Disturbance Attenuation via Nonlinear Feedback for Chemical Reaction Networks

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Abstract: This paper deals with the setpoint control of Chemical Reaction Networks (CRNs) in the presence of disturbances. The addressed control problem is traced back to the output feedback-based stabilization of passive systems. First, the passivity properties of complex balanced CRNs are discussed. Second, it is shown that, by combining the kinetic feedback-based control with the passivity theory-based output feedback approach, arbitrary disturbance attenuation in controlled CRNs can be achieved. A case study is provided to demonstrate the applicability of the proposed control design approach.

Keywords: Chemical Reaction Networks, Passivity, Setpoint Control, Disturbance Attenuation.

1. INTRODUCTION

Feedback control is a fundamental means of ensuring stability and performance properties of process systems containing complex chemical reactions. The dynamical nonlinearities caused by these reactions have to be taken into consideration during the feedback control design (Hangos et al., 2004). As an important sub-class of nonlinear process systems, chemical reaction networks (CRNs, also called kinetic systems) are efficient descriptors of complex nonlinear dynamics having a simple mathematical form and a directed graph structure which is useful for model analysis (Feinberg, 2019).

An emerging field of control studies is the controller design for CRNs. The study (Soustal, 2001) discusses the application of linear state feedback for setpoint control of a class of CRNs. The paper (Cosentino et al., 2013) examines how CRNs can be controlled with such controllers that are themselves realizable as kinetic systems. The paper (Paulino et al., 2018) applies control techniques developed for uncertain linear systems to control nonlinear chemical reactions. The stabilization of nonnegative polynomial models using a kinetic feedback which transforms the closed loop system into a complex balanced CRN was elaborated in (Lipták et al., 2016).

Passivity theory offers systematic control design procedures for nonlinear systems which satisfy particular energy-related properties (Brogliato et al., 2007). Passivity-based control can be used for obtaining relatively simple but robust control loops utilizing the physical interconnection (network) structure of the system (van der Schaft, 2017). These principles can be particularly successfully applied for process systems governed by the laws of thermodynamics (Bao and Lee, 2007). Despite of this application potential, only a few papers are available that use passivity based control for CRNs. The passivity property of detailed balanced CRNs was studied in (van der Schaft et al., 2013). Early results related to the passivity based feedback control in CRNs were reported in (Otero-Muras et al., 2008). Following this line, we have applied the passivity theory for synchronization-based control of interconnected CRNs in (Márton et al., 2018).

In this paper, we first introduce a comprehensive discussion of the passivity properties of CRNs using a logarithmic storage function. A novel control method is then described to ensure the control of a wide class of CRNs in the presence of unknown input disturbances by appropriately setting the $L_2$-gain. The proposed method combines the kinetic feedback-based CRN control method in (Lipták et al., 2016) with a passivity-based control design.

2. PASSIVITY-BASED OUTPUT FEEDBACK CONTROL

In this section relevant notions from passivity theory are reviewed based on the previous studies (Brogliato et al., 2007), (Bao and Lee, 2007) and (Isidori, 1999). Consider a dynamic system which is modeled using an ODE (Ordinary Differential Equation) in the form

$$\dot{c} = f(c) + G(c)u, \quad c(0) = c_0,$$  \hfill (1)

$$y = h(c)$$

where $c \in \mathbb{R}^n$, $y, u \in \mathbb{R}^m$ are the state-, output- and input vectors, $f(\cdot), h(\cdot), G(\cdot)$ are smooth mappings with...
appropriate dimensions, $f(0) = 0$, $h(0) = 0$. Here $0$ is a vector with 0 entries with appropriate dimension.

The condition $f(0) = 0$ implies that $c = 0$ is an equilibrium point of the autonomous system $\dot{c} = f(c)$.

Assign to the system (1) a continuously differentiable, nonnegative storage function $S(c) : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ such that $S(0) = 0$.

**Definition 1.** The system (1) is passive if $\dot{S} \leq y^T u$, $\forall u, c$.

**Theorem 1.** The input-affine system (1) is passive if and only if the following conditions hold:

$$
\begin{align*}
\frac{\partial S}{\partial c} f(c) &\leq 0, \\
\frac{\partial S}{\partial c} G(c) &= h(c)^T.
\end{align*}
$$

**Definition 2.** The system (1) is zero state detectable if $y = 0$ and $u = 0$ implies that the steady-state of $c$ is zero.

**Theorem 2.** Consider that the system (1) is zero state detectable and passive with respect to a nonnegative storage function $S$. Then the control law $u = -K y$, where $K = \text{diag}(k_i) \in \mathbb{R}^{n \times n}$, $k_i > 0$, asymptotically stabilizes the equilibrium state $c = 0$.

**Theorem 3.** Assume that the system (1) is passive with respect to a positive definite storage function $S$, such that $\frac{\partial^2 S}{\partial c^2}$ exists and is continuous. If $\text{rank}[\frac{\partial^2 S}{\partial c^2} G(c)]$ is constant in a neighborhood of $0$, then the system has a vector relative degree $[1,1,\ldots,1]$ at $c = 0$.

3. CHEMICAL REACTION NETWORKS AND KINETIC SYSTEMS

Chemical reaction networks (CRNs) are the generalizations of physico-chemical models describing the transformations of chemical complexes into each other and the change of concentrations of species during chemical reactions (Feinberg, 1987). The nonnegative polynomial ODE models corresponding to CRNs obeying the mass action law are called kinetic system models.

CRNs can be characterized by the sets of species, complexes and reactions as follows.

- **Species**: $\mathcal{A} := \{A_1 \ldots A_n\}$ represent different molecules undergoing chemical reactions.
- **Complexes**: $\mathcal{C} := \{C_1 \ldots C_m\}$ are formally linear combinations of the species with integer coefficients, i.e. $\mathcal{C}_i := \sum_{j=1}^{n} \alpha_{ij} A_j$, where $\alpha_{ij}$ represent the stoichiometric coefficients.
- **Reactions**: $\mathcal{R} := \{R_1 \ldots R_r\}$ where $R_k := (C_i, C_j)$ denoted by $C_i \to C_j$. Here $C_i$ is the reactant (or source) complex, and $C_j$ is the product complex for $k = 1, \ldots, r$.
- **Reaction rate coefficient**: $\kappa_{ij} > 0$ that is associated to $R_k$ for $k = 1, \ldots, r$.

Under the assumption of mass action law, the dynamic behavior of the species’ concentration $(c = (c_i)^T \in \mathbb{R}^n_{>0})$ during the reactions is given by the following ODE:

$$
\dot{c} = M \varphi(c) = YA_k \varphi(c), \quad c(0) = c_0
$$

where $c_0 \in \mathbb{R}^n_{>0}$ is the initial state, $M = Y \cdot A_k$, $Y = [Y_{ij}] \in \mathbb{N}^{n \times m}$, $Y_{ij} = \alpha_{ij}$ is the complex composition matrix, $\varphi_j(c) = \prod_{i=1}^{n} \frac{c_i^{Y_{ij}}}{c_i}$ for $j = 1, \ldots, m$ are monomial functions, and $A_k \in \mathbb{R}^{n \times m}$ is the so-called Kirchhoff matrix containing the reaction rate coefficients:

$$
A_k(i,j) = \begin{cases}
\kappa_{ij}, & \text{for } j \neq i \\
-\sum_{\ell \neq j} \kappa_{ij\ell}, & \text{if } j = i.
\end{cases}
$$

We note that the so-called zero complex for which all the stoichiometric coefficients are zero, is allowed in CRN models (Feinberg, 1987). It is represented by a zero column in the complex composition matrix, and it is primarily used to describe in- and outflows from/to the environment.

A polynomial dynamical system is called kinetic, if it can be written in the form (4), i.e. its coefficient matrix can be factorized as a product of a complex composition matrix and a Kirchhoff matrix.

Let $c^* = (c^*_i) \in \mathbb{R}^n_{>0}$ be an equilibrium state of (4). The CRN is called complex balanced if

$$
A_k \varphi(c^*) = 0.
$$

It is known that, if (6) is satisfied for an equilibrium point, then it is fulfilled for all the other equilibrium points of the CRN model (Horn and Jackson, 1972). Hence complex balance is a property of the whole CRN and not only of the equilibrium point.

If a CRN is complex balanced then the system (4) is at least locally stable in the equilibrium point $c^*$ with the following Lyapunov function (Feinberg, 1987; Sontag, 2001):

$$
S(c) = \sum_{i=1}^{n} \left[ c_i \left( \ln \frac{c_i}{c^*_i} - 1 \right) + c^*_i \right] \geq 0, \quad \forall c.
$$

According to recent results, the stability of complex balanced equilibria is possibly global with respect to the nonnegative orthant (Craciun, 2015).

4. PASSIVITY OF COMPLEX BALANCED CHEMICAL REACTION NETWORKS

Let an open CRN model be given in the form

$$
\dot{c} = M \varphi(c) + u
$$

where $u \in \mathbb{R}^n$ is a general concentration rate input.

Let an equilibrium point $c^*$ of the system (4) such that $c^*_i \geq \epsilon > 0$, $\forall i$ and introduce the error state vector:

$$
c_e = c - c^*.
$$

Its dynamics reads as

$$
\dot{c}_e = M \varphi(c_e) + c^* + u.
$$

The storage function $S$ as a function of $c_e$ has the form:

$$
S(c_e) = \sum_{i=1}^{n} \left[ (c_{ei} + c^*_i) \left( \ln \frac{c_{ei} + c^*_i}{c^*_i} - 1 \right) + c^*_i \right].
$$

The gradient of $S$ satisfies

$$
\frac{\partial S(c_e)^T}{\partial c_e} = \frac{\partial S(c)^T}{\partial c} = \left( \begin{array}{c}
\ln(c_{e1} + c^*_1) - \ln(c^*_1) \\
\vdots \\
\ln(c_{en} + c^*_n) - \ln(c^*_n)
\end{array} \right).
$$
The Hessian of $S$ has the form:
\[
\frac{\partial S^2(c_\delta)}{\partial c^2} = \text{diag}\left( \frac{1}{c_\delta 1 + c^* 1} \ldots \frac{1}{c_\delta n + c^* n} \right). \tag{13}
\]
If $c_\delta = 0$, then $f(c_\delta) = M\varphi(c_\delta + c^*) = 0$, $S(0) = 0$ and $\frac{\partial S(c_\delta)}{\partial c} = 0$.

Recall that if the CRN is complex balanced, then the storage function $S$ for $u = 0$ is non-increasing.

In the case of complex balanced CRNs the following passivity-related properties hold:
- By Theorem 1 the open CRN model (10) is passive from the input $u$ to the output $y = \frac{\partial S(c_\delta)}{\partial c} M\varphi(c) + \frac{\partial S(c_\delta)}{\partial c} u \leq y^T u$. (15)
- The conditions $u = 0$ and $y = \frac{\partial S(c_\delta)}{\partial c} = 0$ imply that $c_\delta = 0$. Hence (10) is zero state detectable and, by Theorem 2, the control $u = -K_y$ asymptotically stabilizes the equilibrium state $c = c^*$ where $c_\delta = 0$.
- Matrix $K$ is defined in the statement of Theorem 2.
- Since $c_\delta^* \geq \epsilon > 0$, the rank of the Hessian (13) in a neighborhood of $c_\delta = 0$ is $n$. As
\[
\text{rank}\left( \frac{\partial y}{\partial c} \right) = \text{rank}\left( \frac{\partial S^2(c_\delta)}{\partial c^2} \right). \tag{16}
\]
by Theorem 3, the CRN (8) has no internal dynamics in the neighborhood of $c_\delta = 0$. Here $I \in \mathbb{R}^{n \times n}$ is the identity matrix.

5. CONTROL DESIGN FOR CHEMICAL REACTION NETWORKS

5.1 The Control Problem

Let the open CRN model with input- and output flows and unknown disturbance be given in the form
\[
\dot{c} = M\varphi(c) + Vc_I - vc + w. \tag{17}
\]
where $w \in \mathbb{R}^n$ is an unknown, time-varying and bounded disturbance rate vector. The control inputs are the concentrations of the inlet substances ($c_I \in \mathbb{R}^n_{>0}$). The rate of supply vector is $Vc_I$, $vc$ is the rate of removal, where $V = \text{diag}(v_1) \in \mathbb{R}^{n \times n}$. By assuming constant volume in the reactor where the reaction takes place, the rate $v$ yields as:
\[
v = \sum_{i=1}^n v_i. \tag{18}
\]

Control objective: Let a setpoint $(c_{SP} \in \mathbb{R}^n_{>0})$ and
\[
y = \text{Ln}(c) - \text{Ln}(c_{SP}). \tag{19}
\]
Design a control input $c_I \in \mathbb{R}^n_{>0}$, which assures that $\lim_{t \to \infty} y = 0$ if $w = 0$. Otherwise, ensure that
\[
\int_0^t y^T y \leq \gamma \int_0^t w^T w + \sigma_0 \tag{20}
\]
for a prescribed $\gamma \geq \varepsilon > 0$. $\sigma_0 \in \mathbb{R}$ is an initial condition-dependent constant.

To achieve the control objective, formulate the control input as the sum of two terms:
\[
c_I = c_I^{(s)} + c_I^{(w)} \tag{21}
\]

The first term $(c_I^{(s)})$ is meant to ensure the complex balance property of the nonlinear CRN dynamics. The role of the second term $(c_I^{(w)})$ is to guarantee the disturbance attenuation objective.

5.2 Kinetic Feedback to Achieve Complex Balanced Realization

The complex balance property of a CRN is strongly related to Lyapunov stability of the CRN models, hence it can be explored during control design. It was shown in (Lipták et al., 2016) that a closed loop complex balanced CRN can be achieved by applying static nonlinear kinetic feedback in the form:
\[
c_I^{(s)} = V^{-1}K_{\varphi^*} \varphi(c). \tag{22}
\]
Here $K_{\varphi} = [k_{ij}] \in \mathbb{R}^{n \times n}$ is the feedback gain matrix such that $k_{ij} \geq 0 \forall i, j$.

The controller can be designed by optimization. For this we give $Y_o$ as a complex composition matrix, $M$ is the open loop coefficient matrix, and $c^* = c_{SP}$ is the given setpoint of the closed loop system. The entries of the feedback gain matrix can be obtained as the solution $(K_{\varphi}, A_\kappa)$ of the following linear optimization problem (Lipták et al., 2016):
\[
\text{Minimize } \sum_{i=1}^n \sum_{j=1}^m |K_{\varphi_{ij}}| \tag{24}
\]
such that
\[
A_\kappa \varphi(c^*) = 0, \tag{25}
\]
\[
\left\{ M + K_{\varphi} = Y_o A_\kappa \right. \tag{26}
\]
\[
1^T A_\kappa \geq 0^T \tag{26}
\]
\[
a_{ij} \geq 0, \quad i \neq j.
\]
where $1 = (1 \ldots 1) \in \mathbb{R}^n$ and $A_\kappa = [a_{ij}]$. The constraint (25) is responsible for the complex balanced equilibrium point, while the constraints (26) are responsible for the closed loop system to be kinetic.

One can see that the constraints (25)-(26) are linear equalities and inequalities in the decision variables $(K_{\varphi}, A_\kappa)$. Therefore, the feasibility of the feedback design can be decided and a solution (if exists) can be found in the framework of linear programming. Obviously, the feasibility (i.e., feedback equivalence to a complex balanced CRN) cannot be guaranteed for any polynomial model, but a larger number of inputs adds more degrees of freedom to the computation.

With such kinetic feedback the CRN model (17) takes the form:
\[
\dot{c} = M\varphi(c) + Vc_I^{(w)} - vc + w \tag{27}
\]
\[ M_0 = M + K \phi. \]  
(28)

The nonlinear term of the model above is complex balanced, hence the passivity-based control design can be applied for disturbance attenuation.

5.3 Nonlinear Feedback for Disturbance Attenuation

Consider the nonlinear output feedback law
\[ c_i^{(w)} = V^{-1}(-K y + v c) \]  
(29)

where \( K = \text{diag}(k_i) \in \mathbb{R}^{n \times n} \) and \( y \) is defined in (19).

With this control, the CRN model has the form:
\[ \dot{c} = M_0 \phi(c) - K y + w. \]  
(30)

As it was presented in section 4, the control (29) guarantees the objective \( \lim_{t \to \infty} c = 0 \) provided that \( w = 0 \).

If disturbances are present in the control system \( (w \neq 0) \), the time-derivative of the storage function (11) in the case of the controlled system (30) reads as
\[ \dot{S} \leq y^T (-K y + w), \]  
(31)
\[ \int_0^t y^T K y d\tau \leq \int_0^t y^T w d\tau + S(0). \]  
(32)

Let \( k = \min_i \{k_i\} \). Since \( k \int_0^t y^T y d\tau \leq \int_0^t y^T K y d\tau \) and \( y^T w \leq \frac{1}{2} (y^T w + w^T w) \) it follows that
\[ 2k \int_0^t y^T y d\tau \leq \int_0^t y^T y d\tau + \int_0^t w^T w d\tau + 2S(0), \]  
(33)
\[ \int_0^t y^T y d\tau \leq \frac{1}{2k - 1} \int_0^t w^T w d\tau + \frac{2}{2k - 1} S(0). \]  
(34)

Let the prescribed attenuation gain be \( \gamma \). It yields that if the controller gain matrix is chosen such that
\[ k > \frac{1}{2} \left(1 + \frac{1}{\gamma}\right) \]  
(35)
then the disturbance attenuation control objective is achieved.

5.4 Rate Adjustment for Positive Control Input

The control input \( c_i^{(w)} \) is a chemical concentration which should always be positive. To ensure its positiveness, the input rates (the entries of the diagonal of the matrix \( V \)) are adjusted as functions of the concentration state vector \( c \). Note that the control algorithm (29) allows non-constant rates.

The problem can be formulated as: design the rate matrix \( V = V(c) \) as a function of the state vector such that
\[ c_i^{(w)} = V^{-1}(c)(v(c)c - K y) > 0 \]  
entry-wise \( \forall K, c, c_{SP} \).

To solve the design problem above, a technical assumption is formulated: each entry of the concentration state vector \( c \) is upper bounded, i.e. \( \exists c_{Mi} > 0 \) such that \( c_i(t) < c_{Mi} \forall i \) and \( t \geq 0 \).

\[ \dot{c} = (M - K_O |Kl|) \left( \begin{array}{c} \phi(c) \\ 1 \end{array} \right) + Vc - vc. \]  
(40)

Here \( K_O = \text{diag}(k_{Oi}) \in \mathbb{R}^{n \times n} \), \( K_I = \text{diag}(k_{Ii}) \in \mathbb{R}^{n \times n} \).

An example of such an open CRN is presented in Figure 1 with its reaction graph, where the zero complex \( \emptyset \) represents the environment. The ODE model of this simple example can be written in the form (40) as
\[
\begin{pmatrix}
\dot{c}_1 \\
\dot{c}_2 \\
\dot{c}_3 \\
\dot{c}_4
\end{pmatrix} =
\begin{pmatrix}
-(k_1 + k_4) & 0 & k_3 \\
2k_1 & -2k_2 & 0 \\
k_4 & k_2 & -k_3 \\
k_4 & k_2 & -k_3
\end{pmatrix}
\begin{pmatrix}
c_1 \\
c_2 \\
c_3 \\
c_4
\end{pmatrix} 
\]

Assume that an estimate of the vector \( K_{O}\phi(c) \) is known with limited precision, i.e., an entry-wise positive vector \( \tilde{\phi}_o(c) \) is available which satisfies entry-wise
\[
|\tilde{\phi}_o(c) - K_{O}\phi(c)| \leq d_o.
\]
The model (40) can be rewritten in the form (17) in which \( \mathbf{w} = K_{I}\mathbf{1} - K_{O}\phi(c) \).

As the addressed CRN is complex balanced (it is weakly reversible with deficiency zero), there is no need to make it complex balanced with feedback. Then the following extended control law is chosen as \( c_I = c_I^{(w)} + V^{-1}\tilde{\phi}_o(c) \), where \( c_I^{(w)} \) is given by (29). With this control the inequality (34), applied for control gain computation, has the form:
\[
\int_0^t y^T y \, dt \leq \frac{1}{2k - 1} \int_0^t \hat{w}^T \hat{w} \, dt + \frac{2}{2k - 1} S(0). \tag{42}
\]
where \( \hat{w} = K_{I}\mathbf{1} + d_o \).

Accordingly, the proposed control approach is applicable for setpoint control of CRNs with constant inflows and mass action kinetics outflows.

6.2 Simulation Results

The performance of the proposed control method were investigated by simulation using the open CRN model presented in subsection 6.1.

Open loop model: By setting \( k_I = k_O = v_i = v = 0 \) in the reaction network model (41), the equilibrium point set of the CRN without in- and outflows obeys the following system of equations:
\[
\begin{aligned}
-(k_1 + k_2)c_i^* + k_3c_3^*c_i^* = 0 \\
2k_1c_i^* - 2k_2c_i^* = 0
\end{aligned} \tag{43}
\]
Figure 2 shows the dynamic response of the CRN model without in- and outflows for the initial values \( c_i(0) = c_i(0) = c_i(0) = 1 \). Note that the steady state values of the chemical concentrations depend on the initial conditions.

The proposed control method was tested on the open system (41) with \( k_I = k_O = 1 \). The other parameters were taken as: \( k_1 = k_2 = k_3 = k_4 = 1 \).

Control experiments: During the control experiments the setpoints were chosen to satisfy the equations (43): \( c_{SP1} = 4 \), \( c_{SP2} = c_{SP3} = 2 \), \( c_{SP4} = 4 \).

The control was tested for two prescribed disturbance attenuation gain values: \( \gamma = 0.05 \), \( \gamma = 0.01 \). In the control

7. CONCLUSIONS

Chemical Reaction Network models are effective tools to analyze the properties and the dynamic behavior of a wide class of nonnegative models. However, during the control design for these nonlinear systems, the modeling uncertainties and external disturbances must often be taken into consideration. The method proposed in this paper gives a solution to setpoint control of Chemical Reaction Networks in the presence of bounded disturbances. The control law has two components: the aim of the first (inner) loop is to ensure the complex balance property of the nonlinear term in the model and to set the desired setpoint by kinetic feedback. The second (outer) loop applies a nonlinear passivity-based feedback, and it guarantees the desired disturbance attenuation in the controlled kinetic system. The simulation results show that the proposed control scheme can be efficiently applied to the setpoint control of CRNs with unknown but bounded disturbances.

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Fig. 3. Trajectories of the CRN with control

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Fig. 4. Control rates

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