East Asian Math. J.
Vol. 38 (2022), No. 3, pp. 357–363
http://dx.doi.org/10.7858/eamj.2022.023

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

Anna Park

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

Received January 9, 2022; Accepted May 14, 2022.
2010 *Mathematics Subject Classification.* 93C23, 34C40, 92B05.
Key words and phrases. Mathematical model, Delay differential equation, Autoinflammatory disease, Stability analysis.
This work was supported by the National Research Foundation of Korea(NRF) Grant funded by the Korean Government(2020R1A6A3A01099888).

(pISSN 1226-6973, eISSN 2287-2833)

response, the human immune system facilitates the occurrence of cancer or the invasion of external viral pathogens, causing cancer or viral and bacterial diseases [4, 5]. When the immune tolerance mechanism becomes stronger, it leads to autoimmune diseases, strong transplant rejection reactions, and inflammatory 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 development 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 mediators is balanced. However, compared with the function of the anti-inflammtory mediator, an increase in the expression of a pro-inflammatory mediator or a decrease in the expression of an anti-inflammatory mediator results in an immune imbalance. Immune/nonimmune cells are stimulation, which can lead to inflammatory 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 significantly 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 practice, 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 elucidate 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:

$$\begin{aligned} \frac{dp}{dt} &= \alpha_1 a \frac{p}{1+p} - d_p p - kp(t-\tau) \\ \frac{da}{dt} &= \alpha_2 pa - d_a a \end{aligned} \tag{1}$$

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 τ 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 τ.

3. Qualitative analysis of the model

We analysis a linear stability in the phase space..

3.1. Steady steats

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

$$\begin{aligned} p^* &= \frac{d_a}{\alpha_2}, \\ a^* &= \frac{\alpha_2 d_p + d_a d_p + \alpha_2 k + d_a k}{\alpha_1 \alpha_2}. \end{aligned}$$

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,

$$\begin{pmatrix} \alpha_1 a/(1+p) - d_p - \alpha_1 pa/(1+p)^2 - ke^{-\tau} & \alpha_1 p/(1+p) \\ \alpha_2 a & \alpha_2 p - d_a \end{pmatrix}$$

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,

$$\begin{aligned} a_0 &= d_p - \frac{\alpha_1 a}{1+p} + \frac{\alpha_1 pa}{(1+p)^2}, \\ a_1 &= \left(\frac{\alpha_1 a}{1+p} - d_p - \frac{\alpha_1 pa}{(1+p)^2}\right)(\alpha_2 p - d_a) - \frac{\alpha_1\alpha_2 pa}{1+p}, \\ b_0 &= k, \qquad b_1 = k(\alpha_2 p - d_a). \end{aligned}$$

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 ω is positive) in the characteristic equation and separating the real and imaginary parts we obtain the system of transcendental equations to determine ω and τ:

$$\omega^2 - a_1 + b_0\omega\sin(\omega\tau) - b_1\cos(\omega\tau) = 0 \tag{2}$$

$$a_0\omega + b_0\omega\cos(\omega\tau) + b_1\sin(\omega\tau) = 0. \tag{3}$$

Squaring and adding (2) and (3) we get,

$$\alpha^2 + A_1\alpha + A_2 = 0 (\alpha = \omega^2)$$

where

$$\begin{aligned} A_1 &= a_0 - 2a_1 - b_0 \\ A_2 &= a_1^2 - b_1^2. \end{aligned}$$

Satisfying (3), there exists a positive ω_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

$$\tau_n^* = \frac{1}{\omega_0}\cos^{-1}\left\{\frac{(\omega_0^2 - a_1)b_0\omega_0 - a_0 b_0\omega_0^2}{(b_0\omega_0)^2 + b_1^2}\right\} + \frac{2n\pi}{\omega_0}.$$

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 $H(s) = s^2 + a_0 s + a_1 + e^{-s\tau}(b_0 s + b_1) = 0$, and η_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 τ increases from zero. Therefore, in this case, the conditions for local asymptotic stability of S_1 give

$$\eta_0^2 - a_1 = b_1 \cos(\eta_0\tau) - b_0\eta_0 \sin(\eta_0\tau) \tag{4}$$

$$a_0\eta_0 > -b_0\eta_0 \cos(\eta_0\tau) - b_1 \sin(\eta_0\tau). \tag{5}$$

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 η_+ on η_0, independent of τ and then to estimate τ so that (4) holds true for all values of η, $0 \geq \eta \geq \eta_+$ 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

$$\eta_0 < \frac{b_0}{a_0}\cos(\eta_0\tau) + \frac{b_1}{a_0}\sin(\eta_0\tau) \tag{6}$$

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

$$(a_0b_1 - b_0\eta_0^2)[\cos(\eta_0\tau) - 1] - (a_0b_0\eta_0 + b_1)\sin(\eta_0\tau) < b_0\eta_0^2 - a_0a_1 - a_0b_1. \tag{7}$$

By using the bounds, we can write

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

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

$$\begin{aligned} L_1 =& \frac{1}{2}|(a_0b_1 - b_0\eta_+^2)|\eta_+^2, \\ L_2 =& |a_0b_0|\eta_+ + |b_1|, \\ L_3 =& b_0\eta_+^2 - a_0a_1 - a_0b_1. \end{aligned}$$

Hence, if

$$\tau_+ = \frac{1}{2L_1}\left(- L_2 + \sqrt{L_2^2 + 4L_1L_3}\right),$$

then for $0 \leq \tau < \tau_+$, Nyquist criterion [13] holds, and τ_+ 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 analysies. 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

[1] Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, THE B7 F AMILY REVISITED. Annual Review of Immunology, 23(1): 515-548, 2005.

[2] Romagnani, Sergio. "Immunological tolerance and autoimmunity." Internal and emergency medicine 1.3 (2006): 187-196.

[3] Goodnow, Christopher C. "Balancing immunity and tolerance: deleting and tuning lymphocyte repertoires." Proceedings of the National Academy of Sciences 93.6 (1996): 2264-2271.

[4] Homey, B., et al., Cytokines and chemokines orchestrate atopic skin inflammation. Journal of Allergy and Clinical Immunology, 118(1): 178-189, 2006.

[5] Bouma, G. and W. Strober, The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol, 3(7): 521, 2003.

[6] Hogquist, K.A., T.A. Baldwin, and S.C. Jameson, Central tolerance: learning self-control in the thymus. Nat Rev Immunol, 5(10): 772, 2005

[7] O'Shea, John J., Averil Ma, and Peter Lipsky. "Cytokines and autoimmunity." Nature Reviews Immunology 2.1 (2002): 37-45.

[8] Baker, Michelle, et al. "Mathematical modelling of cytokine-mediated inflammation in rheumatoid arthritis." Mathematical medicine and biology: a journal of the IMA 30.4 (2013): 311-337.

[9] Seymour, R. M. & Henderson, B. (2001) Pro-inflammatoryanti-inflammatory cytokine dynamics mediated by cytokine-receptor dynamics in monocytes. Math. Med. Biol., 18, 159192.
[10] Jit, M., Henderson, B., Stevens, M. & Seymour, R. M. (2005) TNF neutralization in cytokine-driven dis- eases: a mathematical model to account for therapeutic success in rheumatoid arthritis but therapeutic failure in systemic inflammatory response syndrome. Rheumatology, 44, 323331.
[11] Goronzy, Jrg J., and Cornelia M. Weyand. "Developments in the scientific understanding of rheumatoid arthritis." Arthritis research & therapy 11.5 (2009): 1-14.
[12] H.I. Freedman, L. Erbe, V.S.H. Rao, Three species food chain models with mutual interference and time delays, Math. Biosci. 80 (1) (1986) 5780.
[13] H. Nyquist, Regeneration theory, Bell Syst. Tech. J. 11 (1) (1932) 126147.

Anna Park
Department of Mathematics, Pusan National University, Busan 46241, Korea
E-mail address: annapark@pusan.ac.kr