Some comments on mathematical modelling and biomathematics

Foreword to BIOMATH 2017 Proceedings

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1 Introduction

Both biology and mathematics have existed as well established branches of science for hundreds of years and both, maybe not in a well defined way, have been with the humankind for a couple of thousands of years. Though nature was studied by the ancient civilizations of Mesopotamia, Egypt, the Indian subcontinent and China, the origins of modern biology are typically traced back to the ancient Greece, where Aristotle (384–322 BC) contributed most extensively to its development. Similarly, the ancient Babylonians were able to solve quadratic equation over four millennia ago and we can see the development of mathematical methods in all ancient civilisations, notably in China and on the Indian subcontinent. However, possibly again the Greeks were the first who studied mathematics for its own sake, as a collection of abstract objects and relations between them. Nevertheless, despite the fact that the development of such a mathematics has not required any external stimuli, an amazing feature of the human mind is that a large number of abstract mathematical constructs has proved to be very well suited for describing natural phenomena.This prompted Eugene Wigner to write his famous article *The Unreasonable Effectiveness of Mathematics in the Natural Sciences*, see e.g. [9]. This paper somehow summarizes several centuries of successful interplay of mathematics with engineering and physics where, on one hand, the need to precisely describe the physical world drove mathe-

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matics as a necessary tool for the task and, on the other, mathematical theories gave rise to new physical discoveries. For the former, one could mention the discoveries of Neptune and Pluto on the basis of careful applications of Newton's laws of motion. Also the theory of differential equations, that forms a substantial portion of mathematics created in the 19th and 20th century, was developed to explain newly observed physical phenomena such as electromagnetism, heat conduction or gravitation, as well as to help to understand how fluids flow that is essential for naval and aeronautical engineering. Similarly, functional analysis originally was developed to provide a sound foundation for quantum mechanics. Conversely, purely theoretical equations of General Relativity paved the way to discoveries of physical phenomena such as gravitational lensing or gravitational waves, purely mathematical solutions of the Dirac equations turned out to be physical objects called positrons and the celebrated Higgs boson was predicted on the basis of group theoretical foundations of the Standard Model. On the other hand, [8], for most of its history, biology was being developed using colloquial, everyday language to describe its observations and laws with mathematics playing there at best just an auxiliary role, such routine calculations and statistical analysis of experimental data. However, over the last couple of centuries, biology's five revolutions has brought biology closer to the quantitative sciences and technology, and have changed the way the scientists think about the living matter, [7]. Following *op.cit.*, these revolutions were: the microscope, the linnaean classification, theory of evolution, genetics and the discovery of the DNA structure. If we consider the role played by chance, and hence probability theory, in the theory of evolution, the abstract thinking of Georg Mendel who, on the basis of numerical patterns in the frequencies of particular features of organisms, postulated the existence of agents (now called genes) that are responsible for their occurrence, or the numerical rule observed by Chargaff and Bragg's law of diffraction that paved way to understanding the complex geometry of the double helix of DNA, we see that seeds of the new revolution have been already sown. The author of [7] (any many other books on mathematical biology) Ian Stewart, calls the coming sixth revolution the mathematical revolution.

2 Mathematical modelling

The reason for this is the same as in physical sciences. As we mentioned earlier, many mathematical constructs, for unknown reasons we should be grateful for, are well suited to describe the environment we live in. In other words, there is a correspondence between parts of the real world and objects developed and studied by mathematics. Establishing such relations is refereed to as mathematical modelling. Despite the importance of this concept, it is not well defined and we shall devote a few lines to describe it in detail.

Often by mathematical modelling people understand statistical analysis of the available data and inference based on the found correlations. While very important in many applications, one should not mistake correlations for causations, understanding which is the basis for mathematical modelling. That is, we try to understand the rules governing a particular phenomenon of interest and translate them into mathematical language, which we call a mathematical model. The model often, but not always, takes the form of a system of equations balancing the quantities relevant to the model. Then we apply mathematical methods to analyse it and finally try to understand the implications of the obtained results for the original discipline. For this, we have to interpret the solution, or any other information extracted from the model, as the statement about the original problem so that they can be tested against observations and serve as a basis for the design of further experiments the outcome of which, ideally, should agree with the predictions of the model, serving as it's validation. However, often the constructed model is over-simplified so that there is insufficient agreement between the experimental data and the predictions of the model, or the model turns out to be too complicated to yield itself to any meaningful and robust analysis. Then, in either case, we have to return to the first step of the modelling process to try to remedy the problem. Thus mathematical modelling usually is an iterative procedure, shown on the figure, as it is very difficult to achieve a proper balance between simplicity and accuracy of the model.

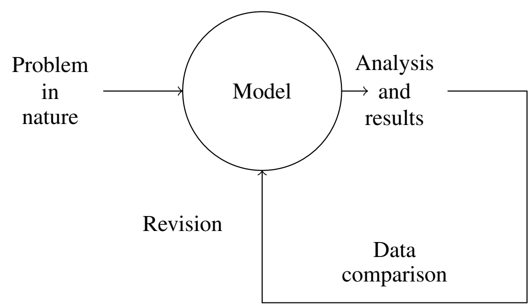

Fig. 1 The process of mathematical modelling.

Mathematical modelling is a difficult subject the reason being that there are no set rules and the understanding of the 'right' way to model only can be reached by familiarity with a number of examples. As mentioned above, a good model should have predictive powers; that is, the model based on an available set of observations should give correct answers when new observations appear. Here a good example is the General Theory of Relativity – it predicted the light deflection by stars, gravitational redshift and gravitational waves, phenomena not known when the theory was developed. A good modelling procedure should also produce nested models – an improved model should contain earlier working models as subcases. For instance, Newton's mechanics is contained in both Special and General Theories of Relativity provided the described objects move with small velocities and away from large masses.

It is important to recognize that mathematical modelling is not a part of mathematics – one cannot prove that a given model is correct and always will give valid predictions. This often is a source of misunderstandings as the decision-makers and the general society, have a tendency to treat results of modelling as universally valid, whereas they always are conditional – one has to understand the assumptions made while building the model to apply it with a reasonable success. A spectacular example of such a misuse of a model is the history of the Long Term Capital Management hedge fund, whose board of directors included the 1997 Nobel Memorial Prize in Economic Sciences winners Myron S. Scholes and Robert C. Merton. The basis of operation of the fund was the famous Black-Scholes equation for determining the value of derivatives. Initially successful, with annualized return reaching over 40%, in 1998 the fund lost 4.6 billion USD in less than four months following the 1997 Asian financial crisis and 1998 Russian financial crisis. The reason for the collapse was that the validity of Black-Scholes model requires the market fluctuations to be small and this assumption fails during large crises.

Thus, it is important to understand that while mathematical models are indispensable tools for cheaply testing various scenarios in engineering or natural, medical, economical, or social sciences, they only give simplified descriptions of real-life problems and should not be used without understanding, like cooking recipes.

3 Mathematical models in biology

As we said earlier, the ability of mathematics to create relatively faithful images of reality has been utilised for years in physics where often, instead of talking about real objects, we talk about their mathematical models. In principle, we should be able to do the same in biology. One can, of course, talk about living matter using the everyday language – indeed, this was the case for most of the history. However, mathematical language offers an array of new constructs together with precise rules of dealing with them, thus allowing for creating of a precise picture of the real world, much richer than that accessible for everyday language description. Thanks to the rules of mathematics we can carry out thought experiments about possible behaviour of the studied objects, that are rather impossible if we restrict ourselves to the word descriptions of them, and the results of these thought experiments can be tested against observational data. Moreover, in contrast to the descriptive word models, the mathematical ones yield quantitative results that add to their applicability and accuracy of the predictions.

Why then do we talk about the mathematical revolution as incoming rather than well established? Why did a great mathematician I. M. Gelfand write, [1],

> Eugene Wigner wrote a famous essay on the unreasonable effectiveness of mathematics in natural sciences. He meant physics, of course. There is only one thing which is more unreasonable than the unreasonable effectiveness of mathematics in physics, and this is the unreasonable ineffectiveness of mathematics in biology.

The reason for this is that biology is incredibly complex. A number of renowned mathematicians and mathematical biologists have tried to explain this. A. Friedman writes in [3] that if the unit in physics is an atom, then the unit of life is a cell, but a cell is much more complex. Not only does a typical mammalian cell contain about 300 million molecules, it also maintains control and order among them. M. Reed elaborates further in [4] by listing the following fundamental difficulties of the field: lack of the fundamental principle such as Newton's Law in physics, diversity and specialization (that can be possibly explained as the fact that, due to evolution, the same functionality does not mean structural similarity), interplay of levels, difficulties of experimentation (due to emergent behaviour coming from interactions of various levels of organisation that disallows studying the system through its isolated parts), as well as the problems of feedback control (that is somehow related to the previous two).

Despite these difficulties, mathematical biology has been growing at a very fast rate, confirming I. Stewart's prediction about the incoming mathematical revolution in biology. The first, and the oldest, role of mathematics is providing a unified language for biological processes. As a mathematical object, diffusion is the same irrespective of whether we are talking about the Brownian motion, spreading of organisms, or transport of molecules across the cell membrane, as long the motion can be interpreted as a random walk. Mathematics has well developed tools for dealing with such problems and it is not necessary to develop a special theory for each process where such a motion occurs. However, our ambitions go further. Mathematics not only should be the language of biology but it should provide a meaningful input into the understanding of biology and, conversely, draw an inspiration from it for its own development. Whether it is possible, currently is a subject of a debate, as shown in the Gelfand's quote. Some minimalists do not believe that mathematics can go beyond being a supplier of auxiliary tools for biologists, but many others, such as I. Stewart, A. Friedman or M. Reed, represent an opposite view. The latter, in [5], argues that there is a true exchange of ideas in both directions. Most people are aware of applications of ordinary and partial differential equations, with a celebrated example of a Nobel Prize winner Sir Donald Ross who, though not a mathematician himself, had a sufficiently mathematical mind to develop the first compartmental model of malaria, [6], possibly launching this way modern mathematical epidemiology. Similarly, in population theory, if certain conditions are satisfied, even simple differential equations, such as the logistic equation, provide results displaying amazing agreement with the data. For instance, it describes the population of the US from 1790 till 1950 with less than 3% error, see e.g. [2]. It is important to emphasize that applications of mathematics to biology are not restricted to differential equations in epidemiology, ecology or population theory. Following [5], [3] and the references therein, we mention applications of graph theory in epidemiology and gene networks, topology in understanding heart fibrillation, algebraic topology in neuroscience or category theory in systems biology, not to mention combinatorics, probability theory, stochastic and, in particular, branching processes that has become central in genetics, or optimal control techniques used to determine the best cancer treatment.

The author of [8] wrote that the measure of mathematization of a particular discipline is its influence on mathematics. While recognizing the mathematization of physics in that sense, in 1992 he was doubtful about mathematization of biology.

In 2015, however, in [5] the author argues that in the 20th century the theory of evolution and genetics influenced the fields of probability theory and stochastic processes, Hodgkin–Huxley equations and Turing's theory of morphogenesis gave a momentum to the theory of reaction–diffusion equations and pattern formation, and sequencing and reconstruction of the human genome created new problems in combinatorics, probability and statistics. While this research continues, new inspirations in mathematics have emerged recently. Again following [5], we mention new problems in conformal geometry created by the question of teeth comparison in paleontology, new results in the theory of dynamical systems prompted by problems posed by such diverse fields as biochemical reactions and central pattern generators in the nervous system; in particular, the coarse-grained methods for classification of dynamical systems is due to the analysis of complex systems with only approximately known parameters.

4 Conclusion

The above description is by no means exhaustive but certainly it shows the breadth of mathematical techniques used at the interface with biology. While, as mentioned earlier, we cannot claim that mathematical thinking and mathematics were not used in biology before, it is clear that the scale of mutual interactions has enormously grown in the last couple of decades to the extent that in some disciplines the research has been determined by mathematical modelling. This justifies the opinion that he mathematical revolution in biology is at our doorstep or, in the words of [3], that mathematics is the future frontier of biology and biology is the future frontier of mathematics.

It is our belief that Africa and, in particular, South Africa are ready to join this revolution. Africa, unfortunately, is the world hub for deadly diseases such as HIV/AIDS, malaria or Ebola and also has a large percentage of the population suffering from malnutrition, with frequently occurring famines. On the other hand, it has an amazing diversity of the environment and wildlife that, properly managed, could be the source of wealth for the whole continent. So, there is a great need for well trained epidemiologists, ecologists and mathematical biologists ready to develop new methods and join the collaboration with health and natural scientists. Fortunately, there is a huge interest among the students across Africa to study mathematical biology and epidemiology. Most bigger universities in Africa offer courses in these topics with some of them having mathematical biology among their Majors. The number of postgraduate students graduating with theses in mathematical biology is growing at a fast rate. The South African government and the National Research Foundation of South Africa have recognized the need to support this endeavour by creating to Research Chairs in the field: in Mathematical and Theoretical Biosciences (jointly held by the Stellenbosch University and the African Institute of Mathematical Sciences in Muizenberg, SA) and in Mathematical Models and Methods in Biosciences and Bioengineering at the University of Pretoria. Through these

Chairs many a further initiatives in the biomathematics have been supported. The Chair in Mathematical and Theoretical Biosciences has been involved in ecological problems and, in particular, in the study biological invasion. The focus of the Chair in Mathematical Models and Methods in Biosciences and Bioengineering is more directed towards population dynamics and epidemiology, where the Chair joined the National Research Foundation Community of Practice project, a national cluster of SARChI Research Chairs working on malaria and, in particular, on developing transmission blocking drugs. These, and many other initiatives, prove that mathematical biology in Africa is on the right track for providing a meaningful support in fight against diseases and designing knowledge based tools for the environmental management, control and protection.

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