A T-Cell Mediated Clonal Selection Algorithm

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Abstract-The two-signal theory of lymphocyte activation was proposed more than thirty-five years ago and since that time has been elaborated and experimentally demonstrated to be a mediation process for the activation of both B and T lymphocytes. Modern names for the theory include associative recognition theory, the ARA model, and co-stimulation for T-cells. This work proposes the integration of T-cell mediation of activated B-lymphocytes into the elaborated clonal selection algorithm (ECSA). The resultant system provides a decoupled condition-action cognitive system that appears to have much similarity with classifier systems and may be an example of the reinforcement-learning paradigm.

Keywords-Clonal Selection Algorithm, Artificial Immune Systems, Two Signal T-Cell Activation, Co-stimulation, ARA model

I. Introduction

Two-signal theories have been proposed in immunology as verification signals permitting the proliferation and differentiation of lymphocytes [3]). Historically developed for the activation of Bself-nonself lymphocytes (in the context of discrimination), the two-signal approach has also been extended to the various classes of T-cells. The theory is also referred to as associative recognition theory (ARA) model), and co-stimulation. This work elaborates on an extension to the clonal selection algorithm (proposed in [1]) that employs a second type of cells to mediate proliferation of high-affinity receptors.

Section II proposes the use of an additional repertoire of cells to mediate those activated B-cells that may proliferate, and discusses the implications of the proposal from a number of perspectives. Section III discusses the implications of two configurations of the approach and suggests potential applications potential extensions of the approach.

II. T-CELL MEDIATED ACTIVATION

The clonal selection algorithm proposes six steps, four of which make up the core algorithmic cycle (Steps 2-5) of antigenic exposure and resultant adaptation. The minimal clonal selection algorithm has been elaborated into a number of specific tasks for each step (in [1]), and is referred to as the elaborated clonal selection algorithm (ECSA)

- Step1: Initialise the system with a set of random bit strings
- Step2: Expose the system to randomly selected antigen
- **Step3**: Select a high-affinity receptor for the antigen
- Step4: Clone the selected receptor with copying errors

Step5: Replace the selected receptor for the clone **Step6**: Repeat steps 2-5 until stop condition

Figure 1 - A minimal clonal selection algorithm

In the elaborated version, Step3 was decomposed into the selection of an activation set, which in turn was provided to Step4 for cloning (maturation). This work proposes that an additional mediation step be introduced to select those receptors of the activated set that may proceed to Step4 for maturation. The mediation process is controlled by a sister repertoire of receptors that also perform a pattern-recognition process using the activated receptors as input signals (much like the clonal selection algorithm responds to antigens).

The Helper T-cell metaphor is adopted such that the repertoire of receptors (first repertoire) represents B-lymphocytes, which require a second verification signal from the helper T-lymphocytes (second repertoire) before proliferating and differentiating. After providing the secondary signal to the activated set of B-lymphocytes, the helper T-lymphocytes proceed with the cloning and maturation of the activated T-cells. Thus, the T-cell repertoire is an application of the clonal selection algorithm that accepts the activated set of another clonal selection algorithm as the antigenic set.

The following list some concerns that must be reconciled in integrating the two repertoires:

- The T-cells must select those B-cells from the B-cells activated set that may proliferate
- The B-cell activated set provides multiple antigens simultaneously to the T-cell repertoire, to which it is possible to generate a T-cell activated set for each member of the B-cell activated set

The modification to the elaborated clonal selection algorithm is as follows:

Step3a: Evaluate the repertoire in the context of the selected antigen

Step3b: *Return* the highest-affinity antigen to meet the needs of the antigen

Step3c: Select a high-affinity set of activated receptors

Step3d: *Verify* the activated set of receptors using a second receptor repertoire **Step4a**: *Clone* each <u>verified</u> receptor in the activated set to create a clonal set

Figure 2 - Modification to the elaborated clonal selection to facilitate mediation of the activated set

The inclusion of a new repertoire to the clonal selection algorithm adds a level of complexity that is less than intuitive to grasp (at least initially). The remainder of this section considers the implications of

the second repertoire from a variety of different perspectives.

A. Mapping Function

The verification signal may be antigen-dependent or antigen-independent. If antigen-dependent, the information provided by the verification signal is a generalisation of the input signals provided to B-cell repertoire. If the verification signal is antigen-independent, then the information provided is a generalization of the receptors themselves in the B-cell repertoire. In the antigen-dependent case, the B-cell receptor provides a delivery mechanism of the antigen to the T-cell repertoire. In the antigen-independent case, the antigen selects the receptor, thus providing the delivery mechanism of the receptor to the T-cell repertoire.

Antigen-Dependent: Verification that the <u>antigen</u> is suitable for a response, using information about the antigen provided by the receptor to mediate a response

Antigen-Independent: Verification that the <u>receptor</u> is suitable for a response, using information about the receptor provided by the antigen to mediate a response

An antigen-dependent mapping from B-cell to T-cell requires that some regularities of the input signal are preserved. The transformation may be of the whole antigen itself, or just the part of the antigen recognised by the B-cell receptor. The T-cell repertoire adapts to a consistent (B-cell invariant) generalization of the input patterns. In keeping with the bit string basis of the clonal selection algorithm, one may specify some example antigen-specific mapping functions.

Passthrough: The antigen pattern is presented by the B-cell to the T-cell unchanged. This approach makes little sense, as the second repertoire would adapt to be a parallel of the first, it is provided here as a baseline mapping (no mapping)

Substring: The B-cell receptors slice the antigen pattern into regular length pieces. A T-cell match may be based on the independent number of pieces it can match for each B-cell receptor.

Figure 3 - Example antigen-dependent mappings between the two repertories

Concern: The concern with antigen-dependent mapping is that the mapping of the input patterns may be achieved in one repertoire, making the second repertoire redundant.

An antigen-independent mapping from B-cell to T-cell receptors disregards the regularities of the input signal, such that the T-cell is performing pattern recognition of B-cell receptors, rather than a pattern recognition of antigen. The result is a T-cell repertoire that is developed independent of antigen, and dependent on the B-cell repertoire (which in turn develops in response to antigen).

Random: Each receptor is associated with a randomly generated pattern (bit string). The T-cell receptors learn the B-cell receptors (and their progeny) that in turn are dominant.

Figure 4 - Example antigen-independent mappings between the two repertoires

Concern: The mapping is arbitrary such that T-cells are complete dependent on specific B-cell lines, and regularity between B-cell patterns has no meaning other

than ancestry (likely to make the mapping harder)

In both the antigen dependent and antigen independent cases discussed, the T-cell repertoire facilitates a mapping and confirmatory verification signal. There is a middle ground for mapping function in which it is possible for regularities of the antigen pattern to be preserved, consistent between cell lines, as well as the introduction of random perturbations. Such approaches are a mixture of antigen-dependent (antigenic regularities) and antigen-independent (receptor regularities).

Reorder: The B-cell receptor may reorder the antigen pattern using a permutation mask. Each receptor would have a unique (randomly generated) mask of the triggering antigen.

Figure 5 - Example of a mixed antigen-dependent and antigen-independent mapping function between the two repertoires

B. Formation of High-Order Structures

Before we can discuss the structures that a second repertoire of receptors facilitates, it is important to understand the structures a single repertoire can facilitate. Receptors respond to input signals, and the structures formed in the receptor repertoire describe the way in which input signal regularities are exploited. The baseline structure is a one-to-one mapping, in which each input signal is represented by a specialised receptor. A natural extension is the generalisation of input signals such that many similar antigen may be represented by one receptor. In this scenario, each receptor represents a common signal feature, which is exploited to compress (generalise) all signals that possess that feature. In both of these cases, antigen exposure results in a small (size one) activated set, and the second scheme is an approximation of the first.

The concept of feature extraction may be extended such that a single input signal may be decomposed into multiple features, such that a given antigen results in an activation set of many receptors. The final scheme generalises the decomposition approach, such that regularities between multiple features extracted from different antigen are exploited. A given antigen thus results in a diverse activation set, and a given receptor may be activated by a diverse set of antigen. For a given configuration (space complexity), it is ideal for a repertoire to specialise as much as possible, although be general enough to exploit the resources of the repertoire. Thus, in conjunction with suitable configuration of pressures and varied antigenic sets, it is possible for all four structure-types to form.

Antigen	B-Cells	Summary
One	One	Perfect mapping (specialisation)
One	Many	Decomposition (feature extraction)
Many	One	Generalisation (pattern compression)
Many	Many	Generalized decomposition (biology)

Table 1 - Summary of the structures that may be formed with a single B-cell repertoire

A second repertoire of receptors adds a second level (in a hierarchy) of complexity to the structures that may form. A given B-cell may be classified as one of the four structure types outlined in Table 1, thus the behaviour of the T-cell repertoire is defined in this context.

Like the B-cell repertoire, a feature-preserving oneto-one mapping may be facilitated in the T-cell repertoire, such that a T-cell is specialised for each Bcell. Following the scheme order presented for the 'antigen and B-cell' discussion, the natural extension is to have a single T-cell receptor activated by a number of different B-cell receptors. In this case, a given T-cell receptor generalises the information content of B-cell receptors. In turn, a given B-cell receptor may activate many different T-cell receptors implying the further decomposition of B-cell receptor information content. The final configuration implies that a given T-cell receptor may be activated by a diverse set of B-cell receptors, and a given B-cell receptor may activated a diverse set of T-cell receptors, such that decomposed features that are regularities across receptors are exploited.

B-Cells	T-Cells	Summary
One	One	Specialisation
One	Many	Decomposition
Many	One	Generalisation
Many	Many	Generalised decomposition

Table 2 - Structure formation between sets of activated receptors between the repertoires

The system may be configured such that the pressures exerted on the receptors purse a structure-formation scheme. For example, it may be desirable to coerce the B-cell repertoire to decompose antigen into regular features (many), and the T-cell receptor to generalise those features toward a specific meaning (few).

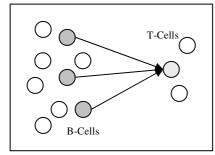


Figure 6 - Depiction of many B-cells activating a single T cell

Alternatively, the B-cell repertoire may be coerced to generalise (compress) based on common antigenic features (few), and the T-cell repertoire to decompose the B-cell information content into a variety of different meanings (many).

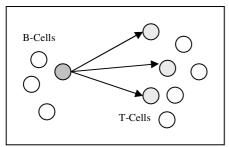


Figure 7 - Depiction of one B-cell activating many T cells

A final point of interest in the formation of higherorder structures is that of concurrency of activation. An activated set (more than one) of B-cells seek a secondary signal from the T-cell population. Rather than treating each activated B-cell independently, the activated B-cells may interact with the T-cell population concurrently, such that multiple B-cells may activate a single T-cell. Further, the T-cell repertoire may be configured such that a T-cell is required to match more than one B-cell before it may become activated (for a given execution cycle). This provides a mechanism in which the T-cell repertoire facilitates the summation (aggregation) of multiple antigenic features (captured in B-cell receptors) into a single T-cell receptor. The effect is a context-recognition system.

C. Receptor Meaning

Receptors may be assigned meaning in addition to that of bland pattern-recognition devises presupposed. Before discussing the meaning imbued by a secondary repertoire of receptors, it is useful to discuss meaning in the context of a standalone B-cell repertoire (as in the clonal selection algorithm).

A traditional view in immunology (implied by the clonal selection theory) is that of self-nonself discrimination. Thus, any signal detected by the receptors is a foreign antigen that requires a response. Other obvious examples include the generalisation of the signal space, and feature extraction of the signal space (which both may be the same thing). A final interesting example is an arbitrary meaning of antigenic signals such as may be achieved via a mapping, for example into another pattern space, or onto a spatial structure.

Meaning	Summary
Self-Nonself Discrimination	Anything detected by the receptors is foreign
	antigen that must be acted against
Feature Extraction	Receptors seek to encode small-regular patterns in the antigenic signals
	1 5
Signal Generalisation	Receptors seek to minimise the information required to represent the antigenic
	environment
Arbitrary Meaning	The arbitrary mapping of receptors, for
	example into another pattern space or onto a
	spatial structure

Table 3 - Summary of some meanings that may be applied to the repertoire of B-cell receptors

The second repertoire facilitates the addition of a second layer of meaning. In the many-to-one case in the previous subsection, a T-cell may represent a high-order concept as an aggregate (summation) of multiple lower-level concepts (B-cell receptors). The meaning is a single or small collection of concepts that are dependent on the presence of specific features (specific context).

Many-to-One: (more likely to be many-to-few) Consensus forming operation in which many lowerorder concepts (such as extracted features) are aggregated together to form a high-order concept (such as a generalisation)

In the case of the one-to-many example of the previous subsection, the collection of T-cells may represent a set of lower-level concepts that emerge from a high-level generalisation (a single B-cell receptor). The meaning is a larger set of lower-order concepts, which may describe a concept, or may be treated together in a

consensus forming operation.

One-to-Many: (more likely to be few-to-many) Descriptive operation in which a high-order concept (such as a generalisation) is decomposed into a number of lower-order concepts (such as descriptive features)

In both of these examples, the meaning implies a mapping that manages to preserve some regularities of the input signal, such that higher-order or lower-order concepts (relationships) may be described. Again, this point highlights the need for a flexible mapping function.

D. Supervised Concept Formation

The application of externally provided feedback provides a mechanism of enforcing (and reinforcing) meaning. Meaning in the B-cell repertoire in the context of the clonal selection algorithm is imposed by pressures of space complexity, maximal resource usage, and genetic diversity. The pressures are imposed through intra-receptor interactions. The result is a maximally used, genetically diverse, specialised set of feature detectors (receptors in the sense of the word, devising for signal reception).

If the B-cell repertoire is coerced to model the input space as a set of low-order features, and the T-cell repertoire is coerced to model activated B-cells as high-order features, what do the resultant high-order features mean? Conversely, if the B-cell repertoire is coerced to model the input space as a set of high-order features, and the T-cell repertoire is coerced to model activated B-cells as low-order features, what does the resultant set of low-order features mean? In both cases, are they merely a remapping of the input space?

The incorporation of external feedback into the algorithm allows an external process to assign meaning and *supervise* the mapping and formation of concepts. For the single repertoire algorithm, T-cell mediation provides an immunological plausible basis for feedback to supervise the selection of activated receptor patterns in response to antigenic exposures. For the dual repertoire algorithm, tissue damage provides an immunological plausible basis for feedback to supervise the selection of concepts formed in the T-cell repertoire, which inturn feeds back to the B-cell repertoire via the mediation process.

Feedback: Tissue damage provides feedback to the T-cell receptors, T-cell mediation of activated B-cells provide a back-propagation of tissue damage feedback from the T-cell repertoire to the B-cell repertoire.

The proposed integration of feedback results in two flows of information through the system. The *top-down* flow of antigenic signals results in B-cell receptors competing for activation, and T-cell receptors competing for activation of the B-cell receptor activated set. Those B-cells that receive the secondary signal proliferate. The *bottom-up* flow of tissue-damage input results in T-cells competing for encouragement that the concepts that they represent are 'correct'. Those T-cells that receive a positive (non-negative, and perhaps non-neutral) feedback, proliferate. Thus, the application of feedback (if available) is to the activated set of T-cells. In the

absence of feedback, there is simply the absence of corrective behaviour: the punishment, or reward of the activated T-cell concept.

Thus, antigen provides a pressure on the B-cell repertoire for recognition (feature extraction) and indirectly on the T-cell repertoire for the activation of concepts in response to activated features. Feedback provides pressure on the T-cell repertoire to form the 'right' concepts to antigenic input, which in turn puts pressure on the B-cell repertoire to reinforce the 'right' mapping between the repertoires. The top-down flow of information may be seen as the usefulness of the pattern recognition, and the bottom-up flow of information may be seen as the meaningfulness of the pattern recognition.

B-cell Pressures: Activation by antigen as <u>useful</u> feature detectors, secondary signal by T-cells as <u>meaningful</u> features

T-cell Pressures: Reinforcement as <u>meaningful</u> concepts from feedback signals, and activation by activated B-cells as useful concepts

III.DISCUSSION

The B-cell repertoire is responsible for approximating the input signals, and the T-cell repertoire is responsible for approximating concepts defined by feedback. Together, both repertoires are responsible for promoting the mapping between these two interconnected concerns. This section discusses the implications of two configurations of the system, and speculates extensions of the approach.

A. Many-to-One Configuration

Perhaps more accurately referred to as the many-tofew configuration, the B-cell repertoire is encouraged to form a repertoire of sub-string features to approximate the input signals. The T-cell repertoire is encouraged to recombine multiple B-cell signals into a limited number of concepts. The B-cell activation set is relatively large, although diverse. The T-cell repertoire accumulates activation, such that the T-cell activation set is defined by those cells that accumulate the most activation from the B-cell activated set. If feedback is available, those Tcells that are 'correct' proliferate, and those B-cell receptors that triggered the 'correct' T-cells are given the secondary signal to proliferate. Thus, the verification signal is a direct pass-through of the feedback signal. In the absence of a feedback signal to preside over the correctness of the activated T-cells, the activated set, or a subset (such as winner take-all for T-cells) is presumed correct, providing a general, unsupervised proliferation signal. This unsupervised signal promotes the generation of a mapping between the repertoires, which may be required prior to the introduction of feedback, and which may reinforce the mapping in the absence of feedback.

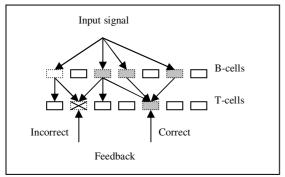


Figure 8 - Depiction of a many-to-few configuration, (fuzzy outlines denote activated receptors, grey fill denotes permission to proliferate)

A result is that the B-cell repertoire is likely larger than that of the T-cell repertoire. Further, there is a higher turnover and maturation (computational effort) of B-cells than there is of T-cells. This configuration may be useful for classification and regression tasks in which the T-cell repertoire models classes or a numerical values.

B. One-to-Many Configuration

Perhaps more accurately referred to as one-to-few configuration. The B-cell repertoire is encouraged to generalise input signals to a few receptors, thus smallactivated sets. The T-cell repertoire is encouraged to recombine many different B-cell receptor activations, such that the small B-cell activated set activates many Tcell receptors. This may be achieved through the promotion of large accumulation of activation of B-cell signals in modelling feature extraction as low-order sequences of bits of B-cells. Those T-cells that accumulate the most B-cell activation makeup the T-cell activated set. If feedback is available, then those cells that are 'correct' receive their secondary signal, which is transmitted back to the triggering activated B-cells, which may proliferate. As is the case for the many-toone configuration, the mapping may be formed, and reinforced in the absence of feedback through the adoption of a greedy winner-take-all or similar T-cell activation set selection (verification) scheme.

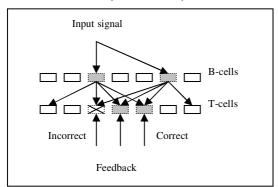


Figure 9 - Depiction of a few-to-many configuration, (fuzzy outlines denote activated receptors, grey fill denotes permission to proliferate)

For this configuration, the B-cell repertoire is likely smaller than that of the T-cell repertoire. The turnover and maturation (computational effort) invested in the T-cell repertoire is higher than that of the B-cell repertoire. This configuration may be suited to regression and function approximation schemes in which the T-cells

may represent concepts such as numerical values or local-functions.

C. Reinforcement Learning

The system that has been proposed, although based on a simple two-signal verification model of lymphocyte activation, appears to offer much in turms of cognitive capability compared to that of the more rudimentary elaborated clonal selection algorithm. The proposed system may be phrased as a reinforcement learning system [2,5], with much commonality to the learning classifier systems [4]. In this phrasing, the system is situated in an environment from which receives input signals via sensors, and manipulates aspects of the environment as output in the form of effectors. Thus, the B-cell repertoire provides a topology preserving representation of the input signals perceived from sensors, the T-cell repertoire is a representation of effectors to trigger based on the inputs perceived The mapping provides the knowledge acquired for the successful application of effectors based on perceived sensor input signals, driven by feedback provided from the environment to the T-cell repertoire.

This system described is reflexive, in that, there is a limitation in the structures that may form as a result. For example, the system does not provide an internal capability to form chains of rules (conditions and actions) in the absence of sensor information. Such chains of rules are desirable for the system to perform independent cognition and environmental tasks achieved through sequential actions.

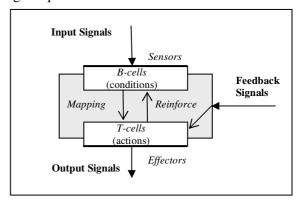


Figure 10 – The two-population scheme embodied in an information processing system with sensors, effectors, and feedback signals

A perhaps un-natural extension to facilitate such processing would be to use a similar model as that which is used during unsupervised learning of T-cells, where the best-matching or historically most 'correct' T-cells are presumed 'correct'. A sensor-invariant B-cell activated-set selection scheme may be used where highly activated B-cells are presumed to be an approximation for sensor input. Such a scheme may be winner-take-all, although perhaps a more T-cell friendly (mapping reinforcing) approach would be to probabilistically select activation sets based on activation and proliferation histories. Such schemes do provide internal-processing, and unsupervised forward and backward flows of reinforcement, although the system remains reflexive.

D. Extensions

In addition to implementation and confirmation of the speculated behaviour, the proposed T-cell mediated clonal selection algorithm suggests some natural extensions

Intra-repertoire recognition: Already suggested in the previous work on the elaborated clonal selection algorithm, a natural extension to achieve rule-chaining is via intra-repertoire recognition, in which activated receptors themselves become input signals to which the repertoire may respond. The feasibility of such an approach requires demonstration in a single repertoire model before integration into a multiple repertoire model.

Spatial repertoire: Another previously proposed suggestion is the use of a spatial repertoire (such as a toroidal lattice). The integration of this proposal into the two-repertoire model implies notions of spatially resident B-cells and T-cells. The system may have to contend with self-organizing two disjoint lattices in addition to adaptation of the mapping between the repertoires. Further, receptor movement (of one population) allows the anchoring of perception and the sharing of actions, or the anchoring of actions and the sharing of perception.

Additional layers (signals): Finally, a natural extension to the two-repertoire model is the addition of further intermediate repertoires. Yet another repertoire may mediate the feedback provided by the environment

to the T-cells, and another repertoire may mediate between the B-cell receptors and antigenic inputs. The forward and backward information flows are compatible with a hieratical (layered) repertoire model. Additional propagation schemes may have to be devised for the incorporation of additional feedback signals, or non-layered repertoire interactions (for example trinary repertoire scheme where the third repertoire interacts with both B and T cells).

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REFERENCES

- [1] Jason Brownlee, "A Clonal Selection Algorithm and Extensions," Complex Intelligent Systems Laboratory (CIS), Centre for Information Technology Research (CITR), Faculty of Information and Communication Technologies (ICT), Swinburne University of Technology, Victoria, Australia, Technical Report: 070521A, May 2007.
- [2] Leslie Pack Kaelbling, Michael L Littman, and Andrew W Moore, Reinforcement learning: a survey *Journal of Artificial Intelligence Research*, vol. 4, pp. 237-285, 1996.
- [3] P. Bretscher and M Cohn, A Theory of Self-Nonself Discrimination *Science*, vol. 169, pp. 1042-109, 1970.
- [4] Pier Luca Lanzi, Wolfgang Stolzmann, and Stewart W. Wilson. *Learning Classifier Systems: From Foundations to Applications*, Berlin / Heidelberg: Springer, 2000.
- [5] Richard S. Sutton and Andrew G. Barto. *Reinforcement Learning: An Introduction*, Cambridge, Massachusetts; London, England: The MIT Press, 1998.