bnAbs paper

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bnAb dose response

The pharmacokinetic and pharmacodynamic properties of bnAbs are well-studied []. In particular it appears there is a biphasic exponential clearance of the antibodies, and the IC50 is approximately 0.33 μg/μL with an average Hill coefficient of 1.3 []. We show simulated results using these parameters in **Fig. 1**.

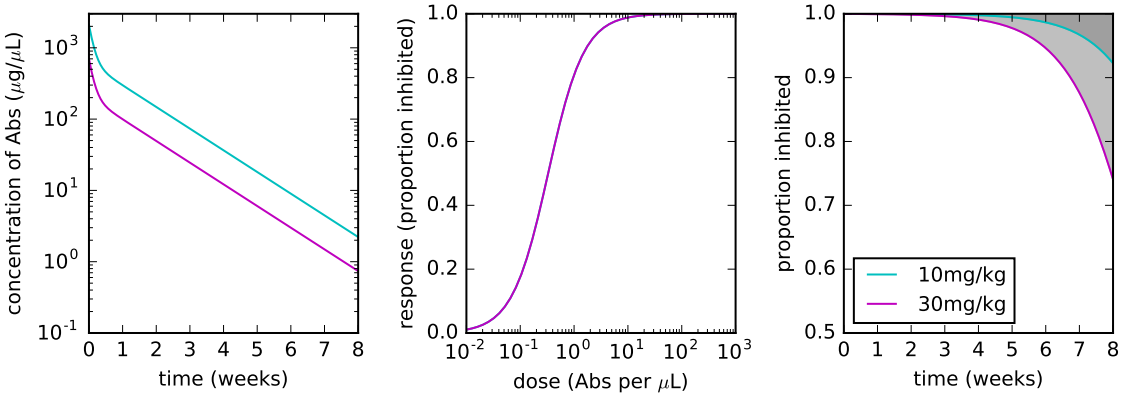

Figure 1: Pharmacokinetic and pharmacodynamic properties of bnAbs.

Mechanistic mathematical model for SHIV viral load dynamics

We designed a mathematical model to quantify the different mechanisms contributing to primary infection given prophylactic treatment with broadly neutralizing antibodies (bnAbs).

The model we employ is shown as a cartoon schematic in **Fig. 2**. We assume that there is a population of HIV virions V that interacts with the susceptible cells S (CD4+ T cells) to create infected cells I. bnAbs Ab decrease the infectivity of virus. However, they do not affect the small proportion of virus that becomes resistant V^*. These viruses infect cells that are then resistant infected I^*. The model is a stochastic branching process model allowing the transitions in Eq. 1. Susceptible cells are born and die with rates α_S and δ_S respectively, viruses and cells meet at rate β to form infected cells dependent on antibody concentration and with probability μ, antibody resistant infected cells are formed. Infected cells die with rate δ_I and burst to generate a Poisson distributed number of virions with mean π. Viruses are also cleared by the innate immune system with rate γ.

$$
\begin{aligned}
\emptyset \rightarrow S & \qquad \alpha_S \\
S \rightarrow \emptyset & \qquad \delta_S \\
S + V \rightarrow I & \qquad \beta_{Ab(t)}(1-\mu) \\
S + V \rightarrow I^* & \qquad \beta_{Ab(t)}\mu \\
S + V* \rightarrow I^* & \qquad \beta_0 \\
I \rightarrow \mathcal{P}_{poiss}(\pi)V & \qquad \delta_I \\
I^* \rightarrow \mathcal{P}_{poiss}(\pi^*)V^* & \qquad \delta_I \\
V \rightarrow \emptyset & \qquad \gamma \\
V^* \rightarrow \emptyset & \qquad \gamma
\end{aligned} \tag{1}
$$

0.1 implementation

$$
\mathbf{r} = \begin{bmatrix} \alpha_S \\ \delta_S \\ \beta_{Ab(t)}(1-\mu) \\ \beta_{Ab(t)}\mu \\ \beta_0 \\ \delta_I \\ \delta_I \\ \gamma \\ \gamma \end{bmatrix}
$$

$$
\Delta\mathbf{x}(\mathbf{E}) = T_{ij}E_i = T_{ij}\mathcal{P}(r_i\Delta t)
$$

$$
\mathbf{T} = T_{ij} = \begin{bmatrix} \Delta S_j \\ \Delta I_j \\ \Delta I_j^* \\ \Delta V_j \\ \Delta V_j^* \end{bmatrix}
$$

$$
\mathbf{x} = \begin{bmatrix} S \\ I \\ I^* \\ V \\ V^* \end{bmatrix}
$$

The values of the rates in the model are shown in **Table 1**. We have obtained values from the literature, either from experimental work, or well established modeling work that fits to data.

Results of simulations

In **Fig. 4** we simulate the model for evenly spaced infection events throughout 2 dosing periods. Infections only persist in ranges where the effective reproductive number is greater than 1 for several days $\mathcal{R}(Ab, t) > 1$.

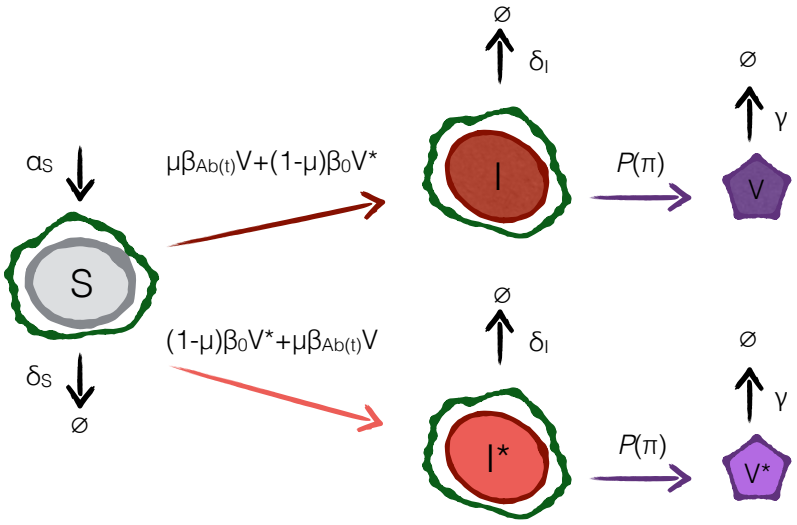

Figure 2: A cartoon model schematic.

parameter	meaning	value [dimensions]	reference
β	viral infectivity	1×10^{-4} [per virus per day]	[]
τ	proportion of productive infections	0.05 []	[1]
δ_I	productively infected cell death rate	1 [per day]	[2]
π	viral burst size	5×10^4 [virions/cell]	[3]
γ	viral clearance rate	23 [per day]	[4]

Table 1: Parameters for the stochastic model Eq. 1

We also simulated the whole trial, and example of the raw data for these follows. The other raw data is shown elsewhere.

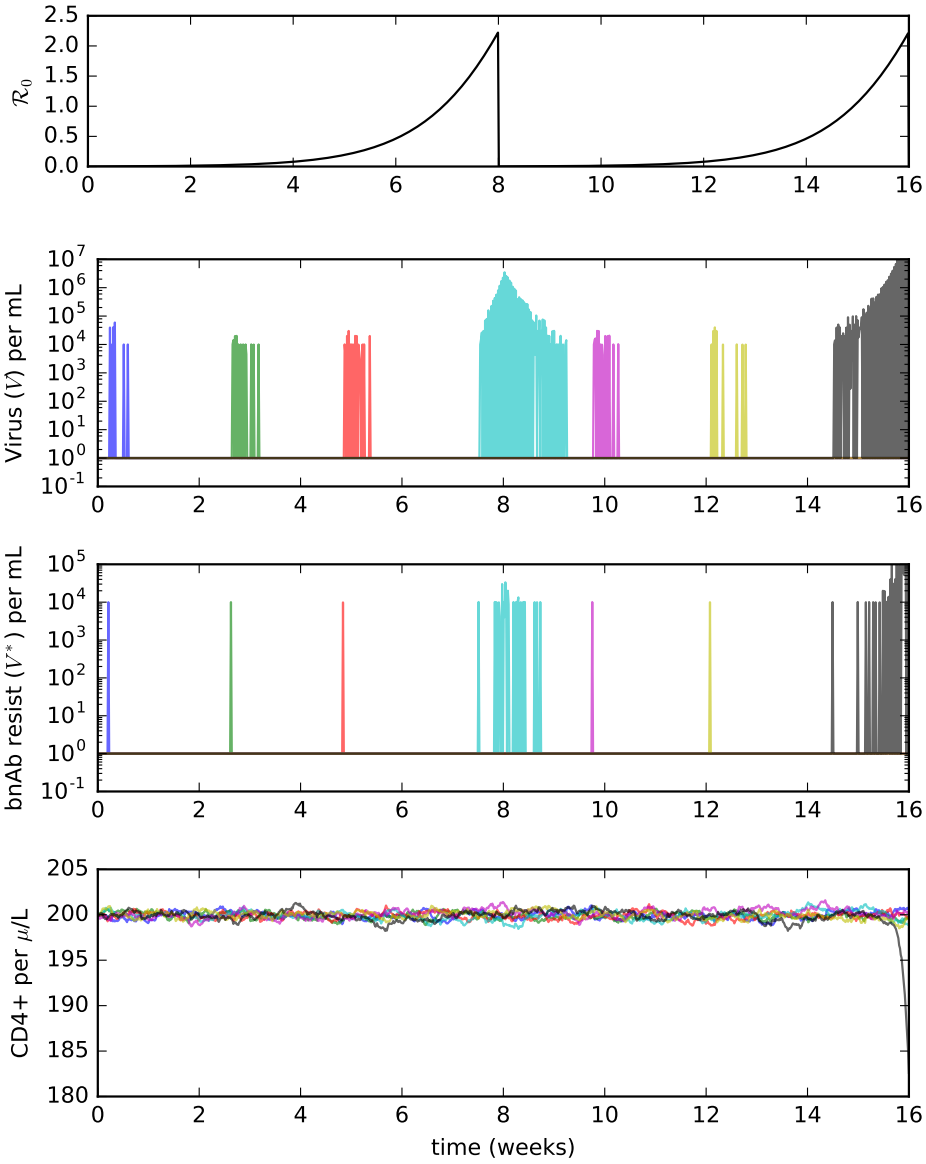

Figure 3: Evenly spaced incidence with 10mg/kg bNab infusion at week 8 and 16. The top panel shows the value of the effective reproductive number $\mathcal{R}(Ab, t)$ over time given the Ab concentration and dose-response kinetics in **Fig. 1**. The remaining panels show stochastic realizations of numbers of virions and Ab resistant virions and CD4+ T cells over time.

References

[1] Gilad Doitsh, Marielle Cavrois, Kara G. Lassen, Orlando Zepeda, Zhiyuan Yang, Mario L. Santiago, Andrew M. Hebbeler, and Warner C. Greene. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. *Cell*, 143(5):789–801, 2010.

[2] Rob J De Boer, Hiroshi Mohri, David D Ho, and Alan S Perelson. Turnover rates of B cells, T cells, and NK cells in simian immunodeficiency virus-infected and uninfected rhesus macaques.

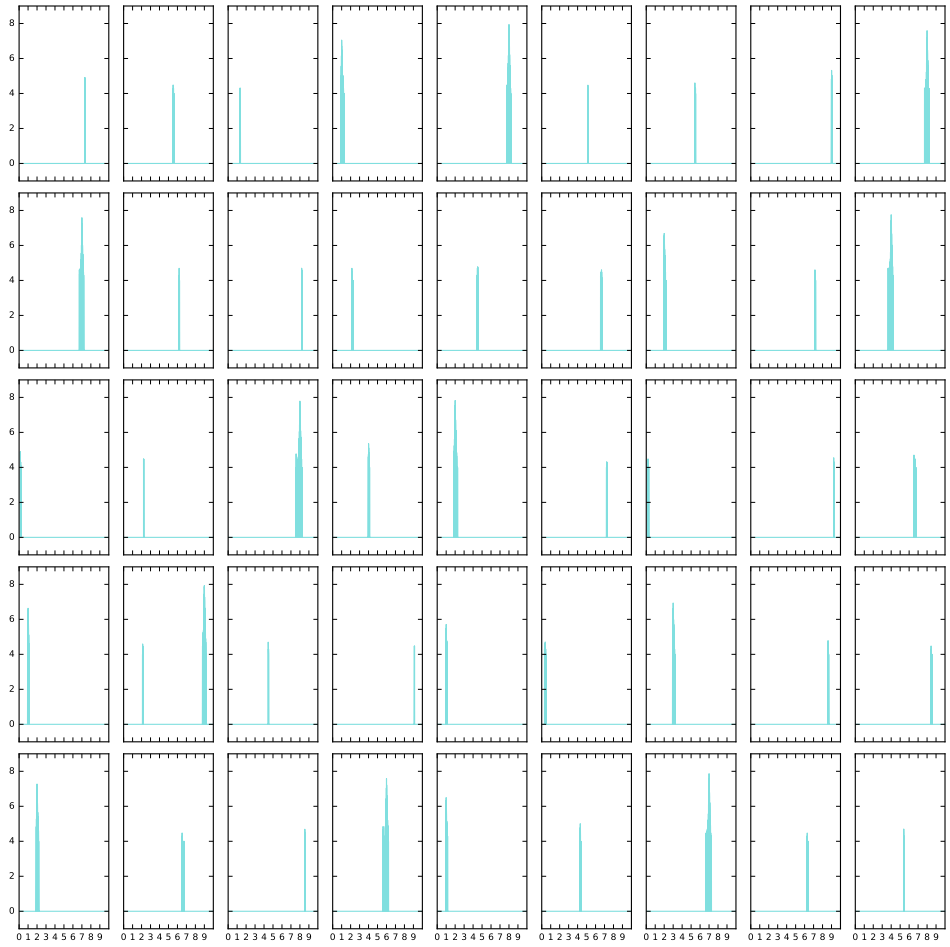

Figure 4: Example clinical trial simulation of the msm 10mg/kg dose arm where incidence is uniform with average annual rate 3%. 800 individuals were enrolled and 45 had outbreak incidents, including a single individual with 2 incidents. No infection was not controlled (though the latent reservoir should have been seeded). The viral load in $\log_{10}$ is monitored over 10 visits, each 4 weeks apart with infusions occurring every 8 weeks.

Journal of immunology (Baltimore, Md. : 1950), 170(5):2479–2487, 2003.

[3] Hannah Yuan Chen, Michele Di Mascio, Alan S Perelson, David D Ho, and Linqi Zhang. Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques. *Proceedings of the National Academy of Sciences of the United States of America*, 104(48):19079–84, 2007.

[4] Bharat Ramratnam, Sebastian Bonhoeffer, James Binley, Arlene Hurley, Linqi Zhang, John E. Mittler, Martin Markowitz, John P. Moore, Alan S. Perelson, and David D. Ho. Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis. *Lancet*, 354(9192):1782–1785, 1999.