# Modeling antibody responses during viral infections

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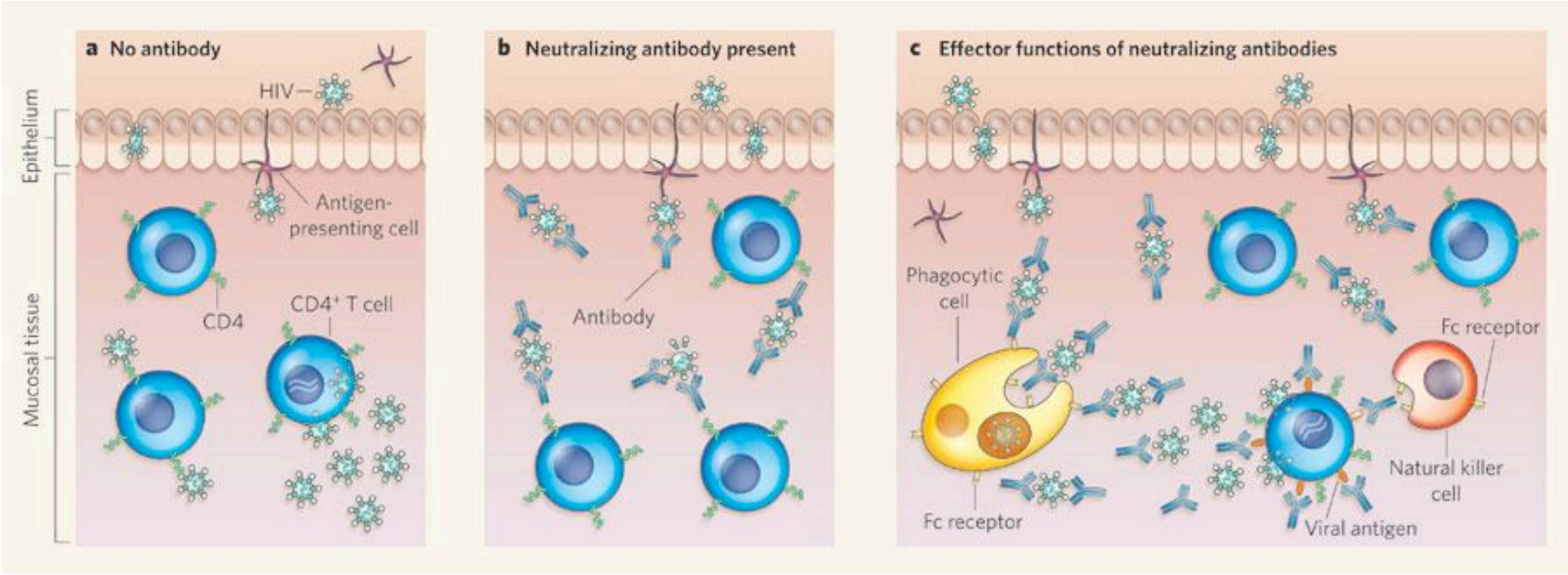
# Antibody functions

- Neutralization of free virus
- Complement-mediated lysis of free virus and infected cells
- Opsonization of virus particles by antibodies and phagocytosis of virus particles via Fc- or complement-receptors
- Antibody-dependent cellular cytotoxicity (ADCC) of infected cells
  - Tissue damage: HIV, HBV, HCV, herpes, Dengue virus, Polio virus, LCMV



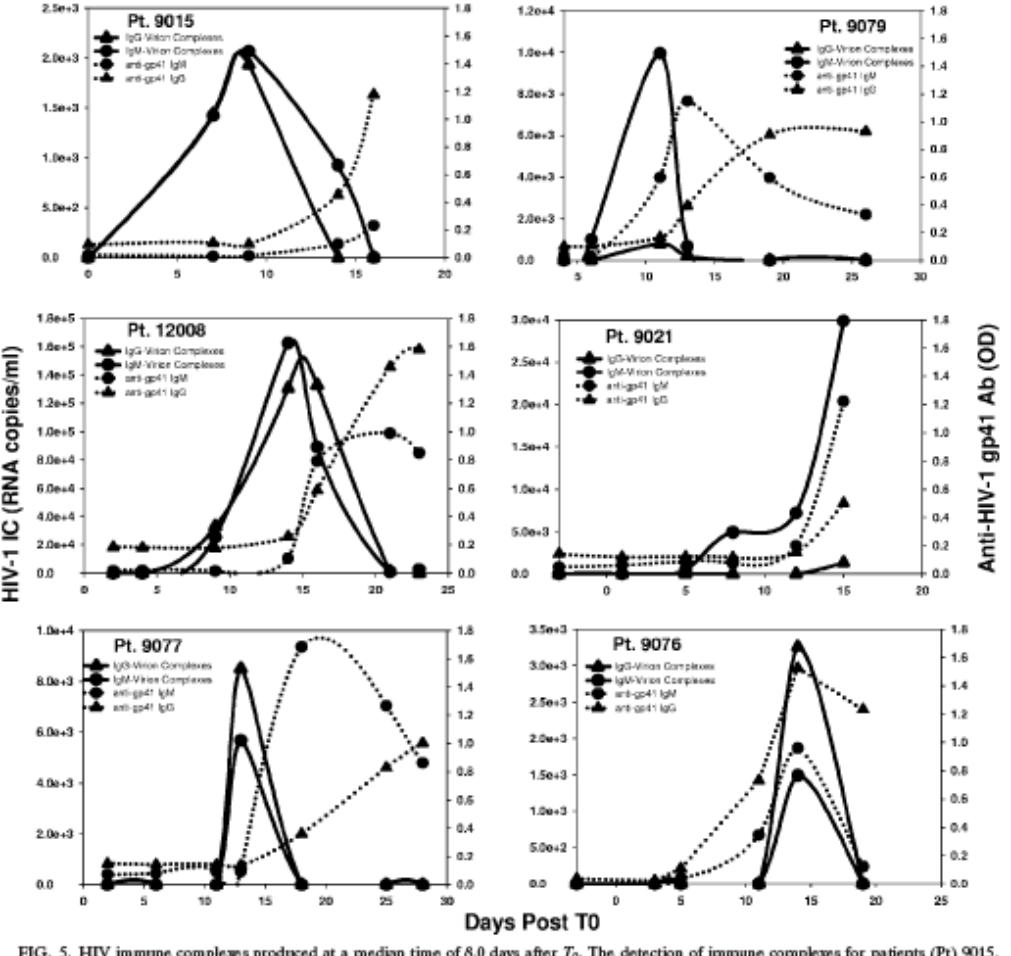



FIG. 5. HIV immune complexes produced at a median time of 8.0 days after $T_0$. The detection of immune complexes for patients (Pt) 9015, 12008, 9077, 9079, 9021, and 9076 are aligned to $T_0$ and plotted in comparison to the detection of free antibody (Ab) responses.

# Competition

- Antibodies can compete with each other for
  - antigen
  - space in the lymph nodes
  - T cell conjugates and/or kinetic prolongation

1. Competition between strain-specific and broadly specific neutralizing antibody in HIV infection.

2. Competition between antibodies directed to virus particles and those directed to empty particles in Hepatitis B infection.

# 1. HIV infection

- Broadly neutralizing antibodies
  - Monoclonal Ab: IgG1b12, 2F5, 2G12, 4E10, Z13, PG9, PG16
  - VRC01 (neutralizes 90% HIV strains)
- Vaccines
  - AIDSVax
    - Rocombinant gp120 protein as vaccine vector
    - Induced strain-specific Ab but failed to induce broadly neutralizing Ab
  - STEP
    - Induction of cellular mediated immune responses
    - Recombinant adenovirus serotype 5
    - Suppressed by pre-existing AD5-specific Ab
    - Enhanced HIV infection
  - RV 144
    - ALVAC-HIV recombinant canarypox + AIDSVax
    - Successful in reducing infectivity rates
    - Believed inefficient for clade C

# What are the challenges?

## Virus

- Extensive viral clade and sequence diversity
- Early establishment of latent viral reservoirs
- Viral evasion of humoral and cellular immune responses

## Antibody

- Responses are strain-specific (ssAb)
- No method exists to elicit broadly reactive neutralizing antibodies in vivo
  - Deleted during selection [Haynes, *Science* 2005, *Nat Struct Mol Biol* 2010]
  - Wrong conformation
  - High rate of mutation (VRC01) [Kwong *Science* 2010]
  - Competition [Zhang, *PNAS* 2009, Clarke, *Evol Applic* 2009]

# Competition

## Hypothesis

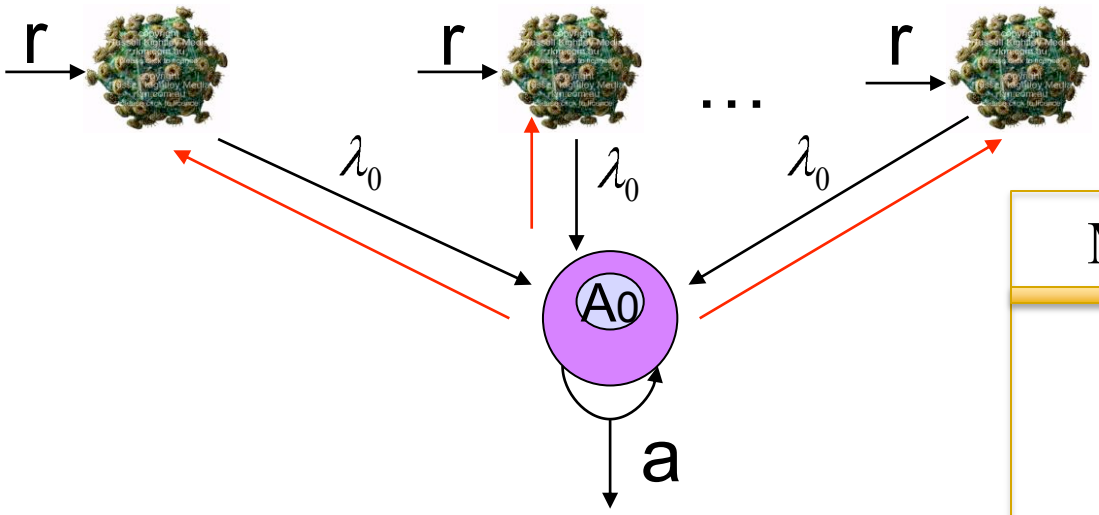
- Presence of strain-specific antibodies doesn't have to exclude the presence of broadly neutralizing ones

## Model

- Competition between the two antibody types.
- Find the parameter region where bnAb is made inefficient by ssAb

# Model without competition

## -continuous immunization




Model equations:

$$\frac{dV_i}{dt} = (r - K_0 A_0) V_i$$

$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0 (a - \beta A_0)$$

$$V_i(t_i) = V_0, \; A_i(t_i) = 0, \; A_0(0) = 0.$$

# Basic reproduction number

$$R_0 = \frac{r}{K_0 \frac{a}{\beta}}$$

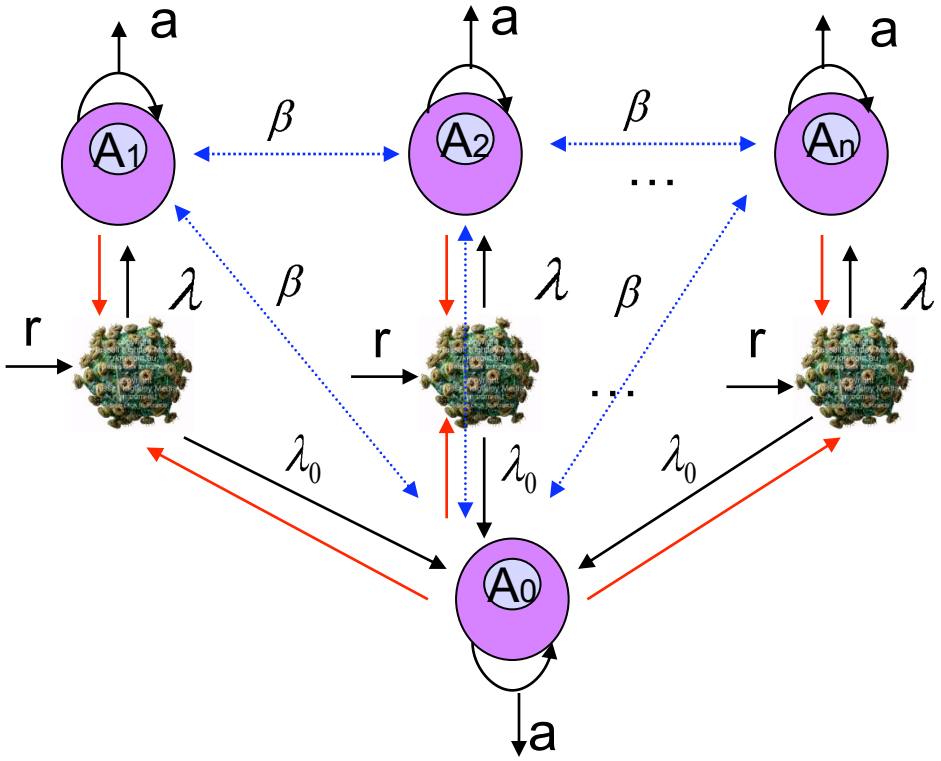
If $R_0 < 1$ then all viruses will be cleared.

If $R_0 > 1$ then at least one virus will persist.

Biological interpretation: When the virus replication rate is smaller then the product between the bnAb affinity rate and the antibody life span viruses will be cleared, otherwise some persist.

# Model with competition

## -continuous immunization




Model equations:

$$\frac{dV_i}{dt} = (r - KA_i - K_0 A_0)V_i$$

$$\frac{dA_i}{dt} = \lambda V_i + A_i(a - \beta A_T)$$

$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0(a - \beta A_T)$$

$$V_i(t_i) = V_0,\ A_i(t_i) = 0,\ A_0(0) = 0.$$

# Basic reproductive number

$$R_0 = \frac{r}{\frac{m\lambda_0 K_0 + \lambda K}{m(\lambda + \lambda_0)} \frac{a}{\beta}}$$ dependent on $m$.

If $R_0 < 1$ for $m = n$ then all viruses will be cleared.

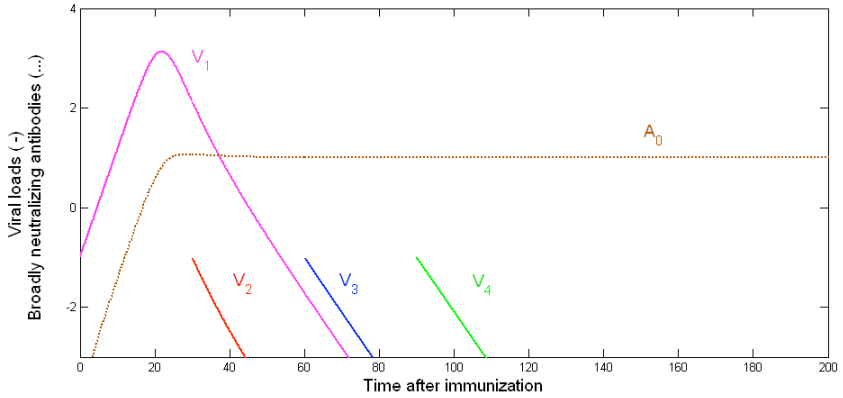
If there exist an m>1 such that $R_0 > 1$ then all viruses will persist.

Biological interpretation: When the virus replication rate is smaller then the product between the combined ssAb and bnAb affinity rate and the antibody life span viruses will be cleared, otherwise some persist.

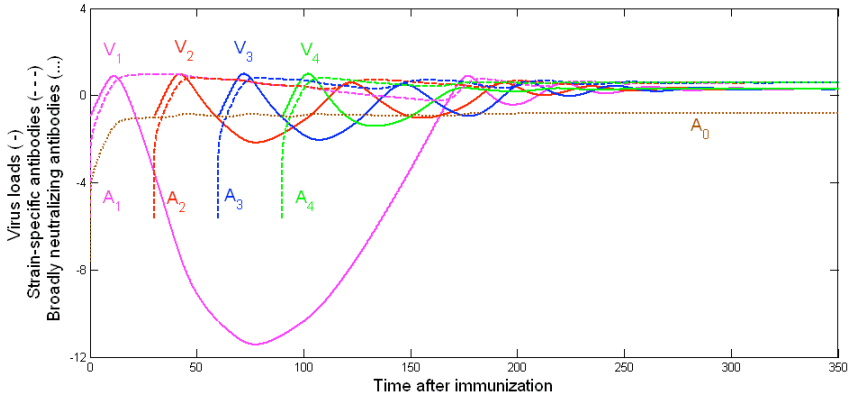
# Model prediction

For any m ≥ 2 for which

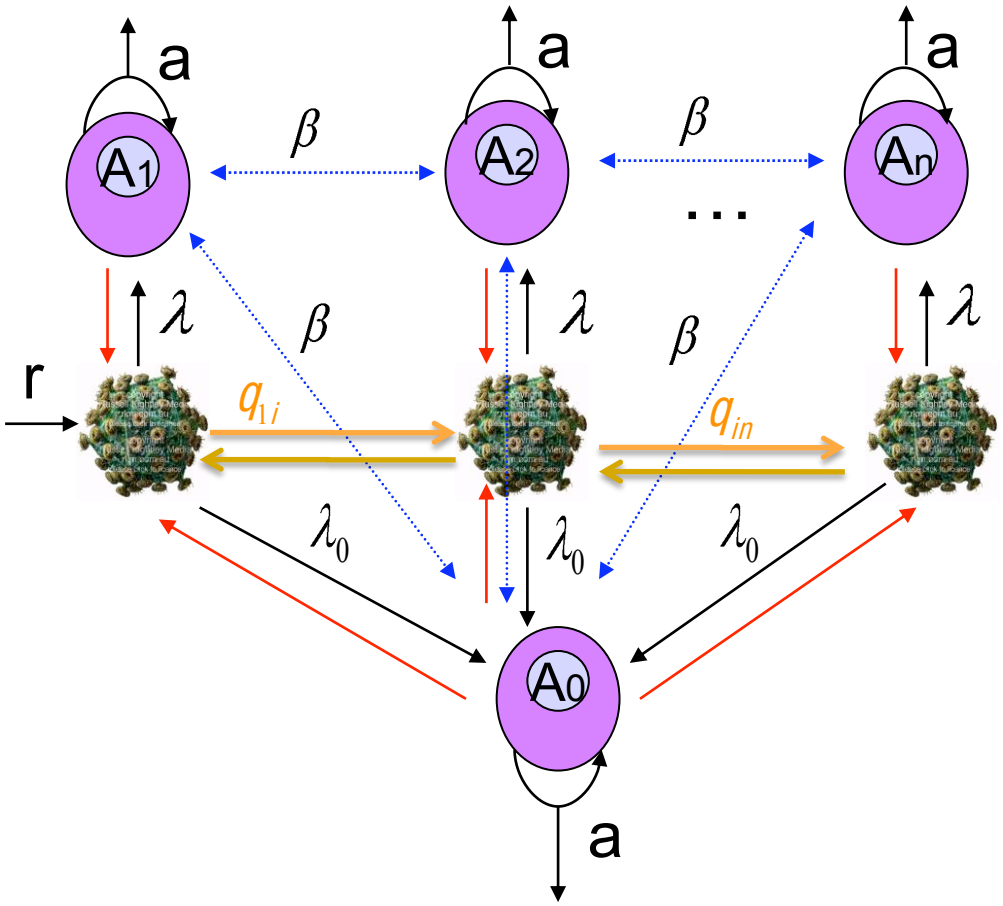
$$\frac{a}{\beta}\frac{mK_0\lambda_0 + K\lambda}{m(\lambda+\lambda_0)} < r < K_0\frac{a}{\beta}$$




- Viruses are cleared with no competition.
- Viruses persist with competition.



# Natural infection - mutations




## Model equations:

$$\frac{dV_i}{dt} = r\sum_{j=1}^{n} q_{ij}V_j - (KA_i + K_0 A_0)V_i$$

$$\frac{dA_i}{dt} = \lambda V_i + A_i(a - \beta A_T)$$

$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0(a - \beta A_T)$$

$$V_1(0) = V_{1,0}$$

$$V_j(0) = A_j(0) = A_0(0) = A_1(0) = 0.$$

$Q = \{q_{ij}\}_{i,j}$ is the mutation matrix:

$$0 \le q_{ij} \le 1 \text{ and } \sum_{i=1}^{n} q_{ij} = 1.$$

# No competition

Let $V = (V_1, V_2, ..., V_n)$ interact with $A_0$.

The dynamics of the systems (1) and (2) are quivalent

(1)
$$\frac{dV}{dt} = (rQ - K_0 A_0 I_n)V$$
$$\frac{dA_0}{dt} = \lambda_0 V_T + A_0(a - \beta A_0)$$

(2)
$$\frac{dV_T}{dt} = (r - K_0 A_0)V_T$$
$$\frac{dA_0}{dt} = \lambda_0 V_T + A_0(a - \beta A_0)$$

when the dominant eigenvalue of $Q=\{q_{ij}\}$ is simple, with corresponding eigenvector $z \geq 0$ s.t. $Qz = z$.

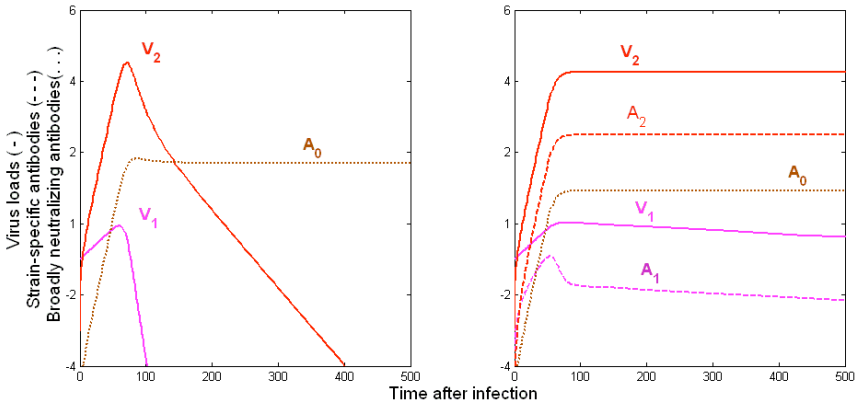
# For example

1. $Q$ is irreducible.

2. $$Q = \begin{pmatrix} 1-q_{12} & 0 & 0 & \dots & 0 & 0 \\ q_{12} & 1\text{-}q_{23} & 0 & \dots & 0 & 0 \\ \dots & & & & & \\ 0 & 0 & 0 & & q_{n-1n} & 1 \end{pmatrix}.$$

Then $R_0 = \dfrac{r}{K_0 \dfrac{a}{\beta}}$ is independent of n and Q.

When $R_0 < 1$ all virus strains are cleared and when $R_0 > 1$ all (dominat) viruses persist.



# Competition

$$R_0 = \frac{r}{\Omega K_0 \frac{a}{\beta}}$$

If $R_0 < 1$ then all viruses are cleared, otherwise some viruses persist.

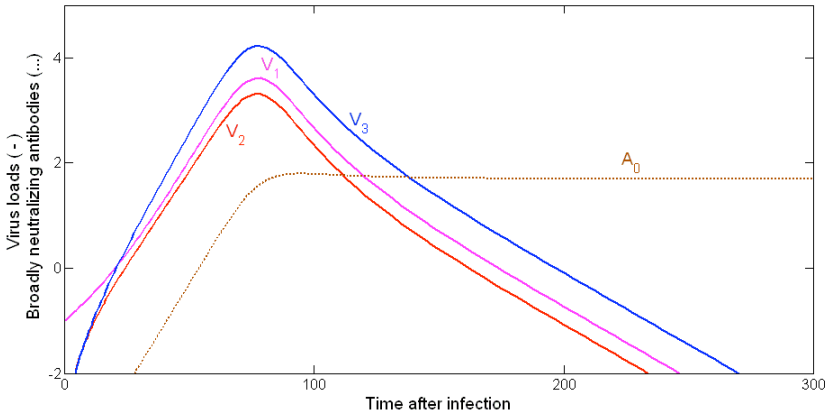
For $n = 2$ and $\mu_{11} = 1-\alpha,\ \mu_{12} = \alpha, \mu_{21} = \mu_{22} = 0$

$$\Omega = \frac{\frac{K}{K_0}\left(\frac{\lambda}{\lambda_0}+\frac{K_0}{K}\right)\left(\frac{\lambda}{\lambda_0}+2\frac{K_0}{K}\right)}{\left(1+\frac{\lambda}{\lambda_0}\right)\left\{\left(3\frac{\lambda}{\lambda_0}+4\frac{K_0}{K}\right)-\alpha\left(2\frac{\lambda}{\lambda_0}+4\frac{K_0}{K}\right)+\sqrt{\left(\left(3\frac{\lambda}{\lambda_0}+4\frac{K_0}{K}\right)-\alpha\left(2\frac{\lambda}{\lambda_0}+4\frac{K_0}{K}\right)\right)^2-8\left(\frac{\lambda}{\lambda_0}+\frac{K_0}{K}\right)\left(\frac{\lambda}{\lambda_0}+2\frac{K_0}{K}\right)(1-\alpha)^2}\right\}}$$

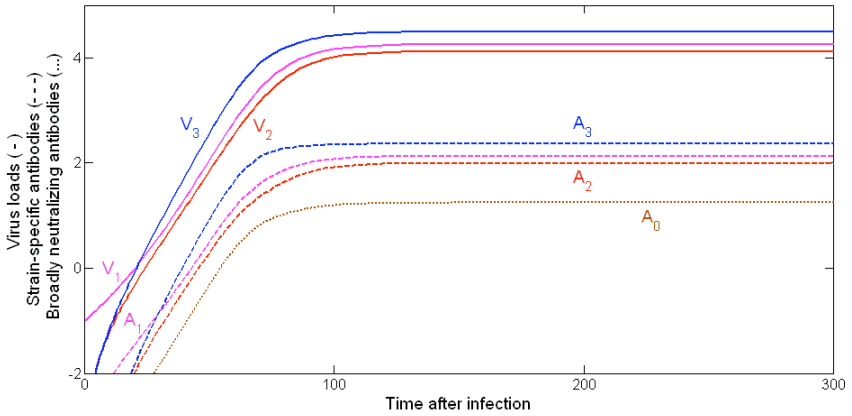
# Model prediction

For parameters

$$\Omega K_0 \frac{a}{\beta} < r < K_0 \frac{a}{\beta}$$




- Viruses are cleared with no competition.
- Viruses persist with competition.



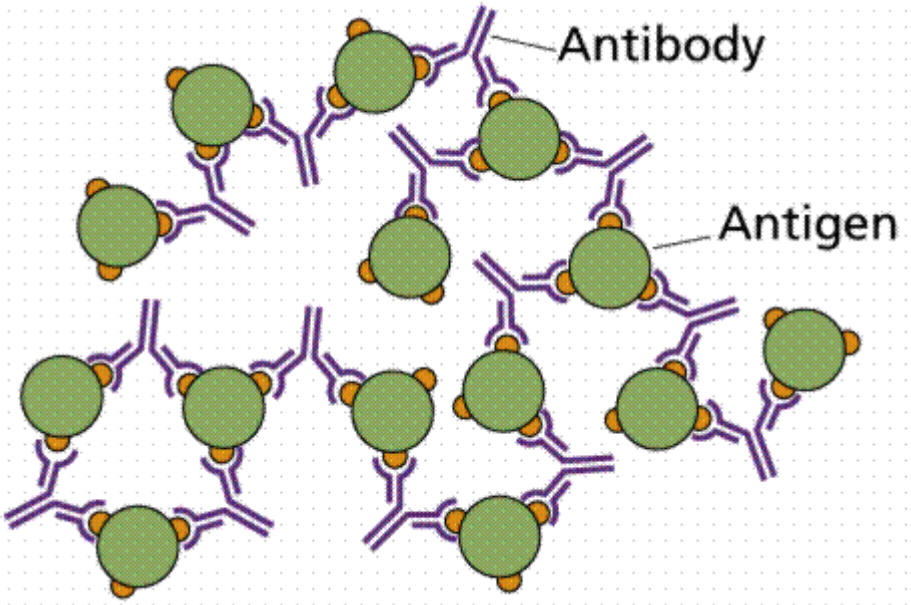
# Summary

- Broadly neutralizing antibodies alone can control multiple HIV infections.
- Additional immune events directed against specific HIV viral strains weaken the immune system defense, by limiting the growth of B cells producing broadly neutralizing antibodies.
- Under global resource limitation, HIV will be controlled only when there is no delay in a viral-specific antibody response. We know that this is not achieved in vivo.
- Inferences:
  - Increase in $K_0$.
  - Decrease in $\lambda_0$.

- How much antibody is needed for protection?

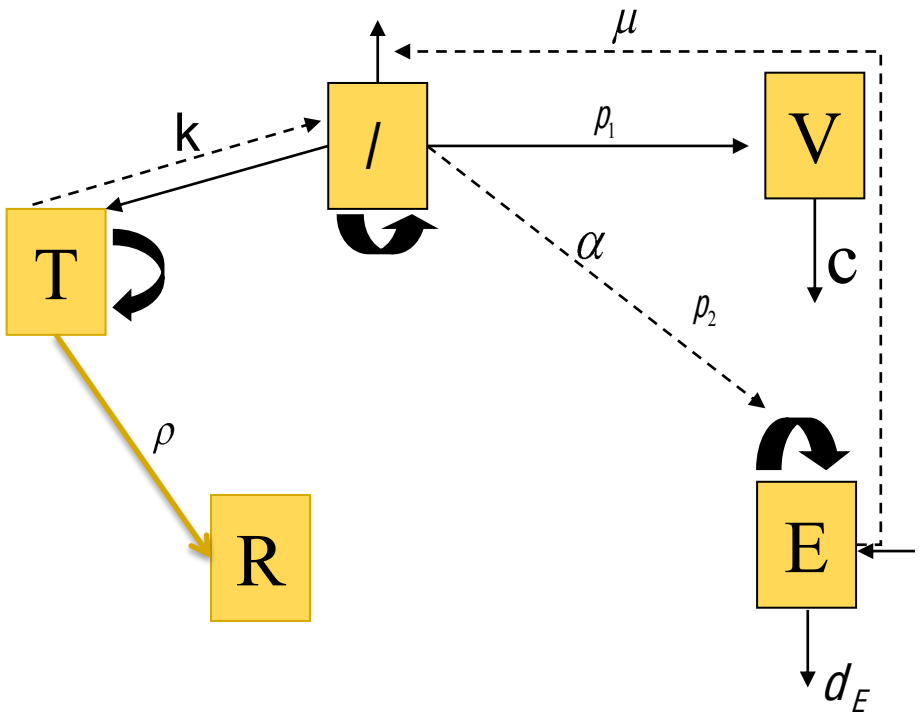
- vitro/vivo

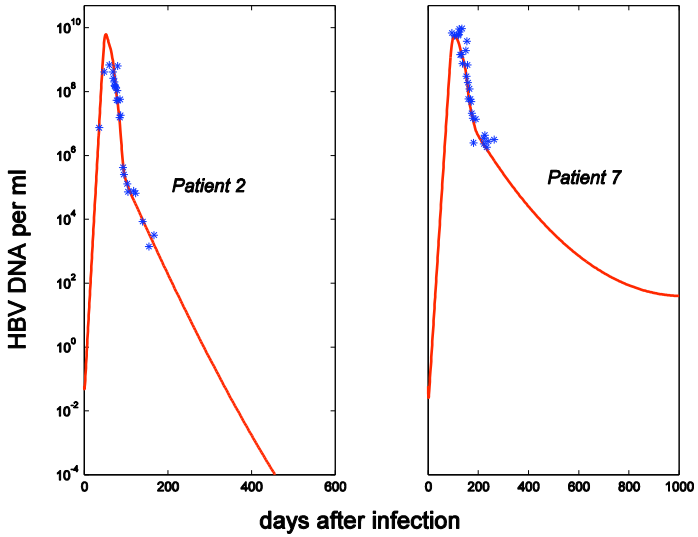
- How many surface antigens have to be occupied by antibodies?




*http://gened.emc.maricopa.edu*

# 2. Hepatitis B

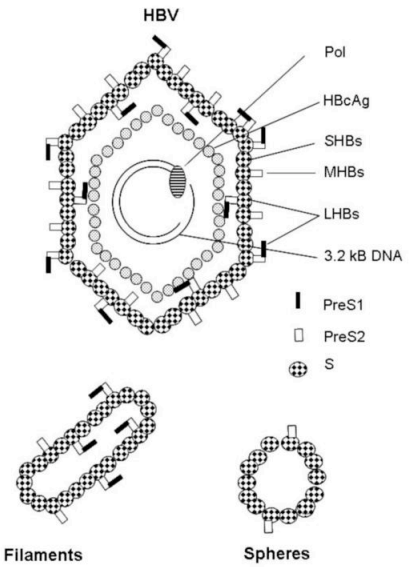


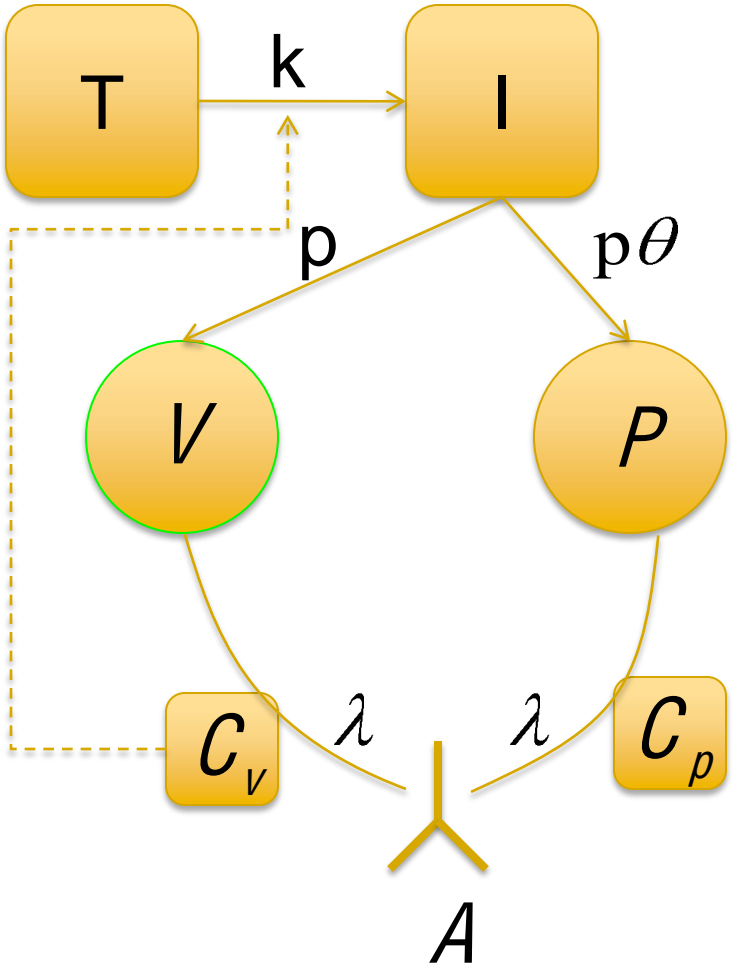

[Ciupe et al, *JTB* 2007, *PNAS* 2007]

# Antibody responses

- Efficient vaccine that induces *anti-HBsAg* antibodies and immune system memory.
- For people already infected
  - Role of antibody in disease pathogenesis.
  - Anti-HBs antibody is detectable after the resolution of acute infection.
  - Inhibit the spread of infection, but do not affect viral replication (Zhang, *J. Virol*, 2004).
  - Subviral particles (1000-10,000 more than virus) may serve as a decoy.



# Antibody model




Model equations:

$$\frac{dT}{dt} = rT(1-\frac{T+I}{T_{max}}) - kVT$$

$$\frac{dI}{dt} = rI(1-\frac{T+I}{T_{max}}) + kVT - \rho I$$

$$\frac{dV}{dt} = pI - cV + k_{-}C_V - k_{+}AV$$

$$\frac{dP}{dt} = \theta pI - cP + k_{-}^{p}C_p - k_{+}^{p}AP$$

$$\frac{dC_V}{dt} = -k_{-}C_V + k_{+}AV - c_{AV}C_V$$

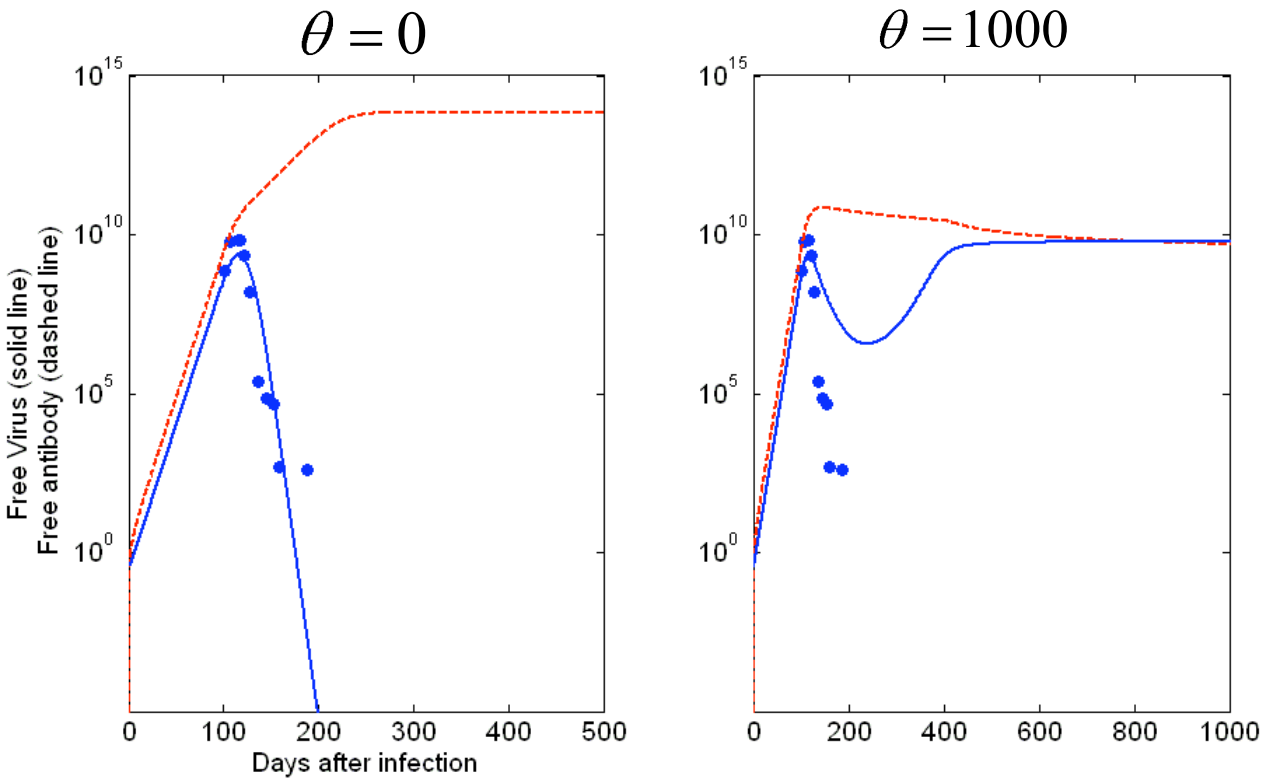
$$\frac{dC_p}{dt} = -k_{-}^{p}C_p + k_{+}^{p}AP - c_{AV}C_p$$

$$\frac{dA}{dt} = \lambda(V+P) + A(a-\beta A) + k_{-}C_V - k_{+}AV + k_{-}^{p}C_p - k_{+}^{p}AP$$

# Things to consider

- Different binding rates
- Different removal rates
- Delay in antibody production
- Increase the binding, so that most antibodies are in complexes
- Combined effect of immune responses

# Numerical results




Antibody responses to subviral particles lower the responses directed at virus particles leading to chronic infections.

# Conclusions

- Competition between antibody producing B cells alone can explain the inefficacy of antibodies to control viral infection
  - Most fit antibody wins
  - Of the limited amount of antibody present, most bind non-infectious particles which exceeds virus titers.
- Use this knowledge in a vaccine trial

# Acknowledgments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