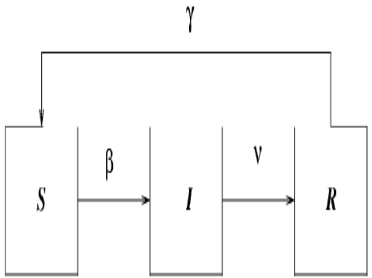
SIRS epidemics

- McKendrick and Kermack, *A Contribution to the Mathematical Theory of Epidemics* (1927)
- we study SIR and SIRS without 'vital dynamics'
- S, I, R - susceptible, infected, removed class (temporary immunity)
- *mass action kinetics* (similar to chemical reactions)
- *conservation law* $(S(t) + I(t) + R(t) = N)$



SIRS model

- the model equations are

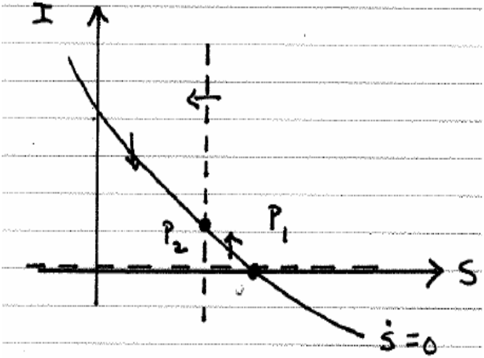
$$\frac{dS}{dt} = -\beta SI + \gamma R \quad (1)$$
$$\frac{dI}{dt} = \beta SI - \nu I \quad (2)$$
$$\frac{dR}{dt} = \nu I - \gamma R \quad (3)$$

- use the conservation law to eliminate R

$$\frac{dS}{dt} = -\beta SI + \gamma(N - S - I) \quad (4)$$
$$\frac{dI}{dt} = \beta SI - \nu I \quad (5)$$

- Nullclines:
  - $\frac{dS}{dt} = 0 \Rightarrow I = \frac{\gamma(N-S)}{\beta S+\gamma}$
  - $\frac{dI}{dt} = 0 \Rightarrow I = 0, S = \frac{\nu}{\beta}$

- Equilibria (S_k, I_k): $P_1 = \left(N, 0\right)$, $P_2 = \left(\frac{\nu}{\beta}, \frac{\gamma(N-S_2)}{\beta S_2+\gamma}\right)$
- I_2 could be also written as $I_2 = \frac{\gamma(N\beta-\nu)}{\beta(\nu+\gamma)}$
- when is equilibrium P_2 physical?



- compute the Jacobian at a stationary point (S_0, I_0):

$$\mathbf{J} = \begin{pmatrix} -I_0\beta - \gamma & -S_0\beta - \gamma \\ I_0\beta & S_0\beta - \nu \end{pmatrix}$$

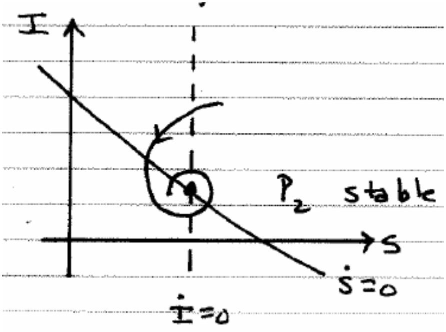
- $a_{11} = -I_0\beta - \gamma$, $a_{12} = -S_0\beta - \gamma$, $a_{21} = I_0\beta$, $a_{22} = S_0\beta - \nu$
- Equilibrium $P_1 = (N, 0)$: use Routh-Hurwitz criterium
  - $a_{11} + a_{22} = -\gamma + (N\beta - \nu)$
  - $det(J) = -\gamma(N\beta - \nu)$

  If $det(J) > 0$ and $a_{11} + a_{22} < 0$, then P_1 is stable (by R-H). However, if we know the eigenvalues, we can say a bit more $(\lambda_1 = -\gamma, \lambda_2 = N\beta - \nu)$.

  if P_2 is physical $\Rightarrow$ P_1 is a saddle
  if P_2 is not physical $\Rightarrow$ P_1 is a stable node

- Equilibrium $P_2 = (S_2, I_2)$: again Routh-Hurwitz criterium (assuming physical P_2)
  - $a_{11} + a_{22} = -(\beta I_2 + \gamma) < 0$
  - $det(J) = \beta I_2(\nu + \gamma) > 0$

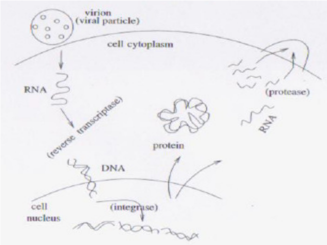
  So P_2 is stable (by R-H). However, to determine for what parameter values there is stable node or stable spiral, tedious algebra is needed.



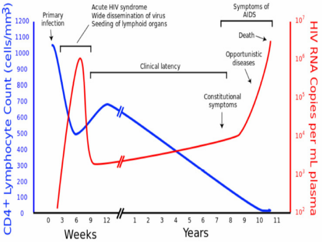
- Suppose that $\beta = \nu = \gamma = 1$. For what values of N does one have stable spirals, or stables nodes, for P_2?

Modelling Human Immunodeficiency Virus (HIV) infection

- RNA virus $\rightarrow$ needs reverse transcriptase to synthesize RNA into DNA
- infects mostly $CD4^+$ T cells
- primary/acute HIV infection, clinically asymptomatic stage, symptomatic HIV infection, AIDS



(a)



(b)

HIV dynamics

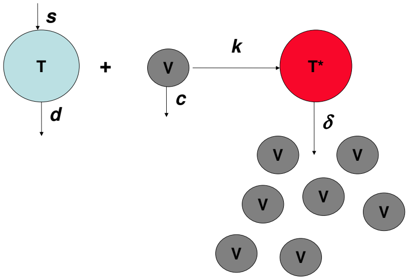
- T, T^* - resting/infected CD4$^+$ T cells, V - HIV virions
- proposed equations:

$$\frac{dT}{dt} = s - dT - kVT \tag{6}$$

$$\frac{dT^*}{dt} = kVT - \delta T^* \tag{7}$$

$$\frac{dV}{dt} = N\delta T^* - cV \tag{8}$$

- cell/mm^3, virions/mm^3, $N \approx 10^2 - 10^3$ virions/cell



Dimensionless model

- introduce $\tau = \frac{T}{\alpha}$, $\tau^* = \frac{T^*}{\alpha^*}$, $v = \frac{V}{\beta}$, $t' = \frac{t}{\gamma}$
- we have

$$\frac{\alpha}{\gamma}\frac{d\tau}{dt'} = s - \underline{d\alpha}\tau - \underline{k\beta\alpha}v\tau$$
$$\frac{\alpha^*}{\gamma}\frac{d\tau^*}{dt'} = \underline{k\beta\alpha}v\tau - \underline{\alpha^*\delta}\tau^*$$
$$\frac{\beta}{\underline{\gamma}}\frac{dv}{dt'} = \underline{N\delta\alpha^*}\tau^* - \underline{c\beta}v$$

- solve for $\beta, \gamma, \alpha^*, \alpha$: $\beta = \frac{d}{k}, \gamma = \frac{1}{c}, \alpha^* = \frac{cd}{N\delta k}, \alpha = \frac{c}{Nk}$
- in canonical form

$$p\frac{d\tau}{dt'} = a - \tau - v\tau \quad (9)$$
$$q\frac{d\tau^*}{dt'} = v\tau - \tau^* \quad (10)$$
$$\frac{dv}{dt'} = \tau^* - v \quad (11)$$

where $p = \frac{c}{d}$, $q = \frac{c}{\delta}$, $a = \frac{Nks}{cd}$ (a is the $\frac{\text{overall production rate}}{\text{overall destruction rate}}$)

Solution behavior in certain parameter regimes

- the dimensionless system only has 3 parameters, but is analytically not trivial
- look at extreme cases - case I: $q \to \infty$ and case II: $q \to 0$

Case I: $q \to \infty \Rightarrow \frac{d\tau^*}{dt'} \to 0$ for all $t' \Rightarrow \tau^* = \tau^*(0)$ is a constant
Also, (11) changes to

$$\frac{dv}{dt'} = \tau^* - v \qquad (12)$$

Solving it, we obtain $v(\tau') = v(0)e^{-\tau'} + \tau^*(1 - e^{-\tau'})$. How would a completely efficient drug modify (12) (to kill all HIV viruses)?

Case II: $q \to 0$

- Subcase I: $p \to 0$
- Subcase II: $p \to \infty$

Subcase I: $q \to 0, p \to 0$

$p \to 0 \Rightarrow a - \tau - v\tau = 0$ by (9)

$q \to 0 \Rightarrow v\tau - \tau^* = 0$ by (10)

Then, $\tau = \frac{a}{1+v}$ and (11) changes to

$$\frac{dv}{dt'} = a\frac{v}{1+v} - v \tag{13}$$

What are the stationary points? Show that the solution of (13) satisfies

$$|v - (a-1)| = Kv^{1/a}e^{-t'(a-1)/a}, \tag{14}$$

where K is a constant. If $a \gg 1$, then $1/a \ll 1$ in (14). Hence,

$$|v - (a-1)| \approx Ke^{-t'},$$

so v approaches $v = a - 1$ exponentially.

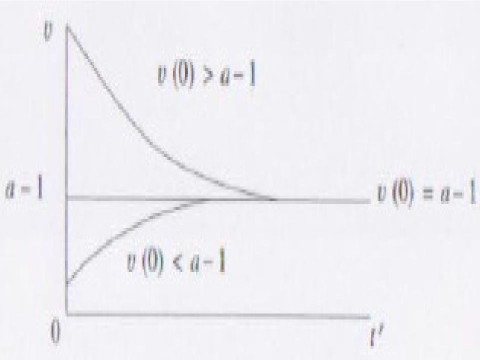


Figure : Time course for $p \to 0$ when $a \gg 1$.

If $a \ll 1$, then $|v - (a-1)| = v + 1 - a$, so (14) changes to

$$v = K'(v+1-a)^a e^{-(1-a)t'} \Rightarrow v \approx K' e^{-t'}$$

That is, if overall production rate is much smaller than overall destruction rate, the infection is suppressed.

Subcase II: $q \to 0, p \to \infty$

$p \to \infty \Rightarrow \frac{d\tau}{dt'} \to 0$ for all $t' \Rightarrow \tau = \tau(0)$ is a constant
$q \to 0 \Rightarrow \tau^* = v\tau$ by (10)
So (11) changes to

$$\frac{dv}{dt'} = (\tau - 1)v$$

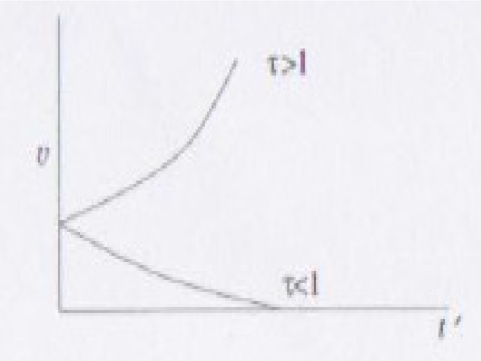


Figure : Time course for $p \to \infty$.

Case II: $q \to 0$, but without the subcases
Recall that $\tau^* = v\tau$ by (10), so let's consider (9) and (11) again:

$$\frac{d\tau}{dt'} = \frac{1}{p}(a - \tau - v\tau)$$
$$\frac{dv}{dt'} = (\tau - 1)v$$

The stationary points are $X_1 = (1, a-1)$ and $X_2 = (a, 0)$, but are they stable or unstable?

Compute the Jacobian at a stationary point (τ_0, v_0):

$$\mathbf{J} = \begin{pmatrix} -\frac{1}{p}(1 + v_0) & \frac{\tau_0}{p} \\ v_0 & \tau_0 - 1 \end{pmatrix}$$

Find the eigenvalues from the characteristic equation $\det(\mathbf{J} - \lambda\mathbf{I}) = 0$.

The eigenvalues corresponding to X_1 are

$$\lambda_1 = \frac{1}{2p}\left(-a+\sqrt{a^2-4(a-1)p}\right), \quad \lambda_2 = \frac{1}{2p}\left(-a-\sqrt{a^2-4(a-1)p}\right)$$

and the eigenvalues corresponding to X_2 are

$$\mu_1 = -\frac{1}{p}, \quad \mu_2 = a-1.$$

Consider how a changes the stability of the stationary points in the following cases:

- Weak source: $a < 1$
- Marginal case: $a = 1$
- Strong source: $a > 1$

Weak source: $a < 1$

X_1: biologically not relevant (why?)

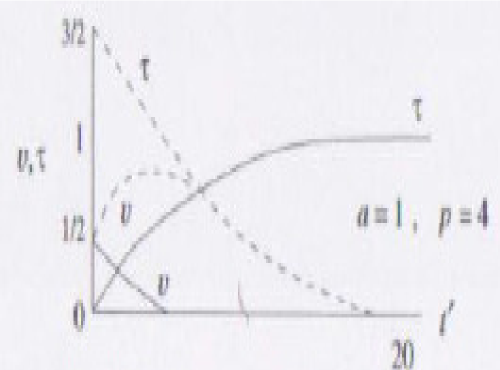
X_2: $\mu_1 < 0, \mu_2 < 0$ - stable node (the virus is eliminated)

Marginal case: $a = 1$

X_1: $\lambda_1 = 0, \lambda_2 = -a/p$ - nonisolated stationary points

X_2: $\mu_1 < 0, \mu_2 = 0$ - nonisolated stationary points

What steady-state is achieved depends on the initial condition (see the Figure).



Strong source: $a > 1$

X_2: $\mu_1 < 0, \mu_2 > 0$ - saddle point

X_1: the discriminant $a^2 - 4(a-1)p$ can change sign

- if $a^2 - 4(a-1)p > 0 \Rightarrow \lambda_1 < 0, \lambda_2 < 0$ - stable node
- if $a^2 - 4(a-1)p = 0 \Rightarrow \lambda_1 = \lambda_2 < 0$ - borderline case (but stable)
- if $a^2 - 4(a-1)p < 0 \Rightarrow \mathrm{Re}(\lambda_1) = \mathrm{Re}(\lambda_2) < 0$ - stable spiral

It is not possible to eradicate the virus.