

INTERSECTION-UNION SYSTEMS*

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In two recent papers the authors introduced some new approaches to the problem of modeling the phenomena underlying immunological reaction tests. These approaches allow one to easily construct the best possible models for a given amount of immunological test data. In the first paper the authors used a purely Boolean approach, i.e., it was assumed that the experimenter signified whether or not a reaction occurred in a given test. In the second paper the authors assumed that the relative strengths of the reactions were available as data for the modeling process. They showed that in this case strictly better models could be constructed. This paper generalizes the approaches taken in the first two papers and provides a unified approach to this whole subject. Many of the results, e.g., the ability to construct the best model, of the first two papers hold in this more general setting. Moreover, this generalization allows one to assess the tradeoffs involved in using data on the relative strengths of reactions. In particular, we see that using relative strengths is equivalent to using an additional intersection factor in a strictly Boolean approach. This intersection factor it turns out, can be obtained experimentally by using elution in addition to the absorption involved in the first two papers. Finally, the duality between fragments and cofragments becomes apparent using this approach.

1. Introduction

Recently, there have been a number of papers [1-10] written suggesting a variety of ways of modeling immunological reaction testing. The authors have put forward some suggestions [1,2,9,10] which avoid some of the ambiguity associated with other approaches. Biological justification for the mathematics involved in [1 and 9] is given in [2 and 10]. The present paper analyzes more deeply the mathematics involved in [1 and 3] and gives a deeper understanding of the tradeoffs involved in using the relative strengths of reactions as input data.

The basic question this paper and [1 and 9] seek to answer is how to discover a binary relation which is observed only indirectly through reaction tests. The next several paragraphs recall some of the definitions and conventions of [1 and 9].

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Throughout this paper G will denote the binary relation between the set of individuals, \mathcal{I} , and the set of antibodies, \mathcal{A} , defined by iGa iff i has some antigen recognized by a . G shall be called the *fundamental relation*. If the reader is unfamiliar with immunology, he need only assume that we are given a binary relation G between two sets \mathcal{I} and \mathcal{A} . G is the relation we seek to reconstruct from the data we are given. The exact nature of this data will be described in greater detail below.

Conventions

The following conventions will be used throughout this paper.

- (a) Iff means if and only if.
- (b) If n is an integer, $n = \{1, \dots, n\}$.
- (c) If X is a set and y an element, $X+y$ denotes $X \cup \{y\}$ and $X-y$ denotes $X - \{y\}$.
- (d) If S is a set, $|S|$ denotes its cardinality and $\mathcal{P}(S)$ its power set.
- (e) If $B \subseteq X \times Y$ and $S \subseteq X$ ($T \subseteq Y$), then $SB = \{y \in Y \mid xBy \text{ for some } x \in S\}$ ($BT = \{x \in X \mid xBy \text{ for some } y \in T\}$). For $x \in X$ ($y \in Y$) we write xB (By) instead of $\{x\}B$ ($B\{y\}$). Thus, iG is the set of all antibodies that recognize some antigen possessed by individual i , and Ga is the set of all individuals possessing some antigen recognized by a .
- (f) If $B \subseteq X \times Y$ and $S \subseteq X$ [$T \subseteq Y$], then $B-S$ [$B-T$] is just $B \cap ((X-S) \times Y)$ [$B \cap (X \times (Y-T))$]. For singleton sets, we omit the set braces as in (e) above.
- (g) To avoid trivialities and uninteresting cases, we assume that $Ga \neq \emptyset$, \mathcal{I} for all $a \in \mathcal{A}$, $iG \neq \emptyset$, \mathcal{A} for all $i \in \mathcal{I}$, and $Ga \neq Gb$ for all distinct a, b in \mathcal{A} .

The goal of the techniques discussed here and in other papers is to uncover the relation G from the results of reaction tests which are given by the relation G^* which will be defined shortly. In general, G^* is not available in its entirety and any technique having practical use must have the ability to extract as much information as possible from parts of G^* . This additional problem will also be discussed in this paper.

Definition 1.1. Let $G \subseteq \mathcal{I} \times \mathcal{A}$ be as above. The *reaction relation associated with G* , denoted by G^* , is a binary relation between subsets of \mathcal{I} defined by TG^*S iff $\bigcap_{i \in T} iG \not\subseteq SG$. For integers j and k , $G^*(j, k)$ shall denote $\{(T, S) \in G^* \mid |T| \leq j, |S| \leq k\}$. \square

Note that $iM(G, w)(j, S)$ in the notation of [1, 2, 9 and 10] iff $\{i, j\}G^*S$. Thus G^* generalizes the concept of reaction relation of [1, 2, 9 and 10].

Notation. For $S, T \subseteq \mathcal{I}$, $\Delta(T, S)$ shall denote $\bigcap_{i \in T} iG - SG$. Here we take $\bigcap_{i \in T} G = \mathcal{I}$ if $T = \emptyset$ and $SG = \emptyset$ if $S = \emptyset$. Note $\Delta(TS) = \{\alpha \mid T \subseteq G\alpha \subseteq \mathcal{I} - S\}$. \square

Thus elements of $\Delta(T, S)$ are obtained as intersections of rows of G (indexed by

T) minus unions of rows of G (indexed by S) and TG^*S iff $\Delta(T, S) \neq \emptyset$. The biological problem of determining G from systematically taken data described in [1,9] translates into the problem of determining a binary relation given whether certain row intersections minus row unions are empty or not.

2. General detectability

The concept of detectability introduced in this section generalizes the concepts of detectability in [1] and that of fc-detectability in [9]. Basically, an antibody is detectable iff its absence changes G^* . The following is a formal definition of this concept.

Definition 2.1. An antibody $a \in \mathcal{A}$ is (j, k) -detectable if $(G - a)^*(j, k) \neq G^*(j, k)$. \square

Theorem 2.2. An antibody a is (j, k) -detectable iff there exist $T, S \subseteq \mathcal{I}$ such that $|T| \leq j$, $|S| \leq k$ and $\{a\} = \Delta(T, S)$.

Proof. Obvious. \square

Theorem 2.3. An antibody a is $(j, |\mathcal{A}|)$ -undetectable iff for all $T \subseteq Ga$ with $|T| \leq j$, there exists $b \in \mathcal{A}$ such that $T \subseteq Gb \subset Ga$. Thus Ga is the union of the Gb . (Such a union is called an undetectable union.)

Proof. Necessity. Let $T \subseteq Ga$ be such that $|T| \leq j$ and let S be $\mathcal{I} - Ga$. Then $a \in \Delta(T, S)$. Since a is $(j, |\mathcal{A}|)$ -undetectable, it follows from Theorem 2.2 that there exists $b \in \Delta(T, S)$ with $b \neq a$. Since $b \in \Delta(T, S)$, $T \subseteq Gb$ and $Gb \cap S = \emptyset$. Thus $T \subseteq Gb \subset Ga$ since $Gb \neq Ga$.

Sufficiency. Suppose a is $(j, |\mathcal{A}|)$ -detectable, i.e., by Theorem 2.2, there exist $T, S \subseteq \mathcal{I}$ with $|T| \leq j$ and $\{a\} = \Delta(T, S)$. Pick b with $T \subseteq Gb \subset Ga$. Clearly $b \in \Delta(T, S)$ which is a contradiction. \square

Note that $(2, k)$ -detectability is simply the k -detectability of [1]. In particular, Theorems 2.2 and 2.3 generalize Theorem 3(b), (c) of [1]. In fact, all the results in Section III of [1] generalize in the same way, but these generalizations shall not be stated explicitly. In the next section, it will be shown that k -fc-detectability of [9] corresponds to $(3, k)$ -detectability.

3. Fragments and cofragments

In [1] fragments were defined from the Boolean reaction relation $G^*(2, k)$ and used to calculate information about G . In [9] cofragments were defined by taking

relative reaction strength into account and both fragments and cofragments were used to calculate information about G . In our more general present setting theorem 3 of [9] furnishes a good approach to the *definition* of fragments and cofragments.

Definition 3.1. Let $T, S \subseteq \mathcal{I}$. Define $F(T, S)$ to be $\bigcap_{a \in \Delta(T, S)} Ga$ and $C(T, S)$ to be $\bigcup_{a \in \Delta(T, S)} Ga$. The $F(T, S)$'s are called *fragments* and the $C(T, S)$'s are called *cofragments*. If $\Delta(T, S) = \emptyset$, $F(T, S) = \mathcal{I}$ and $C(T, S) = \emptyset$. If needed for clarity, the fundamental relation used to derive a given fragment or cofragment will be added to the symbols to yield $F(T, S, G)$ and $C(T, S, G)$ respectively. \square

The k -fragments and k -cofragments of [1] and [9] result from restricting the cardinality of T to be 2 and the cardinality of S to be $\leq k - 1$. The following theorem develops the properties of fragments and cofragments in greater detail and shows their duality more clearly.

Theorem 3.2. Let T and S be subsets of \mathcal{I} . Then the following are true.

- (a) $T \subseteq F(T, S)$.
- (b) $F(T, S) = \{i \in \mathcal{I} \mid \neg TG^*(S+i)\}$.
- (c) $C(T, S) \subseteq \mathcal{I} - S$.
- (d) $C(T, S) = \{i \in \mathcal{I} \mid (T+i)G^*S\}$.

Proof. (a) If $\Delta(T, S) = \emptyset$, the result is obvious. Otherwise, let $a \in \Delta(T, S)$, i.e., $T \subseteq Ga$. Thus $T \subseteq F(T, S)$.

(b) Note that $i \in F(T, S)$ iff $iG \supseteq \Delta(T, S)$ iff $\neg TG^*(S+i)$.

(c) If $i \in S$, $iG \cap \Delta(T, S) = \emptyset$, which means that $i \notin C(T, S)$.

(d) Note that $i \in C(T, S)$ iff $iG \cap \Delta(T, S) \neq \emptyset$ iff $(T+i)G^*S$. \square

Thus both fragments and cofragments can be calculated directly from G^* without the need for using reaction strengths as in the original definitions [9]. Theorem 3.2 shows that in order to calculate the k -cofragments of [9] from G^* one needs to be able to take intersections of three sets. Some biological contexts necessitate the use of relative reaction strengths rather than intersections of 3-sets as suggested by Theorem 3.2. It will be seen that the theory developed in [9] is essentially equivalent to the Boolean theory derived from $G^*(3, k)$ and it turns out that there is an experimental technique (elution) which, when available, can fully utilize the theory derived from $G^*(h, k)$ for $h \geq 3$.

The following definition separates the two notions intertwined in the concept of fragment-cofragment undetectability which was introduced in [9].

Definition 3.3. An antibody a is called (j, k) -*f-undetectable* or (j, k) -*fragment-undetectable* if the fragments $F(T, S, G)$ and $F(T, S, G - a)$ are equal for all T, S with $|T| \leq j$ and $|S| \leq k$. Similarly, a is called (j, k) -*c-undetectable* or (j, k) -*cofragment-undetectable* if the cofragments $C(T, S, G)$ and $C(T, S, G - a)$ are equal for all T, S with $|T| \leq j$ and $|S| \leq k$. \square

Theorem 3.4 relates all the various kinds of detectability and allows us to determine precisely the various trade offs involved.

Theorem 3.4. *Let a be an antibody and j, k nonnegative integers. Then the following are equivalent:*

- (1) a is $(j, k+1)$ - c -detectable,
- (2) a is $(j+1, k)$ - f -detectable,
- (3) a is $(j+1, k+1)$ -detectable.

Proof. The first step is to show that (1) implies (3). If (1) holds, there exist T, S with $|T| \leq j$, $|S| \leq k+1$ and $C(T, S, G) \neq C(T, S, G-a)$. Since the two cofragments are unequal, the first one is a proper superset of the second. Thus there exists an element $y \in C(T, S, G) - C(T, S, G-a)$. This means that $a \in \Delta(T, S, G)$, $y \in Ga$ and $y \notin Gb$ for all $b \in \Delta(T, S, G-a) = \Delta(T, S, G) - a$. Thus $\Delta(T, S, G) = \{a\}$ and (3) holds by Theorem 2.2.

The next step is to show that (2) implies (3). If (2) holds, there exist T, S with $|T| \leq j+1$, $|S| \leq k$ and $F(T, S, G) \subset F(T, S, G-a)$. Proceeding as before, pick $y \in F(T, S, G-a) - F(T, S, G)$. This means that $a \in \Delta(T, S, G)$, $y \notin Ga$ but $y \in Gb$ for all $b \in \Delta(T, S, G-a) = \Delta(T, S) - a$. But this implies that $\delta(T, S+y, G) = \{a\}$ holds by Theorem 2.2.

The final step is to show that (3) implies (1) and (2). If (3) holds, there exist T, S with $|T| \leq j+1$, $|S| \leq k+1$ and $\Delta(T, S, G) = \{a\}$. If $T = \emptyset$, by our conventions, $C(T, S, G) = Ga \neq \emptyset = C(T, S, G-a)$ and (1) holds trivially. If $T \neq \emptyset$, then for each $y \in T$, $y \in C(T-y, S, G)$ since $a \in \Delta(T, S, G)$ implies $y \in Ga \subseteq C(T-y, S, G)$. However, it is impossible for $y \in C(T-y, S, G-a)$, since this would imply the existence of an antibody b , distinct from a which belongs to $\Delta(T-y, S, G-a)$ and for which $y \in Gb$. But this would imply that $b \in \Delta(T, S, G)$ contradicting our initial assumption. Thus (1) holds again.

Similarly, if $S = \emptyset$, $|S| \leq k$, $F(T, S, G) = Ga \neq \emptyset = F(T, S, G-a)$ and (2) holds trivially. On the other hand, if $S \neq \emptyset$, then for each $y \in S$, $y \notin F(T, S-y, G)$ since $a \in \Delta(T, S, G)$ implies $y \notin Ga \supseteq F(T, S-y, G)$. However, it must be true that $y \in F(T, S-y, G-a)$, since the contrary implies the existence of an antibody, b , distinct from a which belongs to $\Delta(T, S-y, G-a)$ and for which $y \notin Gb$. But this would imply that $b \in \Delta(T, S, G)$ contradicting our initial assumption. Thus (2) holds again. \square

4. Recovering the fundamental relation

The purpose of this paper and other work in this area is to show how G may be recovered from G^* or parts of G^* . As the following theorem shows, it is very easy to recover G from all of G^* . As in [1] we can consider G as a relation from \mathcal{J} to $\mathcal{P}(\mathcal{J})$ by identifying an antibody with its reaction range.

Theorem 4.1. Let $\Gamma = \{X \subseteq \mathcal{I} \mid \text{for some } T, S \subseteq \mathcal{I}, X = F(T, S) = C(T, S)\}$. Then $\Gamma = \{G_a \mid a \in \mathcal{A}\}$, i.e., the elements of Γ are just the columns of G . (Recall $G_a \neq G_b$ if $a \neq b$.) Thus the relation $H = \{(i, X) \in \mathcal{I} \times \Gamma \mid i \in X\}$ is identical with G .

Proof. Let $a \in \mathcal{A}$. The first thing to note is that $\Delta(G_a, \mathcal{I} - G_a) = \{a\}$. To see this, assume $b \in \Delta(G_a, \mathcal{I} - G_a)$. Since $b \in iG$ for all $i \in G_a$, $G_a \subseteq Gb$. Since $b \notin iG$ for all $i \in \mathcal{I} - G_a$, $Gb \subseteq G_a$. Thus $Gb = G_a$ and $b = a$ by our initial set of assumptions. From this, it follows easily that $G_a = F(G_a, \mathcal{I} - G_a) = C(G_a, \mathcal{I} - G_a)$.

Conversely if $X = F(T, S) = C(T, S)$, then $\Delta(T, S)$ cannot be empty. Suppose $a \in \Delta(T, S)$. Since $X = F(T, S) \subseteq G_a \subseteq C(T, S) = X$, $X = G_a$. \square

Unfortunately, G^* is usually unavailable in its entirety. In fact, even if it were biologically feasible to generate all of the values of G^* , it is clear that there would rarely be enough time or resources to compute the $2^{2^{|\mathcal{I}|}}$ entries. Thus, the question of most practical interest is determining the 'best' answer given a subset of G^* . The following definition introduces some terms and concepts which generalize the ideas dealing with solutions in [1,2,9,10].

Definition 4.2. Let $W \subseteq P(\mathcal{I}) - \{\emptyset, \mathcal{I}\}$ and $R \subseteq P(\mathcal{I}) \times P(\mathcal{I})$.

(a) The *R-restriction of G^** , is simply $R \cap G^*$, i.e., $X(R \cap G^*)Y$ iff XRY and XG^*Y .

(b) The *fundamental relation generated by W* , $G_W \subseteq \mathcal{I} \times W$, is defined by $iG_W X$ iff $i \in X$. Note that the elements of W play the role of antibodies.

(c) The *reaction relation generated by W* is simply G_W^* . $G_W^* \cap R$ and $G_W^*(j, k)$ have the same meaning as before.

(d) The *G, R -solution space*, denoted by $\text{Sol}(G, R)$, is the set $\{W \subseteq P(\mathcal{I}) - \{\emptyset, \mathcal{I}\} \mid G_W^* \cap R = G^* \cap R\}$. Members of $\text{Sol}(G, R)$ are referred to as G, R -solutions. Here $\text{Sol}(G, j, k)$ means the obvious thing, i.e., $G^*(j, k)$ replaces $G^* \cap R$ in the previous sentence. \square

$\text{Sol}(G, R)$ is thus the set of all solutions to the problem of determining G from the restricted set of data $R \cap G^*$. Note that the above definitions using R reduce to the definitions using the indices j and k if R is assumed to be $\{(X, Y) \mid |X| \leq j, |Y| \leq k\}$. The greater generality resulting from the use of R is useful in those cases where data exists only in irregular forms. Furthermore, the proofs of the theorems do not suffer from an increase in complexity, because of an increase in the generality. Analogous to the results in earlier papers, G, R -solution spaces are closed under unions and consequently contain largest elements.

Theorem 4.3. Let $W_1, W_2 \in \text{Sol}(G, R)$, then $W_1 \cup W_2 \in \text{Sol}(G, R)$.

Proof. If $T, S \subseteq \mathcal{I}$ are such that $T(G^* \cap R)S$, then $T(G_{W_1}^* \cap R)S$. Since $W_1 \subseteq W_1 \cup W_2$ it is clear that $T(G_{W_1}^* \cap R)S$ implies $T(G_{W_1 \cup W_2}^* \cap R)S$.

Conversely, if $T(G_{W_1 \cup W_2}^* \cap R)S$, $(T, S) \in R$, and there exists $X \in W_1 \cup W_2$ such that $T \subseteq X$ and $S \cap X = \emptyset$. Since $X \in W_1 \cup W_2$, $X \in W_1$ or $X \in W_2$, then $T(G_{W_1}^* \cap R)S$. Since $G_{W_1}^* \cap R = G^* \cap R$, $T(G^* \cap R)S$. The argument is identical if $X \in W_2$. \square

Corollary 4.4. $\text{Sol}(G, R)$ contains a largest solution, denoted $\Sigma(G, R)$, which is the union of all elements of $\text{Sol}(G, R)$. \square

Theorem 4.5. $\text{Sol}(G, |\mathcal{J}|, |\mathcal{J}|)$ contains exactly one element: $\{G\alpha \mid \alpha \in \mathcal{A}\}$.

Proof. Let $W \in \text{Sol}(G, |\mathcal{J}|, |\mathcal{J}|)$ and $X \in W$. Note that $XG_W^*(\mathcal{J} - X)$ and thus $XG^*(\mathcal{J} - X)$, i.e., there exists $\alpha \in \Delta(X, \mathcal{J} - X)$. Thus $X \subseteq G\alpha$ and $\mathcal{J} - X \subseteq \mathcal{J} - G\alpha$, whence $G\alpha = X$. This means that $W \subseteq \{G\alpha \mid \alpha \in \mathcal{A}\}$.

The reverse inclusion follows from the fact that $(G\alpha)G^*(\mathcal{J} - G\alpha)$ and thus $(G\alpha)G_W^*(\mathcal{J} - G\alpha)$. This means that there exists $X \in W$ such that $G\alpha \subseteq X$ and $\mathcal{J} - G\alpha \subseteq \mathcal{J} - X$, i.e., $G\alpha = X$. Thus $W = \{G\alpha \mid \alpha \in \mathcal{A}\}$. \square

Theorems 4.1 and 4.5 show that no antibody is undetectable in the sense of being $(|\mathcal{J}|, |\mathcal{J}|)$ -undetectable. Thus the topic of removing undetectables from elements of solutions is more involved and not terribly useful. The final result in the paper is a description of one element of $\text{Sol}(G, R)$. This partially generalizes Theorem 15 of [9].

Theorem 4.6. Let $\theta(G, R) = \{X \subseteq \mathcal{J} \mid \text{for some } (T, S) \in R, F(T, S) \subseteq X \subseteq C(T, S)\}$, and let $\Sigma'(G, R) = \theta(G, R) - \{X \in \theta(G, R) \mid \text{for some } (T, S) \in R, T \subseteq X \subseteq \mathcal{J} - S \text{ but } \neg TG^*S\}$. Then $\Sigma'(G, R) \in \text{Sol}(G, R)$. Furthermore, $\text{Sol}(G, |\mathcal{J}|, |\mathcal{J}|) \subseteq \Sigma'(G, R)$.

Proof. Let $(T, S) \in R$.

First, suppose TG^*S , i.e., there exists $\alpha \in \Delta(T, S)$. This means that $F(T, S) \subseteq G\alpha \subseteq C(T, S)$ and $G\alpha \in \theta(G, R)$. Also if $T' \subseteq G\alpha \subseteq \mathcal{J} - S'$ for some $(T', S') \in R$ then $T'G^*S'$ so that $G\alpha \in \Sigma'(G, R)$ and $TG_{\Sigma'(G, R)}^*S$.

Second, suppose $\neg TG^*S$ but $TG_{\Sigma'(G, R)}^*S$, i.e., there exists $X \in \Sigma'(G, R)$ such that $T \subseteq X \subseteq \mathcal{J} - S$ but $\neg TG^*S$. However, this contradicts the definition of $\Sigma'(G, R)$. Thus $\Sigma'(G, R) \in \text{Sol}(G, R)$. \square

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