Modeling Competition Between Syncytia-Forming and Non-Syncytia-Forming HIV Strains: A Mathematical Approach to Viral Dynamics

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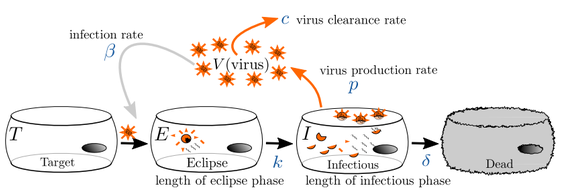
Background

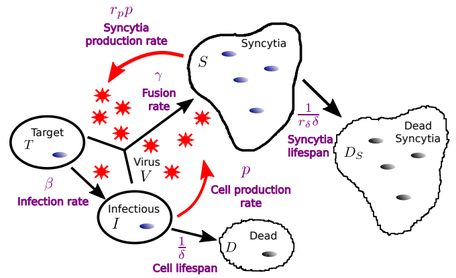
- HIV has a high mutation rate, allowing multiple strains to emerge within a single patient, particularly during the chronic phase of infection.
- Some strains of HIV form syncytia—large, multinucleated cells caused by virus-mediated cell fusion—while others spread exclusively through cell-free transmission.
- Syncytia formation can enhance viral spread by facilitating direct cell-to-cell transmission, potentially altering infection dynamics.
- The competition between syncytia-forming and non-syncytia-forming strains may determine which strain dominates or whether coexistence is possible.
- Mathematical modeling helps analyze infection dynamics and identify conditions favoring one strain over the other.
- Stability analysis and simulations allow for a deeper understanding of how syncytia formation parameters influence viral competition and persistence.

Non-syncytia forming virus model



The non-syncytia forming virus model tracks infection dynamics using parameters like infection rate, virus clearance (c), and production to monitor viral load (V). It emphasizes the eclipse phase (delay before new virus release) and infectious phase duration, which determine cell death or viral clearance and overall spread.

Syncytia forming virus model



The syncytia-forming virus model focuses on cell fusion (via rate γ) and infection dynamics, tracking variables like infection rate (β), virus load (V), and syncytia lifespan (D_s) to explain viral spread. Key factors include cell production, clearance (δ), and syncytia-driven amplification of infections (I), balancing viral persistence and host-cell death (D).

Model equations

1. Target Cells (T):

$$\frac{dT}{dt} = \Lambda - \mu T - \beta_{ns} V_{ns} T - \beta_s V_s T - \gamma(S + I_s)T$$

2. Non-Syncytia-Infected Cells (I_{ns}):

$$\frac{dI_{ns}}{dt} = \beta_{ns} V_{ns} T - \delta_{ns} I_{ns}$$

3. Non-Syncytia Virus Population (V_{ns}):

$$\frac{dV_{ns}}{dt} = p_{ns} I_{ns} - c_{ns} V_{ns}$$

4. Syncytia-Infected Cells (I_s):

$$\frac{dI_s}{dt} = \beta_s V_s T - \gamma(T + 2I_s + S)I_s - \delta_s I_s$$

5. Syncytia Population (S):

$$\frac{dS}{dt} = \gamma T(2I_s + S) + \gamma I_s(2I_s + S) - r_\delta \delta_s S$$

6. Syncytia Virus Population (V_s):

$$\frac{dV_s}{dt} = p_s I_s + r_p p_s S - c_s V_s$$

Methods

- Developed a mathematical model incorporating both syncytia-forming and non-syncytia-forming HIV strains, extending traditional within-host HIV models.
- Performed stability analysis by identifying fixed points of the system and determining their stability to assess conditions for dominance or coexistence.
- Conducted numerical simulations to explore the effects of key syncytia formation parameters (γ, r_p, and r_δ) on infection dynamics and coinfection duration.

Fixed points

Fixed points are values of variables where the time derivative is zero. This means that if you are at a fixed point, the system will stay at that point. Fixed points are presented as $(T, I_{\text{ns}}, V_{\text{ns}}, I_{\text{s}}, S, V_{\text{s}})$.

- **Both Viruses Die Out:**

$$\left(\frac{\lambda}{\mu}, 0, 0, 0, 0, 0\right)$$

- **Only Non-Syncytia-Forming Virus Survives:**

$$\left(\frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}, \frac{\lambda}{\delta_{ns}} - \frac{\mu c_{ns}}{\beta_{ns} p_{ns} \delta_{ns}}, \frac{\lambda p_{ns}}{\delta_{ns} \beta_{ns} c_{ns}} - \frac{\mu}{\beta_{ns} p_{ns}}, 0, 0, 0\right)$$

- **Only Syncytia-Forming Virus Survives:**

$$\left(\frac{\delta_s c_s}{\beta_s p_s}, 0, 0, \frac{\lambda}{\delta_s} - \frac{\mu c_s}{\beta_s p_s \delta_s}, 0, \frac{\lambda p_s}{\delta_s \beta_s c_s} - \frac{\mu}{\beta_s p_s}\right)$$

- **Both Viruses Survive:**

$$\left(\frac{\delta_s c_s}{\beta_s p_s}, \frac{\lambda}{\mu} - \left(\frac{\delta_s c_s}{\beta_s p_s} + \frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}\right), \frac{p_s}{c_s}\left(\frac{\lambda}{\mu} - \left(\frac{\delta_s c_s}{\beta_s p_s} + \frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}\right)\right), 0, 0, 0\right)$$

- **Both Viruses Survive:**

$$\left(\frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}, 0, 0, \frac{\lambda}{\mu} - \left(\frac{\delta_s c_s}{\beta_s p_s} + \frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}\right), \frac{\delta_s c_s}{\beta_s p_s}, \frac{p_s}{c_s}\left(\frac{\lambda}{\mu} - \left(\frac{\delta_s c_s}{\beta_s p_s} + \frac{\delta_{ns} c_{ns}}{\beta_{ns} p_{ns}}\right)\right)\right)$$

Jacobian matrix

$$J = \begin{pmatrix} -\mu - \beta_{ns} V_{ns} - \beta_s V_s - \gamma(S + I_s) & 0 & -\beta_{ns} T & -\gamma T & -\gamma T & -\beta_s T \\ \beta_{ns} V_{ns} & -\delta_{ns} & \beta_{ns} T & 0 & 0 & 0 \\ 0 & p_{ns} & -c_{ns} & 0 & 0 & 0 \\ \beta_s V_s - \gamma I_s & 0 & 0 & -\gamma(T + S + 4I_s) - \delta_s & -\gamma I_s & \beta_s T \\ \gamma(2I_s + S) & 0 & 0 & \gamma(2T + 4I_s + S) & \gamma(T + I_s) - r_\delta \delta_s & 0 \\ 0 & 0 & 0 & p_s & r_p p_s & -c_s \end{pmatrix}$$

- The Jacobian matrix represents the system's stability by analyzing small perturbations around equilibrium points.
- It helps determine conditions under which the syncytia-forming or non-syncytia-forming strain dominates.
- Stability analysis involves calculating eigenvalues of the Jacobian—negative real parts indicate stable equilibria.
- Key parameters influencing stability include infection rates (β_s, β_{ns}), syncytia formation rate (γ), and virus production rates (p_s, p_{ns}).

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This study presents a mathematical model analyzing the competition between syncytia-forming and non-syncytia-forming strains of HIV within a host. HIV exhibits a high mutation rate, leading to the coexistence of multiple strains, some of which spread via cell-free transmission while others spread through cell-to-cell fusion, forming large multinucleated syncytia. Understanding the dynamics between these strains is crucial, as syncytia formation can impact viral replication, immune evasion, and disease progression. These findings provide insight into HIV pathogenesis and could inform future therapeutic strategies aimed at controlling infection.