Evolutionary “Experiments” in Symbiosis: The Study of Model Animals Provides Insights into the Mechanisms Underlying the Diversity of Host–Microbe Interactions

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Current work in experimental biology revolves around a handful of animal species. Studying only a few organisms limits science to the answers that those organisms can provide. Nature has given us an overwhelming diversity of animals to study, and recent technological advances have greatly accelerated the ability to generate genetic and genomic tools to develop model organisms for research on host–microbe interactions. With the help of such models the authors therefore hope to construct a more complete picture of the mechanisms that underlie crucial interactions in a given metaorganism (entity consisting of a eukaryotic host with all its associated microbial partners). As reviewed here, new knowledge of the diversity of host–microbe interactions found across the animal kingdom will provide new insights into how animals develop, evolve, and succumb to the disease.

1. Introduction

It was only about a dozen years ago that next-generation sequencing came on the scene in biology, a breakthrough that rendered nucleic acid sequencing fast and relatively inexpensive. This newly available resource resulted in the international community embarking on a vast number of sequencing projects, notably genomic and transcriptomic analyses, across all corners of the biological world, from viruses to crown-group animals and plants. As the data emerged, it was clear that biology was entering into a new era, one that would change the way we conceive of relationships among the vast array of organisms that comprise the biosphere, as well as our own position as humans within the biological world.[1,2] The most remarkable finding has been that microbes represent the greatest diversity of organisms by far. Using comparative sequence analyses, biologists have gone from recognizing only a few major groups (analogous to divisions or phyla) with a few thousand phylotypes of bacteria to over a thousand major groups with millions of phylotypes. Further, analyses of microbial communities have revealed that the microbial world is at the base of biosphere health, from that of the environment to that of all plants and animals, including humans. The multipartite entity of a host and its associated microbial communities is termed “holobiont”[3] or synonymously “metaorganism.”[4]

In this review, we focus on the impact of these findings on our view of animals. Over the last few years, biologists have realized that persistent associations of microbes with animals, or symbioses, are likely the “rule” rather than “exception.” As all extant animal phyla arose in the microbe-rich seas of the early Paleozoic, it is not surprising that microbes presented a biotic force that, in concert with abiotic forces (e.g., temperature, pressure, and salinity), have shaped the evolution of animal form and function. Within this context, evolution has produced a wide variety of symbiotic systems. Microbes occur i) as intra- or extracellular partners of the host, ii) in relatively simple communities, with one to a few microbial phylotypes, to highly complex systems, with hundreds to thousands of microbes in residence. Further, they can be acquired horizontally (from the environment) or vertically (transovarially) transmitted across generations. Although the speciose insects have many clades with intracellular, vertically transmitted symbionts, perhaps the most diverse and prevalent associations are the colonizations of the apical surfaces of animal epithelia by microbes. For example, portions of most of the 10 vertebrate organ systems (e.g., digestive, integumentary, reproductive, respiratory, etc.) have persistent associations with complex microbial consortia.

Biologists are now tasked with learning the principles that govern this newly discovered, highly complex arena. The questions to be addressed include:

- How are microbes recruited each generation into the tissues where they reside?
• How do metaorganisms develop and how do the interspecific interactions affect development?
• How is the stability of metaorganisms achieved and maintained?
• What are the differences between pathogenic and beneficial associations?
• How do they evolve, that is, what are the conserved features among all animals, and what evolutionary mechanisms drive the diversity of symbiotic systems?
• How do host population dynamics and social structures shape symbioses in metacommunities?
• How do environmental features affect the symbiosis and how do the symbioses affect the environment (e.g., built environment or natural environment)?

Over the history of biology, the practitioners have often been faced with highly complex systems. One mechanism by which to deal with such complexity has been to turn to model systems, i.e., animals that offer unique opportunities to explore the questions at hand. For example, to provide insight into how a fertilized egg becomes a fully mature animal, developmental biologists have used a wide variety of models, for example, Drosophila melanogaster ([D. melanogaster], fruit fly), Caenorhabditis elegans ([C. elegans], worm), Danio rerio ([D. rerio], zebrafish), to name only a few. This approach has been a highly successful strategy; all Nobel prizes awarded in developmental biology have gone to individuals using model systems.[5] Each model has offered a unique set of features that provides a window into specific aspects of developmental biology, such as dynamics of fertilization, the underlying mechanisms of cell determination and differentiation, the cellular pathways that drive organ morphogenesis and body-axis formation.

So, too, are biologists turning to model systems for the study of symbiosis. Fortuitously, many of the powerful models that were important for developmental biology have also been adopted for the study of host–microbe interactions, including Hydra,[6–9] the fruit fly,[10–12] worm,[13–15] zebrafish,[16–18] and mouse.[19,20] In addition to these systems, other model associations have come from a deep history in the field of symbiosis (e.g., the squid–vibrio symbiosis or the parasitic nematode–Xenorhabdus association) or have developed anew (e.g., sponge, starlet anemone, honey bee, leech, and gypsy moth). The systems span the spectrum from inbred strains of the host, which keeps the “noise” of genetic variability low, to natural models that seek to define symbiotic features that are represented across the diversity of a species. In addition, symbioses have various functions in the host, from defense to nutrient management. Further, in some circumstances, the host can be raised without the symbionts (either aposymbiotic, i.e., when other environmental microbes are present, but not the symbiotic partner species; or germ-free or gnotobiotic, no microbes in the environment or an introduction of known microbe(s)). Interestingly, most often, these animals lacking their symbionts are physiologically compromised and rely on the provision of specific constituents or services typically provided by associated microbes (e.g., essential amino acids or vitamins, or protection from pathogens).

2. How Can the Field of Biology Take Advantage of the Species Diversity to Gain a Mechanistic Understanding of Host–Microbe Interactions?

2.1. An Overview of the Model Systems under Development

“Nature has been generous to Science and has provided us with many model systems” (Sydney Brenner in his Nobel Prize Lecture).[21] Our planet is home to an estimated 30 million species of animals. Until recently, lack of genetic resources has hindered research on the mechanisms governing host–microbes interactions outside around a handful of species. This has changed now. Technical powers in modern biology have allowed us to broaden our range of models. Analyzing the genetic underpinnings of a wide variety of animal species is getting easier as sequencing becomes cheaper and more routine. At last count (list of sequenced animal genomes),[22] the genomes of nearly 2500 multicellular organisms had been sequenced, including sponges, sea anemones, and medusozoan cnidarians. These projects from the onset have given some unexpected surprises. For example, the genome of the starlet sea anemone Nematostella vectensis (N. vectensis), an animal that shares the phylum Cnidaria with corals and freshwater polyps, is large and complex and shares more in common with humans and other vertebrates than traditional model organisms like fruit flies or worms.[23] Multilevel omics provides insights into the integrated neurosensory, muscular and organ systems of such model organisms and, in combination with transgenesis, CRISPR/Cas9 genome editing, mathematical and computational modeling, and integrated network analysis, allows us to investigate and interpret interactions between the members of a given metazoans at a mechanistic level.

Below we highlight some of the models (see Figure 1) that are currently providing important clues about how symbioses operate. These examples represent only a small subset of the available systems. They were chosen to lend examples of how the basic questions of the field might be addressed through exploitation of the “experiments” in symbiosis that nature has carried out over the range of animal evolutionary history.

2.2. Symbiosis Models from the Earliest-Branching Animal Phyla

Sponges (Porifera) represent one of the oldest, still extant animal phyla. Fossil evidence dating back 580 million years ago shows their existence in the Precambrian,[24] long before the radiation of all other animal phyla. More than 9000 species have been described taxonomically but the estimated diversity is still much higher. Sponges are globally distributed in all aquatic habitats from warm tropical reefs to the cold deep sea and are even present in freshwater lakes and streams. As sessile filter feeders, they pump many thousands of liters of water per day through the aquiferous canal system that is embedded within the sponge body. Sponges are excellent examples of metaorganisms, because many species harbor enormously dense and diverse communities of symbiotic microorganisms in their tissues. Most sponge symbionts exist extracellularly within the sponge extracellular matrix. In recent years, the field of sponge microbiology has remarkably advanced in terms of curated
Inferred interactions, bacterial isolates with predicted cooperative or competitive behavior were tested for their ability to influence bacterial recolonization dynamics that predicted competitive bacteria can influence community structure at least within a short period of time. The small sea anemone Aiptasia pallida (A. pallida) serves as another sea anemone model system to provide foundational insight for ecologically important species such as stony corals and reef ecosystems that are otherwise hard to study or expensive to maintain in laboratory settings. A. pallida is easy and inexpensive to rear, establish symbioses with the same algal endosymbionts as corals, and their bacterial microbiomes are comparable to those of corals. As an example, salinity-convoyed thermotolerance was recently shown for a group of symbiotic A. pallida anemones. Elucidation of the underlying mechanism showed that abundance of the oxygen-scavenging osmolyte floridoside, produced by the algal endosymbionts, is increased at high salinity and reactive oxygen species (ROS) leakage is reduced. The increased abundance of floridoside at high salinity under high temperatures concomitant with reduced coral bleaching (i.e., increased thermotolerance) could subsequently be confirmed across a broad range of coral species.

The freshwater polyp Hydra vulgaris is an excellent model for studying how metaorganisms function in vivo. The epithelial surface is densely colonized by a stable multispecies bacterial community. The presence and structure of Hydra's microbiota are critical for the tissue homeostasis and health of the polyps. Remarkably, each Hydra species supports long-term associations with a different set of bacteria, suggesting that the host imposes specific selection pressure onto its microbiome. The findings reveal that epithelia and components of the innate immune system play an active role in selecting the inhabitant microbiota via a complex genetic network. The work has contributed to a paradigm shift in evolutionary immunology: components of the innate immune system with its host-specific antimicrobial peptides appear to have evolved in early branching metazoans because of the need to control the resident beneficial microbes rather than because of...
invasive pathogens.\textsuperscript{[7]} The hydra model system also has provided insights of general significance with the discovery of the role of interactions between commensal bacteria in colonization resistance.\textsuperscript{[16]} While so far the epithelial cells of \textit{Hydra} were considered as prime regulators of the microbiome, recent studies uncovered a previously underappreciated role of the nervous system with its rich repertoire of neuropeptides in controlling resident beneficial microbes.\textsuperscript{[37,38]} Recent findings also show that microbes affect the animal’s behavior by directly interfering with neuronal receptors. These observations provide new insight into the original role of the nervous system and suggest that it emerged to orchestrate multiple functions including host–microbiome interactions.\textsuperscript{[9]} In the \textit{Hydra viridisissima} species, a long-term persistence of symbiotic associations is prevalent not only in two-party interactions of \textit{Hydra} and symbiotic algae,\textsuperscript{[99]} but also in more complex systems including stably associated bacteria. Studying symbiotic interspecies interactions in \textit{Hydra}, therefore, may be a paradigmatic example of a complex symbiotic community that influences the host’s health and development.

2.3. Symbiosis Models of Invertebrates with Complex Organ Systems

Among the model organisms used to study reciprocal actions among microbes and hosts, \textit{C. elegans} may be the most advantageous in the context of its unique attributes such as the short life cycle, ease of laboratory maintenance, and the availability of different genetic mutants.\textsuperscript{[40]} In nature, \textit{C. elegans} can be found in soil and microorganism-rich rotting fruit and plant matter.\textsuperscript{[41]} Only very recently efforts have been made to explore the association between \textit{C. elegans} and microbes in nature by profiling the natural microbiome of \textit{C. elegans} and thereby laying a foundation for mechanistic studies of host–microbiome interactions in this genetically tractable model system. Dirksen et al.\textsuperscript{[42]} used 16S rDNA deep sequencing to characterize the natural microbiomes of \textit{C. elegans}, \textit{Caenorhabditis remanei} (\textit{C. remanei}), and \textit{Caenorhabditis briggsae} (\textit{C. briggsae}) isolated from natural environments, including plant stems, fruit, and compost. The study revealed the complexity of native gut microbial taxa of nematodes obtained from natural environments. The association between \textit{C. elegans} and its microbes is much more than a dietary relationship since the intestinal microbiome is distinct from the microbiome in its environment and from the microbiome of \textit{C. remanei}.\textsuperscript{[42]} The microbiomes of \textit{C. elegans} and \textit{C. briggsae} protect each species against infections, but the microbiome of one species fails to protect the other species.\textsuperscript{[43]} The composition and diversity of the microbiome in the environment correlate with developmental stages of the worms.\textsuperscript{[42]} Alphaproteobacteria-rich environments support proliferation, whereas higher levels of Gammaproteobacteria and Bacteroidetes promote nonproliferating dauer-stage development.\textsuperscript{[44]} Bacterial signals affect worm development and aging. \textit{Escherichia coli} folate synthesis reduces \textit{C. elegans}’ life span.\textsuperscript{[45]} \textit{Comamonas aquatica} produces vitamin B12 that affects \textit{C. elegans}’ development and fertility and also breaks down propionic acid to prevent its toxic buildup.\textsuperscript{[46]} The single-species microbe–host interaction model system is instrumental in understanding the function of specific members of the microbiome. Studies using single-species microbes, multimicrobial systems, and humanized worm–microbiome interaction studies reveal metabolic and microbial–microbial interactions relevant in animals with a different body-plan complexity. Taken together, the use of defined synthetic microbiota ecosystems, guided by the natural history of \textit{C. elegans}, should help optimize the development of a relevant model system for host–microbiome interaction studies.\textsuperscript{[44]}

Members of the sepiolid cephalopods are often characterized by two symbiotic associations: 1) the binary light organ symbiosis, where the host harbors a single bacteria symbiont of multiple strains in populations that provide luminescence as a camouflage mechanism for these night-active predators;\textsuperscript{[47]} and 2) the accessory nidamental gland (ANG), which is a female-specific organ associated with reproduction that bears a rich consortium of bacterial phenotypes.\textsuperscript{[48]} The ANG has been under intense study for only a few years, so this review will focus on the light organ association of one particular host, the Hawaiian bobtail squid \textit{Euprymna scolopes} (\textit{E. scolopes}), for which an extensive research community has developed over the last 30+ years.\textsuperscript{[49]} \textit{E. scolopes} forms a symbiotic relationship with light-producing bacteria, \textit{Vibrio fischeri} (\textit{V. fischeri}), that colonize its light-producing organ. Not long after hatching, the squid secretes mucus from a superficial epithelia field of cells. \textit{V. fischeri} is selected in this mucus matrix as the sole symbiont, against the background of other environmental bacteria before it moves into the host crypt spaces where it resides throughout the life of the host. The \textit{E. scolopes} light organ symbiosis offers a rich set of opportunities to study many aspects of symbiosis, from ecology and evolutionary biology to the molecular mechanisms underlying establishment and maintenance of a symbiotic association.\textsuperscript{[50–52]} The binary nature of the relationship and well-developed genetics in the bacterial partner, \textit{V. fischeri}, allow exquisite resolution of the dialogue between partners.\textsuperscript{[52]} The association is highly specific; in the absence of \textit{V. fischeri} in the environment of a hatching, other bacteria do not colonize the organ. In addition, while the association is obligate in the field environment, the host can be raised apsymbiotically in the laboratory (i.e., with other environmental bacteria present, but no \textit{V. fischeri}), with no obvious physiological effects on the host.

Much of the work on this system has focused on the first few days of the association (for review see McFall-Ngai\textsuperscript{[53]}). The newly hatched juvenile animals are small enough (~2 mm total length; light organ, ~400 µm across) and the colonization of the tissues establishes quickly enough (over ~100 µm into six crypt spaces over a few hours) that much of the process can be observed in real time by confocal microscopy. Studies of this model were the first to demonstrate bacteria-induced development in animals\textsuperscript{[49]} and the role of symbionts in driving host circadian rhythms.\textsuperscript{[54]} In addition, in changing the lexicon of host–symbiont molecular interactions from “Pathogen-Associated Molecular Patterns (PAMPs)” to “Microbe-Associated Molecular Patterns (MAMPs),”\textsuperscript{[55]} the squid–vibrio research heralded a conceptual shift that places pathogens in the role of interlopers into a pre-existing “conversation” that an animal has with its beneficial microbial partners. The genome of the squid host has just recently been completed and methods to bring genetics into the squid host are under active study. These advances promise to bring this symbiotic model to a new level.
2.4. Zebrfish to Study the Functional Impact of Microbes on Host Biology

George Streisinger at the University of Oregon established zebrfish *D. rerio* as a vertebrate model system with accessible embryology and simple enough husbandry requirements that it could be used in the forward genetic screen.\(^{[56]}\) The small size and optical transparency of the embryos and larvae have made this animal a premiere model for developmental biologists. The zebrfish research community has invested heavily in developing valuable genetic tools such as transgenic lines that highlight myriad of different cell types during their developmental dynamics and a growing collection of mutants, originally from forward genetic screens and more recently from genome engineering.\(^{[57]}\)

All of these features of accessible embryology, transparency during development, easy husbandry with high fecundity, and available genetic tools have made the zebrfish an excellent model for studying vertebrate interactions with microorganisms. The ex utero embryonic development allows for surface sterilization of the chorion and easy derivation of hundreds of axenic or “germ-free” larval animals at a time,\(^{[58]}\) enabling gnotobiotic experiments on a scale that would be impossible to achieve with mammalian systems. With these large population sizes, it is possible to study the subtle effects of resident microbes on host biology, such as the fine-tuning of intestinal inflammatory tone.\(^{[59–61]}\) Large numbers of germ-free animals can also be used in bioassays for the discovery of novel bacterial effector proteins, such as BefA, which promotes pancreatic β-cell proliferation and AimA,\(^{[62]}\) which reduces intestinal inflammation.\(^{[63]}\) The optical transparency allows visualization of microbial and host cell dynamics in real time during critical process such as intestinal colonization.\(^{[64]}\) Importantly, the larval animal’s small size allows visualization of the entire intestine and quantification of absolute numbers of bacterial residents, providing new insights into parameters that shape population dynamics, such as the forces of gut motility.\(^{[65]}\)

The animal’s small size and large populations also enable explorations of microbiome dynamics at the level of host populations. For example, manipulating host–host interactions through different housing configurations, either in groups or isolation, revealed a profound impact of interhost transmission on the assembly of the intestinal microbiome.\(^{[66]}\) Such co-housing manipulations can also be used to explore the impact of microbes on social behaviors. Because zebrafish are social animals with readily assayed social behaviors,\(^{[67]}\) they provide an attractive model for studying the reciprocal impacts of resident microbes on social behaviors and the impacts of social interactions on microbiome structures.

2.5. Insects as Experimentally Tractable Model Systems to Investigate the Molecular Basis of Animal–Bacterial Interactions

The fruit fly *D. melanogaster* is an exemplary model organism for developmental biology, which has more recently been adopted for studying host–microbe interactions (for an excellent recent review about the use of *Drosophila* in microbiome research see Douglas\(^{[12]}\)). In addition to the wealth of genetic tools available to *Drosophila* researchers, including innumerable transgenic and RNA interference (RNAi) lines, certain features of the fruit fly’s associations with its microorganisms make it amenable to symbiosis studies. First, the communities of bacteria and fungi colonizing the fruit fly intestines in the laboratory and in the wild have been extensively characterized and represent relatively low complexity microbiota of less than a dozen members that are mostly amenable to laboratory culture. Second, the ease with which one can derive axenic or germ-free animals, through surface sterilization of the embryo chorion, has accelerated research with this model.

A prerequisite for symbiosis studies is a clear impact of the members on each other. Germ-free flies exhibit a number of deficits in their intestinal and immune system development and gene expression programs.\(^{[68]}\) One of the most striking phenotypes of *Drosophila* grown in the absence of their associated microbes is the animals’ delayed growth rate: germ-free fruit flies reach the stage of pupation at much later time points than conventionally reared or artificially inoculated counterparts, although these effects can be greatly influenced by nutrient availability. This germ-free growth delay has been exploited by a couple of laboratories to perform what some would consider the holy grail of symbiosis research: forward genetic screens for bacterial traits required for the mutualism. In this case, both groups performed genetic screens in thousands of mono-associated fruit flies looking for transposon-mediated mutations in associated bacteria that rendered them incapable of promoting larval growth and both screens uncovered new bacterial metabolic pathways involved in this process.\(^{[69,70]}\) A limitation of the *Drosophila* model for studying mutualisms is that the gut bacteria studied to date do not establish stable, persistent colonization. Rather they coexist in the fly food and fly gut in equilibrium and if the flies are serially passaged on sterilized food, the bacteria become serially diluted until the flies are essentially sterile. Recently a group studying the microbial ecology of wild flies have identified a persistent gut colonizing bacterium, *Acetobacter thailandicus*.\(^{[71]}\) It will be interesting to see whether this bacterium reveals new facets of symbiosis in *Drosophila*.

In addition, the association between *D. melanogaster* and its endosymbiont *Spiroplasma poulsonii* (*S. poulsonii*), a model system that has been under development over the last ten years, promises to provide insight into the mechanisms underlying endosymbiosis in insects. Most insects harbor bacterial endosymbionts that are vertically transmitted, that is, the microbial partners are incorporated into the egg and the embryogenesis of the host. Depending on the association, the endosymbiotic partners either positively or negatively affect host fitness. The *Drosophila–Spiroplasma* association is the first system in which laboratory culturing and genetic manipulation of both partners have been developed. Among other findings, the study of this symbiosis has already identified the precise mechanisms by which the symbiont is transmitted between generations,\(^{[72]}\) as well as how the symbiont evades the immune system of the host.\(^{[73]}\) Further, the mechanisms by which *S. poulsonii* confer host resistance to parasitoid wasp eggs has been determined.\(^{[74]}\) In addition, the symbiont induces a common host phenotype in insect
endosymbiosis, that is, the killing of male offspring. Genetics on the bacteria symbiont has recently identified the gene responsible for this phenotype and the underlying mechanism by which this gene functions.\(^{[75]}\)

The honey bee is another exciting emerging insect model for host–microbe interaction research (for an excellent recent review see Zheng et al.\(^{[76]}\)). Similar to fruit flies, the honey bees have relatively simple gut bacterial communities that are amenable to culturing. Recently, genetic tools for honey bee bacteria have been developed, including methods for the production of RNAi constructs that target honey bee genes as a strategy for manipulating the host’s biology through symbiotic genetic engineering.\(^{[77]}\) Although lacking the long history of the fruit fly as a genetic model system, the honey bee research field has produced a wealth of knowledge about the biology of this model social insect and commercially important crop pollinator. The microbiota of honey bees has been shown to be important for the animal’s fitness, conferring benefits in development, metabolism, and pathogen resistance. An exciting feature of the honey bee is the possibility of studying the role of microbiota in complex social units such as a hive of workers and queen bee. Interestingly, the hive members have very distinctive gut microbiota, mature queens being dominated by an Alphaproteobacterium enriched in the hypopharyngeal glands of worker bees.\(^{[78]}\) This pattern of microbiota is consistent with the model that worker bees provision the queen with a specialized microbiota, possibly as a strategy to defend this important hive resource from pathogen infection.

2.6. Mining the Species Diversity for Insights into Symbiotic Associations

There are, of course, many other model organisms that provide a unique insight into the origin and function of symbiotic relationships. For example, fungus-growing ants of the genus Atta, form a symbiosis with fungi that they cultivate as the main food source for the colony.\(^{[79]}\) Since in addition to the mutualistic fungus they cultivate for food, fungus-growing ants harbor complex microorganisms,\(^{[80,81]}\) they represent a good model for understanding a multilayered symbiosis. Also, studies in the African turquoise killifish *Nothobranchius furzeri*, one of the shortest lived vertebrate species, revealed that the gut microbiota plays a key role in modulating life span\(^{[82]}\) (see also Finlay et al.\(^{[83]}\) in this issue). Finally, host–microbe interactions using mouse models have a long history,\(^{[84–88]}\) for reviews see Shreiner et al.\(^{[89]}\) and Hugenholtz and de Vos.\(^{[90]}\) Recently, using a closely related wild relative to standard laboratory mouse strains, Rosshart et al.\(^{[91]}\) discovered that the wild mouse gut microbiome not only differed significantly from its laboratory mouse counterpart but, when transferred to and maintained in laboratory mice, also promoted host fitness and improved disease resistance. This finding may promote the discovery of protective mechanisms provided by the natural microbiome and improve the modeling of complex diseases of free-living mammals.

3. Conclusions: Lessons from Models and the Plea for a New Biology

With so many model organisms that can be explored, host–microbe interactions can be analyzed in a diversity of ways. But because there are so many organisms, it can be a real challenge to pick the right one for a particular question and to extract general concepts and rules from comparing different model systems. No single species can ever serve as a universal model; every single species has unique features that will have assets or drawbacks, depending on the question being asked. The models that the community of symbiosis researchers have been developing reveal not only the complexity, but also the ubiquity of such associations. The data continue to accumulate, affirming the idea that the biosphere is truly composed of nested ecosystems of the micro- and macrobiological worlds.

These new findings of the true nature of the biological world come into a complicated intellectual environment. The field of biology has grown enormously over the last several decades, yielding a myriad of phenomenal discoveries. However, its subdisciplines have become increasingly balkanized as they have drilled down into detail. This problem is apparent in the nature of textbooks, the structure of departments and colleges, and even the organization of government funding agencies. Currently, biology is in such strong silos that most biologists have a poor understanding of the relationship of their area to the other areas of the field, i.e., they have no cross-cutting, integrative universal vision. This situation is in sharp contrast to physics and chemistry; these disciplines begin an undergraduate curriculum in the major with a strong unifying set of principles, something that biology could do and should do now. The situation demands a redesign of biology curricula that would integrate microbial biology, as a foundational discipline, into the other fields of biology. It also calls for unprecedented collaboration between macro- and microbiologists, as well as other members of the natural sciences, mathematics, and the social sciences.

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Conflict of Interest

The authors declare no conflict of interest.

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