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Glioma cell fate decisions mediated by Dll1-Jag1-Fringe in Notch1 signaling pathway

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Abstract

Background: The Notch family of proteins plays a vital role in determining cell fates, such as proliferation, differentiation, and apoptosis. It has been shown that Notch1 and its ligands, Dll1 and Jag1, are overexpressed in many glioma cell lines and primary human gliomas. The roles of Notch1 in some cancers have been firmly established, and recent data implicate that it plays important roles in glioma cell fate decisions. This paper focuses on devising a specific theoretical framework that incorporates Dll1, Jag1, and Fringe in Notch1 signaling pathway to explore their functional roles of these proteins in glioma cells in the tumorigenesis and progression of human gliomas, and to study how glioma cell fate decisions are modulated by both trans-activation and cis-inhibition.

Results: This paper presents a computational model for Notch1 signaling pathway in glioma cells. Based on the bifurcation analysis of the model, we show that how the glioma cell fate decisions are modulated by both trans-activation and cis-inhibition mediated by the Fringe protein, providing insight into the design and control principles of the Notch signaling system and the gliomas.

Conclusions: This paper presents a computational model for Notch1 signaling pathway in glioma cells based on intertwined dynamics with cis-inhibition and trans-activation involving the proteins Notch1, Dll1, Jag1, and Fringe. The results show that how the glioma cell fate transitions are performed by the Notch1 signaling. Transition from grade III ∼ IV with significantly high Notch1 to grade I ∼ II with high Notch1, and then to normal cells by repressing the Fringe levels or decreasing the strength of enhancement induced by Fringe.

Keywords: Notch, Fringe, Gliomas, Trans-activation, Cis-inhibition

Background

Notch signaling pathway is an evolutionarily conserved cell-cell communication mechanism governing cell fate decisions during cell development. The signaling pathway includes the Notch transmembrane receptor and its ligands Delta and/or Jagged [1–3]. The Notch inactivation within the same cell is termed as cis-inhibition, which leads to the degradation of both proteins, therefore not generating a signal. The Notch receptor of one cell binds with a Notch ligand of its neighboring cells, i.e., trans-activation, leads to the formation of an active intracellular domain called Notch intracellular domain (NICD), which can translocate to the nucleus and initiate transcription of its target genes [4]. It has been shown that the trans-activation and cis-inhibition play important roles in cell fate decisions, such as neural fate decisions [5].

With only a single type of ligand and a single type of receptor it is relatively straightforward to evaluate Notch signaling's effect. To date, four Notch receptors have been identified (Notch 1-4) in humans, with five canonical ligands including three members of the Delta family (Dll1, Dll3, Dll4) and two members of the Serrate family (Jag1 and Jag2, homologues of Drosophila Serrate) [6]. At the same time, the family of Fringe-related proteins is a major Notch regulator, which can promote or suppresse Notch signaling, depending on the Notch ligands [7, 8]. There is only a single Fringe in Drosophila, while there are three homologues in mammals: Lunatic

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Fringe (LFng), Manic Fringe (MFng) and Radical Fringe (RFng) [6]. Of the three mammalian Fringe proteins, it has been shown that only LFng can enhance Notch1 signaling induced by Dll1 and suppress the signaling induced by Jag1 in coculture reporter assays [9]. It has been also shown that MFng can suppress Jag1 induced signaling through Notch1, while the effects of MFng on Notch1 signaling in response to Dll1 have not been reported [10]. Given the evolutionary conservation of the Notch pathway, three Fringe proteins in human have also been identified [11].

The Notch family of receptors consists of heterodimeric transmembrane proteins intimately involved in the determination of cell fate. Notch signaling can play a positively or negatively role in processes of proliferation, differentiation, and apoptosis, depending on the cell type [12, 13]. Alagille's syndrome in humans, marked by cholestasis/jaundice, characteristic facies, and arterial defects, has been traced to a defect in Jag1 [14, 15]. Dll1 and Jag1 have been found to be up-regulated in cervical cancers [16]. More recently, it has been shown that the Jag1 intracellular domain can up-regulate the activator protein 1 (AP-1) activity [17], a signaling pathway known to be important in many cancers.

To date, it has been shown that Notch1 and its ligands, Dll1 and Jag1, are overexpressed in many glioma cell lines and primary human gliomas. Immuno-histochemistry of a primary human glioma tissue array shows the presence in the nucleus of the Notch1 intracellular domain, indicating Notch1 activation in situ. Down-regulation of Notch1, Dll1, or Jag1 by RNA interference induces apoptosis and inhibits proliferation in multiple glioma cell lines [18]. Glioma is the most common clinical central nervous system malignancies. The patients with glioma have poor effects. The average survival time is short [19]. It has been demonstrated that Notch1 mRNA in human brain gliomas and normal brain tissue can be expressed, but the expression in human gliomas was significantly higher than in normal brain tissue, indicating that the expression levels of Notch1 may be associated with human glioma tumorigenesis and development. Gliomas are divided into four levels: grade I $\sim$ II and grade III $\sim$ IV. The expression of Notch1 mRNA in human gliomas is significantly higher than in normal brain tissue, and the level of Notch1 mRNA in III $\sim$ IV is significantly higher than that of grade I $\sim$ II, wihch indicates the expression levels of Notch1 is associated with not only pathological grade of gliomas, but also the degree of malignancy of gliomas [20]. As for standard therapies, such as chemotherapy, surgery, and radiation, have had limited success in treating patients with high-grade gliomas. Existing results show that the cancer cells may depend on a single Notch ligand and they further suggest a potential Notch juxtacrine/autocrine loop in gliomas [18]. Therefore, Notch1 and its ligands may present novel therapeutic targets in the treatment of gliomas.

The purpose of this paper is to present a computational model for Notch1 signaling pathway in glioma cell lines and primary human gliomas based on intertwined dynamics with cis-inhibition and trans-activation involving the proteins Notch1, Dll1, Jag1, and Lunatic Fringe. Mathematical models of Notch signaling, with different levels of sophistication, have been proposed for different organisms for which sufficient knowledge of molecular biology exists. All these models can produce different results but are not sufficient in several important respects. First, most of the previous models do not include an essential characteristic of Notch signaling, i.e. cis-inhibition [21, 22]. Second, even when cis-inhibition is incorporated, its link to glioma cell lines and primary human gliomas and its effects on cell fate decisions have not been well considered [23]. Most models focus on how Notch signaling plays different roles in various cell fate decisions, but how Fringe affects the fate decisions in glioma cell lines has not been well investigated. Thus, a new model needs to be developed so as to investigate the combinatorial effects of cis-inhibition, trans-activation, and Fringe regulation on glioma cell fate decisions, their operating mechanisms, and potential implications in the treatment of gliomas.

Methods

The regulatory processes between Notch1, Jag1, Dll1, and Fringe are schematized in Fig. 1. Notch1 signaling pathway is involved in glioma stem cells proliferation and differentiation. It has been shown that Notch1 protein is over expressed in human gliomas [19]. Notch1 signaling pathway, including the processes of cis-inhibition, trans-activation, and the regulation mediated by Lunatic Fringe is shown in Fig. 2. It is known that Fringe may play an important role in the treatment of gliomas.

For gliomas, most researchers are currently engaged in the study on related factors of Notch signaling pathway [7, 19], they pay less attention to the relationship between the related factors in terms of mathematical theory. The model presented here involves several aspects. First, the Notch1 binds to Dll1 or Jag1 with the same affinity when the regulation mediated by Fringe is not incorporated. Second, when the Fringe regulation on pathway is incorporated, it can increase the Notch1-Dll1 binding affinity and decrease the Notch1-Jag1 binding affinity. We mainly consider the two-cell system, and the system can be extended to the case where each cell has j-neighbors.

The basic model of Notch signaling incorporating the cis-inhibition and trans-activation was previously developed [24]. Subsequent model by incorporating Jag1 in addition to Delta and the asymmetric effect of NICD which activates Notch and Jag1 but represses Delta was also proposed [25]. Trans-interaction leads to the release

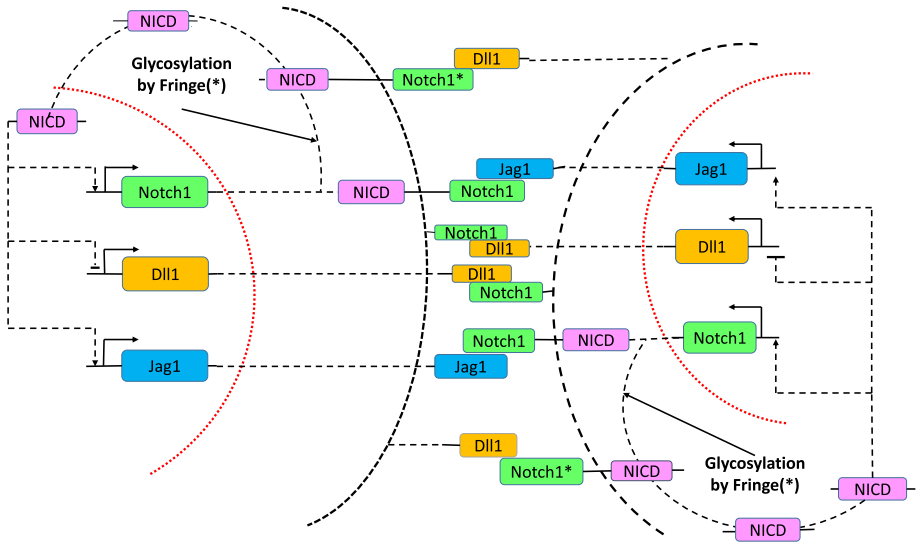

Fig. 1 System for signal integration in the intracellular and intercellular Notch1 signaling pathway. Notch1, the transmembrane receptor of one cell, binds to Dll1 or Jag1, the transmembrane ligands belonging to the neighboring cell. This trans-interaction leads to the cleavage and release of NICD that regulates the production of the two ligands asymmetrically, i.e., it inhibits Dll1 but activates Jag1. Interaction between Notch1 receptor and ligands (Dll1 or Jag1) of the same cell (cis-interaction) leads to the degradation of both the receptor and the ligands. Glycosylation of Notch1 by Fringe modifies Notch1 to have a higher affinity for binding to Dll1 and a lower affinity for binding to Jag1

of the NICD signal into the cytoplasm, resulting in subsequent activation of downstream target genes, while cis-interaction leads to the degradation of both proteins, Notch and Delta, therefore no generation of any signal. Under the assumption that the affinity of Notch1 to Dll1 or Jag1 is the same, when the Fringe regulation is ignored, the dynamics for the Notch1 receptor (N), the ligands Dll1 (D) and Jag1 (J), and the signal NICD (I) are given by the following equations

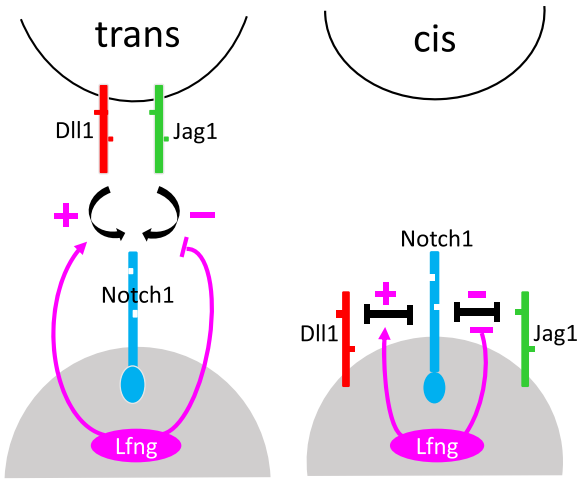

Fig. 2 Regulation diagram. Notch1 could interact by cis and trans with Jag1 and Dll1 ligands, and in which one of the Fringe-related proteins, Lunatic Fringe (LFng), could modulate these interactions. LFng modification of Notch1 enhances trans activation from Dll1 and weakens trans-activation from Jag1 (*left*). LFng modification of Notch1 enhances cis-interactions with Dll1 and weakens cis-interactions with Jag1 (*right*). Interactions are indicated by + and − for positive and negative regulation, respectively

$$\frac{dN}{dt} = \left(1 + \frac{I^2}{I^2 + I_0^2}\right) N_0 - k_c N(D + J) - k_t N(D_{ext} + J_{ext}) - \gamma N, \quad (1)$$

$$\frac{dD}{dt} = \frac{I_0^2}{I^2 + I_0^2} D_0 - k_c DN - k_t DN_{ext} - \gamma D, \quad (2)$$

$$\frac{dJ}{dt} = \left(1 + \frac{I^5}{I^5 + I_0^5}\right) J_0 - k_c JN - k_t JN_{ext} - \gamma J, \quad (3)$$

$$\frac{dI}{dt} = k_t N(D_{ext} + J_{ext}) - \gamma_I I, \quad (4)$$

where N_0, D_0, and J_0 are the innate production rates of Notch1, Dll1, and Jag1, respectively. γ represents the degradation rate of all three transmembrane proteins Notch1, Jag1, and Dll1, which are assumed to be the same. N_{ext}, D_{ext}, and J_{ext} represent the amount of protein available for binding from neighboring cells. k_c and k_t represent the strengths of cis-inhibition and trans-activation, respectively. γ_I stands for the degradation rate of NICD.

Glycosylation of Notch1 by Fringe modulates the binding affinity of the two ligands to Notch1. The glycosylated Notch1 has a higher binding affinity for Dll1 but lower

affinity to bind to Jag1, compared to the unglycosylated Notch1 [6]. Thus, to incorporate this mechanism to our model, while representing effective Notch1 in gliomas cell (sum of glycosylated and unglycosylated Notch1), the model can be rewritten as

$$\frac{dN}{dt} = \left(1+\frac{I^2}{I^2+I_0^2}\right)N_0 - \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right)(k_cND + k_tND_{ext}) - \frac{k_2^n}{k_2^n+[L]^n}(k_cNJ + k_tNJ_{ext}) - \gamma N, \tag{5}$$

$$\frac{dD}{dt} = \frac{I_0^2}{I^2+I_0^2}D_0 - \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right) \times (k_cDN + k_tDN_{ext}) - \gamma D, \tag{6}$$

$$\frac{dJ}{dt} = \left(1+\frac{I^5}{I^5+I_0^5}\right)J_0 - \frac{k_2^n}{k_2^n+[L]^n} \times (k_cJN + k_tJN_{ext}) - \gamma J, \tag{7}$$

$$\frac{dI}{dt} = \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right)k_tND_{ext} + \frac{k_2^n}{k_2^n+[L]^n}k_tNJ_{ext} - \gamma_I I, \tag{8}$$

where L stands for the Fringe. Hill functions are used to show the effects of Fringe on cis-inhibition and trans-activation. The definitions of these parameters, N_0, D_0, J_0, k_c, k_t, γ, and γ_I, are the same as the model (1)-(4). The standard values of all parameters are listed in Table 1. In the two cell model, the adjacent cell means the other cell. But for the hexagonal cell arrangement, the adjacent cells mean the six immediate neighbors, the sum of the expression levels in adjacent cells is divided by six. In order to extend to the multiple cell model, we consider the case where cell i ($i = 1, \ldots, n$) has j-neighbors. These regulatory processes can be expressed by a set of ordinary differential equations as follows

$$\frac{dN_i}{dt} = \left(1+\frac{I_i^2}{I_i^2+I_0^2}\right)N_0 - \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right)(k_cN_iD_i + k_tN_i\langle D_j\rangle_i) - \frac{k_2^n}{k_2^n+[L]^n}(k_cN_iJ_i + k_tN_i\langle J_j\rangle_i) - \gamma N_i, \tag{9}$$

$$\frac{dD_i}{dt} = \frac{I_0^2}{I_i^2+I_0^2}D_0 - \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right) \times (k_cD_iN_i + k_tD_i\langle N_j\rangle_i) - \gamma D_i, \tag{10}$$

$$\frac{dJ_i}{dt} = \left(1+\frac{I_i^5}{I_i^5+I_0^5}\right)J_0 - \frac{k_2^n}{k_2^n+[L]^n} \times (k_cJ_iN_i + k_tJ_i\langle N_j\rangle_i) - \gamma J_i, \tag{11}$$

$$\frac{dI_i}{dt} = \left(1+\frac{a[L]^n}{k_1^n+[L]^n}\right)k_tN_i\langle D_j\rangle_i + \frac{k_2^n}{k_2^n+[L]^n}k_tN_i\langle J_j\rangle_i - \gamma_I I. \tag{12}$$

The notations $\langle D_j\rangle_i$, $\langle J_j\rangle_i$ and $\langle N_j\rangle_i$ refer to the average levels of all j neighbors of the i-th Dll1, Jag1, and Notch1, respectively.

Several studies have reported abnormal activity of Notch1 in human brain tumors. But it is still not clear how Notch1 signaling pathway affects the occurrence and maintenance of gliomas. In the following sections, based on bifurcation analysis of the models, we will analyze how Notch1 signaling pathway modulates glioma cell fate decisions.

Results and discussion

Effect of Dll1-Jag1-Fringe on cell fate decisions for one-cell system

Gliomas may produce neural stem cells which can then differentiate into neurons or glial cells at all stages of tumorigenesis at maturity. Therefore, it could be argued

Table 1 Standard parameter values in the model (5) − (8)

Parameters	Definitions	Values	Unit
N_0	The innate production rates of Notch1	1400	Number of proteins
D_0	The innate production rates of Dll1	1600	Number of proteins
J_0	The innate production rates of Jag1	1200	Number of proteins
I_0	The innate production rates of NICD	200	Number of proteins
γ	The degradation rate of proteins Notch1, Jag1, and Dll1	0.1	time^{-1}(h^{-1})
γ_I	The degradation rate of NICD	0.5	time $^{-1}$(h^{-1})
k_t	The strengths of trans-activation	4.7×10^{-5}	time $^{-1}$(h^{-1})
k_c	The strengths of cis-activation	6.1×10^{-4}	time $^{-1}$(h^{-1})

Values for Figs. 3 and 4

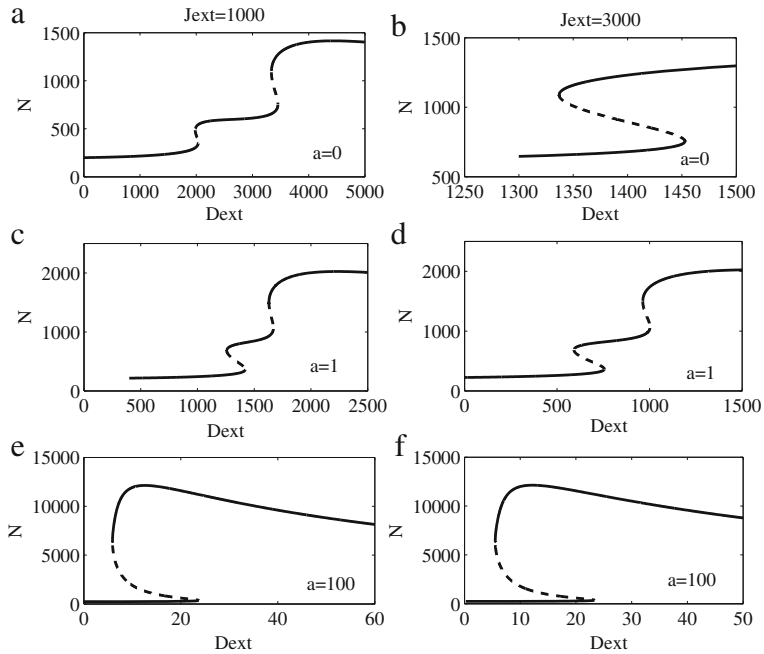

Fig. 3 Bifurcation diagrams for the levels of different proteins. **a**-**b**: Bifurcation diagrams for the one-cell Notch1-Dll1-Jag1 circuit. **c**-**f**: Bifurcation diagrams for the one-cell Notch1-Dll1-Jag1-Fringe circuit. **a**-**c**-**e**: Bifurcation diagrams of Notch1 protein levels when driven by external Dll1 at $J_{ext} = 1000$. **b**-**d**-**f**: Bifurcation diagrams of Notch1 protein levels when driven by external Dll1 for fixed level of $J_{ext} = 3000$

that gliomas produced by cells with different maturity level can show different expression of Notch1 signal cascade of spectrum, which reflects the origin of gliomas [26]. These expression products can also be used to identify different grades of gliomas, including primary and secondary gliomas. Studies have shown correlation of Notch1 expression and glioma grades [27–29].

Immunohistochemistry of a primary human glioma tissue array shows the presence of the Notch1 intracellular domain in the nucleus, indicating Notch1 activation in

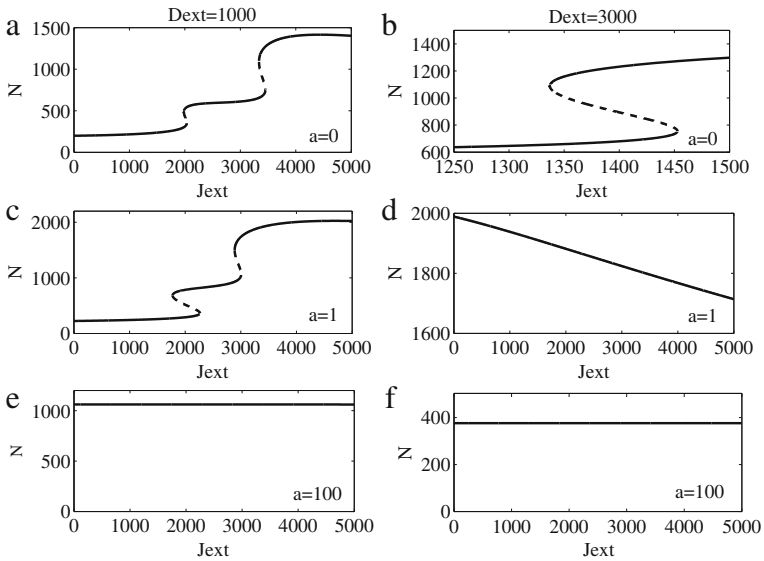

Fig. 4 Bifurcation diagrams. **a**-**b**: Bifurcation diagrams for the one-cell Notch1-Dll1-Jag1 circuit. **c**-**f**: Bifurcation diagrams for the one-cell Notch1-Dll1-Jag1-Fringe circuit. **a**-**c**-**e**: Bifurcation diagrams of Notch1 protein levels when driven by external Jag1 at $D_{ext} = 1000$. **b**-**d**-**f**: Bifurcation diagrams of Notch1 protein levels when driven by external Jag1 at $D_{ext} = 3000$

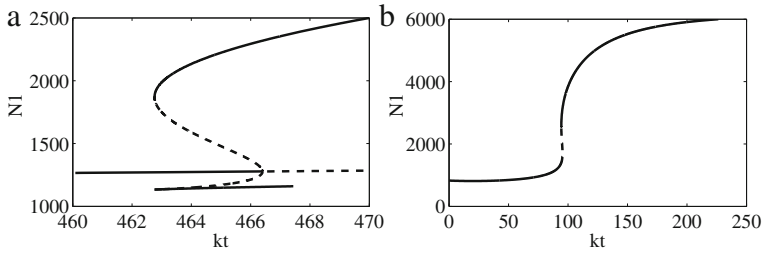

Fig. 5 Dynamical properties of Notch1-Dll1 signaling circuit. **a** Two cells are fully symmetrical. **b** The symmetry of two cells is broken. In Eq. (14), the term $k_c D_2$ is replaced by $3 \times k_c D_2$

situ. Down-regulation of Notch1, Dll1, or Jag1 by RNA interference can induce apoptosis or inhibit proliferation in multiple glioma cell lines. Notch1 and its ligands may present novel therapeutic targets in the treatment of gliomas [18]. Preliminary works in laboratory from phage display biopanning on human glioma cells resulted in the isolation of two peptides that share significant homology to regions of Jag1 and Dll1, two Notch1 receptor ligands. These findings suggested the presence of Notch1 on human glioma cells, which was further supported by cDNA microarray data. All these findings prompt us to study the biological relevance of Notch signaling to the glioma cell fate decisions.

We explore the effects of Dll1-Jag1-Fringe on glioma cell fate decisions by analyzing the model (5)-(8). The effect of ligand Jag1 and Fringe is shown in Fig. 3. As we can see from (a) and (b), for the case of no Fringe, when the value of Jag1 becomes more larger, the system changes from twice transitions to only once. The difference between (a) and (c) is the value of a (on behalf of Fringe existence), which represents the presence of Fringe, but only a small intensity. Stable steady states almost do not change. When the a value is further increased, the transition becomes only once.

The effects of ligand Dll1 and Fringe on the system dynamics are shown in Fig. 4. The standard values of all parameters are listed in Table 1. As we can see from (a) and (b), for the case of no Fringe, when the value of Dll1 becomes more larger, the system changes from twice state transitions to only once. However, when the Fringe regulation is large enough, we can see that on state transitions occur even when J_{ext} is small enough. Compared with Fig. 3, The influence of Dll1 on the system is more larger than Jag1.

From Figs. 3 and 4, preliminary conclusions can be obtained as follows: (1) in the Notch1 signaling system of gliomas, the impact of Dll1 is greater than Jag1; (2) expression of the Dll1 ligand is shown to be increased in gliomas when compared with normal brain tissue; and (3) the appearance of Fringe will change the state transtions in the Notch1 signaling system of gliomas.

Effect of Dll1-Jag1-Fringe on cell fate decisions for the two-cell system

To make a breakthrough and research into the impact of the Notch1 signaling pathway more deeply, we describe the two-cell model of the three cases: Notch1-Dll1 only (N-D), Notch1-Dll1-Jag1 (N-D-J), and the model including the Fringe (N-D-J-F). It has been experimentally shown that given the expression of Dll1 in primary human gliomas, efficient Dll1 were transfected into six glioma lines and their effects assessed. Dll1 knockdown produced dramatic effects, inducing a spindleshaped morphology initially (not shown) with subsequent cell death.

Table 2 Standard parameter values in the model (13)-(18)

Parameters	Definitions	Values	Unit
N_0	The innate production rates of Notch1	500	Number of proteins
D_0	The innate production rates of Dll1	500	Number of proteins
I_0	The innate production rates of NICD	200	Number of proteins
γ	The degradation rate of proteins Notch1, Jag1, and Dll1	0.1	time^{-1}(h^{-1})
γ_I	The degradation rate of NICD	0.5	time^{-1}(h^{-1})
k_t	The strengths of trans-activation	(4.7×10^{-5})※, (10^{-5})*	time^{-1}(h^{-1})
k_c	The strengths of cis-activation	6.1×10^{-4}	time^{-1}(h^{-1})

※ Values for Fig. 5a. *Values for Fig. 5b

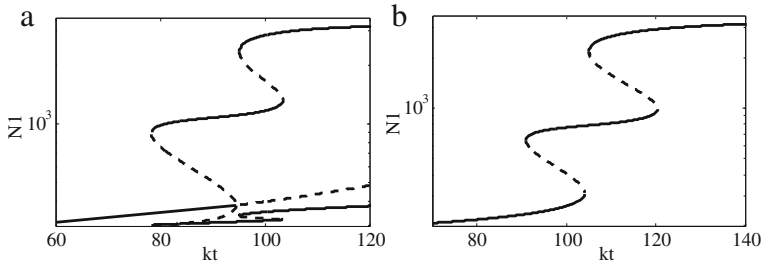

Fig. 6 Bifurcation diagram of Notch1-Dll1-Jag1 signaling circuit. **a** Two cells are fully symmetrical. **b** The symmetry of two cells is broken. The term k_cJ_2 is replaced by $1.2 \times k_cJ_2$ in Eq. (20) and and the term k_tN_1 is replaced by $4 \times k_tN_1$ in Eq. (22)

Significant decreases in viable cell number were evident in all six glioma cell lines as evaluated by alamarBlue assay. We first evaluate the dynamics of N-D signaling for the two-cell system (13)-(18). Bifurcation diagrams with k_t as a control parameter is showed in Fig. 5. The standard values of all parameters are shown in Table 2.

$$\frac{dN_1}{dt} = \left(1 + \frac{I_1^2}{I_1^2 + I_0^2}\right) N_0 - N_1(k_cD_1 + k_tD_2) - \gamma N_1, \tag{13}$$

$$\frac{dN_2}{dt} = \left(1 + \frac{I_2^2}{I_2^2 + I_0^2}\right) N_0 - N_2(k_cD_2 + k_tD_1) - \gamma N_2, \tag{14}$$

$$\frac{dD_1}{dt} = \frac{I_0^2}{I_1^2 + I_0^2} D_0 - D_1(k_cN_1 + k_tN_2) - \gamma D_1, \tag{15}$$

$$\frac{dD_2}{dt} = \frac{I_0^2}{I_2^2 + I_0^2} D_0 - D_2(k_cN_2 + k_tN_1) - \gamma D_2, \tag{16}$$

$$\frac{dI_1}{dt} = k_tN_1D_2 - \gamma_I I_1, \tag{17}$$

$$\frac{dI_2}{dt} = k_tN_2D_1 - \gamma_I I_2. \tag{18}$$

Similarity, it has been shown that Jag1 knockdown can slow growth significantly in several of the glioma lines. Effects of Jag1 on glioma cells can also be assessed. We then analyze the dynamics of N-D-J signaling for two-cell system (19)-(26). The bifurcation diagrams are shown in Fig. 6. The standard parameter values are listed in Table 3.

$$\frac{dN_1}{dt} = \left(1 + \frac{I_1^2}{I_1^2 + I_0^2}\right) N_0 - N_1(k_cD_1 + k_cJ_1) - N_1(k_tD_2 + k_tJ_2) - \gamma N_1, \tag{19}$$

$$\frac{dN_2}{dt} = \left(1 + \frac{I_2^2}{I_2^2 + I_0^2}\right) N_0 - N_2(k_cD_2 + k_cJ_2) - N_2(k_tD_1 + k_tJ_1) - \gamma N_2, \tag{20}$$

$$\frac{dD_1}{dt} = \frac{I_0^2}{I_1^2 + I_0^2} D_0 - D_1(k_cN_1 + k_tN_2) - \gamma D_1, \tag{21}$$

$$\frac{dD_2}{dt} = \frac{I_0^2}{I_2^2 + I_0^2} D_0 - D_2(k_cN_2 + k_tN_1) - \gamma D_2, \tag{22}$$

$$\frac{dJ_1}{dt} = \left(1 + \frac{I_1^5}{I_1^5 + I_0^5}\right) J_0 - J_1(k_cN_1 + k_tN_2) - \gamma J_1, \tag{23}$$

Table 3 Standard parameter values in the model (19) − (26)

Parameters	Definitions	Values	Unit
N_0	The innate production rates of Notch1	1600	Number of proteins
D_0	The innate production rates of Dll1	1800	Number of proteins
J_0	The innate production rates of Jag1	1200	Number of proteins
I_0	The innate production rates of NICD	200	Number of proteins
γ	The degradation rate of proteins Notch1, Jag1, and Dll1	0.1	time^{-1}(h^{-1})
γ_I	The degradation rate of NICD	0.6⁕, 0.5*	time^{-1}(h^{-1})
k_t	The strengths of trans-activation	(7×10^{-6})⁕, (10^{-5})*	time^{-1}(h^{-1})
k_c	The strengths of cis-activation	(4×10^{-4})⁕, (6.1×10^{-4})*	time^{-1}(h^{-1})

⁕Values for Fig. 6a. *Values for Fig. 6b

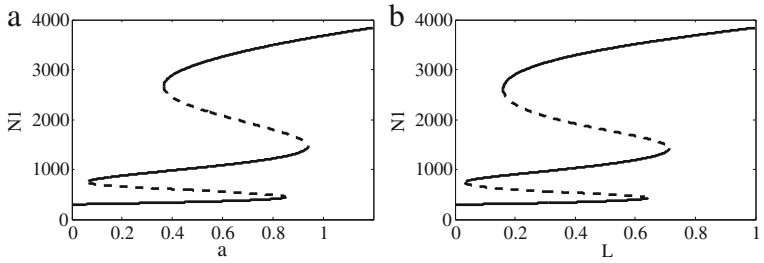

Fig. 7 Bifurcation diagrams for the effect of Fringe protein. **a** The bifurcation with a as a control parameter at $L = 1$. The value a reflects the effect of Fringe on cis-inhibition and trans-activation between Notch1 and Dll1. The term $k_c N_2 J_2$ is replaced by $1.2 \times k_c N_2 J_2$ in Eq. (28) and the term $k_t D_1 N_2$ is replaced by $42 \times k_t D_1 N_2$ in Eq. (29). As a gradually increases, the healthy tissue changes from normal to grade I ∼ II of gliomas. When a is increased to a certain value, the state will switch from grade I ∼ II to grade III ∼ IV of gliomas. **b** The bifurcation diagram with L as a control parameter at $a = 1.2$, which reflects the dynamics of Notch1 signaling pathway after the addition of Lunatic Fringe. When the Fringe is inhibited, the transition from gliomas to a healthy state can be gradually realized

$$\frac{dJ_2}{dt} = \left(1 + \frac{I_2^5}{I_2^5 + I_0^5}\right) J_0 - J_2(k_c N_2 + k_t N_1) - \gamma J_2, \tag{24}$$

$$\frac{dI_1}{dt} = k_t N_1 D_2 + k_t N_1 J_2 - \gamma_I I_1, \tag{25}$$

$$\frac{dI_2}{dt} = k_t N_2 D_1 + k_t N_2 J_1 - \gamma_I I_2. \tag{26}$$

Current data has shown, along with Notch1 expression, the expression of the Notch1 ligands, Dll1 and Jag1, in both glioma cell lines. To our knowledge, this is only the second example described in the literature of Notch1 ligand overexpression in the human malignant disease, with a previous report in cervical cancer. Figures 5 and 6 show a critial role of Dll1 and Jag1 in glioma cells, which reflect the relatively greater efficiency of Dll1 than Jag1 but also indicate a greater role for Dll1 than Jag1 as a Notch1 ligand in glioma cells. At the same time, we can know that the expression of Dll1 increases with increased Notch1 expression. In contrast, the expression of Jag1 has an inverse relationship with the expression of Notch1.

Finally, we analyze the dynamics of Notch1-Dll1-Jag1-Fringe signaling for two-cell system (27)-(34). The dynamics of Notch1 signaling pathway after the addition of Fringe is shown in Fig. 7. The standard parameter values are shown in Table 4. To measure the effect of the Fringe on ligand-induced Notch1 signaling, scholars measured its ability to modulate signaling induced by either Dll1 or Jag1 in 3T3 cells ectopically expressing Notch1 by using a CSL-reporter coculture assay [30]. Consistent with previous findings, LFng potentiated CSL-reporter activity induced by Dll1 and suppressed CSL-reporter activity by Jag1. These findings suggest that Fringe can modulate Notch1 signaling by regulating both Dll1 and Jag1. The link between glycosylation and Fringe activity was also assessed by using mutant cells defective in transferring fucose to proteins. Co-culture of Notch1-expressing and Jag1-expressing cells increased reporter gene activity. While the reporter gene expression was reduced if the Notch1-expressing cells were co-transfected with Manic or Lunatic Fringe [31].

$$\frac{dN_1}{dt} = \left(1 + \frac{I_1^2}{I_1^2 + I_0^2}\right) N_0 - \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right)(k_c N_1 D_1 + k_t N_1 D_2) - \frac{k_2^n}{k_2^n + [L]^n}(k_c N_1 J_1 + k_t N_1 J_2) - \gamma N_1, \tag{27}$$

Table 4 Standard parameter values in the model (27) − (34)

Parameters	Definitions	Values	Unit
N_0	The innate production rates of Notch1	1600	Number of proteins
D_0	The innate production rates of Dll1	1800	Number of proteins
J_0	The innate production rates of Jag1	1200	Number of proteins
I_0	The innate production rates of NICD	200	Number of proteins
γ	The degradation rate of proteins Notch1, Jag1, and Dll1	0.1	time^{-1}(h^{-1})
γ_I	The degradation rate of NICD	0.5	time^{-1}(h^{-1})
k_t	The strengths of trans-activation	7×10^{-6}	time^{-1}(h^{-1})
k_c	The strengths of cis-activation	6.1×10^{-4}	time^{-1}(h^{-1})

Values for Fig. 7

$$\frac{dN_2}{dt} = \left(1 + \frac{I_2^2}{I_2^2 + I_0^2}\right) N_0 - \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right)(k_c N_2 D_2 + k_t N_2 D_1) - \frac{k_2^n}{k_2^n + [L]^n}(k_c N_2 J_2 + k_t N_2 J_1) - \gamma N_2, \quad (28)$$

$$\frac{dD_1}{dt} = \frac{I_0^2}{I_1^2 + I_0^2} D_0 - \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right) \times (k_c D_1 N_1 + k_t D_1 N_2) - \gamma D_1, \quad (29)$$

$$\frac{dD_2}{dt} = \frac{I_0^2}{I_2^2 + I_0^2} D_0 - \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right) \times (k_c D_2 N_2 + k_t D_2 N_1) - \gamma D_2, \quad (30)$$

$$\frac{dJ_1}{dt} = \left(1 + \frac{I_1^5}{I_1^5 + I_0^5}\right) J_0 - \frac{k_2^n}{k_2^n + [L]^n} \times (k_c J_1 N_1 + k_t J_1 N_2) - \gamma J_1, \quad (31)$$

$$\frac{dJ_2}{dt} = \left(1 + \frac{I_2^5}{I_2^5 + I_0^5}\right) J_0 - \frac{k_2^n}{k_2^n + [L]^n} \times (k_c J_2 N_2 + k_t J_2 N_1) - \gamma J_2, \quad (32)$$

$$\frac{dI_1}{dt} = \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right) k_t N_1 D_2 + \frac{k_2^n}{k_2^n + [L]^n} k_t N_1 J_2 - \gamma_I I_1, \quad (33)$$

$$\frac{dI_2}{dt} = \left(1 + \frac{a[L]^n}{k_1^n + [L]^n}\right) k_t N_2 D_1 + \frac{k_2^n}{k_2^n + [L]^n} k_t N_2 J_1 - \gamma_I I_2. \quad (34)$$

Conclusions

Glioma is one of the worst tumors of of central nervous system. The treatment difficulty lies in the relapse, which is related with glioma cells proliferation and invasive growth. In recent years, the Notch1 signaling in proliferation of gliomas for the survival is increasingly concerned. It has been shown the over expression of Notch1 protein in my kinds of cancers, such as skin, lung, and and other caners. Notch1 signaling pathway plays important roles in cell proliferation, differentiations, and apoptosis. Tumor gene therapy and the development of new drugs using Notch1 receptors as targets will open new areas for the tumor therapy. Preliminary research has shown that Notch1 has a good application prospect as an anti-tumor target. Our results confirmed that the regulation between Notch1, its ligands, and Fringe can modulate the glioma cell fate decisions. For the two-cell system, a pitchfork bifurcation occurs due to the symmetry of two cells. Once breaking the symmetry, saddle node bifurcations occur, which is similar to the situation occurred in the single cell system. More importantly, we show that Fringe can modulate the glioma cell fate decisions by regulating the Notch1 signaling, i.e., realizing the transition of grades III $\sim$ IV to grades I $\sim$ II, and then to normal brain tissue. Besides Fringe, Dll1 and Jag1 also play critical roles in glioma cell fate decisions due to combinatorial effects between them.

Although our model provides a new theoretical framework to investigate the effects of Dll1, Jag1 and Fringe in the Notch1 signaling system in glioma cells, it ignores the spatial effects which can be also important. Other limitations of our model include: no distinction between soluble and membrane-bound ligands, no time delays between existence of fringe and its action on Notch1 signaling pathway, and no difference between the Fringe family members. However, the model still presents the first step toward the possible reasons of over expression of Notch1 in gliomas cells, e.g., high Fringe expression, which provides us some possible clinic treatment of gliomas, e.g., inhibition of Fringe expression.

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All data generated or analyzed during this study are included in this published article.

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XS and RW conceived the study. XS and RW performed the numerical experiments and theoretical analysis. Both authors read and approved the final manuscript.

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