

**DYNAMIC ANALYSIS AND CONTROL OF  
CHEMICAL AND BIOCHEMICAL REACTION  
NETWORKS****Irene Otero-Muras\* Gábor Szederkényi\*\*  
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Abstract: Metabolic or cell signalling pathways are examples of biochemical networks exhibiting possible complex dynamics in the form of steady-state multiplicity, sustained oscillations or even deterministic chaos. The origin of these nonlinear phenomena is not always well understood, nor it can be systematically predicted beyond a case by case basis. Despite considerable progress in dynamic aspects, efforts are still needed to develop efficient and robust methods of stabilization and control of reaction networks. In this work, we combine concepts and tools from irreversible thermodynamics and systems theory to explore the underlying dynamic properties of a general class of chemical and biochemical networks. Lyapunov and passivity based methods are given for the systematic design of globally stabilizing feedback controllers in both the concentration space and a novel minimal description of the kinetic networks dynamics: the reaction space.

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Keywords: biochemical reaction networks, passivity, nonlinear control, entropy.

**1. INTRODUCTION**

Complex dynamics of biochemical networks in the form of steady-state multiplicities or sustained oscillations is a recurring theme in the literature due to its decisive role in physiology of living organisms (Thomas and Kaufman, 2001). In this contribution, we make use of concepts and tools from irreversible thermodynamics and systems theory to devise efficient control schemes capable of network stabilization of steady states.

On the one hand, irreversible thermodynamics gives us the necessary physical insight in exploring reaction networks dynamics, which evolution as dissipative systems occurs in terms of the com-

bined action of entropy production and entropy flux. The mass action law establishes the macroscopic reaction rates as proportional to microscopic reactive collisions, connecting in a particular form the concentrations of species with the entropy, and imposing strict constraints on the concentration space (Feinberg, 1979). On the other hand, Lyapunov theory and other control system methods such as passivity which is proved to be useful in process system analysis and control (Alonso and Ystie, 2001), will allow us to explore the intrinsic dynamic properties of chemical and biochemical reaction networks. Furthermore, these methods will be used to construct control configurations ensuring steady state stabilization.

The paper is organized as follows. In Section 2 we explore the structural properties of biochemical networks characterizing them as dissipative systems and define an entropy based Lyapunov function candidate. Connections between thermodynamics and nonlinear stabilizing control are also established here. In Section 3 we define a minimal representation of reaction networks which, being based on a potential structure, will allow us to derive connections with passivity and generalized Hamiltonian systems.

## 2. THE DISSIPATIVE NATURE OF REACTION SYSTEMS

### 2.1 The class of systems under study

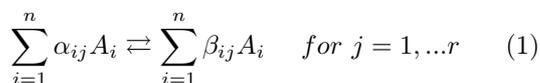
In order to rigorously apply thermodynamic based tools to the dynamic analysis and control of chemical and biochemical systems, we must distinguish between closed and open networks depending on whether there is or not material exchange with the environment. By properly setting the boundary of the domain one defines the control volume of the system. This volume corresponds in classical reaction problems with the volume of the chemostat whereas regarding intra-cell processes it may be enclosed by a virtual boundary.

The general class of systems under study comprises those pure chemical reaction networks and those metabolic, genetic and signalling pathways, which satisfy the following assumptions: *i*) the reaction rates of the kinetic mechanisms obey the *mass action law*, *ii*) the spatial distribution of products can be neglected, *iii*) the process takes place in isothermal conditions, *iv*) all the kinetic steps are reversible, so that irreversible steps will be considered as inflow-outflow terms acting through the control volume.

At this point it is important to note that kinetics of Michaelis-Menten type are in fact reduced order models derived from original mass action law mechanisms.

### 2.2 The basic structure of reaction kinetic networks

In describing the underlying dynamic structure of reaction networks, we adopt the notation employed in (Gorban *et al.*, 2004). Let us first consider a closed and homogeneous isotherm system where  $n$  species participate on a  $r$ -step reaction network, represented by the following stoichiometric mechanism:



with  $\alpha_{ij}$ ,  $\beta_{ij}$  being the constant stoichiometric coefficients for specie  $A_i$  in the reaction step  $j$ .

All reactions are assumed to be reversible, with reaction rates obeying the *mass action law*:

$$W_j = W_j^+ - W_j^- = k_j^+ \prod_{i=1}^n x_i^{\alpha_{ij}} - k_j^- \prod_{i=1}^n x_i^{\beta_{ij}} \quad (2)$$

where  $k_j^+$  and  $k_j^-$  are the constants of the direct and inverse rates of the  $j$ -th reaction step, respectively, and  $x_i \geq 0$  represents the concentration of the specie  $A_i$ . Each concentration evolves in time according to the ordinary differential equation:

$$\dot{x}_i = \sum_{j=1}^r \nu_{ij} (W_j^+ - W_j^-) \quad (3)$$

where  $\nu_{ij} = \alpha_{ij} - \beta_{ij}$  is positive or negative depending on whether the specie  $i$  is a product or a reactant in the reaction  $j$ . The dynamic evolution of the network can be then represented by a set of ordinary differential equations which in compact matrix form is written as:

$$\dot{x} = \mathcal{N} \cdot W(x) \quad (4)$$

where  $\mathcal{N} = [\nu_{ij}]$  is the  $n \times r$  coefficient matrix whose columns are the linearly independent stoichiometric vectors  $\nu_j = \beta_j - \alpha_j$ , and  $W(x) \in \mathbb{R}^r$  denotes the vector of reaction rates.

*The reaction simplex.* In a closed network the amount of each chemically unaltered component  $\mathcal{C}_k$  ( $k = 1, \dots, m$ ) remains constant and the corresponding component mass balances satisfy the following set of algebraic equations:

$$C_k^0 = c_k^T \cdot x \quad \text{for } k = 1, \dots, m \quad (5)$$

where entries of the vector  $c_k \in \mathbb{N}^n$  represent the units of  $\mathcal{C}_k$  in each specie, and  $C_k^0 = c_k^T \cdot x_0$  with  $x_0 = x(0)$ . The intersection of the positive orthant (i.e.  $\mathbb{R}_+^n$ ) with the set of  $m$  conservation laws defines the *reaction simplex*:

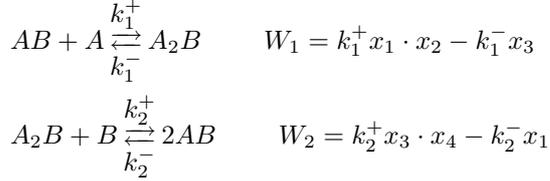
$$\Omega(x_0) = \{x \in \mathbb{R}_+^n / c_k^T (x - x_0) = 0, \quad k = 1, \dots, m\} \quad (6)$$

that is invariant for the system dynamics. The set of vectors  $[c_k]$  forms a basis of  $\ker(\mathcal{N}^T)$  and consequently the number  $r$  of linearly independent reactions in a reaction network is determined by the difference between species and its elementary constituents, i.e.  $r = n - m$ . In addition, it follows that the minimal representation of a chemical reaction system (4) is  $r$ -dimensional, where  $r \leq n$ .

*The equilibrium manifold.* The relationships  $\dot{x} = 0 \Leftrightarrow W(x) = 0$  determine the set of equilibrium points of the closed system. As it will be shown next by means of a direct Lyapunov argument, in a closed reaction network the equilibrium point is unique for every initial condition belonging to the same reaction simplex.

*Example 1.* Let us consider two connected reversible reactions involving four chemical species  $AB$ ,  $A$ ,  $A_2B$  and  $B$ , with concentrations defined

by the state vector  $x = [x_1, x_2, x_3, x_4]$ . These species are composed by two classes of atoms  $A$  and  $B$  representing the chemical unaltered components. The kinetic mechanism is described by two steps with respective rates  $W_1$  and  $W_2$  obeying the mass action law:



The state space description in compact matrix form (4) becomes:

$$\dot{x} = \begin{bmatrix} -1 & 2 \\ -1 & 0 \\ 1 & -1 \\ 0 & -1 \end{bmatrix} \cdot \begin{bmatrix} W_1 \\ W_2 \end{bmatrix} \quad (7)$$

and the atomic conservation balances (5) for this case read:

$$C_A^0 = c_A^T x = x_1 + x_2 + 2x_3, \quad C_B^0 = c_B^T x = x_1 + x_3 + x_4 \quad (8)$$

where  $C_A^0$  and  $C_B^0$  represent the concentrations of each atomic species. Vectors  $c_A$  and  $c_B$  can be grouped into the following matrix:

$$C^T = \begin{bmatrix} 1 & 1 & 2 & 0 \\ 1 & 0 & 1 & 1 \end{bmatrix} \quad (9)$$

which defines a basis for  $\ker \mathcal{N}^T$  so that  $C^T \mathcal{N} = 0$ . Consequently, each vector  $C^0 = (C_A^0, C_B^0)$  is constant along (7) and defines a specific reaction simplex  $\Omega(x_0)$  for every initial condition  $x_0$  satisfying  $C^0 = C^T x_0$ . For this example, the reaction simplex  $\Omega(x_0)$ , defined by the intersection of (8) with the positive orthant is two dimensional. A particular reaction simplex for  $C_A^0 = 10$  and  $C_B^0 = 8$  is depicted in Fig. 1 in the  $x_1 - x_3$  space.

### 2.3 Stability of the equilibrium manifold

The second law of thermodynamics establishes an evolution criterion based on a concave function (the entropy) which never decreases in isolated systems and achieves its maximum at equilibrium. Isolated dissipative systems evolve to equilibrium through irreversible processes that produce entropy, being the rate of entropy production a way to quantify dissipation. The second law formulated as an entropy maximum principle has their counterparts in minimum principles of the thermodynamic potentials. The expression of the corresponding potential that we will use as an entropy-like function is the following function of the species concentrations:

$$S = \sum_{i=1}^n x_i \cdot (\ln x_i - 1) = \sum_{i=1}^n (x_i \ln x_i - x_i) \quad (10)$$

This expression can be derived by starting from the normalized potential for isothermal systems at a constant volume proposed in (Gorban *et al.*, 2004) in combination with the Euler expression for the thermodynamic entropy (Callen, 1980).

In addition, we have that the right hand side term in (4) is Lipschitz continuous. This implies, as discussed in (Alonso *et al.*, 2004), that for any arbitrary reference  $x_1$  there exists a nonnegative function  $L_\lambda(x, x_1)$  associated to a constant  $\lambda \geq 0$ , such that the following relation holds:

$$[\mu(x) - \mu(x_1)]^T \mathcal{N} \cdot W(x) + L_\lambda(x, x_1) = \lambda [\mu(x) - \mu(x_1)]^T (x - x_1) \quad (11)$$

where  $\mu = \nabla_x S = \ln x$ . Systems which, in addition, satisfy that  $L_0(x, x_1) \geq 0$ , are *purely dissipative*. Closed reaction networks are a class of purely dissipative systems for a state  $x_1$  being the equilibrium reference. This can be easily shown by noting that for  $\lambda = 0$  and  $x_1 = x^*$  in (11):

$$L_0(x, x^*) = -(\mu - \mu^*)^T \sum_{j=1}^r \nu_j W_j \quad (12)$$

Equation (12) can be written in terms of the direct and inverse reaction rates (2) as:

$$L_0(x, x^*) = \sum_{j=1}^r \ln \frac{W_j^+}{W_j^-} \cdot (W_j^+ - W_j^-) \quad (13)$$

Since each term at the right hand side of (13) is non-negative we conclude that  $L_0(x, x^*) \geq 0$ .

In order to derive the stability conditions for closed reaction networks we define a positive definite and convex function  $B(x)$ , constructed as the difference between  $S(x)$  and its supporting hyperplane at the equilibrium reference  $x^*$ :

$$B(x, x^*) = \sum_{i=1}^n x_i \left( \ln \frac{x_i}{x_i^*} - 1 \right) + x_i^* \quad (14)$$

Taking the time-derivative  $B(x, x^*)$  along (14) and using (11) with  $\lambda = 0$  we obtain:

$$\dot{B} = (\mu - \mu^*)^T \sum_{j=1}^r \nu_j W_j = -L_0(x, x^*) \quad (15)$$

Since by (13)  $L_0 \geq 0$  we have that  $\dot{B} \leq 0$ . Consequently,  $B$  is a legitimate Lyapunov function which ensures the structural asymptotic stability for the general class of reaction networks under study at the equilibrium reference. In addition, this Lyapunov function  $B$  coincides with the one used by (Feinberg, 1979) in developing the *Chemical Reaction Network Theory* (Gunawardena, 2003). The contours of  $B$  and  $L_0(x, x^*)$ , corresponding to the Example 1 in the reaction simplex  $\Omega(x_0)$  are presented in Fig. 1, where it can be seen that  $B$  is convex and  $L_0(x, x^*)$  negative definite although not convex when far from the equilibrium reference.

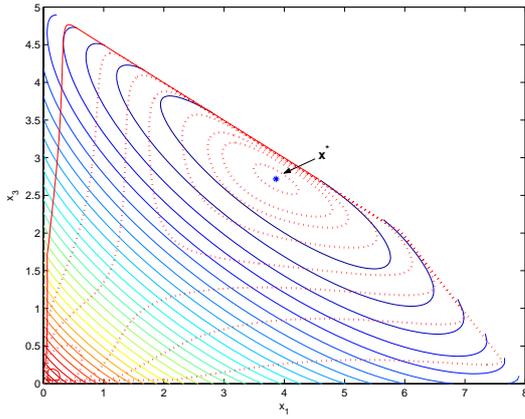


Fig. 1. Reaction simplex and contours of  $B$  (solid lines) and  $L_0$  (dotted lines) for Example 1, where  $x^*$  is the equilibrium point.

#### 2.4 Direct passivation of open reaction systems

The state-space representation of an open reaction system, i.e. a system which exchanges mass with its environment, is constructed by adding a set of input and output convection terms (Hangos and Cameron, 2001) to the closed reaction system (4). In order to handle standard operation conditions in chemostats, we further assume that the overall mass of the system is kept constant by having the same input and output overall mass flow  $\Phi$ . In this way, the set of ordinary differential equations governing the evolution of states becomes:

$$\dot{x} = \mathcal{N} \cdot W(x) + \phi(x^0 - x) \quad (16)$$

where  $\phi = \Phi/V$ , (with  $V$  being the volume of the chemostat), denotes the inverse of the residence time and  $x^0$  is the inlet concentration vector. Regarding intra-cell reaction networks, degradation and generation of components appear to be accommodated in (16) substituting the chemostat by the appropriate control volume.

The material throughput flow introduces non-dissipative contributions in the system, by adding an entropy flux term in the entropy balance. In our formalism, this balance is obtained by computing the time derivative of  $B$  as defined in (14) along (16):

$$\dot{B} = (\mu - \mu^*)^T \sum_{j=1}^r \nu_j W_j + (\mu - \mu^*)^T \phi(x^0 - x) \quad (17)$$

The second term in the right hand side of (17) corresponds with entropy flux and may compensate or even override the natural entropy dissipation, thus undermining the inherent global asymptotic stability of the system. At this point, it should be noted the direct relationship between entropy flux and dynamical complexity. Therefore, in stabilizing open complex reaction systems it seems crucial to act on the non-dissipative contributions by appropriate control configurations.

A simple way of stabilizing steady states is summarized in the following proposition:

**Proposition 1.** Any stationary solution  $x^*$  of (16) can be rendered exponentially stable by a control law of the form  $\dot{x}^0 = x^{0*} - \omega(x - x^*)$  with  $\omega \geq (\lambda - \phi - \alpha)/\phi > 0$  and  $\alpha > 0$

*Proof:* First, let us construct a  $B$  function as in (14) with respect to the stationary solution  $x^*$  associated to the input concentration vector  $x^{0*}$ . Defining  $\bar{x} = x - x^*$ ,  $\bar{x}^0 = x^0 - x^{0*}$  and computing the time derivative of  $B$  along (16) we get:

$$\dot{B} = (\mu - \mu^*)^T \mathcal{N}(W(x) - W(x^*)) + \phi(\mu - \mu^*)^T (\bar{x}^0 - \bar{x}) \quad (18)$$

Since  $B(x, x^*)$  is convex, we also have the following inequality:

$$B(x, x^*) \geq (\mu - \mu^*)^T \bar{x} \quad (19)$$

Substituting (11) and the control law in (18):

$$\dot{B} = -L_\lambda + (\lambda - \phi - \phi\omega)(\mu - \mu^*)^T \bar{x} \quad (20)$$

Since  $L_\lambda > 0$  and  $B$  satisfies (19), equation (20) becomes  $\dot{B} \leq \alpha B$  and the result follows.  $\square$

As a corollary, note that any open network can be made globally exponentially stable by defining a mass flow  $\phi < \lambda$ .

### 3. THE POTENTIAL STRUCTURE OF THE REACTION SPACE

#### 3.1 The dynamics in the reaction space

Systems derived from a potential conform an interesting class of dynamic systems where powerful methods for control design, such as those based on passivity, directly apply. In this section, we demonstrate that a complex reaction network possesses an underlying potential structure on a state space that will be referred to as the *reaction space*, that is homeomorphic to the concentration space in the reaction simplex and is described by defining a new set of variables:

$$z_j = \ln \frac{p_j}{q_j} \quad \text{for } j = 1, \dots, r \quad (21)$$

with  $p_j$  and  $q_j$  being the direct and reverse rates associated to the reaction rate  $j$  ( $W_j^+$  and  $W_j^-$ ). In the new variables, the equation (2) becomes:

$$W_j = p_j - q_j = q_j(e^{z_j} - 1) \quad (22)$$

The right hand side of Eq. (12) can then be transformed through appropriate manipulations into the form:

$$\ell(z, q) = - \sum_{j=1}^r z_j q_j (e^{z_j} - 1) = -z^T W \quad (23)$$

Function  $\ell$  can be easily connected with the so called dissipation function as it is the product of

thermodynamic fluxes (reaction rates) and thermodynamic forces (chemical affinities). In this way, it seems natural to explore the properties of chemical reaction network dynamics in the *reaction space* defined by  $z$ -variables. To that purpose, let us introduce the following notation:

$$S = \mathcal{N}^T \Gamma \mathcal{N} \quad (24)$$

$$\Gamma = \text{diag} \left[ \frac{1}{x_1}, \dots, \frac{1}{x_i}, \dots, \frac{1}{x_n} \right] \quad (25)$$

The particular structure of the reactor vector elements (22) suggests the definition of the potential:

$$H(z) = \sum_{j=1}^r (e^{z_j} - z_j) - 1 \quad (26)$$

and re-writing the vector of reaction rates as:

$$W = F(q)H_z \quad (27)$$

where  $F(q) = \text{diag}[q_1, \dots, q_j, \dots, q_r]$  is a positive definite diagonal matrix and  $H_z$  represents the gradient of (26). Note that by construction, the potential  $H$  is convex and positive definite everywhere except at the equilibrium point  $z^* = 0$ , where  $H(0) = 0$ . Defining  $J = SF(q)$  we obtain the following potential dynamic description:

$$\dot{z} = -JH_z \quad (28)$$

where  $H_z$  is the gradient of  $H$ . Provided that the matrix  $J^T + J$  (and consequently  $J$ ) is a positive definite matrix, Eqn.(28) matches the dynamics in the reaction space with a generalized Hamiltonian system (Van der Shaft, 2000). It is clear from (28) that  $H$  is decreasing in time if the state-dependent matrix  $J^T + J$  is always positive definite. In this case,  $H$  is a Lyapunov-function for the reaction system proving global asymptotic stability in the reaction space. However, it can be shown that there are cases when  $J^T + J$  is positive definite only in a neighborhood (denoted by  $U$ ) of the selected stable equilibrium point of the reaction system.

### 3.2 Passivity and global stabilization in the reaction space

The dynamic evolution of the open reaction network (16) in the reaction space is described as:

$$\dot{z} = -JH_z - \mathcal{N}^T \Gamma \phi(x^0 - x) \quad (29)$$

The potential structure of (28) allows us to establish a straightforward connection with passivity:

**Proposition 2.** *If  $J^T + J$  is globally positive definite, then the system (29) endowed with the function  $H$  (26) is passive with  $y = H_z$  and  $u = \mathcal{N}^T \Gamma \phi(x - x^0)$ .*

*Proof:* We compute the time derivative of the potential (26) along (29) to obtain:

$$\dot{H} = -H_z^T JH_z - H_z^T \mathcal{N}^T \Gamma \phi(x^0 - x) \quad (30)$$

that with the selected inputs and outputs reads:

$$\dot{H} = -H_z^T JH_z + y^T u \quad (31)$$

Since the first term on the right hand side is negative definite, we obtain by integrating (31) in the time interval  $(t, t + \tau)$  the following inequality:

$$H(t + \tau) - H(t) \leq \int_t^{t+\tau} y^T(s)u(s)ds \quad (32)$$

which coincides with the well-known passivity inequality (Van der Shaft, 2000).  $\square$

**Remark 1.** If  $J^T + J$  is not globally positive definite, then open reaction networks can be globally stabilized in the reaction space with a control Lyapunov function  $H$  by nonlinear control laws of the form:

$$u = \mathcal{N}^T \Gamma (\mathcal{N}F + K\Gamma \mathcal{N})y \quad (33)$$

where  $K \in \mathbb{R}^{n \times n}$  is an appropriate matrix. The supply rate is then given by:

$$y^T u = H_z^T \underbrace{\mathcal{N}^T \Gamma \mathcal{N} F}_J H_z + H_z^T \mathcal{N}^T \Gamma K \Gamma \mathcal{N} H_z \quad (34)$$

and substituting (34) in (31) we get:

$$\dot{H} = y^T \mathcal{N}^T \Gamma K \Gamma \mathcal{N} y$$

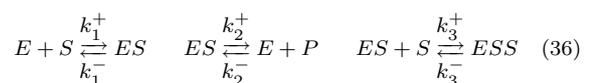
which is clearly negative if  $K$  is negative definite (or zero if  $K$  is skew-symmetric).

**Remark 2.** It must be pointed out that the feedback (33) requires the measurement of the full state vector in the general case. The dimension of the artificial input  $u$  is equal to the dimension of the reaction space (i.e.  $r$ ). However, the physically meaningful manipulable inputs for the system are the elements of either  $\phi$  or  $x^0$ . If a value for  $u$  is computed from (33) then the values of the real physical inputs can be calculated from the relation (see Proposition 2):

$$u = \mathcal{N}^T \Gamma \phi(x - x^0) \quad (35)$$

which is linear separately in  $\phi$  and  $x^0$  (if one of them is arbitrarily fixed). It is clear from the above, that the required number of physical inputs for the stabilization is also  $r$  which is generally less than (or at most equal to)  $n$ . This result is in good agreement with (Sontag, 2001) although the control Lyapunov function is different from  $H$ .

*Example 2.* We use as an example the following Michaelis Menten mechanism of enzymatic catalysis with substrate inhibition:



This mechanism is shown to present multiplicities for the open case and a particular range of the rate constants. The dynamics of the open loop system can be described by the following set of differential equations of the form (4), where

$$N = \begin{bmatrix} -1 & -1 & 1 & 0 & 0 \\ 1 & 0 & -1 & 0 & 1 \\ 0 & -1 & -1 & 1 & 0 \end{bmatrix}^T, \quad (37)$$

$$w_1(x) = k_1^+ x_1 x_2 - k_1^- x_3 \quad (38)$$

$$w_2(x) = k_2^+ x_3 - k_2^- x_1 x_5 \quad (39)$$

$$w_3(x) = k_3^+ x_2 x_3 - k_3^- x_4 \quad (40)$$

and the state vector  $x$  contains the concentrations of the species  $E$ ,  $S$ ,  $ES$ ,  $ESS$  and  $P$ , respectively. In this example, the values for all the kinetic constants  $k_{\{1,2,3\}}^{\{+,-\}}$  were chosen as 1. The initial value of the state vector was  $x(0) = [0.01 \ 0.15 \ 0.01 \ 0.01 \ 0.01]^T$ . We assumed that the manipulable variables are the three inlet concentrations  $x_1^0$ ,  $x_2^0$  and  $x_3^0$  (see eq. (16)). The value of the flux  $\phi$  was 0.01, while the gain matrix  $K$  for the controller was  $-0.1 \cdot I^{5 \times 5}$ . As it is shown in fig. 2, the proposed feedback (33) significantly improves the time-domain performance of the reaction-kinetic system.

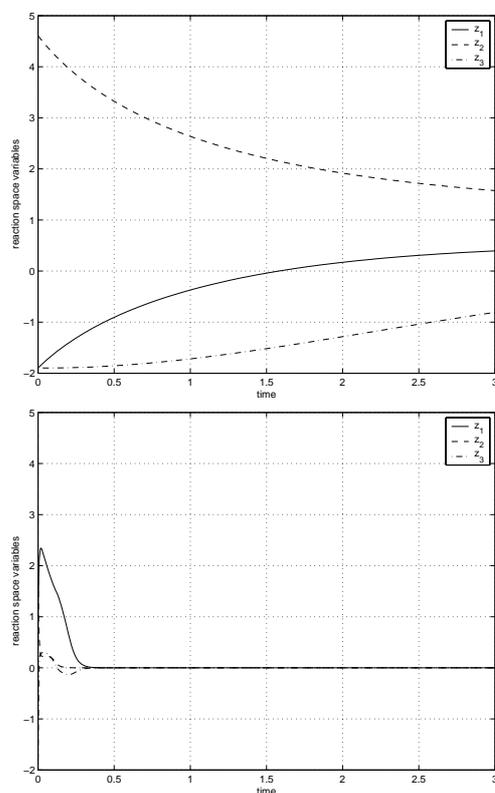


Fig. 2. Reaction space variables in the a) open-loop and b) closed-loop case

#### 4. CONCLUSIONS

In this work, we combined concepts and tools from irreversible thermodynamics and systems and control theory to explore the underlying dynamic properties of a general class of kinetic networks. As a result, we firstly have shown how entropy or a related thermodynamic potential can

be employed as a legitimate Lyapunov function candidate to derive stability conditions for kinetic networks in closed systems. A potential-like structure has been extracted from the network which conducts the evolution of the reaction rates. This enabled us to construct a local Hamiltonian description of the open reaction kinetic system in the reaction space. These results involving entropy and non-linear control design are applied to the efficient stabilization of arbitrary steady-states in open chemical and biochemical networks.

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