Sufficiency Verification of HIV-1 Pathogenesis Based on Multi-Agent Simulation

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ABSTRACT

Researchers of HIV-1 are today, still unable to determine exactly the biological mechanisms that cause AIDS. Various mechanisms have been hypothesized and their existences have been experimentally verified, but whether they are sufficient to account for the observed disease progression is still in question. To better understand the phenomena, HIV-1 researchers turn to scientific models for hypothesis verification. Modeling methods which rely on differential calculus to describe population dynamics, can be inconvenient for predicting nonuniform interactions on a spatial dimension. Multi-Agent (or MA) modeling approaches, on the other hand, views the immune system as a hierarchical structure of cooperating and competing agents, operating with highly coupled behaviours to exhibit emergent complexity. We adopt the latter approach to simulate the pathogenesis of HIV-1. We show the model design and the emergent results for four well-known hypotheses: Direct Effect on CD4+ cells, Rapid Viral Mutation, Syncytium Formation, and Filling of CD4+ Receptor sites under the influence of a null model for an adaptive response to HIV-1. We give the logical basis for our methodology and clarify the semantics for 'model accuracy'. Preliminary simulation results indicate that AIDS is more likely to be caused by either Rapid Viral Mutation or Syncytium Formation.

Categories and Subject Descriptors

I.6.0 [**Simulation and Modeling**]: General; J.3 [**Life and Medical Sciences**] - *biology and genetics*.

General Terms

Design, Experimentation, Theory, Verification.

Keywords

HIV-1, AIDS, immune systems modeling, multi-agent simulation, hypothesis verification.

1. INTRODUCTION

It is a widely accepted fact that HIV-1 causes AIDS, a condition in which the normal human immune system becomes suppressed, rendering the affected individual unable to fight serious or fatal infections. Infection by HIV-1 has many unusual quantitative features. An example is the average 10-year lag from the start of infection till HIV-1 totally dominates the immune system. However, despite years of effort in clinical and laboratory experiments, researchers of HIV-1 are still unable to agree on the explicit causes that result in AIDS [10]. Various mechanisms have been hypothesized and their existences have been experimentally verified, but whether they are sufficient to account for the observed disease progression is unknown. In order to understand the phenomena better, HIV-1 researchers turn to the construction of scientific models to verify these hypotheses.

One of the earlier approaches of HIV-1 modeling uses ordinary differential equation (or ODE) models [19]. For low levels of granularity, they can be inexpensive to construct and allow the prediction of macroscopic dynamics in time dimension. However, to increase model granularity to cover spatial and topological dimension that may contain crucial information with regards to realistic disease progression [26], partial differential equations (PDEs) are usually required. These inadequacies of traditional models to prescriptively elucidate the workings of complex interdependent systems have prompted research in multi-agent based complex adaptive models [7]. The latter approaches conveniently enable the modeling of different entity types through the specification of interaction rules between agents and their environment. By modeling the immune system at cell and molecule level, we analyze in detail each of the four hypotheses [10][25]; namely, Direct Effect on CD4+ cells, Rapid Viral Mutation, Syncytium Formation and Filling of CD4+ Receptor Sites, under the influence of a null model for an adaptive response to HIV-1. Through these experiments, we aim to establish the probable sufficiency of these hypotheses towards the causation of AIDS, individually or in combination.

This paper is organized as follows. Section 2 briefly introduces the human immune system, HIV-1 pathogenesis and the four hypotheses that have been proposed in literature. In Section 3, we review a basic mathematical model of HIV pathogenesis and discuss necessary assumptions for its mathematical tractability. Section 4 describes the design of a CAFISS [9] -based null model for an adaptive immune system and the specific changes for modeling the four abovementioned hypotheses; their MA simulation results are presented in Section 5. Section 6 presents the logical basis for our methodology and clarifies the semantics of 'model accuracy' as specific types of improvements. Section 7 concludes and summarizes our results for future directions.

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2. IMMUNE SYSTEM AND HIV-1

2.1 Immune System Basics

The human immune system can mount a highly specific response against virtually any foreign substance, even those never seen before in the course of evolution. It is able to do so primarily because of cells known as lymphocytes [25]. Lymphocytes are divided into two main classes: B cells that are produced and mature from the bone marrow and T cells that are produced from the bone marrow but travel to and mature in the thymus glands. Cytotoxic or killer T lymphocytes (or CTL) and helper T cells (or T_H) are two important kinds of T cells. Each individual lymphocyte is specific to a particular antigen. This specificity results from the fact that each lymphocyte possesses various probes on its surface, known as receptors, all of which are specific to a particular antigen. Cells maintain contact with each other through surface contact and molecule secretion. When a T cell encounters a target cell, its receptors examine the fragments on the target cell surface. The T cell does not directly recognize a soluble antigen, but the antigen displayed on the surface of an antigen-presenting cell (or APC), e.g., a B cell or a dendritic cell. From the fragments the T cell is able to determine whether the cell is self or non-self. The following is a brief introduction to the functions of some important types of immune cells from a biological perspective [8] but at a level of granularity particular to the models we have constructed in CAFISS.

Helper T Cells (T_H). T_H cells have receptors on their surface for recognition of antigens. The T_H cell is activated when their receptors bind to the antigen presented on an APC. It secretes a variety of stimulatory molecules to activate other immune system cells, for example B cells. T_H cells are also known as CD4+ cells or T4 cells, as they have CD4 molecules on its surface. **Cytotoxic T Lymphocytes (CTL).** CTL cells can kill infected cells upon activation and recognition of antigens on infected cells' surface. **B Cells (B).** B cells have receptors for free antigens. Upon activation by T_H cells, they produce a large amount of specific antibodies, which are the soluble forms of the B cell receptors. **Antibodies (AB).** Antibodies are molecules secreted by B cells. The antibodies are specific to a particular type of antigen (which they are able to match). They bind to the matched free antigens, neutralize the antigen and serve a marker for macrophages (which then perform phagocytosis).

2.2 HIV-1 Pathogenesis: Observations and Hypotheses

Acquired Immune Deficiency Syndrome (or AIDS) is characterized by a combination of opportunistic infections and a markedly reduced circulating helper T_H cell count [21]. That the Human Immunodeficiency Virus (or HIV) is the cause of AIDS has been widely accepted. There are two types of HIV: HIV-1 and HIV-2. Both replicate in T_H cells and are regarded as pathogenic in infected persons although the actual immune deficiency may be less severe in HIV-2 infected individuals [22]. In this paper, we shall refer to HIV-1 as simply HIV. The progression of HIV infection towards AIDS typically follows three phases [15][19], as shown in Figure 1. They are briefly:

1. **Acute Phase**: Within several weeks after infection, there is an early phase with acute symptoms, extensive viremia, and large number of infected helper T cells in blood. With the onset of HIV-specific antibodies and cytotoxic T cells, the amount of virus sharply declines by a factor of 100 or more.
2. **Chronic (Asymptomatic) Phase**: The viral load remains at a relatively low but constant level, while helper T cell count slowly decreases. This period has been known to last for up to 12 years.
3. **Final stage – AIDS**: A normal helper T cell count is 600/µl – 1400/µl. When this concentration falls below 200/µl, it is characterized as AIDS [20]. At this stage the viral load rises exponentially and the immune system collapses, resulting in immunodeficiency and inevitable death.

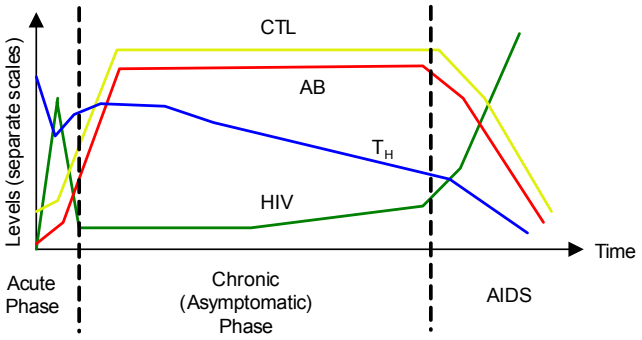

Figure 1. Progression of HIV towards AIDS [15]

Various mechanisms have been hypothesized to explain the HIV infection dynamics. We concentrate on four of them; namely, Direct Effect on CD4+ cell [14], Rapid Viral Mutation [15], Syncytium Formation [23] and Filling of CD4+ Receptor sites [25]. These hypotheses are chosen because of the extensive research and wide acceptance by HIV-1 researchers.

Direct Effect on CD4+ Cell: In the period 1983-1984, Montagnier and Gallo advocated that HIV had a direct cytopathic effect on CD4+ cells [14]. They believed then that HIV could infect and destroy the T_H cell, which in turn causes the immune system to lose its immune function when the T_H cell population level becomes too low.

Rapid Viral Mutation: The immune cells are able to attack the virus only upon recognition [15]. As HIV replication is error prone during reverse transcription which results in mutant strains, the immune system is put at disadvantage since it needs to detect each mutant strain before it is able to activate the specific antibodies. It is postulated that mutation reduces the chance of virus detection and hence allows HIV to persist.

Syncytium Formation: The formation of syncytium involves the fusion of the cell membrane of an infected T_H cell with an uninfected T_H cell [23]. Mature HIV envelope glycoprotein (gp120/gp41) expressed at the surface of infected cells drives cell-to-cell fusion with adjacent uninfected T_H cells [5], which results in formation of multinucleated syncytia. After several rounds of fusion, syncytium attains volumes equivalent to several dozens or hundreds of individual cells. Cell apoptosis (i.e., cell is programmed to death) is then triggered, which contributes to the global loss of T cells.

Filling CD4+ Receptor Sites: HIV can attack CD4+ receptors in at least two ways [25]. First, HIV can attach, via its gp160 "spikes" to CD4+ receptor sites. Second, HIV is capable of releasing or freeing its exterior gp120 envelope glycoprotein, thereby generating a molecule that can actively bind to CD4-bearing cells. T_H cell loses its immune function as a result of receptor site

filling; hence the T_H cells do not have to be infected with HIV to lose their immune function.

There exist experimental evidences that support the existence of the above hypothesized mechanisms, but the *sufficiency* of these hypotheses needs to be further studied, that is, whether the hypothesis alone, or a combination of them, is sufficient to cause the clinical observation as shown in Figure 1 (we will examine the validity of this proposed argument in Section 6). For example, Gallo later admitted that the Direct Effect on CD4+ Cell hypothesis might be too simplistic [10][11] in that very few T_H cells (in the order of 1% [2]) are actually infected versus a T_H cell recovery rate of 5% every two days, indicating that the hypothesis could be insufficient. This reasoning process exemplifies how hypothesis sufficiency could be verified through simple quantitative comparisons. With an explicitly constructed computational model, we can further quantitatively study many types of entities and interactions simultaneously, which would be too complex for simple rationalization. Therefore modeling has great value in assisting in the verification of infection hypotheses. We next review mathematical model construction strategies.

3. REVIEW OF DYNAMICAL MODELS

ODE models have been widely used by researchers to describe immunological dynamics. An extensive survey [26] details the common steps used by researchers to construct ODE models, in summary they are:

1. *Determine the level of model granularity*. Not all types of cells and molecules will be present in the model. The selection reflects the model developers' understanding on what might be important.
2. *Assume causal or correlative relationships*. Identify the probable factors that increase or decrease the population sizes of the selected entities. For example, natural cell death and accelerated cell death due to infection are two different factors contributing to the decrease of population size.
3. *Formulate ODEs*. Each equation describes the change of entity population size with respect to time, which is usually a linear combination of the factors identified in Step 2. Since the factors are usually dependent on the population sizes of other entities, the final set of ODEs become tightly coupled.
4. *Model Analysis and Prediction*. Traditional ODE analysis techniques are applied, for example, the derivation of steady states and associated stability conditions. The analysis is accompanied with interpretations in the immunological context, based on which predictions will be made.

We exemplify this process (particularly Step 4) using a basic ODE model of HIV infection by Perelson [20], given in Eq. 1 to Eq. 3. This model involves three entity populations: healthy T cells (T), infected T cells (I) and HIV virions (V); each described by one differential equation. Healthy T cells are produced at a constant source rate of λ and perish at constant rate d per cell. These cells are susceptible to HIV infection at a rate of k per virion-cell encounter. The above factors constitute the right-hand side of Eq. 1. The infection increases the number of infected T cells, which perish at a rate of δ per cell, as shown in Eq. 2. New virions are produced from infected T cells at rate p per cell, and existing free virions are cleared at a rate of c per virion, as shown in Eq. 3. In terms of HIV pathogenesis hypothesis this model assumes only the Direct Infection Effect on CD4+ cell.

$$\frac{dT}{dt} = \lambda - dT - kVT \qquad \text{Eq. 1}$$

$$\frac{dI}{dt} = kVT - \delta I \qquad \text{Eq. 2}$$

$$\frac{dV}{dt} = pI - cV \qquad \text{Eq. 3}$$

where:

- T : Healthy T cell population size
- I : Infected T cell population size
- V : HIV virion population size
- λ : T cell production rate
- d : Per cell death rate of healthy T cell
- k : Infection rate (per virion-cell encounter)
- δ : Per cell death rate of infected T cell
- p : Virion production rate (per infected T cell)
- c : Virion clearance rate (per virion)

The analysis of ODE models can be analytical or numerical. Analytical techniques involve derivations of steady states, stability conditions [3], and threshold expression [16][17]. The parameter values are determined by curve-fitting to the clinical data using techniques such as nonlinear least-squares estimation [24]. Numerical analysis often includes simulation, where the transient dynamics can be observed. However, despite having convenient tools and robust languages for model construction and analysis, ODE models have several limitations [1][26][27], mainly due to the fact that model entities are treated at *population level*:

1. Assumption of *entity homogeneity*. For example, the basic ODE model given above classifies T cells into two states: healthy and infected. If we wish to increase the model granularity (so as to increase it's realism), more distinguishable states would be needed; such as T cells that are active or quiescent, naïve (just produced) or memory (has been activated before). This would mean dividing the cell population into more subpopulations, each of which is dedicated to one cell state, modeled by a single differential equation. Solving a system of coupled differential equations for as many cell types as there are in the human immune system alone, easily surpasses the capabilities of any modeling tool and its possible computational tractability. As a result, ODE models generally assume homogeneity of entity types so as to limit the number of computable states while compromising on the 'realism' of their predictions.
2. Assumption of *spatial and topological independence*. As only population level factors are considered, spatial (questions of positional effects) and topological (questions of positional responses) dependencies on individual interactions are ignored. The resulting equations imply that entity interactions are uniformly occurring at the same frequency at all places. We believe that this assumption is unjustifiable. As demonstrated in [12], models that explicitly take spatial non-uniformity into consideration can lead to drastically different simulation results.
3. Direct *design* of mathematical expression for macroscopic observables. For example, we can assume infection to be at a constant rate, at a time-dependent variable rate, at an entity-

population-size-dependent variable rate, or a combination of these. In fact, there is no uniquely correct way for such formulation (as is often qualified by researchers themselves). The key problem that underlies this lack of uniquely correct formulation is that macroscopic observables are actually *emergent* properties; they are *results* from microscopic interactions. A directly designed expression of macroscopic observables may approximate observed dynamics well but its results are only as good as the assumptions and mathematical relationships chosen *for* the model. They lack the provision to allow serendipitous discoveries through the causality of microscopic interactions.

Multi-Agent simulation models (or simply MA models) naturally solve the above problems by relaxing the above assumptions [13][18]. MA models treat cells and molecules as 'agents' and allow autonomous interactions in a virtual environment. Such a model explores the level of cell-to-cell and cell-to-molecule interactions, from which the macroscopic behaviors emerge. By doing so we avoid directly making intuition-driven assumptions on macroscopic properties.

4. MULTI-AGENT MODEL DESIGN

As a relatively new approach, MA models differ greatly from each other in both design and implementation. Our implementation is based on CAFISS [9], which differs from one of the early attempts in MA based immune system simulation by Grilo et al. [4] in the method of agent activation regime. In their approach [4], Grilo et al. advanced time by a constant interval, during which agent interactions were examined and carried out in a predefined sequence. In CAFISS, agents are implemented in a multi-threaded fashion; hence the sequence of interaction events is unpredictable. Such a design is intended to eliminate possible artifacts resulting from the implementation itself.

To design the CAFISS MA model, we begin by specifying the agent interaction rules; some of which are specific to the hypotheses, while others are common knowledge specific to the immune system. We first specify a *null model* as a common basis for modeling an adaptive immune response for all four HIV hypotheses. Each hypothesis will then imply a specific set of mechanisms added or parameter changes on the null model.

4.1 A Null HIV Infection Model

Figure 2 gives the individual agent ruleset for the null model. The rectangular boxes represent individual agents. The incoming arrow describes the conditions of the rule. If the condition is met, then the rule is fired, that is, the decision part of the rule is carried out, shown as outgoing arrows. Those outgoing arrows pointing back to the agent indicate that the agent state changes as a result of rule firing. For example, an infection event takes place in the following order. The first rule of HIV says that an HIV virion continuously sends out an "Infection Signal", which does not require any specific conditions to be met. The second rule of T_H says that if a T_H cell receives an "Infection Signal", it changes its own state to "infected", and sends out the "Successful Infection" signal. Upon receiving this signal, the HIV virion is in a situation that satisfies the condition of the third rule, so that the virion starts to reproduce itself. Other events, such as T_H cell activation, antibody secretion, and infected cell killing can be interpreted in a similar way. CAFISS uses a multi-swarm structure for the virtual space: a 'swarm' represents a *spatially localized neighborhood*, within which the above described signals are sent and received. As such, agent interaction topology is based on spatial proximity: they interact only when they are spatially close to each other.

Antigen matching is implemented as follows. Each HIV virion has a specific physical shape, which is computationally represented by a binary string. A T_H cell or B cell successfully detects the antigen only when its receptor (also implemented as a binary string) matches the physical shape of the HIV.

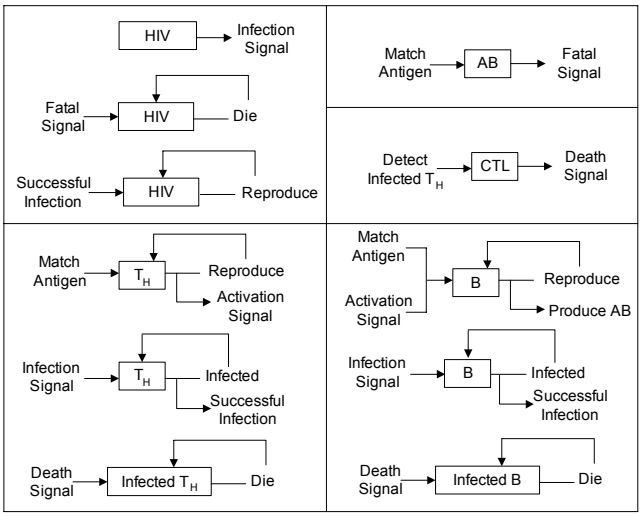

Figure 2. Agent Rules of our Null HIV Infection Model

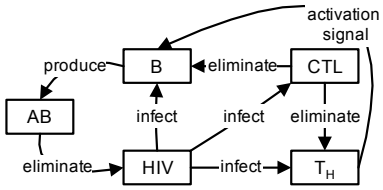

Figure 3. Schematic Diagram of the Null Model

Figure 3 is a simplified schematic representation of the null model, which contains only the key elements of the agent interaction network. It can be seen that the null model simply captures common knowledge about the adaptive immune system, for example, T_H cell sending activation signals, B cell producing antibodies, and humoral elimination of HIV virion; all of which have been described in Section 2.1.

Verification of hypothesis sufficiency means that we need to test whether the modelled mechanisms are sufficient to reproduce the population dynamics observed in Figure 1. A healthy individual has T_H cells measured at 1,000/μl, and the measure falls below 200/μl when AIDS is developed. In the simulation model, the initial population size of T_H cell is set to 100. If the cell count drops to less than 20, the immune system is considered weak and susceptible to opportunistic pathogenesis. Table 1 is a summary of the parameter settings for the null model, including the initial entity counts and production rates (per time unit). The parameters are verified through experimental simulations such that HIV infection appears weak in the face of immune response, and AIDS does not develop in the Final stage (see Section 5.1). As such, if a hypothesis is able to

reproduce the population dynamics similar to Figure 1, we can conclude that it is the part that differs from the null model that is responsible for the alteration in population dynamics. That is, the pathogenesis mechanism specific to the hypothesis indeed plays a vital role in disease progression. However, if a hypothesis fails to exhibit the AIDS-like dynamics, we suspect the sufficiency of this hypothesis in causing AIDS. While other parameter settings that could also give similar null model dynamics; for this preliminary study, we focus primarily on demonstrating the feasibility of MA-based hypothesis verification.

Table 1. Null Model Parameter Setting

Entity Type	T_H	HIV	B	AB	CTL
Initial Count	100	50	120	5	30
Production Rate	5	1*	4	10**	3

* reproduction rate only upon successful infection
** production rate per activated B cell

4.2 Modelling the Hypotheses

The four hypotheses are modelled based on the null model shown in Figure 3 and initialised according to values in Table 1. The differences arise from the addition of new agent rules, or the modification of parameters so that the hypothesis-specific mechanisms are reflected. Figure 4 schematically shows the agent interaction network of each hypothesis. The encircled portion of the diagram denotes the specific differences.

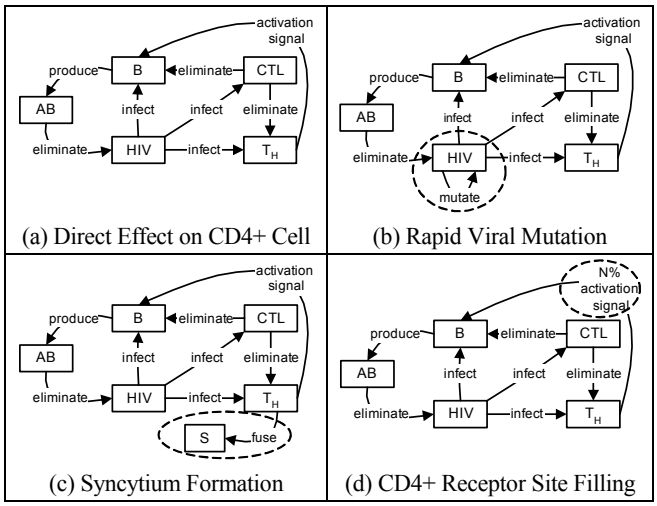

Figure 4. Schematics of Four HIV Pathogenesis Hypotheses

Direct Effect on CD4+ Cell (Figure 4(a)): This hypothesis is essentially the same as the null model in terms of agent rule specification. The difference is that we study this hypothesis under different cytopathic strengths. In particular, we test various settings of two parameters: 1) HIV replication rate and 2) initial HIV virion count, as these are two parameters that collectively reflect the cytopathic strength of HIV in the model.

Rapid Viral Mutation (Figure 4(b)): The mutation mechanism is added by altering the shape from time to time, computationally implemented by toggling a series of binary bits. As such, multiple strains of HIV can coexist in the environment. The antigen matching rules were described in Section 4.1

Syncytium Formation (Figure 4(c)): The additional syncytium formation event takes place when an infected T_H cell gets close to an uninfected T_H cell, or an uninfected T_H cell gets close to an existing syncytium and is conjoined to it.

Filling of CD4+ Receptor Sites (Figure 4(d)): The site filling of a T_H cell is modeled by reducing the activation signals from T_H cells to B cells. The reduction is implemented on a probabilistic basis, that is, only N% of the signals are received compared to the null model.

The abovementioned mechanisms occur within spatial proximities. For example, syncytium forms when an infected T_H cell gets close to an uninfected T_H cell. ODE models do not consider spatial and topological effects; with PDEs however, the dynamics can be specified with respect to x, y and z-axes in space in addition to the time dimension. This results in an increased number of coupled equations, making the model computationally more intensive.

5. EXPERIMENT RESULTS

5.1 Null Model Population Dynamics

The null model serves as a template for all four HIV infection hypotheses. Figure 5 shows the simulation result of the null model based on the agent rule specification in Figure 2 and Figure 3 and the parameter settings from Table 1. HIV is introduced into the system at t=0 with a count of 50. It is quickly eliminated with the fast production of antibodies. Similar patterns are observed for subsequent appearance of HIV (t=35, 53, 70, 90). HIV is controlled and AIDS does not develop.

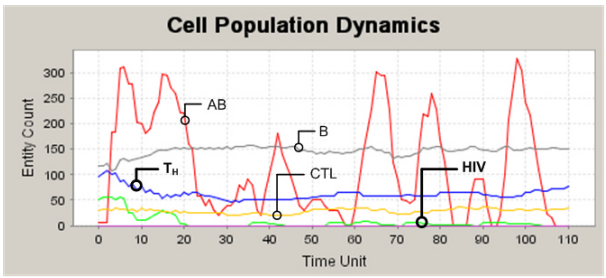

Figure 5. Simulation Result of Null HIV Infection Model

5.2 Direct Effect on CD4+ Cell

The Direct effect on CD4+ Cell hypothesis is investigated by increasing the initial HIV count and the replication rate of HIV. We first look at changes in the former while keeping the latter constant. Figure 6 shows the result of increasing the initial HIV count to 100, twice that of the null model. The resulting dynamics are not significantly different from the null model, that with the increase of antibody count, HIV count drops and remains low. The immune system, in particular the T_H cell count, is not observed to be significantly affected.

The result shown in Figure 7 uses the same setting as that of Figure 6, except that the HIV replication rate is increased to twice that in the null model. Larger scale of 'humps' are observed in HIV population dynamics but these are quickly suppressed by antibodies as can be seen from correlation between the dynamics of antibodies and HIV virions. These initial simulation results suggest that the Direct Effect on CD4+ hypothesis may not be sufficient to account

for the three-stage disease progression of HIV. It is found that when the HIV replication rate is set to 8 times that of the null model, the HIV count easily rises and turns out to be difficult for immune system to control, as shown in Figure 8. However, Figure 8 does not exhibit a 'proper' chronic stage, where HIV counts should remain low for a longer period of time. As a result, we suspect the sufficiency of the Direct Effect on CD4+ Cell hypothesis in explaining HIV's pathogenesis, based on non-correlating dynamical patterns.

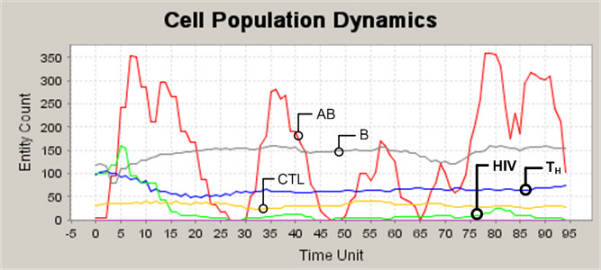

Figure 6. Direct Effect on CD4+ Cell Hypothesis Simulation Result (a): 2x Initial HIV Count

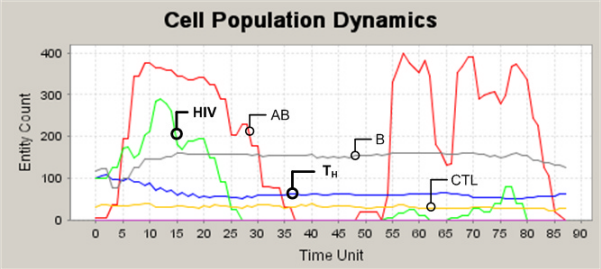

Figure 7. Direct Effect on CD4+ Cell Hypothesis Simulation Result (b): 2x Initial HIV Count & 2x HIV Reproduction Rate

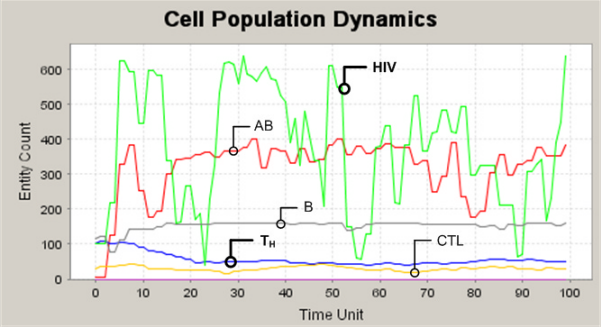

Figure 8. Direct Effect on CD4+ Cell Hypothesis Simulation Result (c): 2x Initial HIV Count & 8x HIV Reproduction Rate

5.3 Rapid Viral Mutation

Figure 9 shows the simulation results of the Rapid Viral Mutation hypothesis. It closely resembles a long chronic stage where the HIV virion count remains low for an extended period, and the Final stage where the HIV count increases exponentially while the T_H cell count drops below 20, indicating the onset of AIDS. Since the model only differs from the null model in its introduction of pattern recognition during antigen detection and virion mutation, it is concluded that these two changes are possible key mechanisms for the observed alteration in disease progression.

Figure 10 is another run where the antibody production rate is increased to 30 per B cell, 3 times that of the null model. Despite the high level of antibodies production, HIV still manages to overcome it, accompanied with T_H cell depletion; therefore the dynamics still correlate with observations in Figure 1.

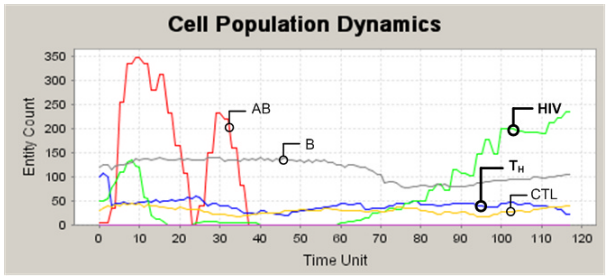

Figure 9. Rapid V. Mutation Hypothesis Simulation Result (a)

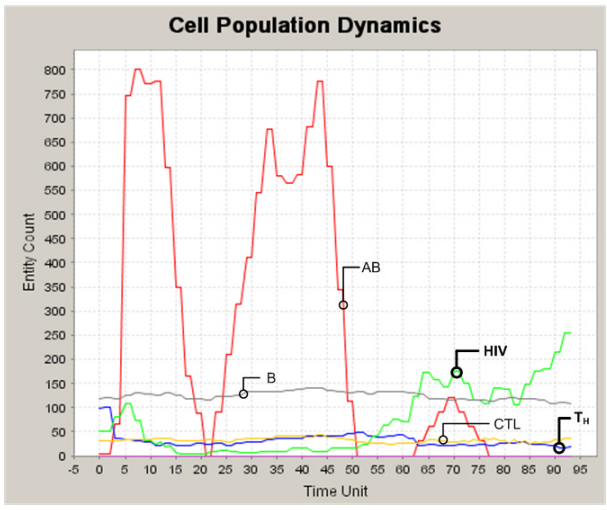

Figure 10. Rapid V. Mutation Hypothesis Simulation Result (b):3x Antibody Production Rate

5.4 Syncytium Formation

Figure 11 is the simulation results of the Syncytium Formation hypothesis.

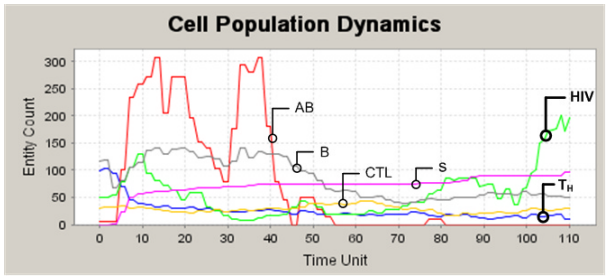

Figure 11. Syncytium Formation Hypothesis Simulation Result

At t=4, syncytium starts to form. Even though the population of syncytium in the system is not large, the dynamics have changed substantially. The HIV virion count decreases, but the syncytium count steadily increases. After a long chronic period, HIV finally starts to increase and T_H cells go depletion. Since the only difference between this model and the null model is the addition of a

syncytium formation mechanism, the final disease development should be attributed to this change, hence we postulate that Syncytium Formation plays an important role in HIV's pathogenesis.

5.5 Filling of CD4+ Receptor Sites

Filling of CD4+ Receptor Sites is implemented by blocking the activation signals sent from T_H cells to B cells on a probabilistic basis. Figure 12 is the simulation result when only 70% of the activation signals are received. The result does not differ significantly in that the HIV virion cannot recover after the initial elimination that occurred during the first 45 time units. The slight rises in virion count at t=55 and t=75 are quickly suppressed by a rise in antibody count.

We further investigate the effect of receptor sites filling by decreasing the activation signal to 30% of the original null model. Figure 13 shows the simulation result. The simulations under this setting consistently show relatively high peaks in virion count, the delay in antibody production in response to virion count rises, and this occasionally results in HIV outbreak. This hypothesis reasons that the activation signal from the T_H cell is an important because it activates B cells to produce the necessary antibodies to neutralize the virus. However, the results suggest that activation signal blocking only becomes a severe problem (i.e., enough to cause AIDS) when the proportion of sent activation signals drastically decrease. If laboratory experiments can show that a large part of the cell receptors are filled and are impeded in producing these activation signals, we can then conclude that this mechanism has a significant role in HIV-1 pathogenesis.

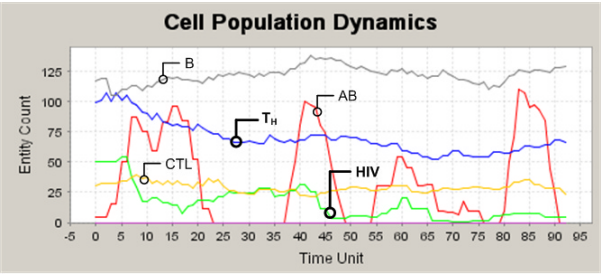

Figure 12. Filling CD4+ Receptor Sites Hypothesis Simulation Result (a): N% = 70%

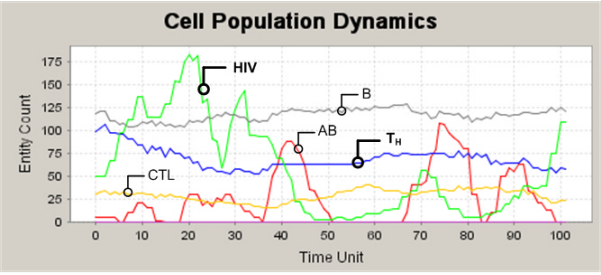

Figure 13. Filling CD4+ Receptor Sites Hypothesis Simulation Result (a): N% = 30%

6. THE LOGICAL BASIS FOR OUR WORK

We have demonstrated how various HIV pathogenesis hypotheses could be captured by MA model as localized agent rules and how the sufficiency of these hypotheses can be tested through MA simulation using CAFISS. We emphasize the need for an initial null model, which should clearly describe the mechanisms of an adaptive immune response known to be accurate. These mechanisms are functionally separate from those specific to the hypotheses. Currently the null model is only required to satisfy that AIDS does not develop, hence any significant alteration in disease progression dynamics can be attributed to the addition of hypothesis-specific mechanisms. This line of argument mirrors a logical proof based on contradiction. The null model represents the base assumptions that we have verified to be true. Additional assumptions in the form of the hypothesis are then added. Through proper deductive logic, *if* we are able to show that an inconsistent result is derived, then since our deductive process is valid, this must imply that the additional assumptions for the hypothesis must be false. *If* however, should we derive consistent results, then we can conclude that the additional assumptions were sufficient to predict viral pathogenesis at a certain level of accuracy. This level of accuracy can be improved by a) Increasing the null model granularity, b) Considering a combination of infection theories, and c) Changing model parameter values based on clinical data. The absolute measure of accuracy and relative improvements would have to be based on statistical regression against clinical data as is commonly done by ODE modelers. In the next subsection, we review some other possible improvements.

6.1 Improvements on Accuracy

There has been ongoing debate among researchers as to whether HIV is the cause of AIDS, or even whether HIV exists [6]. If we take this into consideration, then the present null model requires some redesign. We expect a good null model to be at a higher granularity so that hypothesis-specific elements (entities and mechanisms) can be easily integrated. For example, with antigen matching implemented, the addition of mutation mechanisms is natural and the interpretation becomes straightforward.

By comparing the simulation result against the biological pattern (Figure 1), particularly the dynamics of HIV and T_H cell population, we are able to examine each hypothesis that whether each of them is sufficient to explain the observed disease progression. Of the four, Rapid Viral Mutation and Syncytium Formation produce population dynamics that are consistent with clinical data. Hence we speculate they play more vital roles than the other two; namely, Direct Effect on CD4+ Cell and Filling of CD4+ Receptor Sites. This "null model plus hypothesis" framework of hypothesis verification can be further extended to combined hypotheses, for example, how they weigh in importance with respect to each other, and how they may correlate with each other. This constitutes one of the future extensions as alluded to in improvement (b) above.

Parameter values (improvement (c)) are crucial for both agent rules and overall simulation settings. There are various sources for justification of parameter settings, such as direct clinical data, simulated molecular biological data, and ODE-model-generated data, each requires careful investigations on how to utilize them properly in MA model parameter setting.

7. CONCLUSIONS

In this paper, we present a CAFISS-based Multi-Agent model to verify the sufficiency of four well-known HIV pathogenesis hypotheses that are reported to cause AIDS. We explicate the common processes of traditional ODE models and their inherent limitations that motivate the use of MA models. Our MA model design methodology and the preliminary simulation results are based

on a "null model plus hypothesis" framework of sufficiency verification. Such a methodology is shown to be based on the logic of contradiction proofs; directing us also towards how 'model accuracy' can have definite semantics. We show that among the four hypotheses, Rapid Viral Mutation and Syncytium Formation produce population dynamics that correlate with clinical data on HIV infection stages. The Direct Effect on CD4+ Cell hypothesis fails to exhibit these correlating patterns even under 8 times the infection levels present in the null model, while the result of Filling of CD4+ Receptor Sites hypothesis shows that the activation signals of T_H cells must be impeded up to 70% before similar dynamics can appear occasionally. We show that there is a logical and empirical basis for sufficiency verification of biological phenomena, and propose that more formalized hypothesis verification frameworks and treatments for improving accuracy be constructed so that computer-assisted hypothesis verification tools can become a reality in the near future.

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