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Meeting Report

The first international workshop on the role and impact of mathematics in medicine: A collective account

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Abstract: The First International Workshop on The Role and Impact of Mathematics in Medicine (RIMM) convened in Paris in June 2010. A broad range of researchers discussed the difficulties, challenges and opportunities faced by those wishing to see mathematical methods contribute to improved medical outcomes. Finding mechanisms for interdisciplinary meetings, developing a common language, staying focused on the medical problem at hand, deriving realistic mathematical solutions, obtaining high quality data and seeing things through "by the bedside" are some of the issues discussed by the participants.

Keywords: Mathematics, medicine, interdisciplinary research, therapies

Introduction

This paper is a collective account of the First International Workshop on The Role and Impact of Mathematics in Medicine (RIMM) held at the Poincaré Institute in Paris, June 10-12, 2010. The workshop brought together mathematicians [1-4], physicians [4], mathematical biologists [5], biostatisticians [6], modellers [7] and others with the goal of understanding how mathematics and statistics can better impact medicine.

During the meeting, scientific papers were presented covering a broad range of subjects ranging from mathematical epidemiology to medical imaging. Our goal was to "take stock" and reflect on our methods, our impact, and the need for the mathematical sciences to move from a descriptive to a more prescriptive or predictive role in the medical sciences. This paper brings together contributions on these topics from nine of the twenty participants who attended the meeting.

Background

The role of mathematics and statistics in the clinical and biomedical sciences is ever increasing [8-10]. This is reflected in the growing number of journals and articles devoted to the subject [11]. Today there are a number research institutions devoted exclusively to the interface between mathematics and medicine. The Centre for Mathematical Medicine in Toronto (Canada), the Battelle Center for Mathematical Medicine in Columbus, OH, (USA) and the Centre for Mathematical Medicine and Biology in Nottingham (UK) are just three examples in the English-speaking world.

The three main goals of theoretical modelling of medicine are: (1). elucidation of new understanding; (2). prediction of medical/biological outcomes without the need for complex experiments; (3). derivation of optimal therapeutic solutions.

These three goals rely to various degrees on the collection and description of data and on the construction, optimization and testing of models. Advances in these areas since the Second World War have relied crucially on the advent of computers. This has led to the era of computational mathematics which has greatly extended the scope of standard mathematical models. Rapid developments in computer science also opened new diagnostic frontiers with the development of sophisticated imaging software which rely heavily on advanced numerical methods [12].

The nature of mathematical/medical interactions

Prerequisites

The development of well informed mathematical models in medicine requires deep knowledge and understanding of both mathematics and medicine. A small number of workshop participants had the ideal combination of advanced academic training in both areas, e.g. a Ph.D. in mathematics and a medical degree. This dual training ensures a real commitment to long-term collaborations and an understanding of both languages [13]. It also reassures potential collaborators from both fields that the commitment is genuine. It is important to point out that training in both areas is currently more the exception than the rule, but as the influence of mathematics in medicine continues to grow this situation may change.

Another approach is to train ab initio in an intrinsically interdisciplinary field, such as biostatistics or operations research. The former is self-evident, and in operations research one can specialize in applications to medicine. The most common situation however is when researchers from strictly mathematical or medical backgrounds come together to solve medical problems.

The mathematician's challenge

Researchers with a purely mathematical background need to develop a sustained interest in the applications of mathematics to the health sciences. Minimal training or self-instruction in an area of (bio)medicine compatible with the mathematician's interest is essential. In order to contribute substantive ideas to the field, years of collaboration with a (bio)medical colleague are required. Moreover, the specific application needs to be carefully chosen. For example, a specialist in the theory of partial differential equations could find few direct applications of his/her expertise in modelling global health trends.

The physician's challenge

Practicing medical doctors interested in collaborating with modellers have several hurdles to overcome. First their clinical practice leaves little time for research. Second, the physician needs to be committed to the collaboration even when the research may not have immediate clinical applications. Third, he must be sufficiently well-versed in mathematics. Indeed, doctors are taught basic methods to describe data and perform statistical testing. However, model building, which is of central importance in mathematical medicine, is rarely taught in medical school.

The meeting of minds and talents

When researchers from the same discipline collaborate there may be underlying competition. When a biologically competent mathematician and a numerate physician work together, it is on the contrary all about complementarity and mutual understanding. The physician (or more generally life scientist) must understand the mathematical nature of his problem and be able to communicate it to his mathematical counterpart. The mathematician in turn must find the right tool to solve the problem and be able to explain it to the physician. Ideally the results will have clinical applications and the physician will develop the self-confidence needed to independently use and apply the mathematical solution "by the bedside". This process can take time. While the busy physician gets on with his clinical work the mathematician may spend extended periods of time developing the solutions and making sure they make sense biologically. Such collaboration is rewarding but requires dedication and commitment from both parties as well as a conviction that mathematical techniques can help even if there are risks involved.

Unfortunately such interdisciplinary collaborations are sometimes viewed with some skepticism by both disciplines. However this is changing and there are more and more mechanisms in place to facilitate interactions between researchers from different fields.

Mechanisms for interactions

Research centers, universities and governments need to facilitate and encourage work that takes a project from the modeller's mathematical "drawing board" to the bedside. This can be done by arranging meetings, providing training, funding dedicated positions, etc.

Interdisciplinary meetings

Interactions between the mathematical and medical sciences occur through interdisciplinary conferences and workshops. Conferences involve participants attending talks and engaging in personal discussions over breaks. In general, however, practitioners in the clinical and biomedical areas generally drift towards key conferences in their own areas as do those in the mathematical sciences. There are thus few who endeavour to present mathematical work at biomedical conferences, although this trend is changing. Likewise there are few clinicians who attend a mathematics-in-medicine conference, unless explicitly invited. Thus the conference mechanism does not always ensure the maximum likelihood of interaction between the disciplines.

Workshops are generally smaller, in contrast to conferences, and rely on the organisers actively selecting members from different communities who are amenable or open to interdisciplinary work. Formats for such meetings include talks followed by facilitated periods of discussion. These are either directed by the organizers or participants are left to freely discuss ideas with others in extended discussion/tea breaks? Such a mechanism is successful when problem areas are clearly identified and the participants, particularly those from the life sciences, are open to the ideas and insights that mathematical research can bring.

Given the nature of mathematical research and the complexity of problems in the life science there exist few forums whereby mathematicians are presented with new "open" problems by clinicians and biomedical scientists. One tried and tested workshop format in the United Kingdom and more recently Canada, is the series of Mathematics-in-Medicine Study Groups.

Mathematics-in-Medicine Study Groups (MMSGs)

An MMSG workshop is a week-long gathering. During the first day clinicians and biomedical scientists present their questions/problems to an assembled audience of mathematical modellers. Following this the problem presenter and the mathematicians interested in working on their problem spend the rest of the workshop brainstorming and working on the problem/questions. In this way dialogue between the two disciplines is focused on a specific problem that each is keen to solve. More often than not the questions lead to difficult mathematical problems that are challenging for the mathematical modellers.

Such meetings have a successful track record of creating new collaborations, projects and publications, which are facilitated by further follow-up meetings after the main workshop (www.maths-in-medicine.org). The format is amenable to a wide variation of types of biomedical/clinical problems, and often means a range of mathematical techniques may be applied to a problem thanks to the varied mathematical expertise present.

Jennifer Siggers, of the UK MMSG program gave the participants an impression of what it is like for a mathematician to organise and attend a MMSG. To do this she presented a problem proposed at the 2009 meeting on cardiac arrhythmias. Jennifer described the timeline for organising the group and emphasized the need for early planning and continual discussion with the clinicians. She described the clinical problem of atrial fibrillation and the state of the art in terms of treating it. She also briefly described the approaches that the study group participants had tried to use to solve the problem, and the follow-up work that has been done.

After this the MMSG representatives ran a mini-MMSG. Marcus Tindall, Alexander Foss and Jennifer Siggers presented two problems, chosen for their potential to make some progress in a relatively short time. The audience broke into two groups and discussed possible approaches to tackle the problems. The very short session (30 minutes) produced some surprisingly fruitful and insightful discussions. The session concluded with a brief discussion on the role of mathematics in medicine, particularly the potential opportunities and pitfalls, and also a discussion on how to progress further in this area of research.

Positive comments on the MMSG presentation were received from a number of audience members. Many were surprised and impressed that it is possible to make any decent progress in only one week on a problem for which the participants had little or no prior specialist knowledge.

Challenges

Participants did not shy away from the obstacles and difficulties that impede progress in the applications of mathematics to medicine. The complexity and relevance of mathematical tools applied to medicine were identified as two key challenges.

Simple vs. complex models

Physicians have difficulty appreciating the role of mathematics in their field. At the same time it is important to keep them fully involved in the entire modelling process (e.g. of model creation) and not just consider them as "sources of data to feed the models".

Physicians can be discouraged by some mathematicians' "narrowness" of view and reluctance to stray much beyond their mathematical comfort zone. This can translate into oversimplified models that are easy to understand and tractable but irrelevant. A typical example may be a mathematician's propensity to reduce a three-dimensional problem to one dimension. This may simplify his job, but he needs to convince the physician that the one-dimensional solution is only a first step and/or that it provides at least some useful insights into the more realistic problem.

If physicians can be left unconvinced by oversimplified models, they can, at the other extreme, be overwhelmed by some mathematicians' overly sophisticated models aimed at reflecting complex biological or clinical realities. Such models are hard to convey to the clinical investigators who would ultimately need to adopt the resulting technology. Having said this, there is a “wow” factor that accompanies complex mathematics, and this can be sufficient to have success in publishing the ideas.

To be sure, there is a fine line between developing an overly simple but tractable model which does not mimic reality sufficiently well, and one which is overly complex and which cannot be properly parameterised or used informatively. In any event, as numerical methods improve in parallel with computing power, tractability becomes less critical. The important issues are accuracy, clarity and "relevance by the bedside".

Relevance by the bedside

An unusual characteristic of the workshop is that participants came from various (sub) disciplines and use mathematics in very different ways: modelling cardiac rhythms, optimizing cancer therapies, fine-tuning medical imaging algorithms, or predicting the future number of HIV cases are all worthy endeavours. However they impact patients in different ways, on different time-scales, and in more or less measurable ways. This diversity may complicate any narrative concerning success stories "by the bedside".

Still, the main reason for using mathematical/ statistical methods in medicine is to improve health outcomes and therapies. A model that accurately replicates cardiac rhythms or the spread of cancer cells is inherently interesting as a description of biological processes, even if it has no immediate application. It is still vastly better if the model is realistic, can be fitted to clean data, is predictive and makes a real difference "by the bedside". As examples, cardiac resynchronization therapy and cancer therapy have benefited greatly from collaborative efforts between the medical and mathematical establishments. Clinical trials in those and many other areas are planned or under way.

Outcomes and their measurement

Tangible outcomes

"Downstream" from the modelling effort, it is often the biostatistician or epidemiologist who will evaluate a model from initiation of clinical testing through to clinical trials and outcome studies leading in case of success to clinical applications "by the bedside". Indeed, some relatively simple mathematical/statistical concepts have had a major influence on medical research and its application in the clinic. These include the concept of randomization, which revolutionized the way in which new drugs are tested, the development of genetic models that have led to the identification of numerous genes that influence the risk of major diseases, and the development of predictive models, which are increasingly used by patients, clinicians, and healthy members of the public, to determine individual risk of disease, or of prognosis among patients with a disease.

Perhaps measurable success by the bedside is not the entire story. Outcomes come in various forms and may not always be measurable in tangible ways.

Intangible trickle-down and other effects

A mathematician's biomedical ignorance can have a surprisingly positive effect when extracting the information he needs from a medical scientist. Indeed, more and less naive questions force the medical scientist to think clearly about ideas he may never have articulated before. This thinking process will move things along by kindling new ideas and getting both sides to think together of a problem in converging ways, with converging vocabularies.

For example a mathematical epidemiologist may query the parameters needed to model the usefulness of bed nets to prevent the spread of malaria. The medical entomologist will then struggle to think of how much/how often mosquitoes are found in dwellings, what are the age groups of those most likely to be bitten at night, etc. This can lead both to think of new control strategies such as keeping mosquitoes away from dwellings, which may result in alternative models with different outcomes. The next time the entomologist is in the field he will look at things differently and ponder the possibility of alternative strategies. The team's report to a government or international body (e.g. WHO) can influence policymakers and represents a trickle-down effect that is intangible and goes beyond clear-cut mathematical results on the efficiency of bed nets.

Another example is the mathematical modeller trying to understand the dynamics of cancer cells in a therapeutic rather than purely descriptive perspective. He may challenge an oncologist into thinking of new ways of fighting tumour cells. As an alternative or a complement to attacking them directly with chemicals (cytotoxic drugs), the modeller may suggest limiting their emergence "at their source" e.g., for leukaemia cells, in the bone marrow. In an interactive attitude, the clinician, who usually has already thought of this approach, can provide the principles needed to design optimal strategies at the molecular scale. Such strategies, worked out as a result of the mathematical-life science interaction, will then be applied in cell cultures, in animal experiments and finally in clinical trials. This movement back and forth between fundamental research and clinical trials is essential (**Figure 1**).

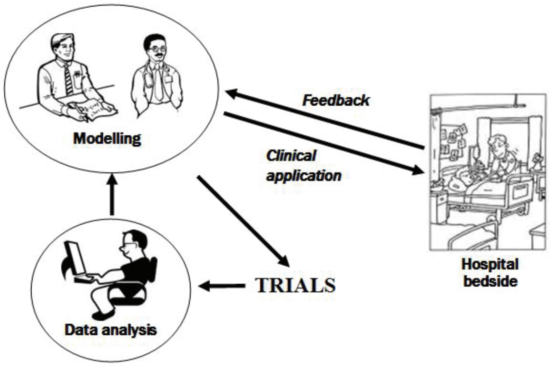

Figure 1. Flowchart of the collaboration between a modeller and clinician (top), leading to clinical trials, data analysis (bottom), and clinical applications (right). Several trials may be required and further iterations necessary after the modeller/clinician team receives feedback from the bedside.

Conclusion

The workshop participants agreed on a number of actions that greatly improve the cross-disciplinary experience of mathematical modellers and medical scientists:

1. Focus on the clinical/biological problem at hand, rather than what is either mathematically tractable or intellectually interesting to the mathematician.

2. Use success stories to convince the medical establishment that mathematics and statistics can contribute much to medicine.

3. Take data seriously: Results are only as good as the data and the methods used to analyze it.

4. Organize Mathematics-in-Medicine Study Groups, which are excellent ways of bringing the two sides together.

5. Be committed: optimal results are obtained only after years of collaboration, when each scientist can make substantive suggestions in the partner's discipline.

6. Be an advocate for inter-disciplinarity which is essential for scientific advances in medicine.

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