Bifurcation dynamics and determination of alternate cell fates in bipotent progenitor cells

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Abstract The gene regulatory networks in which two lineage-affiliated transcription factors, such as GATA1 and PU.1, inhibit each other but activate themselves so as to regulate the choice between alternative cell fates have been extensively studied. These simple networks can generate bistability and explain the transitions between the alternative cell fates. The commitment of a progenitor cell to a new fate corresponds to the occurrence of different types of bifurcations, depending on if a system is symmetrical and how perturbations affect the system. Here we take a general modeling and analyzing approach and show that the lateral inhibition with symmetry and asymmetry can lead to different bifurcation dynamics. Especially, if cell fate decision-making is initiated with asymmetry or symmetry-breaking perturbations, a progenitor cell pre-patterns itself into a polarized cell, depending on the asymmetry or symmetry-breaking perturbations. This study may help us understand the fundamental features of binary cell fate decisions more clearly and further apply to a wider range of decision-making processes.

Keywords Lateral inhibition · Bistability · Cell fate decisions · Symmetry · Asymmetry · Bifurcation

Introduction

Over the past years, much has been learned that hematopoietic stem cells (HSC) give rise to the multi-potent common myeloid progenitors (CMPs), which have the

ability to differentiate toward the erythroid-megakaryocyte and myeloid lineages. Lineage commitment can occur at different levels in the hierarchical hematopoietic development (Seita and Weissman 2010). A mixed lineage gene expression at low levels in progenitors is present as an important pattern accounting for the onset of cell differentiation (Laslo et al. 2006). At commitment states, the expression of lineage-specific genes increases. Determination of cell fates occurs through the function of major transcription factors which positively regulate lineage-specific genes and negatively regulate genes of other lineages (Pina et al. 2012). Lineage-specific transcription factors have been identified as master regulators of commitment and differentiation. For example, C/EBP α is a critical determinant for basophil versus mast cell fate decision (Iwasaki and Akashi 2007). During hematopoiesis, the transcription factors such as PU.1 and GATA-1 are required for the generation of myeloid and lymphoid progenitors (Iwasaki et al. 2005). The antagonistic interplay between these two transcription factors in progenitors is also critical in initial priming states. Similarly, FOG-1 and GATA-1 have been demonstrated to act as master regulators to specify definitive megakaryocytic and erythroid progenitors (Mancini et al. 2012). These transcription factors functionally antagonize one another so as to determine initial choices of multipotent myeloid/erythroid precursors (Nerlov et al. 2000). But the question which remains to answer is how bipotent progenitor cells shift to myeloid or erythroid cells at the expense of the other lineage. Since each of them has a positive auto-regulation, a small change that alters the transcription factor dominance can be amplified to lock in lineage-specific expression. The balance between PU.1 and C/EBP α is a similar case existing in macrophage versus neutrophil cell fate decisions (Reddy et al. 2002). The mathematical model

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integrating both cross antagonism and positive auto-regulation shows another stable state in addition to the classical bistable states corresponding to different cell fates. Experimental observations suggest that a number of relevant transcription factors are expressed simultaneously at a low level at the bipotent stage (lineage priming) (Iwasaki and Akashi 2007). For lineage-specific programs to be activated, the balanced co-expression of these potentially antagonistic transcription factors needs to be broken. Either of the transcription factors needs to be expressed more than threshold amount so that specific commitment occurs, whereas the other transcription is shut down. These observations suggest that a transcription factor network is capable of inducing lineage commitment by changing from unspecific co-expression to committed states of specific expression. However, the general underlying principles of the regulatory mechanisms are currently unknown. Recently, the regulatory mechanisms of two transcription factors antagonistic interdependence together with positive auto-regulation provide a framework for the theoretical investigation of lineage specification control (Huang et al. 2007; Andrecut et al. 2011).

The model describing dynamics of two transcription factor can provide a system view of how one stable state reversibly split into two states through a pitchfork bifurcation, which corresponds well to Waddington's picture (Goldberg et al. 2007). It can provide evidence for better understanding of differentiation mechanisms. However, it is often used in symmetric systems (Andrecut et al. 2011; Lipshtat et al. 2006). Actually, biological systems are more complex, and there is a significant cell to cell variability in molecular concentrations (Raj and van Oudenaarden 2008). Even a small perturbation can change the symmetry of the system and furthermore its dynamics. These facts suggest that nature prefers more complicated regulatory forms which come to be a very exciting question and we need to pay more attention to asymmetric systems. In this paper, we introduce a two-component network in which two lineage-affiliated transcription factors inhibit each other but activate themselves so as to regulate the choice between alternative cell fates. Biologically, many two-component networks are known to be involved in the process of lineage specification (Guantes and Poyatos 2008). In other words, such a network can generate bistability and explain the transitions between the alternative cell fates. By analyzing the dynamical behavior of the mathematical model, we show that the lateral inhibition with symmetry and asymmetry can lead to different bifurcation dynamics. Especially, if cell fate decision-making is initiated with asymmetry or symmetry-breaking perturbations, a progenitor cell pre-patterns itself into a polarized cell, depending on the asymmetry or symmetry-breaking perturbations.

Model description

Two-component network

The gene regulatory network in which two crucial transcription factors X and Y inhibit each other and positively regulate their own expression appears to be a canonical motif controlling binary fate decisions in cell lineage commitment. Many pairs of transcription factors fit for the model have been found, such as GATA-1-PU.1 (Zhang et al. 1999; Huang et al. 2007), PU.1-C/EBP α (Andrecut et al. 2011), Nanog-GATA6 (Chickarmane and Peterson 2008), and Cdx2-Oct4 (Huang 2009). To the best of our knowledge, there are many models, deterministic or stochastic, involving two transcription factors in the process of differentiation (Foster et al. 2009; Guantes and Poyatos 2008; Huang et al. 2007). However, most of the models are based on the polymers binding to gene promoters rather than monomers. In addition, symmetrical models are applied in order to simplify these systems. Actually, the mechanism of fate determination in reality is more complicated. Here we will consider the symmetrical and asymmetrical situations in the absence of cooperativity. The model requires only protein monomers and a heterodimer binding to gene promoter independently to activate the transcription of each transcription factor. Two transcription factors, denoted by X and Y , are involved in our model, as shown in Fig. 1. The two gene loci interact with each other via the repression of their encoded proteins that act as trans-repressors, independent of the auto-activation. A set of distinct elementary chemical reaction kinetics formalism have been mapped into a nonlinear dynamical system previously (Andrecut et al. 2011).

- We will focus on the bifurcation dynamics of the simple mathematical model for the two-component network. Especially, different from the asymmetries in the positions of the initial states, we mainly consider the asymmetries induced by the rate of change of the control parameters.
- In the network, two genes are assumed to have binding sites for effectors in their promoter regions. The translation product of gene X represses the activity of gene Y and vice versa. Both transcription factors, X and Y , can also bind to their own promoter regions, performing a positive feedback independently on their own transcription.
- Different from the model with cooperativity $n \geq 2$, we assume that the formation of XY complex does not have a priori cooperativity between X and Y . Monomers of X and Y binding with their own promoters can activate their own transcription. The sequential binding of two monomers as the second possibility of DNA

Fig. 1 Two-component network for auto-activation and mutual repression. Two transcription factors act as trans-repressors to each other together with positive auto-regulation in lineage specification control. The XY complex in gene promoters does not have a priori cooperativity. Monomers of X and Y binding with their own promoters can activate their own transcription

binding is not considered. The process of DNA binding and dissociation are regarded to be at quasi-steady states.

Model equations

The gene network which governs cell fate decisions is characterized by the mutual inhibition of two opposing fate-determining transcription factors, in which each represses the activity of the other through a variety of molecular mechanisms, as shown in Fig. 1. For instance, the transcription factor pair, PU.1 and GATA-1 controls the binary fate decisions between the erythroid and myeloid lineages in bipotent CMPs. Assuming that the rate constants are the same for the two components leads to a continuous mathematical model which describes the dynamics of this network

$$\frac{dX}{dt} = \frac{aX}{XY + bX + cY + d} - fX, \quad (1)$$

$$\frac{dY}{dt} = \frac{aY}{XY + bY + cX + d} - fY. \quad (2)$$

A detailed derivation of the two-dimensional model, including all assumptions made to get it can be found in Andreucut et al. (2011).

In fact, based on the theory of ‘naked’ DNA which has a low or basal transcription activity, the basic gene regulation has been studied (Widder et al. 2007). The basic transcription activity is often characterized as ‘leaky transcription’ due to the low levels of produced mRNA. In order to take the basal transcription activity into account,

we assume that there is some basal rate of X and Y synthesis, denoted as γ ,

$$\frac{dX}{dt} = \gamma + \frac{aX}{XY + bX + cY + d} - fX, \quad (3)$$

$$\frac{dY}{dt} = \gamma + \frac{aY}{XY + bY + cX + d} - fY. \quad (4)$$

Though the basal transcription activity is incorporated into the equations, the Jacobian matrix is the same with the case of $\gamma = 0$. Since the constant terms vanish through differentiation, the Jacobian matrix only depends on the changes in the positions of the equilibria. Leaky transcription is important for gene activation. In the case of $\gamma = 0$, the origin (0, 0) is an asymptotically stable equilibrium. On the other hand, when $\gamma \neq 0$, the expression of protein at a low level is always going on and the origin is no longer an equilibrium.

Actually, it is impossible for all the gene activation and degradation rates to be the same in reality. The real life process is more complicate than the system above. In order to describe the dynamical system more accurately, we derive a more general system as follows

$$\frac{dX}{dt} = \gamma_1 + \frac{a_1X}{XY + b_1X + c_1Y + d_1} - f_1X, \quad (5)$$

$$\frac{dY}{dt} = \gamma_2 + \frac{a_2Y}{XY + b_2Y + c_2X + d_2} - f_2Y. \quad (6)$$

To gain some insight into the dynamics of the symmetrical and asymmetrical systems, we analyze the bifurcation dynamics of the two systems, i.e., Eqs. (3–4) and (5–6), respectively. The effects of basal transcription are also incorporated in the two systems.

Results

Symmetrical system

To simply analyze the equilibria as well as the potential bifurcation conditions, we restrict the system to the special case of a completely symmetrical one. A symmetrical system is the case in which all parameters for X have values identical to those of the corresponding parameters for Y. Taking c as a bifurcation parameter. The equilibria of Eqs. (3–4) can be solved and plotted as a function of the chosen bifurcation parameter c . Symmetric bifurcations may occur due to the symmetry of the system. When c increases, the levels of X and Y decrease in a symmetrical fashion until c reaches a bifurcation value, at which the single stable equilibrium splits into two stable equilibria, one with X dominating and one with Y dominating, and an unstable equilibrium where X and Y levels are equal. An exploration

Fig. 2 The bifurcation of the symmetrical system with c as the bifurcation parameter. Other parameter values are $a_1 = a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, $\gamma_1 = \gamma_2 = 0$, and $c = c_1 = c_2$. A transcritical bifurcation occurs at $c = 0.5$. The system bifurcates from monostable to bistable regime at $c = 0.5$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

of the system reveals two classes of bifurcations: type I symmetric bifurcation involving transcritical bifurcation (the case of non-leaky transcription $\gamma_1 = \gamma_2 = 0$), and type II symmetric bifurcation involving pitchfork bifurcation (the case of leaky transcription $\gamma_1 = \gamma_2 \neq 0$).

Non-leaky transcription

For the simple case $\gamma_1 = \gamma_2 = 0$, numerical solution leads to three solutions except at $c = b$, which correspond to three equilibria (see the “Appendix”). Geometrically, the condition imposes a transcritical bifurcation which rules the switch of cell differentiation through the variation of parameter c , as illustrated in Fig. 2. The existence of transcritical bifurcation explains the instantaneous onset of gene transcription at the bifurcation point. It sustains two states: (1) a priming state which is uncommitted and (2) a differentiated state which is committed. The transition from the uncommitted to committed state is always through a transcritical bifurcation. Especially, a priming state and a differentiated state coexist at the bifurcation point.

The significance of the transcritical bifurcation is to delineate the transition of cell states in the single parameter space. The equilibria are found where the production and degradation rates are equal. It is easy to evaluate their local stability by calculating their eigenvalues. As c increases, there are always three equilibria except at $c = b$. The equilibrium locus with $X = Y$ is stable for $c < c_t = 0.5$, and becomes unstable for $c > c_t$. On the contrary, the two equilibrium loci with X and Y dominating exchange stability at the transcritical bifurcation point $c = c_t$, i.e., are unstable for $c < c_t$ and stable for $c > c_t$. At the transcritical bifurcation point $c = c_t$, two equilibrium loci with X and Y

Fig. 3 The bifurcation of the symmetrical system with leaky transcription. A pitchfork bifurcation occurs at the value $c = 0.5791$. Other parameter values are $a_1 = a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0.01$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

dominating become stable and the system changes from monostable when $c < c_t$ to bistable when $c > c_t$. The bistable states are robust against variation in the parameter c . In non-leaky transcription, the high expression of one gene inducing specific lineage choice is at the expense of the low expression of the other gene. After crossing the transcritical bifurcation point, the expression of one of the two stable states becomes zero, as shown in Fig. 2 (Andreut et al. 2011), which demonstrates the gene was silenced without basal transcription. Leaky transcription changes this situation, and both genes are activated (Widder et al. 2007). A basal transcription was considered into the symmetrical system in the following section.

Leaky transcription

In the *type II* symmetric bifurcation of the system with leaky transcription, the starting central progenitor state with $X = Y$ is the only one equilibrium which is stable. This monostable state undergoes a pitchfork bifurcation, creating two differentiated states, while the starting central progenitor state becomes unstable, as shown in Fig. 3. Such a bifurcation occurs when c is increased while other parameters are kept at fixed values. In contrast, the *type I* symmetric bifurcation is a transcritical bifurcation and the transition starts from a monostable regime with two unstable states, going into the bistable regime. Different from the two stable states splitting from the single stable state in the pitchfork bifurcation, which are close after crossing the bifurcation point, in the transcritical bifurcation, two unstable states exist and are very different. After crossing the transcritical bifurcation, they become stable.

In summary, to determine the parameter variations that may trigger a symmetric bifurcation, we varied the parameters a, b, d, γ, f and c so that they impinge symmetrically on the two state variables X and Y . We analyze possible bifurcations at which the central attractor state with $X = Y$ disappears and gives rise to a bistable regime with two disparate attractor states ($X > Y$) and ($X < Y$). From the systematical variations of parameters, we find that a symmetric bifurcation in which a central attractor state with $X = Y$ is gradually destabilized and converted into an unstable state. The conversion can be classified into two types: transcritical (Type I) and pitchfork (Type II) bifurcations. The key of the symmetric bifurcations is that the system is symmetrical and the parameter variation that drives the bifurcations impinges symmetrically on the two transcriptional factors. Any imperfection in the symmetry will change the symmetric bifurcations.

The symmetry parameter variations facilitate calculations. However, might such a symmetrical situations be relevant in development? The answer is yes. One example is the deformation of a flat epithelium into one with thickenings and infolding (Oster and Alberch 1982). It is clear that slight or even strong asymmetries are present in reality, which represent the trivial case of instructive symmetry-breaking transitions (Huang et al. 2007).

Asymmetrical system

In the process of cell differentiation, the developmental potential decreases from pluripotent to multipotent, and then to unipotent cells. This developmental potential narrowing is well performed in hematopoietic lineages. During cell lineage specification, uncommitted multipotent progenitor cells might first commit to two classes of cell fates, and then to one specific fate terminally. Both Waddington's model and saddle-node bifurcation account for this phenomenon. Alternative fates remain on the waddington's landscape after passing the pitchfork bifurcation. In contrast, the potential fates disappear completely after transition to the other stable state in a saddle-node bifurcation. A pitchfork or transcritical bifurcation is well known to occur in systems with symmetry. Any imperfection in the symmetry will change the bifurcations occurring in the symmetrical systems. However, we find imperfect pitchfork and transcritical bifurcations may occur in the asymmetrical system. To compare with the symmetric case, we similarly classify the asymmetrical system Eqs. (5–6) into two types: (1) non-leaky transcription ($\gamma_1 = \gamma_2 = 0$) and (2) leaky transcription ($\gamma_1 \neq 0$ and $\gamma_2 \neq 0$).

Non-leaky transcription

When $\gamma_1 = \gamma_2 = 0$, although the system is changed from a symmetrical system to an asymmetrical one, transcritical

Fig. 4 The bifurcation diagram of the asymmetrical non-leaky transcription system with $c = c_1 = c_2$ as a control parameter. **a** The other parameter values are $a_1 = 1.01$, $a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0$. **b** Other parameter values are $a_1 = 1$, $a_2 = 1.01$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

bifurcations may also occur and become more complicated, as shown in Fig. 4. In the symmetrical system, the transcritical bifurcation is symmetrical and the progenitor cells have an equal chance to evolve outwards the two alternative states. But in the asymmetrical system, the situation becomes different. In other words, an uncommitted bipotent progenitor cell pre-patterns itself into a polarized cell that gives rise not to two symmetrical states. For instance, when $a_1 > a_2$, X is likely to win in the competition with Y and the progenitor cell progresses more easily towards a lineage with a higher value of X , as shown in Fig. 4a. In addition, another transcritical bifurcation also occurs in the downregulation direction. This asymmetrical transcritical bifurcation is a transition starting from a monostable state, going into a bistable regime by undergoing twice transcritical bifurcations. On the contrary, when $a_1 < a_2$, the scenario is opposite and the progenitor cell progresses more easily towards a lineage with a lower value of X , as shown in Fig. 4b. Therefore, any imperfection or asymmetry can induce polarized cells which provides an intrinsic possibility to the process of committed differentiation.

Leaky transcription

For the leaky transcription case, i.e., $\gamma_1 \neq 0$ and $\gamma_2 \neq 0$, the imperfection in the symmetry may change the pitchfork or

Fig. 5 Two types of imperfect pitchfork bifurcations for the asymmetrical system with leaky transcription. **a** The pitchfork bifurcation in the symmetric case is replaced by an imperfect pitchfork for the choice of parameters $a_1 = 1.01$, $a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0.01$. **b** The imperfect pitchfork bifurcation for the following choice of parameters $a_1 = 1$, $a_2 = 1.01$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0.01$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

transcritical bifurcation into a saddle-node one. We choose different a_1 and a_2 values but let $c_1 = c_2 = c$ in Eqs. (5–6) to perform the bifurcation set in the parameter space of c . The result will be a saddle-node bifurcation, as shown in Fig. 5. Such symmetry-breaking perturbations may induce loss of transcritical and pitchfork bifurcations (Liu et al. 2007). When $a_1 > a_2$, the up-regulated stable states, i.e., the states with larger X , are created instantaneously by the transformation of the previous stable states, while the down-regulated equilibrium loci form a further saddle-node bifurcation alongside with emergence of unstable states which are not created directly from the original stable states, as shown in Fig. 5a. On the contrary, when $a_1 < a_2$, the progenitor cells pre-pattern themselves into polarized cells with smaller X , as shown in Fig. 5b. This asymmetry in transcriptional activity results in a qualitatively similar symmetry-breaking in the committed states. The pitchfork bifurcation occurring in the symmetrical case is replaced by a remaining stable state alongside with a saddle-node bifurcation forming the up- or down-regulated stable states according to the relationship between a_1 and a_2 . The up-regulated stable states would be interpreted as expression states promoting one of the lineages. We also analyze the effects of other parameters, b_1 versus b_2 , d_1 versus d_2 , f_1 versus f_2 and γ_1 versus γ_2 (see the

Fig. 6 Saddle-node bifurcations for the asymmetrical system with leaky transcription. The choice of parameter are $a_1 = a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $c_2 = f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0.01$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

“Appendix”). According to our analysis, any imperfection in the symmetry will change the perfect pitchfork bifurcation into an imperfect bifurcation. Besides the occurrence of imperfect bifurcation as shown in Fig. 5, the completely asymmetric case of Eqs. (5–6) may also induce the occurrence of saddle-node bifurcation, as shown in Fig. 6. These results indicate that if cell fate decisions are initiated with asymmetry or symmetry-breaking perturbations, an uncommitted bipotent progenitor cell pre-patterns itself into a polarized cell, depending on the asymmetry or symmetry-breaking perturbations.

Discussion

We studied the behavior of a circuit of mutual inhibition with auto-activation which plays important roles in binary cell fate decisions by mathematical models. Comparison of the two systems with changes in bifurcation during differentiation of bi-potent progenitor into specific lineages helps to explain how a progenitor cell commits to a new specific fate. The commitment of a cell to a new fate corresponds to the occurrence of different types of bifurcations, depending on if the system is symmetrical and how the perturbations affect the system. Motivated by the nonlinear dynamical analysis of a symmetrical system, we have detected two types of bifurcation in the model, depending on if the basal transcription activity is incorporated. For both types of the bifurcations, i.e., transcritical and pitchfork bifurcations, the monostable state located before the bifurcation point represents the bi-potent progenitor state. Commitment occurs if cells express more than the threshold amounts of either of transcription factors. Both X and Y are simultaneously expressed at low

amounts at bipotent stages, i.e., lineage priming. When commitment occurs, the dominant transcription factor fur-

The Jacobian matrix at the steady state $(\bar{X}, \bar{Y})$ takes the form

$$J(\bar{X}, \bar{Y}, a, b, c, d, f, \gamma) = \begin{bmatrix} \frac{\partial F}{\partial X} & \frac{\partial F}{\partial Y} \\ \frac{\partial G}{\partial X} & \frac{\partial G}{\partial Y} \end{bmatrix} = \begin{bmatrix} \frac{a(c\bar{Y} + d)}{(\bar{X}\bar{Y} + b\bar{X} + c\bar{Y} + d)^2} - f & \frac{-a\bar{X}(\bar{X} + c)}{(\bar{X}\bar{Y} + b\bar{X} + c\bar{Y} + d)^2} \\ \frac{-a\bar{Y}(\bar{Y} + c)}{(\bar{X}\bar{Y} + b\bar{Y} + c\bar{X} + d)^2} & \frac{a(c\bar{X} + d)}{(\bar{X}\bar{Y} + b\bar{Y} + c\bar{X} + d)^2} - f \end{bmatrix}.$$

ther up-regulates in an auto-regulatory manner, whereas the other transcription is shut down. When the system is symmetrical, which transcription factor becomes dominant depends on the perturbations because the convergence to each lineage has equal possibility due to the symmetry. Different from the equal tendency in the symmetrical system, when asymmetry is present, an uncommitted bipotent progenitor cell pre-patterns itself into a polarized cell, depending on the types of asymmetry or symmetry-breaking perturbations.

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Conflict of interest The authors have declared that no competing interests exist.

Appendix

1. Bifurcation dynamics

To simplify the analysis we focus on the symmetrical system taking the following form

$$\frac{dX}{dt} = \gamma + \frac{aX}{XY + bX + cY + d} - fX \triangleq F(X, Y), \quad (7)$$

$$\frac{dY}{dt} = \gamma + \frac{aY}{XY + bY + cX + d} - fY \triangleq G(X, Y). \quad (8)$$

The steady states of the above equations are given by the solutions of the nonlinear system after setting $dX/dt = 0$ and $dY/dt = 0$. The steady state $(0, 0)$ of Eqs. (1–2) disappears after incorporating the basal transcription activity into the equations.

The eigenvalues of the Jacobian for the steady states of this system are more complicated to calculate than the non-leaky symmetrical system. However, we can numerically show that the system undergoes a bifurcation by increasing c . The system changes from a stable state, when $c < 0.5791$, to bistable states for $c > 0.5791$. The eigenvalues of all the systems are shown in Table 1.

- For the case of non-leaky transcription ($\gamma_1 = \gamma_2 = 0$) in the symmetrical system, the steady states satisfy

$$\frac{aX}{XY + bX + cY + d} - fX = 0, \quad (9)$$

$$\frac{aY}{XY + bY + cX + d} - fY = 0. \quad (10)$$

If $X \neq 0, Y \neq 0$,

$$XY + bX + cY + d = a/f, \quad (11)$$

$$XY + bY + cX + d = a/f. \quad (12)$$

Thus,

$$(b - c)(X - Y) = 0. \quad (13)$$

So, when $b = c$, X and Y have infinitely solutions, as shown in Fig. 2.

- Effects of all parameters on bifurcations

We also analyze the effects of other four pairs of parameters on bifurcations (Fig. 7). From the results, we can see that b_1, d_1, f_1 and γ_2 are likely to promoting differentiation towards cells with larger Y , while the others to larger X .

Table 1 Results of bifurcation analysis of systems

System	c value	X/Y value	Eigenvalues	Bifurcation type
Symmetrical system (non-leaky transcription)	0.500008	0.366024/0.366024	$\lambda_1 = -0.6340, \lambda_2 = 0$	Transcritical
	0.500001	$-2.43256e-05/1.00007$	$\lambda_1 = -0.5, \lambda_2 = 0$	Transcritical
	0.499995	$0.99998/6.69537e-06$	$\lambda_1 = -0.5, \lambda_2 = 0$	Transcritical
Symmetrical system (leaky transcription)	0.579102	0.365567/0.365567	$\lambda_1 = -0.6534, \lambda_2 = 0$	Pitchfork
Asymmetrical system ($a_1 > a_2$) (non-leaky transcription)	0.49022	$1.02/1.17852e-41$	$\lambda_1 = -0.5050, \lambda_2 = 0$	Transcritical
	0.510024	0/1	$\lambda_1 = -0.5, \lambda_2 = 0$	Transcritical
Asymmetrical system ($a_1 < a_2$) (non-leaky transcription)	0.510024	1/0	$\lambda_1 = -0.5, \lambda_2 = 0$	Transcritical
	0.49022	$8.9792e-43/1.02$	$\lambda_1 = -0.5050, \lambda_2 = 0$	Transcritical
Asymmetrical system ($a_1 > a_2$) (leaky transcription)	0.624454	0.203303/0.556441	$\lambda_1 = -0.6368, \lambda_2 = 0$	Saddle-node
Asymmetrical system ($a_1 < a_2$) (leaky transcription)	0.624454	0.556441/0.203303	$\lambda_1 = -0.6368, \lambda_2 = 0$	Saddle-node
Asymmetrical system ($a_1 = a_2, c_2 = 1, c_1$ parameter) (leaky transcription)	0.710291	0.110503/0.663075	$\lambda_1 = -0.6046, \lambda_2 = 0$	Saddle-node
	2.7265	0.660562/0.0546464	$\lambda_1 = -0.5958, \lambda_2 = 0$	Saddle-node

Fig. 7 Effect of parameters on bifurcations for the asymmetric systems with leaky transcription. **a** $b_1 > b_2$, $b_1 = 0.51$. **b** $b_1 < b_2$, $b_2 = 0.51$. **c** $d_1 > d_2$, $d_1 = 0.51$. **d** $d_1 < d_2$, $d_2 = 0.51$. **e** $f_1 > f_2$, $f_1 = 1.1$. **f** $f_1 < f_2$, $f_2 = 1.1$. **g** $\gamma_1 > \gamma_2$, $\gamma_1 = 0.011$. **h** $\gamma_1 < \gamma_2$,

$\gamma_2 = 0.011$. The choice of parameters are $a_1 = a_2 = 1$, $b_1 = b_2 = d_1 = d_2 = 0.5$, $f_1 = f_2 = 1$, and $\gamma_1 = \gamma_2 = 0.01$. Stable and unstable equilibrium loci are indicated by red and black curves, respectively. (Color figure online)

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