Impulsive control of a nonlinear dynamical network and its application to biological networks

Min Luo¹ · Jianfeng Jiao¹ · Ruiqi Wang¹

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Abstract

The control of nonlinear dynamical systems is always a notable problem in science. According to control theory, suitable inputs for a controllable dynamical system are critical. Previous studies have shown some principles to determine control nodes and design control function. In this work, we propose a new control strategy of nonlinear systems by constructing impulsive control functions, i.e., we can realize the transition from an undesired state to a desired one by controlling appropriately chosen nodes in a discrete manner. In order to demonstrate the effectiveness of the strategy, we apply it to two biological networks: the epithelial–mesenchymal transition (EMT) network and the Notch1–Dll1–Jag1 signaling pathway. The strategy can not only be used to guide pharmacological design in a more feasible form but can also be applied into the fields of biological, medical and other multistable dynamical systems.

Keywords Nonlinear dynamical system · Control function · Impulsive · EMT network · Notch1–Dll1–Jag1 signaling pathway

1 Introduction

In recent years, one of the most notable problems in science and engineering has been the control of networks [1]. Although great effort has been devoted to deciphering the interaction between networks and dynamical processes taking place on various natural and technological systems, the control of dynamical biological networks remains an outstanding problem [2]. Previous studies have investigated the controllability of networks with linear dynamics [3] and how to determine the driving nodes [4]. Actually, almost all dynamical processes on networks are nonlinear. Therefore, the control of a nonlinear dynamical network must be considered and the controllability of nonlinear systems is similar to linear systems in many aspects [4, 5]. Many studies have focused on the controllability of nonlinear dynamical systems [6]. For instance, a nonlinear dynamical network, in which the nodes are distinct attractors of the system, has been introduced to investigate the transitions

✉ Ruiqi Wang
rqwang@shu.edu.cn

¹ Department of Mathematics, Shanghai University, Shanghai, China

between different attractors by applying the parameter perturbation technique [7]. Although there have been significant advances in controlling nonlinear dynamics in biological organisms in recent years, more effective and easily realized control strategies remain to be fully investigated.

According to control theory, a dynamical system is controllable if, with a suitable choice of input, it can be driven from any initial state to any desired final state within finite time [8]. A common feature of nonlinear dynamical systems is the existence of a number of distinct attractors [9]. For a disease-related nonlinear system, multiple types of stable states (attractors) can occur. Some of them correspond to healthy (desirable) states, while others are disease (undesirable) states. The main purpose here is to propose a more effective and easily realized control strategy by which the transition from a disease or pre-disease state to a healthy or normal state can be realized. It is hoped that the results presented here will provide a new perspective on how network dynamics is controlled by the impulsive strategy and further guidance for drug design in the biological and medical fields [10].

A previous study proposed a good principle to determine the driving nodes of the biological networks [5]. However, the complexity of the control function makes it difficult to realize in real biological systems. In this paper, we propose an impulsive control strategy by which the transition between two alternative stable states can be realized. Therefore, when multiple stable states corresponding to disease and healthy states exist, the transition from a disease state to a healthy one can be realized when spontaneous transition cannot be performed. We first construct an impulsive control system to model the process of periodically perturbing the driving nodes with appropriate impulsive control amounts, and further study its effects on the dynamics of the controlled system. We can realize the desired transition by changing the frequency and amplitude of the periodic stimuli. The EMT and the Notch1–Dll1–Jag1 networks are used to show the effectiveness of the proposed method. The results not only provide a perspective to understand the interactions between external stimuli and intrinsic physiological dynamics but also may lead to development of realistic artificial control strategy and medical therapy.

2 Theoretical result of impulse control

The nonlinear dynamics of networks can often be represented by a set of nonlinear ordinary differential equations. Without loss of generality, we consider an n -node network whose n -dimensional dynamical state $x(t)$ is described as:

$$\dot{x}(t) = F(x(t)), \quad (1)$$

where $F(x(t)) \in R^n$ is a nonlinear function, which is continuously differentiable with respect to x , $x(t) \in R^n$ is the state vector [11, 12]. If we add a control function $u(t)$ to system (1), we obtain the corresponding control system:

$$\dot{x}(t) = f(x(t), u(t)), \quad (2)$$

where $u(t) \subseteq R^m$ is the control function. It should be noted that system (2) is exactly system (1) when $u(t) = 0$.

Without loss of generality, we assume that nonlinear system (1) exhibits at least two stable steady states (attractors): $\bar{x}_1$ and $\bar{x}_2$ ($\bar{x}_1 \neq \bar{x}_2$). We postulate $\bar{x}_1$ is the ON state and $\bar{x}_2$ is the OFF state. In other words, the ON state is the disease state and we hope to transform it to a desirable and healthy OFF state. Based on the impulsive control theory, an artificial control strategy is proposed. When spontaneous transition from a disease state to a healthy

one cannot be achieved, an external input can be used to compensate the inefficiency of some regulations and thus induce a controlled transition. To address these problems, we consider the following control system:

$$\begin{cases} \dot{x}(t) = F(x(t)) + Bu(t), \\ x(t_0) = \bar{x}_1, t \in [t_0, t_f], \end{cases} \quad (3)$$

where $B \in R^{n \times m}$ ($m \leq n$) is the control input matrix. Matrix $B = \{e_{ij}\}$ consists of m column unit vectors with $e_{ij} = 1$ if controller j directly acts on variable (node) i and $e_{ij} = 0$ otherwise [12]. Without loss of generality, we assume that the first m variables are selected and controlled, i.e., the sub-matrix consisting of the first m row of B is an identity matrix.

For convenience, to prove the following theorem, we use the following notations:

$$\begin{aligned} x(t) &= (X(t), Y(t))^T, \\ \bar{x}_2 &= (\bar{X}_2, \bar{Y}_2)^T, \\ \dot{x}(t) &= (G(x(t)), H(x(t)))^T, \end{aligned}$$

where $X(t)$ and $Y(t)$ represent the controlled and uncontrolled nodes, respectively and

$$\begin{aligned} X(t) &= (x_1(t), x_2(t), \dots, x_m(t))^T \in R^m, \\ Y(t) &= (x_{m+1}(t), x_{m+2}(t), \dots, x_n(t))^T \in R^{n-m}, \\ \bar{X}_2 &= (\bar{x}_{2,1}, \bar{x}_{2,2}, \dots, \bar{x}_{2,m})^T \in R^m, \\ \bar{Y}_2 &= (\bar{x}_{2,m+1}, \bar{x}_{2,m+2}, \dots, \bar{x}_{2,n-m})^T \in R^{n-m}, \\ G(x(t)) &= (F_1(x), F_2(x), \dots, F_m(x))^T \in R^m, \\ H(x(t)) &= (F_{m+1}(x), F_{m+2}(x), \dots, F_n(x))^T \in R^{n-m}. \end{aligned}$$

Theorem 1 *Nonlinear system (3) can be impulsively controlled if there exists a impulsive control function $u(t) \subseteq R^m$ such that the corresponding solution $x(t)$ of system (3) satisfies $\lim_{t \rightarrow +\infty} x(t) = \bar{x}_2$. The time t is divided into a sequence with step size T , i.e., $t = t_0 + jT$ ($j = 1, 2, \dots, \infty$) and we assume that T is sufficiently small.*

Proof The proof includes two main steps. The first step is to determine the control variables that include m variables and the second step is to design the control function $u(t)$ and prove that system (3) can be controlled.

First, we show how to determine the index set of control variables that include m variables. Let K be an index set (possibly empty set) of variables. The purpose of K is to screen out the variables whose partial derivatives are not constantly negative. If there exists a time t and a state $x(t) \in R^n$ such that the following inequality:

$$\frac{\partial F_r(x(t))}{\partial x_r} \geq 0, \quad (4)$$

holds, then $r \in K$.

Let Q be an index set of variables containing q elements, $Q = \{1, \dots, q\}$, where q is the most smallest positive integer satisfying:

$$\begin{cases} N(p) \subseteq C, & p = m + 1; \\ N(p) \subseteq C \cup \{m + 1, \dots, p - 1\}, \\ & p \in \{m + 2, \dots, n\}, \end{cases} \quad (5)$$

where $C = Q \cup K = \{1, \dots, m\}$ is the index set of control variables, $\{m + 1, \dots, n\}$ is the index set of variables that do not need to be controlled and $N(p)$ is the index set of variables that are in the p -th equations of system (3) but exclude the index p . It is obvious

that $m \leq n$ [5]. Actually, the dynamical equation of the remaining variables $(x_{m+1}, \dots, x_n)$ are explicit functions of selected variables $(x_1, \dots, x_m)$.

Second, we design the control function as follows:

$$u(t) = \lambda(X(t) - \bar{X}_2), \quad (6)$$

where $\lambda < 0$.

Recall that the first m rows of B constitute an identity matrix. Substituting (6) into (3), we obtain:

$$\dot{X}(t) = G(x(t)) + u(t) \triangleq \bar{G}(x(t)). \quad (7)$$

Next, we divide time t with step size T , then, $t = t_0 + jT$ ($j = 1, 2, \dots, \infty$). A perturbation u_j is given at instants jT . For any controlled node $x_i(t) \in X(t) \in \mathbb{R}^m$, ($i = 1, 2, \dots, m$), we have:

$$x'_i(t_0 + jT) = x_i(t_0 + jT) + u_j, \quad (8)$$

$$u_j = \lambda(x_i(t_0 + jT) - \bar{x}_{2,i}), \quad (9)$$

where $\bar{x}_{2,i} \in \bar{X}_2$, $i = 1, 2, \dots, m$ [10].

We consider a sequence $x_i(t_0 + jT)$, $j = 1, 2, \dots, +\infty$. We only assess the case of $x_i(t_0) < \bar{x}_{2,i}$, (the proof is similar for the case of $x_i(t_0) > \bar{x}_{2,i}$), then $u_j > 0$. If we assume that T is sufficiently small and by using (9), we obtain:

$$x_i(t_0 + (j+1)T) \geq x_i(t_0 + jT),$$

$$u_{j+1} \geq u_j.$$

When a suitable λ is chosen, we can guarantee that the following equation holds:

$$\begin{aligned} x'_i(t_0 + (j+1)T) &= x_i(t_0 + (j+1)T) + u_{j+1} \\ &\geq x_i(t_0 + jT) + u_j \geq x'_i(t_0 + jT), \end{aligned}$$

which means that $x'_i(t_0 + jT)$ is a monotonically increasing and bounded sequence, therefore, its limit value exists and its supremum is $\bar{x}_{2,i}$, i.e.,

$$\lim_{j \rightarrow +\infty} x'_i(t_0 + jT) = \bar{x}_{2,i}.$$

Due to

$$\begin{aligned} \lim_{j \rightarrow +\infty} u_j &= 0, \\ \lim_{j \rightarrow +\infty} x_i(t_0 + jT) &= \bar{x}_{2,i}. \end{aligned}$$

Therefore, we have:

$$\lim_{j \rightarrow +\infty} X(t_0 + jT) = \bar{X}_2.$$

According to Theorem 3.1 in [5], when the formula $\lim_{t \rightarrow +\infty} X(t_0 + jT) = \bar{X}_2$ is satisfied, we have $\lim_{t \rightarrow +\infty} x(t) = \bar{x}_2$. $\square$

Remark 1 There are two fundamental problems in the control of nonlinear dynamical networks; one is how to identify the driving nodes and the other is how to design the impulsive control function. According to [5], we can obtain a strategy for identifying the driving nodes that are required to ensure that the system is controllable. Compared with [5], the impulsive

control function is more practical due to its simpler form. The impulsive control u_j at each time T is in a discrete form rather than a continuous one, which is more practical in guiding pharmacological design and medical therapy.

Remark 2 In the proof of Theorem 1, the stability of $\bar{x}_2$ is not required. Therefore, if $\bar{x}_2$ is an equilibrium point (no matter whether $\bar{x}_2$ is stable or not), the transition can be achieved. When $\bar{x}_2$ is stable, the impulsive control can be stopped after some times of perturbations due to the existence of an attractive region. Otherwise, the control can never be stopped.

Remark 3 In Theorem 1, we assume that time step T is sufficiently small. Actually, the transition can also be realized even for relatively larger T in simulating some biological networks.

3 Impulsive control of the EMT core network

We first applied the approach to the EMT core network as shown in Fig. 1a [13–15]. Its dynamics can be expressed as:

$$\begin{cases} \dot{x}_1 = \frac{1}{1+K_{12}x_2^2+K_{13}x_3^2+K_{14}x_4^2} - d_1x_1, \\ \dot{x}_2 = \frac{1}{1+K_{26}x_6^2} - d_2x_2, \\ \dot{x}_3 = \frac{x_2^2}{1+K_{32}x_2^2+K_{35}x_5^2} - d_3x_3, \\ \dot{x}_4 = \frac{x_2^2}{1+K_{42}x_2^2+K_{45}x_5^2+K_{46}x_6^2} - d_4x_4, \\ \dot{x}_5 = \frac{1}{1+K_{52}x_2^2+K_{53}x_3^2+K_{54}x_4^2} - d_5x_5, \\ \dot{x}_6 = \frac{1}{1+K_{62}x_2^2+K_{63}x_3^2+K_{64}x_4^2} - d_6x_6, \end{cases} \quad (10)$$

where x_i ($i = 1, \dots, 6$) represents the activity level of CDH1, SNAI1, ZEB1, ZEB2, miR-200, and miR-203, respectively. K_{ij} denotes the regulatory strength from node j to i and d_i is the degradation rate of x_i . The parameter values used to perform numerical simulations are $K_{ij} = 1$, $d_1 = 0.5$, $d_2 = 0.3$, $d_3 = 0.5$, $d_4 = 0.5$, $d_5 = 0.5$, and $d_6 = 0.3$.

The system has two locally stable attractors according to linear stability analysis, i.e., the signs of real parts of eigenvalues of the matrix $Df(x_0)$ (the derivative of $f(x)$ at x_0 , x_0 is an equilibrium point of nonlinear system (10)) [16]. Two stable states are shown in Table 1, which correspond to the epithelial and mesenchymal state, respectively. According to Theorem 1, we can easily determine the controlled nodes of system (10). It is clear that the index set K that satisfies (4) is empty. We rewrite system (10) into the following form:

$$\begin{cases} \dot{x}_1 = G_1(x_2, x_3, x_4) - D_1(x_1), \\ \dot{x}_2 = G_2(x_6) - D_2(x_2), \\ \dot{x}_3 = G_3(x_2, x_5) - D_3(x_3), \\ \dot{x}_4 = G_4(x_2, x_5, x_6) - D_4(x_4), \\ \dot{x}_5 = G_5(x_2, x_3, x_4) - D_5(x_5), \\ \dot{x}_6 = G_6(x_2, x_3, x_4) - D_6(x_6). \end{cases} \quad (11)$$

Fig. 1 The EMT core network and control strategy for its phenotype transition. **a** Diagram of the EMT core network. The arrows and short bars represent activation and inhibition, respectively. **b** The control nodes (genes) for realizing the impulsive control. Mesenchymal cells can be induced from epithelial cells and back by impulsive control of two genes miR-200 and miR-203

By successive evaluation of the dynamical equations, we can obtain the equivalent system as:

$$\begin{cases} \dot{x}_1 = G_1(G_2(x_6), G_3(G_2(x_6), x_5), \\ \quad G_4(G_2(x_6), x_5, x_6)) - D_1(x_1), \\ \dot{x}_2 = G_2(x_6) - D_2(x_2), \\ \dot{x}_3 = G_3(G_2(x_6), x_5) - D_3(x_3), \\ \dot{x}_4 = G_4(G_2(x_6), x_5, x_6) - D_4(x_4), \\ \dot{x}_5 = G_5(x_2, x_3, x_4) - D_5(x_5), \\ \dot{x}_6 = G_6(x_2, x_3, x_4) - D_6(x_6). \end{cases} \quad (12)$$

It is easy to recognize that the values of variables (x_1, x_2, x_3, x_4) at equilibrium are explicit functions of variables (x_5, x_6) , suggesting that the control of x_5 and x_6 can indeed steer system (10) to evolve to a desired attractor as shown in Fig. 1b. According to formula (5), it can be easily obtained that $N(2) = \{6\}$, $N(3) = \{2, 5\} \subseteq \{5, 6\} \cup \{2\}$,

Table 1 Two attractors of the EMT core network with A and B corresponding to the epithelial state and mesenchymal states [15], respectively

x_i	A	B	x_i	A	B
x_1 (CDH1)	1.7924	0.1111	x_4 (ZEB2)	0.0170	1.8169
x_2 (SNAI1)	0.3359	3.2229	x_5 (miR-200)	1.7924	0.1111
x_3 (ZEB1)	0.0522	1.8224	x_6 (miR-203)	2.9873	0.1851

$N(4) = \{2, 5, 6\} \subseteq \{5, 6\} \cup \{2\}$ and $N(1) = \{2, 3, 4\} \subseteq \{5, 6\} \cup \{2, 3, 4\}$. Therefore, we can choose $Q = \{5, 6\}$ and $C = Q \cup K = \{5, 6\}$.

The above analysis indicates that we can realize the transition from epithelial to mesenchymal cells and back by controlling miR-200 (x_5) and miR-203 (x_6). Based on (6), the impulsive control function, $u_j = (u_{1,j}, u_{2,j})^T$ ($t_0 = 0$), for the driving nodes miR-200 and miR-203 takes the form:

$$\begin{cases} u_{1,j} = \lambda(x_5(jT) - \bar{x}_5), \\ u_{2,j} = \lambda(x_6(jT) - \bar{x}_6), \end{cases}$$

where $x_i(jT)$ ($i = 5, 6$) is the level of the i -th component at time jT and $\bar{x}_i$ is the equilibrium of the i -th component of the desired attractor. The successful transition from one stable state to another by impulsive control is shown in Fig. 2.

The parameter λ in the control function may affect the control process. Within a certain range of λ , the higher the absolute value of λ , the shorter time it takes to reach the desired state [5]. Generally, the value of λ should be as small as possible from the viewpoint of medical science. In the numerical simulations, we take the time step T is 10 and λ is -0.35 . After some times perturbations ($j = 15$), the transition is successfully realized. Actually, the control can be stopped after some times of control when the system states fall into the attractive region of the desired attractor.

The size of step size T can affect the control performance. Generally, the smaller T is, the shorter time to reach the desired state, as shown in Fig. 3.

4 Impulsive control of Notch–Delta–Jagged signaling pathway

Next, we apply the approach to the Notch–Delta–Jagged signaling pathway, as shown in Fig. 4, which consists of four nodes. The notch receptor in one cell can interact with both of the ligands, i.e., Delta and Jagged, in the same cell (*cis*-interaction), or with D_{ext} or J_{ext} in the neighboring cells (*trans*-interaction). The *cis*-interaction, also referred to as *cis*-

Fig. 2 The transition from the epithelial state to the mesenchymal state by the impulsive control of the driving nodes x_5 (miR-200) and x_6 (miR-203). The system stays at epithelial state if no perturbation occurs (*blue lines*). When an appropriate impulsive control is performed, the transition from the epithelial state to the mesenchymal state is realized (*red lines*). The *red stars* represent the points at which the control is performed. The *black lines* represent control functions. When the transition is realized, the control can be stopped

Fig. 3 The effect of time step T on control performance. We take numerical simulation on x_6 of the EMT network with different T . **a** $T = 5$; **b** $T = 10$; **c** $T = 15$

inhibition, causes the degradation of both of the interacting proteins. Meanwhile, the *trans*-interaction, also referred to as *trans*-activation, leads to the release of the Notch intracellular domain (NICD), which can translocate to the nucleus and initiate transcription of its target genes [17].

The dynamics of Notch (x_1), Delta (x_2), Jagged (x_3), and NICD (x_4) are given by the following equations:

$$\begin{cases} \dot{x}_1 = (1 + \frac{x_4^2}{x_4^2 + I_0^2})N_0 - k_c(x_2 + x_3)x_1 \\ \quad - k_t(D_{ext} + J_{ext})x_1 - \gamma x_1, \\ \dot{x}_2 = \frac{J_0^2}{x_4^2 + I_0^2}D_0 - k_c x_1 x_2 - k_t N_{ext} x_2 \\ \quad - \gamma x_2, \\ \dot{x}_3 = (1 + \frac{x_4^5}{x_4^5 + I_0^5})J_0 - k_c x_1 x_3 - k_t N_{ext} x_3 \\ \quad - \gamma x_3, \\ \dot{x}_4 = k_t x_1 (D_{ext} + J_{ext}) - \gamma_I x_4, \end{cases} \quad (13)$$

where γ represents the degradation rate of all three transmembrane proteins Notch, Jagged, and Delta and γ_I the degradation rate of NICD. k_c and k_t are the strengths of *cis*-inhibition and *trans*-activation, respectively. N_0 , D_0 and J_0 are the production rates of Notch, Delta and Jagged, respectively. D_{ext} and J_{ext} represent the amount of protein available for binding, which can be on the membrane surface of neighboring cells or in a soluble form. The parameter values used to perform the numerical simulation are: $N_0 = 1600$, $D_0 = 1800$, $J_0 = 1200$, $I_0 = 200$, $k_c = 0.00135$, $k_t = 0.0135$, $D_{ext} = 100$, $N_{ext} = 600$, $J_{ext} = 1000$, $\gamma = 0.1$ and $\gamma_I = 0.5$ [17–19].

System (13) has three stable states, thus, the Notch signaling operates as a three-way switch. The three stable states correspond to a sender cell state (S), a receiver cell state (R) and a hybrid sender/receiver cell state (S/R), as shown in Table 2.

It is clear that there is no set satisfying (4), therefore, K is an empty set. We can rewrite system (13) as:

$$\begin{cases} \dot{x}_1 = G_1(x_4) - D_1(x_1)G_1(x_2, x_3), \\ \dot{x}_2 = G_2(x_4) - D_2(x_2)G_2(x_1), \\ \dot{x}_3 = G_3(x_4) - D_3(x_3)G_3(x_1), \\ \dot{x}_4 = G_4(x_1) - D_4(x_4), \end{cases} \quad (14)$$

Fig. 4 Schematic illustration of the Notch–Delta–Jagged signaling pathway. The *trans*-activation occurs when the receptor (Notch) of the receiver cell interacts with the ligand of the sender cell (Delta or Jagged) or with external ligands in a soluble form (D_{ext} or J_{ext}). The released signal NICD activates the expression of Notch and Jagged and inhibits the expression of Delta. The *cis*-inhibition occurs between the receptor and ligand in the same cell and leads to the degradation of both proteins

where $G_i(x_j)$ and $D_i(x_i)$ indicate the terms related to other variables ($j \neq i$) and itself (x_i) in the i -th equation, respectively. By successive evaluation of the dynamical equations, we obtain the equivalent system:

$$\begin{cases} \dot{x}_1 = G_1(G_4(x_1)) - D_1(x_1)G_1(x_2, x_3), \\ \dot{x}_2 = G_2(G_4(x_1)) - D_2(x_2)G_2(x_1), \\ \dot{x}_3 = G_3(G_4(x_1)) - D_3(x_3)G_3(x_1), \\ \dot{x}_4 = G_4(x_1) - D_4(x_4). \end{cases} \quad (15)$$

As shown in (15), the values of variables x_2, x_3, x_4 at equilibrium are explicit functions of the selected variables x_1 . Therefore, the dynamics of the variables x_2, x_3, x_4 is determined by the variable x_1 . For system (14), according to formula (5), it can easily be shown that $N(4) = \{1\}$, $N(3) = \{1\}$, $N(2) = \{1\}$, and $N(1) = \{1, 2, 3\} \subseteq \{1\} \cup \{2, 3\}$. Therefore, we have $\mathcal{Q} = \{1\}$ and $\mathcal{C} = \mathcal{Q} \cup \mathcal{K} = \{1\}$. Thus, we can choose Notch (x_1) ($t_0 = 0$) as the control node as shown in Fig. 5. The control function can be designed as:

$$u_j = \lambda(x_1(jT) - \bar{x}_1),$$

where $\bar{x}_1$ is the value of x_1 at the target equilibrium. Under the impulsive control of the Notch, the transition among the states S, R, and S/R can be realized. In the numerical simulations, the time step T is 0.1 and the number of pulses performed n is 15. The transition processes are depicted in Figs. 6, 7 and 8, which indicate that the approach can successfully realize the transition between different stable states. These results are consistent with previous experimental results [17].

Table 2 The attractors of the Notch–Delta–Jagged signaling pathway. The attractors A, B, and C correspond to the receiver (R), hybrid sender/receiver (S/R), and sender (S), respectively [17]

x_i	S	R	S/R
x_1 (Notch)	2999.3532	618.4437	184.5724
x_2 (Delta)	20.5765	961.1550	3891.9800
x_3 (Jagged)	568.6468	1647.9910	2793.8860
x_4 (NICD)	888.4379	183.6777	54.8179

5 Parameter control of Notch–Delta–Jagged signaling pathway

The aim of impulsive control is to entrain the driving nodes to their target states and further entrain the whole system to its target. Actually, such a goal can be similarly obtained by perturbing related parameters that significantly affect the dynamics of the driving nodes. For instance, for the Notch–Delta–Jagged signaling pathway, besides the impulsive control of Notch, the perturbation of I_0 can also be used to realize the transition between different steady states because the perturbation can significantly change the dynamics of Notch and further the dynamics of the whole system, as shown in Fig. 9.

6 Discussion

In this paper, we proposed an impulsive control strategy by which the transition between different states can be realized. The process mainly includes two steps: (1) determining the driving nodes and (2) constructing an appropriate impulsive control of the driving nodes. We further apply it into the EMT core network and the Notch1–Dll1–Jag1 signaling pathway to show effectiveness of the approach. Such an impulsive control strategy can be more easily performed in real life. Different from the continuous control in [5], which is so elaborate that it is relatively difficult to perform in the real world, the impulsive strategy is in a discrete form [20] and therefore can be easily performed. For instance, from a medical point of view, patients who need treatment can not be given sustained medication, time intervals of medication are necessarily required. The strategy can not only be used to guide pharmacological design but can also be applied into the fields of biological, medical, and other fields.

Generally, the target is stable. Actually, we can also control a system to an unstable state by the impulsive strategy. As we see in the proof of theorem 1, stability of the target state is not required. For example, for the Notch–Delta–Jagged signaling pathway, we can control the system to an unstable state $x^* = (471, 1475, 1678, 140)$, as shown in Fig. 10. Different

Fig. 5 The transition among different states S, R, and S/R can be realized by impulsive control of Notch

Fig. 6 The impulsive control of the Notch–Delta–Jagged signaling pathway to realize the transition from S to R state by controlling Notch with $\lambda = -0.8$. The blue solid lines show the system stays at the S state when no perturbation occurs. The red lines show the transition from S/R to S state by controlling Notch. The red stars represent the points at which the control is performed. The black lines represent control functions

Fig. 7 The impulsive control of the Notch–Delta–Jagged signaling pathway to realize the transition from R to S/R state by controlling Notch with $\lambda = -1.5$

Fig. 8 The impulsive control of the Notch–Delta–Jagged signaling pathway to realize the transition from R to S state by controlling Notch with $\lambda = -0.6$

Fig. 9 Bifurcation diagram of the Notch–Delta–Jagged signaling pathway with I_0 as a control parameter. The red solid lines represent the stable states R, S, and S/R. The black dotted lines represent the unsteady states. The transition among three types of stable states can be realized by perturbing the parameter I_0

Fig. 10 The transition from S state to the unstable equilibrium point x^* by impulsive control of the Notch with $\lambda = -3$

from the case of stable states, when we control a system to an unstable state, the control can not be stopped because the attractive region does not exist for the unstable state.

In contrast to from the impulsive control approach, the parameter perturbation strategy can also be applied to realize the transition between different states. In the impulse control, we need to calculate the exact value of each steady state in advance, so, we can realize the transition more accurately. While in the parameter control, we do not need to compute the exact value of each steady state but we need to find the bifurcation point between different steady states. Before using any one control strategy, we need to determine the driving nodes in advance. These strategies have significant clinical or experimental implications [21, 22]. For instance, better understanding of the external periodic (impulsive) input may lead to the development of better medical therapies.

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Compliance with Ethical Standards

Conflict of interest This paper has three authors: Min Luo, Jianfeng Jiao, and Ruiqi Wang. We declare that we have no conflicts of interest.

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