Vaccination Alters the Balance between Protective Immunity, Exhaustion, Escape, and Death in Chronic Infections: A Review and Extension

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Vaccination Alters the Balance between Protective Immunity, Exhaustion, Escape, and Death in Chronic Infections[▽]†

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Vaccine Response System

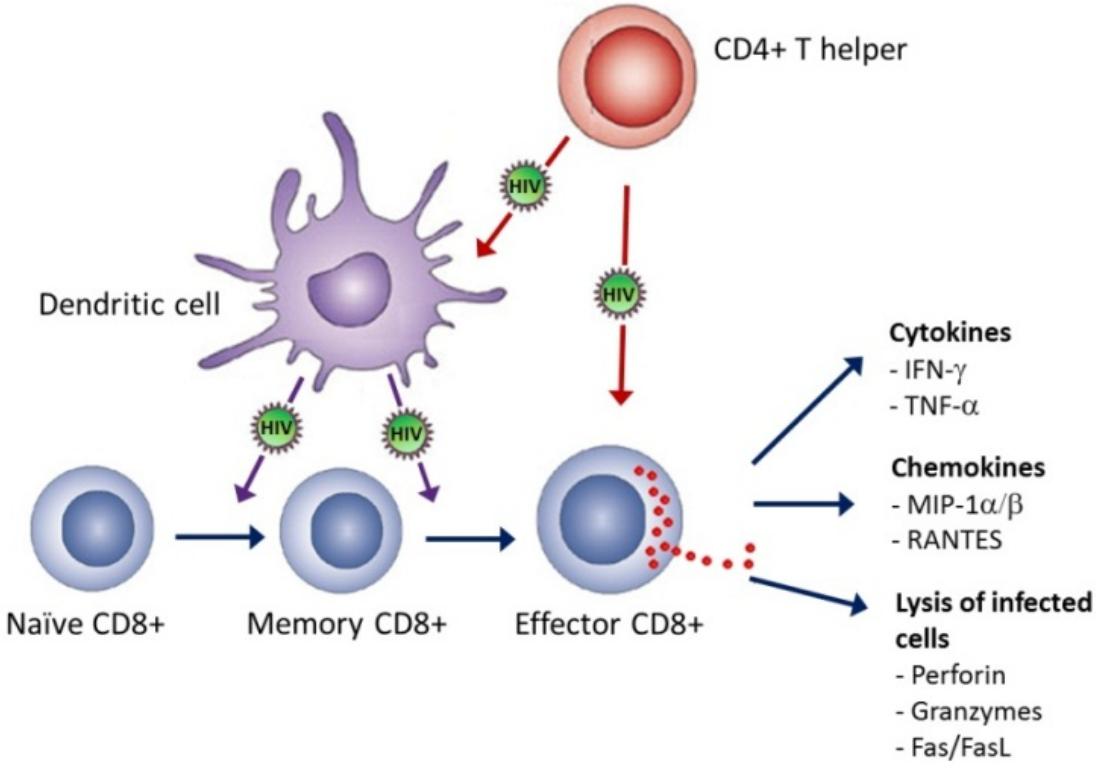

Figure: Dendritic cells signal CD8 T cells which in turn produce cytokines that signal other cells to kill the virus [5].

Biological Mechanisms

- *T cell vaccines*: vaccines for persistent infections that induce a T cell response. Many viruses prevent the signaling of T cells resulting in a decline of immune response.
- *Exhaustion*: progressive loss of immune response cell function (CD8 T cells) culminating in unresponsive cells.
- *Immunopathology*: damage caused by immune mechanisms, in this case induced by vaccines.
- Model based on LCMV virus clinical studies.

Goal: Build a model that describes bodily response to vaccination to inform vaccine development.

Types of responses:

- *Protective immunity*: artificially acquired immunity produced by deliberate exposure.
- *Exhaustion*: progressive loss of immune response cell function (CD8 T cells) culminating in unresponsive cells.
- *Escape*: virus is unaffected by immune response.

Virus/Target Cell System

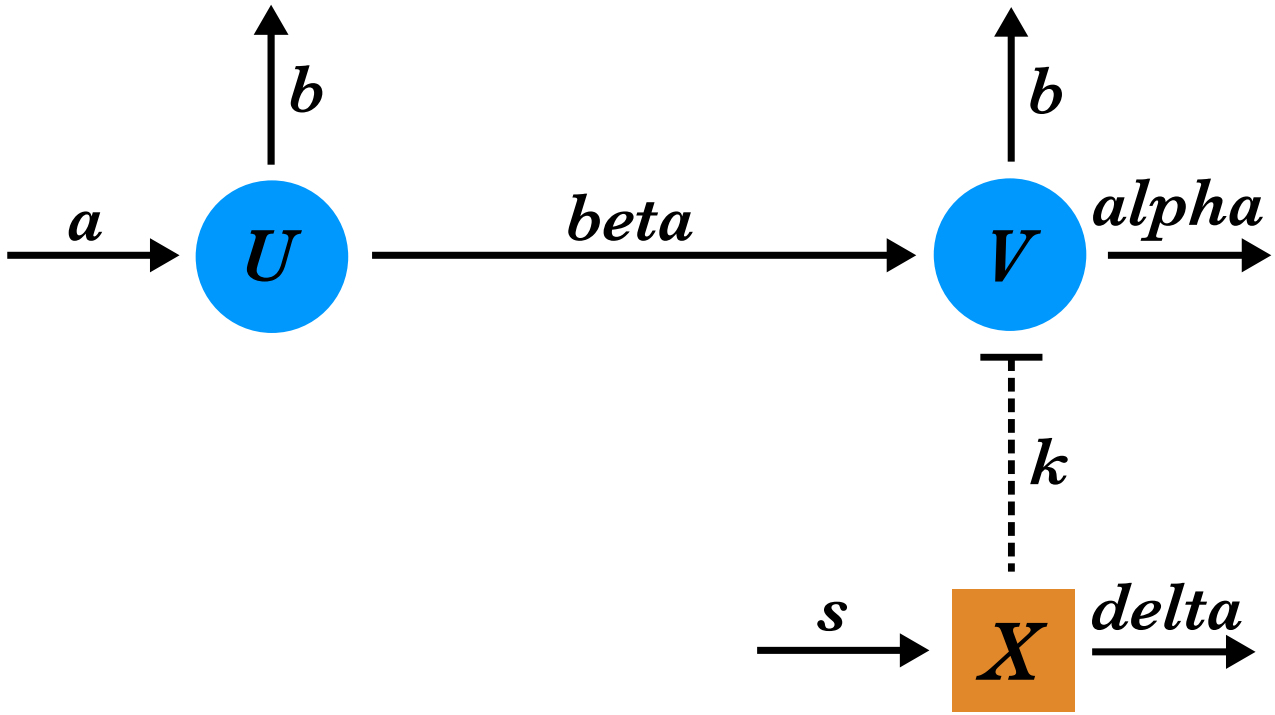

Figure: U: uninfected cells; V: virus-infected cells; X: immune response; X_0: artificially induced by vaccine; δ: exhaustion [2]

ODE System [2]

$$\frac{dU}{dt} = a - \beta UV - bU$$
$$\frac{dV}{dt} = \beta UV - (b + \alpha)V - kVX$$
$$\frac{dX}{dt} = sX\frac{V}{\phi + V} - \delta X\frac{Q^n}{q_c^n + Q^n}$$
$$\frac{dQ}{dt} = \frac{V}{\phi + V} - d_q Q$$

- U: uninfected target cells
- V: virus-infected target cells
- X: magnitude of immune response
- Q: level of exhaustion

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$(b+\alpha)V$: death of infected cells due to infection (α)

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kVX: clearance of infected cells

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$\delta X\frac{Q^n}{q_c^n + Q^n}$: loss of functional immune cells by exhaustion

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- Q: level of exhaustion

$d_q Q$: recovery from exhaustion

Model Simulations

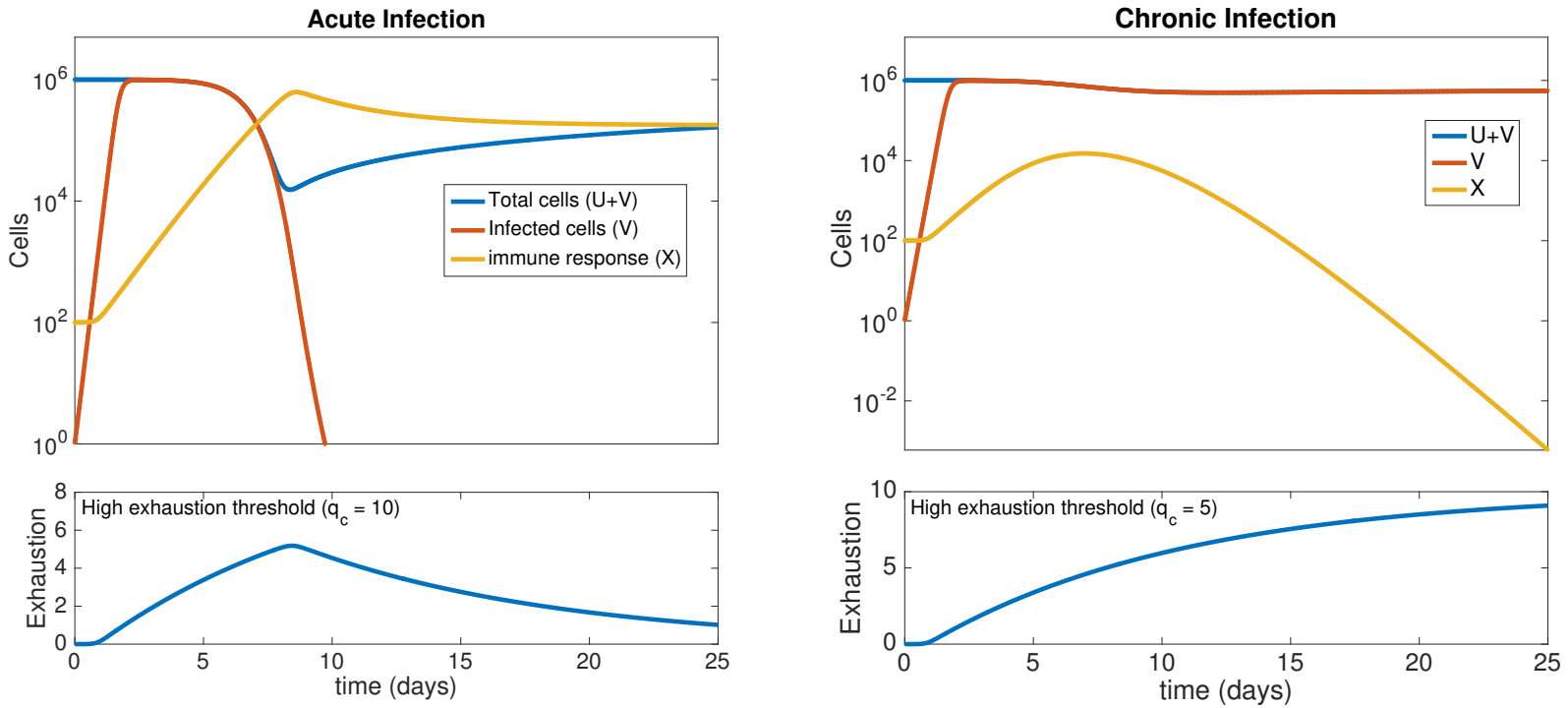


Figure: When q_c is high (L), the immune response clears the virus before exhaustion occurs. When q_c is low (R), exhaustion increases quickly and the immune system fails to clear the virus resulting in chronic infection.

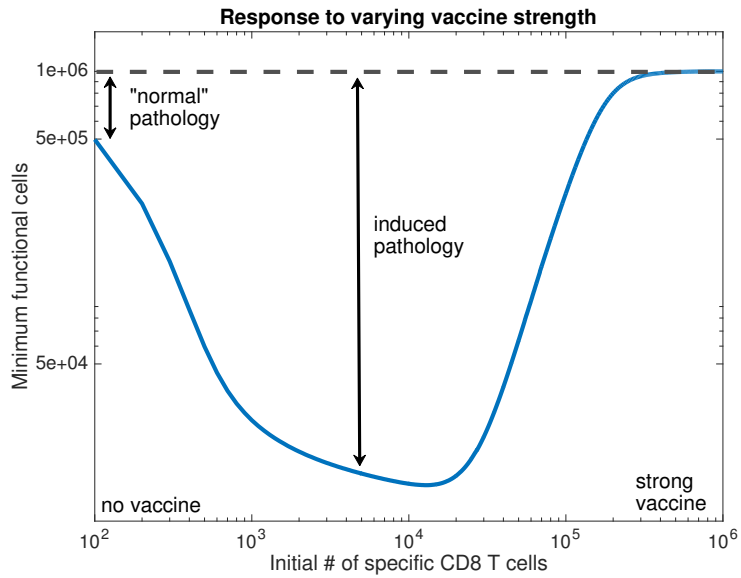
Results

– This model displays the basic features of noncytopathic viruses (HIV, LCMV, etc.) qualitatively including acute vs. chronic viral behavior.

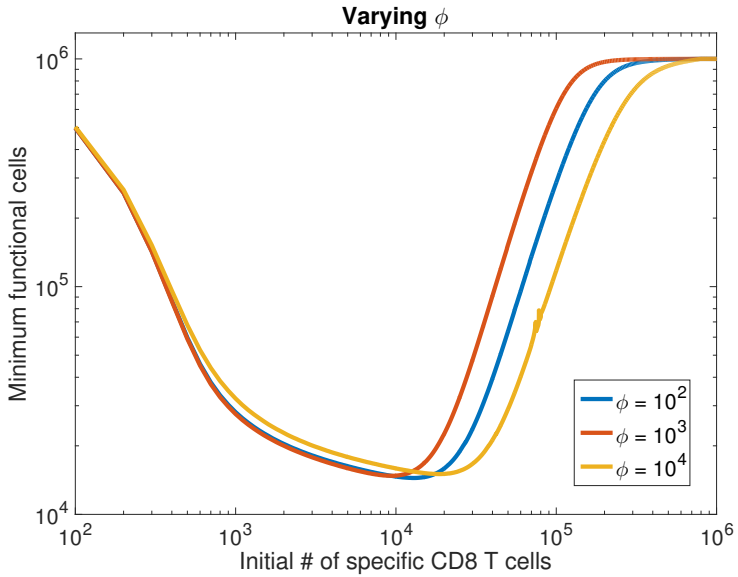
– Does the model display the features of pathology that the data suggests?

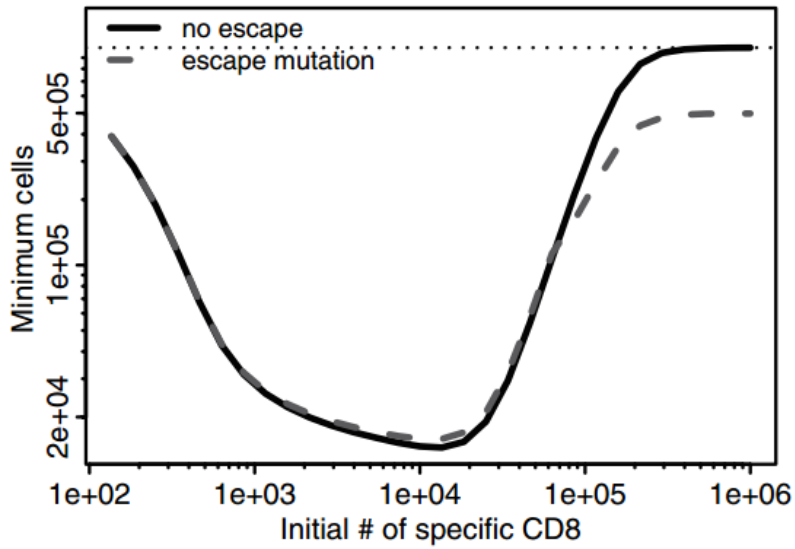
  – Pathology is defined as loss of total target cells ($U + V$)

Qualitative Results



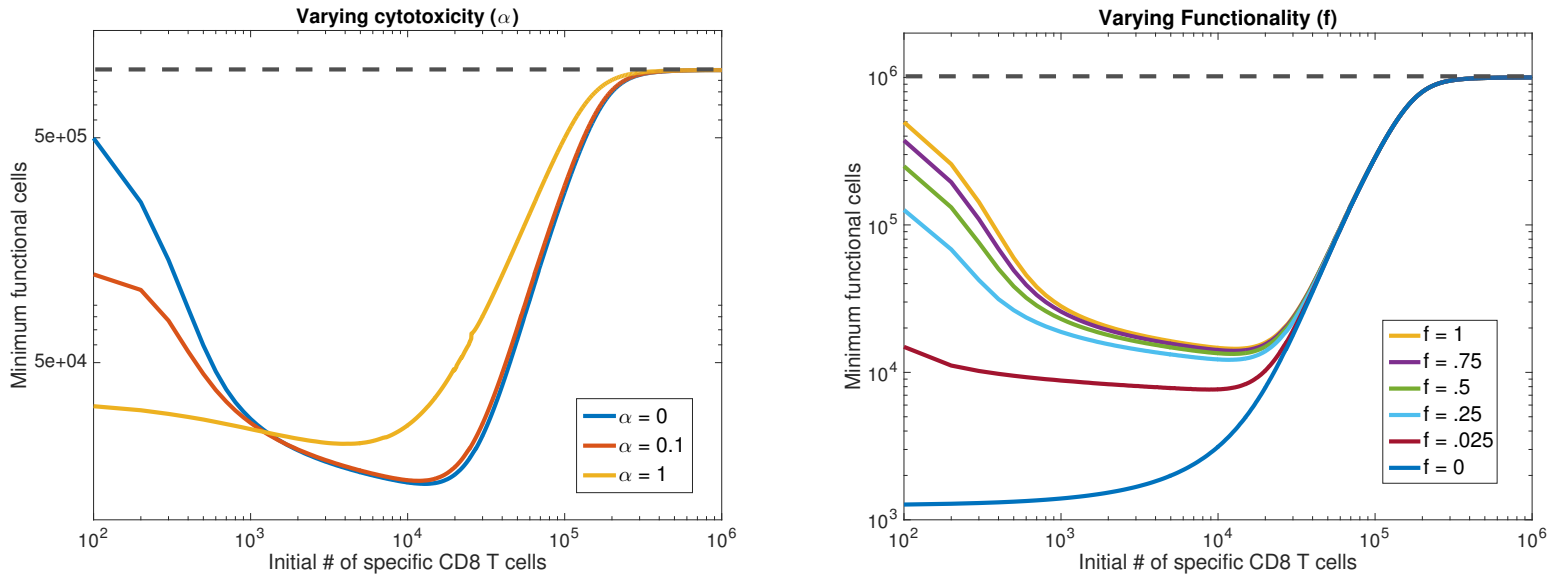
- Initial #(CD8 T cells) $\longleftrightarrow$ vaccine strength
- Pathology $\longleftrightarrow$ low number of functional cells





- Affinity $\longleftrightarrow$ sensitivity of T cell to infected cell
- Escape mutation $\longleftrightarrow$ virus which does not have same primary epitope
- Expanding breadth of immune system

Qualitative Results



(a) (b)

Figure: (a) Cytotoxic viruses kill their host cells while others, as in (b), render their host cells nonfunctional. The model suggests vaccines for both types of viruses will cause pathology.

Limitations and Criticisms

- Purely qualitative model
- Determining escape (main focus) not discussed thoroughly

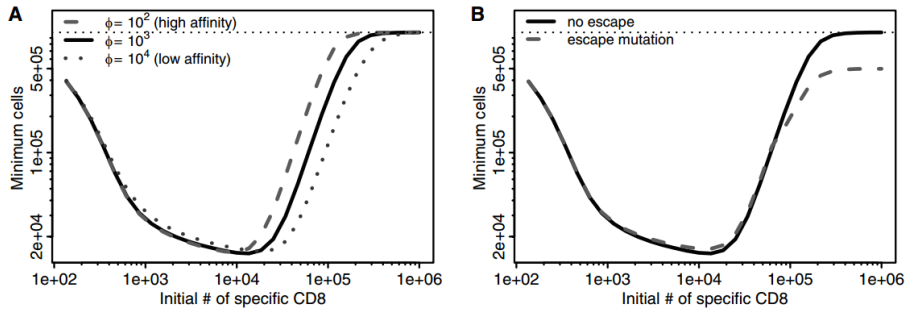


FIG. 3. Pathology results are robust to parameter changes. (A) Pathology is largely independent of altering T cell affinity/sensitivity by manipulating ϕ, where a lower ϕ corresponds to increased sensitivity and a higher ϕ corresponds to decreased sensitivity. (B) Pathology is also minimally affected by immune escape in which a mutant virus that does not display the primary epitope but can still be targeted by a secondary immune response (details for this modified model are in the supplemental material). The dotted horizontal line indicates the number of target cells in the absence of infection. Other parameters are the same as described for Fig. 1B.

HBV ODE System

$$\frac{dT}{dt} = r_T T(1 - \frac{T+I}{K}) - \beta TV$$
$$\frac{dI}{dt} = \beta TV - \delta I - \mu EI$$
$$\frac{dV}{dt} = pI - cV$$
$$\frac{dE}{dt} = sE\frac{I}{\phi + I} - \delta E\frac{Q^n}{q_c^n + Q^n}$$
$$\frac{dQ}{dt} = \frac{I}{\phi + I} - d_q Q$$

- T: Uninfected target cells
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$sE\frac{I}{\phi + I}$: M-M term for growth of immune cells

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$$\frac{dT}{dt} = r_T T(1 - \frac{T+I}{K}) - \beta TV$$
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$\delta E\frac{Q^n}{q_c^n + Q^n}$: loss of functional immune cells by exhaustion

HBV Model Simulations

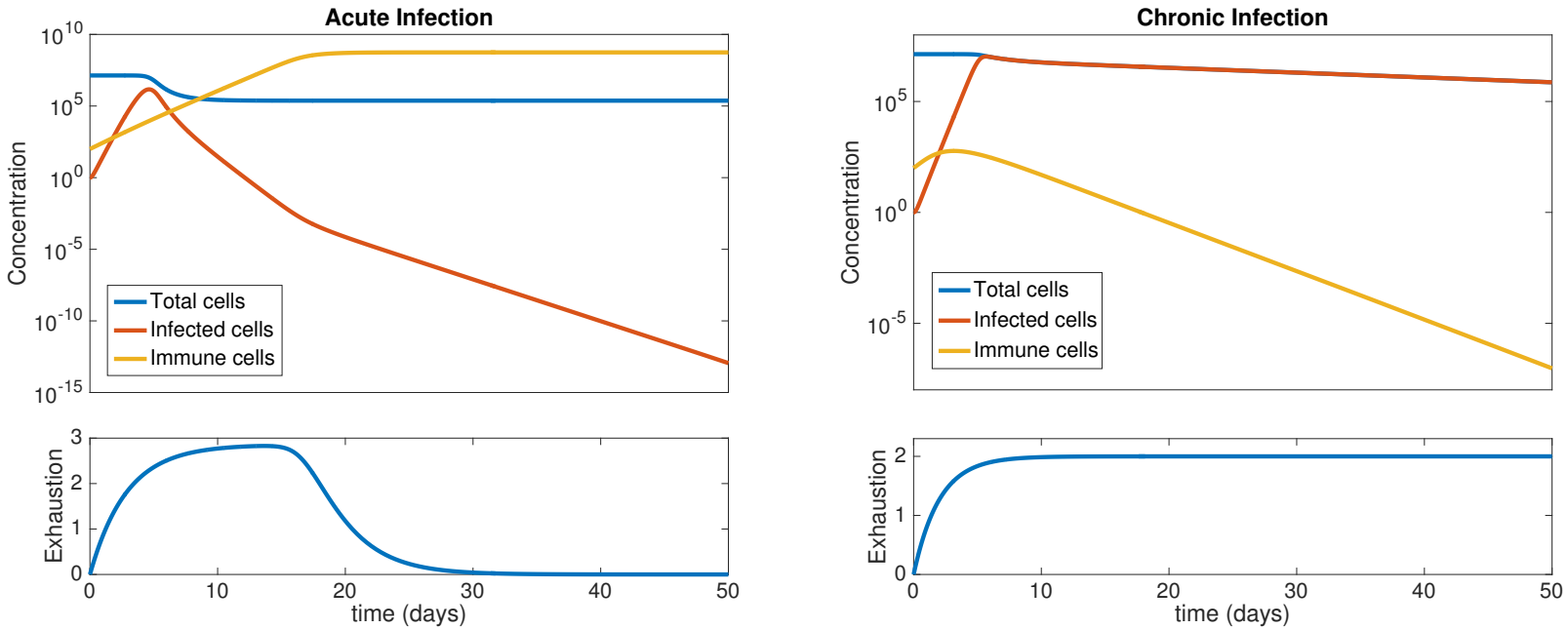
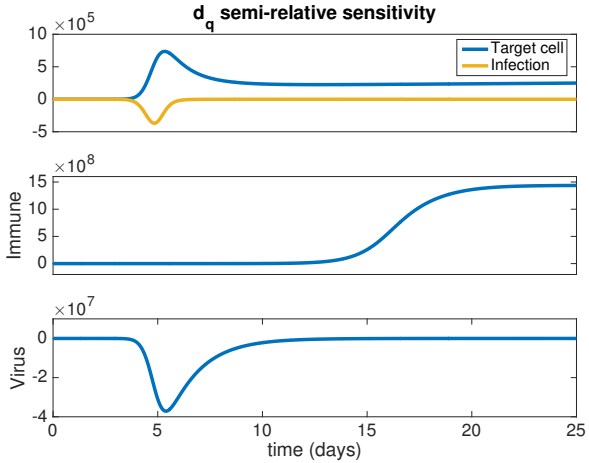
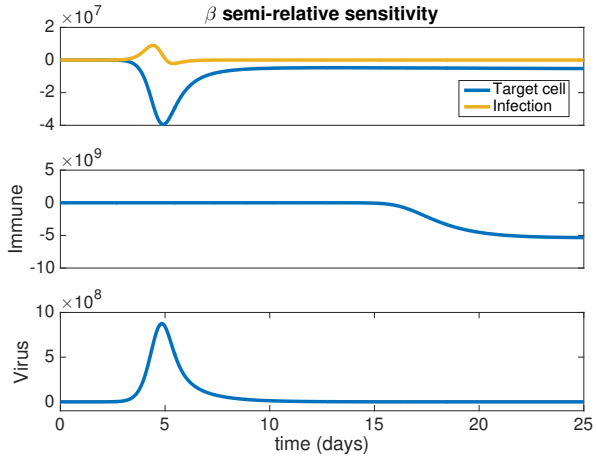
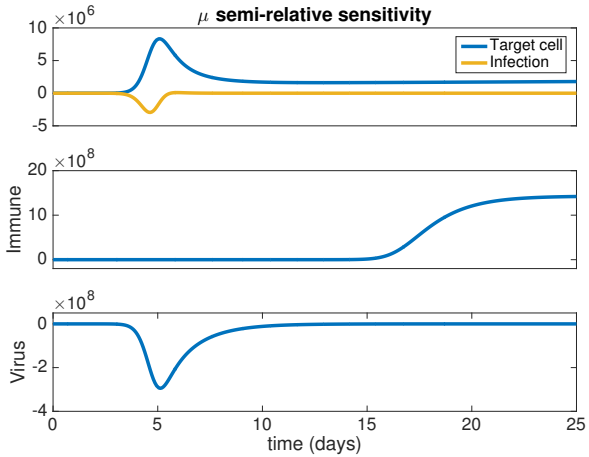


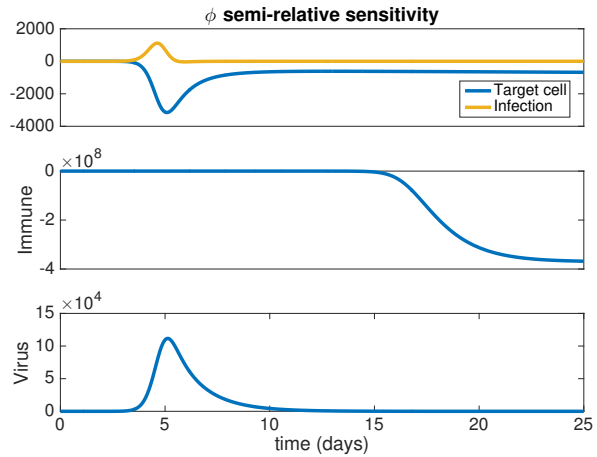
Figure: Both acute and chronic infections are seen in the new model. However, the dynamics of infected and uninfected cells are different from the previous model.

Sensitivity Analysis









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Questions, Comments?

Thank you!