**MATHEMATICAL MODEL AND ANALYTICAL ANALYSIS OF IMMUNE SYSTEM RESPONSES DURING VIRAL EVOLUTION.**

**Abstract:** Viral evolution is the change in the genetic makeup of virus in order to escape from antibody responses. As the viruses mutate and multiply, over time can determine the outcome of the viral infection.As more and more virus strains escape immune responses and accumulate, a given specific immune response can only recognize smaller fractions of the viral population.The unrecognized viruses continue to infect and impair the susceptible cells.This leads to antigenic diversity which can contribute to viral infection progression. The purpose of this study is to analytically elucidate the dynamics of viral evolution towards escape from antibody responses by use and analysis of a mathematical model. To achieve this a discrete mathematical model is developed that captures the following variables: susceptible cells,$n$ virus strain,cells infected by strain $i = 1$ to $i = n$ virus strain, antibody responses specific to strains $i = 1$ to $i = n$ and CTL responses that are taken to be cross reactive and can respond to all virus strains. Analysis of the model is done for two cases: initially weak & un sustained CTL response and strong and sustained CTL response.Stability criteria and parameters combination limiting these cases is established for each of the cases.

**Key words**

- CTL Cytotoxic T Lymphocyte
- Anti bodies
- Pathology

## 1 INTRODUCTION

When a viral pathogen is not resolved by the host immune system, the virus may undergo some genetic changes during its life time. These changes arise from the adaptations, aimed at the survival of the virus within the host, in response to the immune system or the environment. These changes leads to development of new viral variants that can escape detection by the already activated antibody response.Consequently the number of infected cells with different viral mutants will keep growing. This diversification of the virus will gradually stimulate the initially weak CTL and immune responses will shift from non lytic to lytic response. This relationship between the immune system and viral pathogens can result in viral persistence and chronicity, **(author?)** [1].

The presence of ongoing CTL lytic activity that kill the infected cells result in many cells dying, and the infected organ gradually get thinner and weaker in a way that is unhealthy which can lead to its failure of its critical functions in the host,[2].

## 2 Model Development

The model constructed will capture the aspect of viral mutants that escape the antibody responses.

### 2.1 Model assumptions

: The specific biological assumptions taken into account when developing the model equations are based on accepted knowledge of immune system function. The assumptions are;

1. T and B lymphocytes, which are the precursors of the immunocompnent are produced in the bone marrow.
2. Cytotoxic T Lymphocyte (CTL) can kill infected cells or shut down virus replication in the cell.
3. Anti bodies will fight (neutralize) free virus released by infected cells.
4. Pathogen-specific CTL and antibody-specific responses are initiated once the virus is presen
5. Immune responses will decay after some number of encounters with virus or upon virus eradication.
6. The CTL response and antibody response are independent
7. The immune system can recognize pathogens that have been encountered before and those encountered for the first time.
8. $i = 1, ...n$ virus are produced that are different from each other in their epitopes only but otherwise identical in replication rate.
9. $V_i$ and $Y_i (i = 1...n)$ are virus of strain $i$ and cells infected by strain $i$ respectively
10. The virus $i$ of strain can prompt antibody response $A_i$ that is specific for the strain.
11. The CTL responses are considered cross reactive to recognize and respond to all the variants equally.

### 2.2 Model Flow Chart

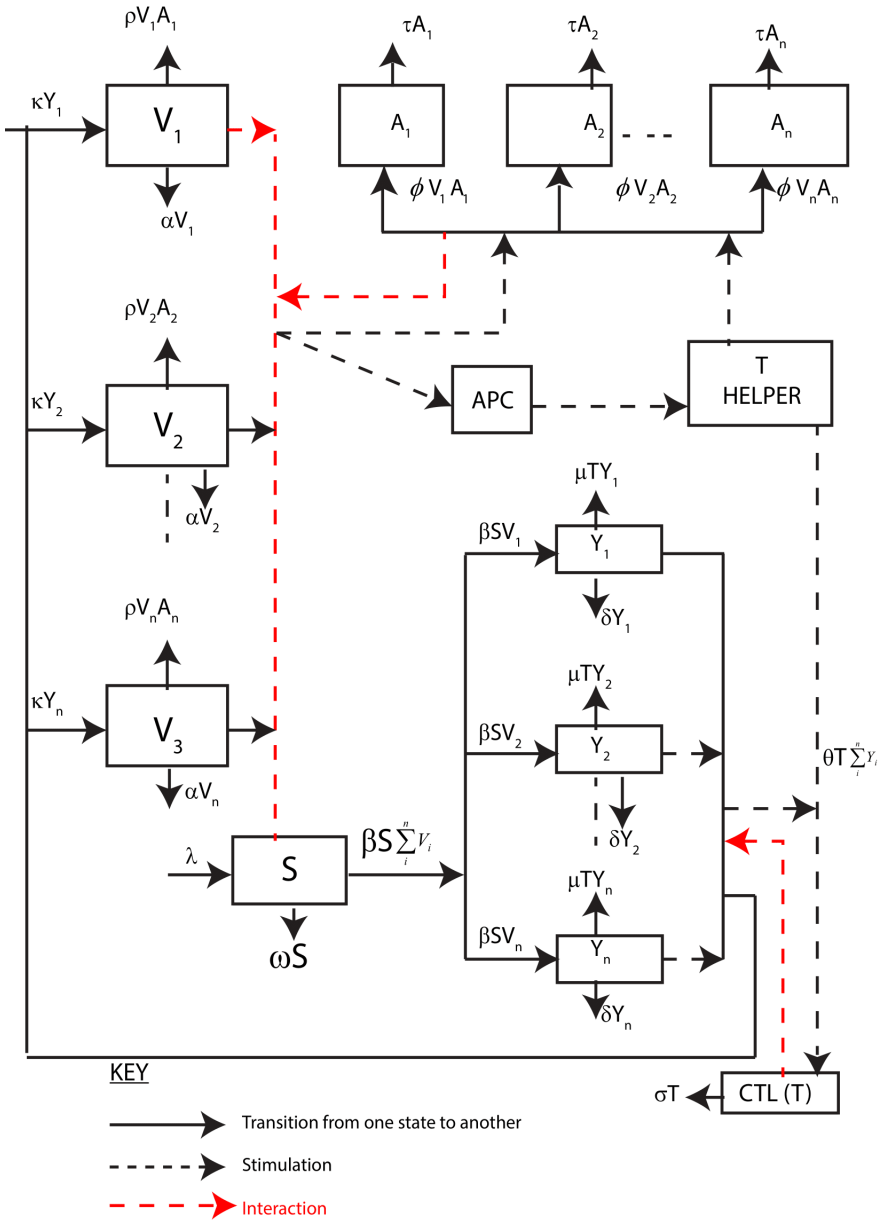


Figure 1: *Schematic representation of viral evolution.*

The following model is deduced:

$$\dot{S(t)} = \lambda - \omega S - \beta S \sum_{i=1}^{n} V_i$$

$$\dot{Y_i(t)} = \beta S V_i - \delta Y_i - \mu Y_i T$$

$$\dot{V_i(t)} = \kappa Y_i - \alpha V_i - \rho V_i A_i$$

$$\dot{A_i(t)} = \varepsilon A + \phi A_i V_i - \tau A_i$$

$$\dot{T(t)} = \nu T + \theta T \sum_{i=1}^{n} Y_i - \sigma T$$

## 3 Analytical Analysis

The following equilibrium describe the outcome of the infection with respect to the number of mutants.

$\varepsilon \approx \upsilon \approx 0$

$$S_{e0} = \frac{\lambda\phi}{\phi\omega + n\beta\tau}, {Y_{e0}}^{i} = \frac{n\beta\lambda\tau}{\delta(\phi\omega + n\beta\tau)}, {V_{e0}}^{i} = \frac{\tau}{\phi}, A^{i}_{e0} =$$

$$\frac{\beta\phi\kappa\lambda}{\delta\rho(\phi\omega + n\beta\tau)} - \frac{\alpha}{\rho}, T_{e0} = 0$$

$$J = \begin{pmatrix} -\omega - \beta\frac{\sigma}{\theta} & 0 & -\beta S_{e0} & 0 \\ \beta V_{e0} & -\delta & \beta S & 0 \\ 0 & \kappa & -\alpha - \rho A_{e0} & -\rho V_{e0} \\ 0 & 0 & \phi A_{e0} & \phi V_{e0} - \tau \end{pmatrix}$$

and $\det(J - \Lambda I) = 0$

$$\Lambda - \beta\delta\kappa\lambda\phi\phi(\phi(\beta\sigma + \theta(\Lambda + \omega)) - \beta\theta\tau) - (\beta \mathrm{n}\tau - \omega\phi)(\delta + \Lambda)(\beta\sigma + \theta(\Lambda + \omega))$$

$$\delta\phi^2(\alpha + \Lambda) - \mu\tau^2 + \beta\lambda\tau\kappa\tau\phi(\mathrm{n}\beta\tau + \omega\phi) +$$

$$\tau^2(\beta \mathrm{n}\tau - \omega\phi)(\delta + \Lambda)(\beta\sigma + \theta(\Lambda + \omega))(\delta\mu\tau - \beta\lambda\tau\kappa\phi(\mathrm{n}\beta\tau + \omega\phi)) = 0 \tag{3.1}$$

Using Routh-Harwitz stability criteria as in, [3].

$$a_0 = 1 \tag{3.2}$$

$$a_1 = \alpha + \frac{\beta\sigma}{\theta} + \delta - \frac{\mu\tau^2}{\phi^2} + \frac{\beta\lambda\tau\kappa\tau(\mathrm{n}\beta\tau + \omega\phi)}{\delta\phi} + \omega \tag{3.3}$$

$$a_2 = -\frac{\beta\kappa\lambda\phi}{\omega\phi - \beta \mathrm{n}\tau} + \frac{\beta\lambda\tau\kappa\tau\omega\phi(\beta\sigma + \delta\theta + \theta\tau + \theta\omega)}{\delta\theta\phi} +$$

$$\frac{\alpha\beta\sigma\delta\phi^2 + \alpha\delta^2\theta\phi^2 + \alpha\delta\theta\omega\phi^2 + \beta\sigma\delta^2\phi^2 - \beta\sigma\delta\mu\tau^2 - \delta^2\theta\mu\tau^2 + \delta^2\theta\omega\phi^2 - \delta\theta\mu\tau^3 -}{\delta\theta\phi^2}$$

$$\frac{\delta\theta\mu\tau^2\omega + \beta\lambda\tau\beta\sigma\kappa \mathrm{n}\beta\tau\tau\phi + \beta\lambda\tau\delta\theta\kappa \mathrm{n}\beta\tau\tau\phi + \beta\lambda\tau\theta\kappa \mathrm{n}\beta\tau\tau^2\phi + \beta\lambda\tau\theta\kappa \mathrm{n}\beta\tau\tau\omega\phi}{\delta\theta\phi^2} \tag{3.4}$$

$$a_3 = \frac{\beta^2\theta\kappa\lambda\phi\tau - \beta\beta\sigma\kappa\lambda\phi\phi - \beta\theta\kappa\lambda\phi\omega\phi}{\theta\phi(\omega\phi - \beta n\tau)} + \frac{\beta\lambda\tau\kappa\tau\omega\phi(\beta\sigma\delta + \beta\sigma\tau + \delta\theta\tau + \delta\theta\omega + \theta\tau\omega)}{\delta\theta\phi} +$$

$$\frac{\alpha\beta\sigma\delta^2\phi^2 + \alpha\delta^2\theta\omega\phi^2 - \beta\sigma\delta^2\mu\tau^2 - \beta\sigma\delta\mu\tau^3 - \delta^2\theta\mu\tau^3 - \delta^2\theta\mu\tau^2\omega - \delta\theta\mu\tau^3\omega +}{\delta\theta\phi^2}$$

$$\frac{\beta\lambda\tau\beta\sigma\delta\kappa n\beta\tau\tau\phi + \beta\lambda\tau\beta\sigma\kappa n\beta\tau\tau^2\phi + \beta\lambda\tau\delta\theta\kappa n\beta\tau\tau^2\phi + \beta\lambda\tau\delta\theta\kappa n\beta\tau\tau\omega\phi}{\delta\theta\phi^2}$$

$$\frac{+\beta\lambda\tau\theta\kappa n\beta\tau\tau^2\omega\phi}{\delta\theta\phi^2} \tag{3.5}$$

$$a_4 = -\frac{\tau^2(\beta\sigma + \theta\omega)(\delta\mu\tau - \beta\lambda\tau\kappa\phi(n\beta\tau + \omega\phi))}{\theta\phi^2} \tag{3.6}$$

This equilibrium is stable if

$$\delta\mu\tau^3(\beta\sigma + \theta\omega) > \beta\lambda\tau\kappa\tau^2\phi(n\beta\tau + \omega\phi)(\beta\sigma + \theta\omega) \tag{3.7}$$

When the CTL responses are weak the increase in antigenic mutants escalates the antigenic drive promoting the expansion of the initially weak CTL
[4]. Below expressions describe this equilibrium .

$$S_{e6} = \frac{\lambda\phi}{\phi\omega + n\beta\tau}, {Y_{e6}}^i = \frac{\sigma}{n\theta}, {V_{e6}}^i = \frac{\tau}{\phi}, {A_{e6}}^i = \frac{\kappa\phi\sigma - n\mu\tau\theta}{n\theta\rho\tau}, T_{e6} =$$

$$\frac{n\beta\tau(\lambda\theta + \delta\sigma) - \delta\theta\sigma\omega}{\mu\sigma(\omega\phi - n\beta\tau)} \tag{3.8}$$

$$J = \begin{pmatrix} -\omega - n\beta\frac{\tau}{\phi} & 0 & -\beta S_{e6} & 0 & 0 \\ \beta V_{e6} & -\delta - \mu T_{e6} & \beta S_{e6} & 0 & -\mu T_{e6} \\ 0 & \kappa & -\alpha - \rho A_{e6} & -\rho V_{e6} & 0 \\ 0 & 0 & \phi A_{e6} & \phi V_{e6} - \tau & 0 \\ 0 & \theta n T_{e6} & 0 & 0 & 0 \end{pmatrix} \tag{3.9}$$

then $\det(J - \Lambda I) = 0$ is

$$\Lambda\mu\sigma(n\beta\tau - \omega\phi)(\rho\tau(n\beta\tau + \phi\omega)(-(n\mu\tau\theta - \kappa\phi\sigma))(\phi(\Lambda + \omega) + n\beta\tau)(-\mu\sigma\omega\phi(\delta)) +$$

$$+\Lambda + \delta\theta\sigma\omega\mu + n\beta\tau(\mu\sigma(\delta + \Lambda) - \delta\sigma\mu - \lambda\theta\mu) - \Lambda\beta\kappa\lambda\phi\mu\sigma n\theta\rho\tau(n\beta\tau) -$$

$$-\omega\phi(\beta\tau + \phi(\Lambda + \omega) + n\beta\tau) - (n\beta\tau + \phi\omega)(\phi(\Lambda + \omega) + n\beta\tau)n\theta\rho\tau(\alpha + \Lambda) +$$

$$(\rho(\kappa\phi\sigma - n\mu\tau\theta))(-\mu\sigma\omega\phi(\delta))$$

$$+\Lambda+\delta\theta\sigma\omega\mu+\mathrm{n}\beta\tau(\mu\sigma(\delta+\Lambda)-\delta\sigma\mu-\lambda\theta\mu)+\theta\mu(\mathrm{n}\beta\tau+\phi\omega)(\delta\theta\sigma\omega)$$

$$-\mathrm{n}\beta\tau((\delta\sigma+\lambda\theta))^2(\phi(\Lambda+\omega)+\mathrm{n}\beta\tau)(\Lambda\mathrm{n}\theta\rho\tau(\alpha+$$

$$\Lambda)-\rho(\Lambda+\tau)(\mathrm{n}\mu\tau\theta-\kappa\phi\sigma))=0 \tag{3.10}$$

$$a_0=-1 \tag{3.11}$$

$$a_1=\frac{-\mu\sigma\mathrm{n}\beta\tau^2\mathrm{n}\theta\rho\tau+\mathrm{n}\beta\tau(\mathrm{n}\theta\rho\tau(-\mu\sigma(\alpha\phi+\delta\phi-\omega\phi+\omega\phi)+\delta\sigma\mu\phi+}{\mu\sigma\mathrm{n}\theta\rho\tau\phi(\mathrm{n}\beta\tau-\omega\phi)}$$

$$\frac{\lambda\theta\mu\phi)+\mu\sigma\rho\phi(\mathrm{n}\mu\tau\theta-\kappa\phi\sigma))+\phi(\mathrm{n}\theta\rho\tau(\mu\sigma\omega\phi(\alpha+\delta+\omega)-}{\mu\sigma\mathrm{n}\theta\rho\tau\phi(\mathrm{n}\beta\tau-\omega\phi)}$$

$$\frac{\delta\theta\sigma\omega\mu)+\mu\sigma\rho\omega\phi(\kappa\phi\sigma-\mathrm{n}\mu\tau\theta))}{\mu\sigma\mathrm{n}\theta\rho\tau\phi(\mathrm{n}\beta\tau-\omega\phi)} \tag{3.12}$$

The coefficient of the polynomial are negative.
The characteristic equation fails to meet the necessary condition of stability by Routh and it is therefore an unstable equilibrium.

## 4 Limiting Parameter combination for CTL induced pathology

Limiting Parameter combination for CTL induced pathology As the virus population continues evolves away from the antibodies, virus load grow and diversification of the antigenic drive increases. The number of cell initially remain the same until a limiting threshold number is attained. This will correspond to absence of pathology. The dynamics will however when the limiting threshold is reached which will indicate the setting in of pathology .This threshold is calculated as given below
Using $F$ and $H$ as defined and equilibrium points $S_{e5}$ , $T_{e5}$ , $V_{e5}$ , $A_{e5}$ and $T_{e5}$ it is found

$$H=\begin{bmatrix} -\delta & \frac{\beta\lambda\phi}{\mathrm{n}\beta\tau+\phi\omega} & 0 & 0 \\ \kappa & -\alpha & 0 & 0 \\ 0 & 0 & \tau & 0 \\ 0 & 0 & 0 & \sigma \end{bmatrix} \tag{4.1}$$

$$F=\begin{bmatrix} 0 & 0 & 0 & \frac{\mathrm{n}\beta\lambda\tau\mu}{\delta(\beta\tau+\phi\omega)} \\ 0 & \rho\left(\frac{\beta\phi\kappa\lambda}{\delta\rho(\mathrm{n}\beta\tau+\phi\omega)}-\frac{\alpha}{\rho}\right) & \frac{\rho\tau}{\phi} & 0 \\ 0 & \phi\left(\frac{\beta\phi\kappa\lambda}{\delta\rho(\mathrm{n}\beta\tau+\phi\omega)}-\frac{\alpha}{\rho}\right) & \tau & 0 \\ 0 & 0 & 0 & \frac{\mathrm{n}\beta\lambda\tau\theta}{\delta(\beta\tau+\phi\omega)} \end{bmatrix} \tag{4.2}$$

$$F.H^{-1} = \begin{bmatrix} 0 & 0 & 0 & \frac{n\beta\lambda\tau\mu}{n\beta\tau\sigma+\delta\sigma\varphi\omega} \\ \frac{\kappa(n\beta\tau\alpha\delta\rho-\beta\varphi\kappa\lambda\rho+\delta\alpha\rho\varphi\omega)}{\delta\rho(n\beta\tau\alpha\delta-\beta\kappa\lambda\varphi+\alpha\delta\varphi\omega)} & \frac{\delta(n\beta\tau\alpha\delta\rho-\beta\varphi\kappa\lambda\rho+\delta\alpha\rho\varphi\omega)}{\delta\rho(n\beta\tau\alpha\delta-\beta\kappa\lambda\varphi+\alpha\delta\varphi\omega)} & \frac{\rho}{\varphi} & 0 \\ \frac{\kappa\varphi(n\beta\tau\alpha\delta\rho-\beta\varphi\kappa\lambda\rho+\delta\alpha\rho\varphi\omega)}{\delta\rho^2(n\beta\tau\alpha\delta-\beta\kappa\lambda\varphi+\alpha\delta\varphi\omega)} & \frac{\delta\varphi(n\beta\tau\alpha\delta\rho-\beta\varphi\kappa\lambda\rho+\delta\alpha\rho\varphi\omega)}{\delta\rho^2(n\beta\tau\alpha\delta-\beta\kappa\lambda\varphi+\alpha\delta\varphi\omega)} & 1 & 0 \\ 0 & 0 & 0 & \frac{n\beta\lambda\tau\theta}{n\beta\tau\delta\sigma+\delta\sigma\varphi\omega} \end{bmatrix} \tag{4.3}$$

The Eigen values of the system are

$$E_3 = \begin{bmatrix} 0 \\ 0 \\ \frac{n\beta\lambda\tau\theta}{n\beta\tau\delta\sigma+\delta\sigma\varphi\omega} \\ \frac{2n\beta\tau\alpha\delta^2\rho-\beta\delta\rho\kappa\lambda\varphi-\beta\varphi\kappa\lambda\delta\rho+2\alpha\delta^2\rho\varphi\omega}{n\beta\tau\alpha\delta-\beta\kappa\lambda\varphi+\alpha\delta\varphi\omega)} \end{bmatrix} \tag{4.4}$$

$$\frac{n\beta\lambda\tau\theta}{n\beta\tau\delta\sigma+\delta\sigma\varphi\omega} > 1 \tag{4.5}$$

from which it follows

$$n > \frac{\delta\phi\sigma\omega}{\beta\tau(\lambda\theta-\delta\sigma)} = \psi \tag{4.6}$$

With weak CTL and strong antibody responses the virus replicates at a higher rate that CTL responsiveness. This means that CTL induced pathology can set in when the number of viral variants reaches a certain threshold. As more variants continue to escape from the antibodies there will be a shift from antibody response dominance to the expanded CTL responses. The antibodies prevent pathology while CTL promotes it the level of pathology will continue to grow with diversification of mutants. When CTL attains maximum dominance relative to antibodies Liver pathology is expected to be at peak also . At this level viral evolution is expected to slow down because most of the target cells will have been infected and any more new variants will have too few cells to infect.

This maximum is calculated using the equilibrium points $S_{e6}, Y_{e6}, V_{e6}, A_{e6}$ and $T_{e6}$ as illustrated below.

$$F = \begin{bmatrix} \frac{\sigma\left(\frac{\alpha\lambda\theta\beta\kappa\sigma}{n\theta\alpha(\alpha\theta\omega+\beta\kappa\sigma)}-\frac{\delta\sigma}{n\theta}\right)}{n\theta} & 0 & 0 & \frac{\mu\sigma}{n\theta} \\ 0 & 0 & \frac{\kappa\rho\sigma}{n\theta\alpha} & 0 \\ 0 & 0 & \frac{\kappa\sigma\phi}{n\theta\alpha} & 0 \\ \frac{\theta\sigma\left(\frac{\alpha\lambda\theta\beta\kappa\sigma}{n\theta\alpha(\alpha\theta\omega+\beta\kappa\sigma)}-\frac{\delta\sigma}{n\theta}\right)}{n\theta\mu} & 0 & 0 & \frac{\theta\sigma}{n\theta} \end{bmatrix} \tag{4.7}$$

$$H = \begin{bmatrix} -\delta & \frac{\alpha\lambda\theta\beta}{\alpha\theta\omega+\beta\kappa\sigma} & 0 & 0 \\ \kappa & -\alpha & 0 & 0 \\ 0 & 0 & \tau & 0 \\ 0 & 0 & 0 & \sigma \end{bmatrix} \tag{4.8}$$

$$F^{-1}H = \begin{bmatrix} \frac{\sigma^2}{n\theta^2} & \frac{\alpha\lambda\theta\beta\sigma^2}{n\theta^2\alpha(\alpha\theta\omega+\beta\kappa\sigma)} & 0 & \frac{\mu}{n\theta} \\ 0 & 0 & \frac{\kappa\rho\sigma}{n\theta\alpha\tau} & 0 \\ 0 & 0 & \frac{\kappa\sigma\phi}{n\theta\alpha\tau} & 0 \\ \frac{\theta\sigma^2}{n\theta^2\mu} & \frac{\alpha\lambda\theta\beta\theta\sigma^2}{\alpha\alpha\theta\omega\mu n\theta^2+\alpha\beta\kappa\sigma\mu n\theta^2} & 0 & \frac{\theta}{n\theta} \end{bmatrix} \tag{4.9}$$

Whose Eigen values are

$$E_4 = \begin{bmatrix} 0 \\ 0 \\ \frac{\theta n\theta+\sigma^2}{n\theta^2} \\ \frac{\kappa\sigma\phi}{\alpha n\theta\tau} \end{bmatrix} \tag{4.10}$$

and found to be

$$n > \frac{\phi\kappa\sigma}{\alpha\theta\tau} = \zeta \tag{4.11}$$

At this point, CTL-induced pathology is expected to be at its maximum. Furthermore, as this threshold is attained, virus evolution is expected to stop, because target cell limitation does not allow invasion of additional virus variants in the face of significant organ cells destruction,[5].

## References


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