The Physics of Physik

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Perspective

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Introduction

> When you can measure what you are speaking about, and express it in numbers, you know something about it. When you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge but you have scarcely, in your thoughts, advanced to the stage of science. *William Thomson, 1st Baron Kelvin*

The discipline of measurement lies at the heart of modern science. Arguably, the most important development in modern medicine is not the development of 'precision medicine' or the emergence of 'big' data, but rather the increasing attention to measurement, across the spatial and temporal scales, which underlies both precision medicine and burgeoning data sets. It is instructive to see how central measurement is to scientific progress by contrasting the development of physics and medicine. Galen, Harvey and many others advanced measurement in medicine; indeed Harvey's work contributed to developing understanding of the physics of fluid flow, in a manner that reflected the cross-disciplinary nature of science in his time.[1,2] Measurement in medicine is difficult: the sheer complexity of biology means that even identifying appropriate measurements to make in medicine can be challenging and, if meaningful variables are identified, it is often technically difficult to make accurate measurements.[3] In physics, key concepts such as mass, charge, distance and force are well-defined and, generally, measurable. They also turn out to be very useful; by combining these measurements with some simple but profound symmetries – the laws of physics – it has proved possible to develop a deep understanding of the fabric of the cosmos. This understanding is framed in the language of physics: mathematics. Measurement and mathematics go hand-in-hand in physics, with mathematics providing what seems at times to be an uncanny ability to provide predictions that may then be tested experimentally. Thus, physics is characterised by two key steps: measurement and the development of mathematical models. The construction of a mathematical model of the system in question represents the theory within which the measurements are understood. This is both informative and useful; for example, the mathematical model enables the system's behaviour to be predicted in conditions beyond those measured. This two-step process –measurement and modelling – is at the heart of physics whereas, until relatively recently, the modelling step in particular has not been commonplace in biology or medicine, in part reflecting the challenges of meaningful measurement noted above.

Given the increasing availability of large amounts of useful data based on careful measurement in biology and medicine, can we now draw useful lessons for the development of medicine from noting how physics has developed historically? Will mathematical models be included as a routine step in clinical research? Is there now a 'Physics of Physik' which reflects converging scientific approaches? Can mathematical models accelerate the pace of medical advances?

This paper offers some reflections on these questions. It draws on several historic and current examples to illustrate the potential impact of a more mathematical approach to medicine, as well as noting some developing areas and possible implications for the medical curriculum. It concludes with suggestions on how interested clinicians might engage with the topic; a short bibliography is provided. Some elements of this paper, including the title, appeared previously in an article on physics and medicine written for *Medicine Matters*.[4]

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Mathematical models in physics

Two recent and prominent examples from physics illustrate the central role that mathematical models – theory – play in physics; the first is the discovery of the Higg's boson. While this was confirmed experimentally at the Large Hadron Collider in 2013,[5] it was predicted in 1964 by three independent groups – Peter Higgs,[6] Robert Brout and Francois Englert,[7] and Gerald Guralnik, Carl Hagen and Tom Kibble[8] – from the mathematical theory of subatomic particles, as a feature of the theory required for the particles to have mass. The 2013 Nobel prize was awarded to Higgs and Englert 'for the **theoretical** discovery of a mechanism that contributes to our understanding of the origin of mass of subatomic particles, and which recently was confirmed through the discovery of the predicted fundamental particle, by the ATLAS and CMS experiments at CERN's Large Hadron Collider.'[9] [bold typeface added].

The second example – the experimental observation of gravitational waves in 2015 at the Laser Interferometer Gravitational-Wave Observatory by an international collaboration including physicists from the Universities of Glasgow and the West of Scotland,[10,11] – is characterised by an even longer gap between mathematical prediction and observation; gravitational waves having been predicted, as ripples in spacetime, by Einstein's general theory of relativity in 1916.[12,13]

It is worth noting that this paper draws a distinction between mathematical models and statistical models; the latter, of course, are already well-established to good effect in medicine and not the subject of this paper. In this context, by 'statistical models' we mean those that determine numerical relationships between data sets but without reference to any underlying biological mechanism. In contrast, by 'mathematical models', we mean those models that are constructed based on a putative understanding of biological mechanism. A historical example from physics illustrates this distinction;[14] in 1543, Copernicus proposed the heliocentric model of the solar system. The Danish astronomer Tycho Brahe assembled a large volume of accurate data which included the relative distances of the planets and sun. Brahe hired a brilliant mathematician, Johannes Kepler, who reviewed the planetary data and noted a series of statistical relationships, including that between the period of the planetary orbit and the distance of the planet from the sun. With characteristic insight, Newton realised that the statistical relationship could be explained as a consequence of an inverse square law of gravitation describing the attractive force between two objects. Newton had thereby constructed a mathematical model based on the earlier statistical model.

These examples of the predictive power of a mathematical theory in physics are clearly impressive and beg the question 'Could predictive mathematical models become commonplace in medicine?' In an era of 'big data', it is not surprising that the answer to this question would appear to be 'yes' and it may well be that this aspect of physics will make an even greater impact on medicine than the well-established role that physics has played in the development of medical technologies.

Developing mathematical models in medicine

Some areas of medicine already have a long and distinguished track record of mathematical modelling; clinical epidemiology of infectious disease[15] and radiotherapy[16] being two examples. However, recent years have seen a significant increase in the number of articles and journals devoted to building mathematical models in medicine and biology; see for example Sneppen,[17] *Physics of Life Reviews*[18] and *Mathematical Biology & Medicine*.[19]

It is worth summarising a few key principles that guide the development of mathematical models.[20] From the outset, it is important to recognise that 'all models are wrong but some are useful'.[21] Models are constructed based on a putative mechanism. In describing the mechanism in mathematical terms, it is important to adopt Occam's razor: that the model is kept as simple as is consistent with the data.[22,23] Models with many parameters that can be adjusted to ensure a good fit to the experimental data – more specifically, where the number of adjustable parameters is comparable to the number of data points – are not good models and do not yield useful insights.

There is a temptation to associate complex data sets with complex underlying models but this is not necessarily so; for example, May's seminal paper[24] confirms that an apparently simple class of mathematical equations can give rise to extremely complex patterns in the data sets being modelled. This also illustrates why intuition can be misleading in trying to understand mechanisms that give rise to observed patterns in clinical data sets: complex patterns do not always lead to complex models.

The mathematical model should also make predictions about how the system would behave under a range of different conditions. Models which simply describe observed behaviours are not informative. The best models become an element in a cyclical exchange between theory and experiment, where experimental data are described by a candidate model capable of predicting the data that should be observed under a different set of experimental conditions. Depending on the outcome of the set of experiments suggested by the model, adjustments are then made to the model and the process of testing repeated.

These aspects of model building – simplicity, predictive power and iterative testing by experiment – are now illustrated by several examples of clinical relevance.

Mathematics in the clinic

Haemodialysis has long been described by mathematical models.[25] Urea is used as a marker of toxicity and urea clearance by haemodialysis is used as a measure of dialysis dose. The process of blood urea clearance during haemodialysis is amenable to compartmental modelling in which the urea is assumed to be distributed in one or more notional body compartments. Urea clearance can then be described in mathematical terms using the principles of mass transport, leading to several mathematical expressions for dose based on the measurement of the blood urea concentration pre- and post-dialysis; see, for example the HEMO pilot study.[26] The precise equation for the dose is dependent in part on the complexity of the underlying compartmental model, but a mathematical approach has permitted the development of more accurate measurements of the dose of dialysis; for example, one approach which was tried used an extra blood sample taken during dialysis, rather than having to wait to measure the post-dialysis equilibrium blood urea level which can be up to 1 h after treatment finishes.[27] Current dialysis treatment guidelines[28] are based on a series of trials that assessed the relationship between dose and mortality, all of which were underpinned by a variety of mathematical models.

The international Physiome project[29] is attempting to provide a comprehensive, multi-scale mathematical model of physiological dynamics and functional behaviour of the human body – a virtual human – and is a particularly ambitious example of potentially clinically-informative mathematical modelling. The Physiome project builds on previous work, including extensive work developing mathematical models of the electrophysiology of the heart. These models have become increasingly useful for clinicians; for example, a recent review article by Trayanova and Chang[30] described how a mathematical model of the heart – implemented as a computer simulation, which is the case for most models – can optimise anti-arrhythmia therapy. The model enables a wide range of different conditions and treatments to be readily simulated and assessed.

The Moffitt Cancer Centre in the USA has an extensive and established research programme in mathematical oncology that entails the careful combination of experiment and mathematics.[31] The Centre is now extending modelling to the selection of treatment strategies for chemotherapy and targeted therapies. The models notably include those based on the evolutionary dynamics of tumours and lead to some novel hypotheses; for example, in a recent paper by Ibrahim-Hashim et al.,[32] it was suggested that identifying and modelling intra-tumoural subpopulations based on their adaptive strategies rather than their molecular properties allows their cellular and environmental interactions to be described mathematically. In turn, these models enable potential therapeutic interventions (for example, manipulation of pH local to the tumour) to be identified which steer the tumour development into a less invasive phenotype.

One of the most elegant recent examples of a mathematical model which describes complex biology is that developed by the Simons group at Cambridge.[33,34] Simons and colleagues use an approach based on the mathematics of branching and annihilating random walks to explain the morphology of branching organs such as the mouse mammary gland, kidney and human prostate. The model demonstrates that complex branching epithelial structures arise due to three simple rules, without reference to a deterministic sequence of genetically-programmed events.

The overall goal of mathematical medicine would be the creation of predictive, patient-specific mathematical models (PSMs), based on a detailed mechanistic description of disease (rather than simply a statistical model) and which draw on large and disparate patient data sets.[35] Such models could then be used to simulate the impact of different treatment regimes and to suggest optimal, tailored treatments. These models would be developed iteratively, drawing on data from detailed regular monitoring of the patient to refine the PSM. If this approach were to be realised more widely, a review visit to the diabetes clinic, for example, might include reference to a PSM based on the patient's blood glucose measurements logged over the previous year and accompanied by cognate clinical data provided by wearable technology. The PSM could suggest adjustments to the treatment regime which would in turn lead to an adjustment of the PSM – the patient data would lead to a recalibration of model parameters – and which might include factors such as diurnal and seasonal variations. The work of, for example, Roman Hovorka[36] suggests that such an approach is not fanciful.

In practice, such PSMs are likely to be hybrid models: a mix of statistical and mechanistic approaches. In cancer, this combined approach is reasonably advanced and draws on work in systems biology.[37]

It is important to note that the development of mathematical models in medicine is not limited to biomedical applications. For example, there is a fast-developing community of health system modellers, comprising mathematicians and clinicians, who are applying mathematics to the study of patient care pathways.[38] This demonstrates the reach of a mathematical approach to understanding healthcare in its broadest sense. In an age when health systems are under particular pressure, the role of mathematics in assessing the merits of different configurations of health systems is increasingly recognised.

New biology and medicine will need new mathematics or, rather, new applications of existing mathematics. A good example of this is the application of network (or graph) theory which was developed in its original form by pure mathematicians, who were not originally motivated by real-world applications.[39] Network theory[40] describes how networks of interacting objects (for example, people, ideas, molecules) behave as a whole system (for example, the internet, transport networks, or gene regulatory networks). Unsurprisingly, given that biology and society are characterised by networks, this branch of mathematics is now contributing significantly to our understanding of many areas including genomics, proteomics, cellular physiology, public health and health systems; see for example Buchanan et al.[41] and Zheng et al.[42]

Barriers to model-building

The first barrier to constructing mathematical models in medicine is that biology is complex. Thus, whereas physics has made immense progress by 'mathematising' the basic symmetries which seem to underlie the cosmos, biology is replete with emergent and contingent phenomena, which cannot be readily reduced to a series of basic laws framed by mathematics. In biology, evolution is the dominant paradigm and this has long been established as a mathematical-grounded theory,[43] which has in turn spawned the applications of evolutionary models to, for example, the emergence of resistance in cancer.[44]

'Emergence' is a rather slippery concept but basically reflects the fact that large numbers of simple interacting objects display collective properties which cannot be easily deduced from the behaviour of an individual entity.[45] The mathematics of emergence was first developed in the physics of condensed matter. A pioneer in the physics of emergence is the Nobel Prize-winning physicist, Philip Anderson, and his paper *More is Different*,[46] is now recognised as being highly relevant to biology.

A second barrier is linked to the quality of clinical and biological data. As mentioned above, Byers notes that the data available to those in the biological and clinical sciences are often rather messy,[3] which often contrasts with data available to theoretical physicists. As Byers notes, messy data sets are more suited to analysis by statistical techniques, including machine-learning, and require an approach to determining underlying models, in which a range of different mathematical models are assessed for agreement with the data using a Bayesian approach. This approach is alien to most physicists. Indeed the physicist Ernest Rutherford is said to have observed that 'If you need statistics then you should have done a better experiment'.[47] This view persists in some quarters of the physics community and must be countered.

The third barrier is cultural; the recent Nurse Review of the Research Councils[48] reflects on the need to foster interdisciplinary science and this is a particular challenge for a mathematically-based science such as physics. Mathematics is a powerful language but, until recently, not one which was taught or deployed routinely by the biological or clinical communities. It is appropriate to briefly outline a number of routes by which this deficit may be addressed.

Routes to engagement

Major funders of research in the UK, including the Research Councils, Cancer Research UK, the Wellcome Trust and the National Institute for Health Research (NIHR) have now created schemes to draw in mathematicians and physicists to biological and population sciences, and to help clinicians engage with other sciences. Examples include:

- The Physics of Life Network – http://www.physicsoflife.org.uk – funded by the Biotechnology and Biological Sciences Research Council and the Engineering and Physical Sciences Research Council (EPSRC). The network is keen to encourage clinician membership and is open to all
- Five Centres for Mathematical Sciences in Healthcare funded by the EPSRC: https://www.epsrc.ac.uk/newsevents/news/newmathscentres. These Centres have established routes to clinical engagement and are keen to increase clinical participation
- Cancer Research UK's Multidisciplinary Award scheme: http://www.cancerresearchuk.org/funding-for-researchers/our-funding-schemes/multidisciplinary-project-award. The scheme is co-funded by the EPSRC and requires at least one investigator from the engineering or physical sciences
- MASHnet – the UK network for modelling and simulation in healthcare: http://mashnet.info
- The Research Councils fund various discipline-hopping awards, see for example: http://www.rcuk.ac.uk/research/xrcprogrammes/otherprogs and https://www.epsrc.ac.uk/funding/calls/htdisciplinehopping
- The Medical Research Council Skills Development Fellowships emphasises the development of quantitative skills: https://www.mrc.ac.uk/skills-careers/fellowships
- NIHR funds fellowships that are open to those wishing to develop quantitative skills applied to health research. See https://www.nihr.ac.uk/funding-and-support/funding-for-training-and-career-development/training-programmes
- Many university mathematics departments have vigorous programmes of research in mathematical modelling in medicine. A reasonably comprehensive list is found at https://www.maths.ox.ac.uk/groups/mathematical-biology/links/groups

University curricula are also responding to the need for improved training in mathematics to extend beyond the physical sciences, although there is more work to be done, not least in strengthening the teaching of mathematics in schools. There are numerous opportunities for mathematicians and physicists to undertake postgraduate training in mathematical modelling in medicine; see, for example the universities of Nottingham[49] and Dundee.[50] The reverse trend – mathematical training for doctors – is not quite so commonplace. The impact of mathematics on medical curricula needs to be thoughtfully reviewed. It makes little sense to expect most medical students to undertake extensive training in mathematics, which is a deeply technical discipline, although there are some who train in medicine following a first degree in physics or mathematics and by whom the potential value of mathematical modelling in medicine is likely to be appreciated. Training in the principles of quantitative analysis is perhaps a better emphasis, as it leads to an appreciation of the power of mathematics to encapsulate clinical understanding and the value to medicine of mathematics, physics and cognate disciplines. Special study modules, intercalated degrees and Masters level courses are emerging, sometimes linked to courses in informatics or statistics: see for example the Farr Institute.[51] Open access resources, including public lecture series (see for example the Institute for Mathematics and its

Applications[52]) are particularly valuable. Such opportunities should be taken by many more clinicians.

Conclusion

The increasing convergence of 'Physics and Physik', based on complementing clinical skills with mathematical insight, offers rich rewards. Indeed, the mathematical model is a key component of what is increasingly recognised as 'Systems Medicine.' As West notes,[53] 'A more integrated, systemic approach is needed to fully understand the processes of health, disease and dysfunction…Integral to this approach is the search for a quantitative, predictive, multilevel, theoretical conceptual framework that both complements the present approaches and stimulates a more integrated research agenda…'.

Predicting the future is fraught with difficulty but drawing an analogy with weather forecasting may reflect the future for medicine; until recently, much forecasting was based on precedent and pattern recognition but the availability of a vast amount of accurate observational data led to the development of large complex mathematical models of the weather system which in turn has led to significant improvements in the accuracy of weather forecasts.[54] Medicine is considerably more complex than weather forecasting but the progress made to date in developing predictive mathematical models that can inform clinical practice suggests that the analogy has some merit.

In conclusion, lest anyone think that mathematical medicine will lead to an unduly narrow view of clinical practice, it is only appropriate to end by tempering Kelvin's apparently rather one-dimensional dictum with a quote attributed to Einstein but which is probably more accurately attributed to the American social scientist William Bruce Cameron:[55]

> Not everything that counts can be counted, and not everything that can be counted counts

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