A Series of Discrete Repertoire Models Inspired by Lymphocyte Migration

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***Abstract*- White blood cells (lymphocytes) are critical to the recognition and response of the acquired immune system. These cells are mobile, migrating from primary lymphoid tissues, recirculating in the blood stream, trafficking though tissues of the body, and homing in to sites of infection and inflammation. Given an understanding of lymphocyte migration in the biological system, three areas of foundational model elements are proposed: (1) a series of architectural lymphatic tissue components, (2) a class system for lymphocyte differentiation based on their functional behaviour, and (3) a series of lymphocyte movement operators. These three major collections of foundational model elements are employed in the definition of a series of discretised repertoire adaptive models that rephrase and elaborate upon two existing discretised repertoire models.**

Keywords- Adaptive Models, Discrete Repertoire, Algorithms, Lymphocyte Migration, Trafficking, Homing, Recruitment, Lymphatic System

I. INTRODUCTION

Lymphocyte recirculation is an integral part of the functioning of the acquired immune system. This work reassesses a pocket of discrete lymphocyte repertoire models proposed in a related work in the context of an understanding lymphocyte migration. Section II reviews the previously stated framework of adaptive models inspired by the acquired immune system, and summarises the contributions and areas of weakness of the previously stated discretised repertoire models. Section III proposed a network topology model of tissues as a formalisation of a discretised repertoire with an abstracted circulation specification representing the edges of the network. Section IV describes the cellular components of the model, which include discrete antigen, and a class system used to differentiate lymphocyte types by their functional behaviour, specifically movement behaviours. Section V presents a set of distinct movement operators employed by the cellular components within the model.

Given the foundation of components and operators specified in the previous sections, section VI proposes a series of four discretised repertoire models two of which a more detailed rephrasing of the discretised models DM1 and DM2. Section VII highlights the pattern of this work re-examining immunological inspired adaptive models in more detail and suggests three other areas of the framework that may benefit from such a treatment. The work concludes with the observation that a test platform is required to begin to evaluate the series of models adaptive models.

II. REVIEW OF FRAMEWORK

In a previous paper, Brownlee [2] proposed a series of adaptive models inspired by the acquired immune system. The proposal began with the definition of a number of simple immunological operators. Using these operators, base clonal selection models were defined, from which further extended models, discrete models, and multiple system models were proposed. Although rudimentary and heavily biased by clonal selection theory, the series of adaptive models provided a framework for both postulating further immunological inspired models and phrasing existing models. This section summarises the series of adaptive models, and focuses on the 'Discrete Models' proposed in that work that will be taken as the basis for the models proposed in this work.

Series of Adaptive Models

The series was made up of five levels of increasing complexity. The first level were the 'Principle Components' that defined seven immunological operators such as clonal expansion, mutation, memory, etcetera. The second level combined these principle components and proposed 'Base Models' that included a cloning algorithm, a mutation algorithm and a culminating clonal selection algorithm (BM3). The following section consisted of a collection of 'Extended Models'. These models built upon the BM3 model and included additional mechanisms such as memory, tolerance, evolving antigen, and helper T cells.

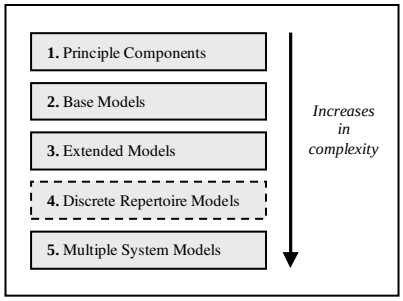

Figure 1 - A summary of the series of adaptive models proposed in [2]

Two 'Discretised Models' were proposed that were extensions of BM3, although with a distributed repertoire. The final section proposed a number of 'Multiple System Models' that subsumed all previous models by raising the level of abstraction to that of multiple instance of the BM3 model. These included a vaccination model, an evolutionary model for gene libraries, and an ontogenetic evolutionary model that combined lifetime learning with the evolutionary learning model.

Distributed Repertoire Models

The series of adaptive models proposed two discrete models: DM1 – Discretised Circulation Model, and DM2 – Discretised Lymphatic Model.

DM1 is an extension of BM3 where the lymphocyte repertoire is discretised into multiple sub-repertoires and the cells circulate around the sub-repertoires. The model introduced the concepts of (1) a mobile population, (2) spatially and temporally distributed antigen stimulation, and (3) autonomous homeostasis. DM2 is an extension of DM1, although, in addition includes (1) the differentiated cell types of effector and memory from the EM1. It further introduces the concepts of (2) differentiated tissue types to distinguish areas of information processing and information preparation, and (3) differentiated movent types: recirculation, homing, and static.

The models raise many unresolved questions, particularly those related to the distributed information processing properties of the systems. Particularly of note are questions related to (1) the properties of the models architecture, (2) a clearer definition of the behaviours of the differentiated cell types, (3) a clearer definition of the differentiated tissue types, and (4) a clearer definition of the differentiated movement types. The remainder of this document attempts to address these points based upon an understanding of lymphocytes migration behaviour outlined in [1].

III. Architecture Components

This section is concerned with the abstraction of the infrastructure of the model, in particular the architectural models for the data structures that represent the discretised repertoire. This section proposed a network topology as a formalism of the discretised repertoire and discusses questions related to the node types, information-process within nodes, and connectivity of the nodes in this model. Architectural components are listed with the notation AC#.

Architecture Component	Summary
AC1 – Discretised Repertoire	(network model) Network topology of tissues and connectivity of the system
AC2 – Tissue Nodes	(node) General tissue location which may house a repertoire of cells, and facilitate antigen-lymphocyte interaction
AC3 – Primary Lymphoid Nodes	(node) Site of cell creation and pre-processing
AC4 – Secondary Lymphoid Nodes	(node) Site of antigen collection and lymphocyte interaction with antigen (information processing)
AC5 – Tertiary Lymphoid Nodes	(node) Site for antigen injection, sentinel lymphocytes, and slow migrating recirculating lymphocytes
AC6 – Germinal Centre	(node compartment) Dynamically created sites of information processing
AC7 – Circulatory System	(edges) connectivity medium between tissues

Table 1 - A summary of the architecture components described in this section

AC1 – Discretised Repertoire

Discretising the repertoire refers to transitioning from an abstracted 'clonal selection' single and self-contained repertoire, to multiple of such repertoires. The direct approach proposed in this work is to focus on the lymphoid tissue (which manages antigen lymphocytes, and their interaction) as the *nodes* in a distributed repertoire and the vascular system (the veins and such that transport the lymphocytes between the lymphatic tissues) as the edges of the network. This network formalism provides an architecture that separates the movement or transport of lymphocytes on the *edges* of a network structure, with the information processing (antigen-lymphocyte reactions) that occur in the nodes of that network.

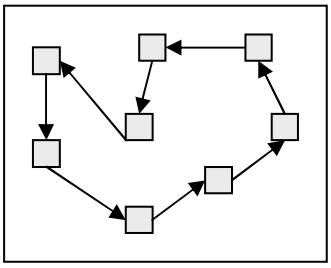

Figure 2 – A depiction of the network topology of a discretised repertoire

AC2 – Tissue Nodes

Tissue is a generic node in the network topology model, and may be specialized to various types of tissue with differentiated functional roles. A tissue may host a repertoire of lymphocytes and facilitates antigen-lymphocyte interaction. Thus, a tissue node is a re-formation of what might be considered the repertoire in the BM3 model. The following sections define some specializations of tissue.

AC3 – Primary Lymphoid Tissues

This node type is an abstraction of primary lymphoid tissue such as bone marrow and the thymus. Such nodes are responsible for the creation of immature lymphocytes using an antigen-independent process. In terms of information processing, this may involve a (1) pre-processing of information such as tolerance (application of a priori domain knowledge), and or (2) maturation of information such as the negative and positive selection of T lymphocytes in the thymus. These nodes would not facilitate direct interaction with antigen (the domain), and the lymphocytes released from this node type would be considered immature or naïve, perhaps requiring further maturation at a secondary lymphatic node. There are few of this node type, and the traffic is limited to outbound lymphocytes.

AC4 – Secondary Lymphoid Nodes

This node type is an abstraction of secondary lymphoid tissue, specifically the lymph node system, and or the spleen. These nodes are the site of information process. They provide a (1) collection site for antigen (domain specific interaction), (2) a collection or stop-over site for recirculating lymphocytes, (3) a holding point for some effector lymphocytes, and (4) a location for maturation of lymphocytes such as the formation and processing within a germinal centre (GC). Such sites may also be considered 'filtration nodes' for streams of information, from which antigen are extracted and houses for interaction with lymphocytes. There are many of this node type and traffic consists of inbound antigen, inbound immature and recirculating lymphocytes, and outbound recirculating lymphocytes.

AC5 – Tertiary Lymphoid Nodes

Tertiary tissue is an abstraction that represents all other (non-lymphoid) tissue in which lymphocytes and antigen may migrate. It may be used to model the site of antigen injection into the system, from which they migrate to secondary lymphoid tissue. Such nodes may also be a location where lymphocytes migrate (crawl) slowly or stand sentinel, awaiting the arrival of antigen. Such sites may be low-probability sites for information process (antigen-lymphocyte interaction). These nodes may be subject to infection and inflammation resulting in the large-scale recruitment of lymphocytes. If such nodes are included in the system there may be many more than secondary lymphoid tissue. Traffic consists of inbound antigen, inbound recirculating or migrating (sentinel) lymphocytes, outbound antigen, and outbound recirculating lymphocytes.

AC6 – Germinal Centre Site

Germinal Centre's (GC's) are locations within secondary lymphoid nodes that are dynamically generated sites for clonal selection, expansion, and maturation (an analogue of the BM3 model). They are founded by a small number of activated lymphocytes and result in high-affinity memory cells, which enter the recirculating pool, and effector cells, which may become resident in the host lymphoid tissue. GC's are an abstraction for the resultant processing that occurs after the activation of a lymphocyte by an antigen. Such sites may also occur within tertiary lymphoid tissue, although less frequently. After the initiation of a GC within a node, the node may (1) close-off outbound traffic resulting in swelling, and (2) recruit additional (more than average) lymphocytes, and (3) involve multiple bouts of the clonal selection, expansion, mutation process.

AC7 – Circulatory System

The circulatory system is an abstraction of the fluid (blood) transport medium of lymphocytes around the body in the vascular system. The connectivity represents the edges of the network model proposed. The connectivity between the nodes defines the topology of the network[1], thus the specification of this connectivity may a critical property of the model. The organisation of primary and secondary tissues may be optimized in the biological model with regard to antigen collection, and lymphocyte movement, thus the organisation of the various node types, and connectivity of the node types of the model may be configured in an a crude abstraction of the biological system. Further, the connectivity between secondary lymphoid tissues is capable of regenerating in the event of damage to the system. This functionality may be modelled with adaptive connectivity between nodes or specific node types. It may also be desirable to adapt such node organisation and connectivity using an evolutionary algorithm and such a model may be an extension of a multiple system model, such as MSM2 – Evolutionary Model.

The clear design decisions include (1) the number and organisation of the various node types, and (2) the connectivity between the selected node types, the combination of which define the network topology of the discretised repertoire model.

IV. Cellular Components

Lymphocyte cells are discrete information packets that collectively in a repertoire (or repertoires) are an internally generated model of the external domain. Antigen may also be considered information packets and or direct interaction with the domain, themselves being of external origin with regard to the lymphocyte model. This section summarises the cellular components of the model that make up the discretised repertoires. In addition to antigen, three cell classes are described which are an abstraction of the commonality in behaviour between B and T lymphocytes. The classes define different information process behaviour, particularly with regard to the mobility of the cells within the network topology architecture described in Section 2. Cellular components are listed with the notation CC#.

Cellular Component	Summary
CC1 - Antigen	Manifestation of the domain in which the lymphocytes interact with
CC2 - Lymphocyte Cell	Generic information packet within the repertoire, divided into three classes.
CC3 - Naïve Cell	Immature cells created within the model without direct regard for antigen, such cells may recirculate or may take residence in secondary or tertiary tissues.
CC4 - Effector Cell	Resultant cells of a cell-antigen interaction that reside in their node of creation performing some function
CC5 - Memory Cell	Resultant cells from an cell-antigen interaction that enter the recirculating pool, manifestation of information dissemination

Table 2 - A summary of the cellular components described in this section

CC1 – Antigen

Antigens embody interaction with the domain, with discrete information packets of external origin representing the simplest example. They may enter the

[1] Alternatively, the geographic placement of nodes may define the connectivity and resultant topology of the network.

system at tertiary nodes, and are collected into secondary nodes for interaction with lymphocytes. Thus antigens may have random temporal and spatial attributes with regard to their arrival into the system, implying that control of the models antigen exposure regime may not be assured. A result may be the spatially and temporally disproportionate (asymmetric) exposure of the model to antigen, which has the potential to overwhelm nodes of the model. This highlights the importance of information dissemination and homeostasis throughout the network topology.

CC2 – Lymphocyte Cell

A lymphocyte cell represents a generic information packet within the system and is an abstraction of B and T lymphocytes in all stages of their lifecycle. In addition to capturing (representing) a piece of knowledge or information with regard to the domain, a cell may posses intra-model information – that is information which influences the cells functional behaviour with other cells, nodes within the model, and antigen.

Lymphocyte – Discrete information quanta of the model, they are the knowledge representation and learning medium. A lymphocyte can interact with an antigen. Information expressed by a lymphocyte is immutable (cannot be changed after creation). Actions upon lymphocytes are also discrete and atomic (operations upon lymphocytes are indivisible, either occur or do not occur).

Figure 3 - Definition of a generic lymphocyte within the model

Lymphocytes are divided into three classes (naïve, effector, and memory) which are general classes abstracted from some commonality in the lifecycles of B and T lymphocyte cells. Such classes broadly describe a given cells 'intentions' and functional behaviour within the system. They are described in the following sub-sections.

CC3 – Naïve Cells

These cells are generated (pseudo) randomly in primarily lymphoid tissue and may be subjected to preliminary (antigen-independent) information (pre)processing. Such cells may be considered immature pre-T cells or pre-B cells. These cells may join the recirculating lymphocyte pool, or may migrate to secondary or tertiary lymphoid tissue for residence or further maturation. Naïve cells are the base cells that make-up a naïve-system, that is a system directly after initialisation before it has been exposed to any antigen. They are also generated in large quantities if the system is subjected to damage or large quantities of lymphocytes are removed – to re-populate the depleted areas.

CC4 – Effector Cells

Effector cells are produced in a Germinal Centre (GC) as the result of an antigen-lymphocyte interaction. This class of cells represents cells whose purpose is to locally interact (perhaps neutralise) with antigen. They may migrate to other nodes within the model, although most likely lodge at their location of creation. Such cells may be considered plasma B cells, or infected-cell killing T cells. These cells have a higher affinity than their parental cells given the maturation process that spawned their creation. Antibody may also be included in this cellular class either manifest the effector proteins themselves (thus subject to recirculation), or plasma cells that produce antibody proteins on a large scale.

CC5 – Memory Cells

Long-lived memory cells, like effector cells, are the product of interaction of lymphocytes and antigen. They are long lived, in that they have a longer innate lifespan than the other two cell types. These cells are the long-term memory of the model and are the basis for information dissemination between nodes. High-affinity information captured at one localised node is shared via memory cells to other nodes of the system. This cell type is highly mobile, and is the dominant cell type in the recirculating lymphocyte pool. Further, these cells may also posses a 'memory' of the geographic node of their instantiation, and an innate intention to preferentially home back to this node.

V. Movement Operators

Movement operators define the fine-grained control of lymphocyte mobility. Without movement, the discretised repertoire may be considered multiple independent instances of some variant of the clonal selection model (BM3). Movement may be considered as a decision process at a per-lymphocyte level involving the interaction of the lymphocyte (lymphocyte class), and its locality (tissue type and location within tissue such as germinal centre). A lymphocyte may posses a movement 'intention' given its class, and so may a node, given its tissue type. Further movement operators may not be limited to lymphocytes, but encompass all so-called cellular components such as antigen.

Movement – Cellular component mobility is controlled in a bottom-up manner, that is, as a fine-grained decision process at the per-cellular-component-level that takes into consideration the 'intention' of the component and the 'intention' of the components locality (context).

Figure 4 - Definition of a generic movement operator within the model

All other aspects of the model being equal, movement influences both the (1) repertoire homeostasis (both discrete repertoire and the aggregate of discrete repertoires), and (2) the dissemination of localised acquired knowledge. Both of these points may be considered to influence a trade-off between *recirculation* and *localisation* of lymphocytes that movement operators must address. A node may have finite capacity for the number of cellular components. Further movement may be quantified in terms of the number of cellular components over time (a rate). This rate may be aggregate or fine-grained by component class. Seeking points of stability or equilibria (homeostasis) may involve direct and dynamic manipulation of these movement rates[2].

[2] An alternative strategy for direct influence of homeostasis is that of cellular component deletion (cellular removal). Implemented models are expected to combine deletion and movement in an effort to seek homeostasis.

Homeostasis (in the BM3 sense) is perturbed by movement operators themselves and can be controlled through the management of aggregate movement rates. Another influence is the dynamic creation of lymphocytes (potentially on a large scale) in germinal centres and the recruitment behaviour at sites of infection and inflammation. Such functional behaviours have a potential to overwhelm the homeostasis capabilities of the model.

This section does not describe operators as much as it describes the movement behaviours of cellular components within the model. Operators are listed with the notation MO.

Movement Operator	Summary
MO1 - Migrating	Movement type used briefly after cellular component inception, component likely has intention
MO2 - Stationary	The lack of movement of a cellular component, such as effector cells.
MO3 - Recirculation	A pool of lymphocytes in transit, in particular those lymphocytes or lymphocyte classes that have a preference for recirculation
MO4 - Recruitment	Decision process for a cellular component to enter a node. This decision process may also be considered from the perspective of a node to sequestering a cellular component. (both perspectives are one and the same)
MO5 - Homing	Increase desirability of a cellular component to enter a node or a node type

Table 3 - Summary of movement operators described in this section

MO1 – Migrating Operator

Migration movement refers to the movement of naïve cells from primary lymphoid nodes to secondary tissue, tertiary tissue, or entry into the recirculating pool. It also describes the movement of antigen from tertiary tissue into secondary lymphoid tissue. It is the movement type of cellular components used briefly after their inception, and the components themselves have an intended location.

MO2 – Stationary Operator

A movement type keeps cells in a location essentially an anti-movement type. This operator may be used to retain effector cells at a node after their creation, or to retain an entire repertoire at a node given inflammation, and a GC reaction.

MO3 – Recirculation Operator

The recirculating lymphocyte pool is an abstraction that refers to a collection of cellular components in transit or that prefer to recirculate around the system. The pool is composed primarily of memory cells, although naïve cells and perhaps effector units also make up its numbers. Cells circulate between nodes of the system, and specific cells and cell types may possess different recirculation intentions (homing, susceptibility to recruitment) resulting in different recirculation circuits through the network topology. Cells in transit may be considered 'at rest' given that they are not capable of information processing until they traffic into lymphoid tissue (a node).

MO4 – Recruitment Operator

The recruitment of a lymphocyte is a decision process at a tissue node that governs the capturing of recirculating lymphocytes. This may be modelled by a tissue having a certain standard desirability to recruit a given cell (perhaps probabilistic), and a cell having a given desirability to be recruited. The recruitment operator refers to the general process of a given cellular component 'entering' (being sequestered by) a given lymphoid tissue (node of the model).

MO5 – Homing Operator

Homing refers to a cell or a cellular class's specific intention to enter a node or tissue type. For example a memory cell may posses an intention to home through the tissue where it was instantiated, naïve cells may intend to home and lodge in a specific tissue type. In the context of recruitment, homing may be modelled as a cellular components increased desirability of being recruited by a given node or node type.

VI. Discrete Repertoire Models

The previous sections have re-examined the components of the discrete (multiple-repertoire) models in the context of lymphocyte migration and expanded them into a series of architecture components, cellular components, and movement operators. This section rephrases the 'Discretised Models' DM1 and DM2 using these expanded components which results in a series of four discrete repertoire models. A notation of DRM# is assigned to listed models.

Discrete Repertoire Model	Summary
DRM1 – Basic Recirculation	Discretised repertoire with generic tissues and generic lymphocytes. A rephrasing of DM1
DRM2 – Differentiated Tissue	Discretised repertoire with differentiated tissues and generic lymphocytes.
DRM3 – Differentiated Cells	Discretised repertoire with differentiated cell types and generic tissues
DRM4 – Differentiated Recirculation	Discretised repertoire with differentiated tissue types and differentiated cell types. A rephrasing of DM2.

Table 4 - Summary of the discretised repertoire models

DRM1 – Basic Recirculation Model

This model employs the network topology discretised repertoire (AC1), with generic tissue nodes (AC2), and a suitable (unspecified) connection scheme (AC7). The model employs the antigen (CC1), and generic lymphocyte (CC2) cellular components. Adaptation occurs within the germinal centres (AC6) of the genetic tissue nodes using the clonal selection model (BM3). Each generic tissue location is responsible for the generation of new generic lymphocytes, as well as the homeostasis of the localised cell repertoire. All lymphocytes are subjected to the recirculation operator (MO3), and recruitment (MO4). This DRM1 model may be considered a rephrasing of the DM1 – Discretised Circulation Model.

DRM2 – Differentiated Tissue Model

This model is an extension of DRM1, although in the place of generic tissue nodes (AC2), the suite of three differentiated tissues is employed. Primary lymphoid tissue nodes (AC3) are responsible for the generation of new generic lymphocytes. Secondary lymphoid tissue nodes (AC4) are responsible for accumulation of antigen, and the dynamic formation of germinal centres (CC6). Tertiary lymphoid tissues (AC5) are responsible for the injection of antigens into the system, and slow migration of lymphocytes. Antigen (CC1) migrate (MO1) to secondary lymphoid nodes (note that new lymphocytes do not migrate, as there is no distinction between new and clonally expanded lymphocytes). Generic lymphocytes are subjected to the recirculation operator (MO3), and recruitment (MO4) into secondary and tertiary lymphoid nodes.

DRM3 – Differentiated Cell Model

This model is an extension of DRM1, although rather than employing generic lymphocytes (CC2), the model employs a full range of differentiated cell types. Generic tissue nodes are still employed (AC2). Naïve cells (CC3) are created at each generic tissue node, and may enter the recirculating pool or lodge at a tissue node. Germinal centres (AC6) may occur at each generic tissue node as in DRM1, although the result of these processes are effector cells (CC4), and memory cells (CC5). Effector cells remain stationary (MO2) at the tissue node of creation, whereas memory cells enter the recirculating memory pool (MO3). Both naïve and memory cells are subjected to recruitment. Memory cells retain an impression of the geographic location in which they were instantiated and express a desire to home (MO5) to that node whilst recirculating.

DRM4 – Differentiated Recirculation Model

This model is an extension of DRM1, although combines the differentiated tissues of DRM2, and the differentiated cells of DRM3. All three differentiated tissue types are employed: primary lymphatic (AC3), secondary lymphatic (AC4), and tertiary lymphatic (AC5) tissue nodes. All three differentiated cell types are employed: naïve cells (CC3), effector cells (CC4), and memory cells (CC5). Thus, each of the specified movement operators are employed. Naïve cells and antigen migrate (MO1) to secondary lymphoid tissues. Effector cells remain stationary (MO2) at their node location of creation. Naïve memory cells, and memory cells recirculate (MO3), and are subjected to recruitment (MO4), and memory cells preferentially home (MO5) their recirculating circuit to the tissue node of their creation. This DRM4 model may be considered a rephrasing of the DM2 – Discretised Lymphatic Model.

VII. Future Work

This work provided a pattern for the re-examination, extension, and ultimately more detailed re-phrasing of acquired immunity models presented by Brownlee [2]. Given the success of this pattern for discrete repertoire models, it is believed that this pattern may be applied to three other areas of the previously presented framework that are expected to benefit from such a re-examination. These areas include, (but may not be limited to): (1) the clonal homeostasis operator (O6), (2) the dynamic antigen model (EM3), and (3) the evolutionary multiple system models MSM2, and MSM3.

(1) A deep understanding of how the biological system seeks equilibrium in terms of lymphocyte numbers and distribution will provide insight into how effective homeostasis may be employed in all immunological inspired adaptive models.

(2) An understanding of the adaptive nature of pathogens such as evolving viruses and bacteria will provide insight into how such dynamic predator-prey interactions may be modelled. Such an understanding would not only permit the EM3 model to be elaborated, but also provide a foundation for how the series of adaptive models may accommodate dynamic antigen.

(3) An understanding of the interplay between the evolutionary processes that formed the biological system, in the context of the systems ontogenetic adaptive behaviour will provide a fertile area for the extension and re-phrasing of the MSM2 and MSM3 evolutionary immune system models. It is believed that the results of the investigation will tie in strongly with the co-evolutionary models that result from (2).

A final important observation and future piece of work is the definition of a test domain (or domains) for the evaluation of the series of adaptive models. It is believed that a generic and meaningful domain and suite of test problems may be defined that effectively demonstrate the intended behaviours of the proposed models. This work would include (although may not be limited to): a) the definition of the general domain(s), (b) a literature review of how such domains have been employed, (c) the clear definition of models to be evaluated, the model properties that will be evaluated, and how such an evaluation will be measured and reported.

Ultimately, there remains a large body of work designing, executing, and evaluating the performance of the series of adaptive models on a problem test suite.

Acknowledgments

Tim Hendtlass for his patience and for providing useful feedback on drafts of this paper

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