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Lyapunov function for irreversible linear metabolic pathways with allosteric and genetic regulation

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***Abstract*— A challenge of great interest in systems biology consists in predicting the behavior of bacteria in response to environmental changes. In this context, the present work analyzes the global stability of more realistic models for bacterial linear metabolic pathways integrating allosteric and genetic regulation. Indeed, we use the composite-system method for analyzing stability of large-scale dynamical systems to build a Lyapunov function for a specific class of bacterial irreversible linear metabolic pathways.**

I. INTRODUCTION

Most bacteria have developed sophisticated mechanisms for the control of their metabolic activities. However, these complex systems exhibit some general control structures widespread in the life kingdom and strongly conserved along the evolution. In this paper, we focus on the stability property of a control structure shared by a large number of metabolic pathways in the cell and which integrates two levels of control: (*i*) enzymatic control through an allosteric effect by a metabolite, (*ii*) genetic control through a transcription factor.

In order to emphasize the interest of such a study, it is important to note that such a control structure is present in the two well studied model bacteria *B. subtilis* and *E. Coli*. In the sequel, we consider an irreversible metabolic pathway where both the genetic control and the allosteric control involve the end product of the pathway. Although this control structure often appears in biosynthesis pathways of various amino acids [1], [2], [3], it is also used in other biosynthesis pathways such as the ones of *purine* and *pyrimidine* [4].

Even if the stability property of bacterial metabolic pathways is central in the cell physiology, most of the various works in the literature focus on the stability analysis of structures having only the enzymatic control. The genetic control was hardly considered. For instance, in [5], [6] and [7] the authors studied the stability issue for control structures where the enzymatic reactions are represented by a linear dynamical system closed by a nonlinear negative feedback corresponding to the enzymatic control. The work of Arcak and Sontag [8] considers the same structure but the enzymatic reactions are presented by a nonlinear dynamical system. Recently, based on the systematic characterization of system equilibrium provided in [3], technical conditions are established in [9] to ensure the global attractivity for more realistic nonlinear models of the linear metabolic pathways, which incorporate genetic and allosteric regulation. In the previous work, monotone system theory [10] allows us to conclude the global attractiveness of the controlled metabolic pathway. In the present study, we will provide conditions establishing the global asymptotic stability of the considered system. By contrast to our previous results, we will explicitly build a Lyapunov function for such biological systems using the composite-system method for analyzing stability of large-scale dynamical systems [11].

This note is organized as follows. Section II introduces a more realistic nonlinear dynamical model of the irreversible linear metabolic pathways integrating both genetic and allosteric regulation. Section III recalls some known results about the boundedness of the state trajectories generated by the kind of nonlinear dynamical systems and the existence of steady state regime. The main contribution of this paper is stated in Section IV as proposition and then proved in Section V. In order to show that our global stability conditions are not restrictive, we demonstrate in Section VI that similar conditions are required in order to guarantee the local stability.

II. IRREVERSIBLE LINEAR METABOLIC PATHWAYS

Let us consider irreversible linear metabolic pathways with the allosteric and genetic regulations depicted in Figure 1. This specific control structure is shared by many metabolic pathways in bacteria, especially the ones associated to most amino acid synthesis pathways. Hereafter, we show how to build a mathematical model for such a set of biochemical reactions.

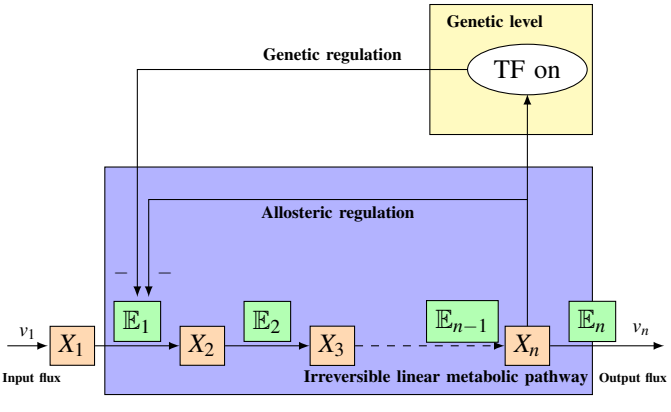

Fig. 1. Genetic and allosteric regulations by the end product. v_1 and v_n represent respectively the input and the output flux. X_i and $\mathbb{E}_i$, $i = 1, \ldots, n$, denote respectively the metabolites and the enzymes.

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A. Enzymatic reactions and allosteric regulation

Let us assume that the concentration $x_1(t)$ of the first metabolite X_1 is maintained by the input flux v_1 which corresponds to the supply flux. Then, we denote by $\bar{x}_1$ the constant concentration of X_1. The output flux v_n represents the cell demand needed for the cell growth. Then, let us consider the first enzymatic reaction,

$$\xrightarrow{v_1} X_1 \xrightarrow{\mathbb{E}_1} X_2 \xrightarrow{\mathbb{E}_2} \dots$$

In the literature, the dynamics of the biochemical reaction is described by the following nonlinear differential equation

$$\dot{x}_2 = E_1 f_1\left(\bar{x}_1, x_n\right) - E_2 f_2\left(x_2\right) \tag{1}$$

where x_2 and x_n represent the concentrations of the second and the final metabolite X_2 and X_n respectively. By E_1 and E_2, we denote respectively the strictly positive concentrations of the enzymes $\mathbb{E}_1$ and $\mathbb{E}_2$. The nonlinear functions $f_1(.,.)$ and $f_2(.)$ describe the reaction rates of the enzymes $\mathbb{E}_1$ and $\mathbb{E}_2$, and have the following properties:

- $f_1(.,.)$ is positive and strictly increasing with respect to x_1 and strictly decreasing with respect to x_n, *viz.* The final metabolite X_n is able to inhibit the factivity of the first enzyme $\mathbb{E}_1$. This represents the allosteric effect by the end product. Moreover, $f_1(.,.)$ is bounded with the known bound M_1.
- $f_2(.)$ is positive strictly increasing with respect to x_2 and bounded with the known bound M_2.

Now, let us consider the remainder enzymatic reactions

$$\dots X_{i-1} \xrightarrow{\mathbb{E}_{i-1}} X_i \xrightarrow{\mathbb{E}_i} \dots$$

which can be modeled by nonlinear differential equations. For $i = 3, \dots, n$, one has

$$\dot{x}_i = E_{i-1} f_{i-1}\left(x_{i-1}\right) - E_i f_i\left(x_i\right) \tag{2}$$

where the concentrations E_i, x_i and the reaction rates $f_i(x_i)$ have the same properties as those of E_2, x_2 and $f_2(x_2)$ respectively.

B. Genetic regulation by the end product

Here we assume that only the first enzyme $\mathbb{E}_1$ of irreversible linear pathway is genetically controlled (by a transcription factor for instance). The variation of its concentration during the exponential growth phase is mostly the result of two phenomena: (*i*) the *de novo* production controlled by the concentration of the end product x_n (*ii*) the *dilution* effect caused by the increase of the cell volume. The dynamics of the first enzyme concentration is then governed by the following differential equation,

$$\dot{E}_1 = g\left(x_n\right) - \mu E_1 \tag{3}$$

where μ is the growth rate of the bacterium assumed to be in the exponential growth phase. The term $g(x_n)$ corresponds to the instantaneous production of the enzyme $\mathbb{E}_1$ modulated by the end product (typically through a transcription factor). The function $g(.)$ is positive strictly decreasing with respect to x_n with $g(0) = g_{max}$ and $\lim_{x\to+\infty} g(x) = 0$. The first enzyme $\mathbb{E}_1$ is more produced when the concentration of the final metabolite X_n is decreasing.

Finally, the irreversible linear metabolic pathway with genetic and allosteric regulation, as depicted in Figure 1, is described by the following set of coupled nonlinear differential equations:

- The dynamics of the metabolite concentrations (linked to enzymatic reactions)

$$\left\{\begin{array}{rcl} \dot{x}_2 &=& E_1 f_1(\bar{x}_1, x_n) - E_2 f_2(x_2) \\ \dot{x}_3 &=& E_2 f_2(x_2) - E_3 f_3(x_3) \\ \vdots & \vdots & \vdots \quad\quad \vdots \\ \dot{x}_n &=& E_{n-1} f_{n-1}(x_{n-1}) - E_n f_n(x_n) \end{array}\right. \tag{4}$$

- The dynamics of the concentration of the first enzyme

$$\dot{E}_1 = g\left(x_n\right) - \mu E_1 \tag{5}$$

Prior to stating our main result about the global stability for such nonlinear systems, we give in the following section the conditions ensuring the boundedness and the existence of the steady state.

III. BOUNDEDNESS AND EXISTENCE OF STEADY STATE REGIMEN

A. Boundedness

We start our demonstration by showing the boundedness of the first enzyme concentration E_1, which is governed by (5). Since, by definition $g(.)$ is positive and bounded, *viz.*

$$\forall x_n \geq 0,\ g(x_n) \in (0, g_{max}]$$

then for any $x_n \geq 0$ the solution $E_1(t)$ of (5) is framed between

$$\check{E}_1(t) \leq E_1(t) \leq \hat{E}_1(t),$$

where $\check{E}_1(t)$ and $\hat{E}_1(t)$ are respectively the solutions of the following stable first-order linear systems with the initial conditions $\check{E}_1(t_0) = \hat{E}_1(t_0) = E_1(t_0)$

$$\dot{\check{E}}_1 = -\mu \check{E}_1, \quad \dot{\hat{E}}_1 = -\mu \hat{E}_1 + g_{max}.$$

Thus, there exists $\overline{E}_1 > 0 \mid \forall t \geq 0,\ E_1(t) \leq \overline{E}_1$.

Once the boundedness of the first enzyme concentration has been proved, the following proposition gives sufficient conditions, which guarantee the boundedness of all state trajectories generated by (4).

Proposition 1: If for each $i \in \{2, \dots, n\}$ the following inequality $\overline{E}_1 M_1 < E_i M_i$ is verified, then all the state trajectories generated by (4) are bounded for any initial state. Here M_i represents the upper bound of the function $f_i(x_i)$. □

Proof: see [9].

B. Existence of the steady state

The steady state $(\mathbf{x}^*, E_1^*)^T$ of the nonlinear system (4)-(5) is obtained when all the time derivatives vanish. Then, by direct computation we obtain:

$$E_1^* = \frac{g(x_n^*)}{\mu}, \tag{6}$$

$$x_n^* = k_n^{-1}\big(\frac{1}{\mu E_n}\big) \tag{7}$$

where $k_n(x_n) = \frac{f_n(x_n)}{f_1(\bar{x}_1, x_n)g(x_n)}$ and for all $i \in \{2, \ldots, n-1\}$

$$x_i^* = f_i^{-1}\big(\frac{E_1^*}{E_i} f_1(\bar{x}_1, x_n^*)\big). \tag{8}$$

As the functions $f_i(.)$, $i = 1, \ldots, n$ are bounded and strictly monotone, the existence of (6), (7) and (8) are guaranteed if the following inequalities are satisfied: $\forall i = 2, \ldots, n \quad \overline{E}_1 f_1(\bar{x}_1, 0) < E_i M_i$, which exactly correspond to the conditions of Proposition 1.

IV. MAIN RESULT

Now, we state the main contribution of the paper about the global stability of the equilibrium point of the coupled nonlinear system (4)-(5).

Proposition 2: Let

$$\gamma_n = \max_{x_n} \big\{ -\frac{\overline{E}_1 f_1'(\bar{x}_1, x_n)}{E_n f_n'(x_n)} \big\} \tag{9}$$

where f_1' (resp. f_n') is the derivative of f_1 (resp. f_n) with respect to x_n. If

$$\gamma_n < \sec(\pi/(n-1))^{n-1} \tag{10}$$

then there exists a diagonal and positive matrix $\mathbf{P} = diag(p_i)$ with order $(n-1) \times (n-1)$ such that

$$\mathbf{PA} + \mathbf{A}^T\mathbf{P} \leq -2\varepsilon\mathbf{I} \tag{11}$$

where

$$\mathbf{A} = \begin{bmatrix} -1 & 0 & \ldots & 0 & -1 \\ 1 & -1 & \ddots & & 0 \\ 0 & 1 & -1 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \ldots & 0 & 1 & -\frac{1}{\gamma_n} \end{bmatrix}, \tag{12}$$

$\mathbf{I}$ is the identity matrix of suitable dimension and ε is a positive real number. Then, the steady state of the irreversible metabolic pathway (4)-(5) is globally asymptotically stable if the following condition is satisfied:

$$\lambda_n = \max_{x_n} \big\{ \frac{g_n'(x_n)}{f_1'(\bar{x}_1, x_n)} \big\} < \frac{\varepsilon\mu E_1^*}{p f_1(\bar{x}_1, 0)} \tag{13}$$

where $p = \max_i(p_i)$. □

To prove our main result let us recall briefly the Lyapunov stability analysis via the composite systems method developed in [11].

A. Outline of the method

Let us consider a dynamical system given by

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, t) \qquad \mathbf{x} \in \mathbb{R}^n, \ t \in \mathbb{R} \tag{14}$$

where $\mathbf{f}(\mathbf{x}, t)$ is assumed uniformly Lipschitz wrt $\mathbf{x}$ and satisfies

$$\mathbf{f}(\mathbf{0}, t) = \mathbf{0} \qquad t \in \mathbb{R} \tag{15}$$

In order to show the global stability of the equilibrium $\mathbf{x} = 0$, one assumes that (14) can be decomposed as follows,

$$\mathbf{f}(\mathbf{x}, t) = \begin{cases} \dot{\mathbf{x}}_1 &= \mathbf{f}_1(\mathbf{x}_1, t) + \mathbf{g}_1(\mathbf{x}, t) \\ \vdots & \vdots \\ \dot{\mathbf{x}}_m &= \mathbf{f}_m(\mathbf{x}_m, t) + \mathbf{g}_m(\mathbf{x}, t) \end{cases} \tag{16}$$

where $\mathbf{x}_j \in \mathbb{R}^{n_j}$, $n_1 + \cdots + n_m = n$, $\mathbf{x} = (\mathbf{x}_1, \ldots, \mathbf{x}_m)^T$. Moreover, one assumes also that the vector functions $\mathbf{f}_j(\mathbf{x}_j, t)$ and $\mathbf{g}_j(\mathbf{x}, t)$ satisfy

$$\mathbf{f}_j(\mathbf{0}, t) = \mathbf{0} \quad j = 1, \ldots, m; \ t \in \mathbb{R} \tag{17}$$

$$\mathbf{g}_j(\mathbf{0}, t) = \mathbf{0} \quad j = 1, \ldots, m; \ t \in \mathbb{R}. \tag{18}$$

Hence, the large-scale nonlinear system (14) is viewed as an interconnection of m dynamical subsystems with input $\mathbf{y}_j$ and output $\mathbf{x}_j$

$$\dot{\mathbf{x}}_j = \mathbf{f}_j(\mathbf{x}_j, t) + \mathbf{y}_j \tag{19}$$

where

$$\mathbf{y}_j = \mathbf{g}_j(\mathbf{x}, t) \tag{20}$$

Thus, it is of great interest to be able to show the Lyapunov stability of the equilibrium point $\mathbf{x} = 0$ of the composite system (14) from the Lyapunov stability of the equilibrium points $\mathbf{x}_j = \mathbf{0}$ of the isolated systems described by

$$\dot{\mathbf{x}}_j = \mathbf{f}_j(\mathbf{x}_j, t) \quad j = 1, \ldots, m \tag{21}$$

In other terms, one expects that the building of Lyapunov functions $v_j(\mathbf{x}_j, t)$ for the isolated systems is easy and one attempts to use their weighted sum

$$v(\mathbf{x}, t) = d_1 v_1(\mathbf{x}_1, t) + \cdots + d_m v_m(\mathbf{x}_m, t) \tag{22}$$

as a candidate Lyapunov function for the composite system (14), where $d_1, \ldots, d_m$ are positive constants. Theorem 1 in reference [11] gives sufficient conditions, which assure that $v(\mathbf{x}, t)$ inherits all the properties of the Lyapunov functions $v_j(\mathbf{x}_j, t)$.

Theorem 1: System (14) is uniformly asymptotically stable if the next three conditions are satisfied,

1) For each isolated system (20), there is a positive-definite and radially unbounded function $v_j(\mathbf{x}_j, t)$ with continuous partial derivatives such that

$$\dot{v}_j(\mathbf{x}_j, t) \leq -\alpha_j\{u_j(\mathbf{x}_j)\}^2 \quad \mathbf{x}_j \in \mathbb{R}^{m_j}; \ t \in \mathbb{R} \tag{23}$$

$$|\bigtriangledown_{\mathbf{x}_j} v_j(\mathbf{x}_j, t)| \leq u_j(\mathbf{x}_j) \quad \mathbf{x}_j \in \mathbb{R}^{m_j}; \ t \in \mathbb{R} \tag{24}$$

where α_j is a positive constant and $u_j(\mathbf{x}_j)$ a positive-definite function and the single bars $|.|$ denote the Euclidean norm.

2) There are nonnegative constants β_{jk} such that

$$|g_j(\mathbf{x},t)| \leq \sum_{k=1}^{m} \beta_{jk} u_k(\mathbf{x}_k) \qquad \mathbf{x} \in \mathbb{R}^m;\ t \in \mathbb{R}. \tag{25}$$

3) The $m \times m$ matrix $C = (c_{jk})$ given by

$$c_{jj} = \alpha_j - \beta_{jj}; \qquad c_{jk} = -\beta_{jk} \quad (j \neq k) \tag{26}$$

is an M-matrix, i.e. all its off diagonal entries are nonpositive and all its eigenvalues have nonnegative real part [12]. □

Proof: see [11].

So, the next section is devoted to show that for the nonlinear system (4)-(5) Proposition 2 is a direct consequence of Theorem 1.

V. PROOF OF THE MAIN RESULT

Let us check all the conditions needed to apply Theorem 1 for the irreversible linear metabolic pathway (4)-(5). To this purpose, first, we make the following change of variables:

$$\forall\ i = 2,\ldots,n, \quad \delta x_i = x_i - x_i^* \quad \text{and} \quad \delta E_1 = E_1 - E_1^*.$$

Then, in the new base of the state variables, system (4)-(5) is equivalent to (27)-(28):

- The dynamics of the metabolite concentrations

$$\begin{array}{rcl} \delta\dot{x}_2 &=& \delta E_1 f_1(\bar{x}_1, \delta x_n + x_n^*) - E_1^* \delta f_1^*(\bar{x}_1, \delta x_n) - E_2 \delta f_2(\delta x_2) \\ \delta\dot{x}_3 &=& E_2 \delta f_2(\delta x_2) - E_3 \delta f_3(\delta x_3) \\ \vdots & \vdots & \vdots \qquad\qquad \vdots \\ \delta\dot{x}_n &=& E_{n-1} \delta f_{n-1}(\delta x_{n-1}) - E_n \delta f_n(\delta x_n) \end{array} \tag{27}$$

- The dynamics of the first enzyme concentration

$$\delta\dot{E}_1(t) = \delta g\big(\delta x_n\big) - \mu \delta E_1 \tag{28}$$

where

- $\delta f_1^*(\bar{x}_1, \delta x_n) = f_1(\bar{x}_1, x_n^*) - f_1(\bar{x}_1, \delta x_n + x_n^*)$,
- $\delta f_i(\delta x_i) = f_i(\delta x_i + x_i^*) - f_i(x_i^*)\ \ i = 2,\ldots,n$ and
- $\delta g(\delta x_n) = g(\delta x_n + x_n^*) - g(x_n^*)$.

To be in conformity with the decomposition (16), we rewrite (27)-(28) as below

$$\left\{ \begin{array}{rcl} \delta\dot{\mathbf{x}} &=& \mathbf{f}_1(\delta\mathbf{x}) + \mathbf{g}_1(\delta\mathbf{x}, \delta E_1) \\ \delta\dot{E}_1 &=& \mathbf{f}_2(\delta E_1) + \mathbf{g}_2(\delta\mathbf{x}) \end{array} \right. \tag{29}$$

where

$$\mathbf{f}_1(\delta\mathbf{x}) = \left\{ \begin{array}{l} -E_1^* \delta f_1^*(\bar{x}_1, \delta x_n) - E_2 \delta f_2(\delta x_2) \\ E_2 \delta f_2(\delta x_2) - E_3 \delta f_3(\delta x_3) \\ \qquad\vdots \qquad\qquad\qquad \vdots \\ E_{n-1} \delta f_{n-1}(\delta x_{n-1}) - E_n \delta f_n(\delta x_n), \end{array} \right.$$

$\mathbf{g}_1(\delta\mathbf{x}, \delta E_1) = \delta E_1 f_1(\bar{x}_1, \delta x_n + x_n^*)$, $\mathbf{f}_2(\delta E_1) = -\mu \delta E_1$, and $\mathbf{g}_2(\delta\mathbf{x}) = \delta g\big(\delta x_n\big)$ that satisfy $\mathbf{f}_1(\mathbf{0}) = \mathbf{0}$, $\mathbf{g}_1(0,0) = 0$, $\mathbf{f}_2(0) = 0$ and $\mathbf{g}_2(0) = 0$. Then, we build hereafter Lyapunov functions for each isolated systems.

A. Lyapunov function for the first isolated system

Consider the first isolated system

$$\delta\dot{\mathbf{x}} = \mathbf{f}_1(\delta\mathbf{x}) \tag{30}$$

Inspired by the results about the diagonal stability given in [13] and [8], we propose for the autonomous dynamical system (30) the following Lyapunov function

$$v_1(\delta\mathbf{x}) = \sum_{i=2}^{n-1} p_i E_i \int_0^{\delta x_i} \delta f_i(\sigma) d\sigma + p_n E_1^* \int_0^{\delta x_n} \delta f_1^*(\sigma) d\sigma \tag{31}$$

where for all $i \in \{2,\ldots,n\}$ $p_i > 0$. By construction, the Lyapunov function has the following properties

1) $v_1(0) = 0$ since $\forall i = 1,\ldots n-1,\ \delta f_i(0) = 0$,
2) $v_1(\delta\mathbf{x}) > 0$ because by definition

$$\forall i = 1,\ldots n-1,\ \delta f_i(\delta x_i)\delta x_i > 0$$

3) $\lim_{|\delta\mathbf{x}| \longrightarrow \infty} v_1(\delta\mathbf{x}) = +\infty$ since for all $i \in \{1,\ldots n-1\}$, $f_i(.)$ is strictly increasing and bounded, and thus

$$\lim_{|\delta x_i| \longrightarrow \infty} \int_0^{\delta x_i} \delta f_i(\sigma) d\sigma = +\infty$$

Hence, the only condition we have to examine is the negative-definiteness of $\dot{v}_1(\delta\mathbf{x})$. To this purpose, we first set

$$\mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T = [E_2 \delta f_2(\delta x_2), \ldots, E_{n-1} \delta f_{n-1}(\delta x_{n-1}), E_1^* \delta f_1^*(\bar{x}_1, \delta x_n)].$$

Then by definition we get $\mathbf{h}(\mathbf{0}, \mathbf{E})^T = \mathbf{0}$ and by direct computation we obtain

$$\dot{v}_1(\delta\mathbf{x}) = \mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T \mathbf{f}_1(\delta\mathbf{x}) \tag{32}$$

In line with the definition of γ_n given in Proposition 2 we have

$$-E_1^* \delta f_1^*(\bar{x}_1, \delta x_n) E_n \delta f_n(\delta x_n) \leq -\frac{1}{\gamma_n} E_1^{*2} \delta f_1^{*2}(\bar{x}_1, \delta x_n)$$

and then we can uppermost bound (32) as follows

$$\dot{v}_1(\delta\mathbf{x}) \leq \mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T \mathbf{P}\mathbf{A}\mathbf{h}(\delta\mathbf{x}, \mathbf{E}) \tag{33}$$

where the matrix $\mathbf{A}$ as defined by equation (12) is diagonally stable if condition (10) of Proposition 2 is satisfied [5], [6]. That means there exist some diagonal positive matrix $\mathbf{P}$ and some positive real number ε such that

$$\mathbf{P}\mathbf{A} + \mathbf{A}^T\mathbf{P} \leq -2\varepsilon\mathbf{I} \tag{34}$$

Therefore, we rewrite (33) as follows

$$\begin{array}{rcl} \dot{v}_1(\delta\mathbf{x}) &\leq& \frac{1}{2}\mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T [\mathbf{P}\mathbf{A} + \mathbf{A}^T\mathbf{P}] \mathbf{h}(\delta\mathbf{x}, \mathbf{E}) \\ &\leq& -\varepsilon \mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T \mathbf{I} \mathbf{h}(\delta\mathbf{x}, \mathbf{E}) \end{array} \tag{35}$$

which proves the negative-definiteness of $\dot{v}(\delta\mathbf{x})$. Moreover, to apply Theorem 1, the Lyapunov function $v_1(\delta\mathbf{x})$ has to satisfy (23) and (24). To check that, let us set

$$\begin{array}{rcl} \gamma_1 &=& \sup_{\delta\mathbf{x}} \left\{ \frac{|\bigtriangledown_{\delta\mathbf{x}} v_1(\delta\mathbf{x})|}{\sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x}, \mathbf{E})^T \mathbf{I} \mathbf{h}(\delta\mathbf{x}, \mathbf{E})}} \right\} \\ &=& \sup_{\delta\mathbf{x}} \left\{ \frac{\sqrt{\sum_{i=2}^n p_i^2 h_i^2}}{\sqrt{\varepsilon \sum_{i=2}^n h_i^2}} \right\} \\ &=& \sup_{\delta\mathbf{x}} \left\{ \frac{p\sqrt{\sum_{i=2}^n h_i^2}}{\sqrt{\varepsilon}\sqrt{\sum_{i=2}^n h_i^2}} \right\} \\ &=& \frac{p}{\sqrt{\varepsilon}} \end{array}$$

where p is the largest entry of the diagonal matrix $\mathbf{P}$. Then, we take

$$\alpha_1 = \frac{1}{\gamma_1^2} = \frac{\varepsilon}{p^2} \tag{36}$$

and

$$u_1(\delta\mathbf{x}) = \gamma_1 \sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x},\mathbf{E})^T \mathbf{I}\mathbf{h}(\delta\mathbf{x},\mathbf{E})} \tag{37}$$

From (35), (36) and (37) it is straightforward to show that

$$\dot{v}_1(\delta\mathbf{x}) \leq -\alpha_1 \{u_1(\delta\mathbf{x})\}^2 \quad \text{and}$$

$$\begin{aligned} u_1(\delta\mathbf{x}) &= \gamma_1 \sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x},\mathbf{E})^T \mathbf{I}\mathbf{h}(\delta\mathbf{x},\mathbf{E})} \\ &\geq \frac{|\bigtriangledown_{\delta\mathbf{x}} v_1(\delta\mathbf{x})|}{\sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x},\mathbf{E})^T \mathbf{I}\mathbf{h}(\delta\mathbf{x},\mathbf{E})}} \sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x},\mathbf{E})^T \mathbf{I}\mathbf{h}(\delta\mathbf{x},\mathbf{E})} \\ &\geq |\bigtriangledown_{\delta\mathbf{x}} v_1(\delta\mathbf{x})|, \end{aligned}$$

and so conditions (23) and (24) of Theorem 1 are satisfied.

B. Lyapunov function for the second isolated system

For the second isolated system

$$\delta\dot{E}_1 = \mathbf{f}_2(\delta E_1) = -\mu \delta E_1 \tag{38}$$

we can associate the following Lyapunov function

$$v_2(\delta E_1) = \frac{1}{2}\delta E_1^2 \tag{39}$$

with

$$\dot{v}_2(\delta E_1) = -\mu \delta E_1^2 \tag{40}$$

Moreover, if we take

$$\gamma_2 = \max_{\delta E_1} \Big\{ \frac{|\delta E_1|}{\sqrt{\mu \delta E_1^2}} \Big\} = \frac{1}{\sqrt{\mu}}, \quad \alpha_2 = \frac{1}{\gamma_2^2} = \mu \tag{41}$$

and

$$u_2(\delta E_1) = \gamma_2 \sqrt{\mu \delta E_1^2} \tag{42}$$

we can show that the conditions (23), (24) of Theorem 1 are also checked by the second isolated system, *viz.*

$$\dot{v}_2(\delta E_1) \leq -\alpha_2 \{u_2(\delta E_1)\}^2 \text{ and } u_2(\delta E_1) \geq \Big|\frac{dv_2(\delta E_1)}{d\delta E_1}\Big| = |\delta E_1|$$

C. Checking the remainder conditions of Theorem 1

To finish the proof of Proposition 2 we must check the two last conditions of Theorem 1. We start by condition (25) with $j = 1,2$. Indeed, we have to determine the nonnegative constants β_{11}, β_{12}, β_{21} and β_{22} such that:

$$|\mathbf{g}_1(\delta\mathbf{x},\delta E_1)| \leq \beta_{11} u_1(\delta\mathbf{x}) + \beta_{12} u_2(\delta E_1) \tag{43}$$

$$|\mathbf{g}_2(\delta\mathbf{x})| \leq \beta_{21} u_1(\delta\mathbf{x}) + \beta_{22} u_2(\delta E_1) \tag{44}$$

To satisfy (43), we have by definition

$$|\mathbf{g}_1(\delta\mathbf{x},\delta E_1)| \leq f_1(\bar{x}_1,0)|\delta E_1| = \beta_{11} \times u_1(\delta\mathbf{x}) + \beta_{12} u_2(\delta E_1)$$

Then, by identification we get $\beta_{11} = 0$ and $\beta_{12} = f_1(\bar{x}_1,0)$.

Now, to check the second inequality (44) we have to compute β_{21} such that

$$\begin{aligned} |\mathbf{g}_2(\delta\mathbf{x})| = |\delta g(\delta x_n)| &\leq \beta_{21} u_1(\delta\mathbf{x}) + 0 \times u_2(\delta E_1) \\ &\leq \beta_{21} \tfrac{p}{\sqrt{\varepsilon}} \sqrt{\varepsilon \mathbf{h}(\delta\mathbf{x},\mathbf{E})^T \mathbf{I}\mathbf{h}(\delta\mathbf{x},\mathbf{E})} \\ &\leq \beta_{21} \tfrac{p}{\sqrt{\varepsilon}} \sqrt{\varepsilon \textstyle\sum_{i=2}^n h_i^2} \\ &\leq \beta_{21} p h_n \\ &\leq \beta_{21} p E_1^* |\delta f_1^*(\bar{x}_1, \delta x_n)| \end{aligned}$$

which implies that

$$\beta_{21} \geq \frac{|\delta g(\delta x_n)|}{p E_1^* |\delta f_1^*(\bar{x}_1, \delta x_n)|}$$

Thus, according to the definition of λ_n given in Proposition 2, we can choose $\beta_{22} = 0$ and $\beta_{21} = \frac{\lambda_n}{pE_1^*}$.

Finally, to complete the verification of the conditions needed to apply Theorem 1 (and the proof of Proposition 2), it remains to show that the matrix

$$C = \begin{pmatrix} \alpha_1 - \beta_{11} & -\beta_{12} \\ -\beta_{21} & \alpha_2 - \beta_{22} \end{pmatrix} = \begin{pmatrix} \frac{\varepsilon}{p^2} & -f_1(\bar{x}_1,0) \\ -\frac{\lambda_n}{pE_1^*} & \mu \end{pmatrix} \tag{45}$$

is an M-matrix. To this purpose, we can use the leading principal minors criteria [12]. We then have to prove that all the leading principal minors of C are positive. By construction we have obtained positive diagonal entries c_{11} and c_{22}, then it remains to show that $\det|C|$ is also positive. By direct computation we obtain

$$\det|C| = \frac{\varepsilon\mu}{p^2} - \frac{\lambda_n f_1(\bar{x}_1,0)}{pE_1^*}$$

and so $\det|C|$ is strictly positive if and only if

$$\lambda_n < \frac{\varepsilon\mu E_1^*}{p f_1(\bar{x}_1,0)}$$

which is exactly the condition (13) stated in Proposition 2. This completes the proof of our main result, namely under conditions (10) and (13) there are two positive constants d_1 and d_2 such that the irreversible linear metabolic pathway (4)-(5) admits the following weighted sum

$$v(\delta\mathbf{x},\delta E_1) = d_1 v_1(\delta\mathbf{x}) + d_2 v_2(\delta E_1)$$

as a well defined Lyapunov function.

VI. CONDITIONS IMPLY EXPONENTIAL STABILITY OF THE EQUILIBRIUM REGIMEN

In fact, the previous conditions (10) and (13) ensure that the stability is actually locally exponential. Beyond its practical interest, it allows us, by classical arguments, to prove that the system is actually globally exponentially stable. In order to prove such a claim, we have first to use the boundedness of system trajectories which ensures that vector field of (4)-(5) is Lipschitz continuous of its arguments (C^1 function of a bounded domain). That allows us to use the classical Gronwall Bellman lemma in order to easily show that the local exponential stability is actually global.

Let us consider the linearized system (46) for the nonlinear system (4)-(5)

$$\begin{bmatrix} \delta\dot{\mathbf{x}} \\ \delta\dot{E}_1 \end{bmatrix} = \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} \delta\mathbf{x} \\ \delta E_1 \end{bmatrix} \tag{46}$$

where

$$A_{11} = \begin{bmatrix} -E_2 f_2'(x_2^*) & 0 & \dots & 0 & E_1^* f_1'(\bar{x}_1, x_n^*) \\ E_2 f_2'(x_2^*) & -E_3 f_3'(x_3^*) & \ddots & & 0 \\ 0 & E_3 f_3'(x_3^*) & -E_4 f_4'(x_4^*) & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \dots & 0 & E_{n-1} f_{n-1}'(x_{n-1}^*) & -E_n f_n'(x_n^*) \end{bmatrix}$$

$A_{12}^T = [f_1(\bar{x}_1, x_n^*), 0, \ldots, 0]$, $A_{21} = [0, \ldots, 0, g'(x_n^*)]$ and $A_{22} = -\mu$ and let us denote by $\mathbf{P}$ some diagonal positive matrix and by p_2 a positive constant. If the following mathematical expression is negative for all $(\delta\mathbf{x}^T, \delta E_1) \neq (\mathbf{0}^T, 0)$

$$\mathscr{C} = (\delta\mathbf{x}^T, \delta E_1)\left[\begin{pmatrix} \mathbf{P} & 0 \\ 0 & p_2 \end{pmatrix}\begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix} + \begin{pmatrix} A_{11}^T & A_{21}^T \\ A_{12}^T & A_{22} \end{pmatrix}\begin{pmatrix} \mathbf{P} & 0 \\ 0 & p_2 \end{pmatrix}\right]\begin{pmatrix} \delta\mathbf{x} \\ \delta E_1 \end{pmatrix}$$

then the equilibrium point of the linear system (46) is stable. Moreover, one can rewrite $\mathscr{C}$ as follows

$$\begin{aligned}\mathscr{C} = {} & \delta\mathbf{x}^T(\mathbf{P}A_{11} + A_{11}^T\mathbf{P})\delta\mathbf{x} + \delta E_1(p_2A_{22} + A_{22}p_2)\delta E_1 \\ & + 2\delta\mathbf{x}^T(\mathbf{P}A_{12} + A_{21}^T p_2)\delta E_1.\end{aligned} \tag{47}$$

In line with the result about the diagonal stability given in [5], [8], we can state that if

$$-\frac{E_1^* f_1'(\bar{x}_1, x_n^*)}{E_n f_n'(x_n^*)} < \sec(\pi/(n-1))^{n-1} \tag{48}$$

then there exist some positive diagonal matrix P and some positive real number ε such that

$$\mathbf{P}A_{11} + A_{11}^T\mathbf{P} \leq -2\varepsilon\mathbf{I} \tag{49}$$

Thanks to (49) we can obtain the following upper bound for

$$\begin{aligned}\mathscr{C} \leq 2\big(& -\varepsilon\delta x_2^2 - \varepsilon\delta x_n^2 - \mu p_2 \delta E_1^2 + \\ & p f_1(\bar{x}_1, x_n^*)\delta E_1\delta x_2 + g'(x_n^*)p_2\delta E_1\delta x_n\big).\end{aligned}$$

where p is the largest entry of $\mathbf{P}$. Note that the previous inequality is of the quadratic form

$$\mathscr{C} \leq (\delta x_2, \delta x_n, \delta E_1)\mathbf{M}(\delta x_2, \delta x_n, \delta E_1)^T$$

where $\mathbf{M}$ is a symmetric matrix,

$$\mathbf{M} = \begin{pmatrix} -2\varepsilon & 0 & p f_1(\bar{x}_1, x_n^*) \\ 0 & -2\varepsilon & p_2 g_1'(x_n) \\ p f_1(\bar{x}_1, x_n^*) & p_2 g'(x_n^*) & -2\mu p_2 \end{pmatrix}$$

Thus, we can claim that if $\mathbf{M}$ is negative definite then $\mathscr{C}$ is negative. Furthermore, $\mathbf{M}$ is negative definite if its principal minors m_1, m_2 and m_3 alternate in sign starting with $m_1 < 0$. Hereafter, we check these conditions,

- $m_1 = -2\varepsilon < 0$, $m_2 = 4\varepsilon^2 > 0$ and
- $m_3 = 2\varepsilon[-4p_2\mu\varepsilon + p_2^2 g(x_n^*)^2 + p^2 f_1(\bar{x}_1, x_n^*)^2]$

Then, $m_3 < 0$ if the inequality is satisfied

$$\mu\varepsilon > \frac{p_2^2 g'(x_n^*)^2 + p^2 f_1(\bar{x}_1, x_n^*)^2}{4p_2} = H(p_2). \tag{50}$$

It is of great interest to replace $H(p_2)$ in (50) by its minimum $H(p_2^*)$ with respect to p_2. To do that, first, we compute p_2^* such that the derivative $H'(p_2) = 0$. By direct computation we obtain

$$H'(p_2) = 0 \Longleftrightarrow p_2^* = \frac{p f_1(\bar{x}_1, x_n^*)}{|g'(x_n^*)|}.$$

and so

$$H(p_2^*) = \frac{1}{2} p f_1(\bar{x}_1, x_n^*)|g'(x_n^*)|.$$

Consequently condition (50) becomes

$$\mu\varepsilon > \frac{1}{2} p f_1(\bar{x}_1, x_n^*)|g'(x_n^*)| \tag{51}$$

Finally, the local stability of the equilibrium point of the nonlinear system (4)-(5) is guaranteed under the conditions (48) and (51). These conditions are similar to the conditions (10) and (13), which allows us to claim that the equilibrium is actually exponentially stable.

VII. CONCLUSIONS AND FUTURE WORKS

In this work we have shown that under some conditions it is possible to build for the irreversible linear metabolic pathway a well defined Lyapunov function, which proves the global asymptotic stability of its equilibrium point. For future works, we try to extend this result to reversible linear metabolic pathways and then to deal with the stability issue for complex metabolic networks viewed as large-scale interconnected linear metabolic pathways.

VIII. ACKNOWLEDGMENTS

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