The Higher Education Academy
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Mathematics as a tool in the Life Sciences

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Abstract
Teaching mathematics to students in the biological sciences is often fraught with difficulty. Students often discover mathematics to be a very 'dry' subject in which it is difficult to see the motivation of learning it given its often abstract application. In this paper I advocate the use of mathematical modelling as a method for engaging students in understanding the use of mathematics in helping to solve problems in the Biological Sciences. The concept of mathematics as a laboratory tool is introduced and the importance of presenting students with relevant, real-world examples of applying mathematics in the Biological Sciences is discussed.

1. Introduction

Life has got more complicated. Actually it has always been complex, but only with the advent of new technologies in the past 50 years to explore well inside living organisms from the atomistic level upwards, have we begun to understand just how complex it is. The advent of the genomic and now post-genomic age and the vast amounts of data being generated by experimental scientists, has seen us reach a paradox in the life sciences where we are data rich, but often understanding poor. Of even more a challenge is integrating this information and being able to ask meaningful and often insightful questions about what the data is showing, how it may lead to understanding the overall picture of what we wish to solve (e.g. a cure for cancer or heart disease) and how one moves forward to the next logical step in solving such problems when surrounded by such data.

Quantitative methods have in the past few decades begun to play an ever more increasing role in the Life Sciences, be it in the design of new machines for increasing the imaging of living tissue, for instance MRI, the development of new therapeutic strategies for drug delivery or manipulating tissue on the single cell scale to better understand diseases such as cancer. The increase in focus on specific genes and proteins in the 1980's and 1990's at the cost of undertanding how their manipulation affects the behaviour of the problem being addressed, led to the development of the field of Systems Biology at the end of 1990's. The field offers an opportunity to bring together what would often be seen as disparate fields, for instance molecular physics and control theory, to answer important biological and biomedical questions. Often it involves developing a mathematical model of a biological system or process to understand how the elements of the system do or do not work together as hypothesised. A well informed mathematical model can allow for the testing of various predictions which would otherwise be impossible or highly costly experimentally.

Whilst Systems Biology emphasises the understanding and elucidation of biological systems, the even newer field of Synthetic Biology focuses on bringing design principles in engineering to biological research. For instance, one may wish to design a cell to undertake a specific task, e.g. to metabolise two harmful constituents with the soil and glow red once it has done so. This involves taking what we know about how genes and proteins function at the intracellular (internal) cell level and designing a new pathway (much like designing an electrical circuit).

Whilst both these fields are in their infancy, it is projected their influence will grow. With it has come the realisation that future research in the Biological Sciences will require its practioners, i.e. today's students, to understand and utilise more quantitative subject material, specifically mathematics. However, the teaching of mathematics to students in the Biological Sciences is often fraught with many difficulties. How do you teach a subject to someone when they may have taken up a specific line of study (e.g. biology) to avoid it? What are the pitfalls and common problems faced in teaching the subject to undergraduate and postgraduate students in the Biological Sciences? Most importantly, how can these be overcome so students in this area can see the benefits of mathematical techniques in understanding biological systems, have respect for its use and thus be motivated to further learn or use these techniques in their daily work, research and teaching?

In this article I advocate the use of mathematical modelling as a useful way in demonstrating to biology students the importance of seeing mathematics as a useful tool in helping to answer questions in the Biological Sciences. Issues discussed include how mathematical modelling, through good examples, can be used to connect with students who have little or no interest in mathematics, how the process of mathematical modelling can be taught without recourse to complicated mathematics, why good examples are important and how this approach can be used to motivate further learning of mathematics in the Biological Sciences. I will also discuss my own experience of implementing this approach at both undergraduate and postgraduate levels.

2. The problem – growing up with mathematics

The outcome of learning mathematics is a very discrete process. Put simply, students either like it or they do not and this discovery is made very early on in, more often than not at primary school. For those who go on to study mathematics in higher education or areas which greatly rely on it, e.g. engineering, physics, computer science, it is often commented that they have a talent for it. For the remainder, mathematics remains allusive – a subject which is often treated with distain ("I could never understand fractions at school") and to some extent a mystery. Students in the Biological Sciences often fall into this latter group and it is the challenge many higher education academics now face, particularly in the UK, of seeking to meet the challenge of increasing the mathematical knowledge of their students, when many may have only completed GCSE mathematics, whilst ensuring they are ready for the future job market, in which understanding and applying quantitative methods is sure to become more of an issue.

3. Mathematics versus mathematical modelling

In presenting work to students and for our purposes here it is important we clearly clarify the difference between mathematics and mathematical modelling. Mathematics is generally defined as

> "the abstract science of number, quantity, and space, either as abstract concepts (pure mathematics), or as applied to other disciplines such as physics and engineering (applied mathematics)." [1]

It is the first part of this definition that many of us are familiar with as a result of our upbringing and education. Indeed a list of mathematical areas and concepts many of us have encountered during our time at school would most probably include the following:

- Number manipulation (addition, subtraction, division, multipication);
- Fractions and their manipulation;
- Decimals;
- Curve sketching (e.g. lines, circles, ellipses);
- Trigonometry;
- Definition of shapes in two and three spatial dimensions (e.g. quadilaterals);
- Concept of area and volume of specifc shapes (e.g. triangle, cube);

- Using and solving algebraic equations (e.g. writing down algebraic equations from word problems, solving quadratic equations);
- Graphing linear functions (e.g. equation of a line $y = 2x + 4$);
- More advanced trigonometric functions (e.g. cos, sin);
- Calculus (integration and differentiation of simple functions); and
- Basic elements of statistics (histograms, idea of frequency and randomness).

For more comprehensive details on the UK primary and secondary curriculumn the interested reader should consult the Department for Education Website [2].

In contrast mathematical modelling is something many people will not be aware of during their life time, but conversely encounter its direct and indirect consequences every day of their lives. By mathematical modelling we mean the second part of the above definition, Applied Mathematics. The field is focused on developing mathematical models of real world phenomena that can be solved and used to provide insight into a process or system being studied. For instance an engineer may wish to build a new car engine, but before doing so calculate the energy and force generated by a specific engine configuration. In today's highly competitive car market one would not even think to begin building a prototype without applying a mathematical model. It is the wide use of such models which permeates our very world, which we see the consquences of, but rarely the process undertaken to develop or use them.

Applied Mathematics utilises mathematical techniques and tools, many learnt at undergraduate and postgraduate university level, and thus the Applied Mathematician relies on developing a core knowledge of mathematics for not only developing mathematical models, but solving them.

4. Mathematical modelling as a laboratory tool

Mathematical modelling is not only a useful for bringing new insight and understanding to real world problems, but it can be used as a very good method for motivating those in other sciences to engage in learning mathematics. The aim here is that once students have been shown how mathematical modelling (underpinned by mathematics) can be useful in their chosen work, they may be further motivated to learn, or at least at the very least, appreciate its usefulness. Such motivation can be achieved by the use of appropriate and relevant examples which students can relate to as discussed in Section 5.

In the Biological Sciences mathematical modelling can be viewed as a useful and insight *tool*, much like any other tool in the laboratory, for helping to solve a problem one is interested in tackling. A model can allow: (i) different hypotheses to be tested and certain ones discounted, thus helping to direct experimental work; (ii) insight to be obtained when actually examing the system at certain spatial or dynamical resolutions is difficult or impractical (e.g. too costly); (iii) be used to develop diagnostic tools for future laboratory use.

Many elements of the mathematical modelling process can be taught without detailed mathematics. These include the following:

- the process of mathematical modelling (as detailed in Figure 1);

- what data is needed to inform the developed models and how one goes about this, e.g. literature search, further experiments, analysing/manipulating current data;

- the various strategies for modelling, e.g. modelling groups or individuals, doing so deterministically or stochastically;

- the methods for solving mathematical models, e.g. can one obtain an analytic solution (by pencil and paper) or does one have to use a computer? If the latter, which method should be applied for solving the model?; and

- how results of the modelling can be used to inform the biological system being studied.

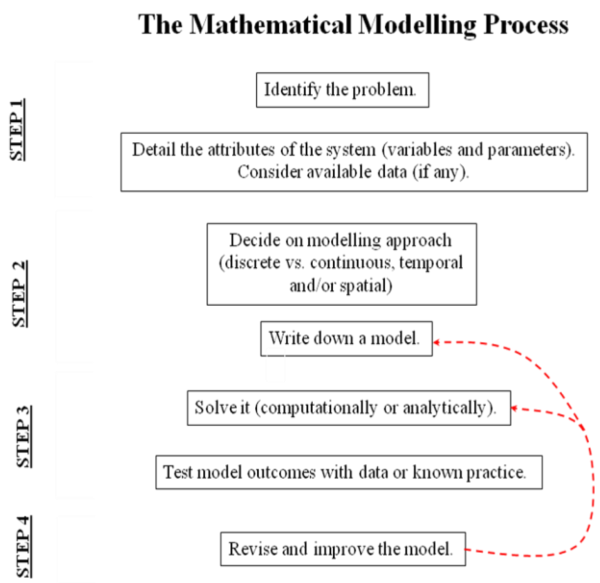

Figure 1: The main steps in developing a mathematical model of a specific problem. The dotted arrows indicate those steps which are required to be reiterated when revising the model

All of these elements can be discussed, and the author has, without the need for presenting or daunting a student audience with overly complicated mathematics. After doing so, it is then important to provide relevant examples of the use of mathematical modelling in helping to understand and/or provide insight into a biological question or problem. In doing so, students can clearly see the application of the process and how it is useful in a biological context.

5. Motivating students through real-world examples

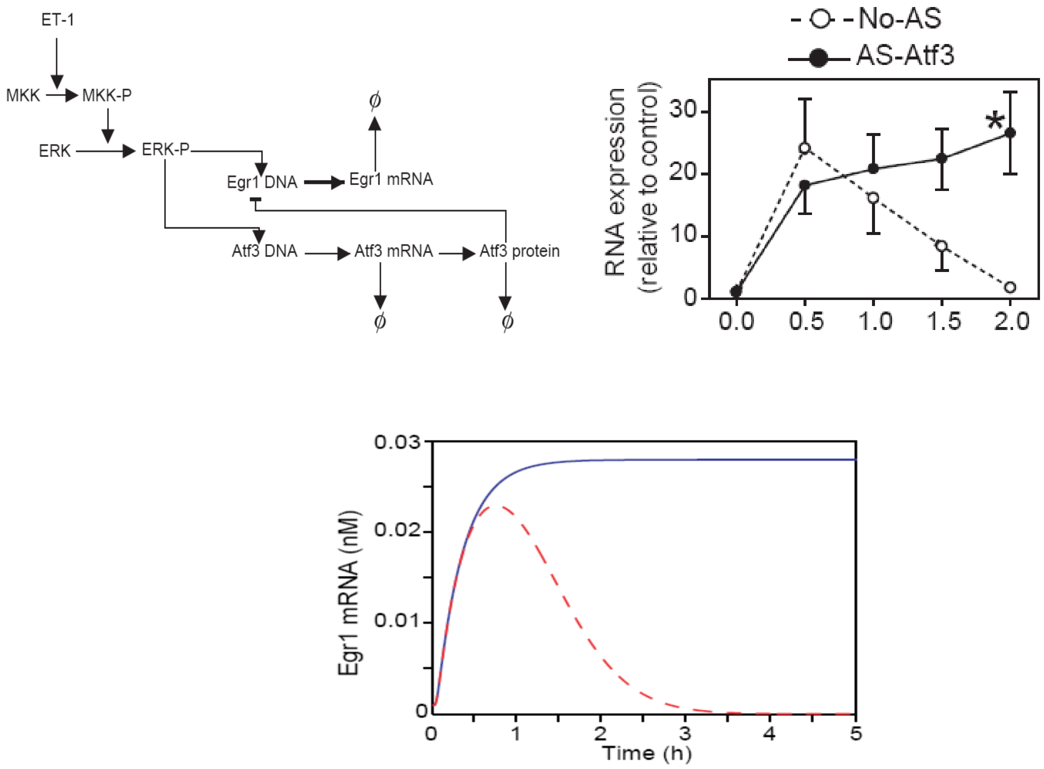

Figure 2: **Modelling the Atf3 – Egr1 expression pathway in cardiac myocytes.** The respective pathway (A) was modelled by formulating a nonlinear ordinary differential equation (ODE) model of the genetic network. This then allowed certain hypotheses to be considered and a good fit (B) to the experimental data to be obtained (C) (here the dotted red-line indicates Egr1 expression levels in the presence of Atf3 protein, whilst the solid lines indicates in the absence of Atf3 protein). For further details see [3].

A critical element of the process outlined here is that students are presented with examples that are directly or indirectly relevant to their areas of interest. For instance, there is no point in presenting an example regarding how mathematical modelling has been very useful in helping design a new circuit board to a group of undergraduate biology students! The author has most recently used the example of understanding the connection between two early gene genetic/protein expression pathways in cardiac myocytes to demonstrate to students how modelling can provide insight into a given problem. The problem was to understand the connection between how the protein Atf3 could possibly affect levels of

Egr1 mRNA, important proteins in the control of cardiac hypertrophy [3]. By developing a mathematical model our work was able to show that competitive binding of Atf3 protein to Egr1 DNA could alone not account for the observed decrease in Egr1 mRNA after a certain time. Instead the process relies on Atf3 protein "removing" phosphorylated ERK bound to Egr1 DNA after that binding process had occurred. Once this process had been identified considerably better fits to the biological data could found, values for the rate of binding could be determined and Atf3 protein was confirmed as the only inhibitor of Egr1 mRNA expression levels as shown in Figure 2.

The authors experience to date in applying the methodology so far outlined here has been in the following areas:

- an MSc in Bioinformatics to students with no or limited background in mathematics;
- Biological Science postgraduate PhD students and industrialists on a one day introduction to mathematical modelling in the life sciences; and
- first year undergraduate biomedical science students.

In each case the lectures covered the process of mathematical modelling detailed in Figure 1, with relevant examples. In the case of (1) and (2) this was then followed by a practical session where students were given a problem with appropriate experimental data and asked to think about how they would model the process to answer the questions posed. This did not require actual mathematics, but just thinking about the mathematical modelling process, what you would do (e.g. Would one model the problem from a population or individual perspective? Where would you get data from?), how you would solve it and how you might revise it. In the case of (3) this was two introductory lectures regarding how biology has become more quantitative and the need for such methods in order to understand data being generated. These lectures form an introduction to the area of quantitative modelling which students can explore in more advanced modules (Systems Biology and Computational Biology) in their third year.

In each case students have been very positive about how the work has been presented to them and been more appreciative of the role mathematics has in helping to understand problems in their area of interest.

6. From mathematical modelling to teaching mathematics

This article does not advocate that teaching mathematical modelling should replace the teaching of mathematics to biological science students. Instead, teaching mathematical modelling, which at the least can be achieved in a few introductory lectures as detailed above, can be used as a motivational tool for engaging students more positively with mathematics with an aim of encouragaging them to understand why learning mathematics is useful. This approach can work at a range of levels – from early undergraduate teaching right through to postgraduate PhD and beyond. Clearly the next stages of teaching mathematics then need to be clearly thought out. For instance, if one is faced with teaching statistical methods to undergraduate students, the idea of presenting relevant examples from genetic testing may well prove a better example than that outlined in Section 5 here. On the other hand, the author has found teaching the basic elements of how ODE models of biochemical reactions can be formulated and solved using mathematical software, a good tool for engaging with undergraduate students in cell biology and biochemistry.

7. Conclusions

Teaching mathematics to Biological Science students without providing clear motivation as to why can prove particularly frustrating and difficult for not only students, but academic practioneers. This paper advocates the use of mathematical modelling in allowing students to appreciate how hypothetical mathematical models can be generated to provide insight into biological problems and questions.

Two key ingredients are:

(i) clearly outlining the mathematical modelling process; and

(ii) providing relevant real-world examples that students can relate to. In doing so students will begin to see modelling as a useful tool at their disposal in tackling questions they may be faced with, not only during their studies, but future endeavours. By positively engaging with and understanding where mathematical modelling can be useful, it is hoped students will be more engaged in learning mathematics both during their studies and beyond.

8. References

[1] Oxford English Dictionary online (www.oxforddictionaries.com). Last accessed 20/01/2011.

[2] Primary and Secondary Mathematics Framework, Department for Education (UK) (www.http://nationalstrategies.standards.dcsf.gov.uk/). Last accessed 20/01/2011.

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