GRAND CHALLENGES

Grand challenges in organismal biology

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Synopsis A renaissance in organismal biology has been sparked by recent conceptual, theoretical, methodological, and computational advances in the life sciences, along with an unprecedented interdisciplinary integration with Mathematics, Engineering, and the physical sciences. Despite a decades-long trend toward reductionist approaches to biological problems, it is increasingly recognized that whole organisms play a central role in organizing and interpreting information from across the biological spectrum. Organisms represent the nexus where sub- and supra-organismal processes meet, and it is the performance of organisms within the environment that provides the material for natural selection. Here, we identify five "grand challenges" for future research in organismal biology. It is intended that these challenges will spark further discussion in the broader community and identify future research priorities, opportunities, and directions, which will ultimately help to guide the allocation of support for and training in organismal biology.

Introduction

Organismal biology is currently experiencing a renaissance. Some have considered it old fashioned, and not an integral part of "modern biology." It is increasingly clear, however, that organisms are the key to organizing and understanding the information in other areas of biology. There is increased recognition of the fundamental importance of the organism as a focal unit for studies at all levels of organization and integration. Organisms assume a similar central role in studies addressing the pressing issues of limited resources and changing environments. The advent of new technologies, methods, and approaches now allow us to tackle long-standing questions in new ways and to ask entirely new ones. In recent decades, most research efforts have focused on the study of basic mechanisms, without regard to the whole organism. There is increasing recognition that to understand life and basic processes, biological information must be understood in the context of the integrated living organism, and not as a collection of systems operating independent of the organism. Indeed, organisms are the central biological unit that integrates and responds to internal and external information. As a consequence, they serve as the bellwethers of environmental change and sentinels of environmental degradation.

The relatively newfound ability to sequence genes and genomes has opened a treasure trove of information about living systems that has led to new areas of research. However, it has become apparent that the path from genomes to functioning organisms and diversity is neither simple nor direct. The processes and products of development, cell division and regulation, protein production, hormone production, regulation, feedback, and homeostasis are all the result of organismal evolution. As Darwin recognized, individual organisms and their integrated phenotypes are the units on which natural selection operates to produce the adaptations and biodiversity

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Integrative and Comparative Biology, volume 49, number 1, pp. 7–14
doi:10.1093/icb/icp034

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that we observe in nature, and attempt to understand.

This is an especially opportune time for scientists to think about the big questions in our fields, to assess the current status of our science and to define the directions we would like it to go in the coming decades. The rapid changes in science and technology, as well as a pressing need for answers to important issues facing society, including environmental and human health, resource depletion, and stressed economies, have led scientists in a range of fields to take stock of the current state of science, and to determine the "grand challenges" faced in a variety of areas of biology (e.g., the iPlant initiative, http://iplantcollaborative.org/the-grand-challenge-identification-process; theoretical biology, NRC 2008). These grand challenges include questions of societal needs, now as well as in the future, and long-standing intellectual challenges in biology that have proven difficult to answer, but now may be within reach.

Given the central role of organisms, it is critical that we now assess the part played by organismal biology in answering fundamental questions in biology, as well as the role of the organism in biological issues of pressing importance to society. The goal of this article is to articulate five grand challenges for the field of organismal biology that have emerged from discussions among organismal biologists. We hope that these challenges will serve as a catalyst for further discussion and as a guide for research needs, as well as opportunities for discovery.

Five grand challenges in organismal biology

Looking to the future, we have identified five areas of research in organismal biology representing important challenges for the field and the promise of significant scientific advances, which will contribute to societal needs (Table 1). Owing to recent advances in theory, methods, techniques, computational power, and knowledge in a variety of fields, this is a propitious time to tackle these particular, synthetic problems. A common thread running through each of the "grand challenges" described here is the call for collaborative, interdisciplinary work that integrates knowledge across fields and levels of biological organization, and which indicates the need to consider how we are to train and provide the best education for the organismal scientists of the future (Wake 2008a,b).

The grand challenges outlined here (Table 1) grew out of discussions among a wide range of organismal biologists, and we emphasize that they are "works in progress." They are intended to stimulate discussion, development, expansion, and refinement by the broader community of organismal biologists.

Understanding the organism's role in organism–environment linkages

The form, function, responses, and performance of organisms at all levels of organization are the result of integration and feedback between internal systems and the external environment, in both the short term and through evolutionary time. We know that the physical environment, physiological and developmental processes, and organismal function are clearly linked, but, at present, we know little about the mechanistic bases of these linkages and how they ultimately translate into changes in populations, communities, and ecosystem function. This knowledge is essential for understanding the consequences of climatic change and environmental degradation, and their impact on human health and welfare. Our reliance on living resources, such as harvestable species, and the services provided by biodiversity and functioning communities and ecosystems, as well as the threats to humans and agriculture posed by emerging diseases, makes it critical that we understand these organism–environment interactions. However, at present, many global and ecosystem models are forced to be overly simplistic due to inadequate knowledge about organismal-level responses to environmental variability and change.

Advances have been made in physical biology such that we are now better able to predict and model the physical environment and the material, mechanical and physical limitations, and constraints (or opportunities) for organisms (e.g., Denny 1988, 1993; Vogel 1994, 2003a, 2003b; Denny and Wethey 2000; Denny and Harley 2006).

Table 1 Five grand challenges in organismal biology—summary

Understanding the organism's role in organism–environment linkages
Organism–environment feedbacks
Organismal responses to environmental changes including climatic change
Mechanisms of organismal resilience or fragility
Responses at different time scales: behavior, acclimation, plasticity, adaptation
Utilizing the functional diversity of organisms
Organisms as successful outcomes of evolutionary testing
Biodiversity as a storehouse of adaptive solutions to environmental and other problems
Improving bioprospecting through integration of AToL and organismal studies
Integrating living and physical systems analysis
Organismal complexity in time and space requires new methods of systems analysis
Application of the theory of mathematical and physical sciences to organismal questions
Application of biological design principles and systems to engineering and computation
Interdisciplinary research and education, e.g., quantitative modeling and robotics
Understanding how genomes produce organisms
Mechanisms of whole organism development from genes and genomes
Generation and evolution of phenotypic diversity
New diverse "model" species and systems, and approaches/techniques for nonmodels
Understanding how organisms walk the tightrope between stability and change
Paradox of evolutionary integration/stability and adaptation/evolvability
Modular organization and overlapping domains
Inter-modular linkages, robustness and adaptive flexibility
Systems-level behavior of organisms

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What is lacking is a mechanistic understanding of how this information is used, sensed, integrated, and translated at the organismal level into function and performance. We need information that is sufficiently detailed to drive predictive population, community, and ecosystem models. In addition, we need to know the capacity of organisms to modulate responses and interactions with the environment to use and protect resources wisely, establish effective means of conservation and restoration, and understand the robustness and resilience (or fragility) of critical species, populations, communities, and ecosystems.

Advances in the area of organismal–environmental research will require interdisciplinary thinking and collaboration to determine the physical, physiological, and genetic factors that constrain, or promote, adjustment to changing environments over different time scales (e.g., behavior, acclimation, plasticity, and adaptation), including the mechanistic bases of feedback systems between organism and environment. Understanding the flexibility and responses of physiological systems to climatic change is also critically important. For all of these research areas, we require an understanding of the functional and systems-level attributes of organisms, the populations they form, and the communities and ecosystems in which they reside, that make them resilient, or fragile, in the face of environmental change.

Utilizing the functional diversity of organisms

Living organisms are historical entities representing the successful outcomes of millions of years of environmental testing applied to different phenotypes and genetic backgrounds. Each species contains a set of unique or novel solutions to many of the same challenges humans presently face, including resource limitation, infectious disease, chemical toxicity, temperature extremes, and drought, to name a few. Basic organismal research has led to countless, often unforeseen, human benefits, including new and better sources of food, building materials, medical treatments, and pharmaceuticals, among others. In other words, organismal diversity (biodiversity) represents a vast, irreplaceable repository of genetic, biochemical, physiological, anatomical, functional, and behavioral strategies with high intrinsic interest and demonstrated value to human beings. Pringle (1966) referred to this as "the treasure-house of nature". The rapid erosion of this 'database' through extinction and loss of diversity creates an urgent need to study a diverse range of organisms, and to create an infrastructural system within which new and existing data can be organized, synthesized, mined, and applied.

The notion of exploiting organismal diversity for human applications is recognized in the nascent practices of "bioprospecting" and organismal "screening" for potential pharmaceuticals and other beneficial products (Spjut 1985), and has met with some success (e.g., bryostatins from the bryozoan, *Bugula*; taxol from the yew tree). However, bioprospecting carries with it ethical dilemmas relating to the potential exploitation of indigenous peoples and developing countries (see the international Convention on Biological Diversity, http://www.cbd.int/), as well as the overexploitation of rare or small-bodied species, as large amounts of tissue are generally required when exploring for new compounds or for human use.

One way to enhance the efficacy of exploring biodiversity may be for organismal biologists to integrate their work with an ongoing NSF initiative, "Assembling the Tree of Life" (AToL), in which systematists are working to piece together the evolutionary relationships of the world's major taxa (Cracraft and Donoghue 2004; http://atol.sdsc.edu). Although one of the stated goals of the AToL project is to help direct organismal research that is of potential human benefit (e.g., Colwell 2004; Yates et al. 2004; Cracraft et al. n.d.), the immediate work of the project is purely systematic. Full exploitation of AToL will require additional, formal collaborations with functional biologists and the integration of evolutionary, phylogenetic information with functional data drawn from all levels of biological organization. This need has also been recognized among plant biologists, and identified as one of the Grand Challenge issues in plant biology (iPlant, http://iplantcollaborative.org/the-grand-challenge-identification-process).

Historical and comparative organismal data allow researchers to make better predictions about where to find suitable organisms and genetic material for particular efforts. For example, alternative energy sources, such as biofuels, are derived from crop plants. The limited genetic diversity of crop plants makes the introduction of genetic diversity from disappearing, wild ancestors and relatives a critical part of enhancing useful attributes of crop plants (e.g., Rick 1974; Iltis 1982, 1988). Without such diversity, artificial selection to increase biofuel production and similar crop breeding projects will quickly grind to a halt. Knowledge about which wild species may be appropriate for a given use and their distribution comes from research by taxonomists, ecologists, and evolutionary biologists who explore and describe the world's flora and fauna. The biological attributes of target species are determined by other organismal biologists. Based on a background knowledge of useful organismal traits (e.g., bioactive chemicals), historical analysis can suggest which related species might be worth examining for similar, or superior, traits.

The vast diversity of functional solutions to environmental problems embodied within organismal systems and perfected through natural selection over evolutionary time provides a rich resource for human needs. New sources of food, structural materials, energy, microbial processes, waste and energy conversion, problem-solving algorithms, and engineering design remain to be discovered, characterized, and developed. Organismal biologists can take a leading role in this process and in organizing and directing the data so that it is maximally beneficial. As Pringle (1966) and Krebs (1975) noted, scientists trained in other fields are often unaware of the possibilities offered by biodiversity and they must depend on comparative, integrative,

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organismal biologists to make this information available.

Integrated approach to analysis of living and physical systems

Organisms operate across spatial scales from molecules to ecosystems and temporal scales from nanoseconds to eons. They are dynamic, multi-dimensional, hierarchical, and nonlinear networks characterized by positive and negative feedback, ill-defined boundaries, and high levels of stochasticity. Further, they operate within dynamic environments that display similar complexity. We need a strong theoretical foundation and a common language to analyze such complex systems involving not only biology, but also the physical sciences. Recent advances in mathematical, physical, and computer sciences make this an auspicious time for inter-disciplinary approaches to biological problems (see NRC 2008). One fruitful direction is the application of "dynamical systems theory" to organismal systems (e.g., Strogatz 1994; Guckenheimer and Holmes 2002). Others include fostering interdisciplinary exchanges and education in areas such as materials science, biomimetics, robotics, neural networks, and evolutionary algorithms.

Organismal biology already borrows extensively from mathematical and physical theory in many respects. For example, most population biology is based on quantitative theories of Mathematics, Physics, and Economics (e.g., May 1974; Levin 1999; May et al. 2008), and many of these theories and models have practical applications, such as the management of wild fisheries (Quinn and Deriso 1999). Environmental physiology and biophysical ecology make extensive use of integrated transport physics models of coupled internal and environmental processes, which are highly relevant to studies of climatic change (Gates 1980). Most ecological theory is, in fact, already driven by quantitative models and approaches borrowed from Mathematics, physical sciences, Engineering, and Economics (e.g., Stephens and Krebs 1986; Gurney and Nisbet 1998; Stephens et al. 2007; McRae et al. 2008). Robotic technology is being applied to problems in organismal biology, including locomotion and evolution (e.g., Schumacher et al. 2005; Lauder et al. 2007; Long 2007). Conversely, biological systems pose challenges to, and provide inspiration for, the mathematical and physical sciences. This is evident, for example, in biologically inspired design and Engineering ("biomimetics") that exploit the factors discussed in Grand Challenge 2, above. Examples include the design of novel robots for human use based on insect locomotion (Koditschek et al. 2000; Lee et al. 2008; Spenko et al. 2008); fish-inspired designs for submersible craft (e.g., Gordon et al. 2000; MacIver et al. 2004; Tangorra et al. 2007); marine mammal hydrodynamics applied to the design of ships (Fish et al. 2008); the hearing mechanism of flies used to design new hearing aids (Miles and Hoy 2006); novel nano-adhesive mechanisms based on geckos' feet (e.g., Autumn et al. 2000; Autumn and Gravish 2008; Lanzetta and Cutkosky 2008; Lee et al. 2008); and the use of biological systems, such as neural networks and evolutionary processes, to develop problem-solving algorithms applied to artificial intelligence, computer science, and robotics (e.g., Floreano and Mattiussi 2008).

It is clear that the integration of biological, mathematical, and physical sciences is highly profitable to all three endeavors, and that current advances put us on the cusp of new successes. However, a shared language and set of common analytical tools would greatly foster this marriage of disciplines. Systems theory, especially dynamical systems theory, may provide this shared language and fruitful avenues of interdisciplinary integration. Biological systems theory takes many forms and approaches, but it has a long history in organismal biology (e.g., Miller 1973a, 1973b; Riedl 1977; Wagner and Schwenk 2000; Kitano 2002; Hood et al. 2004; Baliga 2008), perhaps because organismal biologists have long recognized the dynamic nature of the integrated systems that define an organism, as well as the dynamic interactions linking individuals, species and environment. However, many biological/organismal approaches to systems theory are qualitative or conceptual, and are difficult to generalize or operationalize. Integration of mathematical/theoretical and biological approaches would provide new interdisciplinary insights and advances. The past century has seen remarkable advances in the deterministic theory of systems described by finite sets of states, but much remains to be done. Extensions to stochastic systems (e.g., those subject to random environmental forces), continuum descriptions (e.g., fluid/body interactions in swimming and flying), and to networks of interacting dynamic systems (e.g., neuronal groups and networks, cell–cycle processes, systems of interacting parts; Holmes et al. 2006) pose difficult problems that are not readily amenable to standard methods. Without a solid mathematical infrastructure, biological applications will stall, and without organismal applications, the physical sciences will forfeit the inspiration of evolutionary diversity/creativity and the chance to extend its contribution to the significant biological challenges of the future.

There is a need to encourage and nurture collaborations among scientists from disparate fields. It is also necessary for us to reconsider how we educate our professional scientists. Although the need for intellectual integration is given a lot of attention, in practice scientists tend toward ever-greater specialization and narrower focus in their research. Inter-disciplinary education, synthetic thinkers, and scientists that can collaborate in mutualistic relationships are needed more than ever to see, and exploit, the possibilities revealed by a wider field of view.

Understanding how genomes produce organisms

A long-standing question that has been identified as a grand challenge by many fields of biology is how genes and genomes produce functioning organisms, including the countless phenotypes and responses we see. The mechanisms whereby genes and genomes produce whole organisms with a variety of

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complex phenotypes, fixed as well as plastic, and how these processes regulate and shape organismal function and performance, remain enigmatic. Sequencing of genes and whole genomes was held by many as the silver bullet that would allow us to solve most of the mysteries of biology—if we could just unlock the information held within the genome, major questions in biology would be answered. This notion, however, has proven to be naive.

At present our understanding of how genetic material results in functional organisms, processes of morphogenesis, and the production of complex phenotypes throughout ontogeny is woefully inadequate, despite the progress that is being made. Ultimately, this information needs to be examined not only in terms of generating the phenotypes present within extant species, but also in the context of evolutionary history and the evolution of new organisms, novel phenotypes, and increasing complexity. This is important not only for understanding evolutionary patterns and the production of body plans, but also to define the evolutionary opportunities, limits and constraints that may affect future evolutionary change (Schwenk and Wagner 2004).

Many of the approaches used to date include descriptive, pattern based, gene/genome sequencing, and single-gene responses, including candidate gene approaches, and the mapping of quantitative trait loci (QTLs). Other approaches include new '-omics' fields such as transcriptomics (mRNAs produced), proteomics (proteins produced and their interactions). These include cell-signaling cascades and can incorporate environmental (internal and external) interactions and modulation of responses. A particularly exciting new area is RNA interference systems (RNAi), which help to control which genes are active and modulate their levels of activity (Fire et al. 1998). Advances are also being made through the use of *in vivo* 3D image analysis with fluorescent gene expression (e.g., Emlen et al. 2007) or with cell tracking or lineage mapping with special fluorescent proteins (e.g., Davidson et al. 2002; Livet et al. 2007).

New model species and systems are needed to address many questions, especially those that concern the evolution of body plans, and phenotypic and developmental diversity. The model species currently used are highly derived and were developed because they possess suites of traits that makes them amenable to laboratory studies, including small body size, short generation times, ease of culture in the laboratory, and ease of use with traditional genetics tools. Currently, discussions are underway regarding how to target and prioritize new models to answer this myriad of questions (e.g., Abzhanov et al. 2008). Approaches that allow us to investigate nonmodel systems (e.g., proteomics) are also needed to understand the diversity of living systems, and will allow us to determine and study the most appropriate organism(s) to answer each question at hand. Again, this key area of research is likely to benefit from collaborations between experimentalists and modelers, and include systems and network analysis.

Understanding how organisms walk the tightrope between stability and change

A central paradox in biology is that organisms must remain stable to maintain the integration of complex developmental and functional systems, but they must also adapt to accommodate changing environments. A long period of phenotypic stasis interrupted by a geologically brief period of reorganization to a new stable phenotype is a frequently observed evolutionary pattern. Such a pattern mirrors theoretical systems-behavior where a stable state is buffered against perturbations by system-level properties until some threshold is reached, followed by rapid transition to a new stable state. These properties appear to characterize many organismal systems at all hierarchical levels and across different time scales. A systems-theoretical approach is critical for our understanding of organisms as modular, hierarchical and networked systems (e.g., regulatory networks, cell–cell interactions and signaling pathways, homeostasis, neural networks, functional units, individual and group behavior, and environmental inputs). Interactions with applied mathematicians and engineers could prove productive (Csete and Doyle 2002).

A key element in understanding how organismal phenotypes maintain the balance between integrated stability and adaptive flexibility ("evolvability") is the growing recognition that organisms are modular entities within and across each level of organization (e.g., Wagner 1996; Bolker 2000; Schwenk 2001; Winther 2001; Schlosser and Wagner 2004; Callebaut and Rasskin-Gutman 2005; García 2007; Wagner et al. 2007; Fraser et al. 2009). Modularity can provide buffering, as well as localization of responses to external environmental changes. The advantage of modular organization is that stability, robustness and adaptive flexibility can be provided by within-module integration with relatively small levels of interaction among modules, even in the presence of among-module variation.

An important question is the nature and extent of the linkages among modules. The kinds and strengths of linkages vary among modules (e.g., material, functional, and regulatory interactions, which may be strong or weak). How are changes in the functional outputs of one module coordinated with others and what are the mechanisms that promote coordinated, systemic changes? In addition we need to understand how modules at different hierarchical levels, with overlapping, but noncongruent character domains, interact developmentally, functionally and evolutionarily (e.g., Salthe 1985; Schwenk 2001; McShea and Anderson 2005; Wake 2008b). For example, the vertebrate skull is an anatomical module of tightly integrated, individual bones (see Schwenk 2001). The individual bones, however, derive from different embryonic tissue streams (mesoderm and neural-crest ectoderm) and develop in different ways (endochondrally and intramembranously). The bones and cartilages of the skull are integrated with a variety of soft tissue structures, including the brain,

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nerves, muscles, skin, blood vessels, and sensory organs, themselves deriving from separate developmental pathways. Finally, several components of the head skeleton have independent evolutionary histories, with the derived vertebrate skull representing a complex, developmental melding of the neurocranium, splanchnocranium, and dermatocranium. What are the patterns of integration among these overlapping parts and how are changes in one coordinated with the others? If the importance of modular organization is the relative evolutionary independence of separate modules, what are the constraints on characters participating in more than one putative module?

Finally, an important direction of study is investigation of the functional and system-level attributes of organisms that make them resilient or robust to environmental perturbation (or conversely, sensitive, or fragile). In particular, we need further elucidation of the various mechanisms that mediate phenotypic responses to environmental inputs across different time scales (e.g., DNA methylation, hormonal regulation, physiological acclimation, behavioral and morphological plasticity, and adaptation). Some phenotypic responses are short term and reversible, some occur over ontogeny and are irreversible, and others occur as adaptive, evolutionary responses to sustained selection. We know that some adaptive changes can occur rapidly, such as changes in shape of the beak among Galápagos finches (Grant and Grant 2002), but the relationship between such vacillating microevolution and macroevolutionary patterns remains a critical question.

Conclusions

In this essay, we have highlighted the importance of organismal biology by identifying five grand challenges. Now is the time to begin a dialogue among scientists within and among different fields so that we can initiate the research and infrastructural processes that will help us meet these challenges. It is clear that it will take interdisciplinary research and, possibly, the approaches of integrative systems biology to make real advances in this critical area of science (Wake 2008a,b). This process needs to include the training of new scientists in interdisciplinary fields that are likely to provide important insights and possible solutions to major problems. We also need to identify the tools that we require to make these advances. Some tools can be borrowed from other systems and fields; others will need to be developed. We must stimulate, encourage, and train toolmakers who provide us with the novel approaches to the study of organisms that will open future horizons.

The grand challenges that we have identified are not intended be all encompassing or to limit other important issues within organismal biology. Rather, this perspective marks the beginning of a process that must be continued. Frequent reassessment of our grand challenges with an eye to the future will not only focus efforts of organismal biologists, but will also highlight the advantages of organismal knowledge for those examining different levels of organization and working in other areas of science.

Acknowledgments

We thank William Zamer of the National Science Foundation for inviting discussion of this topic and setting the forces in motion that resulted in this essay and, we hope, future progress. We are indebted to our colleagues on the Executive Committee of the Society of Integrative and Comparative Biology, whose extensive debate and input directly shaped the content: Lou Burnett, Karen Crawford, Ron Dimmock, Tom Hahn, Harold Heatwole, Linda Holland, Anne Maglia, Eduardo Rosa-Molinar, Jim Murray, Michele Nishiguchi, John Pearse, Robert Podalsky, Larry Riley, Rich Satterlie, Stacia Sower, Adam Summers, Brian Tsukimura, Jackie Webb, Mark Westneat, Joe Williams, and Sally Woodin. We thank SICB President, Rich Satterlie and ICB editor, Harold Heatwole, for inviting us to submit this effort to the journal. Finally, we thank our many colleagues whose suggestions, discussions and comments made this essay possible: Eldridge Adams, Greg Anderson, Jody Banks, Bob Denver, Mark Denny, Chris Elphick, R. Geeta, Bruce Goldman, Hugh Iltis, Milica Ivovic, Beth Jake, John True, Don Les, Susan Letcher, Simon Levin, Cory Merrow, Diego Sustaita, Peter Turchin, Mark Urban, and Charlie Yarish.

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