Antibody responses during hepatitis B viral infection - Text S1

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We have shown analytically that when (22) holds, model (7) exhibits bi-stability between the clearance and chronic steady states, S_4 and S_5, respectively. We investigated numerically the individual contributions of r_A, θ and A_0 to the virus long-term dynamics. Since some parameters have synergistic/antagonistic effects, we derived long-term dynamics of V when two of model (7)'s parameters are varied. As seen in Fig. S1, r_A and p_A complement each other, with virus clearance being maintained when the decrease of antigen-independent (-dependent) expansion rate r_A (p_A) is compensated by an increase in the antigen-dependent (-independent) expansion rate p_A (r_A). Conversely, the increase in the subvirus:virus ratio θ requires an increase in the antibody's carrying capacity, A_m, for the clearance to be preserved (Fig. S2).

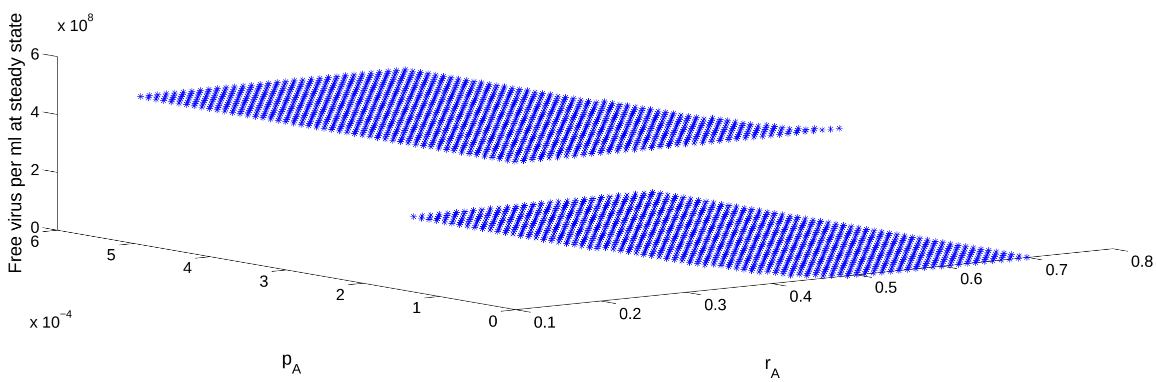

Figure S1: Stable steady state solutions for free virus, V, as given by model (7), as a function of r_A and p_A for $\theta = 10^3$, $A_0 = 0$. The other parameters are as Tables 1 and 2 (median values).

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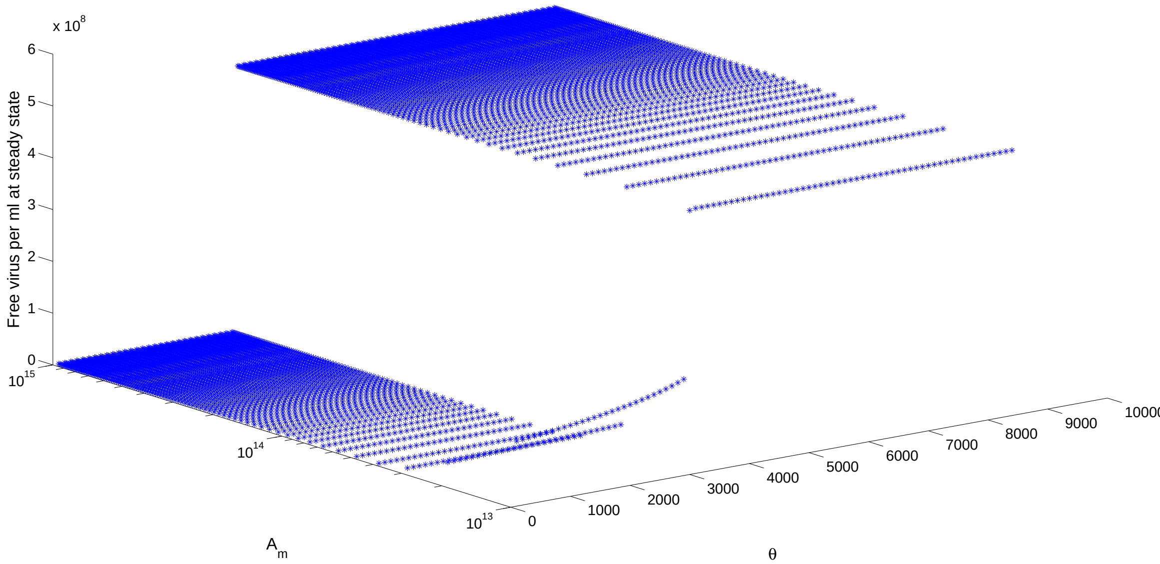

Figure S2: Stable steady state solutions for free virus, V, as given by model (7), as a function of θ and A_m for $\theta = 10^3$, $A_0 = 0$. The other parameters are as in Tables 1 and 2 (median values).

We derived the sensitivity equations for model (7) with respect to $q = \{r_A, p_A\}$ by formally differentiating each equation with respect to q. The resulting curves $q\frac{dV}{dq}$ give the effect on V when q is doubled [1]. We see that the effects of p_A and r_A are proportional with each other throughout the infection (see Fig. S3).

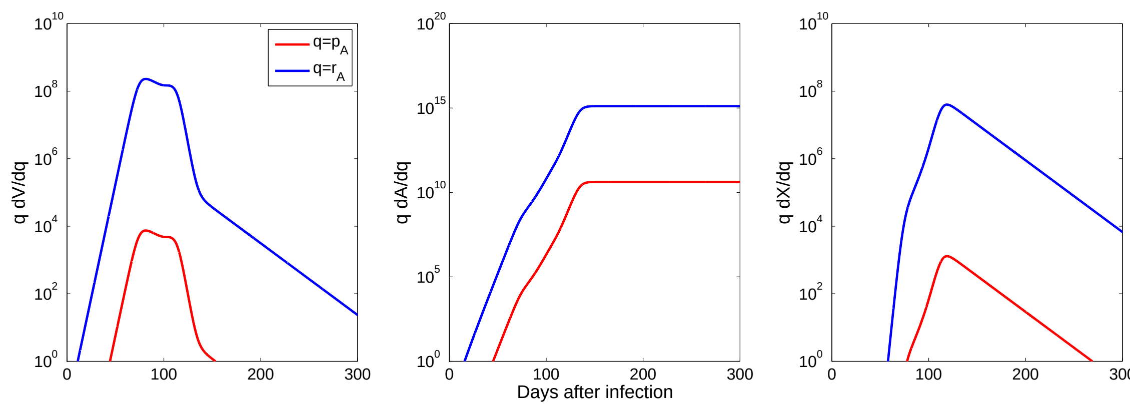

Figure S3: The relative sensitive curves $q\frac{dZ}{dq}$ for $q = p_A$ (red lines) and $q = r_A$ (blue lines) and $Z = V$ (left panel), $Z = A$ (middle panel), $Z = X$ (right panel). The parameters are as in Tables 1 and 2 (median values).

Model (7) assumes that the clearance rate of the virions bound to antibodies is four times higher than the clearance of the virus, *i.e.*, $c_{AV} = 4c$ as in HIV infections [2]. Since the HIV is cleared more rapidly than HBV, the c_{AV} to c ratios may be underestimated. We examined the effects of increasing c_{AV} beyond $4c$ on the free virus population when we are the the clearance region given by equation (19) and $A_5 > \Gamma$ in the main text. As seen in Fig. S4 increasing the clearance of subviral particles reduces the free virus concentration during the second phase decay. In particular, for $c_{AV} = 150c$ (Fig. S4 dotted line) the free virus during the second phase decay is 6.5-times lower than in the $c_{AV} = 4c$ case (Fig. S4 solid line).

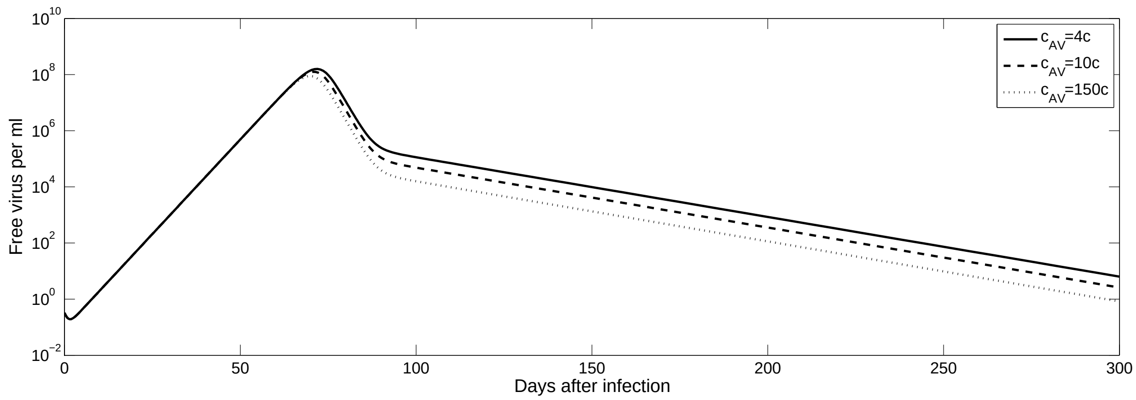

Figure S4: Free virus dynamics as given by model (7) for $c_{AV} = 4c$ (solid line), $c_{AV} = 10c$ (dashed line) and $c_{AV} = 150c$ (dotted line). $\theta = 10^3$, $A_0 = 0$, $r_A = 0.5$, and the other parameters are as Tables 1 and 2 (median values).

References

[1] Bortz D, Nelson P (2004) Sensitivity analysis of a nonlinear lumped parameter model of HIV infection dynamics. Bull Math Biol 66:1009–1026.

[2] Igarashi T, Brown C, Azadegan A, Haigwood N, Dimitrov D, et al. (1999) Human immunodeficiency virus type 1 neutralizing antibodies accelerate clearance of cell-free virions from blood plasma. Nat Med 5:211–216.

Table S1: Patient data

patient	Days	HBV DNA per ml
1	101	7.22×10^8
	107	6.15×10^9
	116	$6.37e \times 10^9$
	117	6.69×10^9
	121	2.16×10^9
	128	1.58×10^8
	137	2.32×10^5
	145	6.79×10^4
	153	4.52×10^4
	159	4.8×10^2
	188	390

patient	Days	HBV DNA per ml
2	36	7.41×10^6
	48	4.16×10^8
	60	6.82×10^8
	69	4.16×10^8
	70	2.59×10^8
	72	2.01×10^8
	73	1.53×10^8
	74	1.44×10^8
	76	1.37×10^8
	78	5.35×10^7
	79	1.09×10^8
	80	6.31×10^8
	81	5.33×10^7
	85	1.55×10^7
	86	5.70×10^7
	87	1.81×10^7
	93	4.21×10^5
	95	2.52×10^5
	103	1.30×10^5
	105	7.27×10^4
	118	7.78×10^4
	123	6.61×10^4
	140	8.52×10^3
	155	1.40×10^3
	167	3.20×10^3

patient	Days	HBV DNA per ml
3	108	3.27×10^8
	120	2.25×10^7
	127	4.85×10^7
	161	3.69×10^4
	193	4.40×10^5
	205	7.68×10^3
	275	9.20×10^3

patient	Days	HBV DNA per ml
4	93	1.11×10^9
	106	7.24×10^7
	110	2.66×10^7
	117	6.06×10^6
	134	1.05×10^5
	151	1.99×10^4
	165	8.40×10^2
	190	1.12×10^3
	213	390
	226	390

patient	Days	HBV DNA per ml
5	66	6.78×10^7
	80	3.58×10^8
	96	1.16×10^9
	110	9.61×10^7
	123	1.35×10^6
	143	7.66×10^4
	172	1.99×10^4
	195	3×10^3
	240	1.6×10^3

patient	Days	HBV DNA per ml
6	99	1.4×10^8
	114	2.05×10^9
	116	4×10^9
	118	1.82×10^9
	120	2.12×10^9
	122	9.65×10^8
	127	1.25×10^9
	129	2.87×10^8
	132	1.88×10^8
	134	1.74×10^8
	136	1.11×10^8
	140	1.15×10^8
	143	4.26×10^7
	145	3.95×10^7
	149	2.59×10^7
	151	3.34×10^7
	157	1.35×10^7
	159	4.73×10^6
	161	4.58×10^6
	163	1.76×10^5
	171	1.14×10^4
	174	2.62×10^4
	177	1.95×10^4
	181	1.30×10^4
	186	6.60×10^3
	198	4.48×10^3
	280	1.22×10^4

patient	Days	HBV DNA per ml
7	95	6.86×10^9
	105	5.66×10^9
	120	5.77×10^9
	122	6.10×10^9
	124	9.15×10^9
	126	7.37×10^9
	128	1.43×10^9
	133	1.43×10^9
	135	9.50×10^9
	137	7.53×10^8
	150	1.94×10^9
	153	3.03×10^8
	155	3.81×10^9
	157	6.87×10^8
	159	1.91×10^8
	161	5.86×10^7
	165	1.22×10^8
	169	5.80×10^7
	172	4.85×10^7
	174	2.10×10^7
	179	1.46×10^7
	181	2.49×10^6
	190	1.38×10^7
	222	3.44×10^6
	223	2.32×10^6
	226	4.33×10^6
	234	1.81×10^6
	240	2.79×10^6
	263	3.16×10^6