A Decision-theoretic Model Of Selection Modulated Intra-host Antigenic Variation For Multi-strain Pathogens

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Abstract—A decision-theoretic approach to modeling the response of multi-strain pathogens to humoral defense is investigated in this paper. The reported theory of language-measure theoretic optimal control is used to compute the optimal response of the invading pathogen. The model is validated by comparison of simulation results with in-vivo observations and contrasted with prominent existing modeling approaches.

Index Terms—Antigenic Drift; Multi-strain Pathogens; Language Measure; Finite Markov Chains; Discrete Event Systems;

1. INTRODUCTION & MOTIVATION

Antigenic variation is a key mechanism by which several known pathogens elude the host immune defense and ensure persistent infection. A detailed classification of pathogens based on the pattern of antigenic variability has been reported in [7]. The five rough categories can be enumerated as follows:

• little intra-host variation, but extensive global variation that is stable in space and time (S. pneumoniae).
• little intra-host variation, but extensive global variation that exhibit spatio-temporal variation (N. meningitidis).
• little intra-host variation, and little variation in the global population at a single time, but rapid evolution over time on a scale of years (influenza A virus).
• extensive replacement of dominant types over time within a single host, with extensive and growing standing diversity in the global population (HIV-1).
• since little or no antigenic variability, naturally acquired immunity and vaccine induced immunity are universal or nearly so.

Pathogens in Category 3 present significant problems to the development of effective long-term vaccines. Influenza A is, in fact, capable of pandemic outbreaks via antigenic shifts to new sub-types in addition to drifting to new strains on a seasonal basis. Recent attempts on developing an universal vaccine for Influenza A that extend cross-protective immunity across subtypes by targeting the extra-cellular domain of the conserved M2 ion channel protein and the nucleoprotein (NP) has met with some success in mice [11]. The most challenging and yet unsolved problem is posed by pathogens in Category 4. Rapid intra-host micro-evolution combined with a large genotype space render the antigen-specific immune response practically ineffective proving almost always, fatal to the host. A number of theoretical models have been proposed over the recent past to elucidate the key dynamics of intra-host antigenic drift with the objective of obtaining valuable insights into the process. The interplay of antigenic mutation with the host immune system manifests as an immensely complex dynamical system making mathematical modeling non-trivial.

Considerable effort has been directed towards developing an acceptable simplification of the complex mechanism of surface antigenic mutation. A few relevant examples of the previously proposed models are:

• The infinite allele model: every mutation creates a new antigen [12]
• The stepping stone model: which is basically a nearest neighbor approach with a 1-D array as the antigenic space [4]
• Antigenic evolution on a 2-D spatial lattice [5]

The infinite allele model may not be portraying an accurate representation of the phenomena observed in vivo. Furthermore, some of the modeling assumptions are oversimplifications of observed facts. For example, [4] assumes that the antigen can transition to only two neighboring states with equal probability, which is too simplistic (as observed by the authors themselves) for actual pathogens such as HIV-1 and EAIV (Equine Infectious Anemia Virus). Even for a spatial 2D lattice based antigen spaces considered in the literature, the situation only slightly improves, allowing 8 transitions from any antigen. The problem is partially addressed by modeling antigens as binary strings in [13], but results in new complications: two variants which are equidistant from the current antigen must appear at the same time implying that the divergence from the initial infecting strain must increase monotonically; which is clearly not what is observed in vivo for EAIV infections [8]. A few key motivating observations for the analysis presented in the sequel can be enumerated as follows:

• The pattern of antigenic drift is not continuous but episodic indicating a discrete rather than continuous driving dynamics: both the substitution rate and the clonal diversity of the HIV population fluctuate over time since infection, associated with the fluctuation in total viral density in a host [14]. Furthermore, the evolution rate and clonal diversity are maximized in periods where viral density is expanding [4].
• Virulence is an important factor in the drifting mechanism which varies with pathogen types and individual hosts, [13] mention why their proposed model fails to apply to “slow” viruses. Observations in vivo [3] further indicate that HIV-1 progresses at different rates in different infected individuals as exemplified by the possible classification of hosts into two groups (rapid and slow humoral escape rates).
• Periodical appearance characterizing EAIV infection also suggests that the antigenic evolution in an infected horse might not be uniform in time and in antigen type space; indeed, the viral variante responsible for consecutive febrile episodes differ in several amino acid residues in the epitope but there is no detectable increase of viral density by the intermediate types.
• Selection modulation of the mutation dynamics is not explicitly considered in most of the reported literature. Models proposed in [13] and [5] assume a random drift defined by one or more differential equations while the B cells proliferate to neutralize the antigens. The traveling wave conclusion made in the cited works may, in fact, be an artifact of the chosen model (which directly leads to the discrete-space wave equation from which the authors derive the continuous counterpart) and possibly mis-represent the actual dynamics. In vivo observations suggest that the evolution is driven by the host immune response [3] and a random drift model may not be portraying an accurate
picture. A detailed discussion to this effect is given in [10] where the authors classify reported models to date into deterministic and stochastic approaches. Models in the former category neglect random drift while the ones in the latter category neglect selection. The authors go on to give an intermediate theory by setting up the Fokker-Plank equation and derive solutions for various parametric regimes. The conceptual basis of the model proposed in this paper is to follow a similar path; investigating the effect of selection modulation of antigenic drift. However, we will refrain from setting up stochastic differential equations and follow a distinct event-driven scheme that allows the pathogen to respond optimally to the selection pressure from the host immune response.

- The importance of the antigen space topology is identified in [6] where a sufficient set of properties of the phenotype space for Influenza A is identified which dictates the latter's peculiar evolution. The concluding remark in the mentioned paper on the necessity of uncovering the actual topology of Influenza strain space highlights a key point; suggesting that a fixed structure for the antigen space (e.g. 1D-array, 2-D lattice) is not sufficient and different pathogens have in fact characteristic strain space topologies which critically impact the antigenic variation.

Motivated by the above discussion, we assume a Erdős-Rényi random graph model of the antigen space. The 1-D array and 2-D lattices are specialized cases of the random graph structure which assumes random connectivity between the graph nodes modeling the individual antigens. This generalization makes the use of differential equations difficult for specification of the drift dynamics. Consequently we investigate a probabilistic discrete event formal approach [1][2] with the antigen modeled to respond optimally to the immune defense by modulating the antigen space topology. The details of the model are described in Section 2.

The organization of the rest of the paper is as follows. Section 2 describes the key formulation. The mathematical details are avoided wherever possible with the interested reader referred to [1], [2]. Section 3 presents results obtained via numerical simulation of the proposed model discusses comparisons with those reported in the literature. The paper is summarized and concluded in Section 4 with recommendations for future work.

2. THE MODEL SPECIFICS

The key objective of the analysis presented in the sequel is two-fold:

- Develop a generalized framework capable of handling the pathogen-specific topology of the antigenic space
- Explicitly take into account the selection pressure exerted by the immune defense on the drift phenomenon

To that effect, the antigenic space is modeled as a Erdős-Rényi random graph with graph vertices denoting the individual antigens and the connecting edges modeling the possible inter-strain mutations. Mathematically, a Erdős-Rényi random graph is defined as follows:

**Definition 2.1:** A Erdős-Rényi random graph \((Q, E)\) is a set of vertices or nodes \(V\) with a corresponding set of connecting edges \(E \subseteq Q \times Q\) such that the probability that an edge exists between any two given nodes is a pre-specified constant.

Literature on the use of random graphs in modeling biological networks is plentiful [REF]. The essential difference from array and lattice based modeling of the antigenic space is illustrated in Figure 1. It is important to note that the former models are (very) special cases of random graphs. For any such chosen structure of the antigen space, the mutation (or transition) probabilities are defined as follows:

**Definition 2.2:** For \(v_i \in V\), denote the outgoing edges from \(v_i\) as \(E(v_i)\). Denote the mutation probability via the edge \(e_j \in E(v_i)\) be denoted as \(\pi(v_i, e_j)\). Then we define:

\[
\forall e_j \in E(q_i), \quad \pi(q_i, e_j) = \begin{cases} 
\frac{1}{\text{CARD}(E(q_i))} & \text{if CARD}(E(q_i)) \neq 0 \\
0 & \text{Otherwise} 
\end{cases}
\]

Thus the mutation probability is defined to be uniform over the existing outgoing edges from any node of the model. We note that the above specification implies

\[
\forall q_i \in Q, \quad \sum_j \pi(q_i, e_j) = 1 
\]

**Remark 2.1:** The assumption of uniform distribution on the outgoing edges is not an intrinsic restriction on the model. It merely reflects the lack of knowledge of the actual distribution; for specific pathogens one can use a better estimate if sufficient immunological data to that effect is available.

Fig. 1. Different topologies of the antigenic space: (a) 1-D array, (b) 2-D lattice and (c) a random graph. Note the circles denote the graph nodes modeling the individual antigenic variants

Using random graphs to model the antigen space makes it difficult to set up approximate continuous domain differential equations to solve the problem. In particular, a random graph, in general, is not embeddable into a line or a plane, implying we will not get nice differential equations (e.g. the wave equation or the diffusion equation). Also keeping in mind that we want to model the role of the immune response as the driving dynamics more explicitly, we propose a discrete event systems based approach as described next.

First we note that the random graph structure along with the specification of the transition probability function \(\pi\) specifies a probabilistic finite state automaton (PFSA). The PFSA formalism is closely related to that of finite state Markov chains and, specifically, the evolution of state occupancy probability distribution can be elegantly specified in terms of the state transition probability matrix which is defined next for the sake of completeness.

**Definition 2.3:** For two states or nodes \(q_i, q_j \in Q\), the transition probability \(\pi(q_i, q_j)\) is defined as follows:

\[
\pi(q_i, q_j) = \sum_{q_k \in \text{outgoing edges from } q_j} \pi(q_k, q_i)
\]

The state transition probability matrix \(\Pi\) is defined as \(\Pi_{ij} = \pi(q_i, q_j)\).

A formal definition of the state transition probability matrix is given in [1]. The occupancy probability evolution can now be stated as:

\[
\psi^{k+1} = \psi^k \Pi 
\]

where \(\psi^k\) is the state vector at the \(k^{th}\) observation instant. We note that \(\psi^0\) is a probability vector satisfying \(\sum_{k=0}^k \psi^k = 1\).

It follows that if \(\psi^0\) is the initial occupancy vector corresponding to the initial infecting strain, then the random dynamical evolution of the antigenic variants, in absence of any immune response can be specified as:

\[
\psi^{k+1} = \prod_{r=0}^{k} \psi^0 \Pi 
\]
To factor in the effect of the selection, we assume that the pathogen is capable of modulating the underlying graph topology as follows:

- Each edge can be disabled to a pre-specified degree (α in Figure 2) to prevent a particular mutation from occurring.
- Such disabling causes a self-loop to appear at the node at which the edge is disabled.

The concept is related to the notion of controllability of events encountered in the control theory of probabilistic discrete event systems [1] and is illustrated in Figure 2. The mathematical argument for the above specification is given in the [1]. We note that the self-loop is necessary to maintain the unity sum of the probabilities of the outgoing edges. The effect of selection can now be stated as follows:

Fig. 2. Probabilistic controllability of event transitions

which is the key modeling assumption of this paper:

The pathogen responds to selection pressure by disabling transitions to nodes with existing humoral immunity.

We consider the development of immunity at the various nodes as a function of the trajectory of the pathogen in the antigen space and, in general, some nodes have partial immunity at any iteration step, making the implementation of the above idea non-trivial. Before we make the concept more precise, we need to formalize the development of the host immune response. Referring to Figure 2, the parameter α ∈ [0, 1] specifies the degree to which the dynamics is driven by selection as opposed to random evolution. The two extreme cases are α = 0 implying perfect response to selection and α = 1 implying a perfectly random case where the graph topology remains unchanged. The immune response on the other hand develops due to pathogenic activity and hence we must specify how to "close the loop".

A. The Immune Response

We assume the host immune response can be attributed as two distinct causes: generation of B-plasma lymphocytes directly by activation of naive B cells and via the response from existing B-memory cells. We treat the two causes separately as follows:

Let $y_{R}^{[k]}$ denote the distribution of B-plasma lymphocytes at the $k^{th}$ iteration which is generated without taking into consideration the effect of memory. Simplifying the activation process, we can write:

$$y_{R}^{[k]} = \mathbf{y}^{[k-1]}$$

where $R$ is the response delay in number of iteration steps. The neutralizing effect due to memory is captured as follows:

Let $y_{imm}^{[k]}$ denote the distribution of B-plasma lymphocytes at the $k^{th}$ iteration step generated via humoral memory. Then we can write:

$$y_{imm}^{[k]} = \mathbf{X} \mathbf{y}^{[k]}$$

where $\mathbf{X}$ is the cross-immunity coefficient matrix, i.e., the immunity to antigen type $j$ from immunity at antigen type $i$ is proportional to the sum of all weighted paths from node $i$ to node $j$ (the weights being the mutation probabilities). It follows that

$$X = \omega \times \left( \mathbf{I} + \Pi_0 + \Pi_0^2 + \cdots \right) = \omega [\mathbf{I} - \Pi_0]^{-1}$$

where $\Pi_0$ is the initial transition probability matrix. However, this leads to the mathematical problem that $[\mathbf{I} - \Pi_0]$ is guaranteed to be singular. Hence, we use the renormalized form to alleviate the singularity [1]:

$$X = \lim_{\theta \rightarrow 0^+} \omega [\mathbf{I} - (1 - \theta)\Pi_0]^{-1}$$

Note $\omega \in [0, 1]$ is the proportionality constant with $\omega = 0$ implying zero cross-immunity. Also note that the initial transition probability matrix is used since there is no reason to assume that cross-immunity is affected by selection.

B. Neutralization

In the above discussion we have specified the evolution of the B cell distribution over the antigen space and have not discussed stoichiometric considerations regarding neutralization. We use the following neutralization model where $L^{[k]}$ is the pathogen density (load) at iteration step $k$:

$$h = \mathbf{y}^{[k]} - \Delta h\mathbf{y}_{mem}^{[k]} = (1 + \Delta h) \left( \frac{1}{\Delta k} \right) y_{mem}^{[k]}$$
where $\Delta_0$ is related to the initial B-cell affinity, $\Delta_0$ corresponds to pathogen clearing rate and $\Delta_0$ is the per capita growth rate of the pathogen. We note that for fully developed humoral memory, $y_{mem}^{[k]} = \varphi^{[k]}$ implying that the pathogen density will fall at a rate bounded below by $\Delta_0$. The effects of affinity maturation and B-cell diffusion can be factored in by considering more complex models of neutralization, which we will refrain from doing in this paper.

C. Optimal Response to Selection Pressure

As mentioned before, the key idea of this paper is to investigate the situation in which the pathogen modulates the topology of the antigen space by selectively disabling connecting edges between the nodes or states. This amounts to altering the mutation probability between the antigen types and requires the notion of "good" and "bad" states from the perspective of the pathogen. A "bad" state or antigen variant is one for which humoral immunity is high. Thus development of memory and generation of B lymphocytes results in selection pressure which is modeled by characteristic weights on the nodes of the underlying graph topology, i.e., on the states of the probabilistic finite state machine. A positive characteristic weight on a particular node reflects the fact that it is a relatively "good" state; a negative weight reflects a bad state. The characteristic weight vector is specified at each iteration step $k$ as follows:

$$\chi^{[k]} = \varphi^{[k-1]} - y^{[k-1]} - y_{mem}^{[k]} - m^{[k-1]}$$

The first term $\varphi^{[k-1]}$ denotes the fact that it is bad for the pathogen to wander around unnecessarily; which would result in the development of humoral memory resulting in rapid extinction. The next two terms denote that states or nodes with active response are bad. The last term denotes that the states at which memory exists are bad with $m$ being a constant model parameter. The definition of $\chi^{[k]}$ completes the specification of the model as a PFSSA with controllable transitions and a state characteristic weights and can be optimized using the language-measure-theoretic optimization technique reported in [2]. It is important to discuss why this optimization is necessary with respect to the problem at hand. Given a particular set of characteristic weights, i.e., a representation of the current selection pressure, we wish to compute the smallest set of alterations required in the underlying graph such that the pathogen population can visit the "good" states most often while minimizing visits to the "bad" states in a probabilistic sense. This is also intuitively true from a thermodynamic perspective since a system under external perturbation will always attempt to reach the most favorable configuration with the least effort. Statistically, this can be stated as to require that the expected value of $\chi^{[k]}$ is to be maximized while number of edge disablings are to be simultaneously minimized resulting in an optimization problem.

Maximize : $$E(\chi^{[k]}) = \varphi^{[k+1]} \chi^{[k]}$$

Minimize : Number of edge disablings

Now, it so happens that this is precisely the problem that is solved in [2]. Hence in each iteration step, we can compute the optimal alteration of the underlying topology using the procedure described in [2]. The formal language theoretic optimization allows one to compute the altered graph connectivity; we still have to figure out how the antigen distribution is affected. This is closely related to the computation of stable distributions of finite state Markov chains which we discuss next.

As mentioned earlier, a given graph with specified state transition probabilities defines a finite state Markov chain as well and the stable distribution over the model states can be computed as follows:

Irreducible Chains : $$\varphi_{stable} = \varphi_{init} \lim_{k \to \infty} \Pi^{[k]}$$

Reducible Chains : $$\varphi_{stable} = \varphi_{init} \lim_{k \to \infty} \frac{1}{j} \sum_{j=0}^{\infty} \Pi^{[k]}$$

It is well known that for irreducible Markov chains, the stable distribution is independent of the initial distribution with $\lim_{k \to \infty} \Pi^{[k]}$ guaranteed to be a rank 1 matrix with identical rows while for reducible chains the final stable distribution is a linear function of the initial distribution. A critical question is whether the pathogen can actually achieve the stable distribution over the antigenic variants after computation of the optimal model alteration at each iteration step. We assume that the stable distribution is only approached, but not necessarily reached:

$$\varphi^{[k+1]} = \varphi^{[k]} (1 - \Pi^{[k]}) S$$

where $S$ is a model parameter which determines to what degree the stable distribution is achieved. Note if $S$ is very large, the distribution is stable for irreducible Markov chains. We summarize the complete computational procedure described in the preceding subsections in Algorithm 1.

The relevant model parameters used is tabulated with brief descriptions in Table I.

```
begin
input : $P$, $X$
output: $\beta^*$
1 begin
2 k = 1;
3 stop = false;
4 while stop == false do
5 Update $\chi^{[k]}$;
6 Compute optimally altered $\Pi^{[k]}$;
7 Compute pathogen distribution $\varphi^{[k]} = \varphi^{[k-1]} (1 - \Pi^{[k]}) S$;
8 Update $y_{mem}^{[k]}$;
9 Update $y^{[k]}$;
10 Compute pathogen distribution after neutralization;
11 Compute pathogen load $L^{[k]}$;
12 if $L^{[k]} < L_0$ then
13  stop = true ;
14 else
15   k = k + 1;
end
```

Algorithm 1: Model Iteration

3. DISCUSSION OF RESULTS FROM NUMERICAL SIMULATION

The first task in this section is to validate the model described in Section 2. To that effect we consider a 100-state antigen space laid out as a random graph with 100 nodes. The chosen model is illustrated in Figure 4. Pathogens encountered in reality may have significantly larger antigen spaces; however we choose a smaller case for simplified exposition. The variation of the pathogen density (load) is encountered in reality may have significantly larger antigen spaces; however we choose a smaller case for simplified exposition. The variation of the pathogen density (load) is plotted in Figure 5 for some chosen values of the model parameters. The pertinent observations are as follows:

- The top plate of Figure 5 shows recurring peaks in the load over the total infection time. This reflects the in vivo observation in EAIV infections as noted in [4]. The host infected by EIAV experiences repeated fevers with roughly
periodical intervals, but the viral density and antigenic diversity do not differ markedly between peaks. More detailed observations of the antigen type that is responsible for each febrile episode showed that two different mutants equally distant from the original type could cause two peaks of viral densities at quite different times [8]. The simulated results in Figure 5 strongly supports this observation.

- The bottom plate shows the load data on logarithmic scale. The initial sharp rise up to the point “A” corresponds to the period before the initial immune response is triggered; the length of which is equal to the response delay R. The load variation continues to increase with a reduced gradient and finally plateaus off. This again corresponds to the load variation predicted by previously reported models [4][3]. The infection eventually subsides due to the finiteness of the antigen space as immunity develops over time. The circled areas in the figure correspond to short time plateauing which may relate to incubation periods observed in vivo in several pathogens. Extensive simulation confirmed the incubation period to be a function of the model parameters chosen.

More detailed simulation results are shown in Figures 6, 7, 8 and 9. Figure 6 shows the variation of the pathogen load with infection time as the response delay increases. The load values are on logarithmic scale. We note that the isolines corresponding to the load confirm the intuitive result that peak loads increase with increasing response time R. The infection time also increases with increasing R. The cross-immunity coefficient \( \omega \) was kept constant at 0.0001 for all the simulation runs plotted in Figure 6. Figure 7 demonstrates the variation of load and infection time for increasing cross-immunity with the response delay kept constant at R = 15. We note that peak load and total infection time falls, as expected, with increasing cross-immunity.

We further note that the peak load is encountered earlier if the the cross-immunity is high. Figure 8 shows the interdependence of the various model parameters. We note that peak load exponentially increases with increasing response delay (follows from the linear increase on logarithmic scale in Figure 8(a)), while infection time increases linearly with significant fluctuations over the range of delays simulated (See Figure 8(b)). With increasing cross-immunity, the peak load encountered falls sharply at first and significantly slowly later as shown in Figure 8(c). This strongly suggests the existence of a threshold which defines a shift in the system response. A similar conclusion was drawn in [4]. This shift in behavior is corroborated by the variation of infection time with increasing cross-immunity (figure 8(d)) showing that the infection time varies very little over the mentioned threshold.

![Figure 4](image-url)  
**Figure 4.** Random Graph of the antigen space used for generating validation results.

![Figure 5](image-url)  
**Figure 5.** Profile of viral load variation with infection time. The top plate shows actual viral load \( \times 10^6 \) particles per unit blood volume; the bottom plate shows the same data in logarithmic scale.

![Figure 6](image-url)  
**Figure 6.** Contour plot showing variation of viral load with increasing Response Delay Vs Infection time. Viral load data is on logarithmic scale.

**The effect of cross-immunity was studied by Haraguchi and Sasaki in a series of papers [12], [4], [13]. The modeling approach proposed in this paper addresses the following simplifying assumptions of the Haraguchi-Sasaki model:**

- The mortality of B cells is ignored, thereby preventing the reappearance of the same antigen type of viruses.
- It is assumed that the antigen type can be indexed in one-dimensional space. In other words, we assume that a pathogen antigen type has only two ways to evade the immune defense. This assumption seems to be too restrictive to apply to the antigenic drift of viruses including HIV,
ELAV and influenza. The model proposed in this paper is significantly more general due to the assumption of Erdős-Rényi random graph connectivity of the antigen space.

- Haraguchi et al. assumes that a single mutation can change the type of antigen only to one of the nearest neighbors; again the proposed model is more general allowing long range interaction between graph nodes.
- The Haraguchi model is applicable for the viruses that cause acute infections, since they seem to contradict to observations on the way slow viruses change their antigen types in a host, e.g., the ELAV case where two different mutants equally distant from the original type could cause two peaks of viral densities at quite different times, is hard to explain by this model. The simulated results shown in Figure 6, however, exhibits this particular characteristic.

4. SUMMARY & FUTURE WORK

We propose a decision-theoretic approach to modeling the response of multi-strain pathogens to humoral defense. The reported theory of language-measure theoretic optimal control is used to compute the optimal response of the invading pathogen. The model is validated by comparison of simulation results with in-vivo observations and contrasted with existing modeling approaches.

Further study needs to be conducted and the model needs to be refined with actual data from known pathogens. Future work will address the issue of very large antigenic space often observed in practice (e.g. HIV) which increases the complexity of the problem. Furthermore, the application of this modeling approach to design optimal drug therapies will be a key area of future research.

REFERENCES