A Hierarchical Framework of the Acquired Immune System

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Abstract-**The acquired immune system provides a general pattern recognition and defence system that modifies itself, adapting to improve its capability with experience. This work elaborates upon and refines the definition of a previously proposed hieratical acquired immune system framework. Rather than trying to fit biological observations in providing a tool for theoretical immunology, the framework is proposed as a tool for computational intelligence (artificial immune systems) for the proposal and investigation of information processing (cognitive and adaptive) models.**

Keywords-Artificial Immune System, Acquired Immunity, Clonal Selection Theory, Framework, Subsumption, Hierarchical

I. INTRODUCTION

A bulk of work has been competed to date based on an ill-defined hierarchical perspective of the acquired immune system, originally proposed [2], emerging out of early work [1]. The philosophy of work proposed in the context of the framework has been the development of information processing (adaptive or cognitive) models inspired by the acquired immune system with the background intent that developed models may be applicable to engineering problems. This work focuses on this hierarchical framework of the acquired immune system, elaborating each level and highlighting some implications for artificial immune system methodology.

Section II elaborates the hierarchical acquired immune system framework, highlighting each tier in turn, proposing additional tiers beyond the traditional three, and highlighting some perspectives of the framework. Section III discusses the pathogenic paradigm in the context of the framework, providing a number of perspectives, which ultimately result in the redefinition (elaboration) of the complementary framework. Finally, the framework is considered when all levels are subsumed into a single system IV, from a spatial perspective V, and some limitations and constraints of the framework are discussed VI.

II. THE IMMUNE SYSTEM AT DIFFERENT SCALES

The field of Artificial Immune Systems (AIS) is predominantly concerned with algorithms inspired by the immune system at the cellular level [18]. This section proposes a broader perspective of the immune system, such that the information properties of this complex biological system may provide metaphor for computational algorithms at multiple scales. A multiple-scales approach in considering the immune system was first proposed in [2], an later elaborated in [4,10], where adaptive models were proposed based on the acquired immune system at the cellular, tissue, and host scales. The focus in these works was the proposal of adaptive models, and later in the realization of algorithms from these models (for example [8,9]). It was not until a later work ([15]) that the potential of the framework was identified.

This section defines a discrete perspective of the immune system at three different scales of abstraction, where each level forms a tier in a hierarchical framework for immune-inspired information processing (artificial immune systems).

Cellular: The cell is the unit of adaptation; processes operate on cells such as selection, proliferation, differentiation, maturation, and decay.
Tissue: The tissue that houses cells in the unit of adaptation; processes operate on cells in tissue such as recirculation, homing, and on tissues, such as inflammation
Host: The host that houses tissues is the unit of adaptation; processes operate on the tissues and cells in hosts such as passive and active immunization, and pressures on tissues and cells such as evolutionary processes

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Table 1 - Summary of the three levels in the immune-inspired information process framework

The processes and components at each scale may be subsumed and augmented by following tiers, or reduced and simplified by previous tiers. The factor that links all three layers is the acquired immune system, that is, learned immunity at the somatic time-scale (clonal selection theory). At the lowest level, the concern is the architecture and processes of acquired immunity at the cellular level. At the tissue level, the concern is groups of cells and tissue types that participate in acquired immunity, and finally at the host level, the concern is the interactions between hosts as they pertain to acquired immunity.

Principle: *The linking principle between all scales of the framework is the acquired immune system and the principle components of adaptation at each level as they relate to this biological system*

In stating this guiding principle, one may define general architectural and process principles at each scale as they relate to the acquired immune system.

Scale	Processes and Operators	Components and Architecture
Cellular	Clonal Selection, Network	Cells, cell population

	theory, cell interactions	
Tissue	Cellular migration, trafficking, homing, inflammation	Lymphoid tissue types, collections of cell populations
Host	Host movement and interaction, host evolution	Collection of tissues in a host, population of hosts

Table 2 - Summary of some general principle processes and components at each scale in the framework

This section proceeds by explicitly defining each level in of the proposed framework with examples, highlighting relationships with existing literature and inter-relationships with neighbouring tiers.

A. *Tier 1 – The Cellular Level*

The base-level tier is the cellular level where the unit of adaptation is a single cell (or cell receptor), and the operations that apply to single cells from a collection of cells. This level has been the most popular in the field of artificial immune systems, with the majority of algorithms and systems inspired by theories and processes that apply to cells and cell receptors, and resultant emergent effects.

The principle components of the system are cells, where cells derive from a genetic composition, and have receptors that may bind to antigen. Cells are the primary component given the proposal of the clonal selection theory in which the cells (with their surface-bound receptors) are responsible for the diversity of the antibody repertoire and tolerance to self. Cells may be substituted for receptors as principle components.

Principle Component: The first tier is cell centric where cells are the units of selection given surface-bound receptors, and may proliferate (divide), change their selectivity (maturate receptors), and change behaviours (differentiate).

Cells exist in a collective in which they may interact with each other and with antigen. This collective structure may be referred to as a population of cells or a repertoire of pattern recognition capability. The collective may be thought to be housed in a tissue which may manipulate cell interactions and mediate behaviours.

Principle Architecture: Cells exist in a collective, which facilitates interaction and mediates behaviour. A tissue environment or architecture may be considered to house the collective (population or repertoire) of cells

Cells exhibit behaviours, thus an agency perspective may facilitate the cells enacting these tasks. From a high-level perspective, processes may be considered to operate upon the cells, for example competition for resources, selection by antigen, and death and removal by attrition and cellular aging.

Principle Processes: Cells are selected for expansion, maturation, and differentiation. Cells compete for resources and die and are removed from the collective.

Immunological inspiration that may be drawn upon from this level of the framework include the traditional cellular-based theories such as (1) the clonal selection theory, (2) the idiotypic network theory, (3) negative selection theory, (4) two-signal theory of lymphocytes, and others. Some algorithms inspired by some of these theories and cast in the context of this tier of the framework include an (1) an elaborated clonal selection [11], (2) a T-cell mediation algorithm [14], (3) an intra-repertoire recognition algorithm [12], and (4) a spatial clonal selection algorithm [13].

Principle	Cellular Tier
Component	Cells and receptors
Architecture	Population or repertoire of cells
Processes	Interactions with other cells and molecules

Table 3 - Summary of the principle aspects of the cellular tier

Given the cellular focus, it is useful for the hierarchical framework to highlight some of the assumptions made regarding the level below, the level above, and the interaction with the pathogenic environment.

Tier Below: The level below this level may be concerned with receptors, with the chemical properties related to binding between a receptor and ligand, and the genetic principles that lead to the different receptor conformations. The cellular level simplifies molecular interaction to matching, receptors and ligands to pattern attributes, and genetics and genetic operations to operations simplified processes directly on the receptor representations.

Tier Above: The level above may be concerned with the tissues that house the cells and receptors, and how antigens may access the different tissues for interaction with the cells. Further, the next level may be concerned with cell mobility and the trafficking of cells between tissues. This level is simplified to that of a single tissue architecture that facilitates cell interactions. These interactions and operations may be applied uniformly across the population of cells.

Pathogenic Exposure: The pathogen may have a uniform chance of interaction with all cells in at this level. Cells are concerned with interacting with the pathogen, and anticipating future exposures based on past exposures, which may be reinforced with clonal expansion processes. Pathogen entry into the host and arrival at the pool is simplified, as is the broader pathogenic environment.

B. *Tier 2 – The Tissue Level*

The second tier is the tissue level, where a single population of cells is scaled to multiple populations. The unit of adaptation shifts from the cell (which may still be a sub-unit of adaptation), to the tissues which house them. The system shifts from that of a tissue of cells, to that of a host that consists of a number of tissues, each of which contains a number of immunological cells.

The principle component is lymphoid tissue, where each tissue is composed of a population of cells and receptors specialised to antigen. Tissue is exposed to pathogen from which it must respond. The exposure may be addressed by the cells housed in the tissue.

Principle Component: Tissues house a population of cells (which may adapt themselves), and are exposed to

pathogen from the environment

A patch of lymphoid tissue belongs to a host organism with a function purpose in the context of other tissues to that host. Tissues have different responsibilities, thus may house different cell types, mediate different cell behaviours and facilitate varied interactions with pathogen.

Principle Architecture*: Tissues are spatially distributed and interconnected to facilitate the broader inter-tissue movement of lymphocytes and interactions with pathogens. The collective of tissues is housed within a single host organism*

Tissues facilitate specific and differentiated behaviours, which are exhibited in the lymphocytes populations that they house. In addition, the collective of tissues provide a network in which lymphocytes may recirculate, traffic, patrol and home. Tissues may be assigned agency in that they facilitate specific information processing manifest in cell interactions and movements, alternatively, the processes may be considered to occur on populations of cells.

Principle Processes*: The principle processes are those, which mediate specific intra-tissue cell interactions, and inter-tissue cell migration*

Immunological inspiration that may be drawn upon for the development of information processing algorithms and system in this level include: (1) lymphoid tissue organization, architecture and function (primary, secondary, and tertiary lymphoid tissue) and (2) lymphocyte movement in the broader context of the host such as recirculation, recruitment, and homing (for example see [3]). Some adaptive models inspired by immunological function at this scale of abstraction have been previously proposed (see [2,4]), as have some algorithms including: (1) a recirculation clonal selection algorithm and homing algorithm [16], and a lymphoid tissue model and lymphocyte recruitment tissue inflammation algorithm [17].

Principle	Tissue Tier
Component	Lymphoid tissues
Architecture	Host of inter-connected tissues
Processes	Movement of cells between tissues

Table 4 - Summary of the principle aspects of the tissue tier

Given the tissue focus of this tier, it is useful to consider the broader context of the hierarchy, not limited to the tier below this tier (cellular tier), the tier above this tier (host tier), and the implications of pathogenic exposures.

Tier Below*: The tier below this level has already been discussed (cellular level). Some concerns not considered include cellular movement within a single tissue (intra-tissue movement) which belongs to the previous tier. This tier simplifies the intra-tissue cell interactions and is concerned with the information content of a tissue, manifest in cells, and how that information may be employed by the entire host (rather than a single tissue).

Tier Above*: The tier below this tissue level (host level) is concerned with collectives of tissue (hosts) as a unit of adaptation. This tier is concerned with a single collective of tissues, thus a single host. The next tier considers the movement of information between hosts and the change in information within a host compared to other hosts. This tier simplifies a host to a collective of tissues without regard for other hosts.

Pathogenic Exposure: In this tier, pathogen may enter any tissue of the host, thus in addition to the systems anticipation of future pathogen based on past pathogen, the system must anticipate which tissues will be infected with which pathogen in the future, based on past exposures. Specific cell-pathogen interaction is simplified (good receptors are reinforced). In addition, the tissues varied spatial exposures as also simplified in that all the system may do is respond the best it can.

C. *Tier 3 – The Host Level*

The third tier is concerned with a single collective of tissues which compose a single host, scaled up to a population of host systems. Thus, each host system is composed of a network of lymphoid (and supporting) tissues, and each lymphoid tissue supports a population of lymphocyte (and supporting) cells. The unit of adaptation shifts from the tissue, to the collective of tissues, although a tissue within the collective, and the cells within a tissue may also be involved in adaptation. The focus moves from a tissue of cells, to a host of tissues that exists in a population of hosts.

The principle component is the host, manifest as a network of tissues, each tissue comprised of cells, and each cell comprised of receptors, ready to be or already specialised for an antigen. A host is exposed to pathogen from the environment. The exposure is addressed by one or more tissues of the host.

Principle Components*: Hosts are composed of a network of lymphoid tissues (which may themselves adapt), and is exposed to pathogen from the environment*

Hosts exist as a member of a population of immune systems. Different hosts have different behaviours, and different specific immune systems, with varied acquired immune traits. The variations between the systems is facilitated by the varied genetic makeup, and the variation in acquired immunity is facilitated by the variation in exposure patterns between hosts over their lifetimes.

Principle Architecture*: Hosts exist within a population (or species) of hosts which all have relatively similar immune systems and relatively similar exposure patterns although they vary on a genetic level and on a specific acquired immunity level*

Hosts are exposed to pathogen at varied rates and doses, thus respond in varied ways and acquire varied immunization characterises. Acquired information may be shared between host systems using passive methods such as via injection and passed from the mother, or actively via infection and vaccination. In addition, the genetic basis for each hosts system may be subjected to evolutionary processes of survival and proliferation.

Principle Processes*: Sharing of acquired immunity may be facilitated by active and passive means. The*

genetic basis for the species immune system may subjected to evolutionary pressures of adaptation.

Immunological inspiration for information processing algorithms and systems in this tier may be drawn from host-level acquired immune system function such as: (1) evolutionary immunology, (2) vaccination theory and other active immunity, (3) maternal immunity and other passive immunity (for example see [7]). Adaptive models inspired by the acquired immune system at this scale of abstraction have been proposed in [2], and elaborated in [10].

Principle	Host Tier
Component	Host of lymphoid tissues (complete immune system)
Architecture	Population of hosts with acquired immune systems
Processes	Sharing and evolution of acquired immunity

Table 5 - Summary of the principle aspects of the host tier

One may consider the previous tier, the tissue tier (already discussed), and the following tier in order to provide context and clarify the functional properties of this tier. In addition, one may consider the relationship hosts have with the pathogenic environment.

Tier Below: The tier below (tissue tier) has already been discussed. In considering a host as a being composed of a set of tissues, one may consider the supporting tissues that may be required, and neglected in the previous tier. In addition, a host is composed of many such lymphoid tissues, thus one may consider the scale (number) of tissues and their connectivity in the previous layer. This layer simplifies the tissues and their connectivity, such that a host is exposed to pathogen and responses by addressing the pathogen and acquiring some level of immunity to the pathogen.

Tier Above: The tier above this tier may be concerned with different species of hosts existing in the same pathogenic environment. Issues may be related to cross-species pathogenic exposure, pathogen crossover between species, and adversarial immune systems between species. The species would become the unit of adaptation, existing in ecology with other species. This tier simplifies this to a single species of hosts.

Pathogenic Exposure: Hosts are concerned with survival, and in turn with survival of the species (all hosts). A pathogen may infect any given host, thus the population must anticipate pathogen exposures, and may be encouraged to share acquired information. Hosts in the species may evolve characteristics of how pathogens are exposed and even if pathogens may be exposed to the host. These characteristics may go beyond evolutionary bias in receptor generation (such as morphology) and ecological niche.

D. *Additional Tiers*

A tier in the framework is given perspective by its context with neighbouring tiers. This have been demonstrated with the three base tiers of the framework, in particular with regard to the assumptions made by each tier, and the specialisation of components, architecture, and processes of each tier.
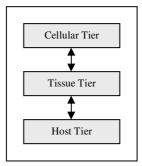

Figure 1 - Depiction of the three-tier hierarchical framework

The immunological theories and functional properties at a given tier (level of abstraction) impose constraints on the tiers that precede and follow a given tier. This observation was originally made in a previous work [15], and is exploited here to propose additional preceding and following tiers for the boundary tiers of the framework (cellular and host). The framework does not fit neatly onto the concerns at the levels outside of the proposed framework. This section proposes some candidates for exploring beyond the boundary tiers.

Below Cellular: Receptor Tier

One may consider the functional aspects of the acquired immune system below the cellular level. Examples include (1) the properties of receptors interacting with a ligand, (2) the intra-cellular processes that occur during and after binding, and (3) the genetic considerations of receptors. Together, these functional aspects may be considered a receptor tier, where the receptor is the unit of adaptation, and a collection of receptors are expressed on a cell.

The receptor level is concerned with the chemical and physical properties of surface bound receptor proteins interacting and binding to ligands (for example, see [5]). In addition to the concerns of molecular interaction are the intra-cellular reactions that describe the chemical processes that occur within a lymphocyte cell after it has been activated. A functional concern is the genetic basis (genes) that define the receptor specificity. The same genome is shared by all cells, and defines the amino-acid sequence and protein conformation of each receptor. Mutations occur to the genome during cell proliferation in the form of copying errors, and mass changes are facilitated by a receptor-rewriting process. Changes to receptors are simplified at the cellular level by direct changes to the resultant receptor conformations rather than the common genetic material that underlies all receptors.
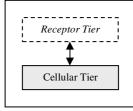

Figure 2 - Example of an extension of the framework below the cellular level

Above Hosts: Species Tier

A population of hosts, each with their own distinct acquired immune system may be considered a species of

organism. A natural extension beyond a species of organisms with immune systems is to that of an ecology of species, where a given species becomes the unit of adaptation, and a species exists in an ecosystem. Co-evolutionary relationships may develop between evolving species. For example, one species may evolve to support another species immune system, to exploit another species immune system, or to develop an adversarial interaction with the species immune system. Other relationships to consider are those of pathogen-interaction such as the spreading of disease between species (cross-contamination), and the prevention of an epidemic of a contagion of one species by another.
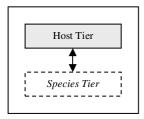

Figure 3 - Example of the framework when it is extended beyond the host level

E. *Additional Perspectives*

The proposed three-tier framework may be considered from a number of perspectives. For example, the perspective used in describing the framework and naming the tiers is the 'unit of adaptation' perspective that focuses on the principle components that change at the scale of interest. Other perspectives include how information is represented, the collectives of principle components, etcetera (see Table 6).

Perspective	Cellular	Tissue	Host
Anticipation	Which receptors	Which tissues	Which hosts
Collectives	Population of cells (tissue)	Population of tissues (host)	Population of hosts (species)
Information	Collective of receptors (a cell)	Collective of cells	Collective of tissues
Interaction	Cells interact with pathogen	Tissues share cells and pathogen	Hosts share immunity and spread pathogen
Redundancy	Cells	Tissues	Hosts
Survival	Tissue	Host	Species
Unit of Change	Cells adapt	Tissues adapt	Hosts adapt

Table 6 - Summary of implicit perspectives of the framework

The tiers are tightly coupled, such that the collective of adaptive principle components on one level themselves become the principle components on the next level. A strict adoption of the framework would be concerned with immunological inspired information processing that fits neatly within each tier. These may be considered the 'low hanging fruit' in adopting the framework to investigate AIS. Such straightforward inspirations include (1) the clonal selection algorithm at the first tier, (2) lymphocyte trafficking at the second tier, and (3) vaccinations at the third tier. In continuing this methodology, application domains for the inspired techniques may also map onto a scale of the framework that most closely matches the level detail in the application. Some domains that match onto the inspired information processing approaches outlined above include: (1) optimization for clonal selection, (2) packet routing for lymphocyte trafficking, and (3) systems anti-virus protection.

Strict Adoption: *A methodology for investigating immunological inspired information processing approaches that fit neatly into the framework, and their application to problem domains that match the same level of detail*

The strict adoption approach for investigating algorithms and applications may be considered a first principles approach in exploiting the framework. It is a base-level methodology that will likely facilitate the bulk of the interesting work that results from the framework.

A closer look at base-level algorithms and applications will reveal assumptions and constraints that spread in both directions on the framework. Thus, an immunological inspired information processing approach that maps onto the framework may implicitly or explicitly constrain the levels above and below the scale at which it is mapped. It is expected that many of the more rewarding inspired approaches will not fit neatly into the tiers of the framework, but will rather spread across the concerns of the tiers in an irregular and asymmetrical manner. The framework remains an effective tool in this methodological approach given its facility in highlighting the perspective of mapped properties. This impact or perspective is give by the context provided by the other immunological characteristics in the same tier, the principle components that contribute to it from the previous tier, and the principle components that the feature contributes to in the next tier.

Irregular Adoption: *A methodology for investigating immunologically inspired information processing that do not fit neatly into the framework, whose concerns spread across the scales in an irregular and asymmetrical manner*

An irregular adoption may be specialised further in a discontinuous mapping. This is the mapping of an immunological function that may have a concern in the boundary tiers, and not in the middle tier. It is expected that such a mapping will likely still impose implicit constraints and or assumptions regarding the middle tier. One example of this type of concern is that of the application of evolutionary processes to receptors. An evolutionary process is an interesting information processing approach to may onto the framework because, although it applies to hosts, it may operate in concert with all other levels. For example, the reproductive fitness of a host may be defined by the ability of the host to survive which may depend on the receptors it can propose (based in the genome) and how those receptors may be moved and applied within the host (morphology based in the genome). As already demonstrated, the reproductive fitness may be defined by as little or as much detail as desired, so a host may be reduced to a single receptor, thus reiterating the discontinuous example above.

Crosscutting Concern: *An immunological inspired (or related) information processing approach that (although may be influenced by) applies to all levels of*

the hierarchal framework

A final consideration in mapping processes to the framework are those immunological inspired information processes that apply to all levels. Unlike evolution that may have an influence at all levels, although is rooted at the host level (host selection and reproduction), there are processes that do not conform to the hieratical reductionist framework. This are referred to as crosscutting concerns or a non-decomposable mapping. They are different from irregular mapping that map onto a tier and spread across surrounding tiers in that a non-decomposable mapping may apply regardless of the tier. Thus, such information processing concerns are beyond the control of the system. A good example (other than esoteric examples such as physics and chemistry) is that of pathogens. Pathogens are exogenous antigens that may be micro-organisms with their own (adversarial) agenda. A host may improve their own or their species defence against a pathogen, although the pathogen may remain a part of the environment. Interaction with a pathogen and the pathogenic environment is a concern at all levels, and thus crosscuts all levels (see the next section for a discussion of pathogens and the framework).

III. PATHOGENIC EXPOSURE PARADIGM

The acquired immune system requires a pathogenic environment as its complement. A pathogenic exposure paradigm has been defined previously [6] in which the stimulus-response relationship was well defined. Exposures were divided into their own hierarchy of complexity: (1) single exposure, (2) multiple exposures, and (3) multiple pathogens. A natural inclination and the intent of this section is to attempt to integrate the two hierarchical frameworks in an immunologically meaningful way. This section proposes a number perspectives on integrating the two frameworks.

A. *Exposure Map Perspective*

A system may have different concerns for different exposures. For example, for a single exposure, the system is concerned with preparing the best set of receptors it is capable of preparing. For multiple exposures, the system attempts the same task, although this is superseded by the goal of anticipating when the system will be exposed. Finally, from multiple pathogens exposing the system multiple times, the two previous goals may be augmented by anticipating which pathogen may arrive. Thus, regardless of the pathogen exposure regime, the system is concerned with building a map of the pathogenic environment. The map is composed of what pathogens (receptor configurations), and the likelihood of exposure (receptor density). The map has nuisances such as the tissue spatial location where the system is exposed and application of the map across the spatial distribution of the host's tissues.

Exposure Map: *An acquired immune system learns a map of the pathogenic environment from experience that is encoded in receptor configuration and receptor densities*

The 'exposure map' perspective highlights the concerns of the systems information gathering via experience at the different scales. The map itself may be considered holistically from the host perspective where the map construction is a side effect of host survival (the map is needed to live). At the tissue level, the map is spread across the host organism, the components of which are recirculated and organised in an attempt to maximise anticipated spatial-exposure payoff. The cellular level provides the map-construction toolkit of acquired immunity in selecting and improving the local repertoire for exposed pathogen. Thus, each exposure type may occur at each level (crosscutting concern), although the meaning of the exposure varies across the levels.

Tier	Pathogen
Cellular	Improve the receptors for whatever arrives
Tissue	Spatially organise the receptors for expected exposures
Host	Prepare a map of the pathogenic environment

Table 7 - Summary of the exposure map perspective of exposures

B. *Delegation of Responsibility Perspective*

The scales of the acquired immune system framework provide a suitable level of detail for each of the levels of detail on the pathogenic exposure paradigm. A single collection of cells may effectively address a given single pathogenic exposure. A tissue may organise a response to multiple pathogenic exposures, and finally, holistically, a host may organise a response to multiple pathogenic exposures. Multiple pathogens exposed to a host multiple times (a pathogenic environment) is addressed by the accumulation of delegated responsibility throughout the tiers of the acquired immune system framework. A tissue can address a given pathogen because its resident lymphocytes can address a given pathogen. Thus, a host may address a given environment, because its tissues can address the given pathogens of that environment.

Delegated Responsibility: *Each tier in the acquired immune system framework takes responsibility for a given tier in the pathogenic exposure framework. Subsequent tiers are addressed by the accumulation of the efforts of the previous tier.*

A single cell may or may not be capable of addressing a single exposure, although a collection of cells provides choice such that selection can discriminate, and maturation can occur on multiple fronts. A single pool of cells may or may not be capable of addressing multiple exposures, although multiple tissues provides the resources and processes for responding to repeat and concurrent exposures. A single host may or may not be capable of addressing a given pathogenic environment, although a population of hosts provides sufficient diversity to survive. This elaborated example demonstrates that all three exposure schemes may occur at all three levels of detail, although the capability provided by resource availably at each tier is required to effectively address the needs of the different scales of exposure.

A single cell can deal with its cognate antigen. A single tissue can deal an exposure of a pathogen of its cells cognate antigen. A host can address multiple exposures to its tissues of a pathogen of its tissues cells

cognate antigen. A species can address multiple exposures of multiple pathogens of the hosts tissues cells cognate antigen.

Tier	Pathogen
Cellular	Address a given exposure, although can address multiple exposures
Tissue	Address a given pathogen with multiple exposures, although can address multiple pathogen
Host	Address a given environment with multiple pathogens, although can address multiple environments

Table 8 - Summary of each tiers delegated responsibility

The point being made is that a given level can address the needs of the next tier although with some constraints. To address the constraints of the additional burden, one most scale to the next level of the framework. For example, a single tissue may address multiple exposures, although in addressing one exposure, resources are taken away from other concurrent or near-concurrent exposures. Thus, in possessing multiple tissues, a system can address multiple exposures. A host can address multiple pathogen, although each additional pathogen exposed to the system consumes more available resources, thus a host has a capacity on the number of varied pathogens it can successfully address. Thus, in scaling to a population of hosts, the species has more resources to address a pathogenic environment.
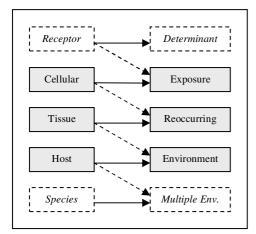

Figure 4 - Depiction of each tiers suitability and capability

C. *Unit of Adaptation Perspective*

The delegation of responsibility implicitly proposes a mapping of units of adaptation. The principle components of a given tier of the acquired immune system are the units of adaptation (cells in a tissue, tissues in a host, hosts in a species). These units are proposed to be the substrate of selection and change. Thus, one may identify aspects of the pathogenic paradigm to which they are being selected by and changing in response too. This is an effective perspective for integrating the two frameworks as it requires an adjustment and refinement of the (newly pressed) pathogenic paradigm.

A tissue of cells may address a given pathogen exposure because a given pathogen has a number of antigenic determinants. Each cell (receptor) may select for and specialise different antigenic determinants on the

pathogen or different perspectives of the same antigenic determinant (or some combination). A population of cells provides multiple varied pathogenic features which may be selected. This basic feature detection premise provides the scalability for addressing (1) variations and combinations of antigenic determinants, and (2) variations in exposures frequencies. A single cell can detect and maturate detection for a single antigenic determining feature. A tissue of cells can detect any pathogen that expresses features that the cells in the tissue can detect. Thus, a host can detect and improve detection for any pathogen its tissues can detect, and the same principle scales for hosts in a population.

Unit of Adaptation: *A single cell with surface bound receptors provides the base-level unit of feature detection and adaptation. Scales beyond a single cell are mealy concerned with organising the receptors for presentation to exposed pathogens.*

This is an organisational perspective. The tissues of the body organise such that a pathogen is exposed to the most likely receptors to detect it in a minimal amount of time. Thus, tissues self-organise internal spatial receptor layout to maximise response efficacy and efficiency (satisfiting an uncountable number of unknown constraints). Once a pathogen is in the host, a response by a tissue is required. Once a pathogen is in a tissue, a response by cells is required. The host may influence the pathogens it is exposed to and when it is exposed to them. Thus, this perspective proposes levels of control over a response in addressing a pathogenic exposure.

Tier	Pathogen
Cellular	Organise which cells to respond to pathogen
Tissue	Organise which tissues respond to pathogen
Host	Organise which hosts are exposed to pathogen

Table 9 - Summary of the levels of control in organising a response

D. *Rephrased Pathogenic Environment*

The default consideration is that a system of cells will encounter stimuli in the form of pathogen regardless of scale. Thus, all three proposed levels of the pathogenic exposure paradigm may be assumed to occur at all scales of the acquired immune system (already proposed in pathogen as a crosscutting concern). Higher scales of abstraction may generally facilitate types of cell-pathogen meetings by organizing cells in the specialized populations or in controlling exposure. Regardless, cell and pathogen interactions still occur. One may consider the behaviours of pathogen at different scales in a similar way that the acquired immune system may be considered at different scales.

A pathogen consists of multiple antigenic determinants (epitope's). A single receptor may be prepared for any one of a given antigenic determinants on a given pathogen. Thus, a pathogen may be considered layered with regard to the types of pattern recognition that may occur of it. A collection of receptors is the natural complement for an aggregate of antigenic determinants, and a single receptor is a natural complement for a single antigenic determinant. At a host level, lymphocytes exist in and migrate between a variety of tissues. Complementarily, a pathogen has a

point of entry, and may employ specific intra-host behaviours in an attempt to survive such as counter-measures, subversion, and tissue destruction. At a species level, hosts may influence individual host exposure patterns and may share acquired immune substrate (cells). Complementarily, a pathogen may use inter-host behaviours to migrate between hosts (influence exposure), facilitating an adversarial relationship with the species for survival. Thus, the pathogenic exposure paradigm may be re-phrased, where the existing three levels may be compressed into a characteristics of a single 'exposure' level of a the new paradigm. This re-phrased framework not only clarifies the relationship of the immune system with pathogen, but conveniently maps onto the existing acquired immune system hierarchical framework.

Immune System	Pathogen
Protein of molecules	Intra-protein (inter-molecular) dynamics of an interaction with a pathogen epitope
Tissue of cells	Intra-tissue (inter-cellular) dynamics of an exposure of pathogen molecule
Host of Tissues	Intra-host (inter-tissue) dynamics of an infection of pathogen
Species of Hosts	Intra-species (inter-host) dynamics of a species of pathogen

Table 10 - Rephrased pathogenic paradigm that maps onto the hierarchal framework of the acquired immune system

The relationship is between one acquired immune system and one pathogen. A species of immune system may provide a pivot such that it must address multiple pathogens. A species of pathogen may provide a pivot such that it may be concerned with multiple species of host. The former case is clearly of more relevance than the latter case.
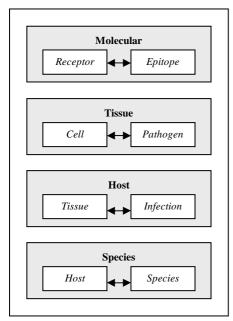

Figure 5 - Depiction of the relationship between an acquired immune system and a pathogen at multiple scales

Thus a tissue may facilitate many cell-pathogen interactions with a variety of receptors and a variety of pathogens. A host may in turn facilitate many tissue-infection interactions again with the same variety. Finally, a species may facilitate many interactions of

hosts with species of pathogen.

IV. A SUBSUMED SYSTEM

The layers of the framework may be compressed into a single system at the host level. Thus, a host has an acquired immune system, which subsumes the tissue level, which in turn subsumes the cell level, and any lower receptor and genetic levels. The difference between a subsumed host system and host from the third tier of the framework is basic-concerns of the previous levels are implemented in the subsumed system, whereas the non-subsumed system may constrain, simplify, or remove the base-concerns of the previous levels. The subsumed system may be considered an implementation of an information processing system at the species level of the framework where the details of the previous two levels are considered in the complete form. In the context of adoptive perspectives, a subsumed system is 'strict and complete' to all layers below. With this refined definition, a strict-complete (subsumed) system may also be defined at the second tier, subsuming the first, although this example will not be discussed.
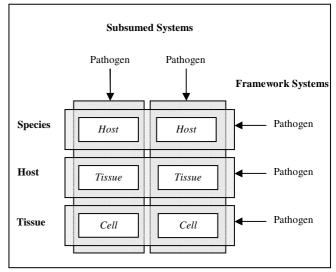

Figure 6 - Depiction of the difference between framework and subsumed systems

This subsumed system provides perspective on the framework and the models that may be proposed within its context. It highlights the emergent effects that may be cultivated and exploited across the tiers of the system, and highlights a strong bottom-up and top-down methodology for considering the acquired immune system.
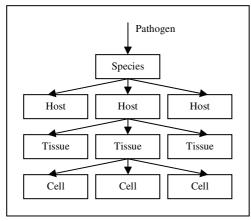
Figure 7 - Depiction of the a subsumption architecture

The primary difference between a subsumed system and a framework system is that the subsumed system is detail. Pathogen is processes by each level of the system as through that level were the only level in the system. This system provides a useful exercise in system roles and responsibility in the context of pathogen (already discussed). The principle problem of the approach is integration. How can one level enact its role and pass on a suitable level of responsibility onto the next level in the hierarchy? Is essence, each of the smaller information processing models proposed in the context of the framework (strict and irregular) provide information on rectifying this problem. The more models, the closer a subsumed system is to realisation. Thus, a background high-level objective of the framework may be a contribution towards a realised subsumed acquired immune system (for whatever plausible information processing needs). Thus, if models in the framework contribute to a subsumed system, the question for further investigation may shift from how; to why (to what information processing needs) such a system may be employed.

V. MAKING IT SPATIAL

A spatial metaphor was used to describe the pathogenic exposure paradigm and its relationship with each 'class' (tier) of system [6]. A tissue of cells is merely exposed, whereas a host of tissues may be selectively exposed, as is a species of hosts. Further, a spatial clonal selection algorithm was proposed in which exposures occur on some discrete spatial geometry and subsequent clonal processes occur in the locality of exposure [13]. This algorithm highlights the fact that in phrasing the information processing systems in the context of a spatial paradigm provides a number of interesting effects.

Pathogen Perspective: Exposures become tied to a location on the geometry (positional exposures). The geometry provides an additional dimension to the system-pathogen relationship, providing an environment in which to house and facilitate interactions.

System Tier	Spatial Pathogen Environment
Cellular	Shape space for all receptor and pathogen variations Affinity landscape for all receptors for a given pathogen Location for clonal expansion
Tissue	Point of system penetration by pathogen (site of exposure)
Host	Vicinity of host susceptibility to contracting a pathogen

Table 11 - Summary of the spatial pathogenic environments facilitated for each tier of the framework

System Perspective: Once adaptive units have a position on a spatial geometry, they may change that position and move about. Positional changes may in turn affect the stimulus-response properties of the system, and adaptive unit interactions. Processes and operations on units of adaptation occur in a local region. Exposures affect units at the site of exposure, proliferation (clonal expansion) displaces cells in the region of location.

A. *Spatial Realization of Subsumption*

A spatial conceptualisation provides a natural realisation of the subsumed host model of the previous section. A one-dimensional subsumed model is used to demonstrate some of the interesting effects that a spatial context may facilitate.
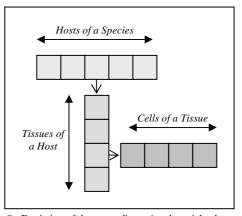

Figure 8 - Depiction of the a one-dimensional spatial subsumption architecture

Perhaps the most important observation from this conceptualisation is that each level of detail may employ the same general principle components (units of adaptation), the same general interface to pathogenic exposure (stimulus-response), and the same general processes of selection, localised adaptation, decay (unit displacement or death), and unit movement. This structure (exemplified in Figure 8) is fractal in that the general properties apply regardless of scale (the level of detail).

VI. DISCUSSION

The proposed three-tier framework lays the foundation for the investigation and application of information processing schemes inspired by the acquired immune system both at the already exploited cellular level and at two scales which have seen very little (if any) specific attention; tissue and host. The framework provides a taxonomy and context for function properties and assumptions of models that provide insight and perspective.

The framework is not all encompassing of the immune system.

1. It is mammal centric and acquired immune

system focused, ignoring the innate immune system

2. It is selection-centric (selectionist) focused on the clonal selection theory which is abstracted and employed at all scales

3. It ignores self antigens and self-nonself discrimination, all stimuli are of exogenous origin, and the information processing in monitoring self and the concerns of generating autoimmunity are ignored

4. It is simplistic and discrete ignoring the morphology and biology of the host, and providing a crude, disjoint abstraction of some acquired immune system observations

In its defence, the framework is not a model of the acquired immune system intended for simulation or any theoretical immunological studies. It is intended as a tool for computer scientists interested in stealing (ripping off) immunological ideas for computational purposes.

The framework may provide a useful tool for interpreting existing work. The level of detail provides a linking perspective that highlights the focused effort of the greater computational intelligence community (artificial immune systems). This may be extended further in devising such a framework for other fields of research. Such work may partially already exist, such as in evolutionary computation, swarm intelligence, and neural networks, although under different guises.

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