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A MATHEMATICAL MODEL OF IMMUNITY

JENS CHRISTIAN LARSEN

Vanløse Alle 50 2. mf. tv.
2720 Vanløse, Denmark

Abstract

The purpose of the present paper is to derive a mathematical model of innate and adaptive immunity. It is an ODE model with variables C for antigen, D for dendritic cells, effector T cells denoted T and memory T cells denoted T_M. For this mathematical model we can prove that for some values of the rate constants it is tristable in the sense that there can be (at least) two stable singular points and an unstable singular point. It is also a mathematical model of a vaccine. To apply the model you need to fit the rate constants to a vaccined individual and also to a possibly different set of rate constants for an individual that has not been immunized. You can then compare the dynamics of the two scenarios.

1. Introduction

D belongs to the innate immune defense and T, T_M belong to the adaptive immune defense. There is a survey article [30] about mathematical models in immunology. See also the references [3], [8], [9], [10], [26], [27], [28], [29], [34], [4], [6], [22], [23]. [33]. There is a monograph for tumor-induced immune system dynamics, see [2]. I am not the first to report bistability in immunity, see [23]. But in this reference the evidence is numerical whereas we prove bistability. There is a monograph on the mathematics of virus dynamics and immunology, see [25]. Consider the following mass action kinetic system of innate and adaptive immunity.

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$$\delta C \to D, \tag{1}$$

$$C + D \to T, \tag{2}$$

$$T \to T_M, \tag{3}$$

$$C \to 2C, \tag{4}$$

$$T_M + C \to T, \tag{5}$$

$$T + \sigma C \to 0, \tag{6}$$

$$T \to 0, \tag{7}$$

$$T_M \to 0, \tag{8}$$

$$D \leftrightarrows 0, \tag{9}$$

$$C \leftrightarrows 0. \tag{10}$$

Here δ, σ are positive integers. We are not modelling B cells. The complexes are

$$C(1) = \delta C,$$

$$C(2) = D,$$

$$C(3) = D + C,$$

$$C(4) = T,$$

$$C(5) = T_M,$$

$$C(6) = 2C,$$

$$C(8) = T + \sigma C,$$

$$C(9) = 0,$$

$$C(10) = T_M + C,$$

$$C(11) = C.$$

Once we have numbered the complexes we have defined the rate constants k_{ij}. For a reaction

$$C(i) \leftrightarrows C(j), \quad i,\ j \in \{1, \ldots, 11\} \setminus \{7\}$$

the forward reaction rate is denoted k_{jz} and the reverse reaction rate is denoted k_{ij}.

(1) says, that antigen potentiate dendritic cells and (2) that antigen binds to dendritic cells and prime T cells to effector T cells. Effector T cells produce memory T cells (3). (4) means that antigen proliferates rapidly. Memory T cells can produce effector T cells in the presence of antigen (5). Effector T cells kill antigen (6). The last four reactions give birth and decay rates for all variables. See [24] figure on page 455.

Define the kinetic matrix A: This is the ten by ten matrix with rate constants

$$K = (k_{21},\ k_{92},\ k_{43},\ k_{54},\ k_{94},\ k_{4,\,10},\ k_{98},\ k_{11,\,9},$$

$$k_{6,11},\ k_{9,\,11},\ k_{29},\ k_{95})$$

and the diagonal terms are minus the sums of rate constants k_{ij} in the corresponding column. That is they are

$$-k_{21},\ -k_{92},\ -k_{43},\ -(k_{54}+k_{94}),\ -k_{95},\ 0,\ -k_{98},\ -(k_{11,\,9}+k_{29}+k_{4,\,10}),$$

$$-(k_{6,\,11}+k_{9,\,11}).$$

Now define the four by ten stochiometric matrix $Y = \{Y_{ij}\}_{i=1,\ldots,4,\ j=1,\ldots,11,\ j\neq 7}$ with matrix elements

$$Y_{11} = \delta, \quad Y_{13} = 1, \quad Y_{16} = 2, \quad Y_{18} = \sigma, \quad Y_{1,\,10} = 1, \quad Y_{1,\,11} = 1,$$

$$Y_{22} = 1, \quad Y_{23} = 1,$$

$$Y_{34} = 1, \quad Y_{38} = 1,$$

$$Y_{45} = 1, \quad Y_{4,\,10} = 1$$

all other $Y_{ij} = 0$. These are the stochiometric coefficients in the complexes $C(1), \ldots, C(11)$.

Now define the vector

$$c^Y$$

with variables $C^\delta,\ D,\ C \cdot D,\ T,\ T_M,\ C^2,\ T \cdot C^\sigma,\ T_M \cdot C,\ C$. Here

$$\begin{aligned} c &= (c_1, c_2, c_3, c_4) \\ &= (C, D, T, T_M). \end{aligned}$$

The definition of c^Y is

$$\{c^Y\} = c_1^{y_1^i} \cdots c_m^{y_m^i},$$

where Y^i is the ith column of Y, m is the number of chemical species, which is four in our case. Then multiply A and c^Y, to get a vector with matrix elements

$$-k_{21}C^\delta,$$

$$k_{21}C^\delta - k_{92}D + k_{29},$$

$$-k_{43}C \cdot D,$$

$$k_{43}C \cdot D - (k_{54} + k_{94})T + k_{4,\,10}T_M \cdot C,$$

$$k_{54}T - k_{95}T_M,$$

$$k_{6,\,11}C,$$

$$-k_{98}T \cdot C^\sigma,$$

*

$$-k_{4,10}T_M \cdot C,$$

$$k_{11,9} - (k_{6,11} + k_{9,11})C.$$

Hence we do not need the qth coordinate of $c^{\tilde{y}}$, since column q is $\tilde{y}$ is the zero column. Now the vector field giving the dynamics with mass action kinetics is

$$f(c) = YAc^Y$$

see [7] which becomes

$$f(c) = \begin{pmatrix} -\delta k_{21}C^{\delta} - k_{43}C \cdot D + (k_{6,11} - k_{9,11})C - k_{4,10}T_M \cdot C - \sigma k_{98}T \cdot C^{\sigma} + k_{11,9} \\ k_{21}C^{\delta} - k_{92}D - k_{43}C \cdot D + k_{29} \\ k_{43}C \cdot D - (k_{54} + k_{94})T + k_{4,10}T_M \cdot C - k_{98}T \cdot C^{\sigma} \\ k_{54}T - k_{95}T_M - k_{4,10}C \cdot T_M \end{pmatrix}.$$

We shall find a polynomial giving candidates of singular points. From $D' = 0$, we get

$$D = \frac{k_{29} + k_{21} \cdot C^{\delta}}{k_{43}C + k_{92}}.$$

From $T' = 0$ and $T_M' = 0$ we get two equations in two unknowns T and T_M,

$$(k_{54} + k_{94} + k_{98}C^{\sigma})T - k_{4,10}C \cdot T_M = k_{43}C \cdot D,$$

$$k_{54}T - (k_{95} + k_{4,10}C)T_M = 0.$$

The Cramer solution formula gives

$$T = \begin{vmatrix} k_{43}C \cdot D & -k_{4,10}C \\ 0 & -(k_{95} + k_{4,10}C) \end{vmatrix} / \Delta,$$

where

$$\Delta = -(k_{54} + k_{94} + k_{98}C^{\sigma})(k_{95} + k_{4,10}C) + k_{54}k_{4,10}C$$

$$< 0.$$

Also

$$T_M = \begin{vmatrix} k_{54} + k_{94} + k_{98}C^{\sigma} & k_{43}C \cdot D \\ k_{54} & 0 \end{vmatrix}.$$

Notice that $T, \; T_M > 0$, when $C > 0$. Insert these expressions in $C' = 0$, and multiply with

$$(k_{43}C + k_{92})\Delta$$

to obtain

$$\begin{aligned} p(C) = &(-\delta k_{21}C^{\delta} + aC + k_{11,\,9})(k_{43}C + k_{92})\Delta \\ &- k_{43}C(k_{29} + k_{21}C^{\delta})\Delta \\ &+ k_{4,\,10}C^2 k_{43}k_{54}(k_{29} + k_{21}C^{\delta}) \\ &+ \sigma k_{98}C^{\sigma+1}k_{43}(k_{95} + k_{4,\,10}C)(k_{29} + k_{21}C^{\delta}). \end{aligned}$$

Positive singular points (C, D, T, T_M) have $p(C) = 0$. Here $a = k_{6,\,11} - k_{9,\,11}$.

2. The Two Dimensional System

We shall consider the subsystem of (1) to (10) with $k_{98} = k_{4,\,10} = 0$, $\delta = 2$,

$$\tilde{f}(C, D) = \begin{pmatrix} -2k_{21}C^2 - k_{43}C \cdot D + aC + k_{11,\,9} \\ k_{21}C^2 - k_{92}D - k_{43}C \cdot D + k_{29} \end{pmatrix}.$$

From $D' = 0$ find

$$D = \frac{k_{29} + k_{21}C^2}{k_{43}C + k_{92}}$$

and insert this in $C' = 0$ to get after multiplying with $k_{43}C + k_{92}$,

$$\begin{aligned} p(C) \triangleq &-3k_{43}k_{21}C^3 + (-2k_{21}k_{92} + ak_{43})C^2 \\ &+ (ak_{92} + k_{11,\,9}k_{43} - k_{43}k_{29})C + k_{11,\,9}k_{92}. \end{aligned}$$

Theorem 1. *Suppose p has three positive mutually distinct roots*

$$0 < C_1 < C_2 < C_3$$

and that

$$k_{21}k_{43}C_3^2 + 2k_{21}k_{92}C_3 - k_{29}k_{43} < 0.$$

Then there exist three positive singular points

$$\left(C_i, \frac{k_{29} + k_{21}C_i^2}{k_{43}C_i + k_{92}}\right) = (C_i, D_i) \quad (i = 1, 2, 3)$$

of $\tilde{f} \cdot (C_1, D_1)$ *and* (C_3, D_3) *are stable and* (C_2, D_2) *is not asymptotically stable.*

Definition. A singular point (C_*, D_*) of $\tilde{f}$ is stable if given $\varepsilon > 0$, there exists a $\delta > 0$ such that every maximal solution c of $\tilde{f}$ with

$$|c(0) - (C_*, D_*)| < \delta$$

is defined on $]0, +\infty[$ and

$$|c(t) - (C_*, D_*)| < \varepsilon$$

for $t \in]0, +\infty[$.

It is asymptotically stable if it is stable and there exists a $\beta > 0$, such that

$$|c(0) - (C_*, D_*)| < \beta$$

implies

$$c(t) \to (C_*, D_*)$$

as $t \to +\infty$, see [32].

Proof. It is clear, that

$$\left(C_i, \frac{k_{29} + k_{21}C_i^2}{k_{43}C_i + k_{92}}\right)$$

are singular points, $i = 1, 2, 3$.

Define two functions

$$D^\infty,\ D^0 : \mathbb{R}_+ \to \mathbb{R},$$

where

$$D^\infty(C) = \frac{aC - 2k_{21}C^2 + k_{11,\,9}}{k_{43}C}$$

giving the ∞ isocline $C' = 0$, and

$$D^0(C) = \frac{k_{29} + k_{21}C^2}{k_{43}C + k_{92}}$$

giving the zero isocline $D' = 0$. We claim that

$$D^\infty(C) > D^0(C)$$

when

$$C_2 < C < C_3, \quad C < C_1,$$

and

$$D^\infty(C) < D^0(C)$$

whenever

$$C_1 < C < C_2, \quad C > C_3.$$

But by the fundamental theorem of algebra we can write

$$p(C) = -3k_{21}k_{43}(C - C_1)(C - C_2)(C - C_3). \tag{11}$$

But

$$D^\infty(C) > D^0(C)$$

is equivalent to

$$(aC - 2k_{21}C^2 + k_{11,\,9})(k_{43}C + k_{92}) > (k_{29} + k_{21}C^2)k_{43}C$$

which is equivalent to

$$p(C) > 0.$$

Now the claim follows from (11).

We start by showing that (C_2, D_2) is not asymptotically stable. Define the region in the plane

$$R = \{(C, D) \in \mathbb{R}^2 \mid C_3 > C > C_0,\ D^0(C) < D < D^\infty(C)\},$$

where $C_0 \in \,]\,C_2, C_3\,[$.

We claim that $\overline{R}$ is positively invariant. But on

$$(C, D^\infty(C)), \quad C \in \,]\,C_2, C_3\,[\tag{12}$$

the vector field is

$$\tilde{f}(C, D) = \begin{pmatrix} 0 \\ K(C) \end{pmatrix},$$

where

$$\begin{aligned} K(C) &= k_{29} + k_{21}C^2 - (k_{92} + k_{43}C)\frac{aC - 2k_{21}C^2 + k_{11,9}}{k_{43}C} \\ &< 0 \end{aligned}$$

which is equivalent to $p(C) > 0$. Now compute

$$\frac{\partial D^0}{\partial C}(C) = \frac{k_{21}k_{43}C^2 + 2k_{21}k_{92}C - k_{29}k_{43}}{(k_{43}C + k_{92})^2}$$

and

$$\begin{aligned} \frac{\partial D^\infty}{\partial C}(C) &= \frac{-2k_{21}k_{43}C^2 - k_{11,9}k_{43}}{k_{43}^2C^2} \\ &< 0. \end{aligned}$$

But by assumption

$$\frac{\partial D^0}{\partial C}(C_3) < 0.$$

Since the numerator of

$$\frac{\partial D^0}{\partial C}(C)$$

is an increasing function of C, we have

$$\frac{\partial D^0}{\partial C}(C_1) < 0$$

and hence

$$\frac{\partial D^0}{\partial C}(C) < 0$$

on an open neighbourhood of C_1 and C_3 and for $C \in \,]C_2, C_3[$.

Let $c(t) = (C(t), D(t))$ denote a maximal integral curve of $\tilde{f}$ defined on $]t^-, t^+[$, $t_- < 0$, $t^+ > 0$. Now when $(C(0), D(0)) = (C(0), D^\infty(C(0)))$, $C(0) \in [C_0, C_3[$,

$$\frac{\partial}{\partial t}(D(t), D^\infty(C(t)))$$

$$= D'(t) - D^{\infty'}(C(t))\frac{\partial C}{\partial t}$$

$$= D'(t)$$

$$< 0.$$

Hence

$$D(t) < D^\infty(C(t)).$$

So the integral curve enters R, except possibly on

$$c_0 = (C_0, D^\infty(C_0)).$$

But if

$$c(t) = (C(t), D(t))$$

is an integral curve of $\tilde{f}$ through $c(0) = c_0$, then we can find

$$\begin{aligned} c_1''(0) &= D\tilde{f}_1(\tilde{f}(C_0, D^\infty(C_0))) \\ &> 0. \end{aligned}$$

Since $c_1(0) = C_0$, we can write by the standard trick from singularity theory

$$c_1(t) = C_0 + t^2 h(t),$$

where h is smooth with $h(0) > 0$. It follows that

$$c_1(t) > C_0$$

for $t \in]0, \varepsilon[$, some $\varepsilon > 0$.

On $C = C_0$, $D < D^\infty(C)$,

$$c_1'(0) > 0.$$

On

$$(C, D^0(C)), \quad C \in]C_0, C_3[\tag{13}$$

we find

$$\tilde{f}(C, D^0(C)) = \begin{pmatrix} \tilde{f}_1(C, D^0(C)) \\ 0 \end{pmatrix},$$

where

$$\begin{aligned} \tilde{f}_1(C, D^0(C)) &= -2k_{21}C^2 - k_{43}C\,\frac{k_{29} + k_{21}C^2}{k_{43}C + k_{92}} + aC + k_{11,9} \\ &> 0 \end{aligned}$$

and this is equivalent to $p(C) > 0$. So the integral curve enters R on (13). In fact, we have

$$\frac{\partial}{\partial t}\left(D^0(C(t)) - D(t)\right)$$

$$= \frac{\partial D^0}{\partial C} C'(0) - D'(0)$$

$$< 0.$$

Hence

$$D^0(C(t)) < D(t).$$

So

$$(C(t),\ D(t)) \in R, \quad t \in \,]0,\ \varepsilon[$$

some $\varepsilon > 0$.

But now let $c(t)$ be the maximal integral curve through

$$c(0) = (C_0,\ D_0) \in \overline{R}.$$

If $(C_2,\ D_2)$ was asymptotically stable, then $t^+ = +\infty$ and

$$c(t) \to (C_2,\ D_2)$$

as $t = +\infty$. But this is incompatible with the fact that $\overline{R}$ is positively invariant. Thus $(C_2,\ D_2)$ is not asymptotically stable.

To show that $(C_3,\ D_3)$ is stable define the open neighbourhood of $(C_3,\ D_3)$,

$$U = \{(C,\ D) \in \mathbb{R}^2 \mid \tilde{C}_1 < C < \tilde{C}_2,\ \tilde{D}_1 < D < \tilde{D}_2\},$$

where

$$\tilde{D}_1 = D^\infty(\tilde{C}_2),$$

$$\tilde{D}_2 = D^\infty(\tilde{C}_1)$$

and

$$\tilde{C}_1 < C_3 < \tilde{C}_2,$$

$\tilde{C}_1$ and $\tilde{C}_2$ near C_3. We claim, that $\overline{U}$ is positively invariant. But on $C = \tilde{C}_1,$ we have

$$c_1'(0) > 0,$$

$c_2(0) \in [\tilde{D}_1, \tilde{D}_2[.$ And when $c_2(0) = \tilde{D}_2,$

$$c_1''(0) > 0.$$

So $c(t) \in R,$ $t \in \,]0, \varepsilon[,$ some $\varepsilon > 0.$ We have the inequalities

$$\begin{aligned} \tilde{D}_1 &\le D^\infty(C) \\ &< D^0(C) \\ &< D_3 \\ &< \tilde{D}_2 \end{aligned}$$

when $C \in \,]C_3, \tilde{C}_2].$ And also

$$\begin{aligned} \tilde{D}_1 &< D_3 \\ &< D^0(C) \\ &< D^\infty(C) \\ &\le \tilde{D}_2, \end{aligned}$$

$C \in [\tilde{C}_1, C_3[,$ because D^0 is decreasing.

Now

$$D' = 0$$

on

$$(C,\ D^0(C)).$$

But

$$\frac{\partial}{\partial D}(k_{21}C^2 - k_{92}D - k_{43}C \cdot D + k_{29}) = -k_{92} - k_{43}C$$

$$< 0.$$

So

$$D' < 0, \quad D = \tilde{D}_2,$$

$$D' > 0, \quad D = \tilde{D}_1.$$

On

$$C = \tilde{C}_2, \quad D > D^{\infty}(\tilde{C}_2)$$

we have

$$c_1'(0) < 0$$

except in $c(0) = (\tilde{C}_2,\ \tilde{D}_1)$. But here

$$c_1''(0) < 0$$

so arguing as before there exists $\varepsilon > 0$ such that

$$c(t) \in U,$$

$t \in\ ]0, \varepsilon[$. But this shows that $(C_3,\ D_3)$ is stable because $\overline{U}$ is positively invariant.

To see that $\overline{U}$ is positively invariant, suppose for contradiction that a maximal integral curve c of $\tilde{f}$, starting in $c(0) \in \overline{U}$, leaves $\overline{U}$. By what we have shown we have that $c(t) \in \overline{U}$, $t \in\ ]0, \varepsilon[$, some $\varepsilon > 0$. Now define

$$A = \{t \in \,]0, t^+[\, \mid c(t) \notin \overline{U}\},$$

$$t_0 = \inf A$$

$$> 0.$$

Then we have that

$$c(t_0) \in \partial U.$$

From what we have shown

$$c(t) \notin \overline{U}$$

for $t < t_0$ close to t_0. A contradiction and c does not leave $\overline{U}$. It follows that $\overline{U}$ is positively invariant. But since $\overline{U}$ is compact c is defined for all $t > 0$, see [1].

To show that (C_1, D_1) is stable define

$$V = \{(C, D) \in \mathbb{R}^2 \mid \tilde{C}_1 < C < \tilde{C}_2, \tilde{D}_1 < D < \tilde{D}_2\},$$

where

$$\tilde{C}_1 < C_1,$$

$$\tilde{C}_2 > C_1,$$

$\tilde{C}_1$, $\tilde{C}_2$, close to C_1,

$$\tilde{D}_1 = D^\infty(\tilde{C}_2),$$

$$\tilde{D}_2 = D^\infty(\tilde{C}_1),$$

and argue as above, to show stability. □

The characteristic polynomial of the linearization F of f at a singular point is

$$\det(F - \lambda\,\mathrm{id}) = \begin{vmatrix} F_{11} - \lambda & F_{12} & F_{13} & F_{14} \\ F_{21} & F_{22} - \lambda & 0 & 0 \\ F_{31} & F_{32} & F_{33} - \lambda & F_{34} \\ F_{41} & 0 & F_{43} & F_{44} - \lambda \end{vmatrix}. \tag{14}$$

Here $\lambda \in \mathbb{C}$ and id is the four by four identity matrix. Also

$$F_{11} = a - k_{43}D - 4k_{98}T \cdot C - k_{4,\,10}T_M - 4k_{21}C,$$

$$F_{12} = -k_{43}C,$$

$$F_{13} = -2k_{98}C^2,$$

$$F_{14} = -k_{4,\,10}C,$$

$$F_{21} = 2k_{21}C - k_{43}D,$$

$$F_{22} = -k_{43}C - k_{92},$$

$$F_{31} = k_{43}D + k_{4,\,10}T_M - 2k_{98}T \cdot C,$$

$$F_{32} = k_{43}C,$$

$$F_{33} = -(k_{54} + k_{94} + k_{98}C^2),$$

$$F_{34} = k_{4,\,10}C,$$

$$F_{41} = -k_{4,\,10}T_M,$$

$$F_{43} = k_{54},$$

$$F_{44} = -k_{95} - k_{4,\,10}C$$

when $\delta = \sigma = 2.$ Decompose (14) after the last column

$$\begin{aligned}
&\det(F - \lambda\, id) \\
&= (F_{44} - \lambda)((F_{11} - \lambda)(F_{22} - \lambda)(F_{33} - \lambda) \\
&\qquad + F_{13}F_{21}F_{32} - F_{31}(F_{22} - \lambda)F_{13} - F_{21}F_{12}(F_{33} - \lambda)) \\
&\quad - F_{14}(F_{21}F_{32}F_{43} + (F_{22} - \lambda)(F_{33} - \lambda)F_{41} - F_{31}(F_{22} - \lambda)F_{34}) \\
&\quad - F_{34}((F_{11} - \lambda)(F_{22} - \lambda)F_{43} - F_{41}(F_{22} - \lambda)F_{13} - F_{12}F_{21}F_{43}).
\end{aligned}$$

If we now take $k_{98} = k_{4,10} = 0$, $\delta = \sigma = 2$, we obtain

$$\det(F - \lambda\,\mathrm{id}) = (F_{33} - \lambda)(F_{44} - \lambda)(\lambda^2 - (F_{11} + F_{22})\lambda - F_{21}F_{12}).$$

Example. Take

$$\delta = 2,$$

$$\sigma = 2,$$

$$k_{21} = \frac{1}{3},$$

$$k_{43} = 100,$$

$$k_{98} = 0,$$

$$k_{4,10} = 0,$$

$$a = 2,$$

$$k_{92} = 1,$$

$$k_{11,9} = 1,$$

$$k_{29} = \frac{3}{2}.$$

Then there are three singular points $(C_1, D_1), (C_2, D_2), (C_3, D_3)$, with

$$C_1 < C_2 < C_3$$

and

$$(C_1, D_1) = (0.023006, 0.454517),$$

$$(C_2, D_2) = (0.253182, 0.057818),$$

$$(C_3, D_3) = (1.7172, 0.014375),$$

where (C_1, D_1) and (C_3, D_3) are stable and (C_2, D_2) is unstable. This example is an example of Theorem 1 because

$$k_{21}k_{43}C_3^2 + 2k_{21}k_{92}C_3 - k_{29}k_{43} < 0.$$

In particular, $D\tilde{f}_{(C_i,\, D_i)},\ i = 1, 2, 3$ is nonsingular.

Let

$$T_i = \frac{k_{43}C_i}{k_{54} + k_{94}} \frac{k_{21}C_i^{\delta} + k_{29}}{k_{43}C_i + k_{92}}$$

and

$$T_M^i = \frac{k_{54}}{k_{95}} T_i.$$

Then we have the proposition

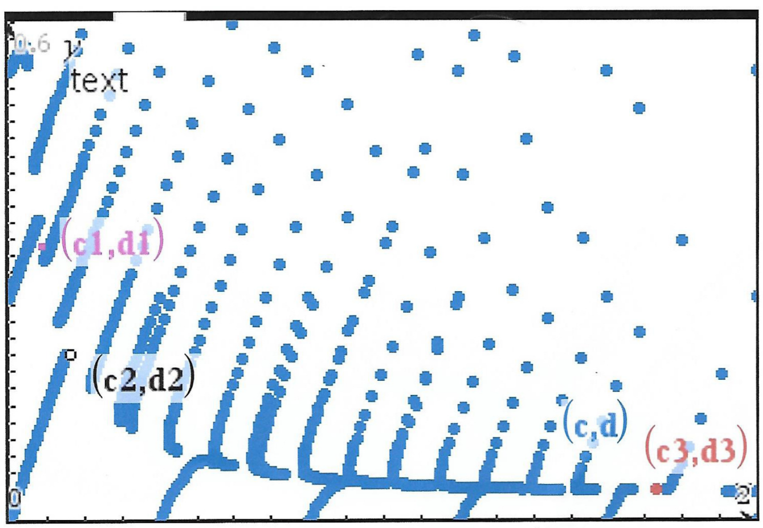

Figure 1. A phase portrait of the two-dimensional ODE model $k_{43} = 40$.

Proposition 1. *Let* (C_i, D_i) *be positive singular points for* $\tilde{f}$, $i = 1, 2, 3$. *If* $D\tilde{f}_{(C_i,\, D_i)},\ i = 1, 2, 3$ *is nonsingular, for* $K = K_0$, $k_{ij}^0 > 0$, *except* $k_{98}^0 = 0$,

$k^0_{4,10} = 0$, *then there exist smooth functions*

$$c^i_*(K),$$

where $i = 1, 2, 3$, *such that*

$$f(c^i_*(K), K) = 0, \quad c^i_*(K_0) = (C_i, D_i, T_i, T^i_M).$$

There are positive values of the rate constants, such that c^1_* *and* c^3_* *are stable and* c^2_* *is unstable, if the linearization of* $\tilde{f}$ *at* (C_i, D_i) *has eigenvalues with negative real part,* $i = 1, 3$ *and for* $i = 2$ *it has an eigenvalue with positive real part.*

This follows from the implicit function theorem and the continuous dependence of roots of a polynomial on its coefficients, see [31].

Tristability can be lost. In the example, above change k_{43} to $k_{43} = 20$. It looks as if only (C_3, D_3) survives see Figure 2.

In Figure 1 and Figure 2, I have plotted phase portraits of $\tilde{f}$. From the phase portrait in Figure 1, you can see, that there is a separatrix which appears to be the unstable manifold of the saddle (C_2, D_2). It separates the basin of attraction of (C_1, D_1) and (C_3, D_3). We also have

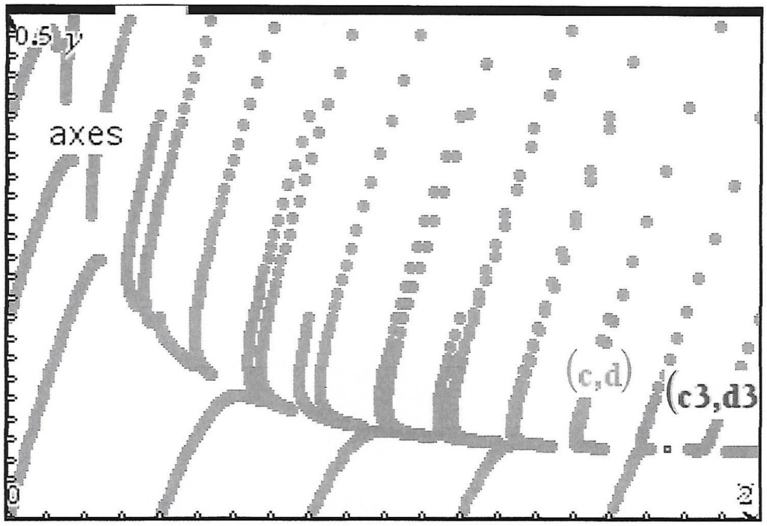

Figure 2. A phase portrait of the two-dimensional ODE model $k_{43} = 20$.

Proposition 2.

$$\det D\tilde{f}_{(C_2,\, D_2)} \leq 0$$

or

$$\operatorname{trace} D\tilde{f}_{(C_2,\, D_2)} \geq 0$$

and

$$\det D\tilde{f}_{(C_i,\, D_i)} \geq 0$$

or

$$\operatorname{trace} D\tilde{f}_{(C_i,\, D_i)} \leq 0,$$

where $i = 1, 3$.

Proof. The linearization of $\tilde{f}$ at a singular point is

$$D\tilde{f} = \begin{pmatrix} -4k_{21}C - k_{43}D + a & -k_{43}C \\ 2k_{21}C - k_{43}D & -k_{43}C - k_{92} \end{pmatrix}.$$

Now the proposition follows from Theorem 1.

In fact, if the eigenvalues λ have $\Re(\lambda) < 0$, then the equilibrium is asymptotically stable, see [32]. Therefore if an equilibrium is not asymptotically stable, then there exists an eigenvalue with $\Re(\lambda) \geq 0$. All eigenvalues λ have $\Re(\lambda) < 0$ is equivalent, by the Routh Hurwitz criterion, to

$$\operatorname{trace} D\tilde{f} < 0,$$

and

$$\det D\tilde{f} > 0.$$

Negating this gives the first two inequalities in the statement of the proposition. Assume, that there is an eigenvalue λ with $\Re(\lambda) > 0$ for

$$D\tilde{f}_{(C_i,\, D_i)},$$

$i = 1, 3$. Then (C_i, D_i) is unstable, see [32, p. 312], which is incompatible with what we have proven. Therefore

$$D\tilde{f}_{(C_i,\, D_i)} = \begin{pmatrix} a_1 & b_1 \\ c_1 & d_1 \end{pmatrix}$$

does not have an eigenvalue λ with $\Re(\lambda) > 0$.

Define

$$\Delta = (a_1 + d_1)^2 - 4(a_1 d_1 - b_1 c_1).$$

We claim, that

(i) All eigenvalues λ have $\Re(\lambda) \leq 0$ is equivalent to

(ii) $a_1 + d_1 \leq 0$ and $a_1 d_1 - b_1 c_1 \geq 0$.

(ii) implies (i). We have the formula

$$\lambda_{\pm} = \frac{a_1 + d_1 \pm \sqrt{\Delta}}{2}.$$

If $\Delta \geq 0$, then $\lambda_{\pm} \leq 0$ and if $\Delta < 0$ we also clearly have $\Re(\lambda_{\pm}) \leq 0$.

(i) implies (ii). If $a_1 d_1 - b_1 c_1 < 0$, then

$$\lambda_{+} > 0$$

no matter what $a_1 + d_1$ is. So we must have

$$a_1 d_1 - b_1 c_1 \geq 0.$$

If $a_1 + d_1 > 0$, then

(1) If $\Delta < 0$, then $\Re(\lambda) > 0$.

(2) If $\Delta \geq 0$, then $\lambda_{+} > 0$.

So we must have $a_1 + d_1 \leq 0$. This proves the proposition. □

We have the following formulas for the trace and determinant of $D\tilde{f}$ at a singular point

$$\begin{aligned} \operatorname{trace} D\tilde{f} = \frac{1}{k_{43}C + k_{92}} \big(&-(5k_{43}k_{21} + k_{43}^2)C^2 \\ &+ ((a - k_{92})k_{43} + k_{92}(-4k_{21} - k_{43}))C \\ &- k_{43}k_{29} + k_{92}(a - k_{92})\big) \end{aligned}$$

and

$$\begin{aligned} \det D\tilde{f} = \frac{1}{k_{43}C + k_{92}} \big(&6k_{21}k_{43}^2 C^3 + (11k_{92}k_{21}k_{43} - ak_{43}^2)C^2 \\ &+ (k_{92}(4k_{21}k_{92} - ak_{43}) - ak_{92}k_{43})C \\ &- ak_{92}^2 + k_{43}k_{92}k_{29}\big). \end{aligned}$$

Suppose we have measeurements

$$c(t_i) = (C(t_i), D(t_i) = (c_1(t_i), c_2(t_i)),$$

where $t_i = t_0 + \varepsilon i$, $i = 1, \ldots, N$, $N \in \mathbb{N}$.

We can fit the rate constants k_{ij} to mesurements by the following well-known approach. Define for $\varepsilon > 0$ the error functions

$$E_1(\varepsilon, k_{21}, k_{43}, a, k_{11,9}) = \sum_{i=1}^{N} (c_1(t_{i+1}) - c_1(t_i) - \varepsilon\tilde{f}_1(c(t_i)))^2,$$

$$E_2(\varepsilon, k_{21}, k_{43}, k_{29}, k_{92}) = \sum_{i=1}^{N} (c_2(t_{i+1}) - c_2(t_i) - \varepsilon\tilde{f}_2(c(t_i)))^2.$$

Then

$$\frac{\partial E_1}{\partial k_{21}} = 0,$$

$$\frac{\partial E_1}{\partial k_{43}} = 0,$$

$$\frac{\partial E_1}{\partial a} = 0,$$

$$\frac{\partial E_1}{\partial k_{11,9}} = 0$$

are four linear equations with four unknowns. If the coefficient matrix is nonsingular, you can solve for the rate constants $k_{21}, k_{43}, a, k_{11,9}$. Then

$$\frac{\partial E_2}{\partial k_{21}} = 0,$$

$$\frac{\partial E_2}{\partial k_{43}} = 0,$$

$$\frac{\partial E_2}{\partial k_{92}} = 0,$$

$$\frac{\partial E_2}{\partial k_{29}} = 0$$

are also four equations in four unknowns and if the coefficient matrix is nonsingular, you can solve for k_{21}, k_{43}, k_{92}, k_{29}.

The two pairs of equations are

$$\begin{pmatrix} -2\sum c_1(t_i)^4 & -\sum c_1(t_i)^3 c_2(t_i) & \sum c_1(t_i)^3 & \sum c_1(t_i)^2 \\ -2\sum c_1(t_i)^3 c_2(t_i) & -\sum c_1(t_i)^2 c_2(t_i)^2 & \sum c_1(t_i)^2 c_2(t_i) & \sum c_1(t_i) c_2(t_i) \\ -2\sum c_1(t_i)^3 & -\sum c_1(t_i)^2 c_2(t_i) & \sum c_1(t_i)^2 & \sum c_1(t_i) \\ -2\sum c_1(t_i)^2 & -\sum c_1(t_i) c_2(t_i) & \sum c_1(t_i) & 1 \end{pmatrix} K_1$$

$$= \frac{1}{\varepsilon}\begin{pmatrix} \sum (c_1(t_{i+1}) - c_1(t_i)) c_1(t_i)^2 \\ \sum (c_1(t_{i+1}) - c_1(t_i)) c_1(t_i) c_2(t_i) \\ \sum (c_1(t_{i+1}) - c_1(t_i)) c_1(t_i) \\ \sum (c_1(t_{i+1}) - c_1(t_i)) \end{pmatrix},$$

where

$$K_1 = \begin{pmatrix} k_{21} \\ k_{43} \\ a \\ k_{11,\,9} \end{pmatrix}$$

and

$$\begin{pmatrix} \sum c_1(t_i)^4 & -\sum c_1(t_i)^3 c_2(t_i) & -\sum c_1(t_i)^2 c_2(t_i) & \sum c_1(t_i)^2 \\ \sum c_1(t_i)^3 c_2(t_i) & -\sum c_1(t_i)^2 c_2(t_i)^2 & -\sum c_1(t_i) c_2(t_i)^2 & \sum c_1(t_i) c_2(t_i) \\ \sum c_1(t_i)^2 c_2(t_i) & -\sum c_1(t_i) c_2(t_i)^2 & -\sum c_2(t_i)^2 & \sum c_2(t_i) \\ \sum c_1(t_i)^2 & -\sum c_1(t_i) c_2(t_i) & -\sum c_2(t_i) & 1 \end{pmatrix} K_2$$

$$= \frac{1}{\varepsilon}\begin{pmatrix} \sum (c_2(t_{i+1}) - c_2(t_i)) c_1(t_i)^2 \\ \sum (c_2(t_{i+1}) - c_2(t_i)) c_1(t_i) c_2(t_i) \\ \sum (c_2(t_{i+1}) - c_2(t_i)) c_2(t_i) \\ \sum (c_2(t_{i+1}) - c_2(t_i)) \end{pmatrix},$$

where

$$K_2 = \begin{pmatrix} k_{21} \\ k_{43} \\ k_{92} \\ k_{29} \end{pmatrix}.$$

For $\delta = 1$, we can preclude tristability.

Theorem 2. *Suppose* $\delta = 1$. *Then there is a unique positive singular point* (C_-, D_-). *If*

$$k_{21}k_{92} - k_{29}k_{43} < 0, \quad a < 0,$$

then it is stable.

Proof. We have

$$\tilde{f}(C, D) = \begin{pmatrix} -k_{21}C + aC - k_{43}C \cdot D + k_{11,\,9} \\ k_{21}C - k_{43}C \cdot D - k_{92}D + k_{29} \end{pmatrix}.$$

Define

$$D^0(C) = \frac{k_{29} + k_{21}C}{k_{43}C + k_{92}}$$

and

$$D^\infty(C) = \frac{(-k_{21} + a)C + k_{11,\,9}}{k_{43}C}.$$

Then

$$(D^0)'(C) = \frac{k_{21}k_{92} - k_{29}k_{43}}{(k_{43}C + k_{92})^2}$$

and

$$(D^\infty)'(C) = -\frac{k_{11,\,9}}{k_{43}C^2}.$$

From $D' = 0$, get

$$D = \frac{k_{29} + k_{21}C}{k_{43}C + k_{92}}$$

and insert it in $C' = 0$, to obtain

$$\begin{aligned} p(C) &= (-2k_{21}k_{43} + ak_{43})C^2 + (k_{11,9}k_{43} + k_{92}a - k_{92}k_{21} - k_{43}k_{29})C \\ &\quad + k_{92}k_{11,9} \\ &= a_2C^2 + b_2C + c_2 \\ &= 0. \end{aligned}$$

By the solution formula for roots of a quadratic equation

$$C_{\pm} = \frac{-b_2 \pm \sqrt{b_2^2 - 4a_2c_2}}{2a_2}$$

give rise to candidates of positive singular points. We can see, that the discriminant is positive and there is one positive root C_- and one negative root C_+. Now define

$$U = \{(C, D) \in \mathbb{R}^2 \mid \tilde{C}_1 < C < \tilde{C}_2, \tilde{D}_1 < D < \tilde{D}_2\},$$

where

$$\tilde{D}_2 = D^{\infty}(\tilde{C}_1), \quad \tilde{D}_1 = D^{\infty}(\tilde{C}_2)$$

and $\tilde{C}_1 < C_- < \tilde{C}_2$, $\tilde{C}_1$, $\tilde{C}_2$ close to C_-.

By the fundamental theorem of algebra

$$p(C) = (-2k_{21}k_{43} + ak_{43})(C - C_-)(C - C_+).$$

So $p(C) > 0$ when $C \in \,]C_+, C_-[$. On $C = \tilde{C}_1$,

$$c_1'(0) > 0$$

when $c_2(0) \in [\tilde{D}_1, \tilde{D}_2[$, and

$$c_1''(0) > 0$$

when $c_2(0) = \tilde{D}_2$. We have

$$\tilde{f}(C, D^\infty(C)) = \begin{pmatrix} 0 \\ K(C) \end{pmatrix},$$

where $K(C) < 0$, when $C \in \,]C_+, C_-[$. On $C = \tilde{C}_2$,

$$c_1'(0) < 0$$

when $c_2(0) \in \,]\tilde{D}_1, \tilde{D}_2[$, and

$$c_1''(0) < 0$$

when $c_2(0) = \tilde{D}_1$. We have inequalities

$$\begin{aligned} \tilde{D}_1 &\leq D^\infty(C) \\ &< D^0(C) \\ &< D_1 \\ &< \tilde{D}_2 \end{aligned}$$

whenever $C \in \,]C_-, \tilde{C}_2]$. Also

$$\begin{aligned} \tilde{D}_1 &< D_1 \\ &< D^0(C) \\ &< D^\infty(C) \\ &\leq \tilde{D}_2 \end{aligned}$$

when $C \in [\tilde{C}_1, C_-[$.

We also have

$$\frac{\partial}{\partial D}(k_{21} - k_{92}D - k_{43}C \cdot D + k_{29}) = -k_{92} - k_{43}C$$

$$< 0. \tag{15}$$

Now $D' = 0$ on

$$(C, D^0(C)).$$

By (15),

$$D' < 0, \quad D = \tilde{D}_2,$$

$$D' > 0, \quad D = \tilde{D}_1.$$

Arguing as in Theorem 1, Theorem 2 follows. □

3. Summary

In the present paper, we developed a four dimensional ODE model of immunity. For some values of the parameters there are two stable singular points and one unstable singular point. This was accomplished by considering a simpler two dimensional model with variables C and D for antigen and dendritic cells, respectively. This model is tristable for some values of the parameters and the implicit function theorem implies tristability of the original four dimensional model. We also proposed a stability test for vaccines.

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