Biomedical Mathematical Modeling

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Abstract

Over the course of the human immunodeficiency virus-type 1 (HIV-1) research, there have been many different approaches by different groups of people. In the mid 1990's, a collaborative effort was made between mathematicians and biomedical scientists in the attempt to accurately model, and thus eventually understand HIV-1. This interdisciplinary unit has performed modeling to reveal new understandings of the disease. One of the greatest discoveries was finding out that the disease incorporates many different time scales. It was further found that those time scales correspond to vital biological processes underlying HIV infection. This led to combination therapy, which has led to the extension of many human lives. But, there is still a far way to go in the modeling process. The models attempt to follow and describe the three variables: uninfected T-cells, infected T-cells, and virus particles. This has been done mainly through deterministic models that develop through the use of differential equations. The difficulty of performing experiments on humans has slowed down the discovery process, but everyday mathematicians and biomedical scientists get closer to clarity and understanding. Our project surveys the recent efforts in these areas, especially those described in a recent paper by Perelson and Nelson.

Keywords: HIV, Math, Biomedical
Introduction

HIV is a dynamic disease that has been researched to a great extent over the last couple decades. A history and biology of the virus is needed for a better understanding of the developments that have already occurred, and the developments that are to come in the future. After one has obtained an understanding of how the virus works in the body, mathematical techniques can be used to help with the treatment of the virus. This is done mainly through differential equations and phase plane analysis. By using these tools, it is possible to describe the different population models inside the human body and the drug therapies that have come into play due to the different time scales that are involved with this complex virus.

It is proven that HIV has been in circulation since 1959. Antibodies for HIV have been detected in frozen blood samples taken from individuals in Zaire in 1959 and the United States in 1968. AIDS was first officially detected in the United States in 1981 in New York and California, whereas HIV was first identified in 1983. As of the end of 2000, an estimated 36.1 million people worldwide were living with HIV/AIDS (34.7 million adults and 1.4 million children under 15 years-old) [2]. More than seventy-five percent of adult infections were as a result of heterosexual contact.

Biology

The major target of HIV infection is a class of lymphocytes, or white blood cells, known as T cells. These cells, also called “helper T cells,” are created in the thymus and secrete growth and differentiation factors that are required by other cell populations in the immune system. When an HIV infected patient’s T cell count, which is normally around 1000 mm$^{-3}$, reaches 200 mm$^{-3}$ or below, then that patient is classified as having AIDS.

Any infectious agent that enters the human body will eventually be taken up in the lymph system. This may happen soon after infection, or it may wait until the infectious agent has found a crevice and begun to replicate. It is in one of the lymph nodes where the infectious agent will come in contact with a macrophage. Once inside of the lymph nodes, the virus will be destroyed by macrophages. Once the macrophage kills the virus particle, it will create viral antigens which immune cells will in turn replicate.

Every microorganism has its own protein specific antigen. These antigens allow the immune system to recognize virus particles that may need to be eliminated. Next the macrophage sends out an immune response, which triggers the T cell response. After the T cells have become activated, the T cells will send out a signal to activate B cells, which also replicates the macrophage’s antigens.

The activated B cell will then produce millions of antibodies. The antibody is a protein that will bind with an antigen. Each antibody is unique and specific. The human body produces antibodies because, given the high concentration of infectious agent that is needed to cause disease, macrophages could not go after the infectious agent alone. However, antibodies will outnumber the infectious agents and will effectively help to get rid of them. The antibodies bind with the infectious agent in a particular manner. The antibody usually provides such a close match that upon contact, the antibody will attach onto the antigen without release. Once an antibody has attached to an infectious agent, it will have other systems take over their complex. A macrophage will then take over the antibody-antigen complex and the body will be rid of the infectious agent.

Eventually, as this process continues, the number of infectious agents will decrease and the process will no longer be necessary. However, the cells are still activated so the immune system must put them to rest. An additional T cell, the T-suppressor cell (or T8) will make those cells inactive. If the T-suppressor cell did not exist, the body would continue trying to fight off a disease that does not exist. This would result in the destruction of the body’s own cells.

In AIDS, this procedure does not work in a suitable manner. Initially macrophages recognize HIV, T cells initiate the response, and B cells produce antibodies. This process is effective at first, but the antibodies do not eliminate the infection. Although some HIV may get killed, many more viruses will actively infect T cells, the very same cells that are supposed to coordinate the defense against the virus. Infected T cells create more viruses, which, if activated, will produce virus instead of the production of more antibodies against it.
Besides T cells, HIV is capable of infecting other cells (macrophages, B cells, monocytes) and crossing the brain-blood barrier, inevitably infecting nervous system cells. Most immune cells cannot cross that barrier. It surrounds the brain and spinal cord. So HIV can go where the immune system cannot.

The immune system is very complex and many of its processes are still not known. Some of the tests used to monitor the health of HIV-positive people show how well the immune system is working, while others show the number of copies of the virus in the body. Monitoring and early treatment can be crucial in determining the course of HIV disease.

**Analysis**

For years many people thought that HIV was a slow moving disease because it takes roughly 10 years to develop. But it is now known that HIV is a dynamic disease encompassing many different time scales. Perturbation techniques combined with mathematical modeling has uncovered these time scales. The modeling issues enclosed will be formed using deterministic, continuous, second order differential equations. A generic system of differential equations may be in the following form:

\[
\frac{dx}{dt} = ax + by \\
\frac{dy}{dt} = cx + dy.
\]  
(1)

The reduction of a first order homogeneous linear system into a second order differential equation results in

\[
\frac{d^2x}{dt^2} - (a + d)\left(\frac{dx}{dt}\right) + (ad - bc)x = 0.
\]  
(2)

A simple way to achieve this formula is to take the trace and determinant of the coefficient matrix, which is represented by

\[
\begin{bmatrix}
\frac{dx}{dt} \\
\frac{dy}{dt}
\end{bmatrix} = \begin{bmatrix}
a & b \\
c & d
\end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}
\]  
(3)

To find the determinant of the matrix take ad - bc = \( \delta \). To find the trace of the matrix take a + d = \( \beta \). Thus the equation looks like

\[
\frac{d^2x}{dt^2} - \beta \left(\frac{dx}{dt}\right) + \delta x = 0.
\]  
(4)

Half-life is an important concept used in the modeling of HIV. Half-life is the period over which the concentration of the virus falls to half of its original concentration level. The generic model is a differential equation of the type (5). Note that the c in this equation is different than the one in equations (1)-(3).

\[
\frac{dx}{dt} = -cx
\]  
(5)
Equation (5) is solvable by a separation of variables into the form:

$$x(t) = x_0 e^{-ct}.$$  \hspace{1cm} (6)

Equation (6) is used to find the half-life of the virus under optimal conditions. That is, it is used to find how fast the virus will eradicate from the body if its production could be completely stopped.

Phase plane analysis is a graphical way to observe the long-term behavior of a system of differential equations without actually solving them. That can be done using fixed points. A fixed point, or steady state, occurs where

$$\frac{dx}{dt} = 0$$
$$\frac{dy}{dt} = 0.$$ \hspace{1cm} (7)

The fixed point can be either stable or unstable. A stable steady state occurs when points are attracted to the fixed point and an unstable steady state occurs when points are repelled from the fixed point. There are many different types of fixed points. A listing of some of these fixed points includes: sink (stable), source (unstable), saddle (unstable), spiral source (unstable), spiral sink (stable), and center (unstable). A well-known theorem can be used to determine what type of fixed point the system contains when in a linear system of equations. This is done by looking at the values of the trace and determinant of the system.

Following Perelson and Nelson [1], the simplest model of virus production has the form

$$\frac{dV}{dt} = P - cV.$$ \hspace{1cm} (8)

In equation (8), P is an unknown function representing the rate of virus production, c is a constant called the clearance rate, and V is the virus concentration. The model predicts that V will fall exponentially if the drug completely blocks viral production (P = 0). This would be symbolized by

$$V(t) = V_0 e^{-ct}.$$ \hspace{1cm} (9)

Linear regression (taking the logarithm) can then be used to determine the slope. At that point, an estimate of c, the clearance rate, and the half-life of the virus in the plasma can be found.

If it is assumed before therapy began that a patient was in a quasi-steady state, which is the stage where the disease appears to be inactive, then dV/dt = 0. If this were the case, then the viral production rate before therapy would be $P = cV_0$. However, these rates would be based on the idea that the prescribed drug would completely block virus production. This is not possible, so instead it measures the rate of virus clearance in the presence of some remaining production. In the above model, the amount of viral decline is only a lower bound, not the true clearance rate. The following models are more polished and will show this result.

HIV modeling occurs by taking account for three different variables. Since it is vital to understand how each one works, a separate equation for each variable is needed. The three populations are: uninfected T cells, T, infected T cells, T*, and virus concentration, V. Such a model is advanced in Perelson and Nelson [1]. We analyze this in the following discussion.

Before developing the equations for the three variables, a background on logistic population models is needed. The simplest model for a growing population $x = x(t)$ is

$$\frac{dx}{dt} = rx$$

where r is the population growth rate. Realistically the growth rate depends upon the population, so $r = r(x)$ can be used instead. This would have a model such that as x gets high, the rate gets small. Occurs razor, which says that all things being equal, the simplest explanation tends to be the correct one, produces a straight-line with decreasing slope. The slope can be given a value of $-\frac{\rho}{k}$. Here the \( \rho \) is the intrinsic population
growth rate and the k is the carrying capacity for the population. By putting that in $mx + b$ form, equation (10) is formed.

$$r = r(x) = -\frac{\rho}{k} x + \rho = \rho \left(1 - \frac{x}{k}\right)$$

(10)

By going back to the original form, and replacing r by $r(x)$, equation (11) develops.

$$\frac{dx}{dt} = px \left(1 - \frac{x}{k}\right)$$

(11)

That is the logistic differential equation that will come into use in the modeling of the three variables that follow.

The formula for uninfected T cell population is

$$\frac{dT}{dt} = s + pT \left(1 - \frac{T}{T_{\text{max}}}\right) - d_{\text{T}} T.$$ 

(12)

The proliferation is represented by the middle term $pT \left(1 - \frac{T}{T_{\text{max}}}\right)$, where p is the maximum proliferation rate. That is the logistic function that was previously discussed. It is the population growth rate of T cells in a healthy person. But the logistic model alone will not suffice. Other ways that cells are created and destroyed need to be factored in. Therefore, the addition of s, which represents the rate at which new T cells are created from sources within the body, is needed. Since T cells, like all cells, have a natural lifespan, the death rate per T cell ($d_{\text{T}} T$) must be subtracted. Note that $d_{\text{T}}$ is simply a proportionality constant representing the “death rate” of healthy T-cells.

The equation above has a single stable steady state, which is given by

$$T = \frac{T_{\text{max}}}{2p} \left[p - d_{\text{T}} + \sqrt{(p - d_{\text{T}})^2 + 4sp T_{\text{max}}^{\text{max}}}ight].$$

(13)

Remember, that the steady state value is found by taking $dT/dt = 0$ and solving for $T$.

T cells become infected when in the presence of HIV. The easiest and most common method of modeling infection is to take into account a “mass-action” term. Here the rate of infection is given by $kVT$, where k is the infection rate constant. This makes sense since virus must come in contact with T cells in order to infect them. The likelihood of virus unexpectedly coming in contact with a T cell at low concentrations can be assumed to be proportional to the product of their concentrations. Thus it is assumed that infection occurs by virus, V, interacting with uninfected T cells, T, causing the loss of uninfected T cells at rate $-kVT$ and the generation of infected T cells at rate $kVT$.

Now that the groundwork has been set up, the rate of change for all three of the population models can be pieced together. The formula for the uninfected cells, T, is the same as the previously developed model except with the mass action term added in. Since this term specifies the rate of infection, it is decreasing the number of uninfected T cells and thus must be subtracted from the original. So the final equation for the rate of change of the uninfected T cell population is

$$\frac{dT}{dt} = s + pT \left(1 - \frac{T}{T_{\text{max}}}\right) - d_{\text{T}} T - kVT.$$ 

(14)

The probability that a T cell will die as a function of time or cell age is not known. Therefore, Occam’s Razor says to choose the rate of death per cell as a constant $\delta$ for infected cells. So $kVT$ represents the generation of infected T cells and $\delta T^*$ represents the death rate per infected T cell. This produces the rate of change of the infected T cell population represented by
The equation for the rate of change of the virus population is

\[
\frac{dV}{dt} = N\delta \Gamma^* - cV. \tag{16}
\]

This equation is developed using different facts about viruses. It is known that productively infected cells produce the virus. It is assumed that on average each productively infected cell produces \(N\) virions, or new HIV virus particles, during its lifetime. The average lifetime of a productively infected cell is \(\delta\); therefore, the average rate of virion production is \(N\delta\). \(kVT\) is small compared to \(cV\) in the average HIV patient, so \(cV\) is used instead of \(kVT\).

From the three previous equations, some conclusions can be drawn. Before therapy, viral loads are for the most part constant. Thus \(dV/dt = 0\), which implies

\[
N\delta \Gamma^*_0 = cV_0. \tag{17}
\]

Since \(V\) is relatively constant for weeks before therapy, this implies that \(\Gamma^*\) must be relatively constant. For \(\Gamma^*\) to be constant, we assume \(dT^*/dt = 0\). Thus,

\[
kVT_\omega T_\omega = \delta \Gamma^*_0. \tag{18}
\]

These two equations imply that in order for \(V\) and \(\Gamma^*\) to be in quasi-steady state then

\[
NK\Gamma^*_0 = c. \tag{19}
\]

The examination of the situation in which \(T = T_0\), but \(\Gamma^*\) and \(V\) vary according to the equations (15) and (16) so the new system (20) must be analyzed.

\[
\begin{align*}
\frac{dT^*}{dt} &= kVT - \delta \Gamma^* \\
\frac{dV}{dt} &= N\delta \Gamma^* - cV
\end{align*} \tag{20}
\]

Phase-plane analysis show that equations \(dT^*/dt = 0\) and \(dV/dt = 0\) define straight lines, which are given by

\[
\begin{align*}
V &= \frac{\delta}{kT_\omega} T^* , \\
V &= \frac{N\delta}{c} T^*.
\end{align*} \tag{21}
\]

From these equations the characteristic equation can be determined to find the distinct eigenvalues of the system. This is done by using the quadratic formula.

Again following Perelson and Nelson [1], the lines can now be graphed and the phase plane diagrams that develop can be analyzed. There are three possible situations that can happen in this instance. First if \(c > NK\Gamma^*_0\), then the phase plane diagram will look like the diagram (Figure 1) shown below.
Here the origin is a stable fixed point when \( c > NkT_0 \). The eigenvalues will both be negative and the virus will eventually be eradicated from the body. This can be viewed as suggesting that the clearance rate of the virus is greater than its rate of production.

Another case is when \( c < NkT_0 \). The phase plane diagram (Figure 2) now looks slightly different as shown below.

This theory predicts that the virus will be eliminated and the infection will not take. This shows a saddle point at the origin.

The last case is when \( c = NkT_0 \) (Figure 3). In this case the two lines in the phase-plane are the same and there exists a line of equilibrium. This has eigenvalues \( \lambda_1 = - (d + c) \) and \( \lambda_2 = 0 \). There is not a point that is stable, but rather the entire line is a possible equilibrium. This model is insightful because the T cell level in patients generally changes very slowly so a relationship similar to this one frequently exists.
Drug Therapies

Through mathematical modeling, drug therapies have changed. The two fields have combined their knowledge to come up with new conclusions. They use the fact that HIV is an RNA virus. When a T cell is infected with the virus, the enzyme reverse transcriptase (RT) makes a DNA copy of its RNA genome. After this occurs, the DNA copy is integrated into the DNA of the infected cell with the help of another virally encoded enzyme, integrase. The new viral DNA, also called the provirus, is duplicated every time the cell divides. Since the enzyme reverse transcriptase and integrase are the main cause of the DNA copy and the integration of the virus into the T cell, they both become the target of today’s drug therapy.

There are two main drug therapies on the market. They are the RT protease and the HIV protease. If RT is used, HIV can enter a cell, but will be unable to make a DNA copy of the viral genome, thus failing in its efforts to infect the cell. If HIV protease is used, viral particles will be created but that lack functional RT, protease, and integrase enzymes. Along with RT inhibitors and protease inhibitors, a combination of the two can be used to try to reduce the concentration of viral particles in the body. By administering one of the two drugs or a combination of each, new math models can develop to better understand the growth or decay of the virus.

Similar to the differential equations used to determine the population growth of the viral particles versus the population decay of T cells, development of new equations to show the effects of the drugs can be found. These drug therapy models represent modifications of the basic HIV model presented in this paper. The interested reader is directed to Perelson and Nelson’s excellent survey [1].

Summary

Over the course of the human immunodeficiency virus- type 1 (HIV-1) research, there have been many different approaches by different groups of people. In the mid 1990’s, a collaborative effort was made between mathematicians and biomedical scientists in the attempt to accurately model, and thus eventually understand HIV-1. This interdisciplinary unit has performed modeling, with their respective experiments, to reveal new understandings of the disease. One of the greatest discoveries was finding out that the disease incorporates many different time scales. It was further found that those time scales correspond to vital biological processes underlying HIV infection. This led to combination therapy, instead of the former monotherapy, which has led to the extension of many human lives. But, there is still a long way to go in the modeling process. The models attempt to follow and describe the three variables: uninfected T cells, infected T cells, and virus particles. This has been done mainly through deterministic models that develop through the use of differential equations. The difficulty of performing experiments on humans has slowed down the discovery process, but everyday mathematicians and biomedical scientists together hope to gain clarity and understanding.
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