

How should biologists engage with controversial mathematical theory?

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Mathematics is beautiful and precise and often necessary to understand complex biological phenomena. And yet biologists cannot always hope to fully understand the mathematical foundations of the theory they are using or testing. How then should biologists behave when mathematicians themselves are in dispute? Using the on-going controversy over Hamilton's rule as an example, I argue that biologists should be free to treat mathematical theory with a healthy dose of agnosticism. In doing so biologists should equip themselves with a disclaimer that publicly admits that they cannot entirely attest to the veracity of the mathematics underlying the theory they are using or testing. The disclaimer will only help if it is accompanied by three responsibilities – stay bipartisan in a dispute among mathematicians, stay vigilant and help expose dissent among mathematicians, and make the biology larger than the mathematics. I must emphasize that my goal here is not to take sides in the on-going dispute over the mathematical validity of Hamilton's rule, indeed my goal is to argue that we should refrain from taking sides.

Keywords: Hamilton's rule, inclusive fitness theory, kin selection, mathematical theory, scientific controversy.

'Do not worry about your difficulties in Mathematics. I can assure you mine are greater still.'

– Albert Einstein

MATHEMATICS is a powerful, precise and beautiful language often described as the queen of all sciences and the language of nature. The language of mathematics is useful and often essential to describe and understand many complex phenomena, and biological phenomena are no exception. But mathematics is unfortunately not a language that everyone can master to the extent necessary to study complex phenomena. Inevitably and quite rightly, empiricists depend on professional mathematicians to build models, do the maths and produce predictions, which they then test with their data, and biologists are no exception to this research strategy. But what if mathematicians disagree among themselves and claim to find fault with a previously accepted mathematical formulation,

model or prediction? This puts the empiricists who have invested their time, money and effort, not to mention their careers, into a potentially incorrect or misleading research agenda. How should they respond to such a situation? In considering this question, let us focus on a specific, recent, real-life example in organismal evolutionary biology – the case of Hamilton's rule.

Inclusive fitness theory and its discontents

Darwinian natural selection prepares us to expect competitive selfishness in the living world, not cooperation and altruism. Therefore, when we see that squirrels endanger themselves while giving alarm calls to warn their neighbours about the approach of a predator or that honey bee workers protect their nests by stinging any marauder even if it means instant death to themselves, we find these phenomena paradoxical. For a long time these unusual phenomena were explained by implicitly assuming that natural selection also acts at the level of the family or colony. However, this kind of 'naïve group selection' thinking became increasingly problematic as it was realized that a few 'selfish' cheaters or free riders could invade the group and drive the altruists to extinction. In the 1950s and 1960s it was also realized that altruism can evolve relatively more easily in groups of relatives because the beneficiaries of the altruism have a high probability of possessing the altruistic genes. This idea has come to be known as kin selection¹. It was perhaps stated most clearly by J. B. S. Haldane when he wrote: 'Let us suppose that you carry a rare gene which affects your behaviour so that you jump into a flooded river and save a child, but you have one chance in ten of being drowned, while I do not possess the gene, and stand on the bank and watch the child drown. If the child is your own child or your brother or sister, there is an even chance that the child will also have the gene, so five such genes will be saved in children for one lost in an adult²'.

In seminal papers in 1964, W. D. Hamilton developed this idea into a formal mathematical model^{3,4}. Hamilton showed mathematically that under certain assumptions, an altruistic allele will be favoured by natural selection if the condition ' $BR > C$ ' holds, where B is the benefit of the altruism to the recipient, C the cost to the altruist and R is the coefficient of genetic relatedness between the

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altruist and the recipient of the altruism. The inequality $BR > C$ has come to be known as Hamilton's rule. In effect Hamilton proposed that altruism evolves because it increases the 'inclusive fitness' of the altruist. Hamilton defined inclusive fitness as the sum of a direct component of fitness gained through offspring production and an indirect component gained through aiding genetic relatives. Initially these ideas were slow to catch on but once they were adopted and popularized by E. O. Wilson in the 1970s (refs 5–7), the overlapping ideas of kin selection, Hamilton's rule and inclusive fitness have led to an explosion of empirical studies ranging from bacteria to humans, and have given birth to the burgeoning fields of behavioural ecology and sociobiology. Thousands of papers, scores of books and several journals have since been inspired by these ideas. Indeed, Hamilton's rule has been called the $e = mc^2$ of sociobiology, even by those who do not necessarily support it⁸.

In a dramatic turnaround, Wilson has now rejected kin selection for being inadequate and unnecessary for understanding the evolution of altruism and eusociality⁹. In a more recent paper two mathematicians Martin Nowak and Corina Tarnita, along with Wilson have questioned the mathematics of inclusive fitness theory and Hamilton's rule¹⁰. They claim to show mathematically that '...inclusive fitness theory is a particular mathematical approach that has many limitations. It is not a general theory of evolution'; 'Inclusive fitness is just another method of computing'; 'the use of inclusive fitness requires stringent assumptions (such as pairwise interactions, weak selection, linearity, additivity and special population structures), which are unlikely to be fulfilled by any given empirical system'; 'Inclusive fitness is not nearly as general as the game theoretic approach based on natural selection'; 'Inclusive fitness is often wrongly defined'; 'Hamilton's rule almost never holds'; '...inclusive fitness theory cannot decide in general if an allele that makes you help a relative is favoured by natural selection or not. Instead we need a calculation that is based on a precise description of population structure and dynamics'; and that 'if we are in the limited world where inclusive fitness theory works, then the inclusive fitness condition is identical to the condition derived by standard natural selection theory'. Thus they ask '... if we have a theory that works for all cases (standard natural selection theory) and a theory that works only for a small subset of cases (inclusive fitness theory), and if for this subset the two theories lead to identical conditions, then why not stay with the general theory?'

These claims have thrown the field into a turmoil¹¹ as they are contrary to prior claims by other mathematicians who have argued repeatedly that inclusive fitness theory requires no special or stringent assumptions and it is as general as natural selection^{12–18}. Since the publication of Wilson and Hölldobler⁹, we have witnessed the publication of papers with the titles 'What's wrong with inclu-

sive fitness?'¹⁹, 'There is nothing wrong with inclusive fitness'²⁰ and 'Kin selection is the key to altruism'²¹. And since the publication of Nowak *et al.*¹⁰, we have witnessed the publication of papers with the titles 'Group selection and kin selection: formally equivalent approaches'²² and 'Group selection and inclusive fitness are not equivalent'²³. We have also seen some authors claim that they 'show that these claims (of Nowak *et al.*¹⁰) are based on false premises, many of which have been exposed more than 25 years ago, such as misrepresentations of the basic components of inclusive fitness and fallacious distinctions between individual fitness and inclusive fitness'²⁴. And finally we have statements from Bossan *et al.*²⁵ that their 'findings, ...could be taken as evidence for the claim (of Nowak *et al.*¹⁰) that the direct fitness approach is superior to the inclusive fitness approach'; that 'conceptual disparities between direct compared with inclusive fitness models can lead to different quantitative predictions...' and that 'Hamilton's rule still provides a useful short cut to understanding the evolution of social traits' but that 'researchers should check carefully for each particular case as to whether this short cut may lead them astray'.

How should biologists respond?

How should empirically-minded biologists respond to these remarkable contradictions that resonate in the literature? I will suggest a four-pronged strategy involving one disclaimer and three responsibilities. It is not my claim that biologists cannot or should not try to fully understand the mathematical foundations of the theory and models they choose to use and test. It is my claim, however, that a full understanding of the mathematical foundations should not be a pre-requisite for procuring a license to use or test a theory. In spite of all the best intentions therefore, it will sometimes (often?) be the case that biologists who set out to use and test a theory will not have fully understood its mathematical foundations. It is for this kind of situation that I suggest the following strategy. Thus my reference below to 'empiricists' or 'biologists' applies only to those who do not fully understand the mathematical foundations of the theory they are using. Such a sharp distinction between mathematicians and biologists need not be made when it is unnecessary, but I believe that it will sometimes be necessary.

The disclaimer

When biologists do not have a full understanding of the mathematical foundations of the theory they are using or testing, they must be cognitively aware of that fact and should publicly admit it. Well-meaning people often tease the ignorant in the hope of raising public standards of literacy in science and mathematics. To take just one example,

Richard Dawkins is credited with the following statement: ‘It has become almost a cliché to remark that nobody boasts of ignorance of literature, but it is socially acceptable to boast ignorance of science and proudly claim incompetence in mathematics’. Yes, but I think the pendulum has swung too far in some quarters – I believe it is better to declare ignorance while it lasts. We should build a publicly recognized consensus that it is acceptable for a biologist to use or test a theory without being able to prove its mathematical correctness. A pilot flies the plane that he did not and cannot build, and the engineer who did build, the plane is not likely to be better than the pilot at flying it. It is easy to see that empirical biologists – both field naturalists and laboratory scientists – perhaps incapable of fully understanding the mathematics behind a theory, are often much better placed to test the predictions of the theory than the mathematicians who built the theory. The availability and acceptance of the aforementioned disclaimer will take away the pressure on biologists to pretend that they understand all the nuances of the mathematics that went into building the theory and will absolve them of blame if the theory turned out to be wrong. It is not my claim here that the mathematics of inclusive fitness theory is wrong or inadequate. It is merely my claim that some of us are entitled to be agnostic about the matter without losing the legitimacy of our empirical research. Indeed the task of the empiricist is to show when and why theories fail, so the mathematicians can build better ones. Nevertheless, the disclaimer will only help if it is availed along with accepting at least the following three responsibilities.

Responsibility 1 – stay bipartisan

Having availed the disclaimer, biologists should then strive to take a bipartisan stand when there is dispute among mathematicians, of the kind that we are witnessing in the context of Hamilton’s rule (described earlier). In the absence of the disclaimer, biologists may feel compelled to pretend that they understand the issues and therefore need to take sides in the dispute. They may also feel that they have a large stake in the mathematical correctness of the theory they have tested and may feel compelled to take sides to protect their (often) life-long careers. More than a hundred people signed a letter to *Nature*²⁶ denouncing the heretical paper by Nowak *et al.*¹⁰. I am aware of some accomplished mathematicians among these, but it is hard to believe that every one of the signatories has a deep enough understanding of the mathematics of inclusive fitness theory to be legitimately able to take sides in the controversy. If we find two people quarrelling with each other in a language that we do not understand, it is quite impossible for us to immediately take sides and declare one of them to be correct and the other to be wrong, and yet, that is what we seem to be

doing. It is my belief that the widespread use of the disclaimer will drastically change the behaviour of biologists in the wake of future mathematical disputes, so that many will indeed be able to stay bipartisan. I have often seen reviewers of mathematical papers use a math disclaimer, stating that they have not checked the maths in any detail, so why not the authors of empirical papers?

Responsibility 2 – stay vigilant

This goes well beyond staying bipartisan after a full-blown dispute spills into the open. It involves a constant vigil for any rumblings under the surface and a commitment to expose and highlight them rather than remain silent or worse, help bury them under the carpet. We have a big stake not in protecting but in exposing the mathematical theories/models we use, to every form of criticism and affront. In the Hamilton’s rule example at hand, there were several missed opportunities for empiricists to blow the whistle. I will cite five examples ranging from 1978 to 2007.

(1) Cavalli-Sforza and Feldman²⁷ developed models ‘for evolution at a single locus affecting altruistic behaviour in which genotypic fitnesses are Darwinian...’, compared fitnesses ‘either in a multiplicative or an additive way’ and showed that ‘The commonly accepted criteria of (Hamilton’s rule) apply only in the additive case.’

(2) Matessi and Karlin²⁸ presented a ‘general model for the evolution of altruism’ and showed that ‘the Hamilton rule has quantitative validity only in the special case of linear fitness functions ... qualitative violation of the rule is also possible’.

(3) Alan Grafen¹⁸ began an influential paper¹⁸ with the words ‘The readers for whom this introduction is intended have met the concept of relatedness and Hamilton’s rule, and find it so unproblematic that they are surprised that any clarification, defence, or exposition is necessary. A fair sized literature ... deals with relatedness and Hamilton’s rule and its very existence is a good indication that there are problems with these ideas. However, this literature is mainly mathematical and I am now to persuade the confident reader, using words only, that clarification, defence, and exposition are, after all necessary for Hamilton’s rule and the concept of relatedness’. And he ends with the following conclusion: ‘In the central case of weak selection in an outbreeding, homogeneous population, later work has abundantly confirmed the validity of the (Hamilton’s) rule as a summary of relevant population genetic models.’ The same cannot be said however of inbred and heterogeneous populations which appear to be problematic. Grafen tells us that ‘The fundamental problem is that the relatedness needed to predict the direction of gene frequency changes differs for dominant and recessive alleles ... (and) that the same problem arises in the case of heterogeneous populations’. He concludes that while ‘...it would not be surprising if the

solutions proposed by Hamilton ... turn out to be close to the truth most or even all of the time ... it is also possible that there are biologically significant exceptions'.

(4) The purpose of a paper entitled 'How to make a kin selection model' by Taylor and Frank¹⁶ appears to 'propose a 'direct fitness' formulation of inclusive fitness which often has a more straightforward derivation'.

(5) Gardner *et al.*¹⁴ state that '...derivation of Hamilton's rule using Price's theorem ... applies very generally. The cost of this generality is that it hides a lot of detail, and so a naïve application of Hamilton's rule may lead to mistakes. For this reason it is easier to use standard population genetics, game theory, or other methodologies to derive a condition for when the social trait of interest is favoured by selection and then use Hamilton's rule as an aid for conceptualizing this result...'

My point is not that these disagreements were altogether ignored by mathematicians, but that empiricists did not adequately seize the opportunity to maintain a healthy dose of agnosticism about the models and press for a swifter resolution of the obvious contradictions. The question here is not about who is right or wrong. The point is that the controversies could have erupted earlier and perhaps clarity might have emerged sooner, paving the way to more fruitful and self-confident empirical research.

Responsibility 3 – make biology larger than mathematics

Our final responsibility is to make biology larger than the mathematical models and theories. The utility of our biological research should not be restricted to the testing of a single class of mathematical results. We should endeavour to make biology to have a life of its own and yet be amenable to testing the prevailing mathematical models or even future models not envisioned today. In this sense, biology may indeed be different from the physical sciences. Since we cannot always choose correctly between rival mathematical theories, we must demand that the mathematicians produce predictions for us to test. We should not shy away from proclaiming that we are more interested in mathematical theories that make predictions, and thus help us better understand our biological systems and care less about purely mathematical nuances. The strategy of developing a wholesome encyclopaedia of natural history from which many different mathematical theories for many different phenomena can be tested, is especially appropriate for organismal biology. There are many glorious examples from the past and we only need to revive good old traditions established by Darwin's notes during his voyage of the *Beagle*²⁹, Alfred Russel Wallace's *Species Note Book*³⁰ or Charles Elton's *Scientific Natural History*³¹. Much inspiration in this matter can be had for beginners and experienced alike from the

memoirs of naturalists, such as E. O. Wilson^{32,33} and India's Salim Ali³⁴ and many paragons worthy of emulation can be sought among the resplendent field notes of naturalists³⁵. There was a time when naturalists had to be chided by mathematicians such as Robert MacArthur who wrote: '...not all naturalists want to do science; many take refuge in nature's complexity as a justification to oppose any search for patterns'³⁶. And yet, I think we should not let the pendulum swing too far. Our natural history should not be captive to the detection of any particular kind of patterns, but should be amenable to the search for patterns and be neutral in terms of what patterns may be or may not be found. Some of my friends who work with honey bees describe Karl von Frisch's magnum opus '*The Dance Language and Orientation of Bees*'³⁷ as a magic well that they dip into every winter and invariably come up with new ideas for experiments with bees the following summer. Armed with a math disclaimer and three kinds of responsibilities, many of us can play the role of agnostic scrutinizers of the validity and utility of diverse genres of mathematical theorizing.

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