A Lymphoid Tissue Model and Lymphocyte Recruitment Algorithms

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***Abstract*-Tissue inflammation is a defensive measure that promotes healing from injury. One symptom of inflammation is the increase in the carrying capacity for blood cells at the site, in particular the increase in the number of supported lymphocytes. This work discusses some of the information processing and information sharing implications of adopting a 'lymphoid tissue architecture' for multiple repertoire models. Previously defined recirculating and homing clonal selection algorithms are phrased as undirected and directed response strategies respectively, which may be enhanced by a proposed tissue inflammation algorithm.**

Keywords-Tissue, Lymphoid, Inflammation, Recruitment, Multiple Repertoire Model, Migration, Artificial Immune System

I. INTRODUCTION

The significant difference between single and multiple repertoire algorithms is that the multiple repertoire approaches introduce a context for lymphocytes (tissue), and movement within the tissue (migration). This work has two aims, the first is to clarify a tissue-based model which defines information processing and information sharing constraints as a context for the previously defined homing and minimal recirculation clonal selection algorithm [4]. The second aim is to phrase the recirculation and homing algorithms as primitive resource allocation strategies, which may be reinforced, by a localised recruitment algorithm.

Section II proposes the layered lymphoid tissue model, highlighting the information streaming and information courier effects within the model. Section III phrases the recirculation algorithm as an undirected response algorithm, and the homing algorithm as a directed response algorithm. A tissue inflammation algorithm is proposed to augment both of these approaches by introducing the tissue as an agent with interests in the response. Finally, section IV proposes some extensions to the work.

II. LYMPHOID TISSUE ARCHITECTURE

The tissues involved in lymphocyte recirculation may be divided into three groups: primary, secondary, and tertiary lymphoid tissues. Primary tissues are responsible for the creation and first-round preparation of lymphocytes (B cells in the bone marrow and T cells in the thymus). Secondary lymphoid tissues provides filters of blood and lymph (such as lymph nodes, and the spleen) for pathogens, as well as microenvironments for the presentation of pathogens to lymphocytes and the subsequent interactions. Tertiary lymphoid tissue is all the other tissue in which lymphocytes may roam. Tissue models have been discussed previously [1], and in the context of lymphocyte migration algorithms in [2,3]. The minimal recirculation clonal selection algorithm [4] is primarily concerned with (1) tissue (node) types, and (2) with movement behaviours. This section discusses some effects specific tissue types may have on lymphocyte movement.

The lymphoid tissue model provides context for the previously proposed minimal recirculation clonal selection algorithm, and the homing clonal selection algorithm. In addition, it proposes an architectural model in which to phrase and investigate the proposed algorithms.

A. *Layered Model*

All three-tissue types may be combined into a single layered model. From an information processing perspective, the role of primary tissue is the guessing of receptor configurations and testing guess feasibility (such as negative selection of T cells in the thymus). The role of secondary tissue is in the presentation of pathogen to pools of lymphocytes (selective application) and in providing a suitable environment for receptor maturation. Finally, the tertiary tissue provides the testing ground for matured receptors for early detection of invading pathogen and subsequent neutralisation.

Tissue Type	Role Summary
Primary Lymphoid	Receptor guessing strategy and guess feasibility testing
Secondary Lymphoid	Pathogen presentation and selective application and maturation of receptors
Tertiary Lymphoid	Mature receptor testing ground for detection and neutralisation of pathogen

Table 1 - Summary of the information processing roles of each tissue type

Thus, different tissue types provide different information processing facilities. With regard to lymphocyte migration, the tissues are arranged in concentric layers. Naïve lymphocytes created in primary tissue migrate to secondary tissue for application. Mature lymphocytes recirculate around secondary tissue seeking their cognate antigen, some of which permeate tertiary tissue where they seek direct interaction with

pathogen. Pathogens penetrate the system in the tertiary tissue, and drain into the secondary tissue where they are collected and presented to the recirculating lymphocyte pool.

Tissue Type	Role Summary
Primary Lymphoid	Migration to secondary lymphoid tissue
Secondary Lymphoid	Recirculation between secondary tissue sites, low-volume migration to tertiary sites. Migration of pathogen from tertiary tissue.
Tertiary Lymphoid	Recirculation and migration back to secondary sites. Penetration of pathogen into the system.

Table 2 - Summary of the lymphocyte and pathogen movement properties of each tissue type

Thus, lymphocytes migrate from the centre of the system outward, increasing in proficiency as they approach the surface, whereas pathogen are housed in the outer layer and seep into the second tier.

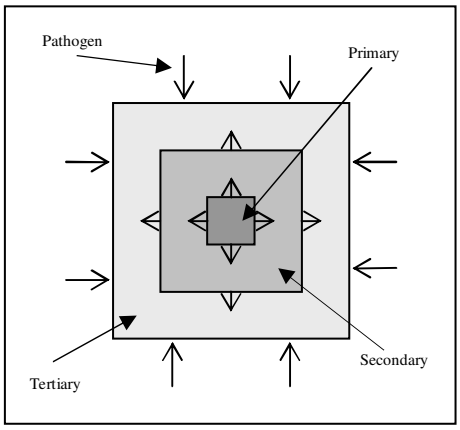

Figure 1 - Depiction of the layered tissue architecture

B. ***Information Streaming***

Pathogens that penetrate the system and manage to take-up residence in the tertiary tissue are drawn to the lymph nodes of the secondary tissue by fluid called lymph. Lymph drains into the lymph nodes, which in turn filter the fluid, collecting antigens, which are presented to local and recirculating lymphocytes. From an information processing perspective, a lymph node is provided an information stream from the regionally located tertiary tissue.

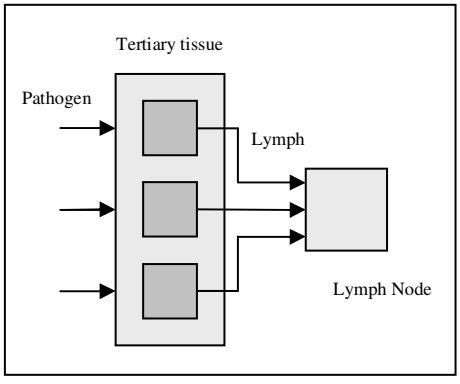

Figure 2 - Depiction of the information streaming providing by lymph collecting in lymph nodes

A proportionally large region of tertiary tissue feeds pathogen to a single lymph node, in effect proving multiple feeding information channels. The information is collected is specialised regions within the node. B cells are exposed to the presented information, and if sufficiently activated may migrate to another specialised region on the node and form a germinal centre in which bouts of selection, proliferation, receptor maturation and ultimately cell differentiation occur. The product of this learning process are effector cells called plasma cells that produce antibodies for the triggering antigen in large numbers, and mature long-lived memory cells. The antibodies enter the blood stream and seek a serendipitous interaction with their cognate antigen. The memory cells recirculate between the secondary tissue and sometimes move into the tertiary lymphoid tissue, with the same mission.

There is no homing effect for the B-cells. Their effectors flood the system, and their memory cells patrol. Importantly, the effectors and the memory cells are created and released in the vicinity of where the pathogen was encountered. Thus, they are more likely to encounter their cognate antigen sooner rather than later. The essence of this behaviour is captured in the minimal recirculation clonal selection algorithm [4].

C. ***Information Couriers***

Another type of cell, called a dendritic cells, patrol tertiary tissue for pathogen. Once detected, these cells collect the material and migrate into the secondary lymphoid tissue (such as lymph nodes). In the secondary tissue, the dendritic cells present the pathogenic material to T-cells that respond, proliferate, and differentiate. The product of this learning process is mature T cells in the form of effectors and likely long-lived memory cells. The effector T cells are imprinted by the dendritic cell as to the location in the tertiary tissue of the pathogen exposure. The effectors recirculate the system and penetrate the tertiary tissue when the specific chemical signature is detected. This behaviour is the basis of the homing algorithm previously described [4].

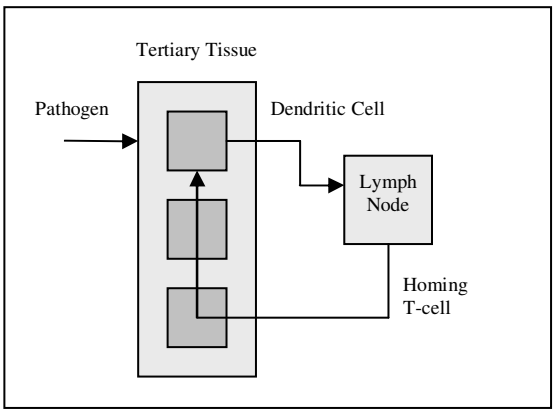

Figure 3 - Depiction of T-Cell education and homing

Information is streamed from the tertiary tissue to the secondary tissue although the streaming is facilitated by courier cells. These cells are aware of where they collected their material and thus are capable of imprinting that information onto the produced effector cells. The result is an effect that differentiates the lymphocyte movement behaviour from that of the B cells (that blindly seek their cognate antigen), to the T cells (that home into the chemical signature of infected

tissue).

III. Lymphocyte Recruitment Algorithms

The B-cell model provides an implicit recruitment of lymphocytes to the site of infection by improving the relationship between the antigen and the receptor and recirculating the receptors in the hope that they find what they are looking for. This is '*prepare and patrol*' response strategy to address the specific needs of a pathogenic invasion. A large amount of resources is required (antibodies) to blanket the system (undirected), although if the pathogen has spread from the area of infection or has arrived on multiple fronts, it will be addressed more effectively than a directed response.

***Undirected Response**: Flood the system with effectors, which will generally address the specific site of invasion and any other sites where the pathogen may have spread or penetrated on multiple fronts*

The T-cell model couriers information about the location of the pathogen invasion to the T-cells which are imprinted with that information. This is a '*fire and forget*' (homing) response strategy. Like the B-cell effectors, the T-cell effectors recirculate the system in search of their cognate antigen, although if the cells detect the signature of the site of infection, they take up residence and provide a local search strategy. Further, less effectors are created than in the B-cell model (mature T-cells as opposed to antibodies), thus the response is both smaller and more directed.

***Directed Response**: Produce a smaller set of effectors that home into the specific site of infection, and have a low chance of addressing additional sites of infection*

Both the undirected B-cell model and the directed T-cell model allocate (recruit) resources to the requirements of a specific pathogen exposure. Further, both strategies address the needs of the distributed information environment (resident receptors and inbound pathogen information). Thus, it is not unreasonable to describe both strategies as distributed recruitment algorithms. The undirected approach is a flooding strategy that does not use any structural information other than the generation of a response in the vicinity of the pathogens first detection. The directed approach is a homing strategy in which structural information is used directly to get the resources to where they are required.

***Distributed Recruitment**: A strategy in which information dispersed across a spatial structure is sought (selected) and employed for a specific task (pathogen neutralisation)*

Recruitment may be phrased as resource allocation with the desire of maximising payoff. The two models previously proposed and discussed both relate to the changing of lymphocyte migration behaviour, treating the lymphocyte as the active agent. An additional important consideration is to consider the properties of the tissue that house the lymphocytes. This section proposes a tissue-based strategy for enhancing lymphocyte recruitment.

A. *Tissue Inflammation Algorithm*

When a tissue is infected by a pathogen that damages the local area, the response is inflammation at the site. Inflammation has many symptoms, not limited to swelling and the increased carrying capacity of lymphocytes in the tissue. In addition, the blood vessels that led to the area dilate, increasing the flow of lymphocytes (information) to the site. Thus, more lymphocytes migrate and home into the tissue and collect there. The increased carrying capacity means that more information is available in the local area to address the infection, and there is less competition between receptors for selection (there is lots of it), and for egress movement (many cells which may leave).

***Increased Carrying Capacity**: The state of the local tissue is adjusted such that more effector cells (more information) can be supported*

This effect may be integrated into the minimal recirculation clonal selection algorithm by temporally increasing the capacity of a tissue for lymphocytes around the time of exposure. The increase in carrying capacity would be stepwise at the time of exposure such that the clones created at the time of exposure may be housed in the repertoire with less competition. This would also have the effect of lessening competition for the inbound lymphocytes from neighbouring tissues. The decrease in carrying capacity would not be stepwise; rather it would decay over time (for example as a linear function of the increased size over time).

Step2a: *Expose* the tissue according to the exposure regime
Step2b: *Decrease* carrying capacity (if capacity more than default)
Step2c: *Increase* carrying capacity (if exposed)

Figure 4 - Summary of the inflammation algorithm

The capacity increase would facilitate the approximate optimal amount of local information needed to address the pathogen. The decay rate would facilitate the approximate optimal amount of time that the local information may be required (for example pathogen endurance or pathogen exposure frequency).

***Inflammation Configuration**: Requires the specification of a resource capacity increase function (for example stepwise) and a resource capacity decrease function (for example linear over increased capacity and time)*

The amount of inflammation (increase in carrying capacity) may be a fixed amount (step size) and the decay function may also be fixed. In addition, an upper limit of lymphocytes for a site is required (upper bound on space complexity). For each exposure, the increase would be applied. The effect would be the allocation of space for lymphocytes *temporally* and *proportional* to exposures. Thus, space is allocated as a resource that is adapted by the system.

***Space-Complexity Resource**: Inflammation allows space complexity to be treated as a resource whose allocation is adapted by the system based on an exposure (needs) basis*

Adaptation of lymphocyte capacity allows not only increases when required, but also decreases when it is

not needed. Thus, the minimal (default) space allocation may be reduced from that of the minimal recirculation clonal selection algorithm, although not so reduced that the system is unable to maintain acquired immunity. The variable repertoire size would decrease replacement pressure in the repertoire and likely facilitate short-term diversity and niching effects.

IV. Discussion

The inflammation algorithm provides a foundation on which the tissue has a vested interest and control over influencing a response. Basic inflammation (increase in carrying capacity) may be augmented with a number of other inflammation-based behaviours, not limited to:

Lymphocyte Trapping: Lymphocytes may be prevented from leaving a site of infection for a temporally time. This provides symmetry to the increase in carrying capacity, which puts less pressure on the cells in the present tissue. This pressure is reduced further by migrating (out-bound) fewer lymphocytes.

Upstream Dilation: The tissues 'upstream' of an exposed tissue may be influenced to increase their down-flow migration of lymphocytes. Upstream and down-stream refers to the uni-directional flow of lymphocytes around the directed cyclic graph structure in which tissues are arranged. Increased flow of lymphocytes provides more localised information to address the exposure.

Effector Discrimination: Tissue behaviour may be extended further such that it may actively discriminate as to the effectors to accept and integrate into the local repertoire from migration, and those that are decidedly not useful during an exposure may be migrated away from the tissue. Thus, tissues may be given the ability to discriminate between effector lymphocytes.

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