Cell Commitment Motif Composed of progenitor-specific TF and Fate-Decision Motif

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***Abstract*—Mutual-inhibition motif is frequently-occuring motif in transcriptional regulatory networks for cell lineage commitment. Stable attractors represent cell commitment state. But how progenitor-specific transcription factors stabilize progenitor cells and commit them to different cell fates remains unexplained. In this paper we represent the motif for cell commitment, composed of mutual-inhibition motif and progenitor-specific transcription factor, and develop associated mathematical model. In the analysis of bifurcation and dynamical simulation, the model could exhibit multiple steady stable states and transition between them, cooresponding to progenitor, committed cell state and different commitment processes. Furthermore, we demonstrate that different commitment patterns, for example that of hematopoitic stem cell and neural stem cell, could be represented with different bifurcation features.**

I. Introduction

In recent years, cell lineage specification has gained great interest. It is generally accepted that the process of lineage specification is governed by the interplay of many different transcription factors(TF), known as developmental transcription networks [1], [2]. The most common motif of cell lineage specification is described as a two-component trancriptioal factors motif, in which two transcription factors inhibit each other [2], [5], [6], [7]. This type of circuits could present bistable feature. The bistable feature of motif allows cells to make irreversible decision and adopt different fates, in which specific sets of genes are expressed and others are silent.

In circuits analysis, mathematical model is developed to explore the circuit features quilitatively. The equilibria in mathematical model of lineage specification define the different stable expression states, each corresponding to a different cell type. As such, cell differentiation is then described as a transition from one stable equilibrium to another [8], [9].

Cell lineage specification from stem cell to terminal mature cell is composed of many stages, and every differentiation stage is viewed as a fate-decision switch. For example, from a single cell type, the hematopoietic stem cell, all mature blood cells emerge through a hierarchical series of lineage decisions via different progenitor cells. Thus, hematopoiesis is often depicted as a hierarchical differentiation tree, with a HSC at the root and the mature blood cells as the leaves [3]. Cell lineage specification is viewed as a hierarchy of differentiation processes(figure hierarchy differentiation), who's basic unit is single branching process, namely fate-decision switch, which is governed by stage-specific genes(transcriptional factors). Here we study the basic constitutive units of hierarchical differentiation process and want to understand the property of these basic units and how they play their roles in lineage specification processes. We represent a three-component motif as the basic unit of hierarchical differentiation process, as shown in Fig. 1. The motif is composed of progenitor-specific factor and fate decision motif. Because of this, it's possible to integrate progenitor state and differentiated sate to a dynamical model corresponding to this three-component motif. While this motif is simple, it helps in the identification of basic princicple for lineage speicification. It might act as basic unit of more complex hierarchical differentiation process and describe more easily dynamical features of lineage tree [4].

The aim of our paper, is as following. We want to
1.use the dynamical model of three-component motif to explore the transition from progenitor state to differentiated states
2.explore the capability of and differentiation in different cell states.

II. Modeling

Mutual inhibition motif is a widespread motif in cell lineage-specification(as described in Fig. 1). The motif is composed of two components as lineage-specific transcriptional factors. The two components inhibit each other's activity and endow this circuit bistability, corresponding to two differentiated states. The two components have auto-activation interaction allowing cells to maintain the lineage-specific expresssion of two trancriptional factors, consolidating two stable steady states. There are various possibilities for autoregulating mechanissms such as autocrine signaling or more extensive signaling loops [5].

Here we represent three-component motif as part of a general framework in relation to a broad number of differentiation scenarios.(Table I) The motif under consideration is a single branching process in a hierarchy of differentiation processes. The single branching process integrate decision-makig motif with progenitor-specific transcriptional factor. The final integrated motif is shown in Fig. 1. This motif consist of two parts, progenitor-specific factor and mutual-inhibition motif, (Fig. 1), each implementing different functions in the commitment

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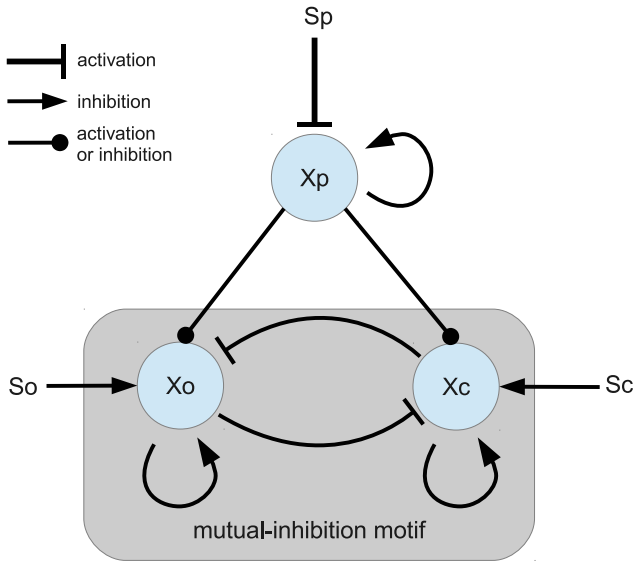

Fig. 1. **genetic circuit topologies of different type for cell lineage commitment**. Sharp arrows and blunt arrows represent activation and inhibition,respectively; and circle-ending arrows are either activation or inhibition.

process: Progenitor-specific TF determines whether the cell is ready to differentiate or remains in the stable progenitor state. Fate-decision switch in turn determines into which cell type the cell will differentiate. The interaction between progenitor-specific TF and fate decison motif is generalized. There are three motif scenarios according to interaction type: two activation, two inhibition or activation-inhibtion mixture. The three motif scenarios are exemplified in Table I.

TABLE I. SOME GENETIC CIRCUITS IN CELL DIFFERENTIATION

System	components	type
pancreas cell [10]	Hnf6(Ptf1a Ngn3)	two activation
pancreas cell [10]	Ngn3(Pax4 Arx)	two activation
myeloid progenitor [3]	GATA-1(Fli-1 EKLF)	two activation
myeloid progenitor [3]	C/EBP(EgrNab Gfi-1)	two activation
helper T cell [11]	TGF-beta(T-bet GATA-3)	two inhibition
human bone precursor [12]	Tweak(RUNX2 SOX9)	two inhibition
myeloid progenitor [3]	GATA-2(GATA-1 PU.1)	activation inhibition

We use mathematical modeling to analyze dynamical behavior of three-component motif(Fig. 1). In this motif, activation and inhibition interactions between components were represented by Hill equations. This is a widely used approximation as molecular interactions are usulally known to behave in a sigmoidal fashion. The similar simplified models have been used to describe the coexistence of several expression states in specific cell fate sysems, such as those involved in hematopoiesis or embryonic stem cell differentiation [4].

Here are the assumptions in modeling: 1. There are three cell types to be captured in terms of stable equilibrium, namely, a progenitor(P), and two committed(O and C) cell types. O and C cell type is recognized by high level of a characteristic TF, denoted as X_p and X_o, respectively, but low level of the other TFs X_o and X_p, respectively. Progenitor cell type is recognized by about equal level of characteristic TFs X_o,X_c. 2. All the polymeriztion is n-meriztion. Here n is a indefinite number. 3. We do not assume that these processes(autoregulation, inhibition) are completely independent of each other, but rather result in an overall activation rate for each component. 4. Stimuli are assumed to enter the system in the following ways. An differentiation-inhibitive stimulus will inhibit progenitor maintenance factor S_p, whereas stimuli acting in the pro-O or pro-C direction enhance the level of the lineage-specific TFs, respectively. The structure of the model and stimulus inputs is depicted in Fig. 1.

These functional relationships can be summarized in a set of ordinary differential equations as follows:

$$\frac{X_p}{dt} = \alpha_p \frac{\nu^p + \nu^p_{sp} S_p + \nu^p_{xp} X_p^n}{1 + S_p + X_p^n} - \delta_p X_p \quad (1)$$

$$\frac{X_o}{dt} = \alpha_o \frac{\nu^o + \nu^o_{so} S_o + \nu^o_{xo} X_o^n + \nu^o_{xc} X_c^n k^o_{xc} + \nu^o_{xp} X_p^n k^o_{xp}}{1 + S_o + X_o^n + X_c^n k^o_{xc} + X_p^n k^o_{xp}} - \delta_o X_o \quad (2)$$

$$\frac{X_c}{dt} = \alpha_c \frac{\nu^c + \nu^c_{sc} S_c + \nu^c_{xp} X_p^n k^c_{xp} + \nu^c_{xo} X_o^n k^c_{xo} + \nu^c_{xc} X_c^n}{1 + S_c + X_p^n k^c_{xp} + X_o^n k^c_{xo} + X_c^n} - \delta_c X_c \quad (3)$$

where the coefficient $n \geq 2$, and for $i, j \in P, O, C$ the state variables x_i and all parameters are non-gegative real numbers. Their basal values are given in Table II. S_p corresponds to a pro-differentiation stimulus, S_o,S_c to pro-O and pro-C stimulus, respectively.

The first term in each equation represents overall production rate, including the contribution of input stimulation, activation and inhibition. The second term in each equation is a first-order decay with rate constant k.

For analysis, we simplify assumptions as following. Fistly, the parameters in the mutual-inhibition switch (Eqs. 2,3) are assigned symmetric values, unless mentioned differently. That means there is no inherent bias of the cell type toward one or the other lineage, as long as no lineage specific stimulus is applied. Secondly, it is assumed that $n = 2$, which is the lowest Hill coefficient producing a sigmoidal shape of the activation term. Qualitative results thereofre apply equivalently for higher Hill coefficients $n \geq 2$, arising from more complex reactions. Thirdly, the rate parameters corresponding to inhibition interactions are assigned zeros.

III. RESULT

We classify the motif into three scenarios according to the type of two interaction between progenitor-specific TF and two lineage-specific TFs, namely two circle-ending arrows in Fig. 1. The three scenarios is two activation scenario, two inhibitioin scenario and inhibition-activation scenario. There are more biological examples in two activation scenario than other scenario in lineage commitment motif. As such, we firstly studies the two activation scenario.

A. Two Activation Scenario

In two activation scenario, transcriptional factor X_p activate X_o ($\nu^o_{xp} \neq 0$), X_p activate X_c ($\nu^c_{xp} \neq 0$). Additionally, the parameters corresponding to rate of inhibition interaction is set to zeros ($\nu^p_{sp} = 0$, $\nu^o_{xc} = 0$, $\nu^c_{xo} = 0$). Other parameters are

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TABLE II. PARAMETER SET USED FOR BIFURCATION ANALYSIS AND SIMULATIONS.

Parameter	Basal value	Parameter	Basal value
α_p	10.25, 10	δ_p	0.02
α_o	0.2	δ_o	0.2, 0.1
α_c	0.2	δ_c	0.2, 0.1
ν^p	1.2, 1	S_p	1
ν^o	0.1	S_o	1
ν^c	0.1	S_c	1
ν^p_{xp}	0.06, 0.0668	K^p_{xp}	0.05, 0.1
ν^o_{so}	1	$K^c_x c$	0.1
ν^o_{xo}	30, 1	$K^o_x o$	0.1
ν^o_{xp}	0.2, 1	$K^o_x p$	0.1
ν^c_{sc}	1	$K^o_x c$	1.8,0.5
ν^c_{xc}	30, 1	$K^c_x p$	0.1
ν^c_{xp}	0.2, 1	$K^c_x o$	1.8, 0.5

The parameters are without units. One value for one parameter is used for both subcritical and supcritical scenario. Two values for the same parameter is used for subcritical and supcritical scenario, respectively.

shown in Table II. Therefore, we can get the final equation set as follows:

$$\frac{X_p}{dt} = \alpha_p \frac{\nu^p + \nu^p_{xp} X_p^2}{1 + S_p K^p_{sp} + X_p^2} - \delta_p X_p \quad (4)$$

$$\frac{X_o}{dt} = \alpha_o \frac{\nu^o + \nu^o_{so} S_o + \nu^o_{xo} X_o^2 + \nu^o_{xp} X_p^2 K^o_{xp}}{1 + S_o + X_o^2 + X_c^2 K^o_{xc} + X_p^2 K^o_{xp}} - \delta_o X_d (5)$$

$$\frac{X_c}{dt} = \alpha_c \frac{\nu^c + \nu^c_{sc} S_c + \nu^c_{xp} X_p^2 K^c_{xp} + \nu^c_{xc} X_c^2}{1 + S_c + X_p^2 K^c_{xp} + X_o^2 K^c_{xo} + X_c^2} - \delta_c X_c (6)$$

The cell states of the system are represented by stable equilibria of Equations, i.e., stable steady states of equations $x^* = (x^*_P, x^*_O, x^*_C)$. Progenitor cell, namely P cell type, is represented by equilibrium with low level of both of lineage-specific TFs. Committed cell, namely O cell type or C cell type, is represented by equilibrium with one lineage-specific TF in high level and the other lineage-specific TF in low level. We split the equation set into two parts for analysis. One part is Eqn. 4, namely progenitor-specific factor. Another part is Eqn. 5 and Eqn. 6 , namely mutual-inhibiton motif. Firstly, we study the mutual inhibition motif. We take the state variable X_p as parameter in system composed of later two equations and get the bifurcation diagram for X_o vs stimuli X_p. According to the bifurcation type in diagram for X_o vs X_p, the diagram could be classfied into two scenarios: subcritical type and supcritical type. We analyze the two scenarios respectively as following.

B. Two Activation Scenario(Subcritical)

We get the bifurcation diagram for X_o vs X_p as shown in Fig. 2 bottom, there is a subcritical bifurcation. We study the dyanmical behavior of X_p. We take the first equation as a system and get the bifurcation diagram for X_p vs input S_p(Fig. 2 top). There is two LP bifurcation point, exhibiting bistable phenomenon. We could get the following intuitive result from two bifurcation diagrams (Fig. 2): When S_p is in low level, X_p is in high level and X_o and X_c is low but equal in balance, corresponding to progenitor P cell type. When S_p is in high level, X_p is in low level and either X_o or X_c is in high level, while the other TF X_c or X_o is in low level, correspondong to O cell type or C cell type.

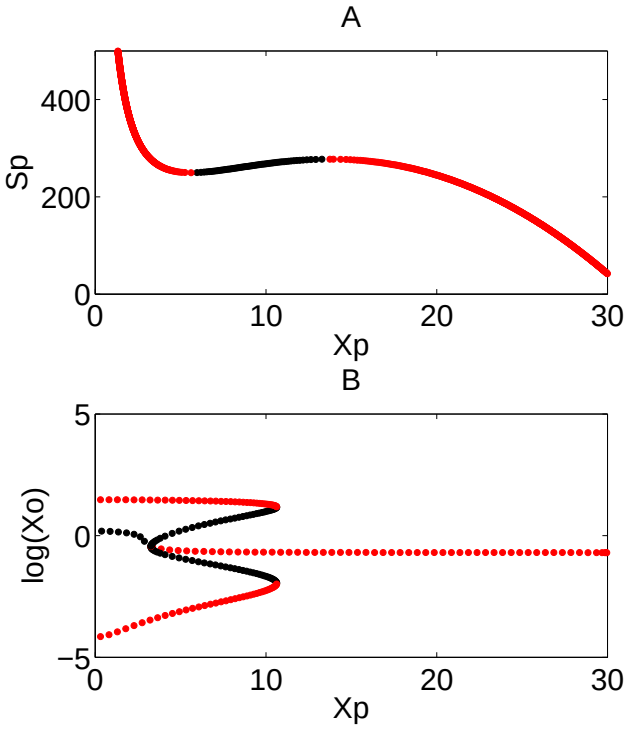

Fig. 2. **bifurcation diagram of system of two activation scenario(subcritical) xp(3.26)**.
A(top): bifurcation diagram for X_p vs the input S_p.
B(bottom): bifurcation diagram for logrithm of X_o vs the input X_p.
Stable equilibrium manifolds are given as red dashed lines, unstable equilibrium manifolds as dark dashed lines.

We implement dynamical simulation to check whether the model could exhibit three cell states and transitions between three states upon stimulating signals. It is possible for cell to commit only if S_p is high enough to reduce X_p in to a low level. So the stimulation S_p is determinant of lineage commitment launch.

In Fig. 3A, S_p and S_o is concomitantly applied. In Fig. 3B, S_p is applied firstly and S_o is applied secondly. In Fig. 3C, S_o is applied firstly and S_p is applied secondly. Application scheme in Fig.3A,B,C could induces escape from the P state and attraction to the O state, correspondint to transition from progenitor state to committed state. In Fig. 3D, the concomitant application of low S_p dn S_o could not induces attraction to the O state. This demenstrate that the committed state could maintain stably only when the progenitor-specific TF is high enough.

Next, we study the relation of the parameter area with capability of commitment. We split the parameter area into three subarea as following: subarea1($X_p > 10.5$), subarea2($3 < X_p < 10.5$), subarea3($X_p < 3$). When parameter X_p switch between different subareas, there would be different patterns in commitment process.

When X_p shift in subarea1 (Fig. 4 A→A+A (A→A)), the model could exhibit the proliferation pattern: progenitor cell could retain the progenitor properties. When a cell divides in this biology enviroment corresponding to this parameter

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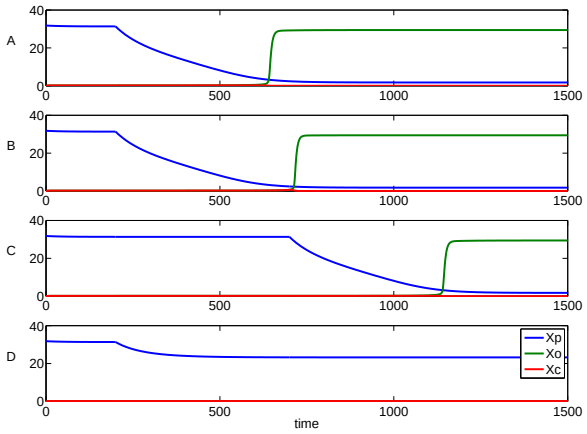

Fig. 3. **dynamics simulation**
Blue line:Xp, green line:Xo, red line: Xc;
A: time(0-200) S=[0,0,0]; time(200-1500) S=[400,10,0];
B: time(0-200) S=[0,0,0]; time(200-700) S=[400,0,0]; time(700-1500) S=[400,10,0];
C: time(0-200) S=[0,0,0]; time(200-700) S=[0,10,0]; time(700-1500) S=[400,10,0];
D: time(0-200) S=[0,0,0]; time(200-700) S=[200,10,0]; time(700-1500) S=[200,10,0];
A:S_p, S_o is added concomitantly. Differentiation to O cell type.
B:S_p is added firstly.Differentiation to O cell type.
C:S_o is added firstly.Differentiation to O cell type.
D:S_p is added concomitantly,but S_p is not sufficient. Not Differentiation.
Data format: $S = [S_p, S_o, S_c]$. "time(200-1500) S=[400,10,0];" indicates that from 200 to 1500, the stimuli input setting is S_p=400, S_o=10, S_o=0;

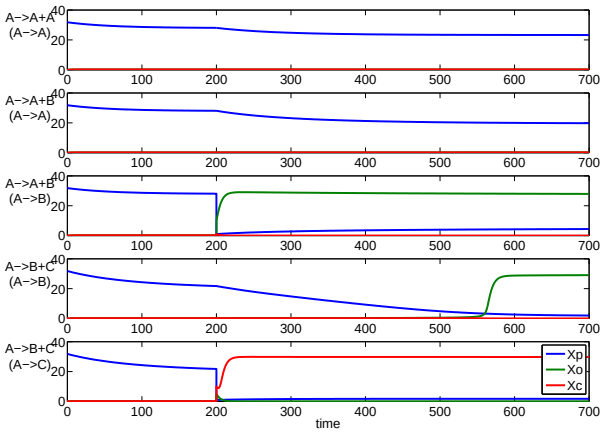

Fig. 4. **three differentiation patterns**
Blue line:Xp, green line:Xo, red line: Xc;
Initial Conditions: [31.8 0 0] for all four subplot;
A→A+A(A→A): time(0-200) S=[100,20,0]; time(200-700) S=[200,20,0];
A→A+B(A→A): time(0-200) S=[100,20,0]; time(200-700) S=[250,20,0];
A→A+B(A→B): time(0-200) S=[100,20,0]; time(200-700) S=[250,20,0]; [Xp,Xo,Xc]=[1 10 1] at time=500;
A→B+C(A→B): time(0-200) S=[250,20,0]; time(200-700) S=[400,20,0];
A→B+C(A→C): time(0-200) S=[250,20,0]; time(200-700) S=[400,20,0]; [Xp,Xo,Xc]=[1 5 10] at time=500;
Data format: $S = [S_p, S_o, S_c]$. "time(200-1500) S=[400,10,0];" indicates that from 200 to 1500, the stimuli input setting is S_p=400, S_o=10, S_o=0;

setting, mother cell could become two daughter cells, both of which are identical to mother cell, as shown in Fig.5.

When X_p shift from subarea1 to subarea2(Fig. 4 A→A+B (A→A), A→A+B (A→B)), the model could exhibit the mix pattern: progenitor cell could retain the progenitor properties, or commit to specific cell type. When a cell divides in this biology enviroment, corresponding to this parameter setting, mother cell could become one commited cell, and one progenitor cells, identical to mother cell, as shown in Fig.5.

When X_p shift from subarea2 to subarea3(Fig. 4 A→B+C (A→B), A→B+C (A→C)), the model could exhibit the commitment pattern: progenitor cell could no longer retain the progenitor properties and must commit to specific cell types. Because there are only two equilibria, corresponding to two differentiation state, in the parameter settings of subarea3. When a cell divides in this biology enviroment, corresponding to this parameter setting, mother cell could become two daughter cells, any of which is committed cell. Which kind of committed cell dauther cell is achieved depends on initial condition and detailed parameter settings, as shown in Fig.5.

When stimulus S_p increase from a low value to a high value, system will jump from subarea1 to subarea2, then jump from subarea2 to subarea3, corresponding to transition from progenitor cell to committed cell. It's worth noting that progenitor cell and committed cell could coexist in biological environment corresponding to the parameter setting of subarea2. The scheme of this commitment patterns is described as in Fig. 5.

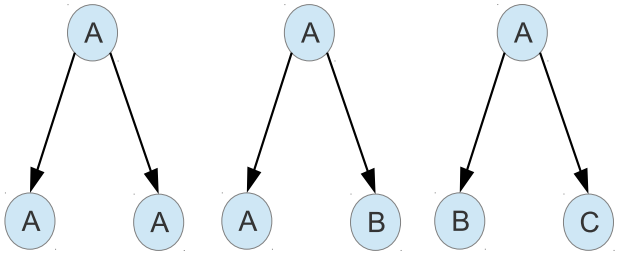

Fig. 5. The committment pattern corresponding to three subarea(subarea1, subarea2, subarea3 for subcritical scenario)

As what are presented in Fig. 4, different level of stimuli S_p was applied to system, there are different response, corresponding to three commitment pattern in Fig. 5. When S_p is low, system is locked in progenitor state. Cell have only ability of proliferation. When S_p is intermediate, system is in intermediate state. Cell have ability of both proliferation and differentiation. When S_p is high, system is in differentiation state. Even if cells in proliferation, after some time, these cells went into differentiation. So all the cells have to differentiate in this condition.

The commitment pattern could be used to qualitatively explain some feature of commitment of the CNS stem cells. CNS stem cell undergo repeated asymmetric cell divisions, first producing neurons then glia [13], [14]. Firstly, single CNS stem cell produce stem cell and neuron through asymmetric division, corresponding to model in subarea2 with S_p

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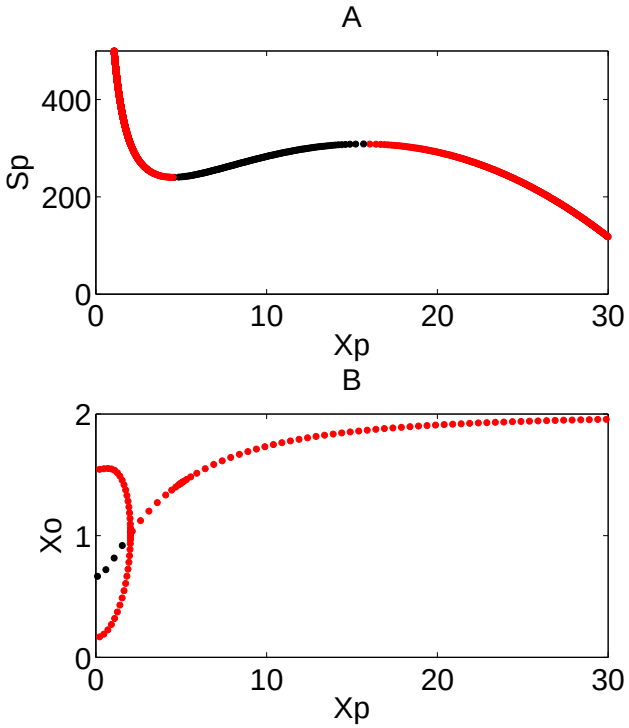

Fig. 6. **bifurcation diagram of system of two activation scenario(supcritical). xp(2.032)**
A(top): bifurcation diagram for X_p vs the input S_p.
B(bottom): bifurcation diagram for logrithm of X_o vs the input X_p.
Stable equilibrium manifolds are given as solid lines, unstable equilibrium manifolds as dashed lines.

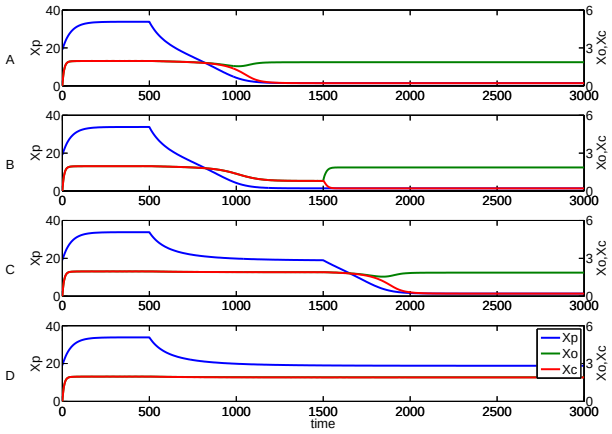

Fig. 7. **dynamics simulation**
Blue line:Xp, green line:Xo, red line: Xc;
Left Y Axis:Xp; Right Y Axis:Xo,Xc;
A: time(0-500) S=[0,0,0]; time(500-3000) S=[400,10,0];
B: time(0-500) S=[0,0,0]; time(500-1500) S=[400,0,0]; time(1500-3000) S=[400,10,0];
C: time(0-500) S=[0,0,0]; time(500-1500) S=[300,10,0]; time(1500-3000) S=[400,10,0];
D: time(0-500) S=[0,0,0]; time(500-3000) S=[300,10,0];
A:S_p, S_o is added concomitantly. Differentiation to O cell type.
B:S_p is added firstly.Differentiation to O cell type.
C:S_o is added firstly.Differentiation to O cell type.
D:S_p is added concomitantly,but S_p is not sufficient. Not Differentiation.
Data format: $S = [S_p, S_o, S_c]$. "time(200-1500) S=[400,10,0];" indicates that from 200 to 1500, the stimuli input setting is S_p=400, S_o=10, S_o=0;

in intermediate level. Subsequently, single CNS stem cell cannot maitain progenitor cell state and produce two glia, cooresponding to model in subarea3 with S_p in high level.

C. Two Activation Scenario(Supcritical)

We get the bifurcation diagram for X_o vs X_p as shown in Fig. 6A) bottom using different parameter from subcritical scenario, there is a supcritical bifurcation. Detailed parameters are shown in Table II. Here we study the dyanmics of X_p. We take the first equation as a system and get the bifurcation diagram for X_p vs input S_p(Fig. 6B). Similar to subcritical scenario, there is also two LP bifurcation point, exhibiting bistable phenomenon. When S_p is in low level, X_p is very high and X_o and X_c is low but equal in balance, corresponding to progenitor cell type. When S_p is in high level, X_p is in low level and either X_o or X_c is in high level, while the other is in low level, corresponding to committed cell type, O cell type or C cell type.

Similar to subcritical scenario, we implement dynamical simulation to check whether the model could exhibit three states and transitions between three states upon stimulating signals.. It is possible for cell to commit only if S_p is high enough to reduce X_p to a low level. So the stimulation S_p is determinant of lineage commitment.

In Fig. 7A, S_p and S_o is applied concomitantly. In Fig. 7B, S_p is applied firstly and S_o secondly. In Fig. 7C, S_o is applied firstly and S_p secondly. The scheme of Fig.7A,B,C could induce escape from the P state and attraction to the O state, corresponding to transiton from progenitor cell to committed cell. In Fig. 7D, the concomitant application of low S_p dn S_o could not induces attraction to the O state.

Next, we study the relation of the parameter area with proligeration and commitment. We split the parameter area into three subareas as following: subarea1($X_p > 2.5$), subarea2($X_p < 2.5$). When parameter X_p switch between different subareas, there would be different scenarios in commitment process.

When X_p shift from subarea1 to subarea1(Fig. 8 A→A+A (A→A), A→A+B (A→A), A→A+B (A→B)), the model could exhibit the proliferation pattern: progenitor could only retain the progenitor properties. When a cell divides in this biology enviroment, corresponding to this parameter setting, mother cell could become two daughter cells, both of which are identical to mother cell.

When X_p shift from subarea1 to subarea2(Fig. 8 A→B+C (A→B), A→B+C (A→C)), the model could exhibit the commitment pattern: progenitor could no longer retain the progenitor properties and must commit to specific cell types. Because there are only two equilibrium, corresponding to two differentiation state, in this parameter settings of subarea2. When a cell divides in this biology enviroment, corresponding to this parameter setting, mother cell could become two daughter cells, any of which is committed cell. Which kind of committed type daughter cell is depend on initial condition

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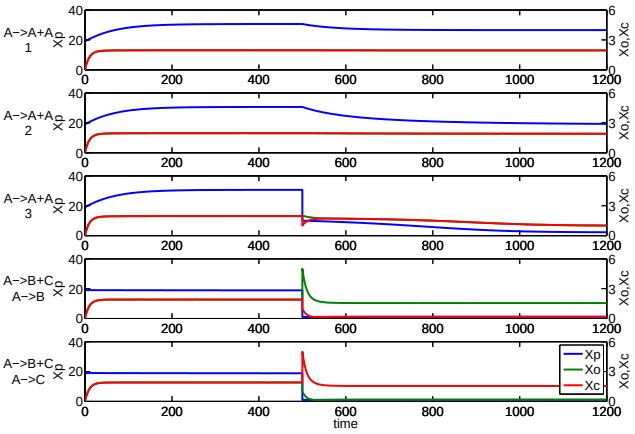

Fig. 8. **three differentiation patterns**
Blue line:Xp, green line:Xo, red line: Xc;
Left Y Axis:Xp; Right Y Axis:Xo,Xc;
A→A+A(A→A): time(0-200) S=[100,0,0], time(200-700) S=[200,0,0];
A→A+B(A→A): time(0-200) S=[100,0,0], time(200-700) S=[300,0,0];
A→A+B(A→B): time(0-200) S=[100,0,0], time(200-700) S=[300,0,0]; time=1500, [Xp,Xo,Xc]=[10,2,1];
A→B+C(A→B): time(0-200) S=[300,0,0], time(200-700) S=[500,0,0]; time=1500, [Xp,Xo,Xc]=[1,5,1];
A→B+C(A→C): time(0-200) S=[300,0,0], time(200-700) S=[500,0,0]; time=1500, [Xp,Xo,Xc]=[1,1,5];
Data format: $S = [S_p, S_o, S_c]$. "time(200-1500) S=[400,10,0];" indicates that from 200 to 1500, the stimuli input setting is S_p=400, S_o=10, S_o=0;

and detailed parameter settings.

When stimulus S_p increase from a low value to a high value, system will jump from subarea1 to subarea3, corresponding to transition from progenitor to differentiated state. Contrary to subcritical scenario, progenitor cell and differentiated cell could not coexist in both biological environments corresponding to the parameter setting of subarea1 and subarea2.

As what are presented in 8, different level of stimuli S_p was applied to system, there are different response, corresponding to two commitment pattern in figure. When S_p is low, system is locked in progenitor state. Cell have only ability of proliferation. When S_p is high, system is in differentiation state. Even cells in proliferation, after some time, these cells went into differentiation. So all the cells have to differentiate in this condition.

The commitment pattern could be used to qualitatively explain the hematopoietic stem cells. Hematopoietic stem cells produce different type of daughther cells undergo asymmetric cell divisions, corresponding to system in subarea2 with S_p in high level.

IV. Discussion

We have developed a general model of cell commitment, based on interaction between progenitor-specific TF and lineage-specific TFs. The well-known motif of two mutually inhibiting TFs is a common motif in lineage commitment studies. Besides mutual-inhibition motif, the motif studied in this thesis contains an additional TF that is responsibile for maintainging the progenitor state. From the analysis in this thesis, this general motif is functionally composed of two switch: one switch responsible for initiating differentiation and the other switch responsibile for fate determination. As we have shown, the model is able to exhibit the biological observations: the existence of three stable equilibria (cell types), and the transitions from the progenitor state to committed lineage.

The motif of two activation scenario is more prevalent than other scenario (two inhibition scenario and inhibiton-activation mix scenario). As such, we studied the two activation scenario in detail in this context. Nevertheless, the two inhibition scenario and inhibition-activation mix scenario need to be explored.

The principle of subcritical and supcritical scenario is as following: When progenitor-specific TF is in high level, both lineage-specific TFs undergo strong self-activation. But when progenitor-specific TF reduce to a level lower than critical value, self-activation of both specific TFs is weaker than cross-inhibition between both TFs, leading to the loss of stability of intermediate equilibrium, corresponding to transition from progenitor cell to committed cell.

Additionally, the subcritical scenarios could be used to explain qualitatively neural stem cell and hematopoietic stem cell, respectively. For neural stem cell, neurons emerge firstly and glia are produced secondly, corresponding to model in subcritical scenario, which have intermediate state with potential to both proliferation and differentiation. For hematopoietic stem cell, different type of daughter cells emerge concomitantly, corresponding to modelin supcritical scenario.

The represented model could apply in the commitment scenario, where cell adopt a binary fate decision, namely transition from a progenitor cell to two kinds of differentiated cells. Furthermore, The model suits the fate decision that is adopted in two steps, the first switch triggering commitment and the second switch deciding which lineage were adopted. The commitment motif studied is only a single commitment process. While the lineage commitment of species is a hierarchy of commitment process like a tree. As such, in the future, we try to integrate single commit motif into bigger lineage tree to explore many properties of lineage tree, including transdifferentiation, dedifferentiation, namely potential of progenitor cell in cell reprogramming.

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