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ScienceDirect
Journal of Computational and Applied Mathematics 205 (2007) 669–686
JOURNAL OF COMPUTATIONAL AND APPLIED MATHEMATICS
www.elsevier.com/locate/cam

Rival approaches to mathematical modelling in immunology

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Received 11 September 2005

Abstract

In order to formulate quantitatively correct mathematical models of the immune system, one requires an understanding of immune processes and familiarity with a range of mathematical techniques. Selection of an appropriate model requires a number of decisions to be made, including a choice of the modelling objectives, strategies and techniques and the types of model considered as candidate models. The authors adopt a multidisciplinary perspective.

Keywords: Mathematics; Immunology; Model selection

1. Introduction

Immunology is the study of the immune system in all its biological, chemical and physical aspects. The immune system is concerned with protection of a host organism from invading pathogens and damaged cells. The immune system comprises a complex set of physical, biochemical and immunological process occurring in time and space with the outcome depending on a large number of intra- and inter-cellular parameters. Two elements of the immune system are recognition and response: recognition is highly specific concerning individual pathogens, altered self and non-self; response comprises the biological, chemical and physical aspects. Immunological research aims at understanding what controls the ability of the immune system to mount a protective response against pathogen-derived foreign antigens, while avoiding a pathological response to self-antigens.

Mathematics is sometimes defined as "*the study of topics such as quantity*, *structure*, *space*, *and change*" (a fairly broad if imprecise definition). However, other definitions include "*the body of knowledge justified by deductive*

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[1] Supported by the Russian Foundation of Basic Research, the Alexander von Humboldt Foundation and through a Leverhulme professorship held at Chester.

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doi:10.1016/j.cam.2006.03.035

reasoning, starting from axioms and definitions". Here, we prefer to interpret "mathematics" as "mathematical sciences" because we seek a term that encompasses a wide range of sub-disciplines, including but not limited to computational mathematics, mathematical modelling, analysis, statistics and probability, inference and information retrieval, and optimization.

It remains to convince some bio-scientists that mathematics can inform their science. The cause may be linked to a statement in Science (April 27, 2001): "*The utility of mathematical models to explain complex biological processes is related to how well their assumptions fit the in vivo situation & whether they accurately encompass actual experimental findings.*" It does not seem too polemical to argue in favour of this as an objective.

It has been observed (for related comments see [37]) that while theoreticians, including mathematicians, studying immunology aspire to influence the work of experimental immunologists in a constructive way, *the impact of theoretical modelling has been negligible* (with, it has been suggested, the exception of work related to HIV and AIDS). In their work on HIV-AIDS, Perelson and Nelson [72] state that mathematical modelling using (see below) both ordinary and delay differential equations, and parameter estimation techniques, has proved useful in understanding the dynamics of HIV infection at both the population and cellular levels, and it has been possible to estimate many quantitative features of HIV-1 infection, the viral infection that ultimately causes AIDS.[1] One can detect the progressive weakening, over the last decade, of statements that emphasize the infancy of mathematical modelling of processes in immunology. Nevertheless, there are specific aspects of the formulation of consistent mathematical models in immunology that have not yet been fully established or evaluated.

The authors are conscious of the impact mathematical models should have, on experimental research and on the provision of building blocks for large-scale models of the immune system. Thus, their main objective in writing this paper was to highlight alternative perspectives on the production of various mathematical models of immune processes, and the need for well-founded methodologies for the construction and selection of such a model. Related objectives are: (1) to convey, throughout, what we see as the need for an interdisciplinary approach; (2) to outline (Section 3) the necessary background for an understanding of the problem; (3) to indicate (Sections 2 and 4–6) the nature of a *model* and to highlight the large variety of types of model available; (4) to emphasize (Section 8) that the selection of a particular mathematical model may be affected by the perspective and context in which the problem is placed and the processes available for discrimination between models.

Since our paper is aimed at a broad and hopefully multi-disciplinary audience, the potential readership includes those who know little about mathematical biology or about immunology, and those knowing little about various types of dynamical systems, information theory, statistics or robust computational methods. This seems to remove unnecessary constraints on the expression of opinions that we hope provoke reaction. Underpinning our thinking are views on the nature of the scientific method and of mathematics (of the mathematical sciences), and general issues in "mathematical biology". Overall, we consider that the key elements of the data- and science-driven application of mathematical modelling to immunology can be summarized as follows:

- More than one model may correspond to (or embody) a particular theory—not least because there may be other independent theories involved. The construction of "candidate" mathematical models, from which one seeks the best embodiment of the data, may be based on (a) *knowledge* of the basic building blocks, (b) *intuition* concerning subjective assessments of likelihood about the underlying scientific possibilities, (c) *mathematical and scientific experience*, and (d) *systems theory approach* (that is, a knowledge of the dynamic structure of the mathematical models and the underlying bio-mechanisms) and (e) the principle of *parsimony*.
- The phenomena are complex and computational techniques permit, where they are apposite, complex rather than basic (naive) mathematical models. Given data of appropriate quality the aim is to discriminate between mathematical models representing differing scientific theories. Reliable techniques are data- (that is evidence-) hungry; one cannot be confident of conclusions on the basis of "slim" or biased evidence. The discrimination between members of a chosen family of models should be based on *observations* (data) and an *objective criterion* formulated on the basis of assumptions about the data. When distinguishing between models on the basis of the data is difficult, the computational results should indicate this.

[1] While AIDS is a disease that occurs on a time scale of about 10 years, there are very rapid dynamical processes that occur on time scales of hours to days, as well as processes that occur on time scales of weeks to months (cf. Remark 2.1). Dynamical modelling has provided a simulation of these features, but much work remains to be done to do justice to the complexity of HIV-AIDS.

Model selection is not simply [22] a matter of parameter estimation. We distinguish a "generic" model, characterized by the form of the equations (e.g., $y'(t) = \lambda y(t)$) that relate to it, and a "parameterized" model in which the equations incorporate actual values of the parameters (with the previous example, $y'(t) = -10y(t)$) rather than "formal parameters" (e.g., λ in $y'(t) = \lambda y(t)$). Given different types of generic equations (e.g., $y'(t) = \lambda y(t)$, and $y'(t) = \lambda y(t - \tau)$) one may (i) for each type, determine a set of actual parameters that is in a well-defined sense optimal, given the data (say, $y'(t) = -5y(t)$ for the first class, $y'(t) = -4.5y(t - 1)$ for the second class); (ii) order, in a rigorous fashion, the optimally parameterized models to obtain "the most appropriate" (say, $y'(t) = -4.5y(t - 1)$).

2. From observations to models

One can find extensive reviews covering various aspects of application of the mathematical models in immunology from the modellers' perspective (e.g., [2,36,64,70,73,74,79,89,91,92]). Most mathematical models of immune responses have no rigorous physical basis, i.e., the equations are not obtained from first principles (the basic laws of physics and mechanics) and therefore have no a priori claim to validity. Multiple models of differing complexity based upon different types of mathematical frame-work (and corresponding scientific hypotheses) have been proposed, in order to address specific phenomena. Examples of such phenomena are the population dynamics of virus infections, the turnover of (specific) (labelled) lymphocytes, the migration and homeostasis of lymphocytes, single lymphocyte regulation and the single cell replication cycle of the virus.

The immune system in an individual may be regarded as a complex example of a population whose individuals co-operate or compete. The system is not static; it evolves with time (though in a healthy individual it stays within certain bounds, referred to as homeostasis). It is not a closed system since the individual exists within a changing environment and can be exposed to infection. It is a multi-dimensional system because the population consists of different types of species (such as B-cells, T-cells and antigens), and it is a compartmental system (in the sense that differing species originate or reside in varying densities in different regions, e.g., the blood or lymphatic system, the skin, liver, etc.). Already, we see the need for (i) a greater familiarity with the underlying science, which we outline in Section 3 and (ii) the specialized vocabularies (the reader may find reputable online dictionaries to be of assistance) used in immunology and in mathematics.

Remark 2.1. The problem of how to develop, in a systematic manner, consistent models that provide a basis for quantitative analysis and prediction in every day immunology research raises a number of challenges. The translation process starting from observations of a particular phenomenon and scientific theories and explanations and ending with a family of mathematical models often appears to be an ill- or vaguely defined process. At the first stage, it involves the conversion of often imprecise assumptions or theories into mathematical variables and relationships between them. The next stage relies on the availability of comprehensive data measuring various aspects of the immune system. When this is available, the process involves the assessment of the accuracy, and explanatory and predictive power, of a particular model and of rival models. *This last stage is not routinely implemented in many efforts at modelling in immunology.*

The term "model" of necessity implies a simplification of the system under study [62], but this simplification must not lose touch with reality. One should not over-simplify models in order to obtain equations that succumb to a preferred mode of investigation. A qualitative analysis of models that have interesting mathematical features but are demonstrably related in only a marginal way to observed phenomena may have intrinsic mathematical interest, but be of limited immunological relevance until investigated further. *Robust computational techniques*, *which embody checks and safeguards*, *permit quantitative investigation of models of greater complexity than those that yield to analytic investigation.* If mathematical modelling is to explain and predict the dynamics of the immune system, it should do so under a range of normal conditions, and in response to perturbations of the internal antigenic homeostasis by various biological agents—viruses, bacteria, tumours, environmental antigens, etc. The relevant dynamics may be in the short-, medium- or long-term (or all of these). A model may be deemed to be qualitatively correct even though its amplitudes or time-scales are incorrect; obtaining a *quantitatively correct* model that will provide accurate estimates of the scale of events can be a challenge.

In order to incorporate the essential features of immunological processes into a mathematical model, *the mathematician has to possess or to have access to the scientific data and insight available to immunologists themselves*. (For comparison: At a very primitive level, one cannot model the mechanics of a ladder leaning against a wall without a

primitive understanding of the laws of Newtonian physics.) In the following section we provide a summary of key aspects of the immune system that have a bearing on the construction of mathematical models.

3. An introduction to immunology

We discuss the *terminology* and *basic facts* underpinning a study of immunology. Since definitions in science correspond to a vocabulary[2] in a language, we review some basic terms and notions of immunology as they are currently understood. The complexity of the interactions indicated in this section may appear daunting (and the description omits many features). The theoretician has to decide what level of complexity must be represented in order to explain specific phenomena.

Some essential scientific aspects of the immune system are briefly summarized in a series of review papers written by the leading experts in the field.[3] The immune system in a mammal is a complex compartmentalized population of different types of humoral factors (e.g., 10^{20} antibody molecules) and cells (10^{13} cells) that migrate spatially, interact with each other (competitively or cooperatively), proliferate, differentiate, mature, age and die. It is organized into compartments—e.g., bone marrow, thymus, spleen, lymph nodes, gut and blood—connected by the vascular system that allows immuno-component cells (lymphocytes) to migrate continuously to or from the compartments during their life. At the basic level, mathematical models relate to the variation over time and location (globally or in specified locations) of the population of the immune environment and the response of the immune system—which is regulated by (delayed) feedbacks that have the possibility of restoring a dynamic equilibrium to the system.

The protection against the invasion of pathogens (agents that causes disease) is provided by a coordinated action of the innate immunity and antigen-specific immunity. The innate immunity refers to the (i) physical, chemical and microbiological barriers, (ii) the responses of natural killer cells, macrophages, dendritic cells (DCs) that lack the memory effect (remain unchanged after antigen encounter) and (iii) the immunologically active substances (e.g., complement, cytokines, acute-phase proteins, interferons). The specific immunity is based upon the use of antigen-specific receptors on lymphocytes to drive targeted effector responses against the pathogens. Viruses and other pathogens display particular molecular signatures (“pathogen-associated molecular pattern”) that are recognized by specific “pattern recognition receptors”. DCs express a vast array of such receptors. Stimulation of DCs through pattern recognition receptors generates swift pathogen-specific innate immune responses and conditions DCs for efficient stimulation of adaptive T-cell responses.

A substance (protein, polysaccharide, glycolipid, virus, bacteria, tissue transplant, etc.) that is capable of inducing *specific* immune response is called an *antigen*. Introduction of an antigen may be through immunization, inhalation, ingestion, etc. Major classes of antigen-specific cells, which have different functions in protecting the host against pathogens (viruses, bacteria, cancer cells), are the $CD8^+$ T-lymphocytes, the $CD4^+$ T-lymphocytes and the B-lymphocytes. $CD8^+$ cytotoxic T-lymphocyte (CTL) responses represent a major immune mechanism of protection against many viral infections and tumors through the killing of altered (infected or tumour) cells. CTLs recognize virus-encoded peptides presented to their T-cell receptor in the context of Major Histocompatibility Complex (MHC) class I molecules. The $CD4^+$ T-cells have special roles as “helper cells”; they facilitate the cellular and humoral responses (the primary responses of the $CD8^+$ T-cells, and B-cells, respectively). In response to exposure to an antigen the B-lymphocytes of the immune system produce and release protein molecules: *antibodies* that have the capacity to bind specifically to the antigen that elicited their production. The chemical nature of the interaction of antigen with antibodies established in the early to mid-1930s (see [44]) suggests that the chemical law of mass action can be used to describe the corresponding process. The specificity of the antigen–antibody interaction is understood to be quantitatively defined by an affinity value. (Actually, the surveillance criteria in the immune system are much more elaborate than this suggests.)

Every antigen-specific lymphocyte displays about 10^5 identical receptors on its cellular membrane recognizing one specific antigen. The antigen-recognizing receptors on a single lymphocyte are identical to each other and can combine strongly with one antigen (the efficacy is characterized by the affinity value); they can recognize/combine with other antigens too, but the affinity of the other interactions is different. A population of lymphocytes with identical antigen-specific receptors is called a *clone*. The repertoire of specificities (number of distinct lymphocyte clones with different

[2] An online dictionary is currently found at http://www.biology-online.org/dictionary.asp.

[3] New England J. Medicine 343 pp. 37–49, 108–117, 338–344, 702–709, 782–786, 1020–1034, 1313–1324, 1703–1714, 1778–1784.

antigen response capabilities) in the immune system is estimated to range in number from 10^5 to 10^7. Selection of the lymphocyte repertoire occurs continuously under conditions of permanent inflow of antigens. The immune system needs to accommodate increasing numbers of newly generated cells within a limited lymphoid population, so a selection process through competition between different subsets of cells and between specific clones presumably takes place.

The interaction between antigen-presenting cells and lymphocytes is regulated at the single-cell level by a complex signal transduction and gene activation machinery[4] and at the cell-population level by various modes of 'communication'. Importantly, signalling molecules are able to activate different genes at different concentrations and, in consequence, the response is not proportional to the stimulus (i.e., *it is nonlinear*). The lymphocytes undergo important changes when exposed to antigens; they express new molecules on their surface and acquire different functional capabilities. As a result, three different stage of lymphocyte maturation can be identified: "naive" cells (cells that have not yet reacted to the antigen), antigen "activated" cells and "memory" cells (cells which have encountered an antigen to which they are specific, and respond faster on re-exposure to that antigen).

Remark 3.1. Regarding the theories outlined above, it is provoking to enquire how scientists (and immunologists in particular) translate the data from their experiments into scientific theories. One assumes that they do so, in the first place, by establishing a correlation between what they see to be a cause and the resulting observable effect. Such a correlation may be inferred rather than established using statistical methods.

A set of principles, governing the immune response regulation, have been proposed in [40]; these have a consequence in terms of the construction of mathematical models in immunology: (1) the immune system responds to a rapid perturbation in its homeostasis (the rate of change rather than the level of stimulation); (2) the lymphocytes respond to a rapid change in the level of stimulation, rather than a stimulation per se; (3) individual cells tune and update their activation thresholds due to the changes in the concentration of and distribution of excitation and de-excitation factors remaining from previous encounters (e.g., the effect of co-stimulatory molecule expression).

4. Rival evolutionary models

We now consider some basic types of equations (cf. [65,78] and, particularly, [57,69]) found in mathematical models. We are generally concerned with evolutionary equations that are causal, i.e., non-anticipative, in the deterministic case—or, in the stochastic case, involve Markovian processes. Included are (ordinary and partial) differential equations, integral and integro-differential equations and functional differential equations, combinations of these, and similar problems with added constraints. The discrete analogues of the continuous equations are recurrence relations, including difference equations, summations equations and difference–summation equations. The solutions of such evolutionary problems depend in general upon initial data that comprise initial values or initial functions. Volterra integral equations and similar functional differential equations are *equations with memory* in which the current state (or its rate of change) depends upon past history (not merely the current state). Some variables represented in models (such as the number of T-cells) are measured in integers and they are, in consequence, not differentiable. In the case of very small numbers (in an in vitro experiment, say), a difference equation may be more appropriate than a differential equation, but if the number of cells is massive (say 10^5) then a differential equation appears appropriate as an approximation. However, *numerical methods* for the approximate solution of differential equations invoke the solution of discrete relations, such as difference equations. In Section 5 we provide an illustration of the roles that may be played by some differing types of models.

We begin by indicating the types of variables that may enter the models. In general, the important variables are the *density* or the *numbers* of bio-organisms (such as B- or T-cells) and *chemical molecules* (such as antigens), each classified according to type and or location. In constructing models in immunology, it is common to adopt a mnemonic notation (e.g., $T(t)$ as the number of T-cells at time t). The number of differing variables is so great that simplification is not only attractive but often appropriate: at one extreme, one may group together the total ensemble of T-cells and adopt a variable that represents the number or the average density of such cells at time t. In the opposite direction, one

[4] For example, the hypermutation process associated with B-lymphocyte division leads to the generation of cells displaying receptors with different affinities; this is followed by selection of those whose receptors have a higher affinity value. Mutation can take place.

may not only indicate the different numbers of distinguishable types of cell (distinguishing them by specific function) but also categorize them by their age, location and past history.

We illustrate various types of equations, commenting on examples of their use. Retaining a context-neutral notation, the index i for a component $y_i(t)$ in the variable $y(t)$ (say) may be an indicator of the type of the variable (there are various types of T-cells, various types of antigens, etc.); alternatively, it may be an indicator of the compartment or location with which the entity is associated (lymph nodes, liver, spleen, bone marrow, etc.).

(a) As examples of *ordinary differential equations* (ODEs), we have a system of linear equations $y_i'(t) = \sum_j \lambda_{i,j}(t) y_j(t) + \gamma_i(t)$ $(i = 1, 2, \ldots, d)$, which can be expressed as

$$y'(t) = \Lambda(t)y(t) + \gamma(t) \quad (t \geqslant t_0), \quad y(t_0) = y_0 \in \mathbb{R}^d \tag{4.1}$$

(using matrix and vector notation); and nonlinear logistic-type equations such as

$$y'(t) = \lambda(t)y(t)(1 - y(t)) + \gamma(t) \quad (t \geqslant t_0), \quad y(t_0) = y_0 \in \mathbb{R} \tag{4.2}$$

and the system

$$y_i'(t) = \sum_k \lambda_{i,k}^{[1]}(t) y_k(t) \left(1 - \sum_j \lambda_{i,j}^{[2]}(t) y_j(t)\right) + \gamma_i(t) \quad (i = 1, 2, \ldots, d; t \geqslant t_0)$$

with prescribed $y_i(t_0)$ $(i = 1, 2, \ldots, d)$. For an example of an application, see [60], where similar equations were used to analyse two hypotheses about the mechanisms for resource competition in B-cell homeostasis on the basis of experimental data.

Models formulated with general non-linear ODEs represent the dominating class of equations in use in mathematical immunology, perhaps because they are easy to simulate on a computer ("*in silico*") and simpler to analyse qualitatively than many other types of model (an exception is certain types of recurrence relation—see below). The constant coefficient homogeneous version of (4.1), $y'(t) = \Lambda y(t)$, is too simple to portray complex short- and long-term dynamics in one model, but it does serve as an introduction to the notion of *slow* and *fast* dynamics (the solution $y(t) = \exp\{\Lambda(t - t_0)\}y(t_0)$ has components whose growth or decay reflects the eigenvalues of $\Lambda \in \mathbb{R}^{d\times d}$). Eq. (4.1), though inhomogeneous and non-autonomous, does not possess the richer dynamics available using non-linear equations. Various more realistic ODE models can be found in reviews and monographs (e.g., [57,69,71]). Large-scale systems of ODEs are increasingly used in so-called systems biology studies of intra-cellular signalling networks associated with the processes of gene up- or down-regulation, virus replication, etc. [31,52,53,81].

(b) The equations $y_{n+1} = \lambda y_n + \gamma_n$ and $y_{n+1,i} = \sum_j \lambda_{i,j}(n) y_{n,j} + \gamma_{n,i}$ $(i = 1, 2, \ldots, d)$ (linear equations) and nonlinear equations such as $y_{n+1} = \lambda y_n(1 - y_n) + \gamma_n$, and

$$y_{n+1,i} = y_{n,i} \left(1 - \sum_j \lambda_{i,j}(n) y_{n,j}\right) + \gamma_{n,i} \quad (i = 1, 2, \ldots, d) \tag{4.3}$$

are examples of *recurrence* or *difference equations*.

Examples 4.1. For recent applications of discrete relations, see (for example) the work of Veiga-Fernandes et al. [86], where a discrete Leslie-type model was used to estimate, from CFSE–labelled lymphocytes, the human *naive* versus *memory* T-cell turnover parameters (parameters such as the average transit time, or lag time, from division 0 to 1, and the average division rate and loss rate in all other divisions).

(c) Presence of a time-lag leads us to consider *delay differential equations* (DDEs), e.g., $y'(t) = g(t, y(t - \tau))$ $(t \in [t_0, \infty))$. Under suitable conditions on g, a solution is specified by an initial condition $y(t) = \varphi(t)$ (for $t \in [t_0 - \tau, t_0]$).

Examples 4.2. A simple modification of the logistic equation (4.2) yields the DDE

$$y'(t) = \lambda y(t)(1 - y(t - \tau)) + \gamma(t) \quad (\lambda \in \mathbb{R}). \tag{4.4}$$

The "delayed logistic equation" (4.4), though simply expressed, has [59] potentially complex dynamics as λ assumes various values. Its dynamics are so rich that some modellers appear to regard it as inappropriate as a model of

real-life biological phenomena. However, "delayed logistic components" appear to have a legitimate role in models. The application of various classes of functional differential equations for problems in immunology has been reviewed in [11,17].

(d) In the case of spatially distributed variables, we shall signify location by a variable $x = [x_1, x_2, x_3]^{\mathrm{T}} \in \mathbb{R}^3$ and represent the quantity of interest by $y(x; t)$. This naturally leads to *partial differential equations* (PDEs). Examples are the *advection–diffusion equation*: $(\partial y/\partial t)(x; t) = \kappa_0 (\partial y/\partial x) y(x; t) + \kappa_1 (\partial^2 y/\partial x^2)(x; t)$ and the one-dimensional *diffusion equation* (set $\kappa_0 = 0$). A simple example of the *reaction–diffusion equation*:

$$\frac{\partial y}{\partial t}(x; t) = \kappa_0 \frac{\partial^2 y}{\partial x^2} y(x; t) + \kappa_1 f(y(x; t)) \quad \text{with} \quad f(y(x; t)) = \{y(x; t)(1 - y(x; t))\} \tag{4.5}$$

(the Kolmogorov–Petrovskii–Piskunov, or KPP, equation [50] where κ_0 is the diffusion constant and κ_1 is the growth rate constant).

Examples 4.3. A modified version of the KPP equation, in which the term $f(y(x, t))$ is replaced by one that depends on the total population size rather than the local population size, has been used recently [88] to model the evolution of bacterial phenotype distribution under the processes of mutation (represented by the diffusion term) and selection. In immunology and physiology, reaction–diffusion equation was used for studying inflammatory responses [4,48], the migration of lymphocytes through solid tissues [58] and T-cell activation dependent on the membrane protein [26]. Recently, it has been shown that the growth kinetics of certain experimental solid tumours is inconsistent with both exponential and Gompertzian growth. The so-called *linear molecular beam epitaxy growth model* based upon a linear fourth-order reaction–diffusion equation has been shown to be compatible with growth processes dominated by surface diffusion and deposition, as in crystal growth [21].

Models based on PDEs are inevitably more complex than those based on ODEs though one may sometimes solve them approximately by associating them with systems of ODEs (semi-discretizing, or through separation of variables). In practice, models include a combination of various types of equations coupled together.

Examples 4.4. (a) A simple discretization of the von Foerster equation $(\partial/\partial t)n(a; t) + (\partial/\partial a)n(a; t) = -\mu(a; t)n(a; t)$ has been related to a model using Leslie matrices (see [41]). High dimensional Leslie matrix models have long been viewed as discretizations of McKendrick PDE models.

(*b*) Semi-discretization of (4.5) leads to the system of ODEs

$$y_i'(t) = \kappa_0 \frac{y_{i+1}(t) - 2y_i(t) + y_{i-1}(t)}{\Delta x^2} + \kappa_1 \{y_i(t)(1 - y_i(t))\} \quad \text{where} \quad y_i(t) \approx y(x_0 + i\Delta x; t).$$

Solution of some PDEs can be achieved through the use of integral equations. A type of Volterra and Abel–Volterra equation can be represented by $y(t) - \int_{t_0}^{t} (t - s)^{-\alpha} k(t, s) g(s, y(s))\, \mathrm{d}s = g(t)$ $(t \geqslant t_0)$ with $\alpha \in [0, 1)$.

(e) The equations above are *deterministic* (the future is precisely determined by the starting conditions). Though the possibility of using stochastic models is recognized in the literature, the majority of models employed are deterministic. Stochastic differential equations relate *stochastic processes*—processes that incorporate some element of randomness [29]—in terms of equations governed by a stochastic calculus (the Itô and Stratonovitch calculus are two of the possible alternatives) and the presence of "noise".

Examples 4.5. The Langevin equation (a stochastic differential equation describing Brownian motion in a potential field) represents an approach to modelling intrinsic fluctuations in dynamics of species, related to additive noise; for a review on modelling the intracellular noise see [77]. More elaborate approaches to modelling the evolution of the probability density function rely upon the Fokker–Planck equation. In [51] the Kolmogorov forward equation was applied to study the evolution of HIV-specific CTL responses. Both approaches refer to a continuous description of the distribution of species. Instead [34] one can consider a discrete state space for the system, and use a stochastic approach based upon a birth–death process equation, which describes the evolution of probability of the system's components to exist in particular states.

Discrete stochastic algorithms are sometimes considered to be appropriate for simulating the interaction of individual cells and molecules. The general approach is based upon the Monte Carlo simulation of a single trajectory through the state space and repeating the simulations of trajectories. Each state of the system is associated with a certain number of species, and the transition to the next state is made using the appropriate probability distribution and a random number generator. Although stochastic simulations of complex systems are able to demonstrate the experimentally observed fluctuating patterns of dynamics, sometimes it appears difficult to interpret them in causal terms. Computational efficiency seems to be the most pressing issue in the application of the individual cell-based versus cell population-based approaches to modelling in immunology.

Examples 4.6. Recent examples include: (i) the use of a 2D cellular automata model in studies of the spatial aspects of influenza A virus infection [13]; (ii) the application of an agent-based model to analyse the specificity versus sensitivity in T-cell recognition [23], the 2D dynamics of granuloma formation in tuberculosis infection [32]; (iii) a stage-structured approach being a simplified version of the well-known Gillespie Direct Method [77] to simulate the multiple CTL responses in LCMV infection [25]; (iv) the Monte Carlo study of the stochastic activation and tuning of the activation thresholds of T-cells [24].

5. Some simple case studies

Flow cytometry analysis of CFSE—or *carboxy fluorescein succinimidyl ester*—labelled lymphocytes using the FACS (fluorescence activated cell sorter) technique is currently the most informative experimental technique in immunology, allowing one to trace labelled cell populations over time in terms of the number of divisions they undergo. The proliferation of CFSE labelled cells is detectable by the halving of the cellular fluorescence with every cell division completed. However, interpretation and analysis of such population-turnover data requires the development of adequate models. The authors' purpose here is to illustrate that a variety of types of model can be used.

Examples 5.1. We review three representative models formulated recently using different types of equations to describe the dynamics of cell populations labeled with CFSE: a heterogeneous ODE model [56], a DDE model [19] and an age-structured hyperbolic PDE model [33].

(a) We first consider *a model based on ODEs*. A general linear compartmental model considered in [56] describes the rate of changes in the numbers of lymphocytes $N_j(t)$ having undergone j divisions and $D(t)$ the number of dead but not disintegrated lymphocytes at time t. The model assumes that the rates of cell proliferation and death, α_j and β_j, respectively, are division number dependent. In generic form, the model equations are as follows:

$$\frac{\mathrm{d}N_0}{\mathrm{d}t}(t) = -(\alpha_0 + \beta_0)N_0(t), \tag{5.1a}$$

$$\frac{\mathrm{d}N_j}{\mathrm{d}t}(t) = 2\alpha_{j-1}N_{j-1}(t) - (\alpha_j + \beta_j)N_j(t), \quad j = 1, \ldots, 7, \tag{5.1b}$$

$$\frac{\mathrm{d}D}{\mathrm{d}t}(t) = \sum_{k=0}^{7} \beta_k N_k(t) - \delta D(t). \tag{5.1c}$$

The birth and death rate parameters were estimated using the in vitro data on the growth of CFSE labeled T-lymphocytes. It appeared that the birth rate as a function of the divisions number is bell-shaped, whereas the death rate function is initially close to zero and increases thereafter.

(b) We now consider *a model incorporating memory*. A well-known biological model for cell cycle data analysis is the Smith–Martin (SM) model, which lumps the cell cycle into two states. The first state (called A) corresponds to G_1 phase of the cycle, and the second one (state B) represents S–G_2–M phases of the cell cycle [83]. The progression through the cell cycle is assumed to have a stochastic component (the recruitment of cells from an A state into B) and a deterministic component (a progression with a fixed time-lag through the B state). In a recent study [19] a DDE-type model was proposed which describes the rate of change of the population of T lymphocytes in the A and B states that

have undergone j divisions:

$$\frac{\mathrm{d}A_0}{\mathrm{d}t}(t) = -(\alpha_0 + \beta_0)A_0(t), \tag{5.2a}$$

$$\frac{\mathrm{d}A_1}{\mathrm{d}t}(t) = 2\alpha_0 A_0(t-\tau_0)\exp^{-\beta_B\tau_0} - (\alpha+\beta_A)A_1(t), \tag{5.2b}$$

$$\frac{\mathrm{d}A_j}{\mathrm{d}t}(t) = 2\alpha A_{j-1}(t-\tau)\exp^{-\beta_B\tau} - (\alpha+\beta_A)A_j(t), \quad j=1,\ldots,\infty, \tag{5.2c}$$

$$B_0(t) = \alpha_0\int_0^{\tau_0} A_0(t-s)\exp^{-\beta_B s}\,\mathrm{d}s, \quad B_j(t) = \alpha\int_0^{\tau} A_j(t-s)\exp^{-\beta_B s}\,\mathrm{d}s, \quad j=1,\ldots,\infty. \tag{5.2d}$$

The parameters of the model characterize separately the division rates and the time-lags of transit through the B state of naive and divided cells as well as the death rates of cells in the A and B states. The range for the division number j in (5.2)—and in the following PDE model (5.3)—was taken to be infinite in order to derive an analytical solution of the models for some special choice of the initial/boundary conditions. In [19] the model variables $A_j(t_i) + B_j(t_i)$ were fitted to in vivo data (extracted from the CFSE profiles—histograms) on T-lymphocyte distributions with respect to the division number.

(c) A *model based on PDEs* which considers the (with respect to the progression through the B state of the cell cycle) age-structured description of lymphocyte division was analysed in [33]. For data fitting, the authors considered the population of cells that have undergone j divisions in the A state and in the B state, the latter being defined using the time distribution of cells at time t in the B state $b_j(t,s)$: $B_j(t) = \int_0^{\tau} b_j(t,s)\,\mathrm{d}s$. The corresponding equations read

$$\frac{\mathrm{d}A_j}{\mathrm{d}t}(t) = 2\alpha b_{j-1}(t,\tau) - (\alpha+\beta_A)A_j(t), \tag{5.3a}$$

$$\frac{\partial b_j}{\partial t}(t,s) + \frac{\partial b_j}{\partial s}(t,s) = -\beta_B b_j(t,s), \quad j=1,\ldots,\infty. \tag{5.3b}$$

To estimate the parameters of the PDE version of the SM model three different parameter estimation approaches (direct fitting, indirect fitting and rescaling method) were examined [33]. The model proved to be consistent with the in vivo data characterizing the CFSE profile of transgenic T-lymphocyte adoptively transferred into irradiated mice. The issue of choosing the right initial conditions for the PDE description received special attention.

6. Key modelling features

The problem of formulating a model explaining a phenomenon specified by data sets is considered to be central to every scientific discipline. In many areas of science, modelling is, in essence, based on the restricting assumption of an isomorphism between the properties of the models and the real system. This allows one make direct inferences about the real system from the properties of the models. In contrast, mathematical modelling in immunology follows a "systems engineering" approach. A conceptual scheme for the system is generated by a priori restricting the model to the "most important" interactions. This defines the selection of the time- and space-dependent variables as well as the set of parameters which characterize the kinetics of the specified processes. The model equations are formulated by putting together elementary functional forms (*building blocks*) for the growth, death, differentiation, etc. processes rather than by deriving constitutive equations from the first principles. Various functional forms and mathematical equations can be used to build up a mathematical model in immunology. Typically, modellers borrow concepts from ecology, enzyme kinetics or epidemiology, making use of the mass action law to formulate equations and describe the dynamics.

Examples 6.1. Modelling the LCMV infection of mice yields an example of the dilemma facing modellers. Three essentially differing mathematical models of the virus-immune response dynamics were developed to explain the phenomenon of CTL exhaustion, reflecting the fact that translation of an immunological phenomenon into a mathematical structure is an ill-defined procedure—see [15,49,90].

In this section, we summarize the mathematical details in the context of the underlying immunological processes. The key features of the immune system that make call for the application of mathematical modelling tools can be summarized as follows: (i) physical complexity; (ii) compartmental structure; (iii) non-linear (bi-phasic) response; (iv) threshold-type of regulation; (v) memory or time-lag effects; (vi) cooperative inter-cellular interaction; (vii) inter-clonal competition and selection; (viii) redundancy.

A mathematical description of the immune processes should address the dynamics of cellular responses to antigens (either at the population or at the single cell level) occurring locally or systemically. To quantify the population dynamics of cells and molecules in one compartment[5] (defined either physically or functionally) one needs to consider the rates of (i) growth, (ii) death, (iii) immigration and (iv) emigration. The relationship can be represented by the following prototype structure of balance equation of the lymphocyte population in a single compartment (e.g., spleen, lymph node):

$$\text{rate of change of population} = \begin{pmatrix}\text{proliferation}\\ \text{or}\\ \text{“ multiplication”}\end{pmatrix} \pm (\text{differentiation}) - (\text{death}) \pm \begin{pmatrix}\text{transport}\\ \text{or}\\ \text{“ transfer”}\end{pmatrix}. \tag{6.1}$$

In the majority of models in immunology, the building blocks (i.e., the individual terms in the differential equations) represent (i) growth of pathogens and cells, (ii) cellular and molecular interactions (e.g., antigen–antibody or receptor–ligand), (iii) activation, division and death of lymphocytes, (iv) homeostasis in the immune system.

Growth and death are to an extent complementary. A number of standard patterns are used to model the growth kinetics of pathogens or lymphocytes: (i) the exponential pattern (associated with a rate of change in $N(t)$ of $b\cdot N(t), b>0$, where b stands for the intrinsic growth coefficient) [57]; (ii) the logistic pattern with a rate of change of $b\cdot N(t)\cdot(1-N(t)/C)$, where $C>0$ is referred to as the carrying capacity [15]; (iii) the “confined exponential” pattern, with rate proportional to $(C-N(t))$ [69,71]; (iv) the Gompertz pattern (with rate proportional to $bN(t)\cdot(\ln(C)-\ln(N(t)))$ [82]; (v) and the time delay or “quasi-exponential” pattern with the growth rate $N'(t)$ proportional to $bN(t-\tau)$; here τ is called for the reproduction time delay [9,67]. Further options for describing the population growth can be found in [12]. The life-span of cells in the immune system is a tightly regulated process. There is a range of mechanisms responsible for cell death or elimination. Most of the mathematical models in immunology restrict the cell death description either to an exponential (“natural” death) or a predator–prey (effector mediated elimination) type kinetics. The functional forms used in the models are:

(α) exponential decay ($N'_{\text{death}}\propto\lambda N(t)$; $\lambda<0$ is the intrinsic death coefficient) [57,69];

(β) the second-order kinetics due to crowding effects ($N'_{\text{death}}\propto\mu N^2(t)$) [71] (the logistic pattern of growth $N'_{\text{death}}\propto|\lambda|N(t)-|\mu|N^2(t)$ may be regarded as an exponential growth mitigated by death from a second-order crowding effect);

(γ) the effector-lymphocyte-mediated elimination with or without saturation effect [14,57,69] (respectively, $N'_{\text{death}}\propto d\{N(t)E(t)\}/\{\theta+E(t)\}$, or $\propto d\,N(t)\,E(t)$);

(δ) the division-number-dependent death rate, which assumes that there is an upper limit (the so-called “Hayflick limit” $n_{\max}$, was observed for cell division in vitro) on the number of cell divisions n: $N'_{\text{death}}\propto d\{(n(t)/n_{\max})^m\}/\{1+(n(t)/n_{\max})^m\}$; here m [27] is an integer similar to the Hill coefficient that determines the steepness of the sigmoidal dependence;

(ε) the fixed-time-delay description [15,14] of antigen-dependent activation-induced cell death ($N'_{\text{death}}\propto d\,N(t)\,A(t)\,A(t-\tau)$).

The interaction between an infectious agent and the immune system is a dynamic process. In ecological models the concept of functional response refers to a function which describes the interaction between predators and preys. The predator–prey framework (and its generalizations [43,68]) leading to Lotka–Volterra type of equations underliess the structure of many low-dimensional models of immune responses. However, the nature of the pathogen–lymphocyte interaction is a more complex one, as the pathogen can also down-regulate the specific immune responses via the induction of anergy (i.e., unresponsiveness) and apoptosis in the responding lymphocytes.

Remark 6.1. There are phenomena observed in various infections, such as lymphocyte exhaustion, or tuning of the activation thresholds, which do not fit into a simple predator–prey interpretation [37,38] and demand more complex models. For example, a *modest* increase in viral load can stimulate an increased immune response, which is similar to

[5] A compartment is defined by a characteristic material which occupies a given volume and which is kinetically homogeneous.

the effect of increase in the prey density on the predator growth. However, an *overwhelming* viral infection results in a suppressed immune response.

The immune system needs to accommodate ever increasing numbers of new cells within a limited lymphoid population, so a selection process through competition between different subsets of cells and between specific clones must take place. The homeostasis in the immune system is maintained by a complex regulatory network leading to cell survival, proliferation and death. These include: (i) spatial control of cell life and death processes, (ii) competition between cells for the limited resources provided by antigen presenting cells like persisting cross-reactive antigens, self-antigens, MHC class I or II molecules, survival factors, etc., (iii) regulation of the level of Bcl-2 expression (whose presence increases cell life), which is increased for memory lymphocytes in comparison with their naive precursors, (iv) regulation of memory cell division by persistent antigen-specific or non-antigen-specific factors. Various functional forms could be employed to represent the structure, such as the antigen/T-cell relationships or the supportive/antagonistic relationships between components; each would imply differing details in the dynamics and the attractors, and distinguishing the optimum choice will rely upon the available data. The homeostatic regulation of the ith lymphocyte clone $N_i(t)$ which maintains the total number of immune cells near the carrying capacity can be described via a density-dependent term [3] of the type $N_i(t)\,[F(\sum_{k=1}^{\sim 10^5} N_k(t)) - d]$, or [57] as constant confined exponential growth.

Lymphocyte response or *activation* is a multi-step process, which includes T-cell receptor mediate signal transduction leading to gene up/down-regulation. The protein–protein and genetic interactions in a single cell during the activation stage are the focus of the systems biology studies. At the cell population levels there were few attempts to derive or infer from data fitting constitutive relationships for the functional dependence of the lymphocyte response on the antigen density [18,20]. Examples of possible forms are:

(α) the second-order reaction kinetics, with no competition and without saturation effects: $N'_{\text{div}} \propto b\,A(t)\,N(t)$;
(β) bounded rate growth (saturation at high antigen load): $N'_{\text{div}} \propto b\,\{N(t)A(t)\}/\{\theta + A(t)\}$;
(γ) inhibitory lymphocyte interaction: $N'_{\text{div}} \propto b\,N(t)(A(t)/\{\theta + A(t)\} - d\,N(t))$;
(δ) antigen-specific resource competition: $N'_{\text{div}} \propto b\,\{N(t)A(t)\}/\{\theta + A(t) + c\,N(t)\}$;
(ε) non-specific resource competition: $N'_{\text{div}} \propto b\,A(t)/(\theta + A(t)) \times N(t)/(1 + c\,N(t))$.

Let us consider *time-lags*. Reactions are either *instantaneous* or *delayed*. The rate of change $N'(t)$ in the population size $N(t)$, at time t, appears to depend on the status of the population at (an) earlier time(s) $t - \tau$. The quantity τ represents a delay in the response and can be either a fixed number or some function of time (replace τ by $\tau(t)$) or time and state (replace τ by $\tau(t, N(t))$). Delays in the mathematical models of immunological phenomena represent the time for signal delivery, transit time through compartments, or cell division/differentiation time. In most applications, a delay is used to represent the effect of some variables and processes (sometimes not visible!) that are not explicitly considered and are hidden in the model. The incorporation of time-lag is an essential feature of realistic models in immunology as it qualitatively improves the consistency with complex patterns of growth and decay processes. The most recent examples include the analysis of: (i) CFSE labelled lymphocyte dynamics [19] based upon the Smith–Martin model of cell division, with the duration of the B-phase described by a time-lag; (ii) the HIV replication model, assuming that the newly infected cell needs some fixed time-lag to start producing the virus particles [66].

We now consider the *compartmental approach*. The immune system can be viewed as being made up of set of compartments, defined either physically (organs) or functionally (states of lymphocyte differentiation). Indeed, as described before, the immune system is a body wide network of interacting lymphoid organs, cells and humoral factors. The organs such as spleen, lymph node, thymus, bone marrow, etc. give examples of physical compartments in the immune system. The compartmental system consistent with the recirculation pattern of lymphocytes is referred to as the mammillary system, where the blood acts as the "mother" or "central compartment" and all other compartments are "daughters". The lymphocyte differentiation process can be properly described using the one-way catenary chain of compartments approach [1,45]. The subject of compartmental analysis emerged in the early 1950s to deal with data on radionuclide tracer measurements. A compartmental system consists of n interconnected compartments. The precise structure is given by a connectivity diagram, and the compartmental model is defined by a compartmental matrix describing the fluxes between any two compartments, and an inflow–outflow vector function describing the exchange of the substances with the external environment. Both processes might depend on time, state and parameters, and compartmental systems can be described using various types of equations, e.g., non-linear autonomous, linear system

with discrete time-lags. In the latter case, the time-lag (τ_{ij}, say) represents a fixed time to move from compartment j to compartment i. The theory of compartmental systems is a well-developed one [1,45]; however, its broad application in immunology is still to come.

Examples 6.2. (a) Recently, it has been shown that using spatially structured models of virus and immune responses result in different estimates of virus–host parameters as well as qualitatively changes the behaviour of system (e.g., eliminates long-lasting oscillations, or reduces the amplitude of an oscillatory solution) [30]. In experimental murine LCMV system understanding the quantitative consequences of the systemic versus peripheral modes of infection and adoptive immunotherapy on virus elimination and immunopathology also requires the extension of analysis from the processes localized exclusively to spleen to those involving other solid tissues and blood [14]. A compartmental model of adoptive immunotherapy with DCs predicted that the recirculation kinetics of the CTL changes dramatically and the transfer coefficients as functions of the DC number in spleen were identified [55].

(b) In order to characterize the kinetics of T-lymphocyte turnover, DNA labelling (BrdU and deuterated glucose) coupled to measurement of Ki-67 expression, cell-surface markers and functional characteristics are used extensively these days. The kinetics of labelled cell sub-populations in blood and other tissues is monitored during labelling and post-labelling. The interpretation of such cell population data in mechanistic terms requires the development of quantitative mathematical models and their careful analysis. It has been shown that the corresponding mathematical models should consider the spatial and temporal structure of lymphocyte proliferation and death as suggested by the clonal burst view. This should allow a consistent interpretation of the data and estimation of the lymphocyte turnover parameters [39]. The models proposed in [61] consider a hierarchy of T-cell differentiation states as well as the spatial structure of the lymphocyte homeostasis, giving an example of genuine compartmental systems.

Conservation laws are well known in physics; they are the statements about certain physical quantities which remain constant with time. In modelling species (chemical or biological) dynamics, conservation of mass, fluxes or connectivity [87] represent practically relevant concepts: if no material is leaving or entering the system then a mass conservation law implies that the total mass remains constant. This is an example of a closed system. Most of the systems modelled in immunology represent open ones. For them, the conservation of fluxes (where the rate of consumption of some species constitutes the same processes as the rate of generation of another species) provides an important constraint that needs to be observed in formulating the modelling and estimating the parameters from the observation data. However, there are numerous examples of models in immunology when the flux conservation is not implemented (e.g., in the description of quasispecies dynamics, where the backward mutations are often neglected to simplify the analysis). To evaluate the consequences of this type of simplification, computational sensitivity analysis is necessary.

The general nonlinear first-order hyperbolic PDE of conservation law has the form $\partial y/\partial t + \partial f/\partial x = 0$ (where f depends nonlinearly on y, and $y = y(x; t)$), and a standard equation for a conserved quantity has the form $(\partial y/\partial t)(x; t) + \sum_i a_i(x; t)\,(\partial y/\partial x_i)(x; t) = 0$ for (x, t) in some region of space and time. This hyperbolic equation of conservation represents the first principle law, which is widely used in studies of cell population dynamics. The corresponding structured population models are associated with the names of Lotka–Sharpe–McKendrick and Gurtin–MacCamy. The second independent variable x may be the age, or size, or mass. The models also consider the increase or decrease in the population size due to death or birth of individuals. For piecewise constant birth and death rates with delta function peaks, the age-structured models give rise to delay or neutral DDEs for some population subsets defined by the features of the birth/death rate functions [16]. In Section 5 we discuss the application of the conservation law based models to the analysis of the dynamics of antigen-stimulated T-lymphocytes labelled with CFSE marker.

The *spatial structure* of the immune system and infection processes plays a decisive role in the dynamics of immune processes and infection outcomes. One of the rules of the immune response regulation suggests that T-lymphocyte ignores antigens (self or foreign) that stay strictly outside of secondary lymphatic organs or reach them only for too short a period of time [93]. The implication of the above rule is that the spatial organization of the immune system is a part of the complex process of immune response regulation. In mathematical immunology the need to consider the dependence of the cell population dynamics not only on time as an independent variable, but also on the spatial position, had been mostly appreciated in the context of modelling the chemotaxis and inflammatory responses [48]. The main problem in advancing spatial–temporal models of the cell population immune response dynamics is a paucity of consistent experimental data.

Examples 6.3. (a) The potential of a PDE model in the description and analysis of the T-cell recirculation experiments in rats was shown in [84]. The model describes the dynamics of T-lymphocytes in blood, spleen, lymphatic and intestinal compartments. Whereas the blood was assumed to be homogeneous well-mixed compartment, the spleen and lymphatic compartments were considered as 1D tubes. The rate at which T-cells move through the compartments was modelled as a bulk movement, with rate of change proportional to $v(\partial N(t,x)/(\partial x))$ (known as convection, or advection, or drift—with v being the velocity of the medium which transfers the lymphocytes).

(b) In a recent study [32] of macrophage response to mycobacterium tuberculosis infection a PDE model was formulated to consider the movement of lymphocytes via diffusion and advection processes. The volume change of the lung granulomas (multicellular lesions) resulting from cell proliferation and death was assumed to generate a velocity field by which (in addition to pure diffusion and chemotaxis-dependent diffusion) cells are transported [32].

Modelling the molecular events that accompany the activation of T-lymphocytes represents another field of mathematical immunology for which the spatio-temporal consideration is important. The PDE models of the T-cell and antigen presenting cell interaction consider 2D binding and dissociation of two types of receptors (antigen- and non-specific) with appropriate ligands, the diffusion mediated and the direct transport of the chemical species on the cell membrane. The time evolution of the membrane separation is described by a Landau–Ginzburg type equation, describing the motion driven by the minimization of the free energy of the membrane. The application of reaction–diffusion models to simulate the formation of the immunological synapse[6] between a T-cell and antigen-presenting cell and the T-cell receptor mediated signalling has recently been reviewed in [26].

7. Experimental data

The formulation of mathematical models of immunological phenomena and estimation of the models' parameters depend on the quality and amount of data. Although experimental data are available in published articles, using it for developing quantitatively consistent models is a problem, as each data set is usually based on an experiment with a different setup. Data on the migratory behaviour of immune cells in lymphoid organs can now be generated [35], due to recent advances with in situ imaging techniques. Light microscopy techniques allow dynamic visualization of T-lymphocyte—antigen presenting cell interaction both in vitro and in intact lymphoid tissue [28] in addition to cell migration through the organs of the immune system. The interpretation of such 4D data calls for further development and application of models based upon reaction–diffusion–advection systems. In general, one assumes that *solid* and *comprehensive* data sets are needed to proceed with mathematical modelling. It is likely that the data arise from several experiments or a series of observations. In this case individual observations have to be summarized in some way. The first problem, which appears to be quite general, is that in most cases the sample sizes in immunology are *small* from a formal statistical point of view, e.g., as few as two to five independent measurements are used to determine the mean and standard deviation of lymphocyte count or virus titer. Secondly, the observation data are summarized either as the mean either of the absolute or of the log-transformed measured quantities. The choice of a particular approach may have a theoretical basis. However, quite often it is made for reasons such as to transform non-linear correlations into linear ones, reduce the effect of the outliers, to describe skewed data, or stabilize the variance when a variable has a constant coefficient of variation. The absolute and geometric means reflect two differing assumptions about the distribution of the measurements, the Gaussian or, as it is frequently called, the normal distribution, and the log-normal (or Gaussian for the log-transformed values) ones, respectively. If the assumed probability distribution is not correct, the results of statistical data processing (mean, confidence intervals, etc.) may deviate from the true ones significantly. Therefore, primary statistical analysis of experimental data has to be carried out in accordance with the genuine underlying probability distribution of the observations errors. Unfortunately, this basic issue has not yet been examined in a comprehensive way, although the statistical frameworks for hypothesis testing and estimation problems in biology and medicine have been advanced systematically since long ago [5].

Remark 7.1. We refer to a recent study in which relatively large samples of data were experimentally obtained (sample sizes containing up to 50 measurements) to estimate the statistical distribution of the percentage of the β-galactosidase

[6] Immunological synapse is a term for the specialized junction between a T-lymphocyte and an antigen-presenting cell, which consists of a central cluster of T-cell receptors surrounded by a ring of adhesion molecules.

specific CTLs (quantified by the tetramer technique) sampled from spleen and blood of genetically identical mice at various times following infection with recombinant adenovirus [7]. The Kolmogorov–Smirnov criterion was used to rank the normal-, log-normal and gamma distribution. It appeared that a log-normal distribution agrees with the samples better than the others. The results suggested that about 20–30 repeated measurements were needed reliably to determine the probability distribution of measurement errors for the percentage of total and tetramer-positive CTLs.

8. How may one choose between different models?

Zinkernagel [93] observed that *the many immunological observations and results from in vitro and in vivo experiments vary and their interpretations differ enormously. A major problem is that within a normal distribution of biological phenomena that are measurable with many methods, virtually anything can be shown or is possible.* The dependence of the results of data analysis on the mathematical model used has been recently referred to by Asquith and Bangham [6] as a worrying aspect of nearly all mathematical modelling in immunology. They wrote: *This lack of detailed knowledge—which extends to virtually every interaction routinely modelled—undermines much theoretical biology because it is difficult to build with confidence on results that are known to be model dependent*.[7] It may have to be recognized that the data available cannot assist in discriminating between theories, either because of the lack of sensitivity of the model (none of the theories is more clearly supported than the others) or because the data are inadequate to make the determination. By such conclusions, the theoretical work may be able to influence the conduct of experiments.

From our viewpoint, a basic requirement of modelling is a methodology for discriminating between rival models (parameterized models) that are constructed from observed data. The problem of identifying a model without imposing any constraints on its form is in general ill-posed; however, selecting the "best" from a collection of models following (for example) the information-theoretic approach is a well defined procedure (in which any non-uniqueness of the outcome is evident from the procedure). Amongst the candidate models should be those that incorporate rival theories, in order to determine which of these theories is best supported by the available data. What we advocate is some procedure that, given a number of generic models of different types (corresponding to different theories or mathematical structures), will: (i) for each type, determine a set of actual parameters that is in a well-defined sense optimal; (ii) order the resulting set of optimally parameterized models to indicate which is most appropriate, given the data. The ability to achieve this aim depends, in part, upon (a) the quality of the observations and (b) the assumptions made about the data for the ranking processes to be valid. The general procedure can be implemented with various *ranking methodologies* (e.g., basic data fitting, information theoretic, systems theory). A feature often considered to have merit is the *parsimony* of the model—the conservation of parameters or of complexity; in effect (and with appropriate definitions), a simple explanation that is consistent with the observations is preferred to a complex explanation that, until evidence to the contrary, does not represent the observations any better.

Data fitting provides the simplest approach to modelling. It is based on a ranking methodology leading to the choice of parameters in a given model that fits the observations in a manner that is "best" in some sense (least-squares fitting is perhaps the most popular). If one has confidence in the forms of candidate models (a subjective judgement), one criterion by which to rank them may be the size of the objective function: optimizing this is the data-fitting approach, which is useful for obtaining a descriptive measure for the purpose of summarizing observed data. See [75] for a succinct critique of data fitting.

Information theoretic methods are more refined. The information-theoretic approach to model building has been presented systematically in [22]. Here, the ranking methodology is that associated with minimum information loss. The latter expression is taken here in terms of the Kullback–Leibler information-theoretic measure of the "distance between" two probabilistic models and it characterizes the information lost when the model is used to approximate the reality or "full truth". (One problem is that the full truth model is not known.) The Kullback–Leibler measure provides a basis for deriving "information-theoretic" criteria, such as the Akaike, Schwarz and Takeuchi indices. Given a family of mathematical models and a data set, the Akaike index uses maximized likelihood estimation to quantify the Kullback–Leibler information loss for each model. The value of the index can be regarded [22] as depending on the so-called *MLE bias* of the data approximation, the *number of parameters in the model* and the *number of observations*.

[7] The solution termed "*pragmatic*" in [6] is the construction of equations having driving terms that contain functions intended to describe interactions of which the details are not known. The main limitation of this approach is the lack of any secure theoretical foundation.

The minimal value of the Akaike index suggests that the preferred model ensures a balance between over-abundance of parameters and over-fitting the data and sparsity of parameters and under-fitting the data. The minimum description length (MDL) provides a selection method that is sensitive to a model's functional form and favours the model that permits the greatest compression of data in its description; the use of MDL for model selection with reduced complexity is reviewed in [42].

Examples 8.1. The computational implementation of an information-theoretic approach (associated with a maximum likelihood treatment) to modelling in immunology was presented in [8]. The analysis was illustrated by modelling CTL response in LCMV infection using a family of models based on systems of ODEs and DDEs. The authors conclude that dealing with a set of plausible mathematical models, ranked according to the information-theoretic criteria, provides an acceptable basis for model selection and multi-model inferences in immunology. However, in real-life the approach is not without difficulties, both practical and conceptual ones, as further discussed in [10,8,80]; Rouzine et al. study the issue of finding a single approximating model for data on SIV and LCMV infections.

In his work in *mathematical systems theory*, Kalman listed fundamental questions related to a general theory of model building [46], and the idea of a *minimal model*. It seems useful to review some basic facts relevant for understanding what is considered to be a minimal model in the mathematical systems theory [76]. Mathematical systems theory is a wide-ranging area of mathematics that includes in its remit the issue of model identification. It defines a mathematical model as a subset of trajectories (behaviour) in a certain space (universum) [76]. The properties of dynamical systems that are the focus of systems theory include system identification, controllability and observability [54,76]. The equations of the model (including the initial conditions) represent an effective but highly non-unique way of specifying a behaviour. The subject of a priori identifiability of models was generally addressed in the context of the ideal conditions of an "error-free model structure" and "noise-free observations", but Kalman [47] proposed an *uncertainty principle*, postulating that inaccurate data give rise to a non-unique (uncertain) mathematical model of the system. The applicability of some of this theory to realistic modelling scenarios (in particular, where one seeks quantitative consistency) merits attention. The mathematical systems approach to modelling in immunology was pursued in an earlier work of the teams lead by Mohler and Bruni; see the comprehensive review [63].

Remark 8.1. An input–state–output (i/s/o) system described by system of differential equations has the generic form $x'(t) = f(x, u)$, $y = h(x, u)$, where u, x and y stand for the input, state and the output, respectively. The map h defines the output value when the system is in state x and the input value applied is u. An input–state–output representation of a given input-output behaviour is minimal if among all possible i/s/o representations its state space has minimal dimension. An observable system is one in which the latent variables can be deduced from the manifest variables. Controllability is related to the question of whether or not the trajectory of the dynamical system can be steered towards another one. For linear i/s/o systems the minimality of the dimension of the state space was shown to be equivalent to observability. Models represented by first-order ODEs in the latent variables and zero order in the manifest variables represent an important class of so-called "state space" models.

An issue that deserves further attention is the following. Immunology deals with processes integrating different levels of complexity as well as the time and space scales. The mathematical models can be used to model a particular phenomenon at different levels. A fundamental question [87] is "... to what degree can the structure and results of lower-level models be incorporated into higher-level model? In other words if a single variable of the higher-level system constitutes an entire system at the lower level, how do the two models relate to each other?" It was shown in [87] that for certain linear models, where the right-hand sides of the ODEs consist of sums of variables and involve S-systems (based on products of power functions of the species), the structure is preserved when variables are exchanged for lower level systems. The issue of model reduction has been addressed in the single cell virus replication model comprising of 43 equations [81]. The effect of lumping and expanding the set of ODEs in a biochemical model on the transient and long-range properties of the solutions was examined in [85].

9. Concluding remarks

Our main message is that an interdisciplinary approach (using mathematical tools to complement experimentation and bioscientific theories in immunology) is required successfully to represent, interpret and predict the observable

immune phenomena and gain further insight (which can either be substantiated or refuted) into the dynamics of immune systems. The development of computational tools for the quantitatively correct and biologically consistent interpretation of data and for prediction (and control) of the immune system has to be informed and influenced by associated experimental work. This approach raises *genuine challenges* in a range of applicable mathematics (e.g., dynamical analysis, numerics, structural stability, identification, statistics, stochastics, information theory, etc.), but especially *the question of model identification*.

Science advances by the development of scientific hypotheses and theories shown to be consistent with observed data (or are revised if shown to be inconsistent). In consequence, it is heavily dependent upon the quality and availability of data and a methodology for demonstrating that some theories fit the observations better (in some objective sense) than others. Some of the rival mathematical methodologies deserve but have not yet received an *objective* evaluation of their success at attaining their respective objectives. The research process can be affected by the attitudes (even special interests) of those who engage in it or sponsor it. History shows that views of the nature and meaning of "science", and of what constitutes an acceptable research outcome, can be influenced by the orientation of strands in society. Research teams that espouse one type of research may seek to promote their own approach, even at the expense of alternatives. (In the context of a discussion of contributions to the study of HIV, Grossman [38] observed "…while the inherent precision of the mathematical language can be used to clearly differentiate among alternative hypotheses in terms of their diverging assumptions, some authors apparently would rather blur the differences than be proven wrong …".) Diversity occurs even within the mathematical community. We see no better way to proceed with application of mathematics to immunology than to formulate mathematical models that correspond qualitatively to the existing theories and to form an ordered (or partially ordered) hierarchy of models—ordered, amongst other characteristics, according to their qualitative and quantitative consistency (in some mathematical sense) with the relevant features of observations.

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