CellPress

Emerging from the bottleneck: benefits of the comparative approach to modern neuroscience

Eliot A. Brenowitz[1] and Harold H. Zakon[2]

[1] Departments of Psychology and Biology, University of Washington, Seattle, WA 98195, USA
[2] Departments of Neuroscience and Integrative Biology, University of Texas, Austin, TX 78712, USA

Neuroscience has historically exploited a wide diversity of animal taxa. Recently, however, research has focused increasingly on a few model species. This trend has accelerated with the genetic revolution, as genomic sequences and genetic tools became available for a few species, which formed a bottleneck. This coalescence on a small set of model species comes with several costs that are often not considered, especially in the current drive to use mice explicitly as models for human diseases. Comparative studies of strategically chosen non-model species can complement model species research and yield more rigorous studies. As genetic sequences and tools become available for many more species, we are poised to emerge from the bottleneck and once again exploit the rich biological diversity offered by comparative studies.

Biological diversity as a resource for neuroscience

Model species such as the fruit fly (*Drosophila melanogaster*), the nematode 'worm' (*Caenorhabditis. elegans*), zebrafish (*Danio rerio*), the rat (*Rattus rattus*), and, most predominantly, the mouse (*Mus musculus*) have played an important role in biology. A given species may offer particular advantages for the study of a biological process, such as rapid embryonic development, accessible nervous systems, or ease of maintenance in the laboratory. The advantages of model species have become more pronounced with the advent of the genomic revolution. Until recently, sequencing genomes was expensive and laborious, limiting the number of species for which genomic sequences were available. As the database of information for a given model species grows over time, there is an increasing incentive to use that species to investigate topics outside the narrow field of inquiry for which the species was initially chosen. 'Repurposing' of model species, however, can raise concerns – as seen in the ongoing debate about the value of inbred mouse (*M. musculus*) strains as models for understanding human mental disorders [1,2]. While the use of model species has clear practical benefits, adherence to a small number of model systems can limit or even distort the research that is conducted. Neuroscience has a rich history of exploiting a wide diversity of taxa, including mollusks, crustacea, fish, amphibians, birds, and 'exotic' (i.e., non-rodent) mammals, as has been commented on previously [3–5]. We contend that comparative studies of strategically chosen non-model species can complement model species research and address some of the limitations inherent in an over-reliance on a small number of model species. Combining the strengths of a comparative approach with the advantages of model systems will lead to more rigorous research in neuroscience.

Potential limitations of the model species approach

Over the past 20 years or so, neuroscience and much of biology in general has coalesced from the traditional embrace of diverse species down to a small number of model species. There are various practical reasons for this process of concentration. Model species tend to be readily available, easily maintained in captivity, and are feasible to breed in large numbers. As a species becomes a well-established model for a research community, there is an exponential growth in the amount of available information that serves as a platform for future research. With the advent of the genomic revolution, and the ensuing development of powerful molecular tools such as combinatorial systems for gene expression and optogenetics, the incentive to concentrate on a small number of species has become even more pronounced. Conservation of orthologous genes across diverse taxa shows that we can understand much about basic genomic structure and function by studying model species.

The current enthusiasm for a model species approach, however, brings with it several limitations that are too rarely acknowledged. The standard model species represent a vanishingly small percentage of the total biological diversity. As Manger *et al.* [6] wrote: '75% of our research efforts are directed to the rat, mouse and human brain, or 0.0001% of the nervous systems on the planet.' In principle, every species has something to offer to our understanding of and progress in biology. We recognize that it is inefficient and impractical in the current funding climate to devote limited resources to the study of all species that appeal to investigators. Nevertheless, it is important to periodically remind ourselves that this coalescence has brought with it a self-perpetuating myopia and amnesia about the past

Corresponding author: Brenowitz, E.A. (eliotb@uw.edu).
Keywords: model; comparative; mouse; translational.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2015.02.008

contributions of diverse species that jeopardize possible future contributions from what are currently non-model species. This myopia affects choice of research topic and funding decisions, and might cause biologists to miss out on novel discoveries.

The history of biology is replete with examples of novel discoveries emerging serendipitously through study of 'exotic' species. Some famous examples include the discovery of green fluorescent protein in jellyfish [7], conotoxins in cone snails [8], nerve growth factor in chicks [9], GABA in crabs [10], *Taq* polymerase from the bacterium *Thermopilus aquaticus* [11], and channel rhodopsins in algae [12,13]. Each of these discoveries led to profound changes in how we study and understand the brain, but it seems unlikely that the pioneering research behind these discoveries would be funded under the current model species approach. Do we believe that all of the far-reaching discoveries to be mined from biological diversity are already in hand, and that we can therefore afford to focus future efforts on a dwindling number of well-studied model species? Prudence would suggest that we continue to cast the net broadly, understanding that we can never predict where the next transformative discovery might emerge.

Repurposing model species from their initial use can distort research programs and funding priorities. An example is the current effort to develop the mouse as a model for visual neuroscience [14]. Vision in mice, in turn, is seen as an entry point for understanding higher processes including perception, consciousness, and decision-making [15]. There are, however, considerable limitations to the applicability of the mouse visual system [16]. Mice are nocturnal animals that rely far more on tactile and olfactory cues than on vision for orientation. They are estimated to effectively have vision on the order of 20/2000, which qualifies humans as legally blind (Niell in [16]). This poor visual acuity precludes mice from behavioral visual tasks such as facial recognition and object discrimination that are so fundamental to human vision. While the mouse visual cortex contains the same basic neural subtypes as the human visual cortex, the mouse cortex is not organized into different functional areas that are homologous to the human cortex. In addition, the mouse 'visual' cortex also serves other functions, unlike the human visual cortex that is dedicated to vision. Thus, while the mouse visual cortex may provide valuable insights into basic principles of cellular connectivity and computational processing in relation to vision, the mouse should not replace other animal models of vision such as cats and primates. Similar arguments apply in general to repurposing model species to the study of neural processes underlying sensory and behavioral processes for which they are not specialized.

Inbreeding of model species leads to extensive homozygosity and massive loss of genetic diversity. This approach ignores the important role of pleiotropy in gene function [17], and the polygenic regulation of most behaviors [18]. This loss of diversity and elimination of alleles will impact phenotypic molecular, physiological, and anatomical traits. Laboratory species are selectively bred to produce sedentary, obese, non-aggressive animals with reduced predator avoidance behavior, and are reared in conditions that lack normal social cues [18,19]. Chalfin *et al.* showed, for example, that laboratory mice are of limited use as models for studying the genetic basis of naturalistic behaviors and for identifying polygenic social traits that are relevant to mental disorders, compared with wild mice. For these reasons, the study of inbred model species can yield a picture of neural function that differs considerably from that seen in their wild ancestors.

The initial choice of a model species may be largely determined by practical considerations rather than for any particular biological reason. This fortuitous choice may then commit future generations of investigators to asking questions of this species that were never envisaged by the originator of the model. T.H. Morgan chose fruit flies as a model because they are easy to rear and maintain, have a short generation time, and reproduce in large numbers, and not for genetic considerations *per se* (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1933/morgan-article.html).

The tremendous value of *Drosophila* for genetic studies established it as a model species, and this led generations of investigators to use it for research only indirectly or completely unrelated to genetics. Current investigators, for example, use fruit flies to study the neural basis of processes such as visually guided locomotion [20], olfaction [21], and courtship singing [22]. Given the small size of these flies, however, it is technically challenging to directly measure the electrical activity of single neurons from awake, behaving flies [23], but progress on this front has been made using larger non-model fly species such as blowflies [24–26].

Convergence on selected model species often carries an implicit assumption that mechanisms observed in one species are characteristic of all related species. A focus on any single species, however, fails to encompass the diversity of mechanistic adaptations present in even closely related species that differ behaviorally. An example can be seen in the coalescence of studies of the neural basis of song learning on the zebra finch (*Taenopygia guttata*) [27–29]. The zebra finch was initially chosen for practical considerations such as breeding readily in captivity, being widely available as a domesticated species, and having a single stereotyped song that is experimentally tractable (A.P. Arnold, personal communication). This species is now the dominant model used for avian studies of mechanisms of vocal learning, sensorimotor integration underlying song production, auditory encoding of biologically-relevant sounds, and mechanisms of sexual differentiation of brain and behavior ([30] for review). There are ~4000 species of songbirds, however, and there is extensive diversity in various aspects of song learning and production. No single species can capture all of this diversity, but the zebra finch in particular falls at one extreme on many dimensions of interest [31,32]. Coalescence on any single model species runs the risk of losing information on the diversity of neural and molecular mechanisms.

A particularly important limitation of a model system approach arises from the effort to use the lab mouse explicitly as a model for human disease, a concept we refer to as the '*homusculus*'. Given the biomedical orientation of much of neuroscience, coerced by the current translational