“The Model Organism is Dead - Long Live the Model Organism”

Patrick S.L. Lim, 2018

I. Introduction

The last century of biological research has been intimately acquainted with a small selection of species commonly referred to as ‘model organisms’. These are particular non-human organisms that have been, for various reasons, designated as archetypal systems for the study of biological processes. For example, they may be able to grow very quickly or display characteristics that simplify experimental observation. Humans lack many of these traits and are relatively difficult to work with; thus, model organisms have become an essential feature of experimental biology.

Despite their legacy, the status of model organisms as experimental staples may be declining. In recent years, technological innovations and widening possibilities for research design have highlighted many shortcomings of model organisms. The sequencing and analysis of understudied species have unleashed remarkable biodiversity, exposing the usefulness of ‘non-model’ systems. Moreover, researchers are compensating for the limitations of physical experimentation through computer modelling and a ‘systems’ view of biology.

In this essay, I will first consider model organisms from a historical perspective, reflecting on their significance in early genetic experiments and modern biological research. Second, in light of technological advances, I will evaluate whether scientists have fallen victim to convention and inertia in continuing to use model organisms. Finally, I will look to the future and envision what a ‘death’ of the model organism would mean for scientists and discuss the implications for biological inquiry as a whole.

II. History of the Model Organism

For more than 2,400 years, humans have observed life around them in order to investigate biological phenomena. The ancient Greeks were perhaps the first to seriously consider what the study of animals could teach us about the nature of all living things. For instance, Aristotle's "On the Parts of Animals" circa 350 B.C.E attempted to describe the 'common elements' of various creatures (Peck and Forster, 1969). Likewise, early anatomical knowledge was derived from the monkey dissections of Galen of Pergamon (Nutton, 2009). Experiments on the guinea pig refined the relationship between disease in humans and

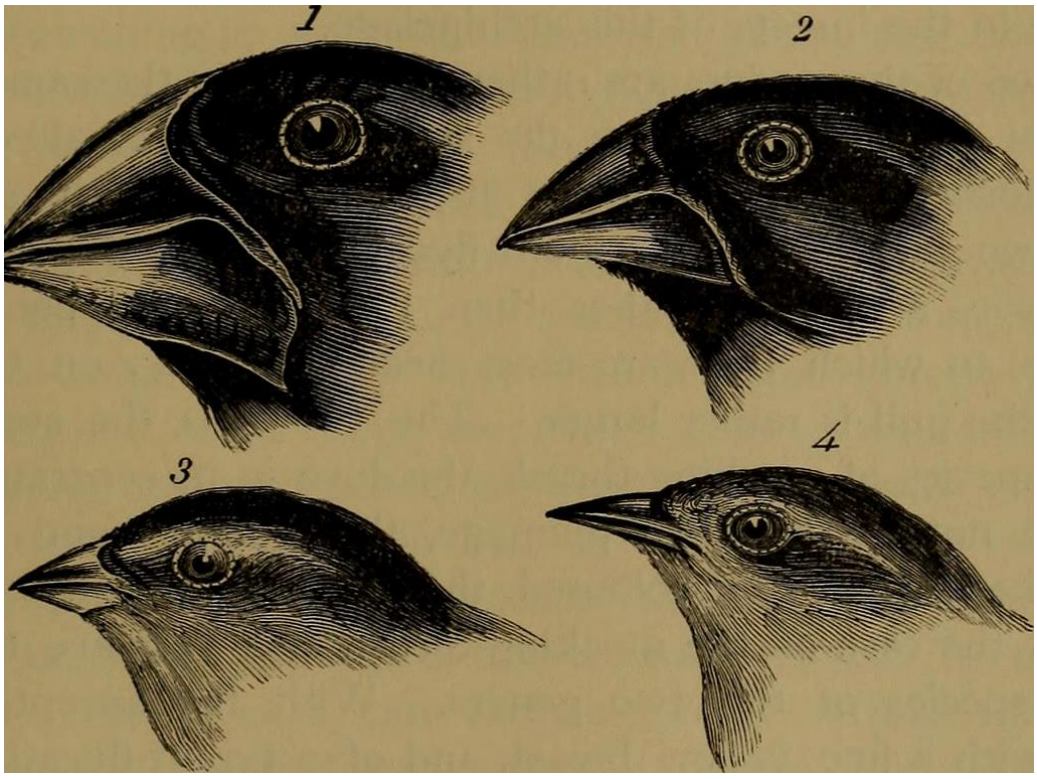

Figure 1. Darwin's Finches. Birds that lived on different islands of the Galápagos archipelago had impressive diversity of beak structure. Charles Darwin would later note the significance of this observation in support of his theory of species transmutation (Darwin, 1890).

animals, leading to acceptance of germ theory (Bynum, 1990). In the nineteenth century, Darwin's descriptions of birds of the Galápagos islands played an important role in his theory

of evolution (Fig. 1) (Lack, 1947). Furthermore, without experimenting with garden peas, the 'father of genetics', Gregor Mendel, would not have discovered his famed laws of inheritance (Suzuki and Griffiths, 1976). Indeed, throughout history, the observation of various organisms has been fundamental to the study of life.

A key distinction, however, between the likes of Darwin or Mendel and the ancient disciplines of anatomy and botany, is that the former were beginning to engage in more active hypothesis-driven experimentation, rather than the descriptive observational methods of their predecessors. This, in part, was driven by the remarkable explanatory power of biological ideas that emerged in the eighteenth- and nineteenth-century. There were now overarching concepts like cell *theory* and *principles* of inheritance—testable assumptions that scientists could work under and elaborate on (Mayr, 1982). This led to a growing appreciation of the generalizations that could be derived from the deliberate manipulation of plants and animals. Following the turn of the twentieth century, scientists became accustomed to asserting that the genetic mechanisms they were discovering could be broadly applicable to all of life—or at least, at the level of a particular taxon. In 1929, the Danish physiologist, August Krogh, remarked on this phenomenon, observing that 'For a large number of problems, there will be some animal of choice, or a few such animals on which it can most conveniently be studied,' (Krogh, 1929). Biology was becoming an organism-oriented science; by the 1940s, geneticists found themselves predominantly working on just three model organisms: corn, mouse or the fruit fly, *Drosophila* (Davis, 2004).

III. The (Coming of) Age of the Model Organism

The major biological findings of the twentieth century were borne on the backs of model organisms. The quick regeneration times and ready availability of *Drosophila*, and bacterium, *Escherichia coli*, facilitated the discovery of principles of heredity, transcription,

translation, and DNA replication—among other central genetic mechanisms (Beckingham et al., 2007; von Hippel, 1998). Similarly, budding yeast, *S. cerevisiae*, was excellent for

Figure 2. Model Organisms from the 'Age of Molecular Biology'. Top left: *Caenorhabditis elegans* (Brenner, 2009). Top right: *Danio rerio* (zebrafish) *(*Grunwald and Eisen, 2002). Bottom: *Arabidopsis thaliana* (Meinke et al., 1998).

functional genetic studies of human genes, possessing many conserved human cellular processes while retaining the manipulability of a microbe (Barnett, 2007). In the latter half of the twentieth century, the rise of molecular biology and sophisticated cloning techniques accompanied the emergence of new model organisms. *C. elegans*, zebrafish, and *Arabidopsis*, for example, found their respective niches in fields of nervous system development, and vertebrate and plant developmental biology (Fig. 2) (Brenner, 2009; Grunwald and Eisen, 2002; Meinke et al., 1998). Experimental success in one or more fields of research was a propelling force for maturation of these species from 'model system' to

'model organism' status. However, this often came at the expense of the development of 'non-model' organisms, which, at least in genetics or molecular biology, were essentially ignored or left behind.

Survival of the Foremost

Success of one species as a 'model organism' over another can be thought to occur in two stages: firstly, selection as an appropriate model for one or several research programmes, and second, its establishment in the scientific community. In general, the initial choice of which organism to use was a question of convenience, tractability, and—depending on the need for functional biological extrapolation—phylogenetic position. Establishment as a

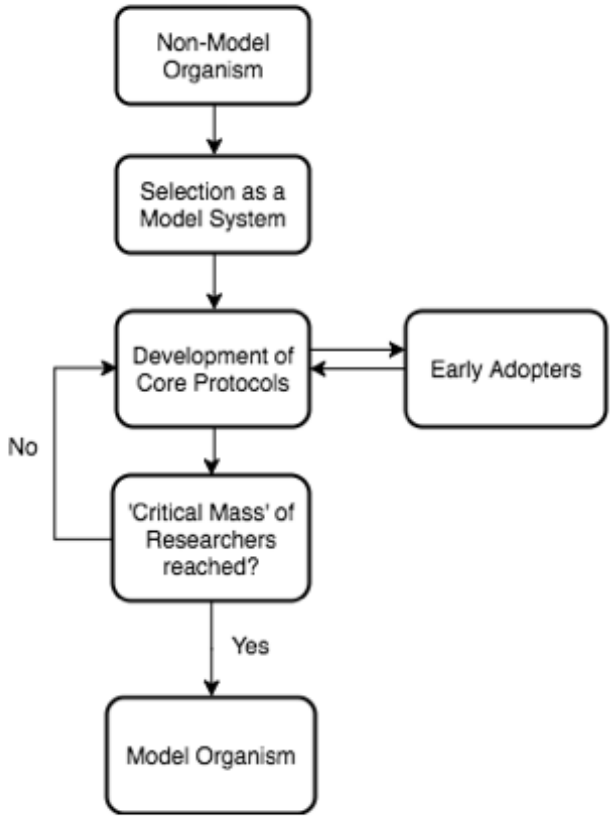

Figure 3. Stages of Model Organism Development. Prior to establishment of a species as a model organism, there must be experimental advantages of the organism in question so as to warrant its use as a model system for a research group or program. Establishment of experimental and technical protocols soon follow, attracting a founding group of researchers. Typically, upon reaching a 'critical mass' of researchers, development of resources and 'know-how' of the organism accelerates its popularity, leading to the establishment of the former experimental system as a new 'model organism' (Müller and Grossniklaus, 2010).

‘model organism’, however, could be attributed largely to inertia; if the development of core protocols for a particular species attracts enough researchers, an eventual amassing of knowledge will, in a similar way, further reduce technical barriers to using the organism in question—ultimately resulting in wide-scale adoption (Fig. 3) (Müller and Grossniklaus, 2010). Furthermore, instead of experimenting with new organisms, scientists often appropriate existing model organisms to other fields of biology. For instance, prior to its contribution to understanding body plan pattern formation, *Drosophila* was known primarily as a model system for studying heredity (Beckingham et al., 2007).

In the absence of immediately favourable alternatives—as in the case of mouse replacing the slower-breeding guinea pig—once ‘domesticated’, model organisms become indispensable and almost monopolize the research programmes that involve them (Crow, 2002). Nevertheless, it was not until the late 1980s, that the phrase, ‘model organism’, had begun to creep into scientific literature—but by this time, model organisms were already embedded in the scientific life of biologists (Ankeny and Leonelli, 2011).

IV. Fall of the Model Organism

Despite the profound contributions that model organisms have made to biological research, we must nonetheless concede a somewhat ironic consequence: as we learn more about life and thereby better understand model organisms, so do we become attuned to the limitations of our efforts. Staunch reliance on model organisms has revealed some potentially grave shortcomings of experimental biology. In this section, I will first propose that scientists may be overestimating the representative ability of popular organisms. I will also describe potential consequences that this misrepresentation may have on biomedical research outcomes. Finally, in light of the many disadvantages of model organisms, I will discuss whether their continued use in modern biology is justified.

What are Model Organisms Modelling?

Researchers have long recognized that the biodiversity represented by model organisms is exceedingly sparse (Russell et al., 2017). There are currently over 1.6 million extant species listed by 'The Catalogue of Life: 2017 Annual Review', and an estimated 100 million yet to be discovered eukaryotes inhabiting the earth—taking prokaryotic life into account, this figure is likely greater by several orders of magnitudes (Species 2000 and ITIS, 2017; Costello et al., 2011). With this perspective in mind, the focus on the ten or so organisms that dominate modern research raises scrutiny for the claim of generalisation that model organisms enjoy, particularly as the establishment of many of these organisms was largely due to convenience. The African clawed frog, *Xenopus laevis*, for example, was previously used in laboratories for pregnancy testing before it was selected as a model for developmental biology (Warkman and Krieg, 2007).

Furthermore, the versions of model organisms in use today are not necessarily wholly representative of their species themselves. For example, the omnipresent K-12 lab strain of *E.*

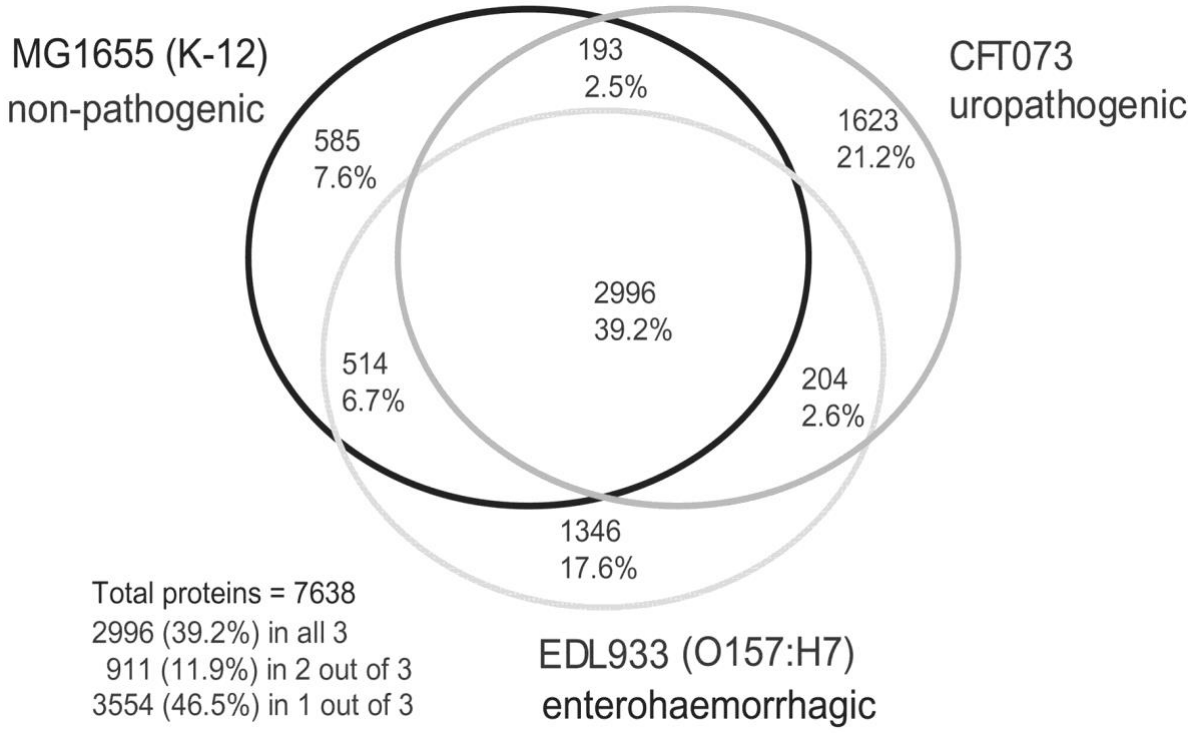

Figure 4. Comparison of Three Uropathogenic Strains of *E. coli.* Two pathogenic strains of *E. coli*, CFT073 and EDL933, were compared with MG1655 (K-12), a non-pathogenic lab strain. Strikingly, the two pathogenic strains were about as different from each other as they were with the non-pathogenic lab strain, K-12. Only 39.2% of proteins were common to all three strains (Welch et al., 2002)..

coli is very different from the ancestral *E. coli* first isolated from a diphtheria patient in 1922 (Bachmann, 1996). One comparative genomic study found remarkable genomic diversity between different '*E. coli'* strains, revealing that conserved *E. coli* 'core' genes appeared to be only a fraction of the total *E. coli* genome (Fig. 4) (Welch et al., 2002). Moreover, modern studies have confirmed that laboratory strains undergo substantial phenotypic and genotypic divergence after repeated subculture (Woods et al., 2006). Similarly, lab strains of *S. cerevisiae* seem to have elevated evolutionary rates relative to wild strains (Gu et al., 2005). Inter-strain variability calls into question the reliability of any single set of data. This is particularly evident in mice, where different strains can significantly affect phenotype. For instance, gene targeting experiments found that EGFR null-mutations had strikingly different effects depending on whether a C57BL/6 or 129/Sv background was used (Sibilia and Wagner, 1995).

Lost in Translation

In the biomedical sciences, animal models are used extensively to mimic disease initiation and progression in humans, as well as in drug development. Thus, overestimating the representative ability of model organisms can have unfortunate implications for biomedical outcomes. The logic that model organisms are 'good enough' for use as model systems is perhaps overextended when applied here, especially as enormous sums of money are spent on a 'frustratingly few clinical advances' (Bolker, 2012, p. 32). In general, the success rate of clinical trials in humans is very low; for instance, fewer than 8% of clinical cancer trials succeed following successful research conducted in animal models (Mak et al, 2014). Furthermore, genome-wide association studies have shown that many diseases are imposingly complex, which is reflected in the limited triumph of animal models for cancer and Alzheimer's. In cancer immunotherapy mouse studies, the failure of the majority of replication attempts in humans is proof of this sobering reality (Ostrand-Rosenburg, 2004).

Similarly, in neurobiological diseases, ‘mouse model results have seemed nearly useless’; for example, major clinical trials found that three drugs that performed well in mice were almost completely ineffective in thousands of human patients with Alzheimer’s disease (Schnabel, 2008).

Are Model Organisms Still Useful?

Clearly, an unexamined loyalty to model organisms can have serious consequences. Yet, it cannot be denied that for most of scientific history, this faithfulness has been well rewarded: model organisms have been sufficient for the fundamental discoveries in molecular biology. Moreover, the model organism tradition may have advantages beyond simply a means to collect data. Research communities that revolve around model organisms provide much in the way of collaboration between investigators, giving rise to the extensive creation and sharing of databases, DNA libraries, and optimization of protocols—among other important resources. As a result, researchers eventually develop ‘a feeling for the organism’—a phrase used by maize geneticist, Barbara McClintock, to describe the general understanding of how particular organisms function as a system (Keller, 1983). When researchers begin to operate under organism ‘infrastructures’, ‘fundamental epistemic changes’ occur—including a more explicit ‘collaborative ethos’ in the pursuit of a holistic overview of model organisms (Leonelli and Ankeny, 2012, p.35). For example, large-scale datasets from *S. cerevisiae* research have been central in providing the gene-centric networks used in predictive biology efforts (Wang and Marcotte, 2010). Arguably, the collective focus on a few model organisms is indispensable for projects of this magnitude. Model organisms may serve to encourage a culture of standardisation and concentration of activity that ultimately aids the larger majority of researchers.

Nevertheless, indirect research benefits notwithstanding, there is thinning justification for the continued everyday use of popular model organisms. For individual scientists, model organisms are considered the most efficient use of available resources—the preferences of funding bodies regularly pressure researchers away from less 'battle-tested' organisms (Maher, 2009). In the current era of genomics, however, this argument is no longer as convincing. Experimenting with new model systems is becoming much cheaper. The costs of sequencing are plummeting and genome-editing technologies such as CRISPR-CAS9 are broadly accessible and easy to use (Buermans and Den Dunnen, 2014; Chen et al, 2014). Moreover, discovery of Yamanaka factors and improvements in culturing of embryonic stem cells have restored experimental utility of neglected species such as rats (Hamanaka et al, 2011).

For all their flaws, model organisms are still used steadfastly by scientists. However, there is no indication that the problems I have described thus far will diminish over time. At least superficially, now that the fundamentals of cells, genes and proteins are well-characterised, biologists are moving towards the more enticing problems of human biology and disease (Fields and Johnson, 2005). Eventually, the limitations of model organisms must be reconciled if current levels of scientific progress are to be maintained.

V. Future of the Model Organism: A Paradigm Shift?

Model organisms are more than just experimental tools. They are firmly entrenched in the tradition and habits of scientists. As such, Thomas Kuhn's theory of scientific revolutions may provide a framework for predicting the future of biological research (Kuhn, 1970). Kuhn postulated that when limitations to a current research 'paradigm' become unsustainable, old scientific assumptions are abandoned to make way for new ones. Although Kuhn was describing an overturning of scientific 'laws' rather than methods of experimentation, an

analogy with model organisms still stands. The model organism paradigm of the twentieth century may be long overdue for an upheaval, technological progress and the mounting complexity of biological questions have opened new avenues for experimental design (Fig. 5). In this final section, I will speculate as to what may replace model organisms in the future and the consequences that this might have for researchers.

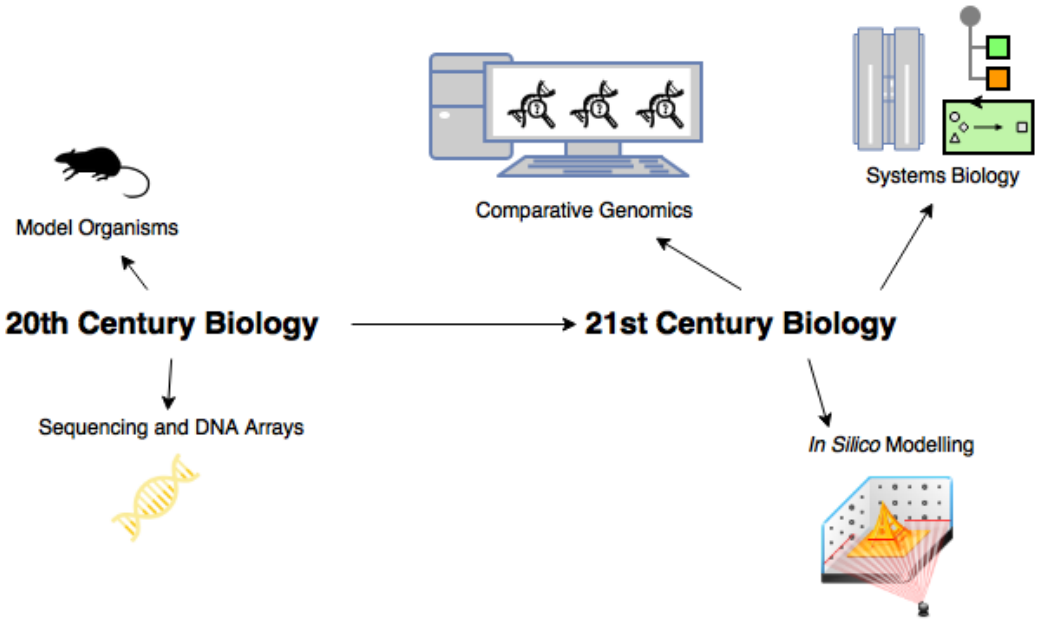

Figure 5. Shifting Experimental Approaches in Biological Research. The twentieth century in biology follows a traditionally 'reductionist' approach, where direct interrogation of model organisms and data from individual experiments are used to study living systems. In contrast, twenty-first century biology exploits high-throughput technology and information processing to study organisms in a more 'integrative' manner, in which organisms treated as complex systems rather than an assembly of components (Palsson, 2000).

The awareness that model organisms are poor representative models may inspire scientists to study organisms straight from their natural habitats. Improvements in efficient genome modification may allow the desirable traits of model organisms to be bestowed *ad hoc* upon non-model or wild organisms. Biologists of the future will be able to select from a much wider range of experimental systems, further obscuring the notion of what makes an organism 'model'. Admittedly, ethical and practical concerns prevent us from applying a similar logic to humans. However, alternatives such as 'microdosing'—exposing human subjects to minute quantities of a drug—provide reliable extrapolation to therapeutic doses, as suggested by a growing body of evidence (Burt et al, 2016). Moreover, microfluidics has

enormous potential for simulating micro-biological environments; devices such as 'organs-on-a-chip' are able to mimic *in vivo* function and may even be combined to form a complete 'human-on-a-chip' (Sackmann et al, 2014; Mehta and Powale, 2013). In his 'Essay on Man', Alexander Pope wrote, 'presume not God to scan; The proper study of mankind is man.' (Pope, 1879). For the biomedical sciences at least, it appears that the English poet's words are gaining significance.

Ultimately, the shortcomings of model organisms perhaps demonstrate the inadequacy of a reductionist approach to biology—an opinion shared by a growing number of researchers (Regenmortel, 2004). Model organisms are not effective at dealing with the increasingly complex questions posed by modern biology. In addition to translational biomedical research, fields within developmental biology, such as eco-devo—which pertains to

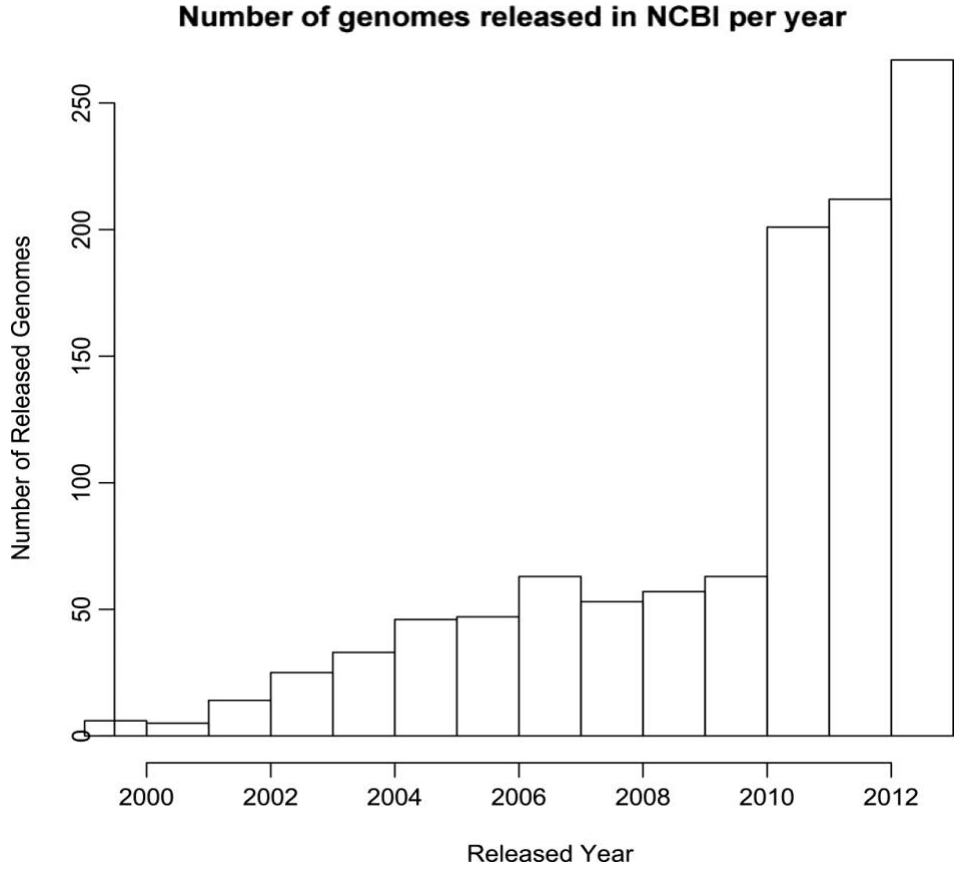

Figure 6. Number of Genomes Published by NCBI From 2000-2012 (Tagu et al, 2014).

environmental effects on phenotype—are not suitably explored by working with individual organisms (Bolker, 2012). In response, viewing organisms as integrated rather than isolated life processes, as exemplified by the field of systems biology, may be a more useful approach to answering biological questions. Disciplines such as comparative genomics are growing in popularity (Davis, 2004). Studying model organisms may become a way to ascertain points of reference from which to compare features of species, rather than as data points in and of themselves.

Furthermore, high-throughput technologies are generating an enormous amount of data; the number of sequenced genomes is growing considerably (Fig. 6) (Tagu et al, 2014). Many important discoveries have resulted from sequence analysis of non-model species; for instance, the platyfish genome has generated a theory for behavioural complexity in fish (Schartl et al, 2013). The sophistication of networks of cellular behaviour is improving via proteomics and information from yeast two-hybrid systems. With the advent of *in silico* experimentation and analysis, it is conceivable that powerful mathematical simulations will one day bypass the need for human or animal subjects altogether (Palsson, 2000).

Regardless of how biologists carry out research in the future, a decreased reliance on model organisms will encourage researchers to broadly interrogate a greater diversity of life. Forays into understudied organisms have already proved invaluable. Premier transposon systems such as Sleeping Beauty and piggyBac used in genetic engineering have been derived from salmon and moth species respectively, not mention the ground-breaking CRISPR-CAS9 system isolated from *S. pyogenes* (Xu, 2016; Chen et al, 2014). A potential treasure trove of insight may be unlocked if scientists relinquish their preoccupation with model organisms in favour of studying ‘life’ more generally—in all its permutations.

VI. Conclusion

In this essay, I have followed the rise of model organisms, challenged their primacy in biology, and argued that future biologists may opt to approach their research differently, taking into account an ever-expanding experimental toolkit. Technical advances are liberating the practical constraints that made model organisms indispensable for more than a century of experimental research. But although the 'model organism' *paradigm* may be dying, for the foreseeable future, it is unlikely that the much-loved models themselves are in danger of obsolescence. Experimental organisms still reign supreme for elaborating on basic genetic mechanisms and gene and protein interactions, as well as for the validation of new technologies (Fields and Johnson, 2005). The accessibility and legacy of popular models will ensure they live on in laboratories, despite forecasts of impending technological or computational revolution. As the famous maxim goes, 'if it ain't broke, don't fix it'.

In any case, model organisms have been a shrewd departure from the millennia of descriptive biology that preceded post-Mendelian research. Poignantly, the biological enterprise may return to its humble beginnings as the next generation of researchers, liberated from the confines of model organisms, once again endeavor to explore the extraordinary diversity of life around them.

References

Ankeny, R.A. and Leonelli, S., 2011. What's so special about model organisms? Studies in History and Philosophy of Science, 42(2), pp.313-323.

Bachmann, B.J., 1996. Derivations and genotypes of some mutant derivatives of Escherichia coli K-12. Escherichia coli and Salmonella: cellular and molecular biology. ASM Press, pp.2460-2488.

Beckingham, K.M., Armstrong, J.D., Texada, M.J., Munjaal, R. and Baker, D.A., 2007. Drosophila melanogaster-the model organism of choice for the complex biology of multi-cellular organisms. Gravitational and Space Research, 18(2).

Barnett, J.A., 2007. A history of research on yeasts: foundations of yeast genetics. Yeast, 24(10), pp.799-845.

Brenner, S., 1974. The genetics of Caenorhabditis elegans. Genetics, 77(1), pp.71-94.

Bolker, J., 2012. Model organisms: There's more to life than rats and flies. Nature, 491(7422), pp.31-33.

Buermans, H.P.J. and Den Dunnen, J.T., 2014. Next generation sequencing technology: advances and applications. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1842(10), pp.1932-1941.

Burt, T., Yoshida, K., Lappin, G., Vuong, L., John, C. et al., 2016. Microdosing and other phase 0 clinical trials: facilitating translation in drug development. Clinical and translational science, 9(2), pp.74-88.

Bynum, W.F., 1990. "C'est un malade": Animal Models and Concepts of Human Diseases. Journal of the history of medicine and allied sciences, 45(3), p.397.

Chen, L., Tang, L., Xiang, H., Jin, L., Li, Q. et al., 2014. Advances in genome editing technology and its promising application in evolutionary and ecological studies. Gigascience, 3(1), p.24.

Crow, J.F., 2002. CC Little, cancer and inbred mice. Genetics, 161(4), pp.1357-1361.

Costello, M.J., Wilson, S. and Houlding, B., 2011. Predicting total global species richness using rates of species description and estimates of taxonomic effort. Systematic Biology, 61(5), pp.871-883.

Darwin, C., 1890. Journal of researches into the natural history etc. Thomas Nelson, London

Grunwald, D.J. and Eisen, J.S., 2002. Headwaters of the zebrafish—emergence of a new model vertebrate. Nature reviews genetics, 3(9), pp.717-724.

Davis, R.H., 2004. The age of model organisms. Nature Reviews Genetics, 5(1), pp.69-76.

Fields, S. and Johnston, M., 2005. Whither model organism research?. Science, 307(5717), pp.1885-1886.

Gu, Z., David, L., Petrov, D., Jones, T., Davis, R.W. et al., 2005. Elevated evolutionary rates in the laboratory strain of Saccharomyces cerevisiae. Proceedings of the National Academy of Sciences of the United States of America, 102(4), pp.1092-1097.

Hamanaka, S., Yamaguchi, T., Kobayashi, T., Kato-Itoh, M., Yamazaki, S. et al., 2011. Generation of germline-competent rat induced pluripotent stem cells. PloS one, 6(7), p.e22008.

Keller, E.F., 1983. A Feeling for the Organism: The life and work of Barbara McClintock. Times Books, New York.

Krogh, A., 1929. The Progress of Physiology, The American Journal of Physiology, 90(2) pp. 243-251

Kuhn, T.S., 1970. The Structure of Scientific Revolutions. University of Chicago Press, Chicago.

Lack, D., 1947. Darwin's Finches. CUP Archive, Cambridge.

Leonelli, S. and Ankeny, R.A., 2012. Re-thinking organisms: The impact of databases on model organism biology. Studies in History and Philosophy of Science, 43(1), pp.29-36.

Mak, I.W., Evaniew, N. and Ghert, M., 2014. Lost in translation: animal models and clinical trials in cancer treatment. American journal of translational research, 6(2), p.114

Maher, B., 2009. Biology's next top model? Nature, 458, pp.695–698.

Mayr, E., 1982. The growth of biological thought: Diversity, evolution, and inheritance. Harvard University Press, Boston

Mehta, S. and Powale, K., 2013. Organ-on-A-Chip. The Bombay Technologist, 62, pp.44-53.

Meinke, D.W., Cherry, J.M., Dean, C., Rounsley, S.D. and Koornneef, M., 1998. Arabidopsis thaliana: a model plant for genome analysis. Science, 282(5389), pp.662-682.

Müller, B. and Grossniklaus, U., 2010. Model organisms—a historical perspective. Journal of Proteomics, 73(11), pp.2054-2063.

Ostrand-Rosenberg, S., 2004. Animal models of tumor immunity, immunotherapy and cancer vaccines. Current opinion in immunology, 16(2), pp.143-150.

Palsson, B., 2000. The challenges of in silico biology. Nature biotechnology, 18(11), p.1147.

Peck, A.L. and Forster, E.S., 1968. Aristotle: Parts of Animals, Movement of Animals, Progression of Animals, HUP, Boston.

Pope, A., 1879. Essay on man. Clarendon Press, London.

Russell, J.J., Theriot, J.A., Sood, P., Marshall, W.F., Landweber, L.F. et al., 2017. Non-model model organisms. BMC biology, 15(1), p.55.

Sackmann, E.K., Fulton, A.L. and Beebe, D.J., 2014. The present and future role of microfluidics in biomedical research. Nature, 507(7491), pp.181-189.

Schnabel, J., 2008. Neuroscience: standard model. Nature News, 454(7205), pp.682-685.

Schartl, M., Walter, R.B., Shen, Y., Garcia, T., Catchen, J. et al., 2013. The genome of the platyfish, Xiphophorus maculatus, provides insights into evolutionary adaptation and several complex traits. Nature genetics, 45(5), pp.567-572.

Sibilia, M. and Wagner, E.F., 1995. Strain-dependent epithelial defects in mice lacking the EGF receptor. Science, 269(5221), pp.234-238.

Shapiro, H.L., 1956. "Galen of Pergamon.". Scientific American, 195(1), pp.130-132.

Species 2000 and ITIS. 2017. Catalogue of Life, 2017 Annual Checklist. Retrieved 31.12.2017 from www.catalogueoflife.org/annual-checklist/2017.

Suzuki, D.T. and Griffiths, A.J., 1976. An introduction to genetic analysis. W.H. Freeman and Company, San Francisco.

Tagu, D., Colbourne, J.K. and Nègre, N., 2014. Genomic data integration for ecological and evolutionary traits in non-model organisms. BMC genomics, 15(1), p.490.

von Hippel, P.H., 1998. An integrated model of the transcription complex in elongation, termination, and editing. Science, 281(5377), pp.660-665.

Wang, P.I. and Marcotte, E.M., 2010. It's the machine that matters: predicting gene function and phenotype from protein networks. Journal of proteomics, 73(11), pp.2277-2289.

Warkman, A.S. and Krieg, P.A., 2007, February. Xenopus as a model system for vertebrate heart development. Seminars in cell & developmental biology,18(1), pp. 46-53.

Welch, R.A., Burland, V., Plunkett, G.I.I.I., Redford, P., Roesch, P. et al., 2002. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic Escherichia coli. Proceedings of the National Academy of Sciences, 99(26), pp.17020-17024.

Woods, R., Schneider, D., Winkworth, C.L., Riley, M.A. and Lenski, R.E., 2006. Tests of parallel molecular evolution in a long-term experiment with Escherichia coli. Proceedings of the National Academy of Sciences, 103(24), pp.9107-9112.

Xu, T., 2016. Sleeping Beauty: Piggyback Transposable Elements in Mammals. Annual Review of Genetics, 50(1).