Department of Applied Mathematics and Statistics
COLORADO SCHOOL OF MINES
MATH484: Capstone - Mathematical and Computational Modeling

Assignment #2, Spring 2015
SOLUTIONS

1. HIV Handout, p. 350, Problem **2**.

The biological interpretation of r is that it represents the per capita rate at which the T-cell population grows logistically due to the clonal selection of T-cells activated by a specific antigen. The percent increase in the T-cell steady state is 3.16% and can be computed with the following code and associated output.

MATLAB Code

```
% 4CM - Latent Model with Logistic growth
clc;clear;

% Parameter Initialization
s = 10;r = 0.03;Tmax = 1500;mu = 0.02;alpha = 2.4;beta = 0.24;
k1 = 2.4e-5;k2 = 3e-3;N = 1400;

%Non-infective equilibrium T-cell count with r
p = r - mu;
T0r = (Tmax/(2*r))*(p + sqrt(p^2 + 4*s*(r/Tmax)));

%Non-infective equilibrium T-cell count with r_n
r_n = 1.1*0.03;
p = r_n - mu;
T0r_n = (Tmax/(2*r_n))*(p + sqrt(p^2 + 4*s*(r_n/Tmax)));

format short g
percent_inc = 100*(T0r_n - T0r)/T0r;
fprintf('The T-cell steady state increases by %3.2f%% \n', percent_inc);

% This part can be used for Problem 2
1 - (alpha*(k2 + mu))/(k1*T0r*[k2*(N-1) - mu])
```

Output

```
The T-cell steady state increases by 3.16%
```

2. One class of antiretroviral drug that is currently used to combat HIV is called a *reverse transcriptase inhibitor* or *RTI*. Such drugs stop virions from copying their RNA within an infected cell by stifling a key viral enzyme that is required for reverse transcription. The overall effect is a decrease in latently, and hence actively, infected T-cells. We will incorporate this into the model. Define $\epsilon_{RTI} \in [0,1]$ to be the efficacy of an RTI, where $\epsilon_{RTI} = 0$ when the drug is not present in the body and $\epsilon_{RTI} = 1$ when the drug is 100% effective. Assume that the person under study is being treated with an RTI and write down the new model. If $\epsilon_{RTI} = 1$ what happens to the condition the ensures the stability of the non-infective state? What efficacy is needed in order to guarantee that the non-infective state is stable? Provide an expression for this efficacy in terms of system parameters, and then use numerical parameter values (p. 350) to compute the ϵ_{RTI} that guarantees stability. Finally, simulate this system for two different values of ϵ_{RTI} to demonstrate that your value is accurate.

Assuming treatment, the model becomes

$$(1) \qquad \begin{cases} \dfrac{dT}{dt} = s + rT\left(1 - \dfrac{T + T_L + T_A}{T_{max}}\right) - \mu T - k_1(1-\epsilon_{RTI})TV \\ \dfrac{dT_L}{dt} = k_1(1-\epsilon_{RTI})TV - \mu T_L - k_2 T_L \\ \dfrac{dT_A}{dt} = k_2 T_L - \beta T_A \\ \dfrac{dV}{dt} = N\beta T_A - \alpha V - k_1(1-\epsilon_{RTI})TV \end{cases}$$

Note that the rate of infection is just decreased and k_1 has merely been replaced by $k_1(1-\epsilon_{RTI})$ throughout. Now, we derived the stability condition in class, namely

$$\frac{Nk_1k_2T_0}{(k_2+\mu)(\alpha + k_1T_0)} < 1.$$

Replacing k_1 with the rate above, we find

$$\frac{Nk_1k_2T_0}{(k_2+\mu)\left[\alpha + k_1(1-\epsilon_{RTI})T_0\right]}(1-\epsilon_{RTI}) < 1.$$

Thus, if $\epsilon_{RTI} = 1$, then the stability condition is satisfied regardless of what the other parameters in the system may be. Hence, perfect drug efficacy ensures that the system always tends to the non-infective equilibrium. To determine the minimal efficacy necessary to ensure that the stability condition is satisfied, we just solve for ϵ_{RTI}, so that

$$\epsilon_{RTI} > 1 - \frac{\alpha(k_2+\mu)}{k_1T_0[k_2(N-1)-\mu]}.$$

Using the parameter values in the handout, we find

$$\epsilon_{RTI} > 0.4494.$$

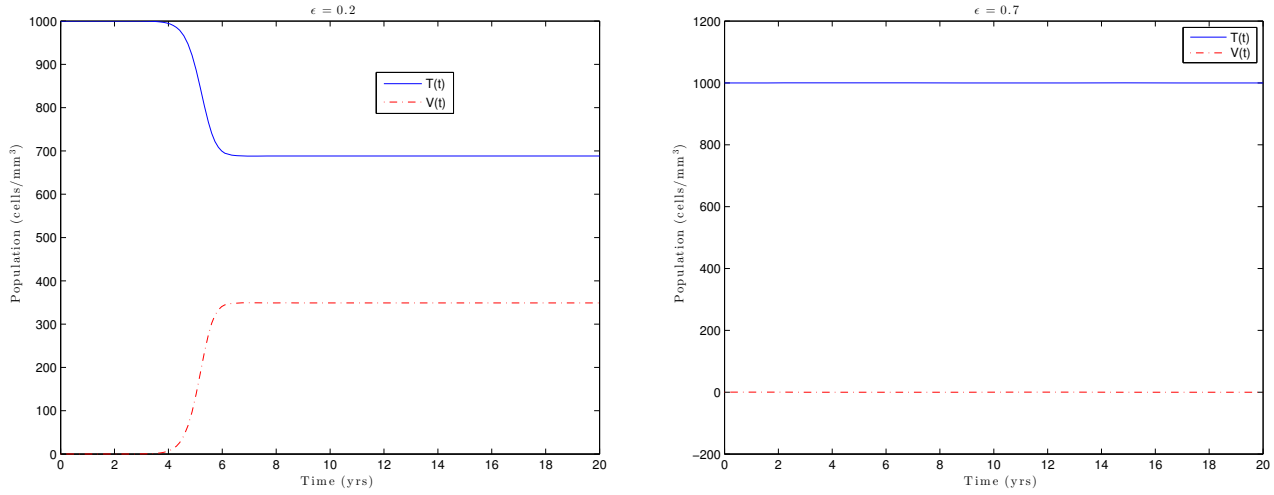

Figure 1: Graphs for Problem 2 with $\epsilon_{RTI} = 0.2$ and $\epsilon_{RTI} = 0.7$, respectively

The simulations are then given by the code below, in which the value of the `eps` variable is altered to produce the necessary graph.

MATLAB Code

```
% 4CM - Latent Model with Logistic growth
clc;clear;

% Parameter Initialization
s = 10;
r = 0.03;
Tmax = 1500;
mu = 0.02;
alpha = 2.4;
beta = 0.24;
k1 = 2.4e-5;
k2 = 3e-3;
N = 1400;

%Non-infective equilibrium T-cell count
p = r - mu;
T0 = (Tmax/(2*r))*(p + sqrt(p^2 + 4*s*(r/Tmax)));

eps = 0.7;% eps_crit = 0.4494

k1 = k1*(1-eps);

R = k1*k2*N*T0/((k2+mu)*(alpha+k1*T0))
```

```
% Let y = [(1) Uninfected T-cell count; (2) Latently Infected T-cell count;
% (3) Actively Infected T-cell count; (4) Virion count];

% Initial condition, time span
y0 = [1e3; 0; 0; 1e-3];
tSpan = [0 365*20];

% Differential Equation
dy = @(t,y) [s + r*y(1)*(1 - ((y(1)+y(2)+y(3))/Tmax))- mu*y(1) - k1*y(1)*y(4);
             k1*y(1)*y(4) - mu*y(2) - k2*y(2);
             k2*y(2) - beta*y(3);
             N*beta*y(3) - k1*y(1)*y(4) - alpha*y(4)];

% Solve ODE
[tOut yOut] = ode15s(dy, tSpan, y0);

fig1=figure('Color',[1 1 1]);
set(fig1,'defaulttextinterpreter','latex');
tOutYr = tOut/365;
plot(tOutYr, yOut(:,1),  tOutYr, yOut(:,4),'-.r');

legend('T(t)', 'V(t)');
xlabel('Time (yrs)');
ylabel('Population (cells/mm$^3$)');
title('$\epsilon = 0.7$')
```

3. Assume $n = 1$ and write down the mutation model. One important class of equilibrium states are triples of the form

$$(v, x, z) = \left(v^*, \frac{g}{k}, \frac{h}{k}\right)$$

where $v^* > 0$ is arbitrary. Show that these equilibria are stable if and only if $N_{div} > 1$. This can be expanded for arbitrary $n \in \mathbb{N}$ to prove Observation 1 (on p. 353)

For $n = 1$, the mutation model is

$$\begin{cases} \dfrac{dv}{dt} = v\,(a - bz - cx) \\ \dfrac{dx}{dt} = v\,(g - kx) \\ \dfrac{dz}{dt} = v\,(h - kz)\,. \end{cases} \tag{2}$$

We denote the equilibrium state by

$$y^* = \left(v^*, \frac{g}{k}, \frac{h}{k}\right).$$

In order to determine conditions for stability of these equilibria, we compute the Jacobian:

$$J = \begin{bmatrix} a - bz - cx & -cv & -bv \\ g - kx & -kv & 0 \\ h - kz & 0 & -kv \end{bmatrix}$$

and evaluate this at the state to find

$$A := J|_{y^*} = \begin{bmatrix} a - \frac{bh}{k} - \frac{cg}{k} & -cv^* & -bv^* \\ 0 & -kv^* & 0 \\ 0 & 0 & -kv^* \end{bmatrix}.$$

Then, we find the eigenvalues of this matrix using

$$0 = \det\left(A - \lambda \mathbb{I}\right) = (kv^* + \lambda)^2 \left(a - \frac{bh + cg}{k} - \lambda\right).$$

Hence, they are

$$\lambda_{1,2} = -kv^* < 0$$

and

$$\lambda_3 = a - \frac{bh + cg}{k}.$$

In order for $\mathrm{Re}(\lambda_3) < 0$, the parameters must satisfy the condition

$$ak - bh < cg$$

or stated another way, $N_{div} > 1$.

4. Assume that the individual in the mutation model (with $n \in \mathbb{N}$ arbitrary) is treated with an RTI of efficacy $\epsilon_{RTI} \in [0, 1]$. How does this alter the model? Determine the efficacy needed to ensure that the infection is controlled - derive both an expression and a number for this by using given parameter values (p. 354) as in Problem 2. Finally, simulate this system with $n = 6$ for two different values of ϵ_{RTI} to demonstrate that your value is accurate.

Introducing a reverse transcriptase inhibitor merely decreases the rate of growth within the virus population. Hence, we replace a in the model with $a(1 - \epsilon_{RTI})$. Since the condition needed to control the infection was

$$N_{div} = \frac{cg}{ak - bh} > n,$$

we replace a as in the model and after some algebra we find

$$\epsilon_{RTI} > 1 - \frac{cg + nbh}{nak}.$$

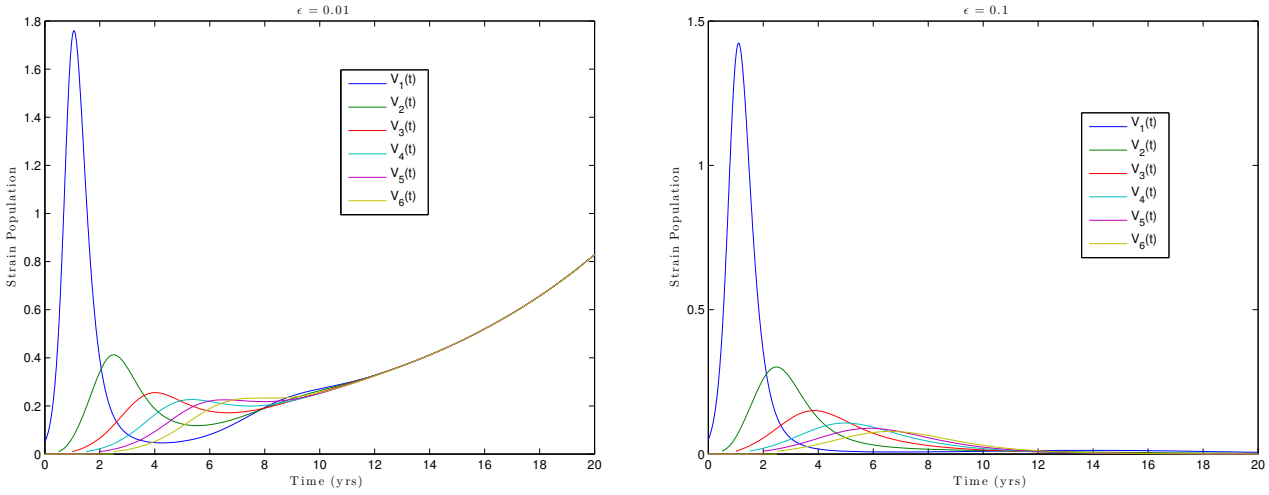

Figure 2: Graphs for Problem 4 with $\epsilon_{RTI} = 0.01$ and $\epsilon_{RTI} = 0.1$, respectively

Using the parameter values given in the handout, this is just

$$\epsilon_{RTI} > 0.033.$$

Alternatively, if $a(1 - \epsilon_{RTI})k < bh$ then the infection is controlled regardless of the value of n, and this occurs for

$$\epsilon_{RTI} > 1 - \frac{bh}{ak} = 0.2$$

Finally, the MATLAB code to simulate the system and produce the associated graphs is given below.

MATLAB Code

```
% HIV Mutation Model with immune response
clear;clc;

% Coefficients
a = 5; b = 4; c = 5; g = 1; h = 1; k = 1;

eps = 0.1;

a = a*(1-eps);

Ndiv = c*g/(a*k - b*h)

% Initial condition, time span
y0 = [0.05; zeros(12,1)];

% Differential Equation
```

```
dy = @(t,y) [(a-b*y(13) - c*y(7))*y(1);
             (a-b*y(13) - c*y(8))*y(2);
             (a-b*y(13) - c*y(9))*y(3);
             (a-b*y(13) - c*y(10))*y(4);
             (a-b*y(13) - c*y(11))*y(5);
             (a-b*y(13) - c*y(12))*y(6);
             g*y(1) - k*y(7)*sum(y(1:6));
             g*y(2) - k*y(8)*sum(y(1:6));
             g*y(3) - k*y(9)*sum(y(1:6));
             g*y(4) - k*y(10)*sum(y(1:6));
             g*y(5) - k*y(11)*sum(y(1:6));
             g*y(6) - k*y(12)*sum(y(1:6));
             (h-k*y(13))*sum(y(1:6))];

fig1=figure('Color',[1 1 1]);
set(fig1,'defaulttextinterpreter','latex');

% Solve ODE up to first mutation
[t1 yOut] = ode45(dy, [0, 0.5], y0);
V = yOut(:,1:6);
S1 = sum(yOut(:, 7:12));
z1 = yOut(:, 13);
plot(t1, V)
hold on

%New "initial" data
y1 = yOut(end,:);
y1(2) = y1(2) + 1e-2;

% Solve ODE to second mutation
[t2 yOut] = ode45(dy, [0.5, 1], y1);
V = yOut(:,1:6);
S2 = sum(yOut(:, 7:12));
z2 = yOut(:, 13);
plot(t2, V)

%New "initial" data
y2 = yOut(end,:);
y2(3) = y2(3) + 1e-2;

% Solve ODE to second mutation
[t3 yOut] = ode45(dy, [1, 1.5], y2);
V = yOut(:,1:6);
S3 = sum(yOut(:, 7:12));
z3 = yOut(:, 13);
```

```
plot(t3, V)

%New "initial" data
y3 = yOut(end,:);
y3(4) = y3(4) + 1e-2;

% Solve ODE to second mutation
[t4 yOut] = ode45(dy, [1.5, 2], y3);
V = yOut(:,1:6);
S4 = sum(yOut(:, 7:12));
z4 = yOut(:, 13);
plot(t4, V)

%New "initial" data
y4 = yOut(end,:);
y4(5) = y4(5) + 1e-2;

% Solve ODE to second mutation
[t5 yOut] = ode45(dy, [2, 2.5], y4);
V = yOut(:,1:6);
S5 = sum(yOut(:, 7:12));
z5 = yOut(:, 13);
plot(t5, V)

%New "initial" data
y5 = yOut(end,:);
y5(6) = y5(6) + 1e-2;

% Solve ODE to second mutation
[t6 yOut] = ode45(dy, [2.5, 20], y5);

V = yOut(:,1:6);
S5 = sum(yOut(:, 7:12));
z5 = yOut(:, 13);
plot(t6, V)

legend('V_1(t)', 'V_2(t)', 'V_3(t)', 'V_4(t)', 'V_5(t)', 'V_6(t)');
xlabel('Time (yrs)');
ylabel('Strain Population');
title('$\epsilon = 0.1$')
```