A NOVEL TELECOMMUNICATIONS-BASED APPROACH TO MATHEMATICAL MODELING OF HIV INFECTION

Aaron T. Sharp

University of Nebraska-Lincoln, atsharp@unomaha.edu

Follow this and additional works at: https://digitalcommons.unl.edu/ceendiss

Part of the Biological Engineering Commons, Digital Communications and Networking Commons, and the Nanoscience and Nanotechnology Commons

https://digitalcommons.unl.edu/ceendiss/14

This Article is brought to you for free and open access by the Electrical & Computer Engineering, Department of at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Theses, Dissertations, & Student Research in Computer Electronics & Engineering by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.
A NOVEL TELECOMMUNICATIONS-BASED APPROACH TO MATHEMATICAL MODELING OF HIV INFECTION

by

Aaron T. Sharp

A THESIS

Presented to the Faculty of
The Graduate College at the University of Nebraska
In Partial Fulfilment of Requirements
For the Degree of Master of Science

Major: Telecommunications Engineering

Under the Supervision of Professor Tadeusz Wysocki

Lincoln, Nebraska
December, 2011
A NOVEL TELECOMMUNICATIONS-BASED APPROACH TO MATHEMATICAL MODELING OF HIV INFECTION

Aaron T. Sharp, M.S.
University of Nebraska, 2011

Adviser: Tadeusz Wysocki

It is well known that biological systems utilize communication in some form, one prolific example of this is the propagation of HIV (Human Immunodeficiency Virus) in the human body. By modeling HIV infection as a communication system, we hope to gain a unique insight into HIV and biological communication systems in general. Such a model would provide researchers a platform for experimenting and simulating various biological communication systems. We have previously developed a layered communication protocol for interpreting biological communication systems using telecommunications paradigms and will apply said model to HIV proliferation. We will also demonstrate the effectiveness of the model by formulating a telecommunications-based mathematical model, and by implementing a simulation of HIV infection based on direct interpretation of this layered protocol.
DEDICATION

I would like to thank my advisers Drs. Tadeusz and Beata Wysocki who have been the driving and creative force behind my work and my family Tim, Cindy, and Andrew for their continued unconditional support. Thank you.
Contents

List of Figures

1 Introduction

2 Motivation

3 Background

4 HIV Communication

5 HIV Mathematical Models
5.2.2 HIV Chemotherapy Treatment ......................... 20
5.2.3 Structured Treatment Interruptions ..................... 23
5.2.4 Antiretroviral Therapy for Low Viral Loads ............. 25
5.3 Parameter Estimation ........................................ 29
5.4 Micro Propagation .......................................... 30
  5.4.1 Standard Model ........................................ 30
  5.4.2 Delay Model .......................................... 31
  5.4.3 Combination Therapy and Delay ....................... 32
  5.4.4 HIV Dynamic Model .................................. 33

6 Telecommunications-based Mathematical Model ............... 43
  6.1 Queuing Networks .......................................... 43
    6.1.1 Exponential Distribution and Poisson Process ........ 44
    6.1.2 Basic Queue Model .................................. 45
    6.1.3 M/M/1 Queue ....................................... 47
    6.1.4 Networks of Queues ................................ 48
  6.2 Queuing Networks for Communication Systems ............ 50
    6.2.1 Bluetooth Queuing Model ............................. 50
    6.2.2 Ad Hoc WLAN Queuing Model ....................... 52
  6.3 HIV Queuing Theory Model ............................... 58
  6.4 Analysis of HIV model ................................... 61
  6.5 Simulation Model ......................................... 62
  6.6 Packet Arrival ........................................... 66
  6.7 Receiver Uptake .......................................... 67
  6.8 Forwarding ............................................. 68
  6.9 Packet and Receiver Shutdown ............................ 68
6.10 Virus Destruction .................................................. 68
6.11 Simulation Parameters .............................................. 69

7 Results ....................................................................... 70

8 Conclusion .................................................................. 74

Bibliography .................................................................. 75
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>HIV Infection Pathway</td>
<td>9</td>
</tr>
<tr>
<td>4.2</td>
<td>Layered Protocol for HIV Infection</td>
<td>13</td>
</tr>
<tr>
<td>5.1</td>
<td>Model of HIV disease progression in adults[18]</td>
<td>37</td>
</tr>
<tr>
<td>5.2</td>
<td>HIV prevalence of women attending public antenatal clinics[18]</td>
<td>38</td>
</tr>
<tr>
<td>5.3</td>
<td>Relationship between transmission probability per act and viral load[60]</td>
<td>38</td>
</tr>
<tr>
<td>5.4</td>
<td>Cumulative risk of HIV tranmission vs number of sexual exposures[60]</td>
<td>39</td>
</tr>
<tr>
<td>5.5</td>
<td>T cell count (A) and viral titer (B)[23]</td>
<td>39</td>
</tr>
<tr>
<td>5.6</td>
<td>Simulation of early infection scenario[2]</td>
<td>40</td>
</tr>
<tr>
<td>5.7</td>
<td>System Diagram of Model[59]</td>
<td>41</td>
</tr>
<tr>
<td>5.8</td>
<td>Model and Induction Therapy Results[59]</td>
<td>42</td>
</tr>
<tr>
<td>5.9</td>
<td>Comparison of Simulated and Measured HIV-1 RNA copies[61]</td>
<td>42</td>
</tr>
<tr>
<td>6.1</td>
<td>Basic Queue Model[3]</td>
<td>46</td>
</tr>
<tr>
<td>6.2</td>
<td>Two-Stage Queuing Network</td>
<td>48</td>
</tr>
<tr>
<td>6.3</td>
<td>Bluetooth Queuing Model[22]</td>
<td>52</td>
</tr>
<tr>
<td>6.4</td>
<td>IEEE 802.11 Organization Model[35]</td>
<td>54</td>
</tr>
<tr>
<td>6.5</td>
<td>WLAN Queue Model vs Simulation - Packet Delay</td>
<td>56</td>
</tr>
<tr>
<td>6.6</td>
<td>WLAN Queue Model vs Simulation - Throughput</td>
<td>57</td>
</tr>
<tr>
<td>6.7</td>
<td>HIV Cellular Pathway Queuing Network</td>
<td>58</td>
</tr>
</tbody>
</table>
6.8 HIV Cellular Pathway Parallel Queuing Network ........................................ 59
6.9 HIV Model Overview .................................................................................. 61
6.10 Physical Layer Pseudo-Code ..................................................................... 65
6.11 Network Layer Pseudo-Code .................................................................... 65
6.12 Transport Layer Pseudo-Code .................................................................. 65
6.13 Application Layer Pseudo-Code ................................................................. 66

7.1 HIV Model Results .................................................................................... 71
7.2 Simulation Results for 1,000,000 T cells ...................................................... 71
7.3 Comparison of Simulation, Mathematical Model, and Measured data[4][24] .. 72
7.4 Scaled Comparison of Simulation, Model, and Measured data [4][24] ......... 72
Chapter 1

Introduction

The basis of this research was the study of communication networks at a nano-scale, where nano-scale networks are defined as all biological or manufactured systems that exhibit some form of communication at a nano-scale. Some prolific examples of nano-scale communication would include drug delivery and viral infection. The author previously helped develop a layered communication protocol for interpreting biological and nano-scale communication networks[47]. This protocol was used to abstract several examples of nano-scale communication including drug delivery for treatment of breast cancer. The author then assisted in the development of a simulation of HIV infection by directly interpreting the previously described layered protocol for nano-scale communication networks (this work has recently been accepted to the Elsevier Journal of Nano Communication Networks). The results of these works demonstrated that telecommunications paradigms can effectively be applied to study biological and nano-scale communication networks. In this thesis, the author will further investigate the results of HIV proliferation by formulating a mathematical model based on similar mathematical models for communication networks.
Chapter 2

Motivation

Biological communication is an exciting new platform for Telecommunications engineers to explore. Recent advances in biomedical technology have given birth to fields such as gene therapy, and nano-scale drug delivery which essentially form basic methods of communication at a biological-scale [45][41][29]. By correctly modeling and understanding the basic principles of biological communication it may eventually be possible to engineer a complete biological communication system. The benefits provided by such a system would be tremendous. Fields such as gene therapy, drug delivery, and cellular-level imaging would greatly benefit from a robust engineered system. From such a system, it would be possible to provide feedback from the nano-scale to the macro-scale, essentially forming bi-directional communication between the macro and nano levels of communication.

The delivery of information in a biological system can mean many things; a system which delivers anti-cancer medication is attempting to deliver information which results in the destruction of a cancerous cell. Conversely, gene delivery vectors deliver information encoded in DNA which attempts to repair an abnormal or mutated gene. A biological system infected with a virus such as HIV (Human Immunodeficiency Virus) is
simply trying to propagate information contained within the virus, albeit it does so in a malicious manner. While the information or application delivered by a particular system may be drastically different, the method of transportation remains similar. For instance, most bio-communication systems employ some sort of protective capsule to protect the information contained therein [52][32][49], resembling a sort of PDU (packet data unit). Likewise, many such systems also contain some method of routing particles based on physical characteristics [46][25][58], similar to any type of packet routing employed in an electrical communication system. The similarities continue, and it is clear that there are distinct sections of the biological system that accomplish specific goals, regardless of their physical construction or implementation.

For these reasons we have chosen to adapt and apply our layered communication protocol [47] for biological communication to study one prolific example of such communication systems. In order to begin application of this layered communication protocol, it is wise to start by considering a succinct system. It is also important that there is a large body of experimental data for basis of simulation. As a result, we have chosen to apply our layered protocol to HIV infection as it is a very well researched topic. In this manner, we will accurately relate the communication principles of HIV proliferation into Telecommunications terminology. This protocol helps abstract the intricate processes involved with HIV infection and lets one focus simply on the communication aspects of the system. We will use this layered protocol to develop a mathematical model and simulation of HIV infection from a communications-based perspective. This mathematical model will describe HIV infection based on common telecommunications-based approaches to modeling communication networks. Our simulation will supplement this mathematical model by demonstrating the effectiveness of the protocol and will in turn develop a platform for experimentation and simulation of biological communication systems both natural and synthetic.
A mathematical model often provides a unique insight into a complex system that a simulation cannot. For this reason, we have chosen to expand our original focus for simulating HIV infection to include a mathematical model based on common telecommunications modeling techniques. In this paper, we shall describe existing HIV mathematical models, formulate a telecommunications-based HIV mathematical model, and compare and contrast the results of this model against our previous simulation. We intend to demonstrate that our model can be used to simplify our existing simulation and provide a different perspective on HIV proliferation.
Chapter 3

Background

Systems which exchange information at a basic biological level have been well studied by biologists for many years [47]. Indeed it is well known that most biological systems utilize communication in some form. While the technology to engineer a complete communication system may currently be out of reach, the tools required to study and experiment with bio-communication are readily available. Some of the simplest forms of biological communication are the exchange of DNA between various organisms, in fact DNA itself can simply be thought of as a packet or container for information. By modeling biological systems as communication networks, one can quickly adapt various well studied Telecommunications techniques and paradigms to the system. In such a manner, telecommunications engineers may eventually be able to develop biological communication networks as well as electrical ones. Before this happens, it is important to understand the basic aspects of biological communication. A layered communication protocol is a succinct method of quickly understanding the abstracted processes involved with communication, and can be used to efficiently understand biological communication [47]. As a result, we will adapt our previously developed protocol to a specific example of biological communication.
We have chosen to investigate the proliferation of HIV. Although there exist simpler forms of biological communication, few are as well studied as HIV. For this reason, we have applied our protocol to this specific virus. Essentially, the goal of HIV is to copy and forward itself back into the communication channel to maximize proliferation. This greatly resembles a multi-cast communication network in that there are many receivers (cells) that are capable of receiving a packet (virus). The prolific amount of research in this field will ease the process of determining constants specific to infection. Although we have currently focused our efforts on HIV, in the future we hope to generalize this model to account for many different types of biological communication systems.

### 3.1 HIV Tutorial

The propagation of HIV in the human body is a relatively straightforward process. HIV spreads by infecting human T cells, which after being infected produce additional viruses \[43\]. The end-destination for the virus is the nucleus of a target cell, where it can change the default operation of the nucleus in order to replicate additional viruses\[8\][\[57\]. In order for a virus to enter the nucleus, it must traverse the cellular pathway performing reverse transcription, and integrating with the nucleus.

However, to infect a target cell an HIV virus must first penetrate and enter the cell. There are two known methods with which a virus can gain entry into a cell. The first is called fusion, where the virus fuses itself to the membrane of the cell and injects its viral contents into the cytoplasm \[10\][\[48\]. The second method involves using the Endocytic pathway to gain entry into the cell \[28\][\[51\]. Endocytosis is a process a cell uses to engulf and eventually consume external particles. A cell performs endocytosis by forming a vesicle around an external particle and pulling this vesicle within the cell \[13\]. A virus may gain entry into a cell by escaping such a vesicle, however, if the virus fails to escape
this vesicle it will typically be destroyed.

After the virus has gained entry into the cell it must assemble its viral genome (RNA) into DNA. This process is referred to as reverse transcription [5]. Mutations occur frequently during reverse transcription and can often strengthen the virus to resist treatment [55]. Our research does not currently consider the effect of mutations on the viral pathway.

Once the virus has entered the cell and the genome has undergone reverse transcription it must enter the nucleus to begin reproducing viruses, a process referred to as integration [57]. Once a target cell’s nucleus is infected by the virus, the virus reprograms the operation of the nucleus, which starts using the cell’s resources to produce more viruses [43]. These replicated viruses are then released into the intercellular fluids and the process repeats itself. An infected cell may produce as many as 100 viruses per day when it becomes productively infected [20].
Chapter 4

HIV Communication

4.1 Layered Protocol for Biological Communication

Previously we have described a layered communication protocol for macro to nano-scale communication systems [47]. This protocol models the communication that takes place when one sends a message from the macro world into the nano-world, an example of such communication would be drug delivery. We have adapted this model for use with generic biological communication systems, specifically how an HIV infection propagates in a biological system. A basic diagram for HIV proliferation is shown in figure 4.1. Although HIV infection is a seemingly straightforward process, it is still necessary to split the model amongst the various aspects of communication. For instance, when a newly produced virus escapes an infected cell via budding, a type of routing is performed to correctly send the virus into the plasma. This routing is considered an external process in that it is performed at various physical structures in the system. As a result, we have chosen to model such routing as an additional communication gateway in the system. In such a manner, there are various layers of communication the virus must traverse in order to be successfully received. The resultant model is similar to that of a multi-cast
Figure 4.1: HIV Infection Pathway

communication network, where there exist many different devices which condition and control the flow of data in the system. The layered protocol for this model is seen in figure 4.2.
The flow of the protocol is somewhat straightforward. There are various junctures in the HIV pathway where routing is performed based on characteristics of the virus. These characteristics help form a sort of error control, which has been represented by a transport layer. Essentially, the end goal of the virus is to switch the receiver (host cell) into a mode of operation where it will copy and forward packets back into the channel [36]. It is important to understand that the protocol forms a communication loop, where the output of the receiver will attempt to forward a packet which will travel to a different host cell. Thus we have described the complete HIV communication pathway with our protocol, since we start and end with an application layer responsible for sending and receiving a message.

4.1.1 Layered Protocol for HIV Infection

The layered communication protocol for this system is illustrated in figure 4.2. Many of the processes involved in this system can be quite complex, however, they ultimately perform a single specific function. The protocol helps one quickly understand the function of a specific phase, even if the physical or molecular implementation is not well understood. Using this paradigm one quickly realizes how similar HIV infection is to a multi-cast communication network. Essentially, each individual virus is a packet which is introduced into the channel, and each target cell is a receiver which is capable of accepting such packets. At some point, with certain probability, a given cell may become infected with a virus and begin to reproduce additional virions at a specified rate (an infected cell is hereby referred to as a productively infected cell). At this time, the cell switches modes of operation, and begins to not only receive packets but also to copy and forward the received message back into the channel. A productively infected cell has a significantly shorter lifespan than a non-infected cell as the virus quickly uses
materials within the cell for reproduction [37]. As a result, the system suffers from the possibility that at any point in time an infected receiver will randomly shut down. This phenomenon is not explicitly demonstrated in the protocol but is accounted for in both theoretical and simulation results.

The protocol itself describes the process a newly produced virus must go through to successfully infect another cell, or in other words, how a packet must traverse the communication network in order to be successfully received. We begin the protocol at the stage where an infected cell produces a virus offspring, note that although the protocol starts at this juncture the virus must somehow be introduced into the system. More succinctly, there must be an initial broadcast of packets into the channel to begin the communication process. After the virus is produced it must escape the host cell which involves routing, or traversing a network layer within the cell itself. Next, the virus must navigate the channel and arrive at a target host cell. It is possible the virus may decay before it arrives at a host cell, however the life span of a virus is typically much longer than the average propagation delay for a virus in the system [37]. The arrival of the virus at the surface of the cell represents another stage of routing in the system and is once again represented by a network layer for the communication medium.

Once a virus arrives at a target cell it must somehow be internalized in order to infect the cell. There are several routes that the virus may take, including fusion, endocytosis, and disassociation [46][54][27]. When a virus is internalized via fusion, it simply attaches itself to the surface of the target cell and injects its contents into the cell[27]. When considering endocytosis (endocytic pathway), the virus is engulfed by the cell for consumption [46]. This engulfing process involves encapsulating the virus in a vesicle within the cell. If the virus fails to escape this vesicle it is quite likely it will be destroyed [46]. Conversely, if the virus escapes the vesicle, it is capable of infecting the cell. Lastly, if a virus disassociates from the cell, it must again attempt to enter via fusion
or endocytosis. It is possible a virus will never correctly associate with a cell, and will fail to deliver its message. Clearly a form of routing is performed to determine which entry mechanism the virus must use. If the virus enters via endocytosis, there is another protocol for routing and error control that is performed in addition to the routing at entry.

At this point, the viral contents have been successfully internalized. Now the virus must assemble its contents (RNA) in order to produce its message. This involves a process called reverse transcription where the RNA genome of the virus is copied into DNA \[36\]. Reverse Transcription is a highly error prone process, and it is quite likely the DNA will mutate or fail to correctly assemble into a proper message \[39\]. It is clear that a form of error control is employed, in that the virus must correctly assemble its message without errors to be successfully received. The last stage of the protocol describes how the message (DNA) must navigate to the nucleus of the cell. While the success of this process is dependent on many factors, it essentially is another form of routing. Once the viral DNA enters the nucleus the cell executes the viral message and begins to replicate additional viruses. The cell must interpret and execute the message which clearly indicates the message must be passed to the application layer of the cell. After this point, the communication pathway is considered complete. Once a cell produces an additional virus, the process begins once again at the application layer of the host cell. Essentially, there is a loop formed between both application layers of the protocol, in that this communication process is a continuous cycle.
Figure 4.2: Layered Protocol for HIV Infection

1. Host cell replicates new virion
2. Virus offspring escapes Host cell
3. Virus arrives at Target cell surface
4. Virus RNA
   - Reverse transcription
5. Virus DNA enters Target cell nucleus
6. Target cell begins to reproduce viruses

- Endocytic pathway
  - Virus enters cell via fusion
  - Lysosomes
    - Physical
  - Virus enters cell via endocytosis
Chapter 5

HIV Mathematical Models

Biologists and virologists have studied HIV in depth for several decades and have formulated countless mathematical models to describe various characteristics of HIV infection. These models range in complexity and focus and are used to describe many important aspects of HIV proliferation both from a macro and micro level. We will review several of these models to formulate a foundation for our model. We have chosen to describe HIV mathematical models by classifying models into the following categories: macro propagation - How HIV is propagated from a macro scale, i.e. how humans contact and deliver HIV in a population; treatment propagation - How HIV propagates when being treated by some external force, such as chemotherapy; parameter estimation - How mathematical models can be used to estimate important characteristics of HIV infection; and micro propagation - The dynamics of HIV propagation in the human body. While some of these categories do not directly describe the communication aspects of HIV proliferation they provide an insight as to existing rigorous methodologies for describing specific characteristics of HIV. As a result, we feel these models can provide a basis for our mathematical model even if they do not explicitly describe the components of HIV proliferation we are most interested in.
5.1 Macro HIV Propagation

Macro HIV propagation refers to the propagation of HIV from a macro standpoint, that is, propagation in a population of HIV carriers. Such models can be useful when determining the dynamics of HIV infection in a population.

5.1.1 South African HIV Projection

Johnson et al\[18\] proposed a model to propagation of HIV in a South African population of HIV carriers. The model was intended to demonstrate how the epidemic would evolve over time and how factors such as prevention and treatment could impact the spread of the disease\[18\]. Unlike other macro models, this approach considered a very specific population and incorporated sample data specific to the population \[18\].

The authors came out with the following set of equations which help model the propagation of HIV in a South African population:

The parameter $T_{tij}(y)$ is defined to be the probability that an HIV-positive $y$-year old female, in stage $t$ of the disease and in risk group $j$, transmits the virus to a partner in risk group $i$ in a single act of sex. The parameter is calculated as follows\[18\]:

$$T_{tij}(y) = r_{ij} \times I_t(1 - [1 - (1 - c_j(y))R_t]e) \quad (5.1)$$

Where

1. $r_{ij}$ is the average probability of transmission from an HIV-positive female in risk group $j$ to an HIV-negative male in risk group $i$, in a single act of unprotected sex.

2. $I_t$ is the factor by which $r_{ij}$ is multiplied if the HIV-positive female is in stage $t$ of disease (see figure 5.1).


3. $c_j(y)$ is the probability that a sero-discordant couple use a condom when the index partner is aged $y$ and in risk group $j$.

4. $R_t$ is the factor by which the proportion that are unprotected is multiplied in stage $t$ of disease (see figure 5.1) (taking into account the effect of knowledge of HIV status).

5. $e$ is the probability that a condom is effective in preventing HIV transmission in a single act of sex.

An identical formula $T^*_tij(y)$ with parameters $r^*_tij, R^*_t$ is also considered for males, which replaces $T_{tij}, r_{ij},$ and $R_t$ which maple-specific parameters.

The probability of HIV infection is then calculated as[18]:

$$1 - 1 - a(x) \sum_{j=1}^{4} w_{ij} \sum_{y=1}^{59} f(x|y) \sum_{t=1}^{6} p_{tij}(y) [1 - (1 - T^*_tij(y))^{n_{tij}S_yD_t}]^{P_iS_x}$$

(5.2)

Where

1. $a(x)$ is the factor by which the per-partners transmission probability is multiplied in women aged $x$.

2. $w_{ij}$ is the proportion of male partners who are in risk group $j$.

3. $p_{tij}(y)$ is the proportion of male partners (aged $y$ and in risk group $j$) who are HIV-positive and in stage $t$ of the disease.

4. $n_{tij}$ is the number of coital acts per partnership between a female in risk group $i$ and a male in risk group $j$.

5. $D_t$ is the factor by which the coital frequency is multiplied in stage $t$ of the disease.

6. $P_i$ is the average annual number of partners for a woman in group $i$.
The author’s then compared their model against measured data for prevalence of HIV in the South African populace and found that their model aligned very well with measured results, see Figure 5.2.

5.1.2 Estimating Viral Infectiousness in a population

Wilson et al. described a mathematical model for estimating if an individual carrying HIV with a certain infection rate was capable of infecting others. Specifically, the authors wanted to determine if a viral load of less than 10 HIV RNA copies per mL plasma could infect other individuals, and if so what the associated risk would be [60].

The authors derived an equation for the transmission probability of HIV infection using the data from a previous study by Rakai et al. This equation states that each ten-fold increment in viral load is associated with a $2 \times 45$ fold increase in the risk of HIV infection [60]:

$$
\beta_1 = 2 \times 45 \log_{10} (V_1/V_0) \beta_0
$$  (5.3)

Where

1. $\beta_0$ - Probability of HIV transmission from a person with a baseline viral load $V_0$
2. $\beta_1$ - Probability of transmission probability corresponding to any other viral load $V_1$

The authors then found the cumulative risk of obtaining HIV from $n$ exposures to be as follows:

$$
1 - (1 - \beta + 1)^n
$$  (5.4)
The authors obtained results from their model which demonstrates the transmission probability, as well as the cumulative transmission probability of an HIV transmission after a given number of sexual exposures, see Figure 5.3.

5.2 Treatment Propagation

Treatment propagation refers to the propagation of HIV when under an external treatment force. This force can be radiation, medicine, or any number of potential treatment programs. These models are extremely useful to those researchers studying HIV treatment and can help determine which aspects of HIV propagation are most susceptible to therapy.

5.2.1 HIV-1 pathogenesis with delay (antiretroviral therapy)

Nelson et al. described a mathematical model for assessing the viral decay of HIV-1 in patients receiving antiretroviral therapy [33]. The authors demonstrate that many similar treatment-based mathematical models fail to consider important aspects of drug-based treatment and consider the treatment to be more or less perfect [33]. As a result, the authors considered the effect of a less than perfect treatment, where the efficacy of the drug may be less than 100%.

The authors derived their model from the general form of the non-delay model, which is found as follows [33]:

\[
\frac{dT}{dt} = \lambda - \delta_1 T - kV_1 T
\]

\[
\frac{dT^*}{dt} = kV_1 T - \delta T^*
\]
\[
\frac{dV_1}{dt} = (1 - n_p)N\delta T^* - cV_1 \tag{5.7}
\]

\[
\frac{dV_{NI}}{dt} = n_pN\delta T^* - cV_{NI} \tag{5.8}
\]

Where

1. $T$ - Uninfected T cells

2. $T^*$ - Infected T cells

3. $V_I$ - Infectious virus

4. $V_{NI}$ - Noninfectious virus

5. $\delta$ - Decay rate of virus producing T cells

6. $c$ - Viral clearance constant

7. $n_p$ - Drug efficacy of protease inhibitor

The authors then introduced an intercellular delay into the model as follows [33]:

\[
\frac{dT^*}{dt} = dT_0V_1(t - \tau) e^{-\mu\tau} - \delta T^* \tag{5.9}
\]

\[
\frac{dV_1}{dt} = (1 - n_p)N\delta T^* - cV_1 \tag{5.10}
\]

\[
\frac{dV_{NI}}{dt} = n_pN\delta T^* - cV_{NI} \tag{5.11}
\]

The eigenvalues of the above equations can be used to determine the rate of viral decline for the model [33]. Extracting these eigenvalues is not a trivial task; a thorough
proof of this can be found in [33]. The result is that the rate of viral decay $\bar{\mu}$ is approximately:

$$\bar{\mu} \sim -\frac{\delta n_p}{1 + (1 - n_p)\delta} = -\delta n_p C(\tau, n_p, \delta) \quad (5.12)$$

$$C(\tau, n_p, \delta) = \frac{1}{1 + (1 - n_p)\delta < 1} \quad (5.13)$$

Thus by assuming a constant intercellular delay the decay rate of virus producing T cells $\delta$ is estimated as

$$\delta \sim \frac{slope}{n_p C} \quad (5.14)$$

Which indicates that the viral decay in HIV patients under antiretroviral therapy was dependent on $\delta$, $n_p$, and $\tau$, which are the decay rate of viral producing cells, the efficacy of treatment, and the intercellular delay.

### 5.2.2 HIV Chemotherapy Treatment

Kirschner et al proposed a mathematical model to study the effect of chemotherapy treatment of HIV infection [23]. The authors used clinical data to fit their model to match the turnover rates and the life spans for sample populations [23].

The authors present the following equations for their model, where $T(t)$ is the uninfected T cell population (at time t), $T_s(t)$ is the drug-sensitive infected T cell population (at time t), $T_r(t)$ represents the drug resistant T cells (at time t), $V_s(t)$ is the drug-sensitive virus population (at time t), and $V_r(t)$ is the drug-resistive virus population (at time t). These populations are all assumed to be measured in blood plasma. The mathematical model without considering treatment is give as [23]:

...
\[ T'(t) = S(t) - \mu_f T(t) + \frac{p T(t) V_s(t)}{C + V_s(t)} - k_s V_s(t) T(t) \]  
(5.15)

\[ T_s'(t) = k_s V_s(t) T(t) - \mu f T_s(t) - \frac{p_i T_s(t) V_s(t)}{C_i + V_s(t)} \]  
(5.16)

\[ V_s'(t) = N p_i T_s(t) \frac{V_s(t)}{C_i + V_s(t)} - k_v T(t) V_s(t) + \frac{G_s V_s(t)}{B + V_s(t)} \]  
(5.17)

\[ S(t) = 10 - 7 \frac{V(t)}{B_s + V(t)} \]  
(5.18)

Where

1. \( \mu_T \) is the mortality rate of uninfected T cells
2. \( \mu_{T_i} \) is the mortality rate of infected T cells
3. \( k_s \) is the rate T cells are infected by drug-sensitive viruses
4. \( k_r \) is the rate T cells are infected by drug-resistant viruses
5. \( k_v \) is the rate T cells kill the virus
6. \( p \) is the proliferation rate of uninfected T cells
7. \( p_i \) is the proliferation rate of infected T cells
8. \( G_s \) is the rate of input of drug-sensitive viruses to the bloodstream
9. \( G_r \) is the rate of input of drug-resistant viruses to the bloodstream
10. \( q \) is the probability of mutation
11. \( N \) is the number of viable viruses produced in bursting
12. C is the half-saturation constant of uninfected T cells

13. \( C_i \) is the half-saturation constant of infected T cells

14. B is the half-saturation constant of external virus input

15. \( B_i \) is the half-saturation constant of constant T cell source

16. \( \mu \) treatment parameter

17. \( \eta \) treatment parameter

18. \( \rho \) treatment parameter

The authors then expanded this model to account for chemotherapy treatment of HIV as follows:

\[
T'(t) = S_0(t) - \mu_T T(t) + \frac{pT(t)V(t)}{C + V(t)} - (\mu k_s V_s(t) + k_r V_r(t))T(t) \quad (5.19)
\]

\[
T_s'(t) = \mu k_s V_s(t)T(t) - \mu_T T_s(t) - \frac{p_i T_s(t)V(t)}{C_i + V(t)} \quad (5.20)
\]

\[
T_r'(t) = k_r V_r T(t) - \mu_T T_r(t) - \frac{p_i T_r(t)V(t)}{C_i + V(t)} \quad (5.21)
\]

\[
V_s'(t) = \frac{\rho q(t) N p_i T_s(t)V(t)}{C_i + V(t)} + \frac{(1 - q(t)) N p_i T_r(t)V(t)}{C_i + V(t)} - k_o T(t)V_s(t) + \frac{G_s V_s(t)}{B + V(t)} \quad (5.22)
\]

\[
V_r'(t) = \frac{q(t) N p_i T_r(t)V(t)}{C_i + V(t)} + \frac{(1 - q(t)) N p_i T_s(t)V(t)}{C_i + V(t)} - k_o T(t)V_r(t) + \frac{G_r V_r(t)}{B + V(T)} \quad (5.23)
\]
The premise of this treatment model explains the inhibition of HIV as similar to reverse transcriptase inhibitor [23]. Figure 5.5 shows a simulation based on this model which shows the effect of treatment on the progression of HIV, where the dashed line is non-treatment.

### 5.2.3 Structured Treatment Interruptions

Adams et al. presented a mathematical model used to study how to best model the structured treatment interruptions (STI) [2]. In this case, STI refers to the process of allowing a patient’s immune system to regain its ability to fight the viral infection [2]. This means that rather than attempt to completely eradicate the virus, treatment should instead focus on trying to suppress it. Numerous methods of STI have been proposed, many of which assess changes in the HIV immune response [2]. As a result, the authors have suggested a mathematical model which incorporates an STI-based methodology. The model is based upon the Callaway-Perelson model and can be described as follows:

\[
\dot{T}_1 = \lambda_1 - d_1 T_1 - (1 - \epsilon) k_1 V T_1
\]  \hspace{1cm} (5.24)

\[
\dot{T}_2 = \lambda_2 - d_2 T_2 - (1 - f \epsilon) k_2 V T_2
\]  \hspace{1cm} (5.25)

\[
\dot{T}_1^* = (1 - \epsilon) k_1 V T_1 - \delta T_1^* - m_1 E T_1^*
\]  \hspace{1cm} (5.26)

\[
\dot{T}_2^* = (1 - f \epsilon) k_2 V T_2 - \delta T_2^* - m_2 E T_2^*
\]  \hspace{1cm} (5.27)

\[
\dot{V} = N_T \delta (T_1^* + T_2^*) - c V - [(1 - \epsilon) p_1 k_1 T_1 + (1 - f \epsilon) p_2 k_2 T_2] V
\]  \hspace{1cm} (5.28)
\[
\dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} - \delta_E E
\] (5.29)

Where \( \dot{T}_1 \) is a type 1 target, \( \dot{T}_2 \) is a type 2 target, \( \dot{T}_1^* \) is a type 1 infected target, \( \dot{T}_2^* \) is a type 2 infected target, \( \dot{\nu} \) are free virions, and \( \dot{E} \) are immune effectors [2].

1. \( \lambda_1 \) target cell type 1 production rate
2. \( d_1 \) target cell type 1 death rate
3. \( \epsilon \) population 1 treatment efficacy
4. \( k_1 \) population 1 infection rate
5. \( \lambda_2 \) target cell type 2 production rate
6. \( d_2 \) target cell type 2 death rate
7. \( f \) treatment efficacy reduction in population 2
8. \( k_2 \) population 2 infection rate
9. \( \delta \) infected cell death rate
10. \( m_1 \) immune-induced clearance rate for population 1
11. \( m_2 \) immune-induced clearance rate for population 2
12. \( N_T \) virions produced per infected cell
13. \( c \) virus natural death
14. \( p_1 \) average number of virions infecting type 1 cell
15. \( p_2 \) average number of virions infecting type 2 cell
16. $\lambda_E$ immune effector production rate
17. $b_E$ maximum birth rate for immune effectors
18. $K_b$ saturation constant for immune effector birth
19. $d_E$ maximum death rate for immune effectors
20. $K_d$ saturation constant for immune effector death
21. $\delta_E$ natural death rate for immune effectors

The authors then presented simulation results which show the virus propagation over time, see figure 5.6.

5.2.4 Antiretroviral Therapy for Low Viral Loads

Wein et al. presented a mathematical model to investigate which factors are most critical for ensuring successful antiretroviral therapy to eliminate HIV-1. [59]. The model is derived from a standard model for HIV proliferation created by Perelson et al [40], but is generalized to introduce two drug-sensitive and drug-resistant viruses, protease inhibitors that are not 100% effective, and incorporates dynamics of uninfected cell populations [59].

The model can be described through figure 5.7, which shows a system diagram of the model [59]. Where A virus V, infects a T cell, T, with rate k and generates productively infected T cells $T^*$. Additionally the virus infects long-lived cells, M, with rate $k^M$ and produces productively long-lived T cells $M^*$. Productively infected T cells die at rate $\delta$ and produce N virions before death. Similarly, productively infected long-lived cells die at rate $\delta^M$ and produce $N^M$ virions before death.

This model may be more rigorously defined as a system of equations, given as:
\[ T(t) = s + \lambda T(t)(1 - \frac{T(t) + T_1^*(t) + T_2^*(t)}{T_{\text{max}}}) - \mu T(t) - k_1(1 - r_1)T(t)V_1^I(t) - k_2(1 - r_2)T(t)V_2^I(t) \]

(5.30)

\[ T_1^*(t) = m_{11}k_1(1 - r_1)T(t)V_1^I(t) + m_{21}k_2(1 - r_2)T(t)V_2^I(t) - \delta_1 T_1^*(t) \]

(5.31)

\[ T_2^*(t) = m_{22}k_2(1 - r_2)T(t)V_2^I(t) + m_{12}k_1(1 - r_1)T(t)V_1^I(t) - \delta_2 T_2^*(t) \]

(5.32)

\[ M(t) = \lambda^M - \mu^M M(t) - k_1^M(1 - r_1)M(t)V_1^I(t) - k_2^M(1 - r_2)M(t)V_2^I(t) \]

(5.33)

\[ M_1^*(t) = m_{11}k_1^M(1 - r_1)M(t)V_1^I(t) + m_{21}k_2^M(1 - r_2)M(t)V_2^I(t) - \delta_1^M M_1^*(t) \]

(5.34)

\[ M_2^*(t) = m_{22}k_2^M(1 - r_2)M(t)V_2^I(t) + m_{12}k_1^M(1 - r_1)M(t)V_1^I(t) - \delta_2^M M_2^*(t) \]

(5.35)

\[ V_1^I(t) = (1 - p_1)N_1\delta_1 T_1^*(t) + (1 - p_1)N_1^M\delta_1^M M_1^*(t) - c_1 V_1^I(t) \]

(5.36)

\[ V_2^I(t) = (1 - p_2)N_2\delta_2 T_2^*(t) + (1 - p_2)N_2^M\delta_2^M M_2^*(t) - c_2 V_2^I(t) \]

(5.37)
\[ V_1(t) = N_1 \delta_1 T_1^*(t) + N_1 M_1^M M_1^*(t) - c_1 V_1(t) \]  
\[ V_2(t) = N_2 \delta_2 T_2^*(t) + N_2 M_2^M M_2^*(t) - c_2 V_2(t) \]  

(5.38) (5.39)

Where

1. \( T \) is the number of uninfected T cells
2. \( T_1^* \) is the number of T cells infected by virus strain 1 (\( V^I_1 V_1 \), drug-sensitive virus)
3. \( T_2^* \) is the number of T cells infected by virus strain 2 (\( V^I_2 V_1 \), drug-resistive virus)
4. \( M \) is the number of uninfected macrophages (long-lived cells)
5. \( M_1^* \) is the number of macrophages infected by virus strain 1
6. \( M_2^* \) is the number of macrophages infected by virus strain 2
7. \( V^I_1 V_1 \) is the number of viruses of strain 1
8. \( V^I_2 V_2 \) is the number of viruses of strain 2

1. \( s \) is the rate of supply of uninfected T cells
2. \( \lambda \) is the maximum growth rate of uninfected T cells
3. \( T_{\text{max}} \) is the maximum number of uninfected T cells
4. \( \mu \) is the death rate of uninfected T cells
5. \( \delta_1 \delta_2 \) are the loss rates of infected T cells
6. \( k_1 k_2 \) is the infectivity rates of the virus
7. $N_1$ is the burst size of strain 1

8. $N_2$ is the burst size of strain 2

9. $c_1, c_2$ is the death rates of the virus

10. $m_{12}, m_{21}$ are the mutation probabilities

11. $\lambda^M$ is the production rate of uninfected macrophages

12. $\mu^M$ is the death rate of uninfected macrophages

13. $\delta_1^M, \delta_2^M$ are the loss rates of infected macrophages

14. $k_1^M, k_2^M$ are the infectivity rates of the virus (in macrophages)

15. $N_1^M$ is the burst size of strain 1 from macrophages

16. $N_2^M$ is the burst size of strain 2 from macrophages

The authors used their model to predict the viral load and T cell count when a patient underwent induction therapy before switching to mainenance therapy at 9 months (solid line) or terminated therapy (dashed-line), see Figure 5.8. Induction therapy as it applies to HIV infection, is the initial treatment process used to rapidly reduce the number of viruses in the body to below some threshold [42]. However, such treatment is very harsh to the patient and is difficult to sustain for long-term treatment [59]. As a result, induction therapy is often followed by maintenance therapy. Maintenance therapy is a treatment process used to sustain the initial treatment, but is not as caustic to the patient [15].

The simulation assumed that the patient switched from induction therapy to mainenance therapy at 9 months or discontinued maintenance therapy altogether [59]. The
authors indicate that had the patient maintained induction therapy regiment the virus would have been eradicated [59].

5.3 Parameter Estimation

Parameter estimation refers to estimating various aspects of HIV proliferation. These estimates can help determine important details of HIV proliferation that can supplement other mathematical models, or simply provide insight into HIV dynamics.

Banks et al. provided a model for determining which parameters of HIV infection models are most influential in the outcome of a given model [6]. The authors examined existing models of HIV proliferation and using sensitivity analysis sought to determine the impact specific parameters have on the model [6]. This technique is advantageous in that many times a researcher cannot always easily describe the specific relationship a given parameter has on the outcome of their model.

The author’s technique for determining sensitivity equations involved taking derivatives of equations with respect to the parameter of interest to find a new system of equations which demonstrate more clearly how a given variable affects the model [6]. Determining the sensitivity equation can be a very challenging task; the authors provide a detailed explanation of their methodology in [6].

To demonstrate how their model could be used the authors determined which parameters most influenced a specific equation in a given mathematical model of HIV proliferation [6]. The authors were able to detail which parameters were most influential in the growth of this model.
5.4 Micro Propagation

Micro propagation refers to describing the in vivo interactions of HIV. Such models are most applicable to our model and as such will form the foundation for any models we describe. Micro propagation is largely concerned with estimating the “state” of the human body under HIV infection. In other words, describing how properties such as the number of viruses or T cells change or can affected by various aspects of infection. These are exactly the type of properties that are most important in our formulation of a mathematical mode, and as such we will focus largely on these types of HIV models. Micro models can be broken into several standard approaches which include: The standard model, delay model, combination therapy and delay [34]. Many of the basis for models presented in section 5.1 and 5.2 can be explained by one of these micro propagation models.

5.4.1 Standard Model

The standard model provides a quintessetial relationship which describes the concentration of virions in plasma as well as the number of T cells. Many models for HIV propagation use this basic identity to describe virus and T cell growth [38]. In this model, the relationship between the concentration of virions in plasma, V, and the number of infected T cells, T*, is described through the following equations:

\[
\frac{dT^*}{dt} = kVT^* - \delta T^* \quad (5.40)
\]

\[
\frac{dV}{dt} = N\delta T^* - cV \quad (5.41)
\]

Where T is the number of uninfected T cells, δ is the rate of loss of infected cells, N is the number of new virions produced per infected cell (during its lifetime), and c is
the rate constant for viral clearance. If one were to use this system of equations alone, then by assuming a constant T cell count for the initial phase of infection and assuming that the number of infected T cells increases linearly, it is trivial to determine the viral concentration. Experimental evidence supports the fact that during the initial infection phase the total number of T cells will remain constant [36]. This simplification of the model eases the calculation of virus and T cell growth.

The model can be further expanded to model the effect of treatment on the system, this is given as follows [34]:

\[
\frac{dT^*}{dt} = kT_0 V_I - \delta T^*
\]

(5.42)

\[
\frac{dV_I}{dt} = (1 - n_p) N \delta T^* - cV_I
\]

(5.43)

\[
\frac{dV_{NI}}{dt} = n_p N \delta T^* - cV_{NI}
\]

(5.44)

Where

1. \(T_0\) is the constant level of target cells
2. \(n_p\) is the efficacy of the protease inhibitor
3. \(V_{NI}\) is a non-infective virus (as rendered by treatment)
4. \(n_{rt}\) is the effectiveness of the reverse transcriptase inhibitor

### 5.4.2 Delay Model

The standard model can be generalized to account for the delay of viruses introduced into a system and the time until the production of new viruses begins [34].
The model expands on the standard model as follows [34]:

\[
\frac{dT^*}{dt} = (1 - n_{rt})kT_0 \int_0^\infty f(\tau) V_I(t - \tau)e^{-m\tau} d\tau
\]  
(5.45)

\[
\frac{dV_I}{dt} = (1 - n_p)N\delta T^* - cV_I
\]  
(5.46)

\[
\frac{dV_{NI}}{dt} = n_pN\delta T^* - cV_{NI}
\]  
(5.47)

\[
f(\tau) = g_{n,b}(\tau) \equiv \frac{\tau^{n-1}e^{-\tau/b}}{(n-1)!b^n}
\]  
(5.48)

The delay is given by a constant \( \tau \), and the term \( e^{-m\tau} \) accounts for cells that are infected at time \( t \) but die before they begin producing additional viruses [34]. The delay distribution \( f(\tau) \) was chosen to be a gamma distribution where the mean delay sets the location of the delay, and \( n \) sets the width of the distribution [34].

### 5.4.3 Combination Therapy and Delay

The combination therapy model suggests that long-term HIV patients have a relatively constant viral count in their plasma [38]. This model accounts for this dynamic by introducing the following relationship:

\[
\frac{dT^*}{dt} = \frac{d}{dt}(V_I + V_{NI}) = 0
\]  
(5.49)

When therapy is first considered, the patient is given a non-infectious viral count of \( V_{NI} = 0 \) and at some time \( t > 0 \) the patient’s system starts to be affected by the treatment [34].
5.4.4 HIV Dynamic Model

Wu et al proposed a dynamic model for HIV propagation that considers a simple sum of exponentials to model the progression of HIV [61]. The model was constructed to be simple, yet robust enough to realistically model HIV proliferation, is based on a non-linear mixed effect model [61].

The model is given by the following equations:

\[
\frac{d}{dt} T_m = (1 - \gamma) \alpha_m k_0 TV_l - \delta_m T_m - \mu_m T_m \tag{5.50}
\]

\[
\frac{d}{dt} T_s = (1 - \gamma) \alpha_s k_0 TV_l - \delta_s T_s - \mu_s T_s \tag{5.51}
\]

\[
\frac{d}{dt} T_l = (1 - \gamma) \alpha_l k_0 TV_l - \delta_l T_l - \mu_l T_l \tag{5.52}
\]

\[
\frac{d}{dt} T_p = (1 - \gamma) \alpha_p k_0 TV_l - \delta_p T_p - \mu_p T_p \tag{5.53}
\]

\[
\frac{d}{dt} V_l = (1 - \eta) P - c V_l \tag{5.54}
\]

\[
\frac{d}{dt} V_{NI} = \eta P + N \delta_m T_m + N \delta_s T_s + N \delta_p T_p - c V_{NI} \tag{5.55}
\]

Where

1. T is an uninfected T cell
2. \( T_m \) infected cells other than T cells
3. \( T_s \) long-lived infected cells
4. $T_l$ cells that are infected but are latent in producing viruses

5. $T_p$ productively infected cells

6. $V_l$ infectious virus

7. $V_{NI}$ non-infectious virus

8. $d_l$ rate at which $T_l$ becomes productively infected

9. $d_m$ rate at which $T_m$ becomes productively infected

10. $d_s$ rate at which $T_s$ becomes productively infected

11. $d_p$ rate at which $T_p$ becomes productively infected

12. $\mu_m$ rate at which $T_m$ dies

13. $\mu_s$ rate at which $T_s$ dies

14. $\mu_l$ rate at which $T_l$ dies

15. $\eta$ proportion of non-infectious viruses produced by infected cells

16. Cell elimination rates of viruses

17. $k$ infection rate

18. $\alpha_m$ proportion of cells which are $T_m$

19. $\alpha_s$ proportion of cells which are $T_s$

20. $\alpha_l$ proportion of cells which are $T_l$

21. $\alpha_p$ proportion of cells which are $T_p$
The final equation for the model is then given by:

\[
V(t) = P_0 + P_1e^{-\lambda_1 t} + P_2e^{-\lambda_2 t} + P_3e^{-\lambda_3 t} + P_4e^{-\lambda_4 t} + P_5e^{-\lambda_5 t} + P_6e^{-\lambda_6 t} + P_7e^{-\lambda_7 t} + P_8e^{-\lambda_8 t}
\]

(5.56)

Where

1. \( P_i | i = 0, \ldots, 8 \) are functions of the parameters in equations that represent the initial viral production rate 5.50 through 5.55

2. \( \lambda_1 = \delta_p \)

3. \( \lambda_2 = \delta_m + \mu_m \)

4. \( \lambda_3 = \delta_s + \mu_s \)

5. \( \lambda_4 = \delta_l + \mu_l \)

6. \( \lambda_5 = c \)

7. \( \lambda_6 = r \)

8. \( \lambda_7 = c + r \)

Although the derivation of the final model is a little involved, the end result is relatively simple and does not require solving a complex series of equations to model the growth of viruses. The authors were able to further simplify their model by ignoring those cells which do not greatly affect the overall virus growth, the model is given as follows [61]:

\[
V(t) = P_0 + P_1e^{-\delta_p t} + (P_2 + P_3 t)e^{-ct}
\]

(5.57)
A simulation demonstrating the effective rate of growth as calculated by the author’s model and compared to measured patient data can be seen in figure 5.9.
Figure 5.1: Model of HIV disease progression in adults[18]
Figure 5.2: HIV prevalence of women attending public antenatal clinics[18]

Figure 5.3: Relationship between transmission probability per act and viral load[60]
Figure 5.4: Cumulative risk of HIV transmission vs number of sexual exposures [60]

Figure 5.5: T cell count (A) and viral titer (B) [23]
Figure 5.6: Simulation of early infection scenario[2]
Figure 5.7: System Diagram of Model[59]
Figure 5.8: Model and Induction Therapy Results[59]

Figure 5.9: Comparison of Simulated and Measured HIV-1 RNA copies[61]
Chapter 6

Telecommunications-based Mathematical Model

It is clear from section the previous section that current HIV mathematical models are extremely diverse, in terms of their focus, complexity, and methodologies. In contrast to these existing methods, we propose a mathematical model of HIV from a telecommunications perspective. Instead of concerning ourselves with the biological interpretation of these processes, we aim simply to describe HIV in the context of a communication pathway. We will rely on existing methodologies of modeling communications networks to describe HIV proliferation. We believe our approach will be quite simple in comparison to many of the aforementioned HIV models, and might give researchers a new perspective on methods with which they could model HIV infection.

6.1 Queuing Networks

In a typical multi-node communication network, packets are sent and routed through many machines where they are buffered, processed and forwarded to their appropriate...
destination. Often, this process can cause packets to become stacked or queued in a specific machine that must process them. As a result, queuing theory has proven very insightful in telecommunications modeling, as a node in a network can be simply and effectively modeled using a queue. We will now explain some of the basic concepts behind queuing theory.

### 6.1.1 Exponential Distribution and Poisson Process

The exponential distribution and Poisson process are essentially the foundation for rigorously describing a queue.

A continuous random variable $X$ has an exponential distribution with parameter $\lambda \geq 0$ if its probability density function is given as follows:

$$f(x) = \lambda e^{-\lambda x} \text{ if } x \geq 0, 0 \text{ otherwise}$$

(6.1)

An important characteristic of the exponential distribution is that it is a *memoryless* distribution, formally stated as follows for a random variable $X$ with parameter $x, t > 0$:

$$P(X > x + t| X > t) = P(X > x) = e^{-\mu x}$$

(6.2)

This property becomes extremely important when considering waiting times in a queue, as the probability of a new arrival is in no way influenced by previous arrivals in the queue [3].

Building upon the exponential distribution, a Poisson process is a *counting process* if $N(t)$ represents the number of arrivals that have occurred in the interval $(0, t)$ [56]. Formally this can be described as follows:

$$N(t) = \sum_{i=1}^{n} 1_{(0, t]}(X_i)$$

where $1_{(0, t]}(X_i)$ is an indicator function that is 1 if $X_i$ falls in the interval $(0, t]$ and 0 otherwise.
The counting process $N(t), t \geq 0$, is a Poisson process with rate $\lambda \geq 0$ if

1. $N(0) = 0$

2. The process has independent increments

3. The number of events in any interval of length $t$ is Poisson distributed with mean $\lambda t$. That is $\forall x, s \geq 0$

$$P(N(t+s) - N(s) = n) = e^{-\lambda t} \frac{(\lambda t)^n}{n!}, \text{ n = 0, 1, 2, ...}$$

Two important properties of the Poisson process are the merging and splitting properties.

The merging property states that if $N_1(t)$ and $N_2(t)$ are two independent Poisson processes with rates $\lambda_1$ and $\lambda_2$ respectively, then the sum $N_1(t) + N_2(t)$ is also a Poisson process with rate $\lambda_1 + \lambda_2$ [3].

The splitting property states that if $N(t)$ is a Poisson process with rate $\lambda$ and each arrival is marked with a probability $p$, that is independent of all other arrivals. Then if we denote $N_1(t)$ and $N_2(t)$ as the number of marked and unmarked arrivals respectively, then $N_1(t)$ and $N_2(t)$ are both Poisson processes with rate $\lambda p$ and $\lambda(1 - p)$ respectively [3].

This properties will again play a critical role in defining and understanding queues.

### 6.1.2 Basic Queue Model

The basic queuing model can be seen in Figure 6.1. The queue consists of a constant input of "customers" (although customers can mean many things), who are waiting to be processed by a "server." Customers arrive in the queue at a given rate and wait to be served. A queuing model must address the following properties[3]:

1. The arrival of “customers.” Often customers in a queue arrive according to a Poisson process.

2. The behavior of customers. In a generic queue customers are free to leave the queue or stay in the queue.

3. The service times. Service times are often modeled using an exponential distribution.

4. The service discipline. The server may choose to serve a certain number of customers, or serve customers in a certain order.

5. The service capacity. The queue may allow multiple servers to process customers.

6. The waiting room. The queue may have limited resources and can only allow a certain number of customers to wait.

Figure 6.1: Basic Queue Model[3]
Queues are often classified into groups by their arrival distribution, the distribution of their waiting time, and the number of servers in the queue [3]. Thus a queue can be referred to using Kendall notation, where the notation is a/b/c. ‘a’ refers to the arrival distribution of customers (M denotes exponential arrival), ‘b’ refers to the service distribution (M denotes exponential as well), and ‘c’ denotes the number of servers in the queue[3].

6.1.3  M/M/1 Queue

The M/M/1 queue is one of the most prolific types of queues, this is largely due to its simplicity (both to model and analyze) and ability to realistically model real-world examples of queues [17].

As previously mentioned an M/M/1 queues has an exponential customer arrival rate \( \lambda \), an exponential service rate \( \mu \), and possesses a single server[3]. An important property of the queue that must be observed is the fraction of working time for the server, or \( \rho \).

\[
\rho = \frac{\lambda}{\mu} < 1
\]  

(6.3)

Without this constraint analysis of the server would queue would produce non-real results.

There are several important properties of the M/M/1 queue that one would wish to analyze. First, the mean number of customers in the queue can be calculated using the following equation [3]:

\[
E(L) = \sum_{n=0}^{\infty} np + n = \frac{\rho}{1 - \rho}
\]  

(6.4)

Also, we may wish to find the mean time a customer spends in the queue. To accomplish this we need a property called ”Little’s Law”, which states simply the following
Using Little’s law we find that the mean time spent by a customer in the queue is as follows:

\[ E(S) = \frac{1/\mu}{1 - \rho} \]  \quad (6.6)

As evident, the simple nature of the queue makes analysis of these properties a straightforward process.

6.1.4 Networks of Queues

A network of queues is defined simply as a system where a series of queues route customers between queues. This routing can be random or dependent on some other property of the queuing network. A queuing network can be used to realistically model a complex system of interconnected nodes, and is often used to effectively model communication networks.

Consider once again the basic queue model as previously defined. A two-stage queuing network is a network which consists of two basic queues connected in tandem, see Figure 6.2[62]. The network consists of two simple queues with service rates \( \mu_0 \) and
\( \mu_1 \), where the external arrival of customers to the network is a Poisson process with rate \( \lambda \). Interestingly, the arrival of customers to queue 1 is also a Poisson process, this is explained by Burke’s Theorem (a proof of Burke’s theorem is outside the scope of this paper, see [62] for a detailed proof). In fact the arrival rate to the second queue is also \( \lambda \).

In order to analyze queuing networks and derive important characteristics it is necessary to analyze the queue using Jackson’s Theorem for Open Queuing Networks. An open queuing network is defined as a queuing network where customers enter and leave the network, this is in contrast to a closed queuing network where customers neither enter nor leave the network[62]. Jackson’s theorem assumes the following characteristics [62]:

1. The network is composed entirely of K first-come first-serve, single server queues
2. The arrival for all K queues is Poisson with rate \( r_1, ..., r_K \)
3. The service times of customers in the \( j^{th} \) queue is exponential with mean \( 1/\mu_j \)
4. When a customer leaves a queue \( i \), it enters another queue \( j \) with probability \( P_{ij} \) or it leaves the system with probability \( 1 - \sum_{j=1}^{K} P_{ij} \). Where \( P_{ij} \) is the probability that a customer will be routed from queue \( i \) to queue \( j \).

Thus, in a Jackson queuing network the arrival rate for each queue is given by the following equation, where the arrival is Poisson[62]:

\[
\lambda_j = r_j + \sum_{i=1}^{K} \lambda_i P_{ij}, j = 1, ..., K
\] (6.7)

It follows that the utilization factor of each queue is then given by the equation[62]:

\[
\rho = \lambda_j / \mu_j, j = 1, ..., K
\] (6.8)
Jackson’s theorem is then stated as follows and assumes that $\rho_j < 1$, and $N_i$ is state of the $i^{th}$ queue[62]:

$$P(N_1...N_K) = P_1(N_1)P_2(N_2)...P_K(N_K)$$  \hspace{1cm} (6.9)

Where

$$P_j(N_j) = \rho_j^{N_j}(1 - \rho_j), N_j \geq 0$$  \hspace{1cm} (6.10)

Jackson’s theorem greatly simplifies the analysis of queuing networks, since one can more easily study specific queues in the network.

### 6.2 Queuing Networks for Communication Systems

Queuing networks have been extensively used to study and model computer networks [14][19]. Such queuing models are used to simulate and account for the limited capacity of networks and often use standard queuing models such as the M/M/1 queue [14]. Such models have been shown to accurately predict network performance and are often the primary tool used to evaluate telecommunications networks [19][16].

#### 6.2.1 Bluetooth Queuing Model

Kibria et all developed a queuing model to analyze multipoint Bluetooth connection systems[22]. The model was designed to study ah-hoc Bluetooth networks and demonstrates how a queuing model can be used to understand performance in terms of efficiency and correctness of data transfers in such an environment [22]. The queuing model used priority queues to categorize Bluetooth devices according to several parameters[22].

The queuing model for this system uses a priority queue of type M/G/1, with one
Bluetooth device as the acting master and several Bluetooth devices acting as slaves. The M/G/1 queue is similar to the M/M/1 queue but is generalized to account for an arbitrary distribution for service times[12]. The generalized service time distribution of the queue allows one to fit the model more precisely to the system of interest. As jobs (devices) arrive in the system they are queued according to their priority groups [22]. These priority queues were categorized by the following parameters: bandwidth, delay, delay variation, throughput, and packet loss [22]. By categorizing Bluetooth users according to these parameters the master is able to utilize its resources more efficiently as it can more accurately determine how to interact with the slave devices [22]. Figure 6.3 shows an overview of the queueing model for this system.

The QoS for this system can be derived from the queueing model. The QoS will be determined in terms of the utilization factor $\rho$, and the mean service time $\bar{X}$. The utilization factor for a job $p$ with arrival rate $\lambda_p$ and mean service time $\bar{X}_p$ is defined as follows[22]:

$$\rho_p = \lambda_p \bar{X}_p \quad (6.11)$$

We now denote the delay or wait time for a specific priority $p$ as $W_p$, and define the average wait time for the queue as $W_0$. It follows that $W_p$ is derived as follows[22]:

$$W_p = W_0 + \sum_{i=p}^{P} \bar{X}_i \lambda_i W_i + \sum_{i=p+1}^{P} \bar{X}_i \lambda_i W_p \quad (6.12)$$

The throughput, denote $\beta$ is then defined as the multiplication of the average arrival rate ($\lambda$) with the packet size to be sent [22]. It then follows that the packet loss can be calculated as follows:

$$\beta_{Packetloss} = TotalDataToSend - DataBeingSent \quad (6.13)$$
Using these equations the authors were then able to derive the optimal throughput of a given Bluetooth network.

### 6.2.2 Ad Hoc WLAN Queuing Model

Özdemir el all developed a queueing model to study the performance of the IEEE 802.11 MAC protocol for wireless LAN [35]. The author’s model is based on the M/G/1/k queueing model. An M/G/1/k queue is an M/G/1 queue with a finite buffer size, namely k [31]. This model often describes a queue more realistically as a queue typically cannot be infinite in length.
The system model is comprised of three entities which include the back-off algorithm, the service time distribution, and the queueing model itself[35]. Back-off algorithms are commonly used within communication networks to avoid collisions and network congestion when transmitting data[7]. This model describes the entire 802.11 MAC protocol and is outlined as follows[35]:

1. Initialize $B_0$ (the steady-state probability that a node is busy or non-empty) and the probabilities that a node is in any of the $m + 1$ back-off stages.

2. Calculate the collision probabilities $c_i$ for each back-off stage and the corresponding transmission attempt probability $\tau$.

3. Given $c_i$ and $\tau$ evaluate the packet service rate $\mu$.

4. Given $\mu$ and $\lambda$ find all the state probabilities in $M/G/1/k$ queueing system.

5. Repeat 2, 3, 4 until the difference between a new and previous value for $b_0$ is arbitrary.

A diagram of this system may be seen in Figure 6.4. Although the authors modeled and described their model of the back-off algorithm, it is outside the scope of this paper, see [35] for details.

The author’s queueing model is based on the $M/G/1/K$ model, with the following parameters $\lambda$ as the packet arrival rate, $B(x)$ as the distribution of the packet service time, $b$ as the expected value of the packet service time[35]. The throughput of the system ($\gamma$) is then defined as follows[35], where $P_k$ is the time average of finding $k$ packets in the system:

$$\gamma = \lambda(1 - P_k)$$

(6.14)
Figure 6.4: IEEE 802.11 Organization Model[35]
and the traffic intensity $\rho$ is defined as:

$$\rho = \lambda b = \frac{\lambda}{\mu}$$  
(6.15)

From [12] and [50] it is shown that $P_K$ can be evaluated in terms of the steady state probabilities as follows:

$$P_k = \frac{\pi_k}{\pi_0 + \rho}$$  
(6.16)

$$P_K = 1 - \frac{1}{\pi_0 + \rho}$$  
(6.17)

Using these equations the authors derived the average packet delay and the throughput of the system. The packet delay $E[T]$ can be found in terms of the average number of packets in the system, $E[l]$ as follows[35]:

$$E[L] = \sum_{k=1}^{K} kP_k = \frac{\sum_{k=1}^{K-1} k\pi_k}{\pi_0 + \rho} + K\left(1 - \frac{1}{\pi_0 + \rho}\right)$$  
(6.18)

then using Little’s Law the packet delay is found as[35]:

$$E[T] = \frac{1}{\lambda} \left[\sum_{k=1}^{K-1} k\pi_k + K(\pi_0 + \rho - 1)\right]$$  
(6.19)

Equation 6.14 can then be modified to find the throughput accounting for packet collisions. The throughput if a packet collides $m$ times is then given as follows, where $c_{i,n}$ is the probability of collision given stage $i$ and $n$ busy nodes:

$$\Gamma_n = \frac{\lambda}{\pi_0 + \rho} (1 - \prod_{i=0}^{m} c_{i,n})$$  
(6.20)
The authors then compared their model against simulation results and found their analysis tracked the expected results quite closely, see Figure 6.5, 6.6.

\[ \Gamma = \sum_{n=1}^{N} \Gamma_n \beta_n \] (6.21)
Figure 6.6: WLAN Queue Model vs Simulation - Throughput
Following the example of telecommunications-centered queuing networks, we have chosen to model the proliferation of HIV as a queuing network. We consider each cell in the system to consist of a queuing network, where customers are viruses and servers are mechanisms in the cellular pathway. Each queue is treated as an M/M/1 queue to simplify the analysis of the network. The result is that each cell in our model forms an open queuing network, see Figure 6.7.

The states in the cell are derived from our layered protocol for HIV proliferation (as seen in Figure 4.2) and are as follows: cell surface, vesicle (endocytosis), cytoplasm, nucleus. Where each state is fed viruses by a queue in the network consisting of each of the possible cellular mechanisms. In our model, there is always a certain probability that a virus will be destroyed before it traverses the entirety of the pathway. Our queuing network models this phenomenon as a virus leaving the network. If a virus successfully traverses the entirety of the network it arrives in the nucleus, where it leaves the network by entering the nucleus. The reproduction of viruses in the nucleus cannot easily be
Figure 6.8: HIV Cellular Pathway Parallel Queuing Network
modeled as a queue, in fact, this process is similar to a sort of pure-birth process. The production of viruses is also not memoryless, i.e. production is triggered when a virus enters the nucleus and ends some time later. For these reasons we have chosen to model viral reproduction separately from the queuing network, and consider this process to be a “Triggered Poisson Process.” We define a Triggered Poisson Process as follows:

The counting process \( N(t), t \geq 0 \), is a Triggered Poisson process with rate \( \lambda \geq 0 \) if given a random variable \( \tau \) such that \( t < \tau \)

1. \( N(0) = 0 \)

2. The process has independent increments

3. The number of events in any interval of length \( t \), such that \( t < \tau \) is Poisson distributed with mean \( \lambda t \). That is \( \forall x, s0 \leq 0 \leq \tau \)

\[
P(N(t+s) - N(s) = n) = e^{-\lambda t} \frac{e^{\lambda t} n^n}{n!}, \quad n = 0, 1, 2, ...
\]

Stated simply, a Triggered Poisson process is a Poisson process which is triggered by an event (in this case the arrival of a virus) and is terminated after a certain duration of time has passed (the death of the infected cell).

HIV represents a highly parallel system, that is, there are numerous viruses and numerous T cells that all interact in concert. Our model accounts for this by forming a parallel set of queuing networks for viruses to infect. Analyzing a set of \( n \) identical parallel queues is not a trivial task, to ease this process we have used the splitting property of the Poisson process to simplify such a parallel network. Consider a queuing network as shown in Figure 6.7, with Poisson arrival rates \( n\lambda_1, ..., n\lambda_K \) for each queue. Then the Poisson splitting property states that a set of \( n \) queues with rates \( \lambda_1, ..., \lambda_K \) (see Figure 6.8) is an equivalent queuing network. Thus we can model \( n \) parallel queues as a single queue with arrival rates scaled for \( n \).
In our model there are two states that are shared by each of the parallel queueing networks; the cell surface and the nucleus. The cell surface is considered the bloodstream where viruses are free to target and invade T cells, clearly this is a shared state. Although the nucleus is specific to each T cell, we consider this state as a shared state as well. This is because we treat the nucleus as a Triggered Poisson Process separate from the queue where each cell feeds into this shared state. When the nucleus produces additional viruses these viruses are fed into the shared surface state, forming a feedback loop. Thus our complete system diagram can be seen in Figure 6.9.

6.4 Analysis of HIV model

In this system we are primarily concerned with the following information: how many viruses are in a specific state at a given time. Since our model forms an open queuing network, that is also a Jackson network, we can derive the arrival rate of the $j^{th}$ queue using equation 6.7. Then using Burke’s theorem we know that this arrival rate is Poisson.
This means that the mean number of viruses to arrive in a state j at time t is simply $\lambda t$. We can further analyze the probability that a queue is in a given state using Jackson’s theorem, however, we will instead perform a simulation of the model.

The system is then treated as a Poisson process with rate $n\lambda_{nu}$ where $n\lambda_{nu}$ is the arrival rate of a virus to the shared nucleus state and n is the number of parallel queues, or cells. When a virus arrives in this shared state it creates a new Triggered Poisson process. While deriving the properties of a Triggered Poisson process is somewhat challenging creating a simulation is a straightforward process. The results of our simulation can be found in section 7.2.

6.5 Simulation Model

The highly parallel nature of HIV suggests that one consider a multi-cast communication network for simulation purposes. In this network, packets are flooded into the channel to maximize the number of successful transmissions. Once a packet is successfully received, the receiver begins to copy and forward this information back into the channel. In order to obtain a pure estimate of the communication efficiency of the virus, we have chosen simply to model the initial infection phase, where virus growth is uninhibited by external factors, such as the body’s immune system. Although the current simulation model does not consider the impact interference would have on communication, it is possible to integrate this information with our simulation. By forming a model for interference and including this in the physical layer of the simulation, one would be able to investigate the impact interference has on the system. We intend to demonstrate this effect once we have fully studied the initial phase of infection and have formulated a model for interference.

In order to determine a threshold for various kinetic constants in our simulation
model, we have used mathematical models for HIV [38][39] as well as models developed from other viruses, such as adenovirus [54]. While these kinetic constants are not necessarily accurate for HIV, they give us an estimate of a realistic time constants for various phases of the simulation. At several stages of the model, there are places where a virus will be routed to another path with a known probability. Fortunately, many biologists have sought to form models which accurately assess these probabilities [11]. Also, at several stages of the protocol, there are events which are driven by errors in the system. We have chosen to model these errors as the result of random noise, and simply generate a random variable to dictate whether an error occurred. This generated error in turn dictates how a given virus is routed in the pathway.

The basic flow of the simulation is described as follows: A group of viruses is introduced into the channel, where each virus is given an appropriate randomly generated arrival time and randomly selected target cell to infect. The physical propagation of the virus in the channel is a complicated process and is currently outside of scope of this project. Instead of attempting to model this process we simply generate a random arrival time to simulate the various delay components caused by the channel the virus must navigate when finding a target cell. Next, the virus will attempt entry into the cell. Depending on various physical properties of the virus this entry could fail, or choose a slower path inside the cell. Next the virus must perform reverse transcription, the process of transcribing its viral RNA into DNA. This process is highly error prone and has once again been appropriately simulated with noise. Next, the generated DNA must navigate into the nucleus of the cell, again assuming an appropriate error rate. Assuming this process has completed successfully, the infected cell will now start to replicate and forward additional viruses into the channel at an appropriate rate. These replicated viruses then attempt to repeat this entire process infecting more cells. It is simple to see why the virus grows so rapidly, since it is not atypical for an infected cell to replicate in
excess of 20 viruses less than 12 hours after becoming infected [9].

The model used for simulation of HIV infection is similar to that of a multi-cast network, where many packets are delivered into the channel to be accepted by many receivers. In contrast to a typical multi-cast network, where packets arrive at neighbor nodes deterministically, the arrival of viruses at target cells is typically a random process. We consider the random arrival of viruses to be similar to multi-casting in a mobile environment, where autonomous sensor networks (e.g. networks with moving nodes) are interconnected through wireless channels experiencing fading and randomly moving in and out of range. Our simulation is concerned specifically with processes that happen once the packet is received by the local gateway (virus attached to the cell membrane). In other words, we are only concerned with the activity of this system from the external gateway to the destination node (cell nucleus). As a result, we will not attempt to simulate the dynamics of HIV infection in the channel, or its formation and introduction into the bloodstream. There are many constants required to determine both the probability for entering certain branches of the HIV pathway, and reasonable time constraints for each path. There is an enormous body of medical research which has accurately assessed many of these constants. Since this is such a highly parallelized system we keep track of information for every virus and every cell at each iteration. Several pieces of information are associated with each virus. For the virus we have the time to next event (virion_event), where the virus is located (virion_state), the T cell the virus has targeted (virion_target). For the T cell we have the time to next event (t_cell_event), and the production stage of the cell (t_cell_state). Using this information we may iterate the simulation at each time-step and simply update the state of each virus and T cell dependent on the event flag.
Algorithm 1 Physical Layer Pseudo-Code

for $t := \text{min} \rightarrow \text{sim\_duration}$ do
    if $t == \text{virion\_event}$ then
        if $\text{virion\_state} == \text{death}$ then
            $\text{virion} \leftarrow \text{destroy}$
        else
            $\text{virion} \leftarrow \text{update\_cell\_state}$
        end if
    end if
    if $t == \text{t\_cell\_event}$ then
        if $\text{t\_cell\_state} == \text{death}$ then
            $\text{t\_cell} \leftarrow \text{destroy}$
        else
            $\text{t\_cell} \leftarrow \text{update\_virion\_state}$
        end if
    end if
end for

Figure 6.10: Physical Layer Pseudo-Code

Algorithm 2 Network Layer Pseudo-Code

$\text{rand\_event} \leftarrow \text{get\_rand}$

for all routes do
    if route $\geq \text{rand\_event}$ then
        $\text{virion} \leftarrow \text{route}$
    end if
end for

Figure 6.11: Network Layer Pseudo-Code

Algorithm 3 Transport Layer Pseudo-Code

$\text{rand\_err} \leftarrow \text{get\_rand}$

if $\text{rand\_err} \geq \text{max\_tolerable\_err}$ then
    $\text{virion} \leftarrow \text{death}$
end if

Figure 6.12: Transport Layer Pseudo-Code
The dynamics of HIV infection in-vivo can be quite complicated. It is difficult to accurately assess the movement of HIV when it proliferates a system. To account for the arrival rate of the packets, we simply randomly generate an appropriate arrival time for each packet and randomly choose a target receiver. It is possible for multiple packets to be processed by a receiver simultaneously, however, this does not significantly impact the production rate of the receiver once it enters production mode. It is also possible that a packet will attempt to navigate to a receiver that has been switched off (destroyed, and no longer viable to facilitate viral production), at which point the packet will be lost or resolve itself to a new host. This time delay accounts for the uncertain movements of the virus at any give time and allows us to realistically simulate these effects without necessarily knowing or predicting their movements.

The Pareto distribution can model packet delay in a communication network quite nicely [63]. Although packets arrive at wide intervals of time, most of these arrival times are clustered close to the origin. The Pareto distribution provides a function for finding such arrival times. The probability density function for an upper-truncated Pareto random variable, $X$, has a distribution [1]:

$$p(X > x) = \frac{\gamma^a (x^{-a} - \nu^{-a})}{1 - \left(\frac{\gamma}{\nu}\right)^a}$$  \hspace{1cm} (6.22)

and density function[1]:

Algorithm 4 Application Layer Pseudo-Code

```plaintext
if t_cell_state == replicate then
    add_virion
end if
```

Figure 6.13: Application Layer Pseudo-Code

6.6 Packet Arrival

The dynamics of HIV infection in-vivo can be quite complicated. It is difficult to accurately assess the movement of HIV when it proliferates a system. To account for the arrival rate of the packets, we simply randomly generate an appropriate arrival time for each packet and randomly choose a target receiver. It is possible for multiple packets to be processed by a receiver simultaneously, however, this does not significantly impact the production rate of the receiver once it enters production mode. It is also possible that a packet will attempt to navigate to a receiver that has been switched off (destroyed, and no longer viable to facilitate viral production), at which point the packet will be lost or resolve itself to a new host. This time delay accounts for the uncertain movements of the virus at any give time and allows us to realistically simulate these effects without necessarily knowing or predicting their movements.

The Pareto distribution can model packet delay in a communication network quite nicely [63]. Although packets arrive at wide intervals of time, most of these arrival times are clustered close to the origin. The Pareto distribution provides a function for finding such arrival times. The probability density function for an upper-truncated Pareto random variable, $X$, has a distribution [1]:

$$p(X > x) = \frac{\gamma^a (x^{-a} - \nu^{-a})}{1 - \left(\frac{\gamma}{\nu}\right)^a}$$  \hspace{1cm} (6.22)

and density function[1]:

Algorithm 4 Application Layer Pseudo-Code

```plaintext
if t_cell_state == replicate then
    add_virion
end if
```
\[ f_x(x) = \frac{\alpha \gamma^a x^{-\alpha - 1}}{1 - \left( \frac{\gamma}{\nu} \right)^a} \] (6.23)

for the parameters \(\delta, \nu,\) and \(a\) being positive reals with \(\gamma < \nu\) being the minimum and maximum values, respectively, and the parameter \(a\) defining the shape of the function.

6.7 Receiver Uptake

Once a packet arrives at a target cell it begins to traverse the HIV pathway (see figures 4.1 and 4.2). The HIV pathway contains several junctures or branches where viruses are routed to a given branch according to some specific physical characteristic. Although these characteristics are not always well understood by researchers, the probability of a virus arriving at a particular state has been determined. As a result, at each juncture of the HIV pathway a random number is chosen which is used to decide where to route the virus (as dictated by the probability of arrival for each branch). The pseudo-code in Algorithm 6.5 demonstrates how routing during HIV infection is performed; note that this procedure is called whenever there is a virion_event, or in other words, when the virion has changed states. Additionally, there are several sections of the HIV pathway where the integrity of the virus is evaluated according to certain physical criteria. This process differs from routing in that a virus which fails to pass a validation routine may simply be discarded, and is no longer viable. The pseudo-code in Algorithm 6.5 illustrates this process. A packet which successfully navigates the entirety of the HIV pathway forces the receiver to switch into production mode, where it begins to forward copies of the packet into the channel.
6.8 Forwarding

Once a receiver (T cell) has been productively infected it begins forwarding additional copies of the infectious virus back into the channel. Viruses are produced at a constant rate, and after sufficient time the receiver will produce an additional virus.

6.9 Packet and Receiver Shutdown

The nature of this system warrants that this simulation take the effects of receiver shutdown and packet timeout into account. When a virus productively infects a cell it causes that cell to produce additional virions. This means that materials within the cell are reconstructed to form additional viruses which are then sent back into the system. This is similar to when a node forwards a message back into a channel, in this case however, the node can still accept incoming messages and forward additional copies. After a sufficient amount of time the infected cell will be destroyed by the virus, at this point the cell is simply eliminated from the simulation.

6.10 Virus Destruction

At any stage of the simulation there is a probability that a virus will simply decay or be eliminated by the human immune system. While antibodies which fight HIV are not in sufficient quantities during the initial stage of infection [36], there is a chance a virus may be eliminated in this manner. Additionally, a virus which fails to internalize into a T cell host has a much higher chance of becoming destroyed. To account for this each virus has a timeout which is randomly selected. If the timeout exceeds the amount of time the virus propagates the channel, then it is destroyed.
6.11 Simulation Parameters

The following section describes the parameters used for our HIV simulation. Finding accurate measurements for these kinetic properties is not an easy task, in fact many of these constants are derived from different viruses and other mathematical models. It is likely that some of these constants are inaccurate, perhaps as much as an order of magnitude, however, we have found discrepancies and variation among numerous sources for given constants. In the future, we would welcome HIV experts to correct these discrepancies as we feel this is the primary reason for the scale discrepancy between our simulation results and measured HIV infection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell Virus Production Rate</td>
<td>10-100 Viruses/day [9][20]</td>
</tr>
<tr>
<td>Infected T cell lifespan</td>
<td>2.2 days [38]</td>
</tr>
<tr>
<td>Virus plasma lifespan</td>
<td>7.2 hours [38]</td>
</tr>
<tr>
<td>Dissociation rate</td>
<td>0.001-.01 Viruses/hour (0.003 average) [26]</td>
</tr>
<tr>
<td>Surface to Cytoplasm (Fusion)</td>
<td>0.001-0.01 Viruses/min [11]</td>
</tr>
<tr>
<td>Surface to Endosome (Endocytosis)</td>
<td>0.003 Viruses/min [11]</td>
</tr>
<tr>
<td>Endosome to Cytoplasm</td>
<td>0.001-0.02 (based on PEG study) Viruses/min [30]</td>
</tr>
<tr>
<td>Cytoplasm to Reverse Transcription</td>
<td>0.001-0.033 Viruses/min [21]</td>
</tr>
<tr>
<td>Reverse Transcription to Nucleus</td>
<td>.17 - .25 Viruses/hour [53]</td>
</tr>
</tbody>
</table>
Chapter 7

Results

We have extracted the following results from our mathematical model and simulation of HIV proliferation (Figures 7.1 and 7.2). Due to the computational intensity of the simulation, we have restricted the total number of receivers (T cells) present in the system. All results were generated with a set of $10^3—10^6$ T cells. While this does not realistically reflect the typical number of T cells in the human body, it allows simulations to be performed in a reasonable time span. Currently, simulated events are happening too quickly or in the incorrect time span as compared against actual measured HIV proliferation rates [4][24] (a time-scale of approximately 30% for the simulation and a time shift of approximately 6 days for the mathematical model), see Figure 7.3. However, when accounting for this time-scale and adjusting appropriately one can see the simulated events align with actual measured viral growth[4][24] quite well (see figure 7.4). It is also visible that the quantity of viruses aligns very well with measured data without any alteration, which is quite impressive.

The simulation model is easily adjustable and may be used to experiment with the effect various simulation constants have on communication efficacy. The results of our simulations indicate that changing constants, even slightly, can have a distinct and often
Figure 7.1: HIV Model Results

Figure 7.2: Simulation Results for 1,000,000 T cells
Figure 7.3: Comparison of Simulation, Mathematical Model, and Measured data[4][24]

![Comparison of Simulation, Mathematical Model, and Measured HIV Viral Copies](chart1.png)

Figure 7.4: Scaled Comparison of Simulation, Model, and Measured data [4][24]

![Scaled Comparison of Simulation, Model, and Measured HIV Viral Copies](chart2.png)

drastic impact on the results. However, despite the sensitivity of certain constants in the simulation the general shape of growth stays somewhat constant. This clearly indicates
that there are parameters for communication which are more critical for successful proliferation than others. Although we have encountered a time-scale discrepancy when applying our model to HIV proliferation, we feel the simulation model works quite well as the reason for said discrepancy is likely due to inaccurate simulation constants.
Chapter 8

Conclusion

Telecommunications models can be applied to HIV infection and this model accurately abstracts the intricate processes involved with HIV communication. The novelty of this model is that it has been used to successfully model and abstract a biological process into a communication network. The preliminary results of our mathematical model and simulation demonstrate that our model is quite capable of predicting the shape of growth for the proliferation of HIV during the initial phase of infection. The simulation model may be easily adjusted and may be used to experiment with the communication aspects of HIV proliferation. The flexibility of the model demonstrates that it may currently be used to model and simulate viruses which are similar to HIV. In the future we hope to enhance the accuracy of the simulation and begin to evaluate other forms of biological communication.
Bibliography


[15] D B Hall, J G Montaner, P Reiss, D Cooper, S Vella, C Dohnanyi, M Myers, J Lange, and B Conway. 5.2.4


[17] Myron Hlynka. The m/m/1 queue, 2010. 6.1.3, 6.1.3


[28] Yuri; Latinovic Olga; Morozov-Vladimir; Melikyan Gregory B. Miyauchi, Kosuke; Kim. Hiv enters cells via endocytosis and dynamin-dependent fusion with endosomes. *Cell*. 3.1


[33] Patrick W. Nelson, James D. Murray, and Alan S. Perelson. A model of intracellular delay used to study hiv-1 pathogenesis.


[40] P; Cao Y; Vesanan-M; Hurley A Markowitz M; Ho DD Perelson, AS; Essunger. Decay characteristics of hiv-10infected compartments. 5.2.4


[43] Francisco; Berzal-Herranz Alfredo Reyes-Darias, JA; Sanchez-Luque. Inhibition of hiv-1 replication by rna-based strategies. Current HIV Research. 3.1


[56] J Virtamo. Queuing theory / poisson process. 6.1.1


