Journal of Theoretical Biology 375 (2015) 13–20

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Understanding the roles of activation threshold and infections in the dynamics of autoimmune disease

K.B. Blyuss [a,*], L.B. Nicholson [b]

[a] Department of Mathematics, University of Sussex, Falmer, Brighton BN1 9QH, UK
[b] School of Cellular and Molecular Medicine & School of Clinical Sciences, University of Bristol, University Walk, Bristol BS8 1TD, UK

ARTICLE INFO

Article history:
Received 31 March 2014
Received in revised form
30 June 2014
Accepted 11 August 2014
Available online 21 August 2014

Keywords:
Autoimmunity
Mathematical model
Virus

ABSTRACT

Onset and development of autoimmunity have been attributed to a number of factors, including genetic predisposition, age and different environmental factors. In this paper we discuss mathematical models of autoimmunity with an emphasis on two particular aspects of immune dynamics: breakdown of immune tolerance in response to an infection with a pathogen, and interactions between T cells with different activation thresholds. We illustrate how the explicit account of T cells with different activation thresholds provides a viable model of immune dynamics able to reproduce several types of immune behaviour, including normal clearance of infection, emergence of a chronic state, and development of a recurrent infection with autoimmunity. We discuss a number of open research problems that can be addressed within the same modelling framework.

1. Introduction

Autoimmune disease occurs when the recognition of self leads to a pathological response. It is widely accepted that the initiating event depends on the recognition of epitopes, derived from proteins produced by the cell, bound to MHC molecules and presented on antigen presenting cells (APCs) to T lymphocytes. The productive engagement of a unique T cell receptor (TCR) elicits proliferation and effector function from the T cell. Each T cell in the whole population of naive T cells (in the mouse about $50–60 \times 10^6$ T cells, González-Quintial and Theofilopoulos, 1992; Jenkins and Moon, 2012; Moon et al., 2007; in humans about 3×10^{11}, Jenkins et al., 2010) carries a population of identical TCRs that recognise a repertoire of epitopes. This allows the immune system to survey the protein universe in real time and with good coverage (Mason, 1998). This cross-reactivity is unfocussed and different ligands are recognised by the same TCR with different affinities (Anderson et al., 2000).

T cells with high levels of self-reactivity are purged from the system in the thymus, but autoreactive cells are readily detected in the peripheral circulation in healthy rodents and humans. In fact, in the laboratory it is possible to produce organ specific immune pathology through immunisation with a combination of self-antigens and adjuvants that enhance immune responses (Anderson et al., 2001; Kerr et al., 2008a). The reason for the normal presence of autoreactive cells is that self-recognition is an essential step in the generation and maintenance of peripheral T cells. In healthy cells the stimulus that self-antigen imparts to select T cells centrally is below the activation threshold needed to initiate activation and cell division of cells in the peripheral circulation, so such encounters do not induce pathological immune responses.

The question of what releases the auto-pathogenic potential of T lymphocytes is at the heart of autoimmune disease. Genes that confer an increased risk of autoimmunity often map to proteins that modulate signal strength or fidelity (Gourraud et al., 2012; International Multiple Sclerosis Genetics, 2013; Ricano-Ponce and Wijmenga, 2013). The environment is also known to play a role. For example, in patients with multiple sclerosis, the relapse of spontaneous autoimmunity has been correlated with infection (Correale et al., 2006). These considerations lead to two models, which are not mutually exclusive, to explain the initiation of autoimmunity. In the first, infection releases autoantigen in an environment rich in cytokines that promote T cell activation, reducing the signal strength requirement for activation, allowing normally unresponsive autoreactive cells to be stimulated by the self-antigens that are present. This is described as bystander activation (Fujinami et al., 2006). In the second model, the introduction of pathogenic peptides that structurally resemble self-peptides, derived from infection, may induce T lymphocytes to proliferate and confer on them the ability to respond to self as well as foreign antigens (Carrizosa et al., 1998; Wucherpfennig and Strominger, 1995). This cross-reactive activation is known as molecular mimicry (Ercolini and Miller, 2008; Fujinami and

* Corresponding author.
E-mail addresses: k.blyuss@sussex.ac.uk (K.B. Blyuss), l.nicholson@bristol.ac.uk (L.B. Nicholson).

http://dx.doi.org/10.1016/j.jtbi.2014.08.019
0022-5193/

Oldstone, 1985; Oldstone, 1998). Both these processes can be conceptualised as depending on an activation induced change in activation threshold making experienced autoreactive cells easier to stimulate than their naive precursors. It is also likely that similar changes occur sub-clinically in healthy individuals, who do not develop autoimmune disease, implying that they are contained by normal regulatory mechanisms.

What are the mechanisms that ordinarily constrain autoimmunity? One explicit hypothesis is that there are fluctuations in activation threshold, in response to environmental conditions and/or stochastic variation, which change the probability that an autoreactive T cell will respond to self. The theoretical concept of tunable activation thresholds (tunable-adaptation threshold model; TAT) was introduced in the context of thymic (Grossman and Singer, 1996) and peripheral (Grossman and Paul, 1992) modulation of T cell behaviour. In these papers, and in models derived from them (Carneiro et al., 2005), persistent subthreshold stimulation is taken to have the effect of making cells more difficult to activate. Therefore if normal regulation depends on tuning, a failure of optimal tuning might promote disease.

Tuning also has the potential to improve the sensitivity and specificity of signalling in a noisy environment (Feinerman et al., 2008; George et al., 2005) and a number of tuning mechanisms have been identified by experiment. CD5 tunes TCR signalling during thymic selection (Azzam et al., 2001) and in autoimmune disease (Hawiger et al., 2004) while co-receptor tuning has been demonstrated and analysed in CD8+ T cells (Park et al., 2007; van den Berg et al., 2007). Activation thresholds vary in the presence of different external signals or as a result of prior activation changing future thresholds. Their regulation is important for successful navigation of the thymus by developing T cells (Fu et al., 2013; Hogquist et al., 1997) and thresholds change in real time as cells circulate within the immune system (Stefanova et al., 2002). In tissues tuning as a result of changes in B7 super-family members' level of expression has recently been reported in responses to antigen over both short (Honda et al., 2014) and longer timeframes (Zinselmeyer et al., 2013).

The other key mechanism of negative feedback in immune responses is supplied by regulatory cells (T regs). The literature on such cells is rich and deep (Josefowicz et al., 2012; Sakaguchi, 2004). In the presence of inflammation these cells are triggered by their recognition of autoantigens, but they function to switch off immune responses. Both direct (T cell to T cell) (Grossman et al., 2004) and indirect (by inactivation of antigen presenting cells) (Alpan et al., 2004; Wing et al., 2008) mechanisms have experimental support. Global impairment of T reg function causes autoimmune disease (Fontenot et al., 2003; Khattri et al., 2003). But whether subtle defects in T reg cells are the root cause of autoimmune disease is less certain. These different mechanisms are summarised in Fig. 1.

One striking property of autoimmune diseases is their chronic relapsing and remitting nature. Remissions in clinical autoimmune disease, even in the absence of treatment are widely recognised. The stuttering nature of the disease process is also reflected in more objective measures of tissue inflammation, for example in the brain in multiple sclerosis (Buljevac et al., 2002; Correale et al., 2006). Exacerbations are significantly associated with the occurrence of infection, but also occur without such an association. Models that capture these chronic and oscillatory properties of the disease process are important if we are to understand the dynamic range of these diseases.

Another characteristic feature of autoimmunity is the localisation of immune cells within the affected tissue. Local inflammation increases the immune cell content of the target organ (Boldison et al., 2014; Kerr et al., 2008b). The TCR specificities of the cells are a mixture of autoantigen responsive and non-autoantigen responsive.

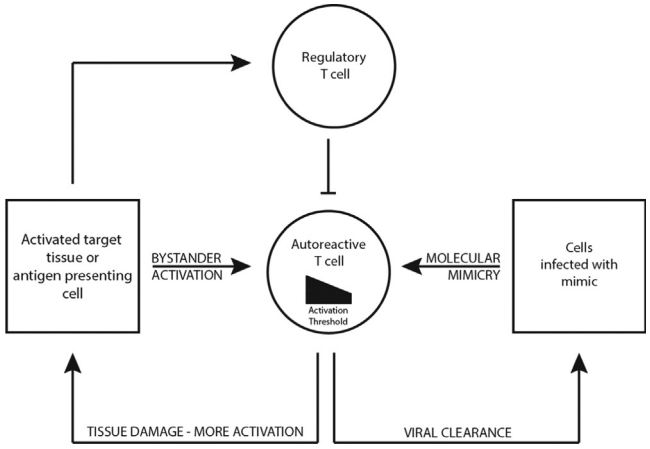

Fig. 1. The activation of autoreactive T cells triggers autoimmune disease. Two major mechanisms are postulated, bystander activation and molecular mimicry. These may be accompanied by changes in the activation threshold which perpetuate the disease state, while the development of naturally occurring regulatory cells and regulatory cells induced within activated target tissue can limit disease.

There is no consensus as to the ratio between these two populations (e.g. Alkemade et al., 2013; Oldstone et al., 2012) but differences in behaviour of these two kinds of cell (specific and non-specific) are beginning to be defined experimentally (Honda et al., 2014). Modelling this type of phenomenology implicitly requires consideration of at least two compartments.

2. Previous mathematical models and results

Mathematical modelling has been very effective in the analysis of different aspects of virus dynamics and the interactions between viruses and the immune system of the host (Bocharov, 1998; Nowak and May, 2000; Perelson and Weisbuch, 1997; Wodarz, 2007). A nice review by Andrew et al. (2007) discusses fundamental modelling and computational issues associated with modelling immune response, especially from the perspective of the possibility of making experimentally testable predictions. While some significant insights have been obtained using mathematical models of underlying processes, theoretical studies of origins and progression of autoimmunity have so far remained quite limited. One test of utility would be the use of model predictions to inform treatment in autoimmune disease, a goal that is so far elusive.

Early models of autoimmunity concentrated on the interactions between effector and regulator cells to understand T cell vaccination (Segel et al., 1995) without addressing causes of autoimmunity. Borghans et al. (1995, 1998) have performed further studies of T cell vaccination and demonstrated how the interactions of autoreactive and regulatory T cells can lead to the onset of autoimmunity or stable oscillations around a vaccinated state. Here (Borghans et al., 1998) autoimmunity is defined by a threshold number of autoreactive cells. Burroughs et al. (2011) have studied cytokine mediated bystander activation in the onset of autoimmunity using a fairly high dimensional model and focusing on asymmetries in the growth rates of different populations. Wodarz and Jansen (2003) analysed autoimmunity in the context of viral cancer by including viral infections indirectly through an increased rate of uptake of self-antigen by antigen-presenting cells. León et al. (2000, 2003, 2004) have studied the dynamics of interactions between different T cells for the purposes of understanding the regulation of immune response and control of autoimmune reaction. In an overview of this work (Carneiro et al., 2005) they have performed a comparative study of two mechanisms of self-tolerance: tuning of activation thresholds

and control by specific regulatory T cells. The authors have shown that these two mechanisms are complementary and together provide a plausible explanation of the observed dynamics of immune tolerance. More recently, Iwami et al. (2007, 2009) derived and studied a model for autoimmunity, which makes explicit account of the virus dynamics and its interaction with the immune system by means of linear or nonlinear immune response. They showed that a specific form of the growth function for susceptible cells can have a significant effect on autoimmune dynamics. Despite its simplicity, this model appears unable to reproduce a normal clearance of virus during a single infection, as it does not allow for a viral expansion. Various roles played by the regulatory T cells in the dynamics of autoimmunity have recently been analysed by Alexander and Wahl (2011), who focus on a model in which the APCs play a key role. Read et al. (2012) and Williams et al. (2013) have shown how one can use agent-based models and simulations to study the dynamics of immune responses and autoimmunity. They showed how model and simulation parameters can be calibrated using available experimental data. The authors illustrated the feasibility of this approach on the specific example of experimental autoimmune encephalomyelitis (EAE) and, in particular, investigated the role of CD8 regulatory T cells in autoimmune dynamics.

When developing mathematical models of autoimmune dynamics, it is important to account correctly for the precise mechanism responsible for the ability of T cells to discriminate between cells presenting self antigens and infected cells. One approach is to include regulatory cells explicitly, which are triggered by autoantigens and inhibit the activity of autoreactive T cells. This approach has been used in models of immune response, see Alexander and Wahl (2011) and Burroughs et al. (2011). Another approach is to consider T cells with tunable activation thresholds, where T cells continually tune their responsiveness to TCR stimulation through stimuli evoked by autoantigens (Grossman and Paul, 1992; Lucas et al., 1999; Nicholson et al., 2000). Grossman and Paul (1992, 2000) and Grossman and Singer (1996) developed models with tunable activation thresholds that were applied to peripheral and to central T cell activation. Altan-Bonnet and Germain (2005) have modelled signalling threshold and showed differences in activation/response threshold that are dependent on the activation state of the T cell. Noest (2000) has shown how the need for activation threshold tuning arises from the first principles of signal detection theory, see also Scherer (2004) for further discussion of this issue. van den Berg and Rand (2004) have studied mathematically two cellular response models of the dynamics of tunable activation threshold. Besides purely theoretical studies, dynamical changes in T cell activation during their circulation have also been shown experimentally both in the mouse and in man, where it has important implications for the outcome of specific therapeutic interventions (Bitmansour et al., 2002; Nicholson et al., 2000; Römer et al., 2011; Stefanova et al., 2002). A more comprehensive model would be one that incorporated both activation thresholds and T regulatory cells.

Models that address the dynamics of infection in different compartments have shown that this approach can have a significant impact on the dynamics of the system (Funk et al., 2005). In this respect, comparing infection in systemic and peripheral tissues provides a much more comprehensive description of the underlying process (Bocharov et al., 2003). In the context of autoimmunity, consideration of the dynamics within the target tissue increases the complexity of modelling but also yields a more realistic representation of the immune dynamics (Nicholson et al., 2012).

In a recent paper (Blyuss and Nicholson, 2012), we proposed a mathematical model of immune response during a viral infection and possible onset and dynamics of autoimmunity. The main focus of this model is on the role of T cells represented as two distinct activated populations, one of which is capable of an autoimmune reaction through having a lower activation threshold to self-antigen. The model also included two distinct populations of susceptible cells to allow for a situation when autoimmunity takes place in a different organ to the one where the original infection occurs. Evidence from some experimental models of autoimmunity suggests that B cells are dispensable, and disease develops when they are not present (Wolf et al., 1996). Furthermore, the development of antibodies depends on prior T cell interactions with bacteria (Wu et al., 2010). To account for these facts, the model concentrated primarily on the T cell dynamics and did not include other aspects of immune dynamics, such as antibody response, regulatory T cells or memory cells.

Fig. 2 illustrates different kinds of immune dynamics that can be exhibited by the model analysed in Blyuss and Nicholson (2012). This includes normal clearance of infection shown in Fig. 2(a), where after the initial peak, the number of infected cells is monotonically decreasing, and eventually the infection is completely cleared. Fig. 1(b) corresponds to a chronic infection where the immune system of the host is unable to clear the infection, and as a result it persists at a constant level. Fig. 2(c) illustrates an autoimmune state characterised by episodes of high viral production (relapses) with long periods of quiescence (remissions). Such dynamics have been observed in a number of autoimmune diseases, such as MS, autoimmune thyroid disease and uveitis (Ben Ezra and Forrester, 1995; Davies et al., 1997; Nylander and Hafler, 2012). An important note here is that none of the subsequent reactivations of the virus requires any exogenous factors, but rather the system itself cycles through periods of relative quiescence and viral release. Fig. 2(d) shows a situation that can be described as T cell exhaustion where virus-specific T cells are rendered ineffective, and therefore their effective population size is reduced to zero.

Since for many viral infections it is realistic to expect multiple exposures of a person to the same virus, we also considered a scenario where someone who has recovered from a primary infection or currently has a chronic viral infection experiences a secondary viral challenge with the same virus. Fig. 3(a) and (b) illustrates the dynamics during a secondary viral exposure. In the case of normal clearance shown in plot (a), one can observe that due to a much slower decay of activated T cells, they still remain at a non-negligible level following the primary infection, resulting in a significantly smaller number of infected cells during secondary infection. Then later a secondary viral challenge occurs, the higher will be the resulting number of infected cells, and correspondingly the higher will be the numbers of activated and autoreactive T cells during a secondary infection. In the case of secondary viral exposure during a chronic infection shown in plot (b), due to the significant amount of activated T cells, the secondary infection does not lead to a major increase in the number of infected cells, and as a result the infection is quickly cleared to the same chronic level as before the secondary infection.

We have also modelled the impact of a therapeutic intervention aimed at reducing the number of autoreactive T cells, as shown in Fig. 3(c)–(f). When infection and autoimmunity affect different cell populations (possibly located at different places), treatment results in a noticeable reduction in the number of autoreactive T cells. For the case when two different cell populations can be targeted by an infection but only one of them is affected by autoimmune response, introduction of treatment leads to elimination of autoreactive T cells, but at the same time leads to an increased level of persistent infection. In the opposite scenario where one cell population is a target of infection but two cell populations are affected by autoimmune response, treatment leads to a suppression of oscillatory dynamics and establishment of a chronic state. Finally, when the treatment is introduced in the case of chronic infection, this again leads to a significant reduction in the number of autoreactive T cells, but at the same time leads to a slight increase in the number of infected cells.

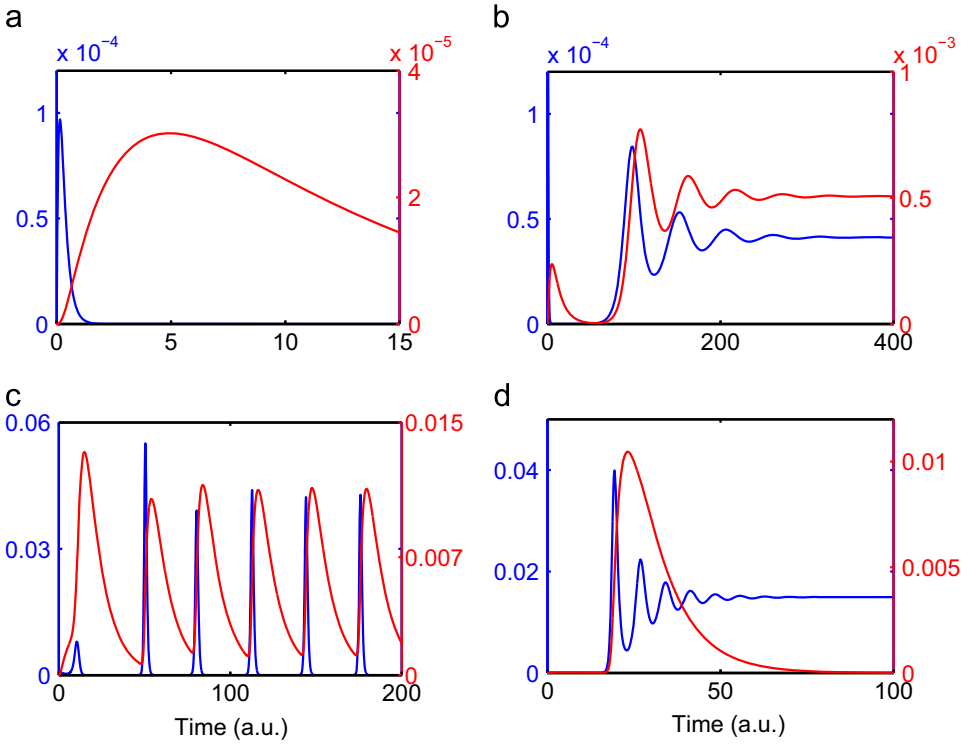

Fig. 2. Numerical simulation of normal clearance of infection (a), chronic state (b), autoimmune state (c), and T cell exhaustion (d). In all plots, blue colour denotes a rescaled number of infected cells, and red colour denotes a rescaled number of autoreactive T cells. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

3. Open problems

The wealth of phenomenology afforded by the immune system presents significant challenges to modelling and to determining what constitutes a useful model. Models that attempt to capture fundamental behavior in the form of low-dimensional dynamical systems are usually susceptible to analytic solutions, but may be difficult to relate to immunity as it is observed in experiment and the clinic. High-dimensional models allow one to incorporate many more observable parameters and behaviors, but high dimensionality of the phase space leads to analyses that rely heavily on numerical simulation, which may be very sensitive to the model parameters and initial conditions. We have recently shown that such high-dimensional models are capable of reproducing many important features of clinically observed behaviour (Nicholson et al., 2012). However, this does not guarantee that these models are capturing all the important aspects of the underlying immune dynamics. Because such models are intractable to analytical analysis and commonly incorporate parameters whose real values are difficult to estimate and to measure, it is often hard to use them to form testable predictions. In fact in practice experimental immunology is relatively data poor, which is a significant challenge for developing models that have the power to predict outcome.

In this section we highlight some of the outstanding research questions in the context of onset and development of autoimmunity with particular interest in tunable activation thresholds and a breakdown of immune tolerance as a byproduct of immune response to an infection.

3.1. Dynamic nature of activation thresholds

Within a modelling framework of tunable activation thresholds, there are several possible ways to formally represent T cell populations with different activation thresholds. One of these is the introduction of distinct compartments for each individual T cell population, where all cells within the compartment have the same activation threshold and functionally perform the same role in controlling immune dynamics (Blyuss and Nicholson, 2012). Although this may be a computationally efficient way of accounting for different activation thresholds, it certainly does not tell the full story, as previous theoretical and experimental work (Altan-Bonnet and Germain, 2005; Alexander and Wahl, 2011; Grossman and Paul, 1992, 2000; Grossman and Singer, 1996; van den Berg and Rand, 2004) has stressed the dynamic nature of the tuning process, which can be observed over timescales of minutes to days (Römer et al., 2011; Stefanova et al., 2002). Since the response of any T cell depends not only on the current level of TCR stimulation, but also on the recent history of TCR stimulation (Gunzer et al., 2000; Iezzi et al., 1998; Rosette et al., 2001), this suggests that activation can itself be included in the analysis as a dynamic variable. One possibility to allow this to be modelled mathematically is to introduce additional differential equations representing activation dynamics in a way similar to van den Berg and Rand (2004). Another option is to include a more detailed kinetics of the activation process (Carneiro et al., 2005), which would allow the investigation of the role of a two-signal mechanism of T cell activation in the development of autoreactive T cell populations. Further biological realism could be achieved by considering activation thresholds as stochastic variables (van den Berg et al., 2001). Analysing dynamic activation thresholds in the context of immune response to a pathogen can provide important insights into the onset of autoimmunity.

3.2. The role of stochasticity

It has been argued that the immune response should be conceived as a multi-factor stochastic process (Perelson and Weisbuch, 1997), and therefore it is not only instructive but also essential to correctly account for the stochastic nature of immune

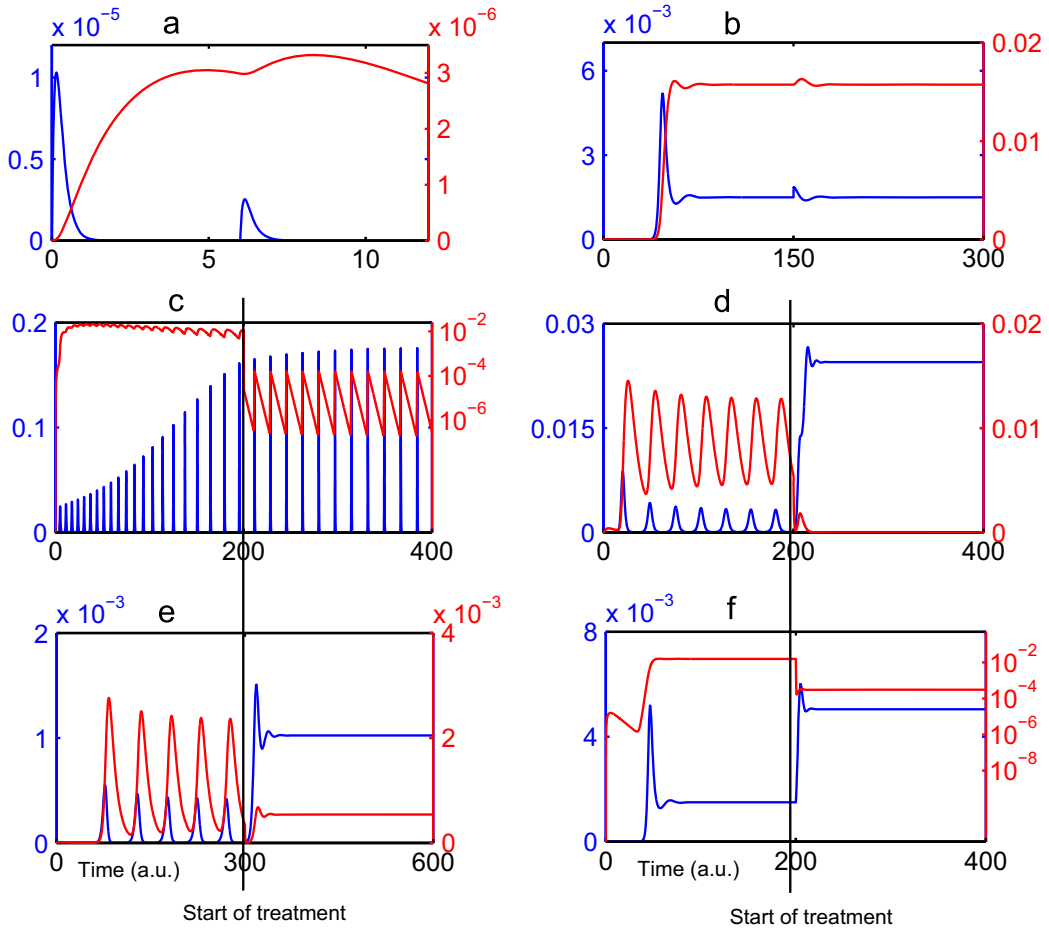

Fig. 3. Numerical simulation of a secondary infection during normal clearance (a) and chronic infection (b). Simulation of treatment of an autoimmune state: (c) infection and autoimmunity target different populations of target cells, (d) infection targets two different populations of target cells, but only one of them is also affected by autoimmune response, (e) one target population is a target of infection but two target cell populations are affected by autoimmunity. (f) Simulation of treatment of a chronic state. In all plots, blue colour denotes a rescaled number of infected cells, and red colour denotes a rescaled number of autoreactive T cells. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

processes when studying the origins and dynamics of autoimmunity. One particular phenomenon that has been identified is that of coherence resonance or stochastic amplification (Alonso et al., 2007; Kuske et al., 2007), whereby a decaying periodic solution of the deterministic system can give rise to sustained periodic oscillations in individual stochastic realisations of the same process. Stochastic analogues of deterministic models would allow one to study both analytically and numerically the effects of noise on the occurrence of sustained oscillations in the numbers of autoreactive T cells. This would correspond to relapses/remissions in clinical manifestations of disease caused by endogenous stochasticity of the immune processes.

Besides their purely theoretical interest, stochastic models would also provide a better understanding of autoimmune disease in clinical practice. Recent experimental data on progression of uveitis in rodent models (Boldison and Nicholson, unpublished data; Kerr et al., 2008a) suggest that upon induction there is often a variation in the way disease develops in the individual eyes of the same animals (Fig. 4). Because from a statistical perspective, the progress of autoimmune disease in two eyes of the same animal can be considered as two independent realisations of the same stochastic process, by considering the level of variation in the progress of disease it should be possible to quantify the level of noise. This would allow one to investigate the contribution of stochastic processes to the unequal distribution of autoimmune disease in identical organs of the same host.

3.3. *Time delays in viral dynamics*

It has already been mentioned that the onset and progression of autoimmune disease is often associated with pathogen-induced breakdown of immune tolerance. While it is difficult to pinpoint the contribution of specific viruses in triggering relapse (Buljevac et al., 2002), it is crucial to take into account the role that is played by the lag phase of virus cycle dynamics. The importance of explicitly including lag phase in the analysis of interactions between viruses and the immune system has been highlighted in earlier work on influenza, HIV and HCV (Beauchemin et al., 2008; Beauchemin and Handel, 2011; Perelson, 1999, 2002). The lag phase of the viral life cycle includes an eclipse phase consisting of virus attachment, cell penetration and uncoating, and a latent phase, which includes virus assembly, maturation and release of new virions. All of these processes result in a delayed production and release of virions, hence it is essential to correctly account for these effects in the model of pathogen-induced autoimmunity.

The lag phase has been experimentally identified in viruses that are known to sometimes cause or exacerbate autoimmune disease, such as Epstein–Barr virus (Krone and Grange, 2011; Ohashi et al., 2011) associated with multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis and autoimmune thyroid disease, HSV-1 virus (Döhner et al., 2006; Maurer et al., 2008) associated with autoimmune stromal keratitis, and the Coxsackie viruses (Hober and Sauter, 2010; Myers et al., 2004) associated with

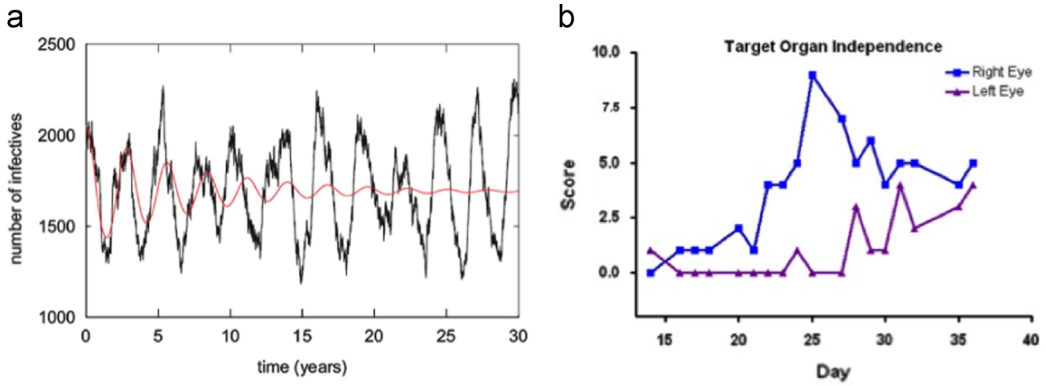

Fig. 4. (Left) Stochastic realisation of an SIR epidemic model showing sustained oscillations (black) versus decayed oscillations in a deterministic simulation (red), from Kuske et al. (2007). (Right) Unequal distribution of experimental autoimmune uveitis in C57BL/6 mice. Clinical disease score (y-axis) was obtained from photographs of the retina obtained throughout the course of disease. These were analysed to produce a disease score by a trained individual, blinded to the origin of the pictures. These results compare two independent realisations of the same stochastic process (unpublished data, Boldison and Nicholson, unpublished data). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

type-1 diabetes. In these cases, precise measurements of different stages of virus life cycle have been performed, and hence the details of the duration of lag phase are available and can be used in testing different time delay effects. Understanding the role of the lag phase in the production of virions on the dynamics of immune responses and possible development of autoimmunity is an important open problem. From mathematical perspective, the lag phase can be represented either through a separate compartment (analogous to an exponentially distributed delay) or through a constant or distributed time delay in the corresponding model equations (Blyuss and Kyrychko, 2010; Campbell and Jessop, 2009; Kyrychko et al., 2011, 2013). Mathematical models with distributed delay have already been efficiently used to study different aspects of viral dynamics (Monk, 2003; Nakata, 2011; Niculescu et al., 2010; Nowak et al., 1997). Infinite-dimensionality of the phase space of delayed equations creates a substantial challenge for analytical computations and numerical simulations, but the added benefit of improved biological realism and the significant insights these models provide would allow us to gain a deeper understanding of the effects of lag phase on the onset and dynamics of autoimmunity.

4. Discussion

In this paper we have considered mathematical modelling of pathogen-induced autoimmune disease with an emphasis on the role played by T cells with tunable activation thresholds. Existing models have demonstrated that by explicit consideration of T cells with different activation thresholds it is possible to qualitatively reproduce many types of immune behaviour. These include normal clearance of infection, emergence of a chronic state, T cell exhaustion, and a temporally periodic state with episodes of high viral production (relapses) and long periods of quiescence (remissions), which is characteristic for these conditions.

The strong evidence that autoimmunity can develop and persist in the absence of infection remains an important challenge for models of autoimmune disease. One straightforward approach that has been used (Borghans et al., 1998) is to define autoimmunity as a threshold event dependent on the number of potentially autoreactive cells present. But the absence of spontaneous autoimmunity in the presence of even large numbers of autoreactive cells (Goverman et al., 1993; Lafaille et al., 1994) means different criteria for autoimmunity will be required to model this situation. This could involve defining two states for cells with the same specificity, one autoimmune competent and one not. In this case the dynamics of activation would control the transition between states.

A complementary issue is that in contrast to models of infection, where clearance is a gold standard for an appropriately tailored immune response, in autoimmunity clearance of antigen does not always occur. Therefore models in which the immune response can terminate without clearing the inciting antigens will need to be developed. Here the application of time delays may have a role to play.

Mathematical models have the potential to contribute to the management of autoimmunity in a clinical setting. As technologies that allow the measurement of autopathogenic cells in the blood of patients are developed (McKinney et al., 2010; Oling et al., 2012), it will be important to produce models that can use such measurements to predict the future dynamics of the disease process. Because accurate prognosis early in these diseases is challenging, identifying and modelling parameters that inform this process can shape clinical decision making with regard to therapy.

Despite the successes of the current models, fundamental issues associated with understanding the onset and development of autoimmune disease remain unresolved. In order to achieve sufficient mathematical tractability, existing models make simplifying assumptions, limiting biological realism and the possibility to relate model predictions with clinical observation. From a modelling perspective, explicit inclusion of the actual dynamics of activation thresholds, as well as a proper account for time delays associated with various stages of immunity and virus life cycle, should result in more comprehensive and robust models of immune response and autoimmunity. We envisage that a more detailed consideration of stochastic aspects of the immune process will provide a better understanding of autoimmunity and will shed light on the recent experimental results that demonstrated unequal distribution of autoimmune disease in different organs of the same host. In the future, modelling the dynamics of the immune response has the potential to realize clinical benefits through the stratification of treatment regimens and their tailoring to individual patients.

References

Altan-Bonnet, G., Germain, R.N., 2005. Modeling T cell antigen discrimination based on feedback control of digital ERK responses. PLoS Biol. 3, e356.
Alexander, H.K., Wahl, L.M., 2011. Self-tolerance and autoimmunity in a regulatory T cell model. Bull. Math. Biol. 73, 33–71.
Alkemade, G.M., Clemente-Casares, X., Yu, Z., Xu, B.-Y., Wang, J., Tsai, S., Wright, J.R., Roep, B.O., Santamaria, P., 2013. Local autoantigen expression as essential gatekeeper of memory T-Cell recruitment to islet grafts in diabetic hosts. Diabetes 62, 905–911.
Alonso, D., McKane, A.J., Pascual, M., 2007. Stochastic amplification in epidemics. J. R. Soc. Interface 4, 575–582.

Alpan, O., Bachelder, E., Isil, E., Arnheiter, H., Matzinger, P., 2004. 'Educated' dendritic cells act as messengers from memory to naive T helper cells. Nat. Immunol. 5, 615–622.

Anderson, A.C., Nicholson, L.B., Kuchroo, V.K., 2001. Experimental autoimmune encephalomyelitis. In: Bona, C.A., Siminovitch, K.A., Zanetti, M., Theofilopoulos, A.N. (Eds.), The Molecular Pathology of Autoimmune Diseases, pp. 734–751.

Anderson, A.C., Waldner, H.P., Turchin, V., Jabs, C., Prabhu Das, M., Kuchroo, V.K., Nicholson, L.B., 2000. Autoantigen responsive T cell clones demonstrate unfocused TCR cross-reactivity towards multiple related ligands: implications for autoimmunity. Cell. Immunol. 202, 88–96.

Andrew, S., Baker, C.T.H., Bocharov, G.A., 2007. Rival approaches to mathematical modelling in immunology. J. Comput. Appl. Math. 205, 669–686.

Azzam, H.S., DeJarnette, J.B., Huang, K., Emmons, R., Park, C.S., Sommers, C.L., El-Khoury, D., Shores, E.W., Love, P.E., 2001. Fine tuning of TCR signaling by CD5. J. Immunol. 166, 5464–5472.

Beauchemin, C.A.A., Handel, A., 2011. A review of mathematical models of influenza A infections within a host or cell culture: lessons learned and challenges ahead. BMC Public Health 11 (Supl. 1), S7.

Beauchemin, C.A.A., McSharry, J.J., Drusano, G.L., Nguyen, J.T., Went, G.T., Ribeiro, R. M., Perelson, A.S., 2008. Modeling amantadine treatment of influenza A virus in vitro. J. Theor. Biol. 254, 439–451.

Ben Ezra, D., Forrester, J.V., 1995. Fundal white dots – the spectrum of a similar pathological process. Brit. J. Ophthalmol. 79, 856–860.

Bitmansour, A.D., Douek, D.C., Maino, V.C., Picker, L.J., 2002. Direct ex vivo analysis of human CD4+ memory T cell activation requirements at the single clonotype level. J. Immunol. 169, 1207–1218.

Blyuss, K.B., Kyrychko, Y.N., 2010. Stability and bifurcations in an epidemic model with varying immunity period. Bull. Math. Biol. 72, 490–505.

Blyuss, K.B., Nicholson, L.B., 2012. The role of tunable activation thresholds in the dynamics of autoimmunity. J. Theor. Biol. 308, 45–55.

Bocharov, G.A., 1998. Modelling the dynamics of LCMV infection in mice: conventional and exhaustive CTL response. J. Theor Biol. 192, 283–308.

Bocharov, G., Klenerman, P., Ehl, S., 2003. Modelling the dynamics of LCMV infection in mice. II. Compartmental structure and immunopathology. J. Theor. Biol. 221, 349–378.

Boldison, J., Nicholson, L.B., Unpublished data.

Boldison, J., Chu, C.J., Copland, D.A., Lait, P.J.P., Khera, T.K., Dick, A.D., Nicholson, L.B., 2014. Tissue-resident exhausted effector memory $CD8^+$ T cells accumulate in the retina during chronic experimental autoimmune uveoretinitis. J. Immunol. 192, 4541–4550.

Borghans, J.A.M., de Boer, R.J., 1995. A minimal model for T-cell vaccination. Proc. R. Soc. B 259, 173–178.

Borghans, J.A.M., de Boer, R.J., Sercarz, E., Kumar, V., 1998. T cell vaccination and experimental autoimmune encephalomyelitis: a mathematical model. J. Immunol. 161, 1087–1093.

Buljevac, D., Flach, H.Z., Hop, W.C.J., Hijdra, D., Laman, J.D., Savelkoul, H.F.J., van der Meché, F.G.A., van Doorn, P.A., Hintzen, R.Q., 2002. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 125, 952–960.

Burroughs, N.J., Oliveira, B.M.P.M., Pinto, A.A., 2011. Autoimmunity arising from bystander proliferation of T cells in an immune response model. Math. Comput. Mod. 53, 1389–1393.

Campbell, S.A., Jessop, R., 2009. Approximating the stability region for a differential equation with a distributed delay. Math. Model. Nat. Phenom. 4, 1–27.

Carneiro, J., Paixão, T., Milutinovic, D., et al., 2005. Immunological self-tolerance: lessons from mathematical modeling. J. Comput. Appl. Math. 184, 77–100.

Carrizosa, A.M., Nicholson, L.B., Farzan, M., Southwood, S., Sette, A., Sobel, R.A., Kuchroo, V.K., 1998. Expansion by self antigen is necessary for the induction of experimental autoimmune encephalomyelitis by T cells primed with a cross-reactive environmental antigen. J. Immunol. 161, 3307–3314.

Correale, J., Fiol, M., Gilmore, W., 2006. The risk of relapses in multiple sclerosis during systemic infections. Neurology 67, 652–659.

Davies, T.F., Evered, D.C., Rees Smith, B., Yeo, P.P.B., Clark, F., Hall, R., 1997. Value of thyroid-stimulating-antibody determination in predicting the short-term thyrotoxic relapse in Graves' disease. Lancet 309, 1181–1182.

Döhner, K., Radtke, K., Schmidt, S., Sodeik, B., 2006. Eclipse phase of herpes simplex virus type 1 infection: efficient dynein-mediated capsid transport without the small capsid protein VP26. J. Virol. 80, 8211–8224.

Ercolini, A.M., Miller, S.D., 2008. The role of infections in autoimmune disease. Clin. Exp. Immunol. 155, 1–15.

Feinerman, O., Germain, R.N., Altan-Bonnet, G., 2008. Quantitative challenges in understanding ligand discrimination by alpha beta T cells. Mol. Immunol. 45, 619–631.

Fontenot, J.D., Gavin, M.A., Rudensky, A.Y., 2003. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat. Immunol. 4, 330–336.

Fu, G., Casas, J., Rigaud, S., Rybakin, V., Lambolez, F., Brzostek, J., Hoerter, J.A.H., Paster, W., Acuto, O., Cheroutre, H., Sauer, K., Gascoigne, N.R.J., 2013. Themis sets the signal threshold for positive and negative selection in T-cell development. Nature 504, 441–445.

Fujinami, R.S., Oldstone, M.B., 1985. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 230, 1043–1045.

Fujinami, R.S., vonHerrath, M.G., Christen, U., Whitton, J.L., 2006. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin. Microbiol. Rev. 19, 80–94.

Funk, G.A., Jansen, V.A.A., Bonhoeffer, S., Killingback, T., 2005. Spatial models of virus-immune dynamics. J. Theor. Biol. 233, 221–236.

George, A.J.T., Stark, J., Chan, C., 2005. Understanding specificity and sensitivity of T-cell recognition. Trends Immunol. 26, 653–659.

González-Quintial, R., Theofilopoulos, A.N., 1992. V beta gene repertoires in aging mice. J. Immunol. 149, 230–236.

Gourraud, P.-A., Harbo, H.F., Hauser, S.L., Baranzini, S.E., 2012. The genetics of multiple sclerosis: an up-to-date review. Immunol. Rev. 248, 87–103.

Goverman, J., Woods, A., Larson, L., Weiner, L.P., Hood, L., Zaller, D.M., 1993. Transgenic mice that express a myelin basic protein-specific T cell receptor develop spontaneous autoimmunity. Cell 72, 551–560.

Grossman, W.J., Verbsky, J.W., Barchet, W., Colonna, M., Atkinson, J.P., Ley, T.J., 2004. Human T regulatory cells can use the perforin pathway to cause autologous target cell death. Immunity 21, 589–601.

Grossman, Z., Paul, W.E., 1992. Adaptive cellular interactions in the immune system: the tunable activation threshold and the significance of subthreshold responses. Proc. Natl. Acad. Sci. USA 89, 10365–10369.

Grossman, Z., Singer, A., 1996. Tuning of activation thresholds explains flexibility in the selection and development of T cells in the thymus. Proc. Natl. Acad. Sci. USA 93, 14747–14752.

Grossman, Z., Paul, W.E., 2000. Self-tolerance: context dependent tuning of T cell antigen recognition. Sem. Immunol. 12, 197–203.

Gunzer, M., Schafer, A., Borgmann, S., Grabbe, K.S., Bröcker, E.-B., Kämpgen, E., Friedl, P., 2000. Antigen presentation in extracellular matrix: interactions of T cells with dendritic cells are dynamic, short lived, and sequential. Immunity 13, 323–332.

Hawiger, D., Masilamani, R.F., Bettelli, E., Kuchroo, V.K., Nussenzweig, M.C., 2004. Immunological unresponsiveness characterized by increased expression of CD5 on peripheral T cells induced by dendritic cells in vivo. Immunity 20, 695–705.

Hober, D., Sauter, P., 2010. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. Nat. Rev. Endocrinol. 6, 279–289.

Hogquist, K.A., Tomlinson, A.J., Kleper, W.C., McGargill, M.A., Hart, M.C., Naylor, S., Jameson, S.C., 1997. Identification of a naturally occurring ligand for thymic positive selection. Immunity 6, 389–399.

Honda, T., Egen, J.G., Lämmermann, T., Kastenmüller, W., Torabi-Parizi, P., Germain, R.N., 2014. Tuning of antigen sensitivity by T cell receptor-dependent negative feedback controls T cell effector function in inflamed tissues. Immunity 40, 235–247.

Iezzi, G., Karjalainen, K., Lanzavecchia, A., 1998. The duration of antigenic stimulation determines the fate of naive and effector T cells. Immunity 8, 89–95.

International Multiple Sclerosis Genetics, C. 2013. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat. Genet. 45, 1353–1360.

Iwami, S., Takeuchi, Y., Miura, Y., Sasaki, T., Kajiwara, T., 2007. Dynamical properties of autoimmune disease models: tolerance, flare-up, dormancy. J. Theor. Biol. 246, 646–659.

Iwami, S., Takeuchi, Y., Iwamoto, K., Naruo, Y., Yasukawa, M., 2009. A mathematical design of vector vaccine against autoimmune disease. J. Theor. Biol. 256, 382–392.

Jenkins, M.K., Chu, H.H., McLachlan, J.B., Moon, J.B., 2010. On the composition of the preimmune repertoire of T cells specific for peptide-major histocompatibility complex ligands. Annu. Rev. Immunol. 28, 275–294.

Jenkins, M.K., Moon, J.J., 2012. The role of naive T cell precursor frequency and recruitment in dictating immune response magnitude. J. Immunol. 188, 4135–4140.

Josefowicz, S.Z., Lu, L.-F., Rudensky, A.Y., 2012. Regulatory T cells: mechanisms of differentiation and function. Ann. Rev. Immunol. 30, 531–564.

Kerr, E.C., ACopland, D., Dick, A.D., Nicholson, L.B., 2008a. The dynamics of leukocyte infiltration in experimental autoimmune uveoretinitis. Prog. Retin. Eye Res. 27, 527–535.

Kerr, E.C., Raveney, B.J.E., Copland, D.A., Dick, A.D., Nicholson, L.B., 2008b. Analysis of retinal cellular infiltrate in experimental autoimmune uveoretinitis reveals multiple regulatory cell populations. J. Autoimmun. 31, 354–361.

Khattri, R., Cox, T., Yasayko, S.-A., Ramsdell, F., 2003. An essential role for scurfin in CD4+CD25+ T regulatory cells. Nat. Immunol. 4, 337–342.

Krone, B., Grange, J.M., 2011. Multiple sclerosis: are protective immune mechanisms compromised by a complex infectious background?. Autoimmune Dis. 2011, 708750.

Kuske, R., Gordillo, L.F., Greenwood, P., 2007. Sustained oscillations via coherence resonance in SIR. J. Theor. Biol. 245, 459–469.

Kyrychko, Y.N., Blyuss, K.B., Schöll, E., 2011. Amplitude death in systems of coupled oscillators with distributed-delay coupling. Eur. Phys. J. B 84, 307–315.

Kyrychko, Y.N., Blyuss, K.B., Schöll, E., 2013. Amplitude and phase dynamics in oscillators with distributed delay coupling. Philos. Trans. R. Soc. A 371, 20120466.

Lafaille, J.J., Nagashima, K., Katsuki, M., Tonegawa, S., 1994. High incidence of spontaneous autoimmune encephalomyelitis in immunodeficient anti-myelin basic protein T cell receptor transgenic mice. Cell 78, 399–408.

León, K., Faro, J., Lage, A., Carneiro, J., 2004. Inverse correlation between the incidences of autoimmune disease and infection predicted by a model of T cell mediated tolerance. J. Autoimmun. 22, 31–42.

León, K., Lage, A., Carneiro, J., 2003. Tolerance and immunity in a mathematical model of T-cell mediated suppression. J. Theor. Biol. 225, 107–126.

León, K., Perez, R., Lage, A., Carneiro, J., 2000. Modelling T-cell-mediated suppression dependent on interactions in multicellular conjugates. J. Theor. Biol. 207, 231–254.

Lucas, B., Štefanová, I., Yasutomo, K., Dautigny, N., Germain, R.N., 1999. Divergent changes in the sensitivity of maturing T cells to structurally related ligands underlies formation of a useful T cell repertoire. Immunity 10, 367–376.
Mason, D., 1998. A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol. Today 19, 395–404.
Maurer, U.E., Sodeik, B., Gruenewald, K., 2008. Native 3D intermediates of membrane fusion in herpes simplex virus 1 entry. Proc. Natl. Acad. Sci. USA 105, 10559–10564.
McKinney, E.F., Lyons, P.A., Carr, E.J., Hollis, J.L., Jayne, D.R.W., Willcocks, L.C., Koukoulaki, M., Brazma, A., Jovanovic, V., Kemeny, D.M., Pollard, A.J., MacAry, P.A., Chaudhry, A.N., Smith, K.G.C., 2010. A CD8(+) T cell transcription signature predicts prognosis in autoimmune disease. Nat. Med. 16, 586–591.
Monk, N.A.M., 2003. Oscillatory expression of Hes1, p53, and NF-kappa B driven by transcriptional time delays. Curr. Biol. 13, 1409–1413.
Moon, J.J., Chu, H.H., Pepper, M., McSorley, S.J., Jameson, S.C., Kedl, R.M., Jenkins, M.K., 2007. Naive CD4+ T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. Immunity 27, 203–213.
Myers, S.E., Brewer, L., Shaw, D.P., Greene, W.H., Love, B.C., Hering, B., Spiller, B., Njenga, M.K., 2004. Prevalent human coxsackie B-5 virus infects porcine islet cells primarily using the coxsackie-adenovirus receptor. Xenotransplantation 11, 536–546.
Nakata, Y., 2011. Global dynamics of a cell mediated immunity in viral infection models with distributed delays. J. Math. Anal. Appl. 375, 14–27.
Nicholson, L.B., Anderson, A.C., Kuchroo, V.K., 2000. Tuning T cell activation threshold and effector function with cross-reactive peptide ligands. Int. Immunol. 12, 205–213.
Nicholson, D., Kerr, E., Jepps, O., Nicholson, L.B., 2012. Modelling experimental uveitis: barrier effects in autoimmune disease. Inflamm. Res. 61, 759–773.
Niculescu, S.I., Kim, P.S., Gu, K., Lee, P.P., Levy, D., 2010. Stability crossing boundaries of delay systems modeling immune dynamics in leukemia. Discr. Cont. Dyn. Syst. B 13, 129–156.
Noest, A.J., 2000. Designing lymphocyte functional structure for optimal signal detection: voilá, T cells. J. Theor. Biol. 207, 195–216.
Nowak, M., May, R.M., 2000. Virus Dynamics. Oxford University Press, Oxford.
Nowak, M.A., Lloyd, A.L., Vasquez, G.M., Wiltrout, T.A., Wahl, L.M., Bischofberger, N., Williams, J., Kinter, A., Fauci, A.S., Hirsch, V.M., Lifson, J.D., 1997. Viral dynamics of primary viremia and antiretroviral therapy in simian immunodeficiency virus infection. J. Virol. 71, 7518–7525.
Nylander, A., Hafler, D.A., 2012. Multiple sclerosis. J. Clin. Invest. 122, 1180–1188.
Ohashi, M., Orlova, N., Quink, C., Wang, F., 2011. Cloning of the Epstein–Barr virus-related rhesus lymphocryptovirus as a bacterial artificial chromosome: a loss-of-function mutation of the rhBARF1 immune evasion gene. J. Virol. 85, 1330–1339.
Oldstone, M.B.A., 1998. Molecular mimicry and immune-mediated diseases. FASEB J. 12, 1255–1265.
Oldstone, M.B.A., Edelmann, K.H., McGavern, D.B., Cruite, J.T., Welch, M.J., 2012. Molecular anatomy and number of antigen specific CD8 T cells required to cause type 1 diabetes. PLoS Pathog. 8, e1003044.
Oling, V., Reijonen, H., Simell, O., Knip, M., Ilonen, J., 2012. Autoantigen-specific memory CD4(+) T cells are prevalent early in progression to Type 1 diabetes. Cell. Immunol. 273, 133–139.
Park, J.-H., Adoro, S., Lucas, P.J., Sarafova, S.D., Alag, A.S., Doan, L.L., Erman, B., Liu, X., Ellmeier, W., Bosselut, R., Feigenbaum, L., Singer, A., 2007. 'Coreceptor tuning': cytokine signals transcriptionally tailor CD8 coreceptor expression to the self-specificity of the TCR. Nat. Immunol. 8, 1049–1059.
Perelson, A.S., 1999. Viral kinetics and mathematical models. Am. J. Med. 107, 49S–52S.
Perelson, A.S., 2002. Modelling viral and immune system dynamics. Nat. Rev. Immunol. 2, 28–36.
Perelson, A.S., Weisbuch, G., 1997. Immunology for physicists. Rev. Mod. Phys. 69, 1219–1267.
Read, M., Andrews, P.S., Timmis, J., Kumar, V., 2012. Techniques for grounding agent-based simulations in the real domain: a case study in experimental autoimmune encephalomyelitis. Math. Comput. Model. Dyn. Syst. Methods, Tools Appl. Eng. Relat. Sci. 18, 67–86.
Ricano-Ponce, I., Wijmenga, C., 2013. Mapping of immune-mediated disease genes. In: Chakravarti, A., Green, E. (Eds.), Annu. Rev. Genomics Hum. Genet., vol. 14; 2013, pp. 325–353.
Rosette, C., Werlen, G., Daniels, M.A., Holman, P.O., Alam, S.M., Travers, P.J., Gascoigne, N.R.J., Palmer, E., Jameson, S.C., 2001. The impact of duration versus extent of TCR occupancy on T cell activation: a revision of the kinetic proof-reading model. Immunity 15, 59–70.
Römer, P.S., Berr, S., Avotaet, E., et al., 2011. Preculture of PBMC at high cell density increases sensitivity of T-cell responses, revealing cytokine release by CD28 superagonist TGN1412. Blood 118, 6772–6782.
Sakaguchi, S., 2004. Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. Annu. Rev. Immunol. 22, 531–562.
Scherer, A., Noest, A., de Boer, R.J., 2004. Activation-threshold tuning in an affinity model for the T-cell repertoire. Proc. R. Soc. B 271, 609–616.
Segel, L.A., Jäger, E., Elias, D., Cohen, I.R., 1995. A quantitative model of autoimmune disease and T-cell vaccination: does more mean less?. Immunol. Today 16, 80–84.
Stefanova, I., Dorfman, J.R., Germain, R.N., 2002. Self-recognition promotes the foreign antigen sensitivity of naive T lymphocytes. Nature 420, 429–434.
van den Berg, H., Rand, D.A., Burroughs, N.J., 2001. A reliable and safe T cell repertoire based on low-affinity T cell receptors. J. Theor. Biol. 209, 465–486.
van den Berg, H., Rand, D.A., 2004. Dynamics of T cell activation threshold tuning. J. Theor. Biol. 228, 397–416.
van den Berg, H.A., Wooldridge, L., Laugel, B., Sewell, A.K., 2007. Coreceptor CD8-driven modulation of T cell antigen receptor specificity. J. Theor. Biol. 249, 395–408.
Williams, R.A., Greaves, R., Read, M., Timmis, J., Andrews, P.S., Kumar, V., 2013. In silico investigation into dendritic cell regulation of CD8Tref mediated killing of Th1 cells in murine experimental autoimmune encephalomyelitis. BMC Bioinform. 14 (Suppl. 6), 59.
Wing, K., Onishi, Y., Prieto-Martin, P., Yamaguchi, T., Miyara, M., Fehervari, Z., Nomura, T., Sakaguchi, S., 2008. CTLA-4 control over Foxp3+ regulatory T cell function. Science 322, 271–275.
Wodarz, D., 2007. Killer Cell Dynamics. Springer-Verlag, New York.
Wodarz, D., Jansen, V.A.A., 2003. A dynamical perspective of CTL cross-priming and regulation: implications for cancer immunology. Immunol. Lett. 86, 213–227.
Wolf, S.D., Dittel, B.N., Hardardottir, F., Janeway Jr, C.A., 1996. Experimental autoimmune encephalomyelitis induction in genetically B cell-deficient mice. J. Exp. Med. 184, 2271–2278.
Wu, H.-J., Ivanov, I.I., Darceet, J., et al., 2010. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 32, 815–827.
Wucherpfennig, K.W., Strominger, J.L., 1995. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 80, 695–705.
Zinselmeyer, B.H., Heydari, S., Sacristán, C., Nayak, D., Cammer, M., Herz, J., Cheng, X., Davis, S.J., Dustin, M.L., McGavern, D.B., 2013. PD-1 promotes immune exhaustion by inducing antiviral T cell motility paralysis. J. Exp. Med. 210, 757–774.