A Series of Adaptive Models Inspired by the Acquired Immune System

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***Abstract*-The acquired immune system is capable of specialising a defence of an organism in response to the its antigenic environment. This complex biological system possess interesting information processing features such as learning, memory, and the ability to generalize. The clonal selection theory is a cornerstone of modern biology in understanding the acquired immune system from the perspective of B-lymphocyte cells and antibody diversity. This work presents a series of computational adaptive systems inspired by features of the biological immune system and the clonal selection theory in particular. Starting with basic clonal operators as principle components, models are presented in increasing complexity from canonical clonal selection models, to discretised architecture models, to finally advanced vaccination, evolution, and ontogenetic models. In addition to providing the basis to an interesting line investigation in the field of artificial immune system, this series of adaptive models presents a hierarchal framework from which existing and future adaptive models inspired by the acquired immune system can be interpreted and related.**

Keywords- Clonal Selection Algorithm, Models, Clonal Selection Theory, Adaptive Systems, Acquired Immune System, Framework

I. INTRODUCTION

This work lists a series of adaptive operators, simple, and distributed models inspired by aspects of the acquired immune system. The intention of this work is not to describe models accurate in the context of biological experimentation and observation, but rather adaptive models that may serve as the basis and inspiration for computational algorithms and systems for addressing complex design, engineering, and information technology problems.

Section II presents a series of general adaptive operators derived from the clonal selection theory of antibody diversity. These operators prove a foundation of principle components, which are employed in the canonical clonal selection models presented in section III. Section IV extends the base clonal selection model with a series of adaptive models that introduce additional operators and processes of acquired immunity. Section V also extends the base model although with a discretised version of the immune systems distributed architecture. Section VI presents advanced multiple immune system models that incorporate larger system ideas such as vaccination and evolution. Finally, section VII describes the presented series of adaptive models as a novel hierarchal framework for which existing and future acquired immunity inspired adaptive models may be interpreted and related.

II. PRINCIPLE COMPONENTS

This section lists a series of principles (operators or mechanisms) that are sufficiently low in complexity to be analysed independently. It is expected that the mechanisms listed in this section may act as component features in larger adaptive models. Operators are assigned a notation of O# and are listed in no particular order. See Table 1 for a quick reference summary of the operators defined in this section.

Operator	Summary
O1 **Clonal Matching**	Matching properties, affinity, and avidity
O2 **Clonal Selection**	Probabilistic selection of lymphocytes
O3 **Clonal Expansion**	Proportional expansion of selected lymphocytes
O4 **Clonal Mutation**	Mutation and affinity maturation of clones
O5 **Clonal Diversity**	Initial and on going repertoire diversity
O6 **Clonal Homeostasis**	Maintenance of repertoire size
O7 **Clonal Memory**	Impression and persistence of antigenic exposures

Table 1 - Quick-reference summary of operators defined in this section

O1 – Clonal Matching

Lymphocytes have receptors with specificity to one surface feature of an antigen, although an antigen will have many different surface features. Thus, a heterogeneous population of lymphocytes vary in their specificity with two general dimensions: (1) The degree to which a given antigen possesses a given surface feature (cells affinity with the antigen), (2) the number of cells with a similar (the same) receptor representing the strength of the response (summed affinity known as avidity).

O2 – Clonal Selection

The clonal selection principle refers to the imperfect selection of 'high affinity' lymphocytes by antigen. The selection may be considered probabilistic, a random event, and perhaps serendipitous. The selected lymphocyte may be considered high-affinity relative to the lymphocytes around it (local vicinity), and or relative to the lymphocytes the antigen may have encountered on its journey (antigen lifetime in vivo).

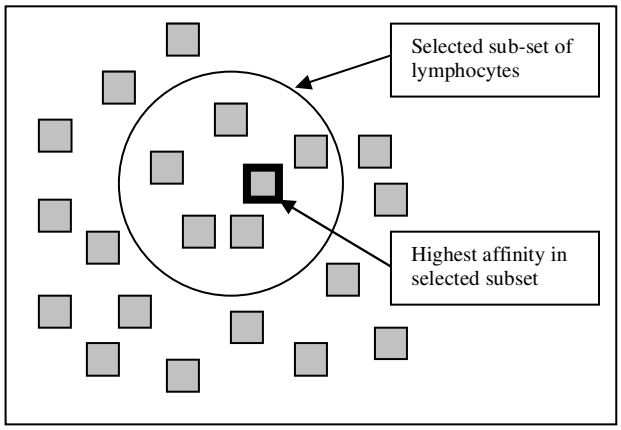

Figure 1- Conceptualisation of probabilistic clonal selection (O2)

O3 – Clonal Expansion

A clone is a group of lymphocytes that divide from the same ancestor, for the most part genetically identical. Consider that an antigen molecule does not arrive alone, but also exists within a clone. Thus, clones of lymphocytes compete, based on specificity for a finite number of antigens (selections) which result in proliferation. Higher-affinity lymphocytes have an increased probability of selection, thus in this scenario we may consider that at a clone level, the proliferation of a clone is proportional to its affinity with the antigen. More accurately, the expansion of a clone is proportionate to its relative avidity to other local clones.

The result is a positive feedback mechanism that may lead to clonal dominance with respect to an antigen epitope (structural feature of antigen the lymphocytes bind to).

O4 – Clonal Mutation

Given the selection and proliferation of a lymphocyte by an antigen, genetic mutations may occur and are expressed in the progeny clone. The errors result in a modified cell receptor, and thus a modified (increased or decreased) affinity to the same antigen that triggered the ancestor's proliferation. Rather than a clone of genetic copies, the process results in a clone of slightly varied (heterogeneous) siblings, some of which, through chance, have an improved affinity for the antigen.

The broader resultant affect in that the clone has a higher avidity for the antigen given both clone size, and the concentrated or refined specificity for the antigen.

O5 – Clonal Diversity

The initial repertoire of cells is heterogeneous with respect to specificity to all antigen given a random generation process that seeded it. The heterogeneity of the repertoire is biased by the antigenic environment of the host. Although, there is an on going random generation of unbiased lymphocytes that fulfil a fraction of the systems original capability of detecting any given antigen. This results in a transition from a random, to biased repertoire, and both on going: (1) random (naive) lymphocyte generation (small fraction) and (2) biasing through clonal selection and expansion (majority of lymphocyte generation).

O6 – Clonal Homeostasis

Lymphocytes have a finite lifetime, and there is a one-to-many relationship between selected ancestor lymphocyte and resultant clonal progeny. This can be reduced to a one-to-many relationship between antigen and resultant clonal progeny. The rate of antigen encounters, the size of progeny clones, and the lifetime (aging) of lymphocytes plays a role in total repertoire size. Another minor contributor is the rate and number of naïve lymphocytes released in the repertoire. Given physiological constraints, the repertoire has a desired equilibrium point as well as an upper limit in size, although the size fluctuates with antigenic encounters with a time lag before returning to the point of equilibrium.

O7 – Clonal Memory

A memory of the antigenic environment, that is, antigens the system has been exposed, is imprinted in the biased lymphocyte repertoire. This memory is refreshed with each identical antigenic exposure, and even refined given affinity maturation. Forgetting occurs given the lack of subsequent exposures, and the reallocation of the repertoire resources. Memory through continued exposure is like having a low-grade chronic infection as a reminder.

III. Base Models

This section lists a series of base adaptive models that are capable of adaptation and posses one or more adaptive operators and components from section II. They are perhaps still low enough in complexity for analytical analysis. The models listed in this section may provide the basis for more elaborate adaptive models through augmentation with additional operators and or processes. The notation BM# is used and models are listed in no particular order. See Table 2 for a quick reference summary of model presented in this section.

Model	**Summary**
BM1 **Affinity Cloning Model**	Perfect and proportionate memory
BM2 **Affinity Maturation Model**	Narrow and specialised memory
BM3 **Clonal Selection Model**	Canonical clonal selection procedure

Table 2 - Quick reference summary of base models

BM1 – Affinity Cloning Model

This model starts with a heterogeneous random repertoire (O5) and assumes clonal matching (O1). The model continually applies the insertion of naïve cells (O5) and the repertoire is subject to clonal selection (O2) and clonal expansion (O3) in the face of repertoire homeostasis (O6). The result is a model that exhibits a perfect and proportional clonal memory (O7) with no ability to adapt.

Random initial repertoire (O5)
Repeated exposure to antigen
    Selection of high-affinity cell (O2)
    Cloning of selected cells (O3)

Generation of naïve cells (O5)
Aging and removal of cells (O6)

Figure 2 - General procedure of the affinity cloning model BM1

Selection and ultimately cloning and clonal numbers are based by the affinity to the antigenic stimulus, thus the name affinity cloning, but the model could just be easily be referred to as selection-cloning as these are the models core adaptive operators. It is the "*make more of something good*" principle where the population or mixing of the repertoire is defined by the antigenic exposures.

BM2 – Affinity Maturation Model

This model starts with a heterogeneous random repertoire (O5) and assumes clonal matching (O1). The model continually applies the insertion of naïve cells (O5) and the repertoire is subject to clonal selection (O2) and clonal mutation (O4) in the face of repertoire homeostasis (O6). The result is a model that exhibits a specialised clonal memory (O7).

Random initial repertoire (O5)
Repeated exposure to antigen
    Selection of high-affinity cell (O2)
    Mutation of selected cells (O4)
Generation of naïve cells (O5)
Aging and removal of cells (O6)

Figure 3 - General procedure of the affinity maturation model BM2

Selection and variation via mutation are the core principles of this model, thus the name affinity maturation (improvement of affinity), but the model could just be easily be referred to as selection-mutation. It is the "*make better that which is already good*" principle where the repertoire becomes highly specialised to antigenic exposures.

BM3 – Clonal Selection Model

This model represents the inclusion of all specified clonal operators and is the union of the two previous models BM1 and BM2.

This model starts with a heterogeneous random repertoire (O5) and assumes clonal matching (O1). The model continually applies the insertion of naïve cells (O5) and the repertoire is subject to clonal selection (O2), clonal expansion (O3), and clonal mutation (O4) in the face of repertoire homeostasis (O6). The result is a model that exhibits a proportional and specialised clonal memory (O7).

Random initial repertoire (O5)
Repeated exposure to antigen
    Selection of high-affinity cell (O2)
    Cloning of selected cells (O3)
    Mutation of selected cells (O4)
Generation of naïve cells (O5)
Aging and removal of cells (O6)

Figure 4 - General procedure of the clonal selection model BM3

This model involves the three core principles of the clonal selection theory: clonal selection, clonal expansion, and affinity maturation and may be considered a canonical clonal selection procedure. The model provides a trade-off between generalist (random repertoire O5), greedy proportionist (BM1 with perfect memory), and narrow specialist (BM2).

IV. Extended Models

This section lists a series of adaptive models with moderate complexity; that is models that combine a number of adaptive operators and or processes from section II in formations that are extensions of the base models of section III (specifically BM3), although include additional operators and or processes. These models may be difficulty to investigate analytically. Models are assigned the notation of EM# and are listed in no particular order. See Table 3 for a summary of the extended models presented in this section.

Model	Summary
EM1 **Memory Cell Model**	Repertoire of plasma and memory cells
EM2 **Tolerance Model**	Feasible and infeasible search space
EM3 **Dynamic Antigen Model**	Non-stationary antigenic environment
EM4 **B & T Lymphocyte Model**	Two-phase selection and co-evolution

Table 3 - Quick reference summary of extended models

EM1 – Memory Cell Model

An extension of the clonal selection model BM3, although rather than amorphous lymphocytes providing the medium of information and adaptation, the repertoire supports both plasma and memory cells. A clonally selected cell proliferates and differentiates into plasma cells and memory cells. Plasma cells provide the immediate effector response and a short lifespan, whereas the memory cells are given a longer, perhaps indefinite lifespan in the repertoire. Both cell types are selectable in terms of clonal selection (O2). Perhaps memory cells persist after the proliferation and differentiation process, whereas plasma cells are destroyed in the process. The extended lifespan of the memory cell type also have an effect on repertoire homeostasis (O6), and improve clonal memory (O7). An indefinite memory cell lifespan may pose problems in the repertoires inability to "forget" antigen.

EM2 – Tolerance Model

This model is an extension of the clonal selection model BM3, although rather than having a random initial repertoire (O5), the repertoire is bias or made tolerant (non-reactive infeasible) to some known sub-space of the possible search space. That is, both in the initialisation of the initial repertoire, and the on-going generation of naïve lymphocytes, those generated cells that are auto-reactive (within the sub-space of the search space deemed self) are adjusted. The adjustment may take on the form of (1) cell death or apoptosis (deletion O6), (2) non-responsiveness or anergy (ignored by clonal selection O2), or finally (3) receptor editing (regenerated O5).

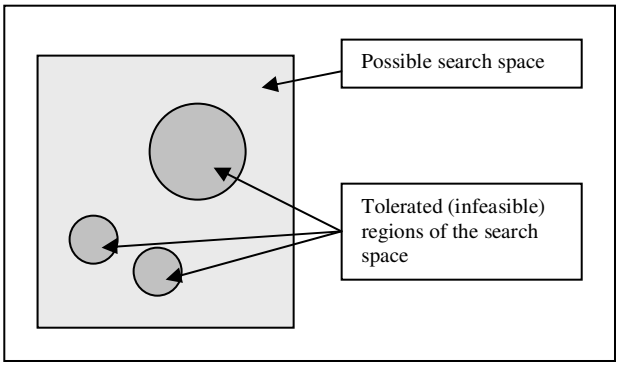

Figure 5 - Conceptualisation of the tolerance model (EM2)

EM3 – Dynamic Antigen Model

An extension of the clonal selection model BM3, although rather than adapting the repertoire to an unknown but static antigenic environment the antigenic environment is dynamic providing a moving target to which to adapt. This model has implications particularly if it were combined with the memory cell model EM1 where the need forgetting antigen would be critical. It is also expected that the number of clones in clonal expansion O3 would be reduced and the generation naïve cells O5 increased in an attempt to minimise the time lag for repertoire adaptation. Critical factors in terms of the antigen include the rate of change in presented antigens, and the likelihood of reoccurrence of old antigens.

EM4 – B & T Lymphocyte Model

An antigen clonally selects (O2) a plasma B cell and the lymphocyte binds to the antigen consuming it, breaking it up and in turn presenting parts of it on the cells surface. Thus, the B lymphocyte becomes an antigen-presenting cell (APC) to other cells such as helper T lymphocytes. Before the plasma cell can begin proliferation and differentiation (clonally expand O3) it must be activated by a helper T cell. Thus, this model provides a two-phase clonal selection process by two different lymphocyte types.

This model is an extension of the clonal selection model BM3. B cells are clonally selected (O2) by the antigen, the selected cells transform or mask the antigen pattern in someway and in turn clonally select (O2) from a second population of T cells before clonally expanding (O2). The two-phase selection provides a richer adaptation process where antigen may be transformed into another search space, simplified using a mask, a many other manipulation processes before being selected upon again. The result is the cooperative-evolution of two complementary lymphocyte repertoires.

V. Discretised Models

This section lists a number of adaptive immune system models that extend the canonical clonal selection model (BM3), although are discretised. Although all models discussed thus far are discrete as opposed to continuous, discrete in this section refers to models of a single immune system that are partitioned into multiple localities as a discrete version of the distributed immune system architecture. These models may be considered a distributed repertoire models of the immune system. Models are assigned the notation of DM# and are listed in no particular order. See Table 4 for a summary of the discretised models presented in this section.

Model	Summary
DM1 **Discretised Circulation**	Distributed and circulating population
DM2 **Discretised Lymphatic**	Lymphatic and normal tissue with memory and plasma cells

Table 4 - Quick reference summary of discrete models

DM1 – Discretised Circulation Model

This model is an extension of the clonal selection model (BM3) that has a distributed repertoire. The repertoire structure is spread out into multiple discrete although connected sub-repertoires in a discretised abstraction of the distributed biological system. Lymphocytes circulate between the localities of the host organism, and antigenic encounters are considered a spatial and temporal random events. Repertoire homeostasis (O6) is varied such that each locality manages its homeostasis autonomously in the context of the circulating nature of the repertoire.

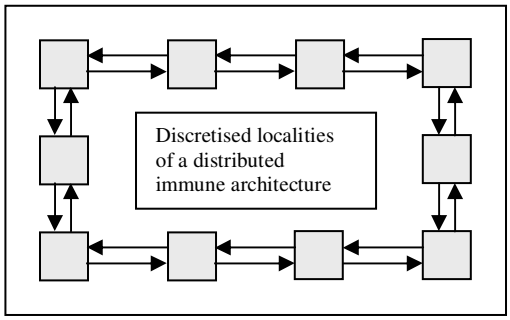

Figure 6 - Conceptualisation of the discretised circulation model (DM1)

DM2 – Discretised Lymphatic Model

This model is an extension of the discretised circulation model (DM1), although incorporates the memory cell model (EM1). The DM1 model is extended to support both normal tissue and lymphatic tissue localities (sub-repertoires). The EM1 model is applied such that the repertoire consists of plasma cells and memory cells. Plasma cells remain in lymphatic tissue localities and may release effectors, which circulate the system. Memory cells and naïve lymphocytes are created in lymphatic tissues although unlike plasma cells may circulate throughout the entire system. Cells, which undergo clonal selection (O2), must migrate or "home" to lymphatic tissue before they may clonally expand (O3). Antigenic encounters may only occur in normal tissue localities.

VI. Multiple System Models

This section lists a number of adaptive immune system models that are composed of multiple instances of the canonical clonal selection model (BM3). They may be considered multiple-immune-system models, and

bare some conceptual similarity to the distributed population models of section V. Models are assigned the notation of MSM# and are listed in no particular order. See Table 5 for a summary of the models presented in this section.

Model	Summary
MSM1 **Vaccination Model**	Multiple systems with lymphocyte vaccinations
MSM2 **Evolutionary Model**	Evolution of the genetic basis that generates an immune systems initial repertoire
MSM3 **Evolutionary Ontogenetic Model**	Evolution of genetic basis of initial repertoire and vertical vaccination of young by parents

Table 5 - Quick reference summary of multiple system models

MSM1 – Vaccination Model

This system contains a number of sub-models, each an example of the clonal selection model (BM3). Each sub-model may be considered an organism with its own immune system, thus the collection of sub-models may be considered a population of organisms. Each organism has a different antigenic environment, specifically in terms of the spatial and temporal properties of antigen exposures.

Vaccination involves training an immune system based on a harmless antigen the effects of which protect the organism from harmful antigens given that both antigens have the same surface features. In this vaccination model, when an organism (specific individual case of BM3) is identified to have addressed (fought off) a specific antigen, a sample of the resultant antibodies/lymphocytes are removed or replicated from the identified organism and "injected" into one or more other organisms in the population. The properties of vaccination include (1) how to identify a good response, (2) how to select lymphocytes to extract/duplicate, and (3) which other organisms to vaccinate.

This system has a conceptual similarity to the discretised circulation model (DM1), although this model possesses larger repertoires and selective (unordered) migrations (vaccinations).

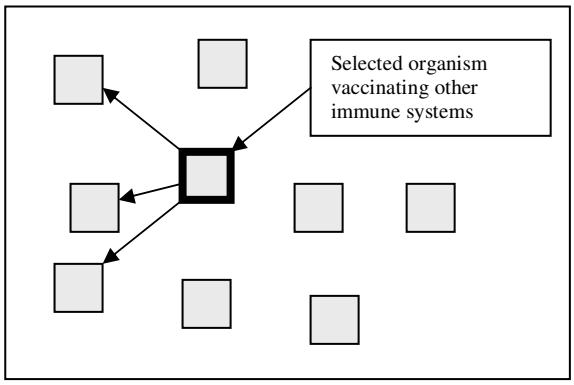

Figure 7 - Conceptualisation of the vaccination model (MSM1)

MSM2 – Evolutionary Model

This model has the same population of immune systems (BM3) approach as the vaccination model MSM1, although without vaccination. This model uses a genetic basis to generate the initial repertoire for each sub-model, and the quality or fitness of the system (organism) is determined based on its performance over its lifetime in the context of a given antigenic environment. An evolutionary process subsumes the population of BM3's and seeks to adapt a population of genetic material that determines the initial repertoire of individual immune systems. Thus, this model describes an adaptive evolutionary process to bias the random generation of the clonal selection models (BM3) initial repertoire (O5).

MSM3 – Evolutionary Ontogenetic Model

This mode is an extension of the Evolutionary Model (MSM2), although in addition, progeny in the evolutionary processes are vaccinated after birth with a small sample of lymphocytes from the mother. This is a mimic of the manner in which mammals pass antibodies to their young through the milk, which young suckle from the mother. This model has similarities with the vaccination model (MSM1), although in this case the vaccinations are directed and vertical through generations, rather than horizontal across a single generation.

VII. Future Work

This work has provided a series of adaptive models inspired by the acquired immune system, starting with simple operators, which provided principle components in the base or canonical clonal selection models that followed. The base models provided the foundation for extended models, distributed models and multiple system models.

Although the series of adaptive models presented did not cover abstractions of all features of the acquired immune system, it introduced a novel hierarchical framework in which existing and future adaptive models of clonal selection and acquired immunity can be interpreted and related to each other. This is an important contribution to the infant field of artificial immune systems (AIS), which is still struggling for clarity and direction.

The utility and behaviour of the proposed models is unknown and may only be conjectured. An important extension of this work is the investigation, implementation, demonstration, and ultimately evaluation of the more promising of the adaptive systems presented in this work, particularly in the context of application to engineering, design and information technology domains. It is speculated that most if not all of the models presented in this work may find utility in application to pattern recognition and optimization domains.

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