Bond Graph Representation of Chemical Reaction Networks

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October 16, 2018

Abstract

The Bond Graph approach and the Chemical Reaction Network approach to modelling biomolecular systems developed independently. This paper brings together the two approaches by providing a bond graph interpretation of the chemical reaction network concept of complexes. Both closed and open systems are discussed.

The method is illustrated using a simple enzyme-catalysed reaction and a transmembrane transporter.

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1 Introduction

The bond graph method for modelling engineering systems [1–6] was shown to provide a thermodynamically consistent approach to modelling biomolecular systems by Oster et al. [7, 8] and further developed by Gawthrop and Crampin [9, 10, 11]. In this context, the relationship between biomolecular systems and electrical circuit theory was explored by Oster and Perelson [12].

In parallel with the seminal work of Oster et al. [7, 8], the mathematical foundations of chemical reaction networks (CRN) were being laid by Feinberg [13], Horn and Jackson [14] and Feinberg and Horn [15]. This approach to chemical reaction network theory was further developed by Sontag [16], Angeli [17], and van der Schaft et al. [18, 19, 20]. General results on stability of both closed and open systems of chemical reactions have been derived and applied to reveal dynamic features of complex (bio)chemical networks [21], dissipation in noisy chemical networks Polettini et al. [22], metabolic networks [23] and multistability in interferon signalling Otero-Muras et al. [24].

As an energy-based method, bond graphs are related to port-Hamiltonians [25–27]. A port-Hamiltonian interpretation of CRNs has been given by van der Schaft et al. [28] and this provides another link between CRNs and bond graphs.

The formal concept of complexes is essential to chemical reaction network theory. Complexes are the combination of chemical species forming the substrate and products of the network reactions. This paper links chemical reaction network theory to the bond graph approach by incorporating the concept of complexes into bond graph modelling of biomolecular systems.

§ 2 introduces the basic ideas of chemical reaction networks from the stoichiometric point of view and § 3 gives a bond graph interpretation. § 4 shows how system equations can be simplified using the complex approach. § 5 discusses thermodynamically open systems. § 6 concludes the paper.

2 The Stoichiometric Approach to Complexes

The notion of complexes was defined by Feinberg and Horn [15]: “By the complexes in a mechanism we mean the set of entities appearing before or after arrows in that mechanism.” where “mechanism” is a generalisation of “chemical reaction”. This section introduces some basic ideas relating to the use of complexes in describing chemical reaction networks by means of the simple reaction network example

$$A + E \underset{r_1}{\overset{r_2}{\rightleftharpoons}} C \rightleftharpoons B + E$$

(1)

This example involves the four species A, B, C and E and the two reactions $r_1$ and $r_2$. It represents the reaction $A \rightleftharpoons B$ catalysed by the enzyme E and with intermediate complex C [29]. The substrate of reaction $r_1$ is $A + E$ and the product is $C$; the substrate of reaction $r_2$ is $C$ and the product is $B + E$. Thus there are three complexes associated
with this reaction network: $A + E$, $C$ and $B + E$; $C$ forms not only the right-hand side of reaction $r_1$ but also the left-hand side of reaction $r_2$.

The standard stoichiometric approach would be to define the species state $x$ and reaction flow $v$ as:

\[
x = \begin{pmatrix} x_A \\ x_B \\ x_C \\ x_E \end{pmatrix} \quad v = \begin{pmatrix} v_1 \\ v_2 \end{pmatrix}
\]

where $v_1$ and $v_2$ are the flows associated with reactions $r_1$ and $r_2$ respectively. The rate of change of species $\dot{x}$ is then given in terms of the stoichiometric matrix $N$ and reaction flow $v$ as\(^1\):

\[
\dot{x} = Nv
\]

where $N = \begin{pmatrix} -1 & 0 \\ 0 & 1 \\ 1 & -1 \\ -1 & 1 \end{pmatrix}$ (3)

In contrast, the complex-based approach uses the complex flows $v^c$ as an intermediate quantity. Thus define

\[
v^c = \begin{pmatrix} v^c_1 \\ v^c_2 \\ v^c_3 \end{pmatrix}
\]

where $v^c_1$, $v^c_2$ and $v^c_3$ are the flows associated with complexes $A + E$, $C$ and $B + E$ respectively.

The rate of change of species $\dot{x}$ is given in terms of the matrix $Z$ and the complex flow $v^c$ as:

\[
\dot{x} = Zv^c
\]

where $Z = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix}$ (5)

and the complex flow $v^c$ is given in terms of the matrix $D$ and the reaction flow $v$ as:

\[
v^c = Dv
\]

where $D = \begin{pmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{pmatrix}$ (6)

If follows from Equations (16) and (18) that $\dot{x} = ZDv$ and thus it follows from (3) that

\[
N = ZD
\]

\(^1\)Although equation (3) is linear, as discussed in § 4 the reaction flow $v$ is, in general, a nonlinear function of the species state $x$. In this particular case the expression for $v$ involves the nonlinear terms $x_1 x_A$ and $x_2 x_B$. 

Figure 1: Digraph corresponding to the $D$ matrix (6) for the system $A + E \rightleftharpoons C \rightleftharpoons B + E$. The three complexes $A + E$, $C$ and $B + E$ appear as nodes connected by a digraph with edges corresponding to the two reactions $r_1$ and $r_2$.

The fundamental motivation for the complex-based approach is that graph theory can be applied to the directed graph formed by taking the complexes to be vertices and the reactions to be edges. In particular, $D$ is the incidence matrix of the graph and has the property that each column of $D$ contains exactly one 1 and exactly one $-1$; the other elements being zero. The corresponding digraph (plotted using graphviz) [30]) appears in Figure 1.

Following Gawthrop and Crampin [9], the stoichiometric matrix $N$ can be written as:

$$N = N^r - N^f$$

(8)

where $N^f$ and $N^r$ connect the forward and reverse sides of the reaction to species. In a similar fashion, $D$ can be written as:

$$D = D^r - D^f$$

(9)

where $D^f$ and $D^r$ connect the forward and reverse sides of the reaction to complexes. $D^f$ and $D^r$ can always be deduced from $D$ as $D^f$ and $D^r$ correspond to the negative and positive elements of $D$ respectively.

The columns of $N^f$ correspond to the substrate complexes and that the columns of $N^r$ correspond to the product complexes. It follows that the columns of both of these matrices contain all of the relevant complexes, possibly repeated. Hence $Z$ can be obtained as follows:

1. Create the matrix $Z_0$ from $N^f$ and $N^r$ and create the corresponding matrix $D_0$

$$Z_0 = \begin{pmatrix} N^f & N^r \end{pmatrix}$$

(10)

$$D_0 = \begin{pmatrix} -I_{n_V \times n_V} \\ \ldots \\ I_{n_V \times n_V} \end{pmatrix}$$

(11)

It follows from Equation (8) that $Z_0D_0 = N$.

2. Delete repeated columns of $Z_0$ to create $Z$ and sum the corresponding rows of $D_0$ to create $D$.  

5
Continuing the example of this section

\[ N^f = \begin{pmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \\ 1 & 0 \end{pmatrix}, \quad N^r = \begin{pmatrix} 0 & 0 \\ 0 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \] (12)

and so

\[ Z_0 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \end{pmatrix}, \quad D_0 = \begin{pmatrix} -1 & 0 \\ 0 & -1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \] (13)

As columns two and three are identical, column three of \( Z_0 \) is deleted to give \( Z \) (5), and rows two and three of \( D_0 \) are merged to give \( D \) (6).

### 3 The Bond Graph Approach to Complexes

Figure 2(a) shows the approach used by Gawthrop and Crampin [9, 10, 11] to represent closed systems. However, following the approach of Gawthrop [31], the Faraday-equivalent potential \( \phi \), with units of V, is used in place of chemical potential \( \mu \) with units of J mol\(^{-1}\). \( C \) represents the \( n_s \) \( \mathbf{C} \) components representing the chemical species; \( \phi \) is the vector of the chemical potentials, and \( \dot{x} \) the corresponding flow rates. \( Re \) represents the \( n_r \) \( \mathbf{Re} \) components representing the chemical reactions with forward and reverse potential \( \Phi^f \) and \( \Phi^r \) and flow rate \( v \). \( \mathcal{T}\mathcal{F}:N^r \) and \( \mathcal{T}\mathcal{F}:N^r \) represent the bond graph transformers encapsulating the system stoichiometry. A key feature of transformers is that they relate both the efforts and flows on the corresponding bonds whilst conserving energy [9–11]. Thus, with reference to Figure 2(a)

\[
\dot{x} = \dot{x}^r - \dot{x}^f = N^r v - N^f v = N v \\
\Phi = \Phi^f - \Phi^r = N^T \phi - N^f T \phi = -N^T \phi
\] (14) (15)

In contrast, Figure 2(b) shows the complex-based approach used here. \( \mathcal{T}\mathcal{F}:Z \) represents the bond graph transformer relating the \( n_s \) species to the \( n_c \) complexes which then become the reaction forward complex (substrates) via \( \mathcal{T}\mathcal{F}:D^f \) and the reaction reverse complex (products) via \( \mathcal{T}\mathcal{F}:D^r \). With reference to Figure 2(b), the transformer equations become:

\[
\dot{x} = Z v^c \\
\phi^c = Z^T \phi \\
v^c = v^r - v^f = D^r v - D^f v = D v \\
\Phi = \Phi^f - \Phi^r = D^T \phi^c - D^r T \phi^c = -D^T \phi^c
\] (16) (17) (18) (19)
Figure 2: A Bond Graph Approach to Complexes. (a) The standard approach given by Gawthrop and Crampin [9, 10, 11]. The bond symbols $\rightarrow$ correspond to vectors of bonds; $C$, $Re$ and $O$ correspond to arrays of $C$, $Re$ and $0$ components; the two $TF$ components represent the intervening junction structure comprising bonds, $0$ and $1$ junctions and $TF$ components. $N^f$ and $N^r$ are the forward and reverse stoichiometric matrices. (b) The complex based approach. $TF:Z$ represents the junction structure connecting complexes and species where $Z$ appears in Equation (16) and $TF:D^f$ $TF:D^r$ represent the junction structure connecting reactions and complexes where $D^f$ and $D^r$ appear in Equations (18) and (9).
3.1 Example: $A + E \rightleftharpoons C \rightleftharpoons B + E$

Figure 3: Example: $A + E \rightleftharpoons C \rightleftharpoons B + E$. (a) A bond graph without explicit representation of complexes. (b) The complex covariables correspond to the three highlighted bonds. The junction structure connecting the three highlighted bonds to the species corresponds to $\mathcal{T}F:Z$ of Figure 2(b) and the junction structure connecting the reaction $\text{Re}$ components to the three highlighted bonds corresponds to $\mathcal{T}F:D^f$ and $\mathcal{T}F:D^r$ of Figure 2(b). Bonds pointing into the $\text{Re}$ components correspond to $\mathcal{T}F:D^f$, those pointing away from the $\text{Re}$ components correspond to $\mathcal{T}F:D^r$.

Figure 3(a) gives the standard bond graph for the reaction $A + E \rightleftharpoons C \rightleftharpoons B + E$ corresponding to the general Figure 2(a) and Figure 3(b) gives the complex-based bond graph corresponding to the general Figure 2(b). The three bonds corresponding to the three complex efforts $\Phi^c$ and flows $v^c$ are highlighted.

4 System equations

This section derives the main properties of the CRN modelled by a bond graph including the complex concept. The notation and concepts of van der Schaft et al. [20, § 2] are used and reversible reactions are used at the outset. Following the notation of van der Schaft et al. [20], $\cdot$, $\frac{x}{y}$, Ln and Exp denote elementwise multiplication, division, natural logarithm and exponentiation of column vectors. In particular for two column vectors $x$ and $y$:

$$x \cdot y = \text{diag}(x)y \quad \frac{x}{y} = (\text{diag}(y))^{-1}x$$

(20)

The basic equation for the potential of species expressed as the Faraday-equivalent
potential [31] is
\[ \phi = \phi^\circ + \phi_N \ln \frac{x}{x^\circ} \]  
(21)

where \( \phi_N = \frac{RT}{F} \approx 26 \text{ mV} \)  
(22)

Alternatively, (21) can be rewritten as
\[ \phi = \phi_N \ln (K^* \cdot x) \]  
(23)

where \( K^* = \frac{\exp \phi^\circ}{x^\circ} \)  
(24)

4.1 Properties of the complexes

The basic bond graph notion of transformers as expressed in Figure 2(b) means that the potential of the complexes can be expressed as:
\[ \Phi^c = Z^T \phi \]  
(25)

hence \( \Phi^c = \Phi^c^\circ + \phi_N \ln \frac{X}{X^\circ} \)  
(26)

where \( \Phi^c^\circ = Z^T \phi^\circ \)  
(27)

\[ X = \exp (Z^T \ln x) = \prod_{j=1}^{n_x} x^j_z \]  
(28)

and \( X^\circ = \exp (Z^T \ln x^\circ) = \prod_{j=1}^{n_x} x^\circ_j z \)  
(29)

Alternatively, using Equation (23)
\[ \Phi^c = \phi_N \ln (K^c \cdot X) \]  
(30)

where \( K^c = \exp (Z^T \ln K^*) = \prod_{j=1}^{n_x} k^*_j z \)  
(31)

Using Equation (20), Equation (30) can also be written as
\[ \Phi^c = \phi_N \ln (\text{diag} K^c \cdot X) \]  
(32)

4.2 Mass-action Kinetics

Mass action kinetics correspond to the Marcelin-de Donder formula [8, 9, 32]:
\[ v = \kappa \cdot \left( \exp \frac{\Phi^f}{\phi_N} - \exp \frac{\Phi^r}{\phi_N} \right) \]  
(33)

where \( \Phi^f = N^f^T \phi = D^f^T \Phi^c \)  
(34)

and \( \Phi^r = N^r^T \phi = D^r^T \Phi^c \)  
(35)
Using Equation (30), (33) becomes:

\[ v = \kappa \cdot \left( \frac{\text{Exp} D_f^T \Phi^c}{\phi_N} - \frac{\text{Exp} D_r^T \Phi^c}{\phi_N} \right) \quad (36) \]

Because the matrices \( D_f^T \) and \( D_r^T \) are simply selecting the appropriate complexes for each reaction, each row has exactly one unit element and the rest zero. Hence Equation (36) becomes:

\[ v = \kappa \cdot \left( D_f^T \text{Exp} \Phi^c - D_r^T \text{Exp} \Phi^c \right) / \phi_N \]

\[ = -\kappa \cdot D^T \text{Exp} \Phi^c \quad (37) \]

Using Equation (32) Equation (37) becomes:

\[ v = K^v X = K^v \text{Exp} \left( Z^T \ln x \right) \quad (38) \]

where \( K^v = -\kappa \cdot \left( D^T \text{diag} K^c \right) \quad (39) \)

Hence the system state equation for mass action kinetics is:

\[ \dot{x} = ZDK^v X \]

\[ = NK^v X \]

\[ = NK^v \text{Exp} \left( Z^T \ln x \right) \quad (40) \]

This is essentially Equation (4) of van der Schaft et al. [20]. Note that the term \( \text{Exp} \left( Z^T \ln x \right) \) appearing in equations (38) and (40) is, in general, nonlinear. As will be seen in the following section, this term leads to products of species states.

### 4.3 Example: \( A + E \rightleftharpoons C \rightleftharpoons B + E \) (continued)

Substituting the numerical values from the example of § 2 into Equation (31):

\[ K^c = \text{Exp} \left( Z^T \ln K^s \right) \]

\[ = \text{Exp} \left( \begin{pmatrix} 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{pmatrix} \right) \begin{pmatrix} \ln K^s_A \\ \ln K^s_B \\ \ln K^s_C \\ \ln K^s_E \end{pmatrix} \]

\[ = \text{Exp} \begin{pmatrix} \ln K^s_A + \ln K^s_E \\ \ln K^s_B \\ \ln K^s_C \end{pmatrix} \begin{pmatrix} K^s_A K^s_E \\ K^s_B K^s_C \\ K^s_C K^s_E \end{pmatrix} \quad (41) \]
Similarly:

\[
X = \begin{pmatrix}
    x_A x_E \\
    x_C \\
    x_B x_E
\end{pmatrix}
\]  

Substituting the numerical values from the example of § 2 into Equation (39)

\[
K^v = -\kappa \cdot (D^T \text{diag} K^e)
\]

\[
= -\kappa \cdot \begin{pmatrix}
    -1 & 1 & 0 \\
    0 & -1 & 1
\end{pmatrix} \text{diag} K^e
\]

\[
= \begin{pmatrix}
    \kappa_1 K^*_A K^*_E & -\kappa_1 K^*_C \\
    0 & \kappa_2 K^*_C & -\kappa_2 K^*_B K^*_E
\end{pmatrix}
\]  

Hence, using (38)

\[
v = K^v X = \begin{pmatrix}
    \kappa_1 (K^*_A K^*_E x_A x_E - K^*_C x_C) \\
    \kappa_2 (K^*_C x_C - K^*_B K^*_E x_B x_E)
\end{pmatrix}
\]  

4.4 Example: Transporter

The seminal book “Free energy transduction and biochemical cycle kinetics” of Hill [33] contains an example of a membrane transporter which is discussed in detail by Gawthrop and Crampin [11]. The bond graph is given in Figure 4(a) and the bond graph redrawn to expose the complexes is given in Figure 4(b); the ten bonds corresponding to the ten complex efforts \( \Phi^c \) and flows \( v^c \) are highlighted.

The ten complexes are: E, Mi + E, EM, Li + EM, LEM, Lo + EsM, EsM, Mo + Es and Es. They are connected by the seven reactions em, lem, lesm, esm, es, e and slip. The corresponding digraph (plotted using graphviz [30]) appears in Figure 6(a).

4.5 Michaelis-Menten Kinetics

Enzyme-catalysed reactions such as (1), § 2 can be approximated to give Michaelis-Menten kinetics. In particular, in the bond graph context, Gawthrop and Crampin [9] show that the two reactions of (1), generalised to allow multiple products and reactants, can be replaced by a single reaction with equivalent rate-constant \( \kappa_e \) given in terms of the rate
Figure 4: Example: Transporter [33]. (a) The bond graph without explicit representation of complexes [11]. (b) The ten complexes correspond to the ten highlighted bonds. The junction structure connecting the ten highlighted bonds to the species corresponds to $TF:Z$ of Figure 2(b) and the junction structure connecting the reaction $Re$ components to the ten highlighted bonds corresponds to $TF:D^f$ and $TF:D^r$ of Figure 2(b).
constants $\kappa_1$ and $\kappa_2$ of the reactions $r_1$ and $r_2$ as

$$\kappa_e = \frac{e_0 K_c}{k_m + \sigma_v}$$  \hspace{1cm} (45)

where $k_m = \frac{K_c}{K_e}$ \hspace{1cm} (46)

$$\bar{\kappa} = \frac{\kappa_1 \kappa_2}{\kappa_1 + \kappa_2}$$ \hspace{1cm} (47)

and $\sigma_v = \begin{cases} \exp \frac{\Phi_f}{RT} + \exp \frac{\Phi_r}{RT} & \kappa_1 = \kappa_2 \\ \exp \frac{\Phi_f^2}{RT} & \kappa_1 \gg \kappa_2 \end{cases}$ \hspace{1cm} (48)

where $\Phi_f$ and $\Phi_r$ are the overall forward and reverse reaction potentials and $e_0$ is the total amount of enzyme both free and bound to C. In particular, in the case of the reactions of (1):

$$\sigma_v = \begin{cases} \frac{K_A x_A + K_B x_B}{2} & \kappa_1 = \kappa_2 \\ K_A x_A & \kappa_1 \gg \kappa_2 \end{cases}$$ \hspace{1cm} (49)

When dealing with networks of enzyme catalysed reactions such as (1) there are two choices: either explicitly model the intermediate species C and use two reactions with constant values of $\kappa$ or use a single reaction approximation without intermediate species C and an equivalent rate-constant $\kappa_e$ which is a function of the species states $x$.

However, as discussed by Gunawardena [34], this approximation should be used with care to avoid violating the fundamental laws of thermodynamics. For example, when modelling networks such as the mitogen-activated protein kinase (MAPK) cascade where enzymes compete and are themselves reaction products, it has been argued [35, §9.5] that the mass-action approach is preferable. This discussed in detail by Gawthrop and Crampin [10].

Nevertheless, the bond graph representation of chemical reaction networks used in this paper, although developed in the context of mass-action kinetics, can equally be applied to systems approximated using Michaelis-Menten kinetics. The difference is that the rate constant $\kappa$ is replaced by an expression $\kappa_e(x)$ dependent on species states $x$.

5 Open systems & Chemostats

There are a number of ways of converting closed systems to open systems whilst retaining the basic closed system formulation. Horn and Jackson [14] use the concept of a *zero complex* to act as a generalised source and sink of chemical species and this idea is followed up by van der Schaft et al. [20]. Polettini and Esposito [36] use the concept of a *chemostat* to act as a source and sink of chemical species at fixed concentration and this idea is followed up by Gawthrop and Crampin [10]. The chemostat has three interpretations:
1. one or more species is fixed to give a constant concentration [37]; this implies that an appropriate external flow is applied to balance the internal flow of the species.

2. an ideal feedback controller is applied to species to be fixed with setpoint as the fixed concentration and control signal an external flow.

3. as a C component with a fixed state.

The chemostat approach is used here.

As discussed by Gawthrop and Crampin [10], for each species set to be a chemostat, the corresponding row in the stoichiometric matrix $N$ is replaced by a zero vector to form the chemodynamic stoichiometric matrix $N^{cd}$. Using the same motivation as that leading to equation (7), $N^{cd}$ is written as:

$$N^{cd} = Z^{cd}D^{cd} \tag{50}$$

In this case, the closed-system equations (16)–(19) are replaced by

$$\dot{x} = Z^{cd}v^c \tag{51}$$
$$\phi^c = Z^T\phi \tag{52}$$
$$v^c = v^{cr} - v^{cf} = D^{cd}v \tag{53}$$
$$\Phi = \Phi_f - \Phi_r = D_f^T\phi^c - D_r^T\phi^c \tag{54}$$

Note that it is the flow equations (51) and (53) that are changed; the potential equations (52) and (54) remain the same as those for the closed system (17) and (19). In particular, some complexes associated with $Z$ and $D$, and thus the potential equations (52) and (54) are not associated with $Z^{cd}$ and $D^{cd}$, and thus the flow equations (51) and (53). Hence the digraph associated with $D^{cd}$ does not necessarily contain all of the complex nodes associated with $D$.

5.1 Example: A + E ⇔ C ⇔ B + E (continued)

Figure 5: Digraph corresponding to the $D^{cd}$ matrix (56) for the system A + E ⇔ C ⇔ B + E of § 2 and § 3. Compared to Figure 1, setting the species A and B to be chemostats reduces the number of complexes to two and the digraph is cyclic.
In the case of the system \( A + E \xrightarrow{r_1} C \xrightarrow{r_2} B + E \) and choosing the two species \( A \) and \( B \) to be chemostats, equation (3) is replaced by:

\[
\dot{x} = N^{cd}v \quad \text{where} \quad N^{cd} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ 1 & -1 \\ -1 & 1 \end{pmatrix} \tag{55}
\]

Thus the two chemostats have constant state \( x_A \) and \( x_B \). The decomposition of Equation (50) gives:

\[
Z^{cd} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 1 \\ 1 & 0 \end{pmatrix} D^{cd} = \begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix} \tag{56}
\]

The digraph corresponding to \( D^{cd} \) is given in Figure 5; this corresponds to the flow equations (51) and (53). On the other hand, the digraph corresponding to \( D \) is given in Figure 1; this corresponds to the potential equations (52) and (54). Thus the cyclic flow associated with the digraph of Figure 5 is driven by the potentials associated with the digraph of Figure 1.

5.2 Example: Transporter (continued)

The closed system digraph, corresponding to \( D \) and the potential equations of the open system, is given in Figure 6(a).

As discussed by [11], the open system is created by choosing the four species: \( Li, Lo, Mi \) and \( Mo \) to be chemostats. The flow digraph with incidence matrix \( D^{cd} \) of Figure 6(b) has six nodes corresponding to the complexes: \( E, EM, LEM, LEsM, EsM \) and \( Es \). This digraph still has the seven connecting reactions listed in § 4.4.

The cyclic flow associated with the digraph of Figure 6(b) is driven by the potentials associated with the digraph of Figure 6(a).
Figure 6: Digraphs corresponding to the $D$ matrix (18) for the closed and open systems for the transporter system. (a) The ten nodes corresponding to the ten complexes are connected by three disjoint linear graphs. (b) The four chemostats reduce the number of complexes to six and the corresponding six nodes are connected by a cyclic digraph.
6 Conclusion

The complex approach to modelling chemical reaction networks as introduced by Feinberg [13], Horn and Jackson [14] and Feinberg and Horn [15] and expanded by van der Schaft et al. [18, 19, 20, 28] has been given a bond graph interpretation thus enabling results from the complex approach to be applied to the bond graph approach and vice versa. In particular, the decomposition of the stoichiometric matrix $N$ into the complex composition matrix [20] $Z$ and the complex graph incidence matrix $D$ (where $N = ZD$) is given a bond graph interpretation.

The approach is developed for closed systems, but extended to open systems via the previously developed notion of chemostats [10, 36]. The corresponding chemodynamic stoichiometric matrix $N^{cd}$ [10] is decomposed into the chemodynamic complex composition matrix $Z^{cd}$ and the chemodynamic complex graph incidence matrix $D^{cd}$ (where $N^{cd} = Z^{cd}D^{cd}$). The complex graph incidence matrix $D$ determines both the flow and potential of closed systems, but in open systems the flow is determined by $D^{cd}$ and the potential by $D$. As, in general $D^{cd} \neq D$, the digraph for the flow of open systems is not the same as the digraph for potentials. In particular, with reference to Figure 6, the flow and potential digraphs for open systems may be structurally different.

The combination of the explicit energy-compliance feature of the bond graph modelling approach with the generic results of the graph-theory based chemical reaction network approach will, it is hoped, lead to new results and methods for the analysis and synthesis of biomolecular systems.

7 Acknowledgements

Peter Gawthrop would like to thank the Melbourne School of Engineering for its support via a Professorial Fellowship. This research was in part conducted and funded by the Australian Research Council Centre of Excellence in Convergent Bio-Nano Science and Technology (project number CE140100036). The authors would like to thank Ivo Siekmann for alerting them to references [18–20] and the anonymous reviewers for helpful comments on the manuscript.

References

[1] H. M. Paynter. Analysis and design of engineering systems. MIT Press, Cambridge, Mass., 1961. 3

[2] F. E. Cellier. Continuous system modelling. Springer-Verlag, 1991.

[3] P. J. Gawthrop and L. P. S. Smith. Metamodelling: Bond Graphs and Dynamic Systems. Prentice Hall, Hemel Hempstead, Herts, England., 1996. ISBN 0-13-489824-9.
[4] Peter J Gawthrop and Geraint P Bevan. Bond-graph modeling: A tutorial introduction for control engineers. *IEEE Control Systems Magazine*, 27(2):24–45, April 2007. doi:10.1109/MCS.2007.338279.

[5] Wolfgang Borutzky. *Bond graph methodology: development and analysis of multidisciplinary dynamic system models*. Springer, Berlin, 2010. ISBN 978-1-84882-881-0. doi:10.1007/978-1-84882-882-7.

[6] Dean C Karnopp, Donald L Margolis, and Ronald C Rosenberg. *System Dynamics: Modeling, Simulation, and Control of Mechatronic Systems*. John Wiley & Sons, 5th edition, 2012. ISBN 978-0470889084. 3

[7] George Oster, Alan Perelson, and Aharon Katchalsky. Network thermodynamics. *Nature*, 234:393–399, December 1971. doi:10.1038/234393a0. 3

[8] George F. Oster, Alan S. Perelson, and Aharon Katchalsky. Network thermodynamics: dynamic modelling of biophysical systems. *Quarterly Reviews of Biophysics*, 6(01):1–134, 1973. doi:10.1017/S0033583500000081. 3, 9

[9] Peter J. Gawthrop and Edmund J. Crampin. Energy-based analysis of biochemical cycles using bond graphs. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Science*, 470(2171):1–25, 2014. doi:10.1098/rspa.2014.0459. Available at arXiv:1406.2447. 3, 5, 6, 7, 9, 11

[10] P. J. Gawthrop and E. J. Crampin. Modular bond-graph modelling and analysis of biomolecular systems. *IET Systems Biology*, 10(5):187–201, October 2016. ISSN 1751-8849. doi:10.1049/iet-syb.2015.0083. Available at arXiv:1511.06482. 3, 6, 7, 13, 14, 17

[11] Peter J. Gawthrop and Edmund J. Crampin. Energy-based analysis of biomolecular pathways. *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, 473(2202), 2017. ISSN 1364-5021. doi:10.1098/rspa.2016.0825. Available at arXiv:1611.02332. 3, 6, 7, 11, 12, 15

[12] G. Oster and A. Perelson. Chemical reaction networks. *Circuits and Systems, IEEE Transactions on*, 21(6):709 – 721, November 1974. ISSN 0098-4094. doi:10.1109/TCS.1974.1083946. 3

[13] Martin Feinberg. On chemical kinetics of a certain class. *Archive for Rational Mechanics and Analysis*, 46(1):1–41, 1972. ISSN 0003-9527. doi:10.1007/BF00251866. 3, 17

[14] F. Horn and R. Jackson. General mass action kinetics. *Archive for Rational Mechanics and Analysis*, 47(2):81–116, Jan 1972. ISSN 1432-0673. doi:10.1007/BF00251225. 3, 13, 17

18
[15] Martin Feinberg and Friedrich J.M. Horn. Dynamics of open chemical systems and the algebraic structure of the underlying reaction network. *Chemical Engineering Science*, 29(3):775 – 787, 1974. ISSN 0009-2509. doi:10.1016/0009-2509(74)80195-8. 3, 17

[16] E.D. Sontag. Molecular systems biology and control. *European Journal of Control*, 11:1–40, 2006. 3

[17] David Angeli. A tutorial on chemical reaction network dynamics. *European Journal of Control*, 15(34):398 – 406, 2009. ISSN 0947-3580. doi:http://dx.doi.org/10.3166/ejc.15.398-406. 3

[18] A. van der Schaft, S. Rao, and B. Jayawardhana. On the mathematical structure of balanced chemical reaction networks governed by mass action kinetics. *SIAM Journal on Applied Mathematics*, 73(2):953–973, 2013. doi:10.1137/11085431X. 3, 17

[19] Arjan van der Schaft, Shodhan Rao, and Bayu Jayawardhana. Complex and detailed balancing of chemical reaction networks revisited. *Journal of Mathematical Chemistry*, 53(6):1445–1458, Jun 2015. ISSN 1572-8897. doi:10.1007/s10910-015-0498-2. 3, 17

[20] A. J. van der Schaft, S. Rao, and B. Jayawardhana. A network dynamics approach to chemical reaction networks. *International Journal of Control*, 89(4):731–745, 2016. doi:10.1080/00207179.2015.1095353. 3, 8, 10, 13, 17

[21] Carsten Conradi, Dietrich Flockerzi, Jörg Raisch, and Jörg Stelling. Subnetwork analysis reveals dynamic features of complex (bio) chemical networks. *Proceedings of the National Academy of Sciences*, 104(49):19175–19180, 2007. doi:10.1073/pnas.0705731104. 3

[22] M. Polettini, A. Wachtel, and M. Esposito. Dissipation in noisy chemical networks: The role of deficiency. *The Journal of Chemical Physics*, 143(18):184103, 2015. doi:10.1063/1.4935064. 3

[23] Oleksandr Ivanov, Arjan van der Schaft, and Franz J. Weissing. Steady states and stability in metabolic networks without regulation. *Journal of Theoretical Biology*, 401:78 – 93, 2016. ISSN 0022-5193. doi:10.1016/j.jtbi.2016.02.031. 3

[24] Irene Otero-Muras, Pencho Yordanov, and Joerg Stelling. Chemical reaction network theory elucidates sources of multistability in interferon signaling. *PLOS Computational Biology*, 13(4):1–28, 04 2017. doi:10.1371/journal.pcbi.1005454. 3

[25] G. Golo, A.J. van der Schaft, P.C. Breedveld, and B.M. Maschke. Hamiltonian formulation of bond graphs. In R. Johansson and A. Rantzer, editors, *Nonlinear and Hybrid Systems in Automotive Control*, pages 351–372. Springer, London, 2003. 3

[26] D. Vink, D. Ballance, and P. Gawthrop. Bond graphs in model matching control. *Mathematical and Computer Modelling of Dynamical Systems*, 12(2-3):249 – 261, 2006. doi:10.1080/13873950500068278.
[27] Alejandro Donaire and Sergio Junco. Derivation of input-state-output port-Hamiltonian systems from bond graphs. *Simulation Modelling Practice and Theory*, 17(1):137 – 151, 2009. ISSN 1569-190X. doi:10.1016/j.simpat.2008.02.007. Bond Graph Modelling.

[28] A.J. van der Schaft, S. Rao, and B. Jayawardhana. On the network thermodynamics of mass action chemical reaction networks. *IFAC Proceedings Volumes*, 46(14):24 – 29, 2013. ISSN 1474-6670. doi:10.3182/20130714-3-FR-4040.00001. 1st IFAC Workshop on Thermodynamic Foundations of Mathematical Systems Theory.

[29] James P Keener and James Sneyd. *Mathematical Physiology: I: Cellular Physiology*, volume 1. Springer, 2nd edition, 2009.

[30] Emden R. Gansner and Stephen C. North. An open graph visualization system and its applications to software engineering. *SOFTWARE - PRACTICE AND EXPERIENCE*, 30(11):1203–1233, 2000.

[31] P. J. Gawthrop. Bond graph modeling of chemiosmotic biomolecular energy transduction. *IEEE Transactions on NanoBioscience*, 16(3):177–188, April 2017. ISSN 1536-1241. doi:10.1109/TNB.2017.2674683. Available at arXiv:1611.04264.

[32] Pierre Van Rysselberghe. Reaction rates and affinities. *The Journal of Chemical Physics*, 29(3):640–642, 1958. doi:10.1063/1.1744552.

[33] Terrell L Hill. *Free energy transduction and biochemical cycle kinetics*. Springer-Verlag, New York, 1989.

[34] Jeremy Gunawardena. Time-scale separation – Michaelis and Menten’s old idea, still bearing fruit. *FEBS Journal*, 281(2):473–488, 2014. ISSN 1742-4658. doi:10.1111/febs.12532.

[35] Eberhard O. Voit. *A First Course in Systems Biology*. Garland Science, New York and London, 2013.

[36] Matteo Polettini and Massimiliano Esposito. Irreversible thermodynamics of open chemical networks. I. Emergent cycles and broken conservation laws. *The Journal of Chemical Physics*, 141(2):024117, 2014. doi:10.1063/1.4886396.

[37] Peter J. Gawthrop, Joseph Cursons, and Edmund J. Crampin. Hierarchical bond graph modelling of biochemical networks. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 471(2184):1–23, 2015. ISSN 1364-5021. doi:10.1098/rspa.2015.0642. Available at arXiv:1503.01814.