



Introduction

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Mathematical methods in medicine: neuroscience, cardiology and pathology

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The application of mathematics, natural sciences and engineering to medicine is gaining momentum as the mutual benefits of this collaboration become increasingly obvious. This theme issue is intended to highlight the trend in the case of mathematics. Specifically, the scope of this theme issue is to give a general view of the current research in the application of mathematical methods to medicine, as well as to show how mathematics can help in such important aspects as understanding, prediction, treatment and data processing. To this end, three representative specialties have been selected: neuroscience, cardiology and pathology. Concerning the topics, the 12 research papers and one review included in this issue cover biofluids, cardiac and virus dynamics, computational neuroscience, functional magnetic resonance imaging data processing, neural networks, optimization of treatment strategies, time-series analysis and tumour growth. In conclusion, this theme issue contains a collection of fine contributions at the intersection of mathematics and medicine, not as an exercise in applied mathematics but as a multidisciplinary research effort that interests both communities and our society in general.

This article is part of the themed issue 'Mathematical methods in medicine: neuroscience, cardiology and pathology'.

1. Introduction

The history of mathematics in the biomedical sciences can be traced back at least to 1798, when Thomas Malthus

published his famous growth law of the human population [1], modified in 1838 by Pierre-François Verhulst [2] to account for the limited amount of available resources in reality. The ‘logistic’ growth rate proposed by Verhulst carried over to other models in population dynamics, e.g. animal dispersal and spatial spread of an advantageous gene, while its discrete-time version is the epitome of a parametric dynamical system with regular and chaotic behaviours. Further milestones include (i) Volterra’s prey–predator model to explain the decrease of fish stocks in the Adriatic Sea after the First World War [3], (ii) Turing’s explanation by means of reaction–diffusion differential equations of how spatial patterns in morphogen concentrations form [4], and (iii) the study of swarm behaviour and its connections with self-organization, collective intelligence, emergent behaviour and evolutionary models [5]. Among the instances directly related to modern medicine let us mention another three: (a) the transmission models of Sir Ronald Ross for malaria [6], later extended by Kermack and McKendrick to the so-called susceptible–infected compartment model, (b) the Hodgkin–Huxley equations for the action potential at a neuron axon, which marks the beginning of computational neuroscience [7], and (c) the advent of computerized tomography, made possible by the Radon integral transform.

Nowadays mathematics is being successfully applied to a number of important fields in medicine including biofluids, cardiovascular diseases, clinical schedules and tests, data analysis, drug design and discovery, epidemiology, genetics, image processing, immunology, instrumentation, microbiology, neuroscience, oncology, virology and more. The list of tools includes virtually the whole of applied mathematics. To cite the most familiar ones: difference equations and discrete-time dynamical systems, information and coding theory, graph and network theory, integral transforms, numerical and computational mathematics, ordinary differential equations and continuous-time dynamical systems, partial differential equations, stochastic and time-delay differential equations, statistics, probability and time-series analysis. All this research has contributed to and continues to increasingly contribute both to better understand medical phenomena and to finding practical ways of action. In the wake of this endeavour, new branches of applied mathematics have emerged, e.g. biomathematics and computational neuroscience. But the most important consequence has been the improvement in healthcare and life quality that results from, say, early and accurate diagnoses, more efficient drugs, control of epidemics, and biotechnological know-how.

The ultimate reason for the ubiquity of mathematics in modern science is the necessity of mathematical thinking to understand complex phenomena. The mathematical approach includes quantification of observations, modelling, classification, optimization, data processing, analysis, prediction and validation. Eugene Wigner, the great mathematical physicist, spoke of ‘the unreasonable effectiveness of mathematics in the natural sciences’ [8] to express the power of the mathematical approach. In turn, it is also true that mathematics owes much of its inspiration and vigorous development to the natural sciences and, increasingly, also to biology, psychology, economy, social sciences and medicine. Classical examples are statistics, actuarial mathematics, stochastic differential equations and time-series analysis, along with biologically inspired classification, optimization and computation algorithms such as neural networks, genetic algorithms and DNA computation. As data collection and data processing capabilities advance, the potential for mathematics to have an impact in the biological and other ‘soft’ sciences is going to continue to increase. All this underlines the central role that multidisciplinary collaboration plays in the development of science in general, and of mathematics in particular.

This having been said, it should be clear that the medical applications of mathematics belong to a large number of branches. Rather than zooming in on a specific one, we have selected a sample of distinct contributions in neuroscience, cardiology and pathology to show the possibilities of the mathematical approach and how it can enrich topics of different nature. These three branches are not disjoint, nor are their borders sharp from the point of view of applied mathematics. What really matters for our purposes is that they build the core of an important research activity, especially by the impact of the results. Finally, let us point out that the application of mathematics to medicine is going through a time of great scientific interest.

2. This issue

This theme issue on the applications of mathematics to medicine is composed of six papers belonging to the area of neuroscience [9–14], three papers belonging to cardiology [15–17] and four papers belonging to pathology [18–21], totalling 13 papers from collaborations among 55 scientists.

Next, we present briefly the mathematical contents of all these papers. Rather than doing this one by one, we prefer to collect them (somewhat arbitrarily) according to their mathematical subject area in order to allow a more general perspective. The reader will find more specific information in the references of the papers.

(a) Cellular automata

The relation of cellular automata to biology can be recognized already from the name. Indeed, cellular automata were introduced in the 1940s by Stanislaw Ulam [22] and John von Neumann [23] as simple models for machine self-reproduction. Two-dimensional binary cellular automata became very popular in the 1970s, also outside the computing community, thanks to John Conway's Game of Life, which was popularized by Martin Gardner in [24]. More recently, the publication of Stephen Wolfram's book [25] brought one-dimensional binary cellular automata to the fore, culminating two decades of work on their properties and classification. From a formal point of view, cellular automata may be considered discrete-time, continuous (topological) dynamical systems.

López *et al.* [21] model the limited nutrient growth of an immunogenic tumour by means of a hybrid cellular automaton. The model includes four types of cells: healthy cells, tumour cells, immune effector cells and dead cells. Depending on the immunogenicity of the tumour, the transient and asymptotic dynamics of the cellular automaton exhibits three main types of dynamics, which are interestingly closely related with the three phases of the theory of immunoediting, to wit: elimination, equilibrium and escape. It is shown that the immune system can keep a tumour dormant for long periods of time but this dormancy is based on a fragile balance between the mechanisms behind the immune response and the growth of the tumour. Thus, the authors question the capacity of the cell-mediated immune response to sustain long periods of dormancy. This study illustrates how an integrated approach, involving numerical evidences and theoretical reasoning, can enhance our understanding of biologically motivated models and stimulate new research on possible therapeutic strategies.

(b) Computational fluid dynamics

The application of computational fluid dynamics to medicine is quite natural although highly nontrivial, mainly for the following two reasons. First, most biofluids (e.g. blood, semen, lymph) are non-Newtonian, i.e. unlike the more familiar Newtonian fluids such as water, their behaviour is not described by the Navier–Stokes equation. Second, the boundaries of the vessels and cavities conveying and containing fluids in the human body are flexible (veins and arteries), time-varying (heart), porous (brain ventricles) or have a complex geometry (lungs), which makes numerical modelling even more challenging.

In [20], Giménez *et al.* extend previous work on the design of ventricular catheters for the treatment of hydrocephalus, a medical condition characterized by an excess of cerebrospinal fluid in the brain ventricles. In a series of papers, some of the authors optimized the geometry and configuration of the catheter holes in order to obtain a uniform flow pattern along the perforated area. Such catheters are less prone to obstructions caused by the macromolecules and tissues present in the cerebrospinal fluid than the standard catheters in use. As compared to a general fluid-mechanical problem, this particular case is simpler because (i) the cerebrospinal fluid is Newtonian to a high degree of accuracy and (ii) the influence of the ventricle geometry on its

flow through the catheter may be assumed negligible with the caveat that the catheter has been correctly placed in the ventricle. Furthermore, the authors assumed constant inlet flow. In this follow-up paper, the authors take into account the pulsatile nature of the cerebrospinal fluid owing to the heart beating and blood flow, and quantify the corresponding corrections. This way they validate their catheter designs under more realistic conditions. As in their previous work, the authors use OpenFOAM[®] [26], an off-the-shelf computational tool for fluid dynamics [18], along with auxiliary meshing and graphical tools.

(c) Data processing

Data processing refers to any method for extracting valuable information from a dataset. At variance with time-series analysis (see §2g), the data need not be observations of a time-evolving phenomenon. Data processing is a multidisciplinary field with intersections with statistics, time-series analysis, machine learning, artificial intelligence and, as we will see shortly, with statistical physics and algebra (e.g. graph theory) too. Owing to the data deluge enabled by the new information technologies, data processing (sometimes under the catchy name of big data analysis) has currently become one of the most active fields of applied mathematics.

The data analysed by Ezaki *et al.* [9] are voxels obtained by functional magnetic resonance imaging of some regions of the brain. The scope is to represent that information in such a way that alterations in brain dynamics can be easily identified. For this purpose, the authors resort to the maximum entropy model, a major variant of which is also known as the Ising model and Boltzmann machine. As a result, the authors map the brain dynamics to the movement of a particle on an ‘energy landscape’ inferred from the neuroimaging recordings. In particular, the authors determine the parameter values more efficiently than a conventional gradient descent method. More generally, the maximum entropy model is a useful method to represent multivariate data that are repeatedly observed and derive the structure of interaction between variates.

Lord *et al.* [11] provide a thorough review of integration and segregation from the perspective of whole-brain connectomics. Importantly, they push the boundary from static network structure to time-varying systems. A wide range of psychiatric and neurophysiological states can be characterized by the degree to which signals from different brain regions are either coupled or separated. This review provides an overview of how various physiological states can be interpreted through whole-brain computational models—and how those computational models involve either segregation or integration. Moreover, they go on to describe how integration and segregation may be quantified. They conclude by speculating that such measures are likely to yield biomarkers or practical therapeutic targets of clinical relevance. They clearly show that approaching an understanding of whole-brain behaviour from computational and mathematical models contributes to the emergence of a stratified neuropsychiatry, and potential for personalized therapeutics.

Clustering is a usual task in statistical data analysis, especially important in information classification and retrieval, pattern recognition and image processing. Borrowing the definition from Lorimer *et al.* [12], clustering is the partitioning of a set of objects into subsets, or clusters, that express, among themselves and compared to objects not in the cluster, an increased degree of similarity. As an example, think of the identification of malicious tissue on a positron emission tomography scan of a part of the body. Lorimer *et al.* compare and discuss two biologically motivated clustering methods: the Phenograph approach and the Hebbian Learning Clustering. Both algorithms represent the data points as nodes of a k -nearest neighbour graph, with distances encoded as edge weights, and, most importantly, are unbiased with respect to the assumption of Gaussian data clouds or clusters itself. On the other hand, the selection of the relevant features of the clusters introduces necessarily bias in the results. In view of their numerical results with synthetic and natural data, the authors elaborate on the importance of selecting features consistent with the sought data classification.

(d) Differential equations/dynamical systems

Ordinary and partial differential equations are ubiquitous in applied mathematics because they describe time-depending phenomena; a simple example is the demographic evolution given by the equations of Malthus and Verhulst. In particular cases, differential equations have to be supplemented to cope with memory effects (integro-differential equations or time-delay differential equations) and noise (stochastic differential equations). If for convenience time ticks in a discrete way (e.g. from generation to generation in population dynamics), then one deals with difference equations, which is a stand-alone branch of mathematics and the formalism underlying the theory of dynamical systems in discrete time. While the theories of ordinary differential equations and difference equations (or dynamical systems in continuous and discrete time for that matter) are well developed and understood, not surprisingly the theory of (nonlinear) partial differential equations lacks so far a unified approach. This shortcoming is circumvented in practice with numerical methods; a typical example was considered in §2b: computational fluid dynamics. Let us note in passing that the discretization of a differential equation via finite differences produces a difference equation.

In this section, we address the papers on computational neuroscience [14] and on cardiac dynamics [15]. Other models described also by differential equations will be addressed in §2e,f. Maslennikov *et al.* [13], which uses difference equations, is also included in §2e.

The synchronization of neuronal networks plays an important role in brain dynamics, a typical study case being epilepsy. In this setting, Reimbayev *et al.* [14] analyse the interplay between excitatory and inhibitory synaptic connections, and how they combine to create both synchronized and unsynchronized neural activity. More specifically, they describe a novel mechanism of synchronization in networks of coupled bursting neurons, based on a combined electrical and inhibitory coupling, that will certainly contribute to the understanding of the collective dynamics of oscillating neuronal networks. The results are tested in small networks and shown to hold in larger ones.

In [15], Boccia *et al.* deal with low-energy control methods (far field pacing) for defibrillation. Specifically, they study numerically the unpinning and termination of spiral waves around an ischemic heterogeneity, modelled as a small circular patch in a two-dimensional sheet of cardiac tissue, by means of phase I of the so-called Luo–Rudy action potential model. Two cases are studied and compared: the simplified isotropic medium (in which the extracellular and intracellular conductivities parallel and transversal to the fibres are set to be equal) and the realistic anisotropic medium (in which those conductivities are different). As a result, the authors show that the range of far field pacing resulting in successful termination of pinned spiral waves is larger in the second case.

(e) Networks

Papers featuring techniques from network science feature prominently in this theme issue. Network models are, of course, a very natural way to describe the interaction dynamics in a wide variety of physiological systems. The papers in this issue focus on network approaches to modelling interaction in neurophysiological settings [10,13] and in disease transmission [18]. The choice of these applications is quite deliberate because these are instances where the network structure is intrinsic to the dynamical behaviour of interest.

In the case of [10,13] we see two different studies of emergent behaviour in neurophysiological models that are highly dependent on the structure of the network itself. Maslennikov *et al.* [13] study an adaptive network of spiking neurons. Starting with simple biologically inspired elements, and a small core network of these elements, they describe a model whereby the elements respond to stimulus to modify their connectivity. This allows the network of neurons to create complex responses to particular stimuli. They characterize this structure in terms of a core network existing within a hypernetwork.

Conversely, in [10], Li *et al.* address neuronal avalanches in a spiking neural network model. Networks of physiologically inspired neurons have been observed to self-organize into a critical state where the resultant dynamics of the system can exhibit a mixture of ordered and disordered patterns. Curiously, the critical region which may exhibit strongly ordered performance is narrow for systems of spiking neurons. In [10], we have a study of this problem from the perspective of a liquid state machine. They show that the performance of the liquid state machine is optimal when the neuronal pool is operating at that critical state.

Complex networks appear in a very wide range of applications, and this is demonstrated within this theme issue with our third contribution from this area. Fu *et al.* [18] examine the problem of disease transmission on complex networks. There is now a substantial body of literature in the area of diseases (and other propagation processes) on complex networks. The particular contribution of Chen *et al.* [18] is to consider two competing strains and to derive analytic expressions for the epidemic threshold and corresponding conditions for endemic transmission. They extend the probability generating function approach to the case of (necessarily) pair-wise approximation across the transmission model. Competing virus strains are, of course, of relevance across a wide range of disease and also treatment.

(f) Optimization

Optimization is a basic task in many areas of mathematics, science and technology. For this reason, it has been the subject of much interest and labour over the last centuries. As a result, whole new branches of mathematics such as calculus of variations, convex optimization and operations research emerged. Nowadays optimization remains a very active research field in which novel techniques are developed to deal with old and new challenges.

Christodoulides *et al.* [19] provide an interesting application of classical optimal control theory for the design of medication and treatment regimes for (in this case) atopic dermatitis. Their paper is a neat example of how classical applied mathematics (and in this case dynamical systems theory) can be applied to informed personalized medicine. As with many diseases, a patient's response to atopic dermatitis is not constant but behaves as a dynamical system. By characterizing this system they are able to tune the timing and dosage of their treatment to arrive at an optimal solution. Their example is a neat one because it relies on fairly simple mathematics to obtain an elegant solution to a real-world problem.

(g) Time-series analysis

Time-series analysis is a useful tool in the study of time-evolving phenomena whose governing equations are unknown or too complex to attempt a detailed analysis. In the linear (or statistical) approach, the usual scope is to find a random process that fits the observations. In nonlinear time-series analysis, the working hypothesis is that the observations are output by a stationary, dissipative nonlinear system. The scope this time is to characterize the attractor of the system by means of dynamical and/or geometrical parameters such as the Lyapunov exponents and a variety of fractal dimensions. In the case of multivariate time series, a further scope may be the causal relations (also called coupling or information directions) between pairs of components. See [27] for a general introduction to nonlinear time-series analysis with applications.

In applications, the scope may actually be more modest. A typical example is the discrimination of different dynamical states or 'regimes' of the system under scrutiny. Think of a medical analyst who wishes to distinguish in an electroencephalogram of an epileptic patient the normal health condition from the abnormal condition (epileptic seizure). An observable that is up to this task is sometimes called a biomarker in medical applications whatever its mathematical nature. Thus, one can find in the literature biomarkers ranging from the traditional statistics, several sorts of entropy, the count of some kind of symbols, to even properties of graphs constructed from the data. Concrete implementations of this strategy can be found in [16,17], as we explain in the following.

Given L consecutive (or, more generally, equidistant) data of a time series, one can assign a symbol to them. In particular, if $L > 1$ this symbol can be the permutation obtained by ordering those data according to their size. By repeating this assignment with sliding blocks of data one trades the original time series for a series of permutations which are aptly called ordinal patterns and are being used in time-series analysis, ergodic theory and dynamical systems for a number of purposes [28]. In [16], this symbolization procedure is brought a step further to construct an associated *ordinal network* to the data as follows: the $L!$ possible ordinal patterns are the nodes of the network and a link goes from node A to node B if the ordinal pattern B follows pattern A in the symbolized series. This technique makes available the power of network theory to the data analyst. For example, using entropy-like complexity measures defined from the ordinal network, McCullough *et al.* [16] are able to discriminate between electrocardiograms characterized by normal sinus rhythm, ventricular tachycardia and ventricular fibrillation. Other interesting applications and the numerical issues involved in the analysis are also thoroughly discussed.

The paper by Porta *et al.* [17] is related to [16] in that it also uses an entropy-like quantity (transfer entropy, a popular measure of causality), but this time to assess the strength of cardiac and sympathetic baroreflex. Causality analysis provides an ideal framework to assess the strength of the physiological interactions aiming at the maintenance of arterial blood pressure during an orthostatic challenge in the presence of relevant nonlinear relations and confounding factors blurring the causal link from sympathetic neural activity to arterial blood pressure (e.g. direct effect of respiration on both variables). Porta *et al.* [17] exploit and compare a model-based and a model-free approach to transfer entropy estimation grounded, respectively, on multivariate autoregressive model and k -nearest neighbour technique to evaluate the strength of the causal relation from sympathetic activity to arterial blood pressure and vice versa in a multivariate framework accounting for heart rate and respiration as covariates.

3. Conclusion

The previous section illustrates the breadth and depth of the mathematical methods currently applied in medicine, specifically in neuroscience, cardiology and pathology, as reflected in the contributions of this theme issue. Thus, differential equations model the action potential of spiking neurons [14], the treatment effect on a pathogenesis [19] or the flow of cerebrospinal fluid in the ventricular system [20]. It also illustrates nicely how different mathematical subject areas usually concur in the modelling and analysis of a specific topic. For example, networks are used in a particular clustering algorithm [12], represent a symbolic time series [16], and are the framework of an infection spreading model [18].

As for the potential implications of the results reported in this issue, they can be classified in the following categories:

- better data analysis and diagnoses [9,12,16,17];
- better therapies or instrumentation [15,19–21];
- better understanding of biological processes [10,13,14]; and
- better understanding of medical disorders [11,18].

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