2011 American Control Conference
on O'Farrell Street, San Francisco, CA, USA
June 29 - July 01, 2011

Dynamic Modeling of Viral Infections in Spherical Organs

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Abstract— **A general mathematical model of viral infections inside a spherical organ is presented. Transported quantities are used to represent external cells or viral particles that penetrate the organ surface to either promote or combat the infection. A diffusion mechanism is considered for the migration of transported quantities to the inner tissue of the organ. Cases that include the generation of latent infected cells and the delivery of anti-viral treatment are analyzed. Different anti-viral mechanisms are modeled in the context of spatial variation. Equilibrium conditions are also calculated to determine the radial profile after the infection progresses and therapy is delivered for a long period of time. The dynamic and equilibrium solutions obtained in this paper provide insight into the temporal and spatial evolution of viral infection for optimal therapies.**

I. INTRODUCTION

The development of virus dynamic models under different infection scenarios has gained attention during recent years [1] [2] [3]. Analysis of the progression of an infection has provided insight into the optimization of anti-viral therapies. [4] [5]. Nevertheless, most virus dynamic models are developed for well-mixed environments, which does not account for the migration of immune system cells, virus particles and anti-viral molecules to the infected areas of the host organ.

Viruses circulate in the host blood stream, and their concentration may vary depending on the susceptibility of some host cells to the infection. Viruses can also target solid organs made of susceptible cells, as is the case for the Hepatitis C virus (HCV), in which a chronic liver infection is established for more than 85% of patients [6]. The penetration and migration of the virus into the inner portion of a susceptible organ have not been modeled using spatial coordinates and partial differential equations. Here we present a model of the progress of a viral infection in a spherical organ where immune cells and viral particles may penetrate and migrate to the inner organ tissue.

Organ viral infections are characterized by a high number of localized infected cells or virus particles in specific tissues. In such cases spatial variability is vital to understanding the disease progression [7]. A diffusive transport mechanism is considered for the virus particles to penetrate to the inner portion of a susceptible organ in order to replicate and proliferate [8]. Immune system cells may also penetrate the infected tissue to combat the infection, but their ability to diffuse and proliferate within solid tissue is limited. In practice, organ vascularity improves immune cell reach to the infected tissue to the extent that the immune system response to infections could promote vascular endothelial growth [9] [10].

The diffusive mechanism of migration, also known as motility [11], incorporates second order spatial derivatives into the well established nonlinear system of differential equations for virus dynamic models [12]. The specification of boundary conditions decouples the organ infection from the compartment that surrounds it. The numerical solution to the resulting partial differential equation model is demonstrated here using radial profiles of the virus dynamic and equilibrium profiles for the virus particles, infected cells and immune system cells.

This paper is organized as follows. Section II presents the mathematical formulation of the organ dynamic model response to a viral infection. The use of active and latent infected cells in virus dynamic modeling is introduced in Section III. Different anti-viral mechanisms of action are explained and modeled in Section IV. The radial profiles of the virus and infected cells show how the infection diminishes in time during anti-viral therapy. Conclusions are provided in Section V.

II. MATHEMATICAL FORMULATION

The infected organ is of spherical shape such that the radial coordinate r is used to describe the spatial variations of the stationary and transported quantities. Stationary quantities are the density of the different types of cells that compose the infected organ. Transported quantities represent external cells or particles that penetrate the susceptible organ surface and travel radially following a diffusive mechanism of transportation,

$$\frac{D^\circ}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right), \tag{1}$$

where $T(r,t)$ represents a transported quantity, D° is its diffusion coefficient and t denotes time. Such a partial differential term requires two boundary conditions. These conditions are given by the penetration of the transported quantity at the surface boundary and the radial symmetry at the center of the organ.

In general all stationary and transported variables are contained in the vectors $\vec{S}$ and $\vec{T}$, respectively,

$$\vec{S} = [S_1 \quad S_2 \quad \cdots \quad S_m]^T \qquad \vec{T} = [T_1 \quad T_2 \quad \cdots \quad T_l]^T,$$

where m and l represent the number of stationary and transported variables necessary to describe the infection dynamics. The evolution equations for stationary variables are given by,

$$\frac{\partial \vec{S}}{\partial t} = \vec{F}\left(\vec{S},\vec{T}\right),$$

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where $\vec{F}$ is a vector of nonlinear functions that represent the generation and consumption terms of the stationary variables. Note that $\vec{F}$ is a function of $\vec{S}$ and $\vec{T}$. Each stationary quantity requires an initial condition.

The partial differential equations (PDE's) for the transported variables include the diffusion term defined in equation 1,

$$\frac{\partial \vec{T}}{\partial t} = \vec{D^{\circ}}.\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \vec{T}}{\partial r}\right) + \vec{G}\left(\vec{S},\vec{T}\right),$$

and each PDE requires two boundary and one initial condition. The vector operator $(.)$ represents an element by element product of two vectors with the same dimension. The function vector $\vec{G}$ denotes the generation-consumption terms for the transported variables.

TABLE I
MODEL PARAMETERS AND VARIABLES WITH INITIAL CONDITIONS (IC).

	Parameter	Value
a	death rate of active infected cells	0.5
a_L	death rate of latent infected cells	0.1
u	clearance rate of free virus	10
k	virus replication rate	1000
β	infection rate of host cell	0.001
λ	production rate of host cells	1
d	death rate of host cells	0.1
p	infected cells elimination rate by the immune system	0.3
b	death rate of immune cells	0.2
c	production rate of immune cells	2
D_v	virion diffusivity factor	0.01
D_z	immune cells diffusivity factor	0.001
D_w	anti-viral diffusivity factor	0.02
P_v	virus penetration factor	33.5
P_z	immune cells penetration factor	50
P_w	anti-viral penetration factor	10
α	activation rate of latent infected cells	0.1
q	portion of active infected cells	0.75
e	anti-viral clearance rate	0.3
g	virus elimination rate by anti-viral	0.5
ϕ	viral infection reduction parameter	0.05
ψ	viral replication reduction parameter	0.05
	Variable	IC
V	free virus concentration	0
W	population of anti-viral particles	0
X	volumetric density of organ uninfected cells	10
Y	volumetric density of organ infected cells	0
Z	density of immune system cells	0

It is convenient to normalize the spatial coordinate r between $[0 \quad 1]$. For this reason, the dimensionless variable $\eta = r/R$ is used as the radial coordinate, where R represents the radius of the infected organ. The infection dynamic response is given by the solution of a system composed by $m + l$ differential equations,

$$\frac{\partial \vec{S}}{\partial t} = \vec{F}\left(\vec{S},\vec{T}\right), \tag{2}$$

$$\frac{\partial \vec{T}}{\partial t} = \vec{D}.\frac{1}{\eta^2}\frac{\partial}{\partial \eta}\left(\eta^2\frac{\partial \vec{T}}{\partial \eta}\right) + \vec{G}\left(\vec{S},\vec{T}\right), \tag{3}$$

where the elements of the vector $\vec{D} \equiv \frac{1}{R^2}\vec{D^{\circ}}$ have inverse time units. These equations are subject to the initial conditions $\vec{S}(\eta,0) = \vec{S}_0$ and $\vec{T}(\eta,0) = \vec{T}_0$, while the boundary conditions are

$$\frac{\partial \vec{T}(\eta,t)}{\partial \eta}|_{\eta=0} = 0,$$

$$\frac{\partial \vec{T}(\eta,t)}{\partial \eta}|_{\eta=1} = \mathbf{P}\left[\begin{array}{c}\vec{S}\\ \vec{T}\end{array}\right]_{\eta=1},$$

The constant matrix $\mathbf{P}$ represents the penetration factor matrix. The specific model parameters used in this study are presented in Table I. The equilibrium conditions for the stationary and transported variables are obtained by setting the time derivatives in Eqs. 2 and 3 to zero, which results in

$$\vec{F}\left(\vec{\bar{S}},\vec{\bar{T}}\right) = \vec{0},$$

$$\vec{D}.\frac{1}{\eta^2}\frac{d}{d\eta}\left(\eta^2\frac{d\vec{\bar{T}}}{d\eta}\right) + \vec{G}\left(\vec{\bar{S}},\vec{\bar{T}}\right) = \vec{0},$$

where $\vec{\bar{S}}$ and $\vec{\bar{T}}$ are the stationary and transported variable vectors at their equilibrium conditions, respectively. Notice that the equilibrium conditions represent a differential algebraic system of equations in η, where the radial boundary conditions need to be satisfied.

Finally, tt is convenient to express the distributed spatial solution obtained from Eqs.(2,3) using an average spatial response in time,

$$\hat{Q}(t) = 3\int_0^1 Q(\eta,t)\eta^2 d\eta,$$

where Q represents a generic quantity.

III. ACTIVE AND LATENT INFECTED CELLS

Immune system cells acknowledge the presence of the virus as it penetrates and replicates inside the organ cells. Part of the virus survival mechanism consists of remaining in a latent state inside susceptible cells. This type of infected cell, also known as latent cells, carries the infection without triggering replication or destroying the cells. In this manner, the immune system can not detect them or combat a virus that remains in such a dormant state. At later stages of the infection, latent infected cells can become active replicators of the virus. What activates the viral response in a latent cell is still considered a topic of investigation [13].

A. Dynamic Response

The parameter $q \in [0 \quad 1]$ determines the probability of an infected cell to be active or become latent from the first moment of the infection. This parameter is used to split the infection term βXV into a portion that generates active infected cells $q\beta XV$ and a portion that engenders latent infected cells, $(1-q)\beta XV$. Latent infected cells are denoted by Y_L and represent a stationary quantity. The generation-consumption terms for the stationary and transported variables that include latent cells are given by the following

expressions,

$$\vec{F}\left(\vec{S},\vec{T}\right) = \begin{bmatrix} \lambda - dX - \beta XV \\ q\beta XV - aY - pYZ + \alpha Y_L \\ (1-q)\beta XV - a_L Y_L - \alpha Y_L \end{bmatrix},$$

$$\vec{G}\left(\vec{S},\vec{T}\right) = \begin{bmatrix} kY - uV \\ -bZ \end{bmatrix},$$

where $\vec{S} = [X \quad Y \quad Y_L]^T$ and $\vec{T} = [V \quad Z]^T$. The initial condition assumes all cells are susceptible at $t = 0$. It is important to emphasize that the immune system cell penetration is proportional to the active infected cells at the organ surface. Because not all infected cells are active, the penetration of immune cells into the infected organ is reduced in the presence of latent infected cells at the surface. A large population of latent cells compared to active cells at the organ surface becomes a natural tendency for the viral infection because active infected cells are effectively eliminated at the organ surface, where immune cell concentration tends to be large. At the same time, the immune system cell penetration is diminished due to low active infected cell density at the surface. Therefore, high density of latent infected cells at the organ surface diminishes immune cells penetration, while high density of the active infected cells at the organ core replicates virus particles.

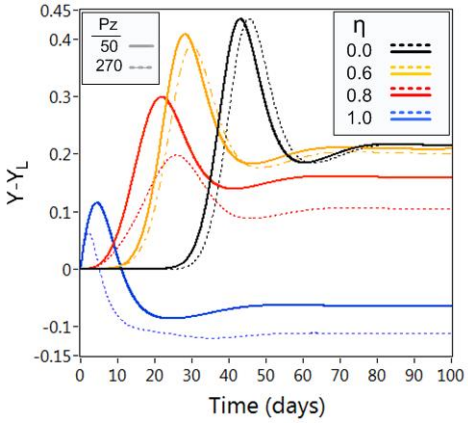
The solid line responses in Figure 1 illustrate the population difference between active and latent infected cells $(Y - Y_L)$ at different radial locations. The response at the organ surface demonstrates that the difference $Y - Y_L$ remains negative after 10 time units of simulation, while the profile at all other locations shown in the figure remains positive. Such a solution corroborates that latent infected cells prevail at the surface of the infected organ because they are not eliminated by the immune system.

The increase of the penetration factor P_z increases the amount of immune cells at the organ surface, which reduces the amount of active infected cells at that location. Such an effect limits the immune system cell propagation to the inner portion of the organ, especially when D_z is small. Figure 1(a) shows how the increase of P_z makes the profile of $Y - Y_L$ more negative at the surface, while the profiles at inner locations remain unaffected.

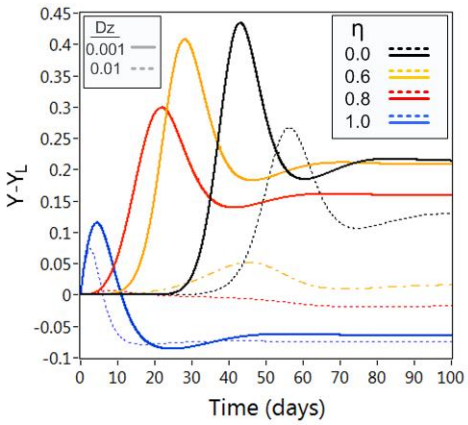
The larger D_z is the larger is the larger the amount of immune cells transported to the organ inner region. Such a phenomenon propagates the elimination of active infected cells in the organ's inner portion. Therefore, the latent infected cells may become more dense than the active cells, as the former are not diminished by immune system cells. Figure 1(b) illustrates how the increase of the immune cells diffusivity factor makes the profile $Y - Y_L$ negative at $\eta = 0.8$, which indicates a better chance of survival for the latent than for the active infected cells.

B. Equilibrium Condition

The coefficient for the generation of latent infected cells $(1 - q)$ and the factor that determines the rate at which latent cells are reactivated (α) represent decision variables for the virus to perpetuate the infection. Many infections



(a) Effect of the immune system penetration factor



(b) Effect of the immune system diffusivity factor

Fig. 1. Profiles of the difference between active and latent infected cells at different radial locations.

remain latent in a hostage organ until the hostage immune system weakens. At this stage, the viral infection's chances of proliferating are enhanced by either generation ($q \to 1$) or reactivation (α increases).

The dynamic model presented here considers q and α constant during simulation. Their influence on the equilibrium conditions is described by solving the following system of algebraic differential equations

$$\bar{X} = \frac{\lambda}{d + \beta\bar{V}},$$

$$\bar{Y} = \frac{\beta\bar{X}\bar{V}}{a + p\bar{Z}} f, \tag{4}$$

$$\bar{Y}_L = \beta\bar{X}\bar{V}\left(\frac{1-q}{\alpha + a_L}\right), \tag{5}$$

$$\frac{d^2\bar{V}}{d\eta^2} + \frac{2}{\eta}\frac{d\bar{V}}{d\eta} = \frac{\bar{V}u}{D_v}\left(1 - \tilde{R}_L\right).$$

$$\frac{d^2\bar{Z}}{d\eta^2} + \frac{2}{\eta}\frac{d\bar{Z}}{d\eta} = \frac{\bar{Z}b}{D_z},$$

where

$$f = q + (1-q)\left(\frac{\alpha}{\alpha + a_L}\right) \quad , \quad \tilde{R}_L = \tilde{R}_I f,$$

$$\tilde{R}_I = \frac{R_I}{1+\bar{V}\frac{\beta}{d}} \quad , \quad R_I = \frac{R_0}{1+\bar{Z}\frac{p}{a}}.$$

subject to

$$\frac{d\bar{V}(\eta)}{d\eta}|_{\eta=0} = 0 \quad , \quad \frac{d\bar{Z}(\eta)}{d\eta}|_{\eta=0} = 0,$$
$$\frac{d\bar{V}(\eta)}{d\eta}|_{\eta=1} = P_v\bar{X}(1) \quad , \quad \frac{d\bar{Z}(\eta)}{d\eta}|_{\eta=1} = P_z\bar{Y}(1).$$

where R_0 is the basic reproductive ratio. The ratio of the expressions 4 and 5 provides the effect of q, α and $\bar{Z}(\eta)$ for the amount of active and latent infected cells at equilibrium conditions,

$$\varphi(\eta) \equiv \frac{\bar{Y}}{\bar{Y}_L} = \frac{a_L q + \alpha}{(a + p\bar{Z})(1-q)} \tag{6}$$

which clearly shows that by either increasing q or α the generation or transformation to active infected cells is being promoted by the viral infection. Furthermore, the larger the number of immune system cells at equilibrium conditions ($\bar{Z}$), the less the value of φ. An analytical expression for the index φ is given by

$$\varphi(\eta) = \frac{a_L q + \alpha}{(a + 2p\frac{Sinh(\sqrt{\sigma_z}\eta)}{\eta}\tilde{P}_z)(1-q)}, \tag{7}$$

where

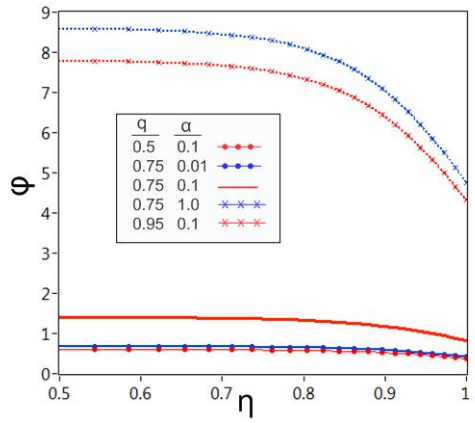
$$\tilde{P}_z = \frac{P_z\bar{Y}(1)}{2Sinh(\sqrt{\sigma_z}) + 2\sqrt{\sigma_z}Cosh(\sqrt{\sigma_z})}.$$

Notice that φ depends on $\bar{Y}(1)$, which in turn is a function of $\bar{V}(1)$.

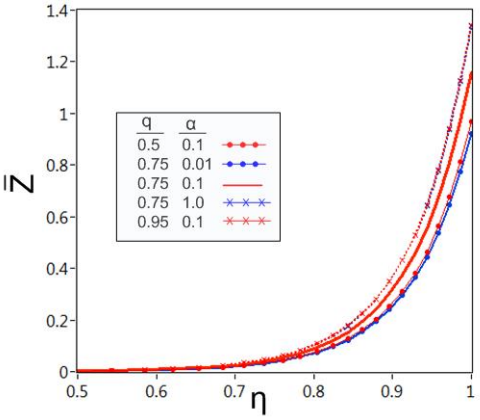
Figure 2(a) illustrates the effect of q and α on φ. Note that the effect of both parameters is significant and very similar. Therefore, q and α have a large influence on φ when equilibrium conditions are analyzed. An important feature of all plots shown in Figure 2(a) is that the index φ drops towards $\eta = 1$ because the number of latent cells tends to increase close to the surface when compared to the active ones. The drop of φ towards $\eta = 1$ is triggered by the large concentration of immune cells at the organ surface. Figure 2(b) demonstrates the immune cell profile for the same parameter changes defined in Figure 2(a). The large concentration of immune cells towards the surface favors the survivorship of latent infected cells at the same location.

The immune system cell profile is impacted by the equilibrium distribution between latent and active cells at the surface, as is illustrated in Figure 2(b). Immune cell penetration is enhanced for cases where $\varphi(1)$ is elevated. This is the case of having large values of q and α, which corroborates the results obtained from the dynamic response analysis in Section III-A.

Medication is required to combat viral infections in situations where the infection can not be controlled by the natural immune system defense. The next section demonstrates the effect of such medication on the virus dynamics equations.



(a) $\varphi = \frac{\bar{Y}}{\bar{Y}_L}$



(b) Immune system cell

Fig. 2. Effect of q and α on the equilibrium condition profiles

IV. Effect of Anti-Viral Drug Therapy

The virus mechanism of engendering latent infected cells in order to extend the existence of a viral infection in a hostage represents a major threat to the life of the host. Viral infections tend to flourish in patients with low immune defenses. This is typical in organ transplant cases, where the patient's immune system is reduced to avoid organ rejection [14]. Chemotherapy also reduces the amount of immune cells in the human body. Therefore, patients treated for cancer or undergoing organ transplants are usually under anti-viral therapy prevents viruses from becoming active and replicating.

There are different ways to account for the effect of anti-viral therapy in such infections. The anti-viral drug can reduce the virus's ability to either infect susceptible cells or to replicate inside active infected cells. The presence of anti-viral particles can also be modeled by adding a consumption term in the virus PDE. These different ways to adjust the dynamic model in order to account for anti-viral therapy are presented next.

Anti-viral doses are periodically provided via the blood stream compartment. They penetrate into the different host organs and are cleared by the host's natural mechanisms for reducing external agents. The population of anti-viral

particles in the host is denoted by W and represents a transported quantity with no generation term inside the solid organ. This work assumes that anti-viral particles tend to penetrate inside the solid organ at a rate proportional to the concentration of virus at the surface, $V(1,t)$. This assumption is acceptable for the mathematical study of virus dynamics in infected organs. Nevertheless, hosts treated with anti-viral drugs present significant concentration of anti-viral particles in organs that are not necessarily infected.

The generation-consumption vectors of viral organ infection undergoing anti-viral therapy are given by,

$$\vec{F}\left(\vec{S},\vec{T}\right) = \begin{bmatrix} \lambda - dX - \beta_W XV \\ q\beta_W XV - aY - pYZ + \alpha Y_L \\ (1-q)\beta_W XV - a_L Y_L - \alpha Y_L \end{bmatrix},$$

$$\vec{G}\left(\vec{S},\vec{T}\right) = \begin{bmatrix} k_W Y - uV - gVW \\ -bZ \\ -eW \end{bmatrix},$$

where $\vec{S} = [X \quad Y \quad Y_L]^T$ and $\vec{T} = [V \quad Z \quad W]^T$. Anti-viral particles can diminish the viral infections through three different mechanisms. These are:

1) Attenuating the virus's capacity to infect susceptible cells by reducing the infection factor β. This mechanism is equivalent to the reverse transcriptase inhibitors for anti-HIV drugs. A simple expression that characterizes the effect of W in β is given by
$$\beta_W = \beta e^{-\phi W}$$
where ϕ is a constant parameter that determines how effective the anti-viral drug is in preventing healthy cells from being infected. Note that this parameter influences the generation of latent and active infected cells in equal proportion.
2) Diminishing the virus replication by reducing the number of new virus particles that an active infected cell can replicate. This effect is similar to the protease inhibitors in HIV treatment, and can be modeled by diminishing k with a similar expression to the one considered for β_W,
$$k_W = ke^{-\psi W}$$
where the larger ψ is the more effective W is in reducing replication in active infected cells.
3) Reducing the amount of the virus inside the solid organ. This effect is achieved by adding a consumption term in the virus partial differential equation. This term is made proportional to the number of virus and anti-virus populations, gVW. The proportional factor g determines how effective is the therapy is at eliminating virus particles.

Specific anti-viral drugs affect one of the three mechanisms listed above. Viral infection treatment tends to provide more than one kind of anti-viral drug at a time in order to combat the virus population using simultaneous mechanisms [15]. Such a strategy increases the effectiveness of the therapy in cases of virus mutations that may enhance their resistance to one particular drug mechanisms. Nevertheless, this work will only consider one of the mechanism above at a time.

The initial conditions for the dynamic simulation depends of how promptly the treatment is administrated to the host after infection has been detected. For simplicity equilibrium conditions are considered for the initial profile before the anti-viral drug is delivered. Such initial conditions correspond to a hostage with a weakened immune system, i.e with an immune penetration factor five times less than the one provided in Table I.

Figures 3(a) and 3(b) illustrate the time progression of the infected organ undergoing therapy for the case where the virus ability to infect is diminished by the anti-viral drug. Figure 3(a) shows how susceptible cells increase their number from the initial condition ($t = 0$ profile) to an equilibrium profile close to their normal value of ten. Most of these transitions occur in a lapse of 50 units of time with minor oscillations at $\eta < 0.6$.

Figure 3(b) shows the drop in the amount of virus to about one third of their initial value. Even though the anti-viral treatment shows effective to control the disease, the infection does not disappear completely due to the persistent penetration of virus into the organ. A model that includes the organ vascularity and the blood compartment that surrounds the infected organ is required to illustrate the complete disappearance of the disease. Figure 3(c) demonstrates the time progression of infected cells for the case where the virus replication is reduced by the anti-viral drug. Latent cells follows a very similar progression than the active ones because the anti-viral therapy affects equally both type of cells. Figure 3(d) shows that the number of immune cells inside the infected organ decreases during anti-viral therapy because the number of active cells at the organ surface is reduced considerably. Recall that a reduced number of active cells at the organ surface diminishes the penetration of immune cells into the infected organ.

The expressions for the equilibrium conditions in the presence of antiviral therapy are similar to the ones obtained in Section III. The PDE related to the anti-viral population is given by:

$$\frac{d^2\bar{W}}{d\eta^2} + \frac{2}{\eta}\frac{d\bar{W}}{d\eta} = \frac{\bar{Z}e}{D_w},$$

which indicates that the solution has the form,

$$\bar{W}(\eta) = 2\frac{Sinh(\sqrt{\sigma_w}\eta)}{\eta}\tilde{P}_w, \tag{8}$$

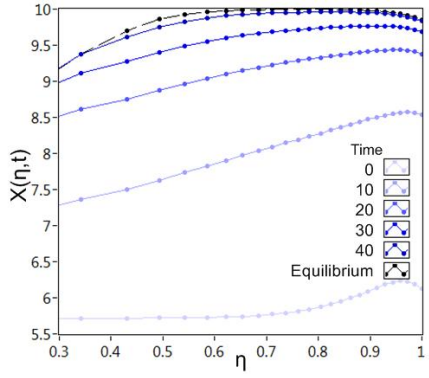
where $\sigma_w = e/D_w$ and

$$\tilde{P}_w = \frac{P_w\bar{V}(1)}{2Sinh(\sqrt{\sigma_w}) + 2\sqrt{\sigma_w}Cosh(\sqrt{\sigma_w})}.$$

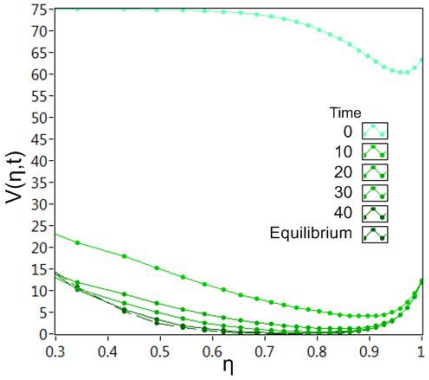
The dimensionless form of the anti-viral concentration is defined by,

$$\bar{W}^\star(\eta) \equiv \frac{\bar{W}(\eta) - \bar{W}(0)}{\bar{W}(1) - \bar{W}(0)},$$

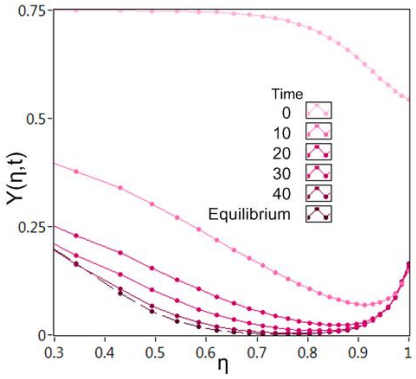
and its profile resembles the one for the immune system cells.



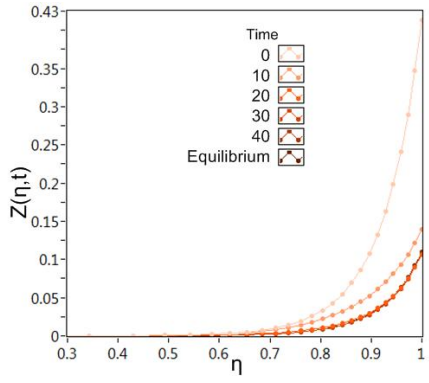
(a) Effect of β_W in susceptible cells



(b) Effect of β_W in virus concentration



(c) Effect of k_W in active infected cells



(d) Effect of virus consumption term in immune cells

Fig. 3. Time progression in an infected organ undergoing anti-viral therapy

V. CONCLUSIONS

This work demonstrates the advantage of representing the viral infection dynamics in solid organs using stationary quantities that characterize the organ tissue cells and transported quantities that penetrate from an external source and populate the susceptible organ. Such a representation provides the flexibility to consider a variety of viral infection cases following a common line of reasoning and notation. Equilibrium conditions in the radial direction are used to determine areas of high concentration of virus or infected cells that could propagate the infection at later stages of the disease. The use of a spatial-coordinate in organ viral infection dynamics helps to visualize the distribution of each quantity along the radial coordinate. The effects of diffusivity coefficients, penetration factors and anti-viral treatment parameters are here analyzed with the temporal and local evolution of viral infections for optimal therapies.

VI. ACKNOWLEDGMENTS

The authors acknowledge the guidance given by Dr. Marisol Fernandez from the infectious disease staff at Dell Children's Hospital in Austin, Texas.

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