Embedding-Based Comparison of Reaction Networks of Wnt Signaling

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Abstract

This work introduces a new method for comparing two reaction networks of the same or closely related systems through their embedded networks in terms of the shared set of species. Hence, we call this method the Common Species Embedded Networks (CSEN) analysis. Using this approach, we conduct a comparison of existing reaction networks associated with Wnt signaling models (Lee, Schmitz, MacLean, and Feinberg) that we have identified. The analysis yields three important results for these Wnt models. First, the CSEN analysis of the Lee (mono-stationary) and Feinberg (multi-stationary) shows a strong similarity, justifying the study of the Feinberg model, which was a modified Lee model constructed to study an important network property called "concordance". It also challenge the absoluteness of discrimination of the models into mono-stationarity

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versus multi-stationarity, which is a main result of Maclean et al. (PNAS USA 2015). Second, the CSEN analysis provides evidence supporting a strong similarity between the Schmitz and MacLean models, as indicated by the "proximate equivalence" that we have identified. Third, the analysis underscores the absence of a comparable relationship between the Feinberg and MacLean models, highlighting distinctive differences between the two. Thus, our approach could be a useful tool to compare mathematical models of the same or closely related systems.

1 Introduction

Reaction networks have recently been used to perform parameter-free analyses of mathematical models individually and comparatively [7,16,17]. The structure of the network's independent decompositions [5,9,10], equilibria parametrizations [8,11], and a standard toolbox for reaction networks [6] are some of the important tools that are used to analyze the models. The crucial properties studied include multi-stationarity, absolute concentration robustness (ACR), and concordance. Multi-stationarity is the capacity for a network to admit two or more positive equilibria with the same conserved quantities [3]. On the other hand, a system exhibits ACR in a particular species if the equilibrium value for a particular species has the same value at any equilibrium regardless of any set of initial conditions [24]. Finally, concordance property is a structural feature of a network that enforce duller and more restrictive behavior despite what might be great intricacy in the interplay of many species [23].

Embedded networks of reaction networks were first introduced in 2013 by Joshi and Shiu in [14] and were used to study continuous flow stirred tank reactors (CFSTR). Embedded networks are also the basis for embedded representations of Biochemical Systems Theory (BST) systems [2]. In particular, Farinas et al. [4] used embedded representations to study a model of Mycobacterium tuberculosis growth. More recently, Meshkat et al. [19] applied the concept to derive a necessary and sufficient condition to determine whether a reaction network has ACR property for a class of mass action systems.

In this work, we analyze the structural and kinetic relationships of

reaction networks through their embedded networks relative to their set of common species. This was motivated by our analysis of Wnt signaling models in biochemistry. Wnt signaling is a vital mechanism that regulates crucial development processes and maintenance of tissue homeostasis.

Wnt signaling pathway have been analyzed via reaction networks by MacLean et al. [18] primarily to investigate bistability, i.e., existence of two stable positive equilibria for a particular set of rate constants. They compared the previous models of Lee [15] and Schmitz [22] with their proposed model [18], which we call MacLean model in this paper. The species and reaction networks of the models are provided in the Appendices A and B, respectively.

The Lee model focuses on the formation of the destruction complex from its constituent parts and how its subsequent ability to degrade β-catenin is altered by the presence and absence of an external Wnt stimulus. The model assumes that all species are uniformly distributed throughout the cell and hence does not distinguish between the nucleus and the cytoplasm. The Schmitz model focuses on the effect that shuttling of β-catenin and destruction complex between the cytoplasm and the nucleus has on T-cell factor binding to β-catenin in the nucleus. The MacLean model focuses on both β-catenin degradation and protein shuttling between the cytoplasm and nucleus that may serve as a possible mechanism for governing bistability in the pathway [18].

Feinberg [5] modified the Lee model by considering a complex of three species into a single species, making the reaction containing this complex a reversible one, and eliminating a single species. In this paper, we call this network the Feinberg network. When the pair of reversible reaction that does not contribute much to the network except to produce a species that does not play any other role in the Wnt signaling network is removed, the concordance property is achieved from an originally discordant network.

The analysis yields three important results for the Wnt signaling models. First, the CSEN analysis of the Lee, which is mono-stationary, and Feinberg, which is multi-stationary, shows a strong similarity. This justifies the study of the Feinberg model, which was a slightly modified Lee model. Furthermore, it challenges the absoluteness of discrimination of the mod-

els into mono-stationarity versus multi-stationarity. Second, the CSEN analysis suggests a strong similarity between the Schmitz and MacLean models. This is indicated by the "proximate equivalence" that we have identified. Third, the analysis underscores the absence of a comparable relationship between the Feinberg and MacLean models. This highlights the distinctive differences between these two models.

The rest of the paper is organized as follows: Section 2 provides the background necessary to understand the flow of this paper. Section 3 outlines the new method of comparing reaction networks via common species embedded networks. Sections 4, 5, and 6 provide our CSEN analyses for the Lee and Feinberg models, the Schmitz and MacLean models, and the Feinberg and MacLean models, respectively. Finally, a summary and recommendation are given in Section 7.

2 Preliminaries

2.1 Chemical reaction networks and systems

We start by introducing a formal definition of a chemical reaction network (CRN).

Definition 1. A *chemical reaction network*, denoted by $\mathscr{N}$, is a triple of nonempty and finite sets $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ where

  a. $\mathscr{S} = \{A_1, A_2, \ldots, A_m\}$ is the set of m *species*,

  b. $\mathscr{C} = \{C_1, C_2, \ldots, C_n\}$ is the set of n *complexes*, which are non-negative linear combinations of the species, and

  c. $\mathscr{R} = \{R_1, R_2, \ldots, R_r\} \subset \mathscr{C} \times \mathscr{C}$ is the set of r *reactions*.

We usually denote a reaction (y, y') using $y \to y'$. In this reaction, y is called a *reactant complex* and y' is called a *product complex*. An inflow reaction, denoted by $0 \to A_i$, means a constant supply of species A_i. On the other hand, an outflow reaction, denoted by $A_j \to 0$, means degradation of species A_j.

A *reaction vector* of the reaction is the difference $y' - y$. Hence, a reaction vector is a linear combination of species. The linear subspace of $\mathbb{R}^m$ spanned by the reaction vectors is called the *stoichiometric subspace* of $\mathscr{N}$, defined as $S = \text{span}\{y' - y \in \mathbb{R}^m \mid y \to y' \in \mathscr{R}\}$. The $m \times r$ matrix, where the ith column contains the coefficients of the associated species in the ith reaction vector associated with the ith reaction, is the *stoichiometric matrix* of the network.

To describe the dynamics of the temporal evolution of the concentrations of the species, a CRN is endowed with kinetics. Kinetics is defined as follows.

Definition 2. A *kinetics* for a reaction network $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ is an assignment to each reaction $y \to y' \in \mathscr{R}$ of a continuously differentiable rate function $K_{y \to y'} : \mathbb{R}^{\mathscr{S}}_{\geq 0} \to \mathbb{R}_{\geq 0}$ such that the following positivity condition holds: $K_{y \to y'}(c) > 0$ if and only if $\text{supp } y \subset \text{supp } c$, where $\text{supp } y$ refers to the support of the vector y, i.e., the set of species with nonzero coefficient in y. The pair $(\mathscr{N}, K)$ is called a *chemical kinetic system*.

Definition 3. A kinetics for a CRN $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ is *mass action* if for each reaction $y \to y'$ (i.e., $[y_1, y_2, \ldots, y_m]^\top \to [y'_1, y'_2, \ldots, y'_m]^\top$),

$$K_{y \to y'}(x) = k_{y \to y'} \prod_{i \in \mathscr{S}} x_i^{y_i}$$

for some $k_{y \to y'} > 0$.

Definition 4. The *species formation rate function* (SFRF) of a chemical reaction system $(\mathscr{N}, K)$ is given by $f(x) = \displaystyle\sum_{y \to y' \in \mathscr{R}} K_{y \to y'}(x)(y' - y)$.

Note that the SFRF can be written as $f(x) = NK(x)$ where N is the stoichiometric matrix of the network and K is the vector of rate functions. The system of *ordinary differential equations* (ODEs) of a chemical kinetic system is given by $\dfrac{dx}{dt} = f(x)$ where x is a vector of concentrations of the species that evolve over time.

Definition 5. A *steady state* or an *equilibrium* is a vector c of species concentrations such that $f(c) = 0$. A *positive equilibrium* is an equilibrium where each concentration is positive.

Definition 6. A CRN is said to *admit multiple (positive) equilibria* or is *multi-stationary* if there exist positive rate constants such that the ODE system admits more than one stoichiometrically-compatible equilibria.

2.2 Embedded networks and network transformations

In this section, we briefly review the concepts of embedded networks and network transformations. First, the definition of embedded networks from [14] is as follows:

Definition 7. Let $\mathscr{N} = \{\mathscr{S}, \mathscr{C}, \mathscr{R}\}$ be a CRN.

1. Consider a subset of the species set $S \subset \mathscr{S}$, a subset of the complexes set $C \subset \mathscr{C}$, and a subset of the reactions set $R \subset \mathscr{R}$.

   - The *restriction of R to S*, denoted $R|_S$, is the set of reactions obtained by taking the reactions in R and removing all species not in S from the reactant and product complexes. If a trivial reaction (one in which the reactant and product complexes are the same) is obtained in this process, then it is removed. Extra copies of repeated reactions were also removed. The *restriction of C to R*, denoted $C|_R$, is the set of (reactant and product) complexes of reactions in R.

   - The *restriction of S to C*, denoted $S|_C$, is the set of species that are in the complexes in C.

2. The network obtained from $\mathscr{N}$ by *removing a subset of species* $\{X_i\} \subset S$ is the network $\left\{\mathscr{S}\backslash\{X_i\}, \mathscr{C}|_{\mathscr{R}|_{\mathscr{S}\backslash\{X_i\}}}, \mathscr{R}|_{\mathscr{S}\backslash\{X_i\}}\right\}$.

3. A subset of the reactions $\mathscr{R}' \subset \mathscr{R}$ defines the *subnetwork*

$$\{\mathscr{S}|_{\mathscr{C}|_{\mathscr{R}'}}, \mathscr{C}|_{\mathscr{R}'}, \mathscr{R}'\}.$$

4. Let $\mathscr{N} = \{\mathscr{S}, \mathscr{C}, \mathscr{R}\}$ be a CRN. An *embedded network* of $\mathscr{N}$ is defined by a subset of the species set $S = \{X_{i_1}, X_{i_2}, \ldots, X_{i_k}\} \subset \mathscr{S}$, and a subset of the reactions set $R = \{R_{j_1}, R_{j_2}, \ldots, R_{j_l}\} \subset \mathscr{R}$, that involve all species of S, is the network $(S, \mathscr{C}|_{R|_S}, R|_S)$ consisting of the reactions $R|_S$.

Example 1. Models in BST have two types of variables: dependent (state variables that change with time) and independent (constants that describe aspects of the process environment). Arceo et al. [1] introduced a power law kinetic realization, whereby the species set of the underlying network—called a total representation—consists of the corresponding dependent and independent species. In a subsequent work [2], they also defined the embedded representation of a BST model, which is the embedded network of the total representation relative to the dependent species. The embedded representation corresponds to the popular technique in BST of "lumping the independent variables to the rate constants".

The concept of network transformation originated in Nazareno et al. [21] and was recently extended by Talabis and Mendoza [25] in their study of network operations. The most well-known example of network transformation is the network translation of mass action systems introduced by Johnston in 2014 [13]. Hong et al. recently showed that any network translation can be composed from three network operations: shifting, dividing, and merging [12]. In this work, we will use shifting and "splitting by reaction vector" to define the network transformations necessary for our study.

We first recall the definition of dynamical equivalence of kinetic systems:

Definition 8. Two kinetic systems $(\mathcal{N}, K)$ and $(\mathcal{N}', K')$ with stoichiometric matrix N and N', respectively, are *dynamically equivalent* if

   i. $\mathcal{N}$ and $\mathcal{N}'$ have the same set of species;

   ii. K and K' have the same definition domain $\Omega = \Omega'$; and

   iii. $NK(x) = N'K'(x)$ for all $x \in \Omega$.

The last condition implies that the ODE systems of $\mathcal{N}$ and $\mathcal{N}'$ are identical.

We now define several classes of network transformations:

Definition 9. A dynamical equivalence between $(\mathcal{N}, K)$ (with stoichiometric subspace S) and $(\mathcal{N}', K')$ (with stoichiometric subspace S') is called

i. *S-extending transformation* if S is contained in S'.

ii. *S-including transformation* if S contains S'.

iii. *S-invariant transformation* if $S = S'$.

iv. *Network transformation* (or simply *transformation*) if one of (i), (ii), or (iii) holds.

Network operations are network transformations that change a single reaction or a pair of reactions in a network. Hence, they can be viewed as "building blocks" of transformations. Two useful operations are as follows:

Definition 10. 1. *Shifting* the reaction $q : y \to y'$ results to $q' : y + z \xrightarrow{r} y' + z$ with kinetics $K_{q'} = K_q$ where $z = z_1 X_1 + \cdots + z_m X_m$ and $z_i \in \mathbb{Z}$ for all $i = 1, \ldots, m$.

2. *Splitting* [via reaction vector] (RV-splitting) the reaction $q : y \to y'$ results to the pair of reactions $q' : x \xrightarrow{r} x'$ and $q'' : z \xrightarrow{r} z'$ with the same kinetics (i.e., $K_q = K_{q'} = K_{q''}$) and $y' - y = (x' - x) + (z' - z)$.

Note that shifting is an S-invariant transformation while splitting is an S-extending one. More examples and applications of network operations and transformations can be found in [25].

3 The method of comparing reaction networks via common species embedded networks

In this section, we introduce a new method for comparing reaction networks of the same or closely related biological systems. We call this method the *Common Species Embedded Networks (CSEN)* analysis. This approach allows us to determine a possible relationship between embedded networks of two CRNs via network operations or transformations, such as dynamical equivalence.

Before we formulate the steps of the CSEN analysis, we introduce some new concepts as follows.

Definition 11. Let $(\mathscr{N}, K)$ and $(\mathscr{N}^*, K^*)$ be kinetic systems. They are *proximately equivalent* if there are kinetics $\widetilde{K}$ and $\widetilde{K}^*$, differing (at most in inflows) from K and K^*, respectively, such that $(\mathscr{N}, \widetilde{K})$ is dynamically equivalent to $(\mathscr{N}^*, \widetilde{K}^*)$. When the dynamical equivalence between $(\mathscr{N}, \widetilde{K})$ and $(\mathscr{N}^*, \widetilde{K}^*)$ is a network transformation, we speak of a *proximate transformation* from $(\mathscr{N}, K)$ to $(\mathscr{N}^*, K^*)$.

Remark.   1. Two kinetic systems differ at most in inflows if they share the same set of reactions, but one system includes at least one inflow $0 \to A_i$ that is absent in the other.

2. The domain of the chosen proximate transformation is the set of proximate reactions of $\mathscr{N}_E$. Its image is the set of proximate reactions of $\mathscr{N}_E^*$.

Example 2.

    i. Dynamically equivalent systems are proximately equivalent.

    ii. Let $\mathscr{N}_E$ and $\mathscr{N}_E^*$ be CSEN. A maximal proximate transformation from $\mathscr{N}_E$ to $\mathscr{N}_E^*$ is a proximate transformation defined by a subset of non-common reactions of $\mathscr{N}_E$ with the maximal number of elements. Note that there may be more than one such subset; hence, more than one maximal proximate transformation.

We now carry out the method in three steps. The first step is to construct the embedded networks $\mathscr{N}_E$ and $\mathscr{N}_E^*$ of two networks $\mathscr{N}$ and $\mathscr{N}^*$, respectively, with respect to their set of common species $\mathscr{S}' = \mathscr{S}_{\mathscr{N}} \cap \mathscr{S}_{\mathscr{N}^*}$.

In the second step, we classify the reactions of each embedded network into 3 subsets or reaction classes:

1. Common reactions of $\mathscr{N}$ and $\mathscr{N}^*$: $\mathscr{R}_{\mathscr{N}} \cap \mathscr{R}_{\mathscr{N}^*}$

2. Common reactions of the embedded networks which are not in the first class: $(\mathscr{R}_{\mathscr{N}_E} \cap \mathscr{R}_{\mathscr{N}_E^*}) \backslash (\mathscr{R}_{\mathscr{N}} \cap \mathscr{R}_{\mathscr{N}^*})$

3. Reactions of $\mathscr{N}_E$ and $\mathscr{N}_E^*$ for further classification into the proximate and non-equivalent subsystems (see Definition 11)

The third step consists of the following task: identify a maximal proximate transformation from $\mathscr{N}_E$ to $\mathscr{N}_E^*$ (if it exists).

4 CSEN analysis of the Lee and Feinberg models

In this section, we compare the reaction networks of the Lee and Feinberg models by first constructing their embedded networks with respect to the set of common species. We then identify network operations that transform the remaining distinct reactions of the Lee network into those of the Feinberg network. Our result shows that the two networks are dynamically very similar and points to a relative aspect of the "model discrimination" by MacLean et al. [18] into mono- and multi-stationary systems.

We now illustrate the approach using the Lee and Feinberg networks. Since the species sets of the Lee and Feinberg networks are

$$\mathscr{S}_L = \{A_1, A_2, A_4, A_6, A_7, A_8, A_{10}, A_{12}, A_{13}, A_{22}, \dots, A_{28}\} \backslash \{A_{28}\}$$

and

$$\mathscr{S}_F = \{A_1, A_2, A_4, A_6, A_7, A_8, A_{10}, A_{12}, A_{13}, A_{22}, \dots, A_{28}\} \backslash \{A_{22}\},$$

then both networks have 15 species with 14 in common. Table 1 presents the results of Steps 1 and 2 of the CSEN analysis.

Theorem 1. *Let $\mathscr{N}_{LE}$ and $\mathscr{N}_{FE}$ be the embedded networks of $\mathscr{N}_L$ and $\mathscr{N}_F$, respectively, with respect to their set of common species. Then $\mathscr{N}_{LE}$ with mass action kinetics is dynamically equivalent to $\mathscr{N}_{FE}$ with mass action kinetics except for an inflow reaction. The dynamical equivalence is via an S-extending network operation.*

Proof. The common reactions of $\mathscr{N}_{LE}$ and $\mathscr{N}_{FE}$ consist of the 21 reactions listed in Table 1. The other remaining reactions in Feinberg become $A_{13} + A_2 \to 0 \to A_{13} + A_{23}$. This is the transform by RV-splitting (an S-extending network operation) from $A_{13} + A_2 \to A_{13} + A_{23}$ in the Lee network. Furthermore, the rank of $\mathscr{N}_{LE}$ is one less than that of $\mathscr{N}_{FE}$. ∎

Table 1. Reactions of the embedded networks ($\mathscr{N}_{LE}$ and $\mathscr{N}_{FE}$) of the Lee ($\mathscr{N}_L$) and Feinberg ($\mathscr{N}_F$) models with respect to their common species. Reaction numbers without the superscript E do not change after getting the embedded networks with respect to their common species.

Common to $\mathscr{N}_{LE}$ and $\mathscr{N}_{FE}$	
$R_1 : 0 \to A_4$	
$R_4 : A_1 + A_4 \to A_8$	
$R_5 : A_8 \to A_1 + A_4$	
$R_{12} : A_{10} \to 0$	
$R_{14} : A_1 \to A_2$	
$R_{15} : A_2 \to A_1$	
$R_{18} : A_{12} \to A_{13}$	
$R_{19} : A_{13} \to A_{12}$	
$R_{38} : A_4 \to 0$	
$R_{43} : A_{24} + A_{26} \to A_{23}$	
$R_{44} : A_{23} \to A_{24} + A_{26}$	
$R_{45} : A_8 \to A_{25}$	
$R_{46} : A_{25} \to A_1 + A_{10}$	
$R_{47} : 0 \to A_{26}$	
$R_{48} : A_{26} \to 0$	
$R_{49} : A_4 + A_6 \to A_7$	
$R_{50} : A_7 \to A_4 + A_6$	
$R_{51} : A_{24} + A_4 \to A_{27}$	
$R_{52} : A_{27} \to A_{24} + A_4$	

Embedding-derived common reactions	
$R_{41}^E : A_{23} \to A_2$	
$R_{42}^E : A_2 \to A_{23}$	

Unique to $\mathscr{N}_{LE}$	Unique to $\mathscr{N}_{FE}$
$R_{40}^E : A_{13} + A_2 \to A_{13} + A_{23}$	$R_{53}^E : A_{13} + A_2 \to 0$
	$R_{56}^E : 0 \to A_{13} + A_{23}$

Remark. 1. The aberrant kinetics on the inflow $0 \to A_{13} + A_{23}$ is given by $kA_{13}A_2$ (versus the usual constant kinetics convention). The choice of this kinetics is due to splitting the reaction $A_{13} + A_2 \to A_{13} + A_{23}$ (with the usual kinetics $kA_{13}A_2$) into $A_{13} + A_2 \to 0$ and $0 \to A_{13} + A_{23}$ (with the same kinetics) as seen, in general, in Definition 10.

2. The expansion of the stoichiometric subspace potentially explains

the mono-/multi-stationarity difference, as equilibria previously in separate stoichiometric classes can fall into the same larger class. Since the embedded networks describe the projection of processes in the larger (different) 15-dimensional species space onto the common 14-dimensional subspace, our result shows the strong dynamical similarity between the Lee and Feinberg systems.

For Step 3 of the CSEN analysis, it is shown in the proof of Theorem 1 that the subnetworks of the non-common reactions are proximately equivalent. Thus, the embedded networks of the Lee and Feinberg models are proximately equivalent. In other words, there is a proximate transformation from $\mathscr{N}_{LE}$ to $\mathscr{N}_{FE}$.

5 CSEN analysis of the Schmitz and MacLean models

The coincidence of many structo-kinetic (e.g., multi-stationarity) and kinetic (e.g., ACR) properties of the Schmitz network ($\mathscr{N}_S$) and the MacLean network ($\mathscr{N}_M$) suggests a structural relationship between them. In this section, we use CSEN analysis to derive such a relationship between their embedded networks, denoted by $\mathscr{N}_{SE}$ and $\mathscr{N}_{ME}$, induced by the subset of common species. More precisely, we show that

- A network transformation of $\mathscr{N}_{SE}$ coincides with $\mathscr{N}_{MEA}$ ($:= \mathscr{N}_{ME}$ less 2 outflows plus 1 reversible pair of "flow" reactions); and

- The kinetics of $\mathscr{N}_{SE}$ is mass action, and that of $\mathscr{N}_{ME}$, while generalized mass action, is mass action except for 3 "flow" reactions.

Remark. In mass action systems, the rate function of a reaction is based on the stoichiometric coefficients in the reactant complex. For example, under mass action kinetics, the reaction $A_5 + A_3 \rightarrow A_9$ has the rate function ka_5a_3. However in generalized mass action systems, introduced by Stefan Müller and Georg Regensburger [20], the rate function is not necessarily based on the stoichiometric coefficients in the reactant complex. In the example above, under generalized mass action kinetics (GMAK), the rate

function can have the form $ka_5^\alpha a_3^\beta$ where α and β can be any positive real number.

Table 2 shows the results of the CSEN analysis Steps 1 and 2.

Table 2. Reactions of the embedded networks ($\mathscr{N}_{SE}$ and $\mathscr{N}_{ME}$) of the Schmitz ($\mathscr{N}_S$) and MacLean ($\mathscr{N}_M$) models with respect to their common species. Reactions without the superscript E do not change after getting the embedded networks with respect to the common species.

Common to $\mathscr{N}_{SE}$ and $\mathscr{N}_{ME}$	
$R_1 : 0 \to A_4$	
$R_2 : A_4 \to A_5$	
$R_3 : A_5 \to A_4$	
$R_4 : A_1 + A_4 \to A_8$	
$R_5 : A_8 \to A_1 + A_4$	
$R_6 : A_5 + A_3 \to A_9$	
$R_7 : A_9 \to A_5 + A_3$	
$R_8 : A_6 + A_5 \to A_7$	
$R_9 : A_7 \to A_6 + A_5$	
Embedding-derived common reactions	
$R_{10}^E : A_8 \to A_1$	
$R_{11}^E : A_9 \to A_3$	
Unique to $\mathscr{N}_{SE}$	Unique to $\mathscr{N}_{ME}$
$R_{14} : A_1 \to A_2$	$R_{38} : A_4 \to 0$
$R_{15} : A_2 \to A_1$	$R_{39} : A_5 \to 0$
$R_{16} : A_1 \to A_3$	$R_{22}^E : A_2 \to 0$
$R_{17} : A_3 \to A_1$	$R_{23}^E : 0 \to A_2$
	$R_{24}^E : A_3 \to 0$
	$R_{25}^E : 0 \to A_3$
	$R_{30}^E : A_1 \to 0$
	$R_{31}^E : 0 \to A_1$

For the embedded Schmitz network, the common species comprise a large subset (9 in $\mathscr{N}_{ME}$ out of the 11 in $\mathscr{N}_S$) and the reactions generate a large subnetwork ($\mathscr{N}_{ME}$ has rank 7 while $\mathscr{N}_S$ has rank 9). This observation already suggests an "inclusion/extension-like" relationship between the networks.

The set of new common reactions is $(\mathscr{R}_{SE} \cap \mathscr{R}_{ME}) \backslash (\mathscr{R}_S \cap \mathscr{R}_M) = \{A_8 \to A_1, A_9 \to A_3\}$. Hence, the total of common reactions make up 11 of the 15 reactions in $\mathscr{N}_{SE}$.

The results of Step 3 are as follows: the following table defines two maximal proximate transformation from $\mathscr{N}_{SE}$ to $\mathscr{N}_{ME}$:

Reaction	Operation	Parameter
$A_1 \to A_2$	Splitting	$A_2 - A_1 = (A_2 - 0) + (0 - A_1)$
$A_2 \to A_1$	Splitting	$A_1 - A_2 = (A_1 - 0) + (0 - A_2)$
$A_1 \to A_3$	Splitting	$A_3 - A_1 = (A_3 - 0) + (0 - A_1)$
$A_3 \to A_1$	Splitting	$A_1 - A_3 = (A_1 - 0) + (0 - A_3)$

The top two rows define the first maximal proximate transformation, the bottom two the second. We choose the first and, hence, consider the reactions $\{A_3 \rightleftarrows A_1\}$ and $\{A_3 \rightleftarrows 0, A_4 \to 0, A_5 \to 0\}$ as the non-equivalent reactions of the CSEN.

Defining the augmented MacLean CSEN as $\mathscr{N}_{MEA} := \mathscr{N}_{ME} \cup \{A_1 \rightleftarrows 2A_1\}$, we can extend the previous considerations to a "structural-kinetic relationship" as follows:

Theorem 2. *The (mass action) system $\mathscr{N}_{SE}$ transforms to the subnetwork $\mathscr{N}_{MEA} \backslash \{A_4 \to 0, A_5 \to 0\}$, a generalized mass action system, which is predominantly mass action (14 of 19 reactions). Moreover, the transformation is the identity in 11 of the 15 reactions of $\mathscr{N}_{SE}$.*

Proof. The following table describes the GMAK details. We set $K_i = k_i A_i$ where $k_i > 0$, i.e., linear kinetics for the species A_i:

Reaction	Transformation 1/ Kinetics/Type	Transformation 2/ Kinetics/Type
$A_1 \to A_2$	$0 \to A_2$/ K_1/ GMAK	$A_1 \to 0$/ K_1/ MAK
$A_2 \to A_1$	$0 \to A_1$/ K_2/ GMAK	$A_2 \to 0$/ K_2/ MAK
$A_1 \to A_3$	$0 \to A_3$/ K_1/ GMAK	$A_1 \to 0$/ K_1/ MAK
$A_3 \to A_1$	$0 \to A_1$/ K_3/ GMAK	$A_3 \to 0$/ K_3/ MAK
$0 \to A_1$	$A_1 \to 2A_1$/ K_3/ GMAK	
$A_1 \to 0$	$2A_1 \to A_1$/ K_3/ GMAK	

The rest of the reactions (and their mass action kinetics) in $\mathscr{N}_{SE}$ remain unchanged. This proves the claim that $\mathscr{N}_{MEA}$ is a network transformation of $\mathscr{N}_{SE}$. ∎

6   CSEN analysis of the Feinberg and MacLean models

Table 3 presents the species and reactions of the Feinberg ($\mathcal{N}_F$) and MacLean ($\mathcal{N}_M$) models. The Feinberg and MacLean networks have eight common species: A_1, A_2, A_4, A_6, A_7, A_8, A_{12}, and A_{13}, and six common reactions: R_1, R_4, R_5, R_{18}, R_{19} and R_{38}. Following the discussion in Section 2.2, the embedded networks of the two models induced by their common species are given in Table 4.

Despite extensive systematic search, we were unable to identify any proximate equivalences. This points to a limitation of the relationship of the two embedded networks to the purely structural coincidence of 10 of the 15–16 reactions.

7   Summary and recommendation

We presented a novel method, which we call the Common Species Embedded Networks (CSEN) analysis, to compare reaction networks in closely related systems. We applied this approach to assess existing reaction networks associated with Wnt signaling models (Lee, Schmitz, MacLean, and Feinberg).

The CSEN analysis produced three interesting results. Firstly, the analysis revealed a strong similarity between the Lee (mono-stationary) and Feinberg (multi-stationary) models. This result challenges the absolute discrimination of models into mono-stationarity and multi-stationarity by Maclean et al. Second, our analysis provided evidence supporting similarity between the Schmitz and MacLean models, highlighted by the identified "proximate equivalence." Lastly, the analysis emphasized the absence of a comparable relationship between the Feinberg and MacLean models, emphasizing distinctive differences between the two. Situations where the search for proximate transformations become challenging (as was the case in Section 6) present further research opportunities.

The CSEN analysis introduced in this study offers a valuable tool for comparing mathematical models in related systems. This approach may

Table 3. Species and reactions of the Feinberg ($\mathscr{N}_F$) and MacLean ($\mathscr{N}_M$) Wnt signaling models

Common to $\mathscr{N}_F$ and $\mathscr{N}_M$	
$A_1, A_2, A_4 \; A_6, A_7, A_8, A_{12}, A_{13}$	
$R_1 : 0 \to A_4$	
$R_4 : A_1 + A_4 \to A_8$	
$R_5 : A_8 \to A_1 + A_4$	
$R_{18} : A_{12} \to A_{13}$	
$R_{19} : A_{13} \to A_{12}$	
$R_{38} : A_4 \to 0$	

Unique to $\mathscr{N}_F$	Unique to $\mathscr{N}_M$
$A_{10}, A_{23}, \ldots, A_{28}$	$A_3, A_5, A_9, A_{14}, \ldots, A_{21}$
$R_{12} : A_{10} \to 0$	$R_2 : A_4 \to A_5$
$R_{14} : A_1 \to A_2$	$R_3 : A_5 \to A_4$
$R_{15} : A_2 \to A_1$	$R_6 : A_5 + A_3 \to A_9$
$R_{43} : A_{24} + A_{26} \to A_{23}$	$R_7 : A_9 \to A_5 + A_3$
$R_{44} : A_{23} \to A_{24} + A_{26}$	$R_8 : A_6 + A_5 \to A_7$
$R_{45} : A_8 \to A_{25}$	$R_9 : A_7 \to A_6 + A_5$
$R_{46} : A_{25} \to A_1 + A_{10}$	$R_{20} : A_{13} \to A_{14}$
$R_{47} : 0 \to A_{26}$	$R_{21} : A_{14} \to A_{13}$
$R_{48} : A_{26} \to 0$	$R_{22} : A_2 \to A_{15}$
$R_{49} : A_4 + A_6 \to A_7$	$R_{23} : A_{15} \to A_2$
$R_{50} : A_7 \to A_4 + A_6$	$R_{24} : A_3 + A_{14} \to A_{19}$
$R_{51} : A_{24} + A_4 \to A_{27}$	$R_{25} : A_{19} \to A_3 + A_{14}$
$R_{52} : A_{27} \to A_{24} + A_4$	$R_{26} : A_{19} \to A_{14} + A_{15}$
$R_{53} : A_{13} + A_2 \to A_{28}$	$R_{27} : A_{15} + A_{17} \to A_{21}$
$R_{54} : A_2 \to A_{23}$	$R_{28} : A_{21} \to A_{15} + A_{17}$
$R_{55} : A_{23} \to A_2$	$R_{29} : A_{21} \to A_3 + A_{17}$
$R_{56} : A_{28} \to A_{13} + A_{23}$	$R_{30} : A_{13} + A_1 \to A_{18}$
	$R_{31} : A_{18} \to A_{13} + A_1$
	$R_{32} : A_{18} \to A_{13} + A_2$
	$R_{33} : A_2 + A_{16} \to A_{20}$
	$R_{34} : A_{20} \to A_2 + A_{16}$
	$R_{35} : A_{20} \to A_1 + A_{16}$
	$R_{36} : A_8 \to A_1$
	$R_{37} : A_9 \to A_3$
	$R_{39} : A_5 \to 0$

be useful in uncovering structural similarities and differences between reaction networks. Further exploration and application of the CSEN analysis

Table 4. Reactions of the embedded networks ($\mathscr{N}_{FE}$ and $\mathscr{N}_{ME}$) of the Feinberg ($\mathscr{N}_F$) and MacLean ($\mathscr{N}_M$) models with respect to their common species. Reactions without the superscript E do not change after getting the embedded networks with respect to the common species.

Common to $\mathscr{N}_{FE}$ and $\mathscr{N}_{ME}$	
$R_1 : 0 \to A_4$	
$R_4 : A_1 + A_4 \to A_8$	
$R_5 : A_8 \to A_1 + A_4$	
$R_{18} : A_{12} \to A_{13}$	
$R_{19} : A_{13} \to A_{12}$	
$R_{38} : A_4 \to 0$	

Embedding-derived common reactions	
$R_{46}^E : 0 \to A_1$	
$R_{54}^E : A_2 \to 0$	
$R_{55}^E : 0 \to A_2$	
$R_{56}^E : 0 \to A_{13}$	

Unique to $\mathscr{N}_{FE}$	Unique to $\mathscr{N}_{ME}$
$R_{14} : A_1 \to A_2$	$R_8^E : A_6 \to A_7$
$R_{15} : A_2 \to A_1$	$R_9^E : A_7 \to A_6$
$R_{45}^E : A_8 \to 0$	$R_{20}^E : A_{13} \to 0$
$R_{49} : A_4 + A_6 \to A_7$	$R_{30}^E : A_{13} + A_1 \to 0$
$R_{50} : A_7 \to A_4 + A_6$	$R_{31}^E : 0 \to A_{13} + A_1$
$R_{53}^E : A_{13} + A_2 \to 0$	$R_{32}^E : 0 \to A_{13} + A_2$
	$R_{36}^E : A_8 \to A_1$

could enhance our understanding of the dynamics of closely related systems and contribute to refining mathematical models in biological and chemical contexts.

Appendix A Definition of variables

Table 5 provides the species in the Wnt signaling networks that we consider.

Table 5. Species and corresponding biomolecules that can occur in the Wnt signaling models considered

Species	Meaning
A_1	destruction complex (DC) (active form)
A_2	DC (inactive form)
A_3	active DC residing in the nucleus
A_4	β-catenin
A_5	β-catenin in the nucleus
A_6	T-cell factor (TCF)
A_7	β-catenin-TCF complex
A_8	β-catenin bound with DC
A_9	β-catenin bound with DC in the nucleus
A_{10}	β-catenin (for proteasomal degradation)
A_{11}	β-catenin (for proteasomal degradation) in the nucleus
A_{12}	dishevelled (inactive form)
A_{13}	dishevelled (active form)
A_{14}	active dishevelled in the nucleus
A_{15}	inactive DC in the nucleus
A_{16}	phosphatase
A_{17}	phosphatase in the nucleus
A_{18}	active DC bound with dishevelled
A_{19}	active DC bound with dishevelled in the nucleus
A_{20}	active DC bound with phosphatase
A_{21}	active DC bound with phosphatase in the nucleus
A_{22}	GSK3β
A_{23}	axin-APC complex
A_{24}	APC
A_{25}	β-catenin bound with DC (for proteasomal degradation)
A_{26}	axin
A_{27}	β-catenin-axin complex
A_{28}	a complex considered as a single species (in [5]): $(A_{13} + A_{22} + A_{23} = A_{28})$

Appendix B   Reaction networks of Wnt signaling models

B.1   Lee Model

The following is the reaction network for the Lee model:

$R_1 : 0 \to A_4$

$R_4 : A_1 + A_4 \to A_8$

$R_5 : A_8 \to A_1 + A_4$

$R_{12} : A_{10} \to 0$

$R_{14} : A_1 \to A_2$

$R_{15} : A_2 \to A_1$

$R_{18} : A_{12} \to A_{13}$

$R_{19} : A_{13} \to A_{12}$

$R_{38} : A_4 \to 0$

$R_{40} : A_{13} + A_2 \to A_{13} + A_{22} + A_{23}$

$R_{41} : A_{22} + A_{23} \to A_2$

$R_{42} : A_2 \to A_{22} + A_{23}$

$R_{43} : A_{24} + A_{26} \to A_{23}$

$R_{44} : A_{23} \to A_{24} + A_{26}$

$R_{45} : A_8 \to A_{25}$

$R_{46} : A_{25} \to A_1 + A_{10}$

$R_{47} : 0 \to A_{26}$

$R_{48} : A_{26} \to 0$

$R_{49} : A_4 + A_6 \to A_7$

$R_{50} : A_7 \to A_4 + A_6$

$R_{51} : A_{24} + A_4 \to A_{27}$

$R_{52} : A_{27} \to A_{24} + A_4$
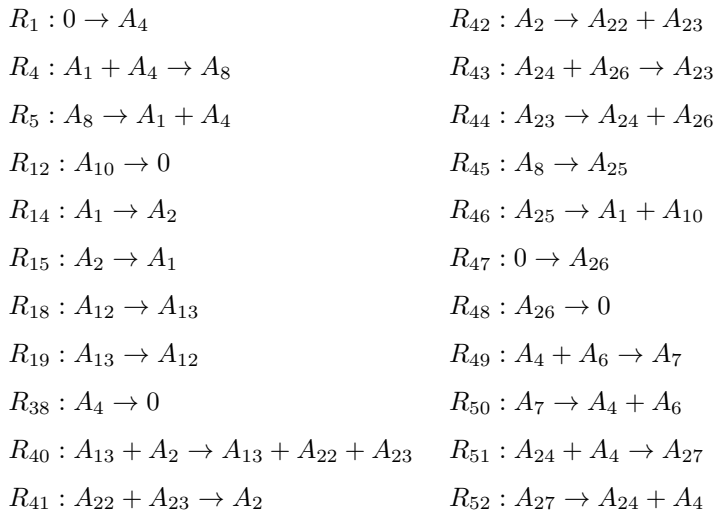
B.2   Feinberg Model

The following is the reaction network for the Feinberg model:

$R_1 : 0 \to A_4$

$R_4 : A_1 + A_4 \to A_8$

$R_5 : A_8 \to A_1 + A_4$

$R_{12} : A_{10} \to 0$

$R_{14} : A_1 \to A_2$

$R_{15} : A_2 \to A_1$

$R_{18} : A_{12} \to A_{13}$

$R_{19} : A_{13} \to A_{12}$

$R_{38} : A_4 \to 0$

$R_{43} : A_{24} + A_{26} \to A_{23}$

$R_{44} : A_{23} \to A_{24} + A_{26}$

$R_{45} : A_8 \to A_{25}$

$R_{46} : A_{25} \to A_1 + A_{10}$

$R_{47} : 0 \to A_{26}$

$R_{48} : A_{26} \to 0$

$R_{49} : A_4 + A_6 \to A_7$

$R_{50} : A_7 \to A_4 + A_6$

$R_{51} : A_{24} + A_4 \to A_{27}$

$R_{52} : A_{27} \to A_{24} + A_4$

$R_{53} : A_{13} + A_2 \to A_{28}$

$R_{54} : A_2 \to A_{23}$

$R_{55} : A_{23} \to A_2$

$R_{56} : A_{28} \to A_{13} + A_{23}$
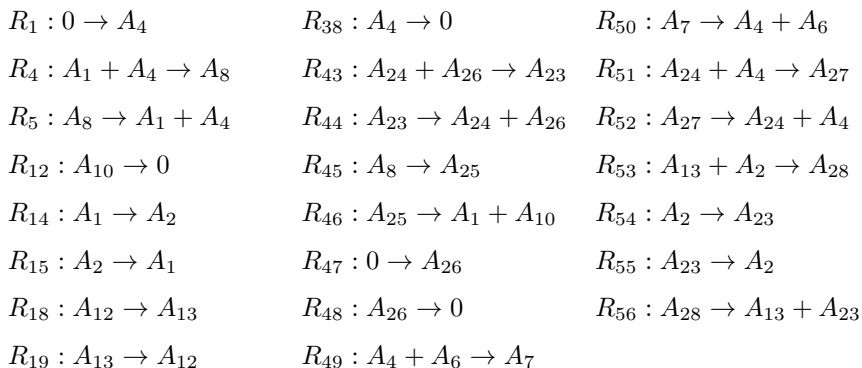
B.3 Schmitz Model

The following is the reaction network for the Schmitz model:

$R_1 : 0 \to A_4$ $R_7 : A_9 \to A_5 + A_3$ $R_{13} : A_{11} \to 0$

$R_2 : A_4 \to A_5$ $R_8 : A_6 + A_5 \to A_7$ $R_{14} : A_1 \to A_2$

$R_3 : A_5 \to A_4$ $R_9 : A_7 \to A_6 + A_5$ $R_{15} : A_2 \to A_1$

$R_4 : A_1 + A_4 \to A_8$ $R_{10} : A_8 \to A_1 + A_{10}$ $R_{16} : A_1 \to A_3$

$R_5 : A_8 \to A_1 + A_4$ $R_{11} : A_9 \to A_3 + A_{11}$ $R_{17} : A_3 \to A_1$

$R_6 : A_5 + A_3 \to A_9$ $R_{12} : A_{10} \to 0$
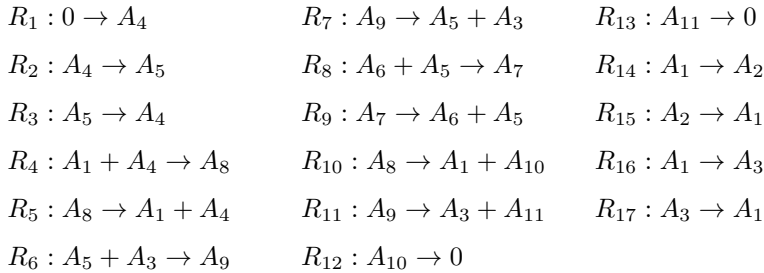
B.4 MacLean Model

The following is the reaction network for the MacLean model:
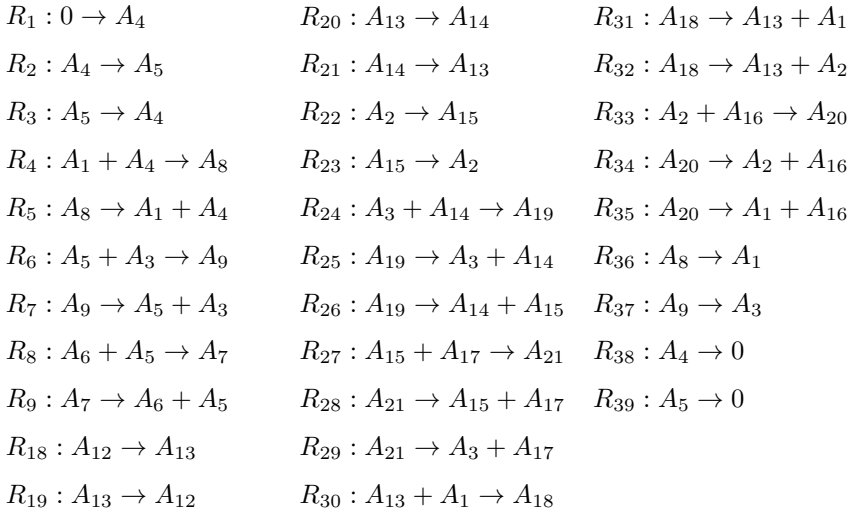
$R_1 : 0 \to A_4$ $R_{20} : A_{13} \to A_{14}$ $R_{31} : A_{18} \to A_{13} + A_1$

$R_2 : A_4 \to A_5$ $R_{21} : A_{14} \to A_{13}$ $R_{32} : A_{18} \to A_{13} + A_2$

$R_3 : A_5 \to A_4$ $R_{22} : A_2 \to A_{15}$ $R_{33} : A_2 + A_{16} \to A_{20}$

$R_4 : A_1 + A_4 \to A_8$ $R_{23} : A_{15} \to A_2$ $R_{34} : A_{20} \to A_2 + A_{16}$

$R_5 : A_8 \to A_1 + A_4$ $R_{24} : A_3 + A_{14} \to A_{19}$ $R_{35} : A_{20} \to A_1 + A_{16}$

$R_6 : A_5 + A_3 \to A_9$ $R_{25} : A_{19} \to A_3 + A_{14}$ $R_{36} : A_8 \to A_1$

$R_7 : A_9 \to A_5 + A_3$ $R_{26} : A_{19} \to A_{14} + A_{15}$ $R_{37} : A_9 \to A_3$

$R_8 : A_6 + A_5 \to A_7$ $R_{27} : A_{15} + A_{17} \to A_{21}$ $R_{38} : A_4 \to 0$

$R_9 : A_7 \to A_6 + A_5$ $R_{28} : A_{21} \to A_{15} + A_{17}$ $R_{39} : A_5 \to 0$

$R_{18} : A_{12} \to A_{13}$ $R_{29} : A_{21} \to A_3 + A_{17}$

$R_{19} : A_{13} \to A_{12}$ $R_{30} : A_{13} + A_1 \to A_{18}$

References

[1] C. P. Arceo, E. C. Jose, A. Marin-Sanguino, E. R. Mendoza, Chemical reaction network approaches to biochemical systems theory, *Math. Biosci.* **269** (2015) 135–152.

[2] C. P. Arceo, E. C. Jose, A. R. Lao, E. R. Mendoza, Reaction networks and kinetics of biochemical systems, *Math. Biosci.* **283** (2017) 13–29.

[3] A. Dickenstein, M. Millán, A. Shiu, X. Tang, Multistationarity in structured reaction networks, *Bull. Math. Biol.* **81** (2019) 1527–1581.

[4] H. F. Fariñas, E. R. Mendoza, A. R. Lao, Chemical reaction network decompositions and realizations of S-systems, *Philipp. Sci. Lett.* **14** (2021) 147–157.

[5] M. Feinberg, *Foundations of Chemical Reaction Network Theory*, Springer, 2019.

[6] M. Feinberg, P. Ellison, H. Ji, D. Knight, The chemical reaction network toolbox version 2.35, `https://zenodo.org/record/5149266#.YSE_3d8pCUk`

[7] N. T. Fortun, E. R. Mendoza, Comparative analysis of carbon cycle models via kinetic representations, *J. Math. Chem.* **61** (2023) 896–932.

[8] N. T. Fortun, E. R. Mendoza, L. F. Razon, A. R. Lao, A deficiency zero theorem for a class of power-law kinetic systems with non-reactant-determined interactions, *MATCH Commun. Math. Comput. Chem.* **81** (2019) 621–638.

[9] B. Hernandez, D. Amistas, R. De la Cruz, L. Fontanil, A. de los Reyes V, E. Mendoza, Independent, incidence independent and weakly reversible decompositions of chemical reaction networks, *MATCH Commun. Math. Comput. Chem.* **87** (2022) 367–396.

[10] B. Hernandez, R. De la Cruz, Independent decompositions of chemical reaction networks, *Bull. Math. Biol.* **83** (2021) #76.

[11] B. Hernandez, P. Lubenia, M. Johnston, J. Kim, A framework for deriving analytic steady states of biochemical reaction networks, *PLoS Comput. Biol.* **19** (2023) #e1011039.

[12] H. Hong, B. S. Hernandez, J. Kim, J. K. Kim, Computational translation framework identifies biochemical reaction networks with special topologies and their long-term dynamics, *SIAM J. Appl. Math.* **83** (2023) 1025–1048.

[13] M. D. Johnston, Translated chemical reaction networks, *Bull. Math. Biol.* **76** (2014) 1081–1116.

[14] B. Joshi, A. Shiu, Atoms of multistationarity in chemical reaction networks, *J. Math. Chem.* **51** (2013) 153–178.

[15] E. Lee, A. Salic , R. Krüger, R. Heinrich, M. W. Kirschner, The roles of APC and Axin derived from experimental and theoretical analysis of the Wnt pathway, *PLoS Biol.* **1** (2003) #e10.

[16] P. V. N. Lubenia, E. R. Mendoza, A. R. Lao, Comparative analysis of kinetic realizations of insulin signaling, *J. Theor. Biol.* **577** (2023) #111672.

[17] P. V. N. Lubenia, E. R. Mendoza, A. R. Lao, Reaction network analysis of metabolic insulin signaling, *Bull. Math. Biol.* **84** (2022) 129–151.

[18] A. MacLean, Z. Rosen, H. Byrne, H. Harrington, Parameter-free methods distinguish Wnt pathway models and guide design of experiments, *Proc. Natl. Acad. Sci. U.S.A.* **112** (2015) 2652–2657.

[19] N. Meshkat, A. Shiu, A. Torres, Absolute concentration robustness in networks with low-dimensional stoichiometric subspace, *Vietnam J. Math.* **50** (2022) 623–651.

[20] S. Müller, G. Regensburger, Generalized mass action systems: Complex balancing equilibria and sign vectors of the stoichiometric and kinetic-order subspaces, *SIAM J. Appl. Math.* **72** (2012) 1926–1947.

[21] A. L. Nazareno, R. P. L. Eclarin, E. R. Mendoza, A. R. Lao, Linear conjugacy of chemical kinetic systems *Math. Biosci. Eng.* **16** (2019) 8322–8355.

[22] Y. Schmitz, K. Rateitschak, O. Wolkenhauer, Analysing the impact of nucleo-cytoplasmic shuttling of β-catenin and its antagonists APC, Axin and GSK3 on Wnt/β-catenin signalling, *Cell. Signal.* **25** (2013) 2210–2221.

[23] G. Shinar, M. Feinberg, Concordant chemical reaction networks, *Math. Biosci.* **240** (2012) 92–113.

[24] G. Shinar, M. Feinberg, Structural sources of robustness in biochemical reaction networks, *Science* **327** (2010) 1389–1391.

[25] D. A. S. J. Talabis, E. R. Mendoza, Analysis of biochemical systems via reaction network operations (2023, in preparation)