Antibodies and Syncytia Formation

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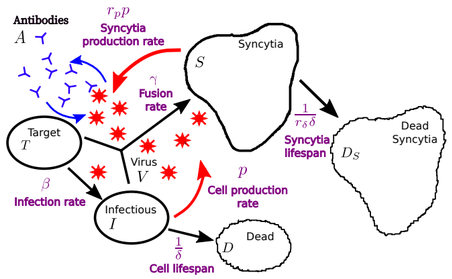
Background

- Several viruses have the ability to cause cells to fuse into large multi-nucleated cells called Syncytia.
- Syncytia allow the virus to spread without entering the extracellular space where an immune response would be present.
- Thus the presence of syncytia should hinder the effectiveness of antibodies.
- There is evidence that antibodies can hinder the fusion process and may be more effective than thought.
- We use a mathematical analysis and model to investigate different possible outcomes and parameter regions.

Mathematical model



In this model, target cells T are generated at rate λ and die at rate μ. The virus V infects healthy target cells at a rate β. The target cells become infected (I) and produce more virus at rate p, or fuse with other cells to create syncytia (S) at rate γ. These syncytia then produce virus at a rate $r_p p$. Both infected cells and syncytia continue to produce virus until they die, after lifetimes of $1/\delta$ and $1/r_\delta\delta$, respectively. The virus is cleared from the system at rate c. Antibodies A remove free viruses at rate k_V. Antibodies are produced in response to the virus at rate α, are naturally cleared at rate δ_A, and are removed due to binding with the virus at rate k_A. Antibodies can lower the fusion rate, with the strength of this effect controlled by ϵ.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \mu T - \beta TV - \frac{\gamma}{\epsilon + A} T(I + S) \\
\frac{dI}{dt} &= \beta TV - \frac{\gamma}{\epsilon + A} I(T + 2I + S) - \delta I \\
\frac{dS}{dt} &= \frac{\gamma}{\epsilon + A} T(2I + S) + \frac{\gamma}{\epsilon + A} I(2I + S) - r_\delta \delta S \\
\frac{dV}{dt} &= pI + r_p pS - cV - k_v VA \\
\frac{dA}{dt} &= \alpha V - \delta_A A - k_A AV
\end{aligned}$$

Fixed Points

Fixed points are points where all the time derivatives are zero. This means that if the system lands on a fixed point, it will stay there. Solutions are presented as $(T^*, I^*, S^*, V^*, A^*)$.

- Null equilibrium:

$$(0, 0, 0, 0, 0)$$

- Disease-free equilibrium:

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

- No virus present equilibrium

$$\left(\frac{\lambda}{\mu + \frac{\gamma}{\epsilon + A^*}\left(S^* - \frac{r_p p S^*}{p}\right)}, -\frac{r_p p S^*}{p}, S^*, 0, \right.$$

$$\left. \frac{\gamma\left(\frac{r_p p S^*}{p}\left(\frac{\lambda - S^*(r_\delta \delta + \delta(\frac{r_p p}{p}))}{\mu} - 2\frac{r_p p S^*}{p} + S^*\right)\right)}{\delta - \frac{r_p p S^*}{p}} - \epsilon \right)$$

- No syncytia present equillibrium

$$\left(\frac{\lambda}{\mu + \beta V^* + \frac{\gamma V^*\left(c + k_v \cdot \frac{\alpha V^*}{\delta_A - k_A V^*}\right)}{p\left(\epsilon + \frac{\alpha V^*}{\delta_A - k_A V^*}\right)}}, \frac{V^*}{p}\left(c + k_v \cdot \frac{\alpha V^*}{\delta_A - k_A V^*}\right), \right.$$

$$\left. 0, \frac{c\delta_A}{ck_A - k_v \alpha}, \frac{\alpha V^*}{\delta_A - k_A V^*} \right)$$

- Chronic infection

$$\left(\frac{\lambda - r_\delta \delta S^*}{\mu}, C - r_p S^* \right.$$

$$\frac{-U \pm \sqrt{U^2 - \frac{4\gamma r_p(1 - 2r_p)}{\epsilon + A^*}\left(\frac{2\gamma\lambda}{\mu(\epsilon + A^*)} C + \frac{2\gamma C^2}{\epsilon + A^*}\right)}}{\frac{2\gamma r_p(1 - 2r_p)}{\epsilon + A^*}},$$

$$\left. V^*, \frac{\alpha V^*}{\delta_A + k_A V} \right)$$

where

$$C = \frac{cV^*}{p} + \frac{k_V \alpha V^{*2}}{(\delta_A + k_A V^*)p}$$

and

$$U = \frac{1 - 2r_p}{\epsilon + A^*}\left(\frac{\lambda\gamma}{\mu} - \frac{\gamma}{\mu} + \gamma C\right) - \frac{2C\gamma}{\epsilon + A^*}\left(\frac{r_\delta \delta}{\mu} + r_p\right) - r_\delta \delta$$

Note that since some of these fixed points are negative, they are not biologically relevant.

Basic Reproduction Number (R_0)

The basic reproduction number measures the number of target cells infected by a single infected cell. $R_0 = 1$ represents the boundary between the disease-free equilibrium and the chronic infection.

$$\begin{aligned}
R_0 &= \frac{\beta T_0 p + \frac{2\beta T_0 r_p p \gamma T_0}{(\epsilon + A_0)\left(-\frac{\gamma T_0}{\epsilon + A_0} + r_d \delta\right)}}{\left(\frac{\gamma T_0}{\epsilon + A_0} + \delta\right) c} \\
&+ \frac{\beta T_0 r_p p}{c\left(-\frac{\gamma T_0}{\epsilon + A_0} + r_d \delta\right)} + \frac{\beta T_0}{c}.
\end{aligned}$$

Simulating RSV

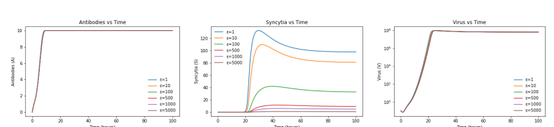
We use parameters to replicate the dynamics of respiratory syncytial virus (RSV), a common respiratory virus that reasily forms syncytia.

Parameter	Value
p	4.66×10^6 (RNA/ mL)$\cdot$ h^{-1}
β	$2.04 \times 10^{-}8\ (RNA/\ mL)^{-1} \cdot\ h^{-1}$
c	.0763 / h
δ	.0735 / h
γ	[01, 1 / h]
r_δ	$[1 \times 10^{-3}, 1 \times 10^3\ ]$
r_p	$[1 \times 10^{-3}, 1 \times 10^3\ ]$

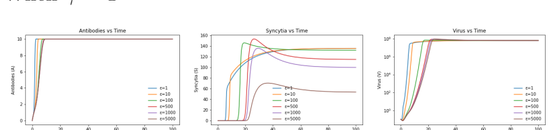
Results Antibodies, Syncytia, and Virus vs. Time

γ represents the rate at which the virus fuses with the target cell to create syncytia. So, $\gamma = .01$ represents a low syncytia formation rate, while $\gamma = 1$ represents a high one. ϵ represents the strength of the antibody suppression of the syncytia formation rate.

When $\gamma = .01$



When $\gamma = 1$



Jacobian Matrix

The Jacobian Matrix consists of all the partial derivatives of the system and can be used to determine the stability of fixed points.

$$J = \begin{bmatrix}
-\mu - \beta V - \frac{\gamma(I+S)}{\epsilon+A} & -\frac{\gamma}{\epsilon+A}T & -\frac{\gamma}{\epsilon+A}T & -\beta T & \frac{\gamma T(I+S)}{(\epsilon+A)^2} \\
V\beta & -2\frac{\gamma I}{\epsilon+A} - \frac{\gamma(2I+S+T)}{\epsilon+A} - \delta & -\frac{\gamma I}{\epsilon+A} & T\beta & \frac{\gamma I(2I+S+T)}{(\epsilon+A)^2} \\
\frac{\gamma(2I+S)}{\epsilon+A} & \frac{\gamma(4I+S)+2T\gamma}{\epsilon+A} & \frac{\gamma(I+T)}{\epsilon+A} - r_{\delta\delta} & 0 & -\frac{\gamma(T(T+2I+S)+I(2I+S))}{(\epsilon+A)^2} \\
0 & p & r_p p & -k_v A - c & -k_v V \\
0 & 0 & 0 & \alpha - k_a A & -\delta_a - k_a V
\end{bmatrix}$$

Conclusions

- For antibodies and virus production, at a low γ value, the value of ϵ makes no or only a slight difference in production.
- At a high γ level, the value of ϵ makes a difference in when the antibodies and virus start to be produced. A higher ϵ value delays the production of the virus and antibodies
- At a low γ value, a high value of ϵ significantly reduces the amount of syncytia, but does not change when syncytia starts to be produced
- At a high γ value, a high value of ϵ changes when syncytia starts to form. However, the difference is that the amount of syncytia is less affected than at a low γ value. Additionally, the values of ϵ affect the max syncytia production

Future Directions

- Find the eigenvalues of the Jacobian to determine the stability of the fixed points.
- This will help us understand if a small disturbance will cause the system to stay on track or send the system off course.
- Run a sensitivity analysis to see which parameter impacts the system most.

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Syncytia are formed by individual cells fusing to create a multinucleated cell. They can spread between cells and avoid antibodies from the immune system. However, some antibodies may directly affect the fusion process. Our study used mathematical analysis to better understand the parameters and possible outcomes at which syncytia formation happens. Our findings can help guide strategies to target viral spread effectively.