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OPTIMIZATION OF PARAMETERS IN MATHEMATICAL MODELS OF BIOLOGICAL SYSTEMS

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ABSTRACT. Under pathological stress stimuli, dynamics of a biological system can be changed by alteration of several components such as functional proteins, ultimately leading to disease state. These dynamics in disease state can be modeled using differential equations in which kinetic or system parameters can be obtained from experimental data. One of the most effective ways to restore a particular disease state of biology system (i.e., cell, organ and organism) into the normal state makes optimization of the altered components usually represented by system parameters in the differential equations. There has been no such approach as far as we know. Here we show this approach with a cardiac hypertrophy model in which we obtain the existence of the optimal parameters and construct an optimal system which can be used to find the optimal parameters.

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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],[6]-[8],[10]). But if a biological system is under pathological stimuli such as hypertension, ischemic heart disease and cardiomyopathy, values of some parameters are changed depending on a specific disease; thereby system dynamics are also changed to another one no longer normal. In this case, to restore the undesired (diseased) responses into the nominal ones, we should consider the control of the parameters altered by stress condition but generally changing all these parameters is not physical or pharmacological approach to treat disease([2],[4],[11]). Thus, we

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must determine how to obtain the desired profiles by changing only a portion of the altered parameters.

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. Although there are a large number of studies based on optimization, there are few studies on this topic as far as we know. Joshi[9] studied on the mathematical model describing the interaction of HIV and T-cells by using optimization. Consider the differential equations

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

with initial conditions

$$y_i(0) = y_i^0 \tag{1.2}$$

where n, m are natural numbers, the state vector $y = (y_1, \cdots, y_n)$ with state variables y_i's and the control vector $u = (u_1, \cdots, u_m)$ with control terms u_j's$(1 \leq j \leq m)$.

The objective functional is defined as

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

where I is an index subset of $\{i|1 \leq i \leq n\}$ and $\tilde{y}_\ell$ is the index function of interest such as the profile of action potential or calcium concentration under non-stress condition.

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

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

where U is a control set.

In this paper, a general type of differential equations for describing dynamics of biological systems is considered. In section 2, we introduce the theorem used to prove the existence of optimal control terms and an example which satisfy the conditions of the theorem. In section 3, 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.

2. Existence of optimal control terms

In order to construct the existence theorem of optimal control terms, we recall the theorem in Fleming and Rishel[5] which is used to prove the existence of optimal control terms. Consider a control problem with system equations $\dot{x} = g(x(t), u(t)), t_0 \leq t \leq t_1, u \in U$ and objective functional $J(u) =$

$\int_{t_0}^{t_1} L(x(t), u(t))\, dt$, where the vector valued function g is defined on D. Let $\|\cdot\|$ be the L^2-norm. Then the following theorem holds.

Theorem 2.1. *Assume that for some positive constant $C_i (i = 1, 2, 3, 4)$, $\gamma > 1$, function $g_i (i = 1, 2)$, and all $x, x_1, x_2 \in D$, $u \in U$,*

(a) *g and L are continuous;*
(b) $\|g(x, u)\| \leq C_1(1 + \|x\| + \|u\|)$;
(c) $\|g(x_1, u) - g(x_2, u)\| \leq C_2\|x_1 - x_2\|(1 + \|u\|)$;
(d) *The set of controls and corresponding state variables is non-empty;*
(e) *The control set U is convex and closed;*
(f) $g(x, u) = g_1(x) + g_2(x)u$;
(g) *$L(x, \cdot)$ is convex on U;*
(h) $L(x, u) \geq C_3\|u\|^\gamma - C_4$.

Then there exists an optimal control vector u^* minimizing $J(u)$ on U.

Note that $g_2(x)u$ means the linear function in u and has values in the codomain of the function g_2.

We assume that

$$0 \leq u_j(t) \leq a_j, \quad f(y(t), u(t)) = \alpha(y(t)) + \beta(y(t))u(t) \tag{2.1}$$

where $a_j (1 \leq j \leq m)$ are positive constant and α, β are continuous functions satisfying the Lipschitz condition in every closed bounded subset of R^n. The assumption (2.1) is satisfied in many mathematical models of biological systems. Under the assumption (2.1), the control problem (1.1)–(1.2) satisfies (a),(d)–(h) of Theorem 2.1 with $g = f$, $x = y$, $g_1 = \alpha$ and $g_2 = \beta$. Thus we obtain the following existence theorem of the optimal control vector to the problem (1.1)–(1.3).

Theorem 2.2. *Assume that the condition (2.1) and the followings hold.*

(i) $U = \{u = (u_1, \cdots, u_m)) \mid u_j$ *is measurable,* $0 \leq u_j(t) \leq a_j,\ t \in [0, T], 1 \leq j \leq m\}$.
(ii) *The solutions of (1.1)–(1.2) are bounded. That is, there exists a bounded subset D_f of R^n containing all the solutions of (1.1).*
(iii) *f is defined on D_f and satisfies (b)–(c) of Theorem 2.1.*

Then there exists an optimal control vector u^* minimizing $J(u)$ on U.

Conventional equations for biochemical reactions are based on the law of mass action. Thus there are a large number of mathematical models of biological systems satisfying mass conservation which makes the solutions of these equations bounded in finite time intervals. In addition, the nonlinear terms of f are usually products of state variables or Hill-types like y_1y_2 or $\dfrac{y_1y_2^h}{k + y_2^h}$ for constants k and h. The boundedness of solutions and this nonlinear form of (2.1) make f satisfy (b)–(c) of Theorem 1 on a bounded domain containing all the values of the solutions. For example, the following mathematical equations describe the calcineurin-NFAT(nuclear factor of activated T-cells) signaling pathway which plays crucial roles in development of cardiac hypertrophy, in particular, under the pathological stress stimuli that mediate elevation of intracellular calcium([12]). Cardiac hypertrophy is a thickening of the heart muscle (myocardium) which results in a decrease in size of the chamber of the heart, including the left and right ventricles:

$$\begin{aligned}
\frac{d[CaN_{free}]}{dt} &= -k_{a1}[CaN_{free}][Ca^{2+}] + k_{d1}[CaN_{act}], \qquad (2.2)\\
\frac{d[CaN_{comp}]}{dt} &= k_{a2}[CaN_{act}]\frac{[MCIP]^{16}}{k_{th}^{15}+[MCIP]^{15}} - k_{d2}[CaN_{comp}]\frac{[CaN_{act}]^5}{k_{m3}^5+[CaN_{act}]^5},\\
[CaN_{tot}] &= [CaN_{free}] + [CaN_{act}] + [CaN_{comp}],\\
\frac{d[NFAT_{cyt}]}{dt} &= \frac{k_{c1}[NFAT_{cyt}^p][CaN_{act}]^5}{k_{m1}^5+[CaN_{act}]^5} - (l_{ctu}+k_{r1})[NFAT_{cyt}]\\
&\quad + l_{utc}[NFAT_{nuc}],\\
\frac{d[NFAT_{nuc}]}{dt} &= l_{ctu}[NFAT_{cyt}] - l_{utc}[NFAT_{nuc}] - \frac{k_{c2}[GPP][NFAT_{nuc}]}{k_{m2}+[NFAT_{nuc}]},\\
[NFAT_{tot}] &= [NFAT_{cyt}^p] + [NFAT_{cyt}] + [NFAT_{nuc}],\\
\frac{d[MCIP]}{dt} &= \frac{v([NFAT_{nuc}]+cof)^{17}}{k_{nuc}^{17}+([NFAT_{nuc}]+cof)^{17}} - k_{d2}[CaN_{act}]\frac{[MCIP]^{16}}{k_{th}^{15}+[MCIP]^{15}}\\
&\quad + k_{d2}[CaN_{comp}]\frac{[CaN_{act}]^5}{k_{m3}^5+[CaN_{act}]^5} - k_{deg}[MCIP].
\end{aligned}$$

Here the state variables are $[CaN_{free}]$, $[CaN_{comp}]$, $[NFAT_{cyt}]$, $[NFAT_{nuc}]$, $[MCIP]$. And $[CaN_{free}]$, $[CaN_{comp}]$, $[CaN_{act}]$, $[CaN_{tot}]$ are the concentrations of free, complex, active and total calcineurin, respectively, and $[NFAT_{cyt}]$, $[NFAT_{nuc}]$, $[NFAT_{cyt}^p]$, $[NFAT_{tot}]$ are the concentrations of cytoplasmic, nuclear, phosphorylated cytoplasmic, and total NFAT, respectively, $[MCIP]$ is the concentration of MCIP(Modulatory calcineurin-interacting protein), and $[CaN_{tot}], [NFAT_{tot}]$ are positive constants. For more details, refer to [12].

In this example, the index function can be $[NFAT_{nuc}]$ which is the profile of the concentration of the protein NFAT in the nucleus under non-stress condition because the nuclear NFAT can incur a hypertrophic response. Then the control terms can be l_{ctu}(import rate constant of NFAT from cytoplasm to nucleus) and l_{utc}(export rate constant of NFAT from nucleus to cytoplasm). Using the existence theorem of solutions of ODEs, the equations (2.2) and objective functional (1.3) satisfy the conditions in Theorem 2.2 so that there exists an optimal control vector.

3. Optimal system

Without loss of generality, we assume $I = \{1\}$ and $m = 2$ in (1.1)–(1.4). To find the optimal control vector u^* and its corresponding state vector y^*, we introduce another state variables called adjoint variables which satisfy some ODEs.

Theorem 3.1. *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*

$$\dot{\lambda}_1(t) = -2\{\tilde{y}_1(t) - y_1^*(t)\} - \sum_{i=1}^{n} \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_1},$$
$$\dot{\lambda}_j(t) = -\sum_{i=1}^{n} \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_j}, \ 2 \le j \le n$$

with the transversality condition

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

And the optimal control terms u_1^* and u_2^* satisfy

$$u_k^*(t) = -\frac{1}{2} \sum_{i=1}^{n} \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial u_k}, \ k = 1, 2.$$

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,

$$\begin{aligned} J(u) &= \int_0^T \{\tilde{y}_1(t) - y_1(t)\}^2 + \sum_{j=1}^{2} u_j^2(t) + \sum_{i=1}^{n} \lambda_i(t)\{f_i(y(t), u(t)) - \dot{y}_i(t)\}dt \qquad (3.1) \\ &= \int_0^T \{\tilde{y}_1(t) - y_1(t)\}^2 + \sum_{j=1}^{2} u_j^2(t) + \sum_{i=1}^{n} \lambda_i(t) f_i(y(t), u(t)) + \sum_{i=1}^{n} \dot{\lambda}_i(t) y_i(t)dt \\ &\quad + \sum_{i=1}^{n} \lambda_i(0) y_i^0. \end{aligned}$$

Since $y_i(t)$ varies depending on the values of u, replace $y_i(t)$ in (3.1) with $y_i(t, u)$ and apply $\frac{d}{dx} J(u^* + xh)|_{x=0} = 0$ for all h in an open ball centered at $0 \in R^m$. Then we can obtain the desired result. □

Using Theorem 3.1, we get the optimal system and optimal control terms of (2.2):

$$\dot{\lambda}_1 = -2(\tilde{y}_4 - y_4^*) - \lambda_1\Big(- k_{a1}[Ca^{2+}] - k_{d1}\Big) - \lambda_2 \left\{ -k_{a2}\frac{(y_5^*)^{16}}{k_{th}^{15} + (y_5^*)^{15}} - k_{d2}y_2^*\delta_3^{act} \right\}$$
$$- \lambda_3 k_{c1}[NFAT_{cyt}^p]\delta_1^{act} - \lambda_5 \left\{ k_{a2}\frac{(y_5^*)^{16}}{k_{th}^{15} + (y_5^*)^{15}} + k_{d2}y_2^*\delta_3^{act} \right\},$$
$$\dot{\lambda}_2 = +\lambda_1 k_{d1} - \lambda_2 \left\{ -k_{a2}\frac{(y_5^*)^{16}}{k_{th}^{15} + (y_5^*)^{15}} - k_{d2}\left(\frac{(z^*)^5}{k_{m3}^5 + (z^*)^5} + y_2^*\delta_3^{act} \right) \right\}$$
$$- \lambda_3 k_{c1}[NFAT_{cyt}^p]\delta_1^{act} - \lambda_5 \left\{ k_{a2}\frac{(y_5^*)^{16}}{k_{th}^{15} + (y_5^*)^{15}} + k_{d2}\left(\frac{(z^*)^5}{k_{m3}^5 + (z^*)^5} + y_2^*\delta_3^{act} \right) \right\},$$
$$\dot{\lambda}_3 = -\lambda_3 \left(k_{c1}\frac{(z^*)^5}{k_{m1}^5 + (z^*)^5} - u_1^* - k_{r1} \right) - \lambda_4 u_1^*,$$
$$\dot{\lambda}_4 = -\lambda_3 \left(k_{c1}\frac{(z^*)^5}{k_{m1}^5 + (z^*)^5} + u_2^* \right) - \lambda_4 \left\{ -u_2^* - k_{c2}[GPP]\frac{k_{m2}}{(k_{m2} + y_4^*)^2} \right\} + \lambda_5 v\delta_4,$$
$$\dot{\lambda}_5 = -\lambda_2 k_{a2} z^* \delta_5 + \lambda_5(k_{d2}z^*\delta_5 + k_{deg})$$

and

$$u_1^* = -(-\lambda_3 + \lambda_4)y_3^*/2, \quad u_2^* = -(\lambda_3 - \lambda_4)y_4^*/2$$

where

$$y_1 = [CaN_{free}],\ y_2 = [CaN_{comp}],\ y_3 = [NFAT_{cyt}],$$
$$y_4 = [NFAT_{nuc}],\ y_5 = [MCIP],\ z = [CaN_{act}],$$
$$\delta_i^{act} = \frac{5k_{mi}^5 z^4}{\{k_{mi}^5 + (z^*)^5\}^2}(i = 1,3),\quad \delta_4 = \frac{17k_{nuc}^{17}(y_4^* + cof)^{16}}{\{k_{nuc}^{17} + (y_4^* + cof)^{17}\}^2},$$
$$\delta_5 = \frac{(y_5^*)^{15}\{16k_{th}^{15} + (y_5^*)^{15}\}}{\{k_{th}^{15} + (y_5^*)^{15}\}^2}.$$

Following the idea of [9], we obtain the uniqueness theorem of the optimal system.

Theorem 3.2. *Assume that f satisfies the conditions of Theorem 2.2 and $\dfrac{\partial f_i(\cdot, u(t))}{\partial y_j}(1 \le i,j \le n)$ satisfies the Lipschitz condition in the domain D_f. Then 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 3.1 with optimal control terms v^*. Then we obtain

$$\begin{aligned}
\dot{\lambda}_1(t) - \dot{\mu}_1(t) &= -2\{z_1^*(t) - y_1^*(t)\} \\
&\quad - \sum_{i=1}^{n} \left\{ \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_1} - \mu_i(t) \frac{\partial f_i(z^*(t), v^*(t))}{\partial z_1} \right\}, \\
\dot{\lambda}_j(t) - \dot{\mu}_j(t) &= -\sum_{i=1}^{n} \left\{ \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_j} - \mu_i(t) \frac{\partial f_i(z^*(t), v^*(t))}{\partial z_j} \right\}, \\
&\quad 2 \le j \le n, \\
\dot{y}_i^*(t) - \dot{z}_i^*(t) &= f_i(y^*(t), u^*(t)) - f_i(z^*(t), v^*(t)), \quad 1 \le i \le n,
\end{aligned}$$

where $u_k^*(t) = -\frac{1}{2} \sum_{i=1}^{n} \lambda_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial u_k}$ and

$$v_k^*(t) = -\frac{1}{2} \sum_{i=1}^{n} \mu_i(t) \frac{\partial f_i(z^*(t), v^*(t))}{\partial v_k} (k = 1, 2).$$

Note that $\frac{\partial f_i(y^*(t), u^*(t))}{\partial u_j} = \frac{\partial f_i(z^*(t), v^*(t))}{\partial v_j}$ since f is linear in u.

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

$$\begin{aligned}
&- \{\dot{\hat{\lambda}}_1(t) - \dot{\hat{\mu}}_1(t)\} + s\{\hat{\lambda}_1(t) - \hat{\mu}_1(t)\} \qquad (3.2) \\
&= -2e^{2st}\{\hat{z}_1^*(t) - \hat{y}_1^*(t)\} - \sum_{i=1}^{n} \left\{ \hat{\lambda}_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_1} - \hat{\mu}_i(t) \frac{\partial f_i(z^*(t), v^*(t))}{\partial z_1} \right\}, \\
&- \left\{\dot{\hat{\lambda}}_j(t) - \dot{\hat{\mu}}_j(t)\right\} + s\{\hat{\lambda}_j(t) - \hat{\mu}_j(t)\} \qquad (3.3) \\
&= \sum_{i=1}^{n} \left\{ \hat{\lambda}_i(t) \frac{\partial f_i(y^*(t), u^*(t))}{\partial y_j} - \hat{\mu}_i(t) \frac{\partial f_i(z^*(t), v^*(t))}{\partial z_j} \right\}, \\
&\dot{\hat{y}}_i^*(t) - \dot{\hat{z}}_i^*(t) + s\{\hat{y}_i^*(t) - \hat{z}_i^*(t)\} \qquad (3.4) \\
&\quad = e^{-st}\left\{ f_i(y^*(t), u^*(t)) - f_i(z^*(t), v^*(t)) \right\}.
\end{aligned}$$

Multiplying (3.2), (3.3) and (3.4) by $\hat{\lambda}_1(t) - \hat{\mu}_1(t)$, $\hat{\lambda}_j(t) - \hat{\mu}_j(t)$ and $\hat{y}_i^*(t) - \hat{z}_i^*(t)$, respectively, integrating the results, and using the boundedness of $\lambda_i, \mu_i, y_i^*, z_i^*$ and the Cauchy-Schwarz inequality, we obtain for some constant C_1 and C_2,

$$\sum_{i=1}^{n}\left[\frac{1}{2}\{\dot{\hat{\lambda}}_i(0)-\dot{\hat{\mu}}_i(0)\}^2+\left\{\hat{y}_i^*(T)-\hat{z}_i^*(T)\right\}^2\right.$$
$$\left.+s\int_0^T\{\dot{\hat{\lambda}}_i(t)-\dot{\hat{\mu}}_i(t)\}^2+\{\hat{y}_i^*(t)-\hat{z}_i^*(t)\}^2dt\right]$$
$$\leq\left(C_1+C_2e^{2sT}\right)\sum_{i=1}^{n}\int_0^T\left\{\dot{\hat{\lambda}}_i(t)-\dot{\hat{\mu}}_i(t)\right\}^2+\left\{\hat{y}_i^*(t)-\hat{z}_i^*(t)\right\}^2dt.$$

It follow from the just above inequality that for $1\leq i\leq n$,

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

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

Remark 1. We can take the proposed approach to finding optimal system for delay differential equations: Consider the following delay differential equations

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

with initial conditions

$$y_i(t)=g_i(t)\qquad -\tau_i\leq t\leq 0$$

and the object functional

$$J(u)=\int_0^T\{\tilde{y}_1(t)-y_1(t)\}^2+\sum_{j=1}^{2}u_j^2(t)\ dt.$$

Here $y_\tau(t)=(y_1(t-\tau_1),\cdots,y_n(t-\tau_n))$ and $u(t)=(u_1(t),u_2(t))$.

Then the optimal control terms u_1^* and u_2^* satisfy

$$u_k^*(t)=-\frac{1}{2}\sum_{i=1}^{n}\lambda_i(t)\frac{\partial f_i(y^*(t),y_\tau^*(t),u^*(t))}{\partial u_k},\ k=1,2,$$

subject to

$$\dot{y}_i^*(t)=f_i(y^*(t),y_\tau^*(t),u^*(t)),$$
$$\dot{\lambda}_i(t)=-2\{\tilde{y}_1(t)-y_1^*(t)\}\delta_{i1}$$
$$-\sum_{j=1}^{n}\left\{\lambda_j(t)\frac{\partial f_j(y^*(t),y_\tau^*(t),u^*(t))}{\partial y_i}\right.$$
$$\left.+\mu_i(t)\lambda_j(t+\tau_i)\frac{\partial f_j(y^*(t+\tau_i),y_\tau^*(t+\tau_i),u^*(t+\tau_i))}{\partial y_{\tau,i}}\right\}$$

with the initial and transversality conditions

$$y_i(t) = g_i(t), \quad \lambda_i(T) = 0, \quad -\tau_i \le t \le 0,\ 1 \le i \le n$$

where $y_{\tau,j}(t) = y_j(t-\tau_j)$, $\delta_{i1} = \begin{cases} 1, & (i=1) \\ 0, & otherwise \end{cases}$ and $\mu_i(t) = \begin{cases} 1, & (t \le T-\tau_i) \\ 0, & otherwise \end{cases}$.

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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