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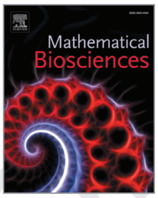

# Reaction networks and kinetics of biochemical systems

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ABSTRACT

This paper further develops the connection between Chemical Reaction Network Theory (CRNT) and Biochemical Systems Theory (BST) that we recently introduced [1]. We first use algebraic properties of kinetic sets to study the set of complex factorizable kinetics $\mathcal{CFK}(\mathscr{N})$ on a CRN, which shares many characteristics with its subset of mass action kinetics. In particular, we extend the Theorem of Feinberg-Horn [9] on the coincidence of the kinetic and stoichiometric subsets of a mass action system to CF kinetics, using the concept of span surjectivity. We also introduce the branching type of a network, which determines the availability of kinetics on it and allows us to characterize the networks for which all kinetics are complex factorizable: A "Kinetics Landscape" provides an overview of kinetics sets, their algebraic properties and containment relationships. We then apply our results and those (of other CRNT researchers) reviewed in [1] to fifteen BST models of complex biological systems and discover novel network and kinetic properties that so far have not been widely studied in CRNT. In our view, these findings show an important benefit of connecting CRNT and BST modeling efforts.

## 1. Commutative algebra of chemical kinetics

In this Introduction, we review concepts and results from Chemical Reaction Network Theory from a new point of view, namely in terms of properties of subsets of chemical kinetics. We provide the underlying definitions in Appendix A.1 together with a nomenclature section in Appendix B.

In view of the fact that some kinetic functions are not defined on the entire boundary of $\mathbb{R}^{\mathscr{S}}_{\geq}$ and the trend to apply a reaction network approach to non-chemical areas, following the formalism and terminology of Wiuf and Feliu [26], we introduce a slightly more general definition of a kinetics.

**Definition 1.** A kinetics for a network $\mathscr{N}=(\mathscr{S},\mathscr{C},\mathscr{R})$ is an assignment to each reaction $r_j \in \mathscr{R}$ of a rate function $K_j : \Omega_K \to \mathbb{R}_{\geq}$, where $\Omega_K$ is a set such that $\mathbb{R}^{\mathscr{S}}_{>} \subseteq \Omega_K \subseteq \mathbb{R}^{\mathscr{S}}_{\geq}$, $c \wedge d \in \Omega_K$ whenever $c, d \in \Omega_K$, and

$$K_j(c) \geq 0, \forall c \in \Omega_K.$$

A kinetics for a network $\mathscr{N}$ is denoted by $K=(K_1, K_2, \ldots, K_r) : \Omega_K \to \mathbb{R}^{\mathscr{R}}_{\geq}$.

In the definition, $c \wedge d$ is the bivector of $c$ and $d$ in the exterior algebra of $\mathbb{R}^{\mathscr{S}}$. Our work is focused on the following subset:

**Definition 2.** A chemical kinetics is a kinetics $K$ satisfying the positivity condition: for each reaction $r_j$: $y \to y'$, $K_j(c) > 0$ iff $\operatorname{supp} y \subset \operatorname{supp} c$.

**Remark 1.** If $\Omega_K = \mathbb{R}^{\mathscr{S}}_{>}$, then the additional condition for a chemical kinetics simply says that $K_j(c) > 0$ for all $c$, hence the name "positivity condition".

We denote the set of kinetics of a CRN $\mathscr{N}$, defined on $\Omega_K$ with $\mathcal{K}(\mathscr{N}, \Omega_K)$. For $\Omega_K = \mathbb{R}^{\mathscr{S}}_{\geq}$ and $\Omega_K = \mathbb{R}^{\mathscr{S}}_{>}$, we often write $\mathcal{K}_{\geq}(\mathscr{N})$ and $\mathcal{K}_{>}(\mathscr{N})$, respectively.

For any two elements of $\mathcal{K}(\mathscr{N}, \Omega_K)$, the sum and product are defined by componentwise addition and multiplication of their non-negative values. With these operations, it turns out that the whole set as well as various subsets of interest in CRNT have nice algebraic properties.

For the rest of this subsection, for simplicity, we set $\Omega_K = \mathbb{R}^{\mathscr{S}}_{\geq}$ and denote $\mathcal{K}_{\geq}(\mathscr{N})$ with $\mathcal{K}(\mathscr{N})$.

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We recall some concepts from Algebra that we will use: a semigroup is a set $S$ together with a binary operation "$\circ$" such that associativity holds: $x \circ (y \circ z) = (x \circ y) \circ z$ for all $x$, $y$, $z$ in $S$. If there is an identity element, i.e. $id$ such that $x \circ id = id \circ x = x$ for all $x$ in $S$, then the semigroup $S$ is called a monoid. Furthermore, a set $R$ with two binary operations " $+$ " and "$\circ$" is called a semiring if $(R, +)$ and $(R, \circ)$ are semigroups and distributive laws hold, i.e. $a \circ (b + c) = a \circ b + a \circ c$ and $(b + c) \circ a = b \circ a + c \circ a$ for $a$, $b$, $c$ in $R$. A semiring is called a semifield (or "proper semifield") if $(R^*, \circ)$ is a group, where $R^* = R \backslash \{0\}$ if $R$ has an additive identity 0, and $R^* = R$ otherwise. The basic example for a semifield is the set of positive real numbers $R_>$.

The following proposition is the basis of our "commutative algebra" approach to chemical kinetics.

**Proposition 1.** *$(\mathcal{K}(\mathscr{N}), +, \circ)$ is a commutative semifield.*

**Proof.** We first need to show that the positivity condition "for each $r$: $y \to y'$, $K_r(x) > 0$ iff $\operatorname{supp} y \subset \operatorname{supp} x$" holds for $K_1 + K_2$ and $K_1 \circ K_2$ if $K_1$, $K_2$ are in $\mathcal{K}(\mathscr{N})$. But this is clear since the operations are defined component-wise: $\operatorname{supp} y \subset \operatorname{supp} x \Rightarrow$ both $K_{1,\, r}(x)$, $K_{2,\, r}(x) > 0$, hence sum and product are both positive. Conversely, $\operatorname{supp} y$ not contained in $\operatorname{supp} x$ implies both $K_{1,\, r}(x)$, $K_{2, r}(x) = 0$, hence both sum and product are equal to 0.

To show that $(\mathcal{K}(\mathscr{N}), \circ)$ is a group, we define the identity element $1_K$ and the inverse element $1/K$ for each reaction $r$: $y \to y'$ as follows:

"For $\operatorname{supp} y \subset \operatorname{supp} x$, $(1_K)_r(x) := 1$ and $(1/K)_r(x) := 1/K_r(x)$. Otherwise both functions are equal to 0." Both functions are chemical kinetics and have the corresponding properties of an identity and inverse, respectively. ☐

A number of kinetics subsets, familiar from the CRNT literature, display interesting algebraic structures. We summarize these in the following proposition and indicate them in the "Kinetics Landscape" from our previous paper (Fig. 1 of [1]).

**Proposition 2.** *Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN and $\Omega_K = \mathbb{R}_{\geq}^{\mathscr{S}}$. Denote $\mathcal{K}(\mathscr{N}, \Omega_K)$ with $\mathcal{K}(\mathscr{N})$.*

1. *The set of continuous kinetics $\mathcal{CK}(\mathscr{N})$ and of differentiable kinetics $\mathcal{DK}(\mathscr{N})$ are sub-semirings of $\mathcal{K}(\mathscr{N})$.*
2. *The set of weakly monotonic kinetics $\mathcal{WMK}(\mathscr{N})$ is a sub-semiring with a multiplicative identity. The set of differentiably monotonic kinetics $\mathcal{DMK}(\mathscr{N})$ is a sub-semiring of $\mathcal{WMK}(\mathscr{N})$.*
3. *The set $\mathcal{PLK}(\mathscr{N})$ of power law kinetics is a multiplicative subgroup of $\mathcal{K}(\mathscr{N})$. Its subset of mass action kinetics $\mathcal{MAK}(\mathscr{N})$ forms an additive subgroup of $\mathcal{K}(\mathscr{N})$.*

**Proof.**

1. Both properties follow directly from the well-known facts that the sums and products of continuous and differentiable real functions are also continuous and differentiable, respectively. However, the multiplicative identity in general has neither property at points of the boundary of the definition domain.
2. We first derive the semiring with identity property of $\mathcal{WMK}(\mathscr{N})$: If $(K_1 + K_2)_r(x^{**}) > (K_1 + K_2)_r(x^*)$, then, for at least one of the summands, say $K_1$, we have $K_{1r}(x^{**}) > K_{1r}(x^*)$, so there is a species $s$ with $x_s^{**} > x_s^*$. Similarly, if $K_1 + K_2(x^{**}) > K_1 + K_2(x^*)$ and $K_i(x^{**}) = K_i(x^*)$ does not hold for both $i$, then for at least one, say $K_1$, there is a species $s$ with $x_s^{**} > x_s^*$ . For the other, the converse inequality holds, so there is a species $s'$ such that $x_{s'}^{**} < x_{s'}^*$. Hence the sum of weakly monotonic kinetics is also weakly monotonic. $1_K$ is also in $\mathcal{WMK}(\mathscr{N})$. The same argument holds for the product. For the multiplicative identity, only the second condition with equality for all species holds.
   $1/K$ is not necessarily weakly monotonic if $K$ is, since $1/K(x^{**}) > 1/K(x^*) \iff K(x^*) > K(x^{**})$, so there is a species s with $x_s^* > x_s^{**}$, but necessarily the other way around. Though, interestingly, $1/K$ fulfills the equality condition.
   We next confirm the subsemiring property of $\mathcal{DMK}(\mathscr{N})$ in $\mathcal{WMK}(\mathscr{N})$. We first show that it is a subset using the Mean Value Theorem for the component function $K_j : \Omega_K \to \mathbb{R}_{\geq}$. We have $K_j(c^{**}) K_j(c^*) = \langle grad(K), c^{**} - c^* \rangle$, and since the left hand side is greater than 0 and all the partial derivatives are $\geq 0$, there must be at least one $s$ such that $c_s^{**} - c_s^* > 0$. Similarly, if the left hand side is 0, either all $c_s^{**} = c_s^*$ or there is a pair of $s$ and $s'$ satisfying both $c_s^{**} > c_s^*$ and $c_{s'}^{**} < c_{s'}^*$.
   The additivity of differentiation shows that if $K_1$, $K_2$ are differentiably monotonic, then $K_1 + K_2$ is too. Similarly, the differentiation rule for a product shows that the product is also differentiably monotonic. Clearly, the (constant) identity function does not fulfill the strict monotonicity condition.
3. The (multiplicative) subgroup property of $\mathcal{PLK}(\mathscr{N})$ is straightforward: note however, that the inverse may be defined on a smaller domain. The additive subgroup property of $\mathcal{MAK}(\mathscr{N})$ also follows directly from the set's definition. ☐

**Remark 2.** The set $\mathcal{MAK}(\mathscr{N})$ maps bijectively onto the set of $\mathbb{R}_{>}^{\mathscr{R}}$: the latter is a semifield. In [13], J. Gunawardena essentially used the semifield properties of this image of MAK systems, (i.e. building sums, products, ratios of rate constants) to establish a linear method for model reduction. This, together with considerations of approximating novel kinetics possibly with sums and products of known ones, inspired us to consider algebraic properties of kinetics sets.

Other well known sets of kinetics on a network, such as those with special equilibria, e.g. the set of complex balanced kinetics $\mathcal{CBK}(\mathscr{N})$ or those with a particular representation form, e.g. the set of Hill-type kinetics $\mathcal{HTK}(\mathscr{N})$, do not have good algebraic properties, i.e., are not closed under addition and/or multiplication.

The "kinetics subsets" viewpoint also allows a compact way of expressing the equivalence of structural and kinetic properties, which we call a "network-kinetic sets relation (NKSR)". Here are two well known examples [6]:

- $\mathscr{N}$ is weakly reversible iff $\mathcal{MAK}(\mathscr{N}) \cap \mathcal{CBK}(\mathscr{N}) \neq 0$.
- $\mathscr{N}$ is weakly reversible and has deficiency zero iff $\mathcal{MAK}(\mathscr{N}) \subset \mathcal{CBK}(\mathscr{N})$.

In the next section, we show further examples, apparently new, of such relationships.

## 2. The (multiplicative) subgroup of complex factorizable kinetics

### 2.1. Duality of the reactant and reactions mappings and related properties

We first (re)state some definitions and basic results relevant for our discussion of complex factorizable kinetics in this and the next section.

**Definition 3.** The reactant map $\rho : \mathscr{R} \to \mathscr{C}$ maps a reaction to its reactant complex. $|\rho(\mathscr{R})|$, the number of distinct reactant complexes, will be denoted by $n_r$.

Two upper bounds for $n_r$ are well-documented in the CRNT literature: the number of complexes $n$ and the number of reactions $r$ with the inequalities $n \geq n_r$ and $r \geq n_r$, respectively. The maximal values translate to interesting network classes as stated in the following.

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