

## 1 Model Organisms

### 1.1 Introduction

This Element presents a philosophical exploration of the concept of the ‘model organism’ in contemporary biology. Thinking about model organisms enables us to examine how living organisms have been brought into the laboratory and used to gain a better understanding of biology, and to explore the research practices, commitments, and norms that have made such understanding possible.<sup>1</sup>

We contend that model organisms are key components of a distinctive way of doing research. This way of doing research parallels broader trends in contemporary biology, including moves towards ‘big science’ approaches, particularly in relationship to the large-scale genomic sequencing projects of the 1990s. It also is unique due to its emphasis on projecting data beyond their original domain and establishing their broader applicability, especially to questions relating to human health and disease. We focus on what makes model organisms an important type of model within the contemporary life sciences, and how the use of these models shapes biological knowledge.

The Element is thus centred on six sets of interrelated questions. First, what do model organisms represent? How does this role compare to others that organisms play in biological research, and in particular how does it relate to non-representational functions of model organisms (such as their use as tools for intervention)? Second, how do model organisms represent, and how do processes of idealisation and abstraction contribute to and warrant the use of such organisms? Third, for whom do they represent? What is the relationship between such organisms and the experimental contexts within which they are utilised? How do the epistemic structures and shared scientific practices within the communities of scientists focused on these organisms influence the ways in which research is conducted and how these organisms are understood? Fourth, why are model organisms accepted as credible representations of biological phenomena? When and why are arguments about projectability of data and other results well founded? Fifth, in what sense can model organisms be thought of as a scientific model? How is knowledge created using these models, and how do the representational and interventionist roles of these models intersect? Finally, what is likely to be the legacy of these models, and what scientific roles are they likely to play in the future?

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<sup>1</sup> For a systematic analysis of the role of commitments and modelling in achieving scientific understanding, see Leonelli (2009).

## 1.2 What Are Model Organisms?

Particularly since the advent of large-scale genomic sequencing associated with the international Human Genome Project (HGP), the term ‘model organism’ has become ubiquitous in contemporary biological discourse. It is difficult to trace the precise point in history at which the actual term was introduced. Use of aspects of the underlying concept can be traced back within organism-based research programmes, particularly in the 1960s and 1970s, in part due to the rise of the techniques associated with molecular biology. Formalisation of the terminology occurred in the 1990s via the HGP which, in turn, resulted in increased numbers of publications associated with certain organisms (Dietrich, Chen, & Ankeny 2014). In the most general terms, model organisms are non-human species that are extensively studied in order to understand a range of biological phenomena. The hope is that data and theories generated through use of the model will be applicable to other organisms, particularly those that are in some way more complex than the original model, especially humans. The most widely acknowledged inventory of these organisms includes those officially recognised by the US National Institutes of Health (NIH 1999) as model organisms for biomedical research, which ultimately listed thirteen species, including mouse (*Mus musculus*), rat (*Rattus norvegicus*), zebrafish (*Danio rerio*), fruit fly (*Drosophila melanogaster*), nematode (*Caenorhabditis elegans*), baker’s yeast (*Saccharomyces cerevisiae*), and thale cress (*Arabidopsis thaliana*).<sup>2</sup>

Much biological research aims at extrapolating knowledge beyond the organisms that are actually being studied. The study of an individual specimen is taken to provide understanding about all other members of the same species. Further, it is often expected that the study of a single species will provide biological insights into many other species, though this type of claim is necessarily contingent and requires empirical justification in any particular case. This idea is grounded in evolutionary theory, according to which all life forms are related through a common evolutionary history and thus share a smaller or greater amount of genetic make-up and a number of developmental features. Evolutionary or phylogenetic conservation can be both genomic and also developmental and mechanistic (Love & Trevisano 2013). It is therefore used to justify the treatment of an organism as a sample of a larger class of organisms that are phylogenetically related to that species and hence display significant

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<sup>2</sup> We generally provide both common and scientific names for organisms, but also use genus only, for instance when a range of species within a genus is being studied, and genus only or common names with reference to the usual designator associated for a particular community of researchers (e.g., the worm or the *Arabidopsis* community), or otherwise where more appropriate.

morphological, structural, developmental, or other types of similarities with it (Weber 2005). As a consequence, a model organism can represent other species: we discuss precisely how this representational role works in more detail in Section 2.

Model organisms have a variety of well-recognised experimental and pragmatic advantages. For instance, they are typically easy to breed and maintain in large numbers under laboratory conditions. Model organism research characteristically involves the standardisation of the organism in question and the accumulation of knowledge and resources on the organism on a large scale. These resources include relevant networks, organism-focused conferences, stock centres, and cyberinfrastructures. Such research is done with a view to creating a platform for interdisciplinary integration across biological disciplines and a reference point for comparative research across species. Many features of model organisms are thus the result of human interventions, including domestication. One of their main functions is to support scientific and technological interactions with the biological world. Indeed, a well-recognised characteristic of model organisms is their usefulness as tools for biological intervention, for example when they are employed to investigate and test techniques for genetic modification or phenotypic imaging.

In this Element, we contend that the representational and interventionist roles of model organisms are deeply linked. Even in situations where model organisms are used primarily as tools to intervene in the biological world, the representational commitments associated with this type of modelling (which we discuss subsequently) persist and underpin their use in research practices. In other words, we argue that there can be no adoption of hybridisation probes or gene-mapping techniques developed on model organisms without also making the representational commitments involved in using those organisms as models. These commitments have thus become entrenched in biology in ways that are often difficult to challenge, despite novel findings that draw the representativeness of model organisms into question, such as gene–environment interactions.

### 1.3 The Significance of a Label

The term ‘model organism’ has come to serve not only as a descriptor for organisms used in biological research that have certain attributes but also as a label with prescriptive power. Large amounts of attention and funding were poured into model organism–related research in the 1980–2010s, with the HGP sequencing efforts providing a crucial incentive and rallying point for the need to focus on a limited number of species. Partly as a consequence of such investments, model organisms have played the role of reference point or

touchstone for a wide variety of research questions and approaches to biological practice (Ankeny & Leonelli 2011). Some critics have argued that the model organism concept is ‘swamping out’ contemporary biological research agendas, particularly in terms of funding, making it difficult to pursue biological research on organisms not considered to be official ‘model organisms’ and to use techniques and methods that do not include or prioritise molecular approaches (Bolker 1995; Davies 2007), although empirical data on publication patterns do not tend to support these claims (Dietrich, Chen, & Ankeny 2014). Others have criticised what they have termed ‘organismism’, namely over-reliance on model organisms without sufficient attention to whether particular organism-based models are adequate (Robert 2008).

Given the significance of the label, questions about whether and in what sense a particular experimental organism is a ‘model organism’ require explorations that go beyond abstract philosophical analyses or laboratory boundaries; answers to these questions have clear epistemic, social, political, and economic implications with regard to how science is conducted and how knowledge is constructed. Hence, we provide a philosophical examination of the model organism concept that is grounded in the extensive body of previous scholarly work on relevant contemporary and historic scientific practices in the biological and biomedical sciences (for a detailed historiographic overview of this literature, see Ankeny & Leonelli 2018). This analysis makes a critical contribution to the literature on the philosophy of biology and has important implications for the conduct of contemporary science, including how we understand the underlying epistemic structures and scientific practices relating to this type of research.

#### 1.4 Grounding Philosophy in the Study of Research Practices

This Element identifies and analyses philosophical issues associated with the concept of a ‘model organism’ against the backdrop of in-depth empirical study of the history of these organisms within biology and the practices within the fields associated with this type of research (although we do not develop any detailed historical accounts about particular organisms in this context). We therefore intertwine descriptive and normative analysis of scientific practices in developing and presenting our account. This approach is necessary because understanding how model organisms work as scientific models involves understanding how scientists use them in their everyday work and reasoning practices, and how those uses and associated arguments have changed over time.

This type of scientific practice cannot be documented using published articles alone, which typically provide a line of reasoning and a set of conclusions

without reporting all of the processes through which these were developed. Given the limits of published literature for analysing how organisms are actually used, it was essential for our account that we develop and utilise a range of rich descriptive materials using techniques from history and the social sciences. In this Element, we rely on previously published scholarly literature, archival material, scientific records (such as grant applications and institutional records), and grey literature (such as newsletters, reports, guidelines, ‘how-to’ documents released by stock centres, and databases). We also carried out interviews with researchers and others involved in scientific practice. These included administrators and technicians from various labs, at different career stages, from diverse fields, and working in different geographic locations. Additionally, we made ethnographic visits to observe practices in laboratories, field sites, funding institutions, scientific conferences, and other settings.<sup>3</sup> Finally, we draw on our long-term collaborations with practising scientists through common projects and publications, membership of expert working groups, and advisory positions in steering committees and stock centres relating to model organism biology. These activities have increased our exposure to laboratory life both at the policy and organisational level – through the perspectives of relevant funders, learned societies, and institutions – and at the level of researchers’ own interests and strategies, including the constraints and impediments that they face.

This philosophical study of model organisms thus exemplifies the value and importance of fostering collaboration between humanists and scientists, as well as constructive dialogues across subfields that focus on the contemporary life sciences within the history and philosophy of science (HPS) and science and technology studies (STS). Understanding how an organism can function as a scientific model means delving into questions concerning the value, epistemic pay-offs, and skills involved in manipulating a physical object (rather than a mathematical construct or a simulation). It also requires reflection on ways that the relationships between researchers and organisms, which include familiarity and affect, may shape biological understanding and resulting knowledge. Equally critical are the roles played by instruments, techniques, institutions, and infrastructures organised around the organism in channelling and entrenching particular ways of doing research. Finally, it is important to consider the extent

<sup>3</sup> For some of the archived materials on which this Element draws, see the Zenodo data collection ‘Exeter Data Studies’ (<https://zenodo.org/communities/datastudies>) which includes interview materials with researchers who work on *Arabidopsis* and various types of yeast; the Bermuda Principles data archive which includes interviews relating to the model organism projects within the Human Genome Project, housed within the DukeSpace Archival Collections, Center for Public Genomics Research Files (<https://dukespace.lib.duke.edu/dspace/handle/10161/7407>); and the Organisms and Us website at <https://arts.adelaide.edu.au/organisms-and-us/>.

to which historically rooted commitments and social dynamics contribute to the development, use, and interpretation of these models. Far from a matter of logical reconstruction informed solely by the study of scientific publications, elucidating the epistemic role of model organisms within biology requires situating these research components in their material, social, and historical contexts.

## 2 What Do Model Organisms Represent?

### 2.1 Introduction

Model organisms help to create knowledge that can be projected beyond the immediate domain in which it was produced. We argue that this projection happens simultaneously in two respects: in terms of the range of organisms being represented (what we call ‘representational scope’) and the type of phenomena that model organisms are used to study (‘representational target’). We then consider the implications of this claim for understanding the representational power of model organisms as scientific models and comparing it to other ways in which organisms are used and interpreted within research. This account emphasises the characteristics associated with model organisms that are necessary to ground their abilities to serve as models (but does not yet address the question of what makes a *good* model, which we confront in Section 5). These characteristics are simultaneously biological and epistemic, and are shared by all model organisms to a greater or lesser extent.

### 2.2 Representational Scope

Why do biologists study fruit flies, worms, or mice, when they are actually interested in humans or biological processes in general? Some species may well be of interest to biologists in and of themselves. But when specific organisms are selected and studied as model organisms, researchers are typically claiming that they will provide some information or understanding about forms of life beyond the original focal organism. We use the term ‘representational scope’ to describe how extensively the results of research conducted on a group of specimens (tokens) can be projected onto a wider group of organisms labelled through reference to a type (e.g., a taxonomic class), a classic form of the problem of induction. The projection can vary from a single species for which the organism is serving as a proxy (notably humans) to a wider class of organisms such as a family or a kingdom (say all mammals or animals), or perhaps even to all organisms, if a process or phenomenon is thought to be universal or common. The extent of representational scope assumed by researchers is often related to the criteria for the selection of the organism in

the first instance, together with the particular context of use and the questions or processes to be investigated. This concept is a critical epistemological feature that shapes which organisms are selected as a research focus and how they are developed for research.

The representational scope of an experimental organism can be very narrow and extend only to its own species or those that are closely related: for instance, red-eared terrapins are used to study turtle shell development (Maher 2009) and tamar wallabies are used as a model for reproduction and development in kangaroos, and marsupials more generally (Hickford, Frankenberg, & Renfree 2009). Researchers may hope that the study of these organisms reveals something about behaviour or physiology that is generalisable. However, this outcome is rarely attained, particularly for research that does not rely on previous empirical evidence about evolutionary or phylogenetic conservation.

By contrast, model organism research programmes share an underlying interpretation of the representational scope of their organisms; the assumed or hypothesised representational scope is broader and more inclusive in the case of model organisms than the representational scope assigned to other experimental organisms. It is common for the results of *D. melanogaster* genetics or *C. elegans* physiology, for example, to be interpreted as applying to a much wider range of organisms, often including humans. Even in the cases of *A. thaliana* and *S. cerevisiae*, findings have been projected well beyond the realm of plants and fungi respectively.

Model organisms serve as the basis for articulating processes that are thought to be common across all (or most) other types of organisms, particularly those processes whose molecular bases can be articulated. Hence, it is often claimed that processes in model organisms are representative of processes shared by higher level organisms, especially humans: in other words, ‘the fish is a frog . . . is a chicken . . . is a mouse’ (Kimmel 1989, as paraphrased in Grunwald & Eisen 2002, 721). The most common sense in which these organisms are ‘representative’ relates to their use in the HGP and, in most cases, as models which provide the basis for biomedical research. Model organisms thus lie at one extreme of the spectrum associated with representational scope, namely being associated with a high degree of generalisability.

### 2.3 Representational Target

Another sense in which findings from research on organisms can be generalised is the number and type of phenomena to which organisms allow experimental access. What are being studied using model organisms? We utilise the term ‘representational target’ to indicate the collection of phenomena that are to be

explored through the use of an organism. By ‘phenomena’, we refer to the labels used by researchers to define concepts, entities, and processes related to their research interests. Whether understood as observable or unobservable, deeply theory-laden, or ‘mirroring’ reality in an objective way, phenomena constitute for us the object of scientific claims. Thus, anything from ‘metabolism’ to a ‘hox gene’ constitutes a phenomenon and can become the representational target (cf. Meunier 2012).

What is epistemologically distinct about model organisms is their representational target: they serve as models for a relatively wide range of systems and processes that occur in living organisms, including those studied within genetics, development, physiology, evolution, and ecology. This approach allows pursuit of one key goal associated with this type of research: to perform large-scale, comparative work across species, integrating a range of disciplinary research approaches. This goal is achieved using a specific strategy, initially gathering resources and building infrastructure on individual whole organisms, and integrating a range of disciplinary approaches, followed by work on comparisons between these organisms using the model organism as a reference point. For example, a number of homologous genes have been identified across a range of model organisms. Researchers conceptualise identification of these homologs as a key step in producing knowledge about the molecular basis of phenotypes across very different types of organisms, and particularly of variations associated with disease (e.g., the gene *BRCA1*, which is associated with human breast cancer and whose homolog has been found in variant forms in *C. elegans* and *M. musculus*).

Another example of the fruits of such a research strategy can be found in the elucidation of the mechanisms associated with programmed cell death, which is a regulated process that generally confers some sort of advantage during an organism’s life cycle. Using the nematode worm *C. elegans*, researchers identified key genes regulating the processes of cell death in this organism (for a summary, see Wood et al. 1988). It was subsequently shown that corresponding homologous genes exist in higher species, including human beings, and that the basic morphological and biochemical features of programmed cell death are conserved in both the plant and animal kingdoms. In these sorts of research programmes, understanding molecular and developmental processes in the model organism is the initial focus of research which then serves as a building block or platform (e.g., *C. elegans* Sequencing Consortium 1998) for a more general investigation of developmental processes together with molecular and other processes across a much wider range of organisms.



What, then, distinguishes model organisms from the general class of experimental organisms in terms of their targets? The difference does not lie solely in the capacity of these organisms to support human interventions or in their use as tools in research practice; all experimental organisms are, to a greater or lesser extent, used as scaffolds for developing techniques for the control and manipulation of biological processes. Rather, what defines model organisms as a specific subclass of experimental organisms is the representational power attributed to them. This representational power is in turn grounded in the specific modes of intervention and standardisation used to establish and develop these organisms over the past few decades.

Model organisms explicitly represent whole organisms; they simultaneously allow access to specific processes and are investigated using a range of disciplinary approaches with the intention of integrating these approaches to develop a multi-level understanding of their evolution, structures, and behaviours. In contrast, experimental organisms are models for specific phenomena, to be investigated through a particular discipline or approach with its accompanying set of techniques and practices. Thus, experimental organisms need not be as versatile as model organisms in order to be useful and successful for particular types of research. For instance, even if it would be extremely difficult to study dogs in genetic terms due to their relatively large genome size and long generation times, these limitations make them no less valuable for the study of behaviour or disease.

We should note that while mechanisms are clearly an important target for many explanations derived from research with model organisms, and biologists place high value on elucidating mechanisms as an epistemic goal, we do not view mechanistic reasoning as the only type of reasoning associated with model organism research. Precisely due to the emphasis on multi-level integration, causal-mechanistic approaches are combined with mathematical models and simulations of dynamic processes both within and beyond the cellular scale (e.g., intercellular transport and protein folding: see O'Malley et al. 2014). Moreover, understandings of gene functions have benefitted from increasingly data-intensive analysis of the correlations between metabolic and gene expression profiling and phenotypic differences across specimens, which may well underpin causal reasoning but do not necessarily involve the formalisation of mechanisms or even a molecular gene concept (Waters 2013). Since we do not take mechanistic reasoning as the sole goal or the primary means of model organism research, we will not delve here into related philosophical debates on causal reasoning and reductionism, which have been well covered in the existing philosophical literature (for a summary, see Brigandt & Love 2017).

## 2.4 What Is Represented: The Whole Organism *and* Other Organisms

In our view, the distinctive representational power of model organisms stems from the simultaneous attribution of wide representational scope and wide representational target. They are at the same time models of (many) higher organisms, thus instantiating properties common to many other species, *and* models of the complex interrelations of processes and entities that occur in and make a whole organism, thus instantiating the interdependencies and links between different biological phenomena and diverse levels of analysis.

By contrast, consider Jessica Bolker's account (2009), which distinguishes two types of animal models: what she calls 'exemplars' (or 'proxies'), which are examples of a larger group such as a taxon or other more extensive groups, and 'surrogates', which are substitutes for another entity of special interest, particularly humans in the biomedical sciences. She stresses that when researchers take elucidation of shared fundamental patterns as their aim, organisms are used as exemplary models; this type of goal would be present in most model organism work, and most often occurs in 'basic' research (in our view, any stark, principled distinction between 'basic' and 'applied' or even 'translational' research is difficult to maintain, but detailed discussion of this issue is not necessary for our current purposes). In contrast, Bolker maintains that organisms used as surrogates are substituted for what would be the ideal target (in many cases humans) for ethical or pragmatic reasons, but that those using such models do not necessarily seek to understand underlying biological processes or mechanisms since this is not necessarily required to develop applications such as medical treatments and therapies.

This way of distinguishing the functions served by various animal models does not apply cleanly to model organisms, even though it may initially appear that Bolker's categories can be directly mapped onto our distinction between representational scope and representational target. Her notion of a 'surrogate model' exemplifies a very specific type of representational target (one that has a clear translational role and is most commonly associated to biomedical research on rodents, as we discuss in 4.6), and one that simultaneously implies a limited representational scope. Taking a wider spectrum of model organisms into account, and particularly the common features characterising thale cress (*A. thaliana*), fruit fly (*D. melanogaster*), nematode (*C. elegans*), baker's yeast (*S. cerevisiae*), and zebrafish (*D. rerio*), we contend instead that both the target and the scope of model organisms are typically broad, and that focus on projecting results across a wide range of species does not diminish researchers' interest in targets including molecular, developmental, and evolutionary