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Parametric analysis of dynamically equivalent reaction network models*

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Abstract— **Using the results related to dynamically equivalent realizations of reaction kinetic systems, we analyze the dynamical properties of mass action reaction networks on which the well known structure based theorems of reaction kinetics are not directly applicable with respect to given range of certain rate coefficients. We introduce a transformation matrix to describe parametric changes, and show that if the appropriate transformation matrix has been found, parameter ranges for which certain dynamical properties can be ensured may be determined via the solution of a linear programming problem. The method is illustrated by numerical examples.**

I. INTRODUCTION

Reaction kinetic systems [1] are widely used on both macroscopic and microscopic scales, describing chemical/biotechnological and molecular biological phenomena respectively. The theory of chemical reaction networks (CRNs) or reaction kinetic networks (RKNs) has significant results relating network structure and the qualitative properties of the corresponding dynamics [2], [3]. It is well known that the network structure corresponding to a given dynamics is generally not unique [1], [4], in other words, structurally different CRNs may correspond to the same polynomial differential equations. In this context it is appropriate to call a CRN a realization of the underlying dynamics. Recently, optimization-based computational methods were proposed for dynamically equivalent network structures with given preferred properties [5], [6].

Since the theorems related to the qualitative dynamic behavior of kinetic systems are formulated for the CRNs, it is possible that for certain CRN realizations of a given dynamics, structural properties can be proved. Therefore, a possible approach for dynamical analysis is to determine multiple possible structurally different realizations of a given dynamics, to determine whether a realization exists for which a stability related result is valid [7], [8]. The aim of this paper is to extend this approach to CRNs where some rate coefficients are uncertain.

II. KINETIC SYSTEMS: MODELS AND PROPERTIES

The notations used in this introductory section are based on [3], [2] and [5].

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A. Basic components of reaction networks

Let us suppose $\mathbf{X}_i,\ i = 1, ..., m$ chemical species taking part in r chemical reactions. The concentrations $x_i,\ i = 1, ..., m$ form the state vector the elements of which are non-negative. *Elementary reaction steps* are defined in the following form [9]:

$$\sum_{i=1}^{m} \alpha_{ij}\mathbf{X}_i \rightarrow \sum_{i=1}^{m} \beta_{ij}\mathbf{X}_i, \quad j = 1, ..., r \tag{1}$$

where α_{ij} is the so-called *stoichiometric coefficient* of component $\mathbf{X}_i$ in the jth reaction, i.e. the number of colliding $\mathbf{X}_i$ molecules, and $\beta_{i\ell}$ is the stoichiometric coefficient of the product $\mathbf{X}_\ell$. The linear combinations of the species in eq. (1), namely $\sum_{i=1}^{m} \alpha_{ij}\mathbf{X}_i$ and $\sum_{i=1}^{m} \beta_{ij}\mathbf{X}_i$ for $j = 1, \ldots, r$ are called the complexes and are denoted by $C_1, C_2, \ldots, C_n$. Note that the stoichiometric coefficients are always non-negative integers in classical reaction kinetic systems.

According to the extended molecular picture, the reaction rate of the above reactions can be described as

$$\rho_j = k_j \prod_{i=1}^{m} [\mathbf{X}_i]^{\alpha_{ij}} = k_j \prod_{i=1}^{m} x_i^{\alpha_{ij}} \quad , \quad j = 1, ..., r \tag{2}$$

where $[\mathbf{X}_i] = x_i$ is the concentration of the component $\mathbf{X}_i$, and $k_j > 0$ is the *reaction rate constant* of the jth reaction, that is always positive.

If the reactions $C_i \rightarrow C_j$ and $C_j \rightarrow C_i$ take place at the same time in a reaction network for some i, j then this pair of reactions is called a reversible reaction (although it will be treated as two separate elementary reactions).

B. Graph representation of mass-action systems

Similarly to [10], we can assign the following directed graph (see, e.g. [11]) to the reaction network (1) in a straightforward way. The directed graph $D = (V_d, E_d)$ of a reaction network consists of a finite nonempty set V_d of vertices and a finite set E_d of ordered pairs of distinct vertices called directed edges. The vertices correspond to the complexes, i.e. $V_d = \{C_1, C_2, \ldots C_n\}$, while the directed edges represent the reactions, i.e. $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j in the reaction network. The reaction rates k_j for $j = 1, \ldots, r$ in (2) are assigned as positive weights to the corresponding directed edges in the graph. A set of complexes $\{C_1, C_2, \ldots, C_k\}$ is a *linkage class* of a reaction network if the complexes of the set are linked to each other in the reaction graph but not to any other complex [3].

C. Differential equations of mass-action systems

There are several possibilities to represent the dynamic equations of mass action systems (see, e.g. [10], [12], or [4]). For our computations, the following factorization is the most practical one:

$$\dot{x} = Y A_k \psi(x) \tag{3}$$

where $x \in \mathbb{R}^m$ is the concentration vector of the species, $Y \in \mathbb{R}^{m \times n}$ stores the stoichiometric composition of the complexes, $A_k \in \mathbb{R}^{n \times n}$ contains the information corresponding to the weighted directed graph of the reaction network, and $\psi : \mathbb{R}^m \mapsto \mathbb{R}^n$ is a monomial-type vector mapping defined by

$$\psi_j(x) = \prod_{i=1}^{m} x_i^{y_{ij}}, \quad j = 1, \ldots, n \tag{4}$$

where $y_{ij} = [Y]_{ij}$. Y and A_k are characterized as follows. The ith column of Y contains the composition of complex C_i, i.e. Y_{ji} is the stoichiometric coefficient of C_i corresponding to the specie $\mathbf{X}_j$. A_k is a column conservation matrix (i.e. the sum of the elements in each column is zero) defined as

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1}^{m} k_{il}, & \text{if} \quad i = j \\ k_{ji}, & \text{if} \quad i \neq j \end{cases} \tag{5}$$

In other words, the diagonal elements $[A_k]_{ii}$ contain the negative sum of the weights of the edges starting from the node C_i, while the off-diagonal elements $[A_k]_{ij}$, $i \neq j$ contain the weights of the directed edges (C_j, C_i) coming into C_i. Based on the above properties, it is appropriate to call A_k the *Kirchhoff matrix* of a reaction network.

D. Important properties of kinetic systems

A CRN is called *reversible*, if for each reaction $C_i \to C_j$, there exists the reverse reaction $C_j \to C_i$, too. A CRN is called *weakly reversible*, if whenever there exists a directed path from C_i to C_j in the reaction graph, there also exists a directed path from C_j to C_i. In such a case, all components of the reaction graph are *strongly connected*. A complex set is called *terminal* if there is no reaction leading out of it.

Using the notation

$$M = Y A_k, \tag{6}$$

equation (3) can be written in the compact form

$$\dot{x} = M \psi(x) \tag{7}$$

We can associate an n-dimensional vector with each reaction in the following way. For the reaction $C_i \to C_j$, the corresponding reaction vector denoted by e_k is given by

$$e_k = [Y]_{\cdot,j} - [Y]_{\cdot,i}, \ k = 1, \ldots, r, \tag{8}$$

where $[Y]_{\cdot,i}$ denotes the ith column of Y. The *rank* of a reaction network denoted by s is defined as the rank of the vector set $H = \{e_1, e_2 \ldots, e_r\}$ where r is the number of reactions. The elements of H span the so-called *stoichiometric subspace*, denoted by S, i.e. $S = \text{span}\{e_1, \ldots, e_r\}$. The positive *stoichiometric compatibility class* containing a $x_0 \in \mathbb{R}^n$ is the following set [3]:

$$(x_0 + S) \cap \mathbb{R}^n_+,$$

where $\mathbb{R}^n_+$ denotes the positive orthant in $\mathbb{R}^n$. The *deficiency* d of a reaction network is defined as [10], [3]

$$d = m_{ni} - l - s, \tag{9}$$

where m_{ni} is the number of non-isolated vertices in the reaction graph, l is the number of linkage classes and s is the rank of the reaction network. The deficiency is a very useful measure for studying the dynamical properties of reaction networks and for establishing parameter-independent global stability conditions.

E. Structural theorems of reaction kinetic systems

The following results and conjectures illustrate the potential of applying the theory of kinetic systems in nonlinear control.

- The *Deficiency Zero Theorem* [3] shows a very robust stability property of a certain class of kinetic systems. It says that deficiency zero weakly reversible networks possess well-characterizable equilibrium points, and independently of the weights of the reaction graph (i.e. that of the system parameters) they are at least locally stable with a known logarithmic Lyapunov function that is also independent of the system parameters. Moreover, they are input-to-state stable with respect to the off-diagonal elements of A_k as inputs [13], it is straightforward to asymptotically stabilize them by additional feedback [14].
- The *Deficiency One Theorem* [3] formulates a similar statement. Consider a chemical reaction network with deficiency d and l linkage classes. Let d_i, $i = 1, \ldots, l$ denote the deficiencies of the individual linkage classes considered as their own networks. Suppose the following conditions:
  - $d_i \leq 1 \ \ \forall i = 1, \ldots, l$
  - $\sum_{i=1}^{l} d_i = d$
  - Each linkage class contains a single terminal strongly linked component (i.e. such strong component in the reaction graph out of which there are no outgoing directed edges).

  Then, if a mass action system corresponding to the network with a specified rate set admits a positive equilibrium concentration, there exists precisely one equilibrium concentration in each positive stoichiometric compatibility class. Furthermore, if the network is weakly reversible, every mass action system permitted by the network has a positive equilibrium.

To shortly summarize these dynamical properties, we say that the CRNs for which the deficiency zero or the deficiency one theorem is valid exhibit the def0- or def1-property, respectively.

In [15], the authors give necessary and sufficient conditions for a set of polynomial ODEs to be kinetic. The constructive proof contains a procedure that defines a possible

(Y, A_k) pair (and thus $\psi(x)$ as well) for realizing a kinetic dynamics. In other words, it provides one realization from the multiple possible ones that we often use as a starting point for finding other structures.

F. Dynamical equivalence of mass-action networks

It is known [2] that CRNs with different structures and/or parametrization can give rise to the same kinetic differential equations. Therefore, we will call two CRNs given by the matrix pairs (Y^1, A_k^1) and (Y^2, A_k^2) *dynamically equivalent*, if

$$Y^1 A_k^1 \psi^1(x) = Y^2 A_k^2 \psi^2(x) = f(x) \tag{10}$$

In this case, the (Y^i, A_k^i) pairs for $i = 1, 2$ are called realizations of a kinetic vector field f (see, e.g. [15] for more details). It is also appropriate to call (Y^1, A_k^1) a realization of (Y^2, A_k^2) and vice versa. We will assume throughout the paper that the set of complexes (i.e. the stoichiometric matrix Y) is fixed and known before the computations. In this case (since $\psi(x)$ is determined by Y as well - see Eq. (4)), the condition (10) for dynamical equivalence can be written as

$$Y A_k^1 = Y A_k^2 = M \tag{11}$$

This implies that by fixing Y, the matrices A_k^i are in one to one correspondence with the realizations, and it makes sense to say that A_k^i is a realization of (Y, A_k). Furthermore, we will say that the realizations A_k^1 and A_k^2 are structurally equivalent, if

$$(A_k^1)_{i,j} = 0 \quad \Leftrightarrow \quad (A_k^2)_{i,j} = 0 \quad \forall \ (i,j)$$

III. RESULTS

To better highlight the applied transformation, firstly, an example is shown.

Example 1: Let us consider the CRN depicted in Fig. 1

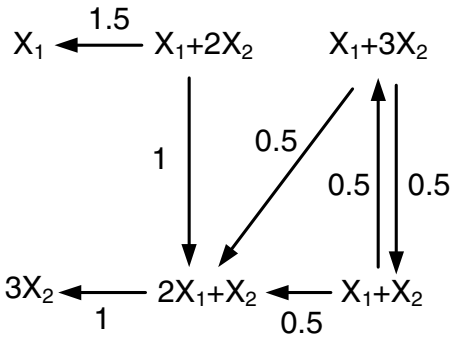

Fig. 1. The basic realization of the example network 1

which corresponds to the matrices

$$Y = \begin{pmatrix} 1 & 1 & 2 & 0 & 1 & 1 \\ 2 & 0 & 1 & 3 & 3 & 1 \end{pmatrix}$$

$$A_k^1 = \begin{pmatrix} -2.5 & 0 & 0 & 0 & 0 & 0 \\ 1.5 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0.5 & 0.5 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0.5 \\ 0 & 0 & 0 & 0 & 0.5 & -1 \end{pmatrix}$$

Considering A_k^1, the deficiency of the network is 3, this means that none of the deficiency theorems apply.

On the other hand (e.g. with the algorithm described in [8]), we can find the reversible structure described by A_k^2 (depicted in Fig. 2). In this realization the complexes X_1 and $3X_2$ do not take part in any reaction. In this case we get that the deficiency of the system is equal to 1, and reversibility ensures the one terminal strong linkage class, so the deficiency one theorem applies. Furthermore, the boundedness conjecture (proved for the one linkage class case in [16]) ensures the boundedness of trajectories, and one may also conclude persistence [17] for the network.

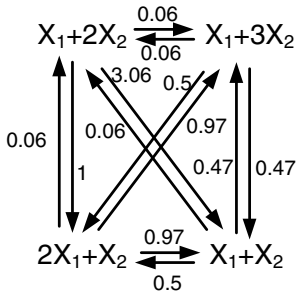

Fig. 2. The second realization of the example network 1

$$A_k^2 = \begin{pmatrix} -4.12 & 0 & 0.06 & 0 & 0.06 & 0.06 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -2 & 0 & 0.5 & 0.5 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0.06 & 0 & 0.97 & 0 & -1.03 & 0.47 \\ 3.06 & 0 & 0.97 & 0 & 0.47 & -1.03 \end{pmatrix}$$

We have to note that the deficiency one theorem applies not for A_k^1, but only for the reversible realization A_k^2. In general, If we change a parameter (a rate constant) in the CRN depicted in fig. 1, it is not guaranteed that the dynamical equivalence with a deficiency one reversible network will still hold. However, as we will see, realization theory can be used to analyze the parameter intervals in which the original system described by Y and A_k^1 will be dynamically equivalent to a reversible deficiency one network.

Let us consider a change of parameters in A_k^1 as follows, described by the variable α.

$$\hat{A}_k^1 = \begin{pmatrix} -2.5 & 0 & 0 & 0 & 0 & 0 \\ 1.5 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0.5 & 0.5 + \frac{\alpha}{2} \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0.5 - \alpha \\ 0 & 0 & 0 & 0 & 0.5 & \frac{\alpha}{2} - 1 \end{pmatrix}$$

One may ask what is the minimal and maximal value of α, for which we still may guarantee the existence of a

dynamically equivalent reversible deficiency 1 CRN. We will use the transformation below to address this question.

A. The transformation matrix

The A_k matrices are Kirchoff-matrices that have the column conservation property. It is clear that multiplying a Kirchoff matrix with any matrix from the right, the column-conservation property remains unaffected (however, the sign pattern of the elements is not guaranteed to remain). This implies the following. Let us assume that we have two structurally different realizations of the same CRN, namely A_k^1 and A_k^2. It is possible that for one of these realizations, let's say, for A_k^2 an important structural property applies (see Example 1).

Consider a transformation matrix $T \in \mathbb{R}^{n\times n}$ which leaves the structures (i.e. the positions of zero and non-zero elements) and the sign-patterns of both A_k^1 and A_k^2 unaffected. Since $YA_k^1T = YA_k^2T$, $(Y, \hat{A}_k^1)$ - where $\hat{A}_k^1 = A_k^1T$ - will be also dynamically equivalent to (Y, A_k^2T) (which is structurally equivalent to A_k^2). A possible candidate for such a T matrix is an identity matrix with one nonzero off-diagonal element as follows.

$$T = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & \alpha \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \tag{12}$$

Our aim is to determine the possible values of α, at which T leaves the structure of both A_k^1 and A_k^2 unaffected.

The (i,j)th element, ith row and jth column of any matrix A will be denoted by $A_{i,j}$, $A_{i,.}$ and $A_{.,j}$, respectively. To keep the structure unaffected (keep the corresponding elements positive, negative or zero) we shall consider the following. Let us consider for example $(A_k^1)_{3,6} > 0$. This will imply that $(A_k^1T)_{3,6}$ should be also greater than zero. We may write the element $(A_k^1T)_{3,6}$ as the product of the corresponding columns/rows to derive the constraint

$$(A_k^1T)_{3,6} = (A_k^1)_{3,.}T_{.,6} = (A_k^1)_{3,.} \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \alpha \\ 1 \end{pmatrix}$$

which results in

$$(A_k^1)_{3,6} + (A_k^1)_{3,5}\alpha > 0$$

This way for positive and negative elements we derive inequality type constraints, while for every zero element we will have an equality type constraint. These constraints secure the structure invariance of T for A_k^1 and A_k^2. Since if α is in the j-th column of T, it will affect only the j-th column of the product. This means that altogether $2n$ constraints may be derived (n for A_k^1 and n for A_k^2). Following the derivation of the constraints, the maximum and minimum value of α can be determined via the solution of the linear programming (LP) problem. In the case of our example this is the following.

$$min/max\ \alpha \quad \text{subject to:} \quad \begin{pmatrix} -0.5 \\ 1. \\ 0.5 \\ -0.06 \\ -0.5 \\ 1.03 \\ 0.47 \end{pmatrix} \alpha < \begin{pmatrix} 0.5 \\ 0.5000 \\ 1. \\ 0.06 \\ 0.5 \\ 0.47 \\ 1.03 \end{pmatrix}$$

As mentioned, we would have 12 constraints, but because of the position of the zero elements, the 5 equality constraints corresponding to the zeros in the last column of A_k^1 and A_k^2 in this example are trivial.

In the proposed example if $\alpha = T_{5,6}$, the structure of A_k^1 and A_k^2 remains unaffected if $\alpha \in (-1, 0.4563)$. In other words the CRN described by A_k^1 exhibits the def1-property for the parameter values implied by the T transformation matrix, if α is in the above range.

Since the deficiency zero and deficiency one theorems depend only on structural properties, the generalization of the proposed approach may be formulated as follows.

Let us have the matrices Y, A_k^1 and A_k^2 such that $YA_k^1 = YA_k^2$. Let us suppose that for A_k^2 a structural property (def0- or def1-property) applies. If we can find a T such that A_k^1 is structurally equivalent to A_k^1T and A_k^2 is structurally equivalent to A_k^2T, $(Y, \hat{A}_k^1 = A_k^1T)$ will be dynamically equivalent to A_k^2, and will hold the corresponding structural property as well.

Example 2: Let us consider the CRN depicted in Fig. 3, described by the matrices

$$Y = \begin{pmatrix} 1 & 2 & 0 & 3 \\ 0 & 1 & 2 & 1 \end{pmatrix}$$

$$A_k^1 = \begin{pmatrix} -1 & 3 & 0 & 0 \\ 1 & -7 & 0 & 0 \\ 0 & 1 & -3 & 2 \\ 0 & 3 & 3 & -2 \end{pmatrix}$$

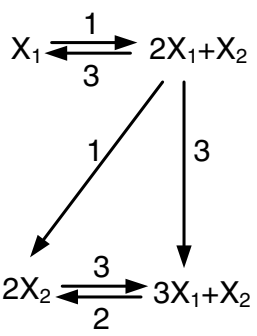

Fig. 3. The basic realization of the example network 2

In this case A_k^1 represents a network of deficiency 1, however the deficiency one theorem does not hold, since multiple terminal strongly connected components are present in the reaction graph. On the other hand, another realization of the network may be found with the Kirchhoff matrix

$$A_k^2 = \begin{pmatrix} -1 & 2 & 0 & 0 \\ 1 & -2 & 0 & 0 \\ 0 & 0 & -3 & 2 \\ 0 & 0 & 3 & -2 \end{pmatrix}$$

In this representation, depicted in Fig. 4, the system contains two linkage classes instead of one, it is reversible (so weakly reversible as well), and thus the deficiency zero theorem holds. Furthermore, the global attractor conjecture ensures the global stability of equilibria [17].

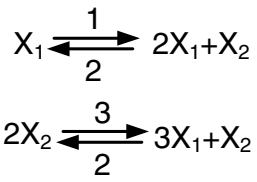

Fig. 4. The two linkage class realization of the example network 2

Let us suppose the following transformation matrix:

$$T_1 = \begin{pmatrix} 1 & \alpha & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \tag{13}$$

Similarly to the previous example, we may derive a LP problem to determine the maximal range of α for which the CRN described by

$$\hat{A}_k^{1a} = A_k^1 T_1 \begin{pmatrix} -1 & 3-\alpha & 0 & 0 \\ 1 & \alpha-7 & 0 & 0 \\ 0 & 1 & -3 & 2 \\ 0 & 3 & 3 & -2 \end{pmatrix}$$

will exhibit the def0-property. In this case the result of the optimization shows that $0 \leq \alpha < 2$. Furthermore if we consider the transformation matrices

$$T_2 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & \alpha \\ 0 & 0 & 0 & 1 \end{pmatrix} T_3 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & \alpha & 1 \end{pmatrix} \tag{14}$$

we may similarly conclude that

$$\hat{A}_k^{1b} = A_k^1 T_2 \begin{pmatrix} -1 & 3 & 0 & 0 \\ 1 & 7 & 0 & 0 \\ 0 & 1 & -3 & 2-3\alpha \\ 0 & 3 & 3 & 3\alpha-2 \end{pmatrix}$$

and

$$\hat{A}_k^{1c} = A_k^1 T_3 \begin{pmatrix} -1 & 3 & 0 & 0 \\ 1 & 7 & 0 & 0 \\ 0 & 1 & 2\alpha-3 & 2 \\ 0 & 3 & 3-2\alpha & -2 \end{pmatrix}$$

will show the def0-property for $0 \leq \alpha < \frac{2}{3}$ and $0 \leq \alpha < \frac{3}{2}$ respectively.

IV. CONCLUSIONS AND FUTURE WORK

We have shown that if we consider dynamically equivalent realizations of kinetic systems, and a structural property (e.g. def0- or def1-property) holds for one of them, then we may analyze the dynamical properties of the system regarding some of its parameters with the help of parameter-dependent transformation matrix T. If we are able to find a post-multiplication transformation matrix, which leaves the structure of both Kirchhoff matrices unaffected, then $\hat{A}_k^1 = A_k^1 T$ will exhibit the same structural property as A_k^2. The minimum and maximum value of the parameter can be determined by solving a linear system of equalities and inequalities that can be handled in the framework of linear programming.

A. Future work

A possible straightforward generalization of the approach may be if we do not look for one T transformation matrix, but for T_1 and T_2 corresponding to A_k^1 and A_k^2 respectively. If T_1 is structure invariant for A_k^1 and T_2 is structure invariant for A_k^2, $(Y, \hat{A}_k^1 = A_k^1 T_1)$ will be dynamically equivalent to $(Y, \hat{A}_k^2 = A_k^2 T_2)$ where $\hat{A}_k^2 = A_k^2 T_2$ will have the same structure as A_k^2, thus the same structural dynamical theories will apply.

A further challenge is to extend the results to stability related theorems which are not only structure, but also parameter dependent, like balancedness [18].

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