A New Organismal Systems Biology: How Animals Walk the Tight Rope between Stability and Change[1]

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Synopsis The amount of knowledge in the biological sciences is growing at an exponential rate. Simultaneously, the incorporation of new technologies in gathering scientific information has greatly accelerated our capacity to ask, and answer, new questions. How do we, as organismal biologists, meet these challenges, and develop research strategies that will allow us to address the grand challenge question: how do organisms walk the tightrope between stability and change? Organisms and organismal systems are complex, and multi-scale in both space and time. It is clear that addressing major questions about organismal biology will not come from ''business as usual'' approaches. Rather, we require the collaboration of a wide range of experts and integration of biological information with more quantitative approaches traditionally found in engineering and applied mathematics. Research programs designed to address grand challenge questions will require deep knowledge and expertise within subfields of organismal biology, collaboration and integration among otherwise disparate areas of research, and consideration of organisms as integrated systems. Our ability to predict which features of complex integrated systems provide the capacity to be robust in changing environments is poorly developed. A predictive organismal biology is needed, but will require more quantitative approaches than are typical in biology, including complex systems-modeling approaches common to engineering. This new organismal systems biology will have reciprocal benefits for biologists, engineers, and mathematicians who address similar questions, including those working on control theory and dynamical systems biology, and will develop the tools we need to address the grand challenge questions of the 21st century.

Introduction

What will allow some animals to respond to climate change, while others not? How can animals maintain function and develop through ontogeny when environments or conditions change? How can animals respond quickly when moving, or building new neural pathways, but still maintain their abilities and regular functions? These, and other important questions, have perplexed organismal biologists for decades. Knowledge in the biological sciences is growing at an exponential rate. The use and incorporation of new technologies has greatly accelerated our

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capacity to ask, and answer, new questions. The molecular revolution, along with advances in electronics and computing, have now opened entire fields of biological inquiry, and now let us address questions that were not possible 50 years ago. Similarly, graduate students are now trained in more specialized areas of research, such as genomics, transcriptomics, proteomics, neural networks, and endocrinology. With increased specialization in research fields we are now able to ask, and answer, questions at all levels of biological organization with greater precision. As a consequence, we can make great strides within subfields, but, what about the big questions of organismal biology? Will ever-increased specialization and detailed information help us answer ever-pressing important questions about organisms and their responses to environmental change, or help address new and urgent needs for information to address current needs of society? Will new massive datasets allow predictions of organismal responses to climate change?

On April 2, 2013, President Obama called on research universities, companies, philanthropists, and foundations to help identify and pursue the grand challenges of the 21st century (www.whitehouse. gov/administration/eop/ostp/grand-challenges). What are grand challenges? According to the White House office of Science and Technology Policy, they are ‘‘ambitious but achievable goals that harness science, technology, and innovation to solve important national or global problems that have the potential to capture the public’s imagination.’’ This call was made broadly across all fields of science, engineering, and technology. Thus, a goal of this call was to have different scientific communities identify the grand challenge questions in their field, and develop research agenda and plans to frame innovative research by 2020 and beyond—both to enhance fundamental knowledge and to develop targeted benefits to society. As a result, major initiatives have been developed to revolutionize understanding of the human mind and the function of the brain, make solar energy cost-competitive with fossil fuels in the next decade, find all asteroid threats to humans and find solutions to deal with them, and to find ways to save lives at birth by the development of treatments for women and newborns in low-resource communities.

What about organismal biology? The Society for Integrative and Comparative Biology took a leadership role in identifying and articulating the grand challenges of organismal biology (Fig. 1). These are the big questions that are yet to be answered, and questions that have emerged as important because of current pressing needs, such as responses of organisms to climate change. As a result, an initial paper by Schwenk et al. (2009) articulated five grand-challenge questions, for organismal biology. These included:

(1) Understanding the organism’s role in organism–environment linkages.

(2) Utilizing the functional diversity of organisms.

(3) Integrating living and physical systems analysis.

(4) Understanding how genomes produce organisms.

(5) Understanding how organisms walk the tight rope between stability and change.

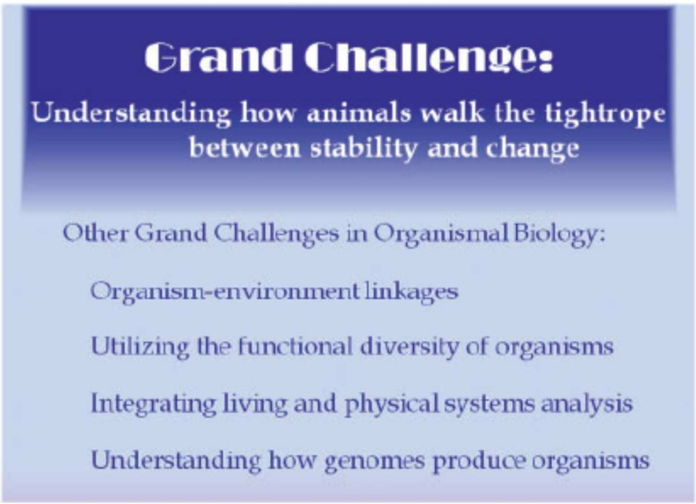

Fig. 1 The grand challenges of organismal biology identified by Schwenk et al. (2009).

This initial paper was followed by a series of papers published in Integrative and Comparative Biology and other journals (Denny and Helmuth 2009; Robinson et al. 2010; Mykles et al. 2010; SIAM 2010; Tsukimura et al. 2010; Zamer 2011; Kültz et al. 2013) that identified challenges and articulated the need to find a way forward to build community consensus and develop research agenda to answer these questions.

Developing research agenda for grand Challenges

How do we, as organismal biologists, meet these challenges, and develop research strategies that will allow us to address grand challenge questions? What is clear is that addressing these major questions will require the collaboration of a wide range of experts. Research programs designed to address grand challenge questions will require not only deep knowledge and expertise within subfields of organismal biology, but also collaboration and integration among otherwise disparate areas of research, including the physical sciences, mathematics, and engineering. Many argue that that the best path forward is to incorporate more quantitative and modeling approaches, especially those from engineering and applied mathematics (Padilla DK, Daniel TL, Dickinson P, Grünbaum D, Hayashi C, Manahan DT, Marden J, Swalla BJ, Tsukimura B. unpublished data. Addressing Grand Challenges in organismal biology – the need for synthesis. BioScience). Different communities of biologists often do not regularly collaborate, let alone work with engineers and mathematicians. However, we are seeing exciting advances being made at the interface of traditionally separate fields, such as eco-immunology, transcriptomics and stress physiology, and biomechanics. Integrating across all of these fields, and including engineers and mathematicians requires that we develop a common dialog and lexicon. For example, biologists and engineers often have very different definitions

for important terms such as adaptation. To work effectively, we must find ways to work through the barriers. Mechanisms that have been proposed to increase collaborations across different fields and make the most of existing data is through the use of a synthesis center-type approach, designed specifically to facilitate such collaborations. There have also been calls for cross-training of students and postdoctoral fellows, and for special, intensive classes, symposia, and workshops, which have proven to be very important for burgeoning fields such as biomechanics, evo-devo, and physiology in extreme environments, such as the Antarctic.

This symposium arose from a workshop (Padilla et al. 2013) held in 2013 that tackled the fifth of these grand challenges, understanding how organisms walk the tightrope between stability and change. Our goal was to develop a research agenda that would advance answering this important question about organismal biology in the near future (Padilla et al. 2013). This workshop included organismal biologists from a range of disciplines, and engineers, applied mathematicians, and modelers, all of whom work on complex systems.

Why did we focus on this question?

This grand challenge applies to all aspects of organismal biology and all levels of organization, such as developmental biology, physiology, endocrinology, neural biology, morphology, and structural biology, as well as organismal interactions and responses to their environment. Thus, for each type of organismal biologist, this question will have a different emphasis or focus when viewed through their scientific lens. Each area of research in organismal biology can see some aspect, application, or context for this question. As a consequence, there are likely to be similar and unexpected solutions to these questions across fields.

What were the results of our discussions?

We all agreed that organisms are complex systems, and operate at multiple scales of time and space. The metazoa are made of multiple interconnected elements, each with the capacity to change and respond to environmental conditions through experience. They can have many non-linearities in responses, and, like most complex systems, have emergent properties. That is, the whole is more than the sum of the parts. These essential properties of organisms have limited the progress that can be made using the conventional tools of biologists. The intrinsic integrative nature of organisms and the interaction and feedbacks among the internal processes and systems of organisms, as well as interactions with external environments, require more expertise and information than is typically found in a single research laboratory or by specializing in one field of biology. Also, it is not clear how we can easily integrate the disparate types of biological information we presently collect. New approaches are needed to make progress in answering these important questions.

What is needed to move science forward?

We not only need new knowledge about organismal biology, but we must find ways to integrate existing knowledge. Thus, we must develop and incorporate new approaches to address and integrate these questions, and then we can develop a plan for moving forward.

Organisms and organismal systems are integrated, multi-scale systems, in both time and space. These are the same properties that are faced by engineers and applied mathematicians who deal with complex systems. Using mathematical and engineering modeling approaches to address similar questions is likely to provide insights into stability and change in animal systems. Quantitative and modeling approaches can make exploration of complex systems more tractable (Wolfram 2002). They can be used to both test and generate hypotheses, and, these approaches can be used to identify principles that apply across disciplines and systems. With such approaches we can look for recurrent themes or principles of design across or within scales of organization, or across taxa. Organismal biologists can also determine if there are general characteristics of biological systems that are stable, versus those that are flexible or fragile. We can also look for general transdisciplinary properties of multi-scale systems, such as tradeoffs and feedbacks. Collaborations between organismal biologists and engineers and applied mathematicians not only can contribute to biology, but also to engineering and mathematics. Through long-term natural selection, biological systems have evolved through time. We would expect that these long-term processes likely would have ‘‘weeded out’’ traits or phenotypes that are less robust, favoring those that are more robust to changes in internal and external environments. By studying organisms, we are likely to find biological solutions to solve questions about how complex control systems work. Ciaccio et al. (2014) and Cowan et al. (2014) provided examples of how engineering, applied mathematics, and control theory, can help us answer these important questions in organismal biology, and direct links of what we can learn by using these tools to study questions about organismal biology.

Historically, most biological research has focused on a single level of organization or process. However, we know that organisms are constructed of and regulated by networks, whose organization can be modular. Collaborations with engineers (Fischer et al. 2014) and mathematicians (Nijhout and Reed 2014) are allowing us to examine gene networks in new ways, and detect important general principles about how these networks work. Similarly, networks and modularity are being investigated with new analytical approaches (Ciaccio et al. 2014), and by using detailed data on gene networks from model (Fischer et al. 2014) and non-model (Plachetzki et al. 2014) systems. These approaches are bringing new insights to our understanding of modularity in organismal development, and responses of organisms to changing internal or external environments.

Across a wide range of biological sciences, a common grand challenge is to understand how genomes produce phenotypes and, because natural selection acts on phenotypes of individuals, the links between phenotypes and genotypic change (e.g., Raikhel 2008). Phenotypic plasticity and sensitivity to changing environments has intrigued organismal biologists, for decades, and remains a prominent area of research across a wide array of areas of biology, including

development, genomics, neural plasticity, physiology, and the morphology of organisms (reviewed by Miner et al. 2012; Krubitzer and Dooley 2013; Padilla and Savedo 2013). Phenotypic plasticity is also an area that has direct applications to understanding how organisms can respond in the short term to climate change, and has been linked to important environmental issues such as the impacts of introduced species (Chown and Gaston 2008). What remains a tremendous challenge is to understand the consequences of flexibility or inflexibility of phenotypes of organisms integrated across whole organismal responses. This includes morphological and developmental responses (Applebaum et al. 2014; Hale 2014), integrated physiological plasticity and development (Greenlee et al. 2014), and linking from within-organismal responses to organismal-level behaviors and external environmental patterning (Grünbaum and Padilla 2014). We have yet to discover whether systems with different modes of plasticity share general properties, or if there are common characteristics for systems with tightly regulated plasticity versus those due to lack of regulation.

Conclusions

After decades of research, we still lack an understanding of which characteristics of complex living systems allow them to change in response to either internal or external environments, and which characteristics create inflexibility or fragility in organismal systems. The increased availability of sequencing has resulted in an explosion of research in genomics; however, we still lack an understanding of what these data mean in terms of organismal function, or how genomes are linked to integrated organismal development, form, and function (Applebaum et al. 2014). Addressing the grand challenge of how metazoans walk the tightrope between stability and change requires a transformation of the way animal biologists approach their discipline. We must move beyond the traditional approaches of organismal biology and incorporate methodological tools from other disciplines that also study complex systems, particularly applied mathematics, engineering, and physics. Not only will we gain a better mechanism-based understanding of how organisms can cope with future environmental challenges, but in pursuing this endeavor, we will also reveal nature-inspired solutions to stability and flexibility for change in complex systems.

Animals around the world face unprecedented pressures from expanding human populations, destruction and fragmentation of habitats, acidification of the ocean, and climate change. The viability of wild animal populations and our ability to manage both domesticated and wild populations for human benefit (e.g., for dietary protein, pollination of crops, and sources of medicines) will depend on understanding how animals function and how they respond to environmental change.

This new organismal systems biology will have reciprocal benefits for biologists, engineers, and mathematicians who address similar questions, including those working on control theory and dynamical systems biology. Biological systems pose new challenges for engineers and mathematicians, and more quantitative and modeling approaches will help biologists work with the complexity of organismal biology, and address important questions that integrate levels or

organization within organisms, and their interactions with external environments. Through collaboration, we will develop the tools we need to address the grand challenge questions of the 21st century.

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