Inhibición de VIH-1 por GB Virus C

Inhibition of VIH-1 by GBVC

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RESUMEN

El GB virus C (GBVC) es un virus linfotrófico de ARN positivo, al cual hasta el momento no se le ha asociado patología alguna. El GBV-C se ha encontrado en porcentajes importantes en donadores de sangre sanos, y en promedio se encuentra en el 1.7% de la población. La forma en que este virus se transmite, es muy similar a las vías de transmisión de VIH y HCV, es decir, por vía parenteral, transmisión sexual, incluso se ha estudiado la vía vertical de transmisión y de lactancia materna. Se replica en células sanguíneas, predominantemente en células mononucleares de sangre periférica, en su mayoría en células T (CD4+ y CD8+) y B. El VIH, es el virus que provoca el SIDA, para el cual hasta el momento no tenemos una cura o vacuna, sin embargo, las interacciones entre GBV-C y VIH, han demostrado en los estudios clínicos realizados hasta el día de hoy una progresión más lenta hacia SIDA y por lo tanto una mayor sobrevida y en estudios in vitro, GBV-C es capaz de inhibir in vitro a VIH en un rango del 78% al 98%; sin que hasta el momento se hayan descrito en detalle los mecanismos de esta interacción. En este trabajo construimos un modelo matemático que describe la dinámica de inhibición del VIH por el virus GBV-C. Se desarrolla un sistema de seis ecuaciones diferenciales no lineales que incluye la población de células susceptibles (sanas), células únicamente infectadas (por GBV-C y VIH, respectivamente), partículas virales libres (GBV-C y VIH) y células doblemente infectadas por GBV-C y VIH. El análisis del modelo revela la existencia de cuatro puntos de equilibrio: el punto de equilibrio libre de la infección en el que no hay virus; el punto de equilibrio infectado por el virus GBV-C; el punto de equilibrio infectado por el virus VIH; y otro punto de equilibrio de células infectadas donde coexisten las dos poblaciones virales. Se establece la estabilidad local de los puntos de equilibrios. Se realizan simulaciones numéricas con parámetros obtenidos de la literatura algunos sugeridos por los autores y que complementan los resultados teóricos.
Descriptores: *VIH, GB Virus C, Inhibición, modelo matemático, estabilidad*

ABSTRACT

GB virus C (GBV-C) is a lymphotropic, positive-RNA virus. GBV-C has been found in considerable amounts in healthy blood donors and, in average, it is found in 1.7% of the population. Its transmission is very similar to HIV and HCV i.e. by parental and sexual transmission. The possibility of transmission via breastfeeding has been suggested. GBV-C replicates in mononuclear blood cells, mainly in T (CD4+ and CD8+) and B cells.

HIV is a world health problem that until today we don't have a cure or vaccine. GBV-C and HIV interactions have prove that coinfected patients have slower progression to AIDS and longer survival, in vitro coinfection experiments GBV-C makes a inhibition of HIV replication in the range of 78% – 98%, but there is no description of the specific mechanism of this interaction.

In this paper, we propose a mathematical model describing the inhibition of HIV by GBV-C. This model consists of six non-linear differential equations system taking into account healthy cells, cells infected exclusively by HIV or GBV-C, free GBV-C and HIV viral particles and by cells coinfected by GBV-C and HIV. The analysis reveals the existence of four equilibria: one equilibrium free of any infection, another one infected by GBV-C, one HIV infected equilibrium and an equilibrium of coinfected cells. A local stability analysis was carried out as well as numerical simulations with parameter values taken from the literature.
Keywords: *VIH, GB Virus C, Inhibition, mathematical model, stability*

INTRODUCCIÓN

Mathematical models have made significant contributions to our understanding into the dynamics of viral infections *in vivo* and is very helpful for evaluating the antiviral effectiveness of therapy.

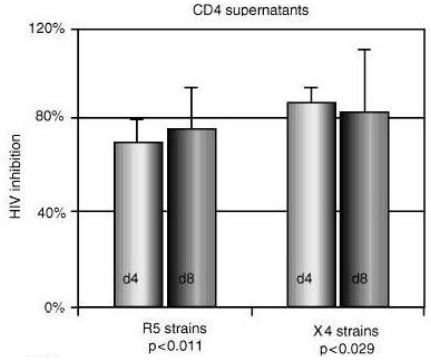


Figure 1: Inhibition of HIV replication on PBMC is induced directly by GBV-C infection and transfection in PBMC.

GBV-C is a ARN virus member or Flaviviridae family, originaly named Hepatitis G virus (HGV), experiments show this as non pathogenic virus [1]. GBV-C in human patients cohorts have demonstrated that patients that are co-infected, have longer survival and slow progression to AIDS [2].
Recently this interaction between both viruses has been studied with interesting founding:
In vitro experiments shows that HIV replication is inhibited by GBV-C, but time condition, the inhibition take place only when GBV-C interact with the cell before HIV [3].
The mechanism of this inhibition is not defined yet, the actual research demonstrated an HIV replication inhibition of 78% to 98%, and indicates that one probable explanation of this phenomenon is the reduction of the HIV co-receptor CCR5 by E2 GBVC protein [4] (figure 1).
Some patients with HIV known as HIV non progressors, have been studied and found that they have lower activation capacity of the lymphocytes this reduced capacity helps the T cell to live longer, and produce a better prognoses in HIV patients.
This activation capacity have been also measured in HIV/GBV-C co-infected patients, founding also a reduction of activation capacity, and this is marked as probably one of the mechanism of HIV patients better prognoses in the presence of GBV-C [5].
In the understand that viral interaction, and in specific case, GBV-C/HIV interaction is apparently a multiofactor problem and very complicated, we can deduce that two big variables are timing and viral load, and we try to define this by mathematical model.

THE BASIC MODEL OF VIRAL INFECTIONS

Nowak developed the basic model to study HIV infection [6], [7], and later adapted to HBV and HCV infection. The model is shown graphically in Fig.2.

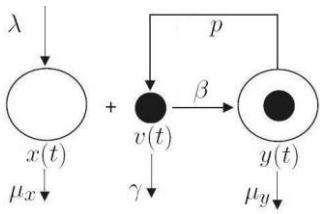


Figure 2: Diagram representing of the basic model of viral infections.

The model is formulated by the following system of non-linear differential equations:

$$\begin{aligned} x'(t) &= \lambda - \mu_x x(t) - \beta x(t) v(t), \\ y'(t) &= \beta x(t) v(t) - \mu_y y(t), \\ v'(t) &= p y(t) - \gamma v(t). \end{aligned} \tag{1}$$

Where x(t), y(t) and v(t) denote the concentration of uninfected cells, infected cells, and free virions, respectively.
In [8] study a most general model that considers various states of infection of cells and estimate the parameters of viral dynamics of HIV-1.

FIGHTING A VIRUS WITH A VIRUS

A mathematical model examined a potential therapy for controlling viral infections using genetically modified viruses [9]. The equations for the full system are:

$$\begin{aligned} x'(t) &= \Lambda - \mu_x x(t) - \beta x(t) v(t), \\ y'(t) &= \beta x(t) v(t) - \mu_y y(t) - \alpha y(t) w(t), \\ z'(t) &= \alpha y(t) w(t) - \mu_z z(t), \\ w'(t) &= p_z z(t) - \gamma_w w(t), \\ v'(t) &= p_y y(t) - \gamma_v v(t). \end{aligned} \tag{2}$$

Where the density w(t) of the recombinant (genetically modified) virus and the density z(t) of doubly infected cells. For biological information see [10].

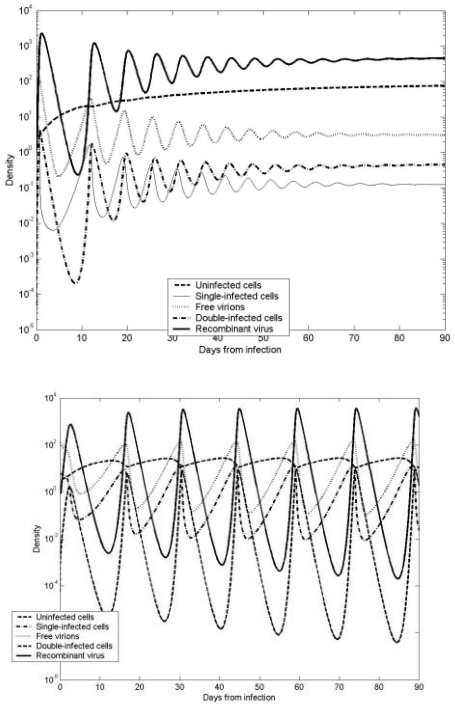


Figure 3: The parameters of simulations of model (2) are given in [9]. (a) System with the double infection. b) Alternative system with the double infection.

Model for a double viral infection by HIV-1 and GB Virus C

We construct a mathematical model describing the dynamics of inhibition of HIV-1 by GB Virus C. Where target uninfected cells, x(t); the virus populations by v(t), w(t) for GBVC and HIV-1, respectively; the only-infected cell populations by GB Virus C and HIV-1 are y(t) and u(t), respectively. The double infected cells by GB Virus C and HIV-1, z(t). The model is shown graphically in Fig. 4, and explained as follows. Where: r+s=1. This is described by the following set of differential equations:

$$\begin{aligned} x'(t) &= \Lambda - \mu_x x(t) - \beta x(t)v(t) - \kappa x(t)w(t),\\ y'(t) &= \beta x(t)v(t) - \mu_y y(t) - \alpha y(t)w(t),\\ z'(t) &= \alpha y(t)w(t) - \mu_z z(t),\\ u'(t) &= \kappa x(t)w(t) - \mu_u u(t),\\ w'(t) &= p_u u(t) + sp_z z(t) - \gamma_w w(t),\\ v'(t) &= p_y y(t) + rp_z z(t) - \gamma_v v(t). \end{aligned} \tag{3}$$

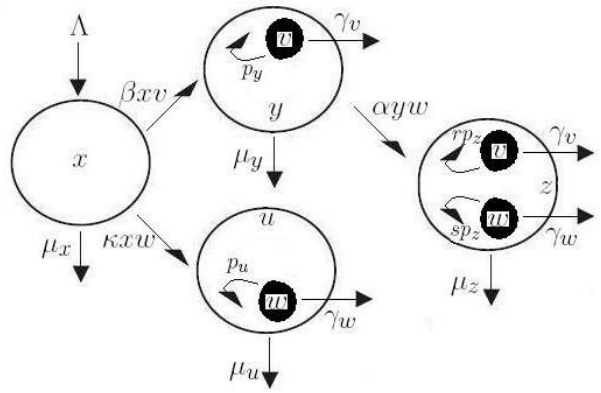


Figure 4: Diagram representing of model for a double viral infection by HIV-1 and GB Virus C.

A more realistic model

Under the assumption of that the double-infected cells only produced GBCV (s=0 and r=1). The system of differential equations is given by:

$$\begin{aligned} x'(t) &= \Lambda - \mu_x x(t) - \beta x(t)v(t) - \kappa x(t)w(t),\\ y'(t) &= \beta x(t)v(t) - \mu_y y(t) - \alpha y(t)w(t),\\ z'(t) &= \alpha y(t)w(t) - \mu_z z(t),\\ u'(t) &= \kappa x(t)w(t) - \mu_u u(t),\\ w'(t) &= p_u u(t) - \gamma_w w(t),\\ v'(t) &= p_y y(t) + p_z z(t) - \gamma_v v(t), \end{aligned} \tag{4}$$

The equilibrium states are obtained by setting the left-hand side of system (4) equal to zero.

1. This new model system (4) always has the all virus-free equilibrium (for *v=0* and *u=0*), therefore *$E^*_0=(\Lambda/\mu_x,0,0,0,0,0)$.*

2. An GB Virus C equilibrium state (for *$v\neq 0$* and w=0): *$E^*_v=(x^*_1,y^*_1, 0,0,0, v^*_1)$,* where

$$x_1^* = \frac{\Lambda}{\mu_x R_0^v},\ y_1^* = \frac{\Lambda}{\mu_y}\left(1-\frac{1}{R_0^v}\right),\ v_1^* = \frac{\Lambda p_y}{\mu_y\gamma_v}\left(1-\frac{1}{R_0^v}\right),$$

Taking

$$\boxed{R_0^v = \frac{\beta\Lambda p_y}{\mu_x\mu_y\gamma_v}}. \tag{5}$$

3. An other HIV equilibrium state (for *v=0* and *$w\neq 0$*) where *$E^*_w=(x^*_2,0,0,u^*_2,w^*_2,0)$*, and

$$x_2^* = \frac{\Lambda}{\mu_x R_0^w},\ u_2^* = \frac{\Lambda}{\mu_u}\left(1-\frac{1}{R_0^w}\right),\ w_2^* = \frac{\Lambda p_u}{\mu_u\gamma_w}\left(1-\frac{1}{R_0^w}\right),$$

and now taking

$$\boxed{R_0^w = \frac{\beta\Lambda p_u}{\mu_x\mu_u\gamma_w}}. \tag{6}$$

4. And fourth possible biologically meaningful equilibria (double-infection equilibrium state) is (for *$v\neq 0$* and *$w\neq 0$*) *$E^*_z=(x^*_3,y^*_3,z^*_3,u^*_3,w^*_3,v^*_3)$*, defined by

$$\begin{cases} x_3^* = \frac{\Lambda}{\mu_x R_0^w},\ y_3^* = \frac{\beta x_3^* v_3^*}{(\mu_y+\alpha w_3^*)},\ u_3^* = \frac{\Lambda\kappa\mu_y}{\alpha\mu_x\mu_u R_0^w}\frac{(R_0^w-R_0^v)}{(R_0^z-R_0^w)},\ z_3^* = \frac{\beta\alpha}{\mu_z}\frac{x_3^* v_3^* w_3^*}{(\mu_y+\alpha w_3^*)},\\ v_3^* = \frac{\mu_x}{\beta}\left((R_0^w-1)+\frac{\kappa\mu_y(R_0^w-R_0^v)}{\alpha\mu_x(R_0^w-R_0^z)}\right),\ w_3^* = \frac{\mu_y(R_0^w-R_0^v)}{\alpha(R_0^z-R_0^w)}, \end{cases} \tag{7}$$

Taking

$$\boxed{R_0^z = \sigma R_0^v}, \tag{8}$$

Where $\sigma = \frac{p_z}{\mu_z}\frac{\mu_y}{p_y}$. The existence condition of *E^*_z* are: (i) If $R_0^w > 1,\ R_0^v < R_0^w < R_0^z$ and $\sigma > 1$. (ii) If $R_0^z < R_0^w < R_0^v$ and $\sigma = \frac{p_z}{\mu_z}\frac{\mu_y}{p_y} < 1$.

The parameters R_0^v, R^w_0 and R^z_0, are called the basic reproductive numbers of the viral infection, are an important concept, especially in the context of viral control. It represents the average number of secondary infected cells produced by each infected cell at the beginning of the infection.

Local stability of the equilibrium states

The stability of the equilibrium points will be determined by the nature of the eigenvalues of the Jacobian matrix evaluated at the corresponding equilibrium state.
We get the following local stability result for the equilibrium states.
Theorem 1 *If* $R^v_0<1$ *and* $R^w_0<1$*, then the infection-free steady state* E^*_0 *is locally asymptotically stable for system (4); if* $R^v_0>1$ *or* $R^w_0>1$*, then it is unstable for system (4).*
Theorem 2 *If* $R^v_0>1$*, and* $R^v_0>R^w_0$*, then the GB Virus C equilibrium state* E^*_v *is locally asymptotically stable for system (4).*
Theorem 3 *If* $R^w_0>1$*,* $R^w_0>R^v_0$ *and* $R^w_0>R^z_0$*, then the HIV equilibrium state* E^*_w *is locally asymptotically stable for system (4).*

3.3 Global stability of the equilibrium states

In recent years, the method of Lyapunov functions has been a popular technique to study global properties of population models. However, it is often difficult to construct suitable Lyapunov functions. The most popular types of Lyapunov functions are the common quadratic and Volterra-type functions.
The common quadratic functions and the Volterra-type functions are of the form

$$F(x)=\sum_{i=1}^{n}\frac{c_i}{2}\left(x_i-x_i^*\right)^2,\quad \widetilde{F}(x)=\sum_{i=1}^{n}c_i\left(x_i-x_i^*-x_i^*\ln\frac{x_i}{x_i^*}\right), \qquad (9)$$

respectively. The Volterra-type function was originally discovered by Vito Volterra as the first integral of a simple predator-prey model. The Volterra-type functions are extensively used to demonstrate the global stability of the steady state of Lotka-Volterra systems and infectious disease. The Volterra type function has been used in [12] to prove global stability of the equilibrium states of basic virus dynamic models. In [12] use this Lyapunov function and studied the global stability of the equilibrium states of model (2). Part of this investigation, we seek the construction of Lyapunov functions for the equilibrium states of the system (4).

4 Numerical simulations of model (4)

In this section, we use numerical simulations to visualize qualitative and quantitative properties of the trajectories of model (4) with respect to different values of the production rate of virus from an infected cell.
The time courses of uninfected cells, infected cells, and free virion populations were obtained by numerical integration using MATLAB 6.5. We use a set of clinical data reported in [13] for the parameter of the viral dynamics of HIV-1 infection and the estimation of the parameter of the cellular infection by GB Virus C is not available in the literature.

We use the values of the parameters given in Table 1 and the definition of basic reproductive numbers, R^v_0, R^w_0 and R^z_0. We perform a series of numerical simulations for model (4). In the following figures 5, 6, 7 and 8 it shows the uninfected target (*x*) cells, infected cells (*y* and *u*), double-infected cells (*z*) and free virions populations (*v* and *w*).

Table 1: Parameter estimates and initial data values for the model of HIV-1 (1) reported in [8]; and used for system (4).

Initial data values and parameters	Values
Initial data values	
$x(0)$ uninfected target cells	10^6 *cells/mL*
$y(0)$ infected cells by GBVC	0
$z(0)$ double-infected cells by GBVC and HIV-1	0
$u(0)$ infected cells by HIV-1	0
$w(0)$ free HIV-1	100 *copies/mL*
$v(0)$ free GBVC	100 *copies/mL*
Parameters	
Λ production rate of uninfected cells	10^5 *cells/(mL.d)*
μ_x death rate of uninfected target cells	$0.1/d$
μ_y death rate of infected cell by GBVC	Assumed identical to μ_u
μ_z death rate of $z(t)$ by GBVC and HIV-1	Assumed identical to μ_u
μ_u death rate of infected cell by HIV-1	$0.5/d$
α rate of infection of $y(t)$ by HIV-1	Assumed identical to κ
β rate of infection of target cells by GBVC	Assumed identical to κ
κ rate of infection of target cells by HIV-1	2×10^{-7} *mL/(copies.d)*
p_u production rate of HIV-1 from an infected cell	Varies
p_y production rate of GBVC from an infected cell	Varies
p_z production rate of GBVC from an $z(t)$	Varies
γ_w clearance rate constant of HIV-1	$5/d$
γ_v clearance rate constant of GBVC	Assumed identical to γ_w

DISCUSSIONS

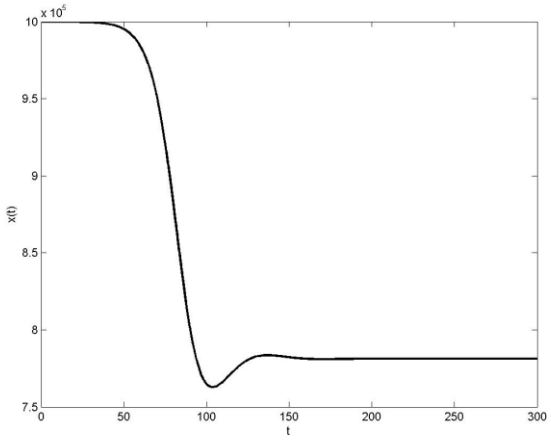
Virus have been difficult to understand in biology, and even more difficult to understand is viral-human interaction. In this paper we pretend to explain the interaction not of just one virus with the human body, but of two viruses interacting between them and with the human body. We use the specific case of GB virus C and HIV, because their implications of co-infection in AIDS disease.

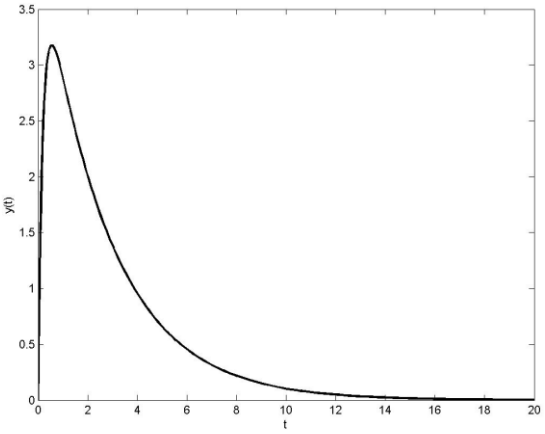
Epidemiological studies describe that HIV/GBV-C co-infected patients have slower progression to AIDS

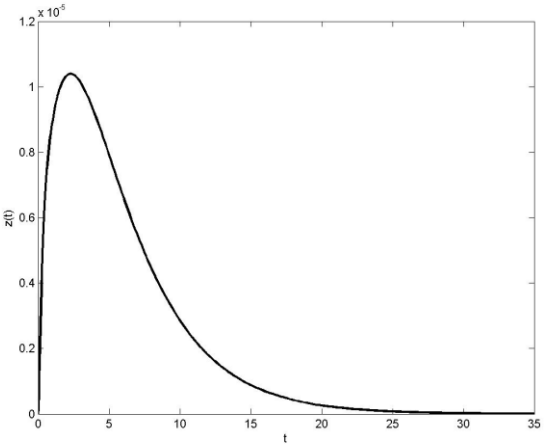
and longer survival. *In vitro* studies demonstrate that GBV-C is able to inhibit HIV replication in levels as high as 98%. To elucidate the phenomenon mechanism different theories have been proposed. HIV enters the cell trough the co-receptors CCR5 and CXCR4 (fusion step). E2 GBV-C protein promotes the expression of MIP1α, MIP1β and RANTES, specific ligands of CCR5 and CXCR4, fomenting the competitive inhibition of HIV fusion. Other explanations include the reduction of T-Cell activation (the same mechanism found in HIV long term non progressors patients) and the blocking of the fusion step by E2 antibodies. However, none of this mechanism can explain completely the inhibition of HIV by GBV-C co-infection.

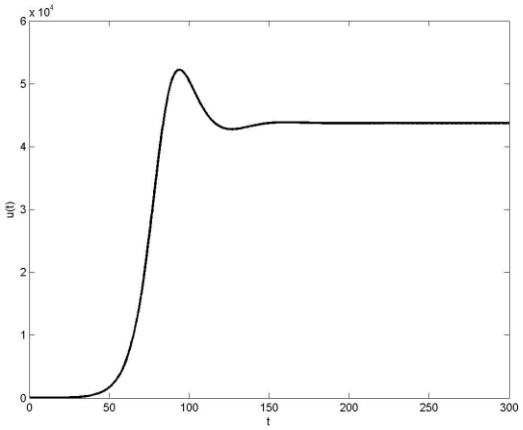
Although the inhibition mechanism or mechanisms are not elucidate, (we are in process). We known that whatever the mechanisms are, it depends of viral loads and infection times.

Due to HIV inhibition mechanism by GB virus C is not completely described, this paper intends to develop a mathematical model to describe the dynamics of coinfection in cell population, depending of GBV-C and HIV viral loads and infection time.









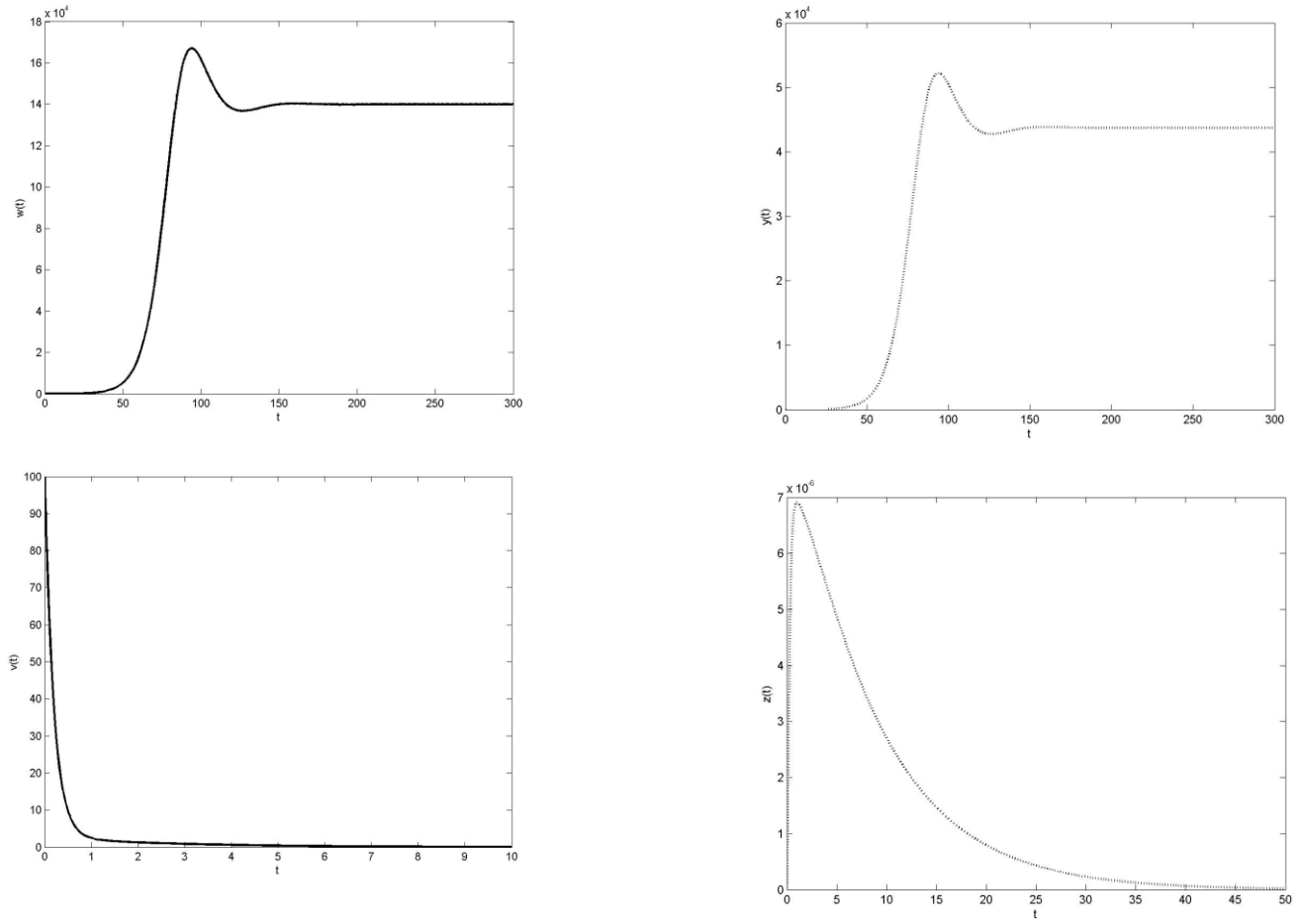


Figure 5: Exclusion Competitive: Only HIV virus. Rw0>Rv0>Rz0. In this case the values of py=3, pu=16 and pz=0.1, then the basic reproductive numbers are Rw0=1.28, Rv0=1.2 and Rz0=0.04, respectively.

On the other hand, the basic reproductive numbers Rv0, Rw0 and Rz0 for model (4) play an important role in the progression of the coinfection. The values of the basic reproductive numbers determine the scenarios of coinfection. The numerical simulations in this paper are based on the assumption that double-infected cells produced only GBV-C. From the figures 5 and 7 we observe that the HIV is able to invade and out-compete the GB virus C replication. And from the figures 6 and 8 we observe that the GB virus C is able to invade and out-compete the HIV replication. This model reveals the scenario of viral competitive exclusion of one of the virus. In the future investigate the possible scenario of the coexistence of viruses, through the qualitative and numerical analysis solutions.

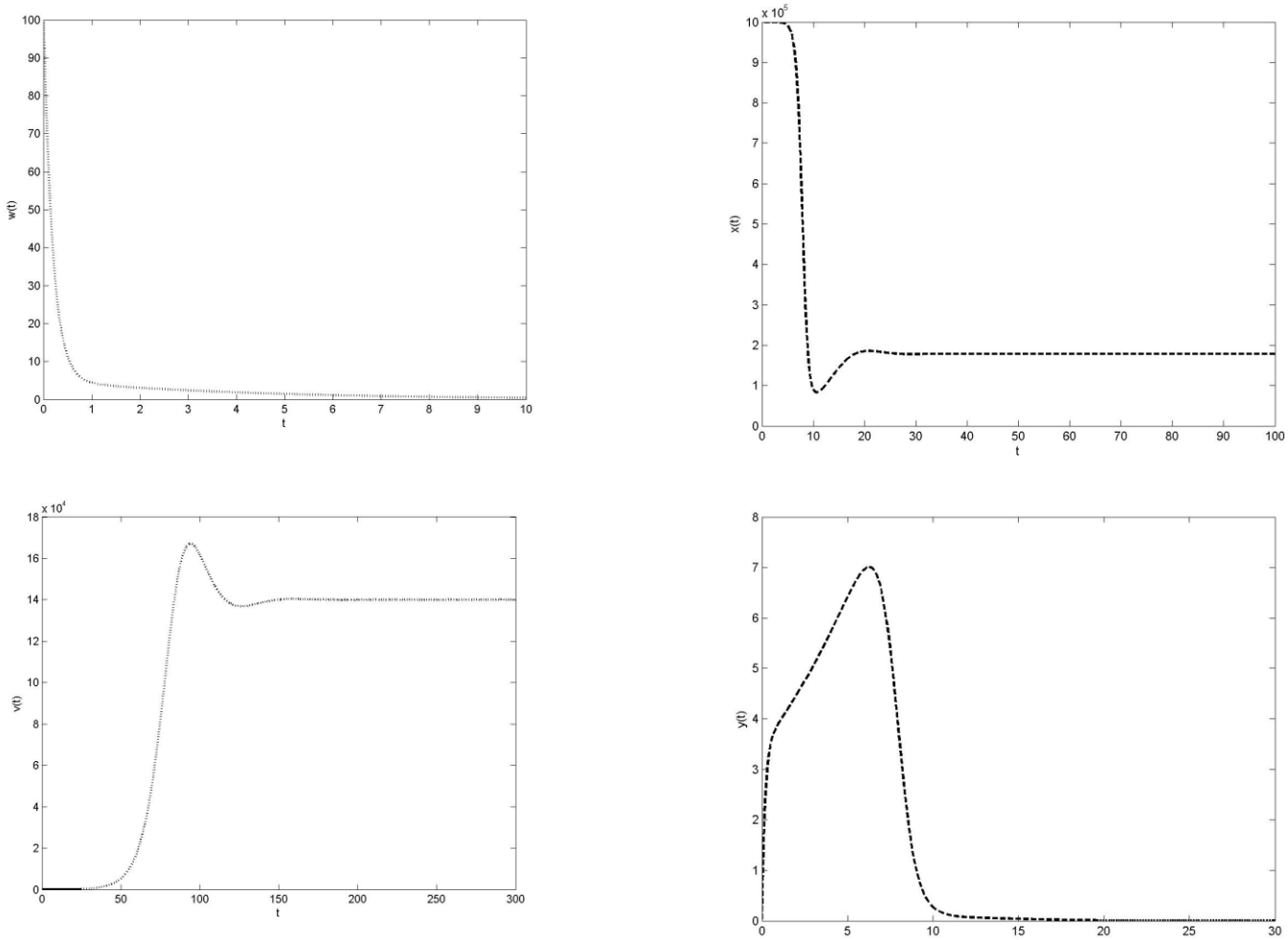


Figure 6: Exclusion Competitive: Only GB virus C. Rv0>Rw0>Rz0. In this case the values of py=6, pu=16 and pz=0.1, then the basic reproductive numbers are Rw0=1.28, Rv0=2.4 and Rz0=0.04, respectively.

The parameters of viral dynamics of HIV are estimated in the literature. The viral dynamics parameters of GB virus C are unknown. Pending determination of the values of the parameters of viral dynamics of GB Virus C, it will be possible to obtain quantitative results to help answer and pose hypotheses of biological trait.

We have been able to culture GBV-C *in vitro*, and in the short future we will begin co-infection experiments with HIV. We expect to get the experimental data needed to feed the mathematical model, and realize further experiments based in the model results; using both the experiments and the model to solve the problem of viral ratio and infection times. We plan in the long term to make a complete mathematical model capable of explaining the deep mechanism of the phenomenon.

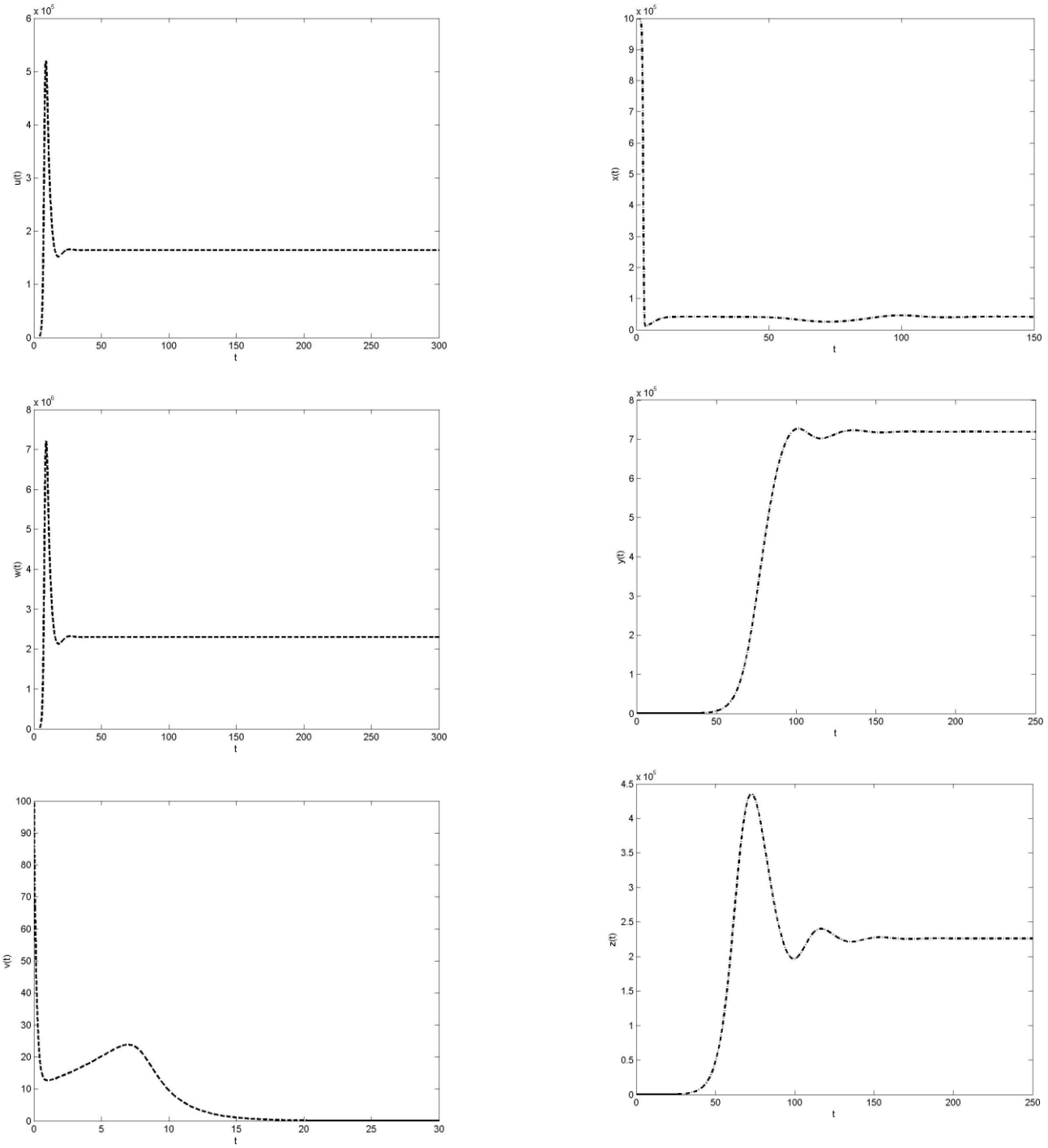


Figure 7: Exclusion Competitive: Only HIV. In this cases, all basic reproductive number are greater than unity, $R^v_0>R^w_0>R^z_0$*. In this case the values of* $\mu_y=\mu_z=0.1$, $p_y=16$, $p_u=70$ *and* $p_z=13$*, then the basic reproductive numbers are* $R^w_0=5.6$, $R^v_0=6.4$ *and* $R^z_0=5.2$*, respectively.*

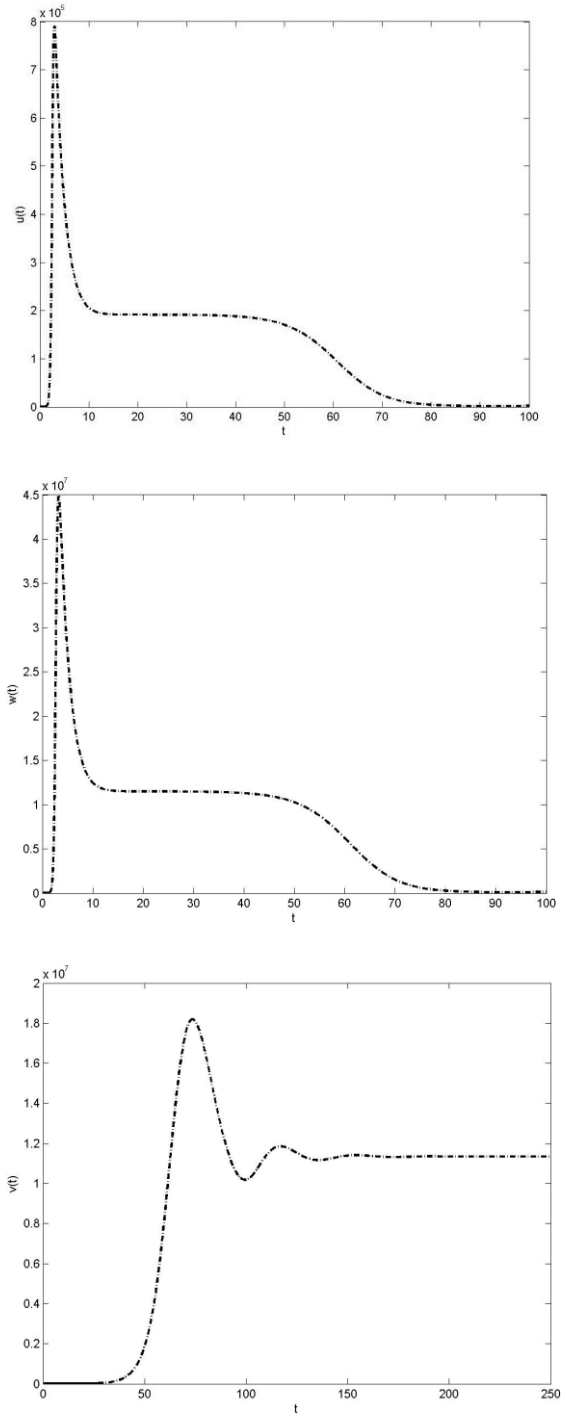


Figure 8: Exclusion Competitive: Only GB virus C. In this cases, all basic reproductive number are greater than unity, $R^z_0 > R^w_0 > R^v_0$*. In this case the values of* $p_y=16$*,* $p_u=300$ *and* $p_z=200$*, then the basic reproductive numbers are* $R^w_0=24$*,* $R^v_0=6.4$ *and* $R^z_0=80$*, respectively.*

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