Exam Task

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Antibody Responses during Hepatitis B Viral Infection

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Exam Task

"SVPs may influence the way the host reacts to HBV infection. In this paper, we aim to determine quantitative features of the antibody responses to virus and subviral particles following HBV infection.

We build on basic chronic virus infection models and determine the antibody characteristics that explain both the high peak and eventual viral clearance observed during acute hepatitis B infections."

Models of virus infection in the absence of antibody responses

$$\frac{d}{dt}T(t) = rT(1 - \frac{T(t) + I(t)}{T_m}) - \beta V(t)T(t) + \rho I(t)$$

$$\frac{d}{dt}I(t) = \beta V(t)T(t) - \delta I(t) - \rho I(t)$$

$$\frac{d}{dt}V(t) = \pi I(t) - cV(t)$$

where uninfected target cells (T), infected cells (I), and virus (V);

$$T(0) = T_m > 0 \quad I(0) = 0 \quad V(0) = V_0 > 0$$

The basic reproductive number

The infection dies out when

$$R_0 = \frac{\pi \beta T_m}{c\delta + c\rho} < 1$$

and the infection takes off and leads to chronic hepatitis when

$$R_0 = \frac{\pi \beta T_m}{c\delta + c\rho} > 1$$

Antigen reaction scheme

We consider the reversible binding of free anti-HBsAg antibody (A), to both free virus (V), and subviral particles (S), described by the reaction scheme

$$A + V \underset{k_m}{\overset{k_p}{\Longleftrightarrow}} X$$

$$A + S \underset{k_m^S}{\overset{k_p^S}{\Longleftrightarrow}} X_S$$

Models of virus infection in the absence of antibody responses

$$\frac{d}{dt}T(t) = rT\left(1 - \frac{T(t)+I(t)}{T_m}\right) - \beta V(t)T(t)$$

$$\frac{d}{dt}I(t) = \beta V(t)T(t) - \delta I(t)$$

$$\frac{d}{dt}A(t) = p_A(V(t)+S(t)) + r_A A(t)\left(1 - \frac{A(t)}{A_m}\right) + k_m X(t) - k_p A(t)V(t) + k_m^S X_S(t) - k_p^S A(t)S(t) - d_A A(t)$$

$$\frac{d}{dt}X(t) = -k_m X(t) + k_p A(t)V(t) - c_{AV}X(t)$$

$$\frac{d}{dt}X_S(t) = -k_m^S X_S(t) + k_p^S A(t)S(t) - c_{AS}X_S(t)$$

$$\frac{d}{dt}V(t) = \pi I(t) - cV(t) + k_m X(t) - k_p A(t)V(t)$$

$$\frac{d}{dt}S(t) = \pi\theta I(t) - c_S S(t) + k_m^S X_S(t) - k_p^S A(t)S(t)$$

where

$$T(0) = T_m > 0 \quad I(0) = 0 \quad A(0) = 0 \quad V(0) = V_0 > 0 \quad S(0) = 0 \quad X(0) = 0$$

Simplification

$$k_m = k_m^S \quad k_p = k_p^S \quad c = c_S \quad c_A V = c_A S$$

$$\frac{V(t)}{S(t)} = \frac{X(t)}{X_S(t)}$$

$$\frac{d}{dt}V(t) + \frac{d}{dt}X(t) = 0 \implies \pi I(t) = cV(t) + c_A VX(t) =$$

$$= c\frac{S(t)X(t)}{X_S(t)} + c_{AV}X(t) = \frac{X(t)}{X_S(t)}(cS(t) + c_{AV}X_S(t))$$

$$\frac{d}{dt}S(t) + \frac{d}{dt}X_S(t) = 0 \implies \pi I(t) = \frac{1}{\theta}(cS(t) + c_{AV}X_S(t))$$

$$S(t) = \theta V(t) \quad X_S(t) = \theta X(t)$$

The model of HBV infection including an antibody response with simplification

$$\frac{d}{dt}T(t) = rT(1 - \frac{T(t) + I(t)}{T_m}) - \beta V(t)T(t)$$

$$\frac{d}{dt}I(t) = \beta V(t)T(t) - \delta I(t)$$

$$\frac{d}{dt}A(t) = p_A(1+\theta)V(t) + r_A A(t)(1 - \frac{A(t)}{A_m}) + (1+\theta)k_m X(t) - (1+\theta)k_p A(t)V(t) - d_A A(t)$$

$$\frac{d}{dt}X(t) = -k_m X(t) + k_p A(t)V(t) - c_{AV}X(t)$$

$$\frac{d}{dt}V(t) = \pi I(t) - cV(t) + k_m X(t) - k_p A(t)V(t)$$

where

$$T(0) = T_m > 0 \quad I(0) = 0 \quad A(0) = 0 \quad V(0) = V_0 > 0 \quad S(0) = 0 \quad X(0) = 0$$

Transformation

$$r_A A(t)(1 - \frac{A(t)}{A_m}) - d_A A(t) = \rho_A A(t)(1 - \frac{A(t)}{\Gamma})$$

where

$$\rho_A = r_A - d_A \quad \Gamma = A_m(1 - \frac{d_A}{r_A})$$

Steady states

a. Infection cleared with liver failure in the absence of immune response

$$S_1 = (T_1, I_1, A_1, X_1, V_1) = (0, 0, 0, 0, 0)$$

b. Infection cleared with liver failure in the presence of immune response

$$S_2 = (T_2, I_2, A_2, X_2, V_2) = (0, 0, \Gamma, 0, 0)$$

c. No-infection steady state

$$S_3 = (T_3, I_3, A_3, X_3, V_3) = (T_m, 0, 0, 0, 0)$$

d. Cleared infection steady state, in the presence of an immune response

$$S_4 = (T_4, I_4, A_4, X_4, V_4) = (T_m, 0, \Gamma, 0, 0)$$

e. Chronic infection steady states

$$S_5 = (T_5, I_5, A_5, X_5, V_5)$$

$$a_1\bar{A}_5^3+a_2\bar{A}_5^2+a_3\bar{A}_5+a_4=0,$$

where

$$\bar{T}_5 = \frac{\delta}{\beta\pi}(c+\xi\bar{A}_5),$$

$$\bar{V}_5 = \frac{\rho_A\bar{A}_5(1-\frac{\bar{A}_5}{\Gamma})}{(1+\theta)(\xi\bar{A}_5-p_A)} = \frac{r(1-\frac{1}{R_0}(1+\frac{\xi}{c}\bar{A}_5))}{\beta+\frac{r}{\pi T_m}(c+\xi\bar{A}_5)},$$

$$\bar{I}_5 = \frac{(c+\xi\bar{A}_5)\bar{V}_5}{\pi},$$

$$\bar{X}_5 = \frac{\xi}{c_{AV}}\bar{A}_5\bar{V}_5,$$

$$\xi = \frac{c_{AV}k_p}{c_{AV}+k_m},$$

$$a_1 = r\rho_A\beta\xi,$$

$$a_2 = \rho_A\beta(\pi\beta T_m+rc)-r\Gamma\xi(\rho_A\beta+\delta\xi(1+\theta)),$$

$$a_3 = r\Gamma\xi c\delta(R_0-1)(1+\theta)+$$

$$\Gamma(r\delta p_A\xi(1+\theta)-\beta\rho_A(\pi\beta T_m+rc)),$$

$$a_4 = r\Gamma p_A c\delta(1+\theta)(1-R_0).$$

When $R_0 > 1$ we have that $a_4 < 0$. Therefore, since $a_1 > 0$, by Decartes' rule of signs, the polynomial in Eq. (14) can have one or three positive roots. Since we require positivity for $\bar{V}_5$, $r(1 - \frac{1}{R_0}(1 + \frac{\xi}{c}\bar{A}_5)) > 0$, which is equivalent to

$$R_0 > 1 + \frac{\xi}{c}\bar{A}_5, \tag{16}$$

and to expression $\frac{\rho_A \bar{A}_5 (1 - \frac{\bar{A}_5}{\Gamma})}{(1+\theta)(\xi \bar{A}_5 - p_A)} > 0$, which is satisfied when

$$\min\{\Gamma, \frac{p_A}{\xi}\} < \bar{A}_5 < \max\{\Gamma, \frac{p_A}{\xi}\}. \tag{17}$$

We cannot give definite conditions for when three roots emerge.

Jacobian matrix

$$\begin{pmatrix} r(1-\frac{2T+I}{T_m})-\beta V-\lambda & -r\frac{T}{T_m} & 0 & 0 & -\beta T \\ \beta V & -\delta-\lambda & 0 & 0 & \beta T \\ 0 & 0 & \rho_A(1-\frac{2A}{\Gamma})-(1+\theta)k_p V-\lambda & (1+\theta)k_m & (1+\theta)(p_A-k_p A) \\ 0 & 0 & k_p V & -k_m-c_{AV}-\lambda & k_p A \\ 0 & \pi & -k_p V & k_m & -c-k_p A-\lambda \end{pmatrix}$$

Proposition 1. The liver failure steady states S1 and S2 are always unstable.
Proposition 2. The no-infection steady state S3 is always unstable.
Proposition 3. The cleared infection steady state S4 is locally asymptotically unstable otherwise and stable when

$$R_0 < 1 + \frac{\xi}{c}\Gamma$$

A new effective basic reproductive number

$$1+\frac{p_A}{c}<1+\frac{\xi}{c}\bar{A}_5<R_0<1+\frac{\xi}{c}\Gamma,$$

$$R_0^a=R_0-\frac{\xi}{c}\Gamma$$

Variables

Variables		
T	Target cells	$T_0 = 13.6 \times 10^6$ per ml
I	Infected cells	$I_0 = 0$
A	Free antibody	molecules per ml (varies)
V	Free virus	$V_0 = 0.33$ per ml
S	Subviral particles	-
X	Virus-antibody complexes	$X_0 = 0$
X_S	Subviral particle-antibody complexes	-

Parameters

Parameters

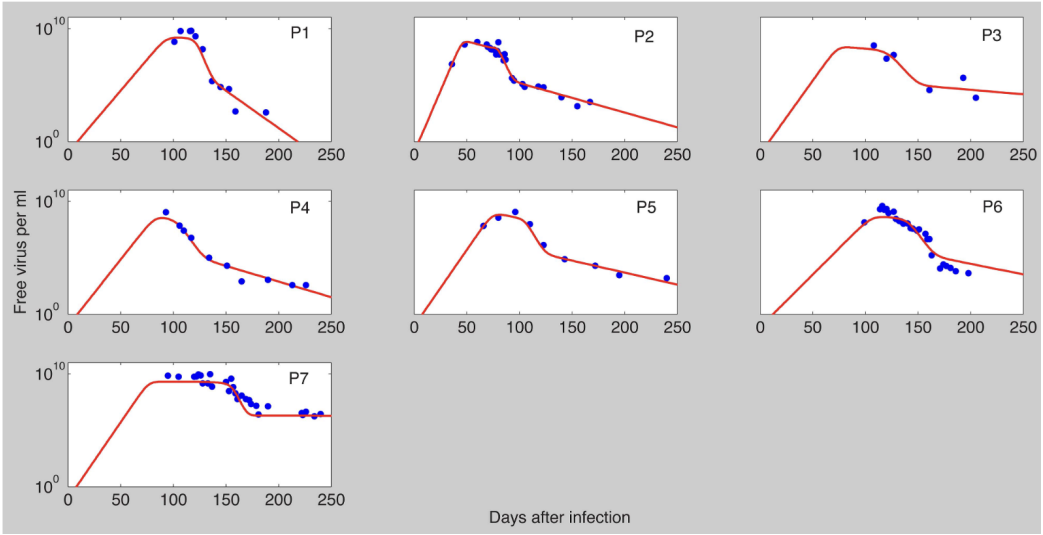
r	hepatocyte maximum proliferation rate	$1\ \mathrm{d}^{-1}$
β	infectivity rate constant	ml d^{-1} (varies)
T_m	hepatocyte carrying capacity	13.6×10^6 cells per ml
δ	infected cell killing rate	d^{-1} (varies)
ρ	cure rate	0
p_A	antibody production	molecules d^{-1} (varies)
r_A	antigen-independent antibody growth rate	d^{-1} (varies)
d_A	antibody degradation rate	$0.033\ \mathrm{d}^{-1}$
A_m	antibody carrying capacity	4×10^{15} molecules per ml
k_p	antibody binding rate	10^{-12} ml d^{-1}
k_m	antibody dissociation rate	$10\ \mathrm{d}^{-1}$
π	virus production rate	d^{-1} (varies)
c	virus clearance rate	$0.67\ \mathrm{d}^{-1}$
c_{AV}	complexes degradation rate	$2.7\ \mathrm{d}^{-1}$
θ	subvirus:virus ratio	varies
η	antibody units conversion factor	2.7×10^{-16} mg/molecule

Parameter best estimates

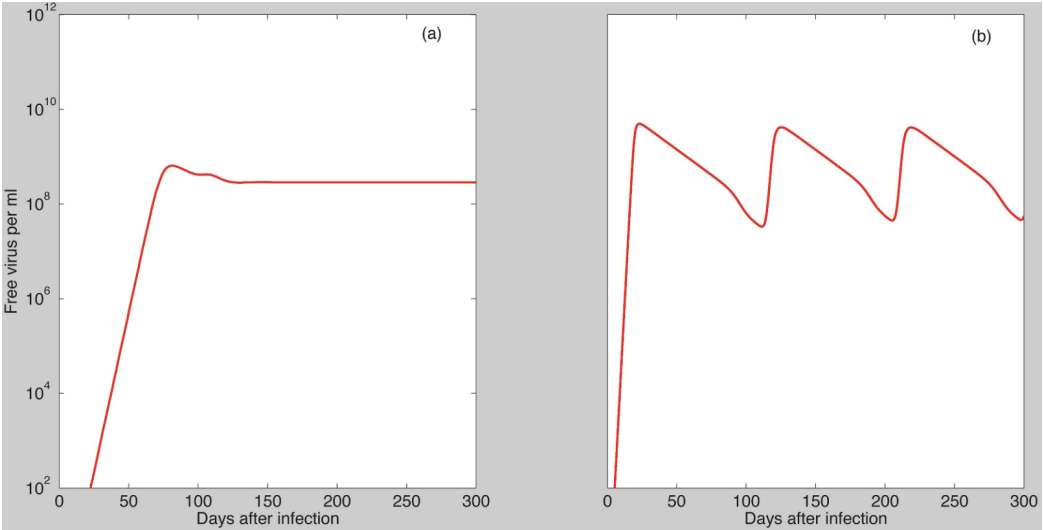
Table 2. Parameter best estimates.

Patient	$\beta \times 10^{-10}$	π	δ	r_A	$p_A \times 10^{-5}$	RSS
1	0.953	297	0.1538	0.4242	0.1	4.8
2	11.1	43.5	0.061	0.4656	0.7	3.5
3	18.2	12.4	0.018	0.2672	9	3.5
4	8.8	26.4	0.064	0.288	520	3
5	6.1	42.5	0.049	0.3578	10	2
6	5.87	28.5	0.043	0.29	1.16	8.1
7	2	113	0.0000998	0.4623	0.41	6.1
median	6.1	42.5	0.049	0.358	1.16	-
average	7.57	80.5	0.056	0.365	77.3	-
stdev	5.87	101	0.049	0.085	195	-

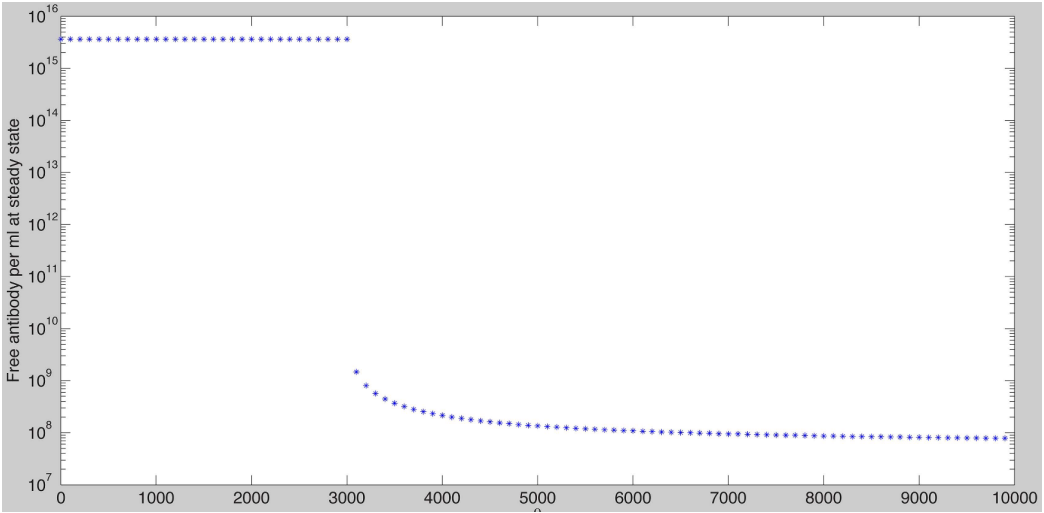
The best fit of V



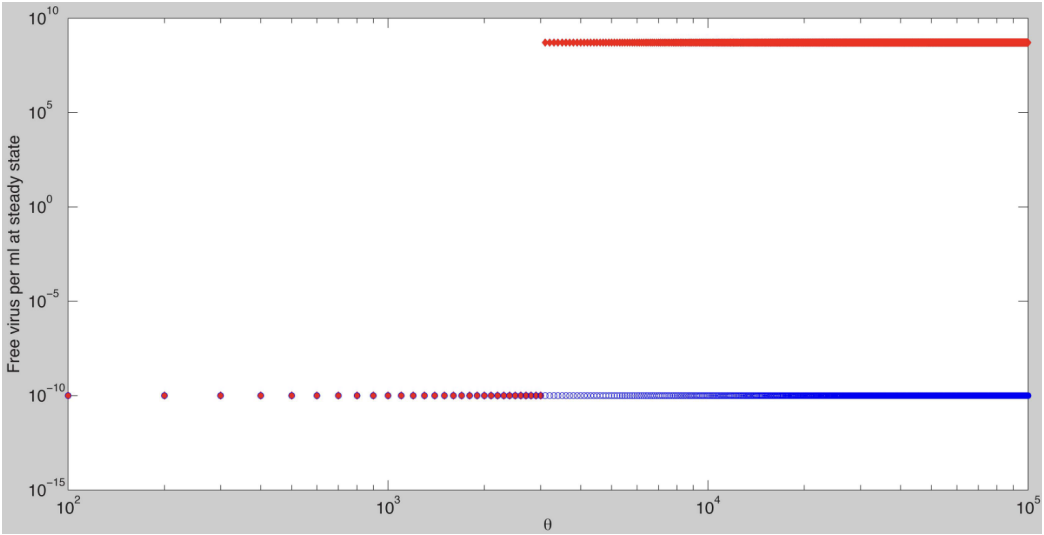
Dynamics of V as when the cleared infection condition fails



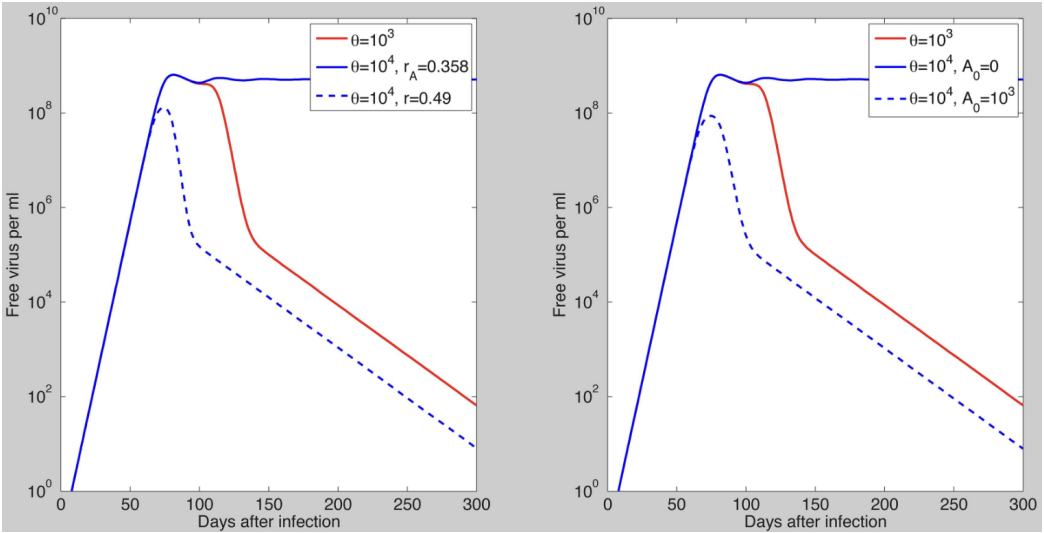
Free antibody at steady state as a function of θ



Stable steady state solutions for V a as a function of θ



Bistable dynamics



Multivalent binding model

$$V_0 + A \underset{1k_m}{\overset{nk_p}{\rightleftharpoons}} V_1,$$

$$V_i + A \underset{(i+1)k_m}{\overset{(n-i)k_p}{\rightleftharpoons}} V_{i+1},$$

$$V_{n-1} + A \underset{nk_m}{\overset{1k_p}{\rightleftharpoons}} V_n,$$

$$\frac{dT}{dt} = rT(1 - \frac{T+I}{T_m}) - T\sum_{i=0}^{n-1} \frac{\beta}{i+1} V_i,$$

$$\frac{dI}{dt} = T\sum_{i=0}^{n-1} \frac{\beta}{i+1} V_i - \delta I,$$

$$\frac{dA}{dt} = p_A(1+\theta)\sum_{i=0}^{n-1} V_i + r_A A(1 - \frac{A}{A_m}) -$$

$$d_A A + (1+\theta)\sum_{i=1}^{n} \{ik_m V_i - (n-i+1)k_p V_{i-1} A\},$$

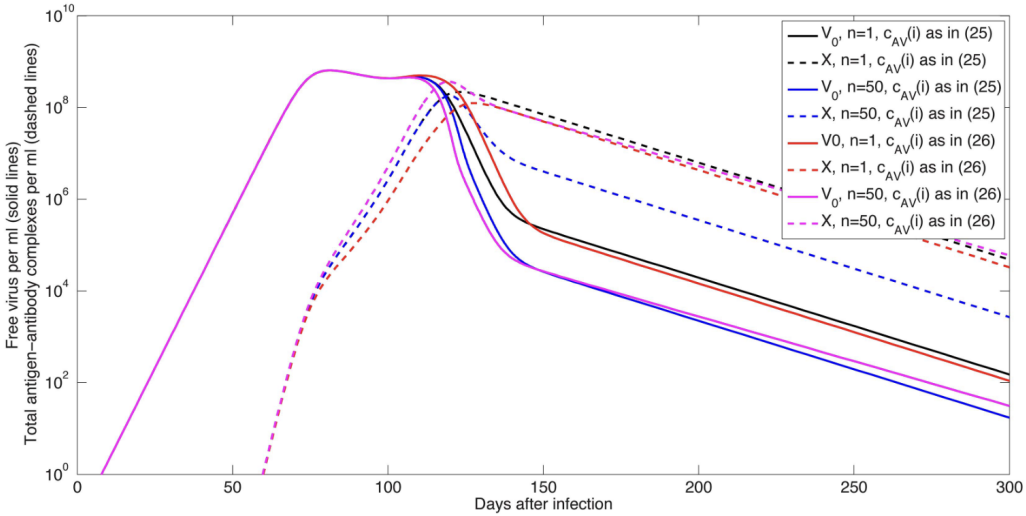
$$\frac{dV_0}{dt} = \pi I - cV + k_m V_1 - nk_p V_0 A - cV_0,$$

$$\frac{dV_i}{dt} = (i+1)k_m V_{i+1} - (n-i)k_p V_i A - ik_m V_i +$$

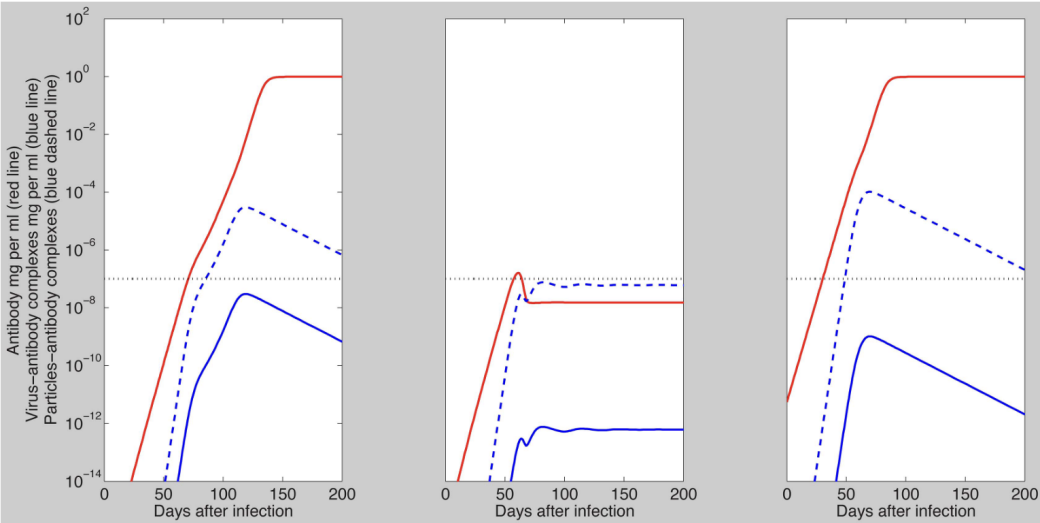
$$(n-i+1)k_p V_{i-1} A - c_{AV}(i)V_i,$$

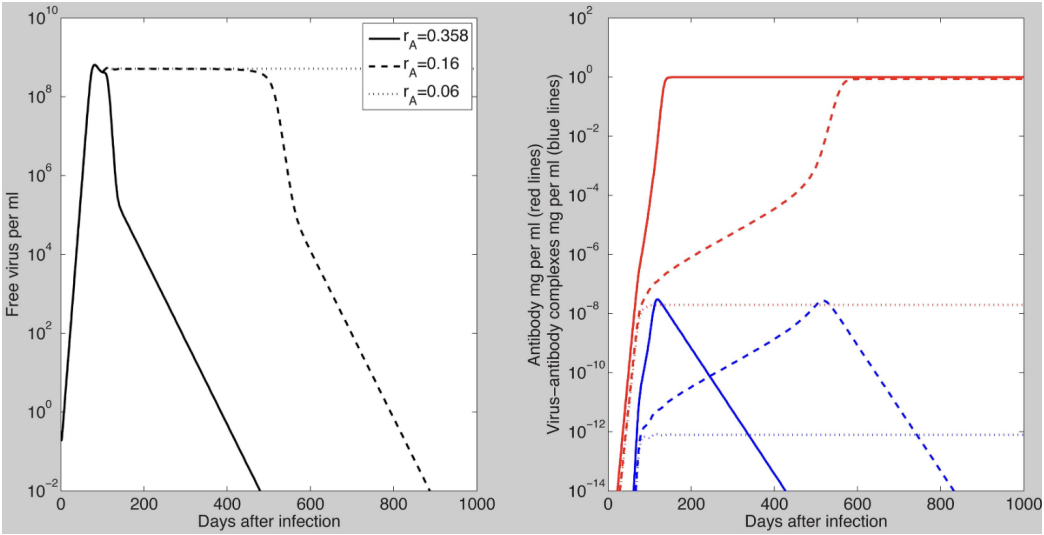
$$\frac{dV_n}{dt} = k_p V_{n-1} A - nk_m V_n - c_{AV}(n)V_n,$$

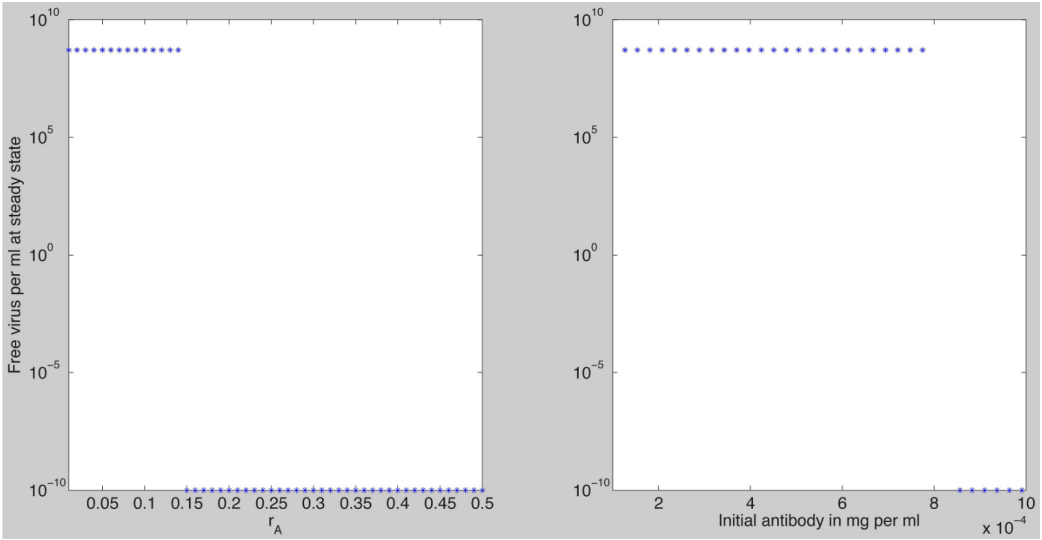
Numerical results



Antibody dynamics




Free virus per ml
Days after infection
r_A=0.358
r_A=0.16
r_A=0.06
Antibody mg per ml (red lines)
Virus–antibody complexes mg per ml (blue lines)
Days after infection


Free virus per ml at steady state
10^{10}
10^{5}
10^{0}
10^{-5}
10^{-10}
0.05 0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5
r_A
10^{10}
10^{5}
10^{0}
10^{-5}
10^{-10}
2 4 6 8 10
Initial antibody in mg per ml
x 10^{-4}