Homeostasis for fiber circuits

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1 Introduction

Considering the formalism presented in [4, 7], given a coupled cell network containing n nodes where the dynamical state of each node is represented by a variable x_i and its internal dynamics is given by the nonlinear function $f_i(x_1,...,x_n)$, we have that the dynamics of the system is represented by

$$\dot{\vec{x}} = \vec{F}(\vec{x}), \tag{1}$$

where $\vec{x} = (x_1,...,x_n)$ and $\vec{F} = (f_1,...,f_n)$. To consider the phenomenon of homeostasis, we add to the system of equations an input parameter $I \in \mathbb{R}$

and also assume that the system has a stable equilibrium at $\vec{x} = \vec{x_0}$ and $I = I_0$ such that we have

$$\dot{\vec{x}} = \vec{F}(\vec{x}(I), I), \tag{2}$$

and

$$\vec{F}(\vec{x_0}(I_0), I_0) = 0. \tag{3}$$

Following [7, 1], we verify the possibility of existence of infinitesimal homeostasis points and, further, the existence of infinitesimal chair points. For this, we first choose one variable $z(I) = x_j(I)$ of the node variables $\vec{x}$ and define this variable as the **input-output map**[1]. The goal is to verify the homeostasis behavior in $z(I)$ as we vary the parameter I around I_0, and this behavior is possible when we satisfy the following conditions:

infinitesimal homeostasis:

$$\frac{\partial z}{\partial I}(I_0) = 0 \tag{4}$$

infinitesimal chair:

$$\begin{aligned} \frac{\partial z}{\partial I}(I_0) = \frac{\partial^2 z}{\partial I^2}(I_0) &= 0, \\ \frac{\partial^3 z}{\partial I^3}(I_0) &\neq 0. \end{aligned} \tag{5}$$

Fortunately, the framework presented in [7] provides a consistent method to obtain the defining conditions for both infinitesimal homeostasis and infinitesimal chairs in a given coupled cell system. Although the authors of [3] provides a generalization for multiple inputs, here we first consider that the input I is provided to only one node of the network. The node depending directly on the input I is called **input node**, while the node j on which we define the input-output map $z(I)$ is denoted as **output node**. The rest of the nodes in the network are the **regulatory nodes**.

Denoting the input and output nodes as $\mathcal{I}$ and $\mathcal{O}$, respectively, while all the regulatory nodes as ρ, we consider the general Jacobian of the system of Eq. 1 as

$$J = \begin{pmatrix} f_{\mathcal{I},\mathcal{I}} & f_{\mathcal{I},\rho} & f_{\mathcal{I},\mathcal{O}} \\ f_{\rho,\mathcal{I}} & f_{\rho,\rho} & f_{\rho,\mathcal{O}} \\ f_{\mathcal{O},\mathcal{I}} & f_{\mathcal{O},\rho} & f_{\mathcal{O},\mathcal{O}} \end{pmatrix}, \tag{6}$$

where $f_{i,j} = \partial f_i / \partial x_j$. Then, we define the homeostasis matrix H as the Jacobian at the equilibrium point $(\vec{x_0}(I_0), I_0)$ without the first row and the last column (regarding the input and output nodes) [7]. Therefore,

$$H = \begin{pmatrix} f_{\rho,\mathcal{I}} & f_{\rho,\rho} \\ f_{\mathcal{O},\mathcal{I}} & f_{\mathcal{O},\rho} \end{pmatrix}. \tag{7}$$

It follows from [7] that the conditions of infinitesimal homeostasis and infinitesimal chair displayed by equations 4 and 5 can be obtained by using the matrix H. Thus, denoting

$$det(H)(\vec{x_0}, I_0) = h(I_0), \tag{8}$$

we have that

infinitesimal homeostasis:

$$h(I_0) = 0 \tag{9}$$

infinitesimal chair:

$$\begin{aligned} h(I_0) = h'(I_0) = 0 \\ h''(I_0) \neq 0 \end{aligned} \tag{10}$$

For general circuits it is possible to obtain the defining conditions for both infinitesimal homeostasis and infinitesimal chair by using the topology of the network and avoiding to solve the determinant of a $(n-1) \times (n-1)$ matrix. This idea is showed by the following equation:

$$det(H) = det(B_1)det(B_2)\cdots det(B_m), \tag{11}$$

where each B_j is a $K \times K$ block submatrix of the matrix H and its determinant is an irreducible polynomial.The connection with the network topology is provided by showing that for each B_j there is a corresponding subnetwork of the original network [7]. Therefore, each $det(B_j) = 0$ defines a homeostasis condition.

2 Example from the literature

We use the following example to demonstrate how we find the homeostasis conditions using mainly the network topology. The example used is original from [7] and showed in Fig.1.

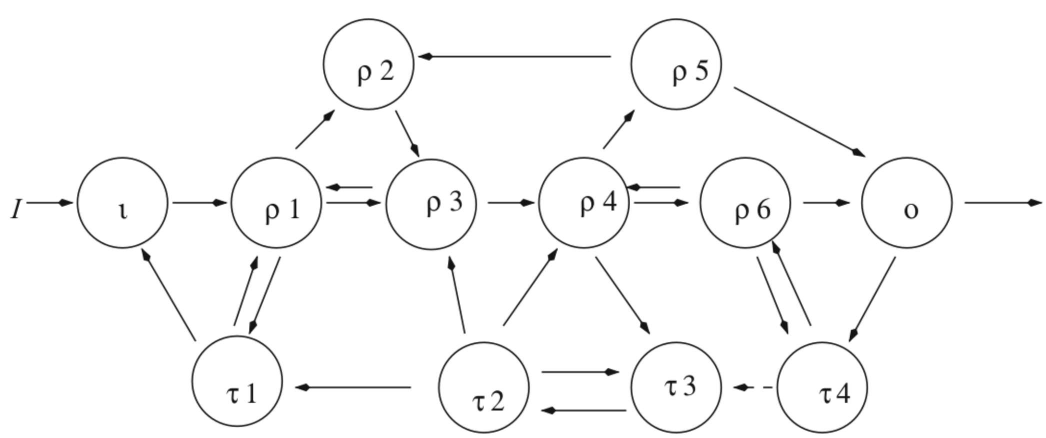

Figure 1: 12-node example. Source: [7]

Using the notation provided by [7] we have that the **simple nodes** are $(\rho_1, \rho_2, \rho_3, \rho_4, \rho_5, \rho_6)$, the **appendage nodes** are $(\tau_1, \tau_2, \tau_3, \tau_4)$ and the **super-simple nodes** are $\mathcal{I}, \rho_1, \rho_3, \rho_4, \mathcal{O}$. The **IO-simple paths** are

$$\begin{aligned}
&\mathcal{I} \to \rho_1 \to \rho_2 \to \rho_3 \to \rho_4 \to \rho_5 \to \mathcal{O}\\
&\mathcal{I} \to \rho_1 \to \rho_2 \to \rho_3 \to \rho_4 \to \rho_6 \to \mathcal{O}\\
&\mathcal{I} \to \rho_1 \to \rho_3 \to \rho_4 \to \rho_5 \to \mathcal{O}\\
&\mathcal{I} \to \rho_1 \to \rho_3 \to \rho_4 \to \rho_6 \to \mathcal{O}
\end{aligned} \tag{12}$$

The classification above allows us to obtain the subnetworks showed in Fig. 2. The subnetworks obtained are either appendage subnetworks or super-simple structural subnetworks (more details is provided in [7], but I can add more here if necessary). Since each subnetwork obtained is associated with the blocks B_j of the homeostasis matrix H, we have that

$$det(H) = det(B_1)det(B_2)det(B_3)det(B_4)det(B_5)det(B_6) \tag{13}$$

where B_1 and B_2 are the Jacobian of the appendage subnetworks A_1 and A_2 and B_3, B_4, B_5 and B_6 are the homeostasis matrices of the super-simple structural subnetworks $H(\mathcal{L}(\mathcal{I}, \rho_1), H(\mathcal{L}(\rho_1, \rho_3)), H(\mathcal{L}(\rho_3, \rho_4))$ and $H(\mathcal{L}(\rho_4, \mathcal{O}))$, respectively. Therefore, we have

$$J_{A_2} = \begin{pmatrix} f_{\rho_2,\rho_2} & f_{\rho_2,\rho_3} \\ f_{\rho_3,\rho_2} & f_{\rho_3,\rho_3} \end{pmatrix}, \tag{14}$$

$$H(\mathcal{L}(\rho_1, \rho_3)) = \begin{pmatrix} f_{\rho_2,\rho_1} & f_{\rho_2,\rho_2} \\ f_{\rho_3,\rho_1} & f_{\rho_3,\rho_2} \end{pmatrix} \tag{15}$$

$$H(\mathcal{L}(\rho_4, \mathcal{O})) = \begin{pmatrix} f_{\rho_5,\rho_4} & f_{\rho_5,\rho_5} & 0 & 0 \\ f_{\rho_3,\rho_1} & 0 & f_{\rho_3,\rho_2} & f_{\rho_6,\rho_4} \\ 0 & 0 & f_{\rho_4,\rho_6} & f_{\rho_4,\rho_4} \\ 0 & f_{\mathcal{O},\rho_5} & f_{\mathcal{O},\rho_6} & 0 \end{pmatrix} \tag{16}$$

and $det(J_{A_1}) = f_{\tau_1,\tau_1}$, $det(H(\mathcal{L}(\mathcal{I}, \rho_1))) = f_{\rho_1,\mathcal{I}}$, and $det(H(\mathcal{L}(\rho_3, \rho_4))) = f_{\rho_4,\rho_3}$. Then, each condition $det(B_j) = 0$ determines an infinitesimal homeostasis type.

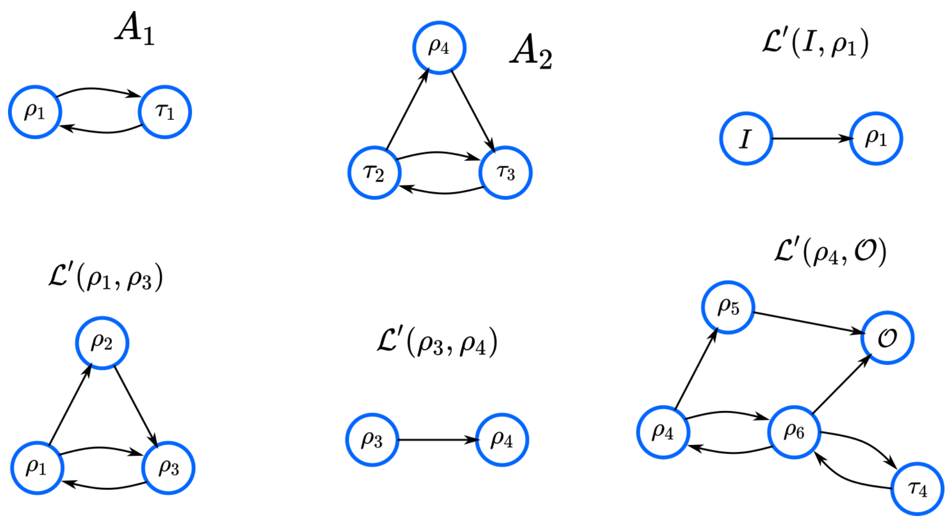

Figure 2: Homeostasis subnetworks of the 12-node network.

3 Broken circuits

In this section, we consider the case where the provided input $\mathcal{I}$ does not preserve the fibration symmetry [2, 6]. For this, we choose one node within the fiber to receive the input, which breaks the fibration symmetry of the network. Note that we only provide input to mRNA nodes in the mRNA/Protein network representation.

3.1 $|n = 1, \ell\rangle$ input-output circuit

Considering the FFF broken circuit, we cannot reduce the network to the quotient form, since the fibration symmetry is broken by the input to x_1^R only. Therefore, we need to verify all the possible regulation combinations for the input-output network shown in Fig. 3.

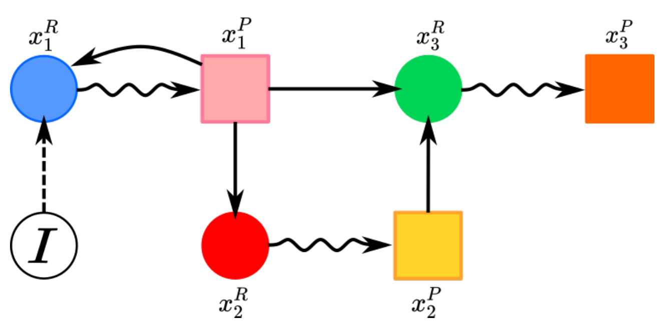

Figure 3:

3.1.1 General vector fields

The general possible dynamics restricted by the topology of this network is given by the following system of admissible equations [4]:

$$
\begin{aligned}
\dot{x}_1^R &= f_{x_1^R}(x_1^R, x_1^P, \mathcal{I}) \\
\dot{x}_1^P &= f_{x_1^P}(x_1^P, x_1^R) \\
\dot{x}_2^R &= f_{x_2^R}(x_2^R, x_1^P) \\
\dot{x}_2^P &= f_{x_2^P}(x_2^P, x_2^R) \\
\dot{x}_3^R &= f_{x_3^R}(x_3^R, x_1^P, x_2^P) \\
\dot{x}_3^P &= f_{x_3^P}(x_3^P, x_3^R)
\end{aligned}
\quad , \tag{17}
$$

where $\vec{F} = (f_{x_1^R}, f_{x_1^P}, f_{x_2^R}, f_{x_2^P}, f_{x_3^R}, f_{x_3^P})$ is the vector of nonlinear functions as described in section 1. The Jacobian of this system is

$$
J = \begin{pmatrix}
f_{x_1^R,x_1^R} & f_{x_1^R,x_1^P} & 0 & 0 & 0 & 0 \\
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 \\
0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & 0 & 0 & 0 \\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 \\
0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 \\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P}
\end{pmatrix}, \tag{18}
$$

where the condition for stability of equilibria is defined over $f_{x_2^R,x_2^R}$, $f_{x_2^R,x_2^R}$, $f_{x_3^R,x_3^R}$ and $f_{x_3^P,x_3^P}$ and the eigenvalues of the 2×2 block matrix defined by the first rows and columns of the Jacobian. Moreover, the homeostasis matrix is given by

$$
H = \begin{pmatrix}
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 \\
0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & 0 & 0 \\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 \\
0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} \\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R}
\end{pmatrix}. \tag{19}
$$

3.1.2 Special model

Considering the $|n = 1, \ell\rangle$ fiber circuits observed in the *E. Coli* genetic regulatory network, we have two possibilities for the regulations within the fiber: the SAT-FFF and the UNSAT-FFF. For each one of the two possibilities there are 4 possibles combinations for the external regulations to node x_3^R:

two with equal types of regulations to the output node (Fig. 4a,b,e,f), and two for the case of alternated types of regulations (Fig. 4c,d,g,h).

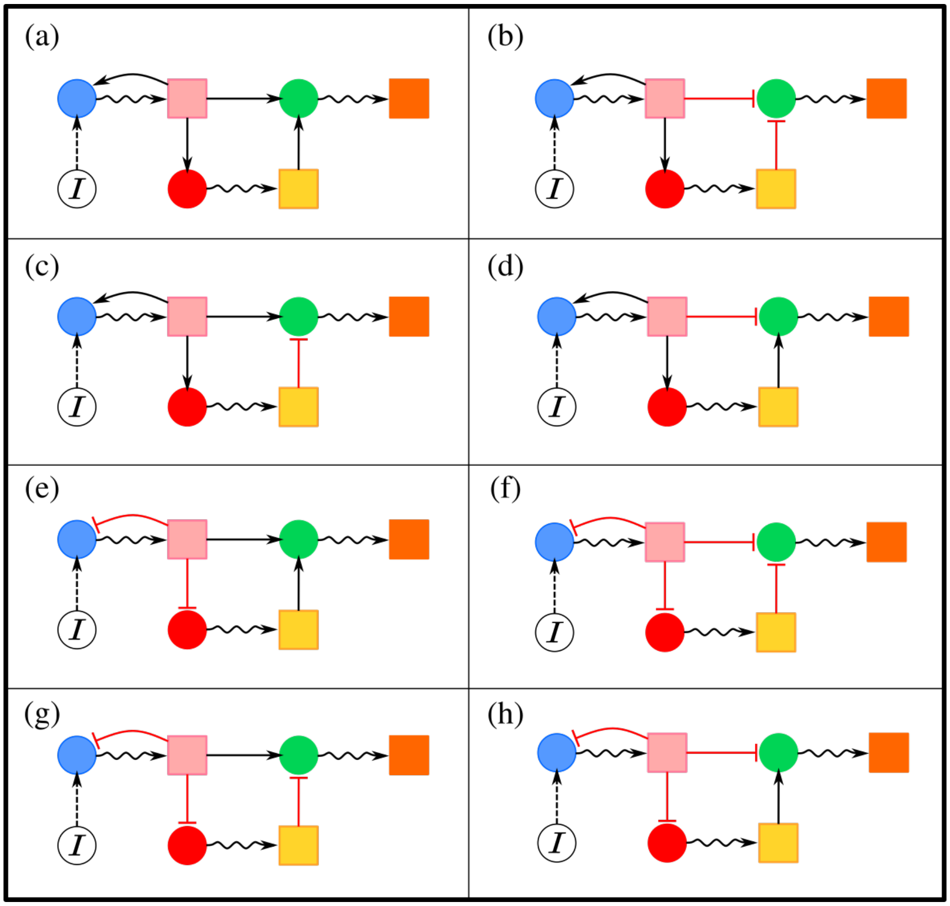

Figure 4:

Now, considering the special equations [5, 1], we have the following core differential equations for all SAT-FFF and UNSAT-FFF circuits:

SAT-FFF	**UNSAT-FFF**
$\dot{x_1}^R = -\delta_1 x_1^R + \gamma_1(1 - S(x_1^P)) + I$ $\dot{x_1}^P = -\alpha_1 x_1^P + \beta_1 x_1^R$ $\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2(1 - S(x_1^P))$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$	$\dot{x_1}^R = -\delta_1 x_1^R + \gamma_1 S(x_1^P) + I$ $\dot{x_1}^P = -\alpha_1 x_1^P + \beta_1 x_1^R$ $\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2 S(x_1^P)$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$

Therefore, we can list all combinations for the external regulated nodes x_3^R and x_3^P as

Circuit	**SAT-FFF**
Fig. 4(a)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3(1 - T(x_1^P + x_2^P))$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(b)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3 T(x_1^P + x_2^P)$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(d)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3 S(x_1^P) + \gamma_3'(1 - S(x_2^P))$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(c)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3(1 - S(x_1^P)) + \gamma_3' S(x_2^P)$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$

Circuit	**UNSAT-FFF**
Fig. 4(e)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3(1 - T(x_1^P + x_2^P))$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(f)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3 T(x_1^P + x_2^P)$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(h)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3 S(x_1^P) + \gamma_3'(1 - S(x_2^P))$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$
Fig. 4(g)	$\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3(1 - S(x_1^P)) + \gamma_3' S(x_2^P)$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$

3.1.3 Stable equilibrium conditions

The general form of the Jacobian assumes two different patterns according to the combination of regulations. These two forms are represented by J_1 and J_2 and are given as follows:

$$J_1 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 & 0 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 \end{pmatrix}, \tag{20}$$

and

$$J_2 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 & 0 \\ 0 & \xi_2\gamma_3 S'(x_1^P) & 0 & -\xi_2\gamma_3 S'(x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 \end{pmatrix}, \tag{21}$$

where we have $\xi_1, \xi_2 \in \{-1, +1\}$. J_1 and J_2 represent both SAT and UNSAT circuits depending on the combinations of ξ_1, while ξ_2 is related to the type of the external regulations. S and T are both Hill functions.

Now, define

$$K = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) \\ \beta_1 & -\alpha_1 \end{pmatrix}, \tag{22}$$

such that we have

$$\begin{aligned} \Delta_k &= det(K) = \alpha_1\delta_1 - \xi_1\beta_1\gamma_1 S'(x_1^P) \\ \tau_k &= Tr(K) = -(\alpha_1 + \delta_1) \end{aligned}. \tag{23}$$

Since the matrix K is the same for both forms of the Jacobian, we have that the stability conditions for J_1 and J_2 are the same. Thus,

$-\delta_2 < 0$	$-\delta_3 < 0$	$-(\alpha_1 + \delta_1) < 0$
$-\alpha_2 < 0$	$-\alpha_3 < 0$	$\alpha_1\delta_1 - \xi_1\beta_1\gamma_1 S'(x_1^P) > 0$

Considering that all parameters are strictly positive, then all conditions depending only on the parameters are satisfied. The last one depending on $S'(x^P)$ is always satisfied for $\xi_1 = +1$ (positive inner regulations). For the case $\xi_1 = -1$(negative inner regulations), the derivative of the Hill function must satisfy the relation

$$S'(x_1^P) > -\frac{\alpha_1 \delta_1}{\beta_1 \gamma_1}. \tag{24}$$

3.1.4 Infinitesimal homeostasis conditions

Since the homeostasis matrix H is not the same for J_1 and J_2, then we define H_1 and H_2 to distinguish between the two cases:

$$H_1 = \begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & -\delta_3 \\ 0 & 0 & 0 & 0 & \beta_3 \end{pmatrix}, \tag{25}$$

and

$$H_2 = \begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 \\ 0 & \xi_2\gamma_3 S'(x_1^P) & 0 & -\xi_2\gamma_3 S'(x_2^P) & -\delta_3 \\ 0 & 0 & 0 & 0 & \beta_3 \end{pmatrix}, \tag{26}$$

To facilitate the calculation of the determinant of the given matrices, we use the method used in section 2 to find the irreducible blocks of $H_{1,2}$ using the topology of the network.

There are only simple nodes in this network, and only three of them are super-simple nodes: x_1^R, x_3^R, x_3^P. Thus, each pair of super-simple nodes defines the subnetworks: $\mathcal{L}'(x_1^R, x_3^R)$ and $\mathcal{L}'(x_3^R, x_3^P)$. From these two subnetworks, we have the following infinitesimal homeostasis conditions:

$$f_{x_3^P, x_3^R} = \beta_3(I_0) = 0, \tag{27}$$

for both H_1 and H_2 combinations. However, we do not expect this to be satisfied because $\beta_i \neq 0$.

For the subnetwork $\mathcal{L}'(x_1^R, x_3^R)$, we have the following conditions. For H_1:

$$det \begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) \end{pmatrix} (I_0) = 0, \tag{28}$$

which gives us the condition

$$\beta_1(\xi_1\xi_2\gamma_2\gamma_3\beta_2 S'(x_1^P)T'(x_1^P+x_2^P)+\xi_2\delta_2\alpha_2\gamma_3 T'(x_1^P+x_2^P))=0, \tag{29}$$

and considering that $\beta_1 \neq 0$, we have

$$\xi_1\xi_2\gamma_2\gamma_3\beta_2 S'(x_1^P)T'(x_1^P+x_2^P)+\xi_2\delta_2\alpha_2\gamma_3 T'(x_1^P+x_2^P)=0, \tag{30}$$

or

$$T'(x_1^P+x_2^P)(\delta_2\alpha_2+\xi_1\gamma_2\beta_2 S'(x_1^P))=0 \tag{31}$$

Following the same procedure for matrix H_2, we have

$$-\xi_1\xi_2\gamma_2\gamma_3'\beta_2 S'(x_1^P)S'(x_2^P)+\xi_2\delta_2\alpha_2\gamma_3 S'(x_1^P)=0, \tag{32}$$

or

$$S'(x_1^P)(\delta_2\alpha_2\gamma_3-\xi_1\gamma_2\gamma_3'\beta_2 S'(x_2^P))=0. \tag{33}$$

3.2 $|\phi_2,\ell\rangle$ input-output circuit

Here, we consider the case where the given input $\mathcal{I}$ turns the Fibonacci fiber of golden ratio ϕ_2 into a broken symmetric circuit. For this, only the dynamics of node x_2^R from Fig. 5 depends explicitly on the input $\mathcal{I}$. Thus, we cannot reduce the circuit to its quotient form.

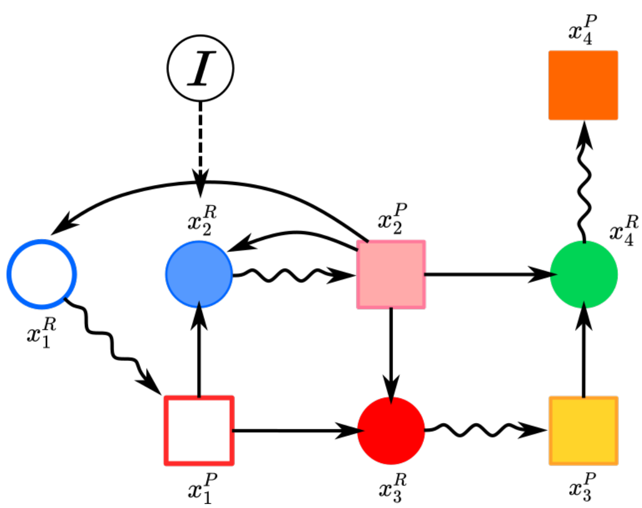

Figure 5:

3.2.1 General vector fields

The general possible dynamics restricted by the topology of this network is given by the following system of admissible equations:

$$\begin{aligned}
\dot{x}_1^R &= f_{x_1^R}(x_1^R, x_2^P)\\
\dot{x}_1^P &= f_{x_1^P}(x_1^P, x_1^R)\\
\dot{x}_2^R &= f_{x_2^R}(x_2^R, x_1^P, x_2^P, \mathcal{I})\\
\dot{x}_2^P &= f_{x_2^P}(x_2^P, x_2^R)\\
\dot{x}_3^R &= f_{x_3^R}(x_3^R, x_1^P, x_2^P)\\
\dot{x}_3^P &= f_{x_3^P}(x_3^P, x_3^R)\\
\dot{x}_4^R &= f_{x_4^R}(x_4^R, x_2^P, x_3^P)\\
\dot{x}_4^P &= f_{x_4^P}(x_4^P, x_4^R)
\end{aligned}\quad , \tag{34}$$

where $\vec{F} = (f_{x_1^R}, f_{x_1^P}, f_{x_2^R}, f_{x_2^P}, f_{x_3^R}, f_{x_3^P}, f_{x_4^R}, f_{x_4^P})$ is the vector of nonlinear functions as described in section 1. The Jacobian of this system is

$$J = \begin{pmatrix}
f_{x_1^R,x_1^R} & 0 & 0 & f_{x_1^R,x_2^P} & 0 & 0 & 0 & 0\\
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & f_{x_1^P,x_2^P} & 0 & 0 & 0 & 0\\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 & 0 & 0\\
0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P} & 0 & 0\\
0 & 0 & 0 & f_{x_4^R,x_2^P} & 0 & f_{x_4^R,x_3^P} & f_{x_4^R,x_4^R} & 0\\
0 & 0 & 0 & 0 & 0 & 0 & f_{x_4^P,x_4^R} & f_{x_4^P,x_4^P}
\end{pmatrix}, \tag{35}$$

where the condition for stability of equilibria is defined over $f_{x_3^R,x_3^R}$, $f_{x_3^P,x_3^P}$, $f_{x_4^R,x_4^R}$ and $f_{x_4^P,x_4^P}$ and the eigenvalues of the 4×4 block matrix defined by the first rows and columns of the Jacobian. Moreover, the homeostasis matrix is given by

$$H = \begin{pmatrix}
f_{x_1^R,x_1^R} & 0 & 0 & f_{x_1^R,x_2^P} & 0 & 0 & 0\\
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 & 0\\
0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 & 0\\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P} & 0\\
0 & 0 & 0 & f_{x_4^R,x_2^P} & 0 & f_{x_4^R,x_3^P} & f_{x_4^R,x_4^R}\\
0 & 0 & 0 & 0 & 0 & 0 & f_{x_4^P,x_4^R}
\end{pmatrix}. \tag{36}$$

3.2.2 Special model

Considering the genes *uxuR*, *lgoR* and *exuR* in the *E.Coli* bacteria, these genes belong to the only Fibonacci ϕ_2 circuit of the bacteria's genetic network, and they only regulate themselves with negative regulations. Therefore, we have four possible combinations by changing the regulations to node x_4^R in Fig. 5. These combinations are shown in Fig. 6.

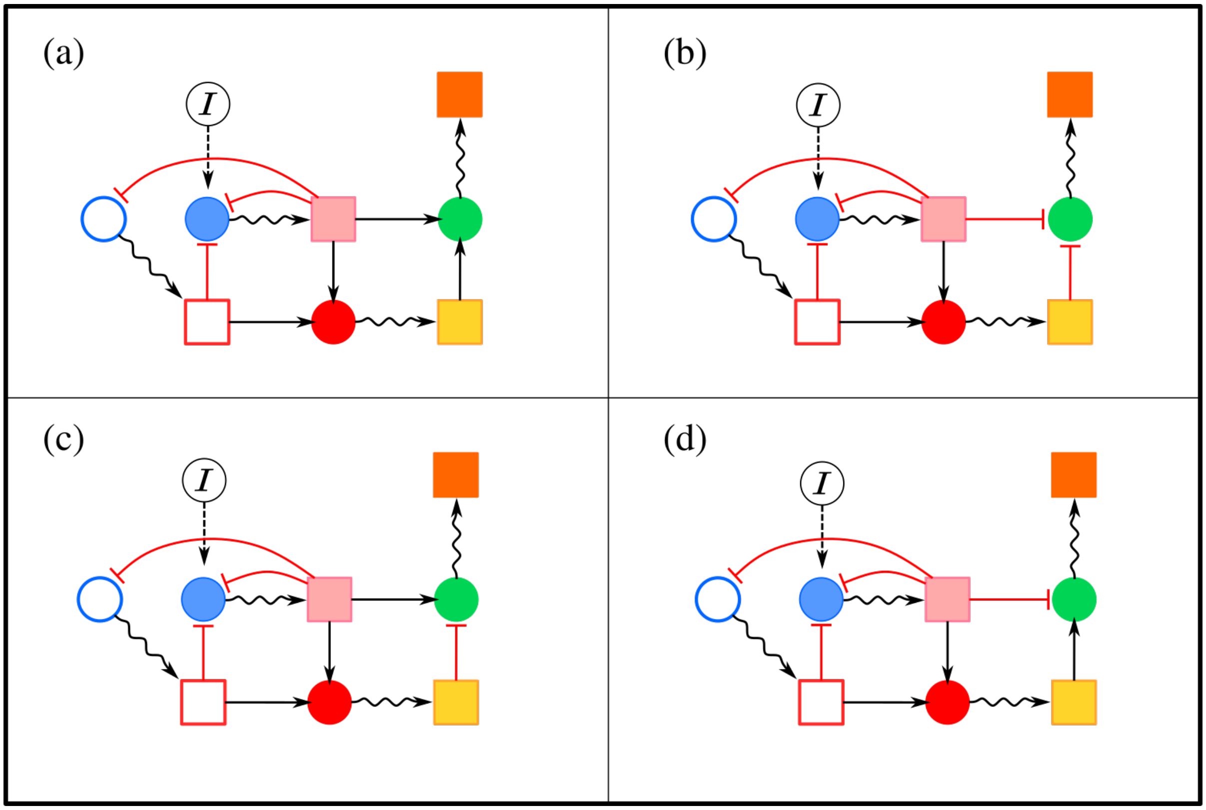

Figure 6:

Now, considering the special equations [5], we have the following core differential equations for the *uxuR*-*lgoR*-*exuR* circuit:

uxuR-*lgoR*-*exuR* **circuit**
$\dot{x_1}^R = -\delta_1 x_1^R + \gamma_1 S(x_1^P)$ $\dot{x_1}^P = -\alpha_1 x_1^P + \beta_1 x_1^R$ $\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2 T(x_1^P + x_2^P) + \mathcal{I}$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$ $\dot{x_3}^R = -\delta_3 x_3^R + \gamma_3 T(x_1^P + x_2^P)$ $\dot{x_3}^P = -\alpha_3 x_3^P + \beta_3 x_3^R$

Therefore, we can list all combinations for the external regulated nodes x_4^R and x_4^P as

Circuit	*uxuR*-*lgoR*-*exuR* **circuit**
Fig. 6(a)	$\dot{x_4}^R = -\delta_4 x_4^R + \gamma_4(1 - T(x_2^P + x_3^P))$ $\dot{x_4}^P = -\alpha_4 x_4^P + \beta_4 x_4^R$
Fig. 6(b)	$\dot{x_4}^R = -\delta_4 x_4^R + \gamma_4 T(x_2^P + x_3^P)$ $\dot{x_4}^P = -\alpha_4 x_4^P + \beta_4 x_4^R$
Fig. 6(d)	$\dot{x_4}^R = -\delta_4 x_4^R + \gamma_4 S(x_2^P) + \gamma_4'(1 - S(x_3^P))$ $\dot{x_4}^P = -\alpha_4 x_4^P + \beta_4 x_4^R$
Fig. 6(c)	$\dot{x_4}^R = -\delta_4 x_4^R + \gamma_4(1 - S(x_2^P)) + \gamma_4' S(x_3^P)$ $\dot{x_4}^P = -\alpha_4 x_4^P + \beta_4 x_4^R$

3.2.3 Stable equilibrium conditions

The Jacobian of the system is a 8×8 matrix where the first six rows and columns are the same for all the 4 possible circuits. Considering the two forms J_1 and J_2 for the Jacobian, we have

$$J_1 = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & 0 & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 & 0 & 0 \\ 0 & 0 & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) & -\delta_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_4 & -\alpha_4 \end{pmatrix}, \tag{37}$$

and

$$J_2 = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & 0 & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 & 0 & 0 \\ 0 & 0 & 0 & \xi_1 \gamma_4 S'(x_2^P) & 0 & -\xi_1 \gamma_4 S'(x_3^P) & -\delta_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_4 & -\alpha_4 \end{pmatrix}, \tag{38}$$

where $\xi_1 \in \{-1, +1\}$.

Now, define

$$K = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_1^P) \\ \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) \\ 0 & 0 & \beta_2 & -\alpha_2 \end{pmatrix}. \tag{39}$$

The stability analysis for the Jacobian J of this system is more complex, since we have a block matrix of dimension 4×4. The other blocks contain in each one only one element. Therefore, for the existence of a stable equilibrium point we require the partial requirements:

$-\delta_3 < 0$	$-\delta_4 < 0$
$-\alpha_3 < 0$	$-\alpha_4 < 0$

.

Moreover, we require that the real part of the eigenvalues of matrix K are negative. The eigenvalues of J are the roots of the characteristic polynomial

$$P(\lambda) = A + B\lambda + C\lambda^2 + D\lambda^3 + E\lambda^4, \tag{40}$$

where we find

$$\begin{aligned} A &= \delta_1\alpha_1(A' + \delta_2\alpha_2) + B' \\ B &= [\delta_1\alpha_1(\alpha_2 + \delta_2) + \delta_2\alpha_2(\alpha_1 + \delta_1)] + A'(\alpha_1 + \delta_1) \\ C &= A' + [\delta_1\alpha_1 + \delta_2\alpha_2 + (\alpha_1 + \delta_1)(\alpha_2 + \delta_2)] \\ D &= \delta_1 + \delta_2 + \alpha_1 + \alpha_2 \\ E &= 1 \end{aligned} \tag{41}$$

with

$$\begin{aligned} A' &= -\gamma_2\beta_2 T'(x_1^P + x_2^P) \\ B' &= -\gamma_1\gamma_2\beta_1\beta_2 S'(x_2^P)T'(x_1^P + x_2^P) \end{aligned}. \tag{42}$$

3.2.4 Infinitesimal homeostasis conditions

We obtain the infinitesimal homeostasis conditions by using the algorithm provided in [7]. For this circuit, all nodes are simple, whereas four are super-simple: x_2^R, x_2^P, x_4^R and x_4^P. Therefore, we can find the subnetworks for the pairs of super-simple nodes: $\mathcal{L}'(x_2^R, x_2^P)$, $\mathcal{L}'(x_2^P, x_4^R)$ and $\mathcal{L}'(x_4^R, x_4^P)$. The infinitesimal homeostasis conditions for $\mathcal{L}'(x_2^R, x_2^P)$ and $\mathcal{L}'(x_4^R, x_4^P)$ are, respectively, $\beta_2(I_0) = 0$ and $\beta_4(I_0) = 0$, which are not feasible since $\beta_i \neq 0$ for the special model.

For the subnetwork $\mathcal{L}'(x_2^P, x_4^R)$ we have the following homeostasis matrices

$$H_1(\mathcal{L}'(x_2^P, x_4^R)) = \begin{pmatrix} -\delta_1 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & \beta_3 & -\alpha_3 \\ 0 & 0 & \xi_1\gamma_4 T'(x_2^P + x_3^P) & 0 & \xi_1\gamma_4 T'(x_2^P + x_3^P) \end{pmatrix}, \tag{43}$$

and

$$H_2(\mathcal{L}'(x_2^P, x_4^R)) = \begin{pmatrix} -\delta_1 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & \beta_3 & -\alpha_3 \\ 0 & 0 & \xi_1\gamma_4 S'(x_2^P) & 0 & -\xi_1\gamma_4' S'(x_3^P) \end{pmatrix}. \tag{44}$$

The infinitesimal homeostasis condition for $H_1(\mathcal{L}'(x_2^P, x_4^R))$ is

$$\xi_1\gamma_4 T'(x_2^P+x_3^P)\big[\delta_1\alpha_1\gamma_3\beta_3 T'(x_1^P+x_2^P)+\delta_1\alpha_1\delta_3\alpha_3+\gamma_1\beta_1\gamma_3\beta_3 T'(x_1^P+x_2^P)\big]=0, \tag{45}$$

and for $H_2(\mathcal{L}'(x_2^P, x_4^R))$ is

$$\begin{aligned} -\delta_1\alpha_1\gamma_3\beta_3\gamma_4' T'(x_1^P+x_2^P)S'(x_3^P)+\delta_1\alpha_1\delta_3\alpha_3\gamma_4 S'(x_2^P) \\ -\beta_1\beta_3\gamma_1\gamma_3\gamma_4' S'(x_2^P)S'(x_3^P)T'(x_1^P+x_2^P)=0 \end{aligned} \tag{46}$$

3.3 Two input nodes $|n=1,\ell\rangle$

Starting from the symmetric circuit $|n=1,\ell\rangle$ where nodes x_1^R and x_2^R receive equivalent inputs I, we now consider the case where the directed edges $I \to x_1^R$ and $I \to x_2^R$ are weighted by two real parameters a and b, respectively. In the special model, we consider that the mRNA concentration of x_1^R is added by $+aI$ while the mRNA concentration of x_2^R is added by $+bI$. When $a \neq b$ the fibration symmetry is broken and there is no more balanced coloring between the pairs $\{x_1^R, x_2^R\}$ and $\{x_1^P, x_2^P\}$. To reduce to one the symmetry parameter, we consider the new parameter $\sigma = a/b$ and redefine the input as $I \leftarrow aI$. Hence, we have the general broken circuit shown at Fig. 7. For $\sigma = 0$ we recover the broken circuit analyzed in subsection 3.1 while for $\sigma = 1$ we obtain the symmetric fiber.

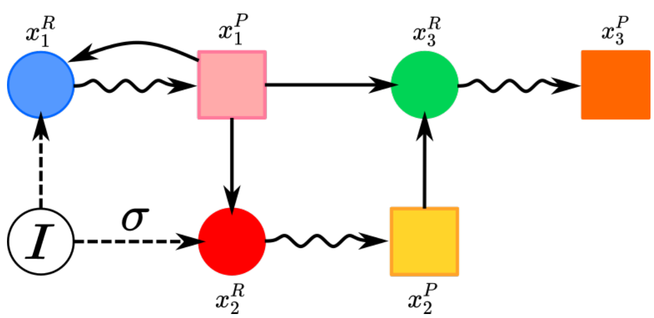

Figure 7:

The general admissible system of equations for this circuit differs from Eq. 17 only in the dependence of the nonlinear function $f_{x_2^R}$, and it is given as

$$\begin{aligned}
\dot{x}_1^R &= f_{x_1^R}(x_1^R, x_1^P, \mathcal{I}) \\
\dot{x}_1^P &= f_{x_1^P}(x_1^P, x_1^R) \\
\dot{x}_2^R &= f_{x_2^R}(x_2^R, x_1^P, \sigma\mathcal{I}) \\
\dot{x}_2^P &= f_{x_2^P}(x_2^P, x_2^R) \\
\dot{x}_3^R &= f_{x_3^R}(x_3^R, x_1^P, x_2^P) \\
\dot{x}_3^P &= f_{x_3^P}(x_3^P, x_3^R)
\end{aligned}, \tag{47}$$

This time, the circuit has two input nodes and we cannot apply the same methodology used before as we need to take into account the generalization of the theoretical framework presented in section 1 based on [7]. This generalization is described in [3].

Therefore, we enumerate the proper classifications for the network of Fig. 7 to find the general infinitesimal homeostasis conditions. First, we denote the input nodes $x_1^R \to I_1$ and $x_2^R \to I_2$, and the output node $x_3^P \to \mathcal{O}$. Then, we have the following $I_1\mathcal{O}$**-simple paths**:

$$\begin{aligned}
I_1 &= x_1^R \to x_1^P \to x_3^R \to x_3^P = \mathcal{O} \\
I_1 &= x_1^R \to x_1^P \to x_2^R \to x_2^P \to x_3^R \to x_3^P = \mathcal{O}'
\end{aligned} \tag{48}$$

while we have one single $I_2\mathcal{O}$**-simple path**:

$$I_2 = x_2^R \to x_2^P \to x_3^R \to x_3^P = \mathcal{O}. \tag{49}$$

There are no appendage nodes, only simple nodes. Thus, we have $\{x_1^R, x_1^P, x_2^R, x_2^P, x_3^R, x_3^P\}$ as I_1-simple nodes and $\{x_2^R, x_2^P, x_3^R, x_3^P\}$ as I_2-simple nodes. Following the notation used in [3] we have that the *absolutely super-simple nodes* are x_3^R and x_3^P. Therefore, from these enumerations, we identify the *absolutely super-simple structural* subnetwork $\mathcal{L}'(x_3^R, x_3^P)$ containing only x_3^R and x_3^P. In principle, this subnetwork can allow only Haldane homeostasis, but following the special model used so far, the factor $\det(H(\mathcal{L}'(x_3^R, x_3^P))) = f_{x_3^P, x_3^R} = \beta_3 \neq 0$. Moreover, we can also determine the *input counterweight* subnetwork $\mathcal{W}_{\mathcal{G}}$ composed by nodes $\{I_1 = x_1^R, I_2 = x_2^R, x_1^P, x_2^P, x_3^R\}$. The homeostasis type supported by this subnetwork is obtained from the determinant relation $det(H'(\mathcal{W}_{\mathcal{G}})) = 0$, where H' is called generalized homeostasis matrix. H' can be obtained from the Jacobian

$J_{\mathcal{W}_{\mathcal{G}}}$:

$$J_{\mathcal{W}_{\mathcal{G}}} = \begin{pmatrix} f_{x_1^R,x_1^R} & f_{x_1^R,x_1^P} & 0 & 0 & 0 \\ f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 \\ 0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & 0 & 0 \\ 0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 \\ 0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} \end{pmatrix}, \tag{50}$$

where for $H'(\mathcal{W}_{\mathcal{G}})$ the last column of $J_{\mathcal{W}_{\mathcal{G}}}$ is replaced by the column resulted from implicit differentiation, such that we have

$$H'(\mathcal{W}_{\mathcal{G}}) = \begin{pmatrix} f_{x_1^R,x_1^R} & f_{x_1^R,x_1^P} & 0 & 0 & -f_{x_1^R,I} \\ f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 \\ 0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & 0 & -f_{x_2^R,I} \\ 0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 \\ 0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & 0 \end{pmatrix}, \tag{51}$$

at the equilibrium point $(\vec{x}_0(I_0), I_0)$. According to [3], we can decompose $H'(\mathcal{W}_{\mathcal{G}})$ into m homeostasis matrices

$$det(H'(\mathcal{W}_{\mathcal{G}})) = \pm f_{x_1^R,I} det(H_1) \pm f_{x_2^R,I} det(H_2) \tag{52}$$

where m is the number of input nodes, and H_i is the homeostasis matrix regarding the input node I_i. Here, we obtain the determinant of H' directly, such that we have

$$\begin{aligned} det(H'(\mathcal{W}_{\mathcal{G}})) = &-f_{x_2^R,I} f_{x_2^P,x_2^R} f_{x_3^R,x_2^P}(f_{x_1^R,x_1^R} f_{x_1^P,x_1^P} - f_{x_1^R,x_1^P} f_{x_1^P,x_1^R}) \\ &- f_{x_1^R,I} f_{x_1^P,x_1^R}(f_{x_2^R,x_1^P} f_{x_2^P,x_2^R} f_{x_3^R,x_2^P} + f_{x_2^R,x_2^R} f_{x_2^P,x_2^P} f_{x_3^R,x_1^P}) = 0. \end{aligned} \tag{53}$$

From Eq. 53 we can recover the case worked in section 3.1 regarding the circuit receiving only one input by setting $\sigma = 0$. In this case, the infinitesimal homeostasis condition is given by

$$det(H'(\mathcal{W}_{\mathcal{G}})) = f_{x_1^R,I} f_{x_1^P,x_1^R}(f_{x_2^R,x_1^P} f_{x_2^P,x_2^R} f_{x_3^R,x_2^P} + f_{x_2^R,x_2^R} f_{x_2^P,x_2^P} f_{x_3^R,x_1^P}) = 0, \tag{54}$$

equivalent to the conditions obtained in section 3.1 for which $f_{x_1^R,I} = 1$.

Considering the form of the Jacobian of the FFF circuit for the special model given by Eq. 20 and Eq. 21, we have that the condition of Eq. 53 is

$$\begin{aligned} &-\sigma\beta_2\gamma_3 T'(x_1^P + x_2^P)\Big[\delta_1\alpha_1 - \xi_1\beta_1\gamma_1 S'(x_1^P)\Big] \\ &-\beta_1\Big[\xi_1\gamma_2\gamma_3\beta_2 S'(x_1^P)T'(x_1^P + x_2^P) + \delta_2\alpha_2\gamma_3 T'(x_1^P + x_2^P)\Big] = 0 \end{aligned}, \tag{55}$$

for the Jacobian J_1, while we obtain

$$\begin{aligned} &-\sigma\beta_2\gamma_3' S'(x_2^P)\Big[\delta_1\alpha_1 - \xi_1\beta_1\gamma_1 S'(x_1^P)\Big] \\ &-\beta_1\Big[-\xi_1\gamma_2\gamma_3'\beta_2 S'(x_1^P)S'(x_2^P) + \delta_2\alpha_2\gamma_3 S'(x_1^P)\Big] = 0 \end{aligned}, \tag{56}$$

for the Jacobian J_2. Both conditions are calculated at $(\vec{x}_0(I_0), I_0)$.

4 References

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