Modeling immunity to malaria

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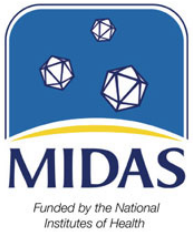
Center *for* Communicable Disease Dynamics



HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Collaborations

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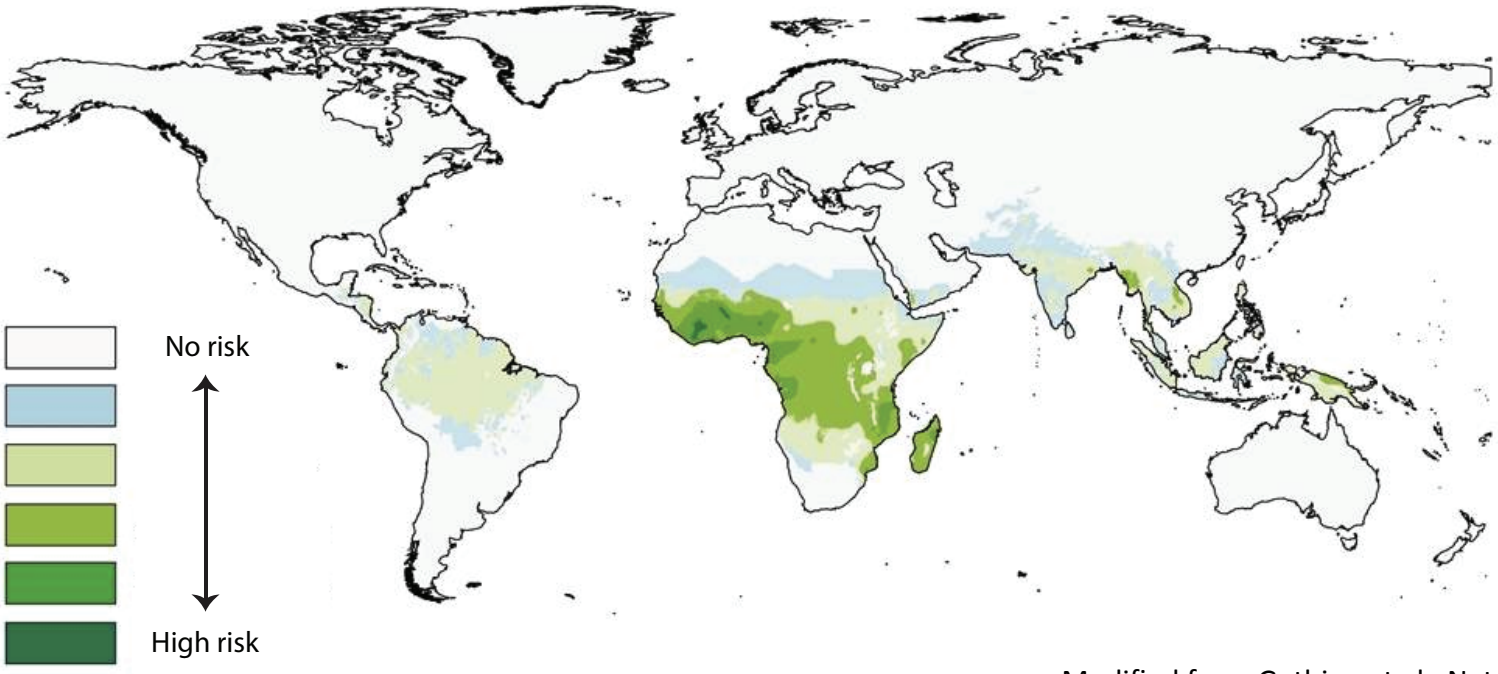
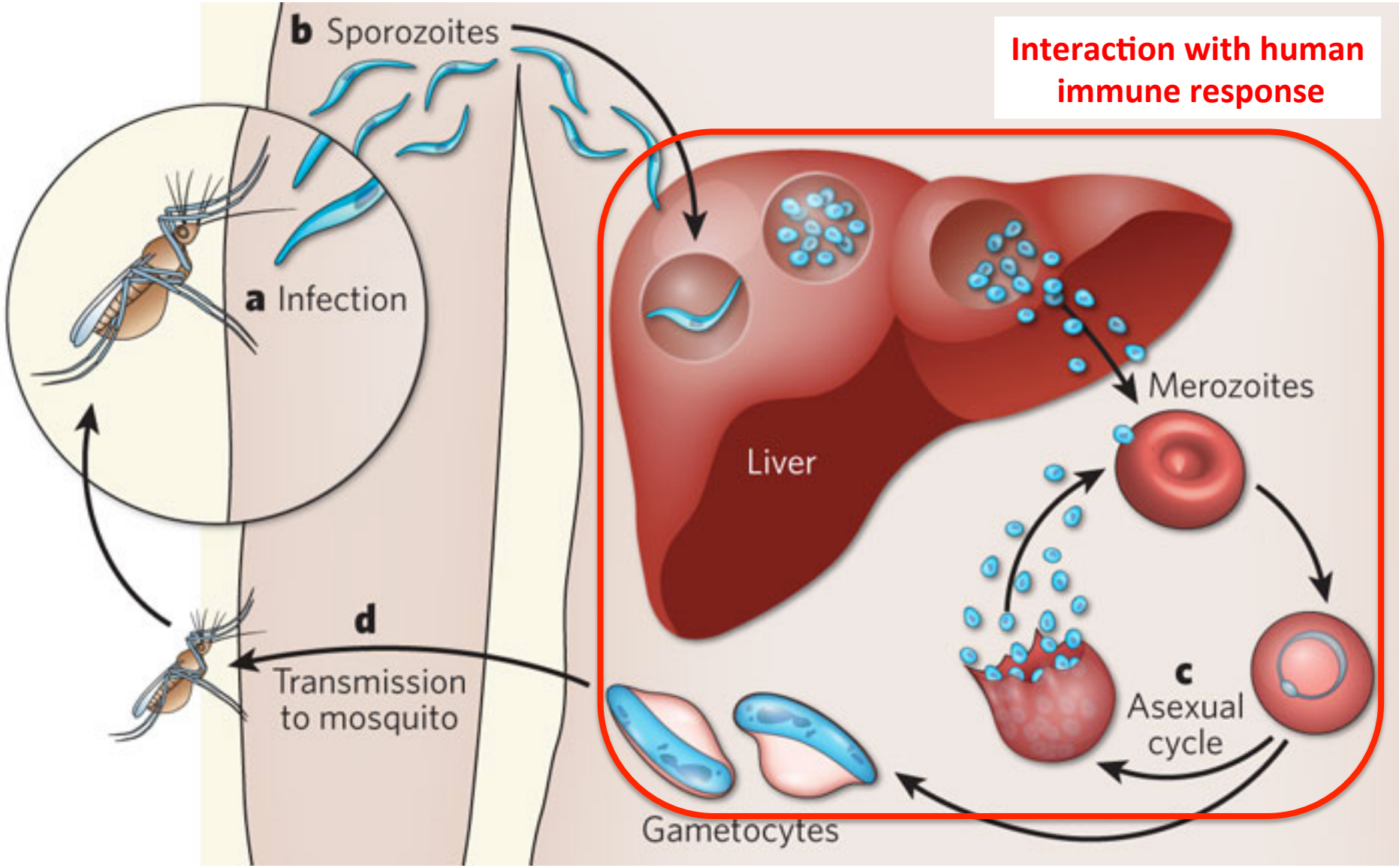
World-wide burden of malaria

- Over 50% of the world population at risk
- More than 200 million cases per year
- Nearly 500,000 deaths per year



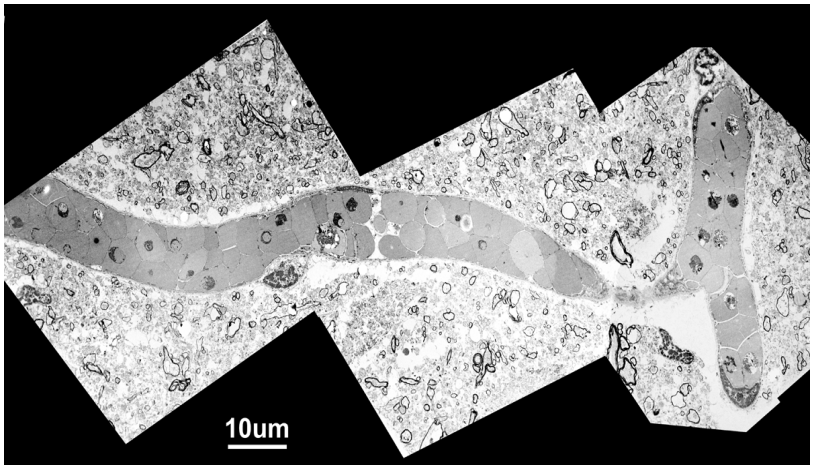
Modified from Gething et al., Nature 2010.

Malaria life cycle in humans and mosquitoes

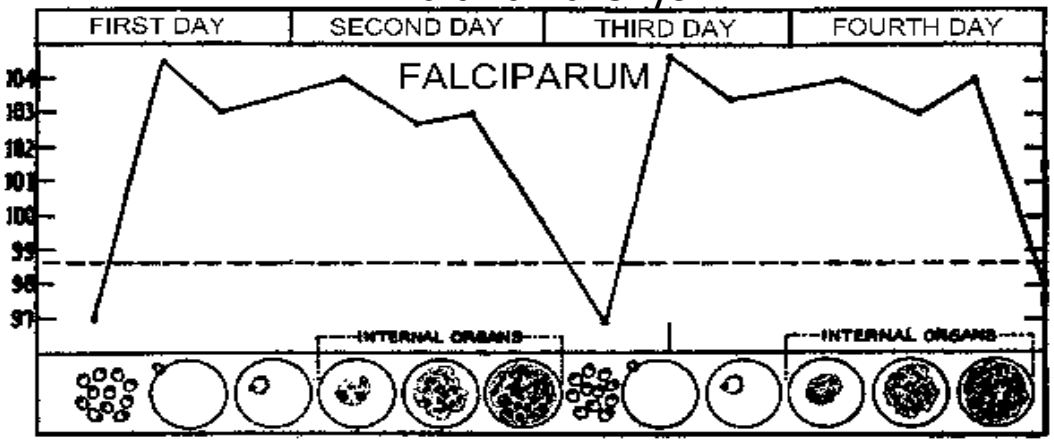


Malaria symptoms and disease

- Pathology occurs during the blood stage of the parasite life cycle
- Common symptoms
  - Fever
  - Flu-like illness
  - Nausea and vomiting
  - Anemia
  - Coma



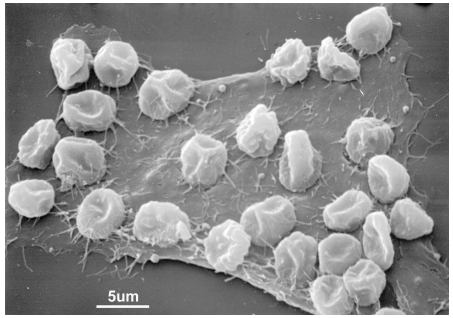
Malaria Paroxysm



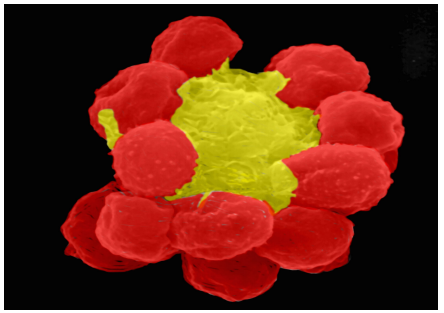
Dual function of varying proteins

- Allow for adhesion to host cells
  - Avoid clearance of parasite

Bind to red blood cells



Bind to endothelium



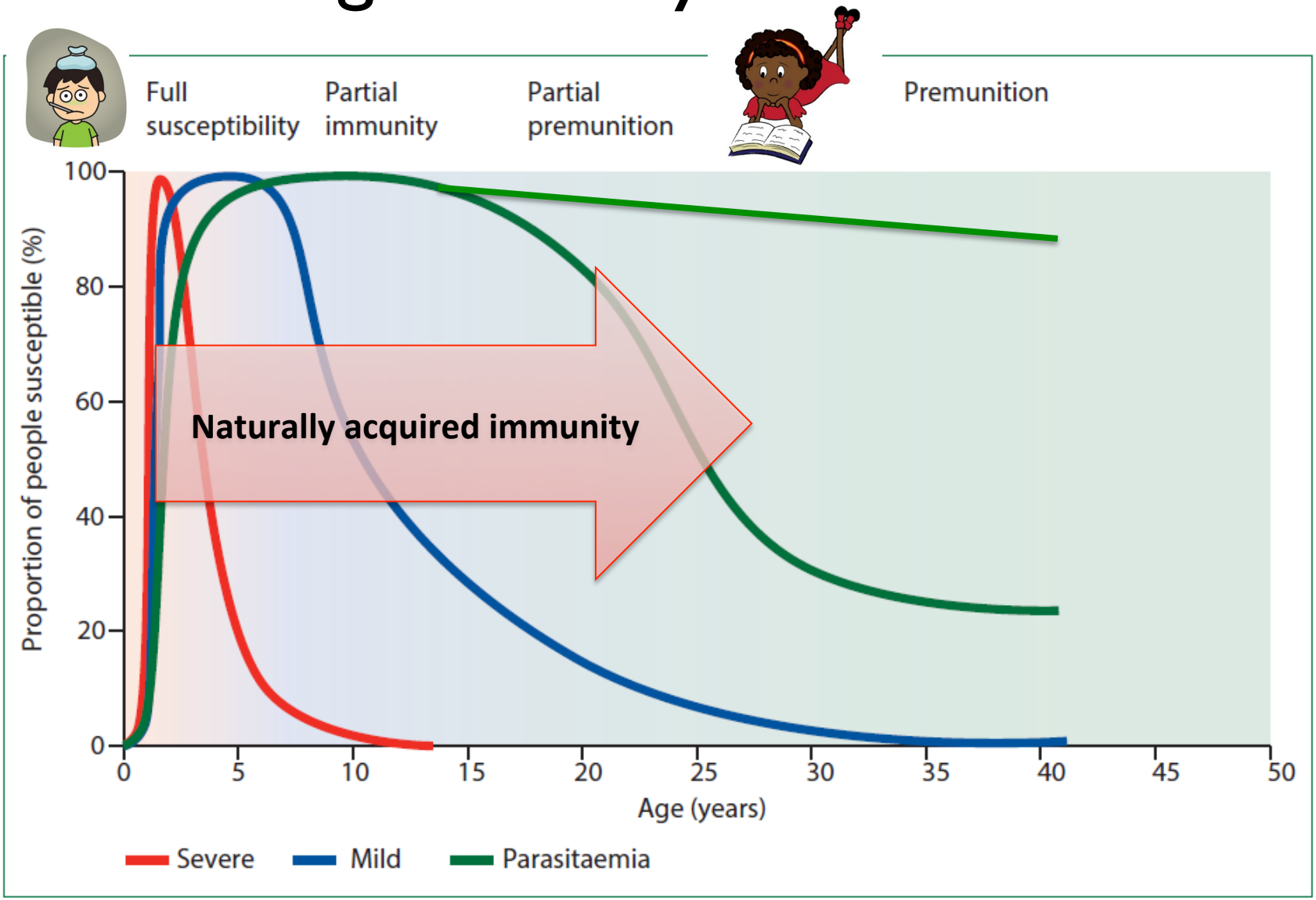
Bind to immune cells

- Elicit strong immune response

- Vary through the course of an infection
  - Synchronized switching of type

EM courtesy of D. Ferguson, Oxford Univ.

No sterilizing immunity to malaria infection

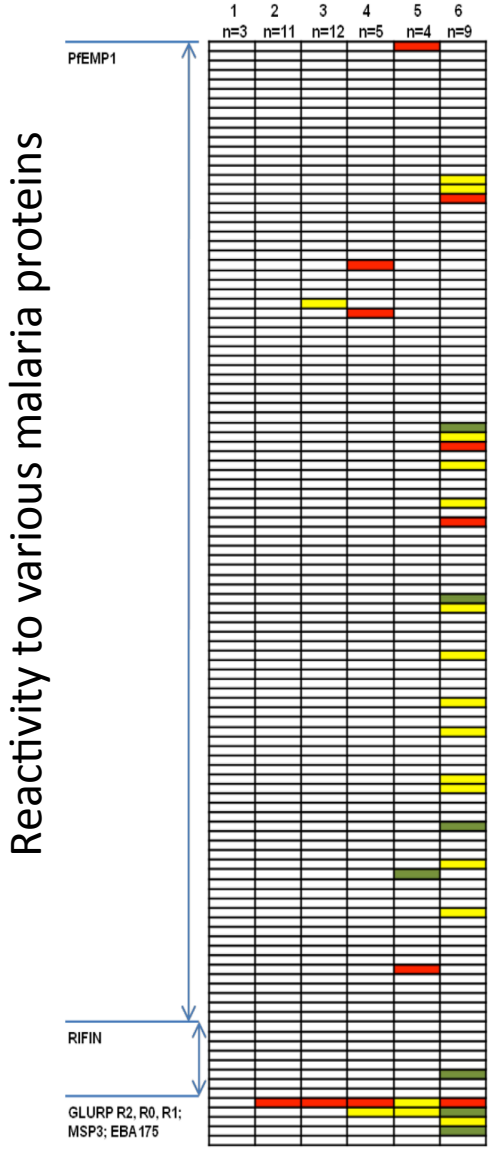


White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. 2014. Malaria. *Lancet 383:723-35*

Difficulties with host immunity

- Hindered by significant parasite diversity
  - Variation between parasite clones
  - Variable presentation of proteins in a single infection
- Lack of understanding on what constitutes protective immunity
  - Immune impairment
  - Variation in antibody levels

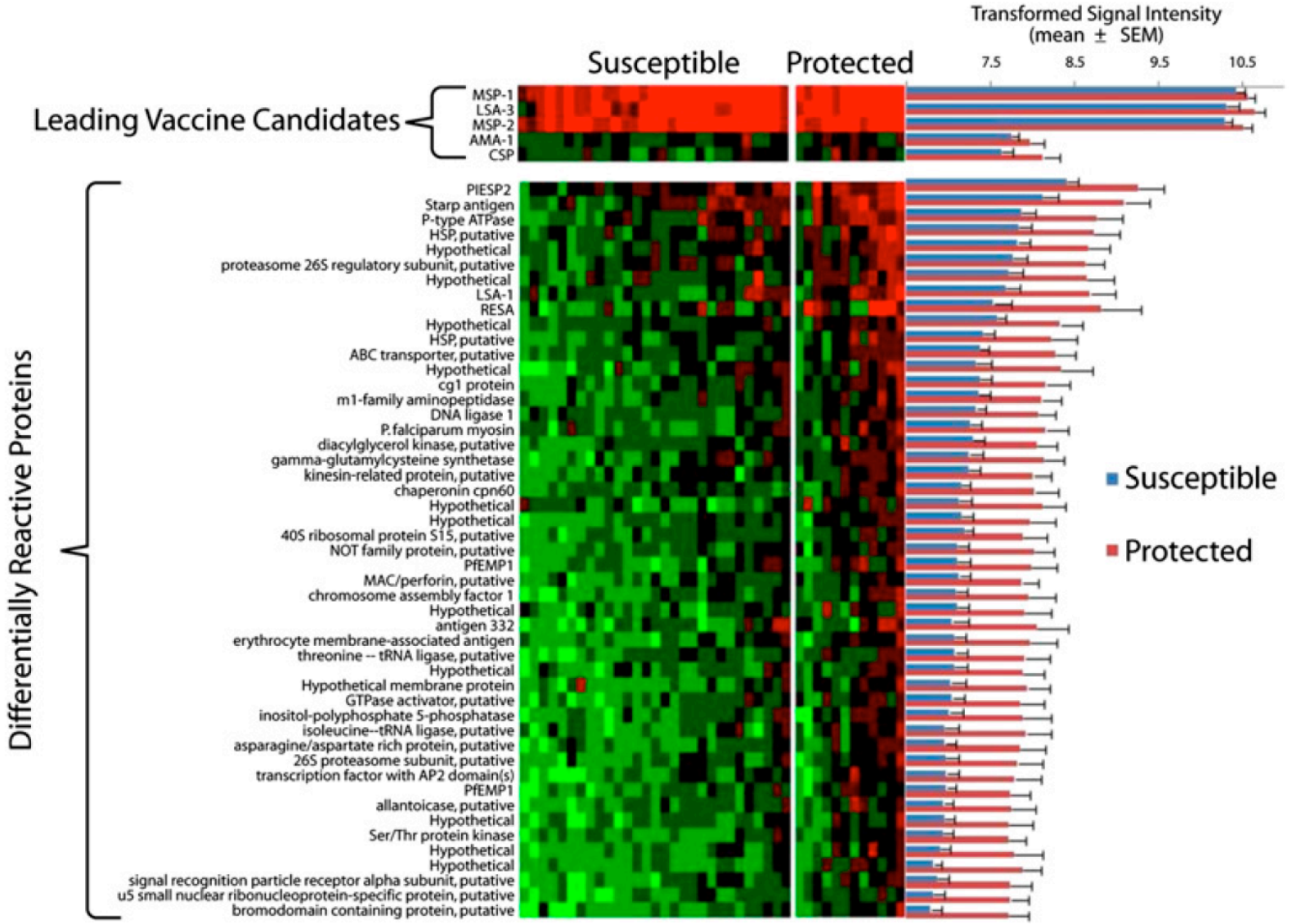
No consistent immune signature



- Individuals respond to a variety of proteins
- Most individuals respond to only a few or none of the proteins
- Final individual is responsive to many proteins

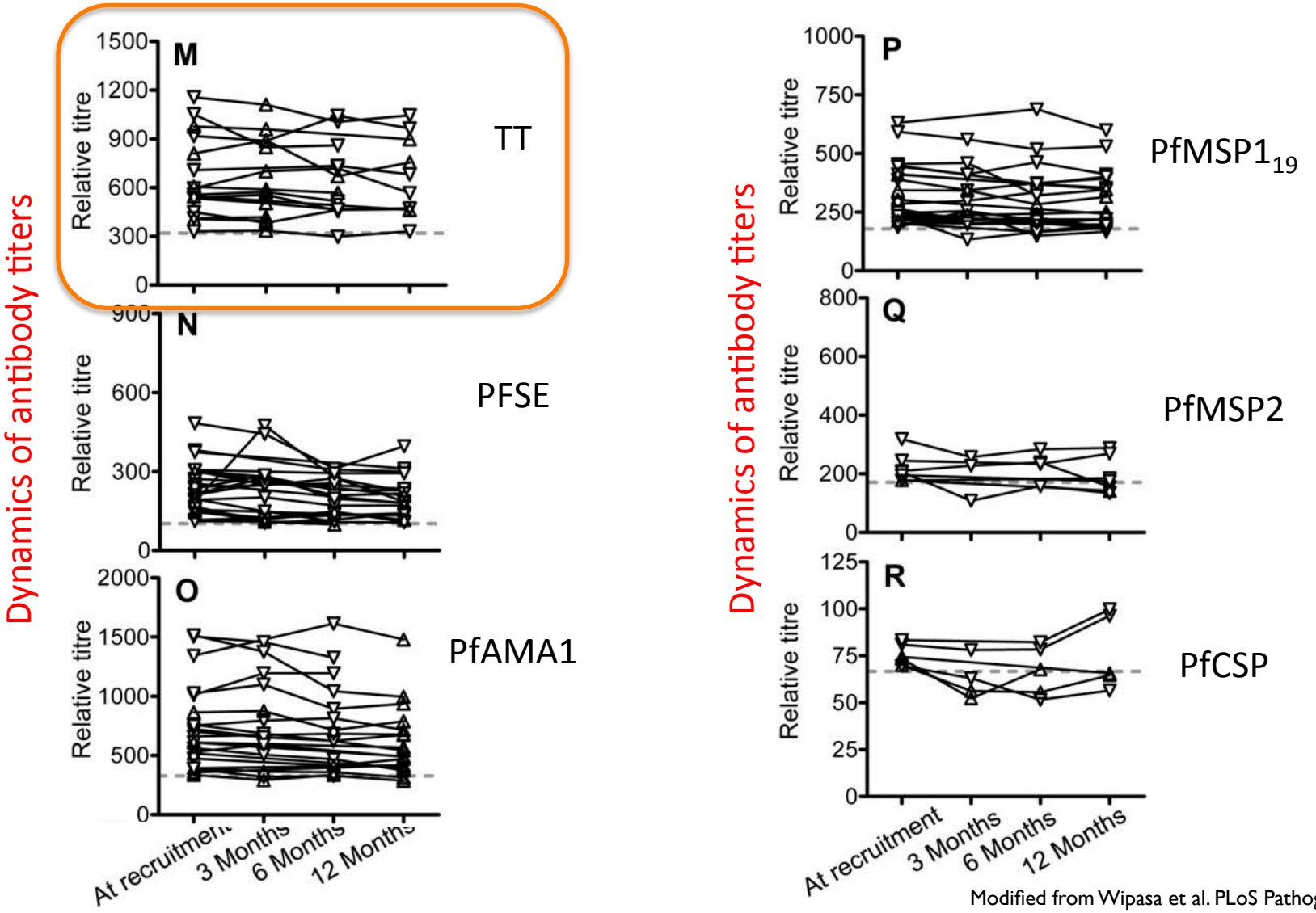
Turner et al. PLOS ONE 2012.

No correlates of protection



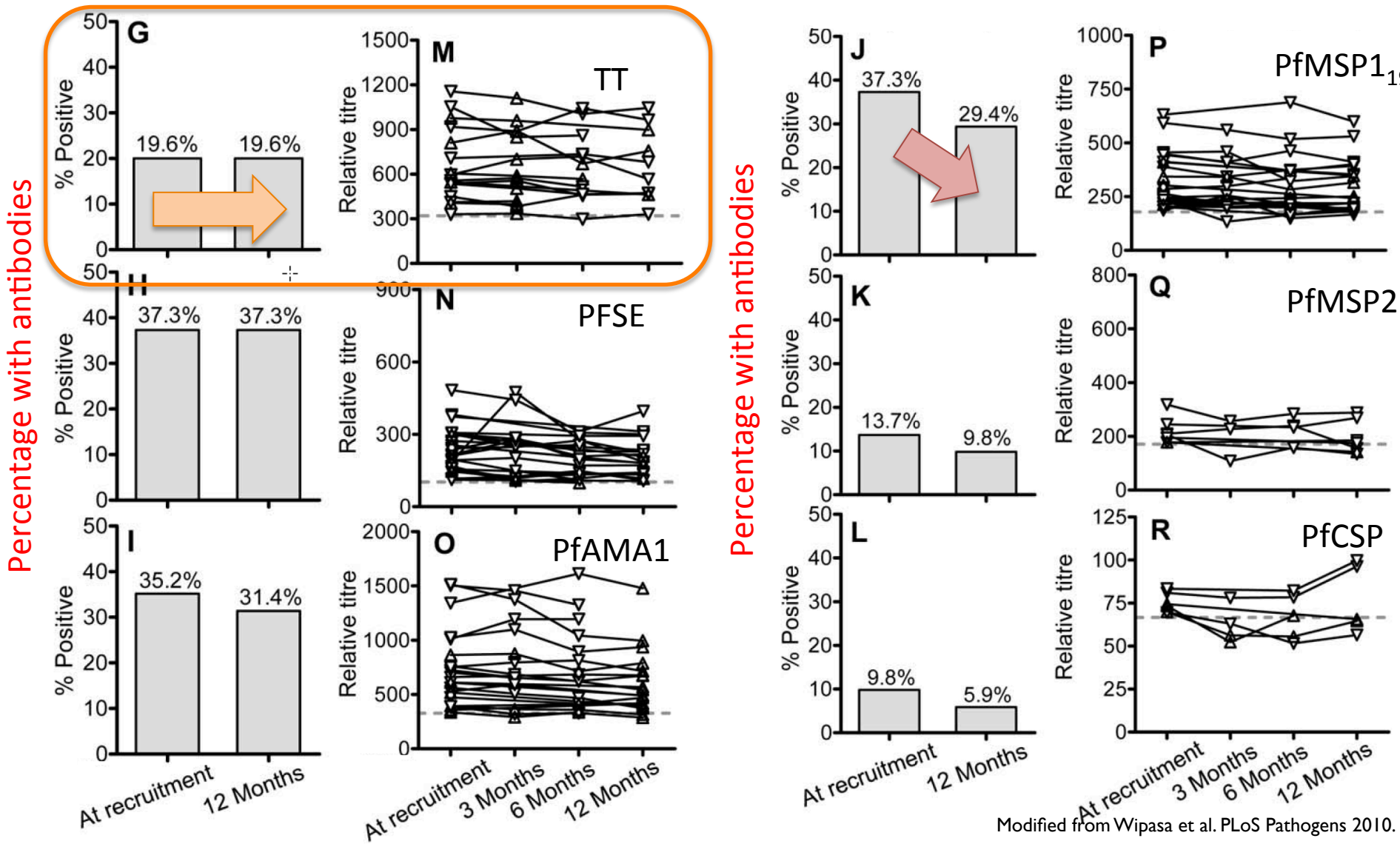
Crompton et al. PNAS 2010

Persistent antibody levels in a low malaria setting



Modified from Wipasa et al. PLoS Pathogens 2010.

Persistent antibody levels for those that retain antibodies in a low malaria setting



Modified from Wipasa et al. PLoS Pathogens 2010.

Big questions in malaria

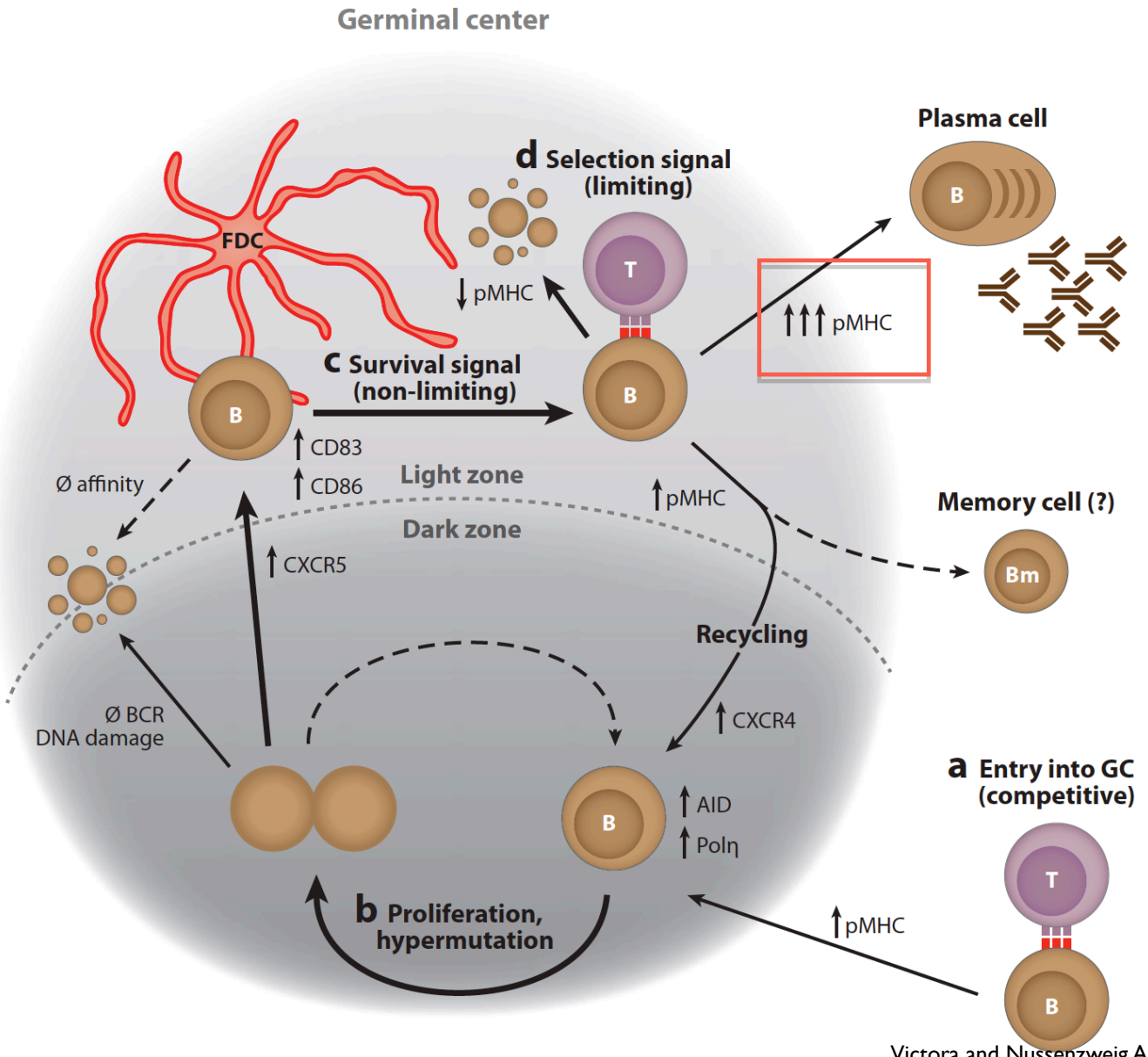
- Why do some individuals get sick while others harbor parasites asymptomatically?
- What constitutes immunity?
- Why is immunity to malaria short-lived?

Development of immune response against malaria

Question: Why do different pathogens elicit vastly different antibody-mediated immune responses?

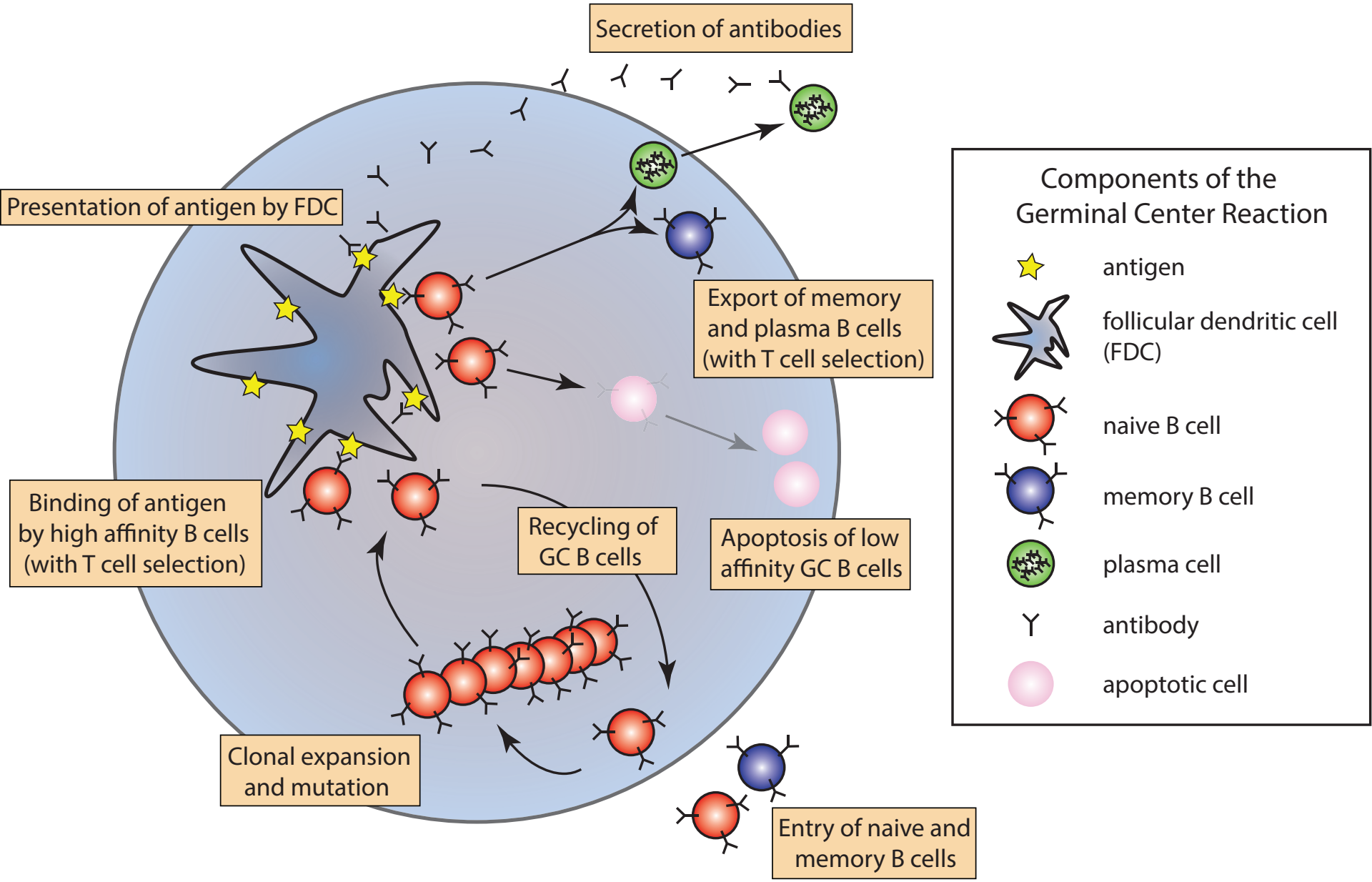
Method: Analyze simulations from a stochastic model of antibody sequence evolution

Germinal center reaction



Victora and Nussenzweig Annu Rev Immunol 2012

Germinal center reaction



Relating BCR sequence to affinity

- Stochastic mapping of genotype to phenotype
- Mutations able to confer large and small effect
- Epistasis and constrained adaptation
- Every BCR has affinity to every epitope
  - Specificity: Epitope to which BCR has highest affinity

Modeling approach

- Stochastic model of GC reaction

  genotype $\longleftrightarrow$ phenotype

  antibody sequence $\longleftrightarrow$ affinity for antigen

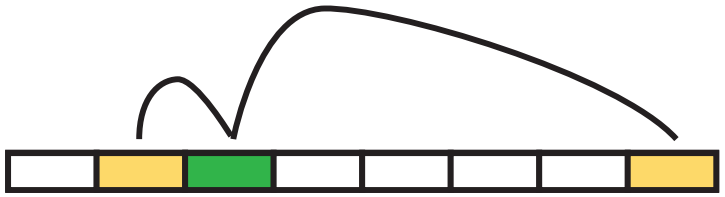
  – NK model

- Assume simple functions
  – Model epistasis
  – Omit some biological features (T cells)

NK model:
"Tunably rugged" energy landscape

N= length of string (sequence)

K = number of associated loci (neighbors)



Value is assigned for each position, based on relationship with the K neighbors.

K controls the amount of epistasis in the model.

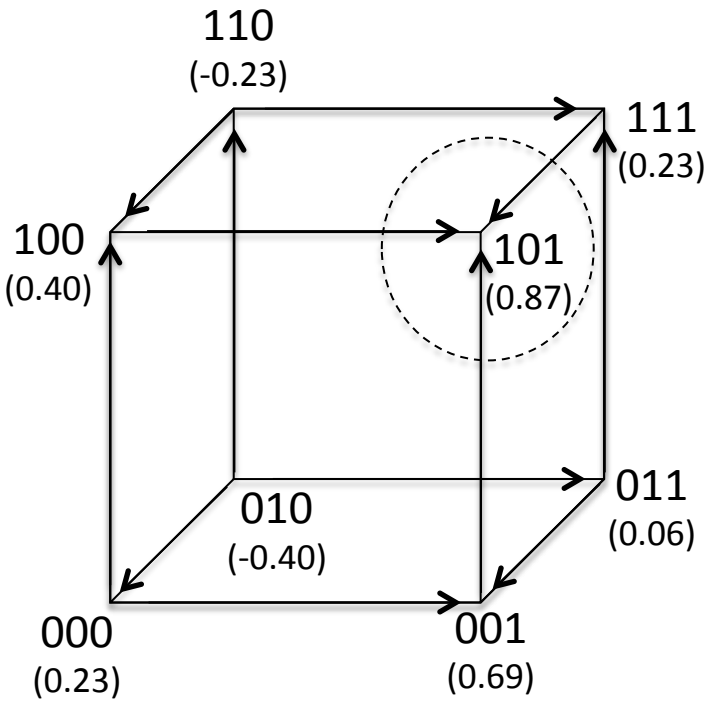
Kauffman and Weinberger 1989

Simple example of NK energy landscape (N=3, K=0)

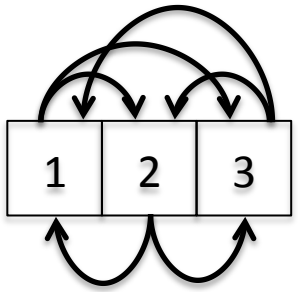
1	2	3

$$W = \frac{1}{\sqrt{N}} \sum_i w_i$$

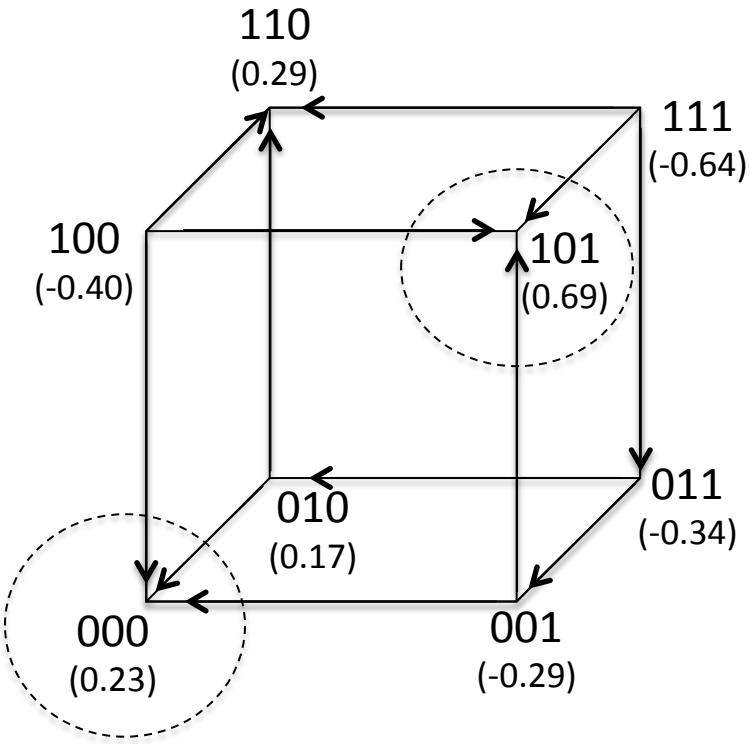
1	2	3	w_1	w_2	w_3	W
0	0	0	0.3	0.2	-0.1	0.23
0	0	1	0.3	0.2	0.7	0.69
0	1	0	0.3	-0.9	-0.1	-0.40
0	1	1	0.3	-0.9	0.7	0.06
1	0	0	0.6	0.2	-0.1	0.40
1	0	1	0.6	0.2	0.7	0.87
1	1	0	0.6	-0.9	-0.1	-0.23
1	1	1	0.6	-0.9	0.7	0.23



Simple example of NK energy landscape (N=3, K=2)



1	2	3	w_1	w_2	w_3	W
0	0	0	0.6	0.3	-0.5	0.23
0	0	1	-0.1	0.5	-0.9	-0.29
0	1	0	-0.4	0.8	-0.1	0.17
0	1	1	-0.3	0.5	-0.8	-0.34
1	0	0	0.9	-0.9	-0.7	-0.40
1	0	1	0.7	0.2	0.3	0.69
1	1	0	0.6	-0.7	0.6	0.29
1	1	1	-0.7	-0.9	0.5	-0.64



Antigenic affinity landscape

- Energy through the sum of single-site contributions:

$$U(x) = \frac{1}{\sqrt{N}} \sum_{i=1}^{N} U_i(\boldsymbol{\nu}_i(\boldsymbol{x}))$$

$$\boldsymbol{\nu}_i(\boldsymbol{x}) = \{x_i, x_{i1}, ..., x_{iK}\}$$

$$U_i(\cdot) \sim \mathcal{N}(0,1)$$

- K neighbors are drawn randomly

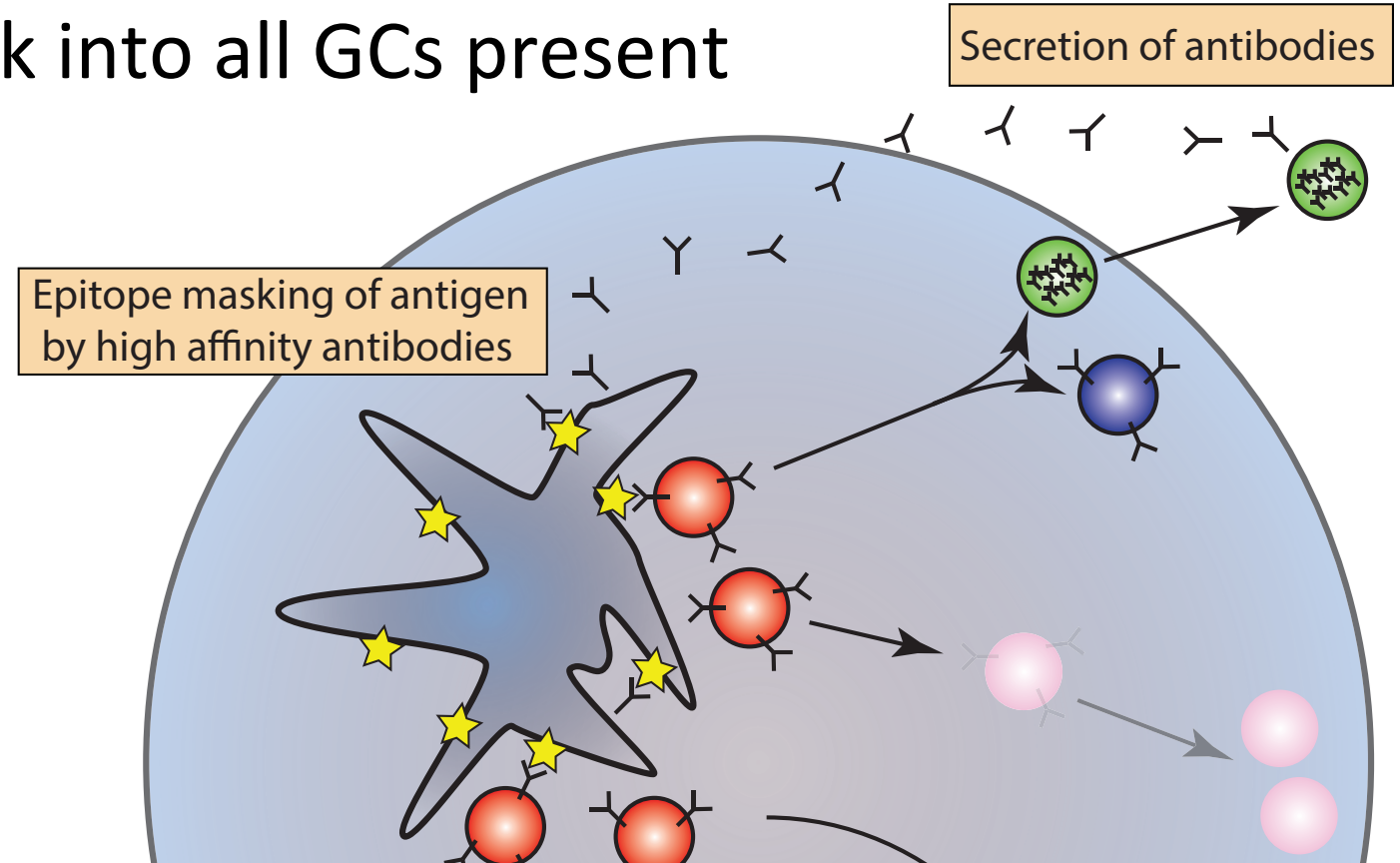
- Translation of energy to affinity: $F = e^{a-bU}$

NK model parameters

- Sequence length, N = 100
  - Length of highly variable positions in antibody
- Neighbors, K = 5
  - Fitted from experimental data
- Amino acid types: 5
  - Group the 20 amino acids based on similarities
- Rounds of mutation and selection: 30
  - Two rounds per day for 15 days
- Single primary infection with one or multiple epitopes

Incorporating epitope masking by Abs

- Reduced ability of B cells to compete in the presence of high affinity Abs
- Feedback into all GCs present

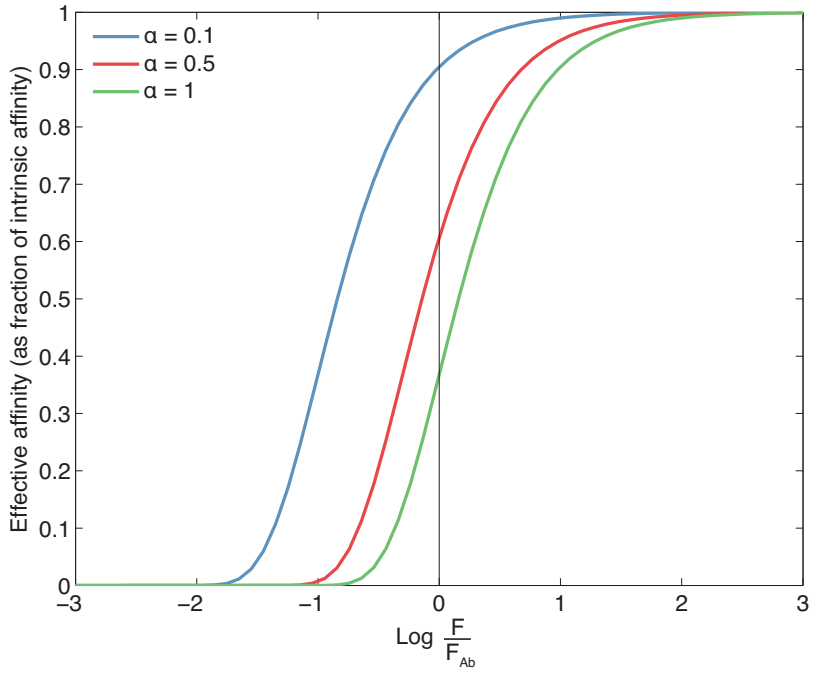


Competition between BCR and Abs

- Abs compete with BCR for antigen
- Competition reduces BCR affinity:

$$E_j(\mathbf{x}) = F_j(\mathbf{x}) \exp\left[-\alpha \frac{F_{\mathrm{Ab}_j}}{F_j(\mathbf{x})}\right] < 1,$$

$$\max_i \left(\frac{C_i F_{\mathrm{Ab}_{i,j}}}{\sum_k F_{\mathrm{Ab}_{i,k}}} \right)$$



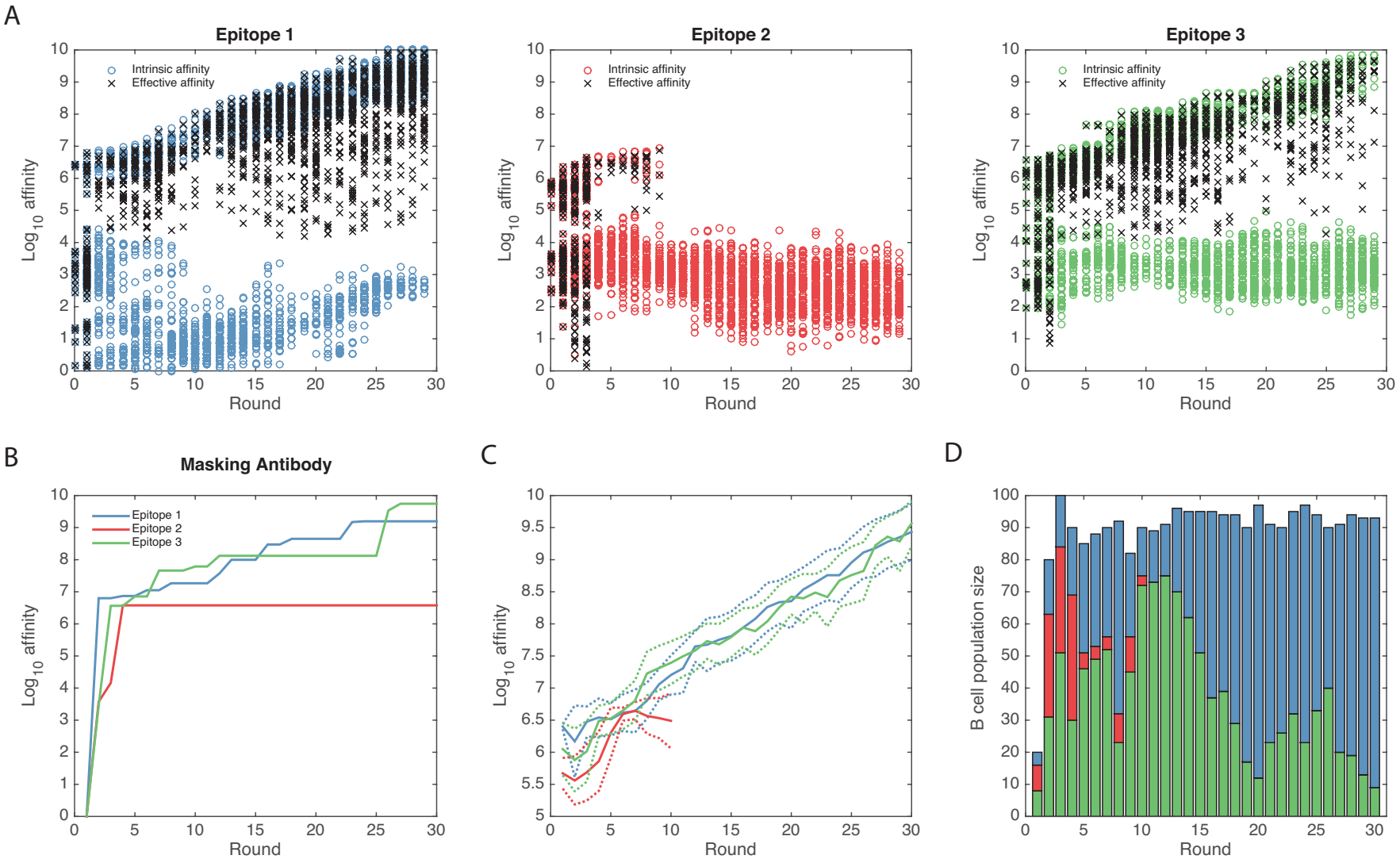
Model parameters

symbol	description	default value	reference
$N_{G,0}$	initial number of GCs per exposure	100[a]	[60]
f	affinity quantile from which to draw GC founders	0.001	[59]
$N_{B,0}$	founding B-cell population size (per GC)	5	[58]
N_B	maximum B-cell population (per GC)	1000[a]	[60]
μ	mutation rate of B cells during affinity maturation	0.01/site/round	[17]
D	maximum number of daughter cells produced per round	4	[16]
m_1	fraction of exported cells becoming memory cells in first round	0.9	text
m_R	fraction of exported cells becoming memory cells in round R	0.1	text
n	fraction of GC cells from which to draw plasma cells	0.1	text
C	initial Ab concentration from plasma cells	1	text
F_T	threshold minimum effective affinity for B-cell removal and GC dissolution	$10^{4.125}$	SI
ϵ	duration of round of affinity maturation	0.5 days	[16]
R	maximum possible number of rounds of affinity maturation	30	[18]
q	number of epitopes per antigen	1	varies
L	B-cell sequence length	100	[52]
K	number of interaction neighbours	5	text
A	size of sequence alphabet	5	[57]
a	tuning parameter for energy-affinity mapping	7.0	text
b	tuning parameter for energy-affinity mapping	2.0	text
α	competition constant for masking Ab and BCR	0.5	text

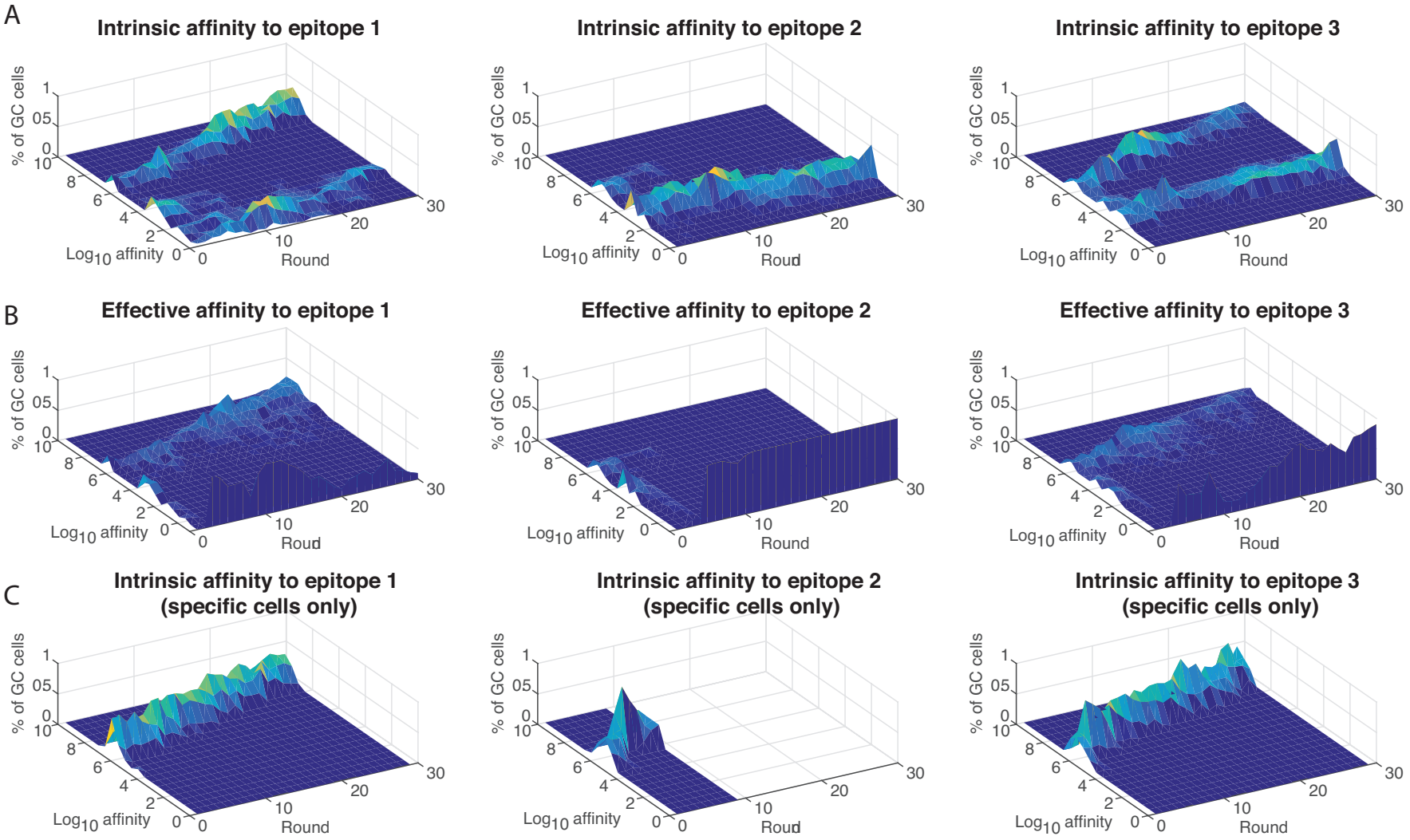
[a]Because the differences in affinity were not dramatic between 10 GCs $\times$ 100 cells/GC and 100 GCs $\times$ 1000 cells/GC, we use 10 GCs $\times$ 100 cells/GC.

Results

Affinity maturation in a single GC



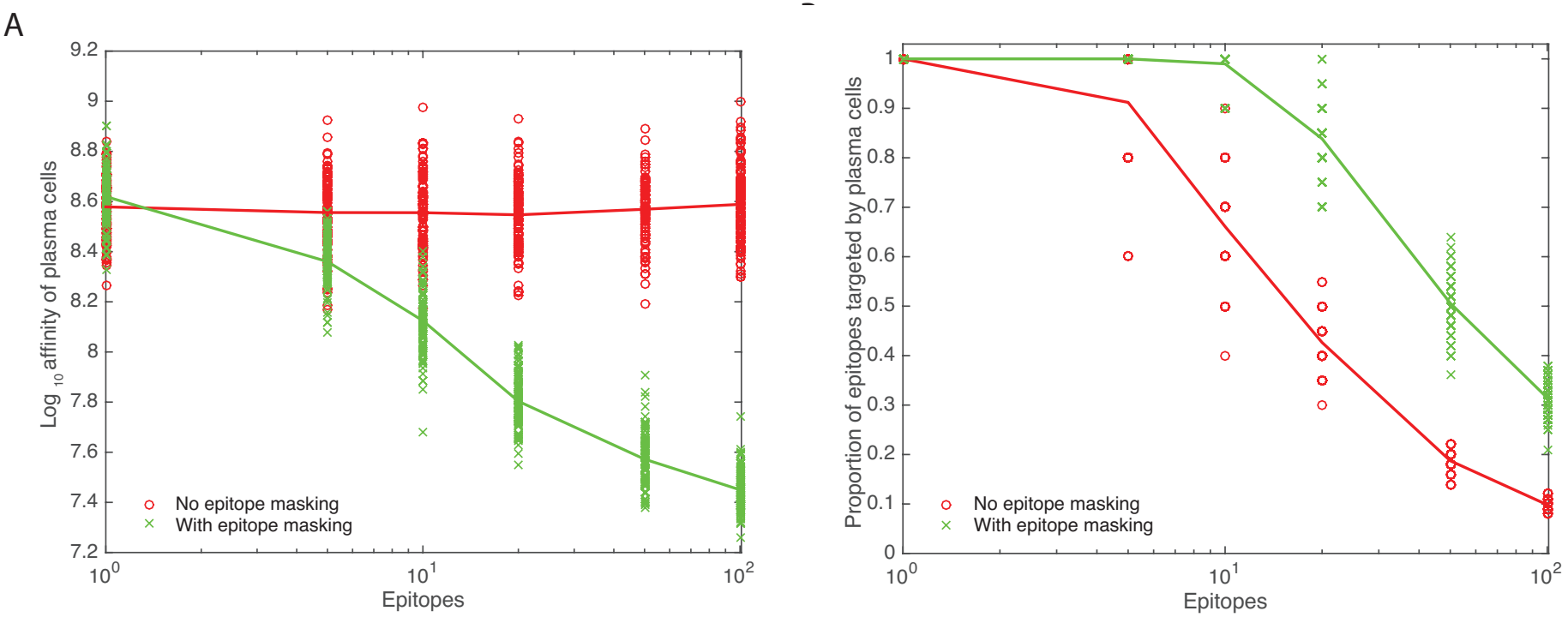
Affinity maturation in a single GC



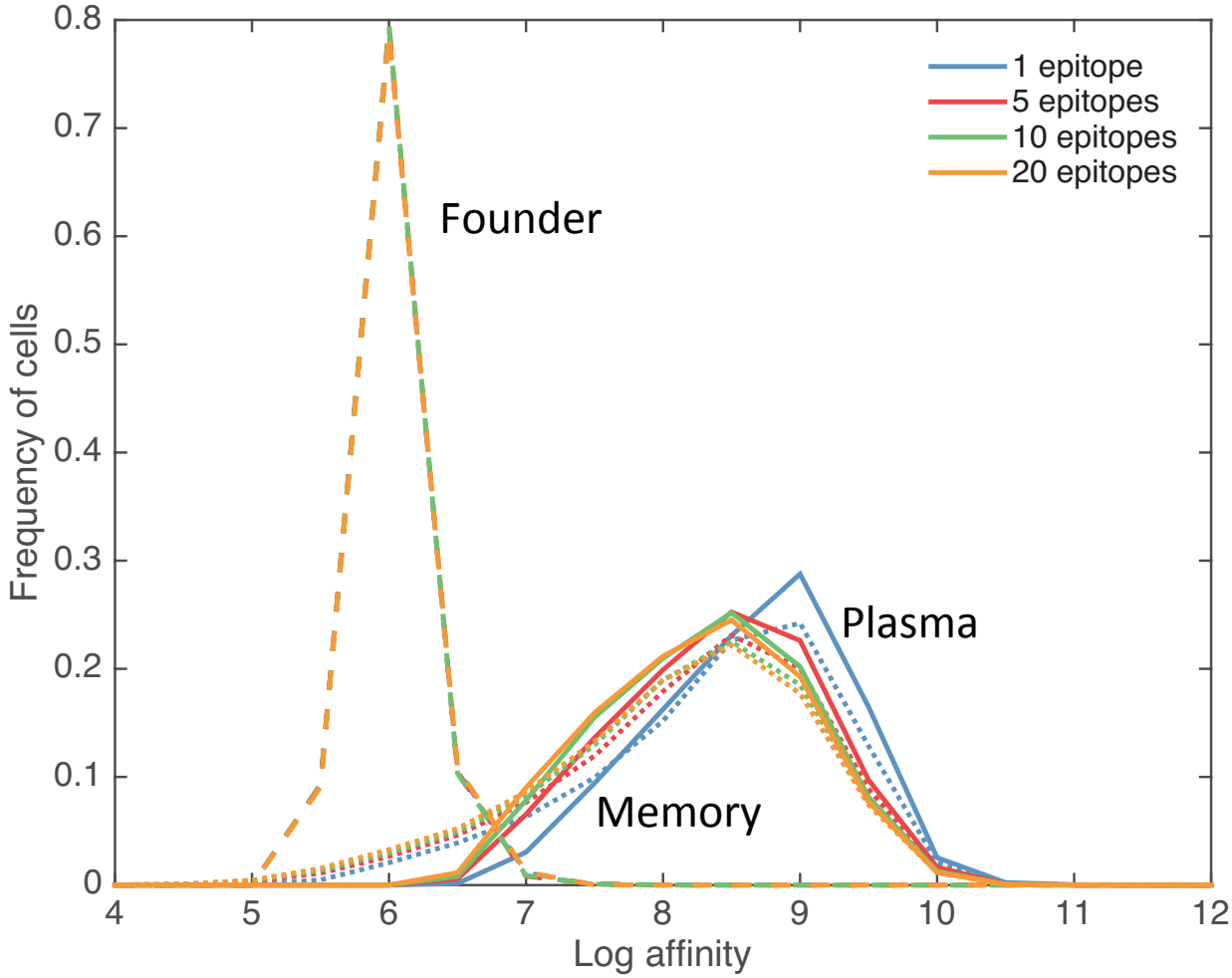
Changes in response with more epitopes

Efficacy

Breadth



Efficacy of response declines



No broadly neutralizing antibodies