A Lymphocyte Homing Algorithm

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***Abstract*-T-lymphocytes are imprinted with chemical information of the general tissue that is exposed to pathogen. T cells express specific receptors for this chemical signature and preferentially traffic from the recirculation pathway to the infected tissue. This effect is referred to as lymphocyte homing and provides a targeted response to pathogenic invasion. This work proposes a minimal recirculating clonal selection algorithm that is specialised such that lymphocytes preferentially home to tissue locations (nodes in a directed cyclic graph) where they are anticipated to be most useful.**

Keywords-Artificial Immune System, T-cell, Homing, Migration, Clonal Selection, Recirculation

I. INTRODUCTION

Naïve T lymphocyte cells are activated by dendritic cells and educated as to the chemical properties of the site of infection. These prepared T cells recirculate around the host organism in search of the cognate antigen, and upon detecting the chemical properties of the site of infection, home into the tissue. The directed trafficking behaviours is called lymphocyte homing [2,3,10,12], and the information which controls the where T lymphocytes traffic is expressed as receptors on the surface of the cell for the chemical properties of the site of infection [1,11]. Inspired by the education and homing processes of T-lymphocytes, this work proposes a lymphocyte homing architecture and algorithm.

Section II discusses some general homing algorithm principles abstracted from the education of T lymphocytes. Section III proposes a minimal recirculating clonal selection algorithm in which lymphocytes migrate around a cyclic directed graph providing information dissemination. Section IV proposes a homing algorithm in which lymphocytes express preferential residence in the tissue of last use, a signature of which is imprinted on the cells. Finally, section V proposes the investigation of inflammation and recruitment extensions of the approach.

II. ALGORITHM PRINCIPLES

High-affinity lymphocytes are selected for a given antigenic exposure. Lymphocytes exist in a spatial environment such that antigenic exposures may occur at different locations in the spatial structure. Thus, in addition to specialising the resources of the system to the antigenic exposures, the specialised resources (lymphocyte receptors for antigen) must be positioned such that they are used in the right locations. The distribution (space and time) of antigenic exposures is unknown, thus the system recirculates specialised resources between the locations of exposure to maximise the chance application of the resource in an exposure event.

***Principle**: Recirculation of lymphocytes provides a strategy in which specialised resources (memory and effector cells) are moved between spatial locations of potential exposure to maximise the chance of interacting with their cognate antigen*

The spatial environment that houses lymphocytes is the tissues of the host. Lymphocytes interact with each other and interact with antigen in this spatial structure. Each tissue type associated with a region of the host has its own unique chemical makeup, which may be used to differentiate tissues types and thus regions of the host.

***Principle**: Lymphocytes interact with each other and with antigen in a spatial tissue structure. Different tissues have different distinct chemical signature*

Lymphocytes may interact with tissues with specialised receptors that detect and differentiate between tissue types. This interaction occurs when the lymphocyte recirculates around the host, and may be used by the cell to travel specific pathways and to enter and remain in a specific tissue in search of its cognate antigen.

***Principle**: Homing receptors on a given lymphocyte, when interacting with tissues using specialised receptors, providing information where to go and how to get there*

These navigation receptors are not expressed in naïve lymphocytes, instead are expressed in matured cells that are produced after an interaction with antigen. A mature receptor (memory or effector) expresses navigation receptors for the tissue surroundings when it is conceived. Thus, mature cells are specialised both for an antigenic stimulus, and for the spatial location (tissue) that is known to have been exposed to that antigenic stimulus.

***Principles**: Homing receptors are imprinted on progeny of a high affinity cell when it proliferates*

The imprinting process occurs irrespective of whether a selected (high-affinity) lymphocyte is mature or naïve. In effect, specialised resources may be re-educated in that their progeny may be imprinted with a different location than themselves (presuming the cell was selected in a tissue different from that it may home

to). This imprinting mechanism facilitates both the spatial anticipation of antigen exposure based on past exposures, and in addition to recirculation, it facilitates the use and re-education of lymphocytes.

***Principle**: Tissue-based imprinting in addition recirculation and re-imprinting provide an adaptive spatial-exposure based mapping mechanism*

III. Recirculating Algorithm

A recirculation algorithm is required in which to phrase a homing algorithm. A minimal recirculation algorithm may be defined as an extension of the minimal clonal selection algorithm [8] generalised to a spatial tissue framework. In this framework, tissues house semi-independent pools of lymphocytes, and the tissues interact indirectly by passing lymphocytes back and forth. Previously this model was referred to by the author as the discrete or multiple repertoire model [4,5,7], although those previous works were concerned with proposing the model as a framework for algorithms, whereas this work is concerned with realising algorithms within that framework. The minimal recirculation algorithm is the simplest possible multiple-pool clonal selection algorithm where each pool is an instance of the minimal clonal selection algorithm (or its extensions) with the augmentation of lymphocyte recirculation (Step6: *Traffic*). A second, and just as important change to the algorithm is the change to exposure (Step 2: *Expose*) in which the exposure of a tissue a antigen is determined by an stimulation routine (for elaboration see [6]).

***Anticipation Principle**: Single repertoire models anticipate <u>what</u> antigen. Multiple repertoire models anticipate <u>what</u> antigen <u>where</u>*

A final note on the modelling framework is that of anticipation. The minimal clonal selection algorithm (and extensions) may be phrased as learning systems concerned with anticipating antigen exposures (in time). The principle for the 'single lymphocyte pool' class of systems is along the lines of '*guess exposures and make some guesses about future exposures based on past exposures*'. The minimal recirculation algorithm (with multiple tissues and inter-tissue movement) must anticipate antigen exposure as well as antigen exposure-location information. Thus, lymphocyte recirculation provides a base process in which to address the concerns of spatial anticipation.

Step1: *Initialise* the repertoire with a set of randomly generated bit strings
Step2: *<u>Expose</u>* the tissue according to the antigenic regime
Step3: *Select* the highest affinity bit string from the evaluated repertoire
Step4: *Clone* the best matching cell with genetic copying errors
Step5: *Replace* the best matching cell with the clone
Step6: *<u>Traffic</u>* lymphocytes in from and out to neighbouring tissues
Step7: *Repeat* steps 2-6 until a stopping condition is triggered

Figure 1 – Minimal lymphocyte recirculation algorithm

The minimal lymphocyte recirculation algorithm implies multiple tissues that are exposed based on regime (not discussed), which accept and send on migrant lymphocytes.

Exposure Regime: A scheme that determines the temporal distribution (iterations), spatial distribution (tissues), and pattern distribution (signals) to expose to a system.
Tissue: A location in which to house lymphocytes and enact the clonal selection principles on housed lymphocytes.
Migration: The movement of lymphocytes between tissues of the system such that lymphocytes are removed from one location and placed into another location (discrete atomic movement)

Figure 2 - Principle components of the minimal recirculation algorithm

A broader systemic-perspective of the multiple tissue (and single tissue) algorithm may defined such that the system is stimulated with antigen (according to a regime), and the system responds to the stimulus (according to clonal selection principles).

Step1: *Initialise* all tissues of the system
Step2: *Stimulate* the system according to the exposure regime
Step3: *Respond* to the exposure according to the clonal selection principle
Step4: *Repeat* steps 2-3 until a stopping condition is triggered

Figure 3 - System-perspective of the minimal clonal selection algorithm

A given tissue may have different properties. For example, some tissues may only facilitate receptor-antigen interactions (tertiary lymphoid), whereas others may be responsible for the creation of naïve cells (primary lymphoid tissues) or for facilitating the clonal selection process (germinal centres in secondary lymphoid tissues). Tissue types are a feature that may be exploited in extensions of the minimal recirculation algorithms, (see [5,7]).

***Dissemination Principle**: Lymphocytes recirculate between tissues in an effort to disseminate acquired information in the form of pre-committed lymphocytes across the system*

Collectively, the lymphocytes in all tissues and thus all tissues represent the acquisition of information (immunity) from antigenic stimuli. The movement process facilitates the dissemination of information between the discrete distributed spatial-structure. Ideally, all acquired information would be available in all tissues in all time. This is not possible given (1) the carrying capacity of tissue locations and (2) the vast quantity of lymphocytes possessed by the entire system. The recirculation mechanism is a strategic exercise in information availability. An antigen must physically contact the receptors of cells to 'test' for a reaction, thus smaller lymphocyte pools may provide some efficiency benefits. In addition, not all information is required everywhere, rather specific information for a given antigen exposure is needed at a specific location at an unknown time. Lymphocyte recirculation provides a trade-off of these concerns.

***Recirculation Strategy**: A mobile repertoire provides an information availability strategy attempts to get the right <u>information</u> (lymphocytes) at the right <u>location</u> (tissue) at the right <u>time</u> (of exposure)*

The amount of movement required/desired is related to the amount of information in the system (number of mature lymphocytes), and the number of spatial locations that may be exposed to antigen (tissues and how they are connected). The minimal recirculation algorithm presupposes that tissues are connected such that cyclic migrations between all antigen-exposure susceptible tissues is possible (a loop for example).

***Directed Cyclic Graph**: Recirculation applies to the migration of mature cells around a graph that provides a directed cyclic connection between tissues that may be exposed to antigen*

The traffic step (Step6) involves the selection of cells to depart a given tissue, and the integration of cells arriving to the tissue. These may be separate decision processes, although they are clearly related. For example, the simplest model involves the removal of a single lymphocyte (posted to a neighbouring tissue) which frees a position in the fixed-size pool for one-arriving lymphocyte (from a neighbouring tissue). Step6 may thus be elaborated into a set of sub-steps as follows:

Step6a: *Select* a subset of the repertoire to move to a neighbouring tissue
Step6b: *Integrate* any arriving lymphocytes from neighbouring tissues

Figure 4 - Elaborated trafficking of lymphocytes

The number and consistency of the sample of lymphocytes posted to the neighbouring tissue should be representative of the acquired information content of the repertoire. Further, the lymphocytes arriving from neighbouring tissue(s) to be integrated into the repertoire should have the same information content, thus meeting the goals of the 'recirculation strategy' principle. In addition to providing a suitable sample of the receptors in the repertoire, the strategy should permit the further development of information in the repertoire. The following provides a number of possible sampling strategies:

Random: Unbiased sample of the repertoire that provides an approximate (depending on sample size) representation of the information content of the repertoire
Activation-based: Sample biased towards activation count is such that highly activated cells are migrated from the repertoire. Applied across all tissues, this would result in the constant cycling of memory-like cells, perhaps inhibiting their formation.
Probabilistic: A probabilistic sample based on cell activation count, sample diversity, or other antigen-independent information.

Figure 5 - Collection of migration selection strategies

Arriving lymphocytes must be integrated into the repertoire. This may be more involved if there is a size mismatch between the number of cells selected and sent compared to the number arriving (for example if cells arrive from multiple tissue locations). Arriving cells may fill the vacant slots provided by the departed cells, and use a replacement strategy (as discussed for clone integration in the elaborated clonal selection algorithm) in the case of overflow.

IV. HOMING AS PREFERENTIAL RESIDENCE

Lymphocyte homing is a natural (first order) extension of the recirculation algorithm. It facilitates the clustering of information at locations where it was previously useful in the face of exposure-neutral lymphocyte movement. Homing empowers individual mature lymphocytes to discriminate their locations and express preference for residence in specific tissues locations. Homing requires an imprinting apparatus, which includes both a unique identity or signature for tissues, and a way lymphocytes to be impregnated with that signature.

A pattern-recognition method may be used that is somewhat similar to the approach used for intra-repertoire recognition (see [9]), although rather than a lymphocyte matching onto other lymphocytes with a mock 'surface feature', lymphocytes are provided with an additional receptor for detecting and matching the tissue they are in. In keeping with the bitstring basis of the minimal clonal selection algorithm (and extensions), a simple and scalable method is to assign each tissue (or tissue group) a random binary string. Each mature lymphocyte (that is a lymphocyte created from a cloning and maturation process) is then assigned (imprinted) with a copy of the tissue bitstring specific to the location of its creation. More interestingly than the imprinting mechanism, is how the mechanism is used to influence the movement process.

***Probabilistic Recirculation**: The probability that a mature lymphocyte is selected in an outbound migration sample is biased by the match between a given lymphocyte and the tissue's signature*

The match information between a given lymphocyte and a tissue may be used to bias the selection of cells from the repertoire to migrate. One may consider a Boolean match/no-match for lymphocytes in their home tissue, and those not in their home tissue. Those progeny lymphocytes created as a result of the clonal selection process are already in their home tissue, thus they have a match to their tissue's signature. All those lymphocytes that migrate from another tissue will not match. Thus, a migration sample selection policy that biases toward no-matches and away from matches (1) exercises a preference for lymphocytes (2) facilitates an 'automatic' recirculation population.

***Recirculating Population**: A tissue-match based migrant selection strategy biases recirculation towards those cells already recirculating, in effect creating, and maintaining an automatic recirculating (homeless) population*

This mechanism facilitates homing but introduces the problem of recruitment into the recirculation pool. Those cells in the recirculating pool will continue recirculating until they get home again, unless they get used or killed elsewhere. The initial recruitment probability will be uniform across the repertoire as there are no migrant cells to consider. If a recirculating cell is replaced (killed) by the proliferation strategy at another (non-home) tissue, then that tissue will fill the gap in the recirculating population.

The mechanism may be implemented in a completely deterministic manner. Given a sample size of S and N tissue locations doing migration, then the recirculating population size would be approximately NS, and the number of iterations for the entire pool to be replaced would be N. Recruitment to the recirculating pool would be probabilistic during the recirculation cycle, subjected to the clonal selection principles in each tissue. Given the lock-step nature of the recirculation (pass-the-parcel), approximately the entire recirculating population would be replaced at the same time (N iterations). This has desirable analysis properties, although the lock-in nature of the pool puts a lot of faith in the random sampling strategy of the repertoire to constitute the pool.

A probabilistic selection scheme adds noise to this selection process at each step, the more noise, the more of the recirculating pool is substituted during a main recirculation cycle.

V. EXTENSIONS

This work has proposed a minimal recirculation clonal selection algorithm in which lymphocytes migrate around a directed graph spatial structure. This algorithm was extended by introducing a homing algorithm to facilitate preferential residence in tissues where lymphocytes are useful (matured, thus the product of selection and proliferation). This section proposes some potentially interesting extensions to the minimal recirculation algorithm.

A. *Inflammation and Recruitment*

When a tissue is exposed to a pathogen, it may become inflamed. This is an immune response in which the local lymphocyte carrying capacity is increased, and lymphocytes are recruited (sequestered) from the recirculating pool to address the pathogen.

One may consider different tissue types in which the access to lymphocytes is restricted. Thus, cells may recirculate and only gain access to specific tissues if the cell and the tissue negotiate and agree. This effect may be exploited by the cells imprint of a tissues signature, as in the homing effect. Some tissues may be more restricted than others, for example, secondary lymphoid tissue may be open to all, whereas tertiary lymphoid tissue may limit access. When tissue becomes inflamed, the restrictions on lymphocyte access to the tissue may be relaxed, thus allowing an influx of cells into the area.

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