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Citation	Kültz, Dietmar, David F. Clayton, Gene E. Robinson, Craig Albertson, Hannah V. Carey, Molly E. Cummings, Ken Dewar, et al. 2013. New Frontiers for Organismal Biology. BioScience 63, no. 6: 464-471.
Published Version	<a href="https://doi.org/10.1525/bio.2013.63.6.8">doi:10.1525/bio.2013.63.6.8</a>
Accessed	February 19, 2015 5:14:23 PM EST
Citable Link	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:12330900">http://nrs.harvard.edu/urn-3:HUL.InstRepos:12330900</a>
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## New Frontiers for Organismal Biology

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*BioScience* 63: XX–XX. ISSN 0006-3568, electronic ISSN 1525-3244. © 2013 by American Institute of Biological Sciences. All rights reserved. Request permission to photocopy or reproduce article content at the University of California Press's Rights and Permissions Web site at [www.ucpressjournals.com/reprintinfo.asp](http://www.ucpressjournals.com/reprintinfo.asp). doi:10.1525/bio.2013.63.6.8

*Understanding how complex organisms function and interact as integrated units with their environment is a long-standing challenge in biology. To address this challenge, organismal biology aims to reveal general organizing principles of physiological systems and behavior—in particular, in complex multicellular animals. Organismal biology also focuses on the role of individual variability in the evolutionary maintenance of diversity. To broadly advance these frontiers, cross-compatibility of experimental designs, methodological approaches, and data interpretation pipelines represents a key prerequisite. It is now possible to rapidly and systematically analyze complete genomes to elucidate genetic variation associated with traits and conditions that define individuals, populations, and species. However, genetic variation alone does not explain the varied individual physiology and behavior of complex organisms. We propose that such emergent properties of complex organisms can best be explained through a renewed emphasis on the context and life-history dependence of individual phenotypes as a complement genetic data.*

*Keywords:* life history, phenotype, evolution, individuality, gene–environment interaction

The organism is the central unit for integration of both of the major determinants of biological form and function—genes and the environment (Lewontin 2000). However, over the past several decades, the focus of biology has shifted considerably to studying genes rather than organisms

by moving in two directions simultaneously. Moving outward from the organism toward broadscale evolutionary issues, the synthesis of Mendelian genetics with Darwinian theory led to a creative focus on mathematics, modeling, and theoretical approaches, giving birth to population and quantitative genetics. Moving inward from the organism toward cellular and molecular biology, reductionist experimental approaches based on DNA technologies allowed the experimental dissection of cause–effect relationships between individual genes and their contribution to cellular and higher-level structure and function. These two movements resulted in many of the monumental discoveries and advances that define the current state of biology. However, they also led to an eclipse of the organism by the gene as the fundamental unit of biology.

A focus on the gene will continue to be a major pillar of biology. In addition, the two broad gene-oriented lines of study outlined above, together with technological advances, have generated extensive fundamental knowledge that now has us superbly positioned for “returning to the organism” (Stillman et al. 2011). The challenge is to extend, integrate, and exploit the insights from “outward” and “inward” gene-oriented biology to develop a deeper understanding of individual organisms’ higher-order emergent characteristics, such as epigenetic mechanisms and complex physiological and behavioral traits, including intelligence. For instance, we need to better understand how individual variation in complex physiological and behavioral characteristics or traits influences ecological and evolutionary processes (Autumn et al. 2002, Gerhart and Kirschner 2007). Facing this broad challenge requires cross-fertilization and integration across traditionally disparate fields of biology, including developmental biology, physiology, microbiology, behavioral biology, neuroscience, phylogenetics, and ecology, and also requires the application of computationally intensive technologies to the emergent traits of the organism (Ungerer et al. 2008). These disciplines are already developing stronger bonds among one another because of their collective growing appreciation of the importance of the individual organism as a fundamental unit of study (Wake 2008).

Organisms and their complex phenotypes represent the units on which selection acts through fitness criteria during the dynamic process of evolution. Therefore, an overarching task for biologists is to properly understand how a specific subset of phenotypes arises from the vast repertoire of possible phenotypes that are in principle attainable from any single genome. To advance this frontier, the principles that govern how the development and life histories of

organisms are shaped by the interplay between genes and the environment need to be elucidated (Callahan et al. 1997, West-Eberhard 2005). A renewed emphasis on organismal biology will reveal the relative roles of exposures to particular environments at different life stages in producing a specific phenotype from the possible repertoire encoded in the genome. It will also provide insight into mechanisms of epigenetic programming, maternal transfer, and phenotypic plasticity that are crucial for determining complex phenotypes (Müller and Newman 2005). A stronger focus on the organism as a unit of study is crucial for understanding how complex phenotypes emerge during development and subsequent life-history stages of individuals.

Whole-animal biology is uniquely positioned to contribute in a substantive way to understanding the influence of life-history experiences and exposures on the processes by which genetic information is decoded into specific physiologies and behaviors. Such knowledge has potentially great relevance for conservation efforts, biodiversity, bioindication, and diagnostic phenotyping in basic biology, medicine, and agriculture. The wealth of behavioral, biomechanical and physiological data on many animal species could reveal novel principles of multicellular animal structure and function. However, intuitive integration of these data with the large and growing base of genetic and molecular information, paralleling significant progress made along those lines in the plant sciences, remains fragmentary for animals other than a few model species. Even though some encouraging and significant efforts toward wider integration are ongoing in animal biology—for example, in biomechanics (Ateshian and Friedman 2009)—they need to be extended to include a much broader spectrum of animals and subdisciplines. Increased emphasis on such efforts might reveal fundamental design principles that are common to all multicellular organisms, which would enhance the potential for applications of that knowledge to develop downstream societal benefits (in, e.g., biomedicine, agriculture, biomimetics, robotics). In the present article, we highlight some important opportunities and challenges for harnessing the full potential of available scientific knowledge and technological toolboxes to aid the study of the biology of complex organisms in the coming decade.

### **Context dependence of organismal life-history trajectories**

Predicting how organisms will respond to adversity and adapt to environmental change is one of the overarching ambitions of contemporary biology, spanning both the applied and the theoretical domains. An urgent need in the context of global change, including climate shifts,

human disturbance, acute environmental disasters, and invasive species, is to gain an understanding of integrated organismal responses to environmental change on very different time scales (e.g., minutes to hours, within an organism's life span, or spanning multiple generations). More knowledge is needed on how organisms respond to acute, catastrophic, and extreme environmental events, including events such as tsunamis, earthquakes, volcanic eruptions, hurricanes, floods, and extreme thermal events. Such acute events are predicted to increase in frequency as a result of climate change and anthropogenic pollution of Earth's atmosphere and oceans (van Aalst 2006, Yasuhara et al. 2011). Biological responses to acute environmental change are based on molecular, physiological, and behavioral mechanisms that rapidly confer plasticity to organismal phenotypes in order to maximize their coping ability under those conditions (Kültz 2005, Wingfield 2012). A central question concerns the determinants of plasticity during changing environmental and social circumstances—that is, to what extent prior life-history experiences and exposures relative to genetic factors influence coping ability. Arguably, the best context for such comparative biological inquiry is the individual organism (figure 1).

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Comparative analyses of how individuals respond to environmental perturbation and social challenges are also of interest in the context of evolutionary medicine (Stearns 2012) and with regard to an organism's microbial symbionts, which have coevolved in close association with their hosts (McFall-Ngai et al. 2013). Moreover, the mechanisms and extent to which organismal plasticity alters the patterns of variation available to natural selection must be investigated on a broader scale and in greater depth (West-Eberhard 2005). On timescales spanning multiple generations, gradual environmental changes such as global warming alter the genomes of populations and species through the effects of differential selection on organismal phenotypes encoded by nonneutral genes. An increasing number of examples show how biologists use phylogenetic patterns and comparisons of contemporary and historical information on the phenology and distribution of organisms to understand and predict the effects of gradual processes such as climate change on populations (Willis et al. 2008). Overall, however, we still know far too little about how the two basic mechanisms of environmental acclimation and adaptation are used by diverse organisms to be able to explain why some populations and species are better than others at coping with acute, extreme, or long-term and gradual environmental

change. Understanding the basis for such differences and the evolutionary trade-offs that counterbalance coping ability in well-suited model organisms will also provide insights into human evolution and medicine.

High-dimensional organismal phenotyping (i.e., the analysis of many phenotypic parameters at high spatiotemporal resolution) is required to understand short- and long-term adaptive responses to environmental adversity and change. In evolutionary theory, high phenotypic dimensionality may provide the solution to understanding how organisms are able to cross from peak to peak in adaptive landscapes, sliding around apparent fitness barriers (Gavrilets 1999, Pigliucci 2008). In human health and development, data-intensive “omics”-based analyses across the life span of individuals may reveal the mechanistic basis for the phenomena of biological embedding (Hertzman and Boyce 2010, Szyf 2011) and predictive adaptive responses (Bateson et al. 2004, Gluckman et al. 2005). Biological embedding and predictive adaptive responses reflect the influence of earlier life experiences on phenotypes at later stages of life (figure 1). The underlying concept is that the physiological and behavioral phenotypes of any organism are contingent on and can be explained by its prior life history (in addition to its genetic predisposition). In the context of climate change and anthropogenic pollution, incorporating the flexible coping abilities of individuals and the capacity for genetic change into population-level models may improve the predictive accuracy of these models (Farrell et al. 2008). Moreover, researchers in the health sciences, having abandoned the notion of “disease genes,” increasingly examine the genetic basis for individual differences in susceptibility to environmental influences and thus actively explore the genomic constraints on plasticity that underlie biological embedding and predictive adaptive responses. These trends will provide data sets of clear relevance for issues central to biology.

It is daunting to confront the difficulties of collecting and analyzing the complex, high-dimensional data sets needed to describe an organism’s phenotype at the necessary spatiotemporal resolution to understand the interplay between genes and the environment in shaping the physiology and behavior of complex organisms. Despite the fact that we are now able to rapidly determine any individual’s complete genotype, when it comes to phenotyping, the reality is all too often “not far removed from previous generations, who took out the calipers, made a single measurement, and wrote it down in a notebook with a pencil” (Houle 2010, p. 1793). Although significant progress in developing high-throughput phenotyping approaches

for some organisms is being made (Mahner and Kary 1997, Freimer and Sabatti 2003), this is an area of great opportunity for future biology research. Increasingly, it is feasible to bring the lab to the field and study organisms in their natural environments, where their exposures and experiences differ from those in artificial lab environments (e.g., Dechmann et al. 2011, Gagliardo et al. 2011). For instance, telemetric applications using micro- or nanosensors allow high-throughput approaches for phenotyping and environmental-exposure assessment of many individuals in diverse environments (Houle 2010, Robinson et al. 2010). In parallel, technological advances enhance opportunities for the simulation of more realistic natural environments in the laboratory to isolate particular environmental parameters of interest and to study their effects on organisms in great depth. Examples that illustrate these emerging opportunities include the use of machine vision algorithms to generate ethograms of many individuals in social groups (Branson et al. 2009), microsenors for motion analysis combined with statistical methods to define behavioral sequences from continuous data (Braun et al. 2010), methodological advances in morphometrics to characterize multivariate organismal features that determine shape (Zelditch et al. 2009, Klingenberg 2010), segmental analysis of iterative subroutines in exploratory behavior in mice (Benjamini et al. 2011), and computer-supported analysis of the developmental trajectories in bird song learning (Lipkind and Tchernichovski 2011) and culture (Fehér et al. 2009).

Collecting and organizing high-dimensional data sets can lead to a new level of knowledge. An example is the burgeoning mapping of neuronal networks in the brain, using functional imaging in humans (Biswal et al. 2010) and high-resolution structural mapping in the simpler insect nervous system (Chiang et al. 2011). Computational models based on these data sets are already predicting novel whole-organism behaviors (Wessnitzer et al. 2012). Another example pertains to the application of proteomics technology, which has developed to such a state that it allows the comprehensive characterization of molecular phenotypes of diverse tissues and cell types of complex organisms (Cox and Mann 2011). This technology platform promises great potential for high-throughput phenotyping, because proteins are the main molecular determinants of phenotype whose abundances are modulated by environmental conditions at numerous levels of regulation (Schwanhäusser et al. 2011). In addition, specific protein posttranslational states, subcellular and tissue-specific compartmentalization, and the composition of multiprotein complexes all reflect the history of prior exposure to particular

developmental and environmental conditions (Weckwerth 2011, Diz et al. 2012). Therefore, proteomics represents a promising toolbox for opening the window into an organism's record of environmental exposures and experiences.

Basic research targeting the overarching principles and mechanisms of coping, acclimation, and adaptation in the face of a changing environment continues to take advantage of existing life strategies and adaptations in particular species. This approach, which is based on August Krogh's principle, emphasizes that there are species especially well suited to address nearly any problem in biology (Krebs 1975). In using this approach, biologists reveal fundamental mechanisms that enable a particular species to thrive under conditions that would be lethal or that would cause severe disease in humans or most other species. Knowledge of such mechanisms is of fundamental importance for better understanding the biological principles on which life is founded, and it entails obvious potential for applications in human medicine, agriculture, and conservation management (Carey et al. 2012). For instance, Antarctic ice fish with no hemoglobin provide a convenient evolutionary example that does not have to be artificially engineered to enable the study of the implications of hemoglobin for organismal responses to environmental challenges (Pörtner et al. 2007). The interaction of complex organisms with the environment requires study in a context-dependent manner on a spatiotemporal scale of sufficient resolution to permit the generation of novel insights into the biological principles that govern such interactions (figure 1). Given that such studies will include a wide variety of species, it will be possible to draw general conclusions and extrapolate knowledge to population, clade, and community levels. Achieving progress toward this ambitious goal requires investments into visionary longer-term research.

### **Importance of individual variability for evolutionary maintenance of diversity**

An important element that needs stronger emphasis in contemporary biology is the individuality of organisms. It is crucial to realize the importance of individual variation, which is far greater at the level of the phenotype relative to the genotype, because each individual has its own unique record of life-history exposures and experiences. This path has been established in developmental psychology and physiology, which provides examples in which the study of individual differences has spawned rather than complicated the development of integrative frameworks. For many biologists, however, embracing individual variation is not trivial and



represents a significant shift in perspective.

Mechanistic approaches to biology have typically worked under the assumption that, for any given trait, there is a common reaction norm, and variations from this norm are often viewed as experimental or statistical noise. Much of experimental biology has aspired to reduce the effects of individual variation and to focus explicitly on the determination of mean values to distill complex phenomena into interpretable entities at the expense of information on individual variation. Even at the cellular level, it is becoming evident that no two cells are alike, and it is increasingly recognized that such variability is of great importance for tissue differentiation during development (Gerhart and Kirschner 2007, Pelkmans 2012). Moreover, clonal lab-reared organisms or highly inbred models, such as certain strains of mice, display “unexpected” phenotypic variation (Crabbe et al. 1999), such that the very concept of a *type specimen* or a *wild type* has been called into question (Mayr 1996, Parichy 2005). In addition, the vulnerability or resilience of populations to environmental change is a function of the genetic diversity of the individuals constituting the population (Hoffmann and Sgrò 2011). In fact, individuals with genotypes that deviate the most from the population mean are often founders of better-adapted populations when the environment changes (Kellermann et al. 2009). A renewed emphasis on individual trait values (in addition to population sampling means) is crucial for assessing the linkages between different traits and the effect of the environment on individual variability. This task will benefit greatly from leveraging high-throughput technologies for genotyping, genomewide epigenetic analysis of chromatin in individual organisms, and comprehensive high-throughput phenotyping.

The importance of individual variation in evolution is perhaps most apparent for behavior, because behavior has long been thought to be at the leading edge of evolutionary change (Mayr 1963). Traditional approaches that identify the mean behavioral tendencies associated with specific genotypes (e.g., quantitative trait loci, genomewide association, human twin studies) have documented multigenic influences for almost all behavioral traits, with each gene contributing small effects (Flint 2003, Kendler and Greenspan 2006). By leveraging high-throughput technology platforms, it is now possible to tease apart the mechanistic differences that underlie specific phenotypes associated with individual variation in behavior. Genomic studies have begun to characterize individual variation in behavioral phenotypes by identifying suites of genes that are dynamically expressed in specific environmental (Whitfield et al. 2003)

or social (Cummings et al. 2008, Ramsey et al. 2012) contexts. The range of behavioral influences associated with specific genes can now be studied in a much broader context, taking into account a more comprehensive array of genomic and life-history backgrounds. Combining high-throughput profiling methods with reverse genetics approaches in individuals with specific genomes and life histories will allow biologists to understand how genetic polymorphisms and environmental exposures contribute to behavioral phenotypes.

### **Development of the organismal biology community**

A larger and more coherent community of biologists who are proficient in both physiological and behavioral whole-organism approaches and in high-throughput genotyping, epigenotyping, and phenotyping technologies is needed to propel organismal biology forward. In addition, students and postgraduate researchers should be given appropriate and state of the art training in the mathematical, analytical, and computational skills that are necessary to comprehend key features for the standardization and analysis of the complex data sets generated by high-dimensional phenotyping technologies. Such training will be crucial for developing a community of organismal biologists that is highly interactive and that can vigorously, creatively, and dynamically communicate and collaborate with computer scientists, analytical chemists, engineers, and experts from other areas that continue to develop new and innovative toolboxes for organismal biology.

Collaborative research in which complementary skill sets of different types of scientists (e.g., biologists, computer scientists) can be brought together in a creative and productive way will benefit from a stronger cross-disciplinary basic training of organismal biologists. Such training should reveal areas and opportunities for cross-fertilization with other scientific disciplines by providing a broad, basic understanding of the current and rising trends and capabilities in other fields. A renewed focus on organismal biology is inevitably interdisciplinary, and it faces all of the well-known challenges of interdisciplinary research.

There is also a need to identify opportunities for advancing our theoretical understanding and intellectual base to a point at which the design of better, more powerful, more holistic, and more integrative approaches is possible. Characterization and in-depth analyses of diverse phenotypic measures (e.g., molecular, morphological, physiological, behavioral) represents an absolute prerequisite for the discovery of the algorithms that describe how order emerges in

complex biological systems (Grimm et al. 2005). Accomplishing such comprehensive phenotyping for many individuals across a large number of species will require strongly interdisciplinary efforts.

Research centers or intellectual focus groups that act as hubs for fostering collaboration on specific projects among scientists with diverse research backgrounds, ideas, and technological expertise would facilitate this endeavor. Such centers could provide cross-disciplinary training to investigators and could allow for better and more efficient integration of high-throughput technologies focused on molecular building blocks (i.e., genes, transcripts, proteins, and metabolites) with studies on the function and responses of complex whole organisms to changing internal and external environments. Examples of initiatives in the United States that could serve as models or nucleation points for such centers include iPlant (Stanzione 2011), NESCent (the National Evolutionary Synthesis Center; [www.nescent.org](http://www.nescent.org)), NCEAS (the National Center for Ecological Analysis and Synthesis; Reichmann 2004), and NIMBioS (the National Institute for Mathematical and Biological Synthesis; [www.nimbios.org](http://www.nimbios.org)). These centers have been highly successful in bringing together scientists with diverse backgrounds and providing interdisciplinary training. They have already generated many invaluable resources, including freely accessible data-processing, deposition, and visualization tools. Corresponding research hubs focused on specific timely aspects of whole-organism biology (e.g., organismal responses to natural disasters, pollution, climate change) could serve to reshape the diverse community of organismal biologists to be more inclusive of the interdisciplinary collaborations needed for future progress. The anticipated payoffs of this inclusive approach promise to add new theories about organisms to basic biological theory and to advance applied science by providing a deeper understanding of how organisms cope with change, challenge, and opportunity—issues of widespread importance in society, sustainability, medicine, and the culture of our world.

### **Development of technology, cyberinfrastructure, and computational tools**

In addition to community development, better and more widely accessible technologies for large-scale rapid phenotyping in physiologically relevant environments are urgently needed to leverage the full potential of organismal biology. For instance, miniaturized and remotely controlled environmental sensors for collecting relevant environmental data over long periods of time in natural environments are needed to understand how specific environmental exposures influence

organismal traits, physiological responses, and complex behaviors. In this case, as well as in others, partnerships and collaborations between academic researchers and industry or businesses should be encouraged in order to most efficiently advance the development and wide distribution of much-needed tools. New and more effective approaches for linking various phenotypes to fitness are also needed. This linkage is currently very difficult and can be accomplished only with a focus on whole organisms, because fitness is ultimately a measure of the reproductive success of an individual. Although a focus on model organisms is necessary in some cases, the development of toolboxes for organismal biology should be more inclusive and widely applicable to a greater number of species to promote larger-scale comparative approaches.

Another area of technology development needed to propel organismal biology involves large-scale phenotypic data storage, accessibility, and computability. Whole-organism data provide two major challenges to the existing infrastructure. First, phenotypic data are typically complex, heterogeneous, and high dimensional. Phenotypic data sets of high spatiotemporal resolution that account for individual variation are needed to learn how particular environmental exposures and experiences at diverse stages of life history influence an organism's traits. Moreover, we need high-dimensional data sets in order to understand how such variability in the traits of individuals is reflected at population, community, and society levels. In particular, physiological and behavioral data and the associated approaches for their acquisition are much more heterogeneous and diverse than are genetic or morphological data.

Therefore, highly flexible data portals and storage solutions that are not restrictive with regard to data structures are urgently needed for accelerating future biology. The Dryad data repository (<http://datadryad.org>) provides a useful model for capturing and preserving primary biological data in which data deposition is integrated into the journal publication process. Dryad has a flexible interface that allows both the flexible deposition of data in any format with minimal metadata requirements and coordinated deposition with other repositories that require structured data types (e.g., Genbank, TreeBASE). Another potential model is the Tranche repository (Hill et al. 2010), which allows the submission of data without predefined formatting requirements. Prepublication data can be password protected to limit access, and a hash code is provided for each data record to facilitate peer-review and data referencing in journals. Data can be downloaded as raw data or visualized through freely distributed viewers (e.g., the Scaffold viewer, the PEAKS viewer; Searle 2010, Zhang et al. 2012). These solutions will require an

enormous storage capacity and a significant investment in the maintenance and management of the associated cyberinfrastructure, as well as in data curation.

A second major challenge is the analysis and computability of phenotypic data. Better computational tools are needed to reduce the high dimensionality of phenotypic data sets into intuitive and interpretable units. Although flexible data formats and metadata standards are important for the a priori capture and documentation of heterogeneous and innovative primary phenotypic data, it is equally crucial to develop and regularly update appropriate data standards. The lack of data standards for many behavioral, physiological, and other phenotypes is a major limitation to integration in organismal biology, because it hinders efficient data interpretation and synthesis. Concerned mainly with fish, the Phenoscope project ([www.phenoscape.org](http://www.phenoscape.org)) provides a useful example and model for the development of the data structures, ontologies (structured semantics), and cyberinfrastructure that relate the anatomical and developmental phenotypes, molecular genotypes, and evolutionary taxonomies. Another excellent example is the PRIDE (Proteomics Identifications Database) repository ([www.ebi.ac.uk/pride](http://www.ebi.ac.uk/pride)), which provides flexible solutions for the conversion, quality control, and visualization of heterogeneous proteomics data (Wang et al. 2012). The challenges are as much cultural as they are technical: Communities of organismal biologists must collectively develop and agree on common standards for terminology and data structures. This will be a particular challenge as organismal biologists increasingly extend genomic, proteomic, and related approaches to a much broader spectrum of species. These advances will also require the continuous development of data analysis tools for novel formats that are emerging and in high demand. In that regard, the iPlant initiative is one step in the right direction and serves as a platform on which to build in the future (Stanzione 2011). Increased digitization of phenotypic and environmental data, which is possible through new museum specimen data portals such as Arctos (<http://arctosdb.org>), will also allow easier access to heterogeneous data associated with organisms and environments.

## **Conclusions**

The strong focus of biology over the last 50 years on gene-oriented approaches has generated a solid foundation for studying the mechanisms that determine the phenotypic diversity of complex organisms from a new perspective. Research on how the phenotypes of complex organisms emerge as a result of gene–environment interactions has great potential to reveal novel principles

that determine fundamental morphology, physiology, and behavior (Bartholomew 2005). Such studies are necessary to understand how the complex properties of higher-order biological systems emerge from simpler building blocks (Pigliucci 2003). Advancing our knowledge of the principles governing the biology of complex organisms requires the study of individual organisms in the context of specific environments and consideration of their unique environmental exposures and experiences over the course of their lives (Lauffenburger 2012). Because of the heterogeneity and high dimensionality of phenotypic data sets, it is necessary to foster community and technology development in the area of organismal biology. Cross-disciplinary training, effective avenues for interdisciplinary communication, and biological databases that span the genotype–phenotype continuum will be key for the development of a stronger community of biologists who focus their efforts on integrating the diverse facets of whole-organism biology. Important foci for technology development efforts include better tracking technologies for monitoring organisms and the associated environmental variables in their natural habitats, more powerful and widely accessible high-throughput phenotyping tools, and a flexible and dynamic cyberinfrastructure framework for large-scale phenotypic data sets. Promising developments in all of these areas are already under way, and intensifying these efforts will advance the biology of complex organisms to a higher level.

### **Acknowledgments**

This article communicates the analyses and discussions of a workshop on the future of organismal biology, which was held on 18–20 September 2011, in Arlington, Virginia. The workshop was supported by National Science Foundation grant no. IOS-1145241 to DK. We apologize to all whose important and long-standing contributions to the topics discussed were not acknowledged because of limited space for references. We would like to thank William E. Zamer and John C. Wingfield for invaluable advice and guidance during the workshop and manuscript preparation and Letitia Cundiff (University of Illinois) for administrative assistance with the logistics of the workshop.

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[Typesetter: In figure 1, please add a closing parenthesis after “exposures”.]

***Figure 1. The three principal factors defining organismal phenotypes are the genotype of the individual, the environment in which the individual is embedded, and the life history experienced by the individual. The life history represents the sequence of environmental exposures during the course of the individual’s life—in particular, during early development—which are recorded as cellular and higher forms of memory. Organisms themselves, through the expression of their individual phenotypes, influence the environment and the propensity for recording life-history events (which depends on the capacity and modes***

*of memorizing those events).*