An Intra-Repertoire Recognition Algorithm

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***Abstract*-The network theory of immunology proposes that antigen receptors themselves provide units for selection by anti-receptor receptors. This work discusses the implication of receptor-receptor recognition in the context of a previously developed elaborated clonal selection algorithm (ECSA). The result is a pattern recognition-based system capable of cognitive tasks that surpass the simple ECSA, and which have strong implications for the previously outlined T-cell mediated algorithm, which is also based on the interaction of receptors although of different casts.**

Keywords- Intra-Repertoire Recognition, Cell-cell recognition, network theory, idiotope, idiotype

I. INTRODUCTION

The network theory (initially proposed by Jerne [3-5]) proposes that a receptor (or antibody) may be selected for by antigen on its combining site (paratope), or be selected by other receptors. One may describe two primary types of receptor-receptor interaction:

(1) The activation of a receptor by the idiotype of another receptor, which results in the creation of more anti-receptor receptors

(2) The activation of a receptor for an antigen, which is triggered, by another receptor, which creates more receptors for the antigen (and anti-receptors for the triggering receptor)

The result is a network of receptors that may interact with antigen and each other providing both an antigen-recognition system and self-regulation of response. This work integrates an abstraction of the receptor-receptor interaction proposed by the idiotypic network theory into the elaborated clonal selection algorithm (ECSA) [1]. Section II proposes the integration of receptor-receptor recognition and discusses the implications of the interactions from the perspectives of relationships, mappings and the meaning of the networks that form. The implications of the approach are discussed when the constraints of a minimal implementation are relaxed facilitating more complex relationship structures such as antigen-independence and branching.

II. RECOGNITION AND RELATIONSHIPS

The complexities of receptor-receptor interaction is a difficult concept to grasp thus, this section begins gently with a discussion of the types of recognition that may occur in an ECSA repertoire with the addition of receptor-receptor recognitions and implications of recognition with regard to the 'intended' targets of the receptors involved.

Receptor-Antigen: (traditional) Receptors for the antigen are created with minor variations, which may improve future recognition
Receptor-Receptor: (idiotypic) Receptors for the matching receptor are created (anti-receptor receptors) with minor variations, which may improve future recognition

Figure 1 - Direct relationships including traditional and idiotypic

Both of the above cases provide examples of *direct* relationships, that of a receptor and an antigen or a receptor and another receptor. In the first case, receptors have an *implicit* relationship with other receptors that also match for the same antigen in that they compete with each other for selection by the antigen. The second case is a lot more interesting, given the recurrent relationships that may result. These relationships will be explored in the context of how a given receptor came to be, assuming a single matching source is responsible for receptor maturation. For example, a receptor may match to another receptor that has been matured for an antigen. Thus, there is a *direct* relationship between the first receptor and the second, as well as a *proportional* relationship with the first receptor and the second receptors antigen.

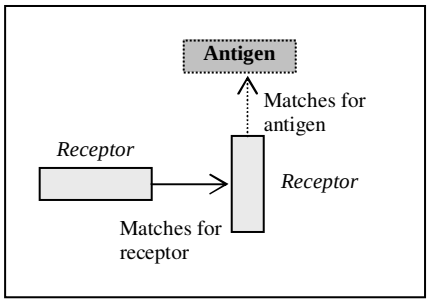

Figure 2 - Example of a receptor that matches for a receptor that in turn matches for an antigen, highlighting a proportional relationship

Another example is that of a receptor that has been matured for a given antigen, may match another receptor. Thus, the first receptor has a *direct* relationship with both the second receptor and the antigen. The second receptor also has an *implicit* relationship with the first receptors antigen.

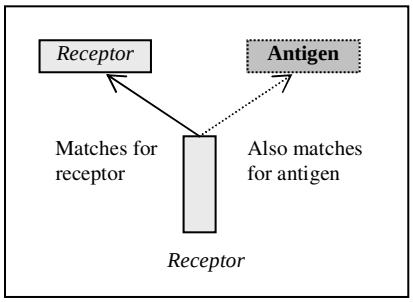

Figure 3 - Example of a receptor that matches for a receptor and also matches for antigen, highlighting an implicit relationship

For clarity the receptor that does the matching is referred to as the *activated receptor* (R1), and the receptor that it matches onto is the *triggering receptor* (R2). If R1 was matured for an antigen, it is denoted R1a, if it was matured for a receptor, it is denoted R1r. The same naming scheme is used for R2, thus R2a and R2r.

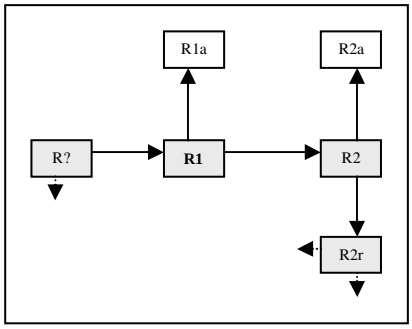

Figure 4 – Example of some relationships between receptors and antigen

The following table provides a summary of the proportional relationships (highlighted by Figure 2) of all the combinations for the causal reasons for each receptors maturation (instantaneous reasoning for its existence). Proportionality in this context refers to the densities of a receptor, which may be abstracted to the amount of activations or prevalence.

Receptors		Proportional Relationship
Activated Target	**Triggering Target**	
Antigen	*Antigen*	$R1 \propto R1a + R2, R2 \propto R2a,$ thus, $R1 \propto R1a + R2a$
Antigen	*Receptor*	$R1 \propto R1a + R2, R2 \propto R2r,$ thus, $R1 \propto R1a + R2r$
Receptor	*Antigen*	$R1 \propto R1r + R2, R2 \propto R2a,$ thus, $R1 \propto R1r + R2a$
Receptor	*Receptor*	$R1 \propto R1r + R2, R2 \propto R2r,$ thus, $R1 \propto R1r + R2r$

Table 1 - Summary of all receptor-receptor interactions as proportional relationships

Thus, the proliferation strategy of the clonal selection principle results in the receptor density (that may be abstracted to maturated image of the signal) to be proportional to the signal frequency. This is a central important relationship for receptor-receptor interaction because the networks that form regulate the information content of the repertoire. In addition to the proportional relationships, there are implicit relationships, highlighted by Figure 3. In this case, the implicit relationship is between the second receptor and the antigen competing for selection by the first receptor. From the first receptors perspective, it is unable to tell the difference.

Direct: A matching relationship that is presently active, such as a the matching of a receptor onto an antigen signal, or the matching of a receptor onto another receptor
Implicit: A relationship facilitated by an intermediate such that the intermediate causes the previously unrelated signals to compete for recognition
Proportional: A relationship in which the prevalence of a receptor is determined by the prevalence of the signal to which it responds

Figure 5 - Summary of the relationship types between receptors and antigen

A. *The Algorithm*

The distinction between antigen and receptor in the context of matching must be abandoned such that receptors simply perform matching of input signals. The reasons for this include the insertion of naïve cells that have no heritage and thus may be a regulatory force (selected by receptors), or a matching force (selecting receptors or antigen). Further, it is natural for the system to exploit regularities between receptors and antigen signals.

***Matching Principle**: Receptors attempt to match against any signal that is presented, regardless of its antigenic or repertoire origin*

The clonal selection algorithm is executed in cycles of signal exposure, and this iterative approach is used for the matching of receptor signals as well. The changes require (1) the selection of receptors to be promoted to antigen-like status, (2) the modification of the exposure regime such that multiple and varied input signals may be received by the repertoire for a given exposure. A natural choice for selecting receptors to promote is to select those receptors that were activated in the previous execution cycle (previous exposure). Another example may be the clonal progeny created from the previous execution cycle. The following list these schemes in addition to some other obvious examples.

Activated Set: The receptors that compose the activated set of the previous exposure (execution cycle), bounded to a fixed size
Progeny Set: The receptors created as a result of the previous exposure (execution cycle)
Random Set: A randomly selected set of receptors from the repertoire
Probabilistic: Receptors may be selected probabilistically from the repertoire proportional to activation history

Figure 6 - Example of some selection schemes for promoting receptors to antigen-like status for a single exposure

The repertoire must be extended from its ability to respond to a single antigenic pattern per exposure, to a potentially large and varied set of input signals. The approach used in a previous work on the integration of T-cell mediation [2] addressed this problem by introducing accumulated activation for exposure to an activated set. This means that a traditional activation scheme (like winner-take-all or similar) is employed for each input signal to which the repertoire is exposed. The selection of the activated set may then be biased towards those repertoire receptors that receive the most activation in aggregate from the exposure set.

***Exposure Set**: An elaboration of the antigenic exposure, that includes a collection of receptors selected from the previous exposure and promoted to antigen-like status, as well as any antigen signals available*

The following specifies the elaboration of the exposure set of the elaborated clonal selection algorithm to select and respond to an exposure set.

Step2a: *Gather* antigen signals available to the system at the given time
Step2b: *Select* receptors from the repertoire to compose the exposure set
Step2c: *Expose* the repertoire to the exposure set (antigen and receptors)

Figure 7 - Modified elaborated clonal selection algorithm to respond to an exposure set

B. ***Matching Function***

The elaborated clonal selection algorithm uses a bit string representation to match antigenic signals. The result is a repertoire that directly models features of the input space (naturally or in complement). When receptors themselves are treated as input signals, a variety of representations may be used in the matching. Mapping functions were discussed in [2] for the matching of B-cell receptors by T-cells.

Natural: Receptors perform matching direct onto other receptors representation.
Random: Each receptor has an associated random bit string that provides the basis for receptor matching
Substring: Each receptor provides substrings of their primary receptor for intra-repertoire matching
Reorder: Each receptor contains a second string that defines a reordering of the receptors primary matching bit string.

Figure 8 - Summary of some mapping schemes for intra-repertoire matching

The network theory proposes that receptors match onto a part of the receptor that is distinct for receptors of that lineage, although different from the receptors combining region (part of the other receptor that does the binding). Thus, a natural scheme is to assign a random or remapping of the primary bit string to each naïve receptor, which, like the primary string is inherited and maturated in progeny. This results in the co-evolution (co-adaptation) of the primary string for activation and the secondary string for secondary effects.

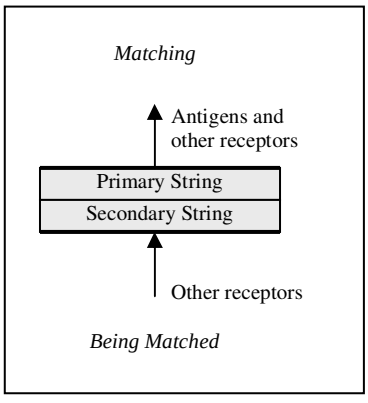

Figure 9 - Depiction of the two-string scheme

A natural representation (using the same string for both) will result in a positive feedback system, where the exposed antigen will be amplified by repeated 'simulated' exposures. Any regularity of the antigenic pattern that is provided on the secondary strings (such as sub-strings or reordering) will likely have this amplification effect, proportional to the fidelity of the mapping of the regularity.

***Amplification Effect**: A positive feedback system that occurs when regularities of the primary string are expressed in the secondary string causing those regularities to be recurrently amplified*

This amplification of input signal may be useful to reinforce the acquisition of knowledge. A natural representation will continue to promote the same instigating signal for as long as activated members are promoted to antigen-like status.

C. ***Relationships***

One may consider a repertoire of receptors after a period of adaptation, such that sufficient time for the formation of relationships is permitted. A steady-state application of this system emphasizes some important properties regarding the formation of relationships as networks (graphs) of activation and exposure. In this implementation, an antigen matches onto and activates a single receptor. The activated receptor is copied from the repertoire and is provided as an input signal in the next cycle. In this next cycle, both a randomly selected antigen and the previously activated receptor are offered as input signals to the repertoire.

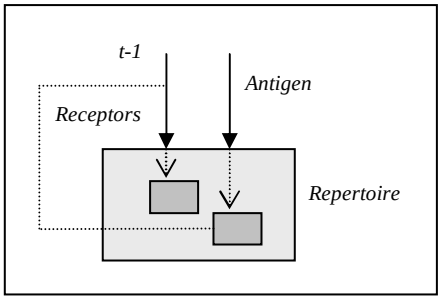

Figure 10 - Example of a simple two-receptor promotion scheme

A queue-based exposure scheme is used such that the more-recent activated receptors (instigation of relationship) are admitted, and older receptors are discarded. Thus, the previously activated receptor is discarded, and the newly antigenic-activated is promoted to the next cycle as an input signal. The behaviour of this scheme may be described with an example (Table 2).

Cycle	Exposed	Activated
1	A1	R1
2	A2, R1	R2, R1a
3	A3, R2	R3, R2a
4	A4, R3	R4, R3a
t	A_t, R_{t-1}	R_t, $R_{t-1}a$

Table 2 - Exposure-activation scheme for a minimal implementation

If a natural mapping is used for string2, then the scheme provides a simple signal-reinforcement scheme that provides a linear amplification (t-1) reinforcement of signals past. If a remapping scheme is used for string2 (such as a random string), then the scheme provides new information in subsequent exposures that may result in the formation of a connection between two different input signals. The simplest example is the selection of R1a by A2. In a natural mapping, if A2 selected R1a

then A1 and A2 would be the same input signal, and R1 and R1a are likely the same receptor or clonal siblings (same ancestor). In a remapping scheme (such as random), it is possible for the remapped string to match for a receptor that is also matched for by an antigen (see Figure 11).

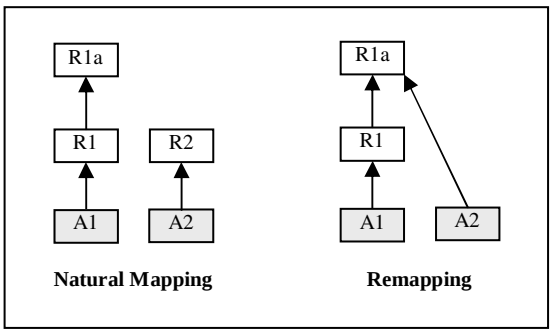

Figure 11 - Depiction of the example difference between a natural and remapping scheme

The remapping example provides an example of a relationship that may form between two different antigen (A1 and A2), facilitated by the remapping of receptors using the two-string scheme. If A2 is withdrawn, the relationship is fostered by A1, which activates R1, which in turn activates R1a. If A2 is withdrawn for all time, then the relationship will deteriorate due to genetic drift[1], thus A2 provides a correcting influence to the relationship. If A1 is withdrawn then the other half of the relationship is reinforced (R1a), and again if A1 is not returned, then R1a may drift such that R1 does not match to it any longer.

***Mapping Principle**: A natural mapping promotes signal generalisation, remapping promotes signal-relationships*

The example relationship is unidirectional, in that the primary string of R1a is a generalisation of A2 and R1's secondary string. A natural extension is to consider the implications of R1a's secondary string. If R1a matches for R1 then both R1 and R1a provides surrogates for A1 and A2 reinforcing each other and the repertoires relationship between A1 and A2. It requires that R1's primary string is a generalisation of A1 and R1s' secondary string. This network may be depicted as follows (R1a is renamed R2).

***Relationship Principle**: A relationship between antigen (facilitated by receptor mapping), may reinforce the related antigen in the absence of their signal.*

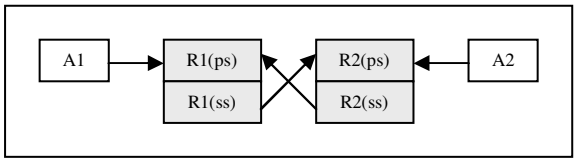

Figure 12 - Depiction of the relationship between remapped antigen and receptors ('ps' is primary and 'ss' is secondary string)

This relationship may be scaled such that circular (cyclic) relationships may form between more than two antigen via a pass-the-parcel connectivity of strings. Each receptor provides surrogate stimulation for another antigen, reinforcing both the receptor for that antigen and the connections of the highly ordered relationship. Such cycles (after creation) once activated, will self-propagate for as long as a single member of the cycle is able to selected and promoted. Alternatively, such structures are fragile in that if a node in the cycle is removed (deleted or corrupted) then the high-order structure fails to function. The robustness of such structures, is that individual (uni-directional) relationships remain and continue to be reinforced.

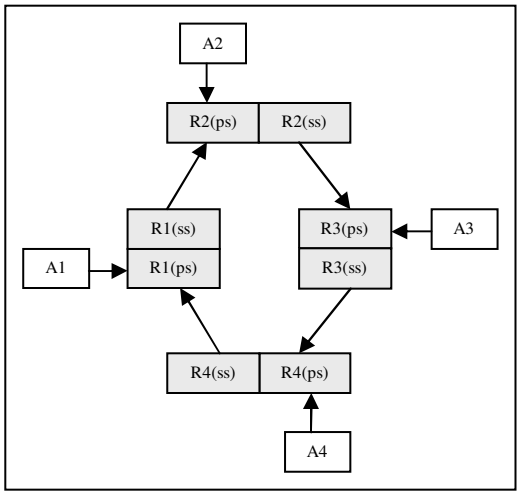

Figure 13 - Depiction of a possible four-antigen relationship facilitated by four different mapping receptors

The relationships discussed thus far are all one-to-one, and structures that are formed are coupled to antigen. In the absence of a reinforcing signal by antigen for the structure (such that a member of structures is promoted to exposure status), the relationship fades from the active-cycle, and given usage-based attrition, it will fade from the repertoire. The following provides an example.

Cycle	Exposed	Activated
1	**A1**	**R1**
2	A2, **R1**	R2, **R1a**
3	A3, R2, **R1a**	R3, R2a, **R1**
4	A4, R3, R2a, **R1**	R4, R3a, R2b, **R1a**
5	A5, R4, R3a, R2b	R5, R4a, R3b, R2c

Table 3 - Example of how the relationships formed are antigen-dependent

The table provides an example of a promotion set of size four, and a structure like that of Figure 12, which is dependent on the initialisation by antigen, but should persist given its own self-referential nature. The structure uses A1 for initialisation and consists of receptors R1 that selects R1a, which in turn selects R1. Given the queue-promotion scheme, the structure persists for four time steps until it is 'phased out'. The example in Table 3 may be adjusted such that another antigen selects for R1a, or that A1 is exposed to the system again (cycle 5 for example), both examples of which would return the structure of interest to a place of prominence in the queue.

***Concern**: If relationships are limited to one-to-one*

[1] The relationship is fostered by activation (usefulness), although here genetic drift refers to the adaptation of receptors (their progeny) in response to activation

mappings then in the context of a queue-based promotion scheme, structures are antigen-dependent

The size of the active queue is a limited resource, thus, for a structure to persist in 'active memory' it must be activated by antigen directly (already discussed), or activated by antigen indirectly. To demonstrate this point, the above example may be adjusted such that A2a's secondary string also detects R1a's primary string (A2a and R1 have similar secondary strings), thus double-promoting R1a. The example prolongs the structure in active memory for an additional cycle, before it again fades.

Cycle	Exposed	Activated
1	**A1**	**R1**
2	A2, **R1**	R2, **R1a**
3	A3, R2, **R1a**	R3, R2a, **R1**
4	A4, R3, **R2a**, **R1**	R4, R3a, **R1a**
5	A5, R4, R3a, **R1a**	R5, R4a, R3b, **R1**
6	A6, R5, R4b, R3c	R6, R5a, R4c, R3d

Table 4 – Extended example of antigen-dependent structures

The following table highlights the structure with the various relationship types.

Relationship	Elements
Direct	A1 = R1(ps)
Direct	R1(ss) = R1a(ps)
Direct	R1a(ss) = R1(ps)
Implicit	A1 = R1a(ss)
Direct	A2 = R2(ps)
Direct	R2(ss) = R2a(ps)
Direct	R2a(ss) = R1a(ps)
Implicit	R2a(ss) = R1(ss)

Table 5 - Relationships of the proposed structure

A larger queue allows more intra-antigen relationships (larger relationship structures in general), which in turn may prolong the activation of structures, but does not facilitate perpetual (antigen-independent) structure formation.

Structure Durability*: The exposure set size defines the durability of a structure in active memory (essentially defining short-term memory), in the absence of renewed promotion*

A final note, these examples do not take into account the proliferation of selected receptors, thus density concerns were subsumed with activation counts that delineated receptor persistence. Additionally, in the structures proposed, the secondary strings became surrogates for antigen strings, thus 'took the form' of antigen signals. This suggests that a mapping, such as substrings or reordering of the primary string may be easier for the system to retrofit for such a purpose rather than a random-based mapping (assuming similarity rather than complementarity of the mapping between receptors and antigen).

D. ***Meaning***

A mash of antigen may be connected via an adaptive receptor mapping, although what do such structured relationship mean?

If competition for limited resources (selection-proliferation for genetic continuance) is considered as a primarily pressure of the naïve minimal clonal selection algorithm, then the relationship structures discussed may provide delayed recurrent antigenic signals resulting in delayed positive feedback. This meaning is only suitable to those secondary strings (mapping) that take the form of (adapt to be similar to) antigenic signals.

Recurrent Antigenic Signals*: Receptors, whose secondary strings take the form (have the same receptor response) to antigenic signals provide a delayed recurrent antigenic signal to the repertoire that provides a positive reinforcement effect*

The interesting aspect of this delayed positive feedback effect is that it is mediated by other antigen either directly or indirectly. Thus, in the structures discussed, the relationships positive regulatory networks (signal amplification) that emerge from the repertoire. Given that the primary pressure on the system is that of competition for resources and feature detection competence, the regulatory networks facilitate signal compression and signal fidelity via *adaptive delayed amplification*. Given that all the examples demonstrated thus far are examples of positive reinforcement of antigenic signals, one questions whether it is possible for the system to develop suppression signals (other than implicit suppression via the selection and expansion of other choices).

E. ***External Meaning (Feedback)***

The relationships that are formed are dependent on the signals received from the antigenic set, and are directed by the pressures imposed on the repertoire. Thus, with the application of additional signals and pressures it is expected that additional and interrelated relationships may form. An example is the integration of feedback into the repertoire to impose meaning, and thus an added layer of usefulness to receptors. Thus, rather than the compression of input signals, the repertoire is responsible for mapping input signals to concepts which are shaped by the feedback mechanism. The result is relationships between input signals that promote the formation and persistence of useful concepts.

Memory*: Relationships allow information (such as a concept associated with a receptor) that is not responsive to antigenic signals to persist via a remapping of input signals*

One may consider a receptor that represents a concept that is meaningful to feedback, but is not directly meaningful to the input signals. The activation of the receptor may occur indirectly, such as a link in a network that is one removed from an input signal. Thus, the existence of the concept is dependent on the receptors that activate it, specifically, receptors in the repertoire whose secondary string matches for the concept receptors primary string. These dependent receptors are themselves dependent on activation by antigenic signals and or other receptors. Thus, the receptors that are matched, may provide a feature detection service, the receptors secondary strings and subsequent receptor interactions to the concept of interest represent a mapping of the feature to the concept.

***Mapping Relationship**: A relationship may represent the mapping of a detected feature onto an internal concept*

The feedback must be integrated into the model such that concepts of interest are promoted over those that are not. Further, a relationship may possess more than one concept, and in fact, a series of receptors may collectively represent a concept. One manifestation of this is to consider that an activated receptor may transmit a signal from the system. This may be embodied the activation of a receptor specific effector function, perhaps mediated by a helper T-cell ([2]). Thus, a relationship of receptor-receptor interactions triggered by an antigen may be considered the activation of a series or chain of effector functions. Further, the activation and subsequent reward (proliferation) of a link in the chain, potentially activates and rewards all links in the chains.

***Receptor Chain**: A relationship of receptor-receptor interactions, in which the activation of a receptor represents the activation of a concept such as a system effector*

The processing of a receptor chain allows a sequence of concepts to be activated. This effect may be exploited by the system to perform interesting higher-order tasks.

Time-Delay: A specific concept on a receptor may be triggered on a time-delay via the processing of the preceding receptors in the chain
Consensus: Two or more different receptor chains may converge to the same concept providing a consensus
Sequences: A set of concepts (tasks) may be processed in a sequence, which may be both directional, and bi-directional (reversible)
Conditions: A secondary signal may or may not be present to which the continuation of a structure is dependent

Figure 14 - Example of some higher-order behaviours the system may achieve with effector-bound receptors

III. DISCUSSION

The queue-based approach limits the relationships in a number of ways, most importantly, relationships are forward-processed chains with a footprint (frontier) of size one, which can be no larger than the size of the exposure/promotion set (if independent of other structures). An alternative promotion scheme may allow additional interesting effects to occur, such as:

1) The formation and processing of antigen-independent structures that persist in the exposure set ('active memory')
2) Structures with a footprint in the exposure set that is larger than one
3) Branching of a structure into sub-structures in the exposure set

The constraint on the size of the queue may be removed, such that the exposure set (at a limit) may be the size of the repertoire in addition to any antigenic signals exposed to the system at that time. Given the proliferation strategy and clone sizes larger than one, there is likely to be much homogeneity in receptor primary strings, thus it is expected that the size of the exposure set will stabilise at a size less than the size of the repertoire, and reduce as the system exploits the regularities and relationships.

***Unbounded Exposure Set**: The limit on the number of receptors that may be promoted per activation cycle is removed which results in the natural stabilisation and ultimate reduction in set size over time as relationships are exploited*

All structures are antigen-dependent, in that the exposure set requires antigen-dependence to grow. After a period of adaptation and structure stabilisation, it is possible for structures to form that are independent of the activation help provided by antigen. If receptors are able to select themselves, then, the smallest example is a single receptor; otherwise, if receptors cannot select themselves, the smallest example is a two-receptor relationship. Such structures self-perpetuate themselves, given that usefulness is based on activation, thus it may be desirable to impose a pressure such that relationships are antigen dependent. Alternatively, a feedback system from the environment may provide sufficient pressures.

***Antigen-Independent Structures**: Relationships that are initially dependent on antigen, which are adapted in such a way that they continue to propagate in the absence of antigen-based selection and promotion*

The unbounding of the promotion set also allows structures with a footprint in the active set larger than a single receptor. A simple example of this is a structure in which each link in the chain as multiple clonal siblings in the repertoire. The result is a diffuse representation of the relationship where the number of parallel choices for a given link in the chain is a measure of the redundancy of the interaction. The result is a parallel processing of the same structure through time.

A smaller structure may facilitate (support) another structure by maintaining receptors to which the second structure is dependent. The supportive role implies that the two structures may be considered one large structure, although it is possible for the first structure to process independently of the second, thus the second structure is a secondary signal-dependent elaboration (extension) of the first structure (so-called conditional processing). The current scheme does not facilitate the branching of a structure into substructures, or the parallel (non-time shifted) interleaving of structures. In order achieve more complex behaviour such as interactive structures and structure branching, a one-to-many relationship is required for a promoted receptor to activated receptors.

***Multiple Receptor Activation**: A promoted receptor must activate more than one receptor in the repertoire in order to achieve more complex behaviours (such as structure branching)*

The activation of more than one receptor requires a receptor selection scheme, as described in the elaborated clonal selection algorithm [1]. One may presume a selection scheme in which a small fixed sized activated set is composed of high-affinity receptors for each member of the exposure set. An alternative scheme may involve the exposure of the repertoire to all members of the exposures set, and probabilistically selecting a fixed-size activated set (without replacement) of the most activated receptors (activation account or perhaps accumulated affinity). Both schemes facilitate (explicitly

and implicitly respectively) the selection of more than one receptor for a given promoted receptor exposed to the repertoire. The branching of a structure facilitates the purist of more than one implication (condition) in parallel. If receptors are representative of a concept or effector action, then such structure branching behaviour (one-to-many structures) allows the execution of two (or more) parallel effector chains in parallel.

Branching, in conjunction with larger footprint structures and antigen-independent chains represents the apex of the receptor-receptor interaction paradigm. Extensions include the integration of T-cell mediation of proliferation (and concept selection), the use of spatial structures to house receptors, and the considerations of integrating feedback (external meaning) into receptor chains.

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