ANALYSIS OF A MATHEMATICAL MODEL FOR INTERACTIONS BETWEEN T CELLS AND MACROPHAGES

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ABSTRACT. The aim of this article is to carry out a mathematical analysis of a system of ordinary differential equations introduced by Lev Bar-Or to model the interactions between T cells and macrophages. Under certain restrictions on the parameters of the model, theorems are proved about the number of stationary solutions and their stability. In some cases the existence of periodic solutions or heteroclinic cycles is ruled out. Evidence is presented that the same biological phenomena could be equally well described by a simpler model.

1. INTRODUCTION

Autoimmune diseases result in a great deal of suffering for affected individuals and huge costs for society. Notable examples are multiple sclerosis, rheumatoid arthritis and type I diabetes. In these diseases the ability of the immune system to distinguish between self and non-self is compromised, with the result that host tissues are attacked and damaged. It is important to get a better understanding of the processes involved and one way to do so is to introduce theoretical models of the immune system, in particular mathematical models.

There has been a lot of work on mathematical modelling of interactions of the immune system with pathogens. See for instance [13] and the book of Nowak and May [11] which concentrate on the case of HIV and present various models. Some deeper mathematical analysis of these models can be found in [1], [5] and [2]. Autoimmune diseases do not need to involve any pathogens, although pathogens might contribute to them indirectly, for instance by molecular mimicry [12]. For this reason it would be interesting to have models for the intrinsic workings of the immune system where non-self antigens play no direct role, in the sense that they are not included among the dynamical variables. Apparently few models of this type exist in the literature. One example is introduced in a paper of Lev Bar-Or [8]. It is a system of four ordinary differential equations which describes the interactions of T cells and macrophages by means of the cytokines they produce. The aim of this paper is to investigate what can be said about the properties of the solutions of this system on the level of mathematical proofs.

Some relevant concepts from immunology will now be introduced. For a comprehensive introduction to the subject see [10]. T cells are white blood cells which

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mature in the thymus. One type of T cell, the T helper cell, helps to direct the activity of other immune cells. These cells are also known as $CD4^+$ since they carry the surface molecule CD4. T cells communicate with other cells by secreting soluble substances known as cytokines. Another important type of blood cell is the macrophage which ingests pathogens and cell debris through phagocytosis. Macrophages also secrete cytokines. Both T cells and macrophages react in various ways to the cytokines which are present in their surroundings. The list of known cytokines is long and each of them has its own characteristics in terms of which types of cells secrete it and what effects it has on cells which detect its presence. An idea of the complexity of this signalling system can be obtained from [8].

It is common to distinguish between two types of T helper cells, known as Th1 and Th2, according to the cytokines they produce. There may be overlaps but roughly speaking it may be supposed that there is one set of cytokines (e.g. interferon γ) which are called type 1 and are produced by Th1 cells and another (e.g. interleukin 4) called type 2 which are produced by Th2 cells. Macrophages produce cytokines of both types. The basic quantities in the equations of [8] are average concentrations corresponding to type 1 and type 2 cytokines produced by T cells and macrophages. These four concentrations are denoted by C_1^T, C_2^T, C_1^M and C_2^M. The populations of different cell types do not occur directly in the system. The quantities which have a chance of being measured directly are $C_1 = \frac{1}{2}(C_1^T + C_1^M)$ and $C_2 = \frac{1}{2}(C_2^T + C_2^M)$.

There are cases where the immune response is dominated by either Th1 or Th2 cells. This may be important in order to effectively combat a particular pathogen. For instance a sufficiently strong Th1 response is necessary for containing or eliminating a tuberculosis infection [15], [9]. An inappropriate balance between these two states can also contribute to autoimmune disorders. It has, for instance, been suggested that multiple sclerosis is associated with an immune response which is biased towards Th1. See [7] for a critical review of this idea. In the context of the model it is said that there is Th1 or Th2 dominance if $C_1 > C_2$ or $C_2 > C_1$, respectively.

Another important function of macrophages which plays a role in the model of [8] is the presentation of antigens. Small peptides which result from the digestion of material taken up by a macrophage are presented on its surface in conjunction with MHC II molecules. (Major histocompatibility complex of class II.) This can stimulate T cells which come into contact with the macrophage.

It has not been possible to give a complete analysis of the dynamics of the system of [8]. A certain inequality on the parameters of the system gives rise to a regime where there is a unique stationary solution which acts as an attractor for all solutions as $t \to \infty$. This is proved in Theorem 2.1. For a more restricted set of parameters it is possible to show (Theorem 2.2) that each solution converges to a stationary solution which in general depends on the solution considered. With further restrictions on the parameters it is shown that there are between one and three stationary solutions and the subsets of parameters for which different numbers of stationary solutions occur are described. This is the content of Theorem 2.3. In Theorems 2.2 and 2.3 the coefficients describing antigen presentation are set to zero. One situation where information can be obtained on the dynamics including antigen presentation is analysed in Theorem 2.4.

The analysis which has been done has uncovered no evidence that the inclusion of the effect of macrophages makes an essential difference to the behaviour of solutions. The types of qualitative behaviour which have been proved to occur in this paper and those which are shown in the figures in [8] can be found in a truncated system which only includes the effect of T cells. This is discussed in section 3.

2. Analysis of the dynamical system

In what follows it will be convenient to use a notation which is more concise than that of [8]. Let x_1, x_2, x_3, x_4, z_1 and z_2 denote C_1^T, C_2^T, C_1^M, C_2^M, $x_1 + x_3$ and $x_2 + x_4$ respectively. The basic dynamical system is:

$$\frac{dx_i}{dt} = -d_i x_i + g(h_i); \quad i = 1, 2, 3, 4. \tag{2.1}$$

The d_i are positive constants. The function g is given by

$$g(x) = \frac{1}{2}(1 + \tanh(x - \theta)) \tag{2.2}$$

where θ is a constant. It satisfies the relations $g(x + \theta) + g(-x + \theta) = 1$ and $g'(x) = 2g(x)(1 - g(x))$. Hence $g(\theta) = 1/2$ and $g'(\theta) = 1/2$. The functions h_i are defined by $h_i = \sum_j a_{ij} x_j$ for some constants a_{ij}. The coefficients in (2.1) satisfy the following conditions

(1) $a_{ij} = b_{ij} + c_{ij}$, $i = 1, 2$, for some coefficients b_{ij} and c_{ij}
(2) $b_{1j} = -b_{2j}$ for all j.
(3) $b_{11} > 0$, $b_{13} > 0$, $b_{12} < 0$ and $b_{14} < 0$
(4) The ratio c_{2j}/c_{1j} is independent of j and positive.
(5) $c_{11} > 0$ and $c_{13} > 0$
(6) $a_{3j} = -a_{4j}$ for all j
(7) $a_{31} > 0$, $a_{33} > 0$, $a_{32} < 0$, $a_{34} < 0$

The sign conditions encode the fact that the effect of type 1 cytokines on cells is to increase their production of type 1 cytokines and to decrease their production of type 2 cytokines, while the effect of type 2 cytokines is exactly the opposite. The coefficients c_{ij} encode the effects of antigen presentation. This is the only role of antigens in the model and the intensity of stimulus due to antigen is not a dynamical degree of freedom in the model. No assumption is made on the signs of c_{12} and c_{14}. There are eighteen parameters in the model which are only constrained by some positivity conditions. The quantities z_1 and z_2 represent total concentrations of type 1 and type 2 cytokines. The biologically relevant region $\mathcal{B}$ is that where all the x_i are non-negative. The function g is strictly positive. Hence if one of the variables x_i vanishes at some time its derivative at that time is strictly positive. It follows that $\mathcal{B}$ is positively invariant under the evolution defined by the system. If some x_i is greater than or equal to d_i^{-1} on some time interval then x_i is decreasing at a uniform rate during that time. It follows that all solutions exist globally to the future and enter the region $\mathcal{B}_1$ defined by the inequalities $x_i \le d_i^{-1}$ after finite time. Thus in order to study the late-time behaviour of any solution starting in $\mathcal{B}$ it is enough to consider solutions starting in $\mathcal{B}_1$. In fact any solution enters the interior of $\mathcal{B}_1$ after finite time.

Theorem 2.1. *For any value of the parameters the system* (2.1) *has at least one stationary solution. If*

$$\sup_i \sum_j |a_{ij}| < 2 \inf_i d_i. \tag{2.3}$$

then there is only one stationary solution and all solutions converge to it as $t \to \infty$.

Proof. That the system always has at least one stationary solution follows from the Brouwer fixed point theorem, cf. [3, Theorem I.8.2]. A stationary solution of the system satisfies

$$x_i = d_i^{-1} g(h_i). \tag{2.4}$$

To prove the second part of the theorem consider the estimate

$$|d_i^{-1} g(h_i(y)) - d_i^{-1} g(h_i(x))| \leq (2d_i)^{-1} |h_i(y) - h_i(x)|$$
$$\leq (2d_i)^{-1} \sum_j |a_{ij}||y_j - x_j|. \tag{2.5}$$

The first of these inequalities uses the mean value theorem and the fact the derivative of g is nowhere greater than one half. If (2.3) holds then the mapping $\{x_i\} \mapsto \{d_i^{-1} g(h_i)\}$ maps $\mathcal{B}_1$ to itself and is a contraction in the maximum norm. Hence it has a unique fixed point. It follows that when the coefficients of the system satisfy the restriction (2.3) the system has exactly one stationary solution. If $x(t)$ and $y(t)$ are two solutions then under the assumption (2.3) it can be shown that $|x - y|$ decays exponentially as $t \to \infty$. Thus all solutions converge to the unique stationary solution as $t \to \infty$. A related statement is that if x_* is the unique stationary solution then $|x - x_*|^2$ is a Lyapunov function. □

A limiting case of (2.1) is that where all c_{ij} vanish. This will be called the zero MHC system. The pattern of signs in the coefficients in the zero MHC system is such that the change of variables $\tilde{x}_i = (-1)^{i+1} x_i$ leads to a system $\frac{d\tilde{x}_i}{dt} = f(\tilde{x}_j)$ satisfying $\frac{\partial f_i}{\partial \tilde{x}_j} > 0$ for all $i \neq j$. This means that the dynamical system for the $\tilde{x}_i$ is cooperative [4]. This pattern of signs corresponds to what is referred to as a 'community with limited competition' or 'competing subcommunities of mutualists' in [14]. It implies, using the Perron-Frobenius theorem, that the linearization at any point of the vector field defining (2.1) has a real eigenvalue of multiplicity one which is greater than the modulus of any other eigenvalue. Notice that in the special case of the zero MHC system where all d_i are equal to d the linearization has two eigenvalues equal to $-d$. As a consequence all the eigenvalues of the linearization must be real in this case. It is not clear how these facts about the eigenvalue structure can be used to help to understand the dynamics. The condition on the coefficients d_i, which says that the rate of degradation of different cytokines is exactly equal, would not be true with biologically motivated parameters. Nevertheless it is not unreasonable to assume that these coefficients are approximately equal and that the model with equal coefficients is not a bad approximation to the situation to be modelled. An assumption of this type is made in the model of [9].

Call the system obtained by assuming $c_{ij} = 0$, $d_1 = d_2$, $d_3 = d_4$ and $\theta = 0$ in (2.1) System 2 while (2.1) itself is System 1. The condition $\theta = 0$ implies that $g(x) + g(-x) = 1$. Adding the equations for $i = 1$ and $i = 2$ then gives

$$\frac{d}{dt}(x_1 + x_2) = -d_1(x_1 + x_2) + 1. \tag{2.6}$$

Similarly

$$\frac{d}{dt}(x_3 + x_4) = -d_3(x_3 + x_4) + 1. \tag{2.7}$$

These equations can easily be analysed. An invariant manifold S_1 is defined by $x_1 + x_2 = d_1^{-1}$ and $x_3 + x_4 = d_3^{-1}$. Substituting this back into the full system gives a two-dimensional system written out below which will be called System 3. The ω-limit set of any solution of System 2 is contained in the invariant manifold S_1. Passing from System 1 to System 3 means setting some parameters to zero and then restricting to a two-dimensional invariant manifold of the resulting system. System 3 may not include all the most interesting dynamics exhibited by solutions of the system of [8] but can be perturbed to get information about cases where the effect of the MHC is small but non-zero. The phase portrait of System 2 follows immediately from that of System 3. The explicit form of System 3 is

$$\frac{dx_1}{dt} = -d_1 x_1 + g((a_{11} - a_{12})x_1 + (a_{13} - a_{14})x_3 + a_{12}d_1^{-1} + a_{14}d_3^{-1}) \tag{2.8}$$

$$\frac{dx_3}{dt} = -d_3 x_3 + g((a_{31} - a_{32})x_1 + (a_{33} - a_{34})x_3 + a_{32}d_1^{-1} + a_{34}d_3^{-1}) \tag{2.9}$$

Note that the coefficients of x_1 and x_3 in these equations which are linear combinations of the a_{ij} are all positive. The constant terms are negative. This is a cooperative system. This fact together with the fact that the dimension of the system is two implies that each solution converges to a limit as $t \to \infty$ [4]. In other words the ω-limit set of each solution is a single point. Furthermore, there are no homoclinic orbits or heteroclinic cycles. What is not clear in general is how many stationary solutions there are. Some of the conclusions of the above discussion can be summarized as follows.

Theorem 2.2. *If $c_{ij} = 0$ for all i, j, $d_1 = d_2$, $d_3 = d_4$ and $\theta = 0$ then every solution of (2.1) converges to a stationary solution satisfying $x_1 + x_2 = d_1^{-1}$ and $x_3 + x_4 = d_3^{-1}$ as $t \to \infty$. There are no homoclinic orbits or heteroclinic cycles.*

Consider now the special case of System 3 obtained by setting $a_{1j} = a_{3j}$ for all j and $d_1 = d_3$. Call it System 4. This corresponds to the assumptions that the T cells and macrophages have identical properties with respect to their death rate and their interactions with cytokines. This system consists of two copies of a single equation. The quantity $x_1 - x_3$ decays exponentially. The further assumption $x_1 = x_3$ on the initial data, which means that there are equal numbers of T cells and macrophages, gives rise to a single ODE, call it the toy model. It is the same equation which occurs twice in System 4. It is of the form

$$\frac{dx}{dt} = -d_1 x + g(ax - b) \tag{2.10}$$

where $a = a_{11} - a_{12} + a_{13} - a_{14}$ and $b = -(a_{12} + a_{14})d_1^{-1}$. Note that a and b are positive. Here the zero MHC condition has been used. This can be simplified by defining $x' = d_1 x$, $t' = d_1 t$ and $a' = a/d_1$. Suppressing the primes leads to

$$\frac{dx}{dt} = -x + g(ax - b) \tag{2.11}$$

Denote the right hand side of (2.11) by $h(x)$, suppressing the parameter dependence. Stationary solutions of the toy model are given by solutions of the equation

$$g(ax - b) = x. \tag{2.12}$$

Since $0 < g < 1$ all solutions of this equation are contained in the interval $(0, 1)$. The right hand side of this equation takes the value zero at $x = 0$ and the value one at $x = 1$. Thus by the intermediate value theorem (2.12) has at least one solution on the interval of interest. Now

$$\frac{d}{dx}(g(ax - b) - x) = 2ag(ax - b)[1 - g(ax - b)] - 1. \qquad (2.13)$$

The first term on the right hand side of (2.13) is symmetric about $x = \frac{b}{a}$ where it attains its maximum value $\frac{a}{2}$. Thus this derivative vanishes at zero, one or two points of the real line according to whether $a < 2$, $a = 2$ or $a > 2$. For $a > 2$ call the zeroes of the derivative x_1 and x_2 with $x_1 < x_2$. It can be concluded that for any value of a there are at most three solutions of (2.12). All these solutions must be within the interval of interest. If there are exactly two solutions then one of them must correspond to a point where the right hand side of (2.11) and its derivative vanish simultaneously. For otherwise the value of this function at one would be negative for large x, a contradiction. For a given value of $a > 2$ there is precisely one value of b for which the equation $-x_1 + g(ax_1 - b) = 0$ holds. Call it $b_1(a)$. Define $b_2(a)$ similarly, replacing x_1 by x_2. Then $b_1(a)$ and $b_2(a)$ are the only values of b for which there is a simultaneous solution of $g(ax - b) = x$ and $ag'(ax - b) = 1$. For all $a > 2$ the inequality $b_1(a) < b_2(a)$ holds. As $a \to 2$ both tend to one. The union of the graphs of b_1 and b_2 divides the (a, b)-plane into two regions. On each of these the number of stationary solutions is constant and equal to one or three. On the region including points with $a < 2$ it is obviously one. Considering points where $b = 1/2$ and a slightly larger than two makes makes it clear that it is three on the other region. Information can also be obtained by simple geometric considerations on the position of the stationary points. If $a < 2$ and $b < a/2$ then the stationary point has $x < 1/2$ while for $b > a/2$ it satisfies $x > 1/2$. If $a > 2$ and there are three stationary points then the central (unstable) one satisfies $x < 1/2$ for $b < a/2$ and $x > 1/2$ for $b > a/2$.

When there is only one solution it is a hyperbolic sink. When there are three solutions the two outermost are hyperbolic sinks while the intermediate one is a hyperbolic source. If the parameter b is held fixed at some value less than one and a is varied then at the value of a where $b_1(a) = b$ there is a fold bifurcation. To see this note that

$$\frac{\partial h}{\partial x} = -1 + ag'(ax - b) \qquad (2.14)$$

$$\frac{\partial h}{\partial a} = xg'(ax - b) = 2xg(ax - b)(1 - g(ax - b)) \qquad (2.15)$$

$$\frac{\partial^2 h}{\partial x^2} = a^2 g''(ax - b) = 4a^2 g'(ax - b)(1 - 2g(ax - b)) \qquad (2.16)$$

From the first equation it follows that at a critical point x the quanitity $ag'(ax - b)$ must be equal to one. Hence the derivative with respect to a does not vanish there. The second derivative with respect to x can only vanish there if $g(ax - b) = 1/2$, which implies that $x = \frac{b}{a}$, $x = 1/2$ and $b = 1$. The situation for $b > 1$ is similar to that for $b < 1$. To understand the case $b = 1$ note that there is a cusp bifurcation

in (a, b) at the point $(2, 1)$. This can be shown using the facts that

$$\frac{\partial h}{\partial b} = -g'(ax - b), \tag{2.17}$$

$$\frac{\partial^2 h}{\partial x \partial b} = -ag''(ax - b), \tag{2.18}$$

$$\frac{\partial^2 h}{\partial x \partial a} = axg''(ax - b) + g'(ax - b), \tag{2.19}$$

$$\begin{aligned}\frac{\partial^3 h}{\partial x^3} &= g'''(ax - b) \\ &= 4a^3 g''(ax - b)(1 - 2g(ax - b)) - 8a^3(g'(ax - b))^2.\end{aligned} \tag{2.20}$$

Hence $\frac{\partial^3 h}{\partial x^3}$ and $\frac{\partial h}{\partial a}\frac{\partial^2 h}{\partial x \partial b} - \frac{\partial h}{\partial b}\frac{\partial^2 h}{\partial x \partial a}$ are both non-vanishing and [6, Theorem 8.1] applies.

If we remove the condition $x_1 = x_3$ then $x_1 - x_3$ decays exponentially. The qualitative nature of the dynamics of System 4 with the given restrictions on the parameters is then clear. This in turn gives information about the phase portrait of System 2 with these values of the parameters. Converting back to the original variables has the effect of replacing a by a/d_i in these criteria. Some of these results are summarized in the following theorem.

Theorem 2.3. *If in Theorem 2.2 it is additionally assumed that $a_{1j} = a_{3j}$ for all j and $d_1 = d_3$ then the number of stationary solutions of (2.1) is between one and three for any values of the parameters. It is one whenever $a_{11} - a_{12} + a_{13} - a_{14} \leq 2$. There is a non-empty open set where it is three. The set where it is two is a union of two smoothly embedded curves which is the boundary between the sets where it is one and three.*

Consider a choice of parameter set for (2.1) for which there are three hyperbolic stationary points. It follows by a simple stability argument that there is an open neighbourhood of this parameter set in parameter space such that for all parameters in this neighbourhood there are precisely three hyperbolic stationary points. If the original set of stationary points consists of two sinks and one saddle then there is an open neighbourhood where this property persists.

In the context of this theorem the question of Th1 or Th2 dominance can be examined for stationary solutions. It is of interest to know whether changing the parameters in the system can cause a switch from one type of dominance to the other. If this happens there must be some values of the parameters for which there is a stationary solution with $z_1 = z_2$. Under the hypotheses of the Theorem 2.2, $x_2 = d_1^{-1} - x_1$ and $x_4 = d_1^{-1} - x_3$ for any stationary solution. Hence $z_2 = 2d_1^{-1} - z_1$. If $z_1 = z_2$ then this implies that $z_1 = d_1^{-1}$ and $x_1 = \frac{1}{2}d_1^{-1}$. In terms of the new variable introduced in (2.11) this means that $x = 1/2$. The above discussion gives information about Th1 or Th2 dominance for various parameter values satisfying the restrictions in the statement of Theorem 2.3. What is of most interest for the applications is the position of the stable stationary points. In particular it is clear that there exist parameter values where there are stationary solutions with both types of dominance.

Now another set of simplified versions of the system will be studied. The phase portraits given in Fig. 2 in [8] relate to one special case of this kind. In the notation used here it is defined by the following restrictions on the parameters: $d_i = 1$ for

all i, $\theta = 0$, all coefficients b_{ij} with $j = 1$ or $j = 3$ are equal, all coefficients a_{ij} with $j = 2$ or $j = 4$ are equal, the coefficients c_{ij} are equal for all i and j. This reduces the number of free parameters to three. To simplify the notation let $A = b_{11}$, $B = -b_{12}$, $C = c_{11}$. These are all positive constants. For Fig. 2 in [8] two sets of values for the coefficients are considered. In both cases $C = 0.5$. In Fig. 2a $A = 0.4$ and $B = 0.5$ while in Fig. 2b $A = 0.6$ and $B = 0.65$. With these assumptions System 1 becomes:

$$\frac{dx_1}{dt} = -x_1 + g((A + C)(x_1 + x_3) + (-B + C)(x_2 + x_4)) \qquad (2.21)$$

$$\frac{dx_2}{dt} = -x_2 + g((-A + C)(x_1 + x_3) + (B + C)(x_2 + x_4)) \qquad (2.22)$$

$$\frac{dx_3}{dt} = -x_3 + g(A(x_1 + x_3) - B(x_2 + x_4)) \qquad (2.23)$$

$$\frac{dx_4}{dt} = -x_4 + g(-A(x_1 + x_3) + B(x_2 + x_4)) \qquad (2.24)$$

Call this System 5. If $A + B + 2C < 1$ then there is at most one stationary point of this system. This can be proved in the same way as Theorem 2.1. Adding the equations in pairs leads to a closed system for the two experimentally accessible quantities z_1 and z_2. These are the variables which are plotted in Fig. 2 of [8].

$$\frac{dz_1}{dt} = -z_1 + g((A + C)z_1 + (-B + C)z_2) + g(Az_1 - Bz_2) \qquad (2.25)$$

$$\frac{dz_2}{dt} = -z_2 + g((-A + C)z_1 + (B + C)z_2) + g(-Az_1 + Bz_2) \qquad (2.26)$$

Call this System 6. Denote the right hand sides of (2.25) and (2.26) by $f_1(z_1, z_2)$ and $f_2(z_1, z_2)$ respectively. For this system uniqueness of the stationary solution follows from the assumption that the coefficients satisfy $A + B + C < 1$. If in addition the coefficient C is assumed to vanish then this reduces to

$$\frac{dz_1}{dt} = -z_1 + 2g(Az_1 - Bz_2) \qquad (2.27)$$

$$\frac{dz_2}{dt} = -z_2 + 2g(-Az_1 + Bz_2) \qquad (2.28)$$

Call this System 7. Note that the system obtained by setting $C = 0$ in System 5 is equivalent to a special case of System 2 and that Theorems 2.2 and 2.3 apply to it. The parameters are related by $a = 2(A + B)$, $b = 2B$. The special cases in [8, Fig. 2] correspond to $a = 1.8$, $b = 1$ and $a = 2.5$, $b = 1.3$. It follows from (2.27) and (2.28) that $\frac{d}{dt}(z_1 + z_2) = -(z_1 + z_2) + 2$ and that $z_1 + z_2$ tends to two as $t \to \infty$. Thus the dynamics is controlled by that on the invariant manifold $z_1 = 2 - z_2$. With the choices which have been made it coincides with the invariant manifold S_1 introduced earlier.

Now consider what happens when $C \neq 0$. Provided $C \leq \min\{A, B\}$ the system consisting of (2.25) and (2.26) is competitive. Thus each solution (z_1, z_2) must converge to a stationary solution as $t \to \infty$ [4]. It can be concluded that the corresponding solution (x_1, x_2, x_3, x_4) tends to a stationary solution. Information about stationary points of the system can be obtained by stability considerations, as was mentioned following Theorem 2.3. This discussion is summed up in the following theorem.

Theorem 2.4. *Any solution x_i $(i = 1, 2, 3, 4)$ of (2.21)-(2.24) with parameter values satisfying $C \leq \min\{A, B\}$ converges to a stationary solution as $t \to \infty$. For fixed values of A and B and C sufficiently small the system has at most three stationary solutions and at most two stable stationary solutions.*

The results which have been obtained are unfortunately not sufficient to give a rigorous confirmation of the qualitative behaviour shown in Fig. 2a and Fig. 2b of [8]. The condition $C < \min\{A, B\}$ is not satisfied by the parameter values in Fig. 2a. It is satisfied in the case of Fig. 2b of [8] but no information is obtained about the number of solutions.

3. Dynamics in the absence of macrophages

In this section it will be shown that all the dynamical behaviour which has been shown to occur in system (2.1) also occurs in a truncated model where the influence of macrophages is ignored. The system has two unknowns x_1 and x_2 with the same interpretation as before. The effect of the macrophages is turned off by setting $a_{ij} = 0$ when i is one or two and j is three or four. This leads to the following closed system for x_1 and x_2:

$$\frac{dx_1}{dt} = -d_1 x_1 + g(a_{11} x_1 - a_{22} x_2) \tag{3.1}$$

$$\frac{dx_2}{dt} = -d_2 x_2 + g(-a_{11} x_1 + a_{22} x_2) \tag{3.2}$$

All the coefficients d_1, d_2, a_{11} and a_{22} are assumed positive, as before. Restricting further to the case that $d_1 = d_2 = d$ and $\theta = 0$ allows the analysis of the dynamics to be reduced to that of a scalar equation as in the previous section. The scalar equation is

$$\frac{dx_1}{dt} = -dx_1 + g((a_{11} + a_{22})x_1 - d^{-1}a_{22}). \tag{3.3}$$

This is essentially the equation (2.11) analysed before and so all the phenomena found previously occur here also.

4. Further remarks

In this paper it has been possible to give a rigorous analysis of the asymptotics of solutions of the system of Lev Bar-Or [8] for some values of the parameters. Unfortunately there are large ranges of the parameters for which no conclusions were obtained or for which those conclusions are incomplete. The latter statement even includes the two cases for which numerical plots were included in [8]. The following questions have not been answered for the system (2.1) with general parameters.

- Are there periodic solutions?
- Are there homoclinic orbits?
- Are there heteroclinic cycles?
- Are there strange attractors?

It should be emphasized that there is no evidence, analytical or numerical, that the answer to any of these questions is yes in the general case. We are left with a picture of a dynamical system where the long-time behaviour seems to be simple but it is quite unclear how to prove it except for a restricted set of values of the parameters.

It is consistent with everything which has been found here that the system of four equations with eighteen parameters produces no qualitatively new phenomena in comparison with a reduced two-dimensional system with three parameters. No effects were found which are specifically dependent on the inclusion of the presentation of antigen by macrophages. The interactions between Th1 and Th2 cells appear to be sufficient. It is seen that under some circumstances the model with T cells and cytokines alone predicts a situation of bistability where either a Th1 or Th2 dominated state can be approached, depending on the initial data.

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