Homeostasis for fiber circuits

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Contents

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 $f_i(x_1, \ldots, x_n)$, we have that the dynamics of the system is represented by

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

where $\vec{x} = (x_1, \ldots, x_n)$ and $\vec{F} = (f_1, \ldots, f_n)$. To consider the phenomenon of homeostasis, we add to the system of equations an input parameter $\mathcal{I} \in \mathbb{R}$ and also assume that the system has a stable equilibrium at $\vec{x} = \vec{x_0}$ and $\mathcal{I} = \mathcal{I}_0$ such that we have

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

and

$$\vec{F}(\vec{x_0}(\mathcal{I}_0), \mathcal{I}_0) = 0. \tag{3}$$

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 $z(\mathcal{I}) = x_j(\mathcal{I})$ 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 $z(\mathcal{I})$ as we vary the parameter $\mathcal{I}$ around $\mathcal{I}_0$, and this behavior is possible when we satisfy the following conditions:

infinitesimal homeostasis:

$$\frac{\partial z}{\partial \mathcal{I}}(\mathcal{I}_0) = 0 \tag{4}$$

infinitesimal chair:

$$\begin{aligned} \frac{\partial z}{\partial \mathcal{I}}(\mathcal{I}_0) = \frac{\partial^2 z}{\partial \mathcal{I}^2}(\mathcal{I}_0) &= 0, \\ \frac{\partial^3 z}{\partial \mathcal{I}^3}(\mathcal{I}_0) &\neq 0. \end{aligned} \tag{5}$$

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

$$det(H)(\vec{x}_0, I_0) = h(I_0), \tag{8}$$

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 it is irreducible. 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.

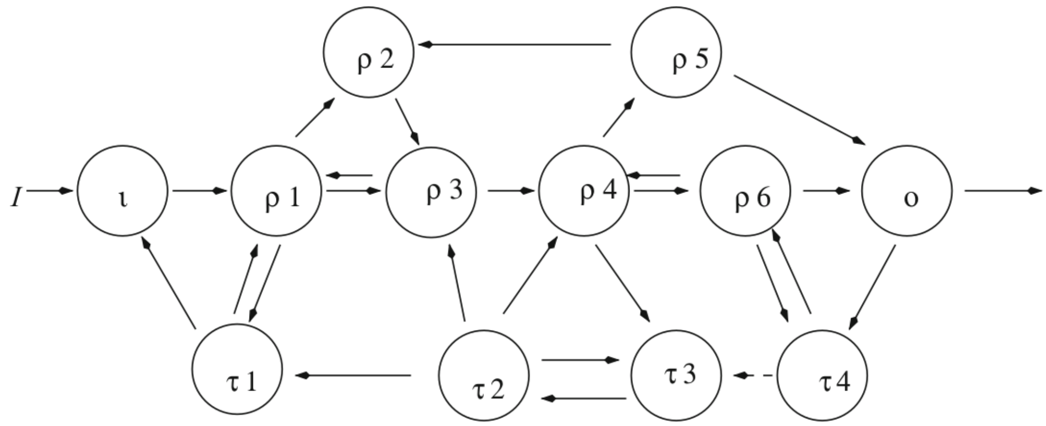

Figure 1: 12-node example. Source: [7]

Using the methodology 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 subnetworks (more details is provided in [7], but I can add more here if necessary). Since each subnetwork obtained is associated with the irreducible blocks B_j of the homeostasis matrix H, we have that

$$\begin{aligned} det(H) = &det(J_{A_1})det(J_{A_2})det(H(\mathcal{L}(\mathcal{I}, \rho_1)))det(H(\mathcal{L}(\rho_1, \rho_3)))\cdots \\ &det(H(\mathcal{L}(\rho_3, \rho_4)))det(H(\mathcal{L}(\rho_4, \mathcal{O}))) \end{aligned}, \tag{13}$$

where

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

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

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

and $det(J_{A_1}) = f_{\tau_1,\tau_1}$, $det(H(\mathcal{L}(\mathcal{I},\rho_1))) = f_{\rho_1,\mathcal{I}}$, and $det(H(\mathcal{L}(\rho_3,\rho_4))) = f_{\rho_4,\rho_3}$.

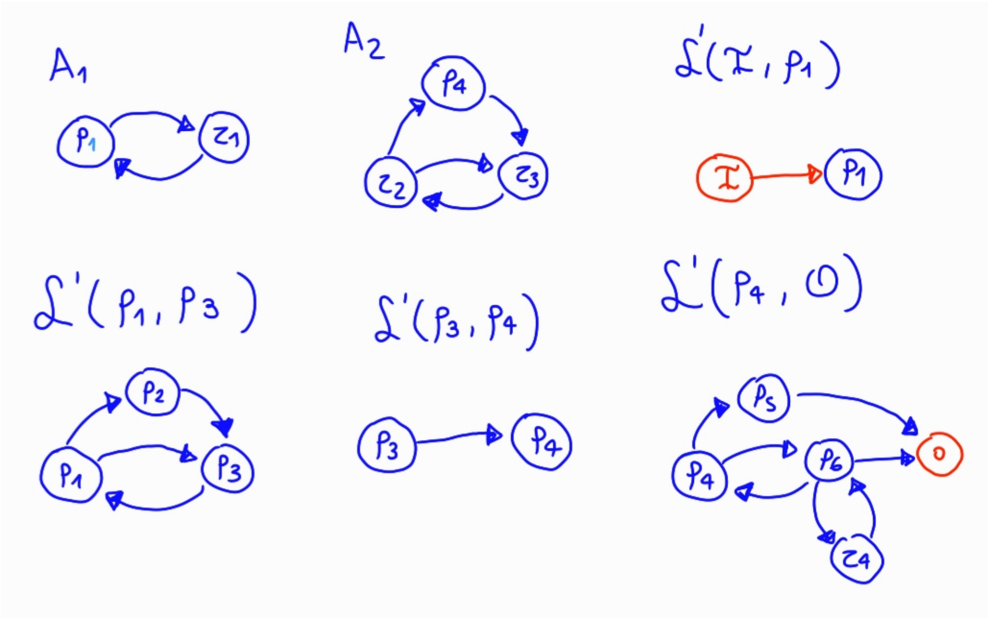

Figure 2: Homeostasis subnetworks of the 12-node network.

3 Quotient circuits

In this section, we consider the cases where $\mathcal{I}$ is the input for all the nodes within a same fiber, such that the fibration symmetry is preserved by the input. In this case, we can simplify the network representation by colapsing nodes belonging to the same fiber into one single node. This simplified representation is referred as *quotient* or *base* network [4, 2, 6]. By performing this transformation, we observe that the possible paths from input to the output of the network are also reduced, specially when we consider the fundamental fibration building blocks. The circuits considered here are defined as follows: given a fiber circuit defined either by n and ℓ for integer branching ratios or by ϕ_d and ℓ for golden ratios of fibonacci circuits, we add an extra node that is going to be regulated by all nodes withing the same fiber. The protein concentration of this external gene is going to be defined as the input-output map, i.e., the output node of the network. Moreover, the input $\mathcal{I}$ regulates all nodes of the fiber. Thus, we reduce the circuit to its quotient form and analyze the nonlinear dynamics of this reduced input-output circuit according to the methods described in the previous sections.

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

Here, we consider the fiber circuit defined by $n=1$, called as Feed-Forward Fiber (FFF)[5]. Depending on the type of internal regulation of the fiber, we denote this circuit either as SAT-FFF (for positive regulations) or UNSAT-FFF (negative regulations). Considering the mRNA/Protein gene expression model (to describe in another section before), we have that the input-output network and its quotient form is shown in Fig. 3.

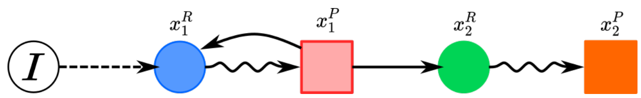

Figure 3:

3.1.1 Admissible vector fields

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

$$\begin{aligned} \dot{x_1}^R &= f_{x_1^R}(x_1^R, \mathcal{I}) \\ \dot{x_1}^P &= f_{x_1^P}(x_1^P, x_1^R) \\ \dot{x_2}^R &= f_{x_2^R}(x_2^R, x_1^P)' \\ \dot{x_2}^P &= f_{x_2^P}(x_2^P, x_2^R) \end{aligned} \tag{17}$$

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

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

where we require that $f_{x_1^R,x_1^R} < 0$, $f_{x_1^P,x_1^P} < 0$, $f_{x_2^R,x_2^R} < 0$ and $f_{x_2^P,x_2^P} < 0$ to permit a stable equilibrium at $\vec{x_0}$. Moreover, the homeostasis matrix is given by

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

3.1.2 Combinations

Considering the $|n=1,\ell\rangle$ fiber circuits observed in the *E. Coli* genetic regulatory network, we have two possibilities, as mentioned before: the SAT-FFF and the UNSAT-FFF, where here we do not take into account the regulators of the fiber defined by ℓ, since here their only purpose is to maintain the fibration symmetry of the network. For each one of the two possibilities there are 6 possibles combinations: two with equal external regulations to the output node (Fig. **??**), and one for the case where the types of regulations are alternated (Fig. **??**).

3.1.3 Special equations

Now, considering the special equations as described in section. **??**, we have the following core differential equations for all SAT-FFF and UNSAT-FFF:

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

Therefore, we can list all combinations for the external regulated nodes x_2^R and x_2^P as

	SAT-FFF	UNSAT-FFF
(a)	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2(1-S(x_1^P))$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2 S(x_1^P)$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$
(b)	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2 S(x_1^P)$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2(1-S(x_1^P))$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$
(c)	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2(1-S(x_1^P)+T(x_1^P))$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$	$\dot{x_2}^R = -\delta_2 x_2^R + \gamma_2(1-S(x_1^P)+T(x_1^P))$ $\dot{x_2}^P = -\alpha_2 x_2^P + \beta_2 x_2^R$

3.1.4 Stable equilibrium conditions

Considering the first four combinations without alternated external regulations, the Jacobian assumes the following form

$$J_1 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \xi_2\gamma_2 S'(x_1^P) & -\delta_2 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 \end{pmatrix}, \tag{20}$$

where $\xi_1, \xi_2 \in \{-1, +1\}$. $\xi_1 = +1$ refers to the UNSAT-FFF circuit, while $\xi_2 = -1$ refers to the SAT-FFF circuit. $\xi_2 = +1$ refers to the both negative regulations to node x_2^R, while $\xi_2 = -1$ refers to the both positive regulations to node x_2^R.

For the case where the external regulations are alternated we have the following Jacobian form

$$J_2 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \gamma_2(T'(x_1^P) - S'(x_1^P)) & -\delta_2 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 \end{pmatrix}, \tag{21}$$

where, again, $\xi_1 \in \{-1, +1\}$. Also, here we consider that T and S are two different 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

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

The stability conditions for J_1 and J_2 are the same. Thus, we have

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

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

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

3.1.5 Infinitesimal homeostasis conditions

Since the homeostasis matrix H is not equivalent between the Jacobians J_1 and J_2, we define H_1 and H_2 as their respective homeostasis matrices:

$$H_1 = \begin{pmatrix} \beta & -\alpha_1 & 0 \\ 0 & \xi_2\gamma_2 S'(x_1^P) & -\alpha \\ 0 & 0 & \beta_2 \end{pmatrix}, \tag{25}$$

$$H_2 = \begin{pmatrix} \beta & -\alpha_1 & 0 \\ 0 & \gamma_2(T'(x_1^P) - S'(x_1^P)) & -\alpha \\ 0 & 0 & \beta_2 \end{pmatrix}, \tag{26}$$

where the infinitesimal homeostasis conditions are given by $det(H_1)(I_0) = 0$ and $det(H_2)(I_0) = 0$:

$$det(H_1)(I_0) = h_1(I_0) = \xi_1\beta_1\beta_2\gamma_2 S'(x_1^P(I_0)) = 0, \tag{27}$$

and

$$det(H_2)(I_0) = h_2(I_0) = \beta_1\beta_2\gamma_2(T'(x_1^P(I_0)) - S'(x_1^P(I_0))) = 0. \tag{28}$$

Again, we consider that all the parameters are restrictely positives, which makes the conditions $\beta_i, \gamma_i = 0$ unfeasible according this special model. Therefore, we have that either $S'(x_1^P(I_0)) = 0$ or $T'(x_1^P(I_0)) - S'(x_1^P(I_0)) = 0$ for the possibility of infinitesimal homeostasis. Beyond the trivial solutions $x_1^P(I_0) = 0$ and $T = S$, these conditions are only possible for large x_1^P, since $S'(x) \to 0$ as $x \to \infty$.

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

Now, we investigate the stability and infinitesimal homeostasis conditions considering the quotient network of a fibonacci circuit with golden ratio $\phi_2 = 1.6184\ldots$. To preserve the fibration symmetry of the original network, the input $\mathcal{I}$ regulates the regulator of the fiber, the one that also receives information from the fiber. Thus, since the symmetry is preserved, we reduce the original network to its quotient, obtaining a new input-output network containing six nodes. The original and reduced network is shown at Fig. 4.

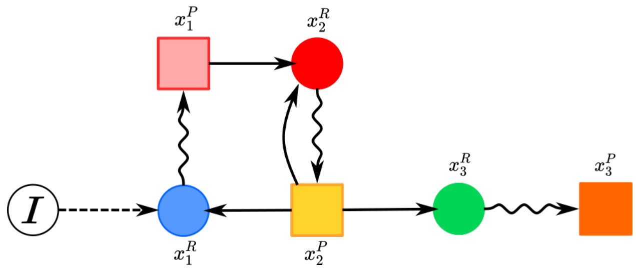

Figure 4:

3.2.1 Admissible vector fields

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

$$\begin{aligned}
\dot{x_1}^R &= f_{x_1^R}(x_1^R, x_2^P, \mathcal{I}) \\
\dot{x_1}^P &= f_{x_1^P}(x_1^P, x_1^R) \\
\dot{x_2}^R &= f_{x_2^R}(x_2^R, x_1^P, x_2^P) \\
\dot{x_2}^P &= f_{x_2^P}(x_2^P, x_2^R) \\
\dot{x_3}^R &= f_{x_3^R}(x_3^R, x_2^P) \\
\dot{x_3}^P &= f_{x_3^P}(x_3^P, x_3^R)
\end{aligned}, \tag{29}$$

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

$$J = \begin{pmatrix}
f_{x_1^R,x_1^R} & 0 & 0 & f_{x_1^R,x_2^P} & 0 & 0 \\
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 \\
0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & f_{x_2^R,x_2^P} & 0 & 0 \\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 \\
0 & 0 & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 \\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P}
\end{pmatrix}, \tag{30}$$

where the condition for stability is defined over $f_{x_3^R,x_3^R}$ and $f_{x_3^P,x_3^P}$ 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

$$H = \begin{pmatrix}
f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 \\
0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & f_{x_2^R,x_2^P} & 0 \\
0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 \\
0 & 0 & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} \\
0 & 0 & 0 & 0 & f_{x_3^P,x_3^R}
\end{pmatrix}. \tag{31}$$

3.2.2 Combinations

Considering the $|\phi_2, \ell\rangle$ fiber circuits observed in the *E. Coli* genetic regulatory network, we have only one possibility, which is the case where all regulations within the fiber and the external loop are negative. For this possibility there are four possible combinations of regulation considering the regulations to the external node x_3^R of the mRNA/Protein network representation. Although we show all these possibilities in Fig. **??** we consider in the following section only the case where all regulations are negative, such that we can observe the general form of the infinitesimal homeostasis condition in the quotient of the fibonacci network.

3.2.3 Special equations and infinitesimal homeostasis

Considering the case where all regulations are negative, we have the following form for the special equations

$$\begin{aligned}
\dot{x_1}^R &= -\delta_1 x_1^R + \gamma_1 S(x_2^P) + \mathcal{I} \\
\dot{x_1}^P &= -\alpha_1 x_1^P + \beta_1 x_1^R \\
\dot{x_2}^R &= -\delta_2 x_2^R + \gamma_2 T(x_1^P + x_2^P) \\
\dot{x_2}^P &= -\alpha_2 x_2^P + \beta_2 x_2^R \\
\dot{x_3}^R &= -\delta_3 x_3^R + \gamma_3 S(x_2^P) \\
\dot{x_3}^P &= -\alpha_3 x_3^P + \beta_3 x_3^R
\end{aligned}, \tag{32}$$

where $S(x)$ is a Hill function of one variable and $T(x+y)$ is the Hill function over two variables. Moreover, since the matrix H is triangular, we have that the infinitesimal homeostasis condition is simply the multiplication of the factors in the principal diagonal of H. Therefore, for the special equations above, we have that

$$det(H)(I_0) = \beta_1 T'(x_1^P(I_0) + x_2^P(I_0))\beta_2 S'(x_2^P(I_0))\beta_3 = 0, \tag{33}$$

which again provides trivial conditions for the occurrence of infinitesimal homeostasis point, since $\beta_i \neq 0$ and the derivative of the Hill function only goes zero for a null argument or asymptotically for $x_1^P + x_2^P$ (or only x_2^P) large enough in the saturation regime. Changing the type of the regulations will only change the sign of the derivative of the Hill functions in the determinant of H.

4 Broken circuits

In this section, we consider the case where the provided input $\mathcal{I}$ does not preserve the fibration symmetry. 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.

4.1 $|n=1,\ell\rangle$ input-output circuit

When we consider this case, we cannot reduce the network to the quotient form, since the fibration symmetry is broken by the input to x_2^R only. Therefore, we need to verify all the combination possibilities for the input-output network shown in Fig. 5.

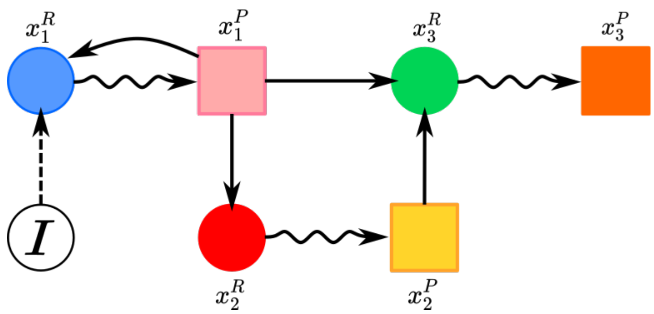

Figure 5:

4.1.1 Admissible vector fields

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

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

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

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

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

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

4.1.2 Combinations

Considering the $|n = 1, \ell\rangle$ fiber circuits observed in the *E. Coli* genetic regulatory network, we have two possibilities, as shown in section **??**: the SAT-FFF and the UNSAT-FFF. This time, 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. **??**), and two for the case of alternated the types of regulations (Fig. **??**).

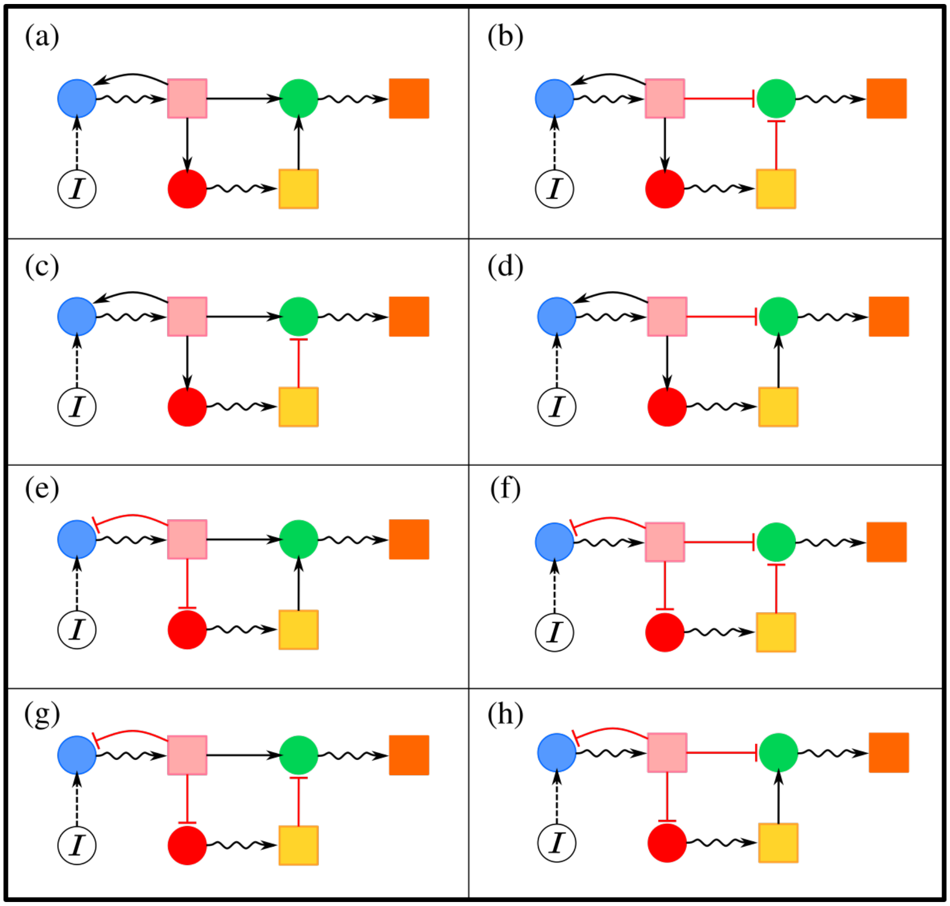

Figure 6:

4.1.3 Special equations

Now, considering the special equations as described in section **??**, 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

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

4.1.4 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:

$$J_1 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 & 0 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 \end{pmatrix}, \quad (37)$$

and

$$J_2 = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 & 0 \\ 0 & \xi_2\gamma_3 S'(x_1^P) & 0 & -\xi_2\gamma_3 S'(x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 \end{pmatrix}, \quad (38)$$

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

$$K = \begin{pmatrix} -\delta_1 & \xi_1\gamma_1 S'(x_1^P) \\ \beta_1 & -\alpha_1 \end{pmatrix}, \tag{39}$$

such that we have

$$\begin{aligned} \Delta_k &= det(K) = \alpha_1\delta_1 - \xi_1\beta_1\gamma_1 S'(x_1^P) \\ \tau_k &= Tr(K) = -(\alpha_1+\delta_1) \end{aligned}. \tag{40}$$

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

$$S'(x_1^P) > -\frac{\alpha_1\delta_1}{\beta_1\gamma_1}. \tag{41}$$

4.1.5 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:

$$H_1 = \begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & -\delta_3 \\ 0 & 0 & 0 & 0 & \beta_3 \end{pmatrix}, \tag{42}$$

and

$$H_2 = \begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 & 0 \\ 0 & \xi_2\gamma_3 S'(x_1^P) & 0 & -\xi_2\gamma_3 S'(x_2^P) & -\delta_3 \\ 0 & 0 & 0 & 0 & \beta_3 \end{pmatrix}, \tag{43}$$

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 $\mathcal{L}'(x_3^R, x_3^P)$ (Fig. **??**). From these two subnetworks, we have the following infinitesimal homeostasis conditions:

$$f_{x_3^P, x_3^R} = \beta_3(I_0) = 0, \tag{44}$$

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

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

$$det\begin{pmatrix} \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \xi_1\gamma_2 S'(x_1^P) & -\delta_2 & 0 \\ 0 & 0 & \beta_2 & -\alpha_2 \\ 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) & 0 & \xi_2\gamma_3 T'(x_1^P + x_2^P) \end{pmatrix}(I_0) = 0, \tag{45}$$

which gives us the condition

$$\beta_1(\xi_1\xi_2\gamma_2\gamma_3\beta_2 S'(x_1^P)T'(x_1^P + x_2^P) + \xi_2\delta_2\alpha_2\gamma_3 T'(x_1^P + x_2^P)) = 0, \tag{46}$$

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

$$\xi_1\xi_2\gamma_2\gamma_3\beta_2 S'(x_1^P)T'(x_1^P + x_2^P) + \xi_2\delta_2\alpha_2\gamma_3 T'(x_1^P + x_2^P) = 0, \tag{47}$$

or

$$T'(x_1^P + x_2^P)(\delta_2\alpha_2 + \xi_1\gamma_2\beta_2 S'(x_1^P)) = 0 \tag{48}$$

Following the same procedure for matrix H_2, we have

$$-\xi_1\xi_2\gamma_2\gamma_3'\beta_2 S'(x_1^P)S'(x_2^P) + \xi_2\delta_2\alpha_2\gamma_3 S'(x_1^P) = 0, \tag{49}$$

or

$$S'(x_1^P)(\delta_2\alpha_2\gamma_3 - \xi_1\gamma_2\gamma_3'\beta_2 S'(x_2^P)) = 0. \tag{50}$$

4.2 $|\phi_2, \ell\rangle$ 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. 7 depends explicitly on the input $\mathcal{I}$. Thus, we cannot reduce the circuit to its quotient form.

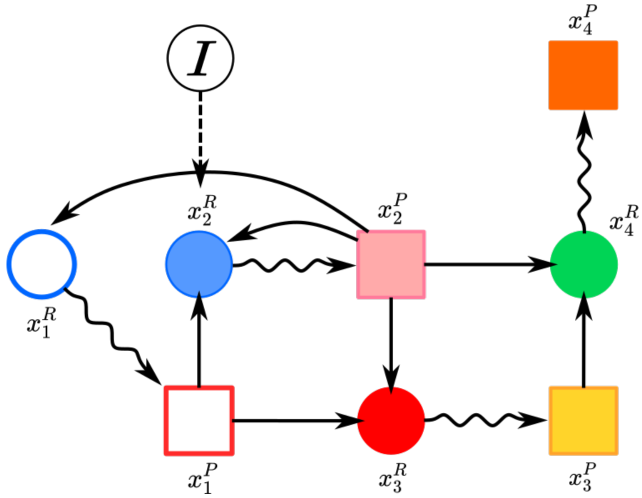

Figure 7:

4.2.1 Admissible vector fields

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

$$\begin{aligned}
\dot{x}_1^R &= f_{x_1^R}(x_1^R, x_2^P) \\
\dot{x}_1^P &= f_{x_1^P}(x_1^P, x_1^R) \\
\dot{x}_2^R &= f_{x_2^R}(x_2^R, x_1^P, x_2^P, \mathcal{I}) \\
\dot{x}_2^P &= f_{x_2^P}(x_2^P, x_2^R) \\
\dot{x}_3^R &= f_{x_3^R}(x_3^R, x_1^P, x_2^P) \\
\dot{x}_3^P &= f_{x_3^P}(x_3^P, x_3^R) \\
\dot{x}_4^R &= f_{x_4^R}(x_4^R, x_2^P, x_3^P) \\
\dot{x}_4^P &= f_{x_4^P}(x_4^P, x_4^R)
\end{aligned} \quad , \tag{51}$$

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

$$J = \begin{pmatrix} f_{x_1^R,x_1^R} & 0 & 0 & f_{x_1^R,x_2^P} & 0 & 0 & 0 & 0 \\ f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & f_{x_2^R,x_1^P} & f_{x_2^R,x_2^R} & f_{x_1^P,x_2^P} & 0 & 0 & 0 & 0 \\ 0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 & 0 & 0 \\ 0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P} & 0 & 0 \\ 0 & 0 & 0 & f_{x_4^R,x_2^P} & 0 & f_{x_4^R,x_3^P} & f_{x_4^R,x_4^R} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & f_{x_4^P,x_4^R} & f_{x_4^P,x_4^P} \end{pmatrix}, \tag{52}$$

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

$$H = \begin{pmatrix} f_{x_1^R,x_1^R} & 0 & 0 & f_{x_1^R,x_2^P} & 0 & 0 & 0 \\ f_{x_1^P,x_1^R} & f_{x_1^P,x_1^P} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & f_{x_2^P,x_2^R} & f_{x_2^P,x_2^P} & 0 & 0 & 0 \\ 0 & f_{x_3^R,x_1^P} & 0 & f_{x_3^R,x_2^P} & f_{x_3^R,x_3^R} & 0 & 0 \\ 0 & 0 & 0 & 0 & f_{x_3^P,x_3^R} & f_{x_3^P,x_3^P} & 0 \\ 0 & 0 & 0 & f_{x_4^R,x_2^P} & 0 & f_{x_4^R,x_3^P} & f_{x_4^R,x_4^R} \\ 0 & 0 & 0 & 0 & 0 & 0 & f_{x_4^P,x_4^R} \end{pmatrix}. \tag{53}$$

4.2.2 Combinations

Considering the genes *uxuR*, *lgoR* and *exuR* in the bacteria *E.Coli*, these genes belong to the only Fibonacci ϕ_2 circuit of the bacteria 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. **??**. These combinations are shown in Fig. 8.

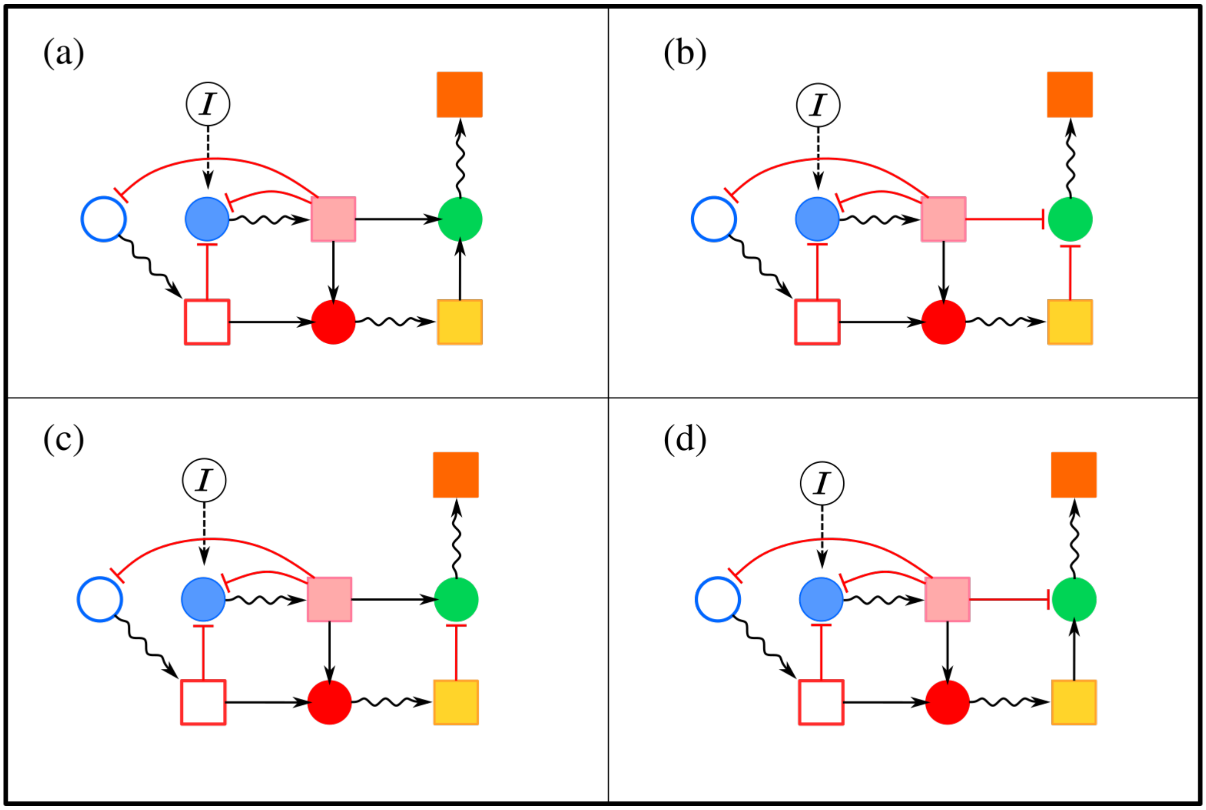

Figure 8:

4.2.3 Special equations

Now, considering the special equations as described in section **??**, 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

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

4.2.4 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

$$J_1 = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & 0 & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 & 0 & 0 \\ 0 & 0 & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) & -\delta_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_4 & -\alpha_4 \end{pmatrix}, \tag{54}$$

and

$$J_2 = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & -\alpha_1 & 0 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & 0 & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_3 & -\alpha_3 & 0 & 0 \\ 0 & 0 & 0 & \xi_1 \gamma_4 S'(x_2^P) & 0 & -\xi_1 \gamma_4 S'(x_3^P) & -\delta_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_4 & -\alpha_4 \end{pmatrix}, \tag{55}$$

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

Now, define

$$K = \begin{pmatrix} -\delta_1 & 0 & 0 & \gamma_1 S'(x_1^P) \\ \beta_1 & -\alpha_1 & 0 & 0 \\ 0 & \gamma_2 T'(x_1^P + x_2^P) & -\delta_2 & \gamma_2 T'(x_1^P + x_2^P) \\ 0 & 0 & \beta_2 & -\alpha_2 \end{pmatrix}. \tag{56}$$

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

$$P(\lambda) = A + B\lambda + C\lambda^2 + D\lambda^3 + E\lambda^4, \tag{57}$$

where we find

$$\begin{aligned} A &= \delta_1\alpha_1(A' + \delta_2\alpha_2) + B' \\ B &= [\delta_1\alpha_1(\alpha_2 + \delta_2) + \delta_2\alpha_2(\alpha_1 + \delta_1)] + A'(\alpha_1 + \delta_1) \\ C &= A' + [\delta_1\alpha_1 + \delta_2\alpha_2 + (\alpha_1 + \delta_1)(\alpha_2 + \delta_2)] \\ D &= \delta_1 + \delta_2 + \alpha_1 + \alpha_2 \\ E &= 1 \end{aligned} \tag{58}$$

with

$$\begin{aligned} A' &= -\gamma_2\beta_2 T'(x_1^P + x_2^P) \\ B' &= -\gamma_1\gamma_2\beta_1\beta_2 S'(x_2^P) T'(x_1^P + x_2^P) \end{aligned}. \tag{59}$$

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

$$H_1(\mathcal{L}'(x_2^P, x_4^R)) = \begin{pmatrix} -\delta_1 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & \beta_3 & -\alpha_3 \\ 0 & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) & 0 & \xi_1 \gamma_4 T'(x_2^P + x_3^P) \end{pmatrix}, \tag{60}$$

and

$$H_2(\mathcal{L}'(x_2^P, x_4^R)) = \begin{pmatrix} -\delta_1 & 0 & \gamma_1 S'(x_2^P) & 0 & 0 \\ \beta_1 & -\alpha_1 & 0 & 0 & 0 \\ 0 & \gamma_3 T'(x_1^P + x_2^P) & \gamma_3 T'(x_1^P + x_2^P) & -\delta_3 & 0 \\ 0 & 0 & 0 & \beta_3 & -\alpha_3 \\ 0 & 0 & \xi_1 \gamma_4 S'(x_2^P) & 0 & -\xi_1 \gamma_4' S'(x_3^P) \end{pmatrix}. \tag{61}$$

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

$$\xi_1 \gamma_4 T'(x_2^P + x_3^P)\big[\delta_1 \alpha_1 \gamma_3 \beta_3 T'(x_1^P + x_2^P) + \delta_1 \alpha_1 \delta_3 \alpha_3 + \gamma_1 \beta_1 \gamma_3 \beta_3 T'(x_1^P + x_2^P)\big] = 0, \tag{62}$$

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

$$\begin{aligned} -\xi_1 \delta_1 \alpha_1 \gamma_3 \beta_3 \gamma_4' T'(x_1^P + x_2^P) S'(x_3^P) + \xi_1 \delta_1 \alpha_1 \delta_3 \alpha_3 \gamma_4 S'(x_2^P) \\ -\xi_1 \beta_1 \beta_3 \gamma_1 \gamma_3 \gamma_4' S'(x_2^P) S'(x_3^P) T'(x_1^P + x_2^P) = 0 \end{aligned} \tag{63}$$

4.3 $|n = 1, \ell\rangle$ for two input node

Starting from the symmetric circuit 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. 9. For $\sigma = 0$ we recover the broken circuit analyzed in subsection **??** while for $\sigma = 1$ we obtain the symmetric fiber.

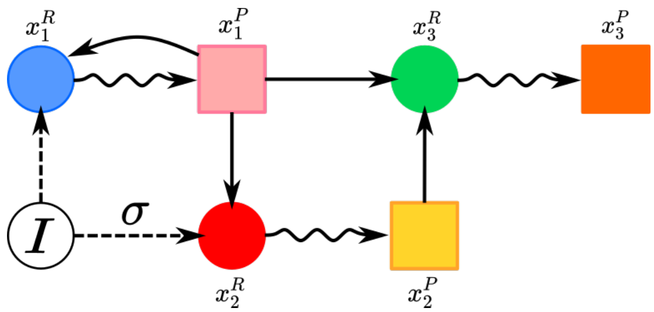

Figure 9:

The general admissible system of equations for this circuit differs from 34 only in the dependence of the nonlinear function $f_{x_2^R}$, and it is given as

$$\begin{aligned}
\dot{x}_1^R &= f_{x_1^R}(x_1^R, x_1^P, \mathcal{I}) \\
\dot{x}_1^P &= f_{x_1^P}(x_1^P, x_1^R) \\
\dot{x}_2^R &= f_{x_2^R}(x_2^R, x_1^P, \sigma\mathcal{I}) \\
\dot{x}_2^P &= f_{x_2^P}(x_2^P, x_2^R) \\
\dot{x}_3^R &= f_{x_3^R}(x_3^R, x_1^P, x_2^P) \\
\dot{x}_3^P &= f_{x_3^P}(x_3^P, x_3^R)
\end{aligned}, \tag{64}$$

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. 9 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**:

$$\begin{aligned}
I_1 &= x_1^R \to x_1^P \to x_3^R \to x_3^P = \mathcal{O} \\
I_1 &= x_1^R \to x_1^P \to x_2^R \to x_2^P \to x_3^R \to x_3^P = \mathcal{O}'
\end{aligned} \tag{65}$$

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

$$I_2 = x_2^R \to x_2^P \to x_3^R \to x_3^P = \mathcal{O}. \tag{66}$$

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

$$J_{\mathcal{W}_{\mathcal{G}}} = \begin{pmatrix} f_{x_1^R, x_1^R} & f_{x_1^R, x_1^P} & 0 & 0 & 0 \\ f_{x_1^P, x_1^R} & f_{x_1^P, x_1^P} & 0 & 0 & 0 \\ 0 & f_{x_2^R, x_1^P} & f_{x_2^R, x_2^R} & 0 & 0 \\ 0 & 0 & f_{x_2^P, x_2^R} & f_{x_2^P, x_2^P} & 0 \\ 0 & f_{x_3^R, x_1^P} & 0 & f_{x_3^R, x_2^P} & f_{x_3^R, x_3^R} \end{pmatrix}, \tag{67}$$

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

$$H'(\mathcal{W}_{\mathcal{G}}) = \begin{pmatrix} f_{x_1^R, x_1^R} & f_{x_1^R, x_1^P} & 0 & 0 & -f_{x_1^R, I} \\ f_{x_1^P, x_1^R} & f_{x_1^P, x_1^P} & 0 & 0 & 0 \\ 0 & f_{x_2^R, x_1^P} & f_{x_2^R, x_2^R} & 0 & -f_{x_2^R, I} \\ 0 & 0 & f_{x_2^P, x_2^R} & f_{x_2^P, x_2^P} & 0 \\ 0 & f_{x_3^R, x_1^P} & 0 & f_{x_3^R, x_2^P} & 0 \end{pmatrix}, \tag{68}$$

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

$$det(H'(\mathcal{W}_{\mathcal{G}})) = \pm f_{x_1^R, I} det(H_1) \pm f_{x_2^R, I} det(H_2) \tag{69}$$

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

$$\begin{aligned} det(H'(\mathcal{W}_{\mathcal{G}})) = &-f_{x_2^R, I} f_{x_2^P, x_2^R} f_{x_3^R, x_2^P} (f_{x_1^R, x_1^R} f_{x_1^P, x_1^P} - f_{x_1^R, x_1^P} f_{x_1^P, x_1^R}) \\ &- f_{x_1^R, I} f_{x_1^P, x_1^R} (f_{x_2^R, x_1^P} f_{x_2^P, x_2^R} f_{x_3^R, x_2^P} + f_{x_2^R, x_2^R} f_{x_2^P, x_2^P} f_{x_3^R, x_1^P}) = 0. \end{aligned} \tag{70}$$

From Eq. 71 we can recover the case worked in section **??** regarding the circuit receiving only one input by setting the $\sigma = 0$. In this case, the infinitesimal homeostasis condition is given by

$$det(H'(\mathcal{W}_{\mathcal{G}})) = f_{x_1^R,\mathcal{I}} f_{x_1^P,x_1^R} (f_{x_2^R,x_1^P} f_{x_2^P,x_2^R} f_{x_3^R,x_2^P} + f_{x_2^R,x_2^R} f_{x_2^P,x_2^P} f_{x_3^R,x_1^P}) = 0., \tag{71}$$

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

5 References

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