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Optimal adaptation of metabolic networks in dynamic equilibrium

Diego A. Oyarzún[†] and Richard H. Middleton[‡]

***Abstract*— We consider the dynamic optimization of enzyme expression rates to drive a metabolic network between two given equilibrium fluxes. The formulation is based on a nonlinear control-affine model for a metabolic network coupled with a linear model for enzyme expression and degradation, whereby the expression rates are regarded as control inputs to be optimized. The cost function is a quadratic functional that accounts for the deviation of the species concentrations and expression rates from their target values, together with the genetic effort required for enzyme synthesis. If the network is in dynamic equilibrium along the whole adaptation process, the metabolite levels are constant and the nonlinear dynamics can be recast as a nonregular descriptor system. The structure of the reduced system can be exploited to decouple the algebraic and differential parts of the dynamics, so as to parameterize the controls that satisfy the algebraic constraint in terms of a lower-dimensional control. The problem is then solved as a standard Linear Quadratic Regulator problem for an unconstrained lower dimensional system. This solution allows for a systematic computation of the optimal flux trajectories between two prescribed dynamic equilibrium regimes for networks with general topologies and kinetics.**

I. Introduction

Metabolic networks convert nutrients into usable energy and synthesize a variety of chemical species required by a cell [1]. A challenging goal is the identification of design principles that underpin their control and regulation [2]. Since it appears that biological systems have evolved so as to optimize their adaptation to external conditions [3], one approach aims at reverse-engineering metabolic systems under the assumption of an underlying optimality principle, as in e.g. [4], [5], [6], [7], [8]. Optimal solutions are then compared with experimental data so as to provide a quantitative justification to the behaviors observed in nature [5], [9], [10]. In this paper we show how to solve a class of metabolic optimization problems using classic Linear Quadratic optimization.

A simple metabolic network is shown in Fig. 1 with the metabolite concentrations denoted as s_i and the chemical reaction rates as v_i. These networks typically operate in a dynamic equilibrium, whereby the rates are stoichiometrically balanced and the metabolites are constant in time [11]. The equilibrium rates (also known as steady state fluxes) define different operation regimes, which in turn correspond to specific physiological states of a cell. For example, in Fig. 1 regimes I and II represent the preferential uptake of nutrient S_A or S_B, whereas regimes III and IV are associated to the preferred synthesis of compound s_2 or s_3. The transition between different regimes is needed to satisfy cellular demands and respond to environmental stimuli within the resource constraints. Such adaptation mechanisms arise, for example, in response to changes in nutritional [9], osmotic [12], and thermal [13] conditions.

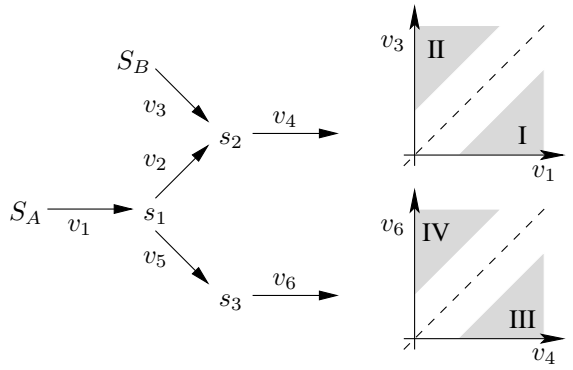

Fig. 1. Metabolic network and different steady state operation regimes.

Metabolic reactions are catalyzed by enzymatic molecules, the availability of which is controlled by genetic expression. This allows the modulation of metabolic fluxes by adjusting the rate at which the enzymes are synthesized. In this paper we address the problem of optimizing the transition between two given metabolic fluxes by means of time-dependent enzyme expression rates. As a way of accounting for the cost/benefit relationship between the genetic effort required for enzyme synthesis and the transition to the new equilibrium, we consider the minimization of a quadratic functional that weighs the time-derivative of the expression rates, together with the deviations of the species concentrations and enzyme expression rates from their target values.

A number of approaches to dynamic optimization of metabolic networks have been developed e.g. [14], [9], [15]. These methods regard the reaction rates as control inputs to be optimized, which makes them applicable in cases where the enzyme kinetics are unknown. This is a great advantage since the identification of enzyme kinetics requires significant experimental effort. This approach, however, overlooks the dependency of the reaction rates on the metabolite and enzyme concentrations. In this paper we avoid this shortcoming and describe the metabolic network as a nonlinear control-affine model with the enzyme concentrations as control inputs. This formulation accounts for a broad class of networks with general topologies and enzyme kinetics. The network model is coupled with a linear model for enzyme dynamics that accounts for protein

[†] Centre for Synthetic Biology and Innovation, Department of Bioengineering, Imperial College London, SW7 2AZ United Kingdom; corresponding author, d.oyarzun@imperial.ac.uk.

[‡] Hamilton Institute, National University of Ireland, Maynooth, Co. Kildare, Ireland; richard.middleton@nuim.ie.

expression and degradation. The complete model describes both metabolite and enzyme trajectories in response to time-dependent enzyme expression rates.

Experimental observations have shown that variations in metabolic fluxes can be accompanied by comparatively small changes in the metabolite concentrations [11]. We study the limiting case of this scenario and address the optimal transition under constant metabolite concentrations. Under this constraint the network remains in dynamic equilibrium along the whole optimization interval and its dynamics can be recast as a nonregular descriptor (linear) system. The structure of the descriptor system is exploited to decouple the algebraic and differential parts of the dynamics. This allows for a parameterization of all controls that satisfy the algebraic constraint in terms of a lower-dimensional control variable. The problem can then be solved with the classic Linear Quadratic Regulator (LQR) theory [16] applied to a purely differential linear system. The analytic nature of this solution makes it promising for large scale networks with complex enzyme kinetics.

II. Problem formulation

A. Control-affine model for a metabolic network

Consider a network of n metabolites $s_1, s_2, \ldots, s_n$ interacting via m reactions. The chemical equation for the j^{th} reaction is

$$\sum_{i=1}^{n} \alpha_{ij} s_i \overset{v_j}{\longleftrightarrow} \sum_{i=1}^{n} \beta_{ij} s_i, \quad j = 1, 2, \ldots, m, \tag{1}$$

where v_j is the reaction rate, and $\alpha_{ij}, \beta_{ij} \in \mathbb{N}$ are the stoichiometric coefficients of the i^{th} metabolite in the j^{th} reaction. The rate of change of s_i is given by the balance between those reactions that have s_i as a product and reactant. This yields

$$\dot{s} = \boldsymbol{N} v, \tag{2}$$

where $s \in \mathbb{R}^n_{\geq 0}$ and $v \in \mathbb{R}^m$ are vectors of metabolite concentrations and reaction rates, respectively. The matrix $\boldsymbol{N} \in \mathbb{Z}^{n \times m}$ is the stoichiometric matrix of the network defined as $\boldsymbol{N}_{ij} = \beta_{ij} - \alpha_{ij}$. Metabolite s_i is consumed (produced) in the j^{th} reaction whenever $\boldsymbol{N}_{ij} < 0$ ($\boldsymbol{N}_{ij} > 0$). For future reference we define $d = \operatorname{rank} \boldsymbol{N}$, so that in the typical case when $n < m$, $n - d$ is the number of moiety conserved cycles in the network.

If the reaction rates are considered as control inputs, the model (2) is a linear time-invariant system with zero state matrix. The linearity of (2) is favorable for the solution of optimal control problems, but this model neglects the dependency of the reaction rates on the metabolite and enzyme concentrations. The reaction rates are typically saturable functions (i.e. sigmoid-like) of the metabolites and linear in the enzyme concentrations [1]. We thus make the following assumption.

Assumption 1: The reaction rates are linear in the enzyme concentrations and can be written as

$$v_i = v_i(s, e_i) = g_i(s) e_i, \quad i = 1, 2, \ldots, m, \tag{3}$$

where $e_i \geq 0$ is the concentration of the i^{th} enzyme, and $g_i : \mathbb{R}^n \to \mathbb{R}$ is Lipschitz continuous.

This assumption is met by most commonly used models for enzyme kinetics, but exceptions can be found, for example, in the case of enzyme-enzyme interactions [1]. The function $g_i(s)$ is the rate per unit of enzyme concentration and depends on the specific chemical kinetics of the enzyme.

Under Assumption 1, the model (2) becomes

$$\dot{s} = \boldsymbol{N} \boldsymbol{G}(s) e, \tag{4}$$

where $e \in \mathbb{R}^m_{\geq 0}$ is the vector of enzyme concentrations and

$$\boldsymbol{G}(s) = \operatorname{diag}\left\{g_1(s), g_2(s), \ldots, g_m(s)\right\}. \tag{5}$$

If the enzyme concentrations are taken as control inputs, the model (4) corresponds to a *control-affine nonlinear system*, which is amenable to control-theoretic analyses [17].

B. Linear model for enzyme dynamics

Enzyme dynamics can be described as the mass balance between enzyme expression and degradation. If the degradation rates are assumed proportional to the enzyme concentration, then we can write

$$\dot{e} = r - \boldsymbol{\Lambda} e, \tag{6}$$

where $r \in \mathbb{R}^m_{\geq 0}$ is the vector of enzyme expression rates, and $\boldsymbol{\Lambda} = \operatorname{diag}\left\{\lambda_1, \lambda_2, \ldots, \lambda_m\right\}$ with $\lambda_i > 0$. The constants λ_i can account not only for enzyme degradation, but also for dilution effects due to cell growth. The full system (4)–(6) can be represented by the block diagram of Fig. 2.

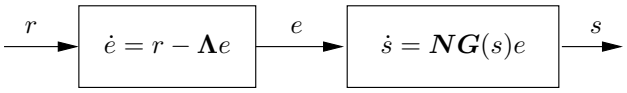

Fig. 2. Block diagram of a metabolic network coupled with enzyme dynamics.

C. Optimal control probem

The objective is to drive the network from an initial steady state to a given flux by means of time-dependent enzyme expression rates. If the steady state metabolite concentration vector is s^i, the initial and target fluxes (v^i and v^f, respectively) are achieved by the following enzyme concentrations and expression rates

$$e^i = \boldsymbol{G_i}^{-1} v^i, \qquad r^i = \boldsymbol{\Lambda} \boldsymbol{G_i}^{-1} v^i, \tag{7}$$

$$e^f = \boldsymbol{G_i}^{-1} v^f, \qquad r^f = \boldsymbol{\Lambda} \boldsymbol{G_i}^{-1} v^f. \tag{8}$$

where s^i is such that $\boldsymbol{G_i} = \boldsymbol{G}(s^i)$ is nonsingular. Note that since v^i and v^f define a steady state, from (2) it must hold that $v^i, v^f \in \ker \boldsymbol{N}$. Since metabolic reactions cannot occur in absence of their substrate, the nonsingularity of $\boldsymbol{G_i}$ limits the problem formulation to those cases in which the metabolite concentrations are nonzero. We will deal with the following optimal control problem.

Problem 1: Let $v^i, v^f \in \ker \boldsymbol{N}$ be two steady state fluxes for the network in (4). Let $s^i \in \mathbb{R}^n_{\geq 0}$ be such that $\boldsymbol{G_i}$ is

nonsingular, and consider the initial conditions $e(0) = e^i$, $r(0) = r^i$, with e^i, r^i given in (7). Define the quadratic functional

$$\mathcal{J} = \frac{1}{2}\int_0^\infty \Big(\left(e - e^f\right)^T \boldsymbol{W_e} \left(e - e^f\right) + \left(r - r^f\right)^T \boldsymbol{W_r} \left(r - r^f\right) + \dot{r}^T \boldsymbol{W_{\dot{r}}} \dot{r} \Big)\, \mathrm{d}t, \tag{9}$$

with e^f, r^f given in (8), $\boldsymbol{W_e}, \boldsymbol{W_r}, \boldsymbol{W_{\dot{r}}} \in \mathbb{R}^{m\times m}$ and $\boldsymbol{W_e}, \boldsymbol{W_r} \geq 0$, $\boldsymbol{W_{\dot{r}}} > 0$. Find a control $r : \mathbb{R}_{\geq 0} \to \mathbb{R}^m$ for the system in Fig. 2 that minimizes $\mathcal{J}$ subject to

$$s(t) = s^i, \forall t \geq 0. \tag{10}$$

Minimization of the cost $\mathcal{J}$ accounts for the combined optimization of the transition to the target steady state together with the genetic effort allocated to enzyme synthesis (as measured by $\dot{r}$). The nonlinearities of the system in Fig. 2 appear only in the matrix function $\boldsymbol{G}(s)$, and hence the dynamics are linear under the constraint (10). Moreover, as shown in the next section, the constraint introduces algebraic dependencies in the state variable.

III. Nonregular descriptor system

The following lemma provides a useful characterization of the constraint (10) in Problem 1.

Lemma 1: Let $s^i \in \mathbb{R}^n_{\geq 0}$ be such that $\boldsymbol{G_i}$ is nonsingular. Define $\boldsymbol{T_1} = \boldsymbol{G_i}^{-1}\boldsymbol{K} \in \mathbb{R}^{m\times(m-d)}$ with $\operatorname{Im}\boldsymbol{K} = \ker \boldsymbol{N}$. Then, $s(t) = s^i$ for all $t \geq 0$ if and only if e satisfies

$$e = \boldsymbol{T_1}\phi, \tag{11}$$

for some function $\phi : \mathbb{R}_{\geq 0} \to \mathbb{R}^{m-d}$.

Proof: Sufficiency follows by substituting (11) in the network (4), which yields

$$\dot{s} = \boldsymbol{N}\boldsymbol{G}(s)\boldsymbol{G_i}^{-1}\boldsymbol{K}\phi. \tag{12}$$

Evaluation of (12) at $t = 0$ implies that $\dot{s}(0) = \boldsymbol{N}\boldsymbol{K}\phi = 0$ for all ϕ and hence $s(t) = s^i$ for all $t \geq 0$ is the unique solution (recall that $\boldsymbol{G}(s)$ is Lipschitz continuous). Necessity can be proven by noting that in (4), $\dot{s} = 0$ holds only when

$$\boldsymbol{G}(s)e = 0, \forall t \geq 0, \tag{13}$$

or

$$e(t) \in \ker\left\{\boldsymbol{N}\boldsymbol{G}(s)\right\}, \forall t \geq 0. \tag{14}$$

Equation (13) holds if $e = 0$ for all $t \geq 0$ (the trivial case) or $\boldsymbol{G}(s) = 0$ for all $t \geq 0$, which can be discarded because $\boldsymbol{G}(s)$ is nonsingular at least for $t = 0$ (recall that $\boldsymbol{G_i}$ is nonsingular). Moreover, $s(t) = s^i$ for all $t \geq 0$ implies that (14) only holds when $e(t) \in \ker\{\boldsymbol{N}\boldsymbol{G_i}\}$, which is equivalent to (11) because the columns of $\boldsymbol{T_1}$ form a basis for the nullspace of $\boldsymbol{N}\boldsymbol{G_i}$. ∎

Define the extended state variable as

$$\bar{x} = x - x^f, \quad x = \begin{bmatrix} e \\ r \end{bmatrix}, \quad x^f = \begin{bmatrix} e^f \\ r^f \end{bmatrix}. \tag{15}$$

By defining the control input as $u = \dot{r}$, the system (6) can be rewritten as

$$\dot{\bar{x}} = \begin{bmatrix} -\boldsymbol{\Lambda} & \boldsymbol{I} \\ \boldsymbol{0} & \boldsymbol{0} \end{bmatrix} \bar{x} + \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{I} \end{bmatrix} u, \quad \bar{x}(0) = x^i - x^f. \tag{16}$$

with $x^i = \begin{bmatrix} e^{i^T} & r^{i^T} \end{bmatrix}^T$. From (11) in Lemma 1 we see that d degrees of freedom need to be dropped in the enzyme vector e. This ensures that $e \in \ker\{\boldsymbol{N}\boldsymbol{G_i}\}$ is satisfied pointwise in time and hence (10) is met. This also implies that $\dot{e} \in \ker\{\boldsymbol{N}\boldsymbol{G_i}\}$ must also be satisfied, which adds another d constraints. Therefore, the algebraic constraints imposed by (10) require dropping $2d$ degrees of freedom in the extended state $\bar{x}$. Hence any $\bar{x}$ that satisfies the algebraic constraints must be of the form $\bar{x} = \boldsymbol{E}z$ with $\boldsymbol{E} \in \mathbb{R}^{2m\times 2(m-d)}$ and $z \in \mathbb{R}^{2(m-d)}$. In view of (16), this implies that z satisfies

$$\boldsymbol{E}\dot{z} = \begin{bmatrix} -\boldsymbol{\Lambda} & \boldsymbol{I} \\ \boldsymbol{0} & \boldsymbol{0} \end{bmatrix} \boldsymbol{E}z + \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{I} \end{bmatrix} u, \tag{17}$$

with $z(0) = \boldsymbol{E}^+\left(x^i - x^f\right)$ and $\boldsymbol{E}^+ = \left(\boldsymbol{E}^T\boldsymbol{E}\right)^{-1}\boldsymbol{E}^T$ being the Moore-Penrose pseudoinverse of $\boldsymbol{E}$. Note that in this case $\bar{x}$ has exactly $\operatorname{rank}\boldsymbol{E}$ degrees of freedom, so in order to avoid introducing further constraints on $\bar{x}$, the matrix $\boldsymbol{E}$ needs to have full column rank. Differential-Algebraic systems of the form (17) are usually referred to as *descriptor* systems. If $\det(\lambda\boldsymbol{E} - \boldsymbol{A}) \not\equiv 0$, $\lambda \in \mathbb{R}$, the system is *regular*, whereas if $\det(\lambda\boldsymbol{E} - \boldsymbol{A}) \equiv 0$ or $p \neq n$ the system is called *nonregular*.

We also note that the cost in Problem 1 can be written as the quadratic form

$$\mathcal{J} = \frac{1}{2}\int_0^\infty \left(\bar{x}^T\bar{\boldsymbol{Q}}\bar{x} + u^T\boldsymbol{W_{\dot{r}}}u\right)\mathrm{d}t, \tag{18}$$

with $\bar{\boldsymbol{Q}} = \operatorname{diag}\{\boldsymbol{W_e}, \boldsymbol{W_r}\}$. The minimization of $\mathcal{J}$ for the descriptor system in (17) is a Linear Quadratic Regulator (LQR) problem [16]. The LQR problem for regular descriptor systems was originally treated in [18], [19], whereas the nonregular case was studied in e.g. [20], [21] and the references therein. The idea behind these methods is to "regularize" the dynamics by introducing suitable state transformations so as to recast the dynamics as a purely differential linear system [22]. In our case, however, the form of the system in (17) can be exploited to choose $\boldsymbol{E}$ in a way that the control minimizing $\mathcal{J}$ in (18) can be explicitly computed in terms of the system matrices $(\boldsymbol{N}, \boldsymbol{G_i}, \boldsymbol{\Lambda})$ and weights $(\boldsymbol{W_e}, \boldsymbol{W_r}, \boldsymbol{W_{\dot{r}}})$. Define the matrix $\boldsymbol{T_2} = \boldsymbol{\Lambda}\boldsymbol{T_1} \in \mathbb{R}^{m\times(m-d)}$ and pick $\boldsymbol{E}$ as

$$\boldsymbol{E} = \begin{bmatrix} \boldsymbol{T_1} & \boldsymbol{0} \\ \boldsymbol{T_2} & \boldsymbol{T_1} \end{bmatrix}, \tag{19}$$

so that the descriptor system (17) becomes

$$\boldsymbol{E}\dot{z} = \boldsymbol{A}z + \boldsymbol{B}u, \quad z(0) = \boldsymbol{E}^+\left(x^i - x^f\right), \tag{20}$$

with $\boldsymbol{A} \in \mathbb{R}^{2m\times 2(m-d)}$ and $\boldsymbol{B} \in \mathbb{R}^{2m\times m}$ defined as

$$\boldsymbol{A} = \begin{bmatrix} \boldsymbol{0} & \boldsymbol{T_1} \\ \boldsymbol{0} & \boldsymbol{0} \end{bmatrix}, \quad \boldsymbol{B} = \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{I} \end{bmatrix}. \tag{21}$$

In next section we solve the problem by using the structure of $\boldsymbol{E}$ to explicitly decouple the algebraic and differential parts of the descriptor system in (20).

IV. Solution of the equivalent LQR problem

Define the matrix $\boldsymbol{E}^* \in \mathbb{R}^{2(m+n-d)\times 2m}$ as

$$\boldsymbol{E}^* = \begin{bmatrix} \boldsymbol{E}^\perp \\ \boldsymbol{E}^+ \end{bmatrix}, \tag{22}$$

where $\boldsymbol{E}^\perp \in \mathbb{R}^{2n\times 2m}$ is given by

$$\boldsymbol{E}^\perp = \begin{bmatrix} \boldsymbol{N}\boldsymbol{G_i} & \boldsymbol{0} \\ -\boldsymbol{N}\boldsymbol{\Lambda}\boldsymbol{G_i} & \boldsymbol{N}\boldsymbol{G_i} \end{bmatrix}. \tag{23}$$

Since $\boldsymbol{E}^\perp\boldsymbol{E} = \boldsymbol{0}$, multiplication of the descriptor system in (20) by $\boldsymbol{E}^*$ yields

$$0 = \boldsymbol{E}^\perp\boldsymbol{A}z + \boldsymbol{E}^\perp\boldsymbol{B}u, \tag{24}$$

$$\dot{z} = \boldsymbol{E}^+\boldsymbol{A}z + \boldsymbol{E}^+\boldsymbol{B}u. \tag{25}$$

The above equations are the algebraic and differential parts of the descriptor system: (24) consists of $2n$ algebraic equations (note that only d of these are nontrivial), whereas (25) comprises $2(m-d)$ differential equations in z. Equation (24) can be used to explicitly find the class of controls that satisfy the algebraic constraint. The products $\boldsymbol{E}^\perp\boldsymbol{A}$ and $\boldsymbol{E}^\perp\boldsymbol{B}$ are given by

$$\boldsymbol{E}^\perp\boldsymbol{A} = \begin{bmatrix} \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & -\boldsymbol{N}\boldsymbol{G_i}\boldsymbol{T_2} \end{bmatrix}, \quad \boldsymbol{E}^\perp\boldsymbol{B} = \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{N}\boldsymbol{G_i} \end{bmatrix}, \tag{26}$$

and thus (24) reduces to the d algebraic equations

$$\boldsymbol{N}\boldsymbol{G_i}\left(-\boldsymbol{T_u}z + u\right) = 0, \tag{27}$$

where $\boldsymbol{T_u} \in \mathbb{R}^{m\times 2(m-d)}$ is given by $\boldsymbol{T_u} = \begin{bmatrix} \boldsymbol{0} & \boldsymbol{T_2} \end{bmatrix}$. Equation (27) implies that a control u satisfies the algebraic constraint if and only if

$$\left(-\boldsymbol{T_u}z + u\right) \in \ker\left\{\boldsymbol{N}\boldsymbol{G_i}\right\}. \tag{28}$$

The columns of $\boldsymbol{T_1}$ span the nullspace of $\boldsymbol{N}\boldsymbol{G_i}$, and thus any u satisfying (28) has the form

$$u = \boldsymbol{T_u}z + \boldsymbol{T_1}\omega, \tag{29}$$

for some $\omega \in \mathbb{R}^{m-d}$. We have obtained a parameterization of the original control u in terms of a lower-dimensional control ω which guarantees that the algebraic constraint is satisfied. The dynamics for z can be rewritten in terms of ω by substituting (29) in (25)

$$\begin{aligned} \dot{z} &= \boldsymbol{E}^+\left(\boldsymbol{A} + \boldsymbol{B}\boldsymbol{T_u}\right)z + \boldsymbol{E}^+\boldsymbol{B}\boldsymbol{T_1}\omega, \\ &= \boldsymbol{E}^+\boldsymbol{E}\underbrace{\begin{bmatrix} \boldsymbol{0} & \boldsymbol{I} \\ \boldsymbol{0} & \boldsymbol{0} \end{bmatrix}}_{\boldsymbol{A_z}}z + \boldsymbol{E}^+\boldsymbol{E}\underbrace{\begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{I} \end{bmatrix}}_{\boldsymbol{B_z}}\omega, \\ &= \boldsymbol{A_z}z + \boldsymbol{B_z}\omega, \end{aligned} \tag{30}$$

where $\boldsymbol{A_z} \in \mathbb{R}^{2(m-d)\times 2(m-d)}$ and $\boldsymbol{B_z} \in \mathbb{R}^{2(m-d)\times(m-d)}$. Since the constraint (10) is satisfied for any ω, the solution of Problem 1 can be obtained by optimizing ω for system (30) without algebraic constraints. To that end, we rewrite the cost $\mathcal{J}$ in (18) in terms of the new state z and control ω. Substituting $\bar{x} = \boldsymbol{E}z$ and (29) in the cost (18) yields

$$\mathcal{J} = \frac{1}{2}\int_0^\infty \left(z^T\boldsymbol{Q}z + \omega^T\boldsymbol{R}\omega + 2z^T\boldsymbol{S}\omega\right)\,\mathrm{d}t, \tag{31}$$

where

$$\begin{aligned} \boldsymbol{Q} &= \boldsymbol{E}^T\bar{\boldsymbol{Q}}\boldsymbol{E} + {\boldsymbol{T_u}}^T\boldsymbol{W_{\dot{r}}}\boldsymbol{T_u}, \\ \boldsymbol{R} &= {\boldsymbol{T_1}}^T\boldsymbol{W_{\dot{r}}}\boldsymbol{T_1}, \\ \boldsymbol{S} &= {\boldsymbol{T_u}}^T\boldsymbol{W_{\dot{r}}}\boldsymbol{T_1}. \end{aligned} \tag{32}$$

It is worth noting that the algebraic constraint on u in (29) translates into $\mathcal{J}$ having a *mixed* term that weighs the product between state and control (via the weight matrix $\boldsymbol{S} \in \mathbb{R}^{2(m-d)\times(m-d)}$). We also see that the dynamics of z in (30) are unstable, since all the eigenvalues of $\boldsymbol{A_z}$ are located at the origin. Define the matrices $\tilde{\boldsymbol{A}}_{\boldsymbol{z}} = \boldsymbol{A_z} - \boldsymbol{B_z}\boldsymbol{R}^{-1}\boldsymbol{S}^T$ and $\tilde{\boldsymbol{Q}} = \boldsymbol{Q} - \boldsymbol{S}\boldsymbol{R}^{-1}\boldsymbol{S}^T$, and assume that the weights satisfy $\boldsymbol{R} > 0$ and $\tilde{\boldsymbol{Q}} \geq 0$. Provided that $(\boldsymbol{A_z}, \boldsymbol{B_z})$ is stabilizable and $\left(\tilde{\boldsymbol{A}}_{\boldsymbol{z}}, \tilde{\boldsymbol{Q}}^{\frac{1}{2}}\right)$ is detectable, the optimal control is stabilizing and given by [16]

$$u = -\boldsymbol{R}^{-1}\left({\boldsymbol{B_z}}^T\boldsymbol{P} + \boldsymbol{S}^T\right)x, \tag{33}$$

where $\boldsymbol{P} \in \mathbb{R}^{2(m-d)}$ is the solution of the algebraic Riccati equation

$${\tilde{\boldsymbol{A}}_{\boldsymbol{z}}}^T\boldsymbol{P} + \boldsymbol{P}\tilde{\boldsymbol{A}}_{\boldsymbol{z}} - \boldsymbol{P}\boldsymbol{B_z}\boldsymbol{R}^{-1}{\boldsymbol{B_z}}^T\boldsymbol{P} + \tilde{\boldsymbol{Q}} = 0. \tag{34}$$

The next result provides conditions under which the above assumptions hold.

Lemma 2: Consider $\boldsymbol{A_z}$ and $\boldsymbol{B_z}$ defined in (30) and $\boldsymbol{Q}$, $\boldsymbol{R}$, and $\boldsymbol{S}$ defined in (32). Then:

(i) $\boldsymbol{R} > 0$,

(ii) the pair $(\boldsymbol{A_z}, \boldsymbol{B_z})$ is stabilizable,

(iii) $\boldsymbol{W_e}, \boldsymbol{W_r} > 0$ implies that $\tilde{\boldsymbol{Q}} = \boldsymbol{Q} - \boldsymbol{S}\boldsymbol{R}^{-1}\boldsymbol{S}^T > 0$, and thus $\left(\boldsymbol{A_z}, \tilde{\boldsymbol{Q}}^{\frac{1}{2}}\right)$ is detectable.

Proof: Claim (i) follows by noting that $\boldsymbol{T_1}$ has full column rank, so that $\boldsymbol{W_{\dot{r}}} > 0$ implies $\boldsymbol{R} = {\boldsymbol{T_1}}^T\boldsymbol{W_{\dot{r}}}\boldsymbol{T_1} > 0$. Claim (ii) follows from the definitions of $\boldsymbol{A_z}$ and $\boldsymbol{B_z}$ we have

$$\begin{bmatrix} \boldsymbol{B_z} & \boldsymbol{A_z}\boldsymbol{B_z} & \cdots & {\boldsymbol{A_z}}^{2(m-d)-1}\boldsymbol{B_z} \end{bmatrix} = \begin{bmatrix} \boldsymbol{0} & \boldsymbol{I} & \boldsymbol{0} & \cdots & \boldsymbol{0} \\ \boldsymbol{I} & \boldsymbol{0} & \boldsymbol{0} & \cdots & \boldsymbol{0} \end{bmatrix}, \tag{35}$$

and so

$$\operatorname{rank}\begin{bmatrix} \boldsymbol{B_z} & \boldsymbol{A_z}\boldsymbol{B_z} & \cdots & {\boldsymbol{A_z}}^{2(m-d)-1}\boldsymbol{B_z} \end{bmatrix} = 2(m-d), \tag{36}$$

which means that the pair $(\boldsymbol{A_z}, \boldsymbol{B_z})$ is completely controllable. To prove claim (iii) we note that, provided that $\boldsymbol{W_e}, \boldsymbol{W_r} > 0$, we have $\bar{\boldsymbol{Q}} > 0$ and so $\boldsymbol{E}^T\bar{\boldsymbol{Q}}\boldsymbol{E} > 0$, which implies that $\boldsymbol{Q} = \boldsymbol{E}^T\bar{\boldsymbol{Q}}\boldsymbol{E} + {\boldsymbol{T_u}}^T\boldsymbol{W_{\dot{r}}}\boldsymbol{T_u} > 0$. Using Schur's complement this implies that $\tilde{\boldsymbol{Q}} = \boldsymbol{Q} - \boldsymbol{S}\boldsymbol{R}^{-1}\boldsymbol{S}^T > 0$ if and

only if

$$\tilde{\boldsymbol{Q}}' = \begin{bmatrix} \boldsymbol{Q} & \boldsymbol{S} \\ \boldsymbol{S}^T & \boldsymbol{R} \end{bmatrix} > 0. \tag{37}$$

From the definitions of $\boldsymbol{Q}$, $\boldsymbol{R}$ and $\boldsymbol{S}$ in (32) we get

$$\tilde{\boldsymbol{Q}}' = \begin{bmatrix} \boldsymbol{E}^T \bar{\boldsymbol{Q}} \boldsymbol{E} + \boldsymbol{T_u}^T \boldsymbol{W_{\dot{r}}} \boldsymbol{T_u} & \boldsymbol{T_u}^T \boldsymbol{W_{\dot{r}}} \boldsymbol{T_1} \\ \boldsymbol{T_1}^T \boldsymbol{W_{\dot{r}}} \boldsymbol{T_u} & \boldsymbol{T_1}^T \boldsymbol{W_{\dot{r}}} \boldsymbol{T_1} \end{bmatrix} > 0. \tag{38}$$

Let $y = \begin{bmatrix} y_a \\ y_b \end{bmatrix}$ with $y_a \in \mathbb{R}^{2(m-d)}$ and $y_b \in \mathbb{R}^{m-d}$, then

$$\begin{aligned} y^T \tilde{\boldsymbol{Q}}' y &= (\boldsymbol{E} y_a)^T \bar{\boldsymbol{Q}} (\boldsymbol{E} y_a) + (\boldsymbol{T_u} y_a)^T \boldsymbol{W_{\dot{r}}} (\boldsymbol{T_u} y_a) \\ &\quad + (\boldsymbol{T_1} y_b)^T \boldsymbol{W_{\dot{r}}} (\boldsymbol{T_1} y_b) + 2 (\boldsymbol{T_u} y_a)^T \boldsymbol{W_{\dot{r}}} (\boldsymbol{T_1} y_b), \\ &= (\boldsymbol{E} y_a)^T \bar{\boldsymbol{Q}} (\boldsymbol{E} y_a) \\ &\quad + (\boldsymbol{T_u} y_a + \boldsymbol{T_1} y_b)^T \boldsymbol{W_{\dot{r}}} (\boldsymbol{T_u} y_a + \boldsymbol{T_1} y_b). \end{aligned} \tag{39}$$

Since $\boldsymbol{E}$ has full column rank, $\boldsymbol{E} y_a = 0$ only for $y_a = 0$, so that $\bar{\boldsymbol{Q}} > 0$ implies

$$(\boldsymbol{E} y_a)^T \bar{\boldsymbol{Q}} (\boldsymbol{E} y_a) > 0, \forall y_a \neq 0. \tag{40}$$

In the case $y_a = 0$, using $\boldsymbol{W_{\dot{r}}} > 0$ in (39) we get

$$y^T \tilde{\boldsymbol{Q}}' y = (\boldsymbol{T_1} y_b)^T \boldsymbol{W_{\dot{r}}} (\boldsymbol{T_1} y_b) > 0, \forall y_b \neq 0 \tag{41}$$

and hence we conclude that $y^T \tilde{\boldsymbol{Q}}' y > 0$ for all $y \neq 0$ and so $\tilde{\boldsymbol{Q}} > 0$, hence claim (iii) follows. ■

From Lemma 2 we conclude that the stabilizability and detectability conditions always hold, provided that the weights $\boldsymbol{W_e}, \boldsymbol{W_r}$ are positive definite. With this result the problem can be solved using the LQR solution for the equivalent system in (30) and the cost in (31). The solution to Problem 1 is given in the next lemma, which is a straightforward application of (33)–(34).

Lemma 3: Assume that the weights in $\mathcal{J}$ satisfy $\boldsymbol{W_e}, \boldsymbol{W_r} > 0$. The solution $x^* = \begin{bmatrix} e^* \\ r^* \end{bmatrix}$ of Problem 1 is

$$x^* = \boldsymbol{E} z^* + x^f, \tag{42}$$

where z^* satisfies

$$\dot{z}^* = \left(\tilde{\boldsymbol{A}}_{\boldsymbol{z}} - \boldsymbol{B_z} \boldsymbol{R}^{-1} \boldsymbol{B_z}^T \boldsymbol{P} \right) z^*, \quad z^*(0) = \boldsymbol{E}^+ \left(x^i - x^f \right), \tag{43}$$

and $\boldsymbol{P} \in \mathbb{R}^{2(m-d) \times 2(m-d)}$ is the solution of the Riccati equation (34).

V. Example

We illustrate our result with the metabolic network in Fig. 1. The stoichiometric matrix of this network is

$$\boldsymbol{N} = \begin{bmatrix} 1 & -1 & 0 & 0 & -1 & 0 \\ 0 & 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{bmatrix}. \tag{44}$$

The enzyme kinetics are assumed to be of Michaelis-Menten type:

$$\begin{aligned} v_1 &= \frac{4 S_A}{1 + S_A} e_1, & v_4 &= \frac{3 s_2}{1 + s_2} e_4, \\ v_2 &= \frac{2 s_1}{1 + s_1} e_2, & v_5 &= \frac{4 s_1}{1 + s_1} e_5, \\ v_3 &= \frac{S_B}{1 + S_B} e_3, & v_6 &= \frac{2 s_3}{1 + s_3} e_6. \end{aligned}$$

All enzymes are assumed to have the same degradation constant $\lambda = 0.1$ and the external substrates are assumed constant with $S_A = S_B = 1$. The weights are chosen as $\boldsymbol{W_e} = \boldsymbol{W_r} = \boldsymbol{W_{\dot{r}}} = \boldsymbol{I}$, whereas the metabolite vector is $s^i = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}^T$, and the initial and target fluxes are

$$\begin{aligned} v^i &= \begin{bmatrix} 2 & 1.5 & 1 & 2.5 & 0.5 & 0.5 \end{bmatrix}^T, \\ v^f &= \begin{bmatrix} 3 & 2 & 1.5 & 3.5 & 1 & 1 \end{bmatrix}^T. \end{aligned}$$

Figure 3 depicts the optimal reaction rates and enzyme expression rates as given by Lemma 3. Note that the reaction rates satisfy constraint (10) and hence $\dot{s} = \boldsymbol{N} v = 0$ for all $t \geq 0$.

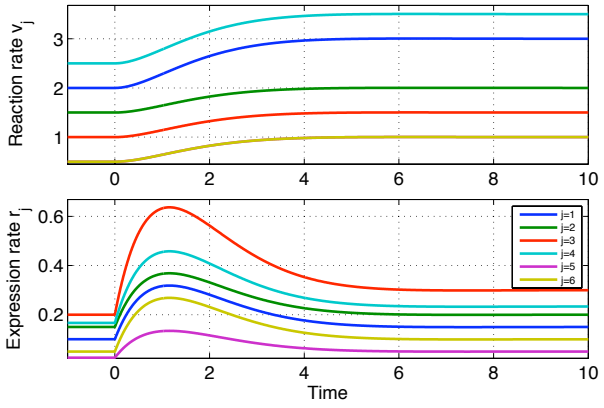

Fig. 3. Optimal reaction rates and enzyme expression rates for the network in Fig. 1.

VI. Discussion and Conclusions

In this paper we have addressed the problem of optimizing enzyme expression rates to drive a metabolic network between different steady state fluxes. Our formulation relies on a control-affine model for a metabolic network coupled with a linear model for enzyme expression/degradation. The objective function is a LQR-type quadratic functional that accounts for the transition to the target flux and the cost of enzyme synthesis. The optimization is carried out under a dynamic equilibrium constraint (constant metabolites) along the whole trajectory, which allows for recasting the dynamics as a nonregular descriptor system. Via a parameterization of all controls satisfying the algebraic constraints, the LQR problem for the differential-algebraic system can be solved as standard one for a purely differential linear system.

The use of optimization principles to reverse-engineer metabolic networks has gained strength with successful case

studies such as growth maximization in *E. coli* [10]. These are based on a static optimization approach known as Flux Balance Analysis (FBA) [23], whereby optimal metabolic fluxes are computed as solutions of a linear program. In view of the results in this paper, our dynamic optimization approach may be combined with FBA within a two-stage optimization setup: Once optimal initial and target fluxes are identified via FBA, our method can be used to compute time-dependent enzyme expression rates that yield an optimal transition between them. By tuning the weighting matrices in the cost function, different cellular objectives can be tested and compared with experimental data. This approach may be useful in systems where the assumption of constant metabolites is sensible; it would also require knowledge on the kinetics, but since only the matrix $\boldsymbol{G_i}$ is needed, these can be estimated from flux and enzyme measurements (the actual metabolite vector s^i and kinetic parameters need not to be known).

Since our solution is analytical and does not assume any specific kinetics or topologies, it shows promise for its application to large-scale networks with complex kinetics, such as allosteric interactions [1]. An important drawback is the lack of state and control constraints. Their inclusion can account for physical limitations inherent to biochemical systems, such as positivity and upper bound constraints on the enzyme concentrations and their expression rates. The use of constrained optimization methods for large-scale kinetic models still needs the development of robust and efficient numerical algorithms, perhaps in the spirit of recent work in the field [9], [24].

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