Systems Biology

Project Report

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Project Proposal

Mathematical Modelling of within-host viral dynamics of SARS-CoV-2 in humans. Implications for Immune response and Antiviral treatments.

Introduction

In December of 2019, the novel pneumonia COVID-19 emerged in the city of Wuhan, in Hubei province, China. Shotgun metagenomics rapidly identified the new pathogen as SARS-CoV-2, a betacoronavirus related to the etiological agent of the 2002 SARS outbreak (SARS-CoV), and of possible bat origin **(Zhou et al. 2020[1]; Andersen et al. 2020[2])**.

The first case of 'coronavirus disease 2019' (COVID-19) was identified in the Chinese city of Wuhan in December 2019. Since then, the novel virus has rapidly spread to 188 countries and territories, infecting more than 60 million people and causing over one million deaths. **(JHU CSSE[3]; WHO[4])** COVID-19 patients develop a 'severe acute respiratory syndrome' analogous to that of the 2002 to 2003 SARS epidemic that spread to 23 countries, infected ~8000, and killed 774 people. The COVID-19 virus was named SARS-CoV-2 by the WHO and is the seventh coronavirus known to infect humans. **(WHO[4]; Corman et al.[5])** Currently, there are no vaccines or antiviral drugs capable of preventing or treating human infections. SARS-CoV-2 belongs to the Betacoronavirus genus of the Coronaviridae family, a group of related enveloped positive-sense single-stranded RNA viruses that infect both mammals and birds. **(Cavanagh et al.[6])**

Approximately 80% of the infected patients are largely asymptomatic or have mild symptoms such as fever or cough, while the rest of the patients display varying degrees of severity of symptoms, with an average mortality rate of 3–4%. Severe symptoms such as pneumonia and acute respiratory distress syndrome may be

caused by tissue damage, which is mostly due to aggravated and unresolved innate and adaptive immune response, often resulting from a cytokine storm.

About SARS-COV-2

Human coronaviruses, first identified in the 1960s **(Kahn et al.[7])**, commonly infect humans. Most coronavirus infections are respiratory in nature and primarily affect the upper respiratory tract and the lungs **(Van der Hoek et al.[8])**. There are 7 identified coronaviruses that have been documented to infect humans—229E, NL63, OC43, HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2. Most human coronaviruses are zoonotic in nature, i.e., these coronaviruses initially infected animals and later gained the ability to infect humans **(Ye et al.[6])**.

SARS-CoV-2 is a positive-stranded RNA virus and has already infected about 60 million people around the globe. With a genome size of ~30000 bases and very high infectivity, the virus has already amassed numerous changes in its genome and acquiring more. The genome organization of SARS-CoV-2 is similar to other coronaviruses. **(Wu et al.[10])** It has Open Reading Frames (ORFs) common to all beta-coronavirus which includes ORF1ab responsible for most of the enzymatic proteins, the surface glycoproteins (S), the envelope proteins (E), the membrane proteins (M), and the nucleocapsid proteins (N). There are also several nonstructural proteins expressed mostly from ORF3a, ORF6a, ORFF7a, and ORF8a. The reference genome of the SARS-CoV-2 also includes ORF10a as part of its genome.

Infecting the Human Body

The CoVID-19 virus, similar to the 2003 SARS-CoV, uses the cell surface receptor ACE2 to gain access to the cells **(Zhang et al.[11])**. Interestingly, there have been reports that the cell surface receptor TMPRSS2 is also required in combination with the ACE2 receptor to gain access to the cells **(Hoffman et al.[12])**. For viral entry into the cell, the viral spike protein first needs to be primed by the host cell proteases, in this case, TMPRSS2, after which the viral spike protein can interact

with the ACE2 protein and can be internalized by the cell. Hence, it is not surprising that both the ACE2 and the TMPRSS2 proteins have been identified as potential candidates that can be targeted for anti-viral interventions **(Zhang et al.[11]; Hoffman et al.[12])**.

The SARS-CoV-2 virus can affect multiple organs like the heart, kidney, gut, etc.—as these organs harbor cells that contain the ACE2 receptor in significant amounts **(Zaim et al.[13])**. The ACE2 levels have been detected in various cell types in different organs both at the transcriptomic as well as proteomic levels using various high-throughput methods. In the lung, the SARS-CoV-2 primarily targets the alveolar type 2 cells **(Chu et al.[14]; Li et al.[15])** a phenomenon similar to the pathogenesis of the previous SARS-CoV **(Mossel et al.[16])**. Hence, it is not surprising to find that the extent of lung damage is a robust marker of disease severity and is often associated with acute respiratory distress syndrome (ARDS) **(Liu et al.[17])**.

Body's Immune Response to the virus

Generally, the body's immune response to SARS-CoV2 and SARS-CoV is closely similar being mediated by cytokines **(Yi et al.[18])**. A case report in Wuhan from 99 COVID-19 patients revealed that there was an increase in the total number of neutrophils, Interleukin-6 (IL-6) serum, and c-reactive protein about 38%, 52%, and 86%, respectively, and a 35% decrease in total lymphocytes **(Chen et al.[19])**. Other research found increased expression of proinflammatory cytokines and chemokines IP-10, MCP-1, MIP-1A, and tumor necrosis factor-alpha (TNFα) **(Huang et al.[20])**. The conditions are correlated with the severity and mortality of this disease which suggests the potential of cytokines forming as found occurring in SARS-CoV and MERS-CoV infections **(Prompetchara et al.[21])**.

The human body has robust mechanisms for clearing infections. Through a series of well-coordinated steps, various immune cells are recruited to the site of the infection to clear out the virus and the virally infected cells. The first step of the response to a SARS-CoV-2 infection is the infected epithelial cells secreting

inflammatory cytokines **(McKechnie et al.[22])**. These molecules result in the recruitment of circulating innate immune cells as well as tissue-resident dendritic cells. Innate immune cells, such as neutrophils and monocytes, clear virally infected apoptotic cells via phagocytosis. These cells also secrete a variety of proteases and produce large amounts of reactive oxygen species that help in neutralizing viruses. Additionally, they also help with the recruitment of additional immune cells through the secretion of cytokines and chemokines. As viral titers at the primary site of infection go down, these cells are also likely to reduce in numbers, thus indicating a self-inhibitory mechanism to resolve the buildup of cytokines and chemokines. Simultaneously, tissue-resident dendritic cells phagocytose apoptotic cells that were infected with the virus, and/or viral antigens that may have been shed, which they then present on their surface resulting in the activation of T cells **(Du et al.[23])**. Simultaneously, activation of other helper T cell subsets and cytotoxic T cells may result in the killing of virally infected epithelial cells **(Chen et al.[24])**. Together, these responses are termed adaptive immune responses and take about 4–7 days to develop following the initial phagocytosis by dendritic cells.

Mathematical Modelling Approaches

A class of mathematical models that focus on the intra-host dynamics of the spread of infectious agents have been studied extensively in the context of HIV-AIDS and influenza, among others. These models, often using a set of coupled ordinary differential equations (ODEs), describe how the virus or the infective agent spreads within the host and the mechanisms within the host to resolve such infections. One of the key parameters tracked by such models is the viral load in the body of the patient. Mathematical models that track the viral kinetics in CoVID-19 patients have also been built recently. However, very few models exist so far that incorporate the interactions of the virally infected cells with different types of immune responses in the body. Such attempts can be powerful for understanding how the different clinical phenotypes appear as manifestations of underlying immune cell interactions with the infected cells.

Target Cell Model (code in 2_tcm.ode)

I started with the Target Cell Model, which has been extensively used in the modeling of the dynamics between the uninfected (target) cells, infected cells, and viral load for diseases like HIV and influenza. **(Ciupe et al.[25])**

The ODE's in the model are as follows:

$$\frac{dU}{dt} = -\beta UV \quad (1)$$

$$\frac{dI}{dt} = \beta UV - \delta I \quad (2)$$

$$\frac{dV}{dt} = pI - cV \quad (3)$$

Equation (1) represents the dynamics of susceptible cells (U) while equation (2) represents the dynamics of infected cells (I). Viral dynamics are represented by (3). Viral particles (V) infect susceptible cells with a rate β ((copies/ml) 1 day 1). Once cells are productively infected, they release virus at a rate p (copies/ml day 1 cell 1) and virus particles are cleared with a rate c (day 1). Infected cells are cleared at rate δ (day 1) as a consequence of cytopathic viral effects and immune responses.

Initial values for infected cells (I(0)) are taken as zero. Note that V cannot be measured if it is below detect able levels (about 100 copies/ml).

Parameters were used as reported in **(Esteban et al.[26])** which used non-linear mixed models to estimate the parameters to fit the patient data they had.

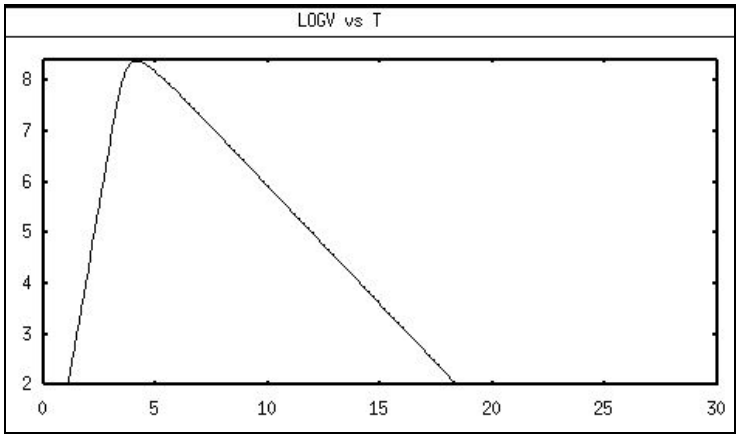
Parameter	Value used
V(0)	0.31 copies/ml
β	4.71×10^{-8}
δ	1.07
p	3.07

c	2.4

Simulations were done using XPPAUT, by writing ODE's.

On running the simulation for 30 days (mean duration of viral presence), the following was observed.

A)



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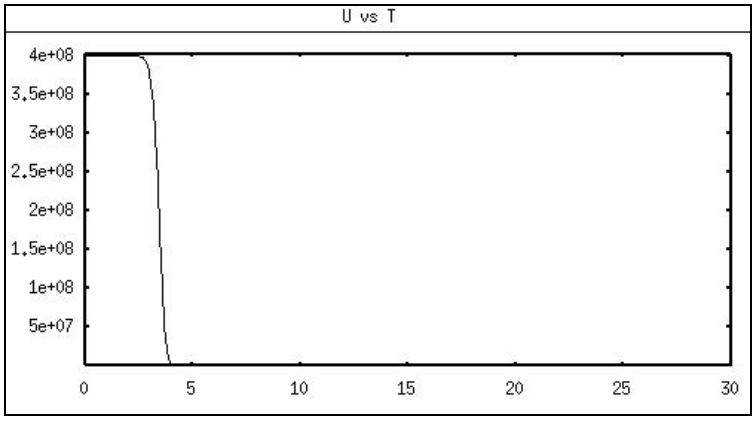


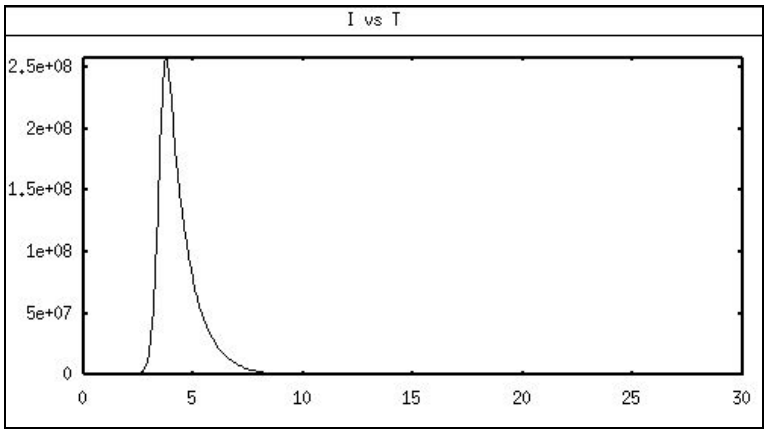
C) 

Fig 1: A) log(viral_load) B) Uninfected cells C) Infected cells plotted against time

Adding Effects of Drugs to this Model: (code in 1_tcm.ode)

I wanted to find out how the dynamics of these variables change when antiviral drugs will be administered to the patient. This is very important as it can help us predict the outcome of drugs even while they are in production. As of now, there is no approved vaccine for the disease, hence these predictive modeling approaches can help us select candidate vaccines from the cohort of many in the production phase.

To simplify the model, making a quasi-steady-state (QSS) assumption, dV/dt = 0, and hence replaced Eq.(3) with V(t) = pI(t)/c . This was done as the numbers of coronavirus RNA copies, V(t), rather than the number of infected cells, I(t), are available. Substituting this into Eq.(2)

Furthermore, defining the ratio of the number of uninfected target cells at time t, U(t) to the initial number of uninfected target cells U(0), that is, f(t) = U(t)/U(0).

Accordingly, obtained the following simplified mathematical model:

$$\frac{df}{dt} = -\beta f V \qquad (4)$$

$$\frac{dV}{dt} = \gamma f V - \delta V \qquad (5)$$

where γ = p β U(0)/c is defined as the maximum viral replication rate

Revaluating the Parameters **(Kwang et al.[27])**

Parameter	Value
f(0)	1
V(0)	0.0014
β	$6.55 * 10^{-6}$
γ	3.89
δ	1.65

Now there can be 3 courses of action for a drug: **(Kwang et al.[27])**

i) Blocking de Novo Infection:

One of the major mechanisms of action for antivirals is blocking de novo infections. This can be induced by human neutralizing antibodies, viral entry-inhibitors, and/or antibodies raised by vaccination.

The antiviral effect of blocking de novo infection therapy (0 < ε ≤ 1. ε = 1 implies de novo infection is 100% inhibited) initiated at t* (0<=t*<=4)days after symptom onset was modeled:

$$\frac{df}{dt} = -(1 - \varepsilon * heav(t - t*))\beta f V \qquad (4)$$

$$\frac{dV}{dt} = (1 - \varepsilon * heav(t - t*))\gamma f V - \delta V \qquad (5)$$

For t* = 2 (that is drug administration started on the 2nd day)

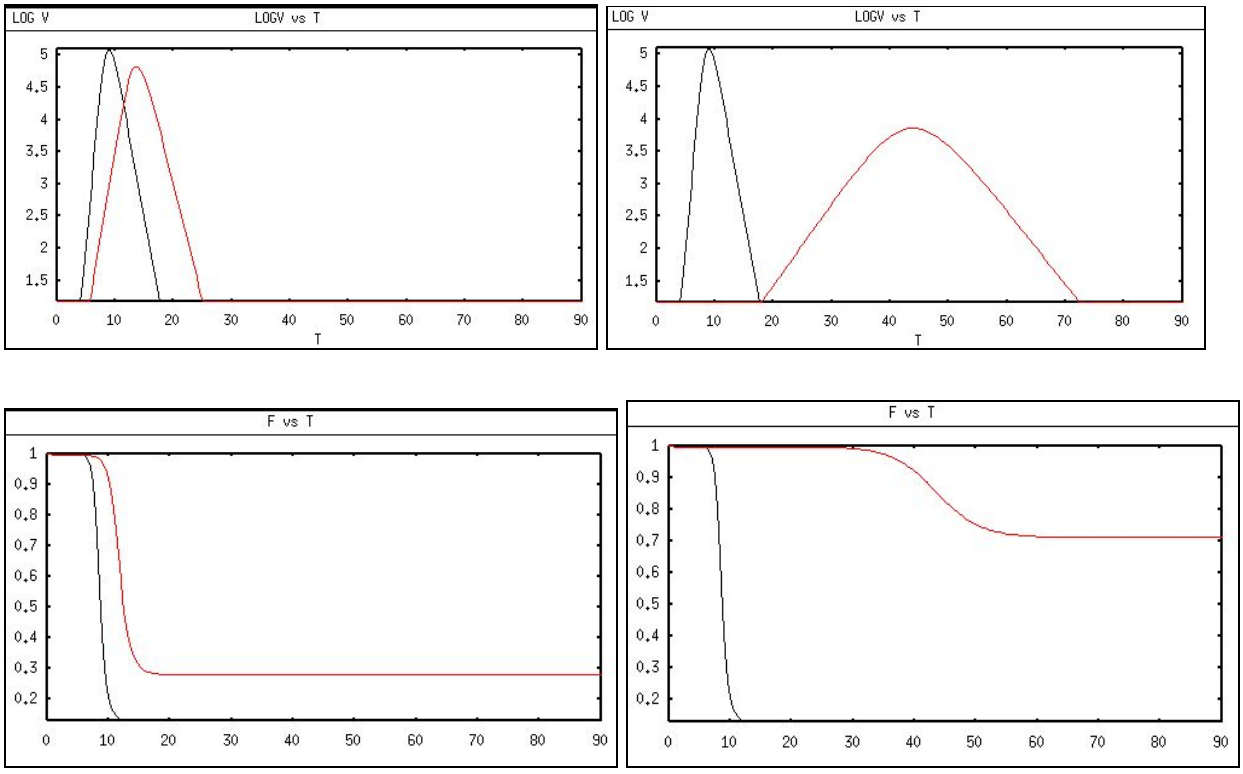
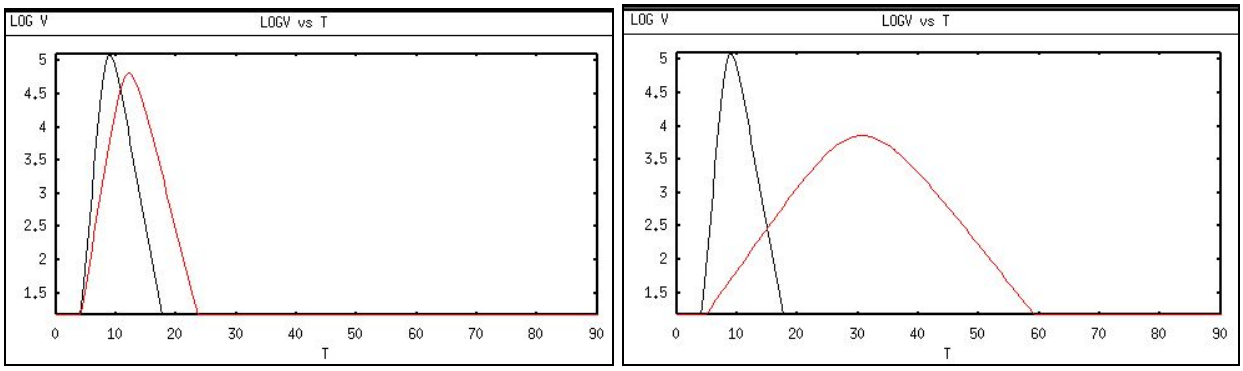


Fig 2: Left) ε = 25% Right) 50% (Black is the original response, Red is with drug)

For t* = 4 (that is drug administration started on the 4th day)



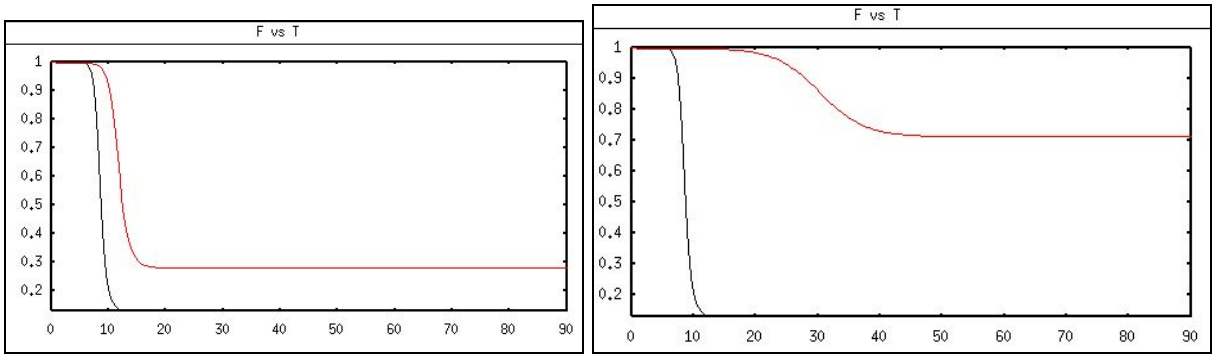
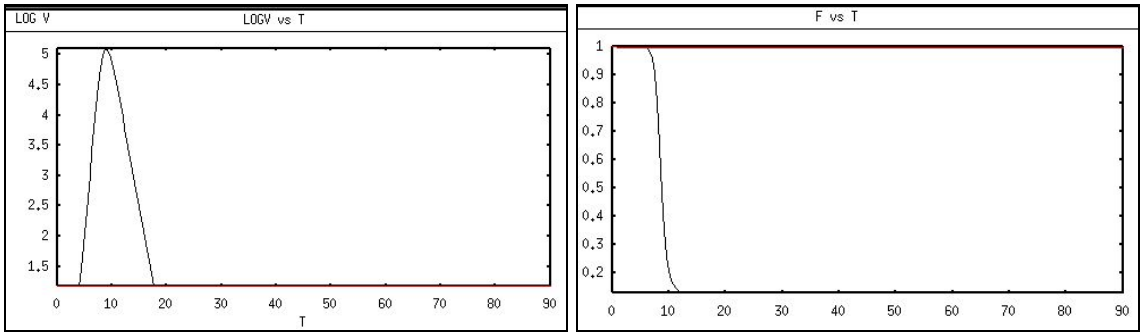
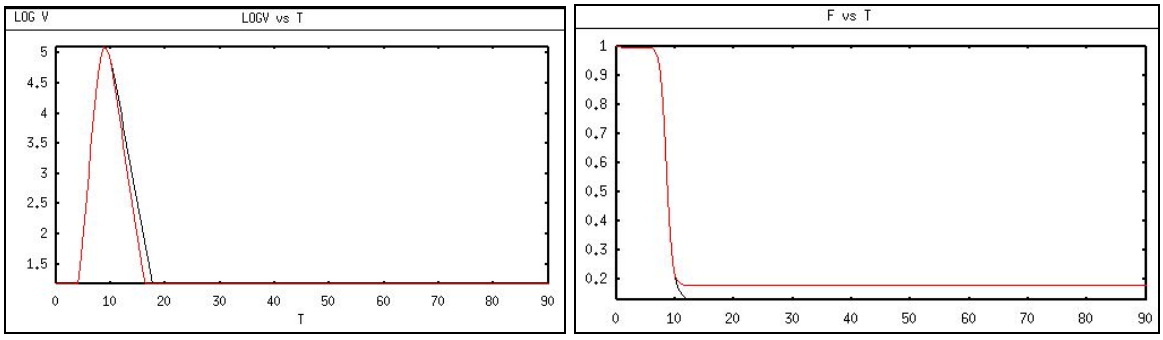


Fig 3: Left) ε = 25% Right) 50% (Black is the original response, Red is with drug)

For both t*=2 and t*=4, it was observed that if drug efficiency was >=57% then no virus above detectible limits was found in the patient



But, if t* >viral peak load (~ 10 days) then not much reduction is seen:



Inference: Even a relatively weak drug (inhibition rates as low as 50%) might effectively reduce the area under the curve of viral load (AUC) because of cytopathic effects due to cell invasion. Also, the fraction of cells left uninfected (f) shows a great reduction on the application of therapy. Therapy of this type

initiated four or more days after symptom onset, on the other hand, is not much effective. Hence, appropriate initiation timing (i.e., before or very soon after symptom onset) is an important factor for suppressing viral load in addition to the therapy having the potential for antiviral effects.

ii) Blocking Virus Production:

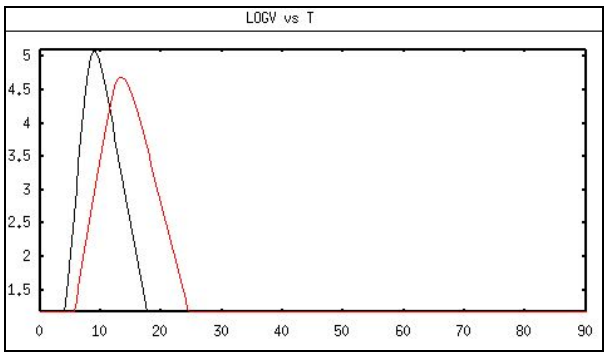
The majority of antiviral drugs inhibit intracellular virus replication. Although their antiviral efficacies need to be confirmed, lopinavir/ritonavir (HIV protease inhibitors), remdesivir (anti-Ebola virus disease candidate), and others have the potential to suppress SARS-CoV-2 by blocking virus production.

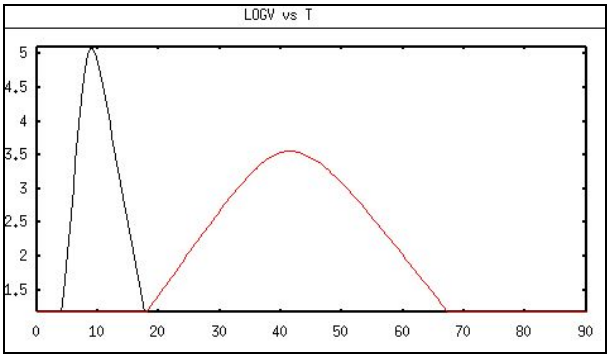
Assuming an inhibition rate of virus production of $0 < \eta \leq 1$.

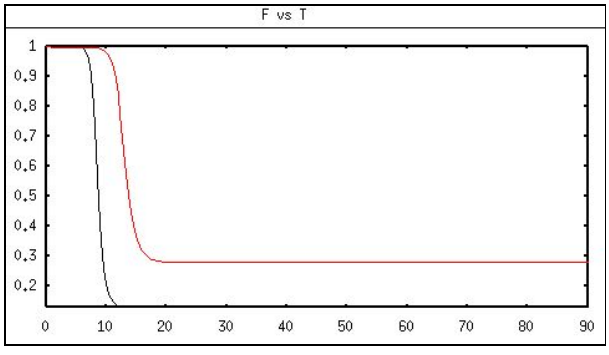
$$\frac{df}{dt} = -\beta f V \qquad (6)$$

$$\frac{dV}{dt} = (1 - \eta * heav(t - t*))\gamma f V - \delta V \qquad (7)$$

For t* = 2 (that is drug administration started on the 2nd day)







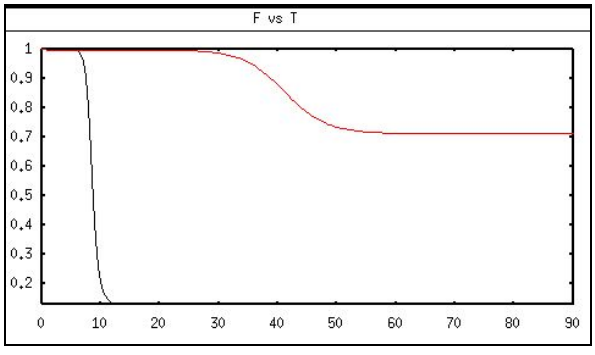


Fig 4: Left) ε = 25% Right) 50% (Black is the original response, Red is with drug)

For t* = 4 (that is drug administration started on the 4th day)

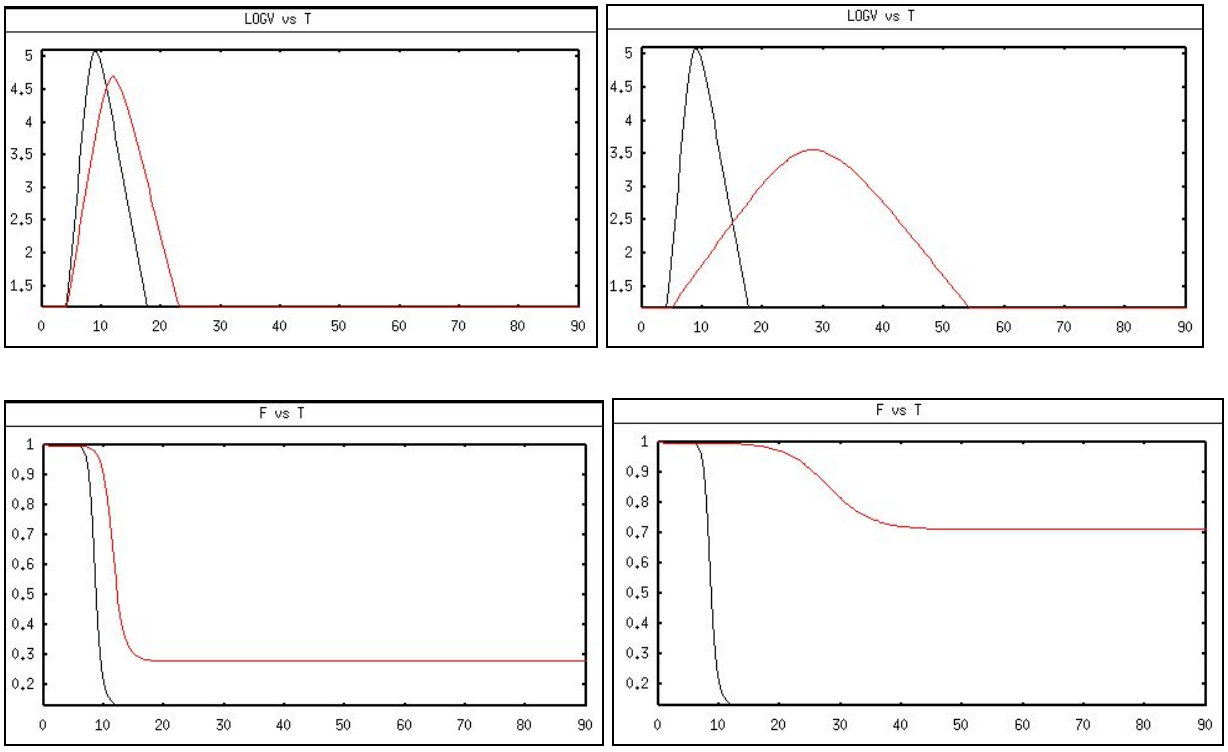
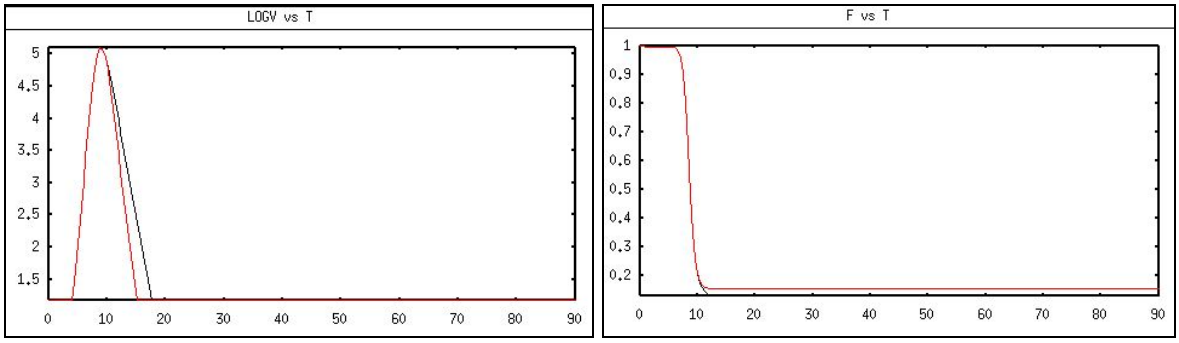


Fig 5: Left) ε = 25% Right) 50% (Black is the original response, Red is the one with drug)

Even a 99% inhibitory drug could not reduce the viral load if it was administered after the viral peak (~10 days):



Inference: Results suggest that even for relatively small inhibition rates of around 25%, the AUC of viral load is partially reduced if therapy is initiated early (within three days after symptom onset). However, if treatment is applied after the peak viral load, even drugs with a 99% inhibition rate are not able to reduce viral loads, which is similar to the predicted outcomes of de novo blocking therapy.

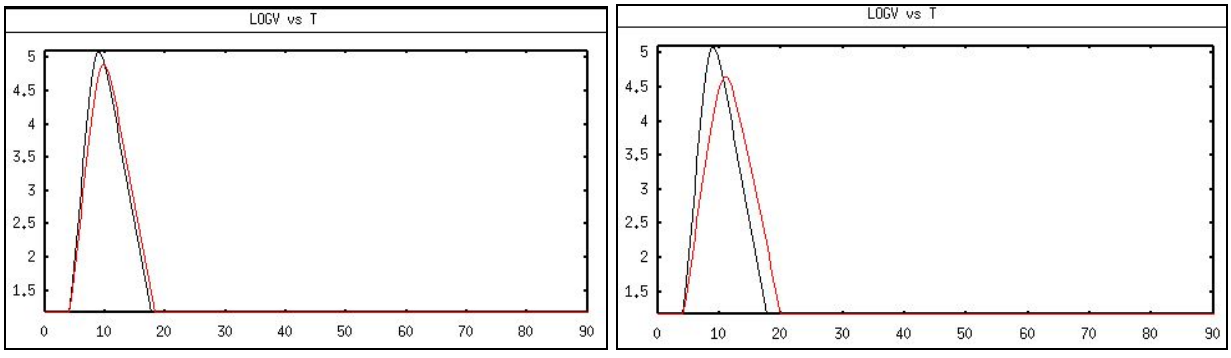
ii) Promoting Cytotoxicity:

Another antiviral mechanism is cytotoxic effects by adaptive immunity including those mediated by cytotoxic T lymphocytes. Here, we assume that promoting cytotoxicity increases the virus death rate by at most two times (i.e., $0.1 \leq \theta \leq 1$), that is, achieves up to 50% reduction of the mean length of virus production).

$$\frac{df}{dt} = -\beta f V \qquad (8)$$

$$\frac{dV}{dt} = \gamma f V - (1 + \theta * heav(t - t*))\, \delta V \qquad (9)$$

For t*=4



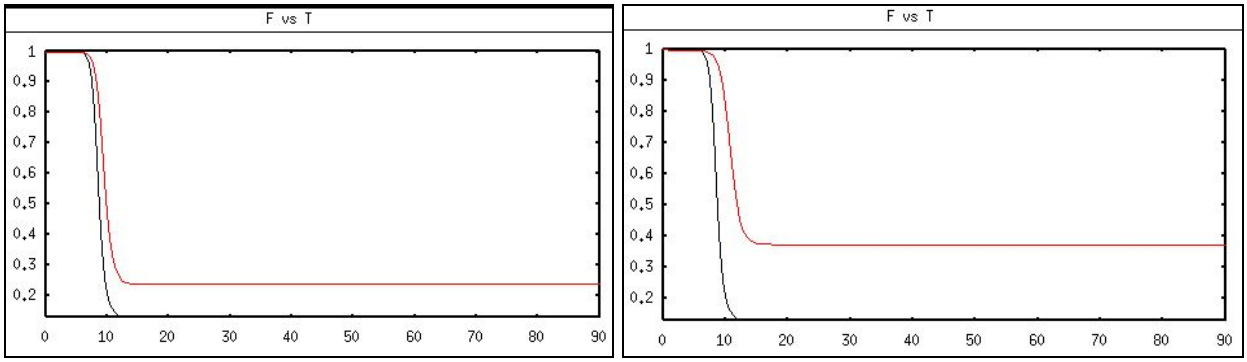
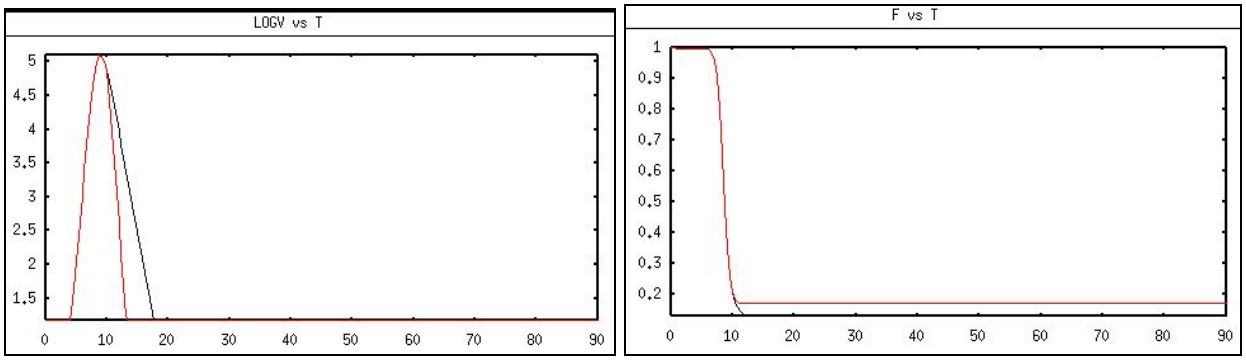


Fig 6: Left) ε = 25% Right) 50% (Black is the original response, Red is the one with drug)

For t*=10



Inference: Compared with the other two therapies (blocking de novo infection and virus production), the induction of cytotoxicity had relatively mild effects on the AUC reduction if initiated before peak viral load. However, cytotoxicity induction initiated after the peak viral load could effectively reduce the viral load AUC as compared to the other two methods.

Conclusion for Therapy :

Therefore there is an optimal time to apply a drug therapy, and that significant antiviral effects are expected unless the promoting rate is too low or therapy is initiated either too early or too late. More than the actual efficiency of the drug, the time of initiation of therapy is important. If a drug with 100% efficiency working de

novo blocking mechanism is initiated after the viral peak load or vice versa, i.e, a drug promoting cytotoxicity is initiated just after the onset of symptoms then, results will not be achieved. Hence, these predictive models, can help the doctors decide when to initiate therapy and with what efficiency drugs.

Target Cell Model with T-cell dynamics (code in 2_tcell.ode)

Many modeling studies have acknowledged the relevance of the immune T-cell response to clear influenza virus. Using a minimalistic model derived by **(Almocera et al.[28])** to represent the interaction between influenza and immune response dynamics. The model assumes that the virus (V) level induces the proliferation of T cells (T) as follows: **(Esteban et al.[26])**

$$\frac{dU}{dt} = -\beta UV \quad (10)$$

$$\frac{dI}{dt} = \beta UV - \delta I \quad (11)$$

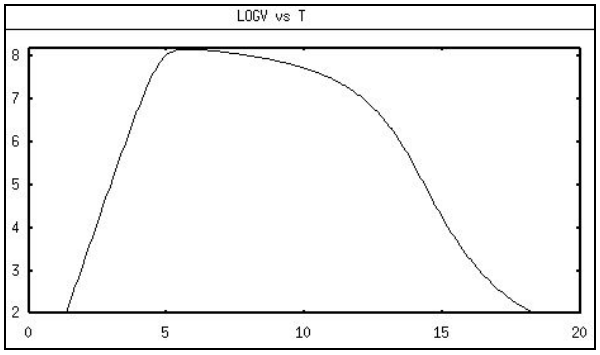
$$\frac{dV}{dt} = pV(1-\frac{V}{K}) - ct * VT - cV \quad (12)$$

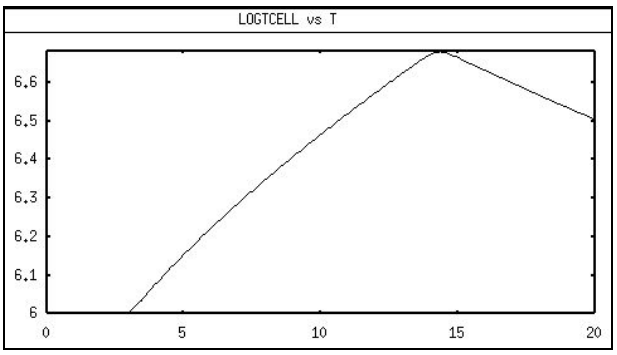
$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m+kt^m}) - \delta t * T \quad (13)$$

Equation (12) refers to the SARS-CoV-2 dynamic. Viral replication is modeled with a logistic function with a maximum carrying capacity K and a replication rate p. The initial viral concentration V(0) is 0.31 copies/ml. The virus is cleared at a rate c, the term c_tVT represents the rate of killing infected cells by the immune response.

Equation (13) represents the T cell response against SARS-CoV-2. T cell homeostasis is represented by $s_t = \delta_t T(0)$, where T(0) is the initial number of T cells and δ_t is the half-life of T cells. It is assumed that the activation of T cell proliferation by the virus follows a log-sigmoidal form with half-saturation constant k_t. The coefficient m relates to the width of the sigmoidal function.

Parameter	Value used
V(0)	0.31 copies/ml
T(0)	10^6 cells
U(0)	4×10^8 cells
β	4.71×10^{-8}
δ	1.07
p	3.07
c	2.4
K	4×10^8
c_t	1.89×10^{-6}
r	0.194
δ_t	0.1
m	2
s_t	10^5
k_t	1.26×10^5





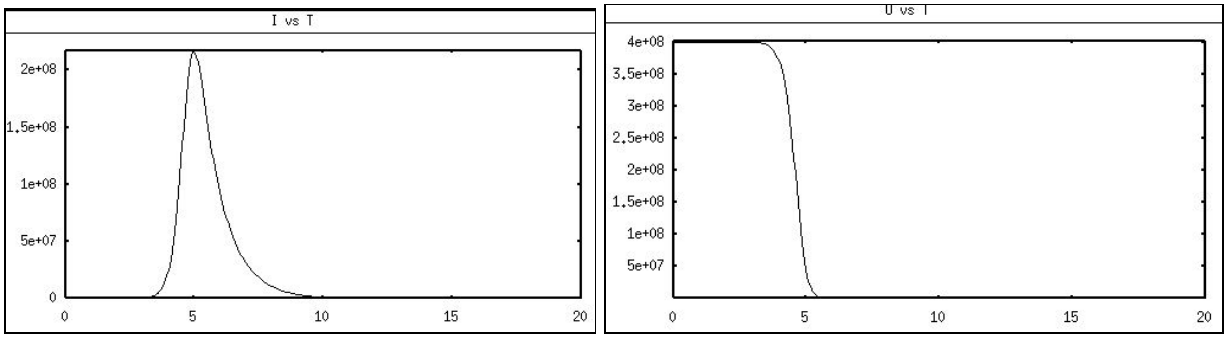


Fig 7: A) Log(Viral_Load) B) Log(T_cell) C) Infected_Cells D) Uninfected_Cells vs t

Adding Effects of Drugs to this Model: (code in 2_tcell.ode)

In the context of COVID-19, our model with the immune response can integrate a term to represent antiviral effects (u_r) as well as immune modulation (u_m) to promote the proliferation of T cells.

Equations are now as follows:

$$\frac{dU}{dt} = -\beta UV \quad (14)$$

$$\frac{dI}{dt} = \beta UV - \delta I \quad (15)$$

$$\frac{dV}{dt} = (1-ur) * pV(1-\frac{V}{K}) - ct * VT - cV \quad (16)$$

$$\frac{dT}{dt} = st + um * rT(\frac{V^m}{V^m + kt^m}) - \delta t * T \quad (17)$$

Modifying u_r: (Reduces Production rate of the virus) (u_m = 2)

From left to right: (0.25,0.30,0.35,0.40)

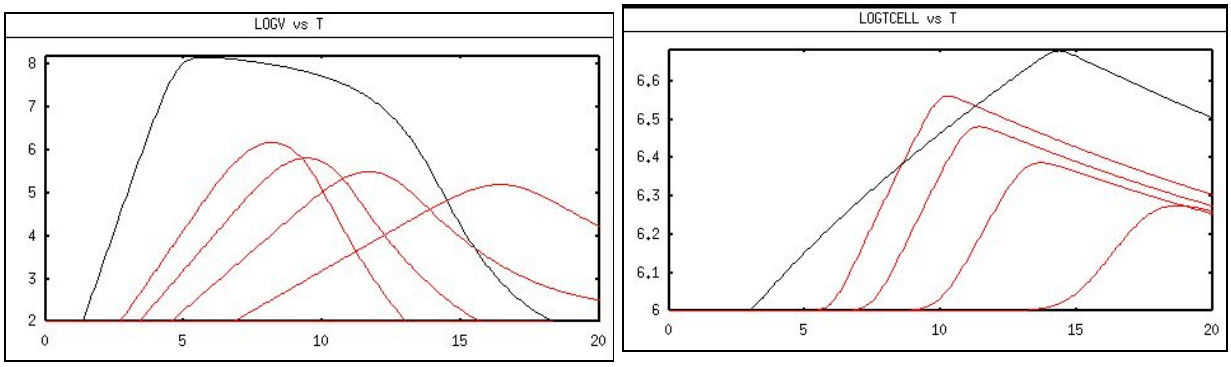


Fig 8: Log(Viral) vs t and Log(Tcell) vs time

Modifying u_m: (Augments Production rate of T-cells) (u_r = 0.25)

For log(V): from left to right, For log(T): from right to left: (3.0, 2.0, 1.5, 1.0),

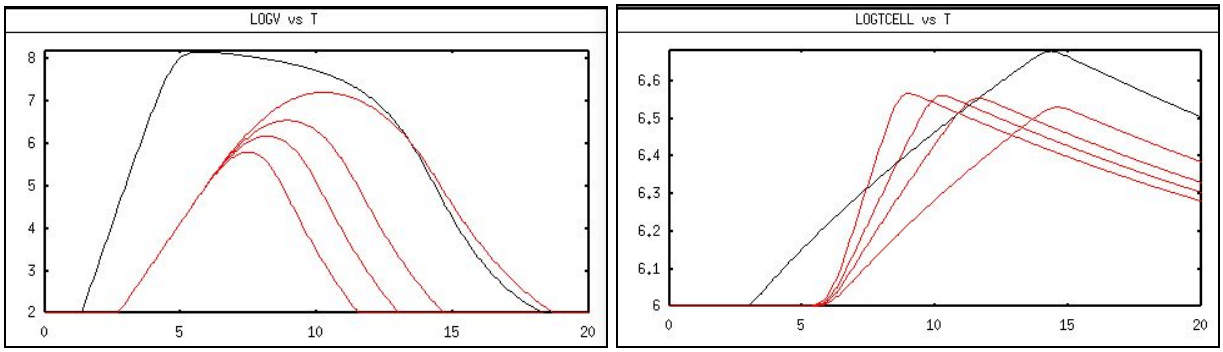


Fig 9: Log(Viral) vs t and Log(Tcell) vs time

Additions to the Target Cell Model with T-cell dynamics **(code in 3_tcell_target.ode)**

Many studies detected the presence of viral particles within the lymphocytes of SARS-CoV and MERS-CoV patients. A new study by **(X.Wang et al.[29])** found that even T lymphocytes get infected by SARS-CoV-2. Therefore, the change in the model that I propose is that T-cells should also be considered a target for the viral particles. Also, many studies have reported a higher number of lymphocytes than

expected in some patients. This has been attributed to a situation called the cytokine storm, which is a sudden acute increase in circulating levels of different inflammation-causing cytokines including IL-6, IL-1, etc. I added a positive autoregulation term on T-cells as cytokines signal T-cells themselves. This Michaelis-Menten hill function term will act as a positive activation of the T-cells.

In this regard, the changed dynamic model is:

$$\frac{dU}{dt} = -\beta UV \quad (18)$$

$$\frac{dI}{dt} = \beta UV + f\beta TV - \delta I \quad (19)$$

$$\frac{dV}{dt} = pV(1 - \frac{V}{K}) - ct * VT - cV \quad (20)$$

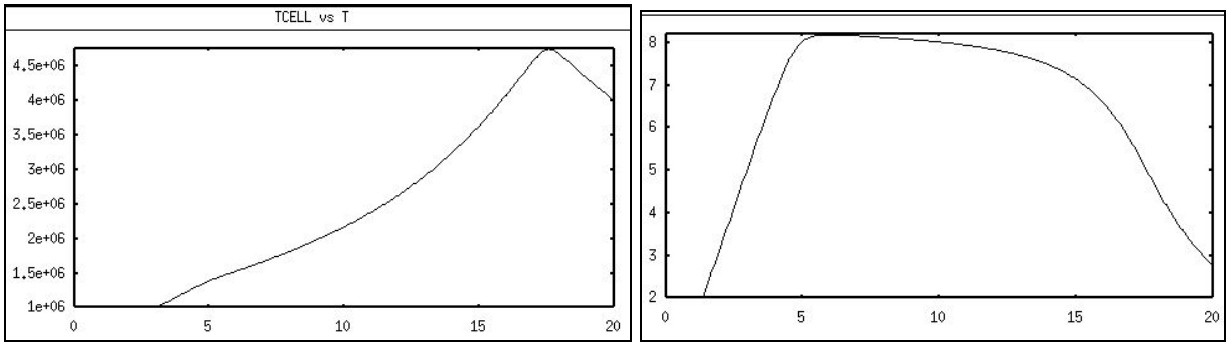
$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m + kt^m}) + par * (\frac{T^m}{T^m + kt^m}) - \delta t * T - f\beta TV \quad (21)$$

Now, the variable f: controls the rate of infection in T-cells as compared to that in other cells (β).

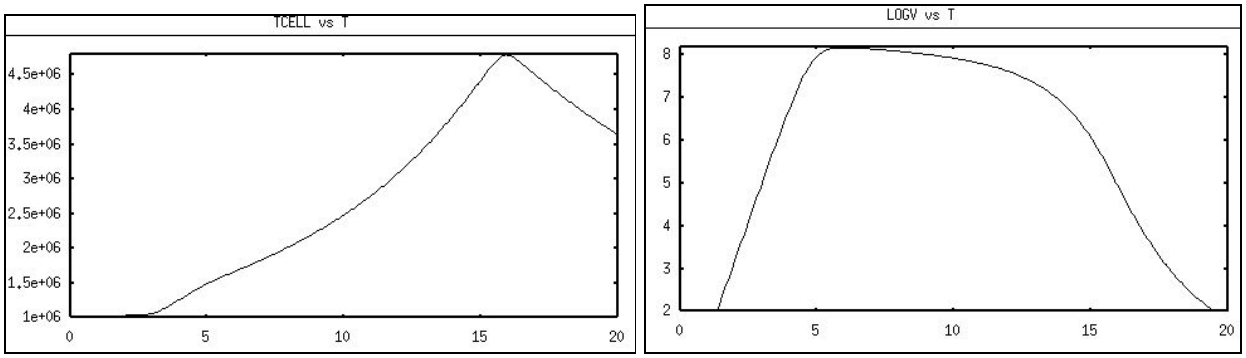
Whether or not a cytokine storm will occur, depends on the value of (par). A large par would mean a strong Positive autoregulation term, which will eventually lead to a cytokine storm, whereas, a small value of PAR would mean that the increment in T-cells due to the PAR term is overshadowed by their death naturally or due to infection by the virus.

Modeling the kinetics with different values of par, we observe:

A) par=0



B) Par = 20000 (horizontal shift in peak for T-cells)



C) par= 40000 (cytokine storm) (T-cell count keeps on increasing)

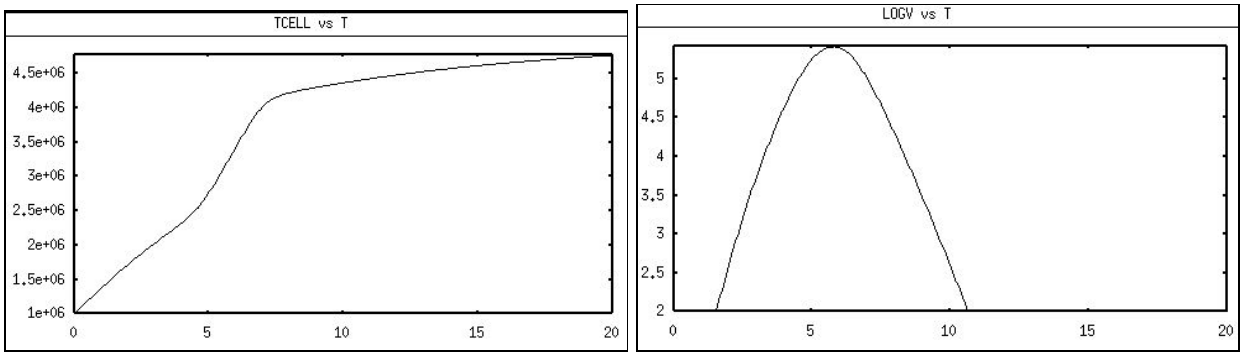


Fig 10: T-Cell & LogV vs time. A) par = 0 B) par = 20000 C) par = 400000

It can be observed from the graphs that when the positive autoregulation coefficient is zero, the value of T-cell rises and then eventually falls down. When the par value is small (20000), then a shift in the peak is seen for the T-cell concentration. But when the value of par is large (400000), then a cytokine storm-like response is seen. The concentration of T-cells explodes eventually leading to the death of the patient. Interestingly, it may appear that the cytokine storm is helping the patient as the viral load in the patient is decreasing with the increasing value of the parameter par. However, it must be noted that the death of a patient suffering from a cytokine storm is not due to the viral infection itself but

rather due to the accumulation of these cytokines resulting in fluid accumulation in the lungs eventually leading to death.

Adding Cytokine dynamics to the previous model

(code in 3_cyto.ode)

In the last model, I added a positive autoregulation term to the dynamics of T-cells, but actually, the mechanism is different. Cytokines instead should have a positive autoregulation term and these cytokines in turn signal T-cells to be deployed at the site. To incorporate this into the model, the PAR term was shifted from T-cells to cytokines and a signal was added in T-cells regulated by cytokines. The dynamics of cytokines were modeled using infected cells (which signal cytokines) and viral particles.

The equations of the model therefore are:

$$\frac{dU}{dt} = -\beta UV \quad (22)$$

$$\frac{dI}{dt} = \beta UV + f\beta TV - \delta I \quad (23)$$

$$\frac{dV}{dt} = pV(1-\frac{V}{K}) - ct * VT - cV \quad (24)$$

$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m+kt^m}) + lc * C - \delta t * T - f\beta TV \quad (25)$$

$$\frac{dC}{dt} = kc * I * (1+\frac{\gamma c}{V}) + storm * (\frac{C^m}{C^m+km^m}) - mc * C \quad (26)$$

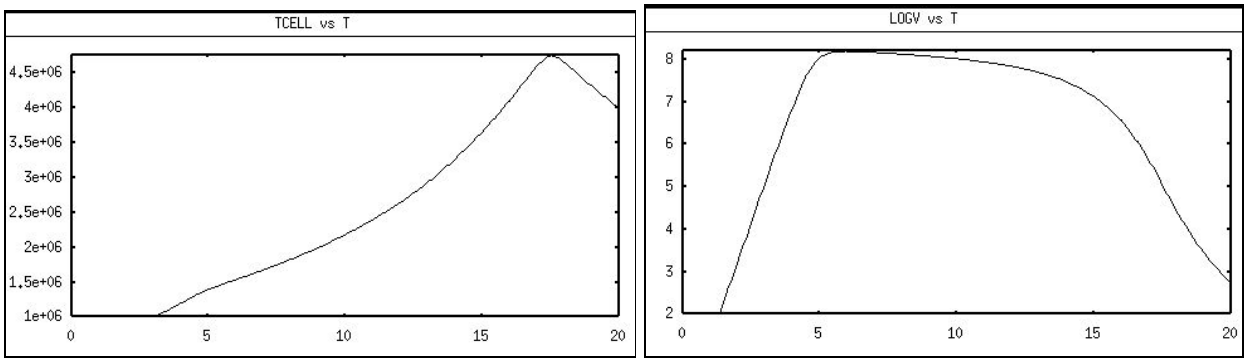
New Parameter	Value used
C(0)	0.01
k_c	5
k_m	100
storm	1000-10000

γ_c	0.5
m_c	0.7
l_c	20

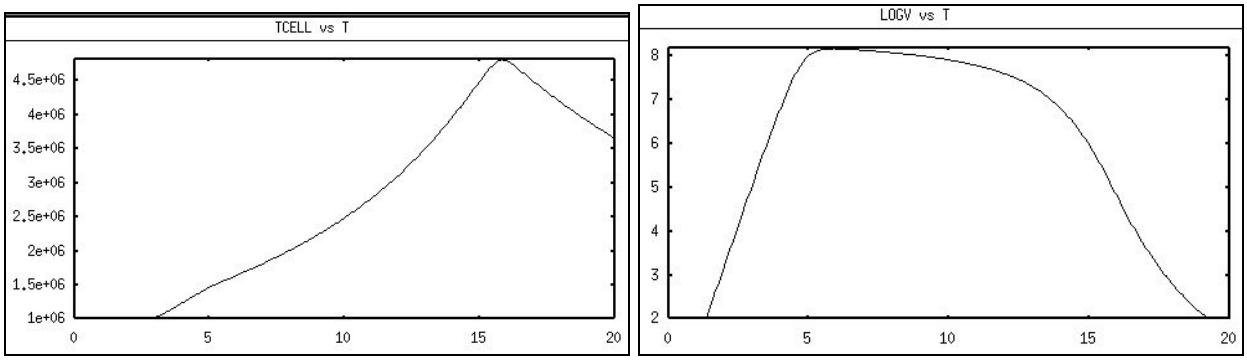
Like previously established, the value of storm controls the cytokine storm. If the value is very huge (10000) a cytokine storm takes place, whereas if it is small (1000) a normal mechanism takes place.

Modeling the kinetics with different values of the storm, we observe:

A) storm=0



B) storm = 10000 (horizontal shift in peak for T-cells)



C) storm= 50000 (cytokine storm) (T-cell count keeps on increasing)

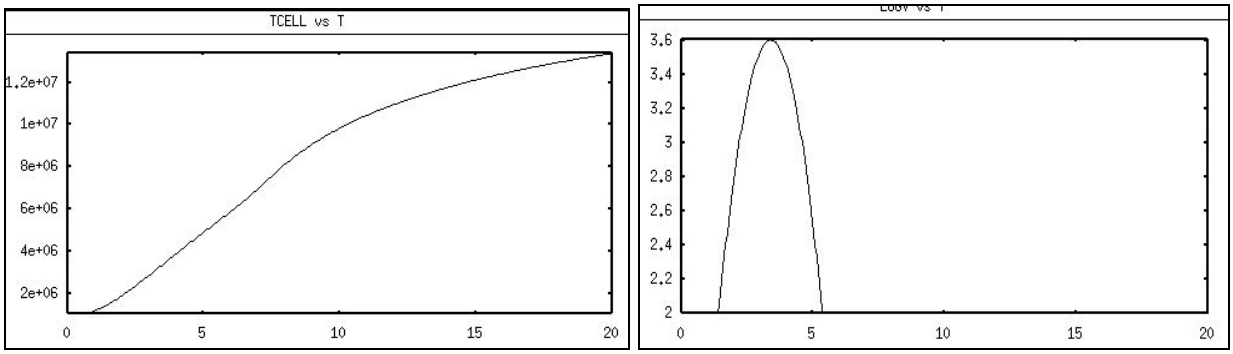


Fig 11: T-Cell & LogV vs time. A) storm = 0 B) storm = 1000 C) storm = 50000

Adding Effects of Drugs to this Model:

As explained before, a possible antiviral drug could act in different ways. Three of them had been elucidated while modeling the drug response in the base target cell model. Another possible drug candidate could be one that suppresses the cytokine storm within a patient if it occurs. Therefore, modeling these 4 types of drugs in the model proposed:

i) Blocking de Novo Infection: (code in 3_cyto_denovo.ode)

$$\frac{dU}{dt} = -(1-\varepsilon * heav(t-t*))\beta UV \quad (27)$$

$$\frac{dI}{dt} = (1-\varepsilon * heav(t-t*))\beta UV + (1-\varepsilon * heav(t-t*))f\beta TV - \delta I \quad (28)$$

$$\frac{dV}{dt} = p(1-\varepsilon * heav(t-t*))V(1-\frac{V}{K}) - ct * VT - cV \quad (29)$$

$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m+kt^m}) + lc * C - \delta t * T - (1-\varepsilon * heav(t-t*))f\beta TV \quad (30)$$

$$\frac{dC}{dt} = kc * I * (1+\frac{\gamma c}{V}) + storm * (\frac{C^m}{C^m+km^m}) - mc * C \quad (31)$$

The term $(1 - \varepsilon * heav(t - t*))$ represents the blocking of new infections and has been added in the dynamics. The 2 new parameters (ε and t*) had been tweaked to see the effect on the model.

Without cytokine storm (storm value = 1000)

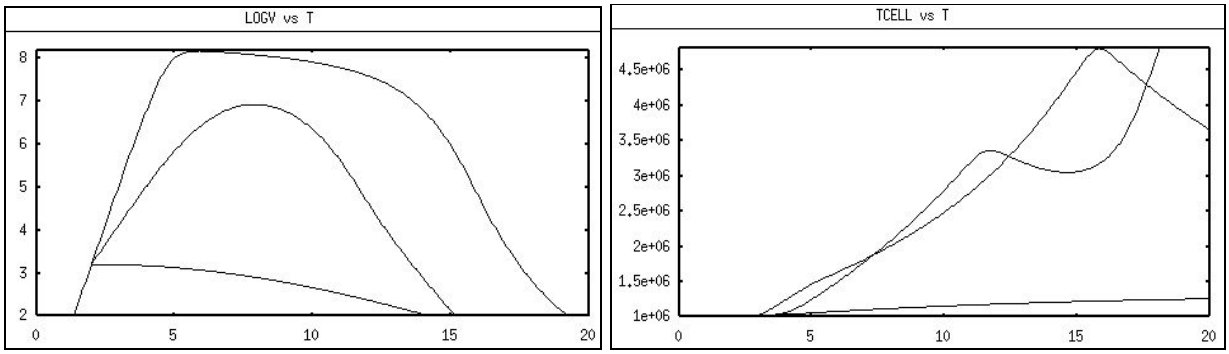


Fig 12: t* = 2; Efficiency ranges from 0, 25%, 50%

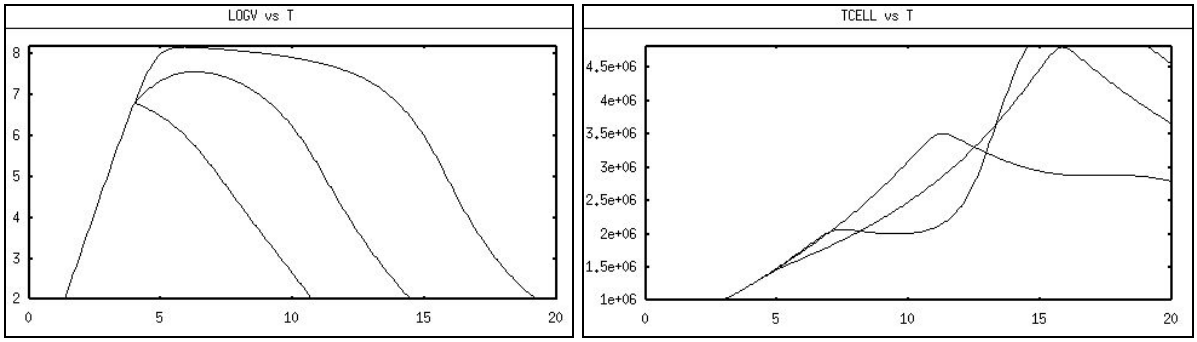


Fig 13: t* = 4; Efficiency ranges from 0, 25%, 50%

As is seen from the plots that in case of a normal infection, a vaccine stopping de novo infection is **very effective** if administered early on after the onset of symptoms as it doesn't change the dynamics of the T-cell much but instead works to reduce the viral load considerably.

With cytokine storm (storm value = 50000)

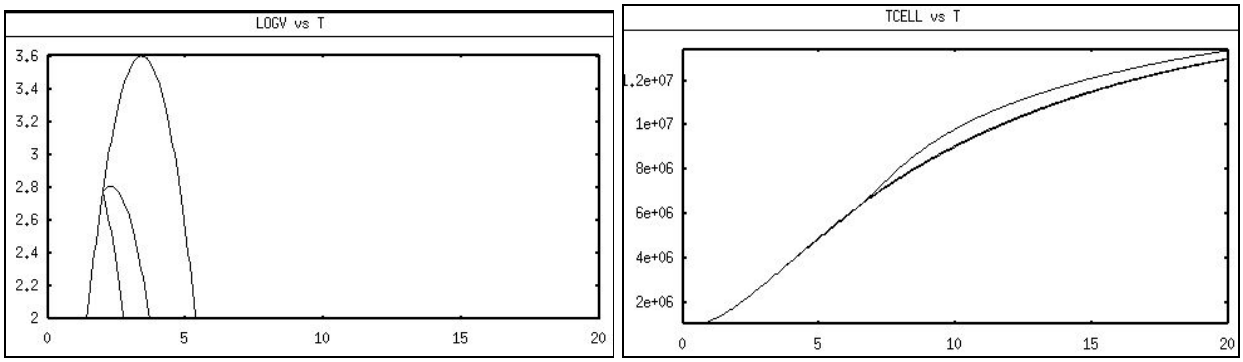


Fig 14: t* = 2; Efficiency ranges from 0, 25%, 50%

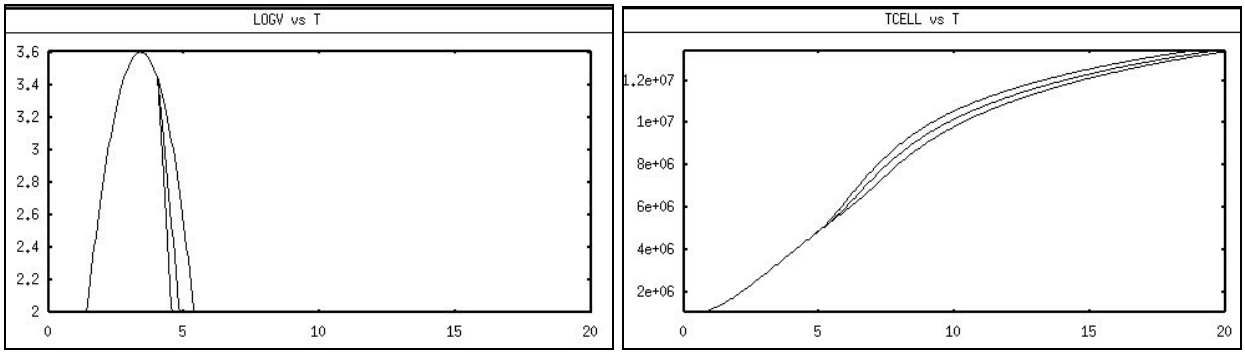


Fig 15: t* = 4; Efficiency ranges from 0, 25%, 50%

As is seen from the plots that in case of a cytokine storm, a vaccine stopping de novo infection is **not of much use**, as it doesn't change the dynamics of the cytokine storm instead works to further reduce the viral load which is not fatal here. Therefore, during a cytokine storm, this vaccine is not useful.

ii) Blocking Virus Production: (code in 3_cyto_blockprod.ode)

$$\frac{dU}{dt} = -\beta UV \tag{32}$$

$$\frac{dI}{dt} = \beta UV + f\beta TV - \delta I \tag{33}$$

$$\frac{dV}{dt} = p(1-\varepsilon * heav(t-t*))V\left(1-\frac{V}{K}\right) - ct * VT - cV \tag{34}$$

$$\frac{dT}{dt} = st + rT\left(\frac{V^m}{V^m + kt^m}\right) + lc * C - \delta t * T - f\beta TV \quad (35)$$

$$\frac{dC}{dt} = kc * I * \left(1 + \frac{\gamma c}{V}\right) + storm * \left(\frac{C^m}{C^m + km^m}\right) - mc * C \quad (36)$$

The term $(1 - \varepsilon * heav(t - t*))$ represents the blocking of virus production and has been added in the rate equation for the virus (dV/dt). The 2 new parameters (ε and t*) had been tweaked to see the effect on the model.

Without cytokine storm (storm value = 1000)

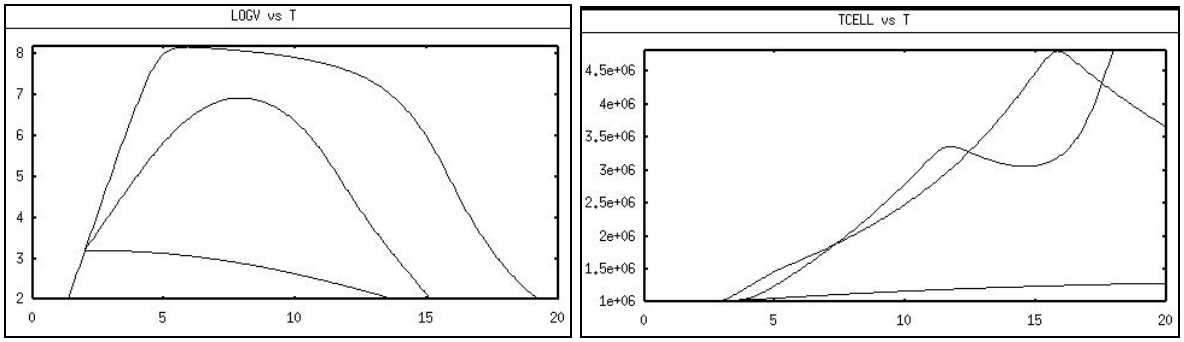


Fig 16: t* = 2; Efficiency ranges from 0, 25%, 50%

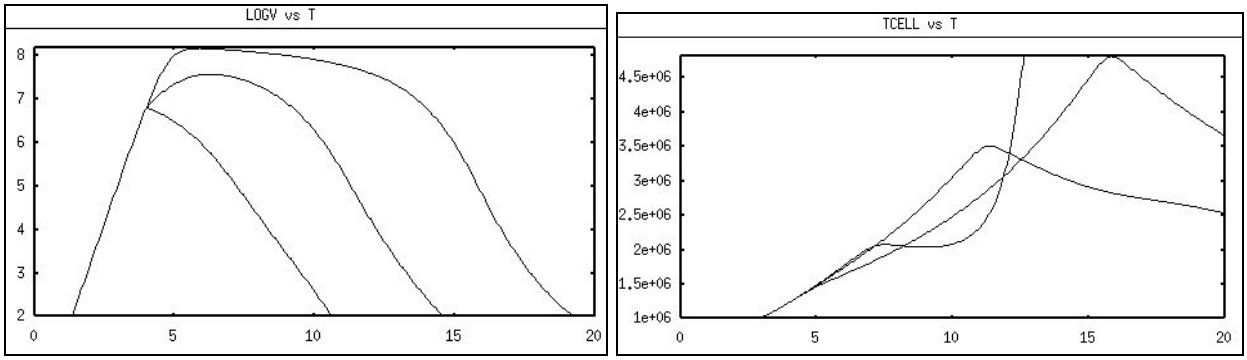


Fig 17: t* = 4; Efficiency ranges from 0, 25%, 50%

As is seen from the plots that in case of a normal infection, a vaccine blocking virus production is **very effective** if administered early on after the onset of symptoms as it doesn't change the dynamics of the T-cell much but instead works to reduce the viral load considerably.

With cytokine storm (storm value = 50000)

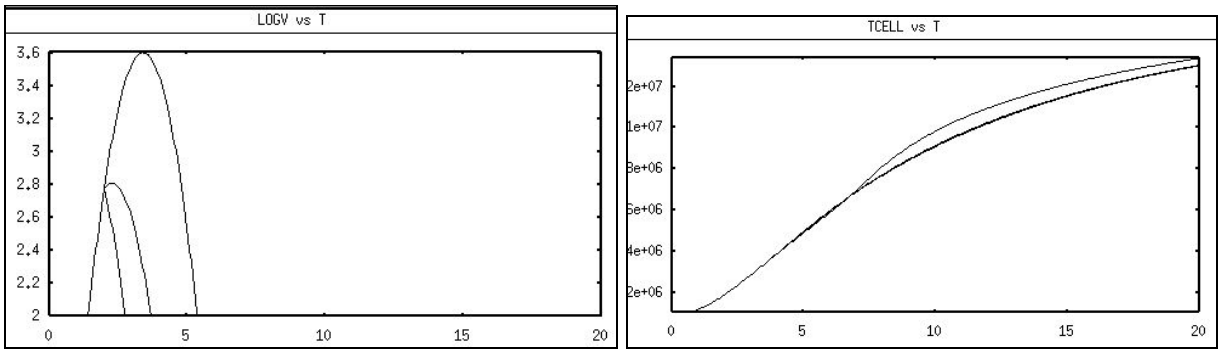


Fig 18: t* = 2; Efficiency ranges from 0, 25%, 50%

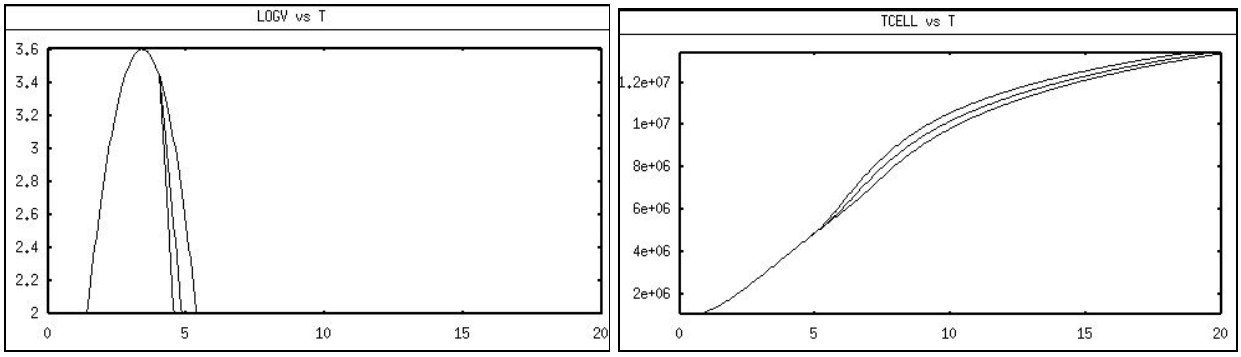


Fig 19: t* = 4; Efficiency ranges from 0, 25%, 50%

As is seen from the plots that in the case of a cytokine storm, a vaccine blocking virus production is **not very effective**, as it doesn't change the dynamics of the cytokine storm instead works to further reduce the viral load which is not fatal here. Therefore, during a cytokine storm, this vaccine is not useful.

iii) Promoting cytotoxicity: (code in 3_cyto_inccyto.ode)

$$\frac{dU}{dt} = -\beta UV \tag{37}$$

$$\frac{dI}{dt} = \beta UV + f\beta TV - \delta I \tag{38}$$

$$\frac{dV}{dt} = pV(1-\frac{V}{K}) - ct * VT - cV \quad (39)$$

$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m+kt^m}) + lc * C - \delta t * T - f\beta TV \quad (40)$$

$$\frac{dC}{dt} = (1+\varepsilon * heav(t-t*))(kc * I * (1+\frac{\gamma c}{V}) + storm * (\frac{C^m}{C^m+km^m})) - mc * C \quad (41)$$

The term $(1+\varepsilon * heav(t-t*))$ represents an increase in the cytotoxicity of the cytokines therefore it has been added in the rate equation for C. Parameters (ε and t*) had been tweaked to see the effect on the model.

Without cytokine storm (storm value = 1000)

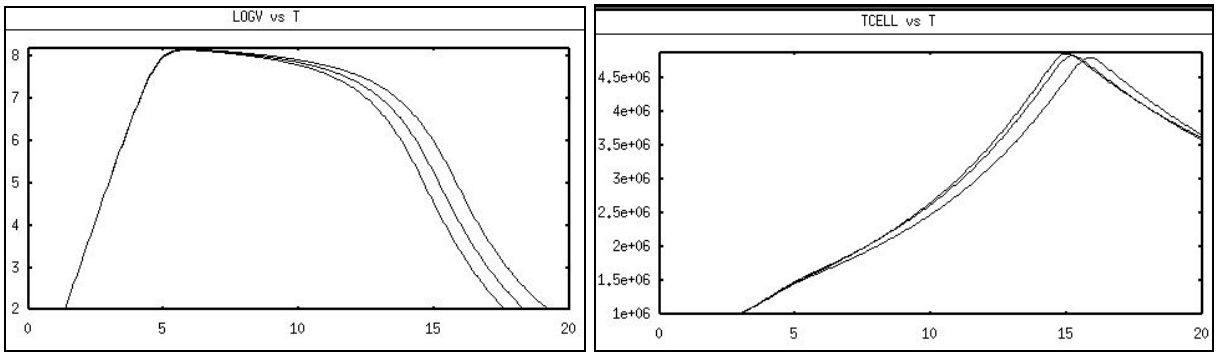


Fig 20: t* = 2; Efficiency ranges from 0, 50%, 100%

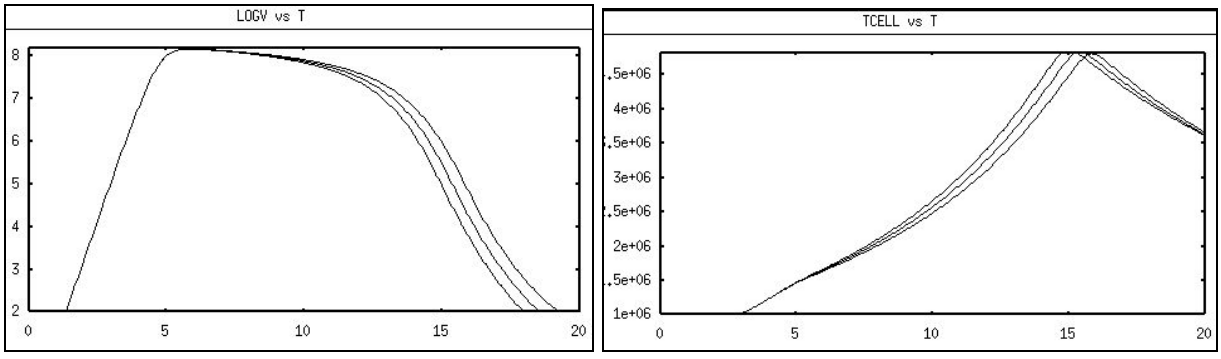


Fig 21: t* = 4; Efficiency ranges from 0, 50%, 100%

A vaccine promoting cytotoxicity is **not very effective** even if administered early on after the onset of symptoms as it doesn't change the dynamics of the T-cell much neither does it reduce the viral load considerably.

With cytokine storm (storm value = 50000)

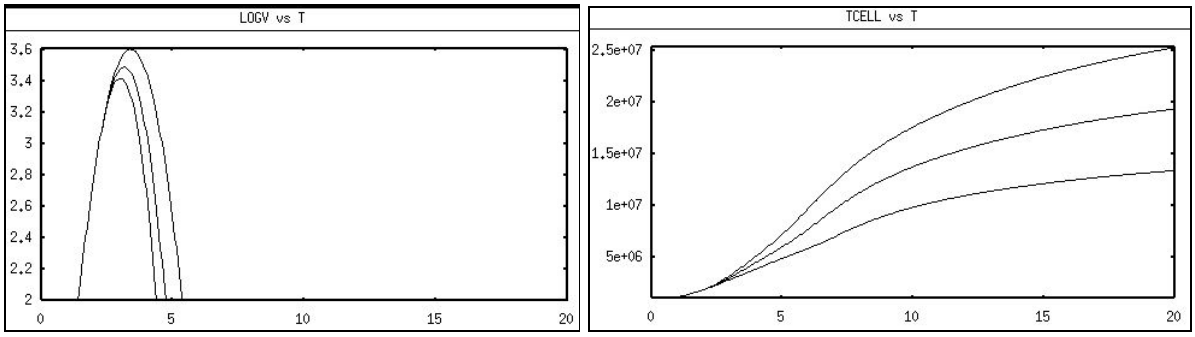


Fig 22: t* = 2; Efficiency ranges from 0, 50%, 100%

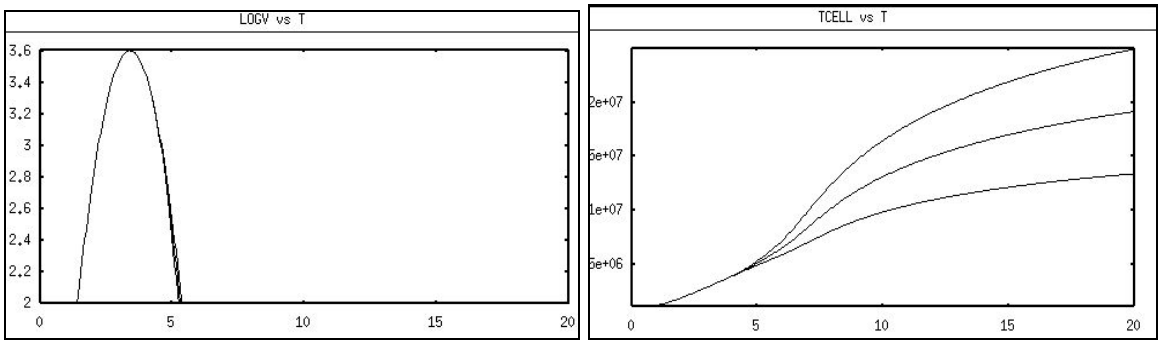


Fig 23: t* = 4; Efficiency ranges from 0, 50%, 100%

A vaccine promoting cytotoxicity is **harmful** to a patient undergoing a cytokine storm as ends up augmenting the severity of the storm also neither does it reduce the viral load considerably.

iv) Kill storm: (code in 3_cyto_kill_storm.ode)

$$\frac{dU}{dt} = -\beta UV \tag{42}$$

$$\frac{dI}{dt} = \beta UV + f\beta TV - \delta I \quad (43)$$

$$\frac{dV}{dt} = pV(1 - \frac{V}{K}) - ct * VT - cV \quad (44)$$

$$\frac{dT}{dt} = st + rT(\frac{V^m}{V^m + kt^m}) + lc * C - \delta t * T - f\beta TV \quad (45)$$

$$\frac{dC}{dt} = kc * I * (1 + \frac{\gamma c}{V}) + (1 - \varepsilon * heav(t - t*))\, storm * (\frac{C^m}{C^m + km^m}) - mc * C \quad (46)$$

The term $(1 - \varepsilon * heav(t - t*))$ represents a decrease in the severity of the cytokine storm therefore it has been added in the rate equation for C. Parameters (ε and t*) had been tweaked to see the effect on the model.

Without cytokine storm (storm value = 1000)

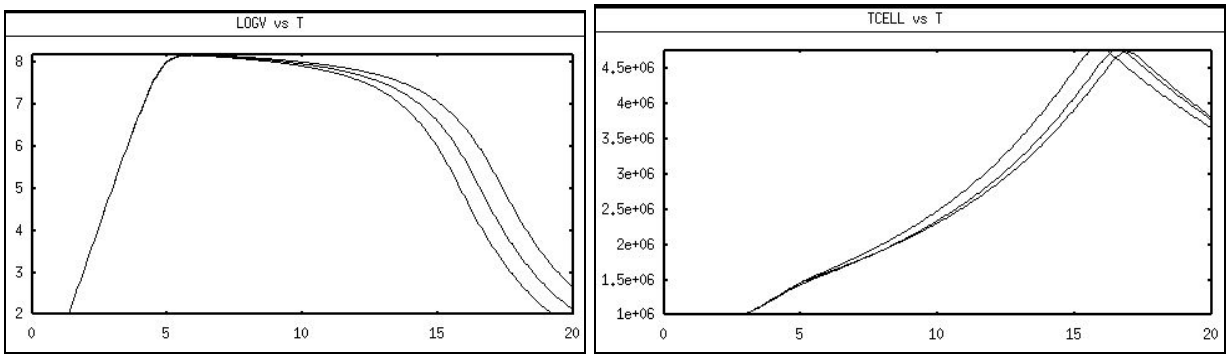


Fig 24: t* = 2; Efficiency ranges from 0, 50%, 100%

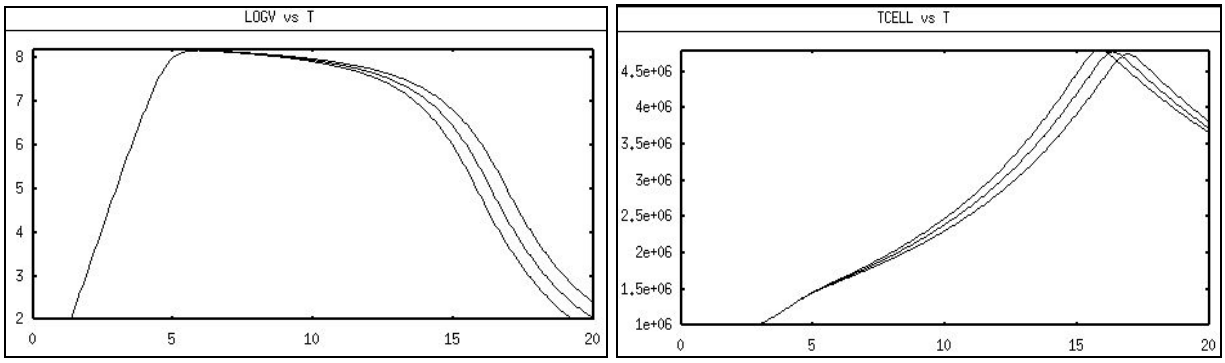


Fig 25: t* = 4; Efficiency ranges from 0, 50%, 100%

A vaccine killing the storm is **not very effective** even if administered early on after the onset of symptoms for a patient with no cytokine storm, as it doesn't change the dynamics of the T-cell instead increases the viral load.

With cytokine storm (storm value = 50000)

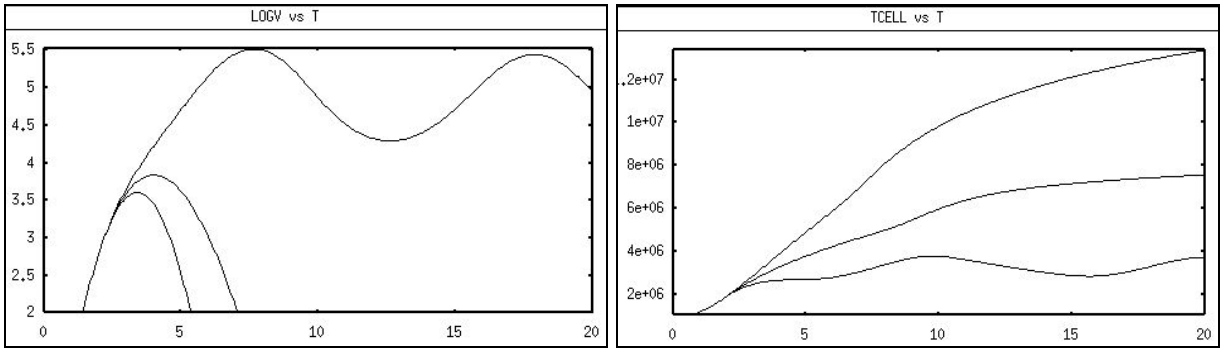


Fig 26: t* = 2; Efficiency ranges from 0, 50%, 100%

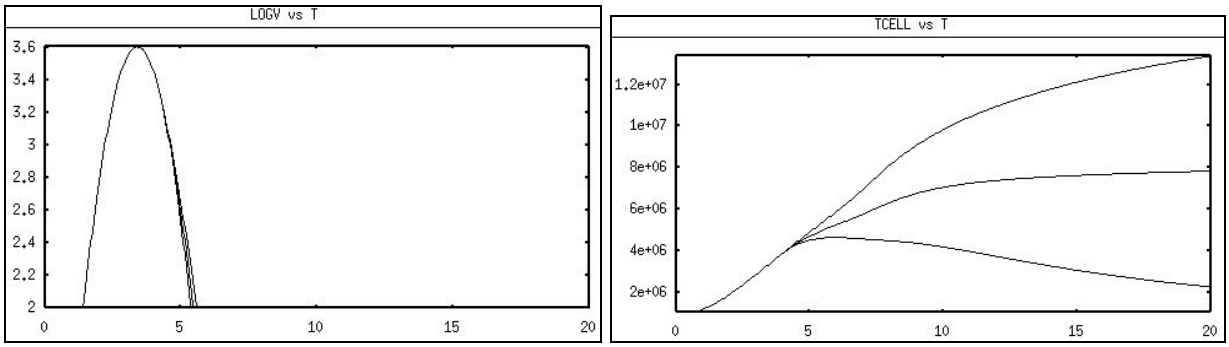


Fig 27: t* = 4; Efficiency ranges from 0, 50%, 100%

A vaccine killing the storm is **very effective** if administered to a patient suffering from a cytokine storm. If it is administered within 2 days of symptom onset, then the viral load increases and the cytokine load decreases. But, the best time to administer this vaccine is 4 days after the symptom onset, on doing so, the viral load remains the same (nearly), while the storm is destroyed and the cytokine concentration starts dropping.

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5) https://link.springer.com/article/10.1007/s41745-020-00205-1
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