The Immune System in Pieces: Computational Lessons from Degeneracy in the Immune System

(Special session: Foundations of Artificial Immune Systems)

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***Abstract*— The concept of degeneracy in biology, including the immune system, is well accepted and has been demonstrated to be present at many different levels. We explore this concept from a computational point of view and demonstrate how we can use computational models of degeneracy to aid the development of more biologically plausible Artificial Immune Systems (AIS). The outcome of these models has lead us to perform an analysis of the receptor dynamics in the model and we discuss the computational implications of a "degenerate" repertoire. Through the use of the Unified Modelling language (UML) we have abstracted a high level immune inspire algorithm that will be used as part of a larger project to develop an immune inspired bioinformatics system.**

I. Introduction

In previous work [1], we have discussed various challenges to the area of Artificial Immune Systems. One area is the further exploitation of the underlying biology, as we argued that AIS have failed to capture the richness and complexity that is inherent in the natural immune system. Indeed, this view is echoed in [2] who propose a methodology to attempt to address this issue. In other work, we have begun to examine alternative views of immunology, away from the *mainstream* immunology [3], [4]. In [3] we explore an alternative view of the immune system as presented by Cohen [5] and how this might be exploited in the context of AIS. Taking that work further in [4], we produced a simple model of the lymph node where T cells interact with antigen presenting cells, the key aspect of this model is that the receptors are *degenerate* i.e. there is no concept of specific receptors in the model. The ongoing work in [4] has provided motivation for the further examination of the notion of degeneracy in the context of AIS, this time with a focus on B cell receptors.

The work in this paper outlines the first stages in developing an immune-inspired classification algorithm for the hierarchical classification of G-Protein coupled receptors (GPCRs) – this work is part of a larger research project whose goal is to develop a state of the art GPCR classification system [15]. Following [2], we first need to develop a model of the biological system in question. We have done this through the use of agent based modelling techniques, which have allowed us to investigate the computational aspects and implications of a degenerate set of B cell receptors (as opposed to a non-degenerate set), in the context of the clonal selection process of the immune response. The next stage is to develop a high-level algorithm that is derived from the model. Independently, recent work by Bersini [6] has highlighted the benefits of adopting object orientated methodologies in the use of modelling biological systems. In our work, we have made use of the Unified Modelling language (UML), not only to represent our agent model, but also to aid the development of a high-level algorithm that we have derived from the model. It should be noted that the model we have developed and the high-level algorithm that we have derived is only the first step towards the development of an actual algorithm for GPCR classification. It is not our intention to implement this high-level algorithm, as at present it does not incorporate the notion of adaptation. The work presented here is the first stage in the development of a more sophisticated system. We report our current progress and discuss what we consider to be interesting lessons that we can learn even from a simple model, and how these can help us in the design of immune inspired algorithms.

The paper is organised as follows. In section II we outline the methodology of [2], this is followed by section III where we discuss the notion of degeneracy in biological systems, with a focus on the immune system. In section IV we present the actual model of degeneracy and the computational results that we have obtained. We then follow in section V with a high level UML diagram of a potential immune inspired algorithm. We conclude with discussions on future work and directions.

II. Modelling through a Conceptual Framework

Work in [2] proposes a conceptual framework that allows for the development of more biologically grounded AIS, through the adoption of an interdisciplinary approach. Metaphors employed within AIS have typically been simple, but somewhat effective. However, as proposed in [2], through greater interaction between computer scientists, engineers, biologists and mathematicians, better insights into the workings of the immune system, and the applicability (or otherwise) of the AIS paradigm will be gained. These interactions should be rooted in a sound methodology in order to fully exploit the synergy. The authors argue that rather than going straight from observing the biology and then to the development of an algorithm, a more principled approach is required to adequately capture the required properties of the biological

system in the engineered counterpart. The methodology is one of abstraction. The first step is to create a mathematical model of the biosystem: a relatively detailed model of the system. In some cases, this model may already have been developed, and indeed with our other work in [4] this is the case. These mathematical models are then used to derive a more abstract computational model: the model can be executed and analysed for properties that are desired in the engineered system we wish to construct. Then a high level algorithm is derived from the model, abstract from any application area. This is then instantiated in the application area, being tailored to the specific requirement of that application area. The result is well-grounded bio-inspired algorithm, that is understood better on a theoretical level (addressing one of the challenges posed in [1]) and capture the *relevant* biological properties for the required application. We have adopted this process in our project, and here report our initial findings.

III. Degeneracy

In the context of biology, degeneracy has been defined by Edelman and Gally [7] as:

> "the ability of elements that are structurally different to perform the same function or yield the same output"

It is ubiquitous property present at all levels of biological organisation (such as the genetic, cellular, system and population levels) being conserved and favoured by natural selection. Examples of degeneracy given in [7] include:

- Genetic code – different base sequences can encode the same polypeptide
- Protein folding – different polypeptides can fold to become structurally and functionally equivalent
- Inter-cellular signalling – parallel and converging signalling pathways of molecules such as hormones are degenerate
- Connectivity in neural networks – connections and dynamics are degenerate
- Body movements – different patterns of muscle contractions can produce equivalent movements
- Inter-animal communication – the same message can be transmitted in different ways, e.g. vocally or via body language

In [8], Tononi *et al.* use information theory to develop measures of degeneracy and complexity in artificial neural networks, showing that an increase in degeneracy leads to an increase in complexity. This has led Edelman and Gally [7] to postulate that in biological systems, degeneracy is invariably accompanied with complexity.

Within immunology, antigen receptor degeneracy is a term that has been used for many decades yet has escaped rigorous definition [9]. A recent and widely held definition that we have adopted for our work is given by Cohen [10], who states that antigen receptor degeneracy is the:

> "capacity of any single antigen receptor to bind and respond to (recognize) many different ligands"

Based on this definition, two problems for immune recognition arise: a single antigen epitope can activate different lymphocyte clones (*poly-clonality*), and a single lymphocyte clone can recognise different antigen epitopes (*poly-recognition*). Poly-clonality can generally be overcome via clonal competition with those lymphocyte clones having the greatest receptor affinity for an antigen epitope proliferating over other activated clones. Poly-recognition, however, causes problems for the traditional clonal selection theory view due to its reliance on the strict specificity of lymphocyte clones [10].

Contrary to the traditional clonal selection theory view, Cohen [10] believes that immune specificity can arise through response patterns of degenerate immune receptors to a particular target. As an example of the power of patterns of degenerate receptors, Cohen [10] discusses the example of colour vision in the human eye. The eye contains millions of colour receptors (cones), each belonging to one of only three types: red, green and blue. Each of these types is highly degenerate, responding in different degrees to a broad range of overlapping light wavelengths. Based on just these three receptor types, the brain can perceive thousands of different specific colours. Colour specificity, therefore, is not encoded in each receptor, but is achieved via the integration of receptor outputs by neuronal firings in the brain. Likewise, Cohen [10] envisages a similar recognition scenario in the immune system.

A. Degeneracy in Practice

In order to understand the concept of degeneracy, consider the following simple example. Using small blocks of letters "ac", "me", "ma", "ca" we can construct words such as "acme", "came" and "mace". However, if we add a further block of letters "ne", this increased the number of words that can be constructed to "cane", "acne", "mane". Therefore, six words can be built using five small blocks of letters. Taking this example as a basis, from a computational point of view we can consider using small sized *detectors* or *receptors* in a recognition system. This has the potential to recognise a large number of patterns (i.e. achieve a high coverage of the data space), but with a low overhead in terms of number of detectors (i.e. the items covering the data space). This is potentially important, as by having multiple, smaller receptors we are able to reduce the *complexity* of cell receptors, when compared to the traditional modelling of one-receptor-to-one-antigen detection. This means that rather than having a single "large" detector and requiring that detector to be activated for pattern recognition to occur (a typical approach in clonal selection based AIS), we can make use of a combination of smaller, simpler receptors, that *together* become activated to recognise a pattern.

To further illustrate the idea, figures 1 and 2 depict a functional view of artificial B cell receptors binding to antigen. Consider, in figure 1, the antigen to be the top set of bars with a diagonal pattern, and the bottom set of bars with a crosshatch pattern, as the artificial B cell receptor. In a typical implementation of a clonal selection based AIS, one would usually represent each of those sets of bars as a numeric

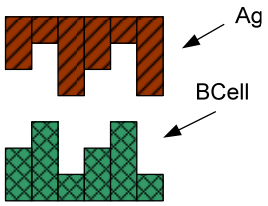
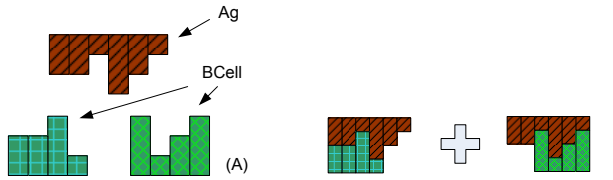


Fig. 1. One to one receptor approach



(a) Smaller receptor approach (b) Smaller Receptor approach combinatorial detection

Fig. 2. Simple Example of Degeneracy

sequence and calculate a distance measure (affinity) between the two.

However, figure 2 shows an artificial B cell receptor which is smaller, and can bind to two different areas of two different antigens: it is the combined recognition of the two receptors that would be the trigger for antigen recognition.

IV. Computational Models

In order to investigate the idea of degeneracy, and following the conceptual framework approach, we need to develop a computational model to facilitate the investigation. For the purposes of this paper, we have developed two models, one that contains receptors that are degenerate, and one where they are not. Both models were implemented in Netlogo (version 3.0.2) which provides a cellular Automata (CA) platform capable of supporting agent based simulations. Given the large number of clonal selection based AIS, we have decided to explore the degeneracy concept in the context of the clonal selection process. We have therefore constructed a simple model of clonal selection, where we focus on the interaction of B cell receptors with antigen. For simplicity at this stage, we have ignored the role of T cells in the response and have examined that independently [4]. We expect to combine this work at a later stage. We will now outline the model developed. Code is available for this model from the project website [15].

A. Model Description

Both B cells and antigens are modelled as agents endowed with a specific set of rules which govern how each agent behaves. Agents are able to move in the CA grid space in random directions one patch (a particular location in the CA) at a time. In both models, B cell agents have a life span governed by Equation 1 and a *death* threshold of 100 (user defined), whilst antigen agents are permanent agents until binding with a B cell which will cause the antigen to be removed from the agent space. As B cell agents have a life span, they must also have a birth rate: this is controlled by Equation 2 and two parameters, *birthrate* and *variation*. *Birthrate* sets how many new cells are introduced on average into the simulation at each step, which alters the dynamics of the population, and *variation* sets the amount of perturbation the population should undergo. The signatures (identifying value) for the B cell receptors and antigen epitopes are randomly generated. In both models, the antigen epitope has a length of six items and each item can take one of 6 values. Usually this would allow us to create 6^6 = 46656 different patterns for the antigen epitope, however, in this case, we impose a restriction on how patterns are generated, which will therefore reduce the total number of patterns available. This restriction is a consequence of the degenerate receptor model, which uses more than one detector to recognise an antigen. If we were to use all possible combinations for generating the antigen epitope signature then some signatures could be *ambiguously* recognised by the degenerate receptors. In this context, ambiguous means that there are certain receptor combinations that can match more than one antigen. This is a potential problem because we can not determine which antigen was recognised. Nevertheless, in the models presented here, we restricted certain patterns in order to be able to create a fair comparison between the models (thus the ambiguity problem does not arise here). Through mathematical analysis, we determined that there were 1296 patterns which are deemed ambiguous. This is the number of patterns where the first two bits are the same as the last two bits of the epitope signature. Therefore, for both models we were able to generate 45360 antigen signatures. For the clonal selection model without degeneracy, the B cell receptors were generated obeying the same restrictions as with the antigen epitope signature allowing for one receptor to be created for each antigen signature.

$$Life = random(death) - (death/2)/10 \quad (1)$$

$$Newcells = birthrate - random(variation) \quad (2)$$

$$variation = birthrate * 0.5 \quad (3)$$

For the clonal selection model with degenerate receptors we used the smaller receptor approach to test degeneracy, as illustrated in figure 2(a). The receptors for this model were of size four, and each bit could take one random value out of six. For recognition to occur successfully full coverage of the antigen is necessary, where coverage means matching all the bits in the receptor. This is enforced, allowing us to calculate the *worst case scenario* within the model. As we are using receptors of size four and recognising a size six signature, the receptors overlap in two places. This overlap reduces the number of potential ambiguous patterns that the use of multiple detectors causes. The number of B cell receptors that can be potentially generate is reduced to 1296 compared

to the 45360 potential receptors used in the clonal selection approach.

In our implementation, the CA grid size is 63 by 63 patches and we begin the simulation with 450 B cells. From the time the simulation begins cells can move in the grid, age, die and new cells can be introduced. The simulation is allowed to run for 120 iterations in order for the population to stabilise, as there is a typical increase in cell population before it stabilises to an average of 445 B cells. Once the B cell population has stabilised, we introduce the antigen that is to be recognised: in our experiments, this is typically at iteration 120. The population usually stabilises around iteration 100 but we allow a 20 iteration buffer before the antigen is introduced. For these experiments, we introduced 85 instances of the same antigen, i.e. 85 antigen agents with the same epitope (the number of antigen is not important at this stage). Antigen agents are allowed to perform a random walk through the grid. When a B cell encounters an antigen (defined as an antigen being within 1 patch of a B cell), a binding check takes place. In the clonal selection model without degeneracy, B cells check if their receptor signature matches perfectly to the antigen epitope signature. If this is the case, then recognition is achieved and the time taken is recorded. The requirement for perfect matching is imposed on the model to allow us to calculate worst case scenarios to cover 100% of the data space (full coverage). Of course, perfect matching is not a requirement in actual biology, and is not a standard requirement in our model or algorithm, but as discussed it has been enforced for worst case scenario analysis. With the clonal selection model with degenerate receptors, the B cells check if their receptor signature matches perfectly either the first four or the last bits of the antigen epitope. If this is the case, then we notify a global tracking mechanism that records that the receptor has bound with a certain antigen and therefore, that part of the antigen's epitope has been covered. Once this tracker has received notification that all parts have been covered then recognition is achieved and the time taken is recorded. This tracker is required as typically in non-degenerative clonal selection models, a simplistic rule is of the type "If a cell is activated over threshold x then recognition is successful", whilst in the degenerate model the rule is "If cell type A and cell type B become activated over threshold x then recognition is successful". The tracker allows for the model (and also corresponding algorithm) to keep track of the activated cells. It is possible to dismiss the tracker if we impose the restriction that successful recognition will only occur if all the necessary cells are activated at the same time.

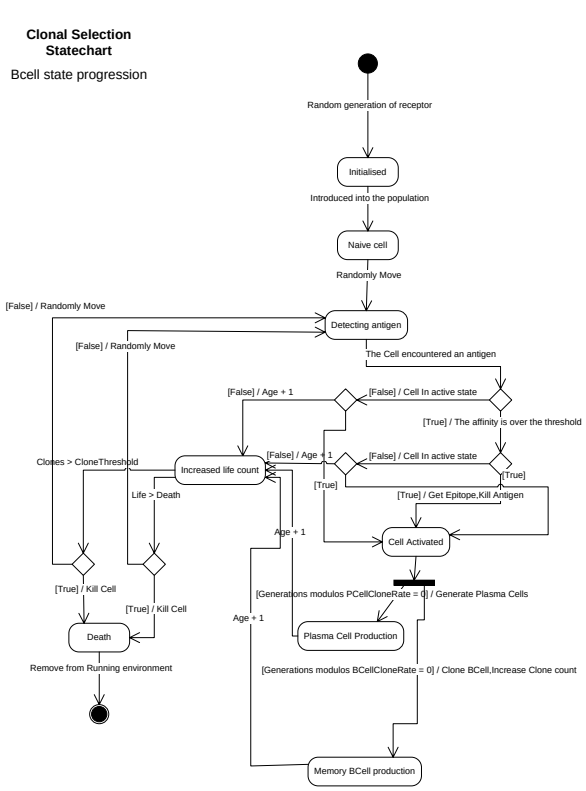
Based on these agent models, we then made use of UML to construct a state chart model of the life of a B-cell. These are shown in Figure 3 where you can see the life of a B cell in the non-degenerate model (figure 3(a)) and degenerate model (figure 3(b)). This state chart model is useful for a number of purposes. First, it allows us to gain an overall insight into the life of a B cell and the stages that are required for it to go through to achieve recognition. This is useful from a computational perspective for when we come to abstract into a high-level algorithm later. Also, by modelling in such a way, any omissions from the agent model can easily be identified and fixed. Finally, it gives a simple representation by which it is possible to communicate between different disciplines: notably computer science and biology. State charts are relatively simple and provide a common language which is required in an interdisciplinary project such as ours.

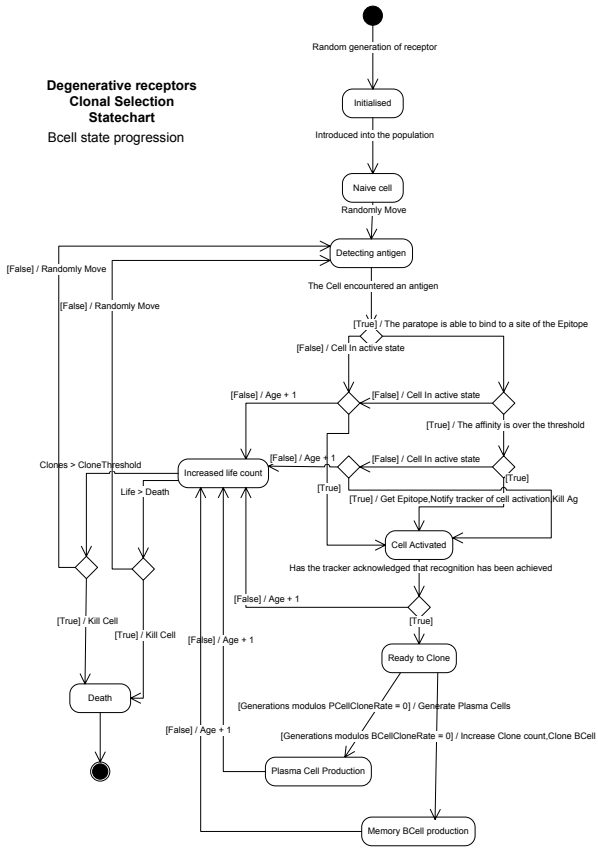
B. Results from the Model

For a baseline experiment, we make use of the clonal selection without degenerate receptors. This allows us to assess the difference the inclusion degeneracy makes in the second model. The main aim of these experiments is to investigate the potential pattern recognition capabilities of the two models i.e. their ability to identify an antigenic pattern from a set of randomly generated patterns. However, further work is directed at identifying classes of antigenic patterns. To allow us to establish meaningful results, due to the random nature of the models, each experiment was performed 1000 times. The parameters were fixed for both experiments (as detailed above) and the restriction is imposed (as previously discussed) that B cell binding with antigen has to be a perfect match as to provide 100% certainty in the recognition. The average size of the population, B cell life span and introduction of new cells was the same for both experiments (as defined above)

Figure 4(a) represents the cumulative frequency graph of the time taken, or how many time steps the B cell population took, to recognise an antigen in a repertoire of 45360 antigens using the clonal selection model without degeneracy. The Diamond point on the graph establishes the mean of the dataset. Figure 4(a) is particularly useful as it demonstrates the sparseness of the data but it also provides information about the frequency of the data at any point in time. The X-axis provides the range for the data and, through the gradient of the graph we can see how dense (steep gradient) or sparse (gentle gradient) the data is at any point in time. The antigen was only released into the system at time step 120, thus allowing the B cell population to stabilise. Each experiment was complete when the appropriate B cell bound to the target antigen. Similarly to figure 4(a), figure 4(b) represents the cumulative frequency of how many time steps the B cell population took to recognise a particular antigen in a repertoire of 45360 antigens using the clonal selection model with degeneracy. Again, the diamond point establishes the mean. As before, the antigen was only released onto the system at time step 120 as to allow the B cell population to stabilise. Opposed to the previous set of experiments where we only required one B cell to bind to the antigen, this set of experiments requires a set of B cells (2 for this particular case) to bind to the target antigen for recognition to occur and the trial time to be recorded.

Both graphs share very similar properties, as they both have similar curve shapes and the mean is approximately at the same relative distance from the median, respectively 13% and 10% of the population. These similarities emphasise the fact that we have not changed the overall behaviour or functionality of models. Although, the striking difference is

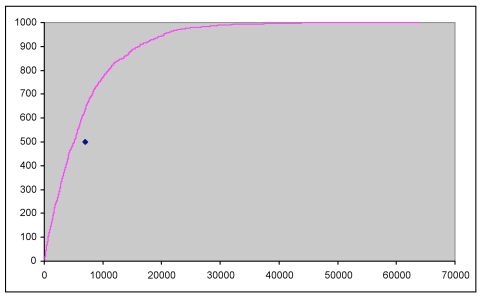




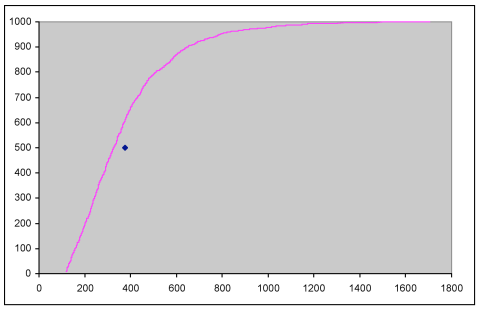
(a) UML State Chart of the life of a B cell in the Model - Non Degenerate Receptors

(b) UML State Chart of the life of a B cell in the Model - Degenerate Receptors

Fig. 3. Two Clonal Selection Models



(a) Cumulative Frequency of the time taken to successfully recognise the antigen, over 1000 runs, using a clonal selection model; X axis number of iterations, in logarithmic scale; Y axis number of trials



(b) Cumulative Frequency of time taken to successfully recognise the antigen, over 1000 runs, using a clonal selection model of B cells with degenerative receptors; X axis number of iterations, Y axis number of trials

Fig. 4. Results from two clonal selection models

on the X-axis scale between the two graphs where the clonal selection model without degeneracy, figure 4(a), is over one order of magnitude greater than the clonal selection model with degeneracy, figure 4(b). Despite both sets of experiments using the same random search approach, the discrepancy can be explained by how each model performs recognition. Due to the imposed restriction for 100% recognition accuracy, the baseline clonal selection model uses one B cell for each antigen in the repertoire, whilst the degenerate receptor model uses two B cells for each antigen in the repertoire. The difference between the B cells in the two models, is that for the typical clonal selection model the receptor in the B cell is the same size as the antigen signature, whilst with the degenerate model the B cell receptors are smaller than the antigen signature and overlap with each other to provide an accurate recognition. For these experiments we employed antigens with a signature length of 6, e.g. '012345'. In the clonal selection model without degeneracy we require a B cell with the receptor '012345' for a perfect match. However, in the clonal selection model with degeneracy we require a B cell with the receptor '0123' and a further B cell with the receptor '2345', providing a two place overlap on the antigen signature. One side-effect of the constraint mentioned above was that a number of patterns had to be removed from the degenerate receptor model. Nevertheless, the total number of potential antigen signatures that could be generated was the same for both experiments.

C. Computational Lessons

Typical approaches within the AIS community to the development of clonal selection based algorithms have met with certain levels of success [11]–[14]. However, through the modelling of a simple clonal selection process, free of any application bias, we have been able to observe the potential computational effects of incorporating new, or modifying existing, properties of a simple clonal selection model. We argue this is of major importance in the development of further immune inspired algorithms. Within the work presented in this paper, the key feature that we have investigated has been the binding and cloning mechanisms which lead to antigen recognition. Through the incorporation of degeneracy into our model at the B cell receptor level, we were able to affect the interaction between B cells and antigens. What this means is from a more traditional view of clonal selection this relation has been a direct one to one mapping between B cell and antigen, whilst the model that incorporates degeneracy this relation becomes a many to one relation. One of the potential benefits of this type of relation is that B cell receptors can possibly extract meaning from the antigen epitope signature and potentially allow for them to be categorised to the type of receptors to which they are able to bind. A further benefit that has already been made clear is the reduction of time taken to recognise an antigen signature when dealing with limited sized populations. Nevertheless, at this stage, there is one significant drawback which involves *ambiguity* in signature patterns. This ambiguity prevents the model with degenerate receptors accurately recognising certain patterns, i.e. if the detectors A and B are used to recognise an antigen epitope signature pattern, have we recognised the pattern AB or the pattern BA? However, in our model it is possible to restrict the patterns that can be used for the antigen epitope signatures, although in algorithmic implementations it would not be feasible to do so. This is one area of future research that is on-going.

V. From Natural to Artificial

In line with the conceptual framework, our next step is to move from a computational model to an algorithm. In order to do this, we have again made use of UML. Based on the agent models we developed, and the subsequent development of the state chart UML diagram, we were able to abstract a high-level algorithm capturing the computational properties of the model i.e. recognition of antigen with and without degeneracy. Figure 5 outline a high-level clonal selection algorithm without degeneracy (figure 5(a)) and one employing degeneracy (figure 5(b)).

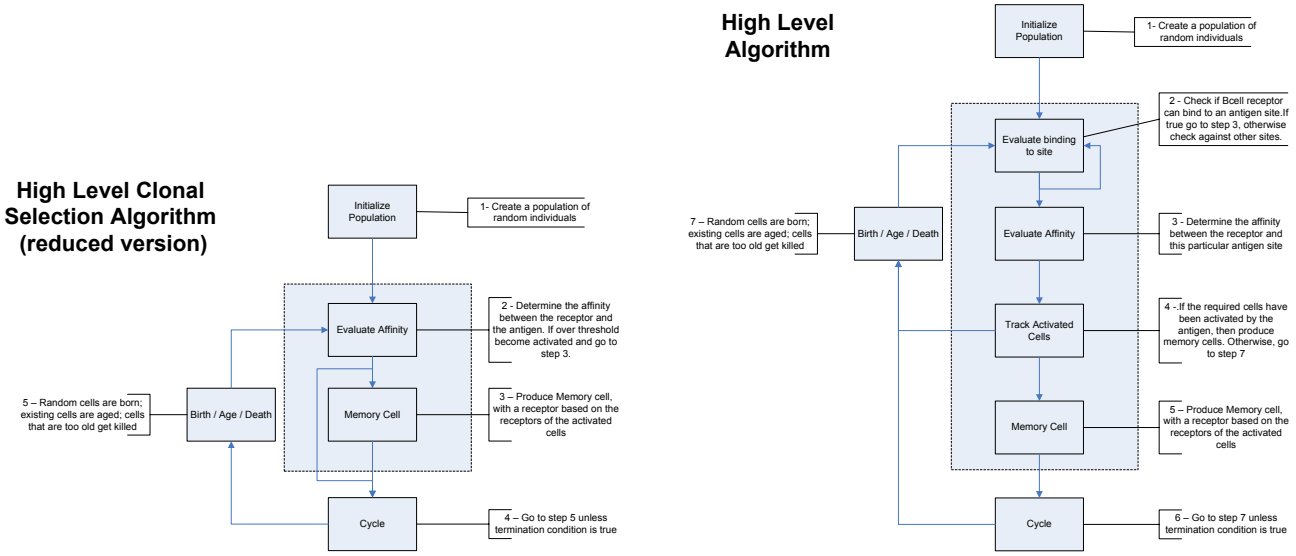
There is a noticeable difference between the two algorithms. As with the clonal selection model with degeneracy, the "degenerate" algorithm is required to make use of a *tracker*, which keeps track of which receptors have been activated (the reason for this is discussed earlier). Therefore, first a check is made to see if a B cell receptor can actually bind to a site (step 2 in figure 5(b)). If this evaluates to be true, then the algorithm proceeds to evaluate the affinity (step 3). Otherwise, the receptor will attempt to bind across all sites on the antigen and if no bind is successful then the next antigen is considered for binding i.e. you jump to step 6 in the algorithm. This is not the case for the clonal selection algorithm without degeneracy.

VI. Conclusion

We have presented the first stages in the development of an immune inspired algorithm, through the use of a conceptual framework [2]. Through the combination of agent based modelling and UML, we have begun to investigate the computational properties of an inherently degenerate recognition system. From our initial studies, we have identified that it is possible to recognise patterns using such degenerate receptors, and when compared to a non-degenerate system, recognition appears quicker. We have begun the first stages in developing an immune inspired algorithm based on these properties. However, the algorithm presented here is by no means complete, and will not be implemented, as many more investigations with the model are required before an algorithm that is capable of being applied to our GPCR data can be developed. Rather, than present a working algorithm, the aim of this paper was to present the process by which it is possible to develop immune inspired systems, taking into account, in a more reasoned way, computational properties of biological systems.

Acknowledgment

This research is supported by EPSRC grant EP/D501377/1. We would also like to thank Alex Freitas, Andy Secker and Darren Flower for their input towards this paper [15].



(a) UML Diagram of Non Degenerate Clonal Selection Algorithm

(b) UML Diagram of Degenerate Clonal Selection Algorithm

Fig. 5. UML Diagrams of High Level Clonal Selection Algorithms

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