Erin

Renee

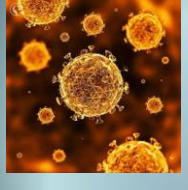
Glencoe High School, Hillsboro, OR

Seattle University, Seattle, WA

AMY

IZZIE

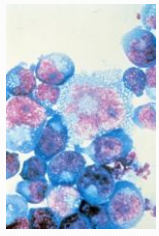
Modeling HIV Infection of T-Cells



Renee, Amy, Izzie, and Erin

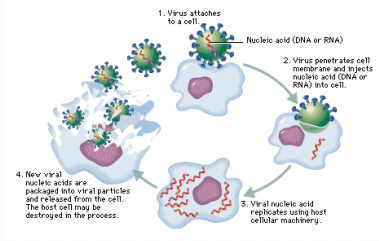
Human Immunodeficiency Virus (HIV)

- Causes Acquired Immunodeficiency Syndrome (AIDS)
  - Failure of the immune system
  - Often a long time period between initial infection and serious symptoms
- Virus transferred through bodily fluids such as blood
  - HIV present as free virus particles and infected immune cells



HIV Mechanism

- Infects important cells of human immune system
  - CD_4+ helper T-cells



Model Background

- The helper T-cells are thought to be particularly vulnerable to attack.
- Ordinary differential equations have been used to model T-cell populations.
- Using delay differential equations can more accurately model virus spread and treatment response.

The ODE System

- Let $T(t)$ represent the concentration of healthy T-cells, $I(t)$ represent that of actively infected T-cells, and $V(t)$ represent that of free HIV virus.
  - $\frac{dT}{dt} = s - d_T T + rT\left(1 - \frac{T+I}{T_{max}}\right) - kVT$
  - $\frac{dI}{dt} = k'VT - d_I I$
  - $\frac{dV}{dt} = Nd_b I - kVT - d_V V$

Parameters and Variables		
Dependent Variables		
T	Uninfected T-cell	$1000\ mm^{-3}$
I	Infected T-cell	0
V	Initial density of HIV	$10^{-3}\ mm^{-3}$
Parameters and Constants		
μ_T	Natural death rate of T-cells	$0.02\ day^{-1}$
μ_I	Blanket death rate of infected T-cells	$0.26\ day^{-1}$
μ_b	Lytic death rate for infected cells	$.24\ day^{-1}$
μ_V	Death rate of free virus	$2.4\ day^{-1}$
k	Rate T-cells become infected	$2.4 \times 10^{-5}\ mm^3\ day^{-1}$
k'	Rate infected cells become active	$2 \times 10^{-5}\ mm^3\ day^{-1}$
r	Growth rate of T-cell population	$0.03\ day^{-1}$
N	Number or virions produced	$Varies$
T_{max}	Maximum T-cell population	$1500\ mm^{-3}$
s	Source term for uninfected T-cells	$10\ (day)^{-1}(mm^{-3})$
Derived Quantities		
T_0	T-cell population for HIV-neg person	$1000\ mm^{-3}$

Healthy T-Cell Equation

$$\frac{dT}{dt} = s - d_T T + rT\left(1 - \frac{T+I}{T_{max}}\right) - kVT$$

- s: T-cells from their source
- d_T : normal death rate of T-cells
- r: growth rate of T-cell population
- T_{max} : carrying capacity for T-cells
- k: rate at which free virus infects healthy cells

Infected T-Cell Equation

$$\frac{dI}{dt} = k'VT - d_I I$$

- k' : rate at which infected T-cells become actively infected
- d_I : death rate of infected T-cells

Free Virus Equation

$$\frac{dV}{dt} = N d_b I - kVT - d_V V$$

- N : number of free viral particles released by bursting of an infected cell
- d_b : rate at which infected cells burst
- k: rate at which free virus infects healthy cells
- d_V : rate at which virus particles die

Non-infected Steady State Solution

- $I(t), V(t) = 0$
- $T(t) = \frac{r - d_T + \left[(r-d_T)^2 + \frac{4rs}{T_{max}}\right]^{\left(\frac{1}{2}\right)}}{2r/T_{max}} = T_0$
- $E_0 = (T_0, 0, 0)$

Note: we will not discuss this steady state any further. We are only interested in the infected steady state.

Non-Zero Steady State

- $\bar{T} = \frac{d_V d_I}{k' N d_b - k d_I}$
- $\bar{I} = \frac{k' \bar{T} \bar{V}}{d_I}$
- $\bar{V} = \frac{d_I\left[\left(s + (r-d_T)\bar{T}\right) T_{max} - r\bar{T}^2\right]}{\bar{T}\left[k' r \bar{T} + k\, d_I\, T_{max}\right]}$
- These values are all known and, thus, $\bar{E} = (260.7, 42.5, 1768.2)$

Stability of the Uninfected State

- A specific value of N defined as $N_{crit} = \frac{d_I(d_V + k\,T_0)}{k' d_b T_0}$ =131. 3 has the following result:
  - If $N < N_{crit}$ the uninfected state is stable and the infected steady state does not exist.
  - If $N > N_{crit}$, the uninfected state becomes unstable and the infected steady state exists.

Stability of the Infected Steady State

- To determine the stability, we linearize the system.
- This gives the characteristic equation:

$$\lambda^3 + a_1 \lambda^2 + (a_2 + a_4)\lambda + (a_3 + a_5) = 0$$

where $a_1, a_2, a_3, a_4,$ and a_5 are dependent on the parameters $d_T, d_I, d_b, d_V, k, k', r, N, T_{max}, s,$ and T_0.

Assessing Stability

- The Routh-Hurwitz criterion tells us when the roots of cubic equations have negative real parts (i.e. stable!). We can apply this to our characteristic equation:

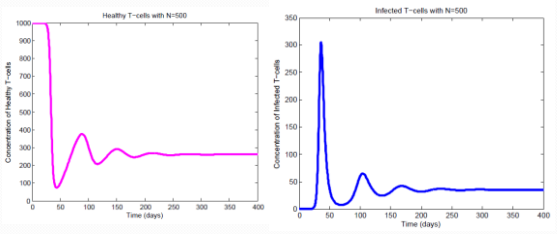
$$\lambda^3 + a_1\lambda^2 + (a_2 + a_4)\lambda + (a_3 + a_5) = 0$$

- Show: $a_1 > 0,\ \ a_3 + a_5 > 0,\ a_1(a_2 + a_4) - (a_3 + a_5) > 0$
- The values of a_i are:
  $a_1 = 2.71\ \ a_2 = .74\ \ a_3 = -.0003\ \ a_4 = -.623\ \ a_5 = .0273$
- Apply the criterion:

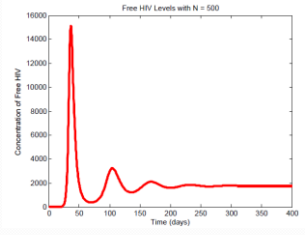
$$a_3 + a_5 = .027 > 0$$
$$a_1(a_2 + a_4) - (a_3 + a_5) = .2928 > 0$$

SUCCESS! STABILITY!

ODE Model – Healthy and Infected Cells

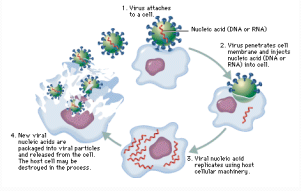


ODE Model – Free Virus



Delay Differential System

- We now include a discrete delay to reflect the time between when a cell becomes infected and when it is itself capable of sending out new virus particles.



Delayed System

- $\frac{dT(t)}{dt} = s - d_T T(t) + rT(t)\left(1 - \frac{T(t)+I(t)}{T_{max}}\right) - kT(t)V(t)$
- $\frac{dI(t)}{dt} = k'T(t-\tau)V(t-\tau) - d_I I(t)$
- $\frac{dV(t)}{dt} = Nd_b I(t) - kT(t)V(t) - d_V V(t)$

Stability of the Uninfected State

- The equilibrium solutions of the delayed system remain the same.
- Adding the delay does not affect the instability of the uninfected state.

Infected Equilibrium

- The stability of the infected steady state equilibrium solution may be affected by the delay.
- We define the perturbations:

$$x(t) = T(t) - \bar{T}$$

$$y(t) = I(t) - \bar{I}$$

$$z(t) = V(t) - \bar{V}$$

Linearized System

- $\frac{dx(t)}{dt} = -\left(d_T + \frac{2r\bar{T}+r\bar{I}}{T_{max}} + k\bar{V} - r\right)x(t) - \frac{r\bar{T}}{T_{max}}y(t) - k\bar{T}z(t)$
- $\frac{dy(t)}{dt} = k'\bar{V}x(t-\tau) - d_I y(t) + k'\bar{T}z(t-\tau)$
- $\frac{dz(t)}{dt} = -k\bar{V}x(t) + Nd_b y(t) - (k\bar{T} + d_V)z(t)$

Characteristic Equation

- From the linearized system, we obtain the characteristic equation:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 e^{-\lambda\tau} + a_4\lambda e^{-\lambda\tau} + a_5 = 0$$

Note: As before, the coefficients are constants which depend on the system parameters (defined in the table)

- This is complex! Transcendental a.k.a hard to solve!

Stability Analysis

- We know that solutions are stable if the real part of λ is negative.
- We know that for $\tau = 0$, the equilibrium is stable. By continuity, we know that in order for the stability to change, there must be a value of τ for which λ is purely imaginary.

Stability

- We assume $\lambda = 0 + yi$ for some real y.
- With much algebraic manipulation, we obtain:

$$y^6 + (a_1^2 - 2a_2)y^4 + (a_2^2 - 2a_1a_5 - a_4^2)y^2 + \left(a_5^2 - a_3^2\right) = 0$$

Stability Analysis

$$y^6 + (a_1^2 - 2a_2)y^4 + (a_2^2 - 2a_1a_5 - a_4^2)y^2 + \left(a_5^2 - a_3^2\right) = 0$$

If we replace values of the above equation with

$w = y^2$
$\alpha = a_1^2 - 2a_2$
$\beta = a_2^2 - 2a_1a_5 - a_4^2$
$\gamma = a_5^2 - a_2^3$

We obtain: $h(w) = \alpha w^3 + \beta w^2 + \gamma = 0$.

Stability Continued

- For our known parameter values, $\gamma > 0$, so we assume $\gamma \geq 0$.
- Then $h(0) = \gamma \geq 0$.
- Also, $\frac{dh(w)}{dw} = 3w^2 + 2\alpha w + \beta = 0$ when $w = \frac{-\alpha \pm \sqrt{\alpha^2 - 3\beta}}{3}$
- If $\beta > 0$, then neither of these values are positive, so h has no positive critical points. Thus h is positive for all $w \geq 0$.
- h has no positive roots, and hence there is no $w=y^2$ which fulfills the characteristic equation.

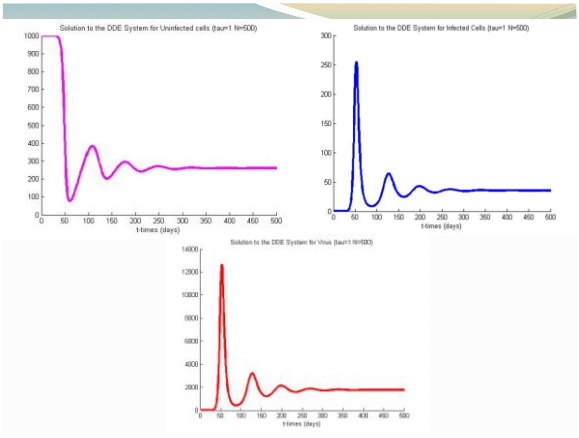
Results

We have that if

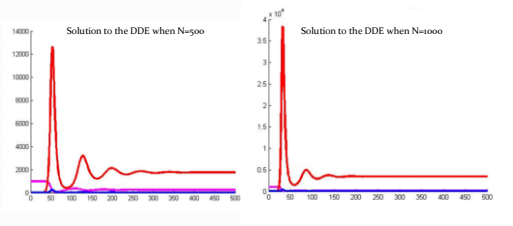
i) $a_1 > 0, a_3 + a_5 > 0, a_1(a_2 + a_4) - (a_3 + a_5) > 0$
ii) $\gamma \geq 0$ *and* $\beta > 0$

Then the infected steady state of the delay model is stable for all $\tau \geq 0$

Recall, the infected steady state: $\bar{E} = (260.7, 42.5, 1768.2)$



Varying the Value of N



Conclusions

- The infected state equilibrium is stable for our known parameter values.
- This indicates that cell populations will initially fluctuate, but will eventually settle to an steady state.
- This analysis holds only for the parameter values given, and could be false if any of the parameters are altered.
- These parameters likely vary among individuals, and possibly over time in the same individual.

Conclusions

- This may provide a partial explanation of why HIV may infect people for years without apparent effect, and then suddenly cause extreme illness or death.
- Delay models can also be used to model other aspects of HIV progression, such as effects of treatment. We can also use other types of delays to model aspects of HIV.

THANK YOU ANGELINA!!

(Angela + Marina)

.....Questions?