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REGULATION OF β-CATENIN IN THE WNT SIGNALING PATHWAY AND EMT VIA OPTIMAL CONTROL

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Abstract. In this paper, we present an optimal control strategy to prevent the EMT process by downregulating the level of overexpressed β-catenin in the cytoplasm. To do this, we propose a mathematical model that expresses relationship between the Wnt signaling pathway and TGF-β in cancer cells. We also define an optimal control problem considering the side effects that occur simultaneously with the method for controlling the concentration of β-catenin. Finally numerical simulations show that treatment effect is quantitatively changes depending on the concentration of core proteins of the Wnt signaling pathway.

1. Introduction

About 90% of cancer patient deaths are caused by metastasis [1]. Metastasis begins when cancer cells separate from primary cancer and infiltrate the surrounding blood vessels, and at this time, the cell's phenotype changes to a mesenchymal phenotype and has the ability to migrate [2]. This process is called epithelial-mesenchymal transition (EMT). Many signal transductions are involved in this process, and Wnt signaling pathway is the most representative [3], [4]. The Wnt signaling pathway is generally involved in cell differentiation and proliferation, but it causes the development and metastasis of cancer when it becomes excessively active [5]. The Wnt signaling pathway causes the accumulation of β-catenin in the cytoplasm. However, excessive accumulation of β-catenin can cause benign and malignant tumors, which is a clinically proven fact [6].

When the Wnt protein binds to a receptor located in the cell membrane, the function of the destructive complex is suppressed, and β-catenin is not decomposed normally. β-catenin accumulates and the concentration in the cytoplasm

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increases. The accumulated β-catenin enters the nucleus and promotes Slug protein, the family of transcription factors [7], [8]. The production of E-cadherin, which tightly connects cells to each other, is suppressed from Slug proteins, resulting in a decrease in adhesion between cells [9], [10]. As a result, the cell obtains ability to mobile and fall from the primary cancer and spreading to other organs. It was well known that the transforming growth factor-β (TGF-β), which is highly expressed in most cancer tissues, targets β-catenin in Wnt signaling pathway and increases the protein concentration in the cytoplasm to cause cancer [11].

Based on this biological perspective, the purpose of our study is to effectively control the concentration of abnormally accumulated β-catenin. To do this, a mathematical model expressing the relationship between the Wnt signaling pathway and TGF-β is proposed. Our result presents a control strategy that effectively reduces the concentration of β-catenin, considering the risks that may arise when reducing the β-catenin concentration. Herein, we consider the optimal control problem with one control using the optimal control theory. The dynamics of β-catenin concentrations are observed and compared using numerical simulations.

2. Mathematical model

In this section, we introduce a modified mathematical model (1) by adding the relationship between TGF-β and β-catenin to a model [12] that expresses the relationship between the core proteins of the Wnt signaling pathway by Hill equation.

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}t} &= \alpha_1 \frac{1}{1+(\frac{S}{IC_S})^{n_1}} - \beta_1 E,\\
\frac{\mathrm{d}B}{\mathrm{d}t} &= \alpha_2 \frac{1}{1+(\frac{E}{IC_E})^{n_2}} + k_1 \frac{(\frac{T}{IC_T})^{n_3}}{1+(\frac{T}{IC_T})^{n_3}} - \beta_2 B,\\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \alpha_3 + k_2 \frac{(\frac{B}{IC_B})^{n_4}}{1+(\frac{B}{IC_B})^{n_4}} - \beta_3 S,\\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_4 - \beta_4 T.
\end{aligned} \tag{1}$$

$E(t), B(t), S(t)$ and $T(t)$ mean as the concentrations of E-cadherin, β-catenin, Slug and TGF-β, respectively.

Within the Wnt signaling pathway in epithelial steady state, the basal production of β-catenin is reduced since the rate of binding of β-catenin-E-cadherin is relatively fast. Conversely, β-catenin, which is not bound to E-cadherin, decomposes naturally. The terms $\alpha_2 \dfrac{1}{1+(\frac{E}{IC_E})^{n_2}}$ and $\beta_2 B$ respectively refer to

this phenomenon. $k_1\dfrac{(\frac{T}{IC_T})^{n_3}}{1+(\frac{T}{IC_T})^{n_3}}$ shows that TGF-β promotes the expression of β-catenin by inhibiting the function of Glycogen synthase kinase-3 (GSK3). β-catenin accumulated above a certain level is translocated to the nucleus through nuclear pores. β-catenin translocated to the nucleus promotes the expression of Slug, which is expressed as the term $k_2\dfrac{(\frac{B}{IC_B})^{n_4}}{1+(\frac{B}{IC_B})^{n_4}}$. $\alpha_1\dfrac{1}{1+(\frac{S}{IC_S})^{n_1}}$ shows the process in which the expressed Slug inhibits the production of E-cadherin while binding to the promoter of E-cadherin, which connects cell-cell. The meaning of the parameters used in the model can be checked in the Table 1.

3. Optimal Control Problem

The goal of this section is to down-regulate the concentration of excessively expressed β-catenin in the cytoplasm, while minimizing side effects. A mathematical model considering a control, $u(t)$, is given by

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}t} &= \alpha_1\frac{1}{1+(\frac{S}{IC_S})^{n_1}} - \beta_1 E,\\
\frac{\mathrm{d}B}{\mathrm{d}t} &= \alpha_2\frac{1}{1+(\frac{E}{IC_E})^{n_2}} + k_1\frac{(\frac{T}{IC_T})^{n_3}}{1+(\frac{T}{IC_T})^{n_3}} - \beta_2(1+u(t))B,\\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \alpha_3 + k_2\frac{(\frac{B}{IC_B})^{n_4}}{1+(\frac{B}{IC_B})^{n_4}} - \beta_3 S,\\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_4 - \beta_4 T.
\end{aligned} \tag{2}$$

The control, $u(t)$, means effort that promotes β-catenin degradation.

Optimal control problem consists of minimizing the objective functional

$$J(u) = \int_0^{t_f}\left(AB(t) + \frac{C}{2}u(t)^2\right)dt$$

with $0 \le u(t) \le 1$. Herein, A and C are weight constants and $\dfrac{C}{2}u(t)^2$ expresses the cost of the treatment promoting β-catenin degaradation.

We search an optimal control function (u^*) such that

$$J(u^*) = min\left\{J(u) \mid u \in \Omega\right\}$$

subject to the system given by (2) and where the control set is

$$\Omega = \left\{u \mid u(t) \text{ is piecewise continuous on } [0, \mathrm{T}],\ 0 \le u(t) \le 1\right\}.$$

To find the optimal solution of the system, we first define the Lagrangian:

$$L = AB(t) + \frac{C}{2}u(t)^2.$$

Next, Hamiltonian function H for the optimal control problem is given as

$$\begin{aligned} H &= AB(t) + \frac{C}{2}u^2 \\ &+ \lambda_1 \left[\alpha_1 \frac{1}{1+(\frac{S}{IC_S})^{n_1}} - \beta_1 E \right] \\ &+ \lambda_2 \left[\alpha_2 \frac{1}{1+(\frac{E}{IC_E})^{n_2}} + k_1 \frac{(\frac{T}{IC_T})^{n_3}}{1+(\frac{T}{IC_T})^{n_3}} - \beta_2(1+u(t))B \right] \\ &+ \lambda_3 \left[\alpha_3 + k_2 \frac{(\frac{B}{IC_B})^{n_4}}{1+(\frac{B}{IC_B})^{n_4}} - \beta_3 S \right] \\ &+ \lambda_4 \left[\alpha_4 - \beta_4 T \right], \end{aligned}$$

where $\lambda_i, i = 1, 2, 3, 4$ are the adjoint variables.

By using Pontryagin's Maximum Principle, we obtain the necessary conditions as follows

$$\begin{aligned} \lambda_1'(t) &= -\frac{\partial H}{\partial E} \\ &= \lambda_1\beta_1 + \lambda_2 \left[\alpha_2 \frac{n_2}{IC_E} \left(\frac{E}{IC_E} \right)^{(n_2-1)} \frac{1}{(1+(\frac{E}{IC_E})^{n_2})^2} \right], \\ \lambda_2'(t) &= -\frac{\partial H}{\partial B} \\ &= -A + \lambda_2\beta_2(1+u(t)) - \lambda_3 \left[k_2 \frac{n_4}{IC_B} \left(\frac{B}{IC_B} \right)^{(n_4-1)} \frac{1}{(1+(\frac{B}{IC_B})^{n_4})^2} \right], \\ \lambda_3'(t) &= -\frac{\partial H}{\partial S} \\ &= \lambda_3\beta_3 + \lambda_1 \left[\alpha_1 \frac{n_1}{IC_S} \left(\frac{S}{IC_S} \right)^{(n_1-1)} \frac{1}{(1+(\frac{S}{IC_S})^{n_1})^2} \right], \\ \lambda_4'(t) &= -\frac{\partial H}{\partial T} \\ &= \lambda_4\beta_4 - \lambda_2 \left[k_1 \frac{n_3}{IC_T} \left(\frac{T}{IC_T} \right)^{(n_3-1)} \frac{1}{(1+(\frac{T}{IC_T})^{n_3})^2} \right], \end{aligned}$$

with the transversality conditions

$$\lambda_i(T) = 0, i = 1, 2, 3, 4.$$

Furthermore, the control function is shown as

$$u^*(t) = \frac{\lambda_2 \beta_2 B}{C}.$$

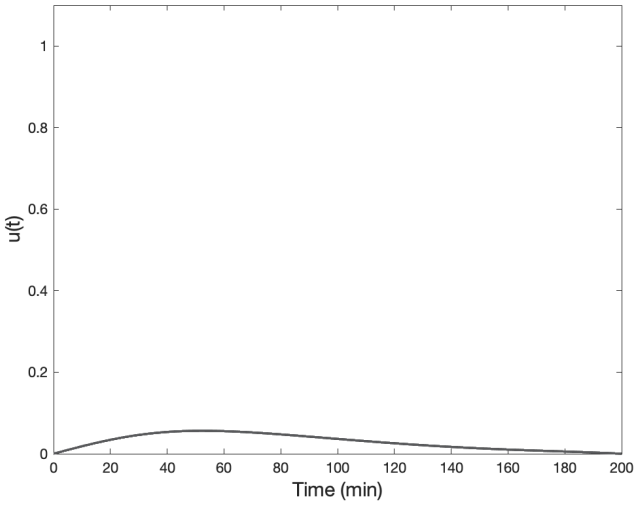
4. Results

In this section, we show the dynamics of β-catenin concentration considering one control by applying optimal control theory. The results are observed by setting $E(0) = 0.33, B(0) = 0, S(0) = 0$ and $T(0) = 0.16$ [12] as initial values and using MATLAB software. The Table 1 shows the meaning the values of the parameters used in simulation.

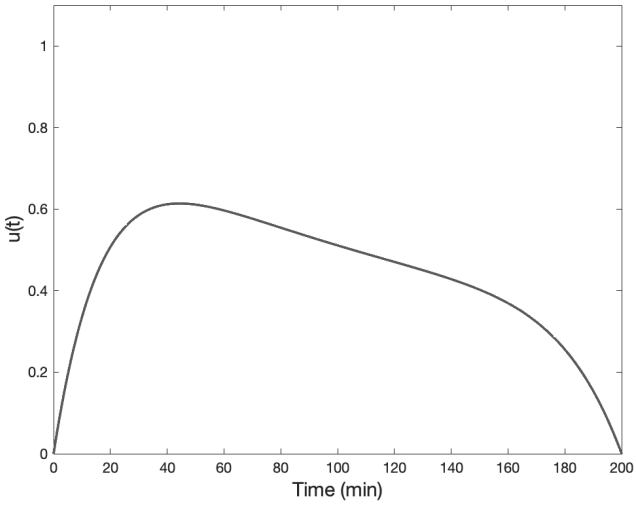
Par.	Description	Value	Unit	ref.
α_1	Basal production of E-cadherin	0.01	nM/min	[12]
α_2	Basal production of β-catenin	0.01	nM/min	[12]
α_3	Basal production of Slug	0.001	nM/min	[12]
α_4	Basal production of endogenous TGF-β	0.001	nM/min	[13]
β_1	Degradation rate of E-cadherin	0.03	1/min	[12]
β_2	Rate at which β-catenin binds to the GSK-3β/Axin/APC complex	0.03	1/min	[12]
β_3	Degradation rate of Slug	0.03	1/min	[12]
β_4	Degradation rate of TGF-β	0.01	1/min	[14]
k_1	Production rate of β-catenin	0.42	nM/min	[15]
k_2	Rate at which β-catenin translocates to the nucleus and activates the Slug	1	nM/min	[12]
IC_E	Half maximal concentration of E-cadherin required for sequestration of β-catenin at membrane	0.033	nM	[12]
IC_B	Half maximal concentration of β-catenin required to upregulate Slug	0.33	nM	[12]
IC_S	Half maximal concentration of Slug required to inhibit E-cadherin transcription	3.3	nM	[12]
IC_T	Half maximal concentration of TGF-β required to upregulate β-catenin	0.67	nM	assume
n_1	Hill coefficient	3	-	[12]
n_2	Hill coefficient	2	-	[12]
n_3	Hill coefficient	3	-	assume
n_4	Hill coefficient	2	-	[12]

TABLE 1. Parameters values

Figure 1 shows the optimal control function for $u(t)$. In the case of figure 1(a), the optimal control function is shown when the weight constant of the control, $u(t)$, is greater than the other constant. It can observe that the control works in very weakly overall. Conversely, the control is applied with a large

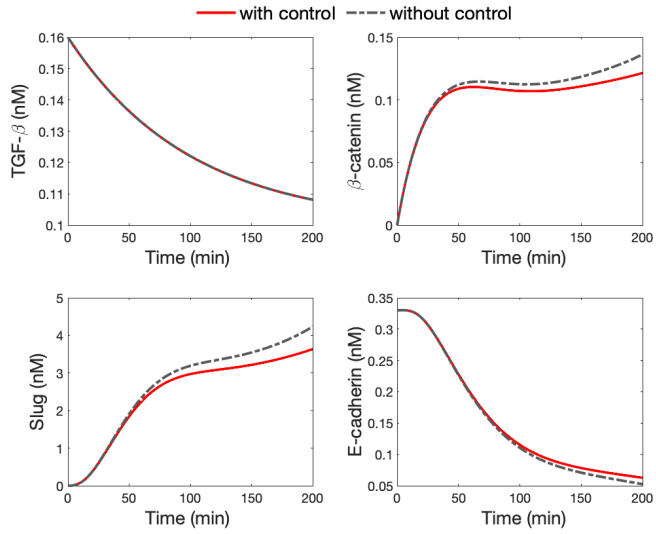


(a)

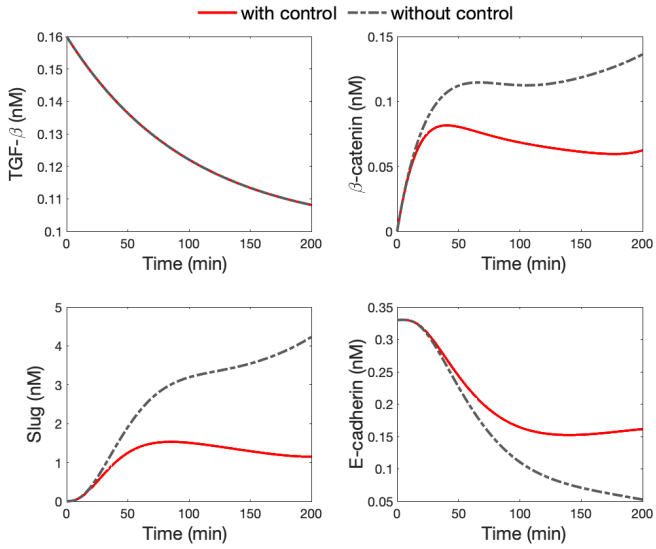


(b)

FIGURE 1. The optimal control function with the weight constant of (a) $A = 1, C = 10$ and (b) $A = 1, C = 0.1$.



(a)



(b)

FIGURE 2. Optimal solution for the concentration of core proteins of the Wnt signaling pathway in cases with the weight constant of (a) $A = 1, C = 10$ and (b) $A = 1, C = 0.1$.

value as a whole when the weight constant of the control is small. The control function initially increases the intensity rapidly to 0.6 and then decreases it from about 40 minutes (Fig.1(b)).

In figure 2, the concentrations of key proteins involved in the Wnt signaling pathway are shown with (solid line) and without (dashed and dot line) control. There is no significant difference between the concentrations of all proteins with control and without control in figure 2(a). However, in figure 2(b), the concentrations of Slug and β-catenin decrease under the influence of the control strategy. The concentration of E-cadaherin decreases at the beginning, but increases again to a certain level with the same effect. We can see that the concentration of β-catenin increases to about $0.14nM$ when not controlled, but finally decreases more than twice to about $0.06nM$ when the control strategy is considered. Conversely, at final time, the concentration of E-cadherin converges to zero when there is no control, but increases only to one-half of the initial concentration when the control is applied.

5. Discussion

Research on metastatic cancer and process is being actively conducted across many fields. However, it is difficult to accurately identify the metastasis phenomenon because the cell signal transduction system is complex, and there are limitations in experimental research on effective measures to prevent metastasis. This study quantitatively presents the effects of β-catenin-targeted treatment. We consider a control in the direction of promoting the degradation of β-catenin. Our goal is to down-regulate the concentration of overexpressed β-catenin in the cytoplasm using the control term. When the control is applied, it can be observed that the concentration of β-catenin is reduced by more than half compared to the situation without control. It also confirms that the concentration of E-cadherin in the cytoplasm, which converges to zero due to the overexpression of β-catenin, is increased to a certain level or more by applying a control.

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