Nonequilibrium antigen recognition during acute infections

by *Roberto Morán-Tovar and Michael Lässig*

Collaborative Research Centre 1310 Predictability in Evolution

Theory and concepts in biology
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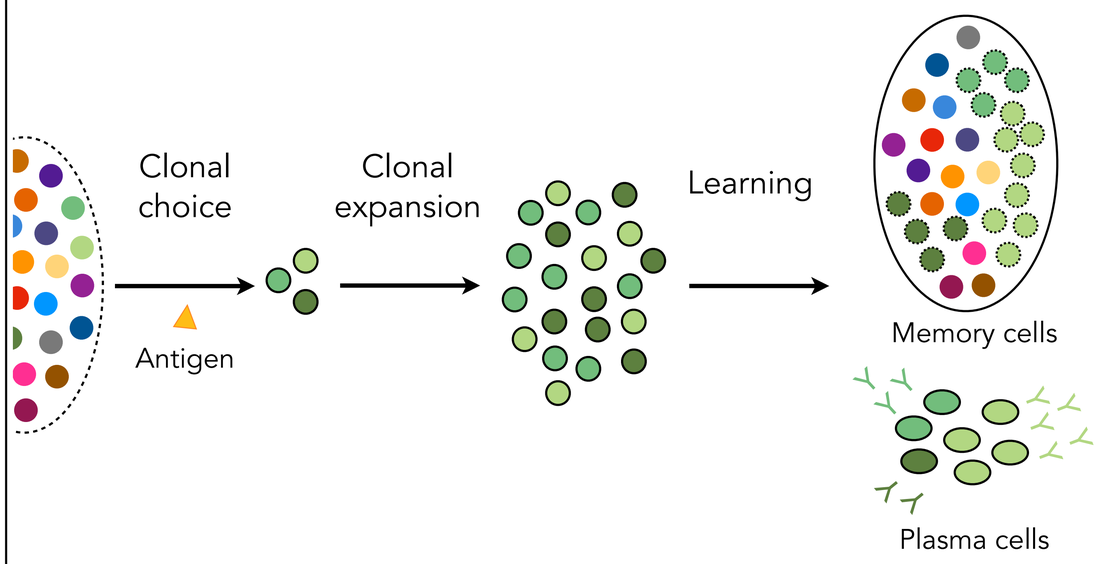
INSTITUTE FOR BIOLOGICAL PHYSICS

I. The problem: a mechanism for *Clonal selection theory*

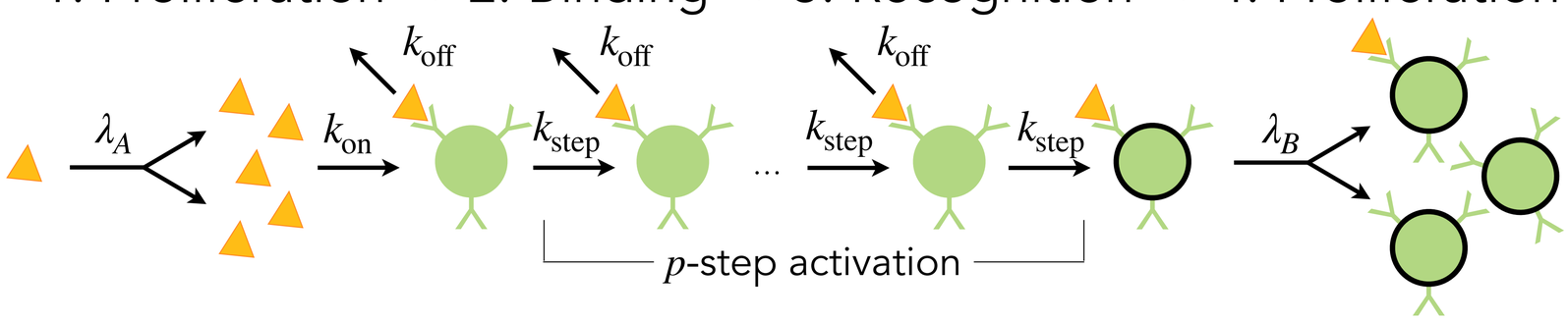


The existing scientific paradigm of acquired immunity and antibody production [1]

- What is the size of the naive repertoire? and of an antigen-specific repertoire?
- How is information stored?
- What constraints the quality of a specific immune response?

II. The model: Generalized Luria-Delbrück dynamics

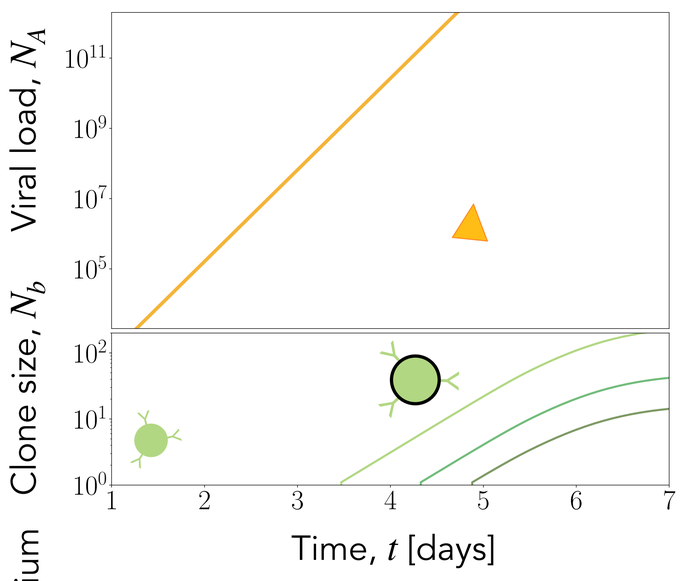
1. Proliferation → 2. Binding → 3. Recognition → 4. Proliferation



We characterize the response of a clone b by $Z_b = N_b/K_b$ with $K_b = k_{\text{off}}/k_{\text{on}} \sim \exp\left[\Delta G_b\right]$, and the total response by

$$Z = \sum_b Z_b \approx p_{\text{binding}}$$

II.a. Exponential proofreading



Time graded clonal activation determined by affinity [2]:

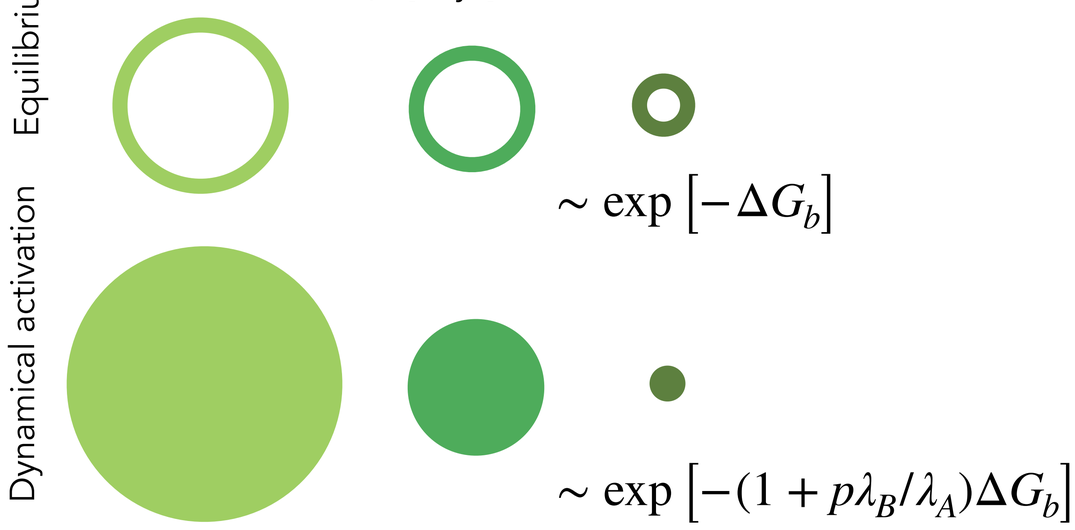
$$N_b \sim K_b^{-p\lambda_B/\lambda_A}$$

The potency becomes

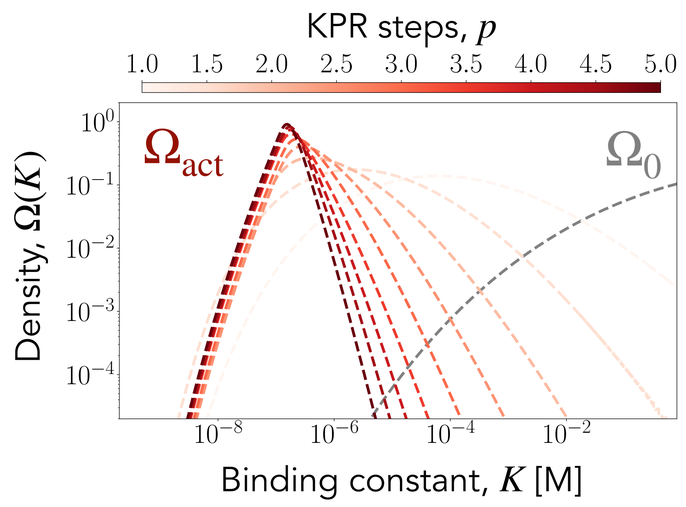
$$Z_b \sim K_b^{-(1+p\lambda_B/\lambda_A)}$$

The model predicts a power law in the clone size rank [2]

$$\langle N_j \rangle \sim j^{-\zeta}$$



II.b. Kinetic proofreading



The level of KPR, p, is tuned to the repertoire complexity, β^*,

$$p \gtrapprox \beta^* = \left.\frac{\partial \log \Omega_0}{\partial \log K}\right|_{K^*}$$

with

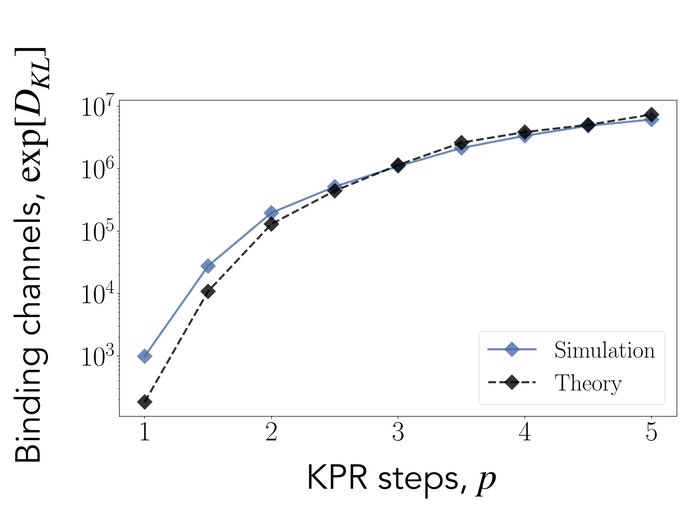
$$\int_{K_{\min}}^{K^*} \Omega_0(K)\, \mathrm{d} \log K = 1$$

For optimal response: a minimum discriminatory power is necessary to beat the large entropy of the naive repertoire [2].

The Kullback-Leibler distance

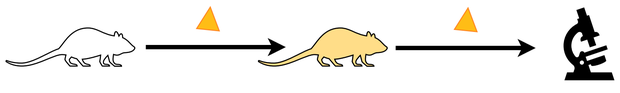
$$D_{KL}(\Omega_{\text{act}} \,|\, \Omega_0)$$

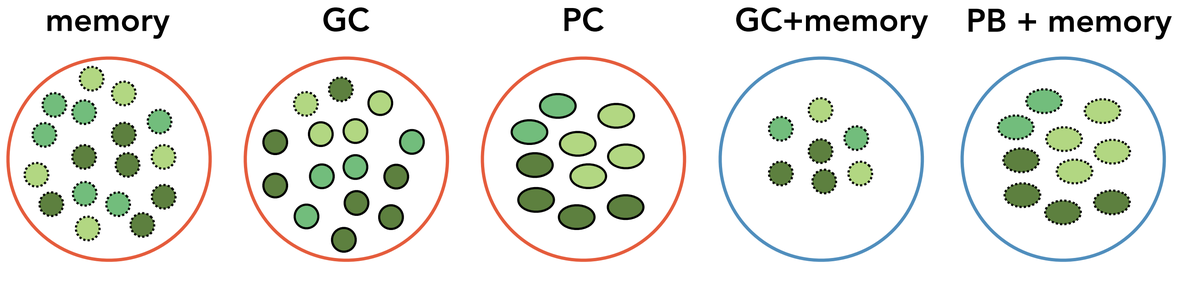
has a diminishing return for larger discriminatory power.

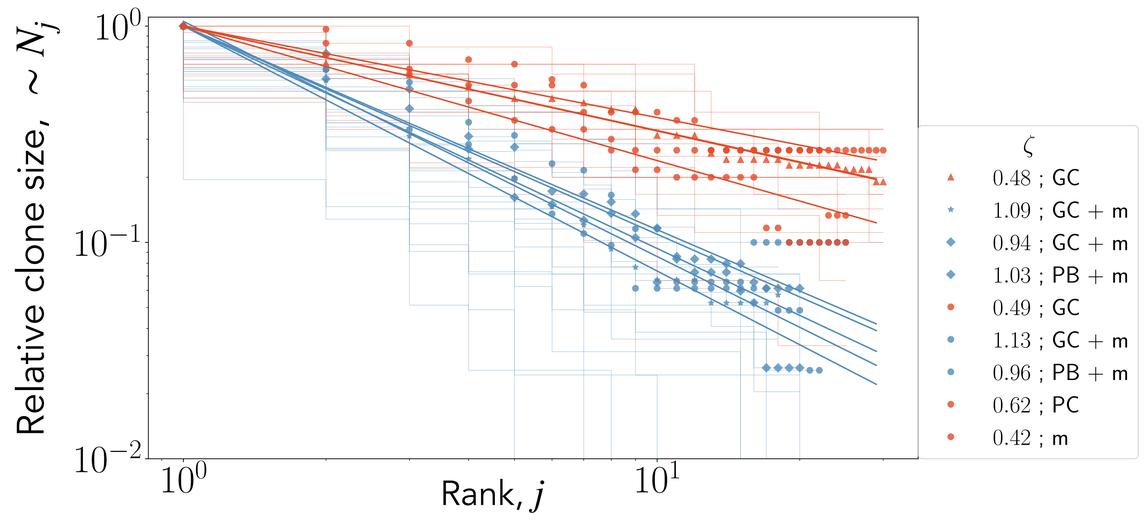


III. Application

Mice experiments with two immunizations with Influenza [3]. After the first immunization, activated population is fate-mapped. During second immunization, it can be distinguished between memory or naive derived response.







Our analysis shows two distinct subsets of subpopulations characterized by different ζvalues [4]. We interpret these two subsets as consisting of subpopulations that have experienced one or two expansion events. The inferred value for one expansion $\zeta \approx 0.5$ is consistent with around $p = 3$ KPR steps.

[1] F. M. Burnet, Au. Jour. Sci. 1957.
[2] R. Morán-Tovar, M. Lässig, PRX 2024.
[3] L. Mesin, A. Schiepers, et.al., Cell 2020
[4] R. Morán-Tovar, M. Lässig, in preparation.