

ON THE BOUNDEDNESS OF LYMPHOCYTES IN
 DETERMINISTIC THRESHOLD MODELS
 OF HUMORAL IMMUNE RESPONSE

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1. **Introduction.** Recently there has been much interest in mathematical models of immune response. To a great extent, the models have been based on the models of Bell [1, 2, 3], who developed the first of such mathematical models.

In this paper we are concerned with models that incorporate thresholds for the various stages of the dynamics. It is a well known property of immune response, that in the case where the antigen is completely eliminated, then the lymphocytes stop growing, i.e., the number of free lymphocyte receptors is bounded. It is the main purpose of this paper to examine several proposed threshold models of humoral immune response and to see to what extent these models have that property. For a complete discussion of the immune process, see Bellanti [4].

In the case of nonreplicating antigen we shall look at a model of Waltman and Butz [7] and extended by Gatica and Waltman [6]. If

$$\begin{aligned}
 (1.1) \quad & x(t) = \text{concentration of free antigen molecules} \\
 & y(t) = \text{concentration of free lymphocyte receptors} \\
 & z(t) = \text{concentration of free antibody molecules} \\
 & w(t) = \text{concentration of bound antigen molecules,}
 \end{aligned}$$

then the system of interest is

$$\begin{aligned}
 (1.2) \quad & x'(t) = -rx(t)y(t) - sx(t)z(t) \\
 & y'(t) = -rx(t)y(t) + \alpha rx(\tau_1(t))y(\tau_1(t))H(t - t_1) \\
 & z'(t) = -sx(t)z(t) - \gamma z(t) \\
 & \quad + \beta rx(\tau_2(t))y(\tau_2(t))H(t - t_2) \\
 & w'(t) = rx(t)y(t), \quad x(0) = x_0 > 0, \\
 & y(0) = y_0 > 0, \quad z(0) = w(0) = 0,
 \end{aligned}$$

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($' = d/dt$) where τ_1 and τ_2 are defined by

$$(1.3) \quad \int_{\tau_1(t)}^t f_1(x(u), y(u), w(u)) du = m_1, t \geq t_1$$

$$\tau_1(t) = 0, t \in [0, t_1]$$

$$(1.4) \quad \int_{\tau_2(t)}^t f_2(y(u) + w(u)) du = m_2, t \geq t_2$$

$$\tau_2(t) = 0, t \in [0, t_2],$$

where t_1 and t_2 are given by

$$(1.5) \quad \int_0^{t_1} f_1(x(u), y(u), z(u)) du = m_1$$

$$\int_0^{t_2} f_2(y(u) + w(u)) du = m_2$$

or by $t_1 = +\infty$, $t_2 = \infty$ if no such t_i exist.

It is assumed that $\alpha, \beta, \gamma, r, s, m_1, m_2$ are positive constants. f_1 and f_2 are the trigger mechanism functions. H is the usual Heavyside function.

In [7], it was shown that if f_1 and f_2 are continuous and locally Lipschitzian, $f_2(\xi) > 0$ when $\xi > 0$, $f_1 > 0$ when $x, y > 0$, then system (1.2) has a unique solution which depends continuously on the initial conditions and parameters. In [6], this theorem was extended to include the case $f_1 = w$.

In the case of replicating antigens, we consider a model proposed by Freedman and Gatica [5]. here the system of interest is

$$(1.6) \quad \begin{aligned} x'(t) &= x(t)g(x(t)) - \beta x(t)y(t) - \gamma x(t)z(t) \\ y'(t) &= -\beta x(t)y(t) + y(t)h(y(t))\hat{H}(t) \\ z'(t) &= -\gamma x(t)z(t) + k(y)H^*(t) \\ w'(t) &= \beta x(t)y(t) + \gamma x(t)z(t) - \epsilon w(t), \\ x(0) &= x_0 > 0, y(0) = y_0 > 0, \\ z(0) &= w(0) = 0, ' = \frac{d}{dt}, \end{aligned}$$

where

$$\begin{aligned}
 & 0, \quad t < \hat{t} \\
 (1.7) \quad \hat{H}(t) = & 0, \quad t \geq \hat{t} \text{ and } \int_{t-\hat{t}}^t \hat{f}(x(u), y(u), w(u)) \, du < \hat{m} \\
 & 1, \quad \int_{t-\hat{t}}^t \hat{f}(x(u), y(u), w(u)) \, du \geq \hat{m},
 \end{aligned}$$

$$\begin{aligned}
 & 0, \quad t < t^* \\
 (1.8) \quad H^*(t) = & 0, \quad t \geq t^* \text{ and } \int_{t-t^*}^t f^*(x(u), y(u), w(u)) \, du < m^* \\
 & 1, \quad \int_{t-t^*}^t f^*(x(u), y(u), w(u)) \, du \geq m^*,
 \end{aligned}$$

where $\hat{t} < t^*$ and are given by

$$\begin{aligned}
 & \int_0^{\hat{t}} \hat{f}(x(u), y(u), w(u)) \, du = \hat{m} \\
 (1.9) \quad & \int_0^{t^*} f^*(x(u), y(u), w(u)) \, du = m^*.
 \end{aligned}$$

Here \hat{m} and m^* are the threshold constants, f and f^* the threshold functions, β, γ, ϵ are positive constants, $g(x), h(y)$ are the specific growth rates of free antigen and lymphocytes respectively, and $k(y)$ is a growth law governing the production of antibody.

In [5], various possible behaviours of the solutions were analyzed for different stages of the model. In particular, for $t < t^*$ the equations governing the dynamics of antigen and lymphocytes resemble competition equations. In general, depending on the parameters, it was shown that coexistence between free antigen, lymphocytes, and antibody is possible. However, it was also shown that the antigen could also be driven to extinction.

2. Nonreplicating antigens. In this section we are interested in the asymptotic behavior of system (1.2). We are assuming here that $t_1 < t_2 < \infty$. Further, from (1.3) and (1.4), note that $\tau_i(t) < t, i = 1, 2$ and that if $(x(t), y(t), z(t), \tau_1(t), \tau_2(t))$ is a solution of (1.2)–(1.4), then $x(t) > 0, y(t) > 0$ and $z(t) \geq 0$ for all $t \geq 0$ and $w(t) > 0$ for all $t > 0$. Also $x(t)$ is a decreasing function and therefore $\lim_{t \rightarrow \infty} x(t) = x^0$ exists. As well, it should be pointed out that if we assume $f_1(x, y, w) > 0$ whenever at least one of the arguments is positive and that $f_2(\xi) > 0$ for $\xi > 0$, then τ_1, τ_2 are strictly increasing functions and $t > t_i \Rightarrow \tau_i(t) > 0, i = 1, 2$.

THEOREM 1. *Suppose that $f_2(\xi) > 0$ if $\xi > 0$ and that $x^0 = \lim_{t \rightarrow \infty} x(t) > 0$. Then*

$$\lim_{t \rightarrow \infty} y(t) = \lim_{t \rightarrow \infty} z(t) = 0.$$

PROOF. First we observe that if $t \geq 0$

$$x(t) - x_0 = -r \int_0^t x(s)y(s) ds - s \int_0^t x(s)z(s) ds$$

and hence the improper integrals

$$\int_0^\infty x(t)y(t) dt, \quad \int_0^\infty x(t)z(t) dt$$

converge. Since the integrands are nonnegative and since $\lim_{t \rightarrow \infty} x(t) > 0$, it must be the case that

$$\liminf_{t \rightarrow \infty} y(t) = \liminf_{t \rightarrow \infty} z(t) = 0.$$

Also, $(y - x)'(t) \geq 0$ for all $t \geq 0$ and therefore $y(t) - x(t)$ is an increasing function. Since there is a sequence $\{t_n\}_{n=1}^\infty$ of positive real numbers such that $\lim_{n \rightarrow \infty} y(t_n) = 0$, it must be the case that

$$\lim_{t \rightarrow \infty} (y(t) - x(t)) = -x^0,$$

i.e.,

$$\lim_{t \rightarrow \infty} y(t) = 0.$$

It follows that $y(t)$ is a bounded function. From the convergence of the improper integral $\int_0^\infty x(t)y(t) dt$ it follows that $w(t)$ is a bounded function. Let $M > 0$ be such that

$$0 < y_0 \leq y(t) + w(t) < M \text{ for all } t \in [0, \infty),$$

and let

$$K = \sup\{f_2(\xi) : \xi \in [0, M]\}$$

$$K = \inf\{f_2(\xi) : \xi \in y_0, M\} > 0.$$

We have, for $t \geq t_2$:

$$f_2(y(t) + w(t)) - f_2(y(\tau_2(t)) + (\tau_2(t)))\tau_2'(t) = 0,$$

so that

$$\begin{aligned} \tau_2'(t) &= \frac{f_2(y(t)) + w(t)}{f_2(y(\tau_2(t))) + w(\tau_2(t))} \\ &\cong \frac{k}{K} > 0. \end{aligned}$$

Hence, by changing variables of integration, we conclude that

$$\int_0^\infty x(\tau_2(t))y(\tau_2(t)) dt < \infty.$$

Now we will show that $z(t)$ is bounded on $[0, \infty)$. Since $z(t)$ is a solution (on $[t_2, \infty)$) of the linear equation

$$z'(t) + (sx(t) + \gamma)z(t) = \beta rx(\tau_2(t))y(\tau_2(t)),$$

we must have

$$\begin{aligned} z(t) &= e^{-\int_{t_2}^t (sx(u)+\gamma)du} \\ &\cdot \left[z(t_2) + \beta r \int_{t_2}^t e^{\int_{t_2}^s (sx(v)+\gamma)dv} \cdot x(\tau_2(u))y(\tau_2(u)) du \right] \\ &\cong z(t_2) + \beta r \int_{t_2}^t x(\tau_2(u))y(\tau_2(u)) du \end{aligned}$$

which is bounded on $[t_2, \infty)$. Hence $z(t)$ is bounded on $[0, \infty)$.

Now we conclude that $z(t)$ is uniformly continuous on $[0, \infty)$ and since $x(t)$ is also uniformly continuous on $[0, \infty)$ we have that $\lim_{t \rightarrow \infty} x(t)z(t) = 0$, since $(x(t)z(t)) \in L^1([0, \infty))$. Hence

$$\lim_{t \rightarrow \infty} z(t) = 0.$$

A possible interpretation of this result is that the model predicts that in case there is no recovery from the action of the antigen, then both the receptor molecules and the free antibody molecules must disappear from the system.

Our next step will be to investigate conditions which insure that if $(x(t), y(t), z(t), w(t), \tau_1(t), \tau_2(t))$ is the solution of (1.2)–(1.4) then $y(t), z(t)$ are bounded functions ($x(t), w(t)$ are always bounded).

THEOREM 2. *Suppose $f_1(x, y, w) > 0$ if $w > 0$ and $f_2(\xi) > 0$ if $\xi > 0$. Then $y(t), z(t)$ are bounded functions if and only if there exists $\eta > 0$ and $t^* \cong t_1$ such that*

$$(2.1) \quad \tau_1'(t) \cong \eta, \text{ for all } t \cong t^*.$$

PROOF. If (2.1) holds, then one obtains the boundedness of $y(t)$ by using a change of variables in order to conclude

$$\int_0^\infty x(\tau_1(t))y(\tau_1(t)) dt < \infty.$$

Having the fact that $y(t)$ is bounded, one can proceed as in the proof of Theorem 1 in order to conclude that $z(t)$ is bounded.

Let us assume now that $y(t)$, $z(t)$ are bounded and observe that $w(t)$ is always bounded and that under our assumptions, if $t^* > t_1$, then $\tau_1(t^*) > 0$ (furthermore, $w(t)$ is a strictly increasing function). Then f_1 is a positive continuous function on $S = [0, x_0] \times [0, M_1] \times [w(t^*), M_2]$, where M_1 is a bound for $y(t)$, M_2 is a bound for $w(t)$.

Let

$$\begin{aligned} &= \inf\{f_1(x, y, w) : (x, y, w) \in S\} > 0 \\ K &= \sup\{f_1(x, y, w) : (x, y, w) \in S\} < +\infty. \end{aligned}$$

We have, for $t \geq t^*$,

$$\begin{aligned} \tau_1'(t) &= \frac{f_1(x(t), y(t), w(t))}{f_1(x(\tau_2(t)), y(\tau_2(t)), w(\tau_2(t)))} \\ &\geq \frac{k}{K} > 0. \end{aligned}$$

COROLLARY. If f_1 depends only on w , say $f_1(x, y, w) = g(w)$ and if $g(w) > 0$ for $w > 0$, together with the condition $f_2(\xi) > 0$ when $\xi > 0$, then $y(t)$, $z(t)$ are bounded functions.

There are other conditions on f_1 that insure boundedness of $y(t)$, $z(t)$.

THEOREM 3. Suppose that $f_1(x, y, w) > 0$ if $w > 0$, $f_2(\xi) > 0$ if $\xi > 0$, that $\lim_{t \rightarrow \infty} x(t) = 0$ and that $y(t)$, $z(t)$ are bounded functions. Then

$$\lim_{t \rightarrow \infty} y(t) \geq 0$$

and

$$\liminf_{t \rightarrow \infty} z(t) = 0.$$

PROOF. First we observe that, as a consequence of Theorem 2, we have

$$\lim_{t \rightarrow \infty} \tau_i(t) = \infty, \quad i = 1, 2,$$

and that $x(t)$, $y(t)$, $z(t)$ have bounded derivatives.

The fact that $\lim_{t \rightarrow \infty} y(t)$ exists and is nonnegative is immediate since $y(t) - x(t)$ is an increasing function and $y(t) > 0$ for all $t \in \mathbf{R}$.

Let $\{t_n\}_{n=1}^\infty$ be any sequence of real numbers such that $t_n > t_2$ for all n and

$$\lim_{n \rightarrow \infty} t_n = \infty.$$

Since $z(t)$ is bounded, we may assume that

$$\lim_{n \rightarrow \infty} z(t_n) = z_0$$

(by restriction to a subsequence if necessary).

Now we define the following sequences of functions:

$$\begin{aligned} X_n(t) &= x(t + t_n), \\ x_n(t) &= x(\tau_2(t + t_n)), \\ y_n(t) &= y(\tau_2(t + t_n)), \\ z_n(t) &= z(t + t_n). \end{aligned}$$

It is clear that

$$\begin{aligned} \lim_{n \rightarrow \infty} X_n(t) &= 0 \text{ uniformly on } [\cdot, \infty) \\ \lim_{n \rightarrow \infty} x_n(t)y_n(t) &= 0 \text{ uniformly on } [0, \infty), \end{aligned}$$

and that $z_n(t)$ is the solution to the initial value problem:

$$\begin{aligned} z'(t) &= -sX_n(t)z(t) - \gamma z(t) + \beta r x_n(t)y_n(t) \\ z(0) &= z(t_n). \end{aligned}$$

Hence $\{z_n(t)\}_{n=1}^\infty$ converges uniformly on compact subsets of $[0, \infty)$ to the solution of

$$(2.2) \quad \begin{aligned} z'(t) &= -\gamma z(t) \\ z(0) &= z_0. \end{aligned}$$

Since the solution of (2.2) tends to 0 as $t \rightarrow \infty$, it follows that

$$\liminf_{t \rightarrow \infty} z(t) = 0.$$

NOTE. The fact that $\liminf_{t \rightarrow \infty} z(t) = 0$ means that if an immune reaction occurs with production of antibody, there will be times in the future when the detection of the antibody will be impossible.

3. Replicating antigens. In this section, we are interested in the asymptotic behavior of solutions of system (1.6). Since there are many possible behaviors of the solutions, (see [5]), we are particularly interested in the case where $\lim_{t \rightarrow \infty} x(t) = 0$. We will show that under reasonable hypotheses on \hat{f} and f^* , then if $x \rightarrow 0$, lymphocyte growth will cease.

First we note that if $\hat{t} = +\infty$, then $y' < 0$, and if $\lim_{t \rightarrow \infty} x(t) = 0$, then $\lim_{t \rightarrow \infty} y(t) = y_1$, where $0 < y_1 < y_0$.

Suppose now \hat{t} is finite, but $t^* = \infty$.

THEOREM 4. *Let $\lim_{t \rightarrow \infty} x(t) = 0$, $t^* = \infty$,*

$$(3.1) \quad f(x, y, w) \leq \kappa xy$$

for some $\kappa \geq 0$, and $|g(x)| \leq A$. Then there exists $T_1 > t$ such that $\hat{H}(t) = 0$ for $t > T_1$.

PROOF. From (3.1), $\hat{I} = \int_{t-\hat{t}}^t \hat{f}(x(u), y(u), w(u)) du \leq \int_{t-\hat{t}}^t \kappa x(u)y(u) du$ which by (1.6), since $z(t) = 0$ when $t^* = +\infty$, is less than or equal to $\beta^{-1}\kappa \int_{t-\hat{t}}^t [x(u)g(x(u)) - x'(u)] du$. Let T_0 be such that for fixed $\xi > 0$, $0 < x(t) < \xi$ for $t \geq T_0$. Then $\hat{I} \leq \beta^{-1}\kappa(A\xi\hat{t} - x(t) + x(t - \hat{t})) \leq \beta^{-1}\kappa(A\hat{t} + 1)\xi$ for $t \geq T_0 + \hat{t}$. Suppose T_0 is so large that ξ can be chosen such that $\xi < \hat{m}\beta/\kappa(A\hat{t} + 1)$. Then if $T_1 \geq T_0 + \hat{t}$, $\hat{I} < \hat{m}$ for $t \geq T_1$, proving the theorem.

NOTE. The above theorem shows that if f_1 is governed by the product of free antigens and lymphocyte receptors, and no antibody is produced, then in the event that the antigen is driven out of the system, the mechanism causing lymphocyte growth will eventually be turned off.

Suppose now that $t^* < +\infty$ and that f^* is essentially governed by the amount of bound antigen, then we can prove a similar theorem.

THEOREM 5. *Suppose $t^* < +\infty$, $0 < f^*(x, y, z, w) \leq \lambda w$, $\lim_{t \rightarrow \infty} x(t) = 0$. Then there exists $T_2 > 0$ such that for all $t \geq T_2$, $H^*(t) = 0$.*

PROOF. Let $I^*(t) = \int_{t-t^*}^t w(u) du$, and let $J(u) = \beta x(u)y(u) + \gamma x(u)z(u)$. Then by (1.6),

$$\begin{aligned} I^*(t) &= \epsilon^{-1} \int_{t-t^*}^t J(u) du - \epsilon^{-1} \int_{t-t^*}^t w'(u) du \\ &= \epsilon^{-1} \int_{t-t^*}^t J(u) du - \epsilon^{-1} I^{*\prime}(t). \end{aligned}$$

Then $I^*(t)$ satisfies

$$(3.2) \quad I^*(t) = -\epsilon I^*(t) + \int_{t-t^*}^t J(u) du.$$

Then

$$(3.3) \quad I^*(t) = e^{-\epsilon(t-T)} I^*(T) + e^{-\epsilon(t-T)} \int_T^t e^{\epsilon(u-T)} \int_{u-t^*}^u J(v) dv du.$$

Now, as before, fix $\eta > 0$ and choose $T > 0$ so large that for $t \geq T - t^*$, $0 < x(t) \leq \eta$. Then from (1.6), $J(v) = x(v)g(x(v)) - x'(v)$ and hence $\int_{u-t^*}^u J(v) dv \leq \eta A t^* - x(u) + x(u - t^*)$, since $u \geq T$, $u - x^* \geq T - t^*$ and so $\int_{u-x^*}^u J(v) dv \leq \eta(A t^* + 1)$. Then from (3.3),

$$I^*(t) \leq e^{-\epsilon(t-T)} I^*(T) + \epsilon^{-1} \eta (A t^* + 1) (1 - e^{-\epsilon(t-T)}),$$

and hence one can find T_2 so large that $e^{-\epsilon(t-T)}$ and η are so small for $t \geq T_2$ that $I^*(t) < m^*/\lambda$. Then $\int_{t-t^*}^t f^* du < m^*$ for $t \geq T_2$ which proves the theorem.

Note that when the antibody production mechanism is turned off, if the hypotheses of Theorem 4 are satisfied, $\dot{H}(t) = 0$ eventually also, in which case the lymphocyte growth will cease as well.

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