Big Biolog Podcast Transcript

Ep 87: Life in the lab, are model organisms an asset or impediment to biology? (with Sabina Leonelli and Rachel Ankeny)

SPEAKERS

Rachel Ankeny, Art Woods, Marty Martin, Sabina Leonelli

Marty Martin 00:08

Welcome to season five of Big Biology.

Art Woods 00:10

We are so excited to be back and we have so many fantastic guests coming this season.

Marty Martin 00:15

Unfortunately, you'll still have to endure Art and me while listening to those excellent guests,

Art Woods 00:20

But we promise to slip in fewer dad jokes and to stop picking on at least some kinds of research.

Marty Martin 00:25

Yeah, not really!

Art Woods 00:26

This season, you'll hear episodes on debunking pseudoscience,

Marty Martin 00:28

The origins of life,

Art Woods 00:30

Deep ocean creatures,

Marty Martin 00:31

The third way of evolution,

Art Woods 00:33

And something called keystone genes, coming up soon.

Marty Martin 00:36

Today on the show, we talk about model organisms. Model organisms have been central to the last 50 or so years of biology, particularly to biomedicine.

Art Woods 00:44

These species,

Marty Martin 00:45

Including fruit flies, thale cress, a nematode called C. elegans, a Sacchromyces yeast, little white mice, and a few others, Have been the focus of almost all molecular and cellular research in the last 50 years, largely because they are physically small, reproduce fast and are easy to keep in captivity. Around the time of the Human Genome Project, the study of these organisms really experienced an explosion of interest. In the US, the National Institutes of Health and the National Science Foundation started identifying model organisms as taxa that were particularly tractable genetically.

Art Woods 01:16

In many ways, research on this small subset of species has been insightful. It's led to improvements in cost reductions in genome sequencing of all species, including the non model organisms that so many biologists study today.

Marty Martin 01:29

Work on model organisms also has led to many technical innovations such as CRISPR modifications of genomes, and has supported the rise of biotech companies, personnel and infrastructure.

Art Woods 01:38

It's also earned its moniker. Model organism work did in fact reveal commonalities among many life forms on Earth. One example is the HOX genes that play important roles in laying out the body plans of animals.

Marty Martin 01:50

Today on the show, we talked with two philosophers of biology, Sabina Leonelli, and Rachel Ankeny, about model organisms then, and now.

Art Woods 01:57

Rachel is a professor in the School of Humanities at the University of Adelaide and Sabina is a professor and director of the Exeter Center for the Study of Life Sciences at the University of Exeter.

Marty Martin 02:07

In 2020, they published a book in the Cambridge Elements philosophy of biology series, entitled,

Art Woods 02:12

Surprisingly,

Marty Martin 02:13

Model Organisms. This book though, was just one of the many contributions they made on the topic.

Art Woods 02:17

In 2011, for instance, they defined model organisms as quote, non human species that are extensively studied in order to understand a range of biological phenomenon, with hope that data and theories generated through the use of the models will be applicable to other organisms, particularly those that are in some way more complex than the original model.

Marty Martin 02:37

This definition has become broadly accepted in biology, but it wasn't the first to propose that some species can be studied in order to understand others

Art Woods 02:45

Take Danish physiologist August Krogh's idea which has become known as the Krogh principle. He said for any biological process, there is an organism best suited to study it.

Marty Martin 02:55

For instance, if we want to understand oxygen uptake through the skin, we don't study grey foxes or flamingos because that's not how they breathe.

Art Woods 03:03

We of course study a species that takes up oxygen through the skin because it's only there that we'll find something interesting and new.

Marty Martin 03:10

In cases like these, the process was the thing to be modeled. Contrast that to the modern approach, which assumes that a genetic model organism is a model in most any sense one wants to use it. Genetic, but also physiological and behavioral.

Art Woods 03:24

During the molecular revolution that started in the 1950s, Krogh's and others perspectives on model organisms were gradually replaced by explicitly genetic perspectives.

Marty Martin 03:34

Genetic tractability started to crowd out physiological and morphological and behavioral suitability, perhaps because so many biologists came to view genes as life whisperers.

Art Woods 03:43

Or maybe just the more utilitarian realization that molecular approaches led to so many stunning breakthroughs.

Marty Martin 03:49

However, and this is where my frustration creeps in, there's a lot of important stuff that the long term focus on genetic model organisms have missed. Take the favorite species of most medical researchers, the lab mouse. For mice, we've learned a lot about components of the immune system, such as the major histocompatibility complex, T cell receptors and the regulatory mechanics of antibody synthesis.

Art Woods 04:12

But overall, and even though we're both mammals separated by perhaps 80 million years of evolutionary time, mice are pretty poor models of humans, especially when it comes to understanding disease.

Marty Martin 04:23

First off, the original reason mice were used as models was to reveal the genetic basis of cancer. And right out of the gate, there were problems, because most mouse tumors tend to originate in an altogether different tissue layer than human tumors.

Art Woods 04:37

And that's just the tip of the iceberg. Our bodies are roughly 2500 times larger than mouse bodies.

Marty Martin 04:42

And this size difference means their metabolic rates are seven times greater per gram body mass than ours.

Art Woods 04:49

They mature super rapidly and have very large litters, whereas human females rarely give birth to more than two babies at a time.

Marty Martin 04:56

We and they are omnivorous, so our diets are somewhat similar, but they also possess intestinal cecae which gives them both a distinct form of digestion and a distinct gut microbiota.

Art Woods 05:06

And finally, mice rely much more on hearing, smell, and touch than we do. In fact, we're largely a visual species. But quality of vision in a,

Marty Martin 05:15

Nocturnal,

Art Woods 05:16

Mouse is equivalent to 20 over 2000 for humans, which qualifies them as legally blind.

Marty Martin 05:23

There's no question that model organisms have and will be important contributors to biology. But we worry that studying them because they're

genetically tractable risks missing major insight offered by organisms living in their natural context.

Art Woods 05:36

As you will know if you've listened to us in the past, phenotypic plasticity is powerful and pervasive in nature, but rarely does work on genetic model organisms account for this.

Marty Martin 05:45

In fact, many model organisms were originally chosen because they are comparatively less plastic than other species, or at least they were assumed to be.

Art Woods 05:52

Critically, too, there have been so many important discoveries in non model organisms that we must keep studying them too.

Marty Martin 05:59

Green fluorescent protein in jellyfish, conotoxins in cone snails, taq polymerase in the bacterium Thermus aquaticus, and channel rhodopsins in algae.

Art Woods 06:07

If we continue to direct so much attention to a few lab bred species, we miss a lot of what biology has to tell us.

Marty Martin 06:13

Organisms are just not machines, as we discussed with Dan Nicholson on a previous show, and genes are but one causal force in the phenotypic diversity we see in nature.

Art Woods 06:22

On today's show with Rachel and Sabina, we discuss the history of the model organism idea,

Marty Martin 06:27

We take a counterfactual detour through what biology might look like today without it,

Art Woods 06:31

And we look into the future of biology on model organisms.

Marty Martin 06:35

I'm Marty Martin.

Art Woods 06:36

And I'm Art Woods,

Marty Martin 06:37

and this is Big Biology season five.

Art Woods 06:41

Welcome back.

Marty Martin 06:51

Rachel and Sabina, thank you so much for coming on the show today, we're really grateful that you agreed to join us and that we can even make this work given that we're in very different parts of the world as we record this. Our chat today is going to be based largely on this really neat book that you had out in Cambridge Elements in the philosophy of biology series entitled model organisms. We're gonna hit some other things through the conversation. But let's start, let's start with that. Sabina, can you tell us what a model organism is?

Sabina Leonelli 07:19

A model organism, we think, is a particular type of experimental organism. So experimental organisms, one may say all of them are types of models, one way or the other. If we think that a model is something that stands for something else that is used to represent something as they want to study, right? So we can agree that to some extent, every time we use an organism in a lab for experimental purposes, then we are dealing with some form of modeling one way or the other. But model organisms, we think, are a particular type of model that has emerged basically, in concomitants, with the rise of genetic sequencing, which has two characteristics really, first of all, it's not just a trying to stand for, say, another set of organisms, a particular group of species, or maybe for humans, but in fact, it's supposed to represent a very wide range of other species. So what we are calling it scope, the scope of that representation is very, very broad. The other characteristic is that the phenomena so the questions that you want to ask, and you want to learn something about biologically, from

studying that model, also tend to be very wide ranging. And so it's not just a case of using an organism to try and answer that particular question. Or to look specifically at questions that come into one domain, say, you know, neurology or developmental biology or physiology. But it's a case of using one organism as a sort of integrated multi level model, where you can look at lots of different questions that may apply to many, many different organisms all at the same time. The value of the model organism is exactly that, that allows you to integrate knowledge that comes from different aspects of it's biology, in addition to one type of organism, one form of life.

Marty Martin 09:15

So I guess, it's hard not to dive deep into this very quickly. But can we can we use some examples here? I think for that latter part of what model organisms are meant to be, like in the case of many model organisms, they are in fact used as models of humans, right? Because so as we'll get to so much of it, model organism use is in biomedical research, right? So really, they are models of humans, maybe others, but definitely models of humans. But what about an example of the second part? What's the kind of thing that is this general phenomenon or general function that models are typically used for?

Rachel Ankeny 09:54

I mean, I'm happy to try. I think the other thing I want to do is just step back a little bit further and even just make one other distinction, which is what Sabina just presented, is sort of the philosophical analysis. But when we think about model organisms, we are also thinking about, you know, in real life, what happened historically. And there was this moment that was very, very important in the human genome projects where there was a process of sort of appointing or anointing certain organisms as model organisms, precisely because they fulfill this sort of role. So our analysis is a conceptual analysis, not what could have been the case, or might have been the case, but of what actually happened historically. Right? So are you using that as a really important spinning off point? Now that spin off point in the Human Genome Project, say in the 1990s, isn't without context in the sense that, you know, before that, as we've talked about, in our book, there's lots of other investigators and biologists who are articulating kind of the components of what makes this kind of biology work well. But in some way, you know, the idea of a model organisms becomes crystallized in that moment of the Human Genome Project, right. And so that's where we get organisms such as mouse rat, C. elegans, the nematode fruit fly, arabidopsis eventually comes into the picture as a model plant. And all of those are really good examples of what is meant by that some of them fulfill that role better or worse. And there were various things on that list that proved to be not very good at what we were just talking about. And so chicken, you know, was initially on there, and it just didn't prove very practical. So I think what's meant by this sort of integrated approach is, is that it's not a question of choosing an

organism and using it, because it's good for one set of questions, you know, so we know that aplysiais is very good for certain sorts of neurobiological work, C. elegans was thought to be iand proved to be not only fairly easy to sequence, fairly easy to start to understand gene function, but you could observe development, you could simultaneously do all sorts of neurobiological kinds of experiments with it. So it had both the quality of being simple enough to be tractable, and simple in terms of its genetics, you could look at cell division in real time, etc, etc. I'm sure your listeners know about this. But it also proved to have a heavy degree of applicability beyond itself, it didn't have real canalised and narrow patterns of, of sequence of gene function or anything else may have proved to be able to be projected from its own domain into other domains. And so, you know, in some way, this is where, in part, we get the gene for kind of talk, right, that we know that there's certain patterns of sequence that allow us and that proved to be conserved across, you know, many different types of organisms.

Art Woods 12:48

That's great. I want to just dwell for a minute on this idea that this word you used earlier said, you know, scope. So you know, I think people are thinking of particular model organisms as having some scope for other species. And sometimes that includes humans, and maybe sometimes not, but like, How broad is that scope? And how reasonable is it to say some things are within the scope, and some things are not, you know, if we had to take an example, like mouse, you know, we're separated from mice by like, 90 million years. And we're clearly within their scope in the sense that they're mammals. And we're mammals, and we share a lot of sort of commonalities, but we also share a lot of differences. So how do you how do you define that scope?

Sabina Leonelli 13:28

So I think that it's very important here to keep in mind that we're looking at a very pragmatic use of the model. Right? And that's partly, I think, part of the tensions that emerge around the notion of model organisms, the fact that people who defend these model organisms think that Well, ultimately, it's just one way we have just one means to try and think in an integrated way around biology. And then once we achieve it for one species, then hopefully we can achieve it for others, if we can kind of expand the comparative work that people that think well, actually, by restricting the focus to this one species, what you're in fact doing is disqualifying the whole of biodiversity and that is free when trying to generalize right. So I think if we take it this pragmatic sense, the scope is, however far you can stretch the findings you do have at any one point in time, or model organisms, and use it almost as a provocation to see whether those particular fundings could extend as far as humans or other types of organisms. And in fact, maybe even easier to think about this done in relation to mice and rats, which are so iconically used as models for humans and biomedicine. Think

about arabidopsis as a model for plants, right? So theoretically, that's, you know, the model plant is supposed to be able to represent all plant forms of life, which of course is itself an incredibly potentially problematic claim. This is a flowering plant is a weed is a very particular type of biology, to which extent can you really make those assumptions but in fact The scope of that model organism has gone well further, is being taken many of the discoveries made on arabidopsis In terms of, for instance, circadian rhythms or particular types of cell division or a cell communication and signaling. Those have been, in fact extended to animals and all the way sometimes even to humans. And then the question becomes, are these assumptions assumptions should be taken as indeed almost provocative claims that is then up to a new generation of researchers in all these different domains working with other types of systems to prove or disprove or to extend? Or is this a completely unwarranted use of an organism as a model for things that, in fact, we cannot really obviously confirm to be within the scope of that representation?

Rachel Ankeny 15:48

But I think I mean, part of the question, I think, is, is there a metric for scope, right. And I think I mean, the claim is that this is a continuum. And model organisms tend to lie at one end of it. But when model organisms were initially used, in any case, historically, including when they started to be used in the context of the Human Genome Project, scope was a promissory claim, right, that's yet to be shown, there was lots of assumptions when many of these organisms were initially used by various labs or various groups about, for example, the degree of conservation without necessarily having a huge amount of data available, a lot of the claims about conservation values date well, before you were actually able to accurately measure them. So scope, in many ways comes to be proven. But model organisms tend to have evidence when they're selected, that they are going to be at this one end of the continuum of having broad scope. And that's something that then plays out in time. And in many ways, some of the ones that didn't work out precisely were because they had processes or particularly genetic processes that were in some way unusual or difficult study or whatever else. And so both, they didn't have as broad scope, as was hoped. And they also weren't able to even investigate that promissory note about what the scope might be.

Art Woods 17:04

So it sounds like you're saying there's been maybe a process of sorting so that some things with narrow scopes have been discarded. The things with the broader scopes that have been more successful at illuminating processes across many taxa are the ones that are persisted.

Rachel Ankeny 17:16

Have persisted kind of more broadly, and at the sort of more quantitative level. But I mean, I think another thing to bring in here is we're interested in model organisms, because we find the reasoning that underlies and fascinating. And when I say that underlies the practices, the very diverse practices that people use, but that's not to say they're the only or the best way to do biology by far, right. And the second thing is, although there is this claim about them being, you know, dominant, there's also lots of evidence, and we've produced this in, in various research articles, that multiple types of organisms persist in many domains as experimental organisms in their own right. And so I do think the dominance of model organism talk is quite overblown. I think if you look at the evidence, it's not the case. And the evidence would be everything from, you know, the sheer numerical hits on how many articles are published in a given year in a given field, but also even the amount of funding that is given to other things. So I think there was a moment where there was a deep fear that everything was going to need to be studied in these canonical model organisms, the ones that the NIH, in many ways appointed through the human genome project process, but that moment disappeared quickly, and didn't necessarily dominate in certain fields and disciplines. So obviously, genomics, genetics, model organisms were extremely popular, particularly in that period of time. But in other fields, you know, there was very quick recognition, they weren't going to allow study of the main focus or the main kind of research question, if you want to go extreme. Think about something like ecology and field based ecology. Well, model organisms are in direct conflict with that way of doing biology, it doesn't make any sense. But even you know, things like developmental biology, depending on processes you want to study, if you're interested in the variant, rather than the typical, well model organisms were not going to be a good way in at first.

Art Woods 19:15

So Thomas Hunt Morgan, let's talk about Thomas Hunt Morgan, he's back in the early 1900s, establishing Drosophila as an very early model species, although he may not have thought of it in those terms. But what did he do and what happened at that time that sort of launched flies as the thing?

Rachel Ankeny 19:32

So he's known as the fly guy, right. But as most people also know, he, he worked on a huge diversity, particularly marine organisms. And I think, you know, that often is overlooked and the logic behind that is often overlooked. And that's, you know, part of what we're thinking about when we're thinking about model organisms is also all the range of experimental organisms and and what they're good for. You know, it's gotten better in maybe the last 10 or 15 years. But I do think there was a period in which the dominance of the model organisms, perhaps was needed at that point in time in order to make certain kinds of goals possible. But that there's been a sort of return to comparative and that was the

sort of thing that that Morgan would advocate. And so I think things like needing to use a model organism in order to get a grant, which may or may not be true, but a lot of biologists think it's the case are the sorts of things that would be very problematic. I think, also, you know, Morgan was was extremely keen on making his people group around, or the people that he worked with group around something and work together and all that sort of thing. I think that does happen in a lot of communities associated with particular organisms. But I also think there is attending to things off the shelf a little bit. And that wasn't at all kind of what Morgan meant by standardizing and using something as a as an experimental or even as a model organism.

Sabina Leonelli 20:57

And he probably would find fascinating to think, what it takes to take the model that he tried to set up in the lab and scale it up. So there's not just one lab, two labs, three labs, but it's hundreds of labs around the world trying to work together. And because then the investment on what are the infrastructures you need to use what are the standards you need to use becomes enormous, you go from spending six months on a newsletter to actually spending years or setting up all these different infrastructures. And of course, that the level of off the shelf services you need to offer to be able to build that community and to get people to talk to each other is really high. And that then becomes very different is a completely is a quantitative shift, that becomes a real qualitative difference in how you think about work in the lab.

Art Woods 21:46

So it sounds almost like you're saying that, you know, he said in, in motion, this process of using particular species as model organisms, and particular fruit flies, but that it was also about sort of developing a model or a style of how to do science with with larger groups of people. Would you say he was a real innovator that way?

Rachel Ankeny 22:05

Absolutely. I mean, I think I wouldn't pin the using a model organism, certainly solely on him, right. So you've got lots of other parallel developments with mice, for example, and the jack's lab and CC little, you've even got people like Claude Bernard long before him who talk in this way. I also think, and we can talk about this in more detail. But Sabina and I both agree that sort of model organism, as we know, it today, really, is fairly modern conception, you know, it dates much later. But I at least would say there's no doubt that the sort of structures of collaboration that gets set up, and what's sometimes called the ecosystem, and Robert Cole is the one who's really written about this, the historian of science, the ecosystem that exists in the mouse room, you know, the labs that Morgan is attached to Columbia, is really unprecedented, that kind of way of doing work.

But also things like, you know, how they, how they choose it, why they choose it, a lot of the narratives that we have around choice and use come from that historical setting.

Sabina Leonelli 23:04

Yeah. And I think novel ideas around what does it mean to communicate, not just the results of scientific work, but methods, procedures, techniques, ways of annotating even, and we already mentioned the newsletter that lab put together to try and bring say, the community of people working on fruit flies in communication with each other. That was a really innovative take on how do we not just communicate formally through the exchange of papers that detail results that we had claims that we want to make on the basis of the evidence, but really, what is actually happening in the lab? What are the everyday issues and techniques and strategies that we may adopt? What have other people observed when they're trying to even just grow and intervene and manipulate their organisms? And what kinds of tricks can people exchange, right. So that level of communication becomes a bit more formalized in that period. And that lab really plays an important role in getting that going. And of course, now, biology is all about thinking very carefully around how to formalize that kind of knowledge. And time, this was basically just starting.

Art Woods 24:13

I do want to ask about the psychology of scientists and this sort of idea of being very proprietary about what you know, versus being very open and sharing. And in my own scientific career, I've mostly had contact with people who are very open and sharing, but I have had contact and I've worked in one lab where people were very proprietary and like they held everything very close to their chest, and were very competitive and didn't want to share stuff. So what what sets is that like a cultural thing? Or is that reflect some sort of like deeper psychological thing just about people's personalities and who the lab head is, and you know.

Rachel Ankeny 24:46

It's all of the above. I think, so the best example that we often use is when you think about mouse, mouse is an incredibly diverse set of practices, right? So you have university labs that use mouse and you know, maybe on the spectrum that you just described everything from being very open all the way out to being proprietary or very even secretive, you might call it. And in those kinds of settings, you know, that's going to depend on a whole range of factors, it depends on what their research question is, what they stand to gain from being open, or being secretive, where their funding structures are, and so on. And you find there that, you know, depending what the subgroup is, I mean, they tend to be associated with a disease group or, you know, maybe an approach, they might

be more on the developmental end and on the, you know, strictly molecular and whatever, you're going to see different norms, and those do tend to be cultural, but that's cultural in all senses, you know, their training will have sort of been cultivated them in a certain way, the lab that they're in now has been in cultivate them in a certain way, the pressures that they're under, you know, are they going for tenure? Are they up for that big grant, you know, whatever it is, but the other end of the spectrum, you know, think about mouse is frequently frequently used in industrial pharmaceutical research, right? And this, this, to a certain extent does cause some issues. There, what we see is, is that that doesn't get out, right, it doesn't have the same mechanisms of credit and reward that say, the more university based kind of setting has, and everything along that spectrum.

Art Woods 26:13

More and more money in patents, right.

Rachel Ankeny 26:15

Yeah. And necessarily they have shareholders they have, you know, things that they need to achieve under certain conditions.

Sabina Leonelli 26:21

one other way to put it is, psychology matters. Like it matters for everything. But really what matters more, we think, is institutional setting. That's really what frames people's individual psychology, it frames the culture, the academic or otherwise, results culture, they're part of it frames the incentives they're subjected to, and ends up having a very, very important role to play on whether people feel proprietary or not, or want to be acting more openly, are allowed even to share some of their materials and feel that they are allowed. And they're not going to damage their colleagues by sharing some of their materials.

Rachel Ankeny 26:59

And to go philosophical. I mean, we actually we have kind of a term that we use for this that we're trying to use to open up the way that people think about this. So we talk about the repertoires that scientists have and the differences amongst repertoires, and repertoires have to do with everything from you know, what you're working on to how you're funded, where you're sitting geographically, institutionally and otherwise. And so, you know, we think that that's a critical part of knowledge production. And it's not ever done in the abstract. It's always done within this push and pull of different aspects of repertoires. And so just working on the same organism, certainly does not assure that you're going to be using the same repertoire of practices.

Marty Martin 27:50

There are so many things, my head's been spinning for the last five minutes about what we've been talking about. There are so many things too many directions to go. I'm not sure which one to tackle. But can you say more about what biology is, is where the money comes from. I mean, that's just largely what it is, can you can you give us more details about support for model organism research? You know, so we've changed since the conception, I mean, at least the 1950s or so we're really started to take traction, how does the allocation of research dollars look?

Rachel Ankeny 28:19

So what we see particularly actually, it's later, it's more like in the 1960s, in some way, model organisms, you know, need to have a lot of the DNA work cemented in behind them. And so part of the trigger is structured DNA, and so on early 60s, right. And then in the 60s, we get a number of big biologists in many ways, who have already made their name in some other way, deciding they're going to pick an organism to work on. And so we've already talked about, you know, Morgan comes a lot earlier, but flies get taken up again, you know, by a whole range of different people for different kinds of things. But in the 60s, these are mostly kind of blue skies, projects, we call it today, you know, they're they're allowing them to do very exploratory investigatory work. And that work then really grounds a lot of more detailed work, say, in the 1970s, in groups around starting to articulate things like what comes to be, you know, genetic sequence or the genetics of an organism. Those projects are largely and I think this is interesting, not particularly well funded. They're kind of too descriptive. They don't really fit a lot of what funders are looking for in the 70s. There's a few exceptions. So National Institutes of Aging, for example, gets interested in C. elegans work. There are, you know, other examples of fruit fly continuing to be kind of on the table, but where the funding really comes in, again, is the genome projects of the of the 90s. Right. By that time, you know, there's really big dollars attached. It's largely through the National Institutes of Health, but in collaboration with the Welcome and the MRC in Britain, and the parallel funders in many other countries. And that project, which is highly global, literally gives chunks of change very large amounts of money to you know, these organisms that they actually establish as the central ones to the Human Genome Project. Now, not all of them are going to have direct payoffs. I think everybody knows that to begin with, but it's a way to refine technology. And it's also a way to get some preliminary, you know, large scale sequence data after the 1990s, then what you see is that once that data is available, there comes to be mandates, many very explicit about using that data, right? And that funding is hooked into using that data. And so there are even questions in grants that say, you know, so which is my whole organism are using more or less, and this includes, and it's particularly the US NIH. But meanwhile, what we see is other funders and other parts of the NIH even are continuing to fund different sorts of projects that do

different sorts of things. And so I think many biologists talk about the fact that swamped out is often used as the terminology that model organisms have swamped out everything else. But the data really doesn't show that, as I mentioned, the data shows that many of these continue to persist, they may not always be funded. And so I want to get someone to take a little issue that the funding leads the work, because the funding leads the work at what you in the US call R1 Universities. Well, we don't even have that distinction anywhere else. Right. So first of all, there's lots of perfectly good and quite important work that goes on in developmental biology, in neurobiology, whatever, even at liberal arts colleges, even an experimental station in little exotic countries like Australia, that isn't necessarily heavily funded in the NIH kind of way, that kind of extremely big funding, or the welcome, you know, kind of funding. And so, you know, it depends on what your priority is, it depends on what the drivers are in your particular setting, you know, what does it mean to be funded? And what does it allow you to do lots of work can go on without a lot of funding, even this kind of work? Because, you know, part of what happens with this work is the costs come down exponentially. And so just during the sequencing project, you're not going to get money for that these days, because it's cheap. It's easy.

Marty Martin 32:05

And that's a fair point. I mean, you know, I think that question definitely came from my position as a scientist at a research one university in the US. So point well taken, let's push it into the conceptual realm. And I'm would like to hear more about this flavor of the things that we're trying to capture with model organism. And where what I mean by that is, there seems to be this tacit assumption that the traits that model organisms are informative about, I think they're mostly sub organismal. Right? They're definitely genetic, in the sense that the origins of model organisms largely are about genetics, right? Their tractability is, you know, animal, an organismal husbandry and all of these kinds of things. They're manipulability, in the genetic sense. But what are the kinds of things that we have modeled that we have used organisms for? And why do we expect that the process that happens in Drosophila is the same that happens in all other flies, when so much else about the organism at the super organismal level is really, really different? I mean, the dances that fruit flies do are profoundly different. What it means to be a mosquito is completely different, above the level of the organism, how it lives its life, its behavior, that timing of all of its activities, so totally different than a fly. Why do we assume that energy metabolism is the same? Where does that come from?

Sabina Leonelli 33:33

I think that the answer to this question is that assumption is not necessarily made directly. Right. The question is, what are people focusing on when they're thinking that working on model organisms is a big conceptual challenge and unnecessary one. And I think, the real focus, I mean, both me and Rachel think

it's, in fact, the idea of working on a whole organism, right at that point in time where there is such an emphasis on molecular approaches and thinking about genetics as foundational. And of course, that's also the case in a lot of model organism work. I mean, historically, we just discussed this, and why this is the case. But at the same time, many of the people that have been involved in really pushing the line of focusing on these few species, but people that were deeply interested in how the genetic level would relate to many other levels of organization, within the organism, deeply interested in developmental biology, deeply interested in physiology, they wouldn't quite go as far as behavior and relationship to the environment, because that would just bring too much complexity in a type of model. And that was really extremely challenging, because, you know, we have to think back to the 1980s 1990s, where actually, knowledge of how we would relate even just the cellular level with a molecular level was very much lacking. I mean, it was a huge challenge, just to think about how do we work our way through different types of omics until we can connect what's happening at the level of the cell and what's happening with the level of molecules in the nucleus. So I think the way in which the challenge was conceived in relation to model organisms was listen, this is a great opportunity to try and bring in so many different disciplines approaches, knowledge coming from different parts of biology, maybe from different relating to different taxa completely different types of organisms. In answering this question, how do we even think about organisms as an integrated whole, where these different levels of organizations are modeled at multiple levels in a way that actually allows us to understand the relationship between structure and function within the organism. Of course, people were very aware of the fact that this was incredibly limiting. It didn't take any account of the behavior of organisms in some way of the revolution in some way, of course, in the environmental stressors and the very different ways in which organisms can exist in the environment, the assumption was that the environment was very, very highly standard, controlled. But all of those controls where we think because the focus was very much on trying to integrate across those levels, within if you want the organism, so you put it very nicely, I mean, within the boundaries of what the individual token organism can reference specimen would be. And then the idea was, well, of course, there's all these other questions around what happens in gene environmental relations, what happened to phenotypes that actually exposed that kind of, you know, to the field and to what's actually happening in nature? But that question will be better answered, once we have a better understanding of these kinds of within organism type biology. I mean, we can be generous to model organism research, and then say, there's some ways in which that work as actually informed approaches that now are pushing the boundaries for how do we think about variation and environmental stressors and the relationship to organismal function?

Marty Martin 36:48

Well, with one and Rachel, I'm interested to hear what you what you say what to say about this, but Art and I have had a little bit of an offline conversation. The problem is we have no counterfactual for this. Yeah, of course, we only have what happened. So it's impossible to know where biology would be without it.

Rachel Ankeny 37:01

That's absolutely right. And I think you know, and so the program can be particularly the Human Genome Project, that way conceptualize things can be accused, and probably often, rightly, of being too deterministic, too reductionistic. These are all slightly different things, or genetisizing sometimes the word comes things that should have been studied in other ways. That's a new one for me, I've never heard that genetisizing when sociologists like sociologists of science, so all of these things are slightly different. Let me see in order deterministic, you know, everything's going to come from the genes. Well, we know that's clearly not true. And it is the case that of course, the people in that point knew that it wasn't true. But if you can hold environment study, because you're doing this in a lab, you start with a wild type. We haven't talked about that before, but you start with what you think is the normal organism. In many ways, you've eliminated a lot of those sources of rich variation, or what others might think of as noise, right? Because you've held these things steady. So I don't think anybody ever thought that you could explain everything this way. They're trying to get to what sometimes people talk about the fundamental building blocks, you know, what a normal gene or genetic sequence read the one that we think is most ubiquitous and produces something that's a healthy and functioning organism? What does that then produce? And in that sense, yes, it's in some sense, reductionistic. But I don't think it ever was about you know, everything is in the genes. There was a lot of rhetoric about that, you know, as a good way to sell to the US Congress that isn't particularly smart, right? It wasn't what anybody actually believed at a deep level. But what they did believe was exactly what Sabina said, this was an incredibly important step at this point in time, because we had technologies that allowed us to attack something at this level, but still start to project both outward to this broader scope of other organisms, and in some way up to the the integrated organism. And so I think, you know, the other thing to keep in mind is, is that even at the point at which these things start things as simple as C. elegans, which is my pet organism, there's already a lot of evidence about its behavior, for instance, and behavior in relation to things we care about like neurological diseases, or arabidopsis which Sabina has looked at it in great detail, you know, there was a lot more attention to ecological factors and interactive factors, and so on. So these things weren't standardized in the lab to the point of what you might call absurdity. I mean, they still were organisms in context. And to a certain extent, that's why they have proven to be quite valuable. All that being said, one of my favorite things that I always like to say is, you know, many people joke about you know, C. elegans is this obscure little organism off to one side of everything in some way, not only the phylogeny, but even the world. You couldn't go out and find what

people study in the lab out there in the dirt. And in fact, it's not important. It's not a agricultural pest. It's not a human pest. Lots of other nematodes probably would have a lot more pragmatic value in that that sense, but C elegans had a lot of value, because it ticked a lot of these other boxes about what it means to be a highly standardized organism that you can just simply, in some ways, dissect at all levels, and then put it back together and see what it actually does, how it behaves, how you know, all these different processes work in an intact organism.

Sabina Leonelli 40:22

So I mean, maybe one way to think about this is a slight touch of schizophrenia, in this kind of program, right? Where, or certainly a very big tension, and that endures and we can still witness it, like between the way of conceptualizing this research, which actually was very much trying to challenge the boundaries of how we think about epigenetics. How do we think about gene expression in a way that's much better contextualized within an organism that will level like all of those kinds of questions that were very challenging intellectually, but at the same time to be able to address them, choosing to standardize infrastructures data collection, very much starting from the genetic level, in a way that almost created I mean, what we sometimes in our field, quote, technological lock in, right, you get so many resources produced at that level, so much is done at the molecular level, partly because that's where the investment is that where the rhetoric is easy to come by. That's where you start to actually get more knowledge that basically gains traction, and it becomes almost an avalanche, it becomes almost unthinkable not to try and bring in some of that knowledge and insight to pretty much whatever question you may ask, conceptually, no matter whether these indeed are the central resources to ask these questions, there's certainly one end, you know, conceptually, you have something that it really is challenging ideas of genetic determinism, say, but at the same time, you're creating an apparatus that can trap people in working in that way. Because, you know, I mean, you just need a reference genome to do anything. And that sort of almost a criterion for what counts as good research. And certainly, it has been for several years. And that creates this tension that I think people have found very difficult to negotiate.

Art Woods 42:14

So let me try to articulate this sort of philosophical disagreement that Marty and I were having offline before we ended up with you online. And let me do it by sort of making the case that I was making the Marty for why I think model organisms are so powerful. And it touches on some of the things that both of you just said in the last last 10 minutes. And that is, you know, that there's just a confluence of resources and tools that happened to be focused on a particular species. And there's a lot of sharing of information and biological discoveries, and like you said, there's just an avalanche of progress. And so why wouldn't

you continue down down that path? And I think the frustration for organismal and comparative biologists like me and Marty, is that it feels like there's too much focus on these individual species and not enough focus on the sort of diversity of life around those species, you know, the things that occupy its its scope, and I was, I was making the case that well, in fact, model organisms are really powerful, because what we get is a lot of understanding and a lot of tools that can then be used in a comparative context. And I'm thinking of like colleagues of mine that are now working on 50 or 100 different species of Drosophila and doing really interesting, comparative evolutionary work by leveraging what's known about about melanogaster. But I'd say the flip side of that is that this this idea, I think, is is kind of bound up with the idea that the genetics and the genomics are so important in establishing model systems and in their power. It has to do with like thinking about where, where the traits come from. And this is like something Marty and I tossed back and forth a lot, and in our sort of evolved idea now is that genes obviously play a role, but there's just super, super important things that are happening with context, you know, with the environment with the choices and the agency that individual organisms exert over the experiences that they have. And when you have like, super highly standardized laboratory conditions, and super standardized genotypes, with which there's there's very little variation, it seems like you're taking out that giant component of, you know, important contributions to the establishment of phenotypes and the flexibility in phenotypes. And so so maybe it's better just to abandon this whole path of using model organisms so that we get back all of that other source of variation. I don't know that that was a long rant. But what do you what do you think about that?

Rachel Ankeny 44:33

I mean, I think art it's not an either or, or maybe I'm answering Marty more. I think it's not an either or, and as you said, the counterfactual what direction might we have gone if we hadn't gone this one is not the case. We're not doing counterfactual history. We don't like to do counterfactual philosophy there. What was the case is all these resources were established and made available. And now that you have them one of the best ways to study variation and phenotypic plasticity, and epigenetics and so on, is to have a baseline from which to work. And in many ways, the classic model organism research has provided that but I'll use this as a jumping off to one of my sort of bugbears and Sabina to certain extent to, which is that it means that experimental organisms are useful. And not everything needs to be a model organism, because to be a model organism has to make a certain kind of set of claims. And so, you know, patch at Cold Spring Harbor, you know, calling everything in emerging model organism, obfuscates the sort of questions and the issues, you can't just call something a model organism and make it one emerging or otherwise, right. And so I think, you know, there's not enough attention. And this is part of why we really push this, not because we think the concept is the best one, or that it was necessarily as well defended when it was introduced as it might have been, but

because it is part of scientific practice, and it's very important to biological practice. But you know, it's not a term to be used lightly. And in fact, it rules all sorts of things out. It also requires that certain things be in the mix to be either meaningful, or, again, a promissory note that can even come some way to be fulfilled. So this is why we're trying to take people to talk of experimental organisms, and experimental organisms that are, you know, in response to certain sorts of questions or certain sorts of levels of investigation, or whatever else, model organisms are something that's quite unique.

Sabina Leonelli 46:29

Yeah, and I mean, just thinking about model organisms as a reference point. And they certainly are, in many ways they do establish reference genomes, they establish particular ways in which one can set up a community or set up standards for people to talk to each other. But that doesn't make them the normal, right, I think that's where the real danger is thinking about a very, very particular kind of model that can act as reference point in very specific and constrained ways, as the biological normal is when things can go very, very wrong. And certainly I really did appreciate your point about traits, because in the reserves that we are doing now, this is something that comes very becomes extremely jarring, and very clear that the moment in which for instance, you think about what is being counting as a relevant trait, the significant biological trait in plant research, very much based on work on arabidopsis related organisms is very little to do with what people who are working in agronomy, in crop science and work maybe with local communities of breeders, regardless very significant, biologically significant traits, which maybe have less to do with particular types of metabolism, metabolic rate, things like that, and have more to do with the shape of leaves, or you know, the color of the pulp of a particular crop or these kinds of elements. And so finding a way to tune down, the predominance now of genetic reference points, as what we need to have to even think about what constitutes a trait, particularly in phenomics, I think is absolutely crucial. And that's, you know, that's where we really do need to get out to this idea of what model organism research has normalized, because as he said, I mean, this is just one part of a much, much wider landscape of biological research that has been ongoing.

Rachel Ankeny 48:24

One thing that model organism research has normalized, and I don't think it introduced it in any strong sense or anything else, is that the sharing ethos that came with a lot of model organism work, which many labs already did, and we talked about Columbia, and the fly room, and so on, and so on. But embedding sharing in the requirements of funding was a really important moment in in contemporary biology, making it a requirement that you deposit your data, and you turn it open access, etc, etc, was something that came along in the model organism projects was consciously implemented. It ran in tandem with a lot of

other efforts towards open science. But that was extremely important. And I guess if I'm going to defend anything about what the model organism projects did, or the concept of the model organism did, it wasn't necessarily all about the biological work that came out of the organism. It was about the infrastructures and the collaborative norms, and the ethos of doing science that these projects tended to support. Now, they don't always work people game the system. There's all sorts of holes even in the formal requirements. But that part of the model organism moment, I think, is a reference point that we don't want to abandon so easily. I think even if we're using a lot of the rest of it as a springboard, that's something that was importantly different, much more refined than it had been previously. and has probably rightly become a bit of a model for lots of other areas of biology and even science at large. And so this, again, is to say model organism work isn't just about the organisms, it is about this whole surround of infrastructures.

Art Woods 50:15

It's about the culture of doing science.

Rachel Ankeny 50:16

Yeah, it was a culture of doing work. And that were quite revolutionary in many ways. Um, I don't want to, you know, hang my hat on any one person or any one moment. But I think the sheer global scale of the work, and the need to be accountable to taxpayers, in multiple countries, really meant that sharing had to happen and had to happen in particular ways that required technological developments. And all of that becomes part of the model organisms story.

Marty Martin 50:43

Okay, this is really useful. I love that we keep kind of going back to the historical context, it underpins model organisms, but at the same time, we're almost referring to this. In the past multiple times. We've talked about model organisms "were"... I mean, it's just an unconscious slip that I think many of us have done. So am I hearing something there in the sense that you think the future for model organism research is going to be profoundly different? What do you think it's going to be like we have had, as Art alluded to many conversations on this show with philosophers, evolutionary biologists, biologists have many different types, including Dan Nicholson that I think you referred to, I love his his idea of of everything flows and are deluded to agency. We talked to Dennis Walsh and Scott Turner about these ideas. But how do the model organisms fit into this? I mean, two things push into systems ways of thinking and moving away from simplistic ways of thinking about genes. And then also the truth that model organisms have created a place where they sort of cause their own demise. The technologies that have been invented for them, like you say, it's

trivial to sequence the genomes of almost anything you want to do now. So what's the future for model organisms?

Sabina Leonelli 51:51

So I think one aspect that probably is getting to be less prominent, that used to be much more central is indeed this idea that this has to be almost a necessary step towards us understanding better what does it mean to understand an organism as an integrated whole? I think now, we have so many different ways of trying to get to that question. So it doesn't necessarily really I don't think that argument holds quite in the same way. Partly, indeed, because of the success of some of the model organism projects, where I think is still incredibly relevant that work is as a sort of reference point for comparison in a way that's much more explicit. And in fact, much more used than it used to be, it becomes one component in a much more diverse, multimodal landscape, where people actually do tend to use different organisms to establish certain claims. And they need some sort of reference point, to think about that comparison. I think model organisms still play a very, very important role in that respect. But that is quite a different situation from what we would have had 20 years ago.

Art Woods 52:59

Is another possibility that we're going to move away from model species and have more like model clades, it's going to be sort of expanded out phylogenetically so that we can work within a much bigger space. Is that Is that coming?

Rachel Ankeny 53:12

I mean, I think, yeah, the comparative work and the broader, you know, more systemic work is clearly coming along much more quickly than it was, say, in the 1990s in the 2000s. Right. But I mean, I hesitate, you know, you can't just call something a model clade, or a model ecosystem, or whatever else, there's a series of kinds of conceptual claims you're making when you do that. Part of what's happening now is that the people who always studied ecosystems, continue to study them, and use the tools you know, that they always use, but also use findings from model organisms from microbiome work from all sorts of other things that have gone on in the intervening period. And you can study ecosystems, not as models, you can study ecosystems, because they're important ecosystems, for whatever reason, you can study a clade because it's interesting in its own right, but a lot of the findings from the model organism work and as I said, all sorts of other different ways of doing biology that have developed in the last 20 years play into those studies now. So what I think we do see increasingly, is much more multidisciplinary work, where you're drawing on methods and techniques and findings from a whole range of things that we might have previously thought of as disciplines. So that the look of the way you study these

things, is tremendously different than it would have been possibly 30 or 40 years ago. And that's only a good thing if it's used, you know, with a clearer view of the question you want to answer. If you're just throwing genetic sequencing at something, or microbiome analysis or whatever, without thinking about how it helps to answer your question. It's just not very good science. But all of these things are tools that if not just taken off the shelf, but used in a way that actually allows greater ability to connect up the different levels well, then it's only a good thing. And model organism research was really critical for a lot of that connecting up that can now go on.

Marty Martin 55:06

So it's getting late to be in I know. And it's early and I don't know how much coffee you've had Rachel, we always end with, did we not give you the opportunity to say something? Is there anything else you'd like to say that we didn't prompt you with a question?

Sabina Leonelli 55:18

I mean, probably, there will be a whole different conversation. But I think that we require another podcast.

Marty Martin 55:25

Part two!

Sabina Leonelli 55:26

The intersection between the culture, ethos and history, model organisms and what they represent now, in the evolution of the Open Science movement. In biology, I think it Rachel hinted at that in a couple of places. But I think that would really deserve a discussion, right? I mean, Rachel has done a lot of work with other colleagues on the Bermuda rules and how they in fact originated very much in tandem and created by many of the key players in in pushing the the model organisms as an approach to biology. And these on the one end, is at a very deep influence on what we now see as the open access movement. And in many people really innovating the ways in which scientists communicate, and particularly how we captured know how, and how we think about the collection of metadata information about the data, I think there's been enormous amount of wonderful work done by committed people in the model organism communities, which has taught a lot to many others in biology wanting to do the same thing. And again, at the same time, it has also pushed a particular style of sharing, that may actually not be appropriate, many other communities that maybe work with different kinds of data. I mean, it's easy to sell genomic data on a variety of respects. And not the same thing could be said for it for phenomic data for certain kinds of imaging data for datasets that actually take

incredible amounts of time and an effort to produce is there are tensions there too, right. But I think that's a whole different space of what the model organism legacy has been, and continues to be that I think is worth also thinking about.

Rachel Ankeny 57:00

I think it's a it's a long conversation, though, because I mean, there are things that we could share. And Sabine has done a lot on data and open access and sharing and etc, as well. I think one of the takeaways is that, you know, it isn't one size fits all. And that applies to the kind of style of doing work that's in the model organism work, but also the open access movement, you know, such as it is or the movements, I would prefer to think about them more generally as movements. And what I think is most interesting in this domain that goes well beyond what we've talked about here is who is excluded, you know, what is left out. And Sabina hinted at that when she talked about the way in which sort of traits are defined what is important is defined, but also what it takes to use what is shared, you can't just take it off, you know, the internet and, quote, use it, that assumes that you're, you know, sitting in a particular type of laboratory with particular types of skills, and so on. So as much as the Human Genome Project is sort of routed and model organisms within them as part of widening kind of the global uptake of science and the ability to work collaboratively at a distance, and so on, there's certain norms embedded in that that are quite problematic and remain problematic today, when we think about what counts is having, quote, unquote, open science sabinas work on this is particularly useful, that locale matters is a really big one. But that goes along with skills and infrastructures and networks and other things. And so again, it's not all that it looks like it achieved very particular goals that were very important at that point in time and remain so. But science is still an in club, right? Don't kid yourself and it's very certain type of in club. And in many ways, as we've realized in the pandemic, all sorts of data points and all sorts of things and norms are very, very different in different locations.

Sabina Leonelli 58:49

Yeah, I suppose it kind of brings us back to almost the beginning of the conversation when we were talking about behavior, organismal behavior, right? The sense in which one of the potential bad legacies of taking model organisms as a normative setup for what biology is, is the reduction of behavior to function, right, where we are interested in biological function as manifested in a mechanical sense within organisms. And we're basically left without tools, or we're not given enough value to the existing tools that we have in collecting data and understanding of the behavior of organisms individually in groups in relation to different kinds of environments, which requires a very different way of intersecting it basically, of relating to the organisms themselves also on this other researchers, right, and that knowledge, which is contextual knowledge, but it's also really essential knowledge about actually how organisms function at

a higher level, you know, developmentally with each other socially. That's something that we need to bring back and kind of really use to complement some of the work that's been done within model organism research, because these are not the kinds of questions that that approach to biology can really come from. It wasn't set up to do so.

Marty Martin 1:00:00

Yeah. Yeah, it's sounds like we need a part two. So at some point.

Art Woods 1:00:04

I know, I think we do. Rachel and Sabina. This has been a super interesting conversation. And I think it's probably a good place to wrap it up. We really appreciate you taking the time and really looking forward to seeing what happens to the idea of model organisms over the next five or 10 years.

Sabina Leonelli 1:00:18

Thank you very much for the great conversation.

Rachel Ankeny 1:00:19

Yeah, thank you so much.

Marty Martin 1:00:30

Thanks for listening to this episode. If you like what you hear, let us know via Twitter, Facebook, Instagram, or leave a review wherever you get your podcasts. And if you don't, we'd love to know that too. All feedback is good feedback.

Art Woods 1:00:40

Thanks to Steve Lane, who manages the website, and Ruth Demree and Brad van Paridon for producing the episode.

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Marty Martin 1:01:03

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