THE IMPACT OF DELAY IN THE TREATMENT OF AUTOINFLAMMATORY DISEASE WITH A MATHEMATICAL MODEL

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ABSTRACT. Immunological imbalance eventually results in the development of various diseases. A typical example is an imbalance of cytokines with immunomodulatory abilities. In this paper, we propose a two-variable delay model to anti-pro-inflammatory cytokine therapy for autoimmune diseases, which are caused by an imbalance between the pro and anti-inflammatory cytokines. The interaction between pro- and anti-inflammatory cytokines were modeled mathematically to investigate the relevance of cytokines in disease processes. The delay time was estimated to maintain the stability of a biologically important steady state. In particular, the effects of delay with anti-pro-inflammatory cytokines therapy in autoinflammatory diseases were studied.

1. Introduction

The immune system builds a defense system composed of various cells to protect the human body from internal and external pathogenic substances. This is achieved through the specific function of each cell and interaction between cells. The human immune system is largely composed of immune tolerance, which is a mechanism that suppresses and regulates immunity, and immune response that enhances immunity [1]. The immune system maintains immunological homeostasis by balancing these two immune actions [2].

However, the immunological balance can be induced by various causes, and this imbalance eventually results in the development of various diseases [3]. Immunological imbalance can occur when the function of immune tolerance is relatively strong compared to the immune response or conversely, when the immune response function is stronger than the immune response function. In addition, when the immune tolerance mechanism is stronger than the immune tolerance...
response, the human immune system facilitates the occurrence of cancer or the
invasion of external viral pathogens, causing cancer or viral and bacterial dis-
eases [4, 5]. When the immune tolerance mechanism becomes stronger, it leads
to autoimmune diseases, strong transplant rejection reactions, and inflamma-
ty diseases such as allergic diseases. From an immunological perspective, a
disease is a result of an imbalance in the homeostasis of the immune system and
thus, the disease can be cured through the regulation of this imbalance.

In addition, an imbalance of immune relay materials can lead to the develop-
ment of inflammatory diseases [6]. Immune relay substances are substances with
immunomodulatory ability; cytokine is a representative example [7]. Cytokines
are cell-signaling molecules that play many roles within the body. In general,
cytokines with anti-inflammatory functions include Interleukin-10(IL-10) and
Transforming Growth Factor-β(TGF-β), and cytokines with pro-inflammatory
functions include Interferon-γ(IFN-γ), Tumor Necrosis Factor-α(TNF-α), and
Interleukin-17(IL-17). During an inflammation, immune responses are mediated
by cytokines, which increase during inflammation before returning to normal
levels. In immunological homeostasis, the expression of these different media-
tors is balanced. However, compared with the function of the anti-inflammatory
mediator, an increase in the expression of a pro-inflammatory mediator or a de-
crease in the expression of an anti-inflammatory mediator results in an immune
imbalance. Immune/nonimmune cells are stimulation, which can lead to inflam-
matory diseases. Therefore, we used it to model this system by incorporating
inflammatory and anti-inflammatory cytokine groups. The proposed model is
based on an activator-inhibitor model for cytokine interactions [8].

Many studies have modelled cytokine-mediated inflammatory processes. In
[9], a four-dimensional model was analyzed to explore the dynamics of cytokines
in infectious and idiopathic diseases and their asymptotic states. They found
runaway Interleukin-1(IL-1) production, multiple stable equilibria, stable limit
cycles, and an exceptionally quasiperiodic behaviour. These behaviours signifi-
cantly depend on the form of the immune cell response. Rheumatoid arthritis
is an inflammatory diseases that is caused by an immune imbalance produced
by excessive pro-inflammatory cytokines. In [10], three types of therapeutic
agents that inhibited pro-inflammatory cytokines were compared and analyzed
using a mathematical model. The main factors were the delayed effects of
anti-pro-inflammatory cytokine input on the system dynamics, in general, and
on the pro-inflammatory cytokine burden, in particular. Some individuals with
autoinflammatory disease inflammatory cytokine inhibitors, also known as anti-
cytokine therapies, are used in the form of pro-inflammatory cytokine receptor
antagonists or antibodies that target pro-inflammatory cytokines [11]. We used
a model to demonstrate the perspective of treatment through a delay. In prac-
tice, it is realistic to assume that the effects of anti-pro-inflammatory cytokines
begin after a certain time delay as treatment is started after the pro- and anti-
inflammatory cytokines reach a stable steady state. This study aimed to eluci-
date the effect of anti-pro-inflammatory cytokine therapy with different immune
thresholds in autoinflammatory diseases. We introduced a modified mathematical model to mathematically examine the effect of autoinflammatory disease treatment using the anti-pro-inflammatory cytokine therapy.

2. mathematical model

The proposed mathematical model consists of a system of two ordinary differential equations, where \( p(t) \) and \( a(t) \) is the concentration of pro-inflammatory cytokine molecules by \( p \) and the concentration of anti-inflammatory cytokine molecules by \( a \), respectively. The corresponding differential equations are expressed as follows:

\[
\frac{dp}{dt} = \alpha_1 a \frac{p}{1 + p} - d_p p - kp(t - \tau) \\
\frac{da}{dt} = \alpha_2 p a - d_a a
\]  

(1)

The degradation of a cytokine concentration was assumed to be linear, where \( d_p \) and \( d_a \) represent the corresponding rates. Moreover, \( \alpha_1 ap/(1 + p) \) denotes the combined effect of pro- and anti-inflammatory stimuli for pro-inflammatory cytokine production [8].

The treatment term \( kp(t - \tau) \) represents the external input of anti-pro-inflammatory cytokine into the system that decreases the concentration of pro-inflammatory cytokines. It is assumed that the external input (treatment term) of anti-pro-inflammatory cytokines into the system is time-dependent and the discrete time delay \( \tau \) indicates the lag after a single dose of anti-pro-inflammatory cytokine is injected. Additionally, we examined the dynamics of treatment through pro-inflammatory cytokines by altering the value of \( \tau \).

3. Qualitative analysis of the model

We analysis a linear stability in the phase space..

3.1. Steady states

To investigate the steady states of biological significance of the system (1), we will consider only the positive quadrant. The steady states are denoted \( S_0 \) and \( S_1 \).

(i) The steady state \( S_0 \) is given by \((0, 0, 0)\).

(ii) The steady state \( S_1 \) is \((p^*, a^*)\), where

\[
p^* = \frac{d_a}{\alpha_2}, \quad a^* = \frac{\alpha_2 d_p + d_a d_p + \alpha_2 k + d_a k}{\alpha_1 \alpha_2}.
\]
Our research will focus solely on the steady states $S_1 = (p^*, a^*)$.
The variation matrix or the Jacobian around the steady state $S_1$ is,
\[
\begin{pmatrix}
\frac{\alpha_1 a}{1 + p} - d_p - \frac{\alpha_1 p a}{(1 + p)^2} - k e^{-\tau} \frac{\alpha_1 p}{1 + p} \\
\frac{\alpha_2 a}{1 + p} - \frac{\alpha_2 p}{1 + p}
\end{pmatrix}
\]

In the case of a positive delay, the characteristic equation for the linearized equation around the steady state $S_1 = (p^*, a^*)$ is given by
\[
\lambda^2 + a_0 \lambda + a_1 + e^{-\lambda \tau} (b_0 \lambda + b_1) = 0,
\]
where,
\[
a_0 = d_p - \frac{\alpha_1 a}{1 + p} + \frac{\alpha_1 p a}{(1 + p)^2},
\]
\[
a_1 = \left( \frac{\alpha_1 a}{1 + p} - d_p - \frac{\alpha_1 p a}{(1 + p)^2} \right) \left( \alpha_2 p - d_a - \frac{\alpha_1 \alpha_2 p a}{1 + p} \right),
\]
\[
b_0 = k, \quad b_1 = k (\alpha_2 p - d_a).
\]

The steady state $S_1$ is stable in the absence of delay ($\tau = 0$) if the roots of the characteristic polynomial
\[
\lambda^2 + a_0 \lambda + a_1 + (b_0 \lambda + b_1) = 0
\]
have negative real parts. Applying the Routh-Hurwitz theorem, one shows that the necessary and sufficient conditions for that are $a_0 + b_0 > 0$ and $a_1 + b_1 > 0$. They are satisfied for the parameter set. Then, the system is stable without discrete time delay.

Now substituting $\lambda = i \omega$ (where $\omega$ is positive) in the characteristic equation and separating the real and imaginary parts we obtain the system of transcendental equations to determine $\omega$ and $\tau$:
\[
\omega^2 - a_1 + b_0 \omega \sin(\omega \tau) - b_1 \cos(\omega \tau) = 0 \tag{2}
\]
\[
a_0 \omega + b_0 \omega \cos(\omega \tau) + b_1 \sin(\omega \tau) = 0. \tag{3}
\]

Squaring and adding (2) and (3) we get,
\[
a^2 + A_1 \alpha + A_2 = 0(\alpha = \omega^2)
\]
where
\[
A_1 = a_0 + 2a_1 - b_0
\]
\[
A_2 = a_1^2 - b_1^2.
\]

Satisfying (3), there exists a positive $\omega_0$. Thus, the characteristic equation has a pair of imaginary roots $\pm i \omega_0$. from (2) and (3), eliminating $\sin(\omega \tau)$ we get the expression for the time delay as
\[
\tau^*_n = \frac{1}{\omega_0} \cos^{-1} \left\{ \frac{(\omega_0^2 - a_1) b_0 \omega_0 - a_0 b_0 \omega_0^3}{(b_0 \omega_0)^2 + b_1^2} \right\} + \frac{2n \pi}{\omega_0}.
\]

For $\tau = 0$ the steady state $S_1 = (p^*, a^*)$ is stable. Hence, from [12], it will remain stable for $\tau < \tau_0$, where $\tau_0 = \tau^*_0$. 
3.2. Estimation of the length of delay to preserve stability

Following the lines of [12] and using the Nyquist criterion [13], it can be shown that the conditions for local asymptotic stability of $S_0$ are given by $Im[H(i\eta_0)] > 0$ and $Re[H(i\eta_0)] = 0$, where $H(s) = s^2 + a_0s + a_1 + e^{-s\tau}(b_0s + b_1) = 0$, and $\eta_0$ is the smallest positive root of $Re[H(i\eta_0)] = 0$. It has already been mentioned that $S_1$ is locally asymptotically stable in absence of delay. Hence, by continuity all eigenvalues will continue to have negative real parts for sufficiently small $\tau > 0$, provided one can guarantee that no eigenvalues with positive real parts bifurcate from infinity as $\tau$ increases from zero. Therefore, in this case, the conditions for local asymptotic stability of $S_1$ give

$$\eta_0^2 - a_1 = b_1\cos(\eta_0\tau) - b_0\eta_0\sin(\eta_0\tau)$$

(4)

$$a_0\eta_0 > -b_0\eta_0\cos(\eta_0\tau) - b_1\sin(\eta_0\tau).$$

(5)

When equation (4) and (5) are satisfied simultaneously, they are sufficiently guarantee the stability. In addition, they can be used to estimate the length of delay. The aim is to find an upper bound $\eta_+$ on $\eta_0$, independent of $\tau$ and then to estimate $\tau$ so that (4) holds true for all values of $\eta$, $0 \geq \eta \geq \eta_+$ and hence, in particular, for $\eta = \eta_0$.

From (4), maximizing the function $a_1 + b_1\cos(\eta_0\tau) - b_0\eta_0\sin(\eta_0\tau)$, subject to $|\sin(\eta_0\tau)| \leq 1$, $|\cos(\eta_0\tau)| \leq 1$, one gets, $\eta_0^2 \leq |a_1| + |b_1| + b_0\eta_0$, which gives $\eta_0 \leq \eta_+$, if

$$\eta_+ = \frac{1}{2}\left[b_0 + \sqrt{b_0^2 - 4(|a_1| + |b_1|)}\right]$$

From the inequality (5) we obtain

$$\eta_0 < \frac{b_0}{a_0}\cos(\eta_0\tau) + \frac{b_1}{a_0}\sin(\eta_0\tau)$$

(6)

As $S_1$ is locally asymptotically stable for $\tau = 0$, therefore for sufficiently small $\tau > 0$, inequality (6) holds. By substituting (4) and (6) and rearranging, we obtain

$$(a_0b_1 - b_0\eta_0^2)[\cos(\eta_0\tau) - 1] - (a_0b_0\eta_0 + b_1)\sin(\eta_0\tau) < b_0\eta_0^2 - a_0a_1 - a_0b_1.$$

(7)

By using the bounds, we can write

$$(a_0b_1 - b_0\eta_0^2)[\cos(\eta_0\tau) - 1] = (a_0b_1 - b_0\eta_0^2)2\sin^2\left(\frac{\eta_0\tau}{2}\right) \leq \frac{1}{2}|(a_0b_1 - b_0\eta_0^2)|\eta_+^2 \tau^2$$

and

$$(-a_0b_0\eta_0 - b_1)\sin(\eta_0\tau) \leq (|a_0b_0|\eta_+ + |b_1|)\tau$$

and simplifying (7), we obtain
\[ L_1 \tau^2 + L_2 \tau < L_3 \]

where

\[ L_1 = \frac{1}{2} |(a_0 b_1 - b_0 \eta_+^2)\eta_+^2|, \]
\[ L_2 = |a_0 b_0| \eta_+ + |b_1|, \]
\[ L_3 = b_0 \eta_+^2 - a_0 a_1 - a_0 b_1. \]

Hence, if

\[ \tau_+ = \frac{1}{2L_1} \left( - L_2 + \sqrt{L_2^2 + 4L_1 L_3} \right), \]

then for \( 0 \leq \tau < \tau_+ \), Nyquist criterion [13] holds, and \( \tau_+ \) estimates the maximum length of delay while preserving the stability.

4. Conclusion

In this paper, an activator-inhibitor model was proposed to investigate the cytokine interactions in autoinflammatory diseases. The delayed effect of the anti-pro-inflammatory cytokine treatment on the higher pro-inflammatory cytokine concentration in autoinflammatory diseases was examined. Consequently, the delay length was studied by conducting mathematical analyses. Although the proposed model is simple, numerical analysis is possible by expanding the obtained results. In addition, this study provided a scientific reference to support clinical trials.

References


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