Evolving antibody repertoire to vaccine and virus

evolutionary arms race and ecological feedback

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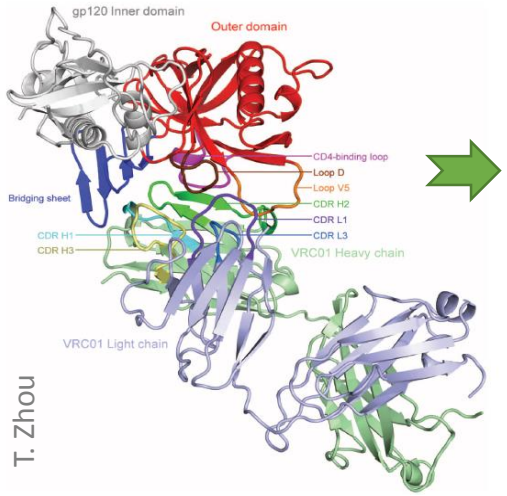
Antibody evolution is a collective phenomenon

Small scale

$10^{-9}m$

second



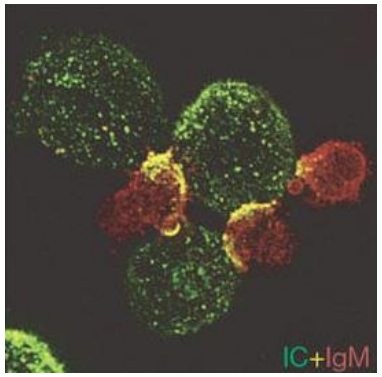
T. Zhou

Molecular interaction (antibody-antigen binding)

Intermediate scale

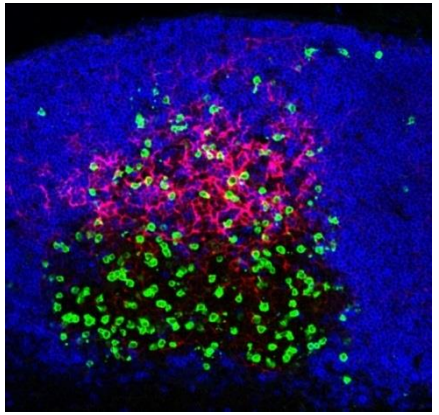
$10^{-6}m - 10^{-4}m$

min to hour



F. Batista

Cell-cell contact (immune synapse)



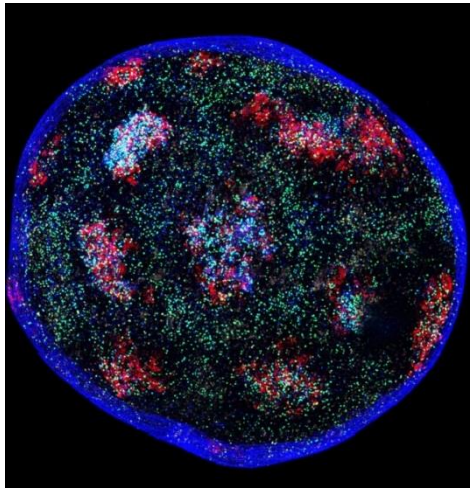
G. Victora

Cell population (germinal center)

Large scale

$10^{-2}m - 1m$

day to month



G. Victora

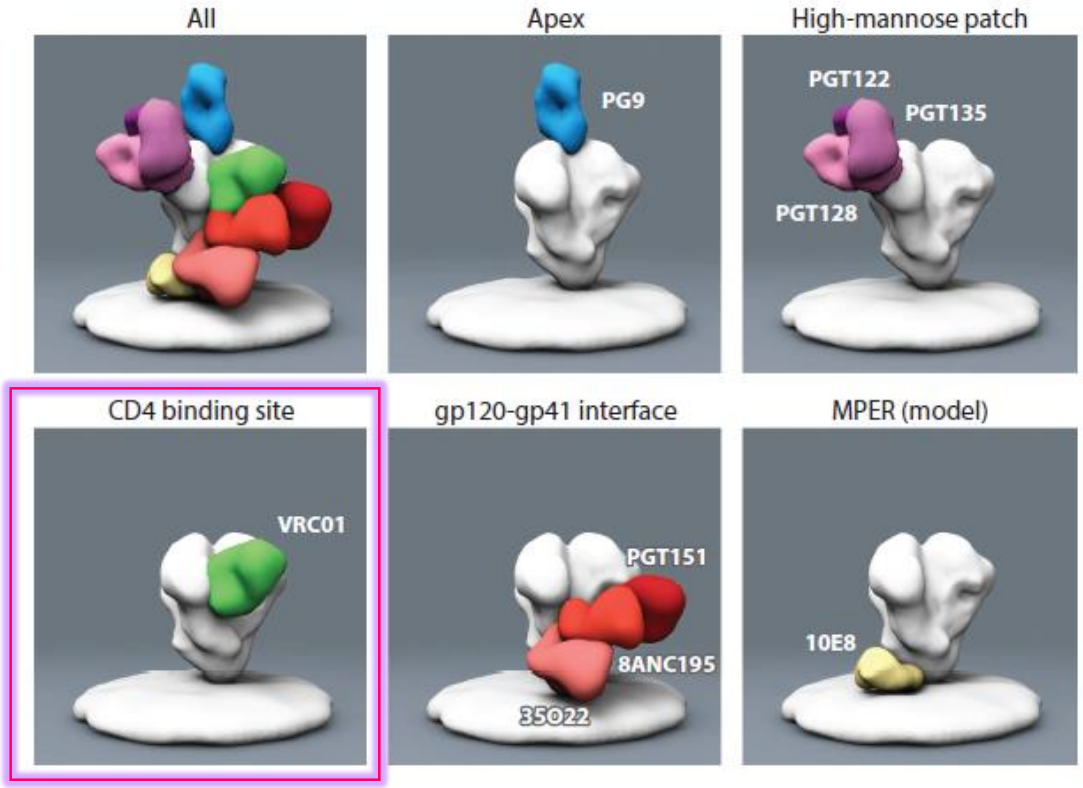
Population ensemble (lymph node)

How does the immune system represent the environment?

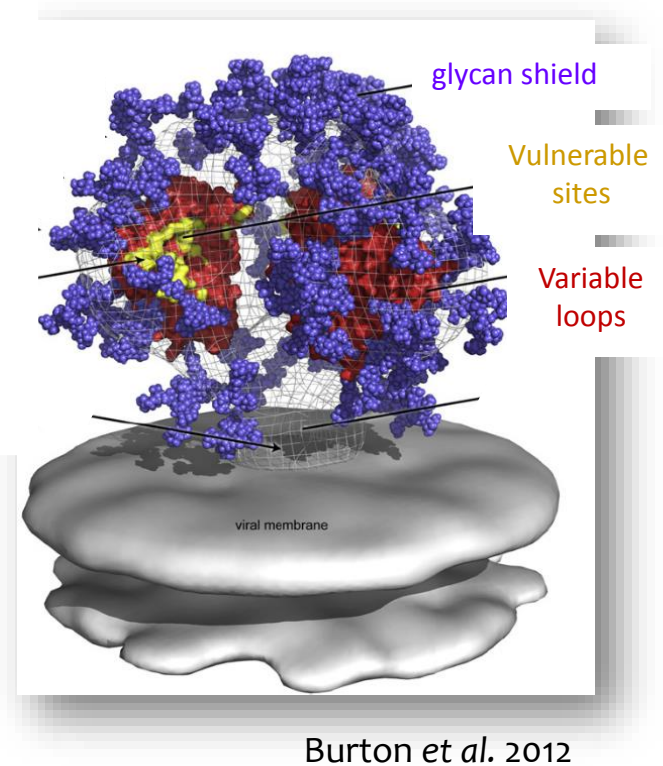
How does adaptation propagate across scales?

Counteracting tremendous antigenic variability

- Broadly neutralizing antibodies (bnAbs) to HIV-1: ‘sites of vulnerability’



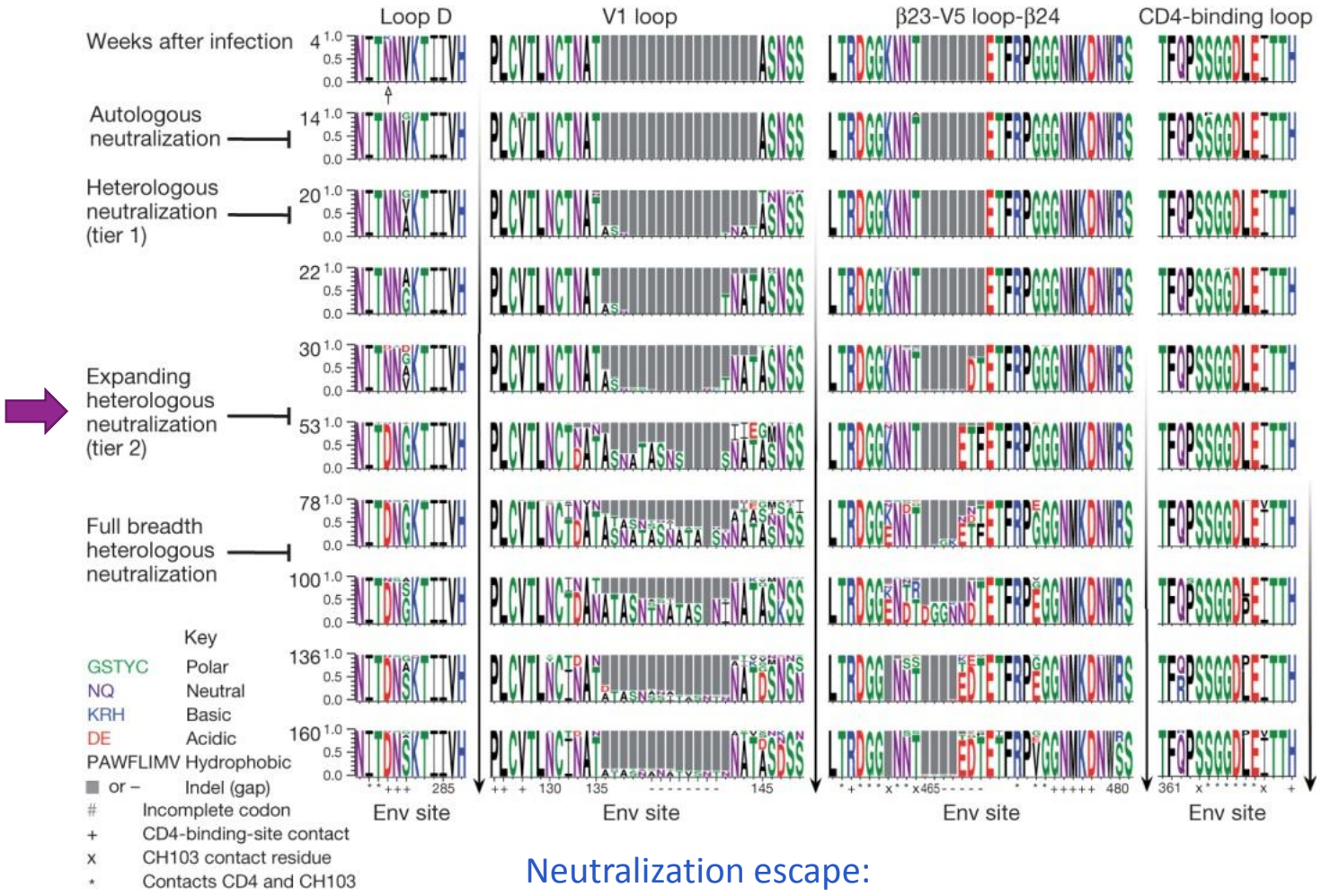
Burton & Hangartner. *Annu. Rev. Immunol*. 2016



Burton *et al.* 2012

Difficult yet accessible

Viral diversification precedes breadth acquisition



Neutralization escape:
insertions (V1, V5) and mutations (loop D)

- Extensive escape-generated epitope diversification
- Plasma breadth evolved in the presence of highly diverse forms of the epitope contact regions
- bnAbs remain capable of neutralizing transmitted/founder virus

Sustained mutual selection
btw engaged B cell & escaping virus

H-X Liao *et al. Nature* 2013

Paths to potent bNAbs are often long and few

- *Persistence is needed*

  Correlation btw mutation load & breadth

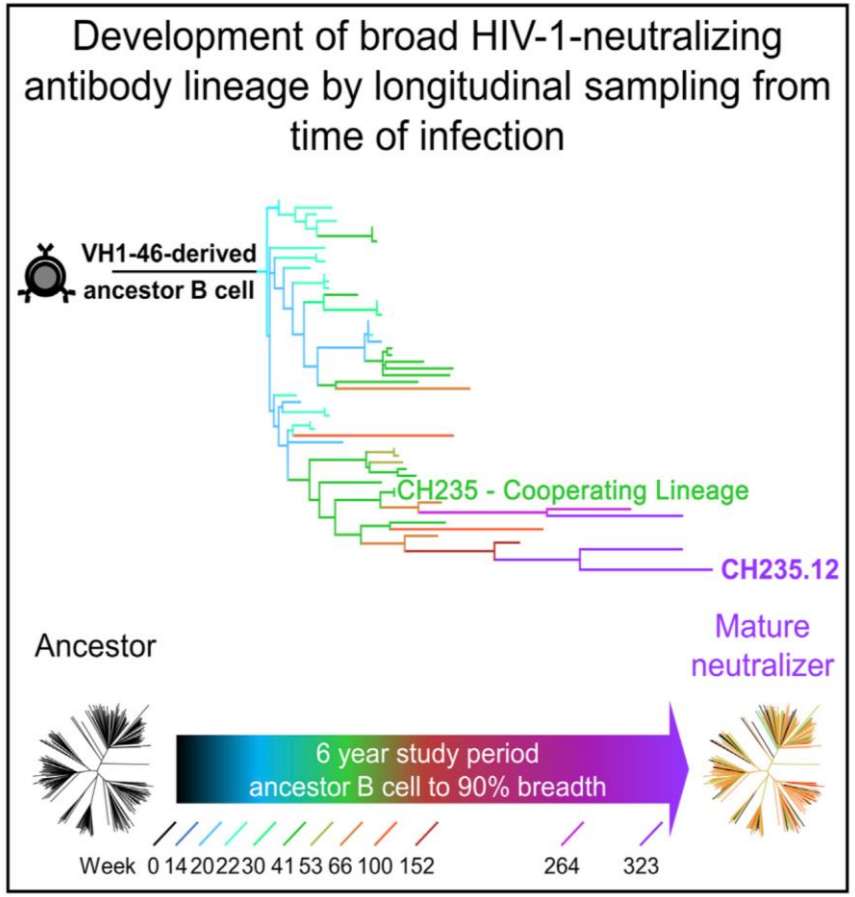
- *Breadth is progressively acquired*

  GL reversion abolishes breadth

- *Lineages can affect one another*

  Helper lineage selects breadth-driving mutants

BnAb lineages can be activated, and yet do not readily expand.



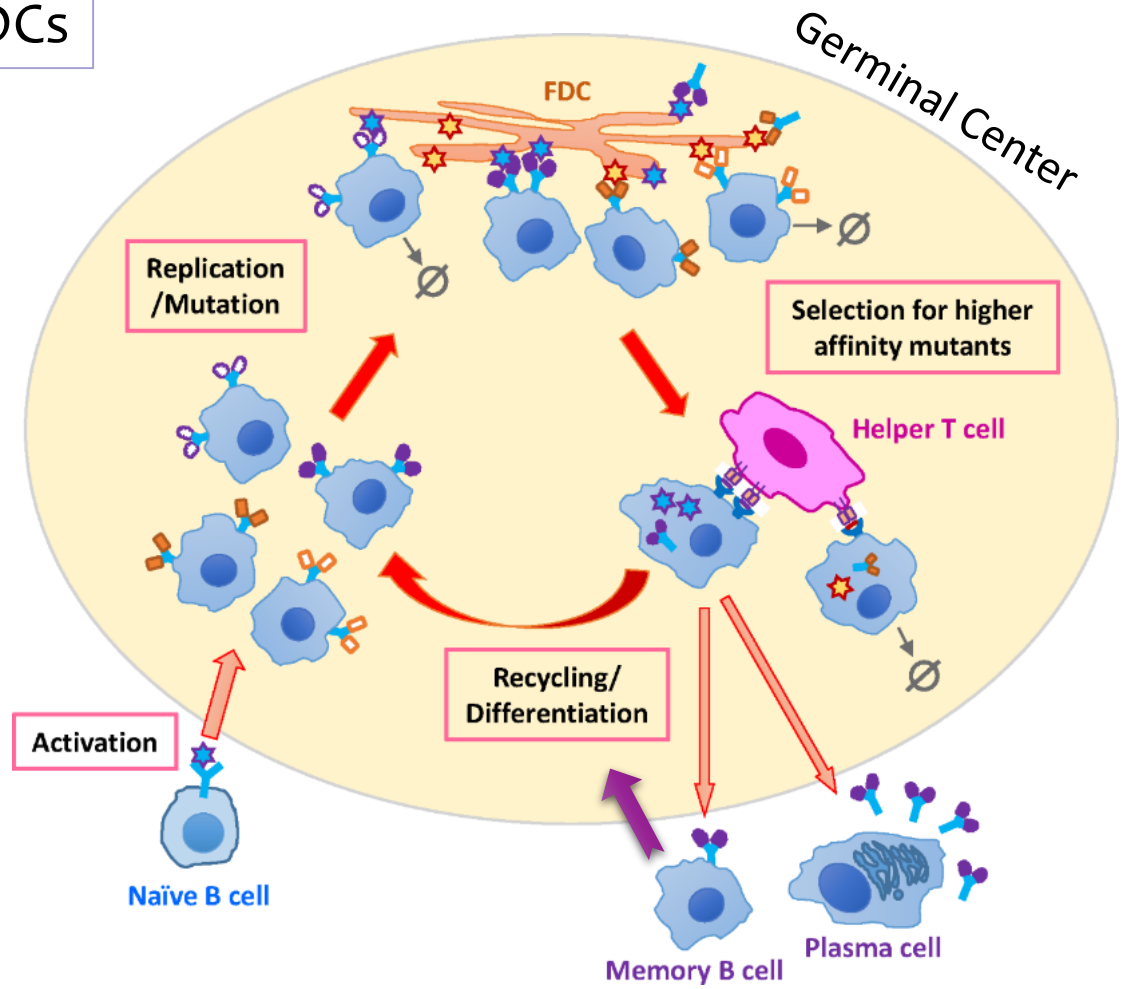
Gao *et al. Cell* (2014)
Bonsignori *et al. Cell* (2016)

Germinal center reaction: affinity maturation of B cells

Presentation of *multiple* Ag variants on FDCs

Agent-based model of GC reaction

- ★ Deleterious mutations more likely
- ★ Stochastic clonal selection
  - competition for Ag and T help
  - affinity-dependent death rate
- ★ Time-varying B cell population size
- ★ Parallel populations

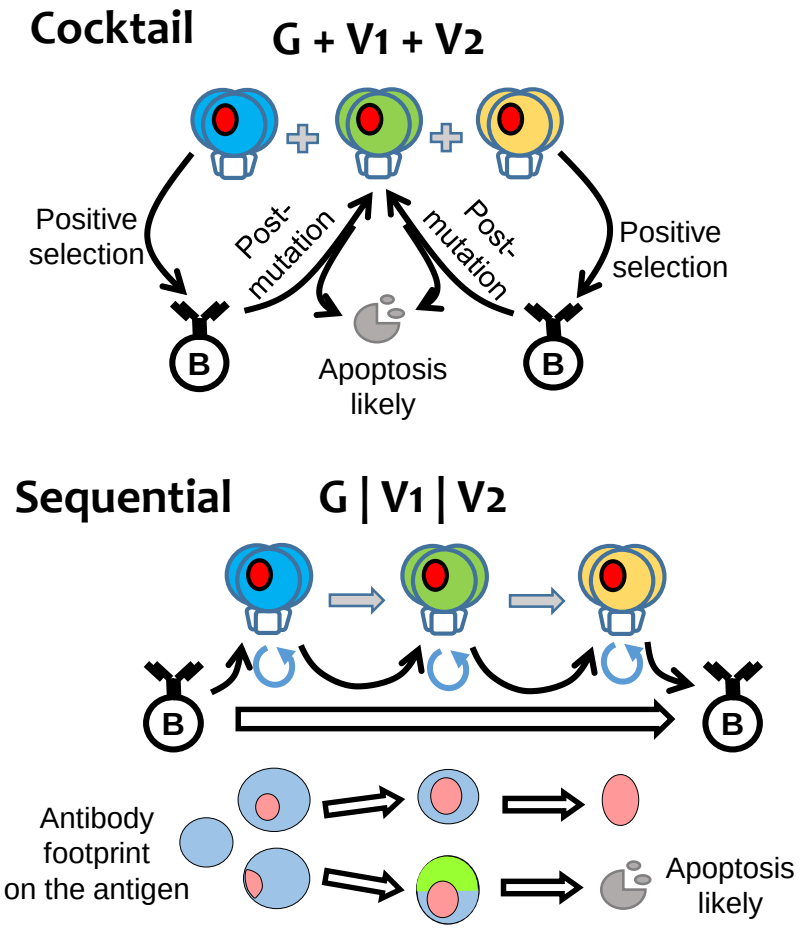


Learning by examples

- Frustrated affinity maturation
  - Mutationally distant targets
  - Spatial heterogeneity => temporal variation
  - B cell lineages either go extinct or stay specific

- Dynamic programming
  - Acquiring new reactivity without degrading earlier ones
  - Extracting recurrent patterns

An evolvable solution



SW ... MK & AKC, *Cell* **160**, 785-797 (2015)

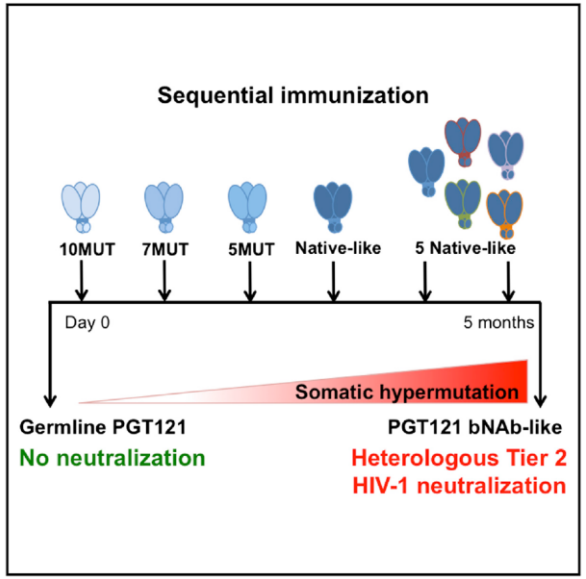
Article

Cell

Sequential Immunization Elicits Broadly Neutralizing Anti-HIV-1 Antibodies in Ig Knockin Mice

Amelia Escolano,[1,6] Jon M. Steichen,[2,6] Pia Dosenovic,[1] Daniel W. Kulp,[2] Jovana Golijanin,[1] Devin Sok,[2,3] Natalia T. Freund,[1] Alexander D. Gitlin,[1] Thiago Oliveira,[1] Tatsuya Araki,[1] Sarina Lowe,[1] Spencer T. Chen,[1] Jennifer Heinemann,[1] Kai-Hui Yao,[1] Erik Georgeson,[2] Karen L. Saye-Francisco,[2] Anna Gazumyan,[1] Yumiko Adachi,[2] Michael Kubitz,[2] Dennis R. Burton,[2,4] William R. Schief,[2,4,*] and Michel C. Nussenzweig[1,5,7,*]

- Mouse antibodies elicited by sequential immunization resemble human antibodies



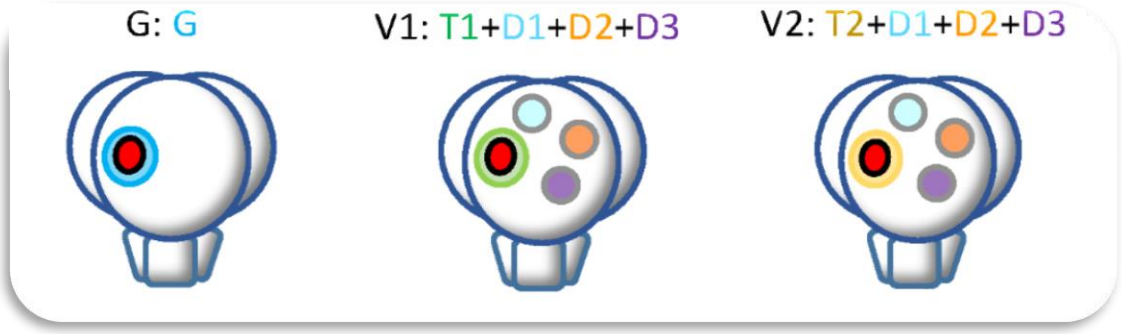
* A. Escolano, *et al.* Sequential immunization elicits broadly neutralizing anti-HIV-1 antibodies in Ig knockin mice. *Cell* **166**:1445-58, September 2016.

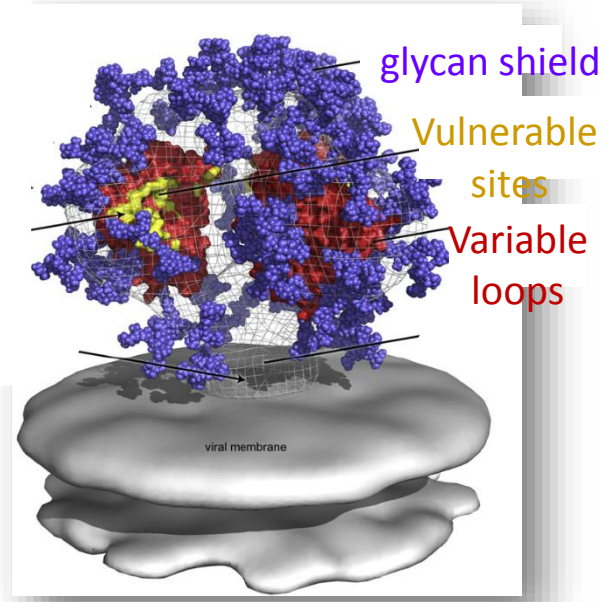
* B. Briney, *et al.* Tailored immunogens direct affinity maturation toward HIV neutralizing antibodies. *Cell* **166**:1459-70, September 2016.

* M. Tian, *et al.* Induction of HIV neutralizing antibody lineages in mice with diverse precursor repertoires. *Cell* **166**:1471-84, September 2016.

Distracting epitopes

Antigen variants with complex epitopes

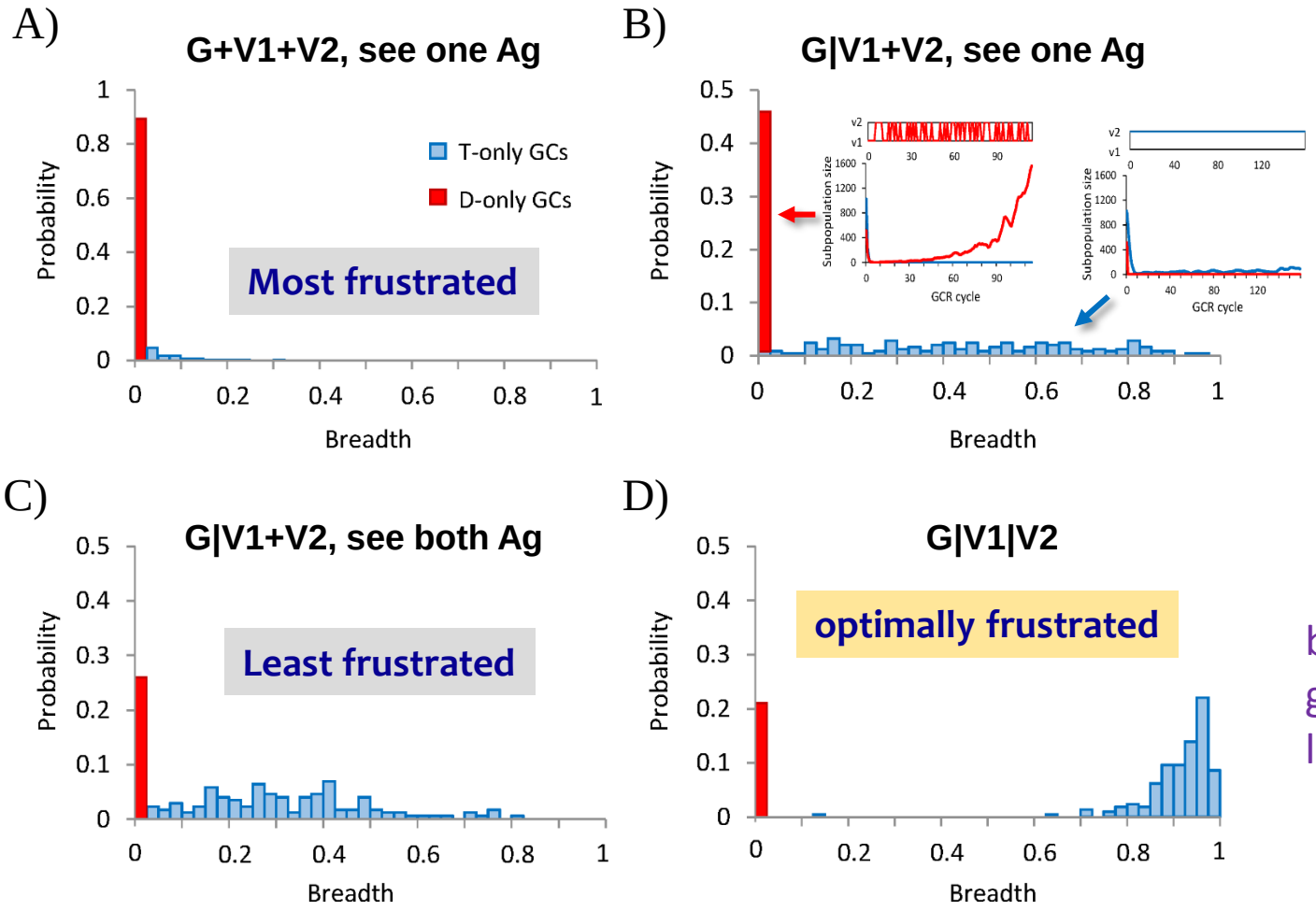




G: germline-activating reference strain
V1 & V2: target-epitope variants

Minimal distraction under optimal frustration

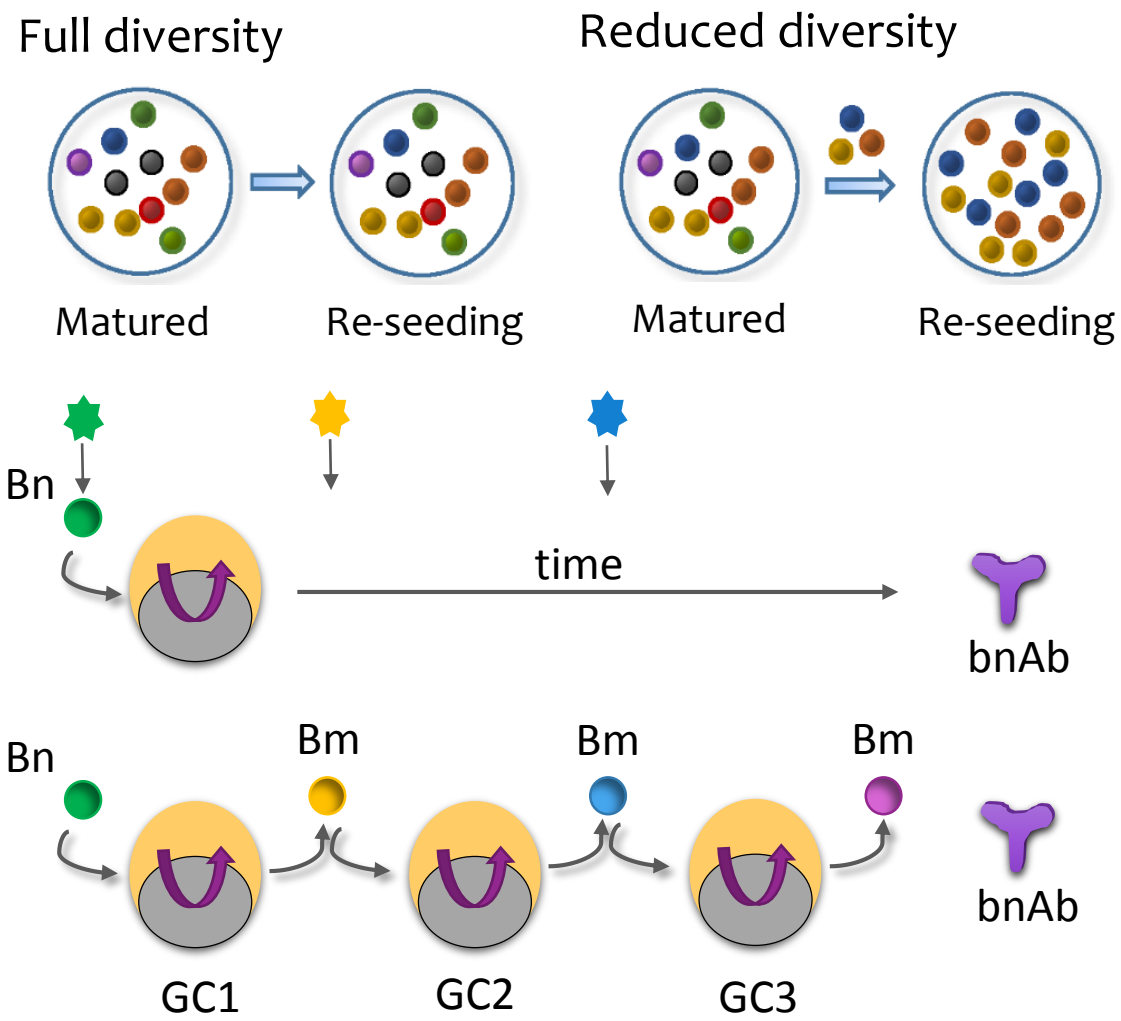
Non-neutralizing Abs dominate early in infection

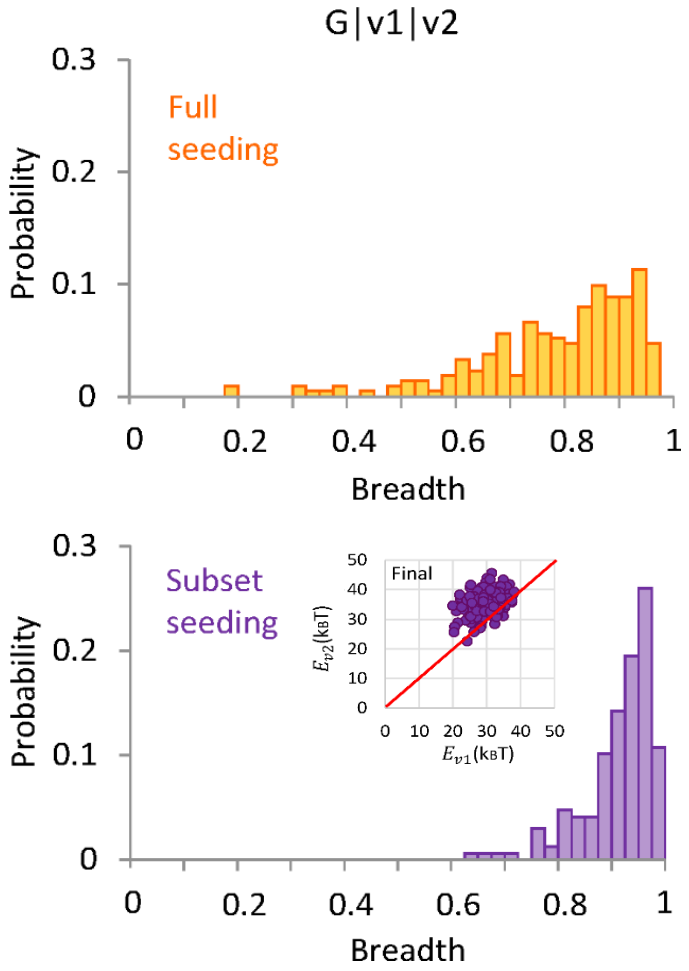


bnAbs, if persist, gain advantage late in infection

SW (2017) *PLoS Comput. Biol.* 13: e1005336

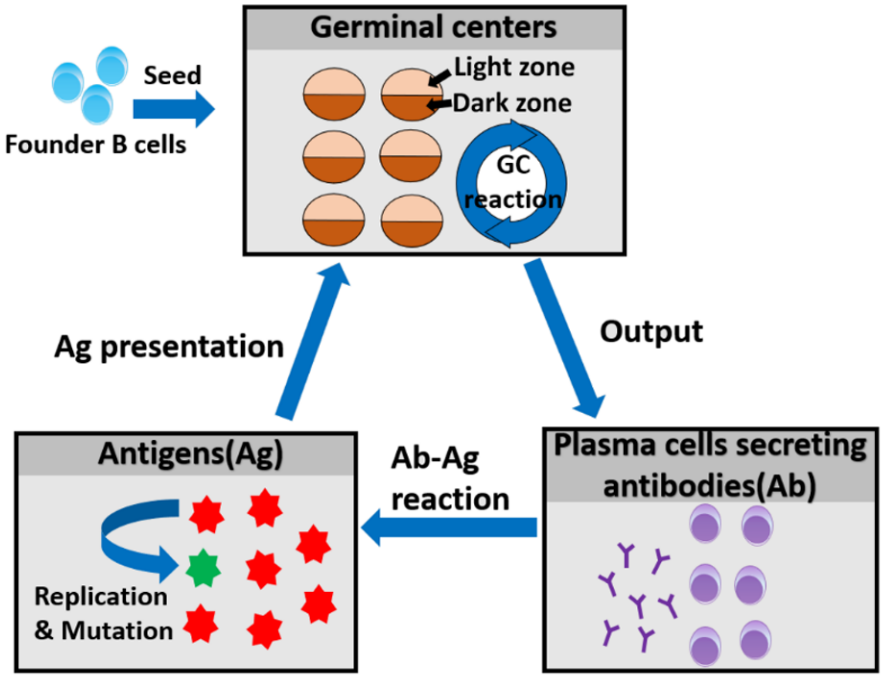
Diversity loss mitigates memory dominance



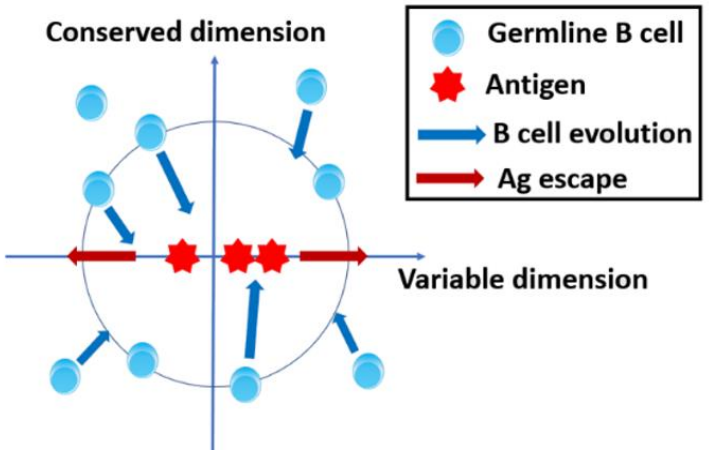


SW (2017) *PLoS Comput. Biol.* 13: e1005336

Host-pathogen co-adaptation

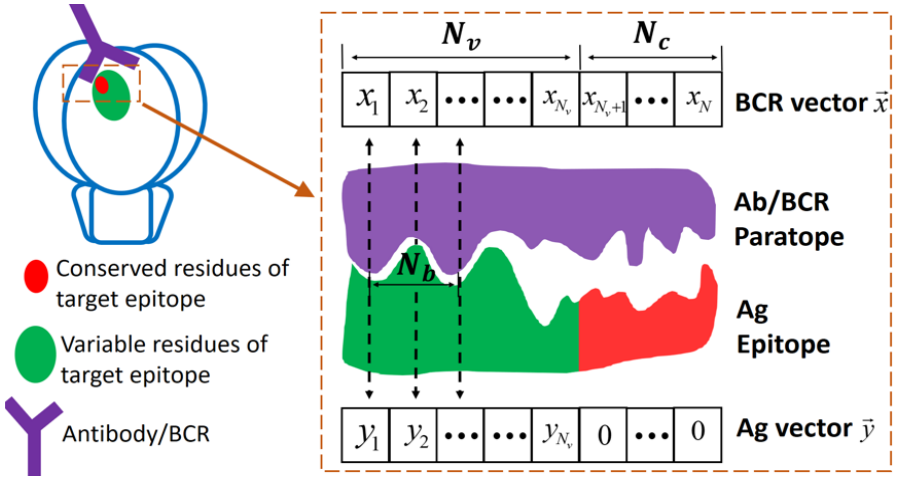


What could be a useful phenotypic space?



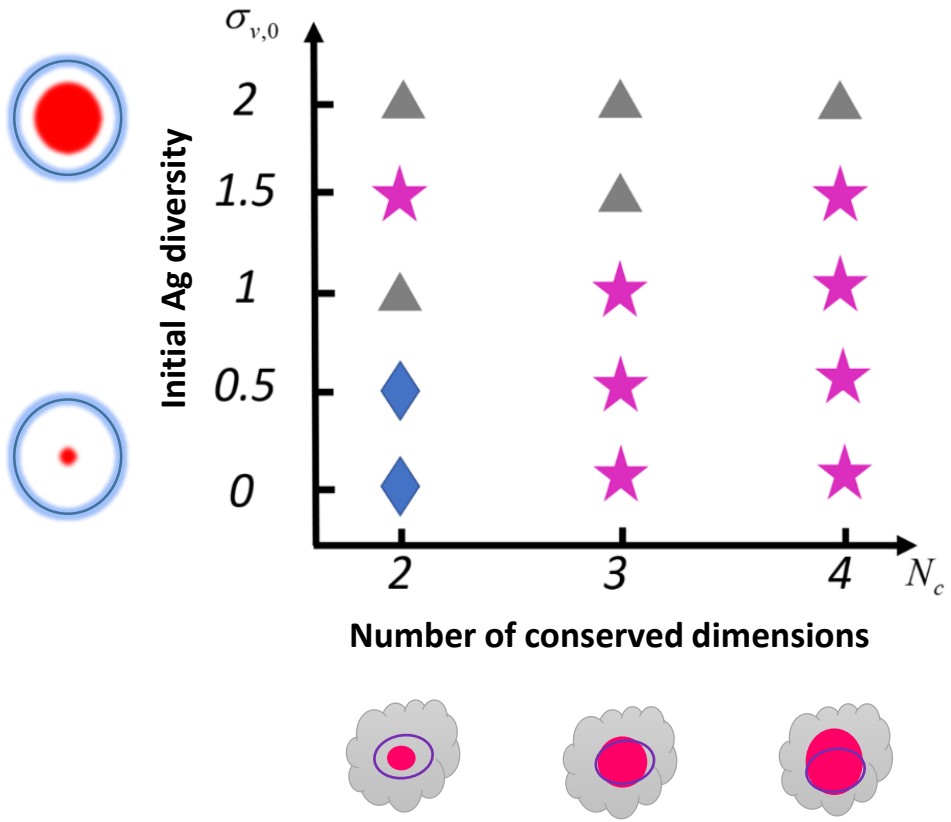
Mutual selection

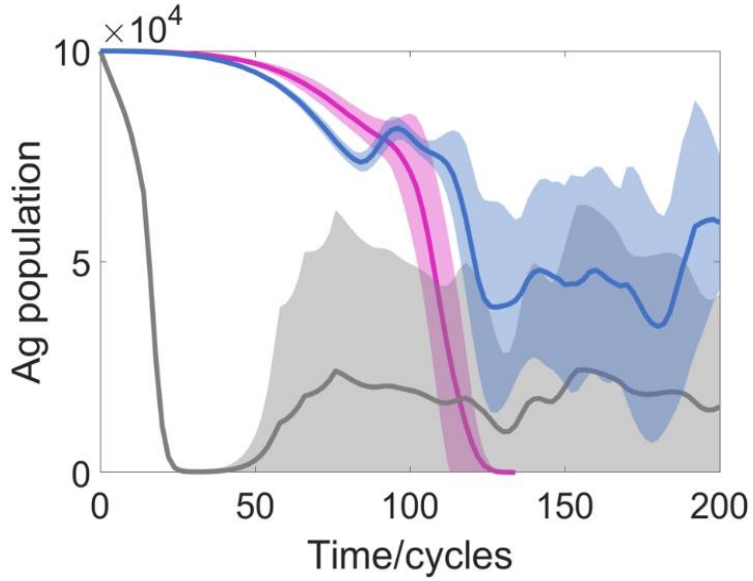
$$P_{surv}(E(||\vec{x}-\vec{y}||))$$



Binding subspaces

Host-pathogen co-adaptation





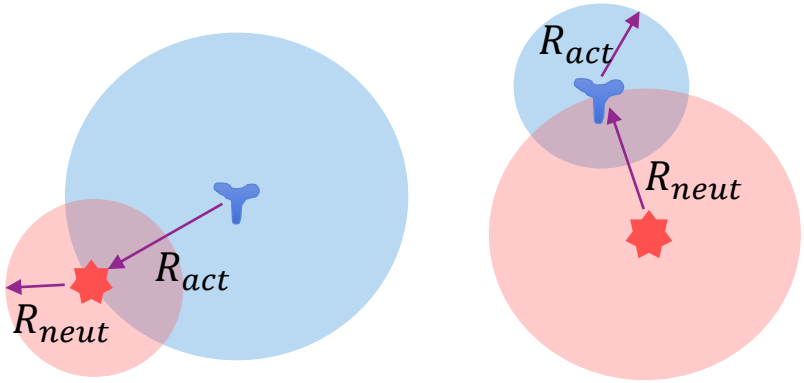
:Ag elimination

: Ag rebound

: Chronic infection

Ecological feedback

‘Sphere of influence’ in the shape space

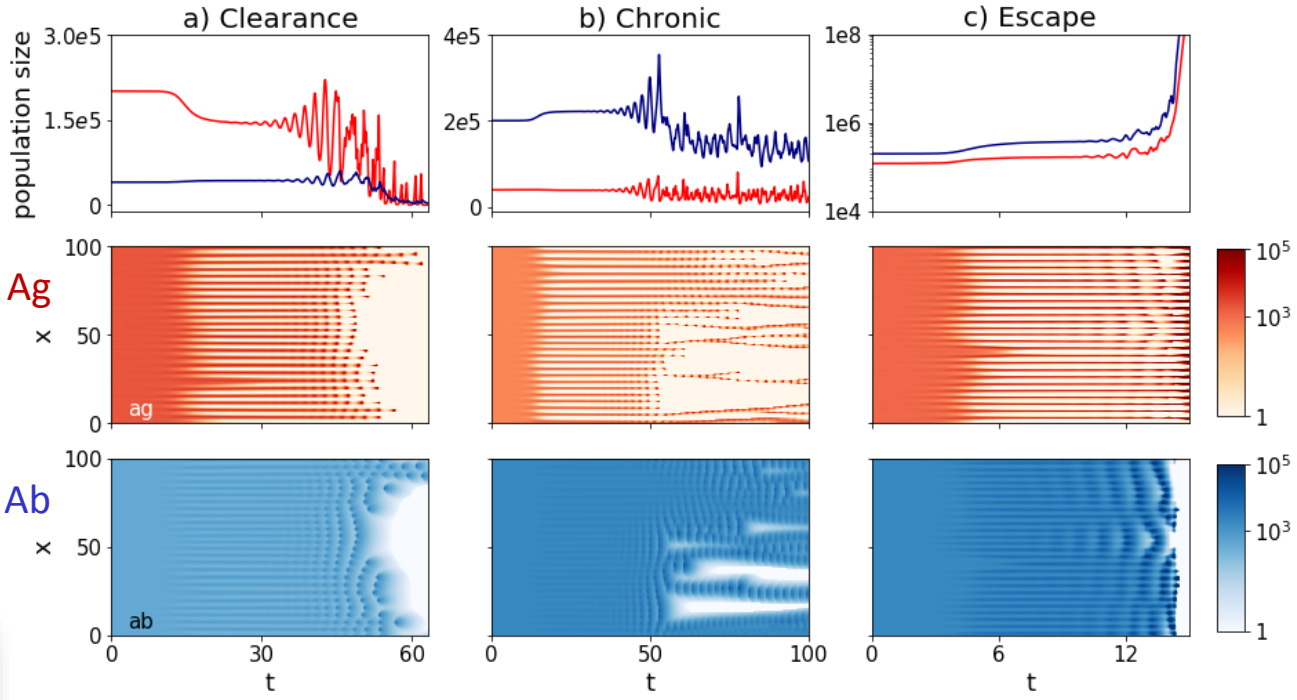


$R_{neut} < R_{act}$ $\quad$ $R_{neut} > R_{act}$

Asymmetry btw activation and neutralization

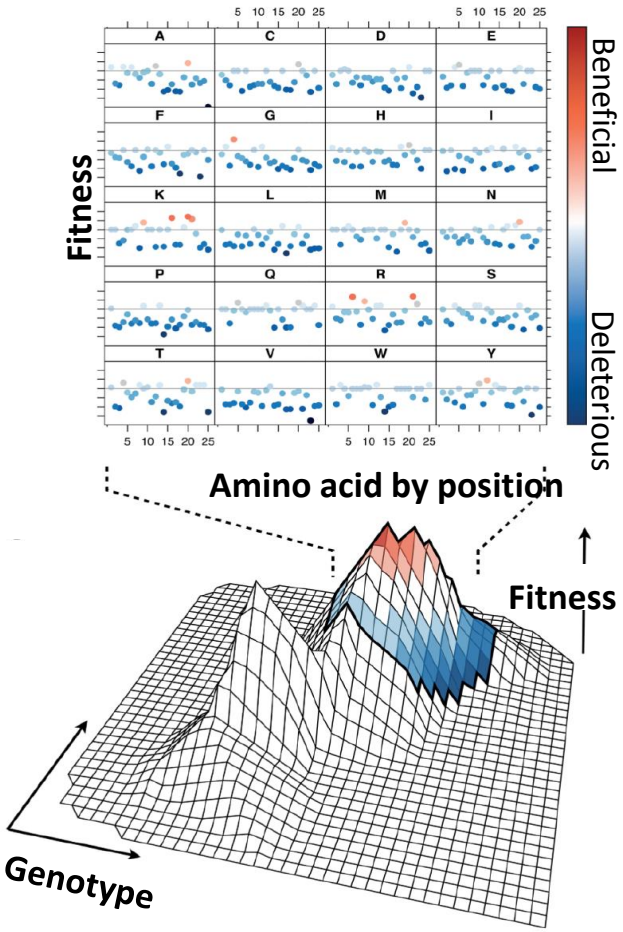
$$\frac{\partial A}{\partial t} = \lambda_1 A - \alpha_1 A B_{eff} + d_1 \nabla^2 A$$

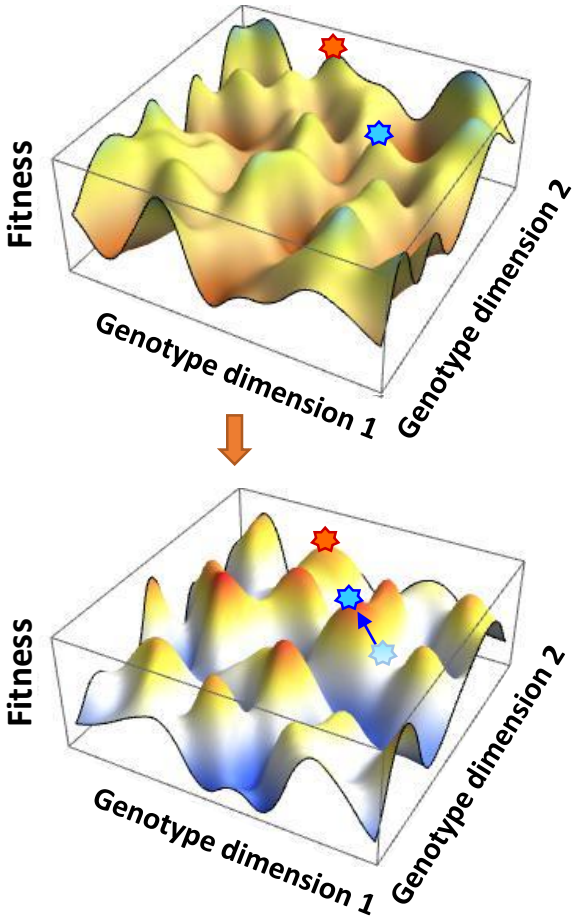
$$\frac{\partial B}{\partial t} = -\lambda_2 B + \alpha_2 B A_{eff} + d_2 \nabla^2 B + \xi\left(1 - \frac{B_{tot}}{\Theta}\right) B + B_{in}$$

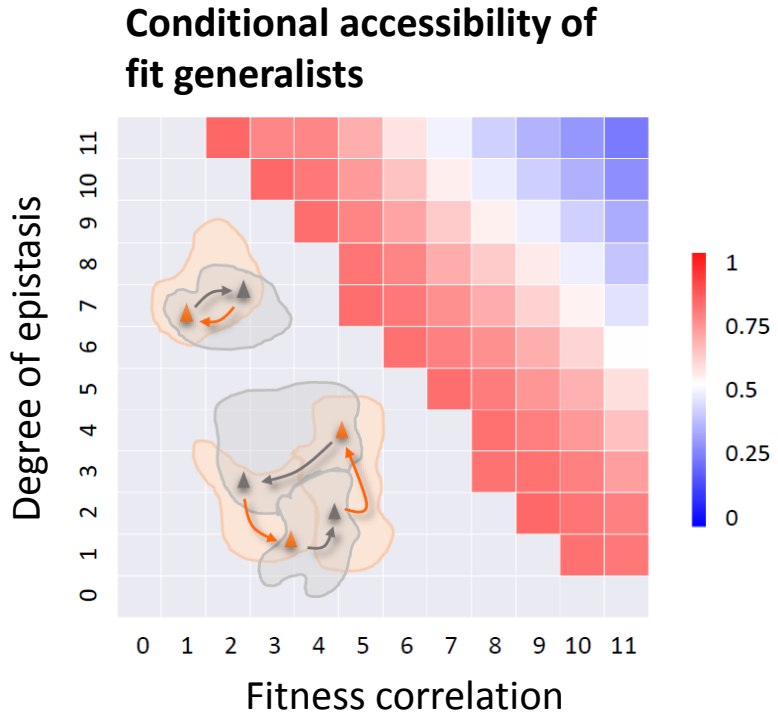


Pattern-forming instability ⇔ population dynamics

Mapping the evolutionary landscape







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EE Wrenbeck, MS Faber & TA Whitehead. *Curr. Opi. Struct. Biol.* 2017

RM Adams, T Mora, AM. Walczak & JB Kinney. eLife, 5:e23156, 2016.
RM Adams, JB Kinney, AM Walczak & T. Mora. arXiv:1712.04000v1.

Collaborating thoughts

- Relative age of host and pathogen
- Memory renewal against aging; modulating memory-naïve competition
- Vaccine-driven viral evolution for delayed aging;
  how may HIV differ from flu (HCV, Ebola, etc.)?
- Spatially varying selection pressure: coevolution on the move