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OPTIMIZATION OF PARAMETERS IN BIOLOGICAL SYSTEMS OF DELAY DIFFERENTIAL EQUATIONS

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Abstract. Biological systems with both protein-protein and protein-gene interactions can be modeled by differential equations for concentrations of the proteins with time-delay terms because of the time needed for DNA transcription to mRNA and translation of mRNA to protein. Values of some parameters in the mathematical model can not be measured owing to the difficulty of experiments. Also values of some parameters obtained in a normal stress condition can be changed under pathological stress stimuli. Thus it is important to find the effective way of determining parameters values. One approach is to use optimization algorithms. Here we construct an optimal system used to find optimal parameters in the equations with nonnegative time delays and apply this optimization result to the Nuclear factor-κB pathway.

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Key words and Phrases : Biological systems,optimization, optimal systems, optimal parameters, delay differential equations.

1. Introduction

Under non-stress condition, biological processes at the level of gene, molecule or physiology can be described by ordinary differential equations with nominal values of parameters that are obtained from experiments([1], [3], [7], [9]–[10], [12], [14]). But values of some parameters are changed depending on specific stress stimuli and can not be measured for the difficulty of experiments. The typical method to obtain the undetermined values is the method of trial and error, making the solutions of the differential equations fit some desired profiles through the trials and errors of changing the values. There are no rule for the process of trial and error. And changing values of many undetermined parameters is not physical or pharmacological approach to treat disease([2], [5], [13]). Thus, it is needed to construct the method to obtain the desired profiles by systematically changing only a portion of the undetermined parameters values.

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We will use the optimization method that is the way to get the desired profiles and optimal values of some parameters in general biological systems with time delay terms. Although there are a large number of studies based on optimization, there are few studies on this topic as far as we know. Joshi[11] studied on the mathematical model describing the interaction of HIV and T-cells by using optimization. Choo and Kim[4] obtained optimal parameters in a biological model without time-delay terms. But biological systems containing both protein-protein and protein-gene interactions can be modeled as differential equations with time-delay terms for the DNA transcription and mRNA translation. Thus we will apply optimization to the differential equations, which can describe the effect of the time delay.

Consider the differential equations.

$$\dot{y}_i(t) = f_i(y_{\tau_i}(t), u(t)), \quad 1 \le i \le n \quad \text{and} \quad 0 < t \le T \tag{1.1}$$

with initial conditions

$$y_i(t) = g_i(t), \ \min\{-\tau_{ji} | 1 \le j \le n\} \le t \le 0 \tag{1.2}$$

where g_i is a known function, n, m are natural numbers, the state vector $y = (y_1, \cdots, y_n)$ with state variables y_i, the control vector $u = (u_1, \cdots, u_m)$ with control terms u_j, and $y_{\tau_i}(t) = (y_1(t-\tau_{i1}), \cdots, y_n(t-\tau_{in}))$ with $\tau_{ik} \ge 0 (1 \le k \le n)$ and $y_{\tau_i,j}(t) = y_j(t-\tau_{ij})$. The equations (1.1)–(1.4) with all time delays $\tau_{ji} = 0$ are the biological model discussed in Choo and Kim[4]. Thus this work is an extension of that in [4].

The objective functional is defined as

$$J(u) = \int_0^T \sum_{\ell \in I} \{\tilde{y}_\ell(t) - y_\ell(t)\}^2 + \sum_{j=1}^{m} u_j^2(t) \, dt \tag{1.3}$$

where I is an index subset of $\{i | 1 \le i \le n\}$ and $\tilde{y}_\ell$ is the index function of interest. In the case that (1.1)–(1.2) are the mathematical model for NF-κB(Nuclear Factor kappaB) pathway, an index function may be the profile of the concentration of nuclear NF-κB, the protein that regulates the expression of numerous genes involved in cell cycle, migration, apoptosis, tumorigenesis, inflammation, and various autoimmune diseases.

The aim of this study is to find an optimal control vector $u^* = (u_1^*, \cdots, u_m^*)$ satisfying

$$J(u^*) = \min_{u \in U} \int_0^T \sum_{\ell \in I} \{\tilde{y}_\ell(t) - y_\ell(t)\}^2 + \sum_{j=1}^{m} u_j^2(t) \, dt \tag{1.4}$$

where U is a control set.

In this paper, a general type of delay differential equations for describing dynamics of biological systems is considered. In section 2, we construct an

optimal system corresponding the control problem (1.1)–(1.4) which is used to find the optimal control terms. And we obtain the uniqueness of the optimal system. In section 3, we give the delay differential equations describing the NF-κB pathway for the application of the results in section 2.

2. Optimal system

In order to construct the existence theorem of optimal control terms, the theorem in Fleming and Rishel[6] was used to prove the existence of optimal control terms in Choo and Kim[4] in which all time delays in (1.1) are zero. Under the assumption of the existence of optimal control vectors satisfying (1.1)-(1.4), we will find the optimal control vector u^* and its corresponding state vector y^* through introducing another state variables called adjoint variables which satisfy some ODEs.

Definig $\delta_{ij} = \begin{cases} 1, & (i=j) \\ 0, & otherwise \end{cases}$ and $\eta_{ji}(t) = \begin{cases} 1, & (t \le T-\tau_{ji}) \\ 0, & otherwise \end{cases}$,
we obtain the following theorem about the optimal system.

Theorem 2.1. *Let u^* and y^* be the optimal control vector and its corresponding solutions, respectively. Then there exist adjoint variables $\lambda_i (1 \le i \le n)$ satisfying the optimal system*

$$\dot{\lambda}_i(t) = 2\{\tilde{y}_i(t) - y_i^*(t)\}\delta_{\ell i} - \sum_{j=1}^{n} \eta_{ji}(t)\lambda_j(t+\tau_{ji}) \frac{\partial f_j(y^*_{\tau_j}(t+\tau_{ji}), u^*(t+\tau_{ji}))}{\partial y_{\tau_j,i}}, \ \ell \in I$$

with the transversality conditions

$$\lambda_i(T) = 0, \ 1 \le i \le n$$

where the optimal control terms u_j^* satisfy

$$u_j^*(t) = -\frac{1}{2}\sum_{i=1}^{n} \lambda_i(t) \frac{\partial f_i(y^*_{\tau_i}(t), u^*(t))}{\partial u_j}, \ j = 1, \cdots, m.$$

Proof. Using new functions $\lambda_i(t)(1 \le i \le n)$ with the transversality condition $\lambda_i(T) = 0$ and integration by parts, we obtain,

$$\begin{aligned} J(u) &= \int_0^T \sum_{\ell \in I} (\tilde{y}_\ell - y_\ell)^2 + \sum_{j=1}^{m} u_j^2 + \sum_{i=1}^{n} \lambda_i \{f_i(y_{\tau_i}, u) - \dot{y}_i\} dt \qquad (2.1) \\ &= \int_0^T \sum_{\ell \in I} (\tilde{y}_\ell - y_\ell)^2 + \sum_{j=1}^{m} u_j^2 + \sum_{i=1}^{n} \lambda_i f_i(y_{\tau_i}, u) + \sum_{i=1}^{n} \dot{\lambda} y_i \ dt + \sum_{i=1}^{n} \lambda_i(0) y_i(0). \end{aligned}$$

Since $y_{\tau_i}(t)$ varies depending on the values of u, replace $y_{\tau_i}(t)$ in (2.1) with $y_{\tau_i}(t,u)$ and apply $0 = \frac{d}{dx}J(u^* + xh)|_{x=0}$ for all h in an open ball centered at $0 \in R^m$. Then we obtain

$$0 = \int_0^T -2\sum_{\ell\in I}(\tilde{y}_\ell - y_\ell)\cdot\left.\frac{\partial y_\ell(t,u^*+xh)}{\partial x}\right|_{x=0} + 2\sum_{j=1}^{m} u_j^* h_j$$
$$+\sum_{i=1}^{n}\lambda_i\left\{\sum_{l=1}^{n}\frac{\partial f_i(y_{\tau_i},u^*)}{\partial y_{\tau_i,l}}\cdot\left.\frac{\partial y_{\tau_i,l}(t,u^*+xh)}{\partial x}\right|_{x=0} + \sum_{j=1}^{m}\frac{\partial f_i(y_{\tau_i},u^*)}{\partial u_j}h_j\right\}$$
$$+\sum_{i=1}^{n}\dot{\lambda}_i\left.\frac{\partial y_i(t,u^*+xh)}{\partial x}\right|_{x=0} dt$$

which implies the desired result. □

Following the idea of [11], we obtain the uniqueness theorem of the optimal system, optimal control vector, and its corresponding state vector.

Theorem 2.2. *Assume that the solutions of (1.1)–(1.2) and the optimal system are bounded and the followings hold.*

(i) $f_i(y_{\tau_i},u)(1\le i\le n)$ *are linear in* u.

(ii) $f_i(\cdot,u)$ *and* $\frac{\partial f_i(\cdot,\cdot)}{\partial\theta_j}(1\le i,j\le n)$ *satisfy the Lipschitz condition*

where θ_j *is* $y_{\tau_i,j}$ *or* u_j. *Then the optimal control vectors and the bounded solutions of the optimal system are unique for a sufficiently small* T.

Proof. Suppose μ_i and $z_i^*(1\le i\le n)$ are also the solutions of the optimal system in Theorem 2.1 with optimal control vector v^*. Then we obtain for $1\le i\le n$

$$\dot{\lambda}_i(t) - \dot{\mu}_i(t)$$
$$= 2\{z_i^*(t) - y_i^*(t)\}\delta_{\ell i} - \sum_{j=1}^{n}\eta_{ji}(t)\left\{\lambda_j(t+\tau_{ji})\frac{\partial f_j(y^*_{\tau_j}(t+\tau_{ji}),u^*(t+\tau_{ji}))}{\partial y_{\tau_j,i}}\right.$$
$$\left. - \mu_j(t+\tau_{ji})\frac{\partial f_j(z^*_{\tau_j}(t+\tau_{ji}),v^*(t+\tau_{ji}))}{\partial z_{\tau_j,i}}\right\},\quad \ell\in I,$$
$$\dot{y}_i^*(t) - \dot{z}_i^*(t) = f_i(y^*_{\tau_i}(t),u^*(t)) - f_i(z^*_{\tau_i}(t),v^*(t))$$

where

$$u_j^*(t) = -\frac{1}{2}\sum_{i=1}^{n}\lambda_i(t)\frac{\partial f_i(y^*_{\tau_i}(t),u^*(t))}{\partial u_j},$$
$$v_j^*(t) = -\frac{1}{2}\sum_{i=1}^{n}\mu_i(t)\frac{\partial f_i(z^*_{\tau_i}(t),v^*(t))}{\partial v_j}(j=1,\cdots,m).$$

Taking $y_i(t) = e^{st}\hat{y}_i(t)$, $z_i(t) = e^{st}\hat{z}_i(t)$, $\lambda_i(t) = e^{-st}\hat{\lambda}_i(t)$ and $\mu_i(t) = e^{-st}\hat{\mu}_i(t)$ for a constant s, we obtain

$$
\begin{aligned}
&-\{\dot{\hat{\lambda}}_i(t) - \dot{\hat{\mu}}_i(t)\} + s\{\hat{\lambda}_i(t) - \hat{\mu}_i(t)\} \qquad (2.2)\\
&= -2e^{2st}\{\hat{z}_i^*(t) - \hat{y}_i^*(t)\}\delta_{\ell i} - \sum_{j=1}^{n}\eta_{ji}\Big\{\hat{\lambda}_j(t+\tau_{ji})\frac{\partial f_j(y^*_{\tau_j}(t), u^*(t+\tau_{ji}))}{\partial y_{\tau_j,i}}\\
&\quad - \hat{\mu}_j(t+\tau_{ji})\frac{\partial f_j(z^*_{\tau_j}(t+\tau_{ji}), v^*(t+\tau_{ji}))}{\partial z_{\tau_j}}\Big\},\\
&\dot{\hat{y}}_i^*(t) - \dot{\hat{z}}_i^*(t) + s\{\hat{y}_i^*(t) - \hat{z}_i^*(t)\} \qquad (2.3)\\
&\quad = e^{-st}\{f_i(y^*_{\tau_i}(t), u^*(t)) - f_i(z^*_{\tau_i}(t), v^*(t))\}.
\end{aligned}
$$

Multiplying (2.2) and (2.3) by $\hat{\lambda}_i(t) - \hat{\mu}_i(t)$ and $\hat{y}_i^*(t) - \hat{z}_i^*(t)$, respectively, integrating the results, and using the boundedness of $\lambda_i, \mu_i, y_i^*, z_i^*$, the condition (i)–(ii), and the Cauchy-Schwarz inequality, we obtain for some constants C_1 and C_2,

$$
\begin{aligned}
&\sum_{i=1}^{n}\Big[\frac{1}{2}\{\dot{\hat{\lambda}}_i(0) - \dot{\hat{\mu}}_i(0)\}^2 + \{\hat{y}_i^*(T) - \hat{z}_i^*(T)\}^2\\
&\quad + s\int_0^T \{\hat{\lambda}_i(t) - \hat{\mu}_i(t)\}^2 + \{\hat{y}_i^*(t) - \hat{z}_i^*(t)\}^2 dt\Big]\\
&\le (C_1 + C_2e^{2sT})\sum_{i=1}^{n}\int_0^T \{\hat{\lambda}_i(t) - \hat{\mu}_i(t)\}^2 + \{\hat{y}_i^*(t) - \hat{z}_i^*(t)\}^2 dt.
\end{aligned}
$$

It follows from the just above inequality that for $1 \le i \le n$,

$$
(s - C_1 - C_2e^{2sT})\int_0^T \{\hat{\lambda}_i(t) - \hat{\mu}_i(t)\}^2 + \{\hat{y}_i^*(t) - \hat{z}_i^*(t)\}^2 dt \le 0.
$$

Choosing s such that $s - C_1 - C_2e^{2sT} > 0$ for sufficiently small T, the equalities $\lambda_i = \mu_i$, $y_i^* = z_i^*$, and $u_i^* = v_i^* (1 \le i \le n)$ hold . Thus the proof is complete. □

3. Application of parameters' optimization to the NF-κB pathway

In this section, we apply optimization obtained in section 2 to the mathematical model for the NF-κB pathway which plays crucial roles in cellular responses to various conditions, such as growth factors, hypoxia, infections, and physical stress stimuli. And the activation of NF-κB is constitutively increased in many types of cancer. Then the NF-κB pathway is one of drug targets for treating cancer.

Under normal conditions, NF-κB is kept in the cytoplasm by the inhibitor protein IκB. When IκB kinase(IKK) phosphorylates IκB, NF-κB is released from its inhibitor IκB and then translocates into the nucleus and activates gene IκB, giving rise to a negative feedback loop. This process can be modeled as follows(see [15]).

$$\begin{aligned}
\frac{dN}{dt} &= -a_1 N \cdot I + d_1 N : I + r_1 N : I : K + g_2 N : I - i_N N + e_N N_n \quad (3.1)\\
\frac{dI}{dt} &= -a_1 N \cdot I + d_1 N : I - a_3 I \cdot K + d_3 I : K + s N_n(t-\tau)\\
&\quad - (g_1 + i_I) I + e_I I_n\\
\frac{dN:I}{dt} &= a_1 N \cdot I - d_1 N : I - a_2 (N:I) \cdot K + d_2 N : I : K - g_2 N :\\
&\quad I + e_{N:I} N_n : I_n\\
\frac{dN_n}{dt} &= -a_1 N_n \cdot I_n + d_1 N_n : I_n + i_N N - e_N N_n\\
\frac{dI_n}{dt} &= -a_1 N_n \cdot I_n + d_1 N_n : I_n + i_I I - e_I I_n\\
\frac{dN_n:I_n}{dt} &= a_1 N_n \cdot I_n - d_1 N_n : I_n - e_{N:I} N_n : I_n\\
\frac{dK}{dt} &= k(t) - a_2 (N:I) \cdot K + (d_2 + r_1) N : I : K - a_3 I \cdot K\\
&\quad + (d_3 + r_2) I : K\\
\frac{dI:K}{dt} &= a_3 I \cdot K - (d_3 + r_2) I : K\\
\frac{dN:I:K}{dt} &= a_2 (N:I) \cdot K - (d_2 + r_1) N : I : K
\end{aligned}$$

where N, I, K, N_n, and I_n represent concentrations of NF-κB, IκB,IKK, nuclear NF-κB, and nuclear IκB, respectively. All lowercase symbols are positive parameters in Hoffman et al[8]. And the symbol "$A \cdot B$" means the product of A and B, and the symbol "$A : B$" the concentration of the complex of A and B.

Let the index function be the known profile $\tilde{N}_n$ of the concentration of nuclear NF-κB and the control terms are the association/dissociation rate constants a_1, d_1 of NF-κB and IκB. Then all $\tau_{ji} = 0$ except for $\tau_{24} = \tau > 0$, so we obtain the optimal system in section 2 with (3.1) and $y_1 = N$, $y_2 = I$, $y_3 = N : I$, $y_4 = N_n$, $y_5 = I_n$, $y_6 = N_n : I_n$, $y_7 = K$, $y_8 = I : K$, and $y_9 = N : I : K$.

$$\begin{aligned}
\dot{\lambda}_1(t) &= 2\{\tilde{N}_n(t) - N_n^*(t)\}\delta_{41} - \sum_{j=1}^{9} \eta_{j1}(t)\lambda_j(t+\tau_{j1}) \frac{f_j(y^*_{\tau_j}(t+\tau_{j1}), u^*(t+\tau_{j1}))}{\partial y_{\tau_j,1}}\\
&= -\big\{\lambda_1 \cdot (-a_1^* I^* - i_N) + \lambda_2 \cdot (-a_1^* I^*) + \lambda_3 \cdot a_1^* I^*\big\},\\
\dot{\lambda}_2(t) &= -\big\{\lambda_1 \cdot (-a_1^* N^* - i_N) + \lambda_2 \cdot (-a_1^* N^* - a_3 K^* - g_1 - i_I) + \lambda_3 \cdot a_1^* N^*\\
&\quad + \lambda_5 \cdot i_I + \lambda_7 \cdot (-a_3 K^*) + \lambda_8 \cdot a_3 K^*\big\},
\end{aligned}$$

$$\dot{\lambda}_3(t) = -\{\lambda_1 \cdot (d_1^* + g_2) + \lambda_2 \cdot d_1^* + \lambda_3 \cdot (-d_1^* - a_2 K^* - g_2) + \lambda_7 \cdot (-a_2 K^*) + \lambda_9 \cdot a_2 K^*\},$$

$$\dot{\lambda}_4(t) = 2(\tilde{N}_n - N_n) - \{\lambda_1 \cdot e_N + \lambda_2(t+\tau) \cdot s + \lambda_4 \cdot (-a_1^* I_n^* - e_N) + \lambda_5 \cdot (-a_1 * I_n^*) + \lambda_6 \cdot a_1 I_n^*\},$$

$$\dot{\lambda}_5(t) = -\{\lambda_2 \cdot e_I + \lambda_4 \cdot (-a_1^* N_n^*) + \lambda_5 \cdot (-a_1^* N_n^* - e_I) + \lambda_6 \cdot a_1^* N_n^*\},$$

$$\dot{\lambda}_6(t) = -\{\lambda_3 \cdot e_{N:I} + \lambda_4 \cdot d_1^* + \lambda_5 \cdot d_1^* + \lambda_6 \cdot (-d_1^* - e_{N:I})\},$$

$$\dot{\lambda}_7(t) = -\{\lambda_2 \cdot (-a_3 I^*) + \lambda_3 \cdot (-a_2 (N:I)^*) + \lambda_7 \cdot (-a_2 (N:I)^* - a_3 I^*) + \lambda_8 \cdot a_3 I^* + \lambda_9 \cdot a_2 (N:I)^*\},$$

$$\dot{\lambda}_8(t) = -\{\lambda_2 \cdot d_3 + \lambda_7 \cdot (d_3 + r_2) + \lambda_8 \cdot (-d_3 - r_2)\},$$

$$\dot{\lambda}_9(t) = -\{\lambda_1 \cdot r_1 + \lambda_3 \cdot d_2 + \lambda_7 \cdot (d_2 + r_1) + \lambda_9 \cdot (-d_2 - r_1)\}$$

where optimal control terms are

$$a_1^* = \frac{1}{2}\{(\lambda_1 + \lambda_2 - \lambda_3) N^* \cdot I^* + (\lambda_4 + \lambda_5 - \lambda_6) N_n^* \cdot I_n^*\},$$

$$d_1^* = -\frac{1}{2}\{(\lambda_1 + \lambda_2 - \lambda_3)(N:I)^* + (\lambda_4 + \lambda_5 - \lambda_6)(N_n : I_n)^*\}.$$

Remark 1. Since the equation (3.1) satisfies the conditions (i)–(ii) in theorem 2.2, the optimal control vectors and the bounded solutions of the optimal system for (3.1) are unique for a sufficiently small T.

Remark 2. Studying numerical schemes for solving the optimal system and applying these results to specific biological systems are future studies.

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