Simplified Model using Ordinary Differential Equations of HIV Infection in a Single Human Patient

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***Abstract*— Model compares T-Cell concentration and Viral Cell concentration over the course of two years with one year of HAART treatment and one year removed from HAART treatment. Results reflect in a step wise fashion, a increase in T-Cell concentration while on treatment, decrease while off and a decrease in viral cell concentration, while on-treatment and increase while off.**

I. Introduction

In the United States alone, 1.1 million people are infected with HIV.[1] There are a variety of FDA-approved treatment drug classes on the market such as Nucleoside Reverse Transcriptase Inhibitors (NRTIs), non-NRTIs, Protease Inhibitors, and Highly Active Antiretroviral Therapy (HAART), just to name a few.[2] Mathematical modeling based on ordinary differential equations (ODEs) have allowed researchers to better understand the dynamics of the disease, and to optimize treatment measures. In this study, a simplified model of an HIV infection in a single human patient is used, and the concentration of T cells and virus cells are analyzed after 1 year on-treatment of HAART and 1 year off-treatment.

II. Procedure for Paper Submission

A. Use of MATLAB

The simulation was conducted in MATLAB. Code is provided in the appendix. The function ode23s was used extensively with reduced tolerance for efficient run time. Logarithmic plots were used as opposed to regular plots to accurately model noise.

B. Model Dynamics

This model uses a patient newly diagnosed with HIV, with initial conditions at the off-treatment infected steady state. Following the initial conditions, they are placed on treatment, and remain on treatment for one year. After one year, the patient goes off treatment and remains off treatment. During this two-year time period, measurements are made once per week of both the concentrations of the virus V and total T-cell count $T+T_I$. Virus measurements were made using 1 mL of blood and have a log-normal error with a standard deviation of 0.2 $\log_{10}$. T-Cell measurements are made using flow cytometry using 1uL of blood and have Poisson noise with the expected count number equal to the concentration of T cells in the blood. In the model, these errors will be reflected as noise on the graph.

III. Math

The mathematical model behind the basis of this experiment is as follows:

$$\dot{x}(t) = \lambda - dx(t) - \beta(1-\eta u)x(t)v(t)$$

$$\dot{y}(t) = \beta(1-\eta u)x(t)v(t) - ay(t) + \lambda_y(t)$$

$$\dot{v}(t) = \gamma y(t) - \omega v(t)$$

This model is a set of differential equations that characterize the viral dynamics of a patient.

A. Maximum Likelihood Parameters

Within the mathematical model provided, a set of parameters are used to accurately measure cell concentration. These parameters include:

- s: regeneration rate of target cells
- d: death rate of target cells
- B: mass-action infection rate
- u_1: death rate of infected cells
- k_I: rate at which infected cells produce virus
- c: death rate of free virus
- L(t): rate at which quiescently infected cells "wake up" and become productively infected cells

Based on previous research performed by Luo and group, the maximum likelihood parameters going into the mathematical model are as follows.

- s = 270 cells/uL/day
- d = 0.1 /day
- B (off treatment) = $1.7*10^{-6}$ mL/cells/day
- B (on treatment) = $3.7*10^{-7}$ mL/cells/day
- u_1 = 1/day
- $k_I = 1*10^{4}$ virions*uL/cells/mL/day
- c = 23/day
- L(t) = $1*10^{-3}$ cells/uL/day

These measurements vary widely from patient to patient, yet for the basis of this experiment, they are assumed to be uniform.

Further on in the experiment, the value for s is optimized for the smallest sum-of-squares error.

B. *Differential Equations*

Given the mathematical model and maximum likelihood parameters, a set of differential equations were produced that reflect the concentration of uninfected target cells (T), the concentration of infected target cells (TI), and the population of the free virus (V).

- $\dot{T} = s - dT - BVT$
- $\dot{T}_I = BVT - u_1 T_I + L(t)$
- $\dot{V} = k_I T_I - cV$

IV. Results

Both figures of T-Cell (1) and Virus (2) concentrations take the form of a stepwise shape. Since the initial conditions are set with beta as off treatment, the initial T-Cell Concentration is very low, and the initial viral concentration is very high.

Following the start of treatment, T-Cell measurements increase to approximately 2700 cells/uL (relatively high) and remain at that level for the rest of the one year of treatment. The concentration of the virus remains rather low, sitting near to 0 cells/uL. This rate remains constant in its true state and is likely due to the body adapting to the treatment. With noise, it is observed that concentrations are sporadic, surrounding the step function of the true state.

Once the patient goes off treatment, the inverse relationship occurs. That is, T-Cell concentration decreases to around 1500 cells/uL and Virus Cell concentration increases to approximately 6,000 cells/uL. This change in concentration occurs 40 days following going off treatment and is biologically discussed later in the discussion.

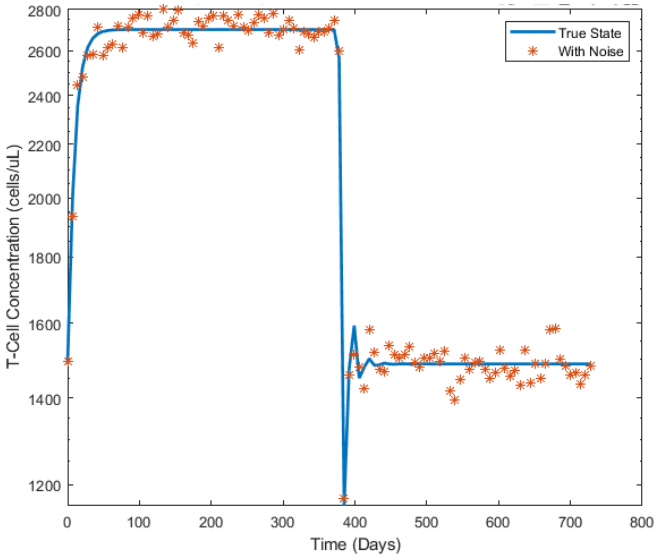

Figure 1: T-Cell concentration (cells/uL) in blood with 1 year on-treatment, 1 year off-treatment. Poisson error noise is reflected by the stars along the true state step function.

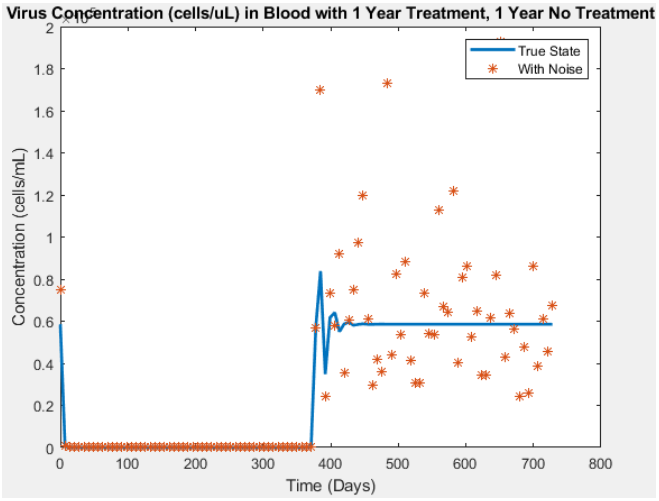

Figure 2: Virus concentration (cells/uL) in blood with 1 year on-treatment, 1 year off-treatment. Log-normal error is reflected by the stars along the true state step function.

One simulation was conducted where s was allowed to vary from 1 to 1000 (see Appendix: sumOfSquares function). The function fmincon was used and the smallest sum-of-squares error between the measured data and noise free values was recorded. Although s was varying, all other parameters were set to their true values. An optimal s of 270 was discovered following the simulation. This s produced the smallest sum-of-squares error. The code ran for approximately 3 hours due to the iterations of ode23s.

V. Discussion

The introduction of combination therapy, known as HAART, has been linked to reductions in the morbidity and mortality associated with HIV-1 infection and AIDS.[3] This medication suppresses viral replication and dramatically reduces HIV-1 viral load to below the limits of detection, as shown in figure 2.[4] This leads to a significant reconstruction of the immune system, as reflected in the increase in circulating $CD4^+$ T-lymphocytes, as shown in figure 1.[5,6,7] HAART reflects the pattern of combination therapy using three antiretroviral agents aimed towards two distinct molecular targets. This biological strategy is the underlying basis for preventing the evolution of drug resistance.

One can speculate the pattern of T-Cell concentration to gradually increase while on-treatment and level off when taken off treatment and for virus concentrations to gradually decrease while on-treatment and level off when taken off treatment. Yet in this model, both concentrations take the form of a step function. This can be contributed to the differential equations used to model the concentrations. The changing value of beta for on and off treatment causes the corresponding spike and drop within the plot.

In biological terms, during the initial 50 days of treatment, the body is attempting to adjust to the HAART therapy and achieve homeostasis. Following the first 50 days, concentrations level out, suggesting the body has achieved homeostasis while on therapy, and the immune system is slowly rebuilding. Once the patient goes off-treatment, it can be assumed that the immune system, which was slowly strengthening while on HAART, becomes overwhelmed by the flux of viral cells and the number of healthy T-Cells begins to decrease, and the number of infected T-Cells and virus begins to decrease, and once the body achieves homeostasis, the numbers begin to plateau.

By just observing the set of differential equations and the beta values, it is worth noting that on-treatment beta is a power 10 smaller than off-treatment beta. Plugging these values into the differential equation yields a smaller rate of healthy T-cell growth and a higher rate of infected T-cell growth while on-treatment, and the inverse relationship while off-treatment. This mathematical note aligns with the step shown in figures 1 and 2 and can be used to explain the mathematical rationale behind the shape of the graph.

VI. Conclusion

This simplified model provided as a good analysis of the effectiveness of HAART treatment on HIV patients. By utilizing differential equations to represent disease dynamics, it was discovered that with one year on-treatment, there was an increase in T-Cell concentration and a decrease in viral cell concentration to zero, and with one year off-treatment, there was an increase in viral-cell concentration and a decrease in T-Cell concentration. Further research must be conducted to determine to efficacy of this model with other diseases, such as cancer dynamics.

Appendix

A. Code for Main Script

```
%Maximum Likelihood Estimates for
Parameters(units are commented)

global s d bOn bOff u1 kI c L tspan
s=270;                %cells/uL/day
d=0.1;                %/day
bOff=1.7e-6;           %mL/cells/day
bOn=3.7e-7;          %mL/cells/day
u1=1;                 %/day
kI=1e4;
%virions*uL/cells/mL/day
c=23;                 %/day
L=1e-3;               %cells/uL/day
tspan = [0:7:730];  %span of 2 years in
weekly increments


%Calculating initial conditions (bOff)
syms T TI V
Tp = s - d*T - bOff*V*T;
TIp = bOff*V*T - u1*TI + L;
Vp = kI*TI - c*V;
[T TI V] = solve([Tp==0, TIp==0, Vp==0],
[T, TI, V]);
x1 = eval(T);
x2 = eval(TI);
x3 = eval(V);
initconds=[double(x1(2)), double(x2(2)),
double(x3(2))];


%Solves the ODEs for concentrations at
each time point
opts = odeset('RelTol',1e-3);
[t,x] =
ode23s(@odeConc,tspan,initconds',opts);


%To be used in sumOfSquares Function
global array1
array1=x;

totalTCell = (x(:,1)+x(:,2));
totalVirus = x(:,3);
noiseVirus =
lognrnd(log(totalVirus),0.2*log(10));
noiseTCell = poissrnd(totalTCell);


%Graphs
figure
semilogy
(tspan,totalTCell,'LineWidth',2)
hold on
semilogy (tspan,noiseTCell, '*')
legend('True State','With Noise')
title('T-Cell Concentration (cells/uL)
in Blood with 1 Year Treatment, 1 Year
No Treatment')
xlabel('Time (Days)')
ylabel('T-Cell Concentration
(cells/uL)')
hold off

figure
semilogy (tspan,
totalVirus,'LineWidth',2)
hold on
semilogy (tspan, (noiseVirus), '*')
legend('True State','With Noise')
```

```
title('Virus Concentration (cells/uL) in
Blood with 1 Year Treatment, 1 Year No
Treatment')
xlabel('Time (Days)')
ylabel('Concentration (cells/mL)')
hold off

%Optimal S calculations given
sumOfSquares function: optimalS=270
optimalS=fmincon(@sumOfSquares,0,1,1000)
```

B. Code for odeConc Function (differential equations)

```
function odes = odeConc(t,xp,y0)

global s d bOn bOff u1 kI c L

%Accounts for on-treatement and off
treatment beta values
if t<366
    B=bOn;
else
    B=bOff;
end

T=xp(1); T1=xp(2); V=xp(3);
Tp = vpa(s-(d*T)-(B*V*T),4);
TIp = vpa(B*V*T - u1*T1 + L,4);
Vp = vpa(kI*T1 - c*V,4);
odes = [double(Tp); double(TIp);
double(Vp)];

end
```

C. Code for sumOfSquares Function

```
function [cost] = sumOfSquares(sNew)
    global s d bOn u1 kI c L tspan
array1

    s=sNew;

    syms T TI V
    Tp = s - d*T - bOn*V*T;
    TIp = bOn*V*T - u1*TI + L;
    Vp = kI*TI - c*V;
    [T TI V] = solve([Tp==0, TIp==0,
Vp==0], [T, TI, V]);
    x1 = eval(T);
    x2 = eval(TI);
    x3 = eval(V);
    initconds=[double(x1(2)),
double(x2(2)), double(x3(2))];

    %Solves the ODEs for concentrations
at each time point

    opts = odeset('RelTol',1e-3);
    [t1,array2] =
ode23s(@odeConc,tspan,initconds',opts);

    count=0;
    for i = [1:1:length(tspan)]
        sOs=(array2(i)-array1(i))^2;
        count=sOs+count;
    end
    cost=count;
end
```

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