Realizing Elementary Clonal Selection Algorithms

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***Abstract*-A series of acquired immunity inspired clonal selection models have previously been proposed that includes principle model components and base (single repertoire) models. Also previously proposed is a contrived problem domain called 'colour space' and a number of scenarios intended for the investigation of adaptive models. This work units these two (until now) isolated streams of work by realizing the clonal selection models as clonal selection algorithms. The components and models are distilled into design principles and testable behavioural expectations. The algorithms are defined and a series of sensitivity analysis and experimental studies are proposed to preliminarily assess the proposed algorithms.**

Keywords- Adaptive Models, Artificial Immune Systems, Clonal Selection Algorithm, Clonal Selection Theory, Experiments, Methodology, Colour Space

I. INTRODUCTION

A series of acquired immunity inspired adaptive models has been defined [2], and elaborated in the context of discrete repertoire models [3] and multiple system models [5]. The core of this series of models is the clonal selection theory, which was interpreted as a collection of principle components for adaptive models and a base model for the series. In addition to the adaptive models, a specially designed (contrived) problem domain was proposed called 'colour space' [1] for evaluating adaptive models. A series of experimental scenarios were proposed in colour space [4] for investigating the various model types.

This work reviews the principle components and base clonal selection models (section II) and distils them into algorithm design principles and behavioural expectations (section III). Section IV elaborates on the base clonal selection model and proposes a series of clonal selection algorithms in sufficient detail that they may be implemented in software for experimentation. Section V unites the colour space and experimental scenarios with the proposed algorithms and behavioural expectations to propose a series of experimental investigations. Finally, section VI suggests algorithm improvements and extensions to this work.

II. SERIES OF ADAPTIVE MODELS

In previous works [2,3,5] Brownlee has proposed a series of adaptive models inspired by the acquired immunity, and the clonal selection theory in particular. The models were conceptualisations intended to provide the basis of computational intelligence algorithms. This section briefly reviews the principle components of the series, and the base clonal selection models that provided the foundation of the series.

Principle Components

The principle components are a collection of clonal selection inspired operators, the aggregation of which reveals a base clonal selection algorithm. This section briefly describes each principle component.

O1 – Clonal Matching: A heterogeneous (diverse) repertoire of lymphocytes individually varying in specificity to an antigen, and in aggregate defining the relative strength of the response. There exists a many-to-many relationship between receptors and antigenic determinants.

O2 – Clonal Selection: A single imperfect (probabilistic) selection event by a pathogen for a relatively high-specificity cell by a pathogen

O3 – Clonal Expansion: The proliferation of selected lymphocytes proportional to their specificity in the context of the number of selection events (pathogenic arrivals)

O4 – Clonal Mutation: Coping errors that are exhibited in progeny during the proliferation (clonal expansion) stage that may result in high or lower affinity for the triggering antigen.

O5 – Clonal Diversity: Randomness of the initial (pre-antigenic exposure) repertoire and the on-going randomness of naïve lymphocytes (antigen exposure independent) introduced into the repertoire.

O6 – Clonal Homeostasis: A maximum cell capability imposed on the repertoire where individual cells have a finite lifetime, and the turn over of cells is driven by the introduction of naïve cells and progeny cells from antigenic exposures.

O7 – Clonal Memory: The repertoire and in particular the clonal densities represent and inductive impression of the pathogenic environment, refined with each subsequent exposure.

Figure 1 - Summary of clonal selection principle components

Base Models

The base models are adaptive models that recombine the principle component, culminating in a quintessential clonal selection model that contains all seven operators.

BM1 – Affinity Cloning Model: Encapsulates selection and expansion resulting in an adaptive model capable of learning and maintaining cell densities in response to pathogenic exposures.

BM2 – Affinity Maturation Model: Encapsulates selection and mutation resulting in an adaptive model capable of refining cells in response to exposures.

BM3 – Clonal Selection Model: Encapsulates all the outlined principle components and embodies the clonal selection theory as an adaptive model.

Figure 2 - Summary of base clonal selection models

III. PRINCIPLES AND EXPECTATIONS

The previously outlined principle components specified the operators for clonal selection models, and the base models provided general prescriptions as to how to arrange the principle components. This section elaborates and extends upon the definitive and prescriptive principle components and base model to outline algorithmic design principles and algorithmic behavioural expectations. The design principles specify the general implementation concerns for the principle components, and the behavioural expectations hypothesize as to the resultant effects that may emerge from such algorithmic implementations.

Design Principles

The design principles provide implementation guidelines for the principle components and base models such that the operators and models may be realised as computational intelligence algorithms. Table 1 provides a summary of clonal selection algorithm design principles.

Design Principle	Summary
DP1 – Pathogenic Environment	The majority of antigen types are exposed to the system early. This results in a pathogenic environment that encourages rapid learning early with long-term refinement
DP2 – Selective Pressure	Selective pressure by antigen on the lymphocyte repertoire is probabilistic and moderate in strength
DP3 – Genetic Representation	A genetic-like representation facilitates replication with copying errors and transcription into phenotypic form
DP4 – Mutation Rate	Variation is introduced via copying errors during proliferation resulting in mutated progeny. Mutation pressure is low-to-moderate in strength.
DP5 – Proliferation Rate	Total expansion is relative to the amount of antigenic stimulation although is stable at the per-event scale
DP6 – Repertoire Size	The size of the lymphocyte repertoire is moderate to large, although operations upon the repertoire are probabilistic and scalable
DP7 – Naïve Cell Creation	The number of naïve cells created and released into the repertoire is stable
DP8 – Cell Lifespan	Lymphocytes have a fixed and short lifespan
DP9 – Population Equilibrium	The clonal size fluctuates with antigenic exposures, resulting in temporal spikes in total repertoire size. A stable population size is sought as a point of equilibrium in the face of the turnover of lymphocytes.
DP10 – Generational Repertoire	The repertoire is simulated in a discrete-time and is generational with regard to the turnover of the lymphocyte population

Table 1 - Summary of clonal selection algorithm design principles

The pressure for learning and adaptation can come from one of a number of different decision points from both within and outside of the system.

Pathogen Novelty: The number of distinctly different pathogens to which the system is exposed
Pathogen Frequency: The time interval between exposures of a given pathogen (distribution function through time)
Pathogen Amplitude: The number of pathogen particles the system is exposed to for a given pathogen exposure

Figure 3 - Decision points for pressures on the system from the environment

One may map problem domains onto this stimulation model of the pathogenic environment. In the case of optimization the novelty is low (there is only one response surface), the frequency is practically infinite (bounded by the number of function evaluations), and the amplitude (at maximum) is the size of the repertoire. In the case of classification the novelty is low (the number of classes represented in the training set), the frequency is practically infinite (the number of exposures of the training patterns to the repertoire). The classification amplitude may be the extent the repertoire is exposed to a pattern (implicit replication of a pattern), or the number of similar (same class) patterns exposed to the system in batch.

	Novelty (*pathogens*)	**Frequency** (*exposures*)	**Amplitude** (*extent of exposure*)
Optimization	Low, one response surface	High, number of function evaluations	Moderate, number of cells selected for evaluation
Classification	Low, number of classes in training data	High, number of presentations of training data	Moderate, number of selected cells selected, or the number of similar patterns exposed in batch

Table 2 - Example of mapping general domains onto the pathogenic pressures

From a system perspective, pathogen frequency (F) and amplitude (A) may be considered the same thing (ignoring what is being learned) in conjunction resulting in ($F \times A$) selection-expansion (stimulation) events. Combinations of pathogen frequency and amplitude result in combinations of temporal lag and concurrency of these events respectively. A high degree of novelty in the pathogenic environment requires a large repertoire to store the acquired immunity. The time lag between pathogen exposures (frequency) defines the extent of memory (long or short term) the repertoire must possess.

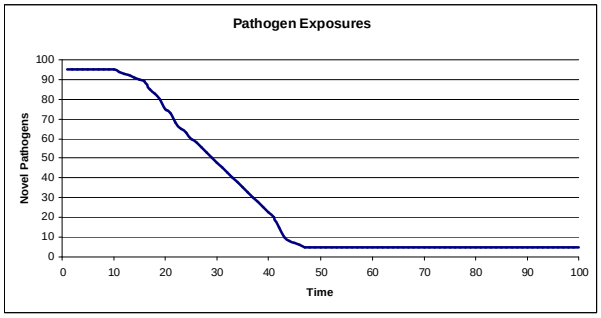

Figure 4 - Example depiction of a pathogen exposure function in time

Pathogen	Effect on System
Novelty	The repertoire size (memory) of the system is a function of the number of novel pathogens it is exposed to (*size or scope of learning*)
Frequency	Pathogen arrival through time (arrival pattern) defines the learning iterations of the system (*learning iterations*)
Amplitude	The degree of exposure defines the concurrent amount of learning the system must do in a single pathogen exposure (*concurrent work in an iteration*)

Table 3 - Summary of the system-perspective of pathogen pressures

The number of selection-expansion events (high frequency and low amplitude, or low frequency high

amplitude) in the system imposes an interesting pressure on adaptation. A large number of these events provide the pressure for improvement perhaps requiring smaller less expansion and mutation (adaptation). A small number of these events perhaps require each event to be exploited with an increase in the expansion size and mutation rate.

Repertoire Size: A small repertoire requires a lot of cell deletion, encouraging large expansion and high mutation in an effort to improve and maintain the best possible repertoire. A large repertoire encourages smaller expansion and refinement although increased selective through more selective-expansion events or through selective pressure.
Selective Precision: Precision of the clonal selection effects the convergence though clonal commitment. Commitment and resultant convergence too early may result in antigenic sin. This is the expansion and refinement of a sub-optimal cell line.
Expansion Size: A large expansion with high mutation provides a large heterogenous clone to integrate into the repertoire. A smaller expansion may be desired if the frequency of expansion events is high.
Mutation Rate: Small mutations are desirable when cells are close to optimal, whereas large mutations are desirable when cells are far from optimal. Pathogens may change and cells are removed through attrition and homeostatic pressures effecting the desirable mutation rate.

Figure 5 - Decision points for configuring pressures within the system

Selective precision has a controlling effect on the maturation (convergence) rate of the system in response to a fixed pathogen. A high selective precision results in the selection and refinement of a dominant clone early, whereas a lower pressure delays this commitment. This pressure may be adjusted through increase in the population size, relaxing of the probabilistic properties of the selection operator, decreasing the expansion rate, or decreasing the mutation rate.

Selective Pressure: This is the selection of the best cell for a given pathogen. The pressure is strongly affected by the repertoire size, and strongly affected by the selection precision (investment for searching). The pressure is weakly affected by the amplitude of pathogen exposure.
Adaptive Pressure: This is the systems property to learn. This is pressure strongly affected by selective pressure, and is influenced moderately by expansion and mutation. The learning of novelty is moderately affected by naïve cell creation and by mutation.
Convergence Pressure: This pressure is the systems property to stabilise in terms of acquired knowledge. This pressure is strongly affected by the selective pressure and the adaptive pressure.

Figure 6 - Summary of general system pressures and their influences

To summarise, the system has a number of decision variables that impose pressures on the efficiency and efficacy of acquiring immunity in different environments. Combinations of pressures facilitate trade-offs and elicit specific effects. The biological immune system may provide an inspiration for interpreting the general configuration for these decision variables although adherence to such general configurations may define only limited applicability of the resultant algorithms.

Behavioural Expectations

The principle components and base models were specified with behavioural expectations in mind, although such expectations have not been delineated other than a brief outline in [4]. This section suggests a series of emergent behavioural expectations of realized clonal selection algorithms, taking the principle components, base models, and design principles into account. Table 4 provides a summary of the behavioural expectations, which may be used later as hypotheses in experimental research questions.

Behavioural Expectation	Summary
H1 – Clonal Convergence	The repertoire rapidly adapts from a random state to quasi-converged state, after which time ongoing adaptation is predominantly in the form of refinement
H2 – Clonal Densities	Adapted clonal densities are representative (proportional) of the pathogenic exposures. **Responses are proportional (size and specificity) to the learned likelihood of exposure**. Densities are learned and maintained.
H3 – Clonal Dominance	Adapted clonal densities result in a clonal dominance effect where a clone will dominate a given antigenic exposure.
H4 – Antigenic Sin	Early clonal dominance by a maladapted line of cells results in an 'antigenic sin' effect, which is the convergence of a clone to a sub-optimal result (a type of premature convergence).
H5 – Novelty Acceptance	The efficiency of acquiring immunity to novel antigenic exposures is reduced after the period of clonal convergence.
H6 – Naïve Cell Utility	The usefulness of antigenic-neutral naïve cells decreases with increased clonal convergence given the clonal dominance effect. Such naïve cells are useful in post-clonal convergence novelty acceptance.
H7 – Approximate Optimality	The improvements achieved as a result of affinity maturation decrease with the increase of clonal dominance. This is because the closer a clone comes to an optimal, the harder it is for mutation produce improvements. This results in each dominant clone achieving approximate optimality for a static pathogen.
H8 – Secondary Response	Secondary and ongoing exposure to an antigen result in an improved response compared to the first exposure. The improvement between the second and subsequent responses is less than that between the first and the second.
H9 – Repertoire Plasticity	The system is capable of general plasticity throughout its lifetime, even after clonal convergence. This is because of selection and competitive learning.
H10 – Repertoire Memory	The clonal densities after clonal convergence may collectively (repertoire in its entirety) represent an impression (fuzzy record) of the pathogenic environment.

Table 4 - Summary of clonal selection algorithm behavioural expectations

Adaptation to the pathogenic environment (convergence) is the core expectation from which the other expectations may relate. This learning adaptation property of the system is considered (1) from the perspective of a mono-pathogen environment, and then (2) from the perspective of the system situated in a poly-pathogen environment

The system improves its response (in terms of densities and specificity) in proportion to the number of pathogenic exposures. The secondary response is improved from that of the primary.

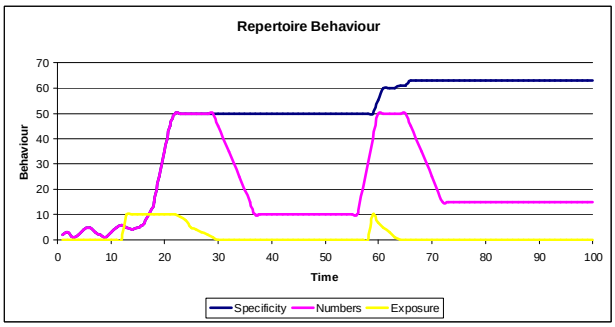

Figure 7 - Repertoire behaviour for primary and secondary exposures

The adjustment of cell densities is a re-allocation of resources allowing a clone of high-specificity cells to dominate future responses. The specificity of this clonal dominance effect is limited as maturation rate (improvement) of expanded cells will decrease and level-off the more the clone matures. This will manifest as a period of improvement in maturation followed by a long period where the majority of mutated cells are of lower relative affinity. There is a tipping-point in the selection of a clone that eventually dominates the response. Selection too early may result in the selection of an ill-fitting clone in what is referred to as antigenic sin (premature convergence). If the dominant clone is selected too early (the sin committed) than the clone will may be maladapted to the pathogen resulting in a less (than was otherwise possible) optimal response.

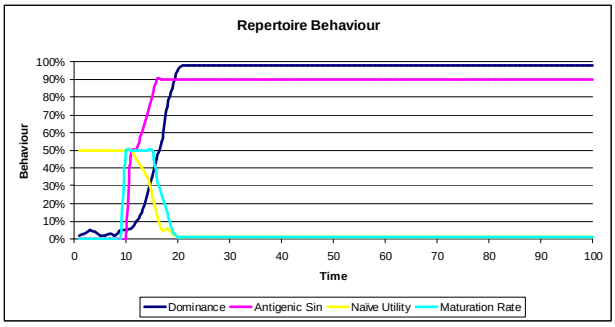

Figure 8 - Repertoire behaviour with regard to clonal dominance

In terms of the entire repertoire in the context of the pathogenic environment, convergence results in a mixture of clonal densities representative of the proportion of pathogen exposures. Thus, the responses are proportional to the likelihood of exposure. In adaptation to the environment the plasticity of the system, its ability to adapt to novel pathogens decreases (although is not complete diminished). Given the pathogen exposure regime outlined in Figure 4, where the majority of novel pathogens are exposed to the system early, the usefulness of naïve cells also decreases with convergence to clonal densities, although the naïve cells facilitate an ongoing minimal repertoire plasticity.

IV. Clonal Selection Algorithms

This section realises the principle components and base clonal selection models as algorithms in the context of the outline design principles. The series of algorithms outlined in this section attempt to isolate the various controls and pressures such that the control trade-offs and expected behaviours may be tested and evaluated independently. The A5 algorithm is the clonal selection algorithm, whereas the leading four algorithms (A1-A4) are simplified variations suitable for investigating design principles and behavioural expectations in relative isolation.

A1 – Steady-State Algorithm

This algorithm exists without external stimulation, in the absence of a pathogenic environment. It provides a baseline algorithm for demonstrating naïve cell creation and repertoire size homeostasis.

Step1: Randomly initialise repertoire
Step2: Age repertoire of lymphocytes
Step3: Introduce random lymphocytes
Step4: Check for stop, otherwise *Step2*

Figure 9 - Summary of A1, the steady state algorithm

A2 – Selection Algorithm

This algorithm is an extension of A1 and introduces a pathogenic environment and clonal selection, although there is no clonal expansion or affinity maturation. Thus, as in A1, the population turns over through time although in this case provides generalist immunity to pathogens. The algorithm encourages the investigation of pathogenic environments and exposures schemes in the context of selective precision.

Step1: Randomly initialise repertoire
Step2: Introduce pathogen to repertoire
Step3: Select high-affinity lymphocyte for pathogen
Step4: Age repertoire of lymphocytes
Step5: Introduce random lymphocytes
Step6: Check for stop, otherwise *Step2*

Figure 10 - Summary of A2, the selection algorithm

A3 – Selection-Cloning Algorithm

This algorithm is an extension of A2 where the system exists within a pathogenic environment, although unlike A2, this algorithm permits the expansion of clonally selected cells. This algorithm permits the investigation of various expansion schemes in the presence of varied exposure schemes and encourages the investigation of clonal dominance and clonal density properties. This algorithm is a realisation of the 'affinity cloning model' (BM1).

Step1: Randomly initialise repertoire
Step2: Introduce pathogen to repertoire
Step3: Select high-affinity lymphocyte for pathogen
Step4: Clonally expand selected lymphocyte
Step5: Age repertoire of lymphocytes
Step6: Introduce random lymphocytes
Step7: Check for stop, otherwise *Step2*

Figure 11 - Summary of A3, the selection-cloning algorithm

A4 – Selection-Mutation Algorithm

This algorithm is an extension of A2, although permits the affinity maturation of selected cells via mutation. Unlike A3, there is no clonal expansion, thus no new clones to integrate into the population. This algorithm provides an improvement algorithm that

encourages the investigation of selective pressures on maturation and maturation utility in proximity to optimality. This algorithm is a realisation of the 'affinity maturation model' (BM2).

Step1: Randomly initialise repertoire
Step2: Introduce pathogen to repertoire
Step3: Select high-affinity lymphocyte for pathogen
Step4: Mutate selected lymphocyte
Step5: Age repertoire of lymphocytes
Step6: Introduce random lymphocytes
Step7: Check for stop, otherwise *Step2*

Figure 12 - Summary of A4, the selection-mutation algorithm

A5 – Selection-Cloning-Mutation Algorithm

This is a realization of a clonal selection algorithm with selection, expansion, and maturation. It encourages the adaptation of both cell densities through clonal expansion, and improvement through the maturation of clones. This algorithm is a realization of the clonal selection model (BM3) and facilitates the investigation of the expectations of acquired immunity with a single repertoire.

Step1: Randomly initialise repertoire
Step2: Introduce pathogen to repertoire
Step3: Select high-affinity lymphocyte for pathogen
Step4: Clonally expand selected lymphocyte
Step5: Mutate selected lymphocyte
Step6: Age repertoire of lymphocytes
Step7: Introduce random lymphocytes
Step8: Check for stop, otherwise *Step2*

Figure 13 - Summary of A5, the selection-cloning-mutation algorithm

V. SERIES OF EXPERIMENTS

The combined effects of the algorithms operators and control parameters are expected to be complex and non-linear. With this in mind, a decomposition-based experimental methodology is adopted that attempts to measure effects of interest through reduction, isolation, and dampening of other system aspects. This section unites the proposed clonal selection algorithms with the colour-space problem domain and the previously outlined colour-space scenarios in an effort to demonstrate the design principles and behavioural expectations previously outlined.

This section specifies a series of optimization control graph and control map experiments (sensitivity analyses) of the A5 algorithm, as well as specialised studies into two important algorithm behavioural expectations.

Sensitivity Analyses 1: Optimization Control Graphs

A control graph is a technique that involves the varied configuration of the algorithm (in one dimension) and the evaluation of the varied configuration in the context of an objective. A Monte Carlo sampling of a configuration parameter is performed and the results are plotted on a two-dimensional plot highlighting performance trends that may be general and transferable.

This section specifies a number of experimental scenarios for evaluating varied control parameters and the effect to be measured for each. All experiments are to be conducted on OS1, and novelty experiments are performed using OS2. Effort to convergence is measured in terms of function evaluations until a steady state is achieved, and efficacy is taken as high-cell scoring in the final repertoire at the time of convergence.

#	Control	Varied	Interest
CG1	*Mutation*	Rate	Effect on effort to converge and resultant efficacy Acceptance rate through time
CG2	*Selection*	Precision	Effect on effort to converge and resultant efficacy
CG3	*Expansion*	Size	Effect on effort to converge and resultant efficacy Acceptance rate through time
CG4	*Repertoire*	Size	Effect on effort to converge and resultant efficacy
CG5	*Insertion*	Size	Effect on effort to converge and resultant efficacy Acceptance rate through time
CG6	*Lifespan*	Length	Effect on effort to converge and resultant efficacy
CG7	*Novelty*	Number	Effect on effort to convergence and resultant efficacy

Table 5 - Summary of control graph experiments

Sensitivity Analyses 2: Optimization Control Maps

A control map is a technique that involves the varied configuration of the algorithm (in two dimensions) and the evaluation of the varied configuration in the context of an objective. A Monte Carlo sampling of both varied configuration parameters is performed and the results are plotted on a three-dimensional plot highlighting performance trends that may be general and transferable.

This section specifies a number of control map experiments intended to reveal general behavioural properties of the system. All experiments are to be conducted on OS1, and novelty experiments are performed using OS2. Effort to convergence is measured in terms of function evaluations until a steady state is achieved, and efficacy is taken as high-cell scoring in the final repertoire at the time of convergence.

#	Controls	Interest
CM1	Selection, Expansion	Combined effect of selection and expansion on clonal convergence
CM2	Selection, Mutation	Combined effect of selection and mutation on clonal convergence
CM3	Expansion-Mutation	Combined effect of expansion and mutation (adaptation) on clonal convergence
CM4	Novelty-Repertoire	Combined effect of amount of pathogenic novelty and repertoire size on clonal convergence
CM5	Novelty-Selection	Combined effect on the amount of pathogenic novelty and selection on clonal convergence

Table 6 - Summary of control graph experiments and interests

Study 1: Clonal Densities

The clonal densities property underlies a large amount of expectation as to how the clonal selection algorithm will behave. The expectation indicates that the mixture of clones (groups of cells with specificity for a pathogen) will converge to be proportional to the proportions of pathogen exposures. The result is that the acquired response offered by the system will be proportional to the likelihood of future exposure with

regard to (1) resources manifest as the number of cells, and with regard to (2) the specificities of those cell densities.

This expectation may be experimentally investigated using the OS2 scenario with a well-configured A5 (using control map results). The system is to be tested against a series of different pathogen exposure distributions (distribution defines total exposure which is temporally neutral). **Variation**: Densities of pathogens

The repertoire may be assessed in the following ways:

Assessment	Expectation
Best pathogen specificity	The 'closeness' of each pathogen will be a relatively proportionate to the amount of exposure to each pathogen.
Aggregate pathogen specificity	The spread of the distribution of specificity of groups of cells within proximity (threshold) of each pathogen will be proportionate to the amount of exposure to each pathogen.
Cell clusters by pathogen	The number of cells within proximity (threshold) of each pathogen will be proportionate to the amount of exposure to each pathogen.

Table 7 - Summary of assessments and expectations of clonal density

Study 2: Novelty Acceptance

Novelty acceptance is required for adaptation, and acquired immunity is a life-long learning process. That being said, exposure to a pathogen that the host (and hosts gene pool) has not seen anything like before may be devastating. Thus, the efficiency and efficacy of late novelty acceptance is lower compared to system behaviour for early novelty acceptance. This expected behavioural transition demonstrates a measurable change in the systems general plasticity.

This system behaviour expectation may be investigated by using a specialised version of OS2. The system is adapted until clonal convergence on a given pathogenic environment of a number of pathogens the exposure of which are density and temporally neutral. After clonal convergence additional pathogens are introduced, and the acceptance of the new pathogens is evaluated.

Variations: (1) the number of pathogens before and after clonal convergence, (2) the similarity of late pathogens to early pathogens, (3) the re-exposure of early pathogens after the exposure to late pathogens

The expectation may be assessed with regard to:

Assessment	Interests
Specificity to late pathogens	The specificity to the late pathogen in the repertoire compared to a system that is only trained on the late pathogen
Specificity to early pathogens	The specificity to the early pathogens in the repertoire after late pathogen exposure compared to specificity of the repertoire before the late pathogen is introduced
Mutated cell usage	The rates of mutated cell usage before, during, and after late pathogen arrival
Naïve cell usage	The rates of naïve cell usage before, during, and after late pathogen arrival

Table 8 - Summary of assessments and interests of novelty acceptance

VI. Discussion

This work has clarified the clonal selection algorithm and outlined: (1) implementation design principles, (2) emergent behavioural expectations, and (3) an experimental framework for investigating the algorithm in the context of the design principles and behavioural expectations. There is much work to do going forward, not limited to the realisation of: extended, discrete repertoire, and multiple system clonal selection algorithms. Some preliminary algorithm extensions that may be interesting to peruse after the A5 algorithm has been investigated may include:

1) Schemes to improve the efficiency of density acquirement through changes to the relationship between pathogen amplitude to clonal expansion. This may involve a specificity proportionate cloning and maturation scheme
2) An organization exposure scheme for arriving pathogens in which a repertoire structure is imposed such that the cells that are most likely to be useful in the exposure event are selected with a higher priority (other than the implicit density-based mechanism). An example may be a hierarchal or spatial data structure such that mature clones or naïve cells are exposed to novel pathogens before the general repertoire
3) A pressure that counteracts the natural premature convergence pressure (antigenic sin). The pressure would represent the penalty for not acting fast enough such as the damage inflicted by the pathogen (danger signals)

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