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Reachability, Connectivity, and Proximity in Chemical Spaces

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Abstract

A chemical universe consists of a set X of chemical compounds and a set of reactions between them. Each reaction transforms a finite (small) multiset of educts in a small multiset of products. In the topological context explored here, stoichiometry is neglected, and products and educts are treated as simple sets. Reactions thus form directed hyperedges on X. Since X can be infinite, it is of interest to consider X not only for a combinatorial point of view but also as a topological construct. Here we argue that generalized reaches and relative closure functions provide a natural framework. These can be seen as generalizations of connected components and are equivalent to a certain class of separation or proximity spaces. We consider notions of strong and weak connected components and derive their basic properties, and we characterize the conditions under which they are equivalent to generalized closure spaces; as it turns out, chemical universes are very different from this more well-behaved type of generalized topologies. The theory presented here provides a solid ground to further investigate concepts related to connectivity in a very general class of models that in particular includes chemistry.

1 Introduction

Over the last two centuries, chemists have explored tens of millions of distinct chemical reactions and synthetized a comparable number of chemical compounds. Still this is just a vanishingly small sample of the molecules that could be produced and that are predicted by means of computational methods [1]. The diversity of chemistry is naturally ordered by means of the chemical reactions that interconnect compounds as individual steps in their synthesis or degradation. This universe of chemistry is far from random, with both molecules and reactions falling into interdependent classes [2]. Explorations of the vastness of chemical space thus have focused both on the combinatorial nature of molecules [1] and on the rules underlying the reactions [3].

From a mathematical point of view, a chemical universe consists of a set X of chemical compounds or species together with a set E of chemical reactions. A chemical reaction is naturally represented as a pair of multi-sets of compounds designating the educts and products, respectively. The multiplicities correspond to the stoichiometric coefficients of the molecules in the reaction formula. The pair (X, E) thus forms a directed, weighted hypergraph [4]. While stoichiometric coefficients of course play an important role in the analysis of fluxes through chemical networks [5], they do not affect whether a reaction can take place in principle or not. For this purpose, knowledge of presence or absence of educts and type of products is sufficient. We therefore model chemical reactions here as unweighted directed hypergraphs and consider the hyperedges as pairs (U, V) of simple sets of educts $U \subseteq X$ and products $V \subseteq X$, respectively. At least conceptually the set X is infinite in general since it may contain for instance polymers of arbitary length. It is of interest, therefore, to consider the pair (X, E) not just as a directed hypergraph but also as a topological structure. So far, there is no generally accepted topological interpretation of directed hypergraphs.

In a series of publications, *closure functions* are proposed as a useful construction to describe accessibility in a chemical space or in evolutionary biology [6–8], see also [9–11] for the origins of these ideas. Given a set A of compounds, it appears natural to consider the sets

$$c(A) := \bigcup \{V | (U, V) \in E \text{ and } U \subseteq A\} \tag{1}$$

of molecules that can be generated from A with the help of a single reaction. By construction, $c : 2^X \to 2^X$ satisfies

(c0) $c(\emptyset) = \emptyset$

(c1) $A \subseteq B$ implies $c(A) \subseteq c(B)$.

Closure functions of this type generalize Kuratowski's topological closures [12] and still support some of the key constructions of classical point set topology. Closure preserving maps $f : X \to Y$ satisfying $f(c_X(A)) \subseteq c_Y(f(A))$, where c_X and c_Y here denote the closure functions on X and Y, resp., play the role of continuous functions in this setting, see e.g. [13, 14].

Closure functions are intimately linked to the notion of self-maintenance and organization in chemical networks. To this end, define

$$C(A) = A \cup c(A) \cup c(A \cup c(A)) \cup \ldots ...c(A \cup c(A \cup c(A \cup c(...)))) \cup ... \tag{2}$$

It is easy to check that $C : 2^X \to 2^X$ satisfies (c0), (c1), as well as

(c2) $A \subseteq C(A)$

(c4) $C(C(A)) = C(A)$

Following [15, 16] a set A of compounds is self-maintaining if all its constituents can be produced from A, that is, if $A \subseteq C(A)$. On the other hand, a chemical reaction system is "closed" if it does not produce new molecular types, i.e., if $C(A) \subseteq A$. This condition is equivalent to $C(A) = A$. A chemical organization in the sense of [17] is closed, and self-maintaining, i.e., requires $C(A) = A$. We refer to [18] for a more detailed analysis.

Before we return to chemical universes, let us briefly consider the problem of imposing a topological structure on undirected hypergraphs. An undirected hypergraph H is a pair $(X, \mathcal{E})$ comprising a vertex set X and a set of hyperedges $\mathcal{E} \in 2^X$. A natural way to endow H with a topological structure is to consider the closure function $a(A) = \bigcup_{\substack{E \in \mathcal{E} \\ E \cap A \neq \emptyset}} E$ [19]. This approach, however, leads to the same type of closure functions as graphs since one easily checks $a(A) = \bigcup_{x \in A} a(\{x\})$. Thus $a(\{x\})$ can also be interpreted as playing the role of the graphtheoretical neighborhood of each vertex $x \in X$. The lack of a widely accepted topological interpretation of hypergraphs is discussed in some more detail e.g. in [20].

An alternative, rather straightforward idea is to treat the hyperedges as a basis of the collection $\mathscr{C}$ of connected subsets of X. A hypergraph is called *simple* if none of its

hyperedges is contained within another. For a simple hypergraph, the edges therefore are the inclusion-minimal connected sets. If the hypergraph is not simple, it is still possible to single out the connected sets that are "relevant" to define hyperedges. We may say that a connected set Z is *redundant* if there is a collection $\mathcal{B}$ of strictly smaller sets $Z_k \in \mathcal{B}$ such that (i) $\bigcup_k Z_k = Z$ and (ii) for every bipartition of $\mathcal{B}$ into two non-empty subsets $\mathcal{B}'$ and $\mathcal{B}''$ there is $Z' \in \mathcal{B}'$ and $Z'' \in \mathcal{B}''$ such that $Z' \cap Z'' \neq \emptyset$. This property guarantees that redundant sets are generated from the smaller connected sets that they harbour.

In this contribution we explore in a more systematic manner a non-symmetric concept of connectedness that, as we argue, describes the topological features of chemical reaction networks, and thus of directed hypergraphs and related set systems, in a satisfactory manner. We start from a generalization of the closure function explored in earlier work and show that "relative closure functions" with three simple properties form a natural and faithful description of the topological structure of chemical universes. Fig. 1 illustrates some of the concepts used in this contribution.

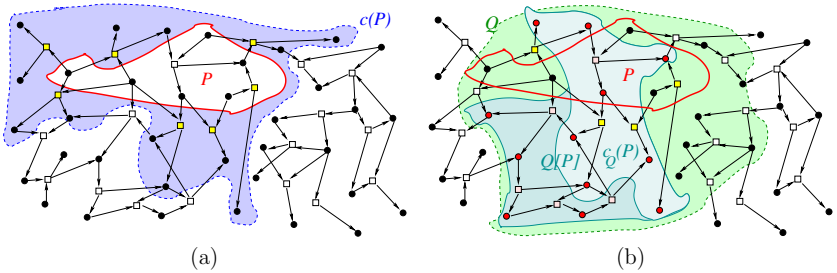

Figure 1. Chemical reaction network bipartite graph notation. Compounds (points) are shown as circles, reactions (hyperedges) are indicated by squares. Arrows connect educts to the reaction node and the reaction node to the products. A "seed set" P comprising five compounds is indicated by the red outline. The two panels illustrate alternative topological constructions: (a) Reactions with all educts in P are highlighted in yellow. The products of these reactions form the closure $c(P)$ shown as blue area. In this example none of the seed vertices is (re)produced within P and hence $c(P) \cap P = \emptyset$. (b) Reaction with all educts in P and all products also restricted to the reference set Q are highlighted in yellow and the corresponding relative closure $c_Q(P)$ is indicated. Their reaction products then iteratively enable additional reactions (with pink squares). The set $Q[P]$ consisting of all compounds eventually reachable from P within Q consists of the circles marked in red. The four black vertices in P are not reachable from P within Q.

2 Relative Closure Functions and Oriented Components

A conceptually very different way to describe the topological structure of a chemical universe is to first fix a reference set $Q \subseteq X$ of compounds of interest and set of "seeds" $P \subseteq Q$. We then consider the *relative closure of P in Q* $c : 2^X \times 2^X \to 2^X$ defined by

$$c_Q(P) := \bigcup \{V | (U,V) \in E,\, U \subseteq P,\, \text{and } V \subseteq Q\} \tag{3}$$

The key difference to the closure functions mentioned in the Introduction is the prescribed reference set Q that limits the allowed products. While it may appear unrealistic from a chemical point of view, the notion may be useful also in practice e.g. when products are to be avoided that are overly dangerous, expensive to dispose of, or legally regulated. Here the concept is introduced primarily as a mathematical device. Comparing equ.(3) with the definition of the closer function we observe $c(P) = c_X(P)$, i.e., the ordinary closure is just the closure relative to the entire space X. This suggest already that $c_Q(P)$ captures more details of the structure of the chemical universe than the topological closure function.

It is important to note that c_Q is not the closure on the subspace Q, which is given by $Q \cap c(P)$ [21]. By construction we have $c_Q(P) \subseteq Q \cap c(P)$. The following three properties are immediate consequences of the definition:

(r1) $P \subseteq P' \subseteq Q$ implies $c_Q(P) \subseteq c_Q(P')$.

(r2) $P \subseteq Q \subseteq Q'$ implies $c_Q(P) \subseteq c_{Q'}(P)$.

(r3) $c_{c_Q(P) \cup P}(P) = c_Q(P)$ for all $P, Q \in 2^X$.

The properties **(r1)** and **(r2)** establish isotony in both variables. Condition **(r3)** reflects the fact that all reactions that contribute to $c_Q(P)$ are entirely contained in $c_Q(P) \cup P \subseteq Q$ and hence the same relative closure is obtained on this smaller set.

Let us now consider an arbitrary relative closure function c_Q satisfying **(r1)**. It is natural to consider its iterations

$$c_Q^{(k)}(P) := c_Q\big(P \cup c_Q(P) \cup c_Q^{(2)}(P) \cup \cdots \cup c_Q^{(k-1)}(P)\big) \tag{4}$$

for $k \geq 1$. By isotony **(r1)** we have $c_Q^{(j)}(P) \subseteq c_Q^{(k)}(P)$ whenenever $j \leq k$, hence there is a simpler recursion

$$c_Q^{(k)}(P) = c_Q(P \cup c_Q^{(k-1)}(P)) \quad \text{for } k \geq 2. \tag{5}$$

It is easy to see that $c^{(k)}$ satisfies **(r1)**. If **(r2)** holds in addition, then $c^{(k)}$ also satisfies **(r2)**.

The sequence of sets $c_Q^{(k)}(P)$ is non-decreasing.Therefore there exists a limit $c_Q^\infty(P)$ that satisfies the functional equation

$$c_Q^\infty(P) = c_Q(P \cup c_Q^\infty(P)) \tag{6}$$

It also satisfies **(r1)**. If c satisfies **(r2)** then this is also true for c^∞.

Lemma 1. *Let c be a relative closure function satisfying* **(r1)**. *Then the associated limit c^∞ satisfies $c_Q^\infty(c_Q^\infty(P) \cup P) = c_Q^\infty(P)$ for all $P \subseteq Q$.*

Proof. We show by induction that $c_Q^{(k)}(c_Q^\infty(P) \cup P) = c_Q^\infty(P)$ for all k. The base case is equ.(6). For the induction step assume that the assertion holds for $k-1$. Then $c_Q^{(k)}(c_Q^\infty(P) \cup P) = c_Q(P \cup c_Q^{(k-1)}(c_Q^\infty(P) \cup P) = c_Q(P \cup c_Q^\infty(P)) = c_Q^\infty(P)$. Since the r.h.s. of the assertion is constant in k and the limit $c_Q^\infty(P')$ exists for all $P' \subseteq Q$, the lemma follows. ■

Lemma 2. *Let c be a relative closure function satisfying* **(r1)**, **(r2)**, *and* **(r3)**. *Then c^∞ satisfies* **(r3)**.

Proof. We first show that $c^{(k)}$ satisfies **(r3)**. We proceed by induction in k. For $k = 1$ we recover **(r3)**. For the induction step we evaluate

$$c^{(k)}_{c_Q^{(k)}(P)\cup P}(P) = c_{c_Q^{(k)}(P)\cup P}\left(P \cup c^{(k-1)}_{c_Q^{(k)}(P)\cup P}(P)\right) \supseteq c_{c_Q^{(k)}(P)\cup P}\left(P \cup c^{(k-1)}_{c_Q^{(k-1)}(P)\cup P}(P)\right).$$

By induction hypothesis, $c^{(k-1)}_{c_Q^{(k-1)}(P)\cup P}(P) = c_Q^{k-1}(P)$. With $W = c_Q^{(k-1)}(P) \cup P$, using $c_Q^{(k-1)}(P) \subseteq c_Q^{(k)}(P)$, and inserting the recursion in the subscript of the first relative closure above, we can rewrite the last term as

$$c_{c_Q(c_Q^{(k-1)}(P)\cup P)\cup c_Q^{(k-1)}(P)\cup P}(P \cup c_Q^{k-1}(P)) = c_{c_Q(W)\cup W}(W) = c_Q(W) = c_Q^{(k)}(P)$$

For the last two equalities we have used **(r3)**, and the definition of W together with the recursion for $c_Q^{(k)}$, respectively. Thus we have shown $c_Q^{(k)}(P) \subseteq c^{(k)}_{c_Q^{(k)}(P)\cup P}(P)$. The isotony condition **(r2)** yields the reverse inclusion $c^{(k)}_{c_Q^{(k)}(P)\cup P}(P) \subseteq c_Q^{(k)}(P)$. Thus $c^{(k)}$ satisfies **(r3)**.

Now we observe that $c^{(k)}_{c_Q^{(k)}(P)\cup P}(P)$ is a non-decreasing sequence of sets indexed by k. Thus the limit $c^{(\infty)}_{c_Q^{(\infty)}(P)\cup P}(P)$ exists and necessarily coincides with $c_Q^\infty(P)$. ■

In the following we will focus on c^∞. To make the connection to earlier work more transparent we simplify the notation and write $Q[P] := c_Q^\infty(P)$. These sets have a simple interpretation: $Q[P]$ is the subset of Q that is eventually reachable within Q from the seed set P. In particular, $X[P]$ enumerates the set of molecules that can be generated at least in principle from a seed stock P.

In [22] such sets were introduced axiomatically:

Definition 3. *A* system of oriented components *is a map* $(Q, P) \mapsto Q[P]$ *with* $P \subseteq Q$ *satisfying the following axioms*

(o1) $Q[P] \subseteq Q$

(o2) $P' \subseteq P$ *and* $P' \subseteq Q' \subseteq Q$ *implies* $Q'[P'] \subseteq Q[P]$

(o3) $(Q[P] \cup P)[P] = Q[P]$

(o4) $Q[Q[P] \cup P] = Q[P]$

Note that **(o1)** holds by construction for c^∞, **(o2)** is equivalent to the isotony conditions **(r1)** and **(r2)** and property **(o3)** and **(o4)** are the assertion of Lemmas 2 and 1, respectively. Axioms **(o3)** and **(o4)** were stated in different form in [22]. There, we also allowed $P \not\subseteq Q$, phrased condition **(o3)** as $(Q[P])[P] = Q[P]$ and used the additional condition **(a)** $Q[P] = (P \cup Q)[P] \cap Q$ that uniquely defines $Q[P]$ for $P \not\subseteq Q$ in terms of the larger reference set $P \cup Q$ that now contains P. Using **(a)** we have $(Q[P])[P] = (P \cup Q[P])[P] \cap Q[P]$. Since $(P \cup Q[P]) \subseteq Q$ by **(o1)** and the assumption $P \subseteq Q$, **(o2)** implies $(P \cup Q[P])[P] \subseteq Q[P]$. Thus $(Q[P])[P] = Q[P]$ if and only if **(o3)** holds as stated in the definition. In [22], axiom **(o4)** was given in the form **(o4')** "If $R \subseteq Q[P]$ then $Q[R \cup P] = Q[P]$". Using **(o2)** we have $Q[P] \subseteq Q[R \cup P] \subseteq Q[Q[P] \cup P]$. Hence our present version of **(o4)** implies $Q[R \cup P] = Q[P]$ and thus **(o4')**; conversely setting $R = Q[P]$ in **(o4')** yields **(o4)**. Thus **(o4)** and **(o4')** are equivalent in the presence of **(o2)**. Together, **(o2)** and **(o4)** also allow us to conclude that $S \subseteq Q[P]$ implies $Q[S] \subseteq Q[P]$.

It is worth noting that we can think of the relative closures c as oriented components that satisfy only **(o1)**, **(o2)**, and **(o3)**. Condition **(o4)** requires that c is iterated until no further compounds are generated, i.e., it holds for c^∞ but, in general, not for c.

The systems of oriented components on X are in 1-1 correspondence with generalized reaches. Formally, a *generalized reach* [22] is a relation $P \succ Q$ on 2^X with $P \subseteq Q \in 2^X$ that satisfies the following axioms

(O) $P \succ Q$ implies $P' \succ Q$ for $P \subseteq P' \subseteq Q$

(U) $P_i \succ Q_i$ for all $i \in I$ implies $\bigcup_{i\in I} P_i \succ \bigcup_{i\in I} Q_i$

(T) $P \succ Q$, $S \subseteq Q \subseteq T$, and $P \cup S \succ T$ implies $P \succ T$.

(A) $P \succ Q$ implies $P \succ Q'$ for all Q' satisfying $Q \setminus P \subseteq Q' \subseteq Q$.

From **(O)** and **(U)** it follows that $P \succ Q$ implies $P' \succ Q$ whenever $P \subseteq P' \subseteq Q$.

The correspondence is established by means of the bijection

$$\begin{aligned} P \succ Q \quad &\text{if and only if} \quad Q[P] = Q \text{ or } Q = \emptyset \\ Q[P] &= \bigcup \left\{ Q' \in 2^X \middle| P' \subseteq P,\, Q' \subseteq Q,\, P' \succ Q' \right\}. \end{aligned} \tag{7}$$

This is also a bijection between set systems satisfying **(o1)**, **(o2)**, and **(o3)** and set systems for which both **(O)** and **(U)** hold [22]. In the light of the discussion above, this is, in turn, equivalent to the relative closure functions. Axioms **(o4)** and **(T)**, which are called **(t+)** and **(T+)** in [22], become equivalent whenever **(o1)**, **(o2)**, and **(o3)** holds. These set systems generalize the reaches and oriented components studied in [23, 24] as axiom systems for oriented versions of connectedness. Condition **(A)** is a mostly technical condition that removes ambiguities. By construction $P \succ Q[P]$. Condition **(A)** allows us to remove (parts of) P from the "image", i.e., in particular $P \succ Q[P] \setminus P$ is also true.

While finite graphs are well understood from a topological perspective as the finite pretopological spaces [7], the question how hypergraphs fit into the framework of point set topology has remained open [20]. Since chemical reaction networks are not necessarily finite, this is a problem of potentially practical importance. Related "constructive systems" have shown that their topological aspects are indeed important. The Scott topology [25] and the Visser topology [26], for instance, are essential for understanding certain aspects of computation as expressed by the λ-calculus.

3 Oriented Components and Separations

3.1 A Galois connection

The main result of [22] can be rephrased in the following manner:

Proposition 4. *The equivalence*

$$A \mid B \iff (A \cup B)[B] \cap A = \emptyset \tag{8}$$

establishes a 1-1 correspondence between systems of oriented components with properties **(o1)**, **(o2)**, **(o3)**, *and* **(o4)** *and "separation relations"* $\mid$ *on* 2^X *that satisfy the following axioms*

(S0) $\emptyset \mid B$ *for all* B

(S1) $A' \subseteq A$, $B' \subseteq B$, *and* $A \mid B$ *implies* $A' \mid B'$

(SR1) $A \mid C$ *and* $B \mid A \cup C$ *implies* $A \cup B \mid C$

(SR2) *If* $A_i \cup B_i = Z$ *and* $A_i \mid B_i$ *for all* $i \in I$ *then* $\bigcup_{i\in I} A_i \mid \bigcap_{i\in I} B_i$.

This equivalence is based on the explicit construction of a Galois connection between the relations $\mid$ and $\succ$.

In [22] we established the following correspondences between properties of oriented components and their associated separation relation:

(g)	$Q[\emptyset] = \emptyset$	**(S0+)**	$A \mid \emptyset$
(m)	$P' \subseteq P \backslash Q[P]$ implies $Q[P'] = \emptyset$	**(SR0)**	$A \mid B$ implies $A \cup B \mid A \cap B$
(d)	$Q[P] = \bigcup_{p\in P} Q[\{p\}]$	**(SR2+)**	$A_i \cup B_i = Z$ and $A_i \mid B_i$ for all $i \in I$ implies $\bigcap_{i\in I} A_i \mid \bigcup_{i\in I} B_i$
(p)	$P \subseteq Q[P]$	**(S3)**	$A \mid B$ implies $A \cap B = \emptyset$

It is easy to see that **(d)** implies **(g)**. Generalized oriented components satisfying **(m)** and **(d)** are in 1-1 correspondence with the reaches of [23, 24], i.e., those that can be explained in terms of sets reachable from a single point. It is worth noting that most of the literature on directed hypergraphs considers hyperedges with hyperedges of the form $(\{p\}, Q)$ or $(P, \{q\})$ [27]. These naturally give rise to reaches. In a chemistry context, axiom **(d)** thus stipulates that all (elementary) reactions are isometrization and fragmentation reactions.

Axiom **(p)** highlights the fact that in our definition of $Q[P]$ we have not assumed that a chemical reaction reproduces its educts, or, using an alternative interpretation of $Q[P]$. For many applications it will be desirable to assume **(p)**. This simplifies the formal structure considerably and for instance, guarantees that each point is reachable from itself, since in particular $\{p\}[p] = \{p\}$ for all $p \in X$. However, in the context of flow systems educts that are not actively recreated will eventually disappear. Hence axiom

(p) must not be assumed e.g. when considering issues of self-maintenance in chemical organizations. We refer to [17, 18] for a more extensive discussion of this topic.

3.2 Strongly connected components

The concept of generalized reaches, which in a sense extends the notion of directed paths in graphs [23, 24] gives raise to natural notions of *connectedness*. In a directed graph, for instance, a set Z of vertices is strongly connected if for every pair $x, y \in Z$ there is path from x to y. The idea can be phrased for generalized reaches in the following manner:

Definition 5. *A set S is* strongly connected *w.r.t. a generalized reach, i.e., a production relation $\succ$, if $P \succ S$ for all $\emptyset \neq P \subseteq S$.*

In particular, thus, S is strongly connected if and only if $\{x\} \succ S$ for all $x \in S$.

Lemma 6. *Let $x \in S \subseteq Q$ and suppose S is strongly connected. Then $Q[\{x\}] = Q[S]$. Furthermore, if $P \subseteq Q$ and $Q[P] \cap S \neq \emptyset$ then $S \subseteq Q[P]$.*

Proof. By definition, we have $y \in S[\{x\}]$ for all $y \in S$, and thus $S = S[\![x]\!] = S[\![y]\!] \subseteq S[\{x\}]$. By **(o2)** $S[\{y\}] \subseteq S[\{x\}]$ for all $y \in S$ and thus **(o4)** implies $Q[S] = Q[\{x\}]$. To see the second statements we pick $y \in Q[P] \cap S$. Then $S \subseteq Q[\{y\}]$ and **(o4)** implies $S \subseteq Q[P]$. ■

The key elementary observation about strongly connected sets is the following

Lemma 7. *The collection $\mathscr{S}$ of strongly connected sets w.r.t. $\succ$ satisfies*

(c1) *If $S_i \in \mathscr{S}$ and $\bigcap_{i\in I} S_i \neq \emptyset$ then $\bigcup_{i\in I} S_i \in \mathscr{S}$.*

Proof. By assumption there is a common point $x \in S_i$ and $\{x\} \succ S_i$ holds for all $i \in I$. Axiom **(U)** implies $\{x\} \succ \bigcup_{i\in I} S_i$. Now fix $j \in I$ and $y \in S_j$. By definition $\{y\} \to S_j$. Since $x \in S_j$ and $\{x\} \succ S_i$, axiom **(T)** implies $\{y\} \succ S_i$. Since this is true for all $i \in I$, we can use **(U)** again to establish $\{y\} \succ \bigcup_{i\in I} S_i$ for all $y \in S_j$ and all $j \in I$, i.e., for all $y \in \bigcup_{i\in I} S_i$. Thus $\bigcup_{i\in I} S_i \in \mathscr{S}$. ■

As shown in [28, 29], the set systems $\mathscr{S}$ satisfying (c1) are in 1-1 correspondence with systems of connected components $(S, x) \mapsto S[\![x]\!]$ satisfying

(o0) $x \notin S$ implies $S[\![x]\!] = \emptyset$

(o1) $S[\![x]\!] \subseteq S$

(o2) $S \subseteq S'$ implies $S[\![x]\!] \subseteq S'[\![x]\!]$

(o3) $(S[\![x]\!])[\![x]\!] = S[\![x]\!]$

(o4) $y \in S[\![x]\!]$ implies $S[\![y]\!] = S[\![x]\!]$

The bijection is established by $S[\![x]\!] = \bigcup\{Z \in \mathscr{S} | x \in Z \subseteq A\}$. By construction $\{x\} \succ S[\![x]\!]$ whenever $x \in S[\![x]\!]$. A key result of [29,30] is

Proposition 8. *There is a one-to-one correspondence between systems of "connected components" satisfying* **(o0)**, **(o1)**, **(o2)**, **(o3)**, *and* **(o4)** *and separations* $\vdots$ *on* 2^X *satisfying* **(S0)**, **(S1)**, **(SR1)**, **(SR2)** *and the symmetry axiom*

(S2) $A \vdots B$ *implies* $B \vdots A$, *where* $A \vdots B$ *iff for all* $Z \subseteq A \cup B$ *we have* $Z \cap A = \emptyset$ *or* $Z \cap B = \emptyset$. *Conversely,* $Z \in \mathscr{S}$ *iff* $Z = A \cup B$ *and* $A \vdots B$ *implies* $A = \emptyset$ *or* $B = \emptyset$.

It is shown in [22], furthermore, that axiom **(S2)** is equivalent to **(m)**, **(d)**, and

(s) $p \in Q$ and $r \in Q[\{p\}]$ implies $Q[\{p\}] \subseteq Q[\{r\}]$.

Spaces of connected sets and their associated systems of connected components have been studied in their own right since the early work of Börger [31] and Serra [28] in the 1980s. Much of the initial interest was motivated by mathematical morphology and image processing [29,32]. Recent investigation such as [33,34] arrive at the same structure from different starting points.

As an immediate consequence of Lemma 7, any set $Q \subseteq X$ decomposes uniquely into strongly connected components Q_i for index set I and residual points that do not belong to any connected component. Now suppose $A \cup B = Q$ and $A \vdots B$. Then $Q_i \cap A = \emptyset$ or $Q_i \cap B = \emptyset$ for all $i \in I$. Write I_A and I_B for the index sets so that $Q_i \subseteq A$ (and thus $Q_i \cap B = \emptyset$ for $i \in I_A$ and $Q_i \subseteq B$ (and thus $Q_i \cap A = \emptyset$ for $i \in I_B$. Obviously $I_A \cup I_B = I$ and $I_A \cap I_B = \emptyset$.

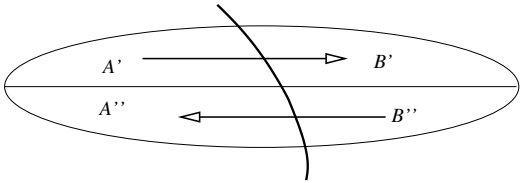

Figure 2. Counterexample. Consider a set Q consisting of 4 strongly connected components such that $Q[A'] = A' \cup B'$, $Q[B'] = B'$, $Q[A''] = A''$, and $Q[B''] = A'' \cup B''$. Set $A = A' \cup A''$ and $B = B' \cup B''$. We have $A \mathrel{:} B$ since arbitray subsets of strongly connected components are $\mathrel{:}$-separated from each other. However, we have neither $A \mid B$ nor $B \mid A$.

The construction of the separation $\mathrel{:}$ associated with strongly connected components suggests to investigate its relationship with the separation $\mid$ of the underlying generalized reach. In immediate consequence of the discussion above is

Fact 9. *$A \mid B$ or $B \mid A$ implies $A \mathrel{:} B$.*

The converse, however, is not true in the general case, as shown by the counter-example in Fig. 2. It does hold, however, between pairs of connected components.

Lemma 10. *Let $Q = A \cup B$, $A \mathrel{:} B$, and let $S_1 \subseteq A$ and $S_2 \subseteq B$ be strongly connected. Then $S_1 \mid S_2$ or $S_2 \mid S_1$.*

Proof. Suppose neither $S_1 \mid S_2$ nor $S_2 \mid S_1$ holds, i.e., $(S_1 \cup S_2)[S_i] \cap S_i \neq \emptyset$ for $i = 1, 2$. By Lemma 6 and using **(o4)** have $(S_1 \cup S_2)[\{x\}] = S_1 \cup S_2$ for all $x \in S_1 \cup S_2$, i.e., $S_1 \cup S_2$ is strongly connected, constradicting $S_1 \mathrel{:} S_2$, which follows immediately from $A \mathrel{:} B$ and **(S1)**. ■

For any two strongly connected components S' and S'' holds that S' is not $\mid$-separated from S'' if and only if $(S' \cup S'')[S''] = S' \cup S''$.

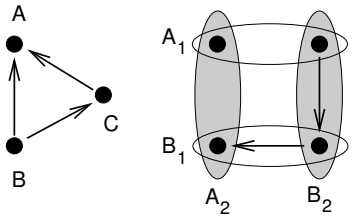

Figure 3. L.h.s.: The relation $\wr$ defined as $A \wr B$ iff "$A \mid B$ or $B \mid A$" does not satisfy **(SR1)**. We have $C \mid A$ and $B \mid A \cup C$, i.e., $A \wr C$ and $B \wr A \cup C$, but neither $A \cup B \mid C$ nor $C \mid A \cup B$ is true.
R.h.s.: $\wr$ does not satisfy **(SR2)**. We have $B_1 \mid A_1$, i.e., $A_1 \wr B_1$, and $A_2 \mid B_2$; but neither $A_1 \cup A_2 \mid B_1 \cap B_2$ nor $B_1 \cap B_2 \mid A_1 \cup A_2$ is true.

Before we proceed, we briefly consider the relation $A \wr B$ defined as "$A \mid B$ or $B \mid A$". It is straightforward to see that $\wr$ is isotonic and satisfies **(S0)**. The counterexamples in Fig. 3, however, show that $\wr$ satisfies neither **(SR1)** nor **(SR2)**. Therefore $\wr$ is not equivalent to a system of connected sets.

3.3 Weakly connected components

Let us now turn to notions of connectedness that are weaker than reachability. In graph theory, *weak connectedness* requires only the existence of a sequence of arcs between two points without regarding their orientation. It does not seem to be immediately clear how this intuitive notion should be generalized to the much more general setting discussed here.

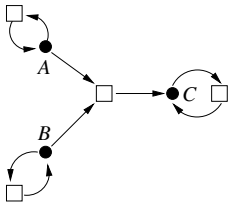

Figure 4. The relation $\parallel$ does not satisfy **(SR1)**. Consider the chemical network on three compounds. It satisfies $\{x\} \succ \{x\}$. Denoting the sets containing a single compound each by A, B, and C, we have the symmetric separations $A \parallel B$, $A \parallel C$, $B \parallel C$, $A \parallel B \cup C$, $B \parallel A \cup C$. In addition $A \cup B \parallel C$. The production $(A \cup B) \succ C$ implies that $C \mid A \cup C$ is not true. This **(SR1)** fails: $A \parallel C$ and $B \parallel A \cup C$ would imply $A \cup B \parallel C$ and thus also $C \mid A \cup C$, a contradiction.

A simple idea would be to consider the separation relation $\parallel$ defined by $A \parallel B$ if and only if $A \mid B$ and $B \mid A$. Clearly $\parallel$ is again isotonic, and hence a separation relation. It

fails to satisfy **(SR1)**, however, as the example in Fig. 4 shows. A similar example on four point $\{u, v, w, x\}$ and the single non-trivial production $\{u, v, w\} \succ \{x\}$ shows that **(SR2)** also fails: Setting $A_1 = \{u, v\}$, $B_1 = \{w, x\}$, and $A_2 = \{u, w\}$, $B_2 = \{v, x\}$ we have $A_1 \parallel B_1$ and $A_2 \parallel B_2$. From $A_1 \cup A_2 = \{u, v, w\}$ $B_1 \cap B_2 = \{x\}$ we should be able to conclude that $\{u, v, w\} \parallel \{x\}$. But, by construction $\{x\} \mid \{u, v, w\}$ is violated, hence **(SR2)** fails.

An alternative approach is to declare reaches as connected sets. The union property, however, is undesirable since it would stipulate that every union of connected sets is again connected, a situation that contradicts our intuition. On the other hand, the idea that an individual chemical reaction should count as connected set is certainly appealing. Let us formalize this idea:

Definition 11. *A production $P \succ Q$ is* redundant *if there is a collection of strictly smaller productions $P_i \succ Q_i$ with $P_i \subseteq P$ and $Q_i \subseteq Q$ such that $\bigcup_i P_i = P$ and $\bigcup_i Q_i = Q$.*

For directed graphs, irredundant productions are their arcs; for directed hypergraphs, irredundant productions are their directed hyperedges.

Now we could construct a collection $\mathscr{B}$ of connected sets by setting $P \cup Q \in \mathscr{B}$ if $P \succ Q$ is not redundant. As discussed in [29, 30] this gives rise to a separation relation $\|^*$ via $A \|^* B$ if and only if there is no $Z \subseteq A \cup B$ such that $Z \in \mathscr{B}$, $A \cap Z \neq \emptyset$, and $B \cap Z \neq \emptyset$. For graphs and hypergraphs, this reproduces the weak connected components and the weak connected components of the König graph representation of the hypergraph. It remains an open question, however, whether this is the only or the most natural construction of weakly connected components.

Consider a tiny network $X = \{u, v, w, x\}$ with reactions $u \to x$ and $v \to y$. Obviously, their sum $u + v \to x + y$ is redundant according to Definition 11. Whether X should be interpreted as weakly connected, by virtue of $u + v \to x + y$, or whether it should be treated as consisting of two weakly connected components $\{u, x\}$ and $\{v, y\}$ depends on the context and the purpose of the model. Assuming that $u + v \to x + y$ is only a formal sum of two elementary reactions, the second interpretation is clearly the better chemical represention. On the other hand, if we assume that $u + v \to x + y$ is an elementary reaction following 2nd order kinetics, it may not be considered redundant from a chemical point of view. It may thus be necessary in general to explicitly specify a basis of elementary, i.e., irredundant reactions, instead of relying on Definition 11. From a mathematical point of

view this issue suggests that there is some freedom in what can naturally be considered weakly connected in a chemical network.

4 Wallace Functions

The connection between separations and closure functions was introduced by Wallace [35] and explored in more detail by Hammer [36]. It provides a natural link between proximity and separation spaces and generalized topologies.

Definition 12. *Let* $\mathfrak{R} \subseteq 2^X \times 2^X$ *be an arbitrary relation on* 2^X. *Then the* Wallace function *or* closure function *associated with* $\mathfrak{R}$ *is* $w : 2^X \to 2^X$ *defined by*

$$w(B) = \bigcap_{(A,B)\in\mathfrak{R}} X \setminus A \tag{9}$$

Equivalently, $w(B) = X \setminus \bigcup_{(A,B)\in\mathfrak{R}} A$ and thus

$$(A, B) \in \mathfrak{R} \text{ implies } A \cap w(B) = \emptyset \tag{10}$$

We note in passing that there is a number of related constructions that various authors have referred to as Wallace functions, most notably the one derived from the transpose of $\mathfrak{R}$ [36].

In this contribution we are interested primarily in separation relations. The isotony property allows a simpler representation of the Wallace function:

Lemma 13. *If* $\mathfrak{R}$ *is hereditary* **(S1)**, *then*

(i) $x \in w(B)$ *iff* $(\{x\}, B) \notin \mathfrak{R}$

(ii) w *is isotonic, i.e.,* $B' \subseteq B$ *implies* $w(B') \subseteq w(B)$.

Proof. (i) $x \in w(B)$ iff $x \in A$ for all A such that $(X \setminus A, B) \in \mathfrak{R}$, i.e., iff $x \notin A'$ for all A' satisfying $(A', B) \in \mathfrak{R}$. By heredity the latter condition is equivalent to $(\{x\}, B) \notin \mathfrak{R}$.

(ii) Suppose $B' \subseteq B$. By heredity $(\{x\}, B) \in \mathfrak{R}$ implies $(\{x\}, B') \in \mathfrak{R}$, i.e., $x \notin w(B)$ implies $x \notin w(B')$. ■

From now on we assume that $\mathfrak{R}$ is hereditary, i.e., **(S1)** holds, and we revert to the notation $|$. The following lemma is well known for the symmetric case, see e.g. (3.3) in [35], thm. 3.2 of [37], the discussion in [38] or thm. 3 of [39]. For completeness we include the simple proof here.

Lemma 14. *If | satisfies* **(S1)**, *then*

(wy) *$A \mid B$ is equivalent to $A \cap w(B) = \emptyset$*

holds if and only if | satisfies

(SY) *$\{x\} \mid B$ for all $x \in A$ implies $A \mid B$.*

Proof. Clearly $A \cap w(B) = \emptyset$ if and only if $x \notin w(B)$ for all $x \in A$, which by definition of the Wallace function is equivalent to $\{x\} \mid B$ for all $x \in A$. By **(S1)** $A \mid B$ implies $\{x\} \mid B$ for all $x \in A$, hence **(SY)** is equivalent to "$A \mid B$ if and only if $\{x\} \mid B$ holds for all $x \in A$", hence $A \cap w(B) = \emptyset$ is indeed equivalent to $A \mid B$. ■

Using the equivalence of separation relations and oriented connected components we can express the Wallace function also in terms of oriented components. Recall that invoking this equivalence amounts to assuming that **(S0)**, **(S1)**, **(SR1)**, and **(SR2)**, and equivalently, **(o1)**, **(o2)**, **(o3)**, and **(o4)** is satisfied. We have $\{x\} \mid B$ if and only if $(\{x\} \cup B)[B] \cap \{x\} = \emptyset$, i.e., if and only if $x \notin (\{x\} \cup B)[B]$. Hence

$$x \in w(B) \quad \text{if and only if} \quad x \in (B \cup \{x\})[B]\,. \tag{11}$$

Therefore we can write

$$w(B) = \bigcup_{x \in X} (B \cup \{x\})[B] \tag{12}$$

as an alternative definition of Wallace functions for oriented components. It is by construction consistent with the definition in terms of separations relations.

Now consider $P \subseteq Q$. Then $x \in Q \cap w(P)$ if and only if $x \in Q \cap (P \cap \{x\})[P]$. For all $x \in Q$ we have $(P \cap \{x\})[P] \subseteq Q[P]$, and thus

$$Q \cap w(P) \subseteq Q[P]\,. \tag{13}$$

Lemma 15. *Let | be a separation with a corresponding system of oriented components $(P, Q) \mapsto Q[P]$ and suppose $P \subseteq Q$. If* **(SY)** *holds, then $Q[P] = Q \cap w(P)$ holds for all $P \subseteq Q$.*

Proof. By equ.(10) and **(SY)** we have $A \mid P$ iff $A \cap w(P) = \emptyset$ and hence in particular $X \setminus w(P) \mid P$. By **(S1)** we therefore have $Q \setminus w(P) \mid P$. Now $P \subseteq Q$ and equ.(8) imply $Q[P] \cap (Q \setminus w(P)) = \emptyset$, and therefore $Q[P] \subseteq w(P)$. Thus equality holds in equ.(13). ■

From equ.(12) we obtain the following

Corollary 16. *If* **(SY)** *holds, then* $w(P) = X[P]$.

This implies, furthermore, $Q[P] = Q \cap X[P]$, i.e., $Q[P]$ is simply the closure $P \mapsto X[P]$ restricted to subspaces.

As an immediate consequence of the basic properties of oriented components we therefore conclude that in the presence of **(SY)** we have $w(w(P) \cup P) = w(P)$. Because of isotony, $w(P) \subseteq w(w(P) \cup P)$, and thus $w(w(P)) = w(P)$, i.e., the Wallace function is idempotent.

Lemma 17. *Let* $|$ *be a separation with a corresponding set of oriented components and let* w *be its Wallace function. If* $Q[P] = Q \cap w(P)$ *for all* $P \subseteq Q$*, then* **(SX)** *holds.*

Proof. Suppose $Q[P] = Q \cap w(P)$. Then $A \mid P$ holds for $A \subseteq Q$ if and only $A \cap w(P) = \emptyset$, i.e., if and only if $x \notin w(P)$, i.e., if and only if $\{x\}|P$ for all $x \in A$. Thus **(SY)** holds. ■

Theorem 18. *Let* $|$ *be a separation with a corresponding set of oriented components. Then* **(SY)** *is equivalent to*

(y) $Q[P] = \bigcup_{x \in Q} (P \cup \{x\})[P]$ *for all* $P \subseteq Q$

Proof. From lemma 15 and 17 we know that $Q[P] = Q \cap w(P)$ for all $P \subseteq Q$ is equivalent to **(SY)**. From equ.11 we have in particular $Q \cap w(P) = \bigcup_{x \in Q} (P \cup \{x\})[P]$, concluding the proof. ■

Lemma 19. *If* **(y)** *then* $(P \cup \{x\})[P] = P[P]$ *for all* $x \in Q \setminus Q[P]$.

Proof. If $x \in P$ then $(P \cup \{x\})[P] = P[P]$. If $x \notin P \cup Q[P]$ then **(x)** implies $(P \cup \{x\})[P] \subseteq Q[P]$ and therefore $x \notin (P \cup \{x\})[P]$, whence $(P \cup x)[P] \subseteq P$. By **(o3)** we have $(P \cup \{x\})[P] = (P \cup (P \cup \{x\})[P])[P] = P[P]$. ■

As a consequence, it suffices to consider the union over the $x \in Q[P]$ in condition **(y)**.

Theorem 18 characterizes the production relations and their systems of oriented components that can specified completely in terms of closure function. Clearly, condition **(y)** is much too restrictive to describe chemical spaces in general.

5 Concluding Remarks

In this contribution we have explored some basic properties of oriented components and their equivalent separation relations. We have shown, in particular, that these mathematical objects provide an essentially faithful topological description of reachability within directed hypergraphs, including (not necessarily finite) chemical reaction networks. Our focus here are the notions of connectedness arising from oriented components. While there is a very natural definition of strongly connected components, it is much less clear how to obtain a concept of weak connectedness. The construction proposed here uses a concept of "irredundancy". Since systems of oriented components are equivalent to certain (non-symmetric) separation spaces, it seemed obvious to consider symmetrization of the separation relations. As it turns out, these are not equivalent to systems of connected sets. It appears promising, however, to consider this question from the point of view of the lattice of separation relations [29, 40].

Chemical reactions are reversible, at least in principle. That is, if $(U, V) \in E$, then $(V, U) \in E$. It is of interest, therefore, to consider how this condition can be expressed in terms of production relations. This is not completely straightforward since $P \succ Q$ implies $P' \succ Q$ for all P' with $P \subset P'$ and thus one cannot simply interpret $Q \setminus P$ as the set of product molecules. Instead, given $P \succ Q$ it seems natural to consider the inclusion-minimal subsets $P' \subseteq P$, for which $P' \succ Q$ still holds, as the sets of necessary educts. In the absence of catalysts, reversibility then requires that there is $\bar{P} \subseteq Q$ such that $\bar{P} \succ Q$ and $\bar{P} \cap P' = \emptyset$. In an elementary reaction, furthermore, we should have $P' \cup \bar{P} = Q$ with both P' and $\bar{P}$ being inclusion minimal. Catalysts, however, require $P' \cap \bar{P} \neq \emptyset$, and in composite reactions it may be the case that part of Q is generated and then used up again by intermediate reactions, so that $P' \cap \bar{P} \subset Q$ does not cover all molecules produced within Q. This topic clearly deserves attention in future work.

One might argue that oriented components are a somewhat crude structure that still fails to represent some of the intricacies. This is, in particular, due to the "transitivity" axiom **(o4)**. This suggests to study the relative closures, which lack **(o4)**, in some more detail. Since these are directly expression in terms of the edge set of the chemical reaction networks, they also seem to be a quite natural structure to capture reversibility in a concise manner.

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