A Series of Multiple Immune System Adaptive Models Inspired by Evolution and Immunization

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Abstract-**The acquired immune system provides a microcosm of Darwinian natural selection at the cellular level. When more than one of these somatic learning systems is considered in a population, an array of interesting effects and interactions become apparent. This work elaborates on a series of multiple immune system models defined in a previous work. A framework for such models is presented that defines mechanisms such as pathogen exposure regimes, immune effector sharing schemes, and evolutionary mechanisms. The previously defined models are re-defined using this framework, although the models described represent a small fraction of the combinations of the defined mechanisms.**

Keywords- Adaptive Models, Artificial Immune Systems, Multiple System Models, Evolution, Vaccination, Immunization, Passive Immunity

I. INTRODUCTION

In raising the level of abstraction from that of whole immune systems, to populations of interacting immune systems, a number of interesting adaptive mechanisms and models are revealed. The intent of this work is to leverage an understanding of immunization of populations of immune systems and the various evolutionary concerns in the systems development highlighted in [3] to design a series of mechanisms and adaptive models. This work provides an natural elaboration of the multiple system models described by Brownlee in [1], and is inspired by the elaboration of discrete repertoire models in [2].

Section II summarises the original series of adaptive models with a particular focus on the contributions of the multiple immune system models presented. Section III describes two pathogen exposure regimes from which the host may learn immunity. Section IV describes two different effector sharing schemes for transplanting a learned immunity between systems. Section V proposes three different evolutionary mechanisms that adapt an immune defence in response to a pathogenic environment. Section VI extends previous vague notions of system stimulus via antigen to define five different pathogen models of behaviour. Section VII elaborates on the three previously defined multiple immune system models, applying the mechanisms and behaviours defined in this work. Finally, section VIII discusses future work extensions of this work.

II. SERIES OF ADAPTIVE MODELS

In a previous work, Brownlee [1] proposed a series of adaptive models inspired by the clonal selection theory of acquired immunity. The series included principle components and base clonal selection models. Extensions of the base models were proposed, as were a discrete repertoire models. The discrete repertoire models were inspired by the spatially distributed architecture of the immune system, and the recirculation and homing behaviours of lymphocytes. These models were elaborated to a series of structural, cellular, and movement behaviours by Brownlee in [2]. The final model type in the original series were multiple immune system models that were perhaps of the highest order of complexity given that they subsumed all previously defined single-system models.

Multiple System Models

The original series proposed three different multiple system models, that were all based on the premise that more than one acquired immune system model (base model BM3) may be aggregated into a population in which they may interact in various ways.

MSM1 (Vaccination Model) contained a collection of BM3 (base clonal selection models) each distinct in terms of base repertoire and pathogenic environment. The model proposed (1) the controlled exposure of individual immune systems to a vaccine to elicit immunity with regard to a pathogen, and (2), the transplantation of effectors developed (learned) in response to the vaccine from vaccinated immune systems to unvaccinated immune systems.

MSM2 (Evolutionary Model) is composed of a collection of BM3 models (like MSM1), although the BM3 model is implemented in such a way that the initial 'random' repertoire and ongoing 'random' naïve lymphocyte generation determined via a transcription process from a genetic basis. This genetic basis is varied and subjected to an evolutionary process where reproductive potential of a given immune system is determined given fitness of the system relative to other systems in the population (lifetime immunological performance in a similar pathogenic environment). The evolutionary pressures encourage a bias in the genetic basis of the lymphocyte repertoire towards those naïve lymphocytes that may be immediately useful in the

populations (species) pathogenic environment.

MSM3 (Evolutionary Ontogenetic Model) is an extension of MSM2, which introduces a form of transplantation of learned immunity effectors that functions vertically between generations rather than horizontally between members of the same generation as described in MSM1.

Multiple System Model Principles

1. Subsume single immune system models (single repertoire) to a collection of single immune systems
2. Individual immune systems in the population are unique and distinct from each other with regard to: a) The initial base repertoire and ongoing naive lymphocyte creation, and b) The temporal (and perhaps spatial) aspects of pathogen exposure (pathogenic environment)
3. Immune systems in the population may interact *explicitly* and *implicitly*: a) Explicitly by sharing immunization information, and b) Implicitly through selection and recombination in an evolutionary process

Figure 1 - Summary of the principles described in the multiple system models

The principles of the multiple system models MSM1-MSM3 are listed in Figure 1, which essentially describe populations of autonomous immune systems that may interact in various ways. The summarized adaptive model principles raise a number of investigatory questions such as: (1) What are the ways in which an immune system may be exposed to pathogens? (2) What are the ways in which learned immune effectors may be transferred between immune systems? (3) In what ways may evolution be used to shape immunity? (4) What are some differing pathogen behaviours?

Given a review of immunization and evolutionary immunology by Brownlee [3], this work elaborates the multiple system models to a framework of immunization and evolutionary mechanisms that addressed the raised questions, and in which the three (and many more) multiple immune system adaptive models may be defined.

III. Exposure Immunization Mechanisms

The acquired immune system learns through exposure to pathogens, thus the pathogenic environment defines *what* is learned and *when*. The immunity that a system receives through recognising and responding to pathogens is called active immunity and may be induced naturally (uncontrolled) and artificially (controlled). Pathogen exposure-based immunization mechanisms are numbered EIM# and summarised in Table 1.

Mechanism	Summary
EIM1 – Uncontrolled	Exposure as a function of environment (pseudo-random)
EIM2 – Controlled	Exposure as a function of intent

Table 1 - Summary of exposure immunization mechanisms

EIM1 – Uncontrolled Exposure

Uncontrolled pathogen exposure is a natural way for a system to achieve active response-based immunity. This form of pathogen (antigen) exposure is an elaboration of the previously defined standard model in [1] as a principle component O1 (clonal matching).

An aspect of the distinctiveness of acquired immune systems in a population is the spatial and temporal variations of pathogen exposures. These varied exposure patterns in conjunction with the varied naïve repertoire of each individual result in distinct initial and learned specificities to pathogens. For a given pathogen, exposure may be described as a function over space and time that may be skewed for many reasons such as pathogen virulence, host density, and other pathogen-behaviour and spatial-population effects.

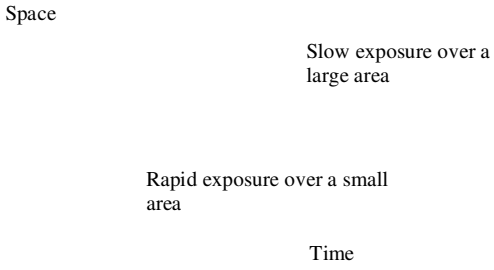

Figure 2 - Example of some aspects of uncontrolled pathogen exposure

EIM2 – Controlled Exposure

Control over pathogen exposure provides control over immunity of individual systems and virtual immunity over the entire population through effects like 'herd immunity'. Artificial exposure of systems to pathogens provides control of (1) *which* systems are exposed to (2) *what* pathogens (3) *when*. A vaccination exposure strategy may involve administering a vaccine to a large number of systems quickly. An inoculation strategy may involve exposing a select few systems to the pathogen in a short amount of time. Control of exposures may also extend to preventative steps such as environment sterilisation or individual system isolation from the pathogenic environment.

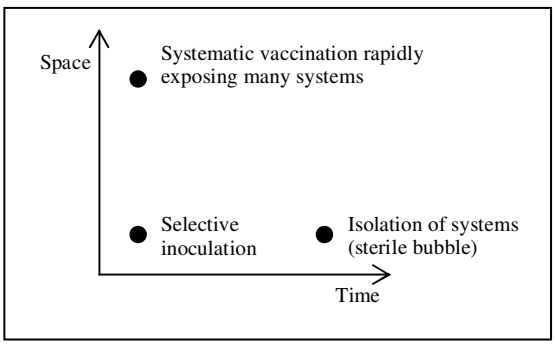

Figure 3 - Example of some aspects of controlled pathogen exposure

IV. Shared Effector Immunization Mechanisms

Immunity is acquired and refined over the lifetime of the host given pathogen exposures and resultant clonal selection and affinity maturation. The effectors produced in this process (antibodies, memory and recirculating lymphocytes) may be shared with other immune systems. This section describes two mechanisms for sharing effectors between systems in what is referred to as passive immunity. Table 2 summarises the shared effector immunity models, which are numbered SEI#.

Mechanism	Summary
SEI1 – Vertical	Learned immunization information is passed between generations
SEI2 – Horizontal	Learned immunization information is passed between systems of a generation

Table 2 - Summary of shared immunization mechanisms

SEI1 – Vertical Sharing

Vertical sharing is inspired by natural passive immunity such as the sharing of antibodies between mother and foetus across the placenta (maternal immunity), and to the infant after birth through breast breastfeed (mucosal immunity). Vertical sharing of immune effectors is a mechanism of inheriting acquired immunity between generations in a Lamarckian manner. A sample of the effectors are removed from a parent system and inserted into a child system. The shared effectors, like all cellular components, have a finite lifetime and may perish before being employed by the receiving system. A natural version of this mechanism is a parent-child relationship, but this is not a requirement. The mechanism does require (1) a generational population structure, (2) the selection of a donator from the previous generation, (3) the selection of a receiver from the next generation, and (4) a sampling method for the donator (effector selection mechanism).

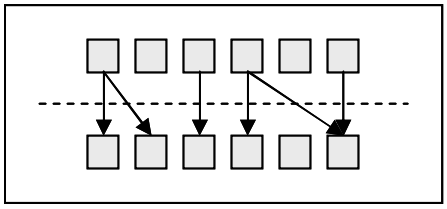

Figure 4 - Depiction of vertical effector sharing

SEI2 – Horizontal Sharing

Horizontal sharing of immunity effectors is inspired by artificial passive immunity where effectors are synthesized and injected into hosts, or removed from one host and injected into another. This method of effector sharing provides a way of transferring learned immunity within a population of immune systems. The mechanism does not require a generational population structure, although, like vertical sharing it does require (1) a donator of effectors (within the population or synthesized externally), (2) a receiver system within the population, and (3) a sampling (selection) method for effector cellular components from the donator.

Figure 5 - Depiction of horizontal effector sharing

V. EVOLVED IMMUNITY MECHANISMS

Another way of sharing immunity is through genetic evolution involving the assignment of immune system fitness, (2) selection of parent immune systems, (3) the recombination of parent genetic material to create children, and (4) the mutation of child genetic material. Those immune systems that demonstrate their relative utility (relative to other immune systems with the same generational population) may proliferate, and those that do not demonstrate utility, perish.

The evolution of immune systems requires that the expressed phenotype (thing being evolved such as immune effectors or response strategy) be transcribed from a genome (representation) on which the evolutionary processes of selection, recombination, and mutation may operate. It provides a generation mechanism for implicitly sharing effectors rather than explicitly as in the case of vertical (SEI1) and horizontal (SEI2) effector sharing. Table 3 summarises the evolutionary immunity mechanisms, which are numbered EIM#.

Mechanism	Summary
EIM1 – Innate	Evolution of a generalized innate immunity
EIM2 – Acquired	Evolution of a generalized acquired immunity
EIM3 – Strategy	Evolution of a generalized immune response strategy

Table 3 - Summary of genetic specificity mechanisms

EIM1 – Evolved Innate Immunity

Although the series of adaptive models is primarily concerned with the acquired immune system, evolution also facilitates the acquiring of an innate immunity. Innate immunity may be thought of as hard-wired defence mechanisms that are learned in response to pathogens within a species over generational time. A simple example is a static recognition and response rule system for a host, which although remains fixed for the lifetime of a single host, evolves to protect the whole species. In this example, the rule system is fast acting on the lifetime scale, although slow to change on the same scale implying perhaps the increased expendability of individuals for the greater good of the species.

EIM2 – Evolved Acquired Immunity

The acquired immune system, although is a somatic learning system rapidly adapting to the hosts pathogenic environment, may also acquire more generalized species level traits via evolution. Evolution may be used to evolve the acquired immune system by biasing the creation of naïve lymphocytes to specific sub-areas of the shape space. This bias may accelerate the acquisition of immunity by individuals, requiring less work by the somatic learning system.

EIM3 – Evolved Response Strategy

The response characteristics of an immune system, such as the timing, strength, and specificity, may be considered a general response strategy. A general defensive response strategy may be evolved for a

species, specialised to the pathogenic environment of the population.

Timing: The speed of the response, such as how quickly the clonal selection and affinity maturation processes occur. They may be fast, triggered as soon as a pathogen enters the system, or slow, allowing the pathogen to linger for a time within the host.
Strength: The strength of the response such as the amount proliferation that occurs, or the number of effectors recruited to the task. High strength may involve a large reallocation of resources for a given response, whereas a low strength may allocate a minimum of resources.
Specificity: The specificity of the response such as the initial affinity of lymphocytes, or the threshold affinity of maturated lymphocytes for the triggering pathogen.

Figure 6 - General characteristics of an immune response strategy

The evolution of the response strategy may involve the generalized refinement any number of parameters responsible for influencing the clonal selection and affinity maturation required of acquiring immunity.

VI. Pathogen Models

An aspect of the series of the acquired immunity inspired adaptive models that has been neglected is the pathogenic environment. In [1] the principle component 'clonal matching' (operator O1) indicated the existence of antigen as stimuli for the immune response, and that there may be a many-to-many relationship between antigen and lymphocytes. Brownlee elaborated on the cellular components in the framework in [2], highlighting the antigen as one such component (cellular component CC1). Antigen is very general, describing anything that may elicit an immune response. In using pathogen to describe stimulation of the system facilitates conceptualisations external ecosystems and adversarial relationships, such as parasite-host.

Without pathogens, the acquired immune system (as described in this series of models) has no function. Selection III demonstrated that the exposure of systems to pathogen may be controlled (EIM2) by an external agent, although the natural case is for exposure to be uncontrolled (EIM1), defined by environmental factors. This section elaborates the antigen cellular component in a series of pathogenic mechanisms. These mechanisms are numbered PM#, and are summarised in Table 4.

Pathogen Model	Summary
PM1 – Environment	A pathogenic environment
PM2 – Static	Pathogen does not change
PM3 – Diverse	Minor variations in pathogen virulence
PM4 – Evolvable	Virulence of pathogen evolves over time
PM5 – Transmissible	Pathogen spreads from host-to-host

Table 4 - Summary of pathogen models

PM1 – Pathogenic Environment

Virulence describes the disease causing characteristics of a pathogen within a host. If a pathogen is of high-virulence it may infect and kill the host before it can be transmitted to other hosts. If a pathogen is not virulent enough it may be out-competed by other pathogens within the host. A simplified model of pathogen virulence is to describe pathogen as existing within shape space. Different distinct pathogens exist within different regions of shape space, and the aggregation of all possible pathogens represents the pathogenic environment in which host immune systems are situated. Given a spatial representation of a population of immune systems, a given pathogen may be considered to have an attack distribution with regard to space and time. This is simply a re-phrasing of the exposure patterns from the host perspective described in EIM1.

The characteristics of a pathogenic environment are as follows:

1. What pathogens are in the environment?
2. For a given pathogen:
    a. How does it select hosts to infect?
    b. When does it infect?
    c. For how long does the infection last?
    d. Does the pathogen change?

The characteristics of a given pathogen may be aggregated to describe a pathogenic strategy. The strategy may be static or may evolve with time, providing an adversary for a population of immune systems.

PM2 – Static Pathogen

A pathogen may be represented a single static coordinate in shape space. This type of pathogen is inspired by a benign molecule that may elicit an immune response, although has no variability in its surface features. An immune system need only learn the static pathogen once to be immune.

PM3 – Diverse Pathogen

A diverse pathogen may be one coordinate from a set of coordinates in shape space that define a region of feasible pathogen instances. Although instances of the pathogen are different, the general characteristic may still be learned, perhaps at a greater expense of resources.

PM4 – Evolvable Pathogen

A pathogen may explicitly evolve or coevolve with the population of immune systems. Evolution may refine the strategy of the pathogen affecting virulence and transmissibility. An individual acquired immune system may be open to multiple infections by the same pathogen during its lifetime if the rate of evolution is sufficiently rapid. Such a pathogen may require tracking and ultimately evolved countermeasures by the host population, perhaps facilitating a host-parasite interaction.

PM5 – Transmittable Pathogen

A pathogen may jump from host-to-host using a number of mechanisms (vectors). Further, transmissibility may be influenced by any number of epidemic-based models such as density-dependence,

spatial models, and genetic-similarity models.

VII. Multiple Immune System Models

This section uses the elaborated mechanisms to specify a number of multiple immune system models. These model are by no means a complete list of the combinations of the mechanisms, rather they represent a reformulation of the previously defined MSM1-MSM3 models, as well a few natural-fit examples of how the mechanisms may be applied. To distinguish these models from the previously defined models they are numbered MISM#, see Table 5 for a summary.

Model	Summary
MISM1 – Population	Generational population of systems that is evolutionary neutral
MISM2 – Evolution	Evolved innate and acquired immunity strategies
MISM3 – Shared	Population with inherited and transplanted effectors
MISM4 – Evolution with Passive Immunity	Evolved immunity and inherited effectors
MISM5 – Evolution and Vaccination	Evolved immunity with artificial vaccination
MISM6 – Arms Race	Arms race between evolving pathogens and evolving immune systems

Table 5 - Summary of multiple immune system models

MISM1 – Population Model

This model is composed of a population on BM3 immune systems, each with a finite lifetime. After the expenditure or death of a model, a new model spawned to take its place in an evolutionary neutral generational process. Models are exposed to a pathogenic environment (PM1), with an uncontrolled exposure regime (EIM1). The random base repertoire and ongoing random naïve lymphocytes results in a population of distinct immune system models that autonomously respond to the pathogenic environment although do not share (explicitly or implicitly) any acquired knowledge. This model provides a baseline for population immune system models.

MISM2 – Evolution Model

This is an extension of the population model (MISM1) although evolution is employed. Each immune system in the population is an instance of BM3, although also has an innate immune system of a static recognition and response. Evolution operates upon the innate immune system (EIM1), the acquired immune system (EIM2), and the response strategy of the acquired immune system (EIM3). Models are exposed to a pathogenic environment (PM1), with an uncontrolled exposure regime (EIM1). This model is an elaboration of the original evolutionary multiple system model (MSM2).

MISM3 – Shared Model

This model is composed of a population of clonal selection models (BM3) and is an extension of the population model (MISM1) with an evolutionary neutral generational process. Acquired immune effectors are passed from parent system to child system using vertical sharing (SEI1), and effectors are transplanted between intra-generation population members using horizontal sharing (SEI2). Exposure to pathogens is uncontrolled (EIM1). This model represents aspects of a rephrased version of the vaccination multiple system model (MSM1).

MISM4 – Evolution with Passive Immunity

This model is an extension of the evolution model (MISM2), although in addition to the passing of genetic material from parents to children, there is also a vertical transfer of effectors (SEI1) in a process that simulates a natural genetic evolution with passive immunity. The pathogenic environment (PM1) consists of uncontrolled exposure (EIM1). This is a rephrasing of the evolution ontogenetic multiple systems model (MSM3).

MISM5 – Evolution with Vaccination

This model is an extension of the evolution model (MISM2), although in addition to the passing of genetic material from parents to children, there is also control over the pathogenic environment (EIM2) in the form of the administration of vaccines. Produced child immune systems are vaccinated shortly after creation with a series of vaccines for known pathogens. The pathogenic environment (PM1) consists of uncontrolled exposure (EIM1). This model represents a rephrasing of aspects of the vaccination multiple systems model (MSM1).

MISM6 – Arms Race

This model is an all-inclusive model that represents a combination of the evolution model (MISM2) and the sharing model (MISM3), as well as vaccinations (EIM2). In addition to the uncontrolled (EIM1) pathogen environment (PM1), there are adversarial pathogens that evolve (PM4) to counter the defences of immune systems in the population. The result of evolving immune systems and evolving pathogens provides a co-evolutionary struggle ('arms race') for survival between the species.

VIII. Future Work

This work has elaborated on previously defined multiple immune system models to provide a framework for designing adaptive models that represent any number of natural or artificial multiple immune system scenarios. The mechanisms of this framework described of high-level, hiding much of the specific model detail. These mechanisms require investigation as adaptive models in their own right before integration to the resultant series of multiple immune system models.

An interesting extension of this work is to re-phrase the movement characteristics of the lymphocytes recirculation models as strategies that may be subjected to generalisation and refinement by an evolutionary process. Evolutionary processes may also be used to refine the architectural aspects of the discrete repertoire models to adapt the recirculation of lymphocytes and optimize presentation of pathogens to effector systems.

Ultimately, much work remains (1) in realizing the series of adaptive models as algorithms, (2) investigating the realised algorithms as adaptive systems, and (3) consolidating the framework provided by the series of models and using it to phrase other works in the field of artificial immune systems.

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