The Art and Ethics of Model Selection

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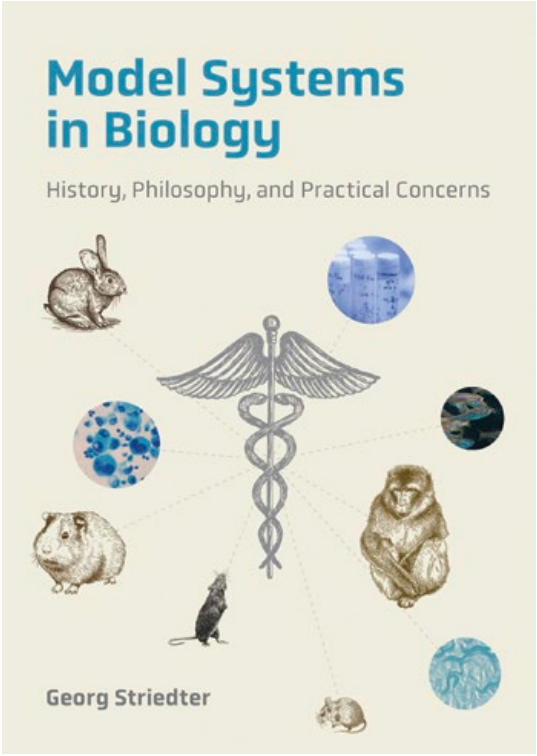

Model Systems in Biology: History, Philosophy, and Practical Concerns
by Georg Striedter. Cambridge, MA: The MIT Press, 2022, 304 pp.

Biomedicine is credited with many achievements, including the increased longevity and enhanced quality of life of those of us fortunate enough to live in the early twenty-first century. In the context of the current pandemic, biomedical advances have facilitated the rapid development of vaccines that have enabled societies to better manage COVID-19. Yet all is not well with biomedicine; there are crises that threaten the field's ongoing success and bring into question some of its past triumphs. Georg Striedter's new book, *Model Systems in Biology*, does a good job of articulating a number of these challenges, particularly around translating animal research to human disease treatments.

Preclinical research carried out on nonhuman animals is intended to assess the safety and effectiveness of new treatments prior to human trials. It may come as a surprise to people unfamiliar with the field, however, that the animal tests often performed in this type of research have proved extremely poor predictors of what will work in humans. A tiny proportion of the drugs that look promising in animal studies holds up when translated into human clinical trials. After investing huge amounts of money and recruiting human participants to research, most potential new drugs are abandoned before they make it to market.

This crisis in translation links to a replicability crisis in biomedicine and science, in which researchers are unable to successfully reproduce the empirical results of earlier studies. Worryingly, even landmark and highly cited studies fall prey to this problem. For example, the ALS Therapy Development Institute retested scores of drug candidates after apparently promising results in animals and found no evidence of benefits, including eight molecules that had progressed to—and disappointed in—human trials.

Striedter devotes the first chapter to establishing the parlous state of biomedical research—its failures in translation, replicability, extrapolation, and generalization—and then spends most of the remainder of the book exploring the reasons behind these failures.

One issue that looms over the book, and which Striedter touches on at various points, is what might be thought

of as a potential crisis in biomedicine's public legitimacy. Although scholars in history and philosophy of science and researchers in the life sciences have been aware of the shortcomings in biomedicine for some time, many of the challenges are not widely appreciated outside the field. The philosophies and methodologies of animal research are implicated in many of these challenges.

Studies on public attitudes toward animal research suggest support for the practice is contingent on the necessity of this research (i.e., that there are no alternatives) and that the suffering of animals is minimized. Translational failures challenge the necessity and value of animal research and call into question whether the suffering of animals involved can be justified. These failures could pose an existential threat to how biomedical research is practiced and funded.

Despite the many problems in translating preclinical animal research to human treatments, the resources involved in animal research are vast: an entire industry supports animal testing for pharmaceutical companies. Governments pour billions of dollars into animal studies every year. Animal research attracts highly skilled scientists, who could arguably be engaged in other, more productive, pursuits. There are also costs for participants enrolled in clinical trials that may end up having little or no therapeutic value; they might otherwise be receiving well established and less risky treatments, or forgo the extra time, procedures, and travel that clinical studies often require.

And beyond the human costs, there are the significant number of animal lives that are impacted and lost as part of this practice. Disappointingly, Striedter falls into predictable patterns when considering the ethics of animal research, reproducing the all-too-familiar caricature of the animal rights position. The view is linked to extremism, with advocates for animal rights apparently unable to distinguish appropriately between a consideration for the interests of human and nonhuman animals; instead, Striedter writes, advocates "tend to believe that animals and humans have roughly the same capacity for suffering and thought." There is the usual charge of inconsistency, that people who argue for animal rights in research supposedly want it both ways: humans and animals are similar enough to deserve the same rights, but so different that scientists cannot gain any knowledge from undertaking research with them.

Further, Striedter makes the allegedly telling comparison between animals used in research and for food. "Compared with the concerns expressed over animal experiments," he writes, "sympathy for animals we use for food is rather limited." The number of animals used in research is, after all, smaller. From this perspective, researchers are unfairly held to a higher standard, while those who raise animals for food get away with their poor practices, including sometimes slaughtering animals in what Striedter calls a "brutal" fashion and without anesthesia.

Like almost all researchers and regulatory bodies, Striedter adopts a consequentialist approach that turns ethics into a kind of calculation. Scientists weigh up the harms to animals compared to the potential benefits to humans, and so long as basic standards of welfare are adhered to and the bulk of animals come from supposedly uncharismatic or pest species, research can continue. Animal use is permissible, and animal lives are expendable, provided some greater human good is at stake.

There are, however, alternate ethical approaches. For instance, looking at how human research is regulated, people generally don't think that it is okay to balance harms to one group against benefits to another, since this conflicts with a basic principle of justice. Other considerations from human research ethics could also be imported to an animal setting, including special protections for vulnerable groups.

The book's lack of sophistication surrounding issues in animal ethics stands in contrast to the nuance and complexity of Striedter's discussion of model selection. The process of model choice—that is, selecting an animal species that can appropriately mimic relevant aspects of a human disease or drug reaction—is complicated. It involves weighing factors such as economic considerations; animal convenience (e.g., availability, housing needs, experimental tractability, size, reproduction rate, and standardization); the supposed higher predictive value of, say, macaques versus roundworms; history and tradition; the popularity of certain models for answering particular questions; researcher training and experience; regulatory requirements (e.g., the lack of regulation of insects); and so on.

It is telling from the kind of considerations outlined here that what might be thought of as strictly scientific reasons are only a part of model selection. This is perhaps why discussion of the reasons for favoring a particular model are not generally aired publicly. "Biologists do occasionally pen thoughtful commentaries or reviews on the pros and cons of various model systems," Striedter writes, "but the vast majority of these papers advocate primarily for the model that the authors themselves are working on. Few are willing to critique the choices of other biologists." While this may seem prudent, the lack of discussion among biomedical researchers themselves is problematic. Opening up this reasoning to explicit consideration is a significant part of the project of *Model Systems in Biology*—a laudable goal indeed, and one which Striedter largely achieves.

The book provides a seemingly helpful checklist of factors for a

researcher to consider when thinking through what model to choose. For example, does the strain of mice proposed become deaf or blind in maturity, limiting its suitability for tests using these modalities? Or if swimming is required as part of spatial memory tasks, rats will likely be preferable over mice. However, it would be difficult in reality to implement such a decisionmaking process. It might appear most promising for relatively junior researchers—Striedter notes he had "young scientists" in mind when writing the book—who don't have entrenched patterns and habits. But given the hierarchy of science, it is unclear that these people always have the autonomy necessary to determine model choices.

And for researchers well established in their practice, many of these choices may effectively be closed off as a consequence of previous decisions to devote time and energy to developing expertise with particular animals in particular institutions. Constraints on space, for instance, mean some facilities that house mice are unable to support comparable numbers of rats, so a researcher cannot simply shift between rodent species. Nonetheless, the book may help these scientists be clearer and more explicit in understanding the factors involved in their research decisions, especially in the context of mentoring the next generation of researchers.

Despite its shortcomings, *Model Systems in Biology* is worth reading. It is an important and timely book that synthesizes a significant body of research across many fields. And it is accessible to nonscientists, meaning it can potentially speak to a broad variety of audiences drawn together by their concerns about biomedical research.

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