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Mathematical Simulations of Competitiondynamics between Cell Mediated and Humoral Branches of Immune System against Hepatitis C Virus.

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Abstract: *This section presents a mathematical simulation that includes two different effectorresponses that fight a viral infection independently: CTL (responsible for cell mediated immune responses) and antibodies (responsible for humoral immune responses).Since it is assumed that both responses rely on antigenic stimulation, the simulationscapture the competition dynamics.This is because the virus population is a resource that both CTL and antibodies require for survival. Competition can result either in the exclusion of one branch of the immune system, or both branches may coexist. We have examined and simulated five different immune dynamics of immune system responses; pathogen free, immunity free, CTL dominant, Antibody dominant and relative equal CTL and Antibody responses. Analytically we have established the minimum conditions required for either of the two branches of immune system to dominate or to coexist equally. We have explored how these competition dynamics can influence acute and persistent phases of infection in the context of hepatitis C virus infection. This is because data indicate that the balance between CTL and antibody responses might determine whether the virus is cleared during acute infection, whether it can establish a persistent, chronic infection, and whether the infection is asymptomatic or pathogenic. HCV primarily infects liver cells. A relatively small percentageof patients clear the virus from the blood, while the rest develop persistent infection that results in liver pathology as long as 10-20 years after infection.*

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I. Introduction

Cognition of the immune response mechanism provides a key to understanding disease processes and methods of effective medical treatment. Again some treatments that are becoming available to medics will become overwhelmingly useless unless we find a way to simulate particular treatment protocols before applying them in practice.

In 1989, HCV was identified by a molecular biological method where researchers induced the expression of DNAs obtained from the blood plasma of a chimpanzee with hepatitis non-A, non-B and screened them with convalescent serum (Choo et al., 1989). HCV was the first virus to be discovered not by the previously used virological methods, but by a molecular biological method**.**

The discovery of HCV had a great impact on the treatment and prevention of liver diseases (Hayashi &Takehara, 2006). It turned out that not only did most patients who had been diagnosed as hepatitis non-A, non-B actually have hepatitis C, but also that there were quite a few hepatitis C patients among those who had been thought to have alcoholic liver disease or autoimmune hepatitis. As the natural history of hepatitis C was clarified, it became clear that the disease is a major risk factor for hepatocellular carcinoma (HCC) .The infection route of HCV is via the blood. Some patients who are exposed to the virus develop overt liver disease, but most of them remain in a latent state. Within six months of being infected, 30% of the patients expel the virus naturally while the remaining 70% enter a phase of persistent infection. Once patients enter in this latter phase, it is very rare for the virus to be expelled naturally, with the estimated annual rate being less than 0.2% at most. Many of the patients with persistent infection show the medical conditions of chronic hepatitis and develop cirrhosis in 20 to 30 years. Patients with cirrhosis develop HCC at a very high annual rate of 8%, while patients with early chronic hepatitis do so at an annual rate of only 0.5%. The estimated number of patients with HCV is about 1.7 million in Japan and about 1.7 billion in the world. It is a serious public health problem as many of these patients belong to a high-risk group for HCC.

Because HCV replication is non-cytolytic, cell-mediated immune (CMI) responses to viral antigens are thought to be responsible for the clearance of virus from infected cells and for the liver damage seen in transient and persistent infections. This is presumed to occur via a direct, cytolytic effect of viral antigen-specific cytotoxic T lymphocytes (CTLs) on infected hepatocytes, or via the non-cytopathic action of inflammatory cytokines. In addition, neutralizing antibodies have been shown to prevent infection by blocking the ability of virus particles to bind to receptors on target cells. Wodarz, D. (2003)

II. Model Description

Susceptible host cells are produced at a rate λ, die at a rate ωS and become infected by virus at a rate βSV. Infected cells die at a rate δY and are killed by the CTL response at a rate μYT .Free virus is produced by infected cells at a rate κY, decays at a rate αV, and is neutralized by antibodies at a rate ρVA. The rate at which pathogen specific antibodies of immunological memory are lost at rate ε ,the antibodies develop in response to free virus at a rate ϕVA and decay at a rate τA. The rate at which pathogen specific CTL of immunological memory are lost at rate υ. CTL expand in response to viral antigen derived from infected cells at a rate θYT, and decay in the absence of antigenic stimulation at a rate σT. εV and υT indicate that even in the absence of pathogen there will always be a (typically small) standing stock of both antibodies and CTL ready to fight an attack. Without this standing stock immune response system would take longer to respond to pathogen. For primary infections we will take $\varepsilon = \upsilon \cong 0$,

$E = \frac{1}{\varepsilon}$ and $G = \frac{1}{\upsilon}$ is the average duration of antibodies and CTL memory cells respectively.

$$\dot{S}(t) = \lambda - \omega S - \beta SV \qquad 4.1$$

$$\dot{Y}(t) = \beta SV - \delta Y - \mu YT \qquad 4.2$$

$$\dot{V}(t) = \kappa Y - \alpha V - \rho VA \qquad 4.3$$

$$\dot{A}(t) = \varepsilon A + \phi VA - \tau A \qquad 4.4$$

$$\dot{T}(t) = \upsilon T + \theta YT - \sigma T \qquad 4.5$$

III. Parameter combination for dominance of either CTL or Antibody responses or both

Here we analytically examine the conditions that must be satisfied to guarantee any of the three possible outcomes described above.

We separate immunological events from non- immunological events in the model equations, where an immunological event is any event involving either CTL or Antibody. Define two matrices f and h which represent immunological events and non- immunological events respectively.

Let

$$f = \begin{bmatrix} \mu Y_e T_e \\ \rho V_e A_e \\ \phi V_e A_e \\ \theta Y_e T_e \end{bmatrix} \text{ and } h = \begin{bmatrix} \beta S_e V_e - \delta Y_e \\ \kappa Y_e - \alpha V_e \\ \tau A_e \\ \sigma T_e \end{bmatrix}$$

Where Y_e, V_e, A_e and T_e are the values of the defined variables at equilibrium points.

Let F and H represent the partial derivatives with respect to each of the variables defined in equation 2 to 5 and H^{-1} be the inverse of matrix H.

$$F = \begin{bmatrix} \mu T_e & 0 & 0 & \mu Y_e \\ 0 & \rho A_e & \rho V_e & 0 \\ 0 & \phi A_e & \phi V_e & 0 \\ \theta T_e & 0 & 0 & \theta Y_e \end{bmatrix} \text{ and } H = \begin{bmatrix} -\delta & \beta S_e & 0 & 0 \\ \kappa & -\alpha & 0 & 0 \\ 0 & 0 & \tau & 0 \\ 0 & 0 & 0 & \sigma \end{bmatrix}$$

$$H^{-1} = \begin{bmatrix} \frac{-\alpha}{\alpha\delta - \beta S_e \kappa} & \frac{\beta S}{-\alpha\delta + \beta S_e \kappa} & 0 & 0 \\ \frac{\kappa}{-\alpha\delta + \beta S_e \kappa} & \frac{-\delta}{\alpha\delta - \beta S_e \kappa} & 0 & 0 \\ 0 & 0 & \frac{1}{\tau} & 0 \\ 0 & 0 & 0 & \frac{1}{\sigma} \end{bmatrix}$$

Substituting the equilibrium points and evaluating $F \bullet H^{-1}$ we have

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

The Eigen values of the system are

$$E_1 = \begin{bmatrix} 0 \\ 0 \\ \frac{\theta^2 + \sigma^2}{\theta^2} \\ \frac{\kappa\rho\phi}{\alpha\theta\tau} \end{bmatrix}$$

It is required for CTL to dominate $\frac{\kappa\rho\phi}{\alpha\theta\tau} > 1$ and hence $\frac{\kappa\rho\phi}{\alpha\theta} > \tau$

Similarly for Antibody responses to dominate the matrix $F \bullet H^{-1}$ is evaluated atthe respective equilibrium points and Eigen evaluated. This is found to be

$$E_2 = \begin{bmatrix} 0 \\ 0 \\ \frac{\beta\lambda\tau\theta}{\delta\sigma(\beta\tau + \omega\phi)} \\ \frac{\beta\tau\delta^3\rho - \beta\delta\rho\kappa\lambda\theta - \beta\phi\kappa\lambda\delta\rho + \delta^3\rho\phi\omega + \alpha\delta^2\rho(\beta\tau + \phi\omega)}{\delta\rho(-\beta\kappa\lambda\theta + \alpha\delta(\beta\iota + \phi\omega))} \end{bmatrix}$$

It is required that $\frac{\beta\lambda\tau\theta}{\delta\sigma(\beta\tau + \omega\phi)} > 1$ and hence $\frac{\beta\lambda\tau\theta}{\delta(\beta\tau + \omega\phi)} > \sigma$

Therefore whenever $\frac{\kappa\rho\phi}{\alpha\theta} < \tau$ and $\frac{\beta\lambda\tau\theta}{\delta(\beta\tau + \omega\phi)} > \sigma$ the CTL will dominate and Antibody response will fail , whenever $\frac{\kappa\rho\phi}{\alpha\theta} > \tau$ and $\frac{\beta\lambda\tau\theta}{\delta(\beta\tau + \omega\phi)} < \sigma$ the CTL will fail and Antibody response will dominate, and whenever $\frac{\kappa\rho\phi}{\alpha\theta} > \tau$ and $\frac{\beta\lambda\tau\theta}{\delta(\beta\tau + \omega\phi)} > \sigma$ both branches of the immune system will mount strongly.

IV. Numerical results

We will then apply this model to investigate how the interactions between these two branches of the immune system can influence infection dynamics during acute and chronic phases.. Theseaspects will be discussed in the context of hepatitis C virus (HCV) infection of humans.A complete list of parameters and their estimated values that we use for numerical simulations of the model are given in Table 1. The majority of the values have been taken from the data found in scholarly articles published in various journals. Much of these parameters were adopted from Perelson*et al.* (1993), Kim, P. S., Levy, D., & Lee, P. P. (2009),Wodarz, D. (2007) and Lewis, C. J. (2011).

These data do not depict a strict situation of the entire patients range but the parameter range is within the plausible and realistic values.

Table 1

Item	Parameter description	Symbol	Value
1	Rate of Proliferation of Healthy hepatic cells	λ	1-10
2	Rate of Natural Loss of healthy hepatic cells	ω	0.1
3	Rate at which Virus Infect Healthy hepatic cells	β	0.01-0.03
4	Death rate of infected hepatic cells	δ	0.1-0.3
5	Rate at which Cytotoxic T-cells Eliminate Infected hepatic cells	μ	1
6	Rate of Proliferation of Virions from Infected hepatic cells	κ	1-2.5
7	Rate of Natural Loss of Virus	α	1-5
8	Rate at which Antibodies Eliminate Virus	ρ	1-10
9	Rate of activation of Antibody activation by virus	ϕ	0.1-2.5
10	Rate of Natural Loss of the Antibody population	τ	0.1-0.25
11	Rate at which Virus Induce Cytotoxic T-cell Proliferation	θ	0.01-4.5
12	Rate of Natural Loss of Cytotoxic T-cell population	σ	0.1-0.2
13	Threshold antibody response	χ	As calculated
14	Threshold CTL response	η	As calculated

Infection free Dynamics

The healthy target cell population is at the disease-free equilibrium value and thenumber of infected cells is zero. The initial values are zeros, except for the supply of healthy cell, representing a state at of no infection

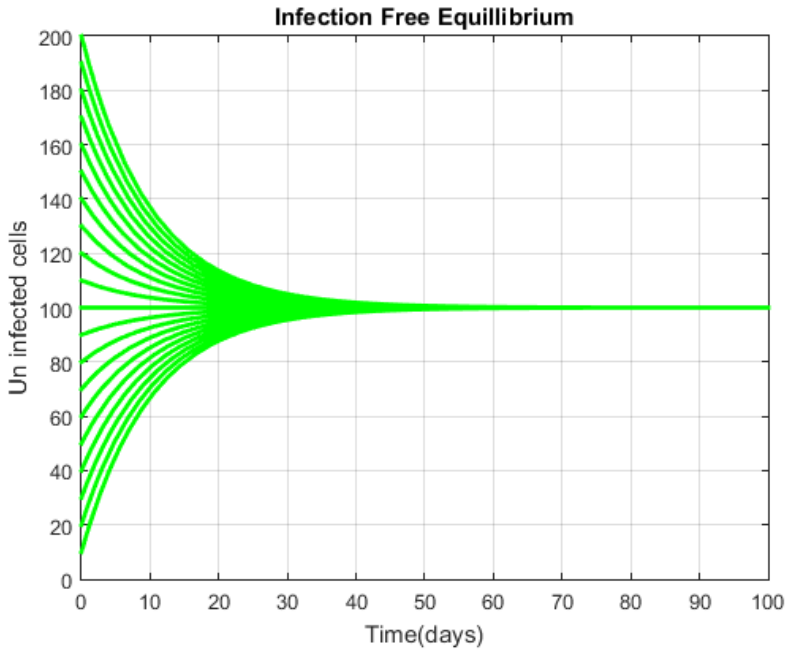

Fig1: *Infection free state of the immune system.*

The parameters are chosen as follows:
$\lambda = 10,\ \omega = 0.1,\ \beta = 0.0,\ \delta = 0.,\ \mu = 0.0,\ \kappa = 0,\ \alpha = 0.0,\ \rho = 0.0,\ \varepsilon = 0.00,\ \phi = 0,\ \tau = 0.0,$
$\upsilon = 0.0,\ \theta = 0,\ \sigma = 0.0$ *The*
initial conditions considered are : $S(0) = 10,\ Y(0) = 0.0,\ V(0) = 0,\ A(0) = 0.0,\ T(0) = 0.0$

Immunity Free System of a single strain virus infection

Immune system disorders cause abnormally low activity or over activity of the immune system. In cases of immune system over activity, the body attacks and damages its own tissues (autoimmune diseases). Immune deficiency diseases decrease the body's ability to fight invaders, causing vulnerability to infections.
A viral load of less than 615 IU/L (international units per liter) means there's no detectable hepatitis C virus, or it's too low to detect. Additionally, a viral load of more than 800,000 IU/L is high, and less than 800,000 IU/L is low.

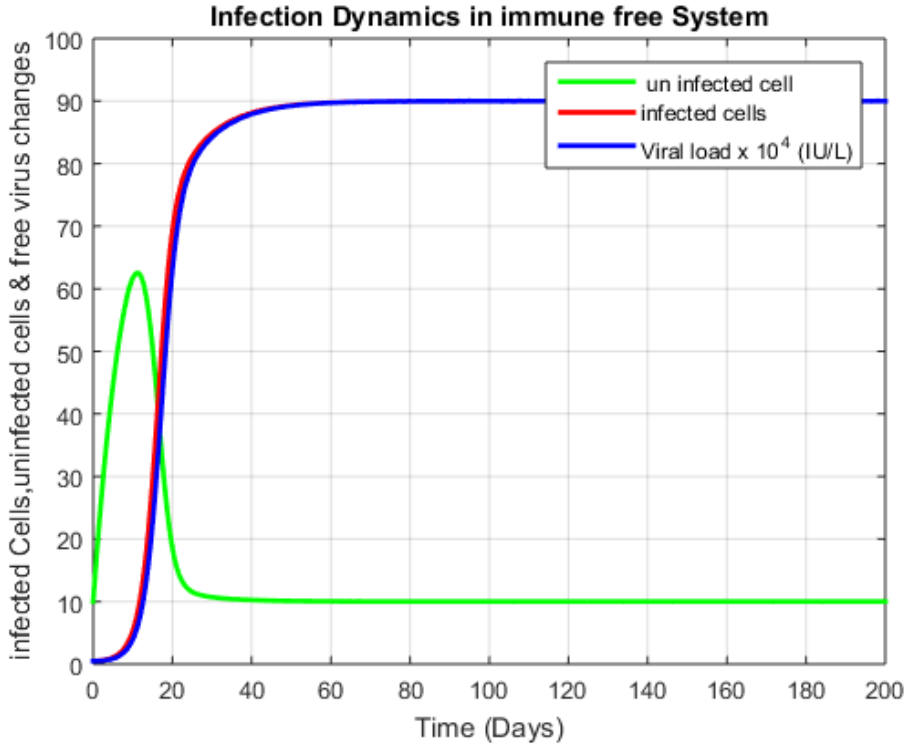

Fig 2:*Immunity free state of the immune system*

The parameters are chosen as follows:
$\lambda = 10,\ \omega = 0.1,\ \beta = 0.01,\ \delta = 0.1,\ \mu = 0.0,\ \kappa = 1,\ \alpha = 1,\ \rho = 0.0,\ \varepsilon = 0.00,\ \phi = 0,\ \tau = 0.0,$
$\upsilon = 0.0,\ \theta = 0,\ \sigma = 0.0$ *The*
initial conditions considered are : $S(0) = 10,\ Y(0) = 0.5,\ V(0) = 0.5,\ A(0) = 0.0,\ T(0) = 0.0$

This represents a high viral load meaning that the body is not able to defend itself against the infection. The overall number of liver cells at equilibrium is, however, predicted to remain constant since HCV is non-cytopathic and death of infected cells is almost the same as the death of un infected cells, which corresponds to absence of pathology. This would however be different for a highly cytopathic virus.

Immune responses dynamics

Now we assume that immune responses can potentially develop. This requires
the following initial conditions;
$\phi V(0) > \tau$ and $\theta T(0) > \sigma$.

This guarantees development of immune response but not dominance of any branch of immunity. The initial values are small, representing a state at the initiation of infection, but they are also chosen to be large enough so that there will be an immune responses, either through the CTL or the antibodies, or both.

In this case, the following three outcomes can be observed. (Stability conditions have been determined by examining the ability of the immune cell populations to grow from low numbers).

CTL only response to a single strain virus infection

As the CTL perform antiviral activity, virus load declines and clearance of the virus from the host occurs in many cases. As the infection is resolved, the population of CTL declines. This is often referred to as the contraction phase. However, it does not decline to the same low levels from where the response started. Instead it settles around an elevated level, and the CTL persist at this elevated level for long periods of time in the absence of any further exposure to the virus. This is called immunological memory and is observed in all branches of the specific, adaptive immune system. If a heightened number of immune cells remains after the resolution of infection, it is thought that the host can react more efficiently if it is re infected with the same pathogen again. Such a secondary infection will not result in much virus growth and the host is protected from symptoms and disease.

The model approximates clearance of the virus between eighth and tenth month. This is supported by the work Grebely, J., Prins, M., Hellard, M., Cox, A. L., Osburn, W. O., Lauer, G., ... & Dore, G. J. (2012) that spontaneous viral clearance occurs within twelve months , no case of spontaneous clearance is reported after this period

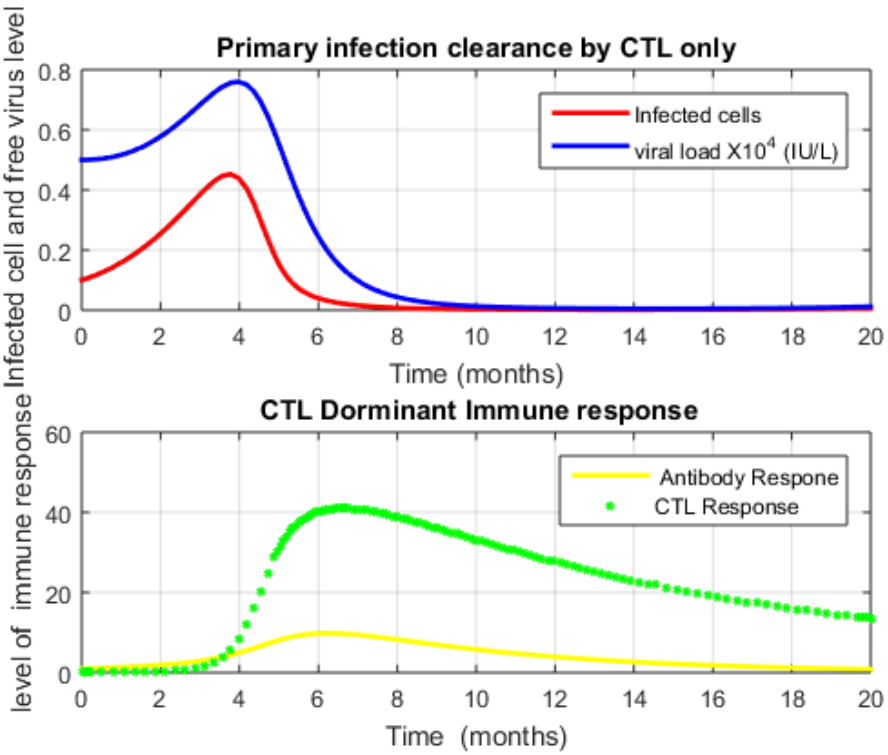

Fig 3: *CTL Dominant the immune response: Before a host is exposed to antigen, there are few specific CTL and specific immune cells in general. The host is said to be naive. Upon exposure to the virus, the CTL divide and expand (clonal expansion). They fight the virus population, and as the infection is resolved, the number of CTL declines to a certain degree. It subsequently settles around an elevated level in the long-term.*

Before the host has encountered a pathogen it is said to be *naive*. This means that the number of immune cells that are specific for this pathogen is relatively low. When the host is infected with this pathogen for the first time (*primary infection*), the population of specific immune cells expands, fights the pathogen, and subsequently settles around a relatively stable level that is much higher than in the naive host. This population of cells is referred to as *memory cells*, and memory persists in the long-term after pathogen clearance. Upon reinfection with the same pathogen (*secondary infection or re-challenge*), this population of memory cells can react more efficiently against the invading virus compared to a naive host. Consequently, the host suffers less harm.

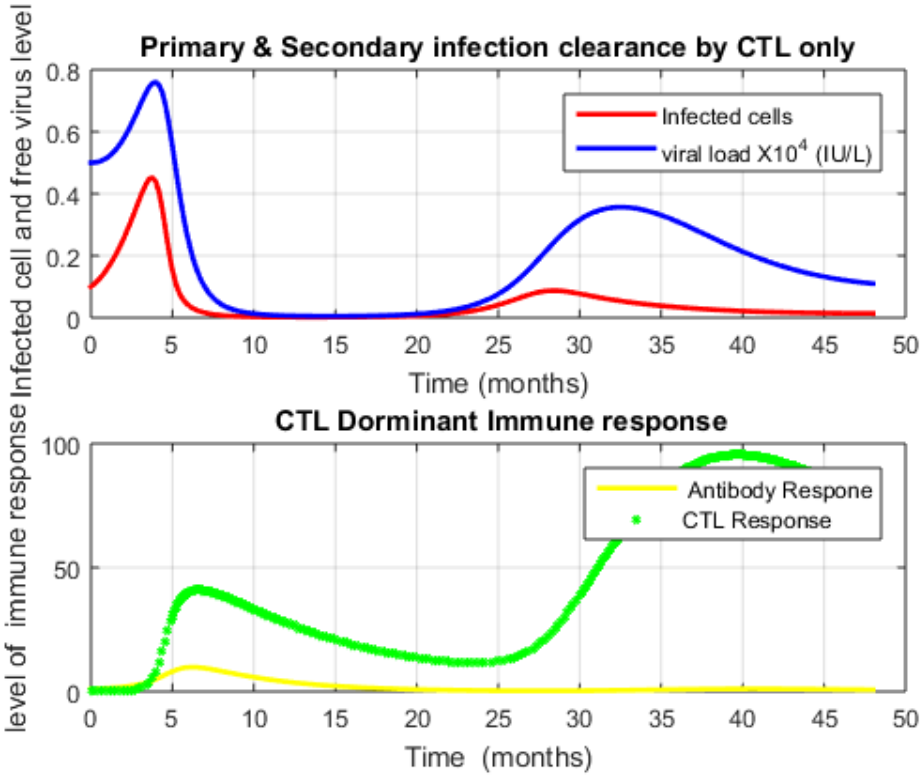

Fig 4 *The elevated number of memory CTL can fight the virus more efficiently if it infects the host a second time.*

The parameters are chosen as follows for fig 3 and 4 ;

$\lambda = 10,\ \omega = 0.1,\ \beta = 0.01,\ \delta = 0.1,\ \mu = 0.1,\ \kappa = 1,\ \alpha = 1,\ \rho = 0.1,\ \varepsilon = 0.0,\ \phi = 1,\ \tau = 0.25,$

$\upsilon = 0.0,\ \theta = 4.5\ \sigma = 0.1$

The initial conditions considered are : $S(0) = 10,\ Y(0) = 0.1,\ V(0) = 0.5,\ A(0) = 1,\ T(0) = 0.1$

$\chi = 0.22 < 0.25$ and $\eta = 11.13 > 0.1$

Antibody Dominant Immune Response

Antibodies inhibit the rate of virus spread, without killing the infected cells. Antibodies are a major branch of the immune system, and contribute significantly to non-lytic.The result is persistent infection in the presence of an ongoing antibody response. The CTL response is not sustained. Most patients do not have viral clearance and viraemia persists after 12 months, leading to chronic infection and progression to cirrhosis in 5–10% of individuals within 20 years. Grebely, J., Prins, M., Hellard, M., Cox, A. L., Osburn, W. O., Lauer, G., ... & Dore, G. J. (2012)Neutralizing pathogens or changed cells is one of the most important tasks of antibodies. To do this, they attach directly to the surface of a virus or bacterium and stop the pathogen from attaching itself to a normal body cell and infecting it. Or the antibody binds to toxins produced by pathogens. These substances can then no longer enter the body cells and damage them. The antibodies however have no ability to control the pathogen once inside the cell

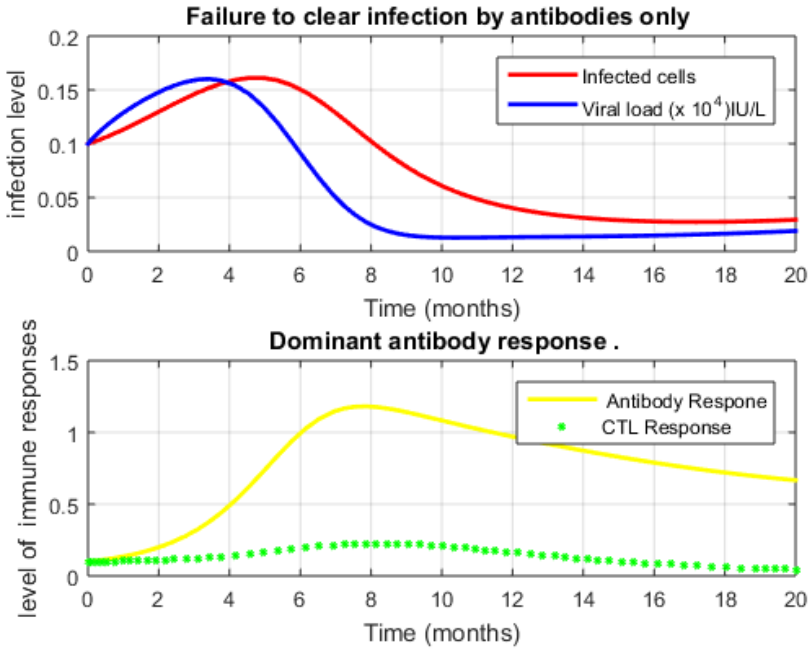

Fig 5:*Antibody Dominant the immune response*

The parameters are chosen as follows:

$\lambda = 1,\ \omega = 0.1,\ \beta = 0.03,\ \delta = 0.1,\ \mu = 1,\ \kappa = 1.5,\ \alpha = 1.0,\ \rho = 1.2,\ \varepsilon = 0.0,\ \phi = 3.5,\ \tau = 0.1,$

$\upsilon = 0.0,\ \theta = 2.5,\ \sigma = 0.24$

The initial conditions considered are : $S(0) = 10,\ Y(0) = 0.1,\ V(0) = 0.1,\ A(0) = 0.1,\ T(0) = 0.1$

$\chi = 2.5 > 0.1$ and $\eta = 0.2125 < 0.24$

CTL and Antibody Mediated Immune Responses

Both CTL and antibody responses are sufficiently strong and become fully established. The outcome is virus clearance, of worth noting is that for patients who mount both CTL and antibody responses strongly the virus is cleared much earlier, by fifth month, such patients are a lower risk of persistence and chronic infection as compared to those who clear the infection by CTL response only.

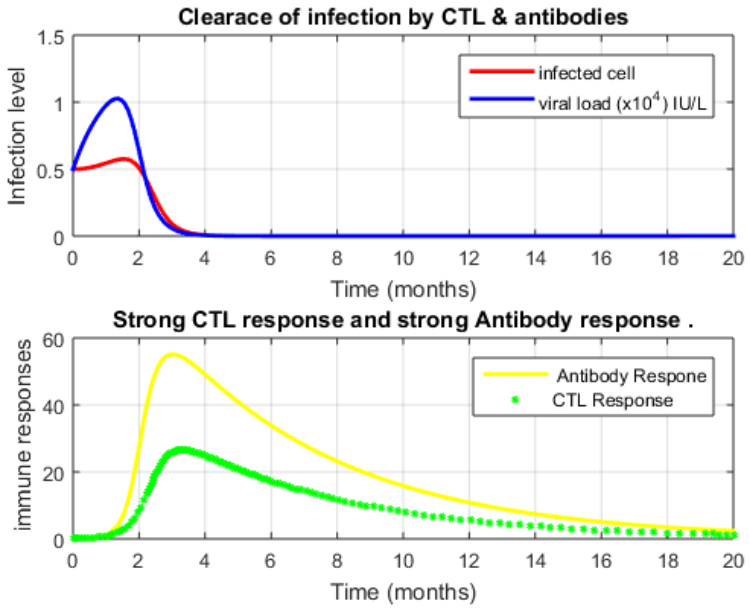

Fig 6*: strong CTL and Antibody responses*

The parameters are chosen as follows:
$\lambda = 10,\ \omega = 0.1,\ \beta = 0.01,\ \delta = 0.1,\ \mu = 0.1,\ \kappa = 1,\ \alpha = 1.0,\ \rho = 0.1,\ \varepsilon = 0.0,\ \phi = 3.5,\ \tau = 0.2,$
$\upsilon = 0.0,\ \theta = 3.5,\ \sigma = 0.2$

The initial conditions considered are : $S(0) = 10,\ Y(0) = 0.5,\ V(0) = 1,\ A(0) = 0.13,\ T(0) = 0.13$

$\chi = 0.1944 > 0.1$ and $\eta = 1.2821 > 0.2$

V. Conclusion

It is the hope of investigators that this system will provide the opportunity to study the essential steps in the HCV life cycle. However, it is also essential that more flexible and even more robust infection models be continuously developed.Continuous research in the human disease mathematical models is essential, as is the continuous development of new molecular tools for dissecting the intriguing bio pathogenesis of chronic hepatitis C in man. Just as the progress on this disease to date has been phenomenal, so too will be the future progress in furthering our understanding of HCV infection, replication, and molecular biology, and in improving the treatment of hepatitis C. The present state of progress and unanswered questions currently facing investigators should act as an impetus to vigorously undertake research aimed at unravelling the grey areas in the understanding of HCV. We postulate that mathematical and computational approaches will be most valuable when coupled with experimental work through collaborations, this should be encouraged.

References

[1]. Choo, Q. L., Kuo, G., Weiner, A. J., Overby, L. R., Bradley, D. W., & Houghton, M. (1989). Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*, *244*(4902), 359-362.
[2]. Hayashi, N., &Takehara, T. (2006). Antiviral therapy for chronic hepatitis C: past, present, and future. *Journal of gastroenterology*, *41*(1), 17-27.
[3]. Wodarz, D. (2003). Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses. *Journal of General Virology*, *84*(7), 1743-1750.
[4]. Perelson, A. S. (2009). Simulation and prediction of the adaptive immune response to influenza A virus infection. *Journal of virology*, *83*(14), 7151-7165.
[5]. Kim, P. S., Levy, D., & Lee, P. P. (2009). Modeling and simulation of the immune system as a self-regulating network. *Methods in enzymology*, *467*, 79-109.
[6]. Wodarz, D. (2007). *Killer cell dynamics* (Vol. 32). Springer Science+ Business Media, LLC.
[7]. Ahmed, M. I., Mardaryev, A. N., Lewis, C. J., Sharov, A. A., &Botchkareva, N. V. (2011). MicroRNA-21 is an important downstream component of BMP signalling in epidermal keratinocytes. *J Cell Sci*, *124*(20), 3399-3404.
[8]. Mitchison, H. M., Bernard, D. J., Greene, N. D., Cooper, J. D., Junaid, M. A., Pullarkat, R. K., ... & Gardiner, R. M. (1999). Targeted disruption of the Cln3 gene provides a mouse model for Batten disease. *Neurobiology of disease*, *6*(5), 321-334.

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