Probabilistic models for pathogen evolution within and between hosts

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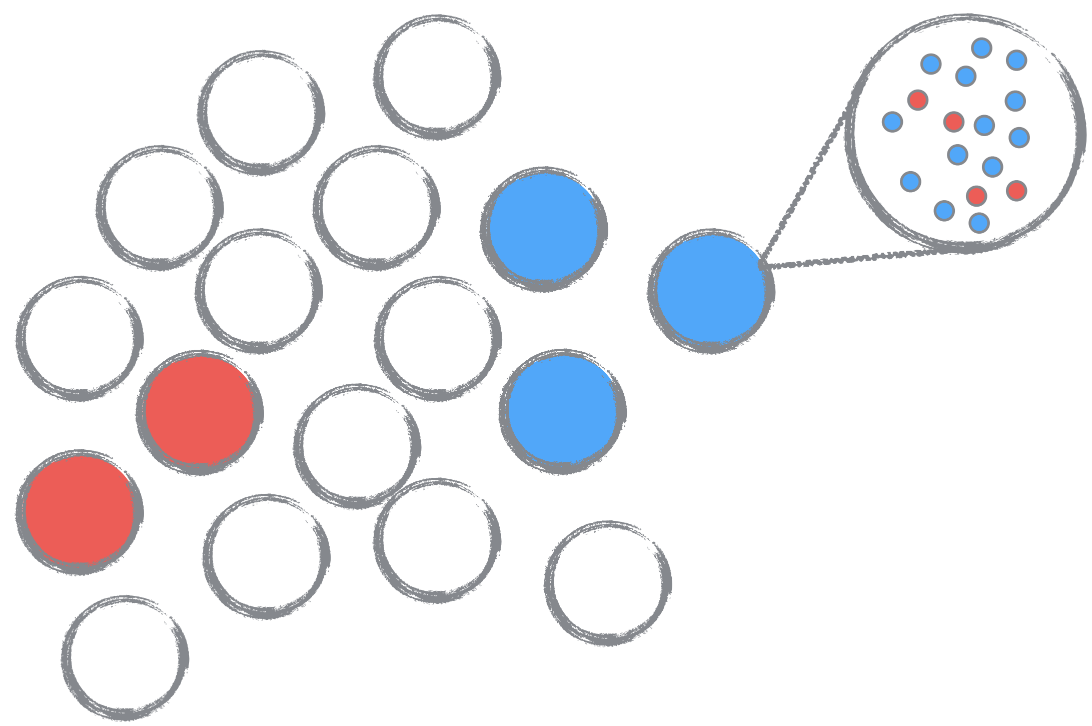
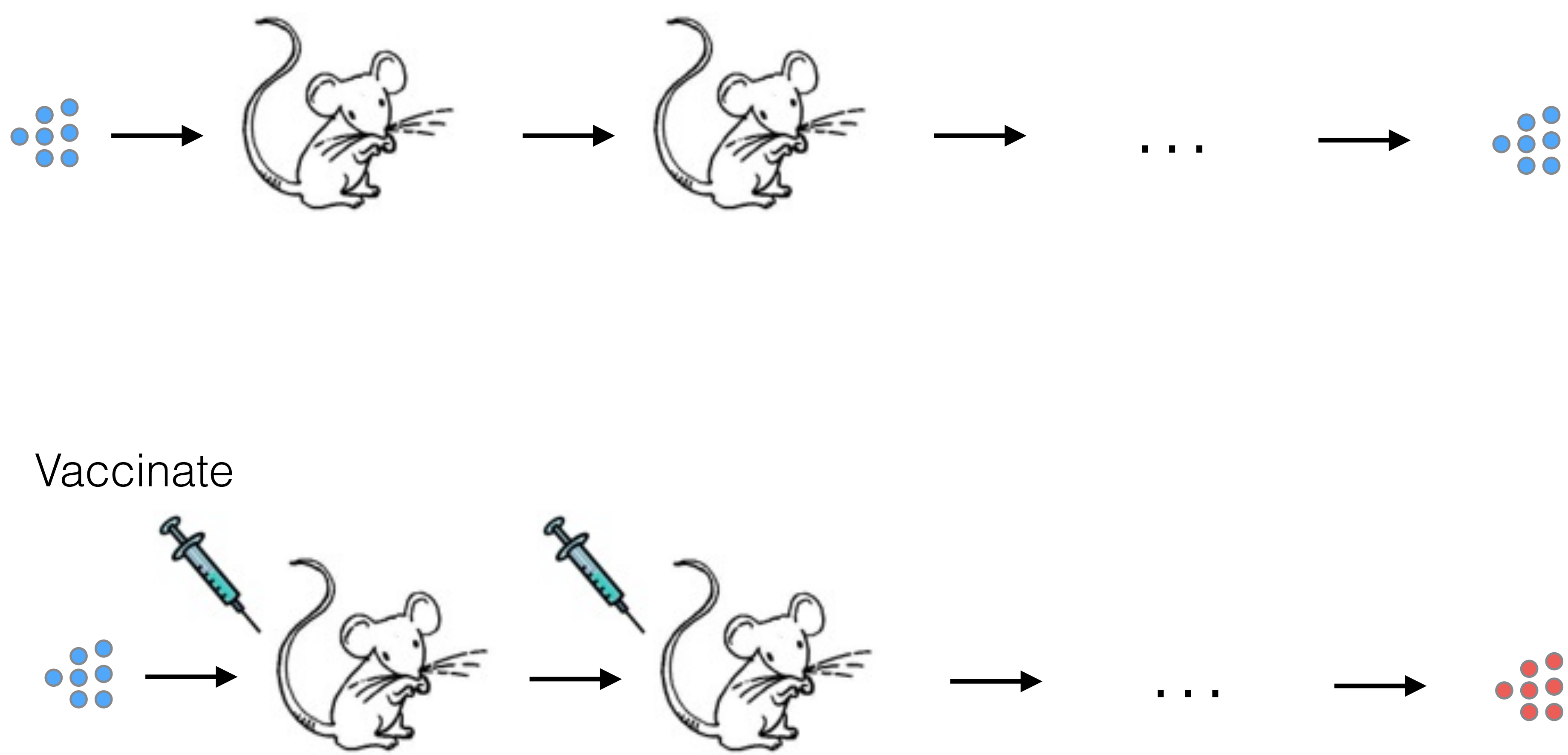
Pathogen evolution



- Influenza
- HIV
- General two-level selection

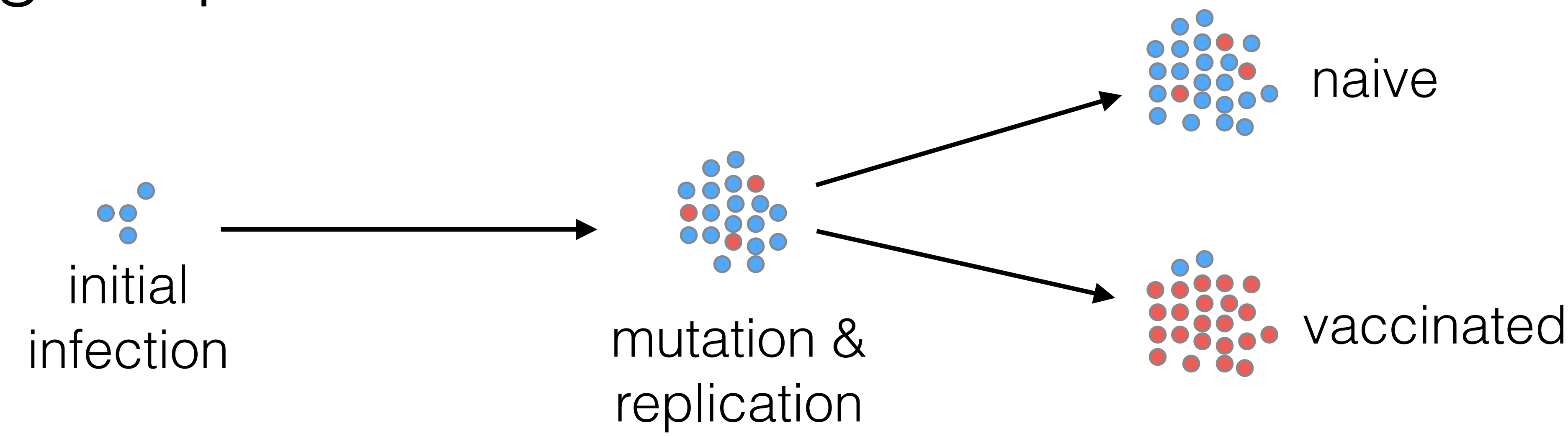
Antigenic drift of influenza

(with K Koelle, JC Mattingly, MC Reed)

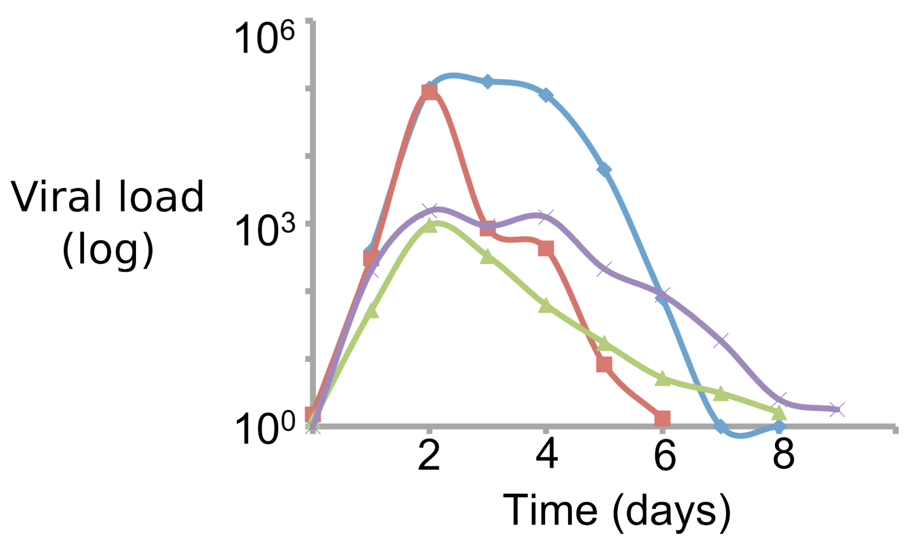


Viral dynamics and evolution

Passage experiments



Within-host influenza viral dynamics (colors are different studies)



ODEs with Poisson mutation

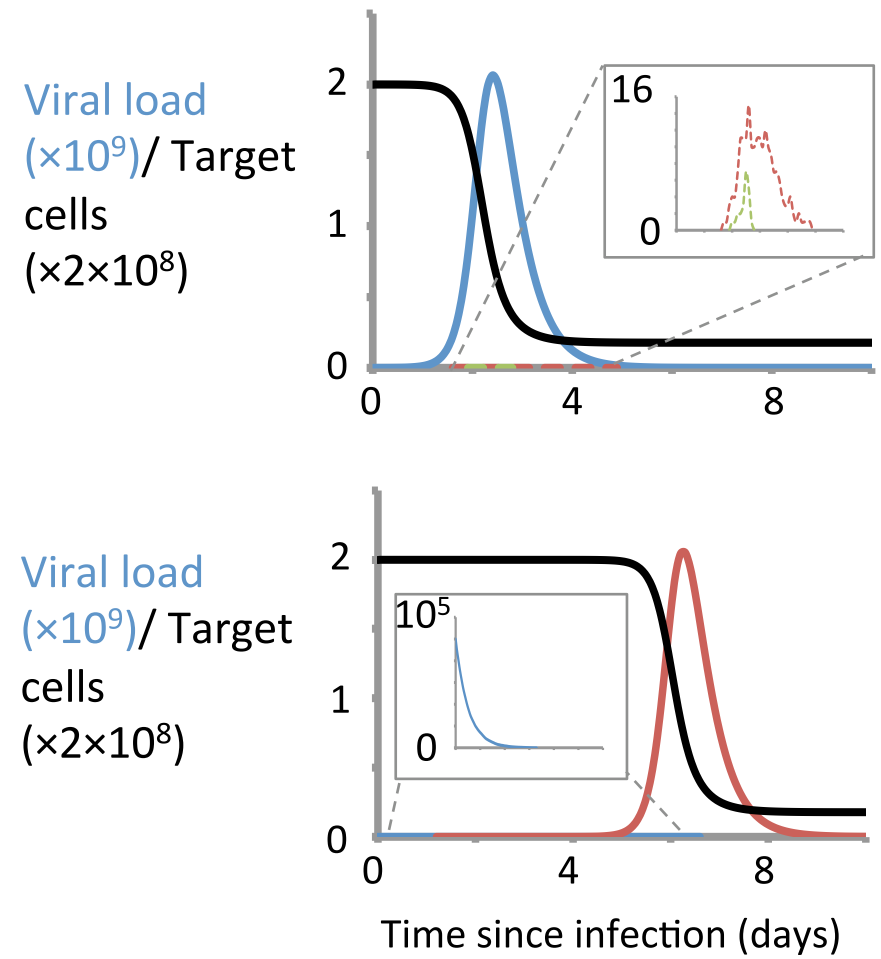
$$\dot{C} = -\beta C V_r - \beta C V_m$$

$$\dot{V}_r = \gamma C V_r - \delta_r V_r$$

$$\dot{V}_m = \gamma C V_m - \delta_m V_m$$

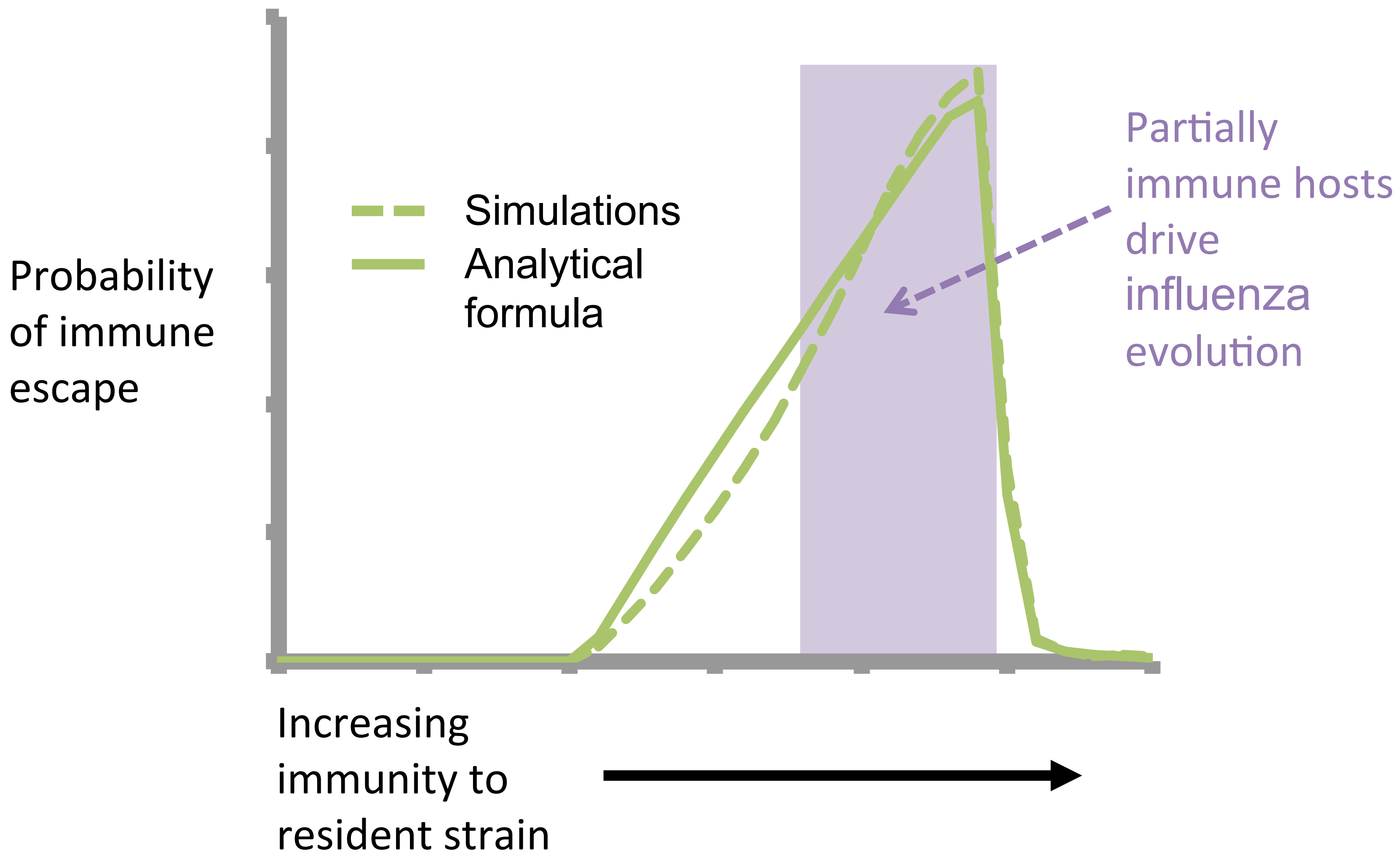
$$V_r(0) = V_0 \qquad C(0) = C_0$$

$$\text{mutations occur at rate } \mu V_r(t)$$

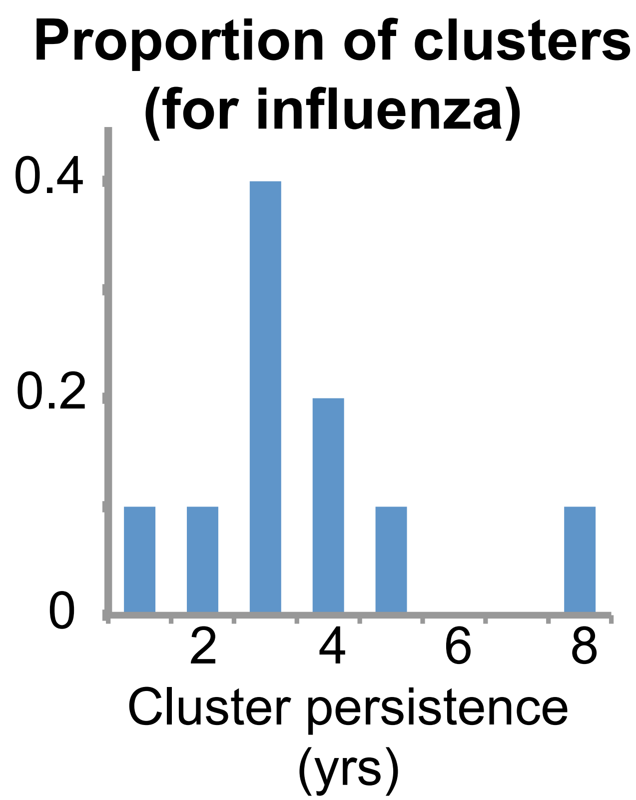


Luo, Reed, Mattingly, Koelle *Interface* 2012

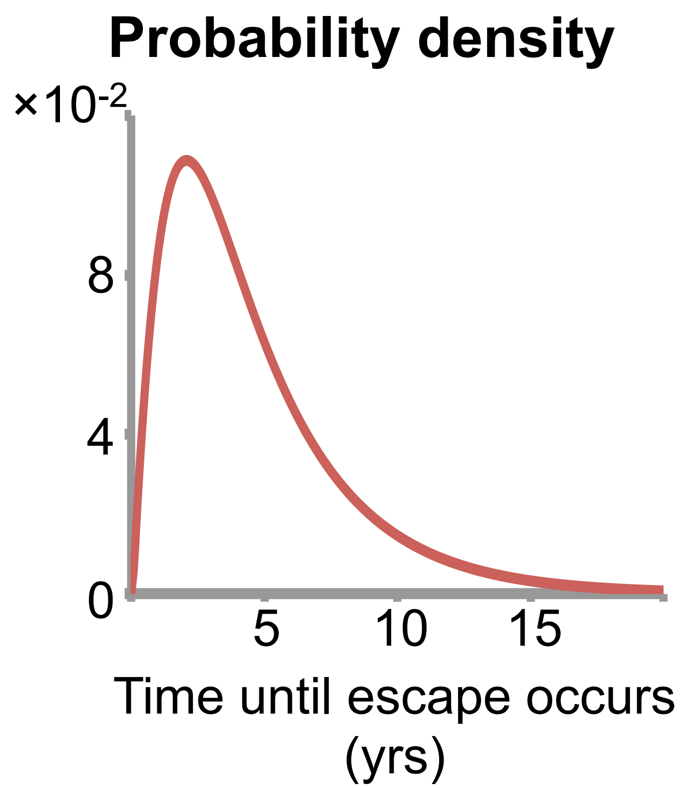
Results: Within hosts



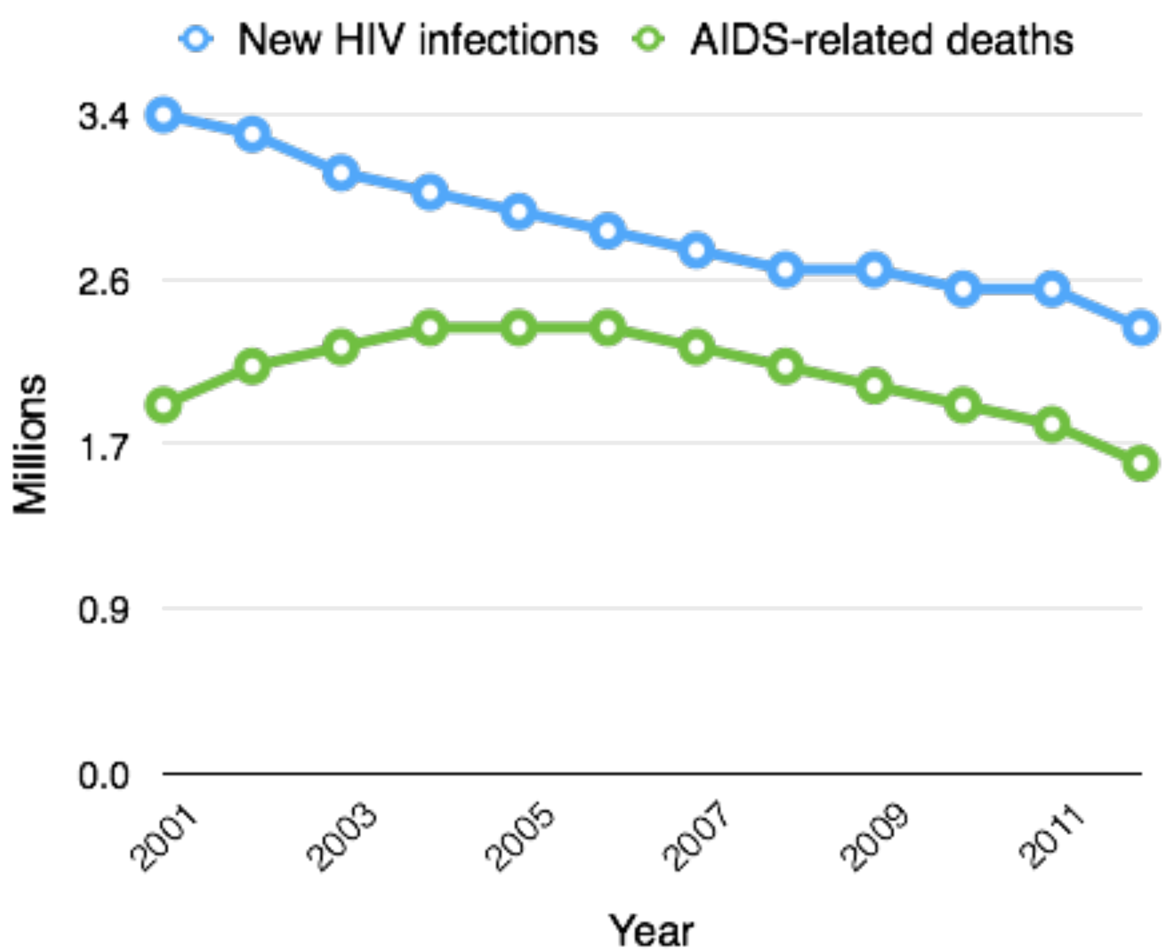
Results: Population level



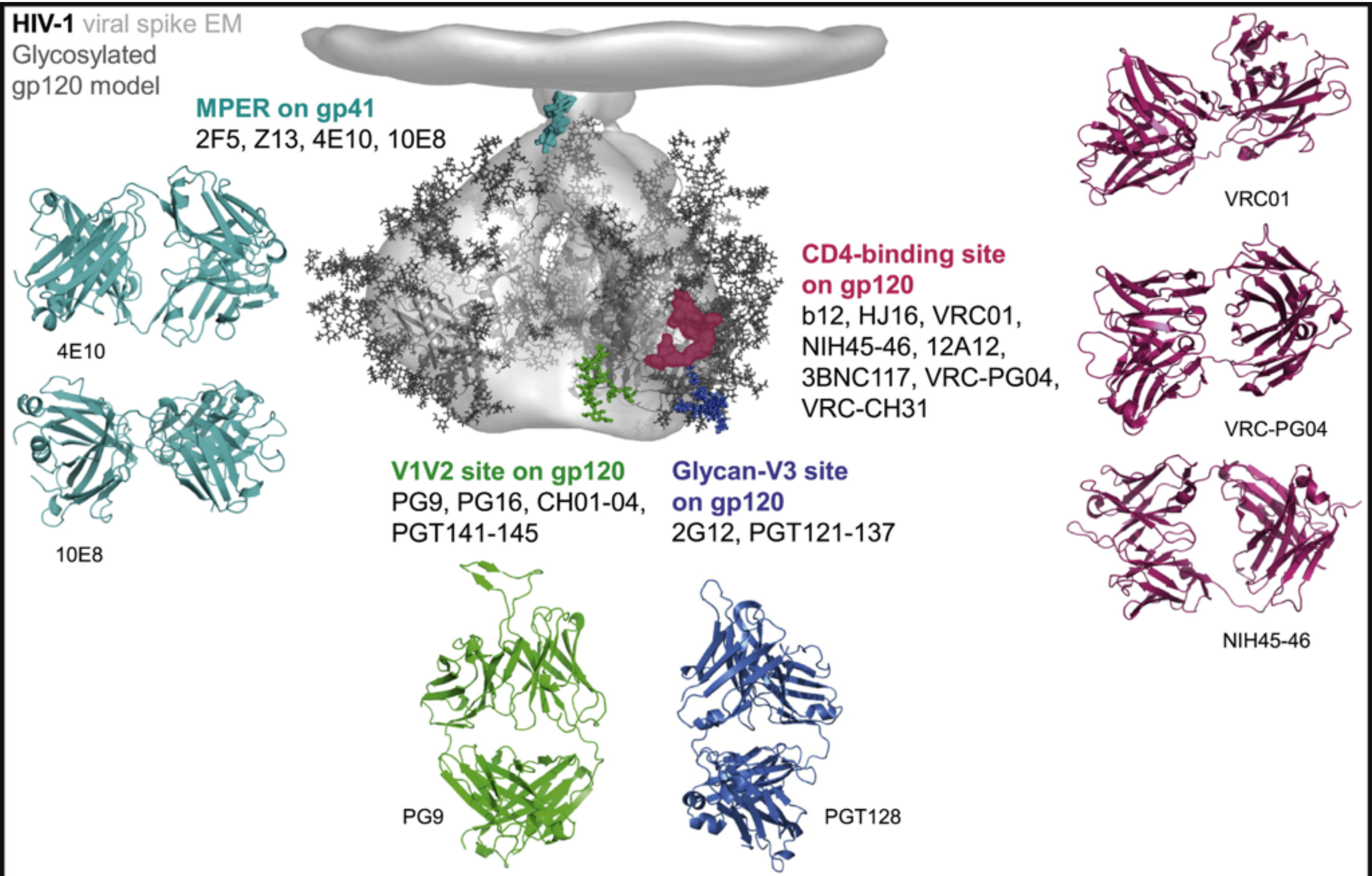
Koelle et al *Epidemics* 2009



Broadly neutralizing HIV antibodies
(with A Perelson)

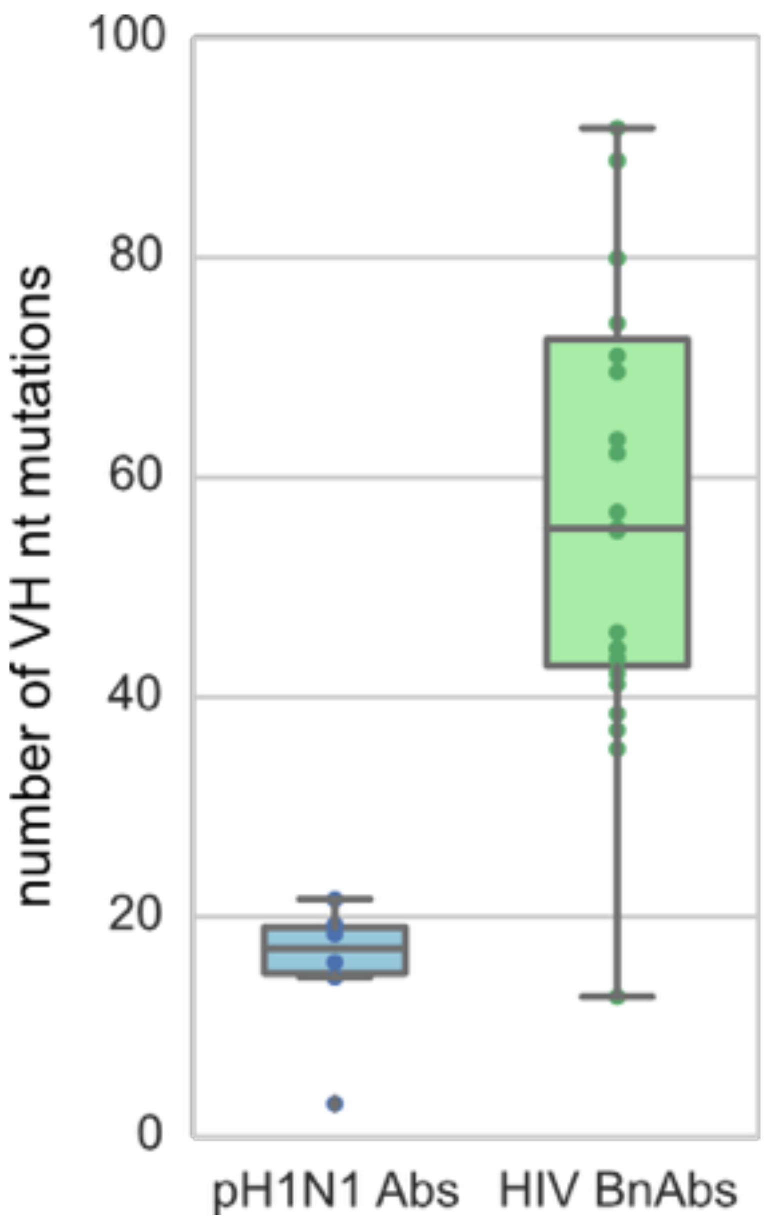


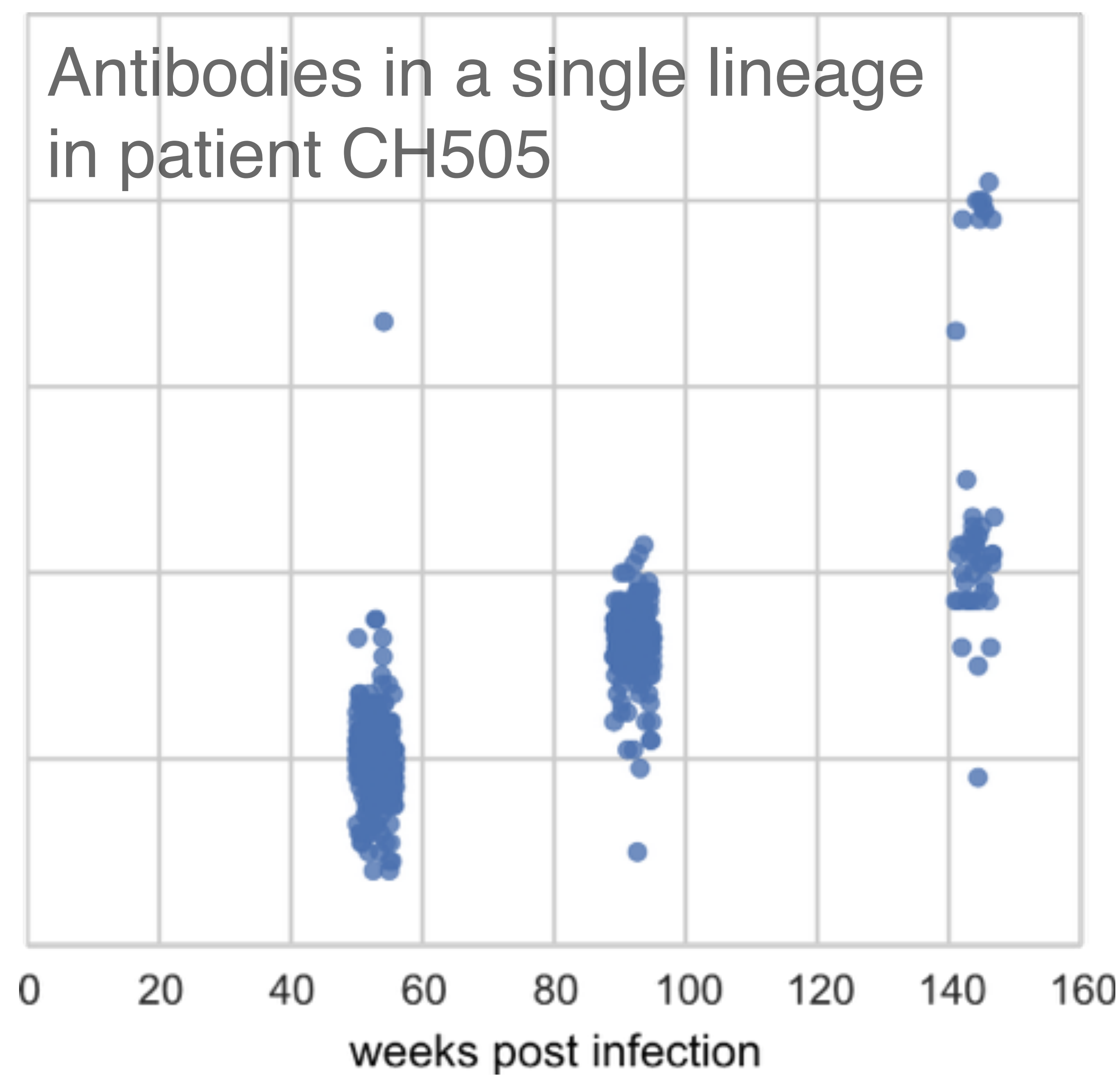
Data from UNAIDS Global fact sheet 2012



Kwong & Mascola *Immunity* 2012

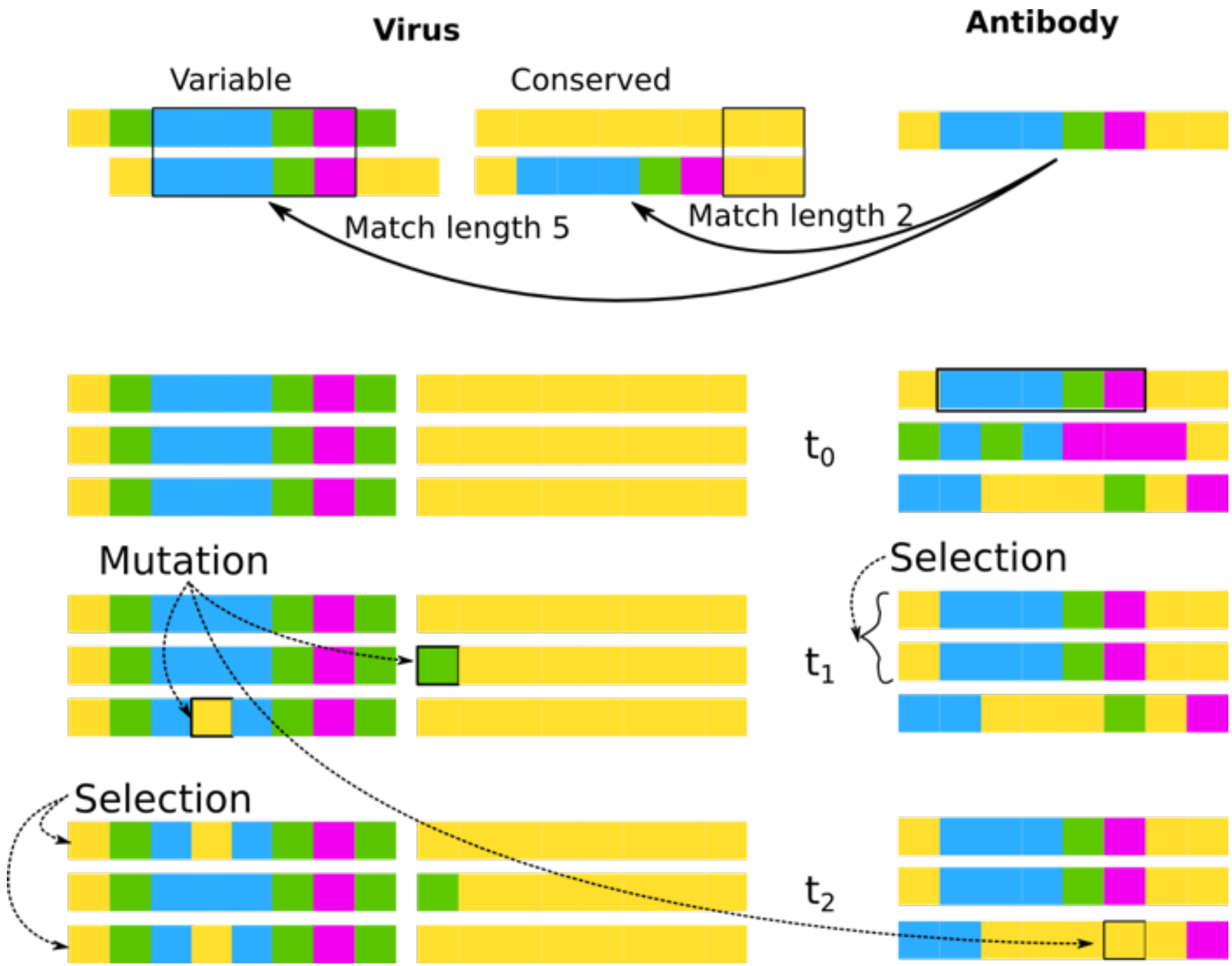
Broadly neutralizing HIV antibodies are highly mutated



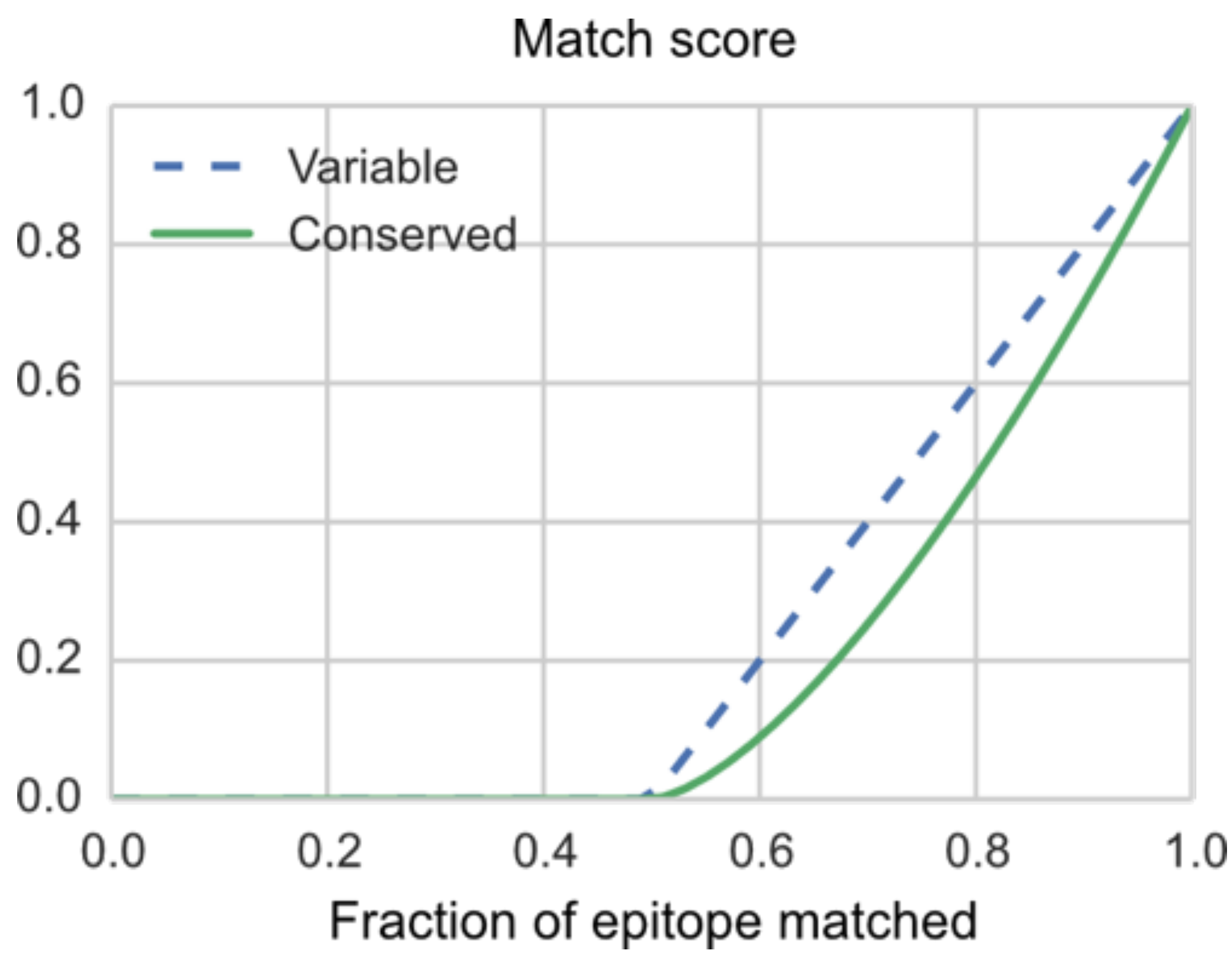


Data from: Wrammert et al J Exp Med 2011, Kwong & Mascola Immunity 2012, hiv.lanl.gov

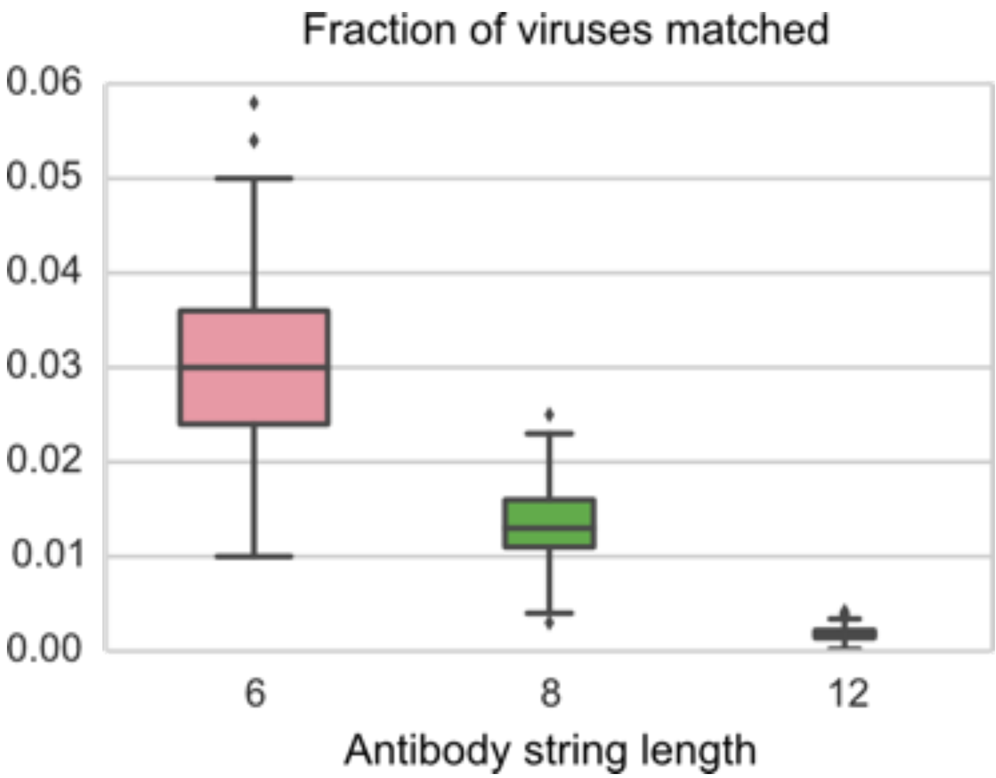
‘Bitstring’ model

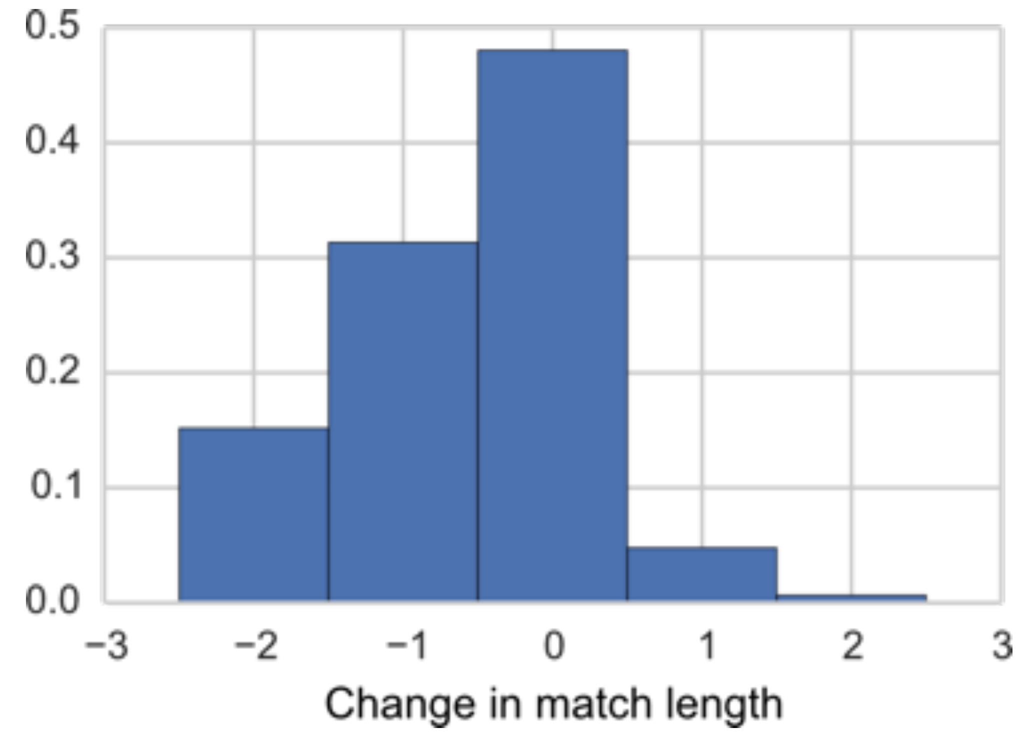


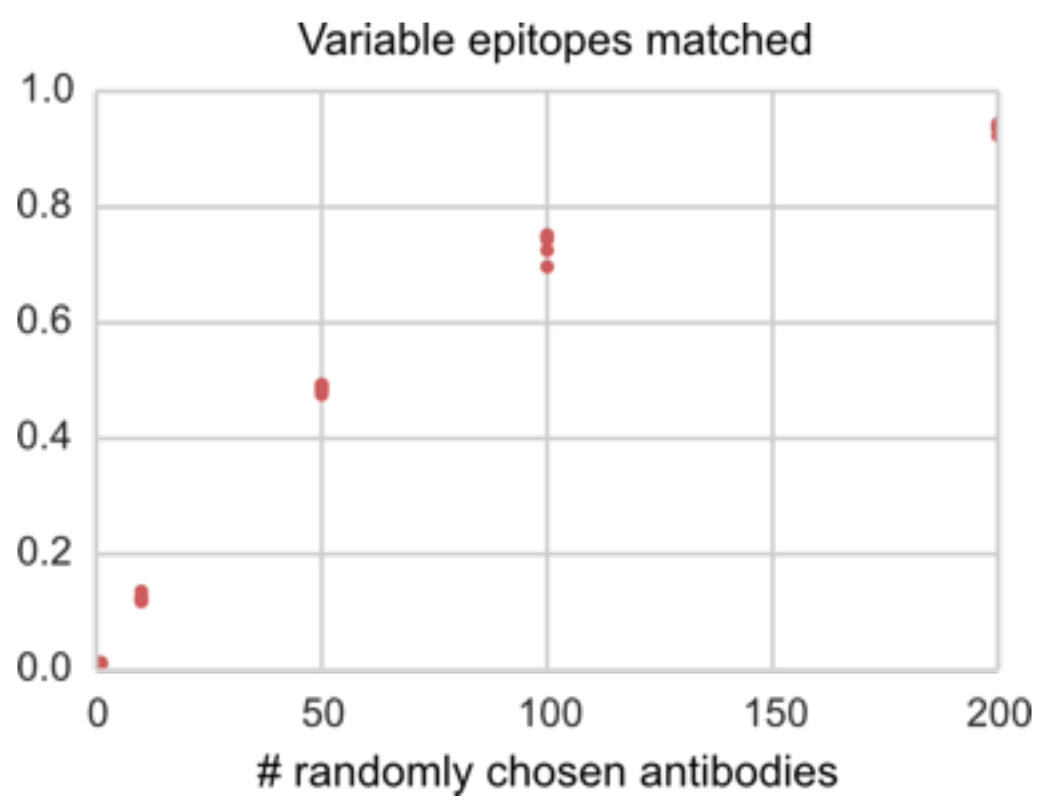
Conserved region is less accessible



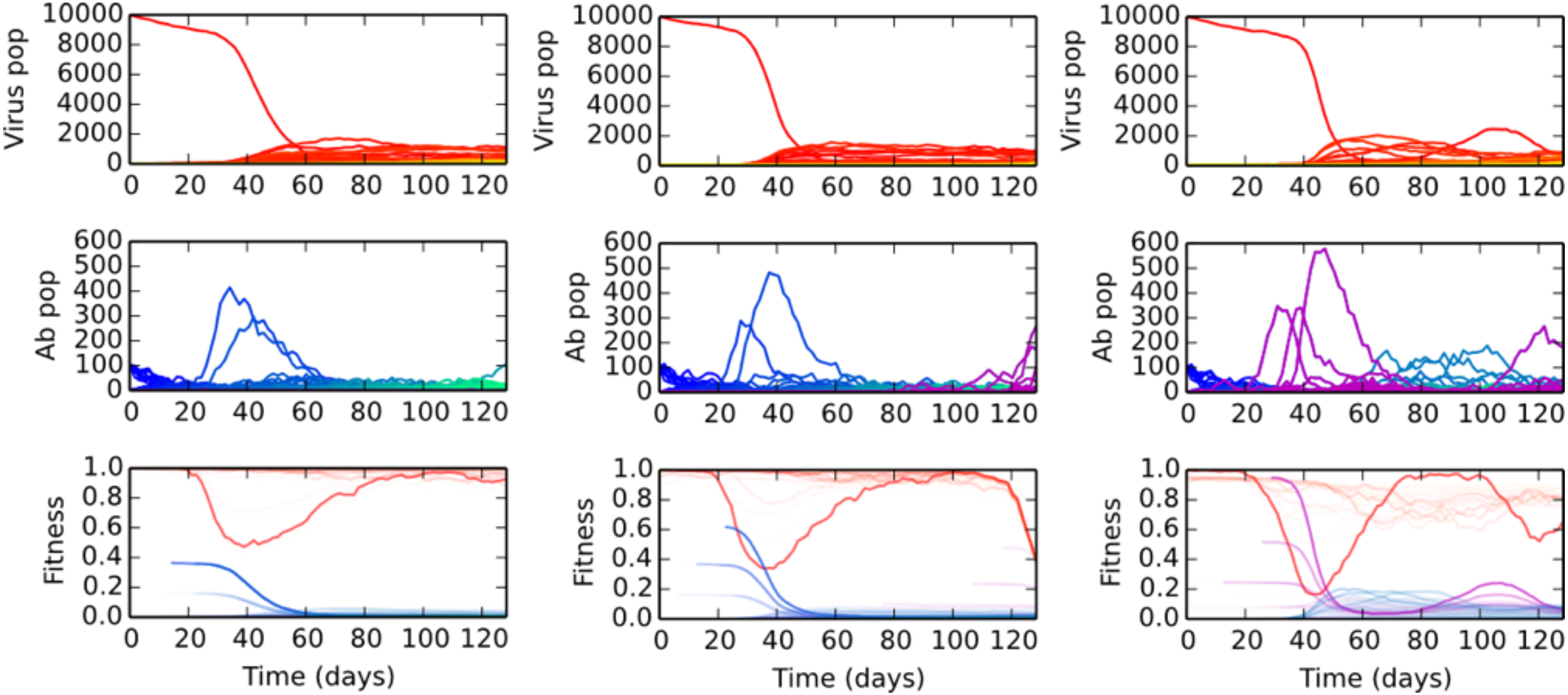
Binding properties





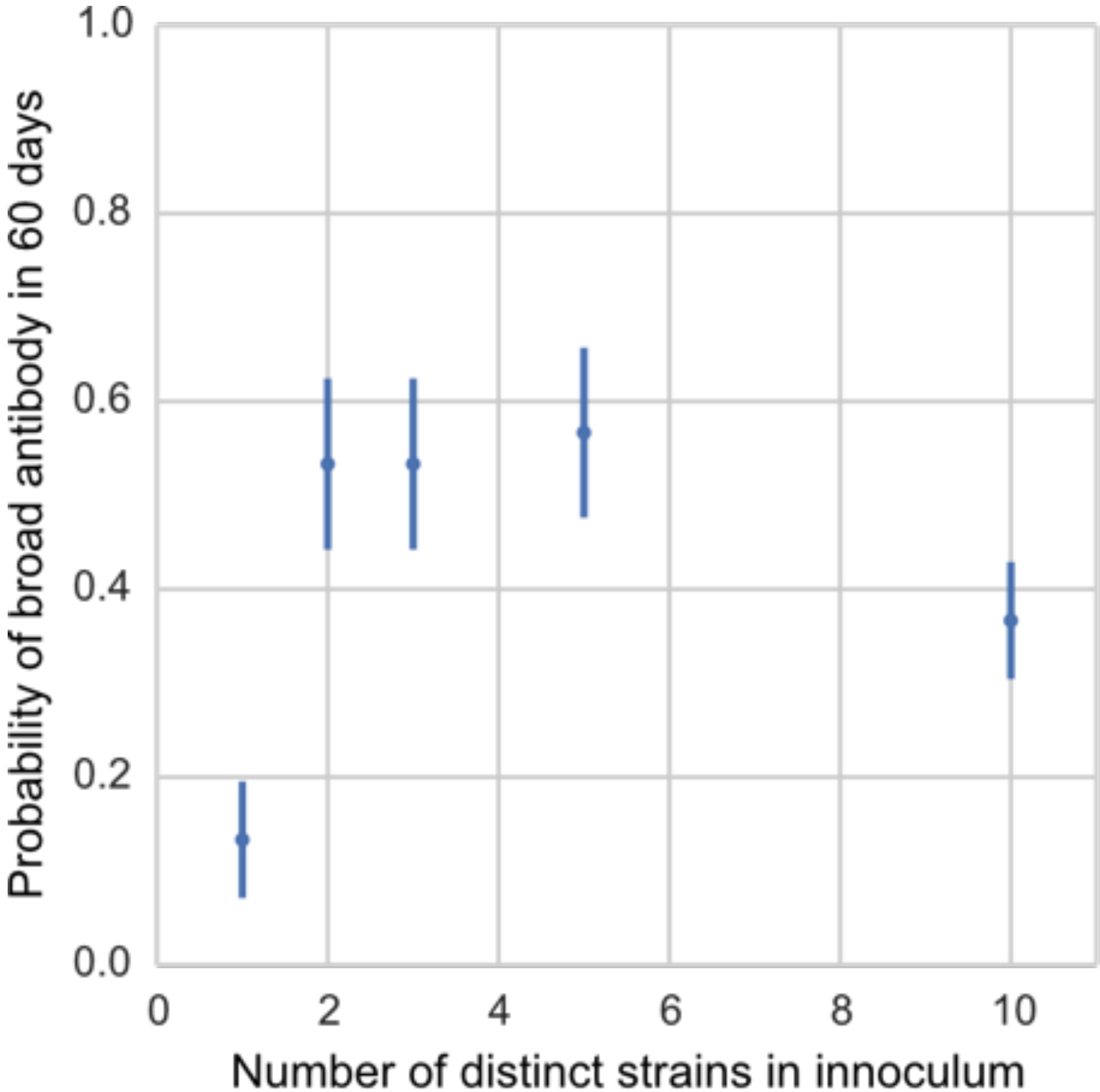


Infection with single strain

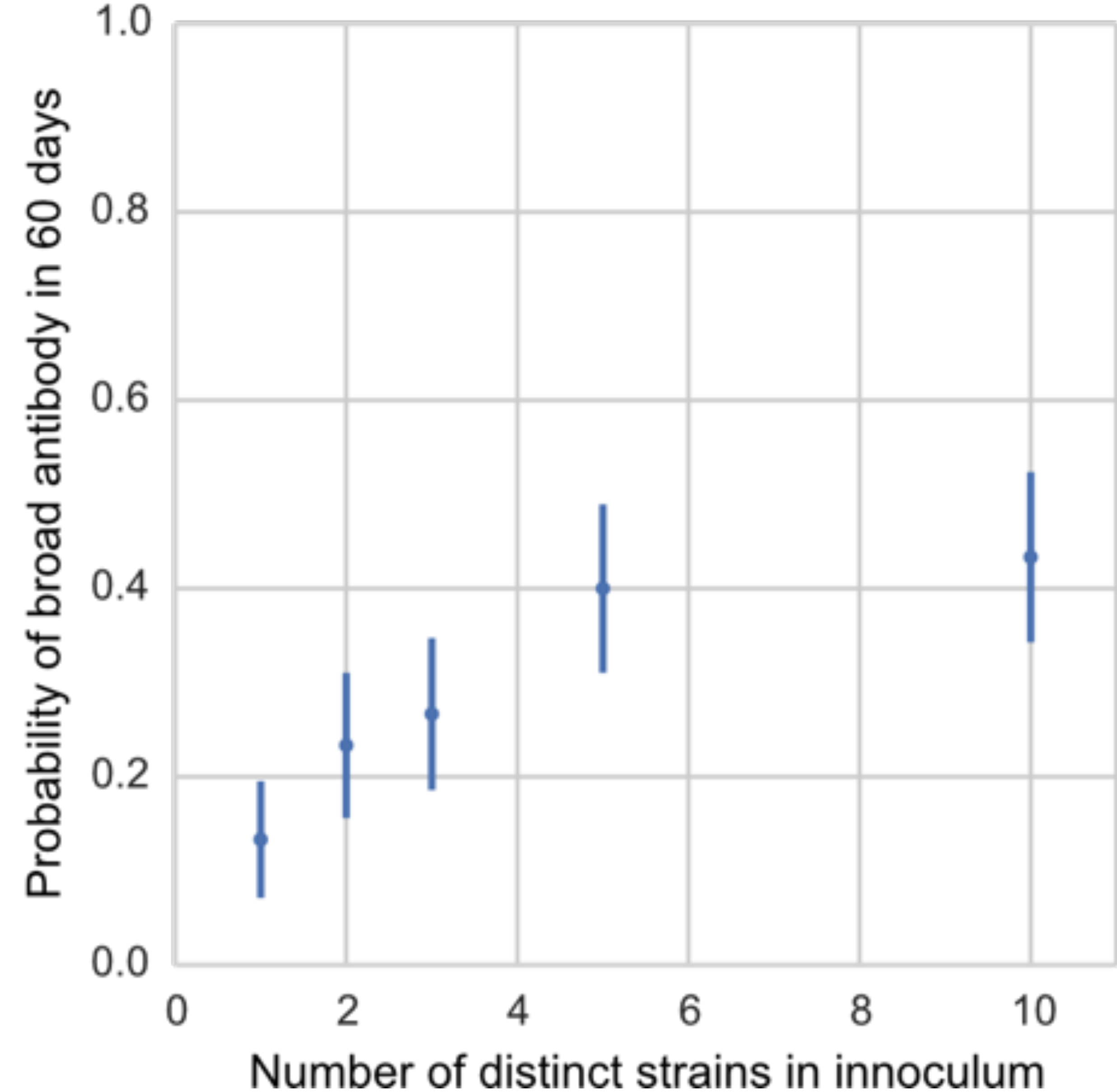


Vaccine strategies

Strains selected uniformly at random



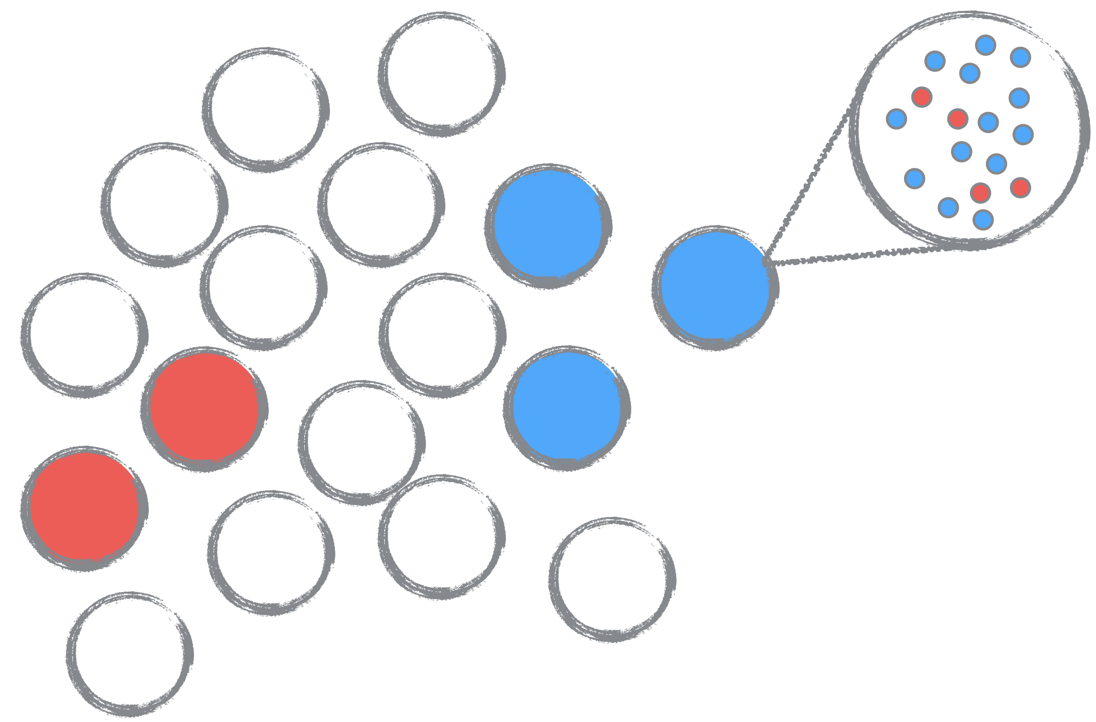
Strains are nearest neighbor mutants



Bars show +/-1 SE

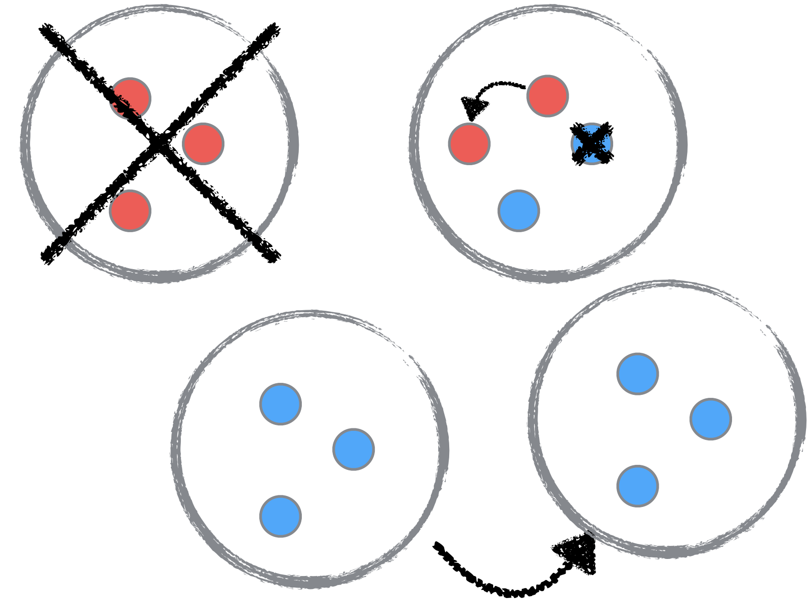
Multilevel selection in host-pathogen systems
(with JC Mattingly)

- myxomatosis-rabbit
- human papillomavirus
- malaria

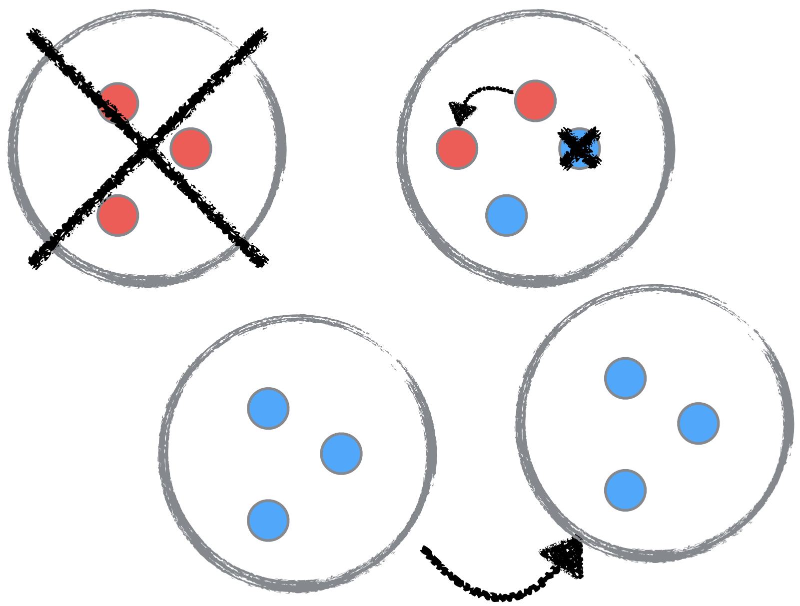


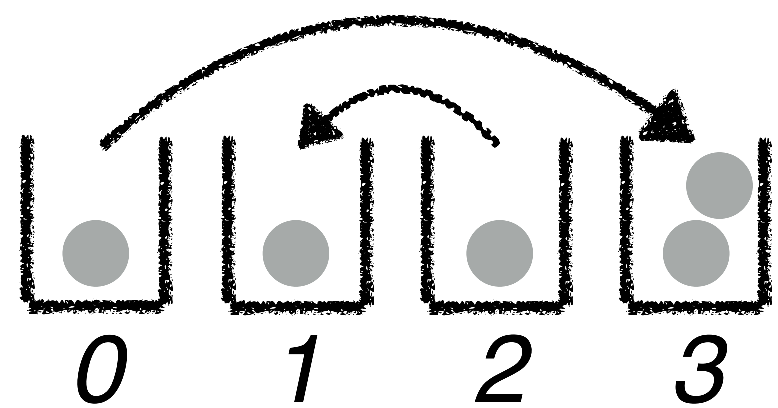
Suppose:

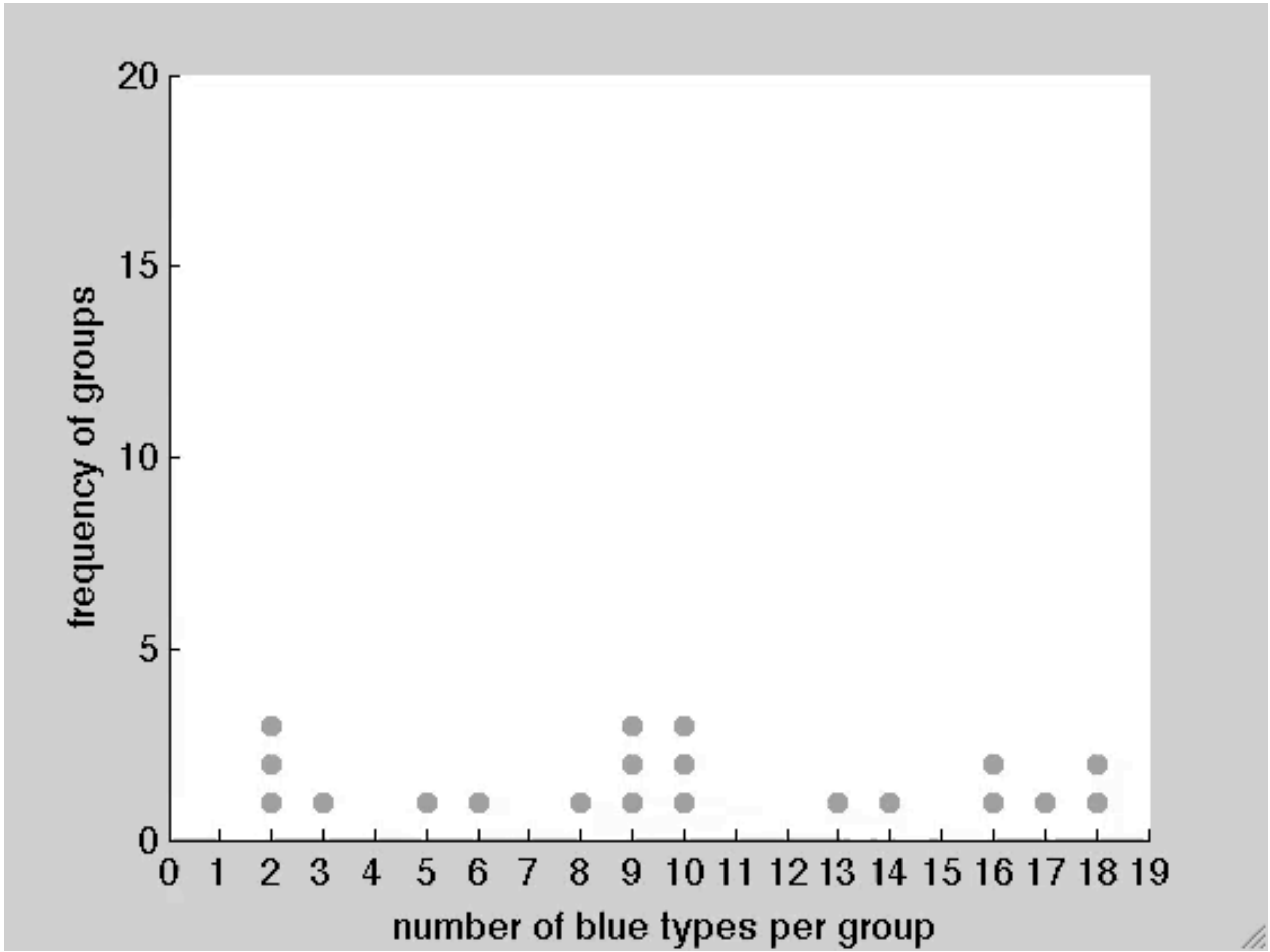
- m groups, n individuals per group
- red beats blue in each group, $1+s$ vs 1
- bluer groups beat redder groups, $1+r\frac{k}{n}$, were $\frac{k}{n}$ is fraction of blue
- $w = \frac{\text{rate of group-level events}}{\text{rate of individual-level events}}$



Luo *J Theor Biol* 2014




0
1
2
3



Recall: blue types beneficial at group level

- Let X_t^j be the position of ball j on the (rescaled) 1-d lattice $\{0, \frac{1}{n}, \ldots, 1\}$ at time t.
- Define the measure-valued process:

$$\mu_t^{m,n} = \frac{1}{m} \sum_{j=1}^{m} \delta_{X_t^j}$$

$\mu_t^{m,n}$ has transition rate matrix $R = R_1 + wR_2$ where:

$$R_1\left(v, v + \tfrac{1}{m}(\delta_{\frac{j}{n}} - \delta_{\frac{i}{n}})\right) = \begin{cases} mv(\frac{i}{n})i\left(1 - \frac{i}{n}\right)(1+s) & \text{if } j = i-1, i < n \\ mv(\frac{i}{n})i\left(1 - \frac{i}{n}\right) & \text{if } j = i+1, i > 0 \\ 0 & \text{otherwise} \end{cases}$$

$$R_2\left(v, v + \tfrac{1}{m}(\delta_{\frac{j}{n}} - \delta_{\frac{i}{n}})\right) = mv(\tfrac{i}{n})v(\tfrac{j}{n})(1 + r\tfrac{j}{n})$$

s: individual-level selection, r: group-level selection, w: relative rate of events, m: number of groups, n: number of individuals in each group

The deterministic limit of $\mu_t^{m,n}$:

$$\frac{\partial}{\partial t}\mu(t,x) = s\frac{\partial}{\partial x}\left[x(1-x)\mu(t,x)\right] + wr\mu(t,x)\left[x - \int_0^1 y\mu(t,y)dy\right]$$

The stochastic (Fleming-Viot) limit:

$$\begin{aligned}\partial_t \nu_t = \sigma\partial_x\left[x(1-x)\nu_t\right] + \partial_{xx}\left[x(1-x)\nu_t\right] \\ + w\alpha\rho\nu_t \cdot \left[x - \int_0^1 y\nu_t(y)dy\right] + w\alpha\sqrt{2\nu_t(1-\nu_t)}\dot{W}_t\end{aligned}$$

Long-term behavior of PDE

Suppose μ_0 is a density and k^* is such that

$$\mu_0^{(k)}(1) = 0 \text{ for all integers } k < k^* \text{ and } \mu_0^{(k^*)}(1) \neq 0$$

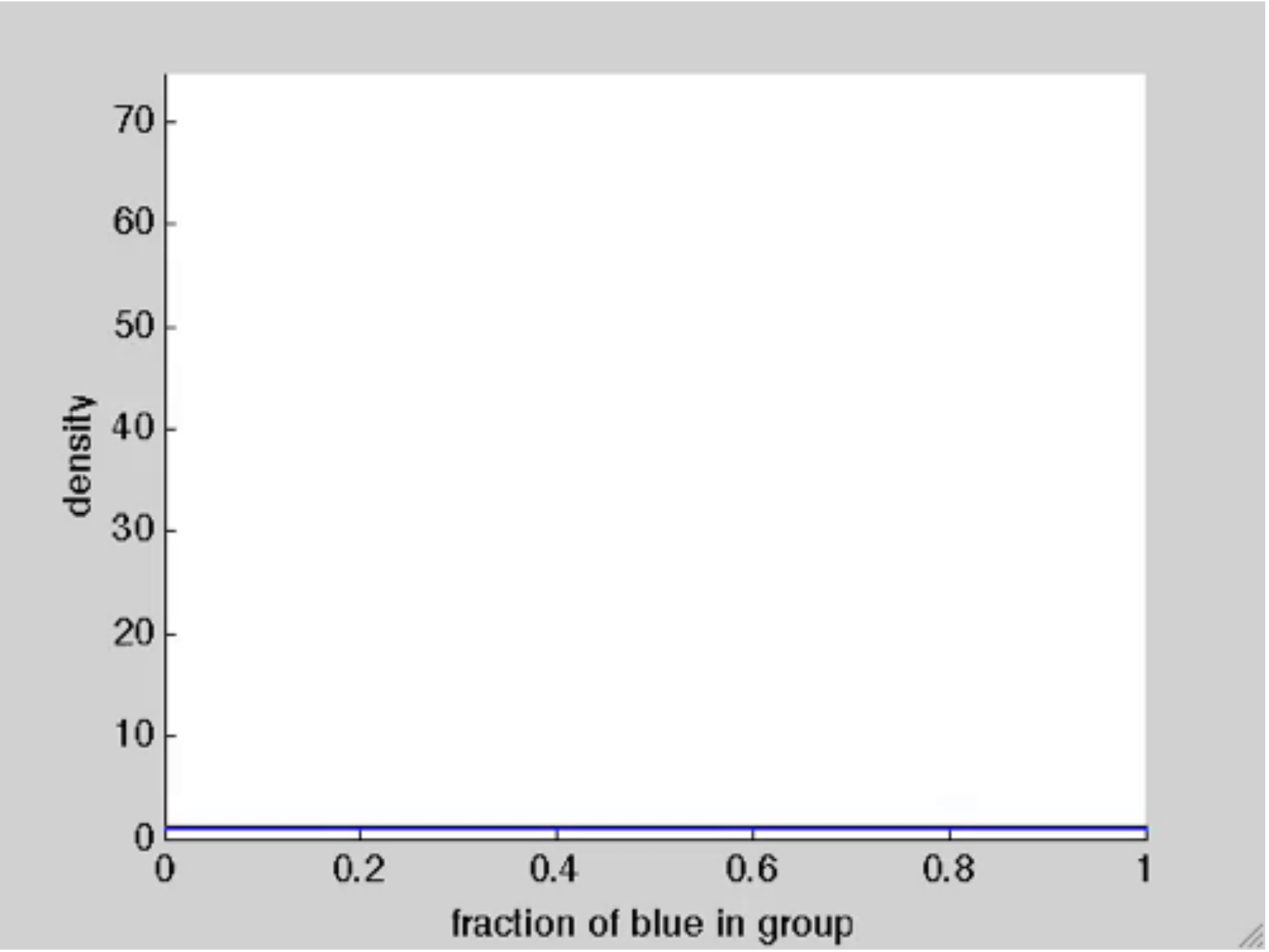
If $\lambda - 1 > k^*$,

$$\mu(t,x) \to \text{Beta}(\lambda - k^* - 1, k^* + 1) \ \text{ as } t \to \infty$$

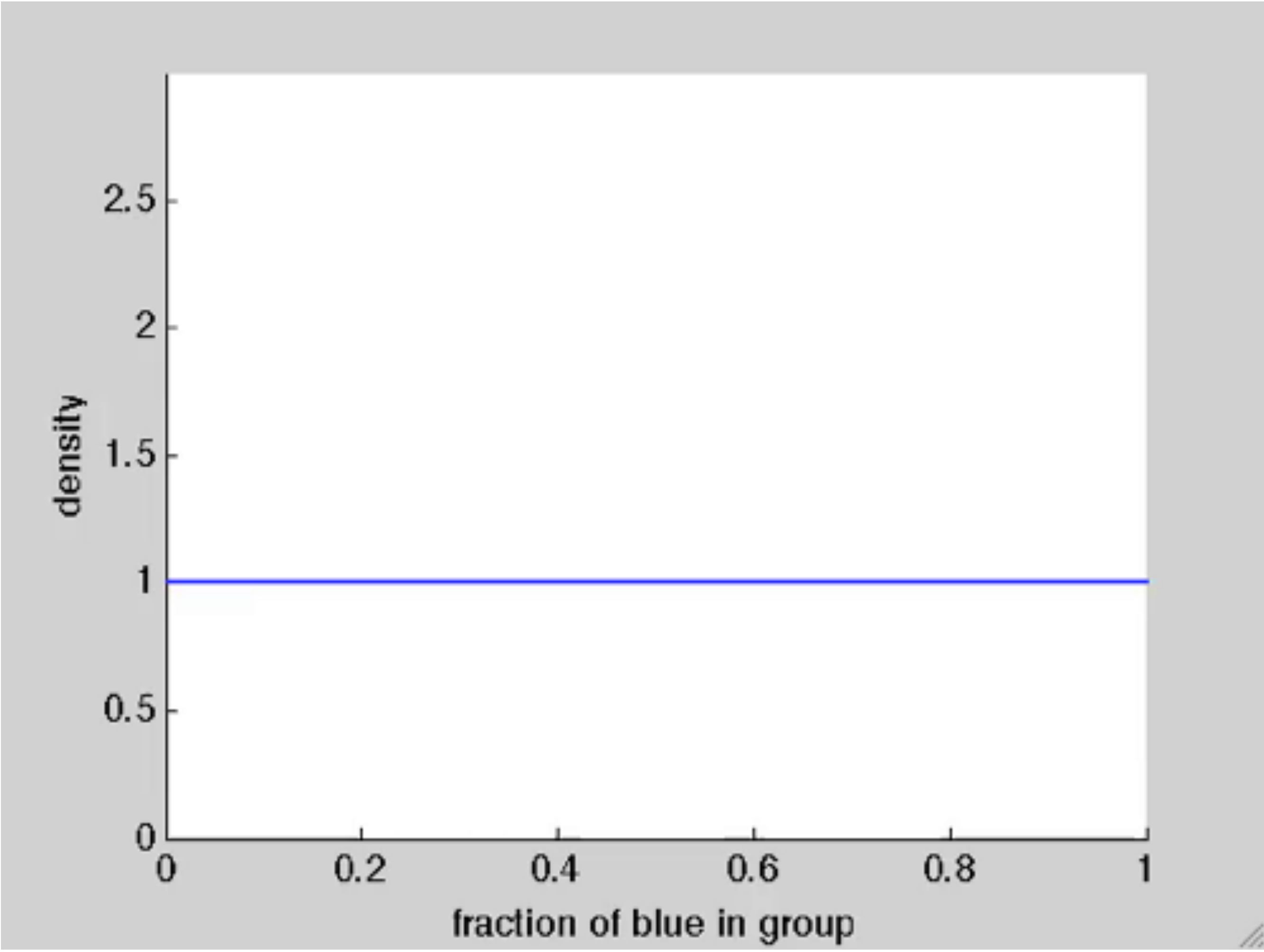
If $\lambda - 1 \leq k^*$,

$$\mu(t,x) \to \delta_0(x) \ \text{ as } t \to \infty$$

$\lambda = 1.5$



$\lambda = 4$

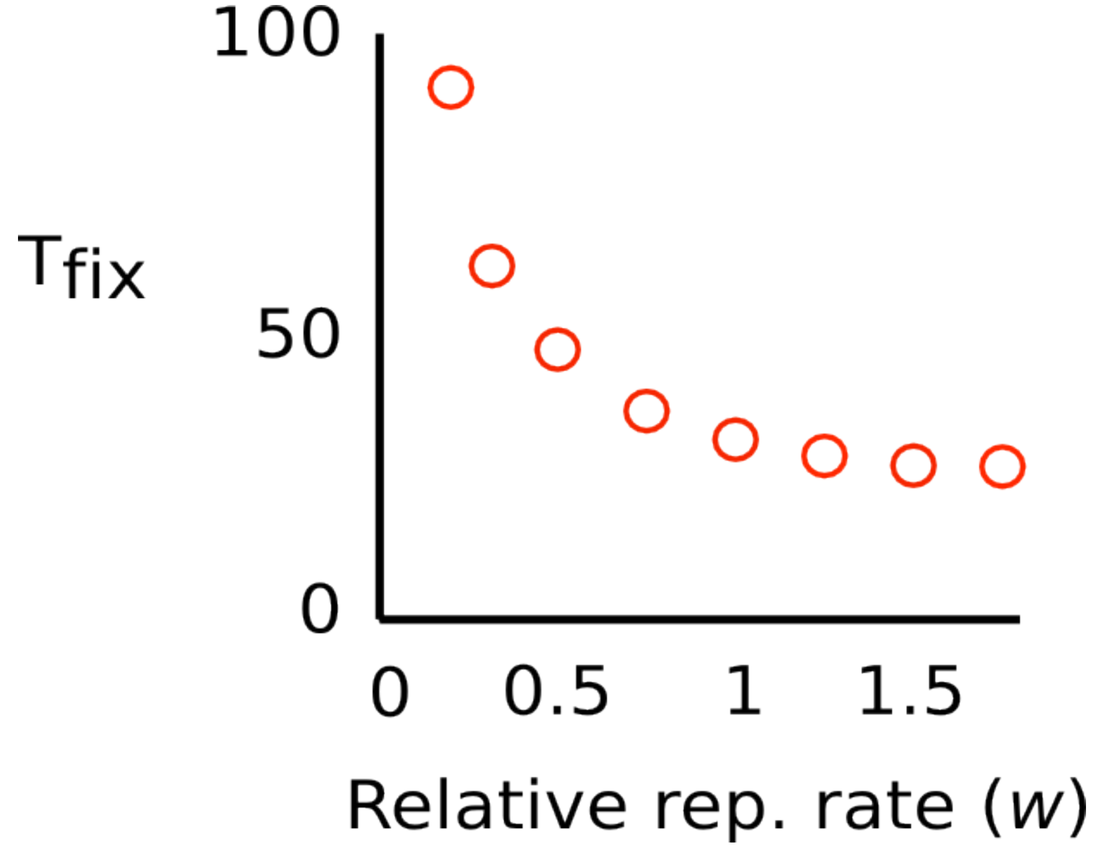


Properties of particle system

Relative rate of replication acts like group-level selection

$$\frac{\partial}{\partial t}\mu(t,x) = s\frac{\partial}{\partial x}\left[x(1-x)\mu(t,x)\right] + wr\mu(t,x)\left[x - \int_0^1 y\mu(t,y)dy\right]$$

$$\lambda := \frac{wr}{s}$$



What if *m* and *n* are finite?

$$\frac{\partial}{\partial t}\mu(t,x) = s\frac{\partial}{\partial x}\left[x(1-x)\mu(t,x)\right] + wr\mu(t,x)\left[x - \int_0^1 y\mu(t,y)dy\right]$$