

## The Importance of Mathematics to Biology

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“(…) I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics, for men thus endowed seem to have an extra sense” from *The life and letters of Charles Darwin, 1887.*, including an autobiographical chapter. London: John Murray.

How important is mathematical biology for Biology? Is it as important as mathematical physics for Physics? In 1928, Paul Dirac made the first prediction for the existence of a new particle. Namely, by putting together quantum theory and special relativity, he was able to show that, somewhere, there should be a particle very similar to the electron but with positive charge. Only four years later, in 1932, Carl Anderson alone found the particle. Higgs Boson had a different story and predicted the existence of the particle responsible for the mass of the other fundamental particles in 1964. However, because there was no idea how much should be its mass, and also because its mass turned out to be very high, it took almost 50 years for thousands of physicists to find it.

There is no doubt that Biology and Physics are very different sciences. In Physics, mathematics plays a fundamental role, whereas, in Biology... keep reading! When should biologists use mathematical models to understand biological systems? There is no doubt that mathematics has played a very important role in Biology, as the discoveries by Mendel, Fisher and many others have testified. Should Darwin have spent a few years studying mathematics? Would Darwin discover many more important things in Biology (and Geology) had he studied more mathematics? We will never know. According to John Maynard-Smith, Haldane once said that “(…) if you are faced by a difficulty or a controversy in science, an ounce of algebra is worth a ton of verbal argument”. Many research papers in Biology show that Haldane was right, but, putting aside statistical treatments, most research papers have no mathematics in them. This is clearly the case in many subjects of Biology, including those of this journal. What are we missing given its absence? There are many kinds of mathematical models in biology but, I wonder whether all of them are useful. It is not important to make a mathematical model of a system “just because”. The mathematical model should be able to explain something that is not intuitive (that is, show that a given phenomenon discussed in the paper is likely) or make some predictions based on the same premises of the mathematical model. What kind of predictions? In her book “*Modelling for Field Biologists (and Other Interesting People)*”, Cambridge University Press, the theoretical biologist Hanna Kokko writes that “Predictions of conceptual models (...) tend to be qualitative rather than quantitative”. Indeed, in Biology, most mathematical models make qualitative rather than quantitative predictions. There are some exceptions of course (e.g., Fisher’s sex ratio theory predicts that “investment” in males should be the same as in females), but, contrary to what happens in Physics, quantitative predictions in Biology are extremely difficult to do. Indeed, it is perfectly fine to use a mathematical model (population genetics) to show that, the more deleterious is a mutation, the less likely it is that it will fix in a finite population of individuals: this is a qualitative prediction based on a well known mathematical equation from population genetics. But it is impossible to predict what will happen really. In Bruce R. Levin’s words, “doing research in population biology without mathematical

and/or computer simulation models is like playing tennis without a net or boundary lines”.

While doing his mathematical model, a biologist has to think very carefully about premises of the model. They have to be realistic. However, that does not necessarily mean that one has to think about all the details. Sometime ago, in a very interesting conference about Cooperation putting together Sociologists, Historians, Economists and Biologists, I was discussing a mathematical model with other mathematical biologists. Then, someone who introduced himself as unprepared in mathematics asked me: if something is proven mathematically, why is it that something is left for discussion? To which I answered ‘Premises of the model’. But how far should we go with details and premises? The more details in the model, the more confusing it is to interpret the outcome of the model. So, one has to think about them very carefully. As the statistician George E. P. Box once put it, “all models are false, but some models are useful”.

How useful? In 1953, Carl Nordling found that the probability of cancer increases with the sixth power of age. Nordling, being someone with an “extra sense” (using Darwin’s words), understood that this means that the development of cancer needs seven (six plus one) consecutive mutations (perhaps or not in seven different genes). Later, in 1971, Knudson showed to the world the first concrete example of this mathematical reasoning. Retinoblastoma is a tumour of the retina that affects two kinds of people at different ages. People with inherited retinoblastoma tend to have the disease much earlier than people without any cases of retinoblastoma in the family. Knudson interpreted this by postulating that this cancer needs two mutations to occur. According to this idea, most people have to get two mutations to develop the disease. However, people belonging to families with cases of retinoblastoma have high probability of having inherited one of the mutations. To develop the disease, they only have to receive one mutation. From this finding, cancer researchers understood that cancer involves the activation of genes that stimulate cell proliferation and deactivation of genes that suppress cell proliferation.

Until very recently, researchers would read only a few journals, at the library, without much access to other “cultures”, other sciences, or even other subjects within their sciences. It is my opinion, however, that open access in general, and OMICS group in particular, help to break cultural barriers, between humanities and sciences or between theoreticians and experimentalists by providing all subjects at the distance of a click.

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