such interactions will not only allow us to advance organismal biology but will also provide important benefits to science and society, examples of which are shown in the left and right margins.

general properties regarding the control of the plasticity, and what are the integrated links among developmental, physiological, and structural systems? Are there common characteristics among traits that have tightly regulated and controlled plasticity and those that lack regulation or that are loosely regulated? Do the 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? Does regulatory modularity enhance or limit the plasticity of different types of traits (e.g., morphological, physiological, life history, behavioral). How do the microevolutionary responses of populations change the set points, sensitivity, response range, or qualitative outcome of phenotypic plasticity?

New opportunities

Many biologists now recognize that integration across biological levels is necessary to broadly understand the workings of whole animals in their natural environments. This integration requires novel approaches that extend beyond gene or protein interactions. A new more-expansive 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 (figure 1). For example, biologists examining the ability of gecko lizards to run on walls and across ceilings collaborated with engineers to understand nanoscale adhesion and how toe pad orientation and gait allow the toes to

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repeatedly grip and release (Autumn et al. 2000, 2002, Arzt et al. 2003, Tian et al. 2006, Wan et al. 2012). This knowledge stimulated engineers and material scientists to develop novel types of dry adhesives (Ge et al. 2007, Lee HS et al. 2007, Lee JH et al. 2009, Murphy et al. 2009, Filippov et al. 2011). Such collaborations have also led to new insight regarding the dynamic control of animal locomotion (e.g., Libby et al. 2012, Dyhr et al. 2013, Mongeau et al. 2013, Sefati et al. 2013), and new strategies for controlling complex and highly dynamic machines (e.g., Dyhr et al. 2012). Combined biology, applied mathematics, and engineering approaches are presently being used to examine the role of feedback in the stability (or change) of dynamical systems, such as regulatory gene networks, cellular metabolic systems, sensorimotor dynamics of moving animals, and even ecological or evolutionary dynamics of organisms and populations (Cowan et al. 2014). Engineers and mathematicians are addressing similar questions with the use of control theory and other dynamic systems modeling tools. Moreover, they are also using biological design and function to inspire new approaches and solutions to long-standing problems. With the increasing availability of data across biological taxa and systems, unprecedented interdisciplinary syntheses will be possible. The discovery of guiding and generalizable principles will rely on the development of robust modeling approaches and tools.

Several challenges exist, including the need for a common scientific language and mechanisms for facilitating interactions and collaboration among organismal biologists, engineers, and mathematicians. We need to identify transdisciplinary principles, approaches, and frameworks that are robust to their context. Examples include the general properties of networks (e.g., Cowan et al. 2012, Fischer et al. 2014, Nijhout and Reed 2014), which can be applied to gene networks, neural networks, and interaction networks and even to social networks. For the development of predictive models and methods necessary to identify general patterns and overarching principles, we need to define and articulate the limits of biological questions such that appropriate modeling techniques can be applied. Examples include the emergence of a metabolic theory of ecology (Brown et al. 2004) and the application of thermodynamics to the configuration of organs (Reis et al. 2004), organisms (Miguel 2006), and animal movement (Bejan and Marden 2006).

We need to facilitate productive communication among engineers, mathematical modelers, and biologists to build bridges and to develop the cross-talk needed for progress. Biologists and control theorists both use terms that have explicit definitions within their disciplines but that are used with quite different meanings in common language or in other disciplines. To effectively work together on common problems, biologists and engineers must agree on a shared lexicon, a common set of definitions for important terms. In addition, it is important that biologists be trained in quantitative and modeling methods, on one hand, and that engineers gain a greater awareness of the biological problems and systems 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.

Solutions and important capacity building

Answering these complex questions will require comparative studies spanning greater taxonomic and disciplinary diversity 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. Therefore, 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.

A call for an organismal biology synthesis center. A synthesis center that provides a venue for organismal biologists, mathematicians, and engineers to collaborate would be the most effective means of finding solutions to the important questions identified here and of training the next generation of scientists. Organismal biologists face challenges similar to those faced by ecologists a number of years ago: They had large amounts of data characterizing ecological processes and ecosystem function across habitats, across geographic space, and through time, but were unable to use those data to the fullest. The National Center for Ecological Analysis and Synthesis 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. The existence of a center allowed the field to grow and develop by training researchers at all stages of their careers, by applying new advanced statistical and modeling methods using existing data to their fullest, and by identifying new important research and data needs. In many ways, the center transformed the field of ecology.

Integrating engineering and mathematics approaches with organismal biology is similarly well suited for development and training through a synthesis center. A synthesis center for organismal biology, involving both biologists and quantitative scientists (engineers, mathematicians, and modelers), would qualitatively enhance communication across the disciplines and collaboration on problems. It would also provide crucial training for new researchers across disciplines and would retool more advanced researchers to work and communicate effectively across disciplines. Such a synthesis center could develop novel frames of reference for organismal biology to discover emergent properties, as

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well as transdisciplinary principles. For example, novel cell-signaling pathways that allow organisms to manage temperature stress may be elucidated from network inference techniques (Ciaccio et al. 2014).

Additional impacts. The impacts of the proposed research agenda's extention beyond advances in our understanding of organismal biology can be divided into two major categories: opportunities to advance the development of mathematics and engineering and benefits to society beyond scientific advances. Developing a deep, quantitative understanding of the complex functions and interactions of many aspects of organismal biology will require the development of new mathematical, computational, and engineering tools—particularly, new types of applied mathematics and new methods for analyzing massive volumes of data of mixed types (the big data problem). At present, we cannot easily model multiscale systems, and our ability to model nonlinear systems is limited. By engaging engineers and mathematicians to work together with biologists on the complex problems that organismal systems provide, advances will be made in each of these fields. These advances may, in turn, lead to the development of new devices, materials, and applications. Simultaneously, a deep understanding of organismal biology at an engineering level can lead to the development of translational principles that can be used in engineering and applied mathematics, which, in turn, can lead to a wide range of technological advances, such as biology-inspired control mechanisms for robots and flight (Dyhr et al. 2012, 2013, Sefati et al. 2013). Organisms have evolved a myriad of solutions to life's challenges; therefore, the potential for biology-inspired design of materials and engineered products is enormous. Evolutionary innovations are excellent starting points for developing novel materials or processes—for example, using plant hairs to deter bed bugs or mass producing spider silk for low-weight, high-strength fabrics or cables. Similarly, these innovations can provide a starting point for the design of products such as robots and low-drag vehicles. 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 and improve recovery from heart attack or stroke.

A new research agenda can capitalize on natural solutions to environmental problems. Examples include using taxonomic diversity to understand whether there are recurring themes among taxa in response to environmental challenges. Invasive species and pests will expand their ranges as climate change occurs, and models that address physiological and functional flexibility, as well as the factors that limit species in new environments, can facilitate the development of management plans that account for species expansion or contraction in response to increasing environmental extremes. Such models may also assist in predicting the responses of organisms to habitat fragmentation and climate change, which is particularly important for endangered species or other species of special concern.

Conclusions

Biology is rapidly becoming more quantitative. Biologists must now deal regularly with massive data sets and the functioning of complex systems at scales from single genes and molecules to whole genomes, as well as the entirety of complex organismal systems, such as the nervous system—for example, in mapping the function of the human brain. Addressing the grand challenge of how animals walk the tightrope between stability and change requires transforming the field of organismal biology. Predicting and understanding whether and how organisms can respond to short- and long-term changes in environments are pressing needs, given the current rates of climate change. Better knowledge of system-level attributes of organisms that make them resilient or robust—or, conversely, sensitive or fragile—with respect to internal or external environmental perturbations is needed in order to understand the dynamics and evolution of complex living systems. Accomplishing these goals will require new approaches that extend beyond our traditional disciplinary comfort zones, 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 will also reveal nature-inspired solutions to stability and agility in complex engineered systems that will benefit science and society.

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