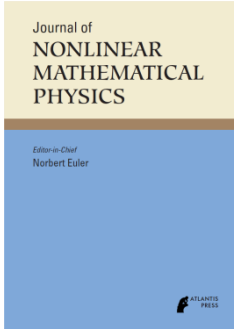

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NAMBU BRACKET FORMULATION OF NONLINEAR BIOCHEMICAL REACTIONS BEYOND ELEMENTARY MASS ACTION KINETICS

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We develop a Nambu bracket formulation for a wide class of nonlinear biochemical reactions by exploiting previous work that focused on elementary biochemical mass action reactions. To this end, we consider general reaction mechanisms including for example enzyme kinetics. Furthermore, we go beyond elementary reactions and account for reactions involving stoichiometric coefficients different from unity. In particular, we show that the stoichiometric matrix of biochemical reactions can be expressed in terms of Nambu brackets. Finally, we solve the sign problem that arises in the context of coupled biochemical reactions.

Keywords: Nambu brackets; biochemical reactions; stoichiometric matrix.

1. Introduction

Nambu mechanics generalizes Hamiltonian mechanics to N-dimensional dynamical systems that involve $N-1$ integrals of motion [18]. Let $\mathbf{x} = (x_1, \ldots, x_N)^T$ denote the (column) state vector of a system of interest and $W_1(\mathbf{x}), \ldots, W_{N-1}(\mathbf{x})$ correspond to the invariants of motion. Then, Nambu mechanics describes dynamical systems that evolve like [18]

$$\frac{\mathrm{d}}{\mathrm{d}t} x_k(t) = \sum_{i_2,\ldots,i_N=1}^{N} \epsilon_{k,i_2,\ldots,i_N} \frac{\partial W_1}{\partial x_{i_2}} \cdots \frac{\partial W_{N-1}}{\partial x_{i_N}}, \quad k = 1, \ldots, N, \tag{1.1}$$

where $\epsilon_{i_1,\ldots,i_N}$ is the N-dimensional epsilon tensor (Levi-Civita tensor) and t denotes time. In order to cast Eq. (1.1) into a concise form, the Nambu bracket $\{\cdot\}$ can be used that is defined by

$$\{f_1, \ldots, f_N\} = \sum_{i_1,\ldots,i_N=1}^{N} \epsilon_{i_1,\ldots,i_N} \frac{\partial f_1}{\partial x_{i_1}} \frac{\partial f_2}{\partial x_{i_2}} \cdots \frac{\partial f_N}{\partial x_{i_N}}, \tag{1.2}$$

for a set of functions $f_i(\mathbf{x})$ with $i = 1, \ldots, N$. Note that the Nambu bracket (1.2) generalizes the Poisson bracket to the N-dimensional case. Using Eq. (1.1), the Nambu dynamics (1.1) can be equivalently expressed by

$$\frac{\mathrm{d}}{\mathrm{d}t} x_k(t) = \{x_k, W_1, \ldots, W_{N-1}\} \tag{1.3}$$

for $k = 1, \ldots, N$, which can be written as vector-valued evolution equation like

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x}(t) = \{\mathbf{x}, W_1, \ldots, W_{N-1}\} = \sum_{i_1,\ldots,i_N=1}^{N} \epsilon_{i_1,\ldots,i_N} \left[\frac{\partial}{\partial x_{i_1}} \begin{pmatrix} x_1 \\ \vdots \\ x_N \end{pmatrix}\right] \frac{\partial W_1}{\partial x_{i_2}} \cdots \frac{\partial W_{N-1}}{\partial x_{i_N}}. \tag{1.4}$$

Nambu mechanics has found various applications in classical physics. Rigid body rotations have been studied from a Nambu perspective equations [9, 18, 21, 23, 25, 27, 29]. Particles moving on two-spheres [2, 5, 6, 8, 33] can be described in terms of Eq. (1.1). Nambu mechanics has been used to examine certain electrodynamic problems [4, 14, 22, 24, 27, 32]. Importantly, the Kepler problem is another benchmark Nambu system [3]. Chiral models [5] as well as the Calogero–Moser system [12, 30] have been investigated. Hydrodynamic problems have been examined [13]. Oscillatory systems such as elliptic oscillators [15, 31], multi-oscillators [3, 20], and other types of oscillators [4, 22] have been studied in the context of Nambu mechanics. Likewise, the motion of a free particle from a Nambu perspective has been examined [4, 22]. Perturbation theoretical calculations of energy levels exploiting Nambu mechanics have been developed [27]. Finally, it has been shown that Nambu mechanics just as Hamiltonian mechanics can be generalized to address so-called canonical-dissipative systems [8, 9] (see also [7, 10, 26]).

Recently, a formulation of biochemical reactions satisfying mass action kinetics in terms of Nambu brackets has been developed [11]. However, this study was rather limited in scope. Therefore, we generalize the Nambu approach to biochemical reaction dynamics to account for more general reaction mechanisms including for example enzyme kinetics. Second, while in [11] only elementary reactions with stoichiometric coefficients equal to unity were considered, we will in what follows consider stoichiometric coefficients different from unity. Most importantly, we will establish a link between Nambu brackets and the stoichiometric matrix of biochemical reactions. This link has not been pointed out in previous works. Finally, we will consider coupled biochemical reactions just as in [11]. By introducing a re-sorting operator we will solve the sign problem that arises in this context and has not been addressed so far.

2. Nambu Bracket Formulation of General Nonlinear Biochemical Reaction Models

We consider a reaction in which L reactants $A_1, \ldots, A_L$ (molecules, macromolecules, components, etc.) produce R products $B_1, \ldots, B_R$ such that the reaction involves $N = L + R$ species. In general, we consider the reversible case that allows for both forward and backward

reactions such that [28]

$$\sum_{i=1}^{L} l_i A_i \leftrightarrow \sum_{k=1}^{R} r_k B_k, \tag{2.1}$$

where $l_i, r_k \in \{1, 2, \ldots\}$ are stoichiometric coefficients different from zero. Let $a_i(t), b_k(t)$ denote the time-dependent concentrations of the reactants and products, respectively. Let $\mathbf{x}(t) = (a_1, \ldots, a_L, b_1, \ldots, b_R)^T$ denote the (column) state vector of the biochemical reaction (2.1). The forward reaction (left to right) occurs with the forward rate $v_f(\mathbf{x})$, while the reverse reaction (right to left) can be observed with the backward rate $v_b(\mathbf{x})$. In general, these rates are nonlinear functions in $\mathbf{x}$. The reaction model (2.1) includes irreversible reactions of the form $\sum_{i=1}^{L} l_i A_i \to \sum_{k=1}^{R} r_k B_k$ as special case. In this case, we have $v_b = 0$. The reaction rate v in general is defined by $v(\mathbf{x}) = v_f(\mathbf{x}) - v_b(\mathbf{x})$. The evolution equation of the state vector $\mathbf{x}$ is given by the nonlinear first-order differential equation [28]

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x}(t) = v(\mathbf{x})\,\mathbf{s}, \tag{2.2}$$

where $\mathbf{s}$ denotes the time-independent stoichiometric vector $\mathbf{s} = (-l_1, \ldots, -l_L, r_1, \ldots, r_R)^T$. For biochemical reactions satisfying mass action kinetics the forward and backward rates read

$$v_f(\mathbf{x}) = k_f \prod_{i=1}^{L} a_i^{l_i}, \quad v_b(\mathbf{x}) = k_b \prod_{k=1}^{R} b_k^{r_k}, \tag{2.3}$$

with reaction coefficients $k_f, k_b \geq 0$. In [11] only elementary reactions with $l_i = 1, r_k = 1\ \forall\, i, k$ were considered. Furthermore, [11] was restricted to address mass action kinetics involving reactions rates of the form (2.3). In this context, it was shown that Eqs. (2.2) and (2.3) can be expressed using Nambu brackets that involve the $N-1$ invariants $H_i = b_1 + a_i$ with $i = 1, \ldots, L$ and $H_{L-1+k} = a_1 + b_k$ with $k = 2, \ldots, R$. More precisely, it was shown that Eqs. (2.2) and (2.3) can be written like

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x}(t) = (-1)^{L+1}\omega(\mathbf{x})\,\{\mathbf{x}, H_1, \ldots, H_{N-1}\}, \tag{2.4}$$

with $\omega(\mathbf{x}) = k_b \prod_{k=1}^{R} b_k - k_f \prod_{i=1}^{L} a_i$.

Our objective is to generalize this result to reactions that involve stoichiometric coefficients different from unity and to reaction models that do not necessarily satisfy mass action kinetics. To this end, we first link the Nambu bracket with the stoichiometric vector $\mathbf{s}$. From Eq. (28) in [11] it follows that for elementary reactions (i.e., $l_i = 1, r_k = 1\ \forall i, k$) we have

$$\mathbf{s} = (-1)^L \{\mathbf{x}, H_1, \ldots, H_{N-1}\}. \tag{2.5}$$

Note that alternatively we arrive at Eq. (2.5) by comparing Eq. (2.4) with Eq. (2.2) taking into account that $v = -\omega$. Next, we consider the invariants $h_1, \ldots, h_{N-1}$ defined by

$$\begin{aligned} h_i(\mathbf{x}) &= -\left(\frac{b_1}{r_1} + \frac{a_i}{l_i}\right), \quad i = 1, \ldots, L, \\ h_{L-1+k}(\mathbf{x}) &= \frac{a_1}{l_1} + \frac{b_k}{r_k}, \quad k = 2, \ldots, R, \end{aligned} \tag{2.6}$$

which reduce to the previously proposed invariants H_j in the case of elementary reactions except for the minus sign for $j = 1, \ldots, L$. For $l_i = 1, r_k = 1\ \forall\, i, k$ it follows that

$$\{\mathbf{x}, h_1, \ldots, h_{N-1}\} = (-1)^L \{\mathbf{x}, H_1, \ldots, H_{N-1}\} = \mathbf{s}. \tag{2.7}$$

Consequently, the minus sign in the first L invariants $h_1, \ldots, h_L$ is used to eliminate the factor $(-1)^L$ used in [11]. Next, let us consider the general case $l_i, r_k \in \{1, 2, \ldots\}$.

Theorem 2.1. *The stoichiometric vector* $\mathbf{s}$ *of the biochemical reaction* (2.1) *can be defined in terms of the Nambu bracket* (1.2) *and the invariants* (2.6) *like*

$$\mathbf{s} = \left(\prod_{i=1}^{L} l_i \prod_{k=1}^{R} r_k\right) \{\mathbf{x}, h_1, \ldots, h_{N-1}\}. \tag{2.8}$$

Proof. For $l_i = 1, r_k = 1\ \forall\, i, k$ from Eq. (2.7) it follows that

$$\{\mathbf{x}, h_1, \ldots, h_{N-1}\} = (\underbrace{-1, \ldots, -1}_{L\,\text{times}}, \underbrace{1, \ldots, 1}_{R\,\text{times}})^T. \tag{2.9}$$

Furthermore, the wth component of the Nambu bracket under consideration is explicitly given by

$$\{x_w, h_1, \ldots, h_{N-1}\} = \sum_{i_2, \ldots, i_N = 1}^{N} \epsilon_{w, i_2, \ldots, i_N} \frac{\partial h_1}{\partial x_{i_2}} \cdots \frac{\partial h_{N-1}}{\partial x_{i_N}}. \tag{2.10}$$

For elementary reactions (i.e., $l_i = 1, r_k = 1\ \forall\, i, k$) it has been shown that there is only one term of the sum on the right-hand side of Eq. (2.10) that is different from zero. This term is either plus or minus one. When we admit for coefficients $l_i, r_k \in \{1, 2, \ldots\}$ then this does not affect the first-mentioned property of the sum. There is again only one term that is different from zero. Moreover, the integer values $l_i, r_k \in \{1, 2, \ldots\}$ do not affect the sign of the non-vanishing term, which implies $\{x_w, h_1, \ldots, h_{N-1}\} < 0$ for $w \in \{1, \ldots, L\}$ and $\{x_w, h_1, \ldots, h_{N-1}\} > 0$ for $w \in \{L+1, \ldots, N\}$. By definition of the epsilon tensor, the non-vanishing term involves partial derivatives $\partial/\partial x_{i_k}$ of all coordinates $x_1, \ldots, x_N$ except for x_w and each partial derivative occurs in the non-vanishing term only once. By definition of the invariants, see Eq. (2.6), each partial derivative $\partial/\partial x_{i_k}$ produces either a factor $1/l_{i_k}$ if $i_k \in \{1, \ldots, L\}$ or a factor $1/r_{i_k}$ if $i_k \in \{L+1, \ldots, N\}$. In short, we conclude that

$$\sum_{i_2, \ldots, i_N = 1}^{N} \epsilon_{w, i_2, \ldots, i_N} \frac{\partial h_1}{\partial x_{i_2}} \cdots \frac{\partial h_{N-1}}{\partial x_{i_N}} = \begin{cases} -\displaystyle\prod_{i=1, i \neq w}^{L} l_i^{-1} \prod_{k=1}^{R} r_k^{-1} & \text{for } w \in \{1, \ldots, L\}, \\ \displaystyle\prod_{i=1}^{L} l_i^{-1} \prod_{k=1, k \neq w}^{R} r_k^{-1} & \text{for } w \in \{L+1, \ldots, N\}. \end{cases} \tag{2.11}$$

From Eq. (2.11) it follows that

$$\left(\prod_{i=1}^{L} l_i \prod_{k=1}^{R} r_k\right) \{\mathbf{x}, h_1, \ldots, h_{N-1}\} = (-l_1, \ldots, l_L, r_1, \ldots, r_R)^T = \mathbf{s}. \tag{2.12}$$

□

Let us illustrate Theorem 2.1 for the chemical reaction

$$\mathrm{N_2} + 3\mathrm{H_2} \to 2\mathrm{NH_3}, \tag{2.13}$$

with stoichiometric coefficients $l_1 = 1$, $l_2 = 3$, and $r_1 = 2$. Let $\mathbf{x} = (a_1, a_2, b_1)$ with the concentrations $a_1 = [\mathrm{N_2}]$, $a_2 = [\mathrm{H_2}]$, $b_1 = [\mathrm{NH_3}]$. The invariants (2.6) read

$$h_1(\mathbf{x}) = -\left(\frac{b_1}{2} + a_1\right), \quad h_2(\mathbf{x}) = -\left(\frac{b_1}{2} + \frac{a_2}{3}\right). \tag{2.14}$$

We calculate $\{\mathbf{x}, h_1, h_2\}$ by means of the identity $\{\mathbf{x}, h_1, h_2\} = \nabla h_1 \times \nabla h_2$, where ∇ denotes the nabla operator $\nabla = (\partial/\partial a_1, \partial/\partial a_2, \partial/\partial b_1)$. We obtain

$$\nabla h_1 = \begin{pmatrix} -1 \\ 0 \\ -1/2 \end{pmatrix}, \quad \nabla h_2 = \begin{pmatrix} 0 \\ -1/3 \\ -1/2 \end{pmatrix}, \quad \nabla h_1 \times \nabla h_2 = \begin{pmatrix} -1/6 \\ -1/2 \\ 1/3 \end{pmatrix}. \tag{2.15}$$

We have

$$\mathbf{s} = l_1 l_2 r_1 \{\mathbf{x}, h_1, h_2\} = \begin{pmatrix} -1 \\ -3 \\ 2 \end{pmatrix}, \tag{2.16}$$

which is the stoichiometric vector of the chemical reaction (2.13). For sake of completeness, we note that the chemical reaction (2.13) is irreversible and satisfies mass action kinetics. Consequently, we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t} \begin{pmatrix} a_1 \\ a_2 \\ b_1 \end{pmatrix} = k_f\, a_1\, a_2^3 \begin{pmatrix} -1 \\ -3 \\ 2 \end{pmatrix}, \tag{2.17}$$

with $k_f > 0$.

Corollary 2.1. *The dynamical system* (2.2) *describing the biochemical reaction* (2.1) *can be formulated in terms of a Nambu bracket like*

$$\frac{d}{dt}\mathbf{x}(t) = (v_f(\mathbf{x}) - v_b(\mathbf{x})) \left(\prod_{i=1}^{L} l_i \prod_{k=1}^{R} r_k\right) \{\mathbf{x}, h_1(\mathbf{x}), \ldots, h_{N-1}(\mathbf{x})\}. \tag{2.18}$$

This formulation applies to general reaction models and is not restricted to reactions satisfying mass action kinetics.

The corollary follows directly from Theorem 2.1 and from the observation that the Nambu bracket $\{\mathbf{x}, h_1, \ldots, h_N\}$ is related to the stoichiometric vector of the reaction (2.1). Consequently, the Nambu bracket $\{\mathbf{x}, h_1, \ldots, h_N\}$ is not linked to reaction velocity as such. That is, it is not related to forward and backward reaction rates. This point was not adequately observed in [11].

Let us illustrate this issue by means of a reversible reaction between the passive A and active B form of a biochemical transcription factor [1]. In sensory transcription networks, so-called transcription factors exhibit two forms: an active and a passive form. Typically,

under baseline conditions, transcription factors are in their passive form. Input signals result in a transformation of the passive form into the active form. The concentration of the active form depends in a sigmoid function on the strength of the input signal [1]. Typically this is due to the fact that the reaction $A \leftrightarrow B$ is an enzyme reaction. Consequently, v_f and v_b exhibit a particular form predicted by the Michaelis–Menten theory of enzyme reactions [19] and are not described by the law of mass action kinetics. For example, the biochemical reaction between active and passive forms of the transcription factor CREB can formally be described by

$$\mathrm{CREB} \leftrightarrow \mathrm{CREB}^*, \tag{2.19}$$

where the star indicates the active form. Let a and b denote the concentrations $a = [\mathrm{CREB}]$ and $b = [\mathrm{CREB}^*]$. The forward rate v_f depends on the time-dependent signal $S(t)$ and the concentration a of the passive form, whereas the backward rate depends only on the concentration b of the active form. We have [17]

$$v_f(\mathbf{x}, S(t)) = V_a\, S(t) \frac{a}{K_a + a}, \quad v_b(\mathbf{x}) = V_b \frac{b}{K_b + b}, \tag{2.20}$$

where $V_a, V_b, K_a, K_b > 0$ are constants and $\mathbf{x} = (a, b)$. Since we have $N = 2$, there is only one invariant, which reads

$$h_1 = -(a + b). \tag{2.21}$$

Using the Nambu bracket approach, the stoichiometric vector is given by

$$\mathbf{s} = \begin{pmatrix} s_a \\ s_b \end{pmatrix} = \{\mathbf{x}, h_1\} = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \begin{pmatrix} \partial h_1/\partial a \\ \partial h_1/\partial b \end{pmatrix} = \begin{pmatrix} \partial h_1/\partial b \\ -\partial h_1/\partial a \end{pmatrix} = \begin{pmatrix} -1 \\ 1 \end{pmatrix}. \tag{2.22}$$

From Corollary 2.1 and Eq. (2.20) it follows that the state vector $\mathbf{x}$ of the signal-dependent enzyme reaction (2.19) satisfies the nonlinear evolution equation

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} &= (v_f(\mathbf{x}, S(t)) - v_b(\mathbf{x}))\{\mathbf{x}, h_1(\mathbf{x})\} \Rightarrow \\ \frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} a \\ b \end{pmatrix} &= \left(V_a\, S(t) \frac{a}{K_a + a} - V_b \frac{b}{K_b + b} \right) \begin{pmatrix} -1 \\ 1 \end{pmatrix}. \end{aligned} \tag{2.23}$$

3. Coupled Biochemical Reaction Equations

We consider next $j = 1, \ldots, M$ coupled biochemical reactions that involve N reactants $X_1, \ldots, X_N$. Note that we do not require that all reactants participate in all reactions. The state vector $\mathbf{x}$ is given by the concentrations $x_i = [X_i]$ such that $\mathbf{x} = (x_1, \ldots, x_N)^T$. Every reaction j is described by a reaction scheme

$$\sum_{i=1}^{N} l_i^{(j)} X_i \leftrightarrow \sum_{i=1}^{N} r_i^{(j)} X_i \tag{3.1}$$

involving the stoichiometric coefficients $l_i^{(j)}, r_i^{(j)} \in \{0, 1, 2, \ldots\}$. Note that if $l_i^{(j)} = r_i^{(j)} = 0$ holds for a particular index i, then the species X_i does not participate in the reaction j.

Each reaction step j exhibits a stoichiometric vector $\mathbf{s}^{(j)}$ defined by

$$\mathbf{s}^{(j)} = \left(r_1^{(j)} - l_1^{(j)}, \ldots, r_N^{(j)} - l_N^{(j)}\right)^T \tag{3.2}$$

and the reaction rate $v_j(\mathbf{x}) = v_f^{(j)}(\mathbf{x}) - v_b^{(j)}(\mathbf{x})$. The change of the state vector due to the jth reaction step is

$$\mathrm{d}_j\,\mathbf{x} = v_j(\mathbf{x})\mathbf{s}^{(j)}\,\mathrm{d}t. \tag{3.3}$$

Accordingly, the total derivative is given by $\mathrm{d}\mathbf{x} = \sum_{j=1}^{M} \mathrm{d}_j\,\mathbf{x}$, which leads us to the evolution equation

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} = (\mathbf{s}^{(1)}, \ldots, \mathbf{s}^{(M)}) \cdot \begin{pmatrix} v_1(\mathbf{x}) \\ \vdots \\ v_M(\mathbf{x}) \end{pmatrix} \tag{3.4}$$

involving the stoichiometric matrix and the vector of reaction velocities as indicated. In [11] a reformulation of Eq. (3.4) in terms of Nambu brackets has been proposed. In this context, we need to distinguish for each reaction step j between the reactants on the left-hand side, the products on the right-hand side, and the non-participating or "silent" molecules. Accordingly, we define the index sets $I_L^{(j)} = \{i \,|\, l_i^{(j)} > 0\}$, $I_R^{(j)} = \{i \,|\, r_i^{(j)} > 0\}$, and $I_S^{(j)} = \{i \,|\, l_i^{(j)} = r_i^{(j)} = 0\}$. Let $|\cdot|$ denote the size of a set. Then, $L^{(j)} = |I_L^{(j)}| \geq 1$, $R^{(j)} = |I_R^{(j)}| \geq 1$, and $S^{(j)} = |I_S^{(j)}| \geq 0$ denote the number of reactants, products, and silent molecules, respectively, for the reaction step j. We have $L^{(j)} + R^{(j)} + S^{(j)} = N \;\forall j \in \{1, \ldots, M\}$. In [11] it has been shown that the invariants of reaction j are those $L^{(j)}+R^{(j)}-1$ invariants that can be constructed from the participating species using the rules discussed in the previous section. In addition, there are $S^{(j)}$ invariants that correspond to the concentrations of the silent species. In doing so, $H_1^{(j)}, \ldots, H_{N-1}^{(j)}$ invariants can be identified for each reaction j. Moreover, the reaction equation (3.4) can be cast into the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} = \sum_{j=1}^{M} (-1)^{L^{(j)}} \omega_j(\mathbf{x})\{\mathbf{x}, H_1^{(j)}, \ldots, H_{N-1}^{(j)}\}, \tag{3.5}$$

with $\omega_j = \pm v_j$. In order to determine whether $\omega_j = v_j$ or $\omega_j = -v_j$ holds it has been suggested to compare separately each term occurring in the sum of Eq. (3.5) with its corresponding single reaction step equation (3.3). In other words, in order to determine the proper sign we need to exploit *a priori* knowledge about the reaction equations under consideration. This is the sign problem to which we referred in the introduction.

In what follows we will show that the sign problem can be solved by considering appropriately defined coordinate systems and by constructing a re-sorting operator that transforms these coordinate systems back into the reference coordinate system defined by the state vector $\mathbf{x}$. Let us define the "adjusted" state vector of the biochemical reaction step j by

$$\mathbf{x}_j^* = (\underbrace{x_{i_1}, \ldots, x_{i_{L^{(j)}}}}_{L^{(j)}\text{ entries}}, \underbrace{x_{p_1}, \ldots, x_{p_{R^{(j)}}}}_{R^{(j)}\text{ entries}}, \underbrace{x_{w_1}, \ldots, x_{w_{S^{(j)}}}}_{S^{(j)}\text{ entries}})^T \tag{3.6}$$

with $i_k \in I_L^{(j)}$, $p_k \in I_R^{(j)}$, and $w_k \in I_S^{(j)}$. The vector $\mathbf{x}_j^*$ defines a coordinate system that is most appropriate for deriving a Nambu bracket for the reaction step j. Let

$$N_j = L^{(j)} + R^{(j)} = N - S^{(j)}. \tag{3.7}$$

The first N_j entries in $\mathbf{x}_j^*$ denote the species participating in the reaction j. Using these species, we define the invariants $h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}$, see Eq. (2.6). In addition, we define the invariants of the silent molecules by

$$h_{S,k}^{(j)} = x_{w_k} \tag{3.8}$$

for $k = 1, \ldots, S^{(j)}$ and $w_k \in I_S^{(j)}$. In other words, the latter type of invariants simply correspond to the last $S^{(j)}$ entries of the vector $\mathbf{x}_j^*$:

$$\left(h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\right) = \left(x_{w_1}, \ldots, x_{w_{S^{(j)}}}\right). \tag{3.9}$$

Theorem 3.1. *In the adjusted coordinate system described by the vector $\mathbf{x}_j^*$ the stoichiometric vector $\mathbf{s}_j^*$ of the reaction step j can be expressed like*

$$\mathbf{s}_j^* = \left(\prod_{i \in I_{L^{(j)}}} l_i^{(j)} \prod_{i \in I_{R^{(j)}}} r_i^{(j)}\right) \{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}. \tag{3.10}$$

Proof. If $S^{(j)} = 0$ then Theorem 3.1 reduces to Theorem 2.1. Let us consider the case $S^{(j)} > 0$. Let $x_{j,1}^*, \ldots, x_{j,N}^*$ denote the coordinates of the vector $\mathbf{x}_j^*$: $\mathbf{x}_j^* = (x_{j,1}^*, \ldots, x_{j,N}^*)^T$. Then, Eq. (3.9) reads

$$\left(h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\right) = (x_{w_1}, \ldots, x_{w_{S^{(j)}}}) = (x_{j,N-S+1}^*, \ldots, x_{j,N}^*). \tag{3.11}$$

Consequently, for the wth component of the Nambu bracket in Eq. (3.10) we obtain

$$\begin{aligned}
&\{x_{j,w}^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\} \\
&\quad = \sum_{i_2,\ldots,i_N=1}^{N} \epsilon_{w,i_2,\ldots,i_N} \frac{\partial h_1^{(j)}}{\partial x_{j,i_2}^*} \cdots \frac{\partial h_{N_j-1}^{(j)}}{\partial x_{j,i_{N_j}}^*} \frac{\partial h_{S,1}^{(j)}}{\partial x_{j,i_{N-S+1}}^*} \cdots \frac{\partial h_{S,S}^{(j)}}{\partial x_{j,i_N}^*} \\
&\quad = \sum_{i_2,\ldots,i_N=1}^{N} \epsilon_{w,i_2,\ldots,i_N} \frac{\partial h_1^{(j)}}{\partial x_{j,i_2}^*} \cdots \frac{\partial h_{N_j-1}^{(j)}}{\partial x_{j,i_{N_j}}^*} \frac{\partial x_{j,N-S+1}^*}{\partial x_{j,i_{N-S+1}}^*} \cdots \frac{\partial x_{j,N}^*}{\partial x_{j,i_N}^*} \\
&\quad = \sum_{i_2,\ldots,i_{N_j}=1}^{N} \epsilon_{w,i_2,\ldots,i_{N_j},N_j+1,\ldots,N} \frac{\partial h_1^{(j)}}{\partial x_{j,i_2}^*} \cdots \frac{\partial h_{N_j-1}^{(j)}}{\partial x_{j,i_{N_j}}^*}.
\end{aligned} \tag{3.12}$$

Consequently, for $w \in \{N_j + 1, \ldots, N\}$ the bracket equals zero, whereas for $w \leq N_j$ the bracket refers to the case discussed in Theorem 2.1 of a single biochemical reaction that

involves N_j species. In short, we obtain

$$\left(\prod_{i\in I_{L(j)}} l_i^{(j)} \prod_{i\in I_{R(j)}} r_i^{(j)}\right)\{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}$$
$$\big(\underbrace{-l_{i_1}, \ldots, -l_{i_{L(j)}}}_{L^{(j)}\text{ entries}}, \underbrace{r_{p_1}, \ldots, r_{p_{R(j)}}}_{R^{(j)}\text{ entries}}, \underbrace{0, \ldots, 0}_{S^{(j)}\text{ entries}}\big)^T = \mathbf{s}_j^*. \tag{3.13}$$

□

Definition 3.1. The re-sorting operator

$$\mathbf{y}^* \to \mathbf{y} : \mathbf{y} = T(\mathbf{x}^* \to \mathbf{x})(\mathbf{y}^*) \tag{3.14}$$

describes a mapping from the N-dimensional vector $\mathbf{y}^*$ to $\mathbf{y}$ and involves the N-dimensional "template" vectors $\mathbf{x} = (x_1, \ldots, x_N)^T$ and $\mathbf{x}^*$, where $\mathbf{x}^*$ is composed of the same coordinates x_i as $\mathbf{x}$ but in general these coordinates are arranged in a different order. That is, we have $\mathbf{x}^* = (x_{i_1}, \ldots, x_{i_N})^T$, where the index vector $(i_1, \ldots, i_N)$ is a permutation of the vector $(1, 2, \ldots, N)$. The re-sorting operator rearranges the coordinates of the vector $\mathbf{y}^*$ according to the coordinate mapping $\mathbf{x}^* \to \mathbf{x}$. For example: $T((b, a, c) \to (a, b, c))((5, 2, 4)^T) = (2, 5, 4)^T$.

Corollary 3.1. *The stoichiometric vector* $\mathbf{s}^{(j)}$ *of the reaction step* j *is given by*

$$\begin{aligned}\mathbf{s}^{(j)} &= T(\mathbf{x}_j^* \to \mathbf{x})(\mathbf{s}_j^*)\\ &= T(\mathbf{x}_j^* \to \mathbf{x})\left[\left(\prod_{i\in I_{L(j)}} l_i^{(j)} \prod_{i\in I_{R(j)}} r_i^{(j)}\right)\{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}\right]\\ &= \left(\prod_{i\in I_{L(j)}} l_i^{(j)} \prod_{i\in I_{R(j)}} r_i^{(j)}\right) T(\mathbf{x}_j^* \to \mathbf{x})\big[\{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}\big].\end{aligned} \tag{3.15}$$

Proof. Corollary 3.1 follows immediately from Theorem 3.1 and the definition of the re-sorting operator T. □

Our next objective is to replace the adjusted coordinate vector $\mathbf{x}_j^*$ by the reference vector $\mathbf{x}$. That is, the next goal is to apply the re-sorting operator within the Nambu bracket to the adjusted state vector $\mathbf{x}_j^*$ without changing the arguments of the invariants. In this context, it is important to note that in the expression $\{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}$ the vector $\mathbf{x}_j^*$ also determines the sequence in which the coordinates appear in the partial derivatives of the bracket, see Eq. (1.4). Due to the nature of the epsilon tensor any exchange of two coordinates results in a sign change. More precisely, if for the vector $\mathbf{y} = (y_1, \ldots, y_i, \ldots, y_k, \ldots, y_N)^T$ and the functions $f_1(\mathbf{y}), \ldots, f_{N-1}(\mathbf{y})$ we obtain

$$\{\mathbf{y}, f_1(\mathbf{y}), \ldots, f_{N-1}(\mathbf{y})\} = (u_1, \ldots, u_i, \ldots, u_k, \ldots, u_N)^T, \tag{3.16}$$

then for $\mathbf{y}^* = (y_1, \ldots, y_k, \ldots, y_i, \ldots, y_N)^T = (y_1^*, \ldots, y_N^*)^T$ with y_i exchanged by y_k we obtain

$$\{\mathbf{y}^*, f_1(\mathbf{y}), \ldots, f_{N-1}(\mathbf{y})\} = \sum_{i_1,\ldots,i_N=1}^{N} \epsilon_{i_1,\ldots,i_N} \left[\frac{\partial}{\partial y_{i_1}^*}\begin{pmatrix} y_1^* \\ \vdots \\ y_N^* \end{pmatrix}\right] \frac{\partial f_1(\mathbf{y})}{\partial y_{i_2}^*} \cdots \frac{\partial f_{N-1}(\mathbf{y})}{\partial y_{i_N}^*}$$
$$= -(u_1, \ldots, u_k, \ldots, u_i, \ldots, u_N)^T. \tag{3.17}$$

An illustration of this property is shown in the Appendix. We assume next that the re-sorting operator T re-arranges the coordinates by exchanging pairs of coordinates. Let $|T|$ denote the number of transpositions required to perform the mapping. Each transposition induces a sign change.

Corollary 3.2. *Alternatively, the stoichiometric vector* $\mathbf{s}^{(j)}$ *of the reaction step* j *is given by*

$$\mathbf{s}^{(j)} = (-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|} \left(\prod_{i \in I_{L(j)}} l_i^{(j)} \prod_{i \in I_{R(j)}} r_i^{(j)}\right) \{\mathbf{x}, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}, \tag{3.18}$$

where $|T|$ *denotes the number of transpositions involved in the coordinate mapping* $\mathbf{x}_j^* \to \mathbf{x}$.

Proof. From Eqs. (3.15)–(3.17) it follows that

$$\begin{aligned}
\mathbf{s}^{(j)} &= \prod_{i \in I_{L(j)}} l_i^{(j)} \prod_{i \in I_{R(j)}} r_i^{(j)} T(\mathbf{x}_j^* \to \mathbf{x})\big[\{\mathbf{x}_j^*, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}\big] \\
&= \prod_{i \in I_{L(j)}} l_i^{(j)} \prod_{i \in I_{R(j)}} r_i^{(j)} (-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|} \{T(\mathbf{x}_j^* \to \mathbf{x})[\mathbf{x}_j^*], h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\} \\
&= (-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|} \prod_{i \in I_{L(j)}} l_i^{(j)} \prod_{i \in I_{R(j)}} r_i^{(j)} \{\mathbf{x}, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}.
\end{aligned} \tag{3.19}$$

□

Corollary 3.3. *The nonlinear dynamical system* (3.4) *describing the coupled biochemical reactions* (3.1) *can be formulated in terms of Nambu brackets like*

$$\begin{aligned}
\frac{d}{dt}\mathbf{x} = \sum_{j=1}^{M} \big(v_f^{(j)}(\mathbf{x}) - v_b^{(j)}(\mathbf{x})\big)(-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|} \\
\times \prod_{i \in I_{L(j)}} l_i^{(j)} \prod_{i \in I_{R(j)}} r_i^{(j)} \{\mathbf{x}, h_1^{(j)}, \ldots, h_{N_j-1}^{(j)}, h_{S,1}^{(j)}, \ldots, h_{S,S^{(j)}}^{(j)}\}.
\end{aligned} \tag{3.20}$$

Proof. This follows immediately from Eqs. (3.4) and (3.18). □

Let us illustrate Corollary 3.3 by means of two examples.

First, we revisit the example of a cyclic three-step reaction address in [11]. We consider the coupled biochemical reactions

$$X + C_1 \to Y, \quad Y + C_2 \to Z, \quad Z + C_3 \to X \tag{3.21}$$

involving the substances X, Y, Z and the substrates C_1, C_2, C_3. We assume that the concentrations of the substrates are held constant. Consequently, we have $N = 3$. The state vector is given by the concentrations $\mathbf{x} = (x, y, z)^T$. The first reaction is characterized by $L_1 = R_1 = S_1 = 1$. In order to determine the invariants of the first reaction step, we do not need to adjust (resort) the state vector. Rather, we put $\mathbf{x}_1^* = \mathbf{x}$. The invariants are $h_1^{(1)} = -(x + y)$ and $h_{S,1}^{(1)} = z$. Using Eq. (3.10), we obtain

$$\mathbf{s}^{(1)} = \mathbf{s}_1^* = \{\mathbf{x}, h_1^{(1)}, h_{S,1}^{(1)}\} = \nabla h_1^{(1)} \times \nabla h_{S,1}^{(1)} = \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix}. \tag{3.22}$$

Assuming that the law of mass action kinetics applies, the reaction rate for the first reaction corresponds to $v_1(\mathbf{x}) = v_f^{(1)}(\mathbf{x}) = k_1 c_1 x$ with $k_1 > 0$ such that

$$\mathrm{d}_1\mathbf{x} = k_1 c_1 x \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix} \mathrm{d}t. \tag{3.23}$$

For the second reaction step we observe that $L_2 = R_2 = S_2 = 1$. As adjusted state vector we use $\mathbf{x}_2^* = (y, z, x)^T$. Accordingly, the invariants are $h_1^{(2)} = -(y + z)$ and $h_{S,1}^{(2)} = x$. Let us determine $\mathbf{s}^{(2)}$ explicitly by means of the two methods described by Corollaries 3.1 and 3.2. From Eq. (3.10) it follows that

$$\mathbf{s}_2^* = \{\mathbf{x}_2^*, h_1^{(2)}, h_{S,1}^{(2)}\} = \nabla^* h_1^{(2)} \times \nabla^* h_{S,1}^{(2)}, \tag{3.24}$$

with $\nabla^* = (\partial/\partial y, \partial/\partial z, \partial/\partial x)^T$. Consequently, we have

$$\nabla^* h_1^{(2)} = \begin{pmatrix} -1 \\ -1 \\ 0 \end{pmatrix}, \quad \nabla^* h_{S,1}^{(2)} = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} \Rightarrow \mathbf{s}_2^* = \nabla^* h_1^{(2)} \times \nabla^* h_{S,1}^{(2)} = \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix}. \tag{3.25}$$

Substituting this result and $T((y, z, x) \to (x, y, z))$ into Eq. (3.15), we obtain

$$\mathbf{s}_2 = T((y, z, x) \to (x, y, z)) \left[\begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix} \right] = \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix}. \tag{3.26}$$

Alternatively, we compute $\mathbf{s}_2 = (-1)^{|T|}\{\mathbf{x}, h_1^{(2)}, h_{S,1}^{(2)}\}$, see Eq. (3.18). We have $|T((y, z, x) \to (x, y, z))| = 2$ such that

$$\mathbf{s}^{(2)} = \{\mathbf{x}, h_1^{(2)}, h_{S,1}^{(2)}\} = \nabla h_1^{(2)} \times \nabla h_{S,1}^{(2)} = \begin{pmatrix} 0 \\ -1 \\ -1 \end{pmatrix} \times \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix}. \tag{3.27}$$

From the law of mass action kinetics we obtain for the reaction step $j = 2$ the reaction rate $v_2 = v_f^{(2)} = k_2 c_2 y$ with $k_2 > 0$ such that

$$\mathrm{d}_2\mathbf{x} = k_2 c_2 y \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix} \mathrm{d}t. \tag{3.28}$$

By analogy, we can discuss the reaction step $j = 3$. Eventually, we obtain

$$\mathrm{d}_3\mathbf{x} = k_3 c_3 z \begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} \mathrm{d}t, \tag{3.29}$$

with $k_3 > 0$. In total we have $\mathrm{d}\mathbf{x} = \sum_{j=1}^{3} \mathrm{d}_j\mathbf{x}$. More explicitly, form Corollary 3.3 and the intermediate results obtained above we conclude that the dynamics of the cyclic reaction (3.21) exhibits the following Nambu bracket formulation:

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} &= \sum_{j=1}^{3} v_f^{(j)}(\mathbf{x})(-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|}\big\{\mathbf{x}, h_1^{(j)}(\mathbf{x}), h_{S,1}^{(j)}(\mathbf{x})\big\} = \sum_{j=1}^{3} v_f^{(j)}(\mathbf{x})\big\{\mathbf{x}, h_1^{(j)}(\mathbf{x}), h_{S,1}^{(j)}(\mathbf{x})\big\} \\ &= \big(\mathbf{s}^{(1)}, \mathbf{s}^{(2)}, \mathbf{s}^{(3)}\big) \cdot \begin{pmatrix} v_f^{(1)}(\mathbf{x}) \\ v_f^{(2)}(\mathbf{x}) \\ v_f^{(3)}(\mathbf{x}) \end{pmatrix} = \begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 1 & 1 & -1 \end{pmatrix} \cdot \begin{pmatrix} k_1 c_1 x \\ k_2 c_2 y \\ k_3 c_3 z \end{pmatrix}. \end{aligned} \tag{3.30}$$

In our second example we consider an enzyme reaction involving substrate molecules S and enzyme molecules E. The enzymes convert the substrate molecules into product molecules P. The enzyme mechanisms can be considered as a two step process.

$$S + E \leftrightarrow C, \quad C \to E + P. \tag{3.31}$$

First, an enzyme molecule E binds to a substrate molecule and forms a complex C. This reaction is assumed to be reversible. Second, the complex C decays into the enzyme E and the product P. This process is irreversible. Note that although the whole two-step reaction (3.31) is an enzyme reaction, the two individual reaction steps satisfy mass action kinetics. For more details see [16]. Let s, e, c, p denote the concentrations of the molecules S, E, C, and P such that $\mathbf{x} = (s, e, c, p)^T$ corresponds to the state vector of the enzyme reaction. For the first reaction we have $L_1 = 2$ and $R_1 = S_1 = 1$. We put $\mathbf{x}_1^* = \mathbf{x}$. Consequently, the invariants are $h_1^{(1)} = -(c + s)$, $h_2^{(1)} = -(c + e)$, and $h_{S,1}^{(1)} = p$, see Eqs. (2.6) and (3.9). From Eq. (3.10) it follows that

$$\mathbf{s}^{(1)} = \mathbf{s}_1^* = \big\{\mathbf{x}, h_1^{(1)}, h_2^{(1)}, h_{S,1}^{(1)}\big\} = \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix}. \tag{3.32}$$

According to the law of mass action kinetics, the forward and backward reaction rates for the first reaction are $v_f^{(1)}(\mathbf{x}) = k_1 se$ and $v_b^{(1)}(\mathbf{x}) = k_2 c$, respectively, with $k_1, k_2 > 0$. Taken together, we find that the state change due to the first reaction step is

$$\mathrm{d}_1\mathbf{x} = (k_1\, s\, e - k_2\, c) \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix} \mathrm{d}t. \tag{3.33}$$

For the second reaction we find that $L_2 = 1$, $R_2 = 2$, and $S_1 = 1$. We put $\mathbf{x}_2^* = (c, e, p, s)$, which implies that the invariants read $h_1^{(2)} = -(e + c)$, $h_2^{(2)} = c + p$, and $h_{S,1}^{(2)} = s$. We can use either Corollary 3.1 or 3.2 to calculate the stoichiometric vector $\mathbf{s}^{(2)}$. For demonstration purposes we will do both. Using Eq. (3.10), we obtain

$$\mathbf{s}_2^* = \{\mathbf{x}_2^*, h_1^{(2)}, h_2^{(2)}, h_{S,1}^{(2)}\} = \begin{pmatrix} -1 \\ 1 \\ 1 \\ 0 \end{pmatrix}. \tag{3.34}$$

Subsequently, Eq. (3.15) yields

$$\mathbf{s}^{(2)} = T((c, e, p, s) \to (s, e, c, p))(\mathbf{s}_2^*) = \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix}. \tag{3.35}$$

Alternatively, we compute $\mathbf{s}^{(2)}$ from $\mathbf{s}^{(2)} = (-1)^{|T|}\{\mathbf{x}, h_1^{(2)}, h_2^{(2)}, h_{S,1}^{(2)}\}$. Since we need two transpositions to transform the sequence (c, e, p, s) into (s, e, c, p) we have $|T| = 2$. A detailed calculation yields

$$\mathbf{s}_2 = \{\mathbf{x}, h_1^{(2)}, h_2^{(2)}, h_{S,1}^{(2)}\} = \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix}. \tag{3.36}$$

The forward rate reads $v_f^{(2)} = k_3 c$ with $k_3 > 0$. In summary, the second reaction step contributes to the change of the state vector like

$$\mathrm{d}_2\mathbf{x} = k_3\, c \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix} \mathrm{d}t, \tag{3.37}$$

while the total change of the enzyme reaction is given by $\mathrm{d}\mathbf{x} = \mathrm{d}_1\mathbf{x} + \mathrm{d}_2\mathbf{x}$. More explicitly, we have

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x} &= \sum_{j=1}^{2} \big(v_f^{(j)}(\mathbf{x}) - v_b^{(j)}(\mathbf{x})\big)(-1)^{|T(\mathbf{x}_j^* \to \mathbf{x})|}\big\{\mathbf{x}, h_1^{(j)}(\mathbf{x}), h_2^{(j)}(\mathbf{x}), h_{S,1}^{(j)}(\mathbf{x})\big\} \\
&= \sum_{j=1}^{2} v_j(\mathbf{x})\big\{\mathbf{x}, h_1^{(j)}(\mathbf{x}), h_2^{(j)}(\mathbf{x}), h_{S,1}^{(j)}(\mathbf{x})\big\} \\
&= (k_1\, s\, e - k_2\, c)\begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix} + k_3\, c \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix} \\
&= \begin{pmatrix} -1 & 0 \\ -1 & 1 \\ 1 & -1 \\ 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} k_1\, s\, e - k_2\, c \\ k_3 c \end{pmatrix}.
\end{aligned} \tag{3.38}$$

4. Concluding Remarks

The objective of the present study was to develop a Nambu formalism for a broad class of biochemical reactions. To this end, we resolved some limitations of an earlier study. In particular, we showed that irrespective of the reaction type (mass action kinetics, enzyme kinetics, etc.) Nambu brackets are directly related to the stoichiometric vector of biochemical reactions and to the stoichiometric matrix of coupled biochemical reactions. Consequently, the formulation of biochemical reactions via Nambu brackets applies to all kinds of reaction models. Moreover, we considered general reactions rather than elementary reactions. In the former case stoichiometric coefficients may be different from unity, while in the latter case they are restricted to being equal to one.

Let us dwell on an interpretation of the Nambu representation of the stoichiometric vector of a given biochemical reaction, see Eq. (2.8) and Theorem 2.1. A biochemical reaction involving N species exhibits $N-1$ invariants $h_1(\mathbf{x}), \ldots, h_{N-1}(\mathbf{x})$. The gradient vectors

$$\mathbf{w}_1 = \nabla h_1(\mathbf{x}), \ldots, \mathbf{w}_{N-1} = \nabla h_{N-1}(\mathbf{x}) \tag{4.1}$$

define particular directions in the state space spanned by the concentrations $x_1, \ldots, x_N$. These directions are "forbidden" directions. Roughly speaking, the reaction dynamics cannot evolve in any of these directions. More precisely, the reaction dynamics must evolve orthogonal to all of the gradient vectors listed in Eq. (4.1). Otherwise, at least one of the invariants h_k would change. In other words, the vector $\mathbf{s}$ (stoichiometric vector) that describes the direction in which the biochemical reaction evolves must satisfy

$$\mathbf{w}_k \cdot \mathbf{s} = 0 \tag{4.2}$$

for $k = 1, \ldots, N-1$. The Nambu bracket $\{\mathbf{x}, h_1, \ldots, h_{N-1}\}$ yields a vector that exhibits exactly the property (4.2). In order to realize that Eq. (4.2) holds, we first note that Nambu

brackets in general possess the fundamental property

$$\nabla f_1 \cdot \{\mathbf{x}, f_2, \ldots, f_N\} = \{f_1, f_2, \ldots, f_N\} \tag{4.3}$$

for functions $f_i(\mathbf{x})$. Furthermore, we have $\{f_1, \ldots, f_i, \ldots, f_{k=i}, \ldots, f_N\} = 0$. Consequently, Eq. (4.2) is satisfied because

$$\mathbf{w}_k \cdot \mathbf{s} = \nabla h_j \cdot \{\mathbf{x}, h_1, \ldots, h_{N-1}\} = \{h_j, h_1, \ldots, h_{N-1}\} = 0. \tag{4.4}$$

We may conclude that the Nambu bracket $\{\mathbf{x}, h_1, \ldots, h_{N-1}\}$ constructs out of the set of gradient vectors $\mathbf{w}_k = \nabla h_k(\mathbf{x})$ a vector that is orthogonal to all of these vectors. In other words, a Nambu bracket can be regarded as an operator that constructs in a given N-dimensional space out of a given set of $N-1$ forbidden directions the very direction that is not forbidden.

Appendix A. Illustration of Sign-Change Due to Coordinate Transposition

Let $\mathbf{y} = (a, b, c)^T$ and f_1, f_2 denote functions of $\mathbf{y}$. Then,

$$\begin{aligned}\{\mathbf{y}, f_1(a,b,c), f_2(a,b,c)\} &= \begin{pmatrix}\partial_a\\ \partial_b\\ \partial_c\end{pmatrix} f_1 \times \begin{pmatrix}\partial_a\\ \partial_b\\ \partial_c\end{pmatrix} f_2\\ &= \begin{pmatrix}\partial_b f_1 \partial_c f_2 - \partial_c f_1 \partial_b f_2\\ -\partial_a f_1 \partial_c f_2 + \partial_c f_1 \partial_a f_2\\ \partial_a f_1 \partial_b f_2 - \partial_b f_1 \partial_a f_2\end{pmatrix} = \begin{pmatrix}u_1\\ u_2\\ u_3\end{pmatrix}.\end{aligned} \tag{A.1}$$

Likewise, let $\mathbf{y}^* = (b, a, c)^T$ and f_1, f_2 denote the same functions as before. That is, we do not change the arguments in f_1 and f_2. Then,

$$\begin{aligned}\{\mathbf{y}^*, f_1(a,b,c), f_2(a,b,c)\} &= \begin{pmatrix}\partial_b\\ \partial_a\\ \partial_c\end{pmatrix} f_1 \times \begin{pmatrix}\partial_b\\ \partial_a\\ \partial_c\end{pmatrix} f_2\\ &= \begin{pmatrix}\partial_a f_1 \partial_c f_2 - \partial_c f_1 \partial_a f_2\\ -\partial_b f_1 \partial_c f_2 + \partial_c f_1 \partial_b f_2\\ \partial_b f_1 \partial_a f_2 - \partial_a f_1 \partial_b f_2\end{pmatrix} = -\begin{pmatrix}u_2\\ u_1\\ u_3\end{pmatrix}.\end{aligned} \tag{A.2}$$

Finally, in this example, using the re-sorting operator T, we obtain

$$\begin{aligned}T((b,a,c) \to (a,b,c)[\{\mathbf{y}^*, f_1, f_2\}] &= (-1)^{|T((b,a,c)\to(a,b,c))|}[\{T((b,a,c) \to (a,b,c)[\mathbf{y}^*], f_1, f_2\}]\\ &= (-1)^{|T((b,a,c)\to(a,b,c))|}\{\mathbf{y}, f_1, f_2\} = -\{\mathbf{y}, f_1, f_2\}.\end{aligned} \tag{A.3}$$

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