Original Research Article

The lost art of mathematical modelling

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A R T I C L E   I N F O
This article is dedicated to the memory of Edmund Crampin

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A B S T R A C T
We provide a critique of mathematical biology in light of rapid developments in modern machine learning. We argue that out of the three modelling activities – (1) formulating models; (2) analysing models; and (3) fitting or comparing models to data – inherent to mathematical biology, researchers currently focus too much on activity (2) at the cost of (1). This trend, we propose, can be reversed by realising that any given biological phenomenon can be modelled in an infinite number of different ways, through the adoption of a pluralistic approach, where we view a system from multiple, different points of view. We explain this pluralistic approach using fish locomotion as a case study and illustrate some of the pitfalls – universalism, creating models of models, etc. – that hinder mathematical biology. We then ask how we might rediscover a lost art: that of creative mathematical modelling.

1. Introduction

The challenges in mathematical biology can be roughly broken down into three activities: (1) formulating models; (2) analysing models; and (3) fitting or comparing models to data. These activities are part of a larger modelling cycle – where modellers work together with biologists to try to better understand the study system – but within that cycle, most of the time, the modeller will be found conducting one of these three activities. Research in mathematical biology has evolved a great deal over the last decades, in particular in response to the rise of machine learning (ML). Indeed, the ML approach – with its emphasis very clearly on activity (3), that of predicting future data – can be seen as a challenge to the essence of the research area. We need to find ways of reconciling a mathematical biology approach, largely built on describing biological mechanisms, with rapid progress in predicting patterns in data [1].

We argue that in response to the rise of ML, mathematical biology needs to refocus on activity (1), the formulation of new models. We start, in the next section, by defining an inherent feature of biological systems, that they are complex. Our definition of complexity differs from (is more radical than) those most often provided by modellers, in that it emphasises the open-ended nature of biological systems. In Section 3, we critique one approach to complex systems, that of unification. This leads us, in Section 4, to propose another approach to modelling biological systems, one which emphasises a plurality of models.

We then argue, in Section 5, that (whether researchers are aware of it or not) the unification and pluralistic approaches emphasise different values. Unification emphasises activity (2), that of analysing models, while plurality emphasises activity (1). We argue that currently, the universalist approach dominates and creation of new models, which is inherent to pluralism, is not sufficiently emphasised. This brings us to, in Sections 6 and 7, a discussion of how mathematical biology has responded with the rise of machine learning. We argue that ML, which emphasises prediction (activity 3), is ill-prepared to deal with complexity without incorporating some form of mechanistic model building. But we also, more controversially for those working in mathematical biology, emphasise how some of the responses to the rise of ML have fallen into the trap of making models of models (or fitting models to data generated by models) rather than innovating by creating new models of biology itself.

We conclude that mathematical biology needs less unification and less analysis of existing models, and more creativity and more creation of new models. We should be creative without fear of them being wrong or producing ideas that are mathematically intractable, with an aim of providing a multitude of tools for better understanding of biological systems.

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2. What is complexity?

Biological systems are complex systems. This statement is so often made, that it can obscure just how radical the consequences of complexity are for the life sciences. To explain why we say radical, consider one of the most common uses of the term complex systems. In physics and applied mathematics, complex systems science has become a name for a set of modelling tools: networks, power laws, phase transitions and the like which purport to capture general properties of systems. This is explicitly not what we mean by complexity. Although complex systems models will come up in this article, we do not consider them useful in defining complexity itself.

Instead, the radical definition of complex systems comes from, what is known as, critical complexity. Work by Paul Cilliers and Alicia Juarrero warned against aggrandising models (even supposedly complex systems models) [3,4]. They emphasise the need to embrace the ambiguous, messy, fluid, non-determinable, contextual, and historical nature of complex systems. They describe complex phenomena as unfinalizable and inexhaustible, which means that we can never capture any given biological system entirety with models [5]. Fig. 1, adapted from Di Paolo et al. (2018), captures the interdependence, fluidity and interactivity of agents and environments in a complex system [2]. Complex systems are open-ended, which means there is no uncontested way of telling whether what we have included in a model is crucial or what we have omitted as irrelevant is indeed so. Models can, according to the critical complexity approach, be contradictory: we can accept two incompatible predictions as both describing the same system.

This approach views a model as a snapshot of a system and no single snapshot tells the whole story. For modelling the human body, for example, “a portrait of a person, a store mannequin, and a pig can all be models” [6]. None is a perfect representation, but each can be the best model for a human, depending on whether one wants to remember an old friend, to buy clothes, or to study anatomy. The critical complexity view suggests that theoreticians should avoid specialising in any one modelling approach and try to find the right set of models to understand a particular system in a given context.

There can, of course, be more than one definition of complex systems. Indeed, Cilliers and Juarrero’s approach to complexity encourages a plurality of definitions (after all, there is no single view of a system). We would, though, emphasise that it is the radical definition of complexity – in which systems always resist a complete description, are open and unfinalizable – which is least well understood by mathematical biologists today. It is therefore important to investigate how complexity should be approached in the study of biological systems.

3. The allure of unification

Precisely because most biological systems are more complex than physical systems, they are also more difficult to model. In another article in this collection, Vittadello and Stumpf outline two broad approaches that might be adopted [7]. The first of these approaches builds on the motto put forward by Philip Anderson, that ‘More is Different’ [8]: suggesting that each level of biological organisation requires different types of approaches. The second of these, which we will critique in this section, suggests that the way forward is greater unification and increased mathematical rigour.

In presenting the second approach, that of unification, Vittadello and Stumpf argue that the success of mathematical modelling of physical systems suggest that further progress in mathematical biology can be best made with even more advanced mathematics [7]. With the complexity of biological systems comes a need for rigorous definitions of biological concepts, and they propose a definition-theorem-proof style as a way forward. Accompanying this idea, comes a focus on unification. In the same way as there are unifying theories in physics – relating to energy conservation, entropy, etc. – there ought to be unifying models for biological systems. Under this view, an increase in rigour is supposed to tame the complexity of biology. Vittadelli and Stumpf suggest that unification and rigour could lead to avoidance of excessive incrementalism in model development, as well as avoidance of a focus on development of simple models of simple systems.

The idea of unification in biology has been echoed by many others [9–12]. For example, van Hemmen claims that some of the universal laws of biology might have already been discovered in neurobiology [12]. Since mathematical models can describe the behaviour of biological systems at certain scales, the equations of the models could be seen as “universal laws”. The question is how to find the appropriate scale for these universal laws. We should, van Hemmen argues, be patient: it has taken humanity hundreds of years to discover the physical laws of the Universe formulated through mathematics; with enough time we will discover the universal laws of biology too [12].

Finding the appropriate scales and determining unifying laws is certainly part of modelling biological systems. For example, a fundamental difference between most biological and physical systems is the conservation of momentum. For self-propelled particle models – which are used for modelling biology on scales ranging from cells to flocks – momentum is not conserved [13], and thus classical kinetic theory used in physics to derive macroscopic equations is not applicable. To get around this problem, Degond introduced the Generalised Collision Invariant [14], from which it is possible to derive macroscopic equations for many self-propelled particle systems used in modelling flocks and other systems in biology [15–18]. This method allows us to show convergence between self-propelled particle systems on microscopic and macroscopic scale, i.e. between the movement of e.g. flocks of birds described by local interactions between a few individuals, and PDEs describing the angular and velocity distributions of the flock as a group.

In the example above, an approach like the Generalised Collision Invariant, when applied to the collective motion of real biological systems, usually fails to provide the answers biologists are looking for. Indeed, the very point of self-propelled particle models is to capture the
rich, varying dynamics of different schools, swarms and flocks. Deriva-
tions of continuum equations for infinitely large populations provide
little insight into these questions. While all of these systems may well
share a common invariant, this is not the key issue at hand. Biologists
want to find the details of shapes of schooling [19], understand how a
wave of fish escape from a predator [20], find the mechanism behind
the V-shape of migrating birds [21], measure the sociability of fish
schooling based on their movement [22], study leadership in flocks
of pigeons [23,24], or understand the mechanisms behind shepherding
sheep [25]; to give just a few examples. We have illustrated this point
with a specific example, but see the point as applying more widely.
While unification in mathematical biology is tempting, it often neglects
the complex nature of biological systems.

Our discussion of the Generalised Collision Invariant is meant to
give one concrete example of how a mathematically appealing univer-
sal idea fails to give insight into range of complexity seen in biology'.
Such approaches may well lead to new, interesting and useful mathe-
matics [26], but there is no reason (a priori) that they will give
deeper biological insight. In biology, experimental results are noisy,
non-stationary and often differ across species and scales. Studies of self-
propelled particles span species from spiders through fish to humans,
as well as sperm and cell interactions. When formalising such models,
we have to ask the question, exactly which biological entity or species
is it that is being formalised? Is the relevant scale the molecules, the
cells, the organs, the animal or the collective? These questions are not
amenable to a universal approach or reducible to a small number of
equations.

A focus on rigour in biology is an example of over-mathematisation,
a phenomena frequently discussed in economics [27–31]. The cri-
tique has been summarised by the Nobel prize laureate Paul Krugman,
who described that “the economics profession went astray because
economists, as a group, mistook beauty, clad in impressive-looking
mathematics, for truth” [30]. A similar phenomenon has occurred in
theoretical physics, where the focus on developing beautiful mathematical
theories has taken precedent over genuine insight into physics [32].
There is a danger, that in trying to find unification, mathematical biol-
ogy gets stuck at analysing/unifying simple models, none of which are
appropriate for any specific system. Moreover, in search for unification
and general methods in biology, we might neglect to study actual
systems because they are too complicated or detailed.

The allure of unification often centres the idea of deriving properties
of the collective from interactions between individuals. Countering
the possibility of unifying biology through such an approach, Sandra
Mitchell argues that microscopic phenomena (cells, molecules, atoms)
are not always suited for capturing the rich variety of relations found
in biological sciences [33]. Scientific representations are abstractions
or idealisations, and thus only represent partial features of individ-
uals or a system [34]. As such, the abstractions/idealisations do not
constitute identical representations across the two levels. Thus, even if
the descriptions at each level is accurate, they may, by being partial,
not represent the same features of nature. As a result, there is no
straightforward derivability or intertranslatability relationship between
levels [33].

Unification is a reductionist approach [35]. Multilevel, multi-
component, complex systems that populate the domain of biology can-
not be reduced to a simple, unified picture of scientific theorising [33].
And even though contributions to mathematical biology can be made
by unification approaches, they do not account for all the explanations
that biologists seek [35]. This view echoes that of Dupré, who explains
unification as another way of arguing for the (flawed) reductionist
hypothesis that all of science can be reduced to a description based
on simple building blocks [36]. Reductionism fails to account for what
Noble calls the ‘relativity principle’, that there is no “privileged scale
at which biological functions are determined” [37].

In summary, there are both philosophical (universalism is another
form of flawed reductionism) and practical (supposedly general equa-
tions do not capture the type of questions biologists ask) arguments
against a unification approach to biology. The question now is what is
the alternative?

4. The pluralistic approach

Given that biological knowledge is fragmented and that biological
systems are complex, we have argued that it is not useful to build
a general theoretical framework or to strive for unification. We now
outline, in this section, an alternative: the pluralistic approach
to modelling biological systems. Pluralism embraces complexity by never
seeking to close a biological system in a single or a small number of
formalisms, but endlessly endeavours to find new ways of looking at
the world. Pluralism reflects the open, unfinalizable nature of complex
systems described in Section 2.

We illustrate the pluralistic approach by focusing on one specific
area of biology, modelling fish locomotion, before broadening out
(in the next sections) to explore the lessons we can learn from this
approach when looking at other systems. Fig. 2 illustrates various ways
that fish locomotion can be modelled. When modelling the behaviour
of fish shoals and schools, self-propelled particle models are widely
used [38–44] (Fig. 2a). The most prominent model, called the Vicsek
model [42], assumes that each fish (or particle) moves with constant
speed, while its direction is updated at each time step to be closer to
the average direction of individuals within its neighbourhood. A noise
term is added to model uncertainty or error in the fish’s direction. These
type of models have proven useful when explaining many aspects of
schooling behaviour, for example, how body size influences shoaling
patterns [45], how large schools switch between different organisa-
tional states [46] and the spread of escape waves in response to a
predator [20].

Although self-propelled particles have been central to the study of
collective motion, both in fish and other species, there are a several,
fundamental ways in which they do not capture the locomotion of fish. For example, rather than updating their angle to turn towards other fish, as assumed in many models [39–41,43], between-fish attraction and repulsion is mainly mediated by speed changes [19]. Even in the absence of interactions, constant speed is not typical swimming behaviour for most fish species. Zebrafish [47], koi carps [48], guppies [49], cod [50], rummynose tetra fish [51] and many other species swim by alternating between accelerated motion and powerless gliding [52] (Fig. 2b).

The discrepancy between how fish are modelled collectively and individually can be seen as an example of logical incompatibility between models [33,53]. After all, fish cannot simultaneously swim both at a constant speed as in the Viscek model and according to a varying speed, as in a burst and glide model! Yet the models in Figs. 2a and 2b might view the same fish in both of these (contradictory) ways. From a unification point of view, logical incompatibility might be seen as an indication that the models are, at least in some aspects, wrong or that we should try to find ways to unify them to make them both approximately correct (possibly on different time scales). Building on our definition of complexity and open systems, however, we would downplay the importance of investigating relationships between models. From the point of view of complexity, since each model is a different snapshot of a system, taken from a different point of view, using a different camera and lens, we should not be surprised to find an element of incompatibility between models. If we accept the idea of complex phenomena as unfinalizable and inexhaustible (as we outlined in Section 2), we cannot expect our models to be logically compatible on every level. Moreover, lack of compatibility should not concern us: it is simply a consequence of taking a different view, of using a different lens, which bends the light of observation in a different way.

Even within the context of intermittent burst and glide motion, we can find several useful and correct, yet logically incompatible approaches to fish locomotion. For example, a range of biomechanical models [50,52,54–59] have been proposed for fish locomotion (Fig. 2c). These have been used to show that there are energetic advantages of burst and glide behaviour, when compared to constant swimming speed. The energetic cost of swimming is minimised during the glide phase, where the body is rigid and the fish decelerate due to water resistance [52]. Other models have focused on a behavioural ecology perspective, since intermittent motion is associated with many ecologically relevant behaviours, e.g. foraging, mating, exploration and predator evasion [60,61]. There are also perceptual benefits that can arise from the pauses in locomotion, such as the sensory system’s capacity to detect relevant stimuli increases [62,63] (Fig. 2d).

Yet another level to the understanding of intermittent locomotion of fish, is to look at why fish use burst and glide when swimming in pairs. Theoretical studies from hydromechanical perspectives show that there are energetic advantages to intermittent motion in this setting [64,65]. However, the hydromechanical models neglect the social aspects of intermittent locomotion when swimming in pairs (Fig. 2e). In fact, burst and glide swimming have been shown pivotal to detect and quantify social interactions between individual fish [49]. Moreover, high burst speed in response to neighbours evolves when subjected to artificial selection [66]. Also, when studying intermittent locomotion of pairs of fish, leadership can become apparent [67]. For example, in pairs of freely exploring eastern mosquito fish, it is possible to categorise the fish into leaders and followers [68].

The locomotion of fish can also be studied in neurobiological settings (Fig. 2f), leading to questions about how different nerve cells affect the initiation of motion seen in fish [69–72]. This can also be linked to genital aspects of fish locomotion. For example, studies on zebrafish show that genetically encoded calcium-indicators provide a direct link between signalling at a cellular level and functional output in the form of swimming behaviour [72,73].

Above we have listed many different approaches to modelling fish locomotion. Depending on what question we want to answer, the model used is different. It is this creation of many different viewpoints which is pluralism. This multiplicity (or plurality) of ways of seeing a system is even stronger than suggested by Philip Anderson’s ‘More is Different’ approach [8]. Anderson emphasised that “psychology is not applied biology, nor is biology applied chemistry”: each level of organisation requires completely new approaches. We would go further, arguing that even within a single biological phenomena, at only one organisational level, we need a whole range of different explanations and models. We simultaneously engage many different frameworks and views of a system, each designed to answer a different sub-question. We take different snapshots of the system and then use each of them to construct a bigger picture of the system. The more snapshots we include, the more comprehensive the bigger picture.

Our approach follows, what Sandra Mitchell calls, integrative pluralism [33–35]. Like us, she argues that complexity in nature, particularly in biology, has direct implications for our scientific theories, models, and explanations. To quote, “nature is complex and so, too, should be our representations of it” [33]. Mitchell’s own examples build on how social insect biologists explained the emergence of division of labour, by focusing on the effects of causes at one level (genetics, single organisms, and colonies), while idealising away the other potentially relevant factors [53]. She argues that scientists do not need unified theories to provide causal explanations. Nor is there a requirement for logical compatibility between explanations. Mitchell’s characterisation of biological research as a whole, we believe, translates even to the mathematical biologist’s approach to creating formal models. To paraphrase her: “biology is complex and so, too, should be our mathematical models of it”.

Comprehensive, integrated understanding of biology does not come from one universal model, but rather the synergy of many different, potentially contradictory models. Having many models helps us understand more.

5. How modelling approaches shape mathematical biology

Our rejecting unification and embracing a pluralistic approach, which emphasises the open nature of biological systems, might be viewed as a purely philosophical exercise. It could also be seen as a question of personal taste. After all, it might be argued, practicing mathematical biologists seldom discuss whether they see the world in terms of unification or integrative pluralism, they just get on with their job.

In this section we reject this last notion and argue that the formalism and unification approach has a strong influence on what is valued in mathematical biology research. To understand this point, let us return to the three activities outlined in the introduction: (1) formulating models; (2) analysing models; and (3) fitting or comparing models to data. Under a unification approach, which emphasises the importance of mathematical formalism, activity (1) is about finding a small number of universal models which explain as many biological phenomena as possible; and activity (2) requires great care in developing a precise formalism to be clear about the universal properties of the model. Under an integrative pluralism approach activity (1) is about producing lots of different models which view a system through different lenses; and activity (2) is important to get right initially, but details are less important, since we are happy to discard the model once it has told us something useful.

Unification and integrative pluralism thus emphasise very different values and practices. Whether or not these values are acknowledged by researchers, we can look at the type of activities carried out by mathematical biology researchers and see which approach is more predominant. This is what we do now.

We have already described a pluralistic approach to fish locomotion (Fig. 2) and emphasised the success of self-propelled particle models in describing schooling patterns. However, while there are valuable empirical studies of bird flocks and fish schools, where variations of
these models are used to understand the details, these are outnumbered by articles reporting on simulations and investigations of theoretical properties of flocking models [74–76]. A similar pattern is seen in evolutionary game theory, which provides insight into how spatial and genetic structure is important to the evolution of co-operation [77–79]. This approach has produced countless theoretical questions about how co-operation evolved in different (artificial) settings [80–83], which are detached from observations in the natural world. This is not to say that evolutionary game theory is not useful in biology, it is just to point out that testable predictions have been accompanied by a massive sub-literature simply analysing model properties.

Similarly, complex systems tools – such as networks [84,85], power laws [86], phase transitions [87] etc. – often purport to capture general properties of systems and suggest that studying these models will give very general insight, in terms of scaling laws or unifying rules. In making claims of universality, modellers sometimes suggest that biology will succumb, like physics, to an understanding based on one or a small number of models. Under the definition of complexity we use here, the more radical definition, such universality is impossible: complex systems are not complex if they can be reduced to a small number of universal rules.

Focusing on network science, Fox-Keller argues that claims that scale-free networks and power law distributions are universal laws of life are problematic on two counts [88]. Firstly, power laws are not as ubiquitous as was originally supposed [89]. Second, and more importantly to Fox-Keller, the existence of these distributions tells us nothing about the mechanisms that give rise to them [88]. Many reported power laws lack either (or both of) statistical and mechanistic support [90]. There are, at least, a dozen distinct ways to derive power laws from theoretical models [91], making them far from universal. And asking questions about how power laws should be measured has led to better practices for model fitting (and identifying cases in which they do not fit) [92]. Again, it is the details that matter in biology. Power laws do not fit everywhere.

We note that it is activity (1), rather than activity (2), which typically provide the biggest steps forward in science. Specifically, it is the initial model (prisoners dilemma, chaos theory [93], Turing’s work on morphogenesis [94], the Fitzhugh–Nagumo model [95], Yule’s power law model [86], Vicsek’s SPP model [42, ...] which provides the most inspiration and insight into the biological world, rather than analyses of small variations of these initial models. Yet, universalism, with its emphasis on formalism, prizing activity (2) over activity (1), remains a dominant force in shaping what constitutes mathematical biology.

We believe that the emphasis on model analyses, rather than creating new models, is caused by a tendency towards universalism. The result is mathematical analysis of small variations of existing models (activity 2) at the expense of creating very novel and different models (activity 1). Admittedly, the observations we make above are qualitative. We have not carried out a comprehensive literature review comparing universalism and pluralism approaches, but instead we appeal to the active mathematical biologist to consider their own research field and think about the theory/application balance. We would imagine for most (leaving activity 3 aside for now) the balance is towards 2, rather than 1.

This imbalance, we believe, is wrong. Small variations of already existing models seldom provide additional insight into biological systems. We would follow Reed, who wrote in his 2004 Essay Why is mathematical biology so hard [96]: “Don’t do mathematical biology to satisfy a desire to find universal structural relationships; you’ll be disappointed. Don’t waste time developing “methods of mathematical biology”, the problems are too diverse for central methods. What’s left is the biology. You should only do mathematical biology if you are deeply interested in the science itself”.

6. Machine learning cannot replace modelling

The distinction between universalism and pluralism has become particularly important with the move away from activities (1) and (2) – model building and analysis – towards methods broadly described as machine learning (ML), which emphasises activity (3). Initially, machine learning methods were proposed primarily for data collection – for example, computer vision was proposed to track movements of fish and cells – but it later became clear that these methods could also be used to pick out patterns in the data. In an early example, Berman and colleagues showed how different types of fruit fly behaviour (grooming with different legs, running, moving of wings etc.) could be categorised without the need for human definitions of these activities [97]. This work has evolved into a field of computational ethology, which Pereira recently claimed will “in the near future, make it possible to quantify in near completeness what an animal is doing as it navigates its environment” [98].

Such claims place activity (3), that of fitting or comparing models to data, as central to the scientific endeavour. The proponents of this approach [99–101] sometimes even go as far as to suggest that activity (1), that of creating models, is now redundant. For example, Rackauckas and colleagues claim that traditional mathematical models are only required because of too small training datasets and that models which are not learnt directly from data have an inductive bias, because they use assumptions about the underlying system being modelled [101].

We reject such claims as yet another form of universalism. As Nurse has recently argued, data should be a means to knowledge, not an end in themselves [102]. Nurse emphasises that the hypothesis free approach of collecting data is just the first step when doing biological research. In order to make advancements in biological sciences, new hypotheses and theories need to be formulated. Reed follows a similar line of argument: “data itself is not understanding. Understanding requires a conceptual framework (that is, a theory) that identifies the fundamental variables and their causative influences on each other” [96].

In the context of machine learning, Birhane and Sumpter make a distinction between closed systems – such as games like Chess and Go, some image analysis tasks and short term nowcasting of the weather – that are entirely defined by the available data, and open systems – like fish schools and other biological systems – similar to those we discuss above, which can be viewed in multiple ways [103]. The only systems which can modelled by data alone, in the way Rackauckas and colleagues propose, are those which are fully closed. Indeed, data-driven models, are just representations of the data itself, rather than insights into that data. To take an example given by Nurse, what if Darwin had just fed in the data of size and shapes of finch beaks into a neural network? The deep learning algorithm would have found clusters and patterns and might have predicted the future development of the beaks on different islands, but would never formulated the theory of natural selection. An ML approach, when employed in the absence of activities (1) and (2), can be characterised as a view from nowhere [104]: without context data analysis becomes meaningless to us, the scientist interpreting the results.

Not only are there (as we have already emphasised) many ways of seeing a system, there are also many other reasons for doing modelling, over and above making predictions. For example, models can also be used to guide data collection for future experiments, or to capture qualitative behaviours of overarching interest and lead to new scientific questions being posed [105]. While pure machine learning models are focused on prediction, a large part of biological understanding focuses on mechanistic explanations [106,107]. There is no consensus definition of mechanisms, but Illari and Williamson offers the following: “a mechanism for a phenomenon consists of entities and activities organised in such a way that they are responsible for the phenomenon” [108]. Thus, for a mathematical model to give a mechanistic explanation to a phenomenon, the model cannot merely summarise and describe the
data, but rather the model should encode a mechanism generating the observed phenomenon [109].

Breidenmoser and Wolkenhauer make a distinction between mechanistic models, which explain a system by describing underlying biological processes, and phenomenological models, which only “save the phenomena” by fitting a curve to the data [106,109]. The key problem with a purely machine learning based approach is that it says little about the processes, i.e. mechanisms, behind the data [110], and instead focuses on “saving the phenomena”, to use Breidenmoser and Wolkenhauer’s term. Phenomenological models, like many ‘view from nowhere’ machine learning models, might be a good start in understanding statistical relationships between variables, and thus a first step towards modelling a phenomena, but these models do not contribute to a deeper understanding [109].

### 7. Are hybrid models the answer?

Moving away from the idea that machine learning can fully replace mathematical modelling, several authors have proposed integration of mechanistic models and machine learning methods in the form of hybrid models [1,7]. These come in many forms, from neural ordinary differential equations [100,111] and biologically informed neural networks (BINNs) [112,113], to symbolic regression [114,115] and equation learning [116,117]. Hybrid models can both have an underlying specified mechanistic model and then use machine learning methods to infer parts of the equations (as in BINNs [112]) or aim to find analytical expressions directly from data (as in equation learning [101]). The end product is thus a mechanistic model, in form of, e.g., a dynamical system [117].

To give a concrete mathematical example, consider a reaction diffusion equation of the following form

\[
\frac{\partial u}{\partial t} = \nabla \cdot (D(u) \nabla u) + R(u),
\]

where \(D\) is a function of \(u\) describing the diffusion process, and \(R\), also a function of \(u\), describing the reaction process. This equation is used in a range of situations in mathematical biology, from pattern formation, to insect dispersal, to spread of epidemics, to tissue growth. Depending on the application, \(D(u)\) and \(R(u)\) take different forms. For example, in the Fisher–KPP equation, which was originally used to describe the spatial spread of a favoured gene, \(D\) is a constant and \(R(u) = ru(1 - u)\) [118].

Choosing the correct form of \(D\) and \(R\) is an open question and the focus of many research efforts [112]. The traditional approach for solving this task is to choose an appropriate form of \(D(u)\) and \(R(u)\) based on first principles and then try to fit the parameters of the model to the data.

Another approach, is not to state the form of \(D(u)\) and \(R(u)\) explicitly, but instead learn the functions directly from data. There are different methods for achieving this. For example, sparse regression [119, 120] and theory-informed neural networks [112] are two of them. Also, \(D(u)\) and \(R(u)\) do not need to be explicitly defined, but can instead just be modelled with data [121]. This approach is sometimes referred to as an equation-free approach as parts of the equations do not need to be explicitly formulated [121]. Other applications of so-called equation free approaches can be found, for example, in ecosystem forecasting [122].

Hybrid models are sometimes presented as defining a complete modelling cycle: doing all three activities – (1) formulating a model, (2) analysing a model and (3) fitting the model to data. But even though parts of the equations do not need to be explicitly formulated in this approach and are directly learnt from the data, the underlying model (in our case the reaction diffusion equation in Eq. (1)) is already specified. Thus, equation-free approaches like these are useful for model selection, validation, and analysis, which is part of activity (2) and (3), but they do not replace activity (1).

Even methods that infer analytical expressions directly from data, with no underlying model like the reaction-diffusion example, cannot be used to replace activity (1). Building mathematical models is more than choosing a set of differential equations that describe data. For example, equation learning would never have formulated inclusive fitness theory in the way Hamilton did after careful across species observations [123]. Nor would symbolic regression produce the Vicsek equations and the idea of self-propelled particles solely from analysing videos of bird flocks.

Thus, while approaches combining machine learning and mechanisms are certainly part of the way forward for mathematical biology, we also need to look critically at whether they are a genuine step away from the universalist thinking, which we have criticised in earlier sections of this article.

One important critique in this direction arises when researchers apply machine learning methods to models, rather than to data from natural systems. For example, parameters and properties of agent-based models can be learnt using machine learning methods [124,125]. In such settings, simulations are seen as a way of generating data on which to test methods for fitting models (i.e. to improve the way we perform activity 3). The limitation, from the perspective of a complexity approach, is that simulated data from known models does not come from a complex system (as defined in Section 2). Models are not in themselves open-ended or unconstrained, in the same way a biological system is. Instead, an already well-established view of a system in the form of one model is studied in the context of another model. This approach implicitly avoids the challenge of formulating new models.

For example, Roesch and colleagues, apply a collocation based method for training neural ODEs, i.e. ODEs where the derivative is learnt directly by a neural network [109]. To demonstrate the applicability to biology, the neural ODE is trained on data generated from the classical Van der Pol oscillator with added Gaussian noise. The authors view the model as a promising hybrid method for biological applications, because it uses machine learning methods to infer a (mechanistic) dynamical system. However, using Breidenmoser and Wolkenhauer’s distinction between phenomenological and mechanistic models, we would argue that, even though coated in terms like “mechanistic”, this method is nothing more than a phenomenological model: a curve is fitted to a derivative, instead of a time series.

A similar critique can be applied to studies in which differential equations are learnt from model simulations [125]. For example, in one paper on hybrid models, Nardini et al. show how differential equations can be learnt from agent-based simulations in order to predict how the latter type of model responds to parameter changes [117]. One justification for this approach is that agent-based models might be computationally expensive to simulate. The approach also allows researchers to compare three approaches – an agent based model, mean field equations derived from the agent based model, and a differential equation model learnt from the data provided by the agent based model – in terms of the insights they offer and how well the methods approximate each other [117]. In terms of the pluralistic approach (which we advocate) the limitation of such a study is that it gives the (false) impression of generating three different views of a system, while it is primarily an exercise in deriving and estimating one model from another. In many studies describing hybrid approaches, data from real-world systems is not included.

The danger here is that hybrid and equation-free modelling has a veneer of doing activities (1) through (3) but are, in fact, limited to activity (2). Real biological data is noisy, non-stationary and can be viewed in a multitude of ways. Understanding biology requires an openness to adopt different view points, rather than an attempt to close our approach down to one self-consistent framework. Fundamentally, any mathematical model or method should provide additional insights to a phenomenon, rather than cement a relationship between models. Hybrid approaches are not a substitute for, and can run counter to, an approach based on integrative pluralism.
We found a way to couple this model to the velocity of the fish membrane potential in a neuron, of fish motion [127]. The FitzHugh–Nagumo equations model the dynamics, the FitzHugh–Nagumo model, with a self-propelled model burst and glide motion by combining a well-studied model of neuronal firing [133], through Hamilton's proposal of inclusive fitness [123] and May's application of chaos theory in ecology [93], to Vicsek's model of collective motion [42] and Hogeweg's models of multi-level selection [134], it is the formulation of models (rather than their in-depth analysis) which has led to progress. Instead, of treating these existing models as sacred Platonic forms, which should be respected with deeper analysis, we should not be scared to look for new ideas and approaches. The inconvenient truth – that biology is itself endlessly rich and varied and never subject to a final analysis – is sometimes dismissed as an unrigorous approach. Such a situation is wrong. We need to rediscover the lost art of creating mathematical models.

Rather than staying safely within the confines of one model, after his PhD, Edmund made sure he created new approaches to a variety of mathematical problems. When we look at his contributions – ranging from multi-cellular modelling of the heart [138,139], through systems biology [140] to biochemical reactions [141,142] and fundamentals of biophysics [143,144] – we see an approach grounded in all three of the activities (modelling, analysis, comparison to data) we have discussed here.

Edmund's self-insight has always stayed with David. And it is this spirit we have tried to adopt in this paper. Edmund may not have agreed with everything we have written – we have taken a very strong
position on what mathematical biology should be – but he would have understood the need to be critical. Most of all, he would have enjoyed, over a long lunch or a vigorous walk, talking (and arguing) about the merits of different approaches to the subject he loved.

Declaration of competing interest

There are no conflict of interest.

References


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Fig. 4. Sketch examples of creating models of complex biological systems. (a) Langton’s (1984) loop is one of the first examples of a self-reproducing cellular automata [129]; (b) Artificial chemistry gives insight into both the origin of life and how complex components arise from simpler units [130]; (c) Nicky Case’s ‘We come what we behold’ is one example of an explorable game that allows the user to actively explore complexity [131]; (d) Inigo Quilez work shows how realistic complex, fractal landscapes can be generated by a few lines of code [132].
A. Birhane, Algorithmic injustice: A relational ethics approach, Patterns 2 (2) (2021) 100205.


P.E. Smalldino, Models are stupid, and we need more of them, in: Computational Social Psychology, Routledge, 2017, pp. 311–331.


