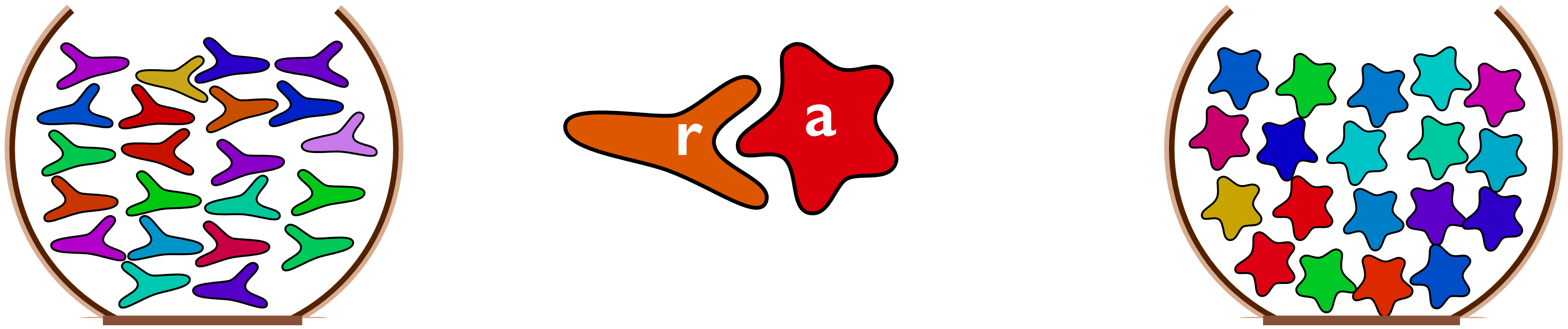

# Predictability and diversity in immune repertoires

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work with
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Olivier Rivoire, UJF
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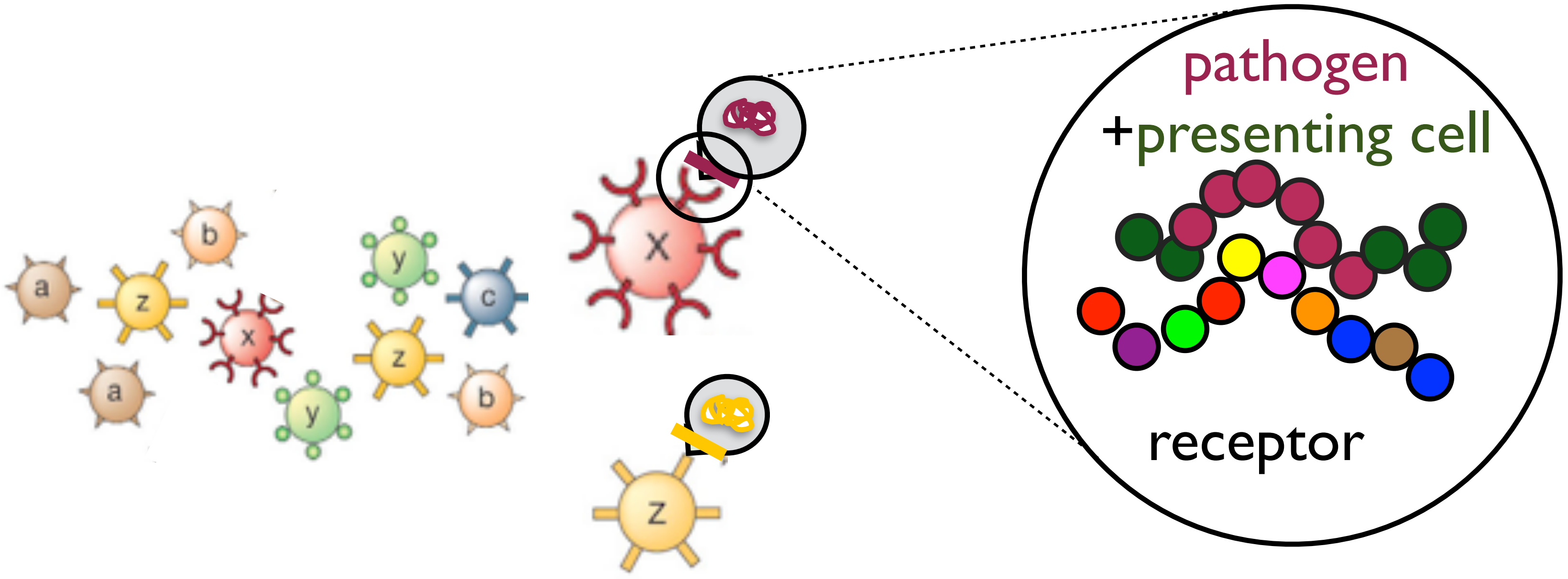
Thierry Mora, ENS

and
Misha Pogorely, RAS Moscow
Dmitriy Chudakov, RAS Moscow
Ilgar Mamedov, RAS Moscow
Yury Lebedev, RAS Moscow

# Immune receptors

- T-cells important actors of immune system



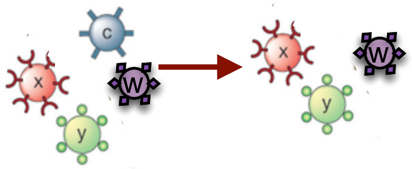
many unique receptors ↔ many different pathogens (virus...)

- triggers immune response

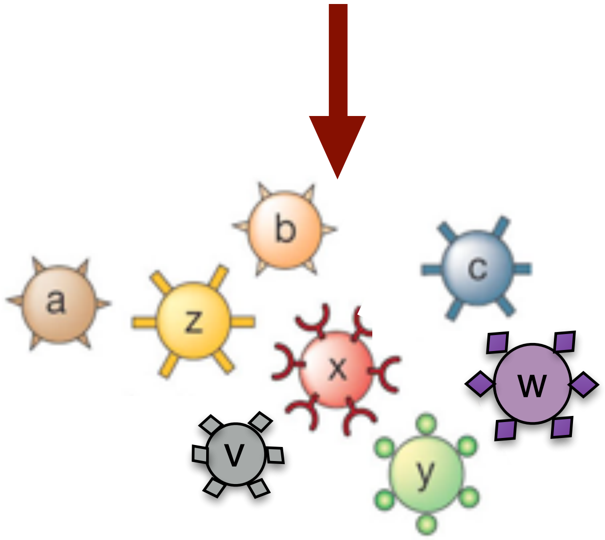
natural, healthy (=“normal”) diversity of immune receptors?

optimal distribution ?

# Repertoire evolution



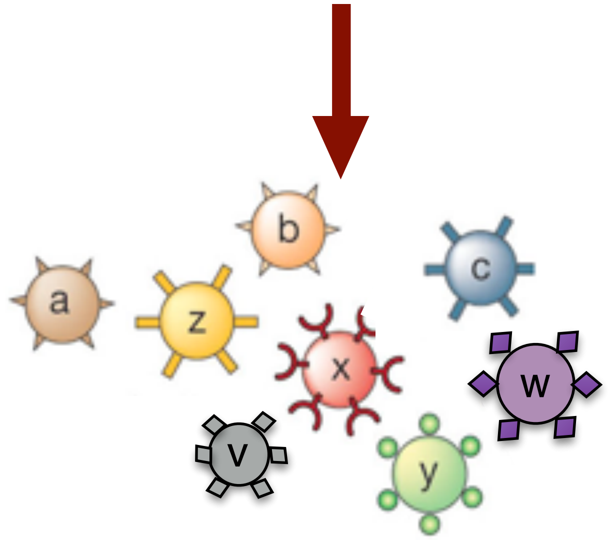
**RECEPTOR GENERATION**



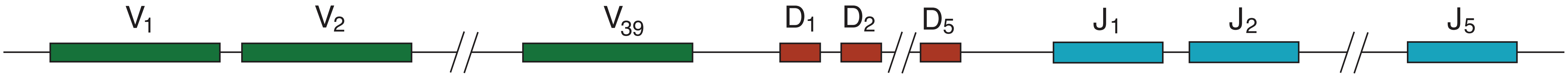
combinatorics + *randomness* → diversity

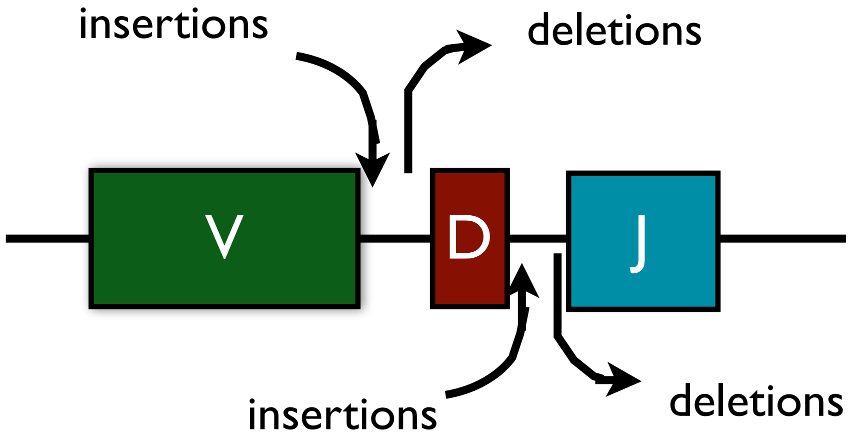
# Repertoire evolution

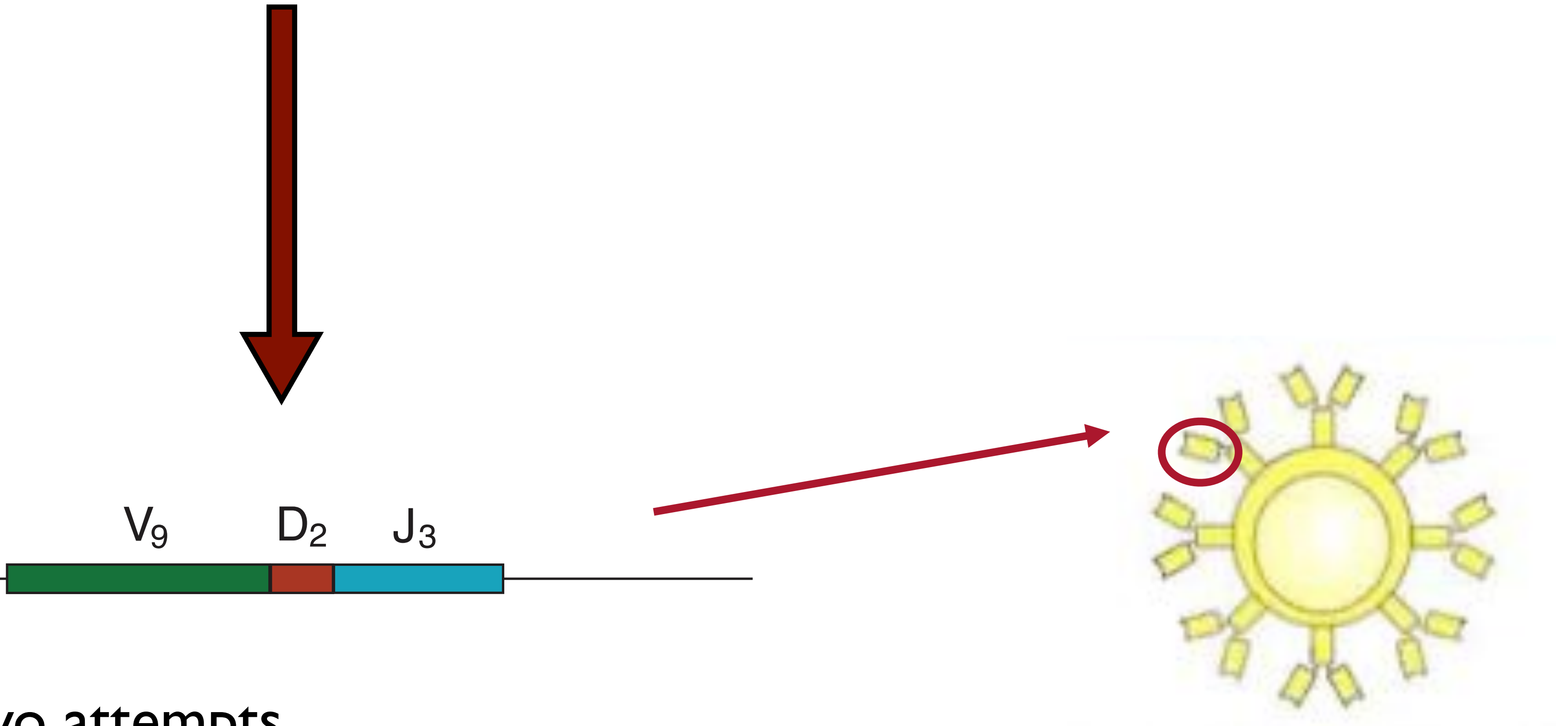
**RECEPTOR GENERATION**



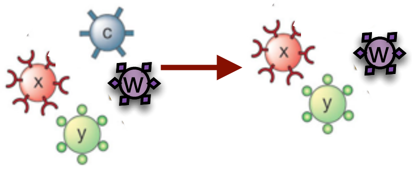
combinatorics + *randomness* → diversity



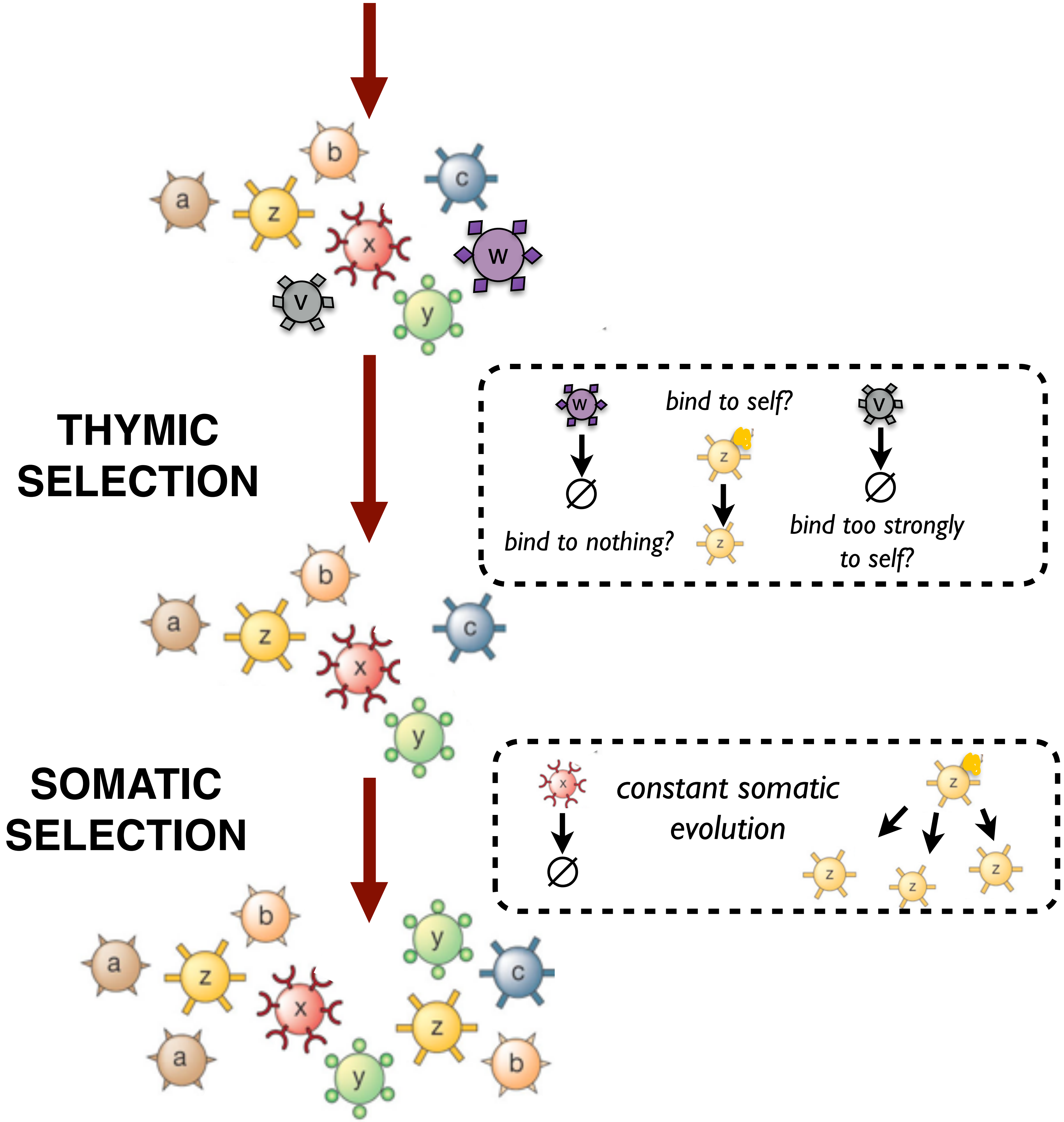




- two chromosomes per cell = two attempts



## RECEPTOR GENERATION



THYMIC SELECTION

*bind to self?*

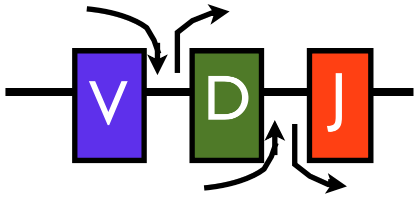
*bind to nothing?*

*bind too strongly to self?*

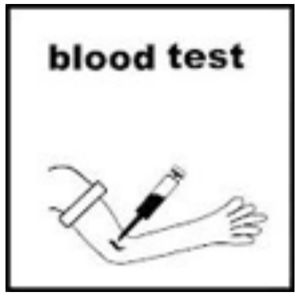
SOMATIC SELECTION

*constant somatic evolution*

# Sequence data



*new data*

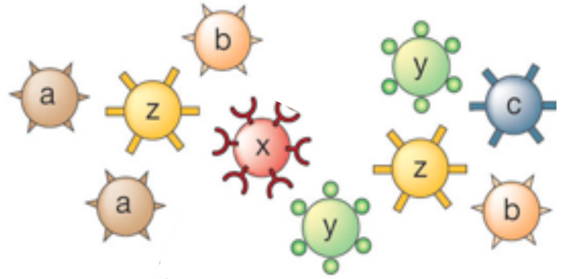


+

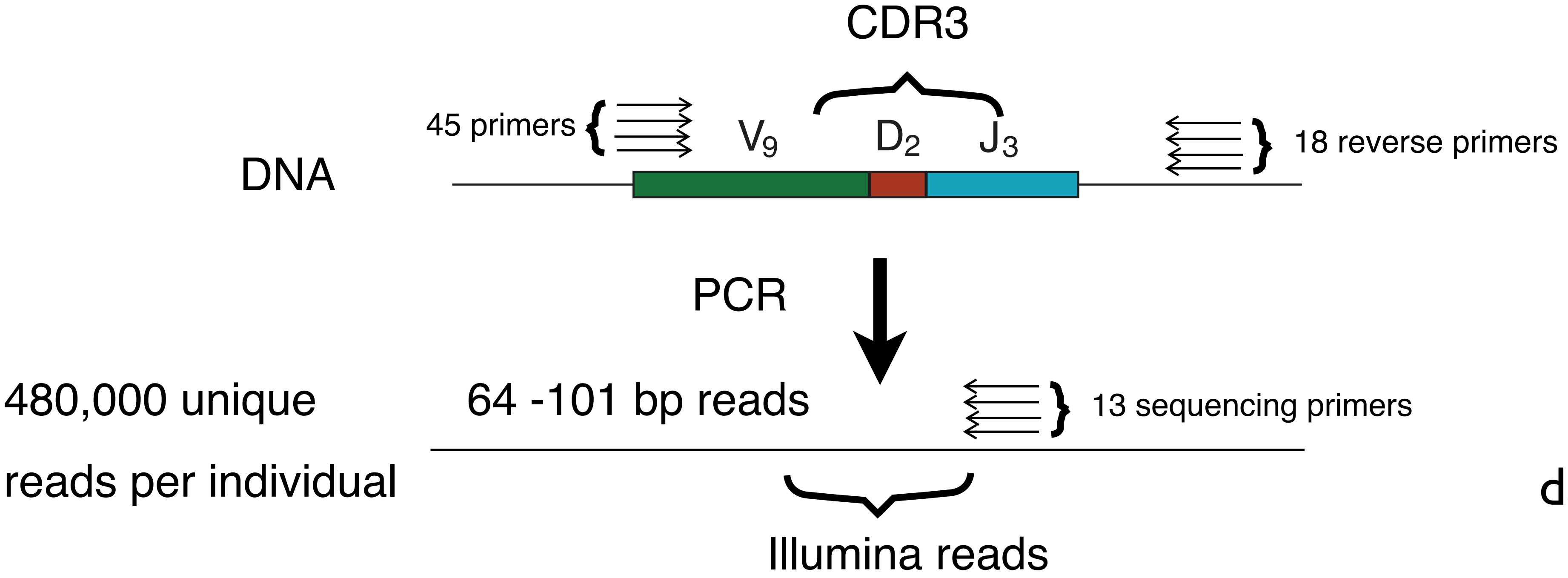
sequencing machine

=

*natural diversity* distribution



- human T-cell beta chain receptor sequences
- 9 people
- out of frame reads (~14% of each type of cells) = 35,000 unique reads ⟶ *generation*
- in frame reads  (~235,000 unique reads) ⟶ *selection*



CDR3

45 primers

$V_9$ $D_2$ $J_3$

18 reverse primers

DNA

PCR

480,000 unique

reads per individual

64 -101 bp reads

13 sequencing primers

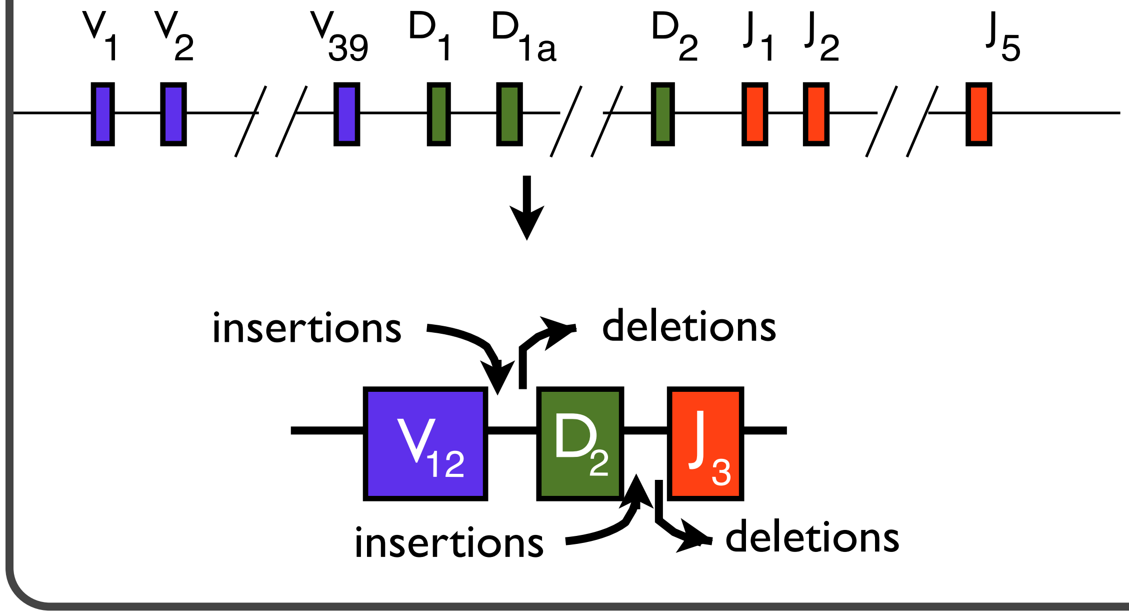
Illumina reads

data from Robins lab and
Chudakov lab

# Probabilistic VDJ recombination annotation

sequence generation:

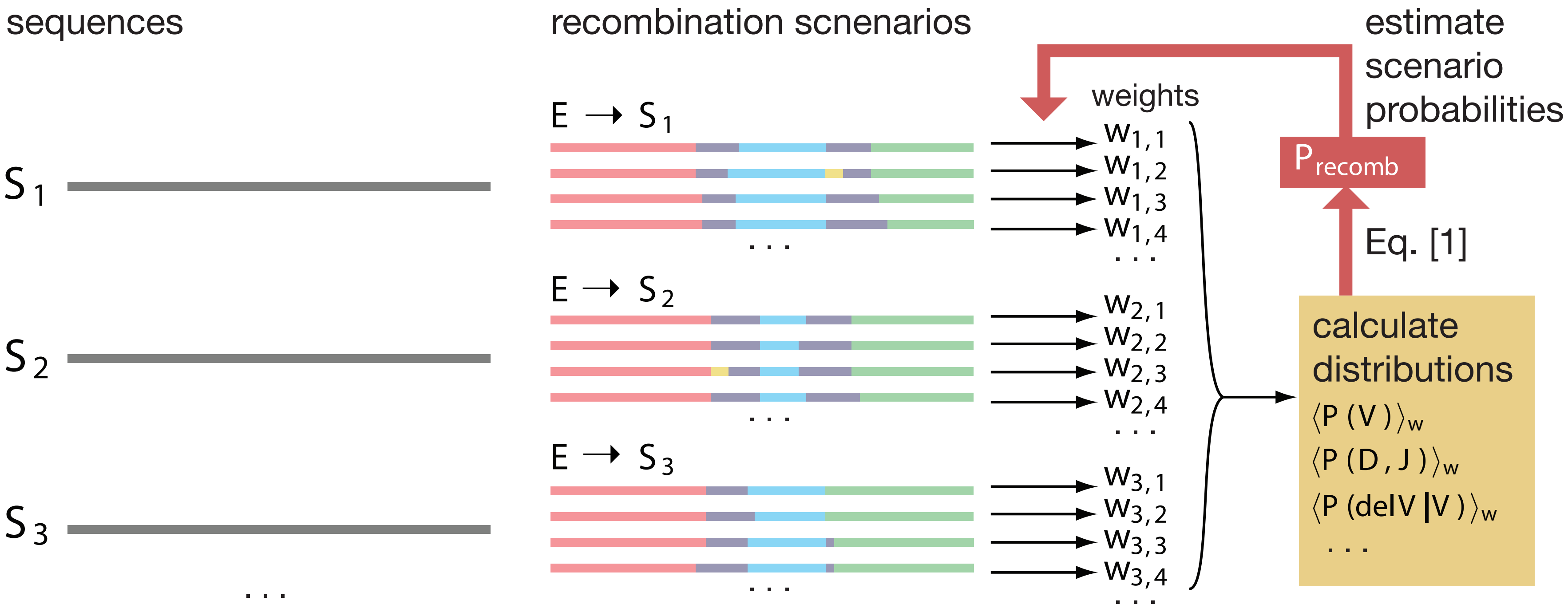
combinatorics + *randomness* → diversity



$\vec{\sigma}$ - receptor DNA sequence

```
TAGGACCTCGGAAACCTCTTCTGCTGGCGCAGAGATACAGGGCTGAGTCTTCTT
TATCTGCCGATGTCGCGAAGGCCCTCCCGCTAAGATCACTGGTGGCACAGAAGT
TAGGGAGAGGTGCCTAACTGCTGGCACAGAAGTACAGAGAGGTCTGGTTGGGGT
TCCGCCGCTAGTCCCTGAAACTACTGGCACAGAGATAGAAAGCTGTCGGGTTCT
CGAAACTGCTGGCACAGAAGTACACAGATGTTTGGGAGGGAGCAGCCGACTCCA
TCTTGGCCGCTAGTCCGAGAAACTGCTGGCACAGAAGTACACAGATGTTTGGGA
TTGTAGGAGCCGGACCGGCCCCCTGTCCCCTTGGCTGCTGGCGCAGAGATACAG
TCATTTAACGTGCGGCCCGCCTGGCACAGAAGTAAAGAGCTGTCTGGTTGTGGT
TAGTAACTCCGCTTCACTGCTGGCACAGAAGTACACAGATGTCTGGGAGGGAGC
TCCCTCCGGTTTGAAGGTCTGCTGGCACAGAAGTACACAGATGTTTGGGAGGG
CCGGTGTTCGCACAGCCCTGGGGACCCTGGCGCAAACCCCGCTTCCCTCGAGGA
```

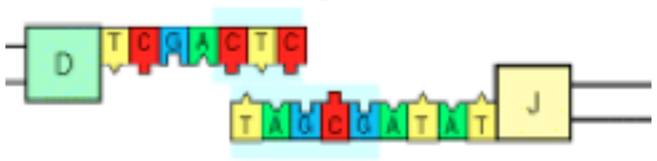
- probabilistic assignment of:



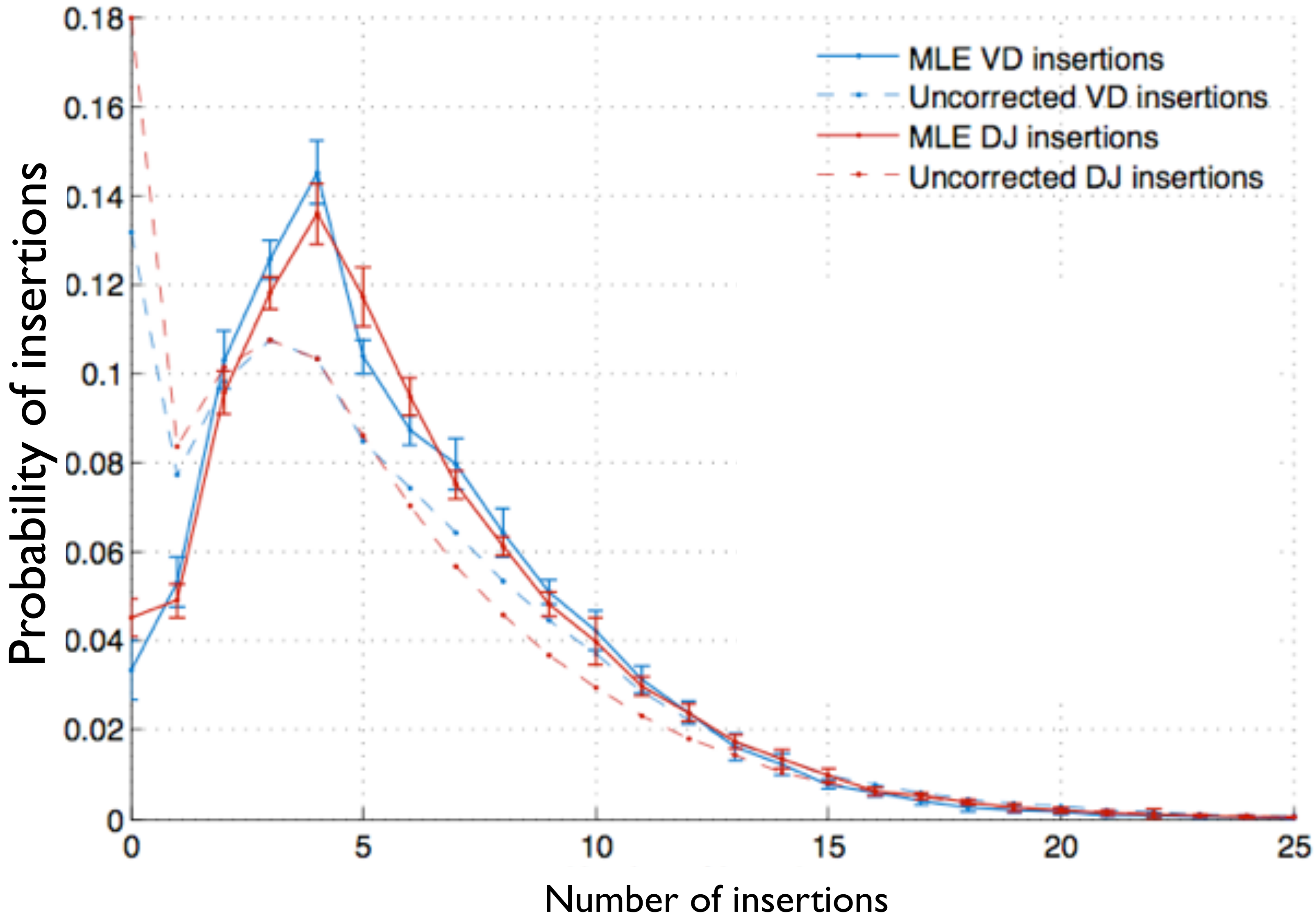
$$P^{\mathrm{recomb}}(\mathrm{scenario}) = P(V)P(D,J)P(\mathrm{deletions}V|V)P(\mathrm{insertions}DJ)... \qquad [1]$$

# Universal insertion profiles

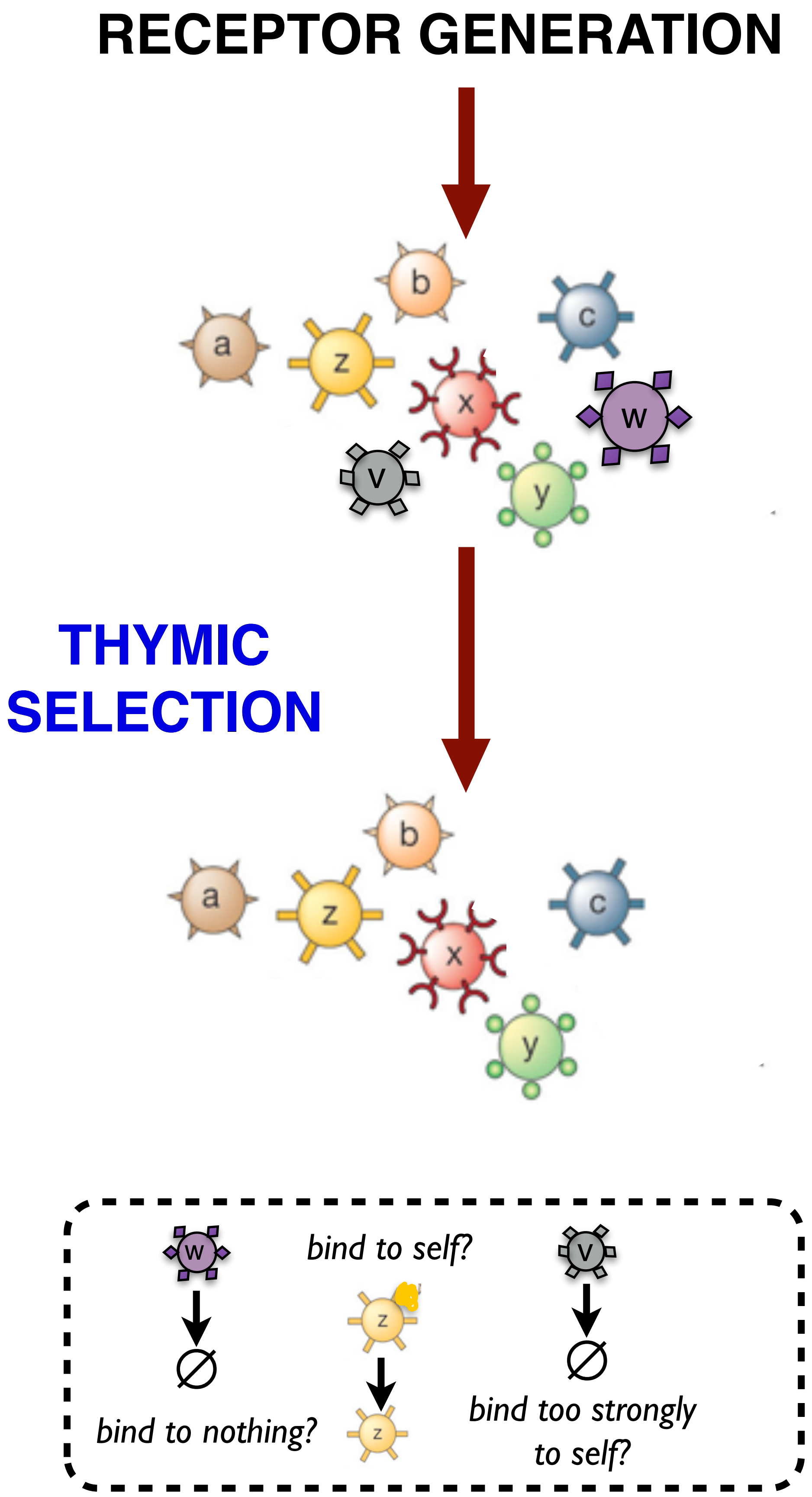
→ universal mechanism for generation



- VD and DJ insertion profiles are identical



# Receptor sharing



RECEPTOR GENERATION

THYMIC SELECTION

bind to nothing?

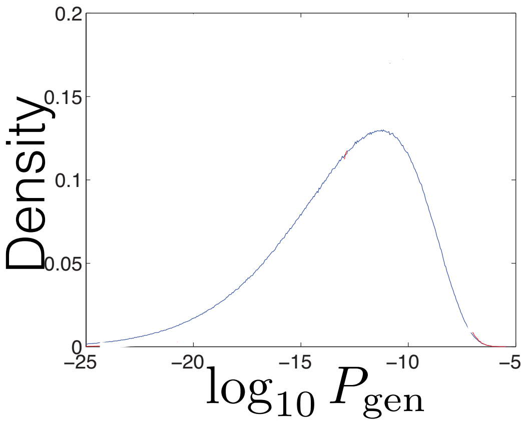
bind to self?

bind too strongly to self?

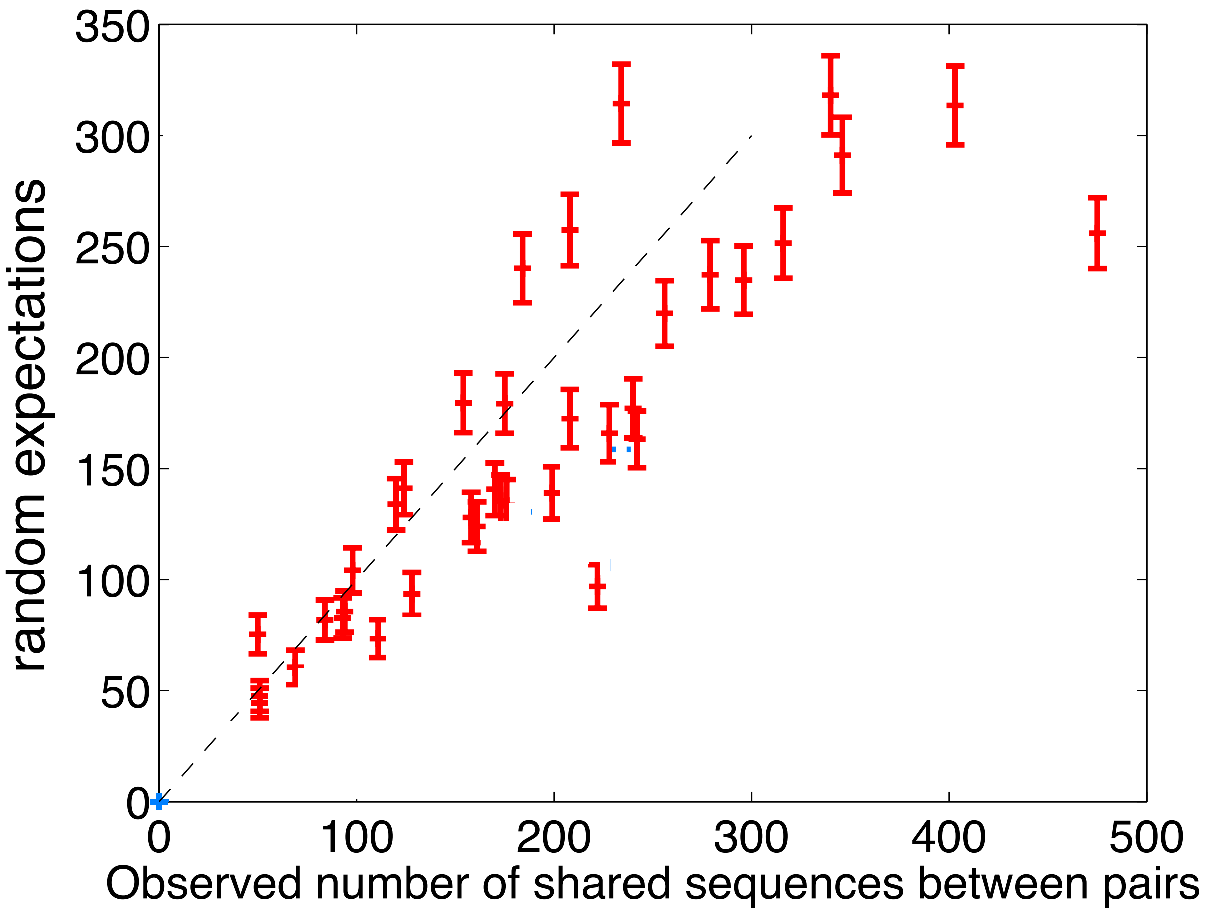
- quantify using selection factors

$$Q(\{\sigma\}) = \frac{P_{\mathrm{post-sel}}(\{\sigma\})}{P_{\mathrm{gen}}(\{\sigma\})}$$

human beta TCR data from Robins lab



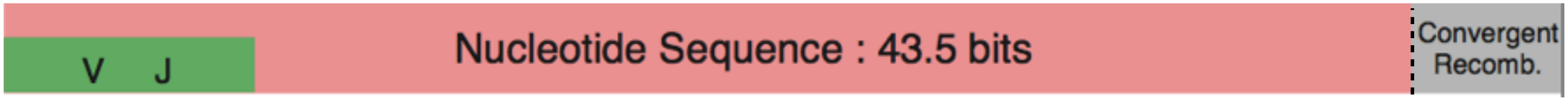
- how many shared receptors between 2 people?



→ close to random expectations

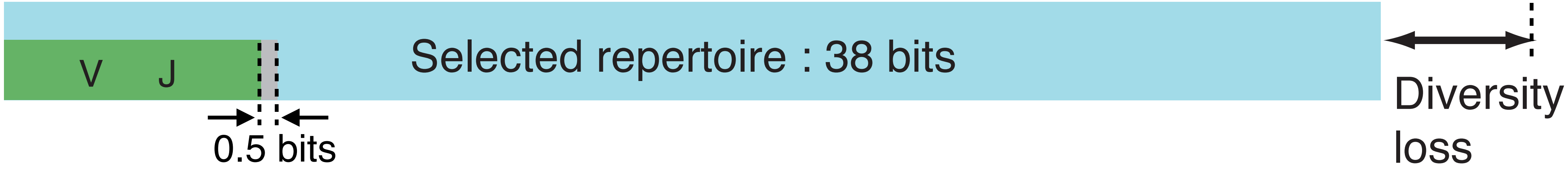
# Entropy of distribution

- entropy of generated repertoire



$\Longrightarrow$ repertoire size $10^{13}$ sequences

- entropy of post-thymic selection repertoire



$\Longrightarrow$ repertoire size $10^{11}$ sequences

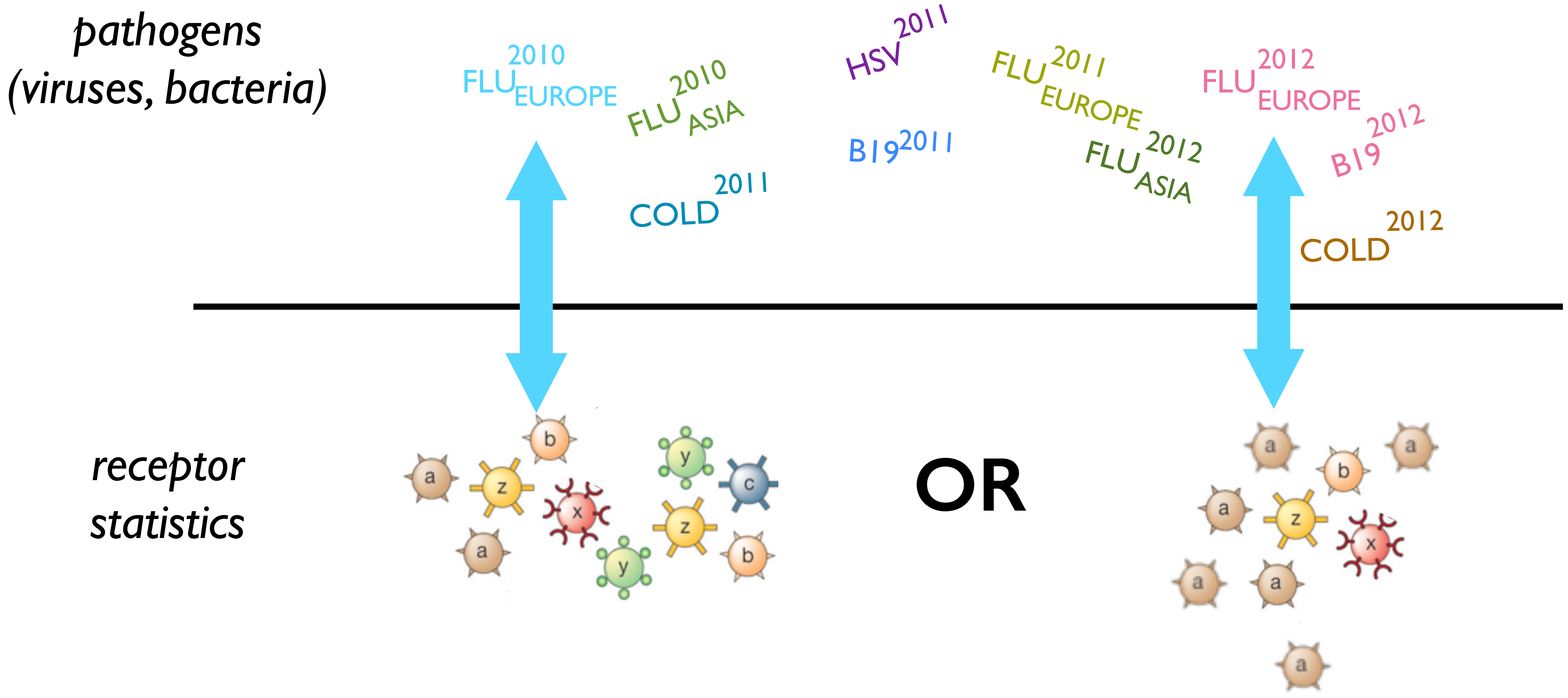
$\longrightarrow$ thymic selection gives 50-fold reduction in diversity

- thymic selection keeps ~15% of sequences but only 2% of diversity

$\longrightarrow$ thymic selection gets rid of rare clones

selection favours clones that are likely to be generated

# Receptor distributions



*pathogens (viruses, bacteria)*

FLU$_{\text{EUROPE}}^{2010}$

FLU$_{\text{ASIA}}^{2010}$

COLD$^{2011}$

HSV$^{2011}$

B19$^{2011}$

FLU$_{\text{EUROPE}}^{2011}$

FLU$_{\text{ASIA}}^{2012}$

FLU$_{\text{EUROPE}}^{2012}$

B19$^{2012}$

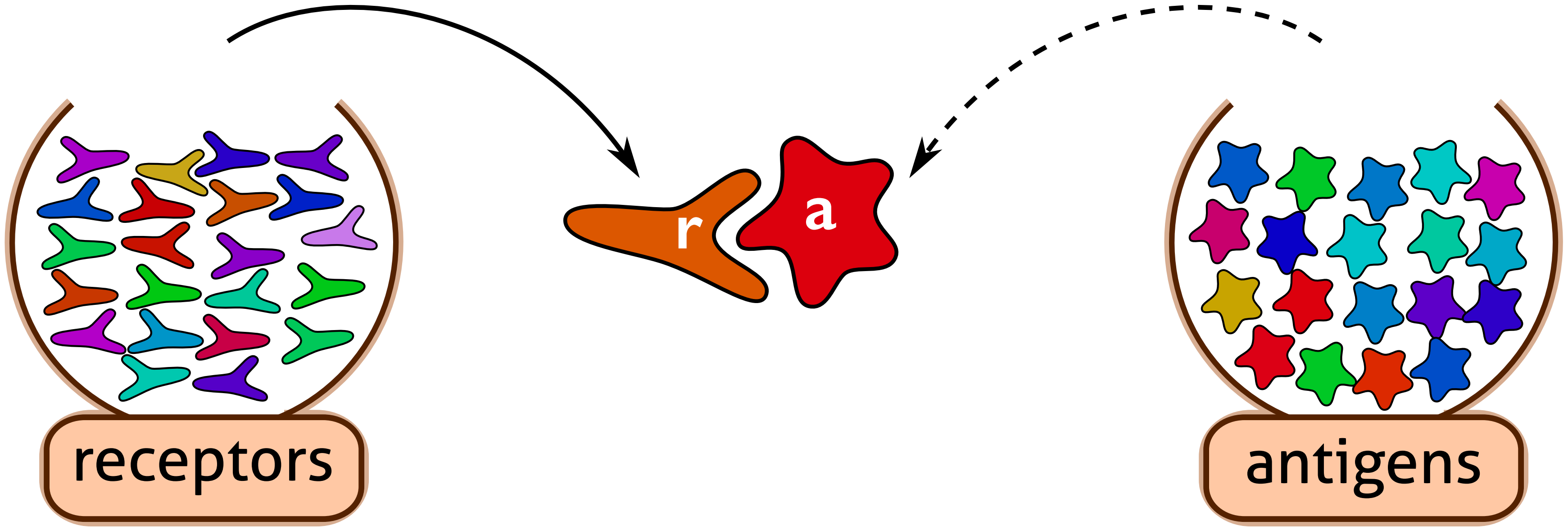
COLD$^{2012}$

*receptor statistics*

OR

optimal distribution ?

# The trade-off

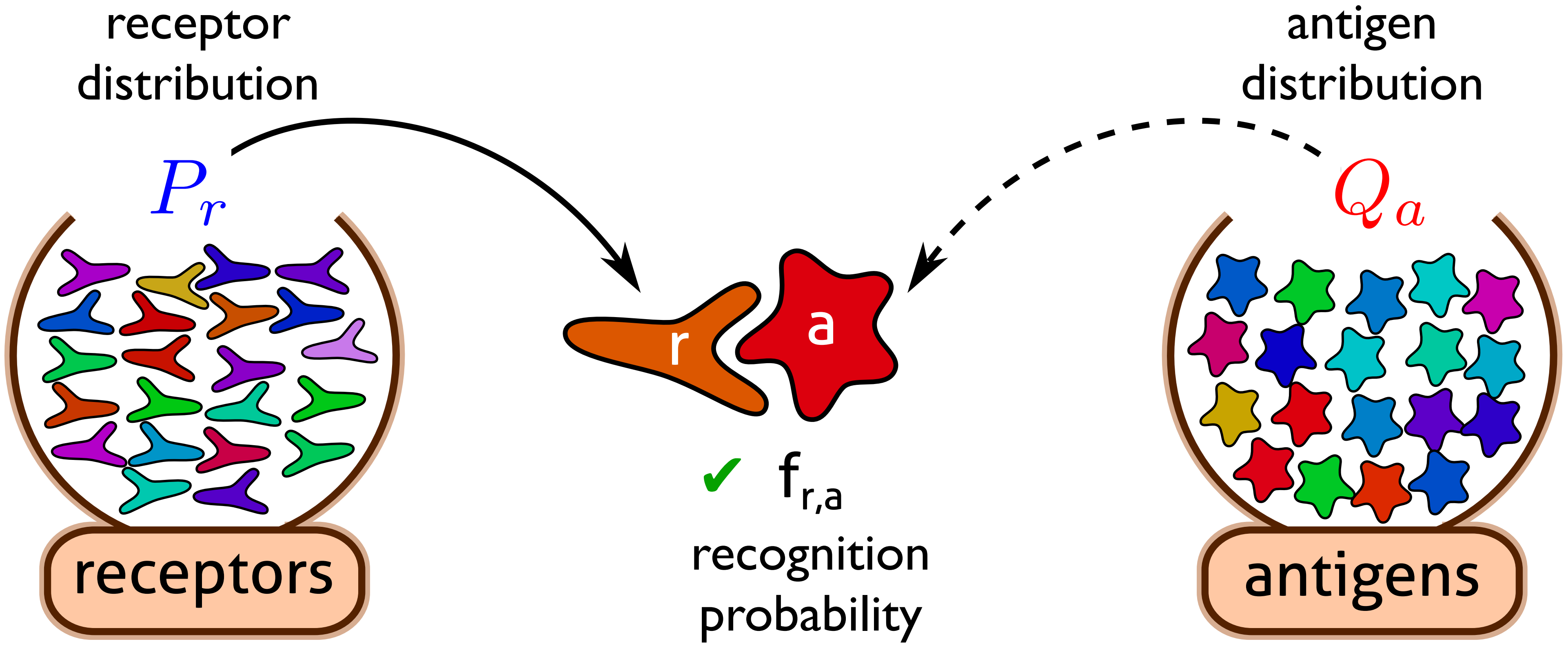


limited number of encounters

**How should immune receptors be distributed to minimize harm from infections?**

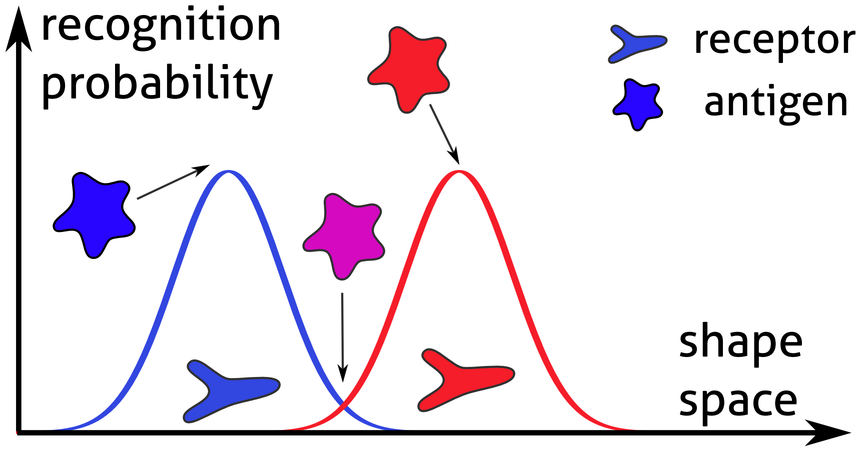
lymphocyte repertoire ↔ antigenic environment

# Cross-reactivity

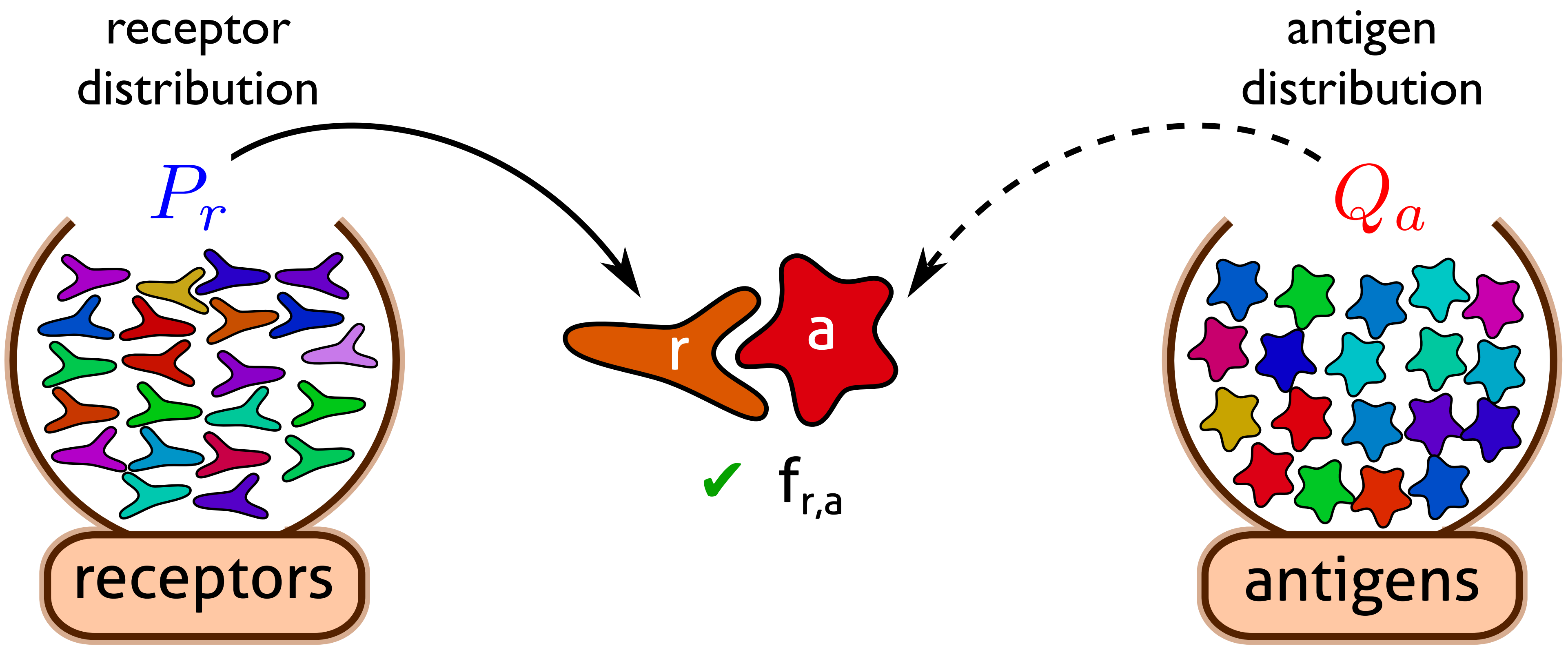


- cross-reactivity - recognition probability
- probability of immune response from encounter with a given antigen

$$\tilde{P}_a = \sum_r f_{r,a} P_r$$



# Receptors - antigens interactions



receptor distribution

antigen distribution

$P_r$

$Q_a$

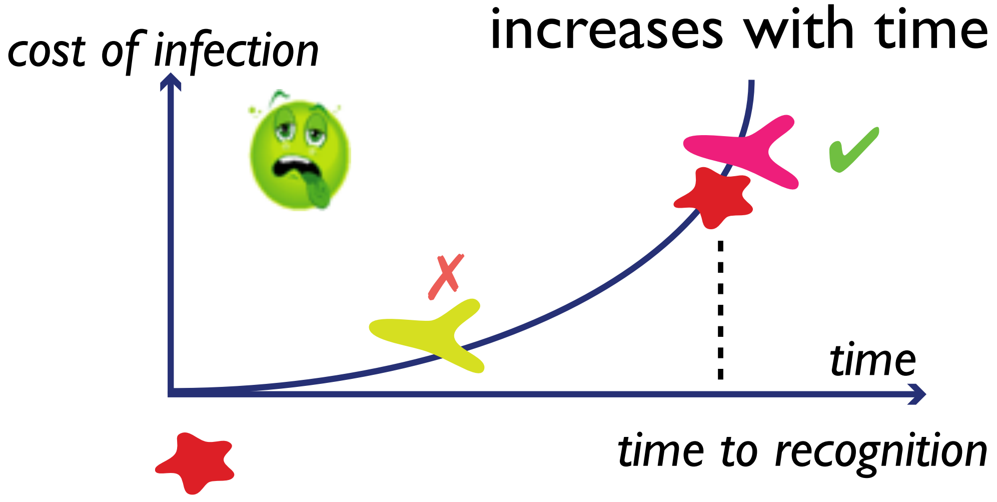
✔ $f_{r,a}$

receptors

antigens

- probability of immune response from encounter with a given antigen $\tilde{P}_a = \sum_r f_{r,a} P_r$
- time measured in mean number of encounters $m$

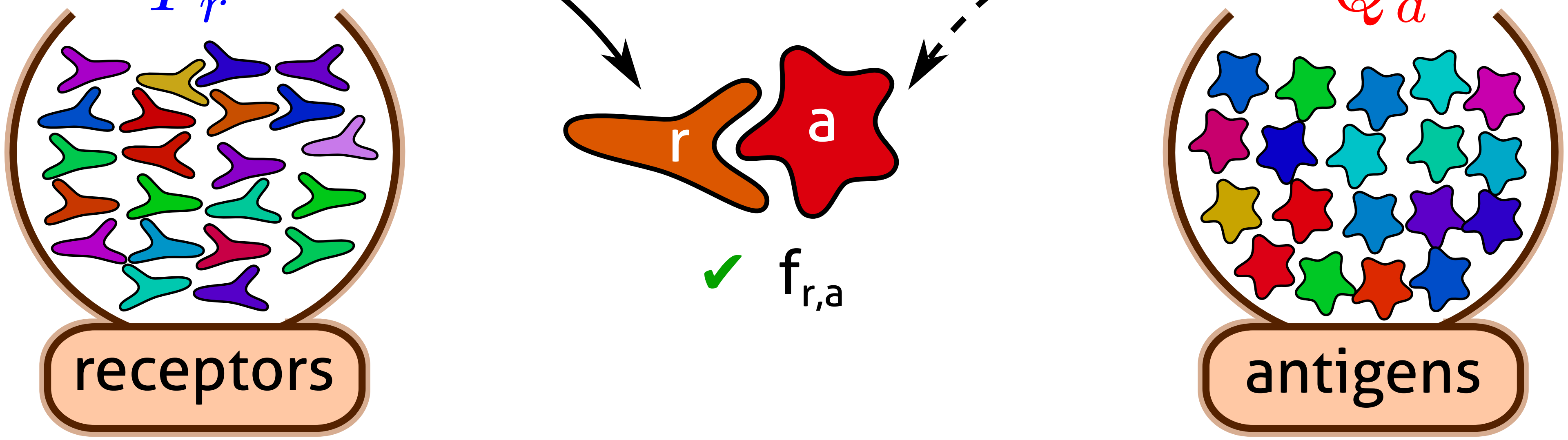
*harm* caused by a given antigen increases with time



$$\bar{F}_a(P_r) = \overset{\text{virulence}}{\mu_a} \int_0^{+\infty} dm\, \overset{\text{effective cost of infection}}{F_a(m)}\, \underset{\text{Poisson distributed recognition}}{\tilde{P}_a e^{-m\tilde{P}_a}}$$

$$\mathrm{Cost}(\{P_r\}) = \sum_a Q_a \bar{F}_a(P_r)$$

# Cost



receptor distribution

$P_r$

antigen distribution

$Q_a$

✓ $f_{r,a}$

receptors

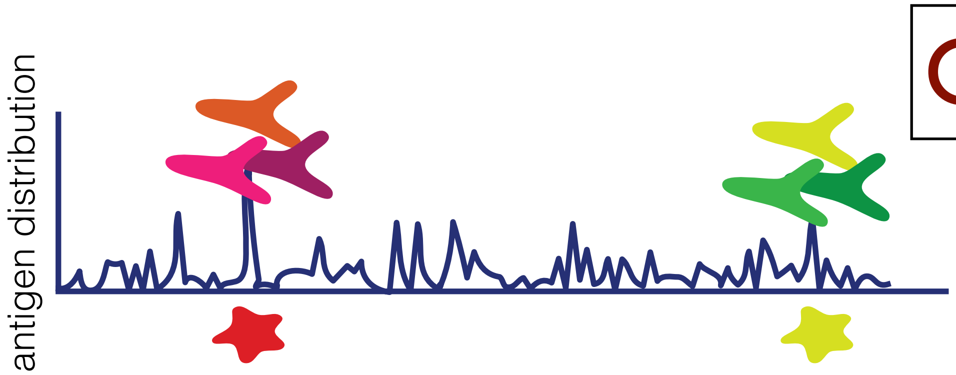
antigens

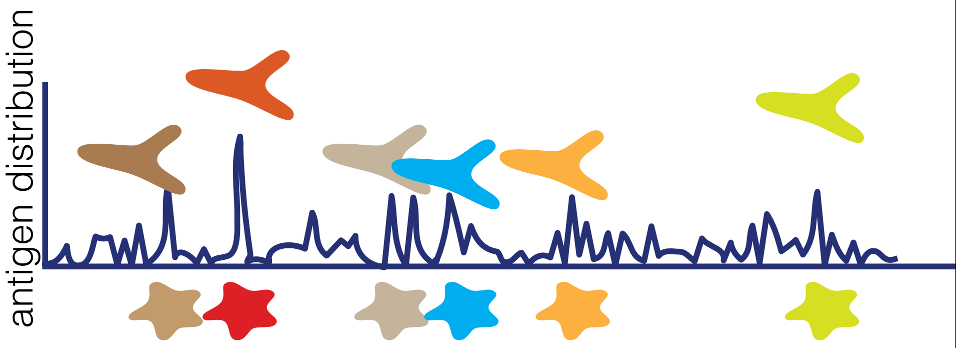
total harm caused by antigen increases with time

$$\mathrm{Cost}(\{P_r\}) = \sum_a Q_a \bar{F}_a(P_r)$$

trade-off: many antigens ↔ limited resources

**Optimal repertoire?**





→ minimize cost given fixed antigen distribution

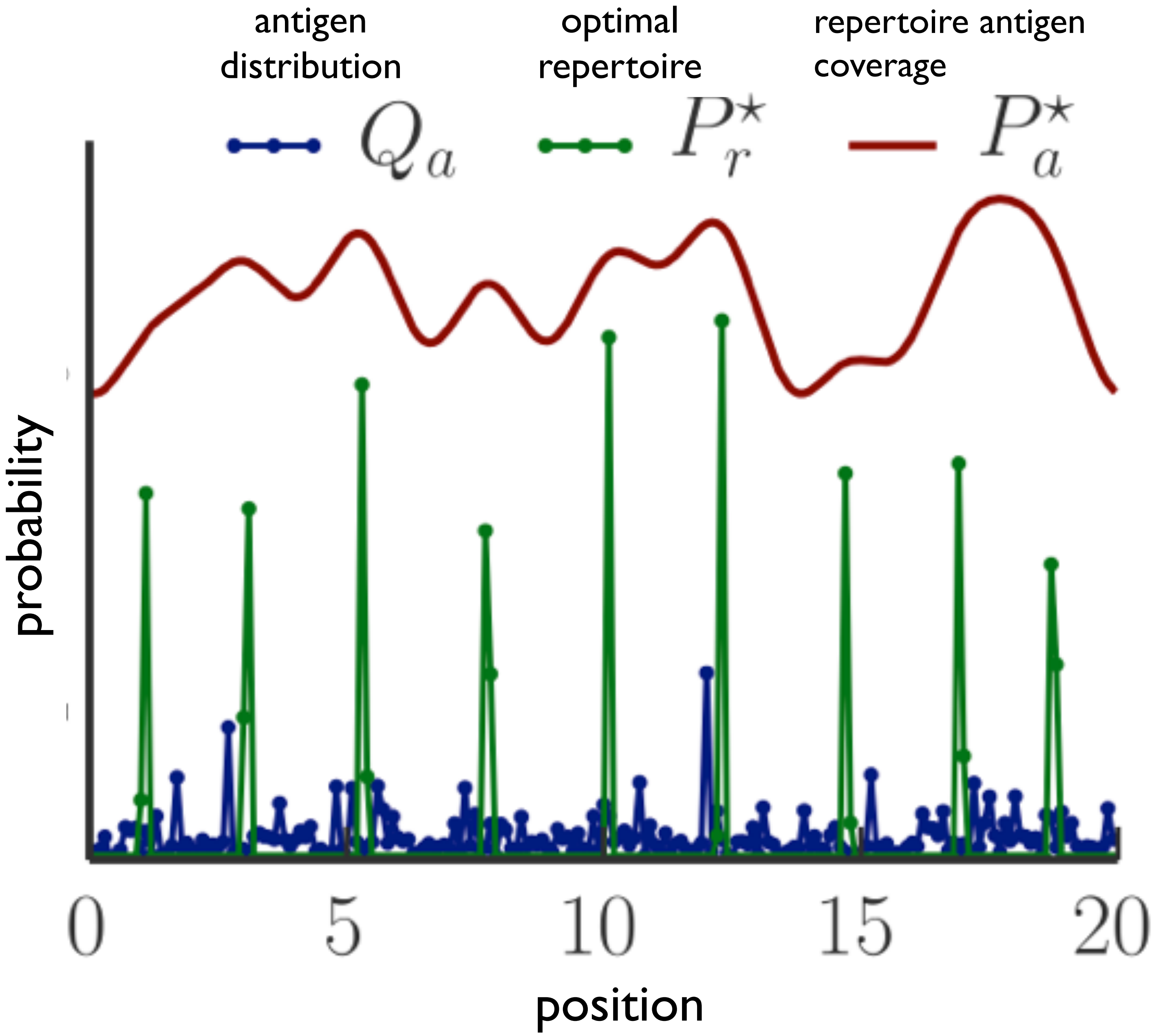
# Peaked optimal repertoires

- exponentially expanding antigen population
  + exponentially growing cost in time

$$F(m) = m$$

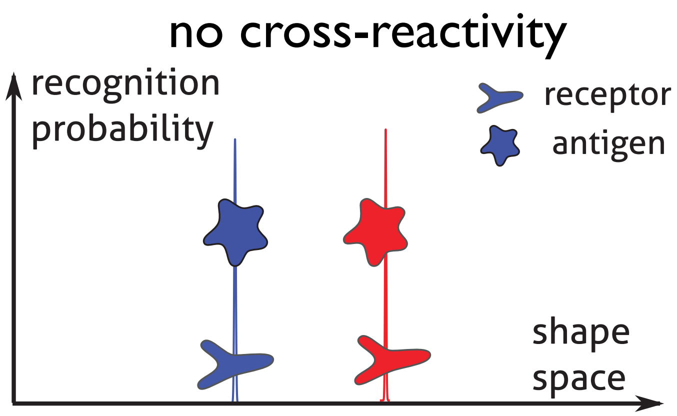
- peaked distributions
- tile space

- coverage follows antigen distribution
- but not exactly



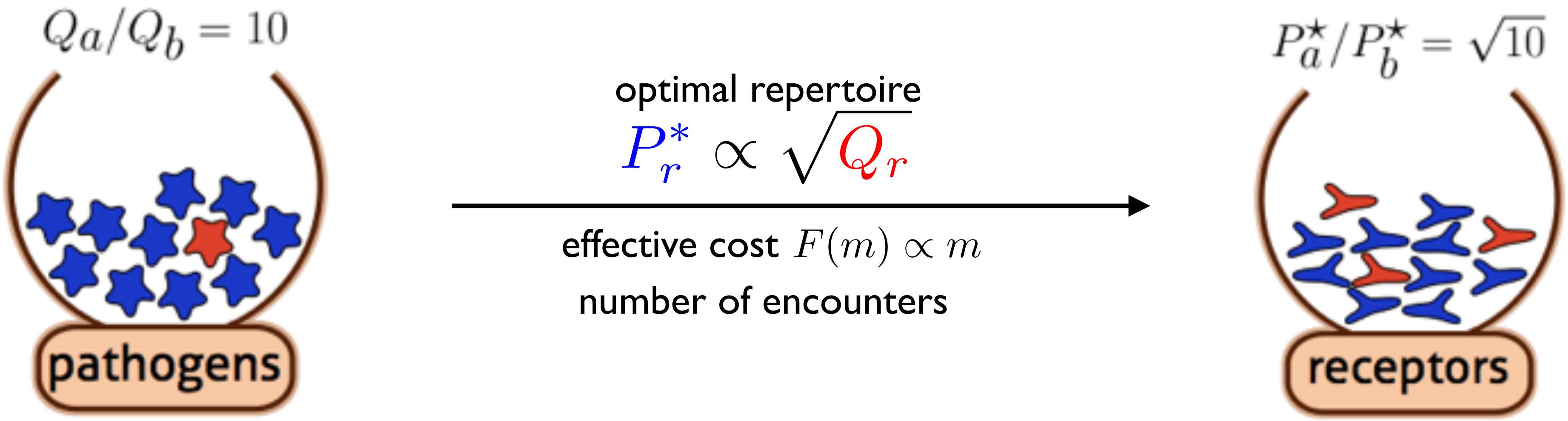
# Covering rare pathogens

How many resources aimed at common/rare antigen?



depends on cost of late recognition ⟶ effective cost function

- exponentially expanding antigen population



optimal repertoire

$$P_r^* \propto \sqrt{Q_r}$$

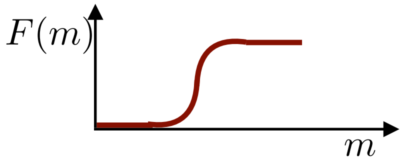
effective cost $F(m) \propto m$

number of encounters

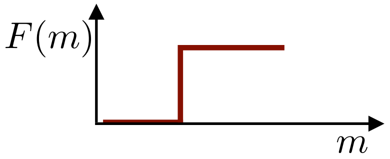
- exponentially expanding antigen population + exponentially growing cost in time

$$F(m) = m^\alpha \qquad \longrightarrow \qquad P_r^* \propto {Q_r}^{1/(1+\alpha)}$$

- saturated cost ⟶ low frequency cut-off

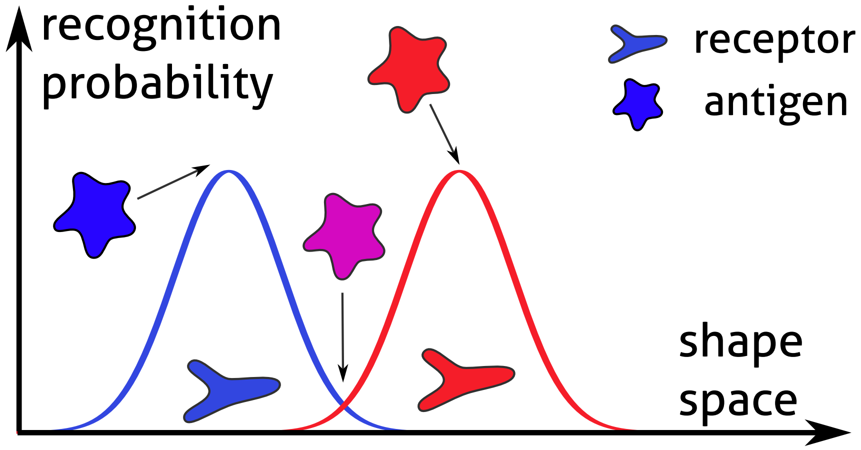


- harm past threshold ⟶ flattened receptor distribution

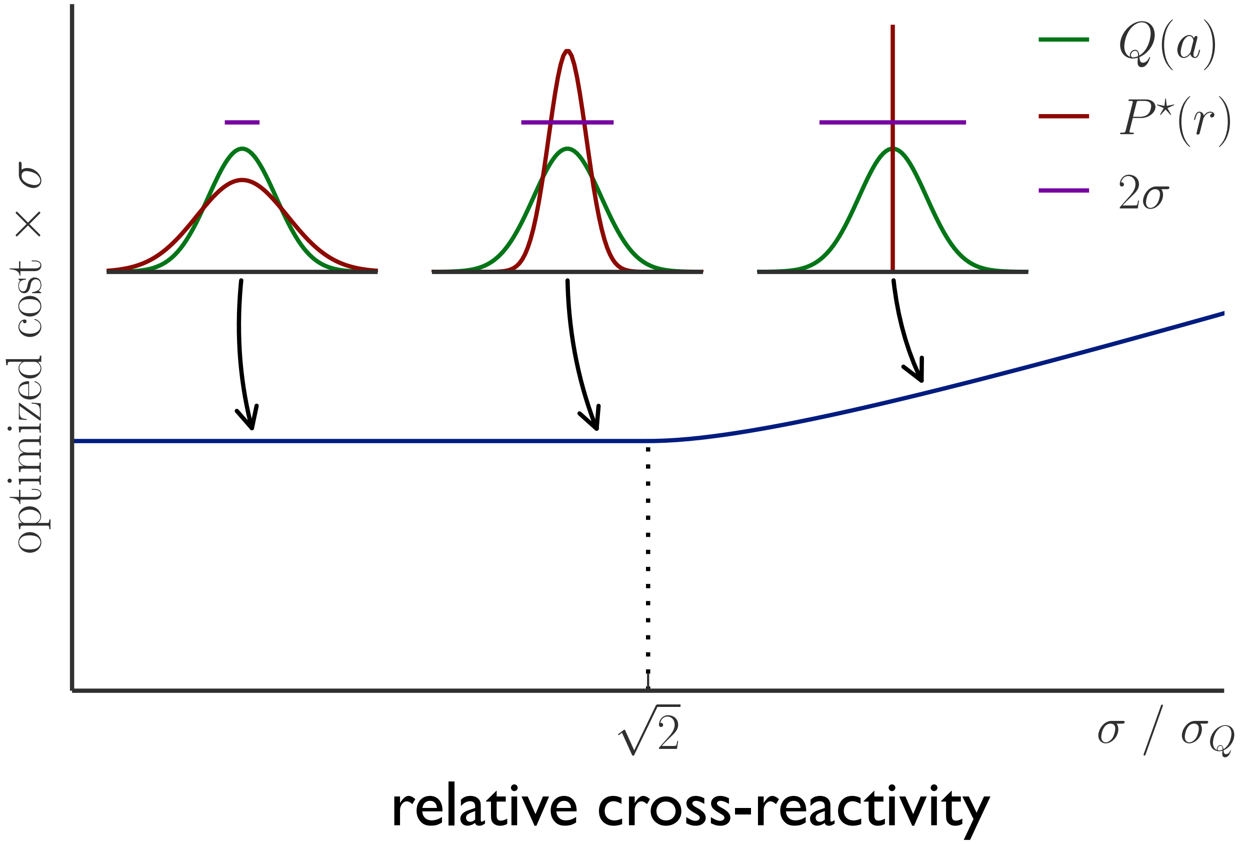


- $P_r^* \propto Q_r \Leftrightarrow$ very slowly increasing cost $F(m) \propto \ln m$

# Cross-reactivity



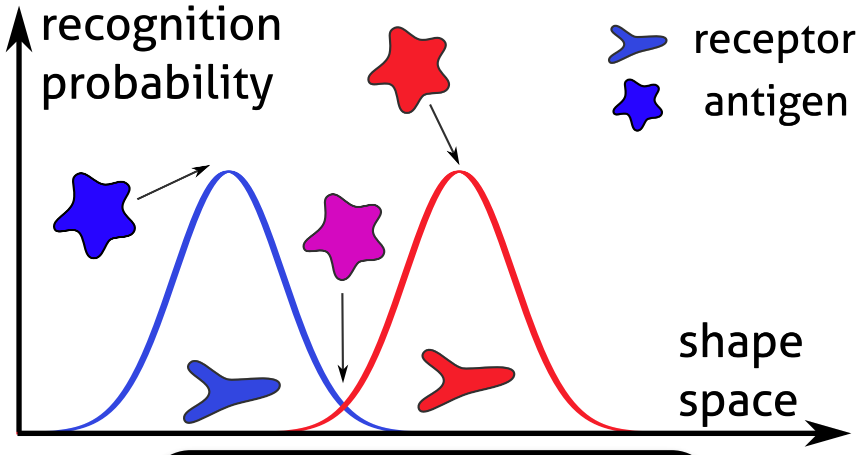
- antigen distribution + cross-reactivity Gaussian



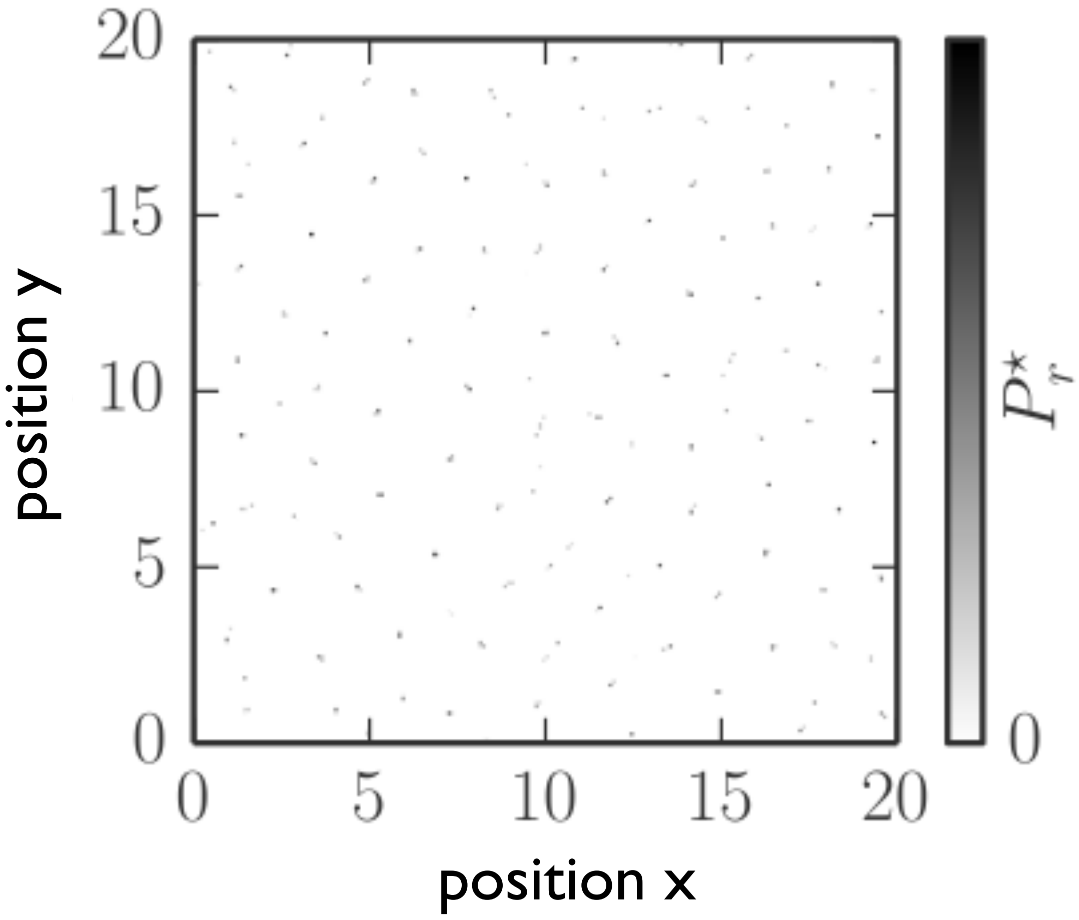
→ large cross-reactivity concentrates distribution

# Peaked optimal repertoires

rare antigens

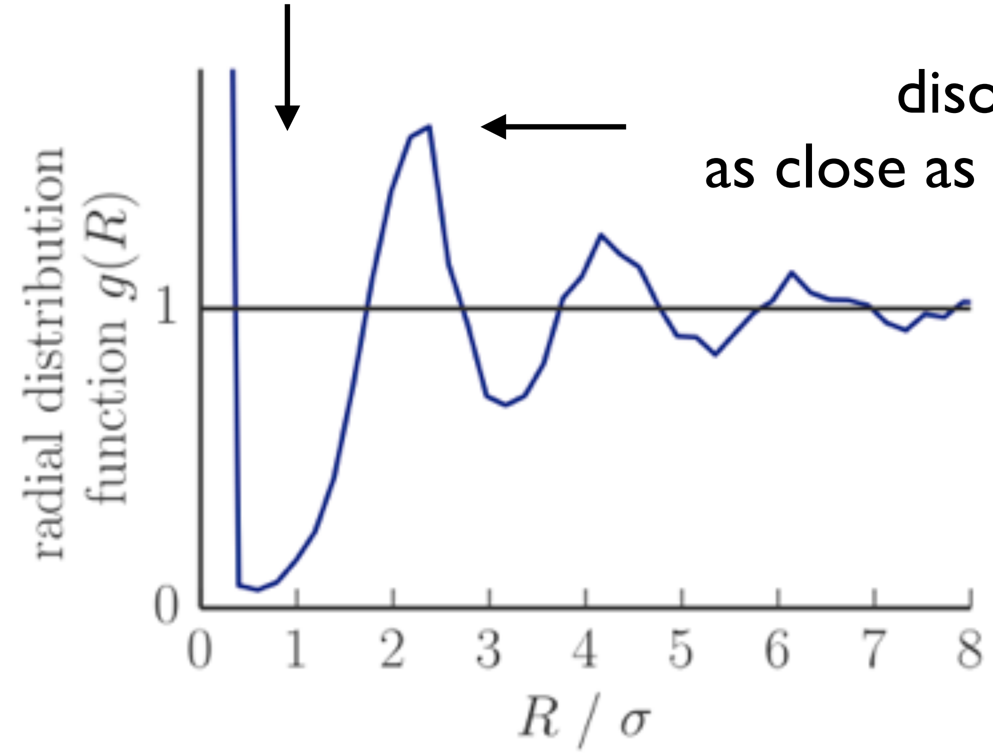


cross-reactivity

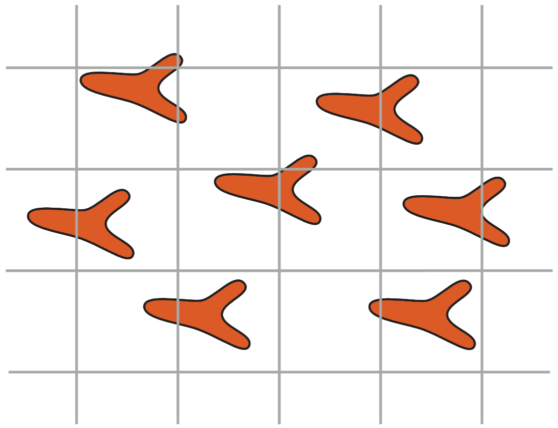


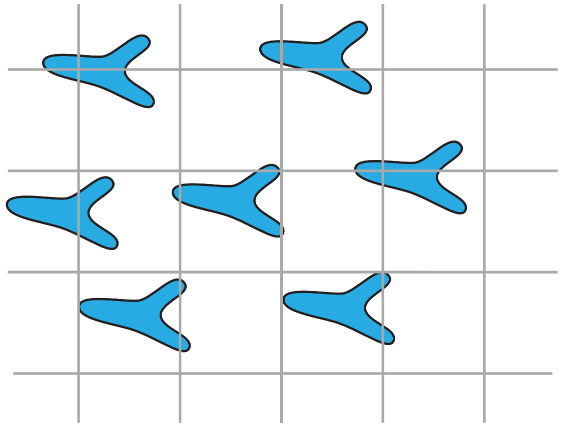
# Disordered hyperuniformity

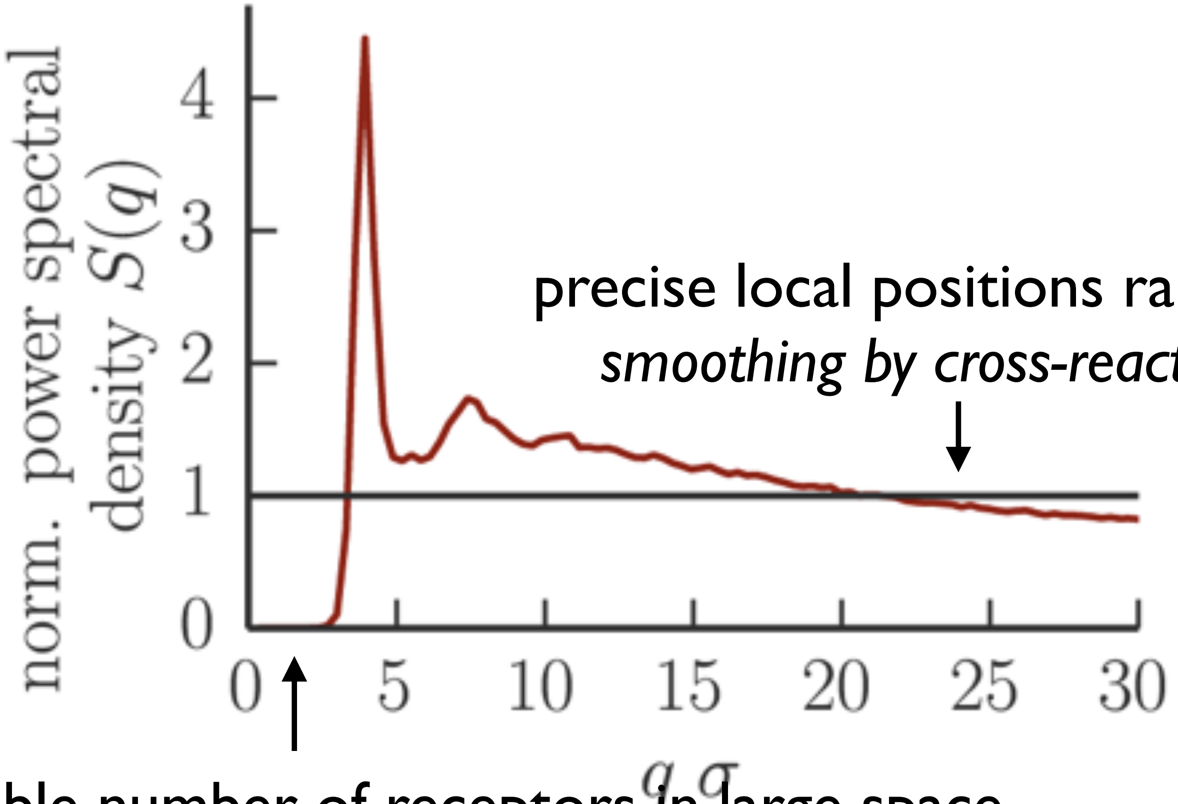
receptors cannot be close to each other



disordered tiling -
as close as possible but excluding





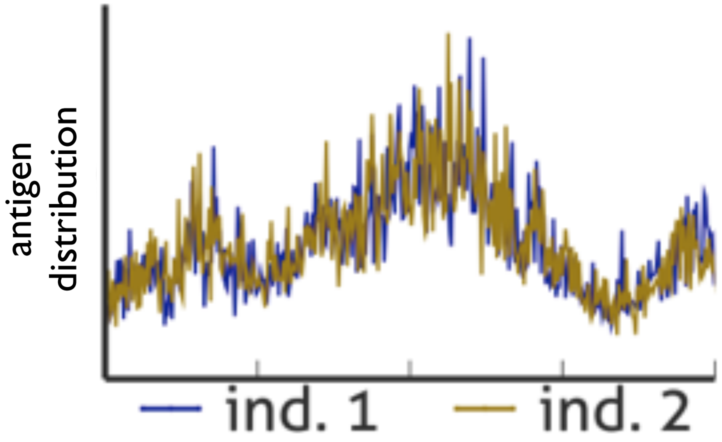


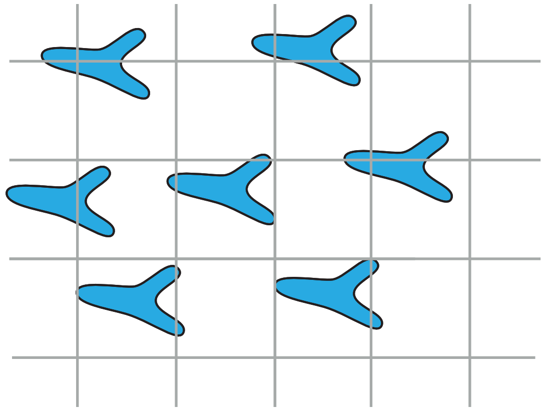
precise local positions random
*smoothing by cross-reactivity*

reproducible number of receptors in large space
*tracking of antigen*

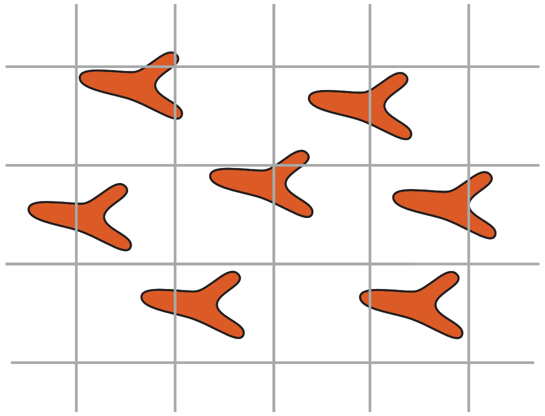
# Personalized responses

two individuals see the environment slightly differently





→ very different repertoires



# Self-organized dynamics

## Can optimal repertoires be reached via dynamics?

$$\dot{N}_r = N_r \left[ b \boxed{\sum_p Q_p f_{r,a} \boxed{A\left(\sum_{r'} N_{r'} f_{r',a}\right)}} - d \right]$$

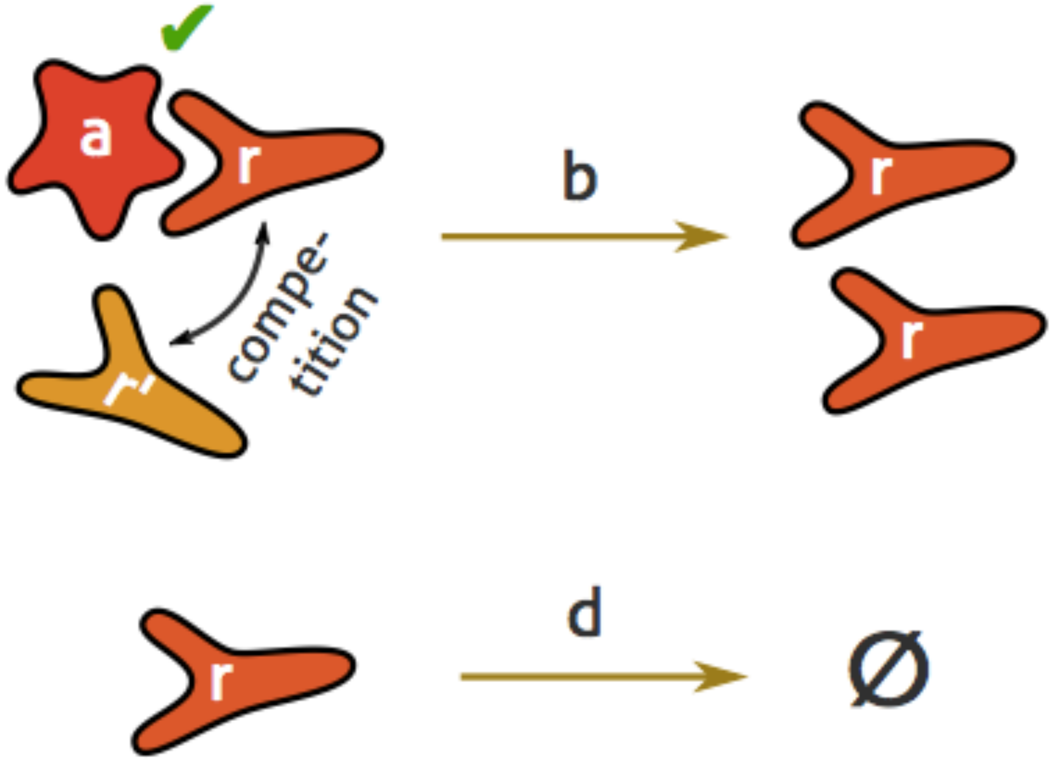
population size

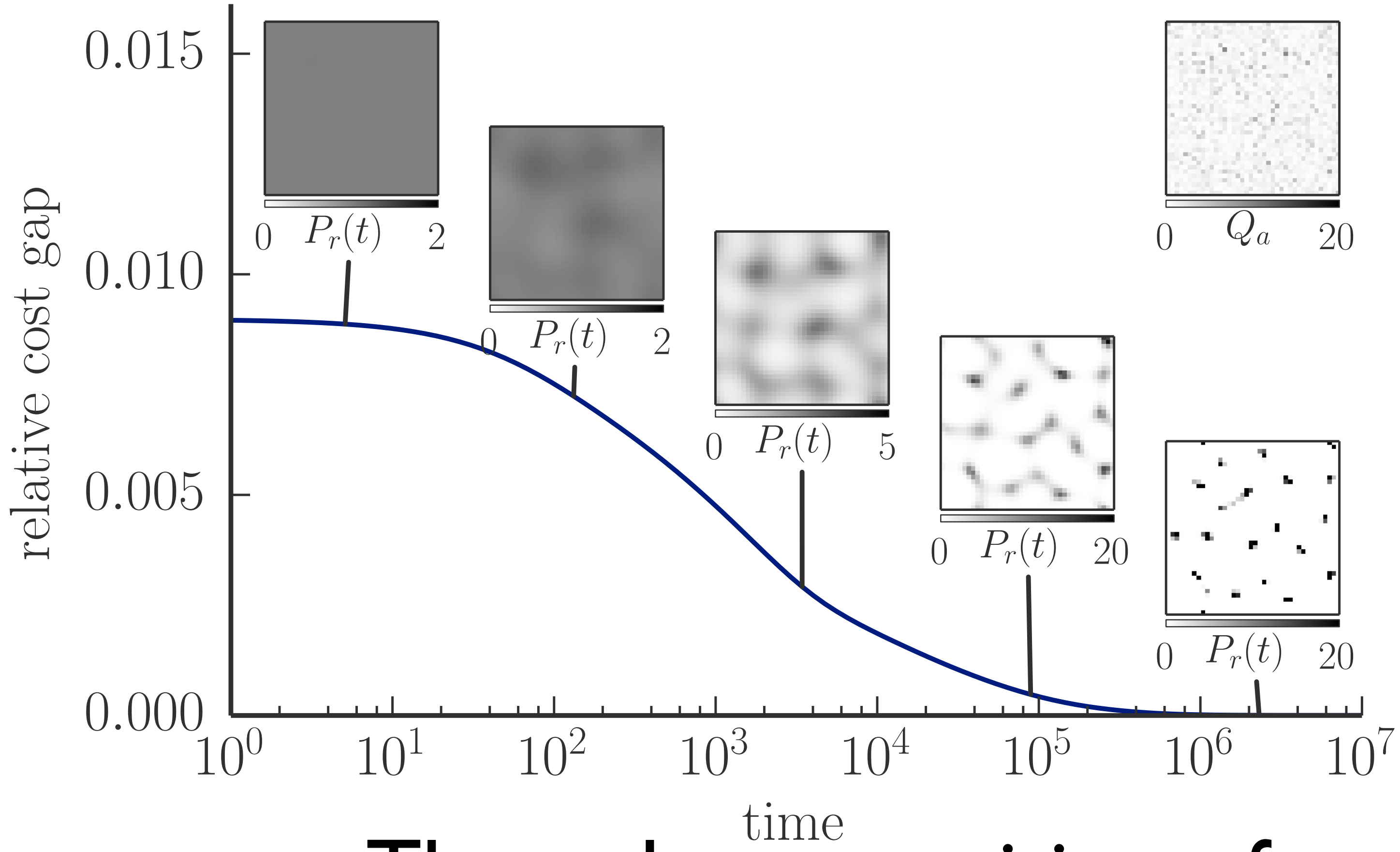
proliferation rate

detectable pathogen

availability of pathogen
→ reduced by competition
e.g. $A(\tilde{N}_a) = \frac{1}{(1+\tilde{N}_a)^2}$

death rate



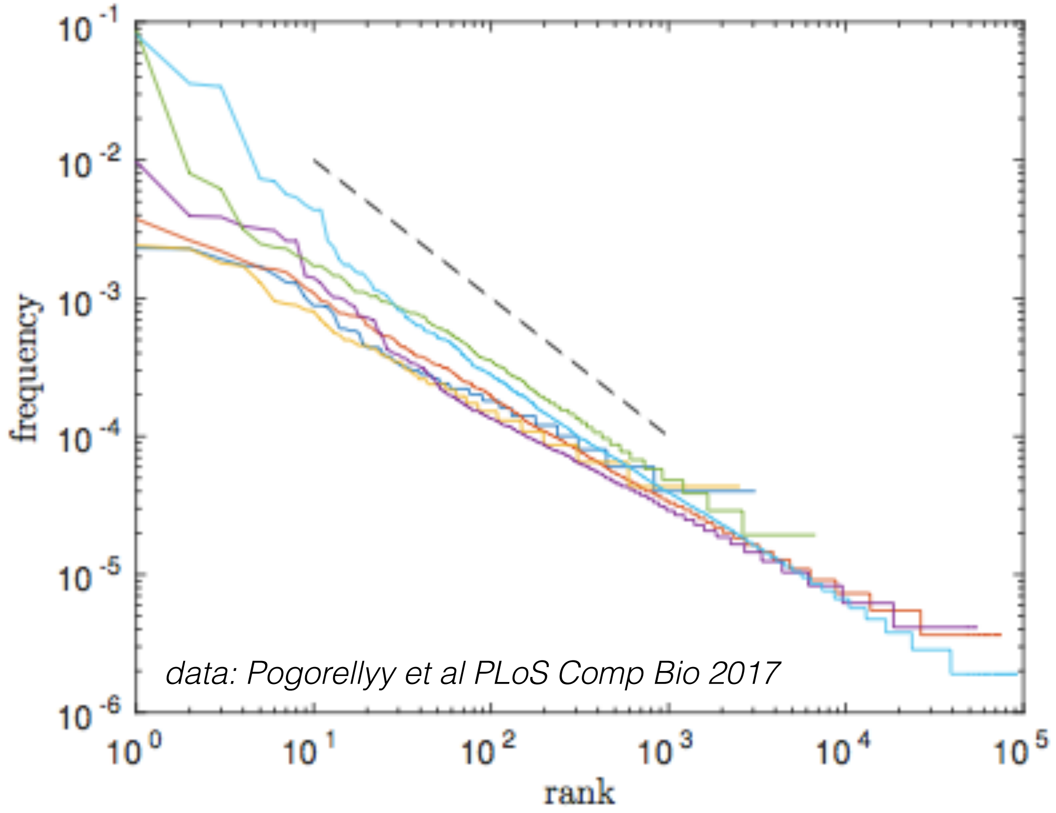


⟶ Through competition of receptors for antigen

# Estimating frequencies

- trying to infer species frequencies

*human T-cells:*

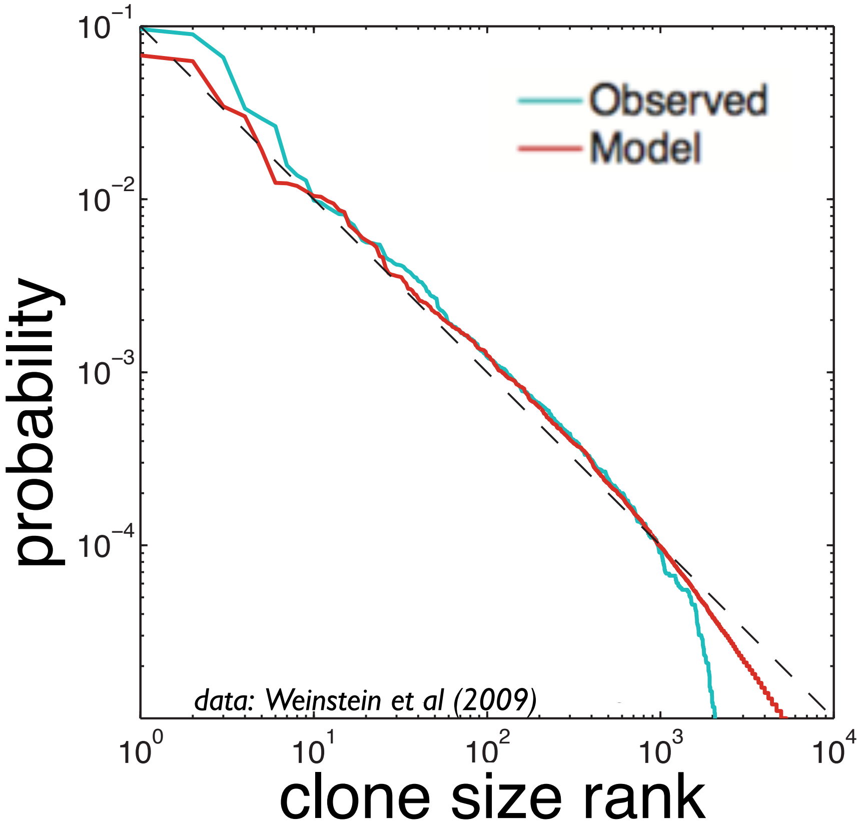


data: Pogorellyy et al PLoS Comp Bio 2017

beta chain

Post-selection: 38 bits

*zebrafish B-cells: clone size distribution*



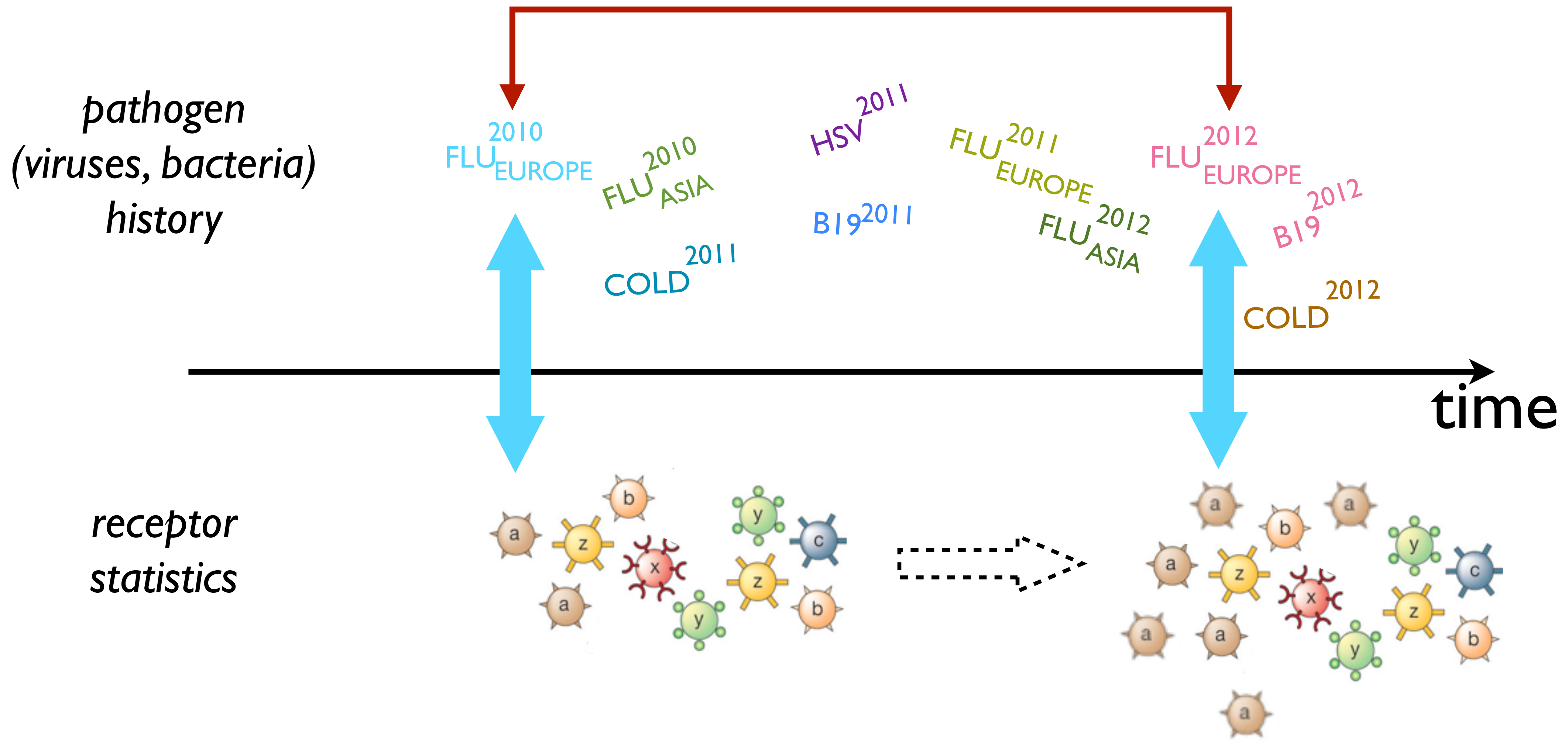
data: Weinstein et al (2009)

- also in other environments (microbiome, ponds, forests)

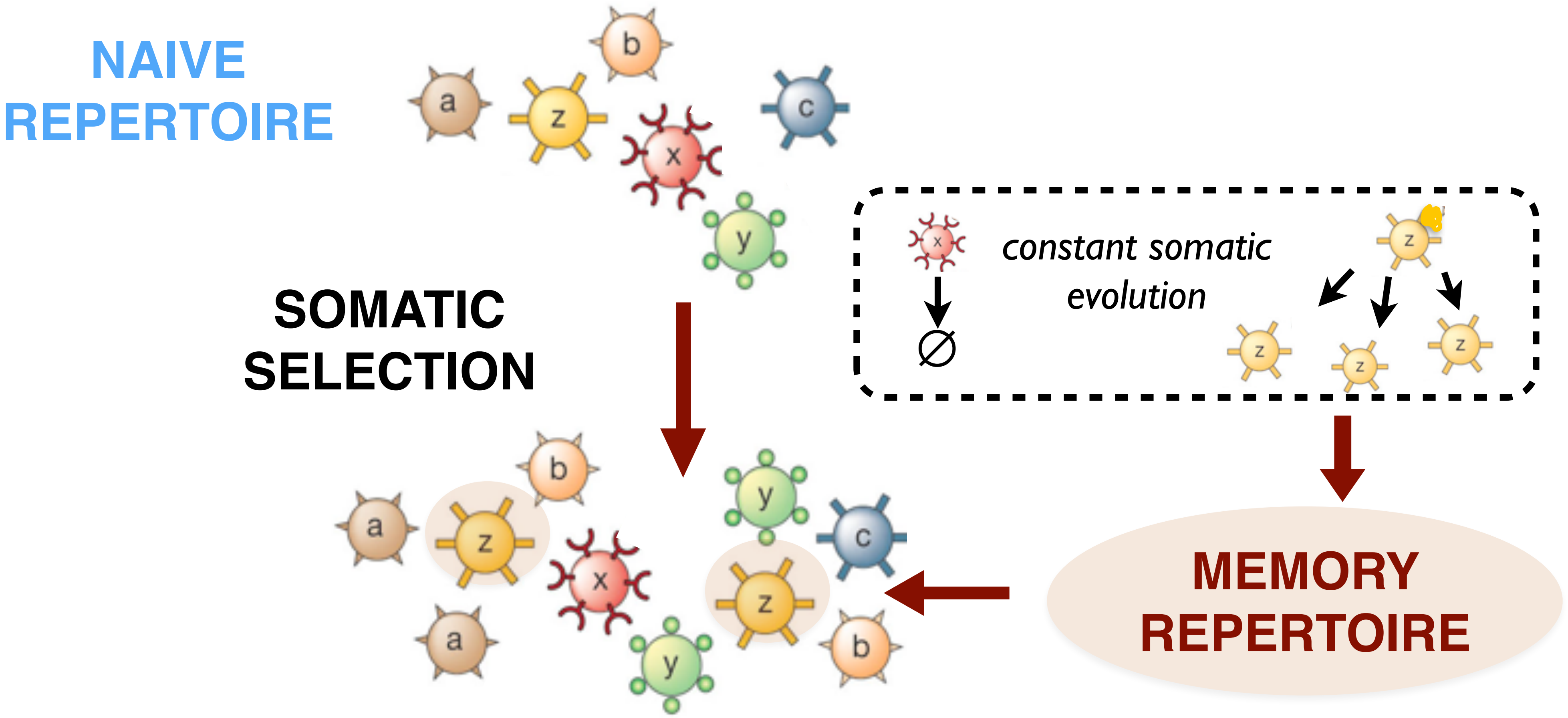
# How to update receptor frequencies?

- *adaptive* immune system - optimal predictor of future pathogens?

pathogen statistics is predictable because ***correlated in time***



# How to remember?

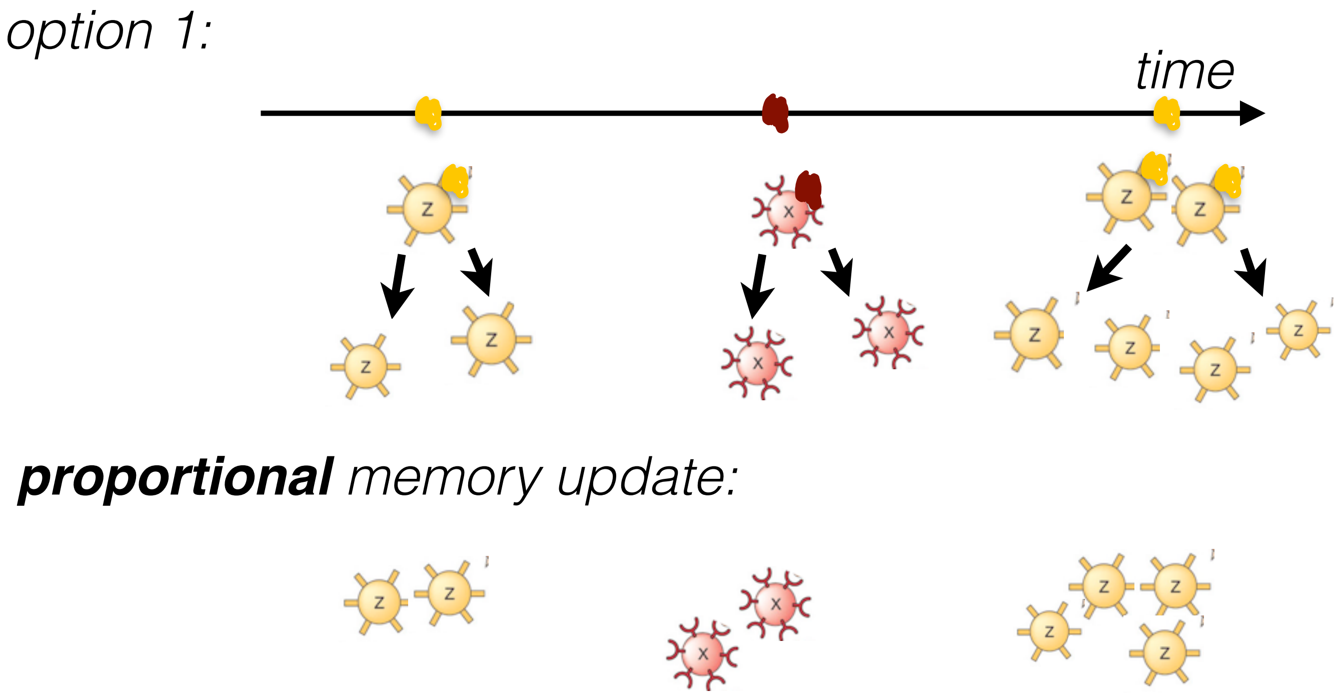

NAIVE REPERTOIRE

SOMATIC SELECTION

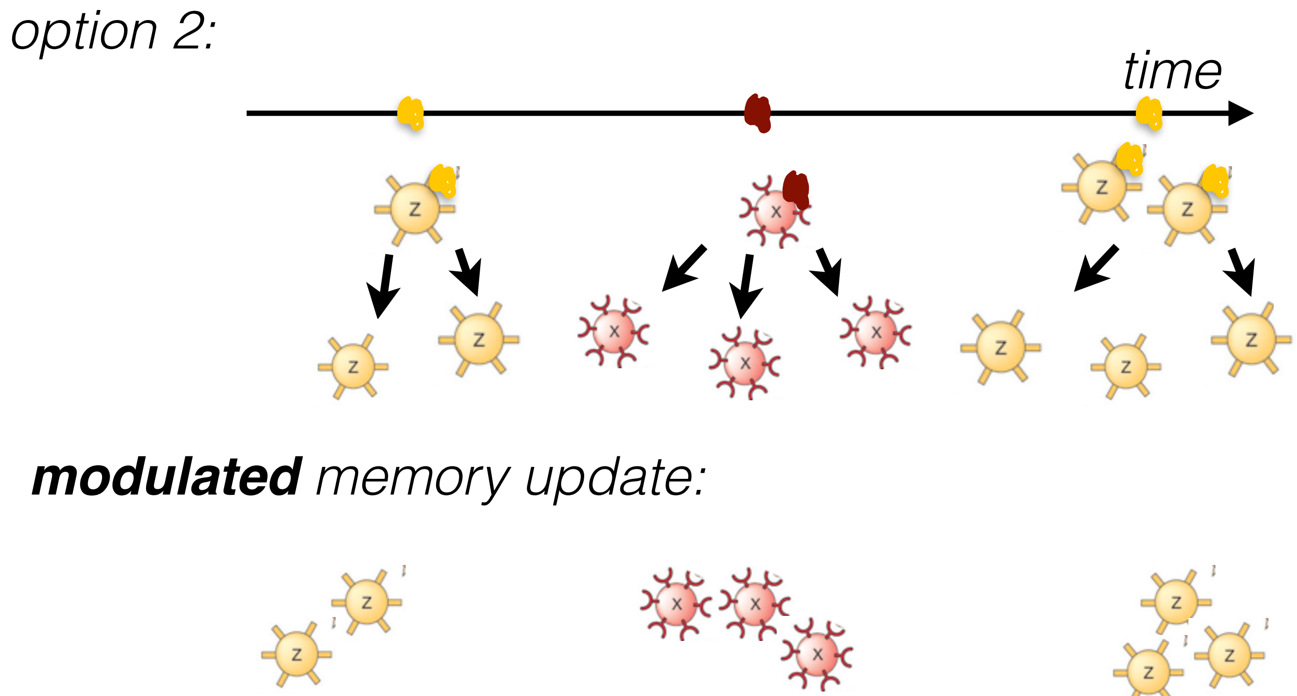
constant somatic evolution

MEMORY REPERTOIRE

is memory useful ?


option 1:

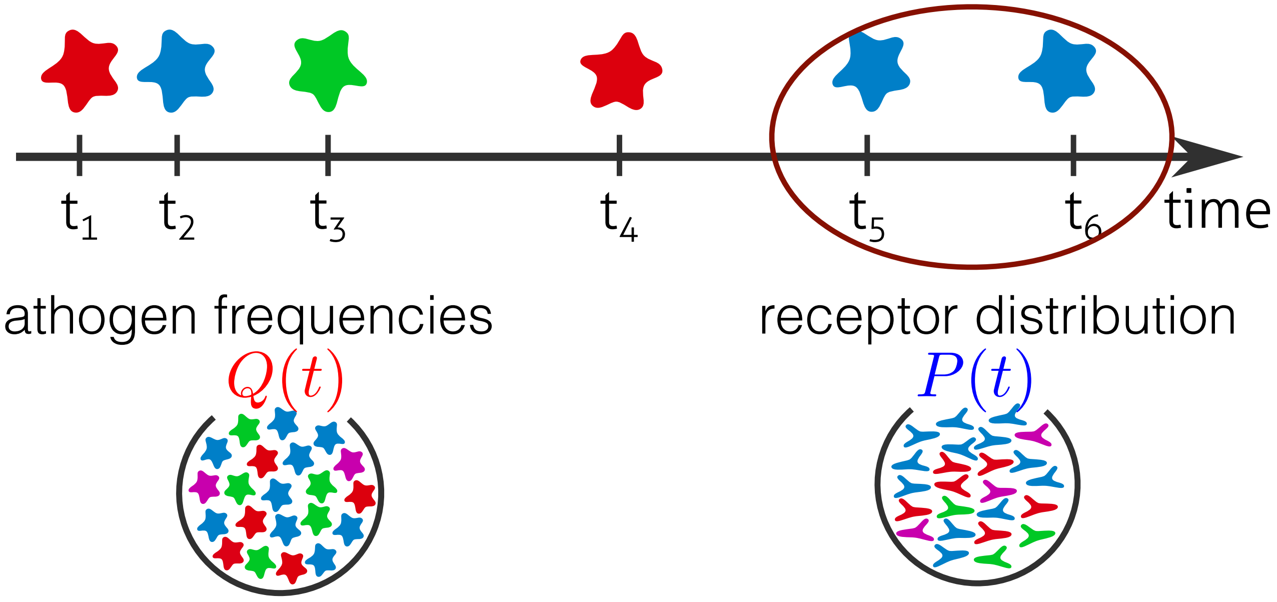
proportional memory update:


option 2:

modulated memory update:

# Estimate pathogen frequencies

$\lambda$ Poisson sampling rate of environment



what receptor distribution P(t) minimizes expected harm?

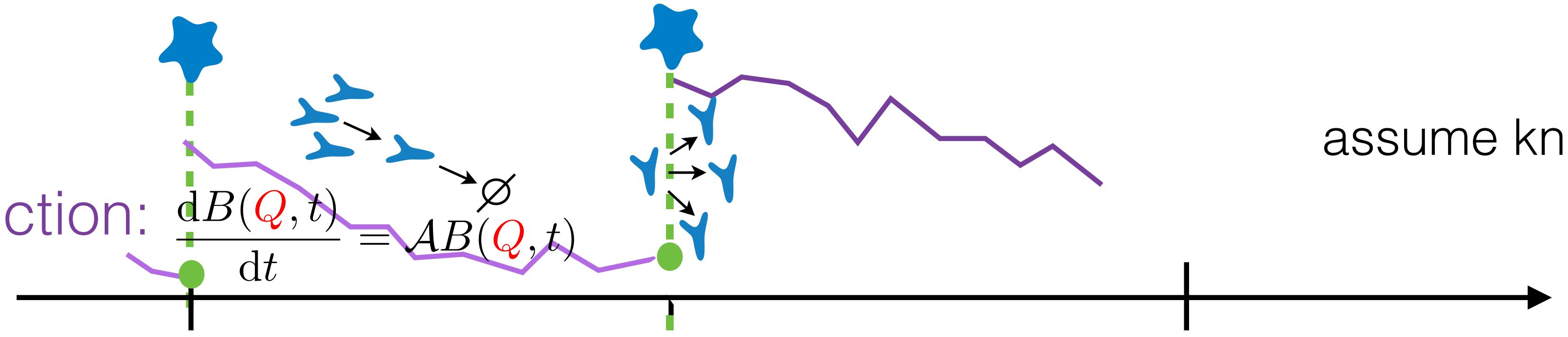
- Q(t) unknown → estimate it

belief of Q(t)

$$\langle \mathrm{Cost}\,(\mathrm{P(t)},\mathrm{Q(t)})\rangle = \int \mathrm{dQ}\ \mathrm{Cost}\,(\mathrm{P(t)},\mathrm{Q})\,\mathrm{B}\,(\mathrm{Q},\mathrm{t}) \xrightarrow{\text{min Cost}} P^{\star}(t) = f\left(\langle Q(t)\rangle\right)$$

expected cost of an infection

- propagate belief in time = encounters + prior



prediction: $\frac{\mathrm{d}B(Q,t)}{\mathrm{d}t} = \mathcal{A}B(Q,t)$

assume know real dynamics $\mathcal{A}$

update: $B(Q,t^{+}) = \frac{\mathcal{L}(a|Q)B(Q,t^{-})}{Z}$

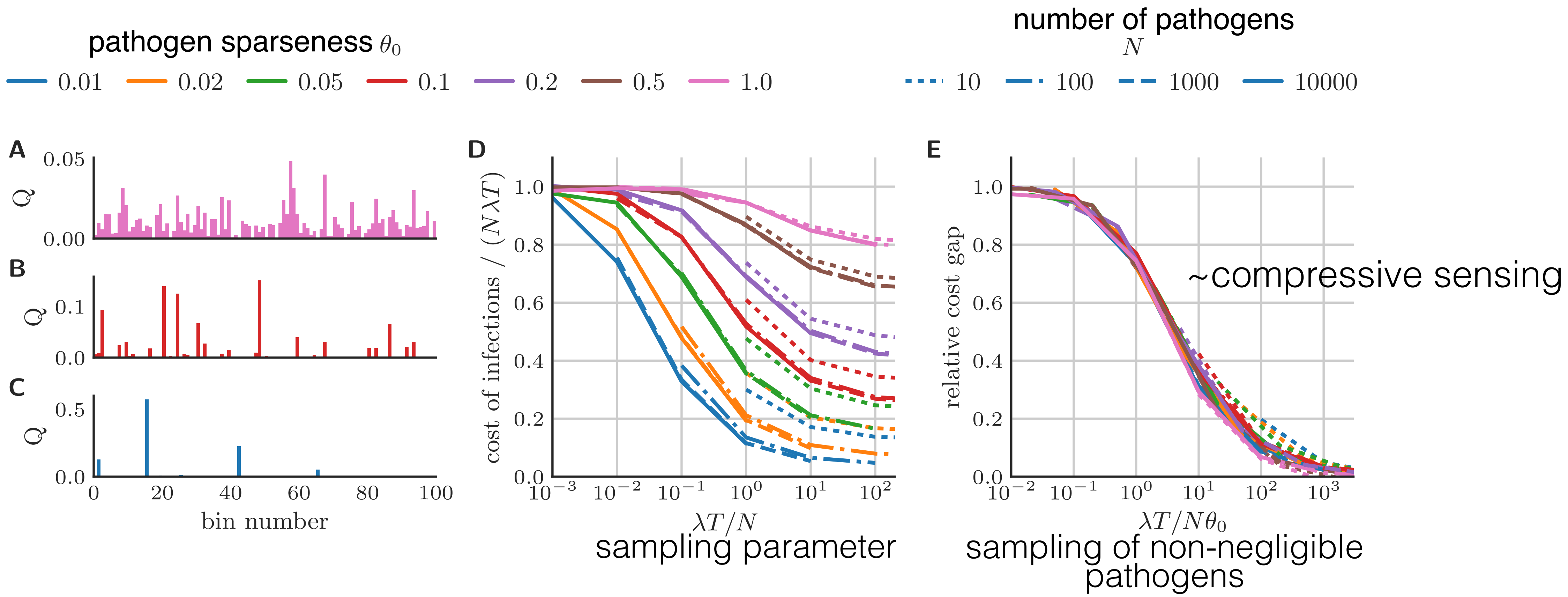
$Q_a(t^{+})$

MEMORY REPERTOIRE

# Memory helps

- memory helps in sparse environments

  → fast detection of few pathogens



~compressive sensing

sampling parameter

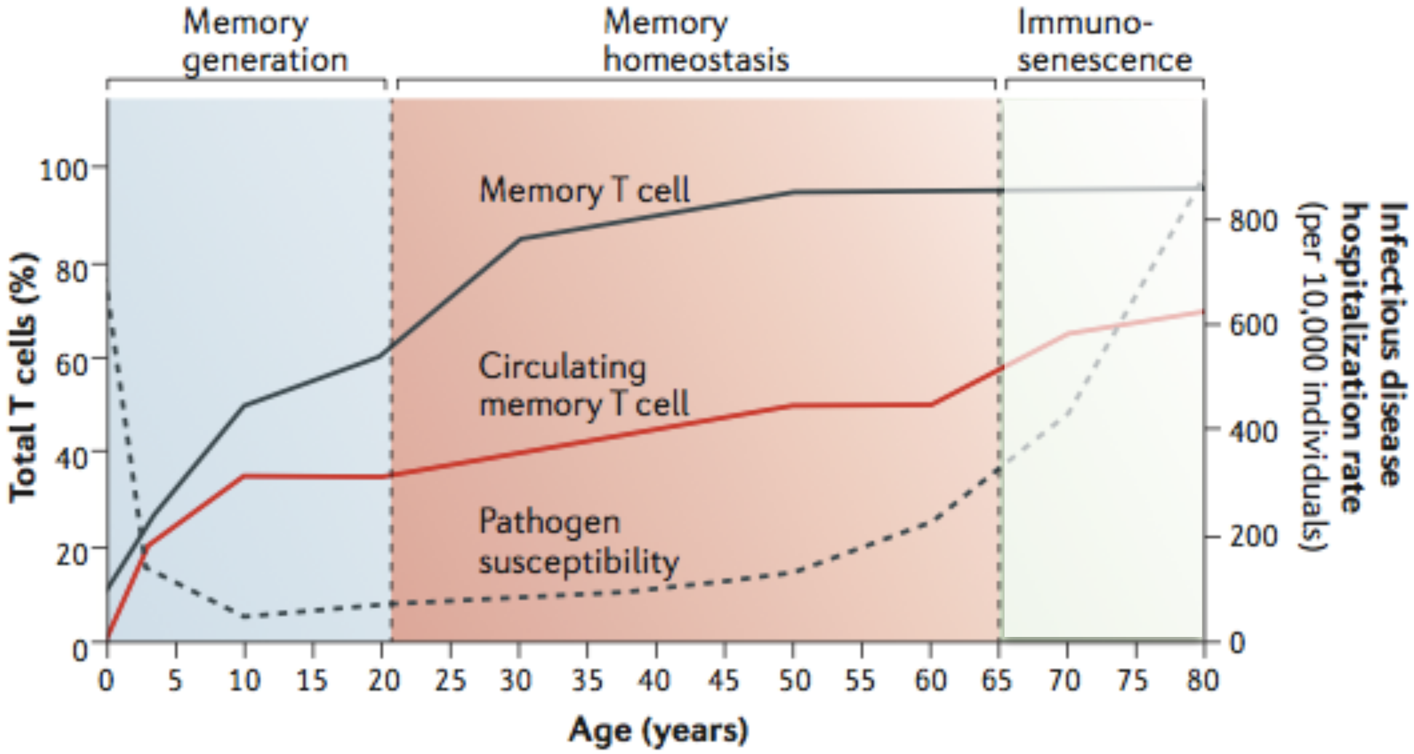
sampling of non-negligible pathogens

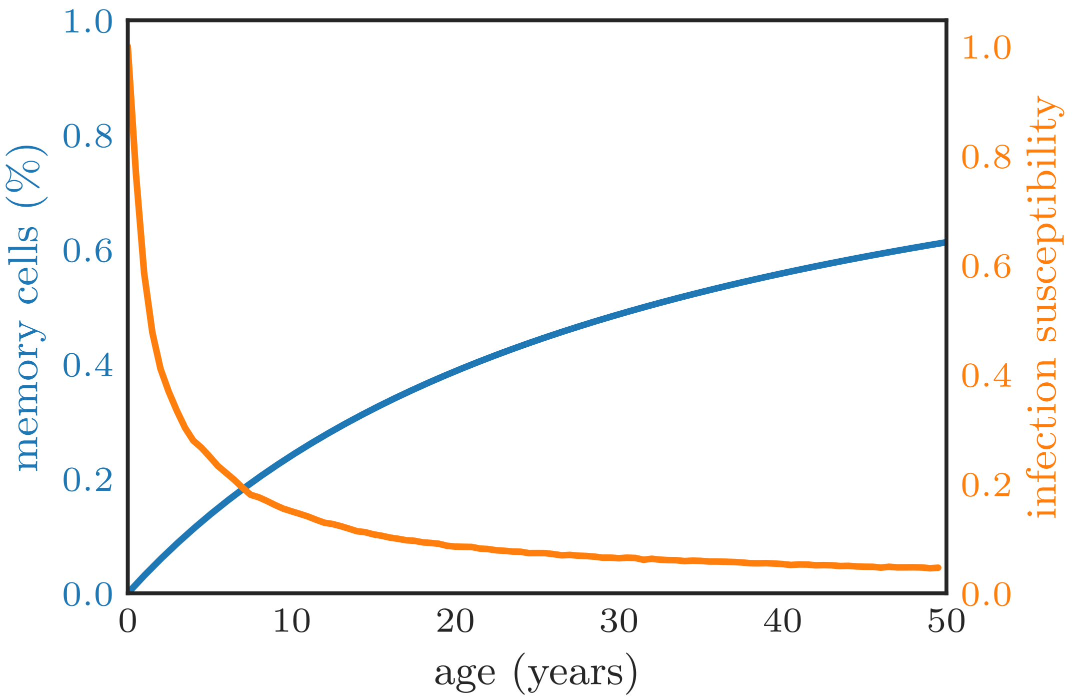
- advantage of memory - depends on sampling

→control theory rationalizes existence of immunological memory

# Rapidly acquired memory

- quickly learn global features of the distribution



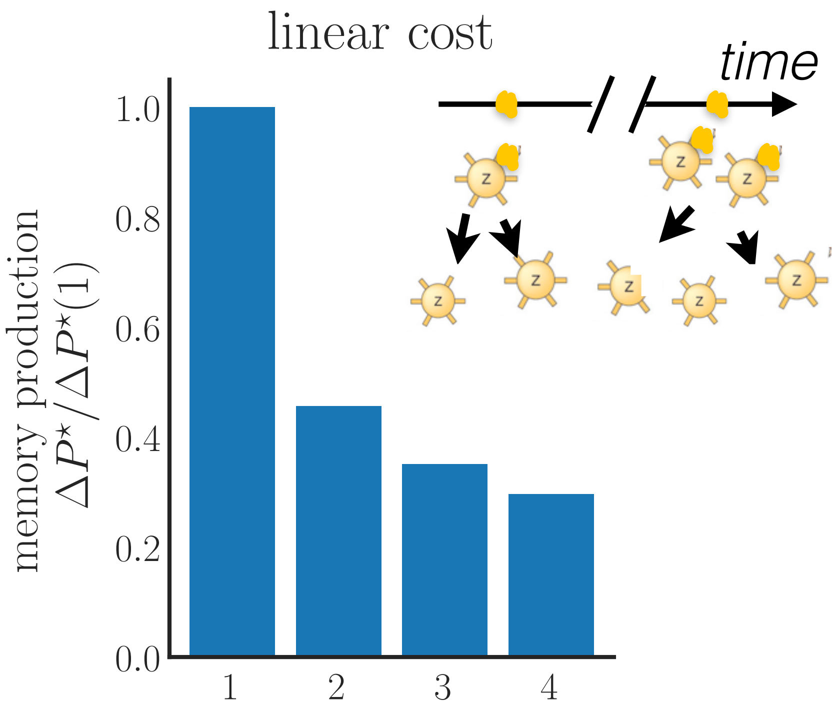


- predictive learning reproduces experimental features

*D. L. Farber, N. A. Yudanin· N. P. Restifo,NATURE REVIEWS | IMMUNOLOGY 2013*

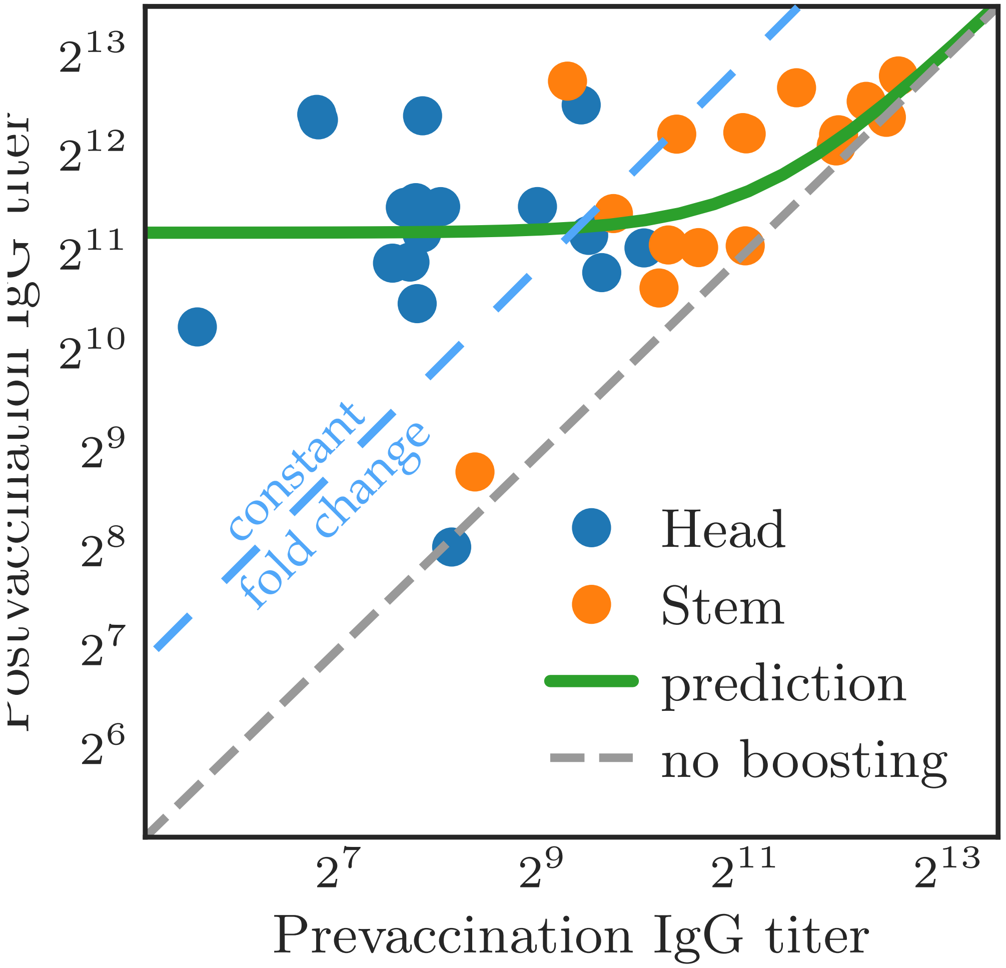
# Learning

- subsequent observations count as less evidence



→ *vaccination*

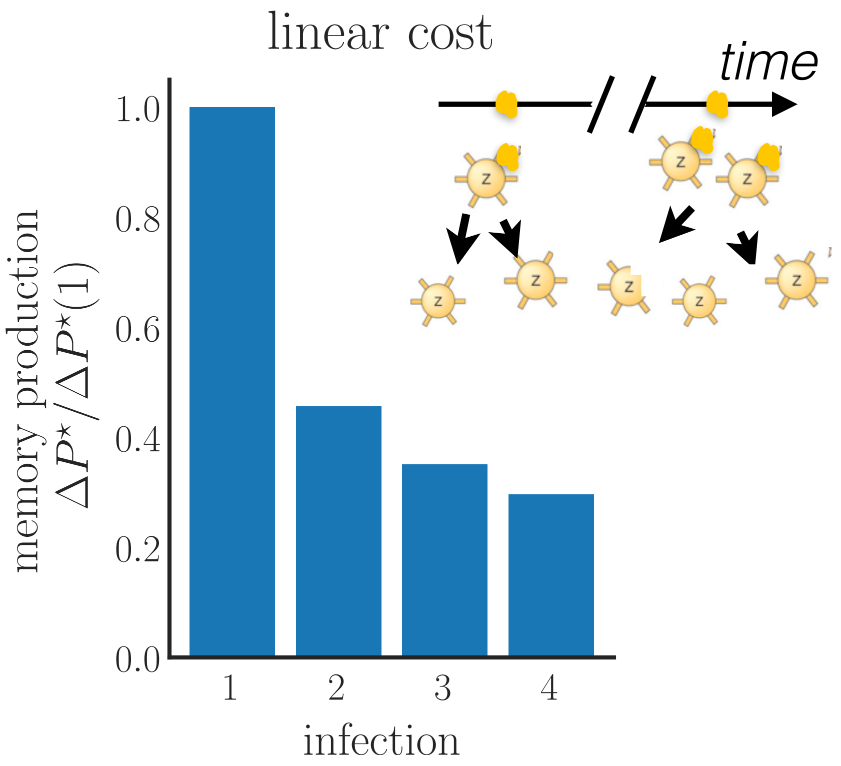
- booster vaccination titers for epitopes of hemaglutanin following vaccination with inactivated H5N1



*data from Ellebedy et al. PNAS 2014*

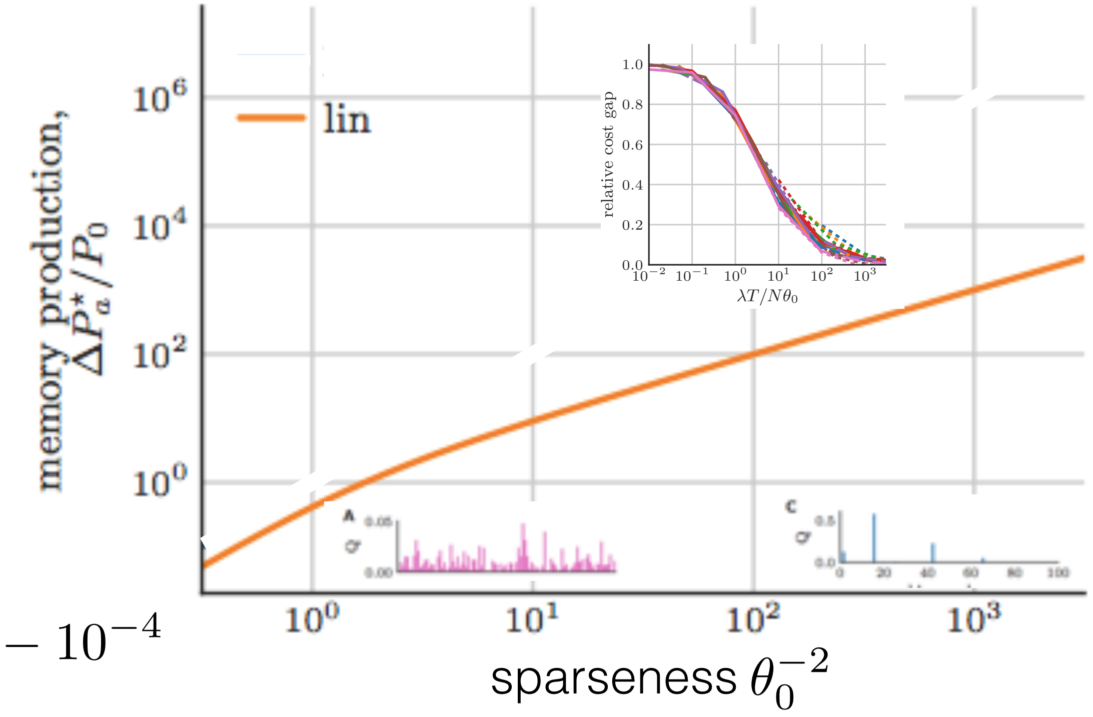
# Learning

- subsequent observations count as less evidence



- stronger response in sparse environments

memory increase ~100-1000*



→ very sparse environment $\theta_0 \sim 10^{-6} - 10^{-4}$

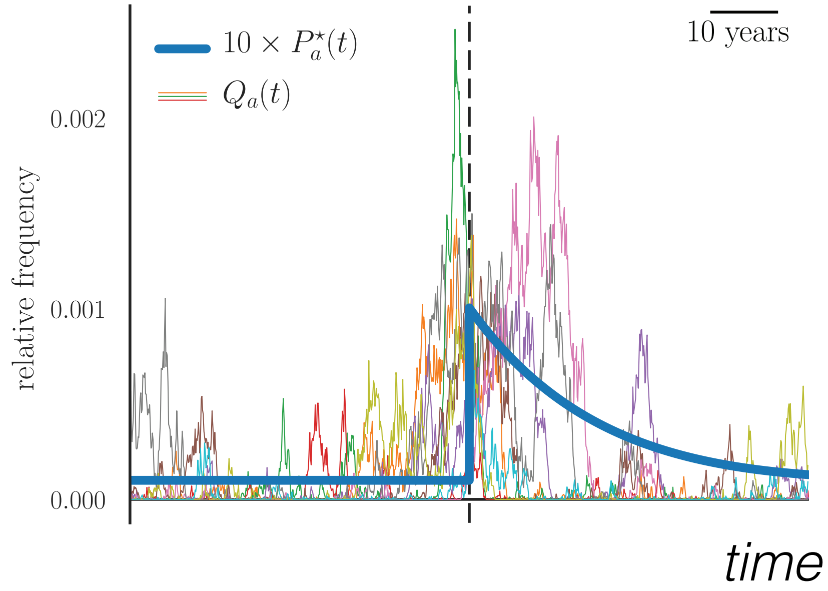
→ pathogen seen once - memory gives ~2 fold cost decrease

*Buchholz et al (2016) An. rev. imm.

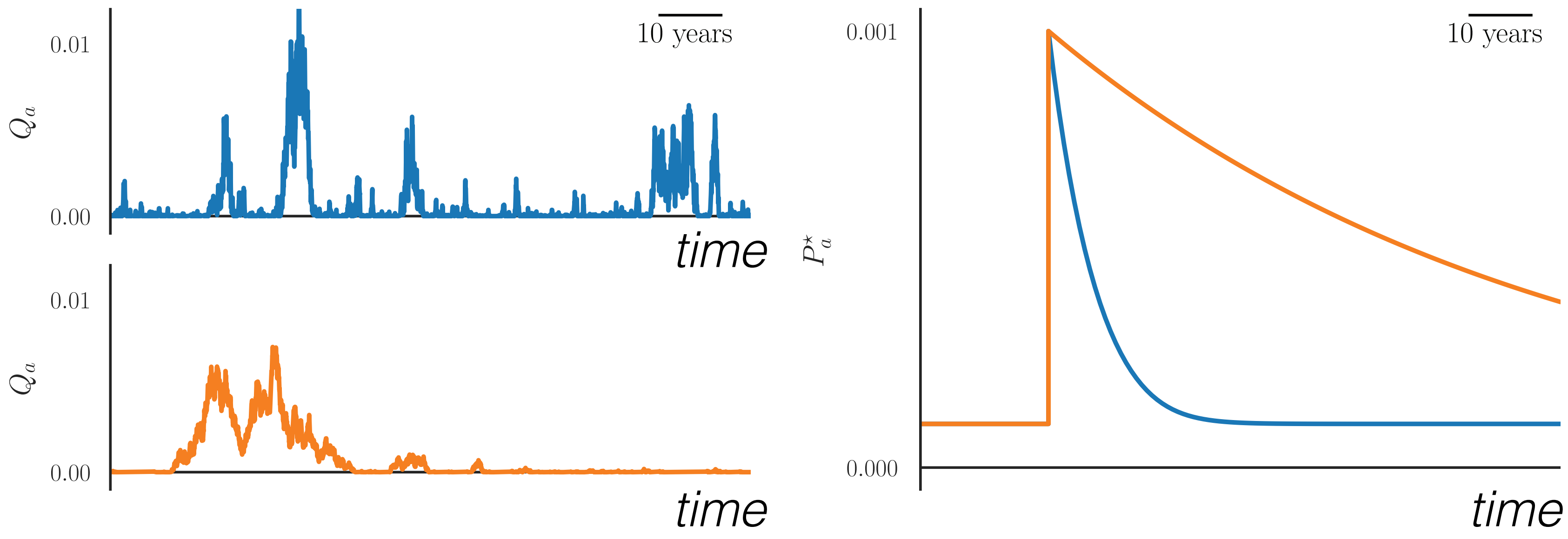
# Forgetting

- changing environment → propagate belief between sampling

- Bayesian prediction of changing environment



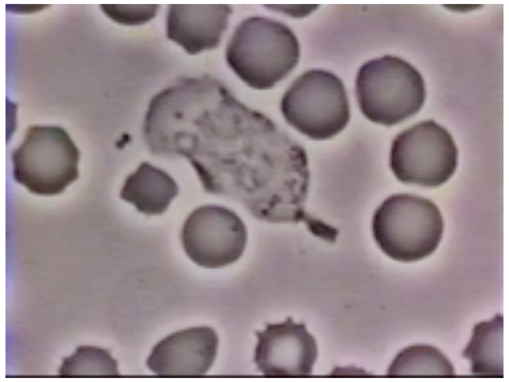
- forget faster in rapidly changing environments



# Different immune strategies

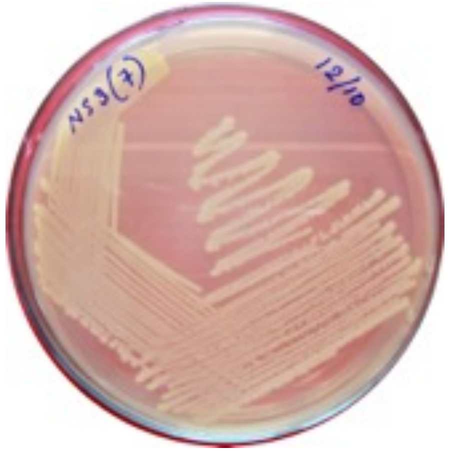
adaptive immunity

# Other immune strategies



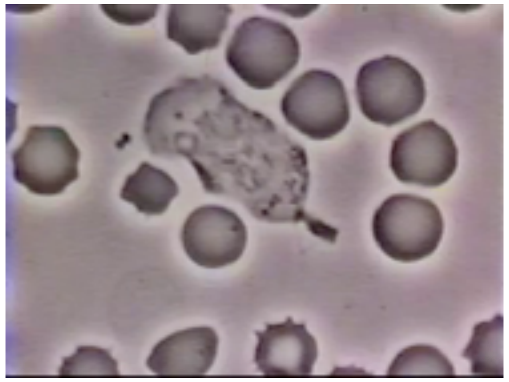
innate immunity

adaptive immunity

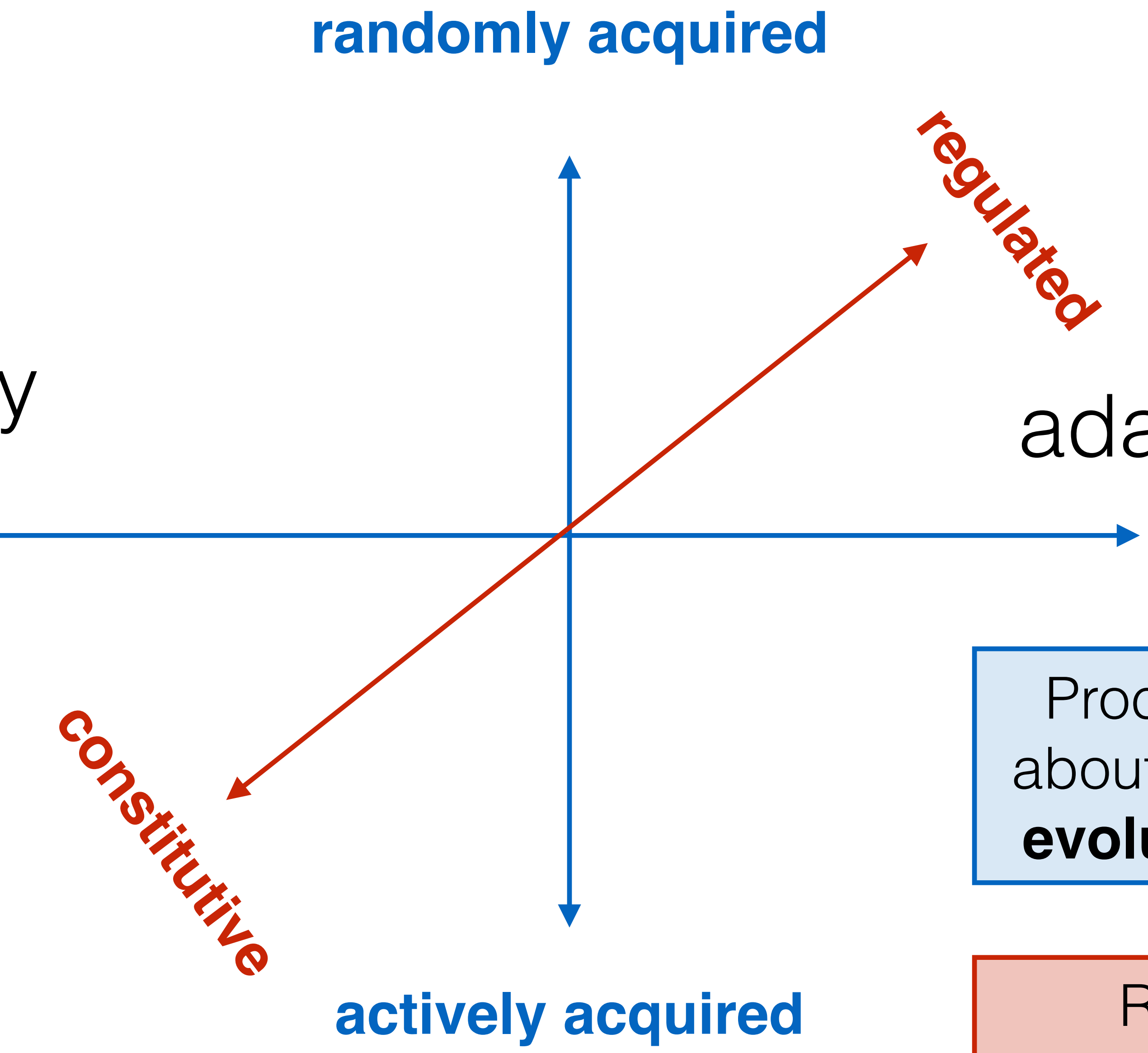


CRISPR immunity

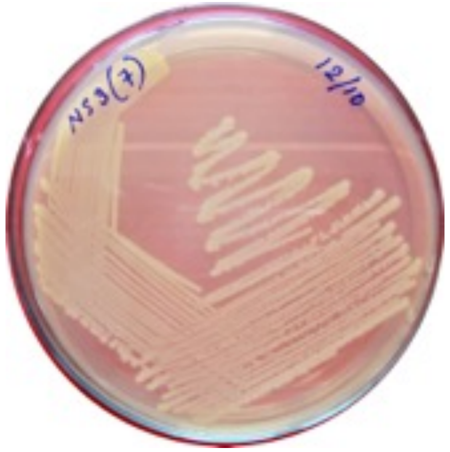
# Common strategic choices



innate immunity



adaptive immunity

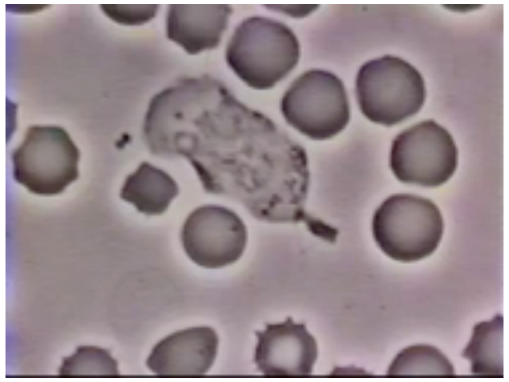


CRISPR immunity

Processing information about the environment on **evolutionary** timescales

Response during **organism** lifetime

# Common strategic choices



randomly acquired

regulate

in

optimal immunity?

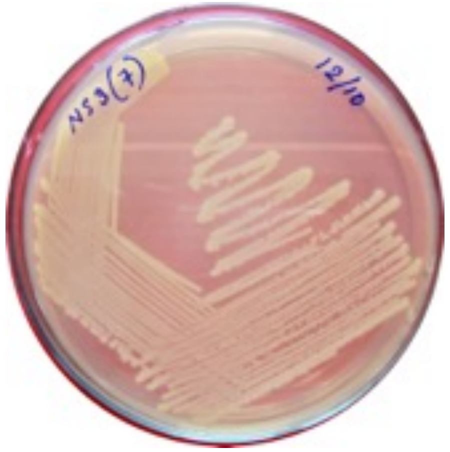
ty

constitutive

Processing information about the environment on **evolutionary** timescales

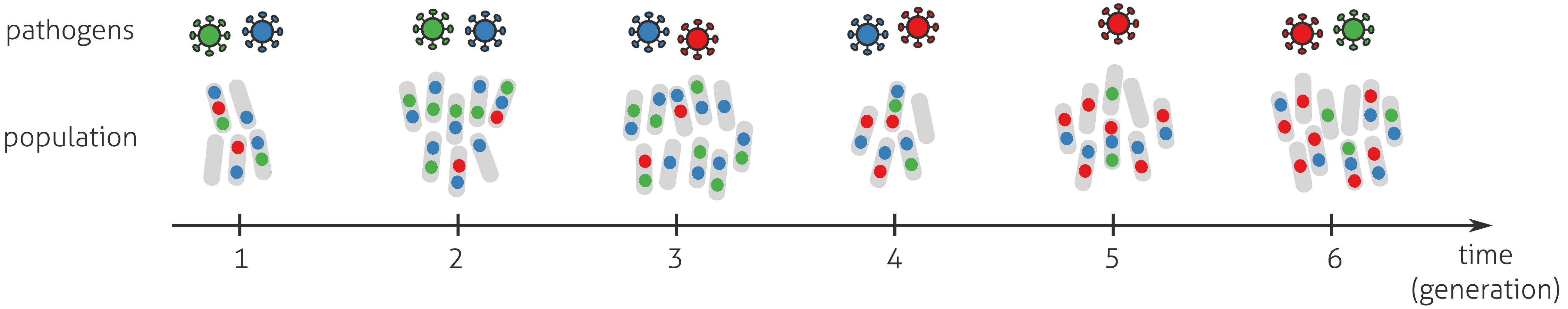
Response during **organism** lifetime

actively acquired



CRISPR immunity

# Optimal immunity

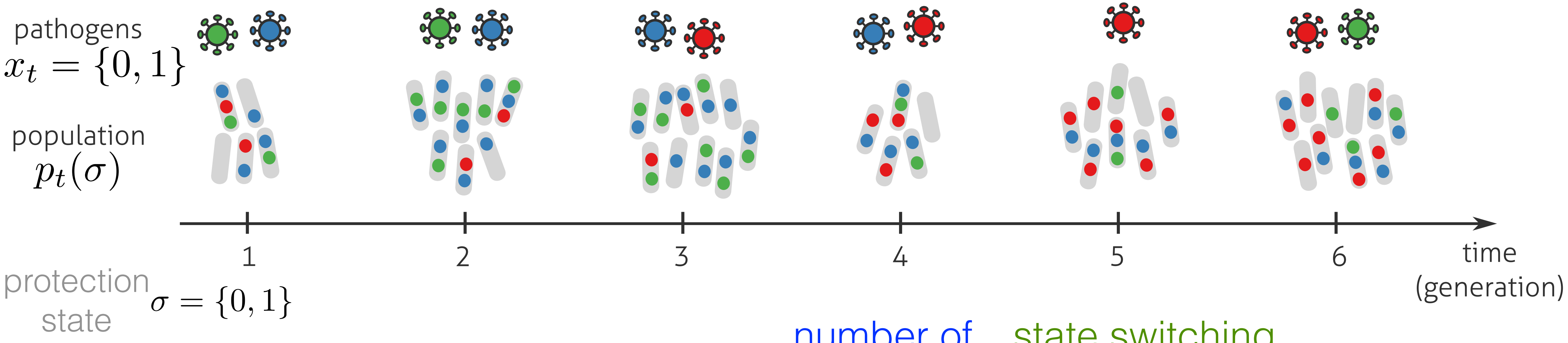


- match environment statistics
- ensure long term population growth

→ immunity as adaptation to pathogen statistics

- consider different strategies
- optimize long term population growth

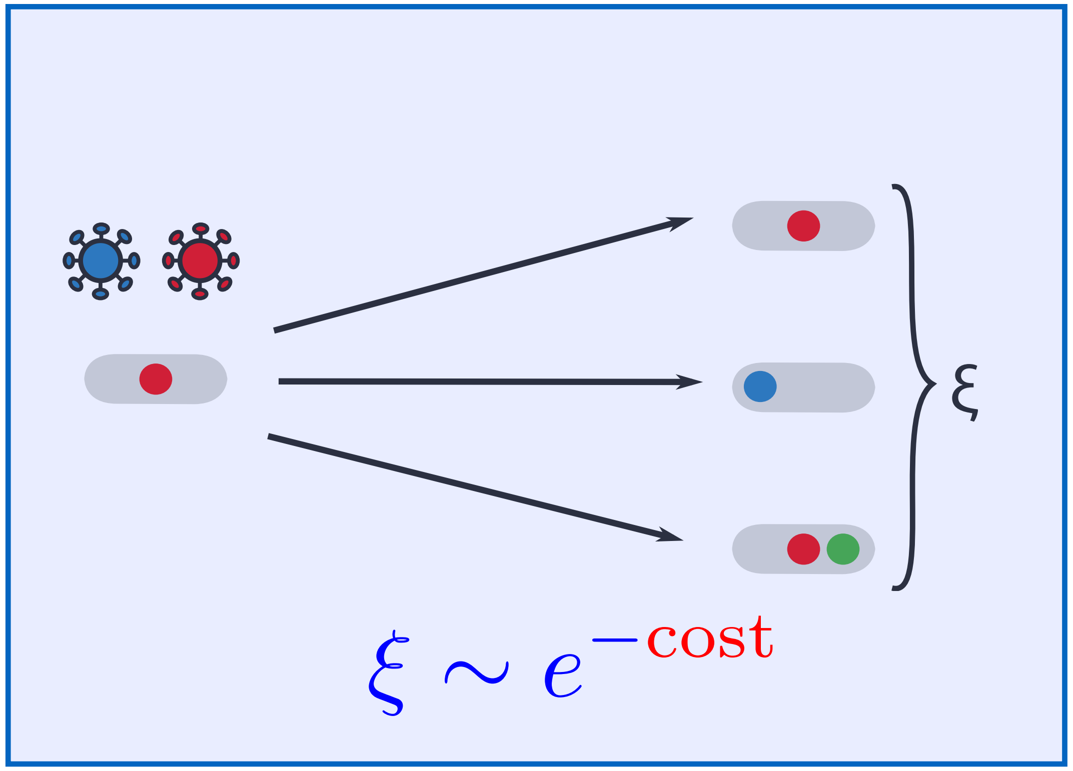
# Population growth



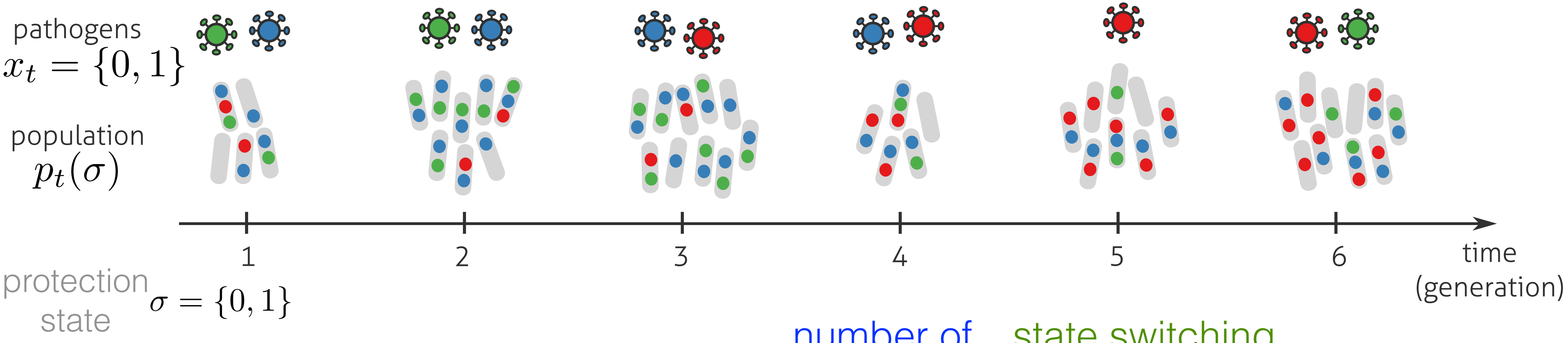
number of offspring

state switching probability

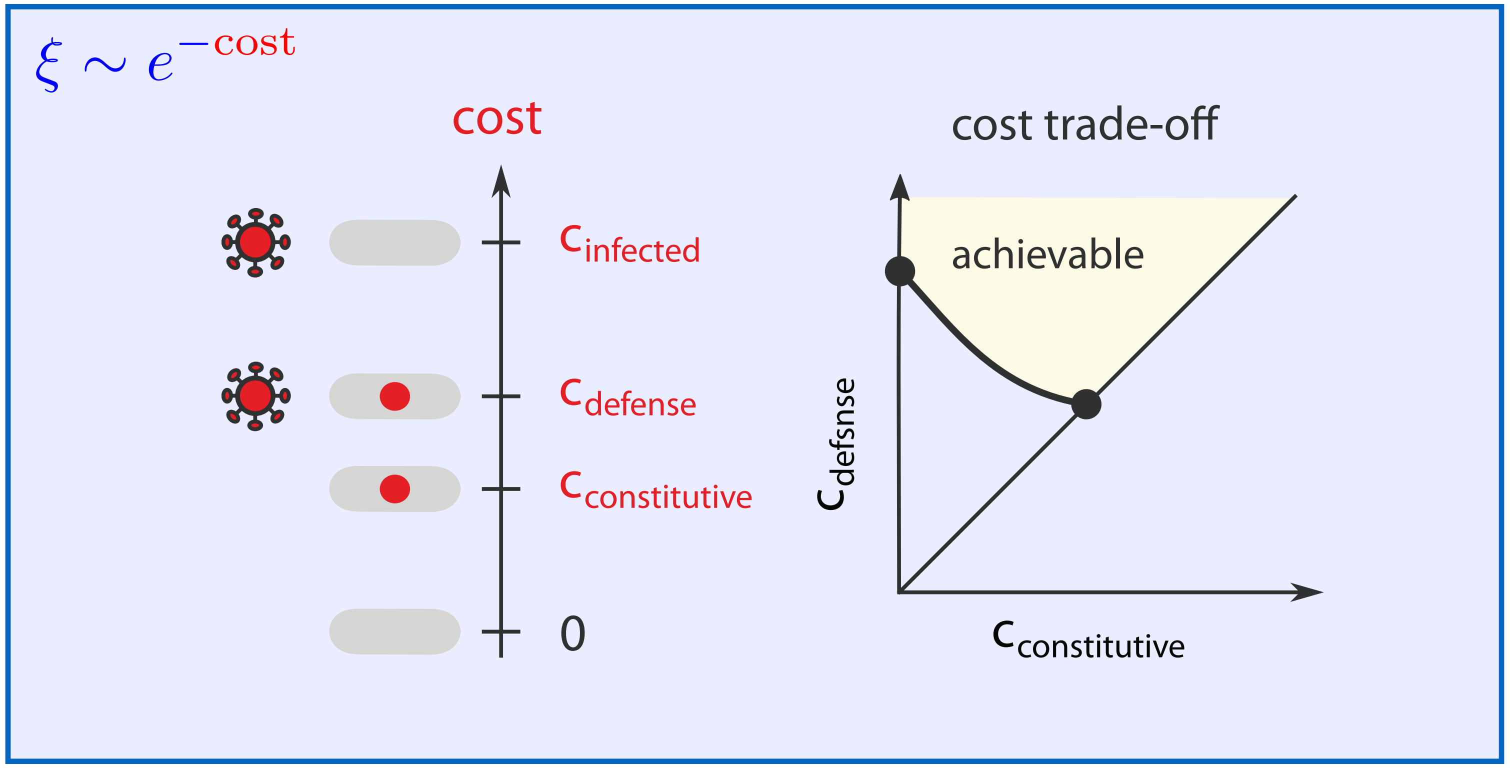
$$p_{t+1}(\sigma) = \frac{1}{Z_t} \sum_{\sigma'} \xi(\sigma', x_t)\, \pi(\sigma|\sigma', x_t)\, p_t(\sigma')$$



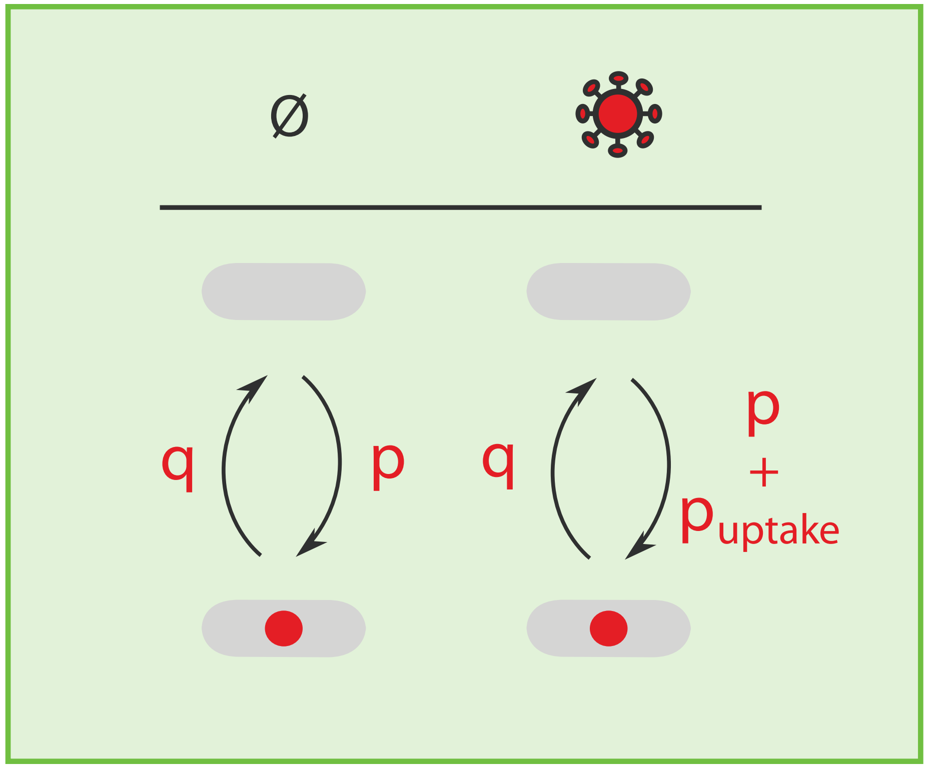
# Population growth



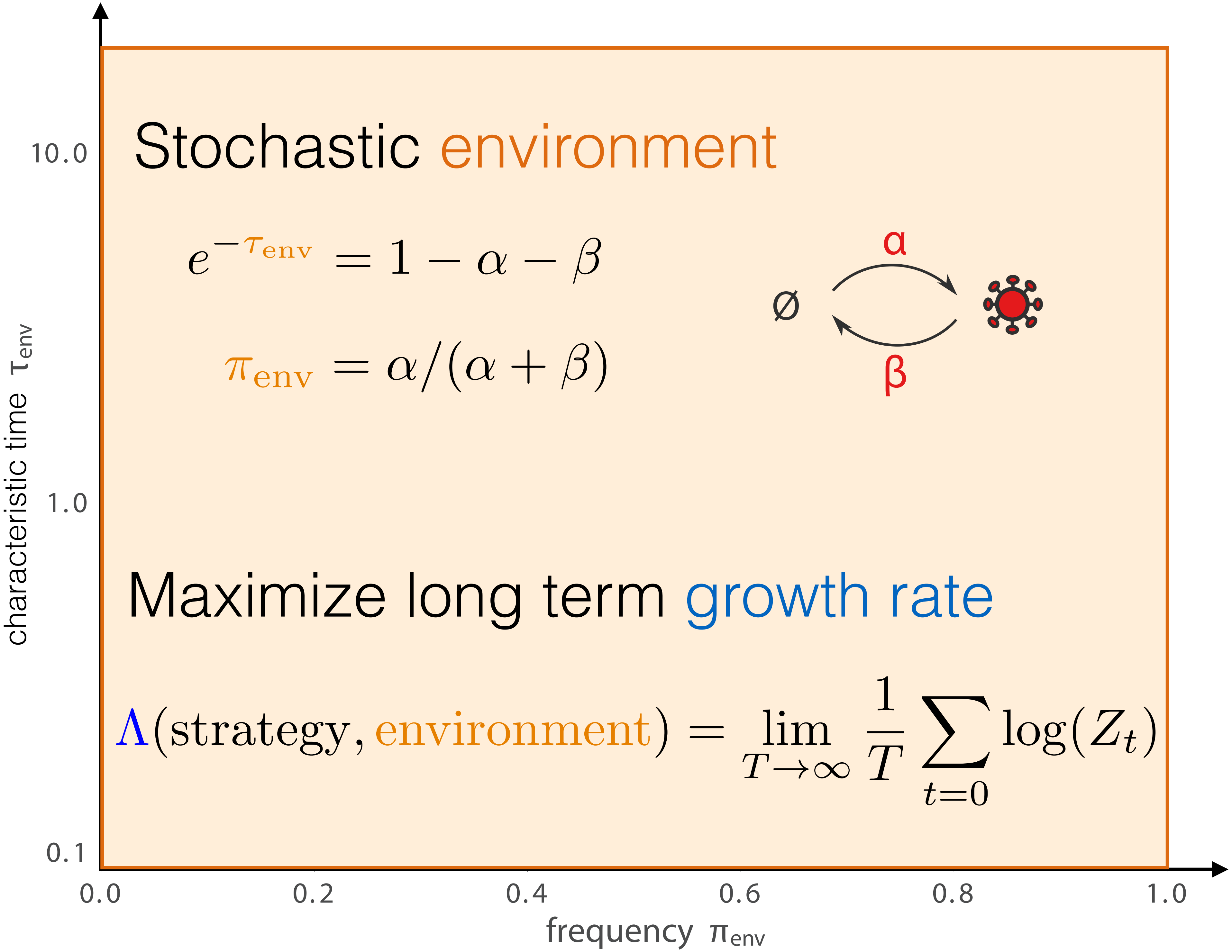
$$p_{t+1}(\sigma) \quad = \quad \frac{1}{Z_t}\sum_{\sigma'} \overset{\text{number of offspring}}{\xi(\sigma', x_t)}\ \overset{\text{state switching probability}}{\pi(\sigma|\sigma', x_t)}\ p_t(\sigma')$$



$\xi \sim e^{-\text{cost}}$



# The environment


10.0
1.0
0.1
characteristic time $\tau_{\mathrm{env}}$
0.0
0.2
0.4
0.6
0.8
1.0
frequency $\pi_{\mathrm{env}}$
∅
α
β

Stochastic environment

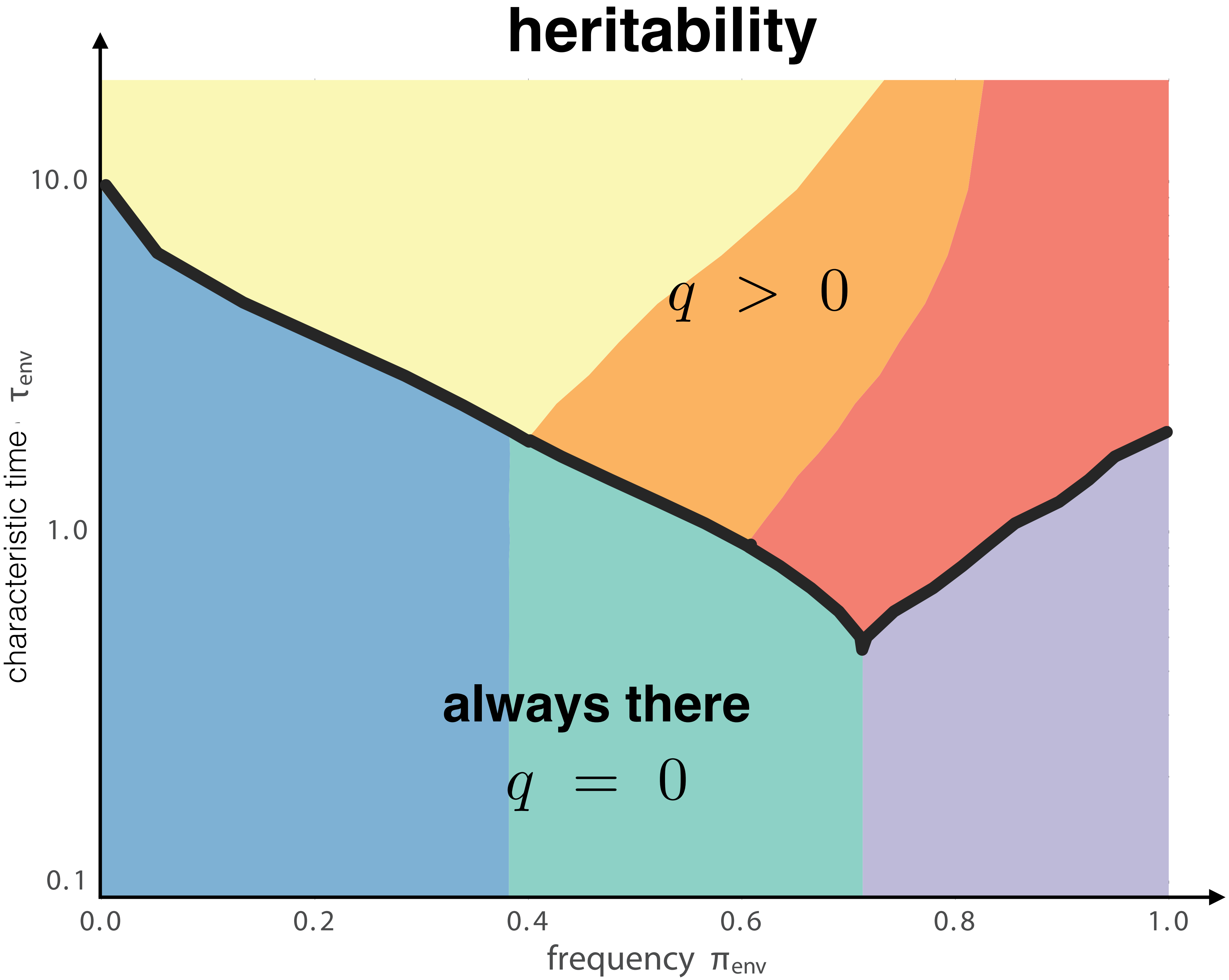
$$e^{-\tau_{\mathrm{env}}} = 1 - \alpha - \beta$$

$$\pi_{\mathrm{env}} = \alpha/(\alpha + \beta)$$

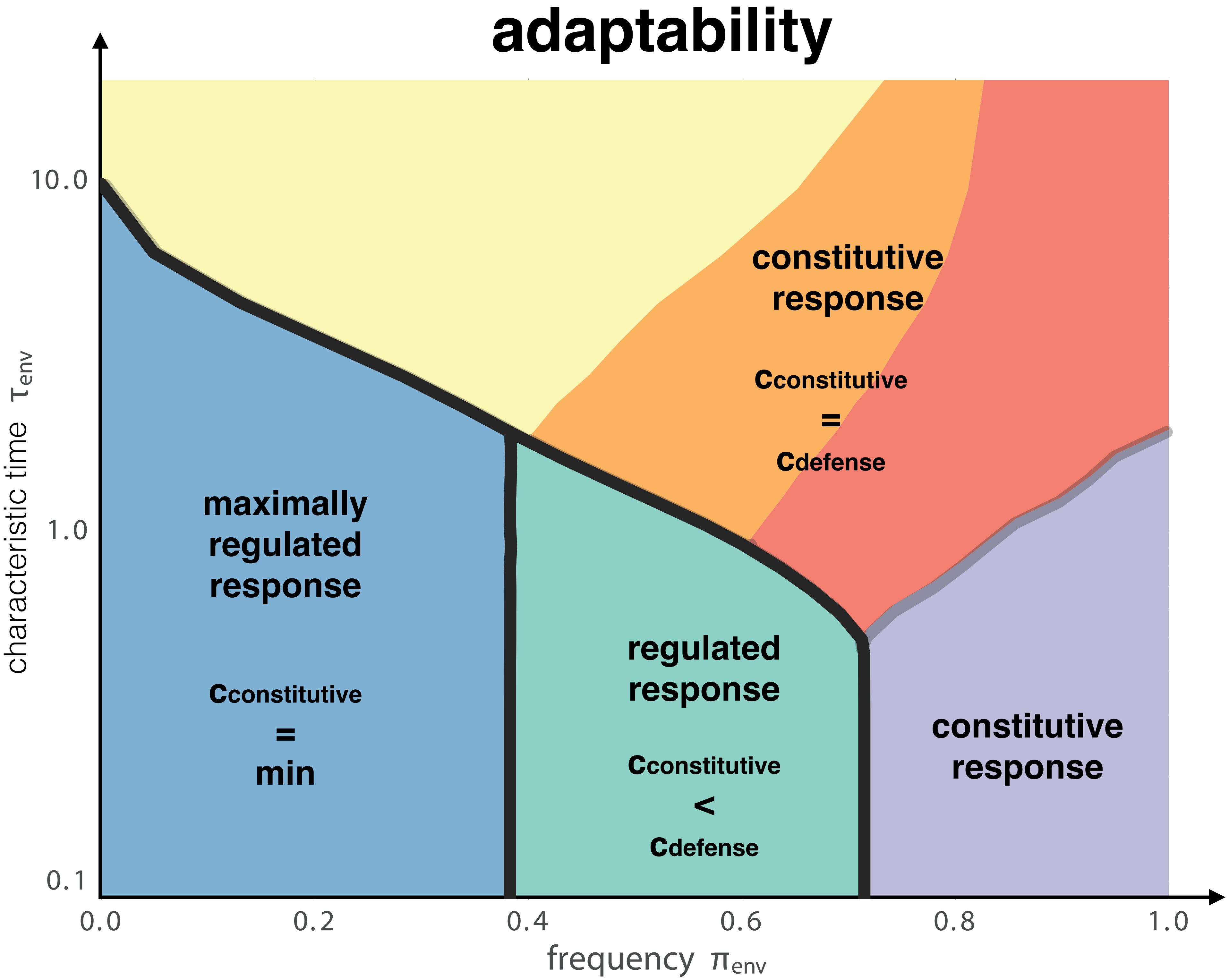
Maximize long term growth rate

$$\Lambda(\mathrm{strategy}, \mathrm{environment}) = \lim_{T \to \infty} \frac{1}{T} \sum_{t=0} \log(Z_t)$$

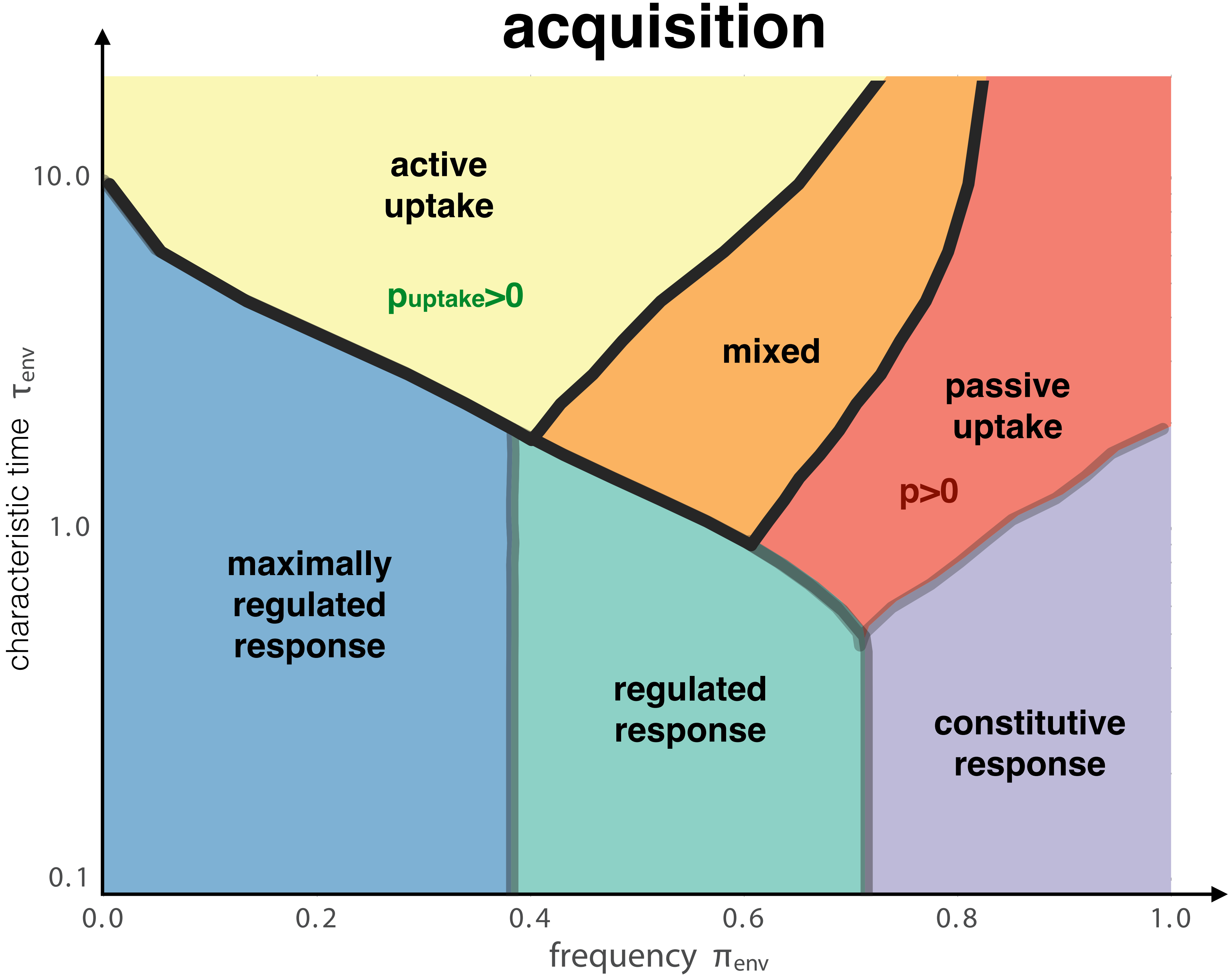
# Optimal strategies



# Optimal strategies

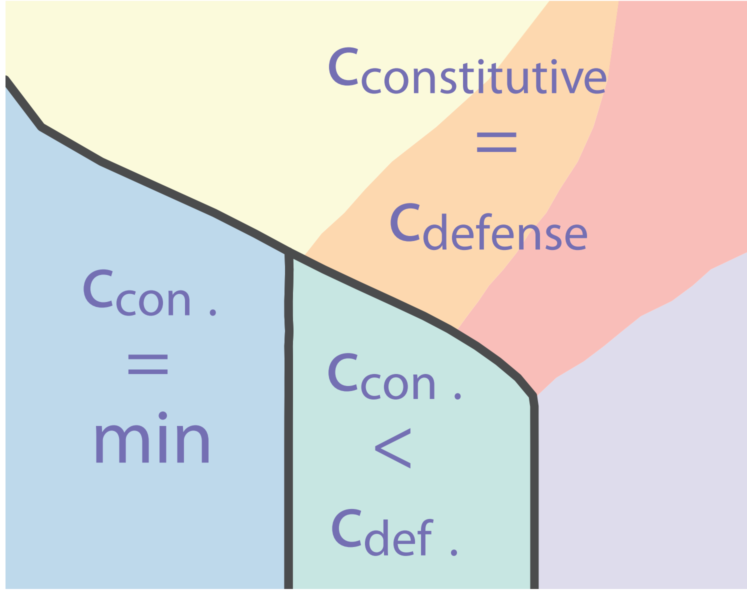


# Optimal strategies

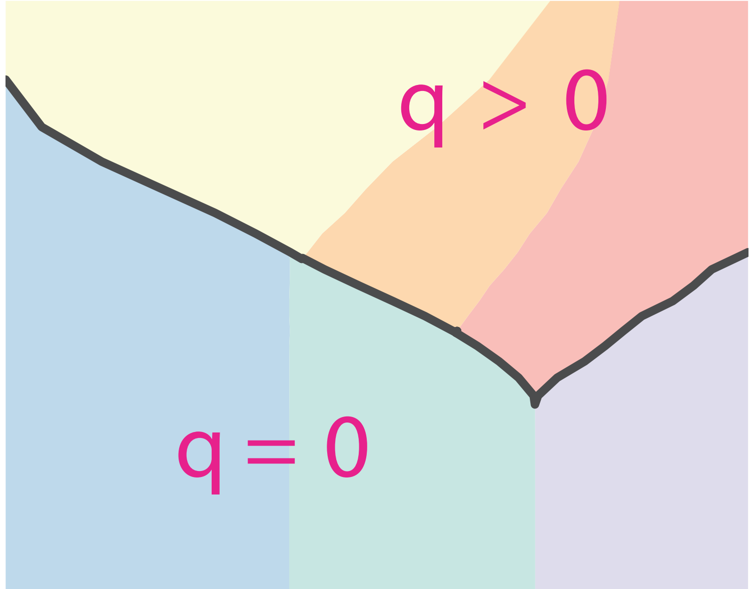


# Three strategy axes

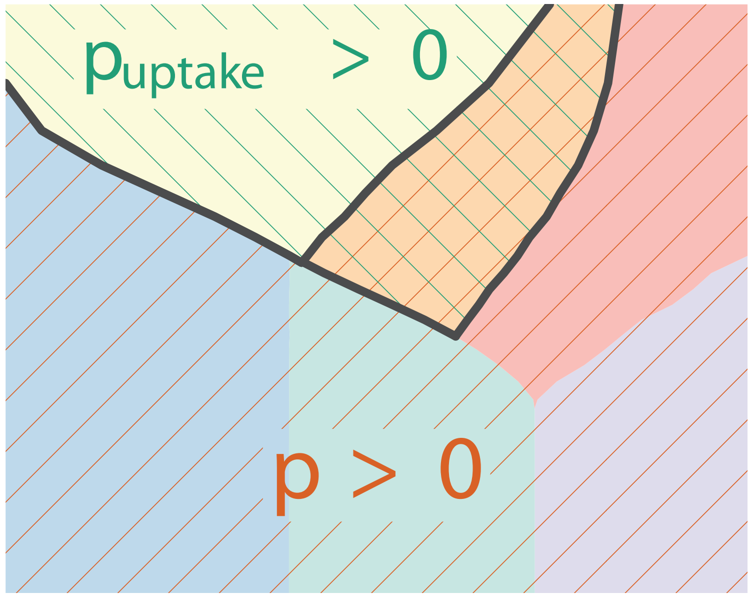
adaptability



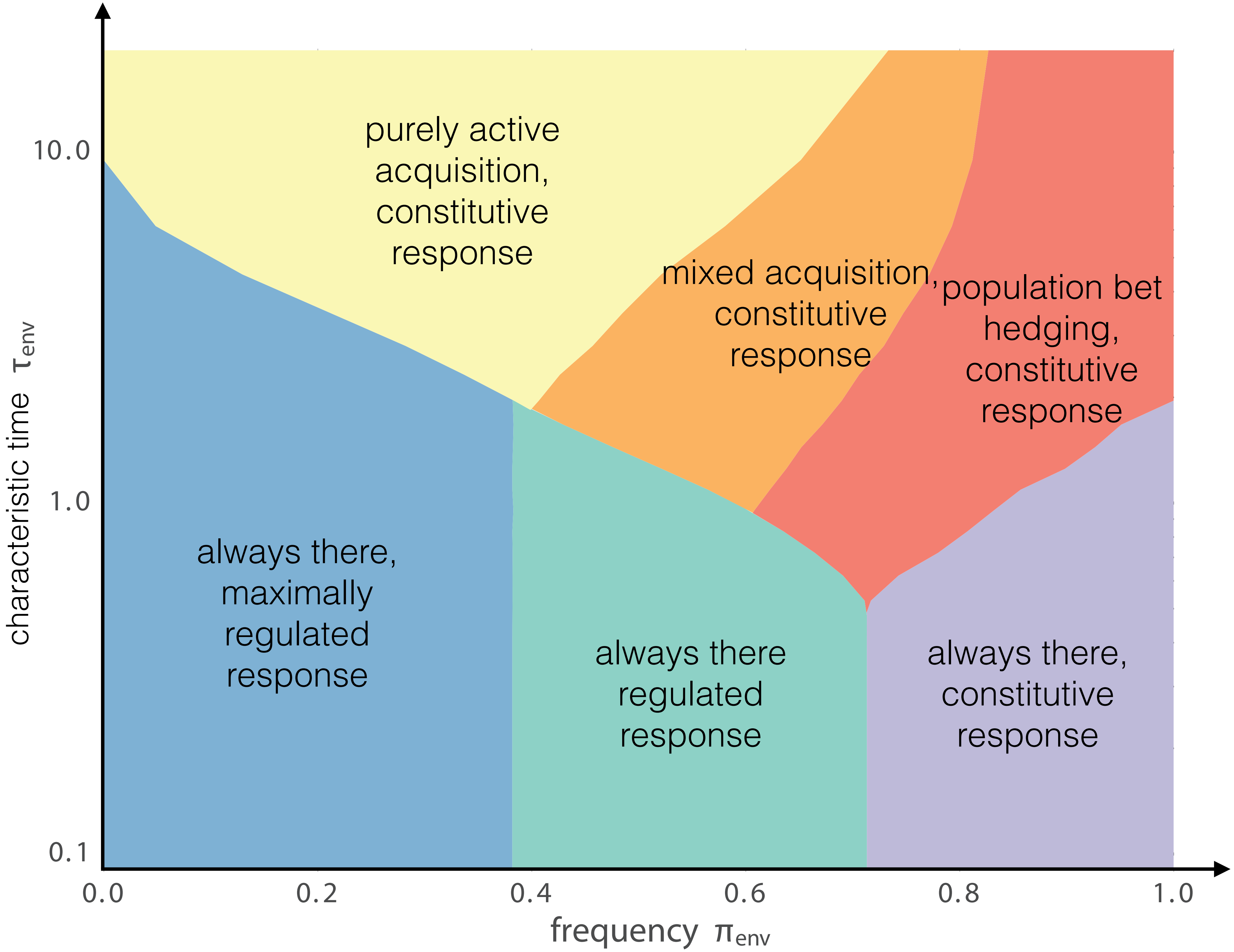
heritability



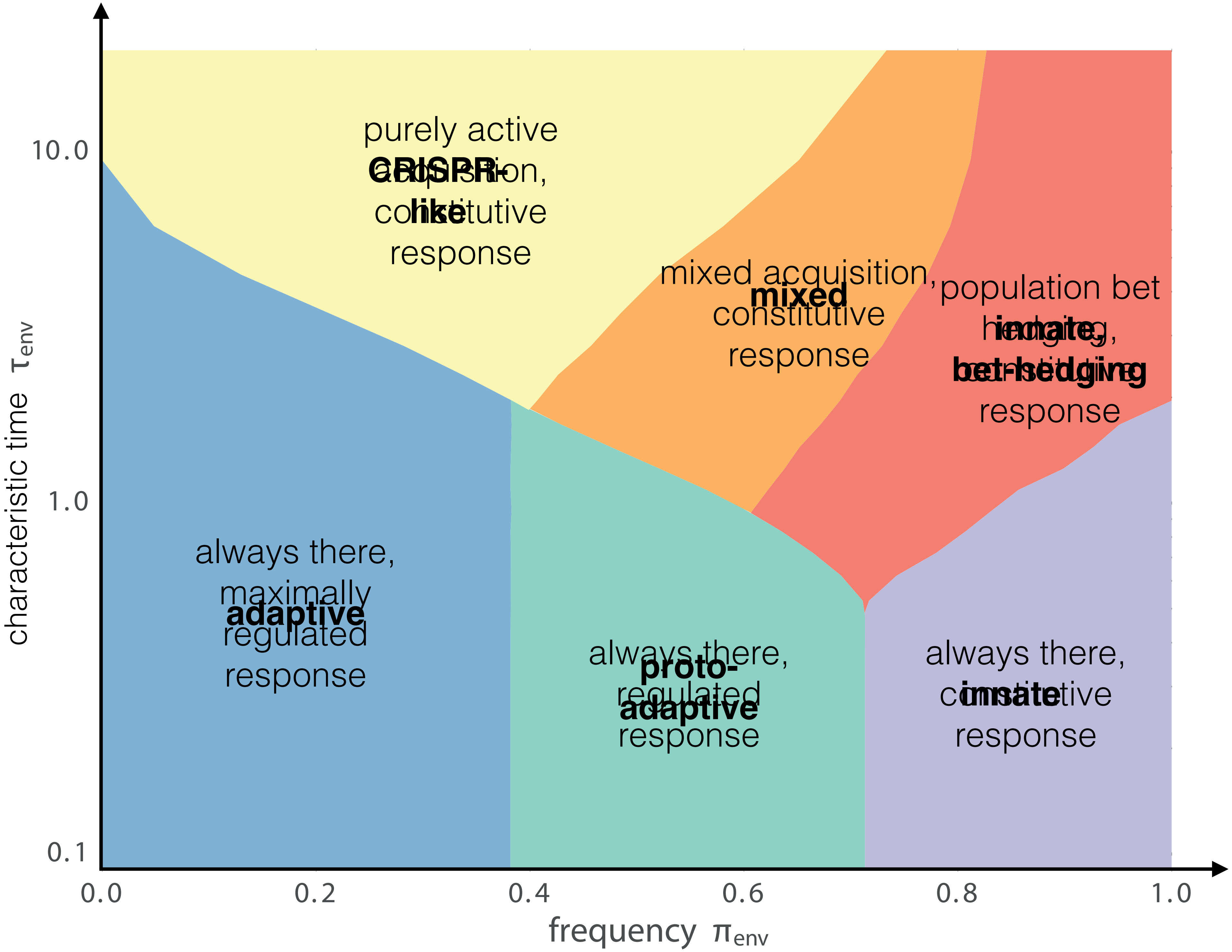
acquisition mode



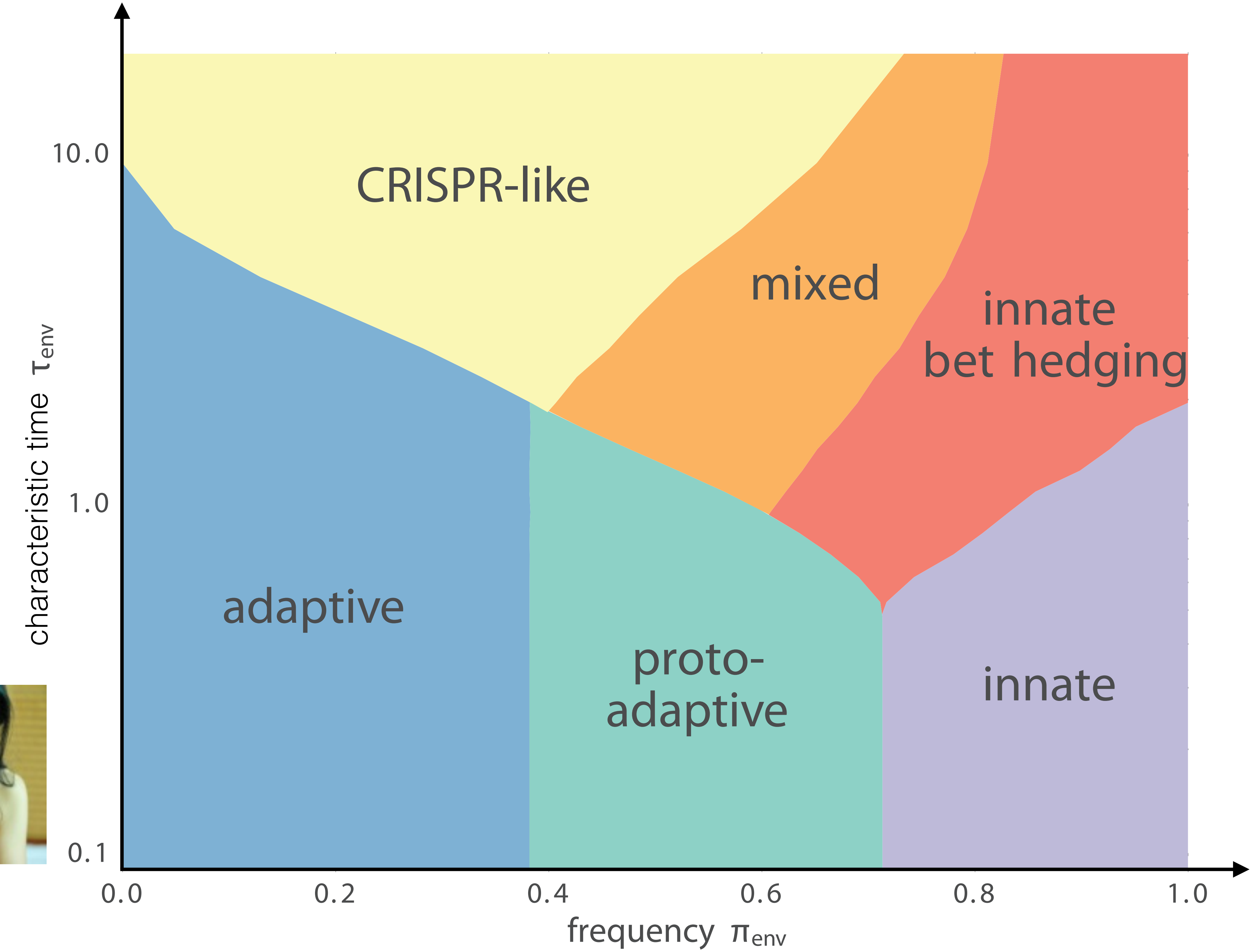
# Optimal strategies



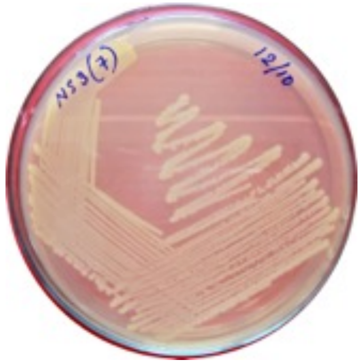
# Optimal immune systems

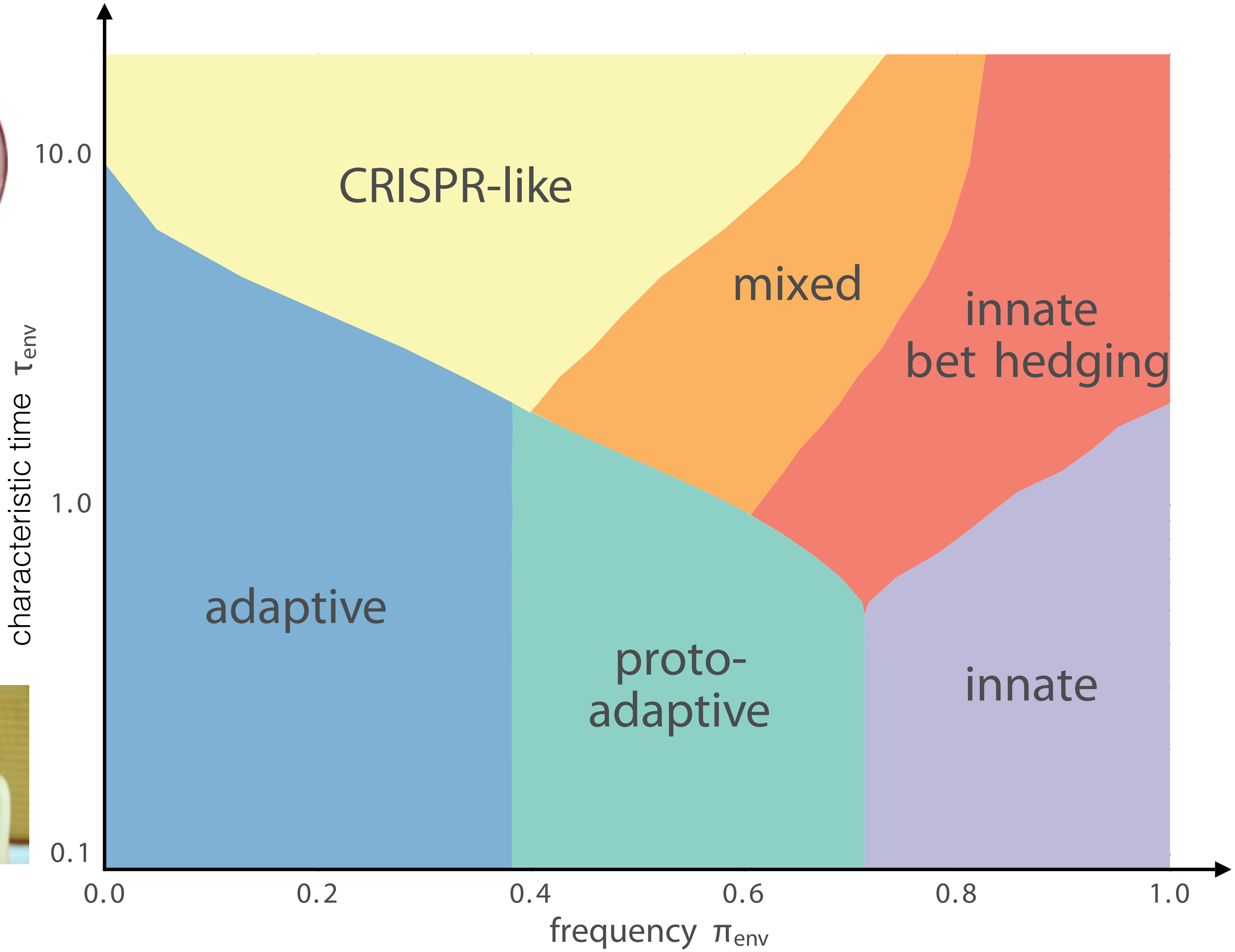


# Optimal immune systems



# Optimal immune systems





# Conclusions

## generating diversity and selection:

- random overlap between (most) individuals
- very long lived clones

## optimal repertoires:

- cover space but are random
- differ in two individuals

## predicting immune systems:

- use dynamics to anticipate frequencies
- memory useful in sparse environments

## optimal immunity:

- known immunity from evolutionary constraints
- depends on environment statistic

T Mora, AM Walczak, W Bialek, CG Callan, PNAS (2010)
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