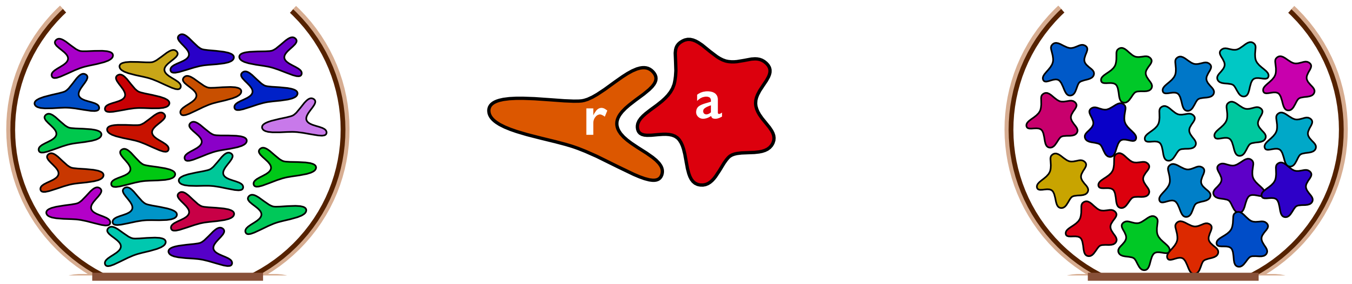


Optimal immune systems

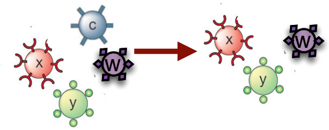
Andreas Mayer (delivered by Aleksandra M Walczak)

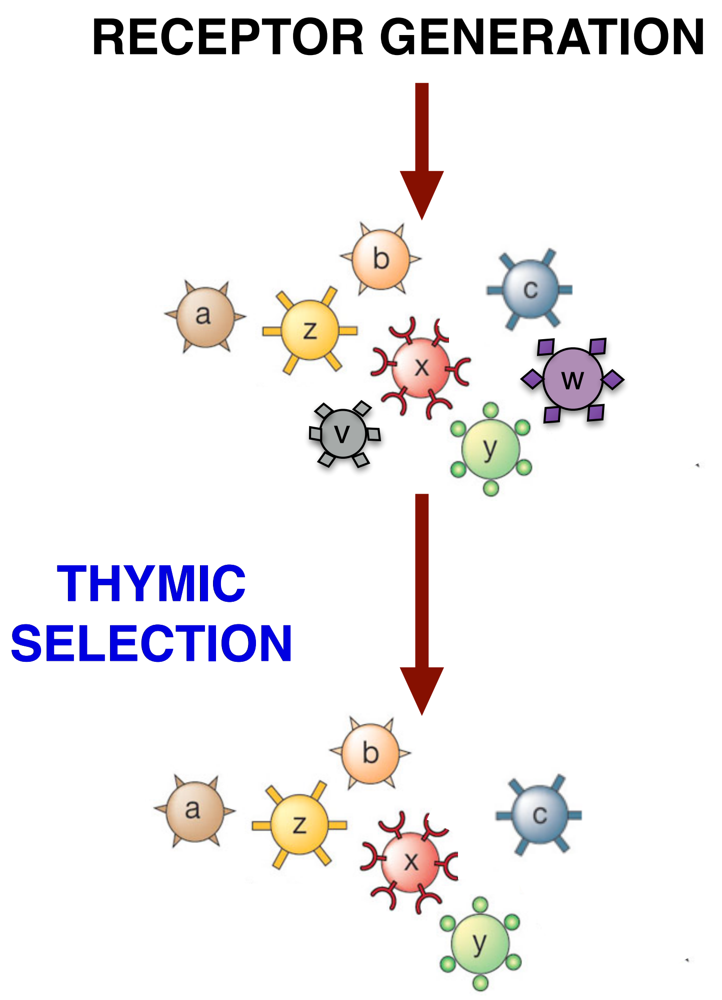
Laboratoire de Physique Théorique - ENS, CNRS

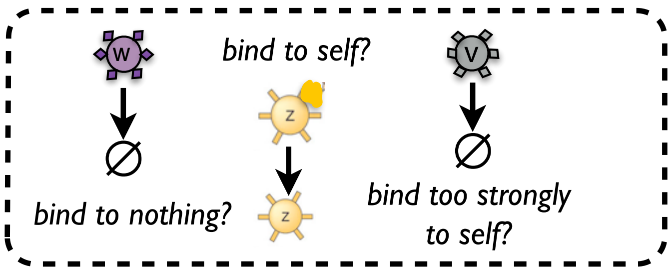
European Research Council
Established by the European Commission

work with
Andreas Mayer, ENS
Vijay Balasubramanian, UPenn
Olivier Rivoire, Grenoble
Thierry Mora, ENS

Receptor sharing



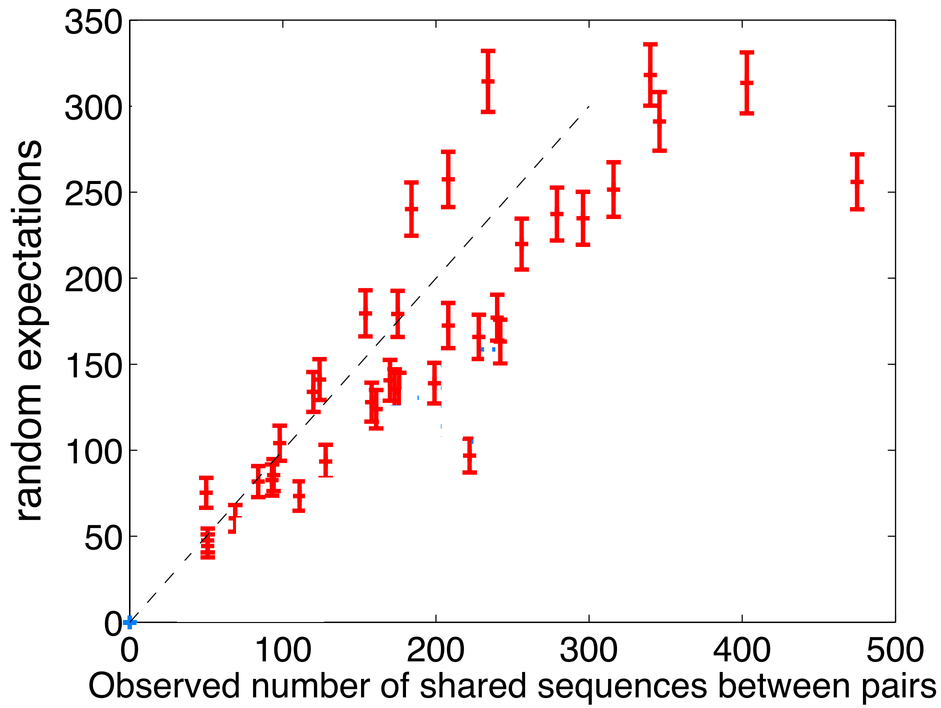




- quantify using selection factors

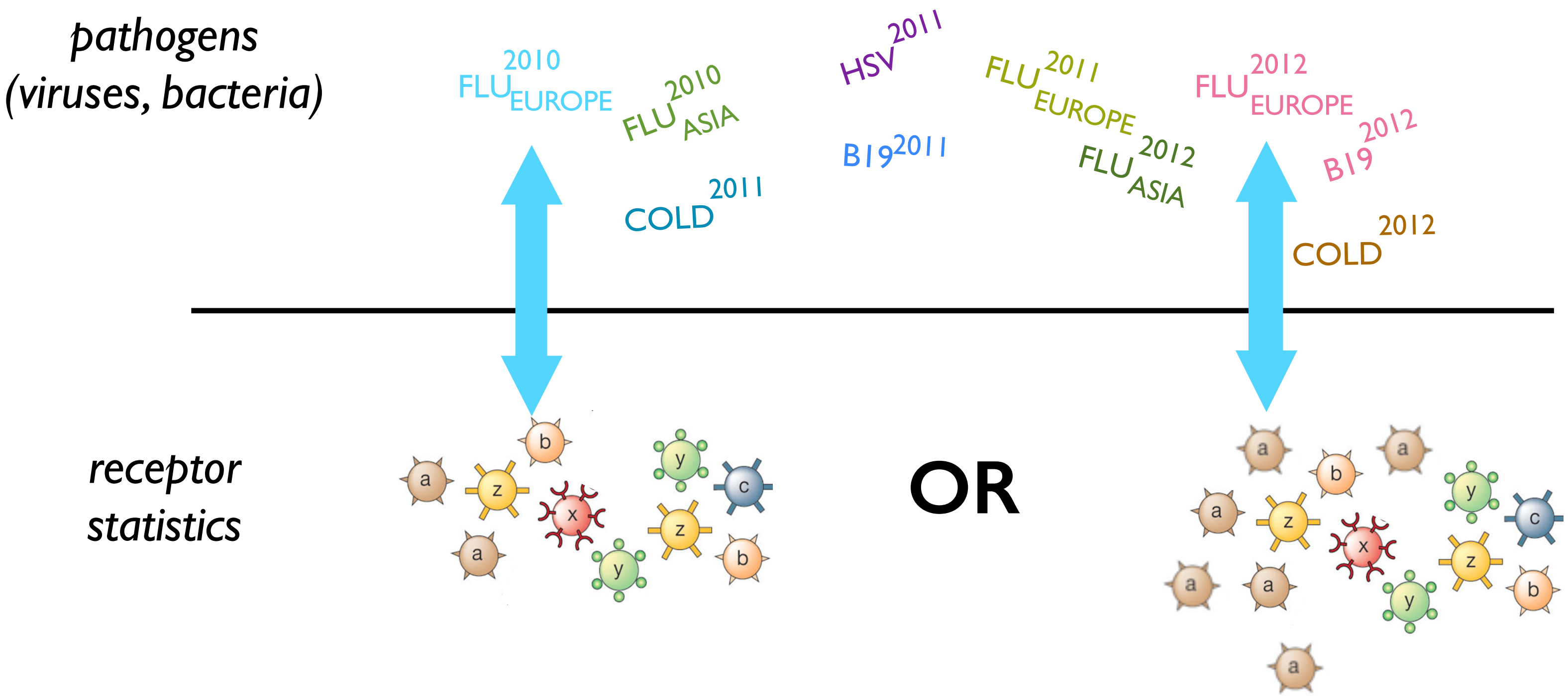
$$Q(\{\sigma\}) = \frac{P_{\text{post-sel}}(\{\sigma\})}{P_{\text{gen}}(\{\sigma\})}$$

- how many shared receptors between 2 people?



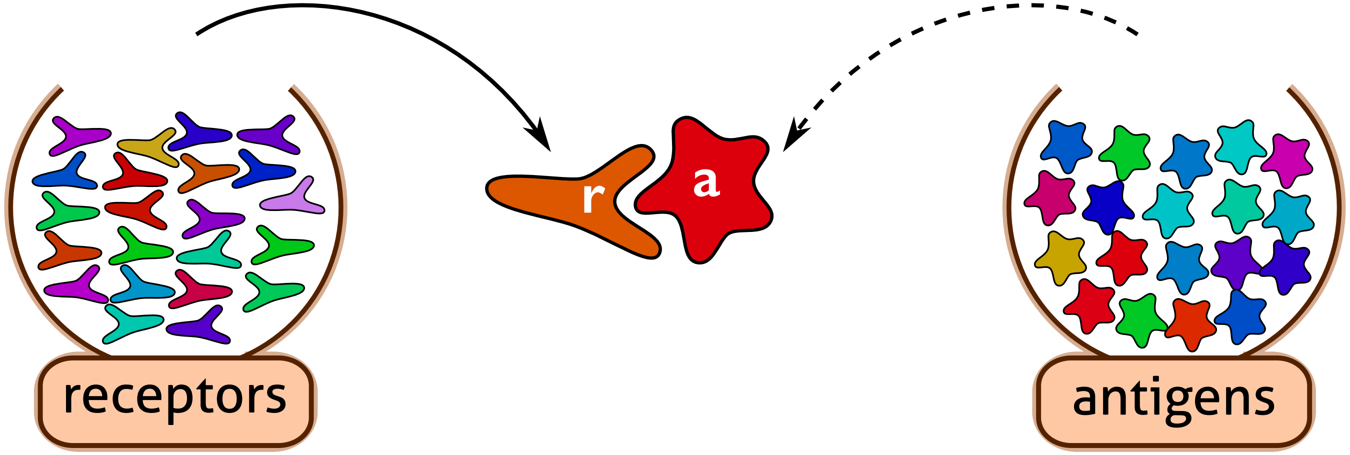
→ close to random expectations

Receptor distributions



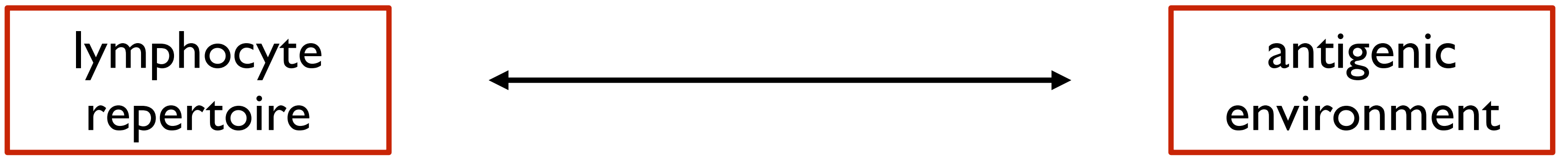
optimal distribution ?

The trade-off

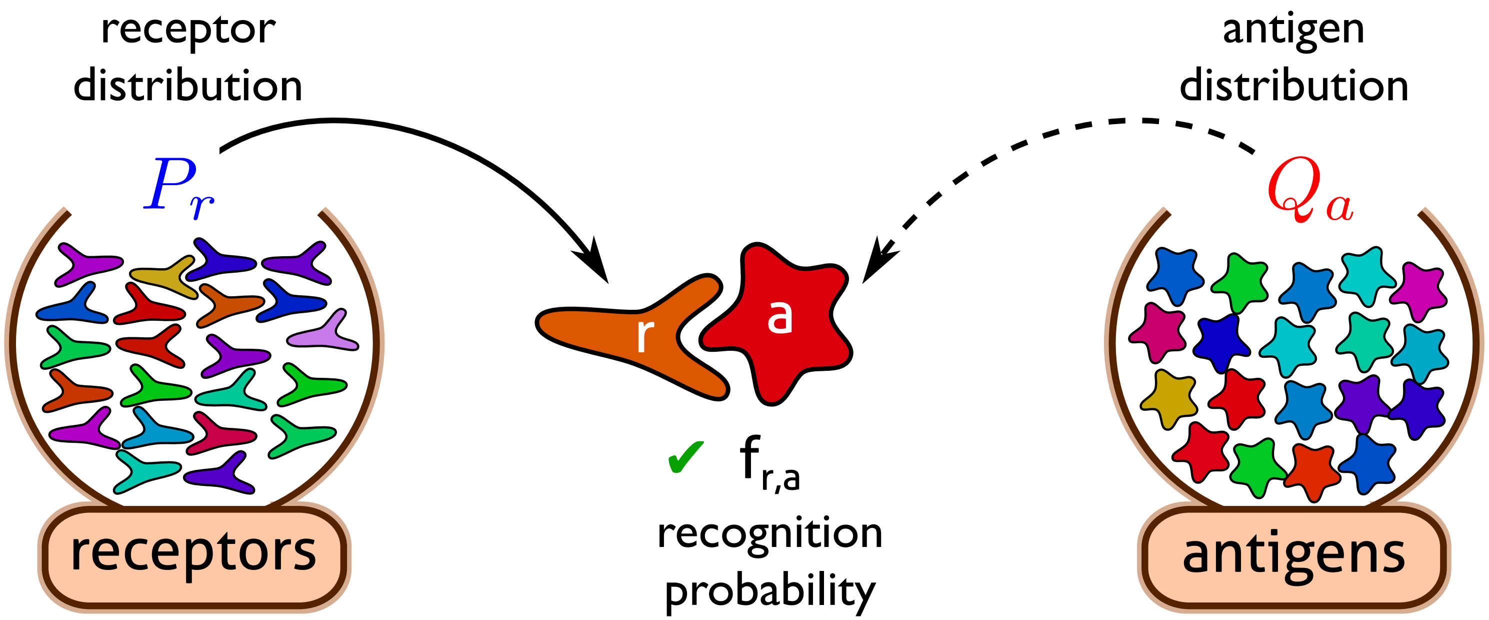


limited number of encounters

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

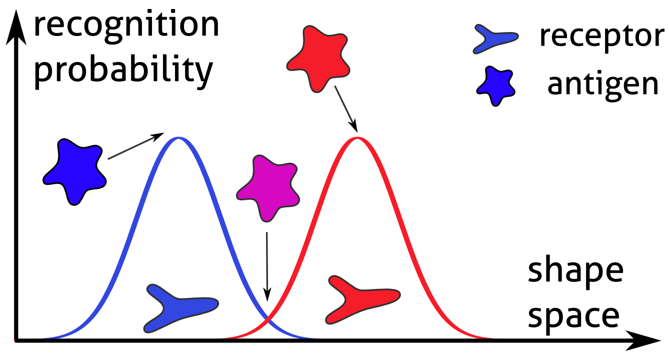


Cross-reactivity

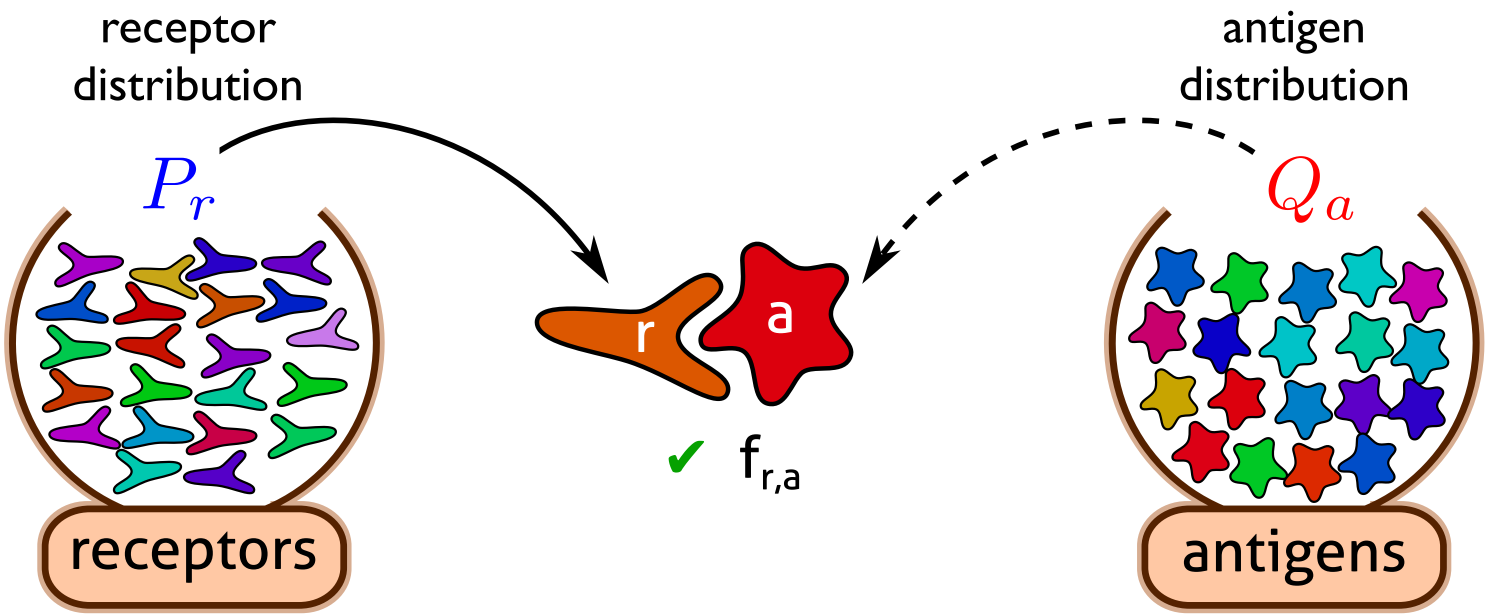


- cross-reactivity - recognition probability
- probability of immune response from encounter with a given antigen

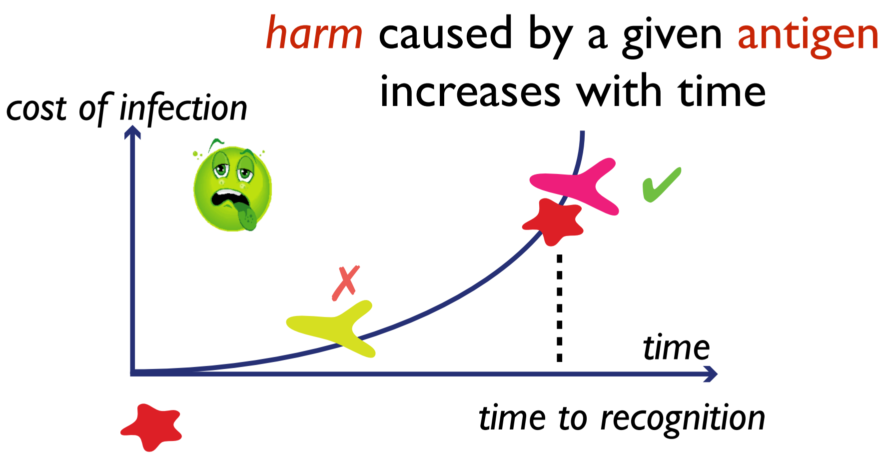
$$\tilde{P}_a = \sum_r f_{r,a} P_r$$



Receptors - antigens interactions



- 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

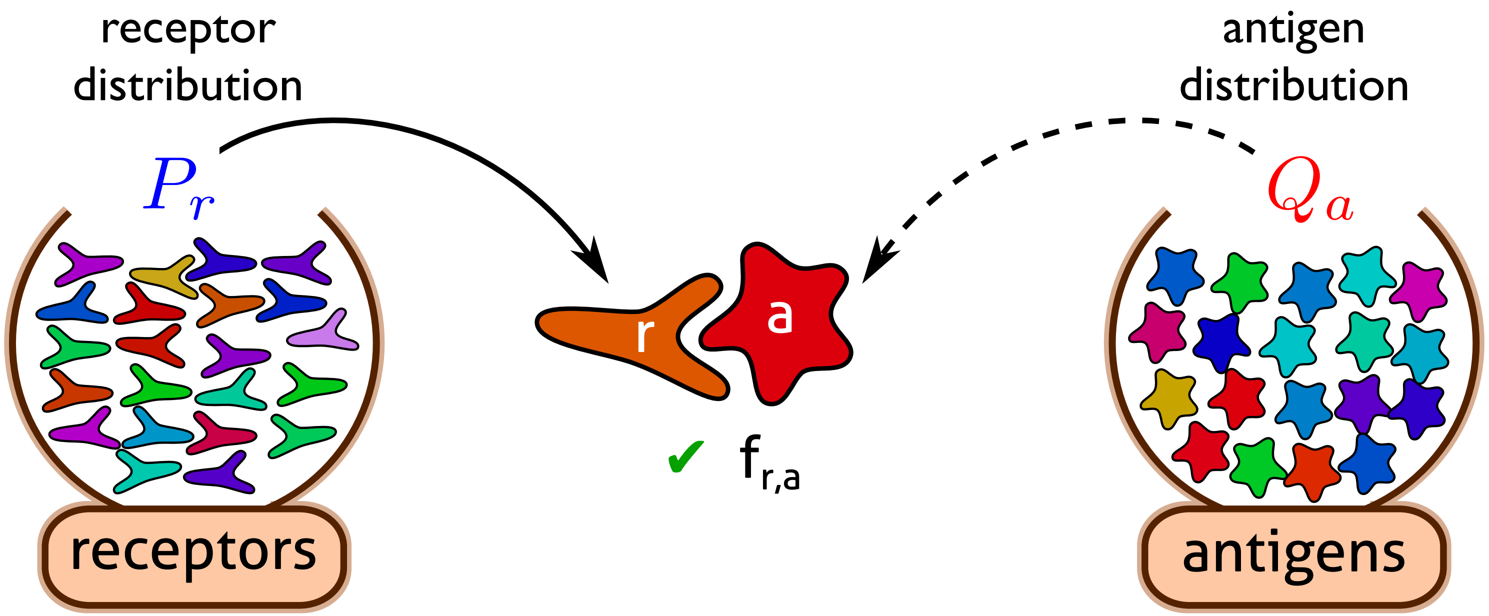


$$\bar{F}_a(P_r) = \mu_a \int_0^{+\infty} dm\, F_a(m)\, \tilde{P}_a e^{-m\tilde{P}_a}$$

virulence (μ_a); effective cost of infection ($F_a(m)$); Poisson distributed recognition ($\tilde{P}_a e^{-m\tilde{P}_a}$)

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

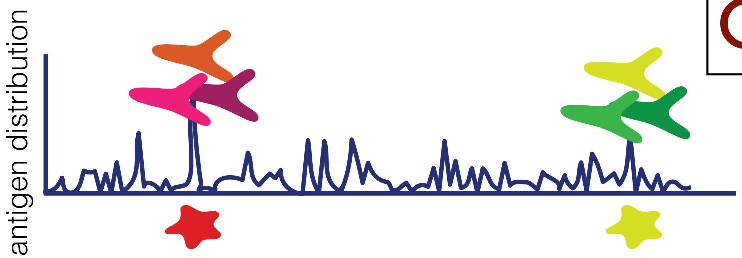
Cost



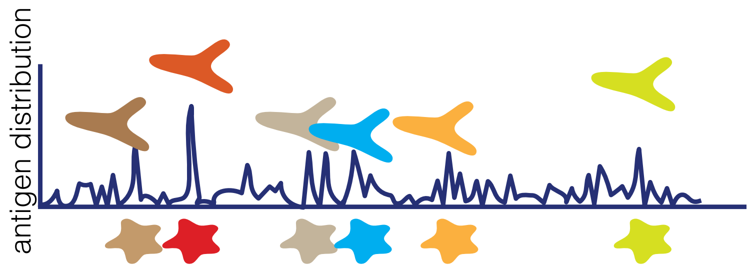
total harm caused by antigen increases with time

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

trade-off: many antigens ↔ limited resources



Optimal repertoire?



→ minimize cost given fixed antigen distribution

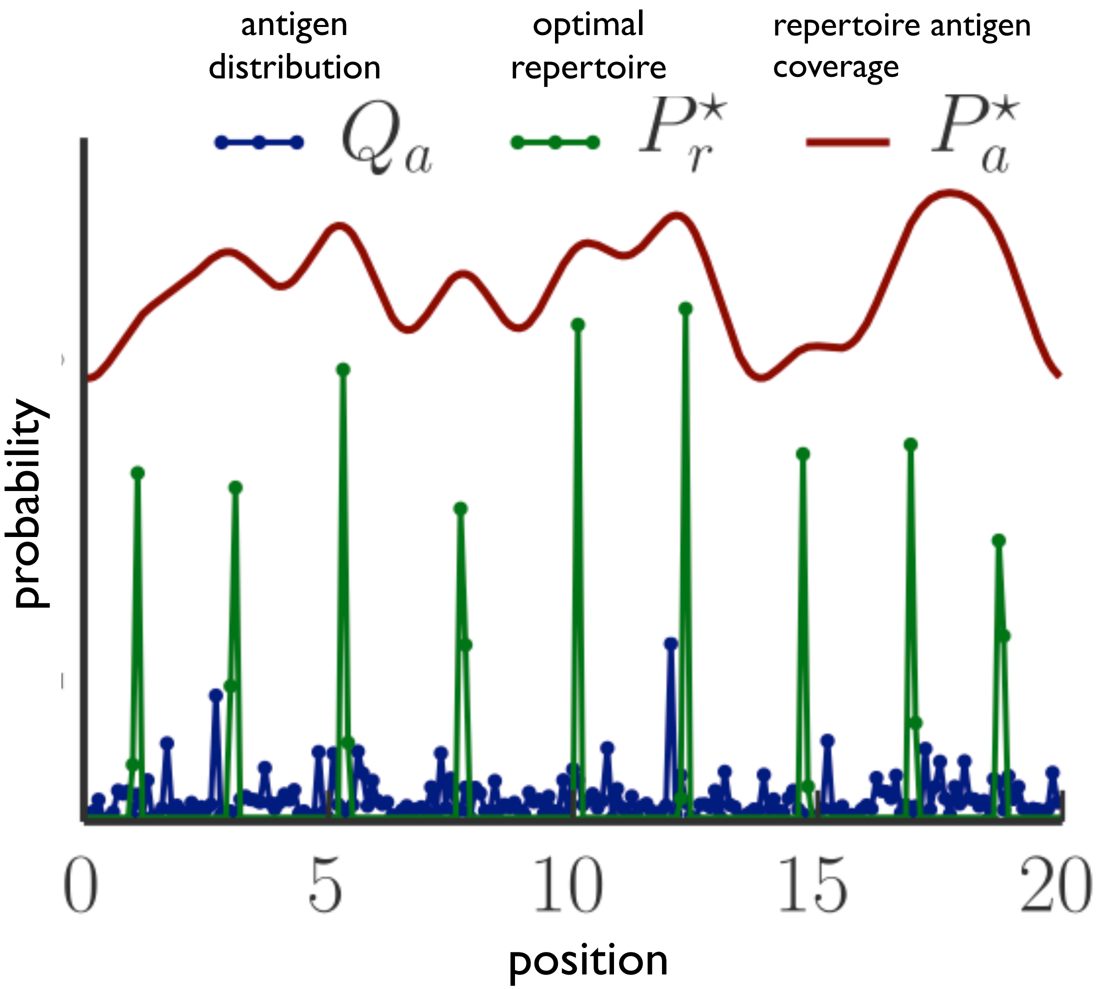
Peaked optimal repertoires

- exponentially expanding antigen population
  + exponentially growing cost in time

$$F(m) = m$$

- peaked distributions
- tile space

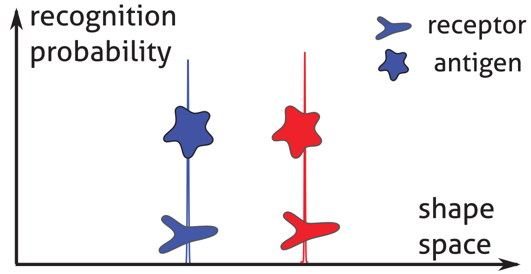
- coverage follows antigen distribution
- but not exactly



Covering rare pathogens

How many resources aimed at common/rare antigen?

no cross-reactivity



depends on cost of late recognition $\longrightarrow$ effective cost function

- exponentially expanding antigen population

$Q_a/Q_b = 10$

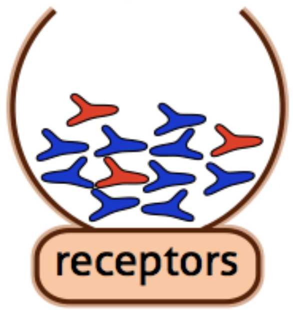
optimal repertoire

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

effective cost $F(m) \propto m$

number of encounters

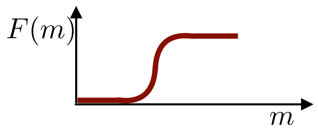
$P_a^\star/P_b^\star = \sqrt{10}$



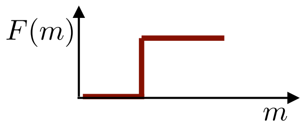
- exponentially expanding antigen population + exponentially growing cost in time

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

- saturated cost $\longrightarrow$ low frequency cut-off

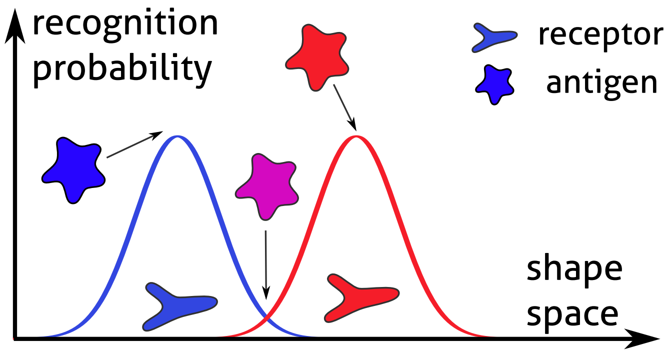


- harm past threshold $\longrightarrow$ flattened receptor distribution

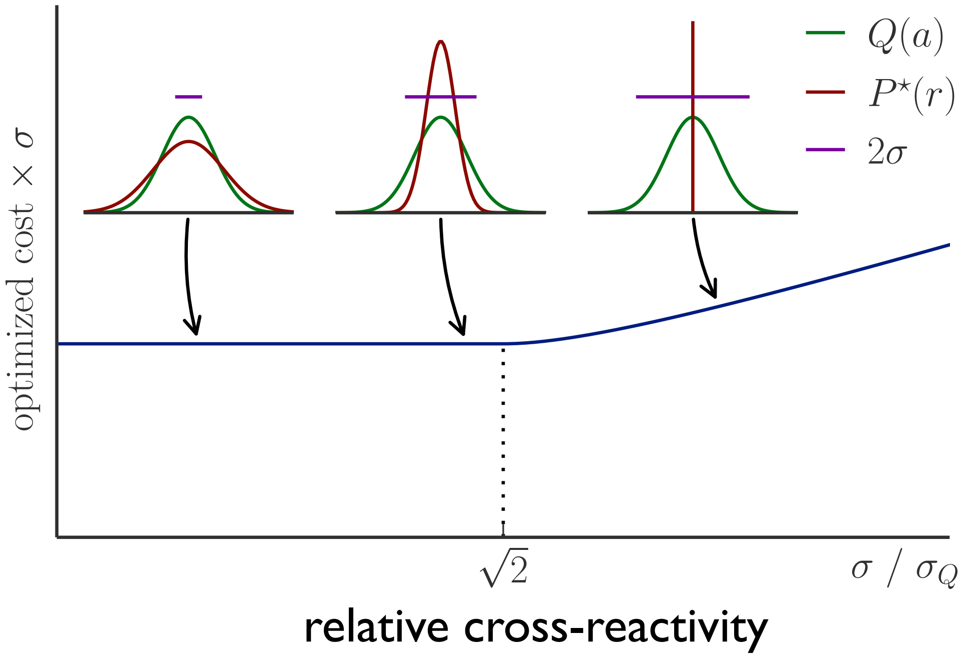


- $P_r^* \propto Q_r \Leftrightarrow$ very slowly increasing cost $\quad F(m) \propto \ln m$

Cross-reactivity

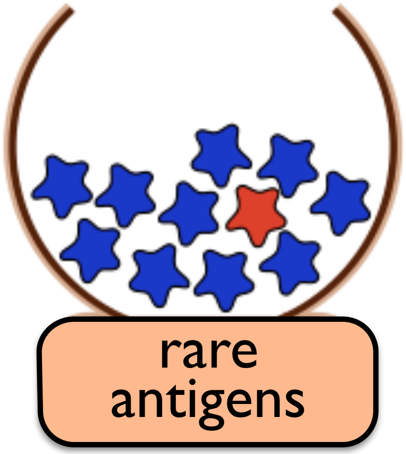


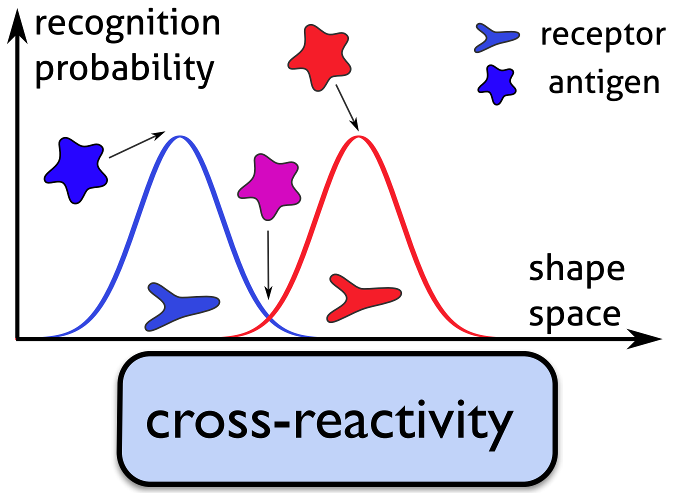
- antigen distribution + cross-reactivity Gaussian

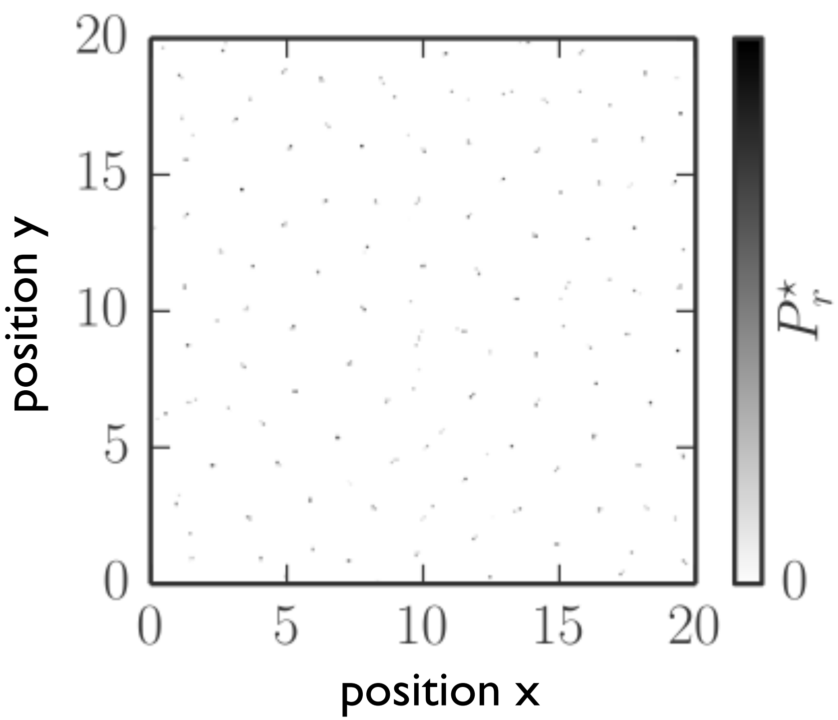


$\longrightarrow$ large cross-reactivity concentrates distribution

Peaked optimal repertoires



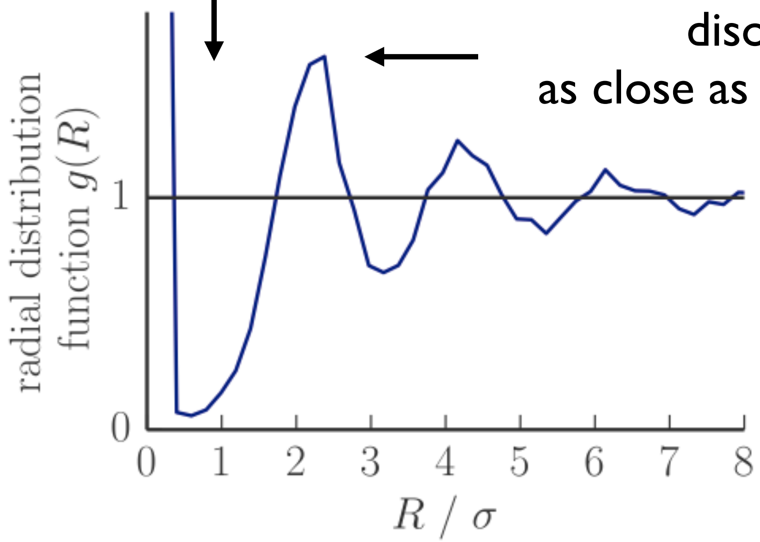


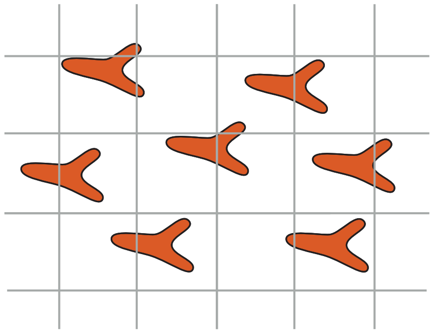


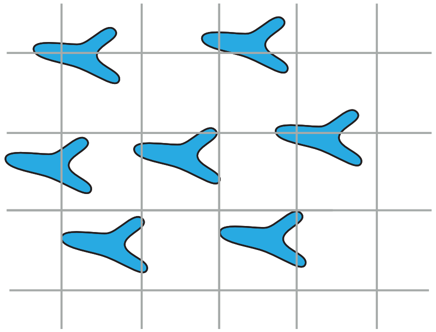
Disordered hyperuniformity

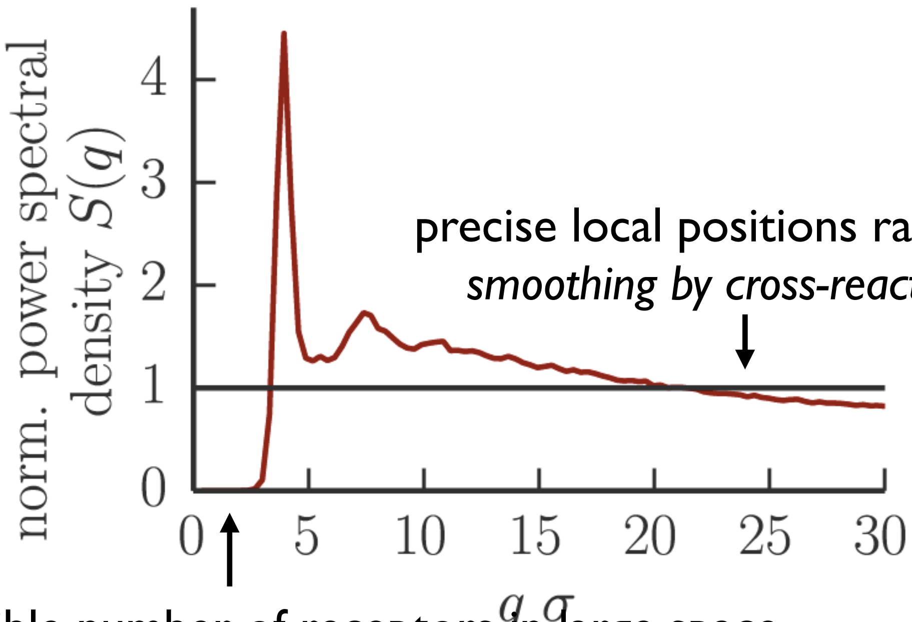
receptors cannot be close to each other

disordered tiling -
as close as possible but excluding







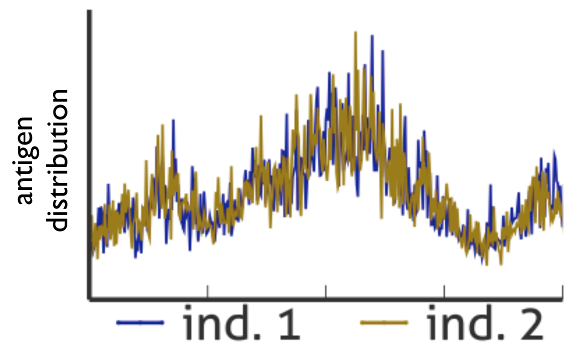


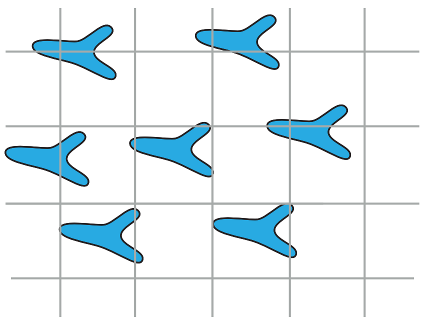
precise local positions random
smoothing by cross-reactivity

reproducible number of receptors in large space
tracking of antigen

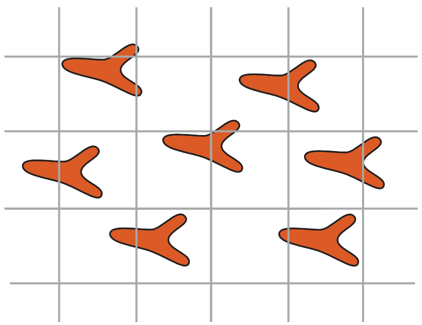
Personalized responses

two individuals see the environment slightly differently





→ very different repertoires

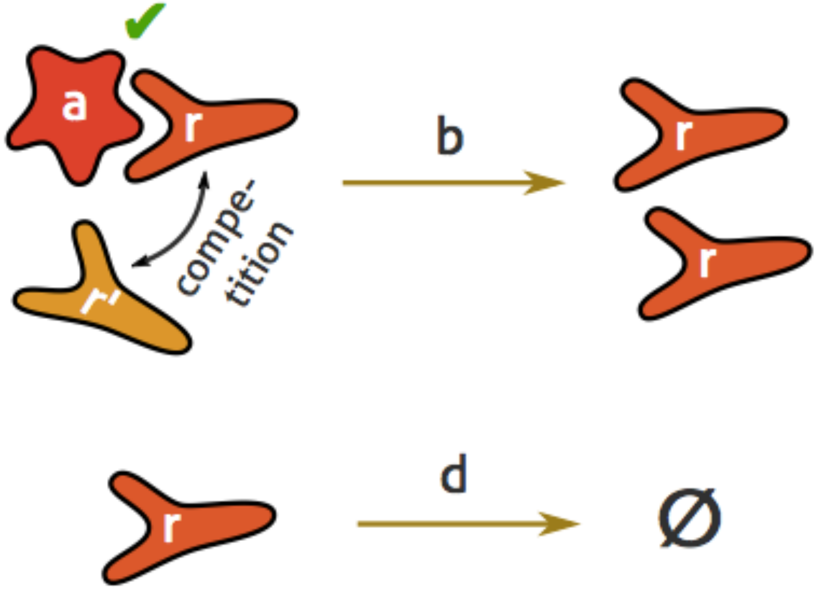


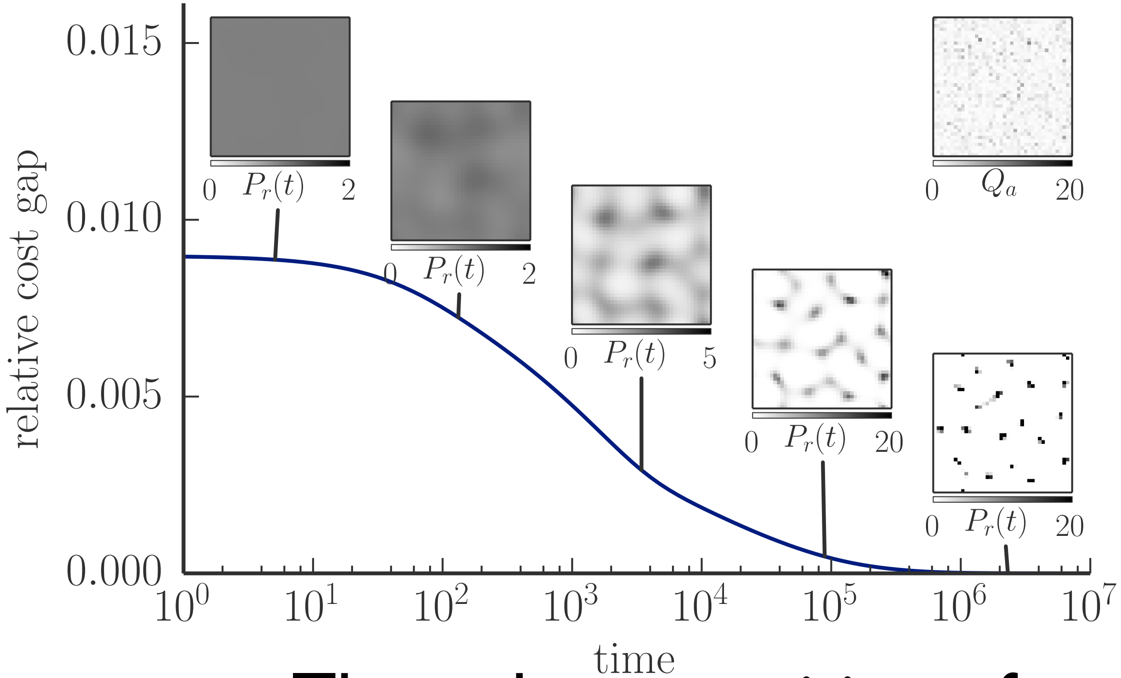
Self-organized dynamics

Can optimal repertoires be reached via dynamics?

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

- N_r: population size
- b: proliferation rate
- $\sum_p Q_p f_{r,a}$: detectable pathogen
- $A\left(\sum_{r'} N_{r'} f_{r',a} \right)$: availability of pathogen → reduced by competition, e.g. $A(\tilde{N}_a) = \frac{1}{(1+\tilde{N}_a)^2}$
- d: death rate



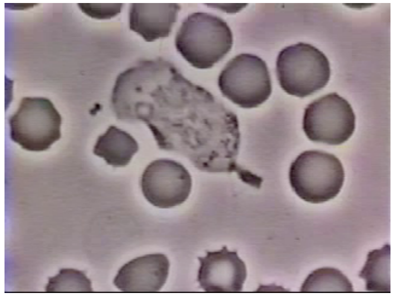


→ Through competition of receptors for antigen

Different immune strategies

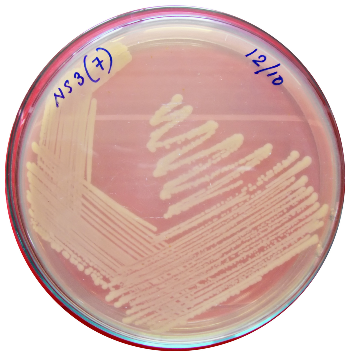
adaptive immunity

Other immune strategies



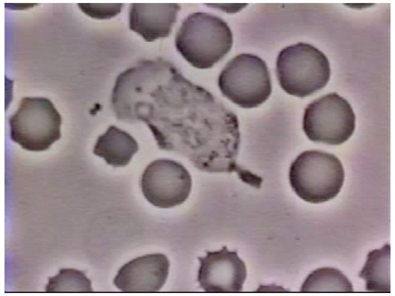
innate immunity

adaptive immunity



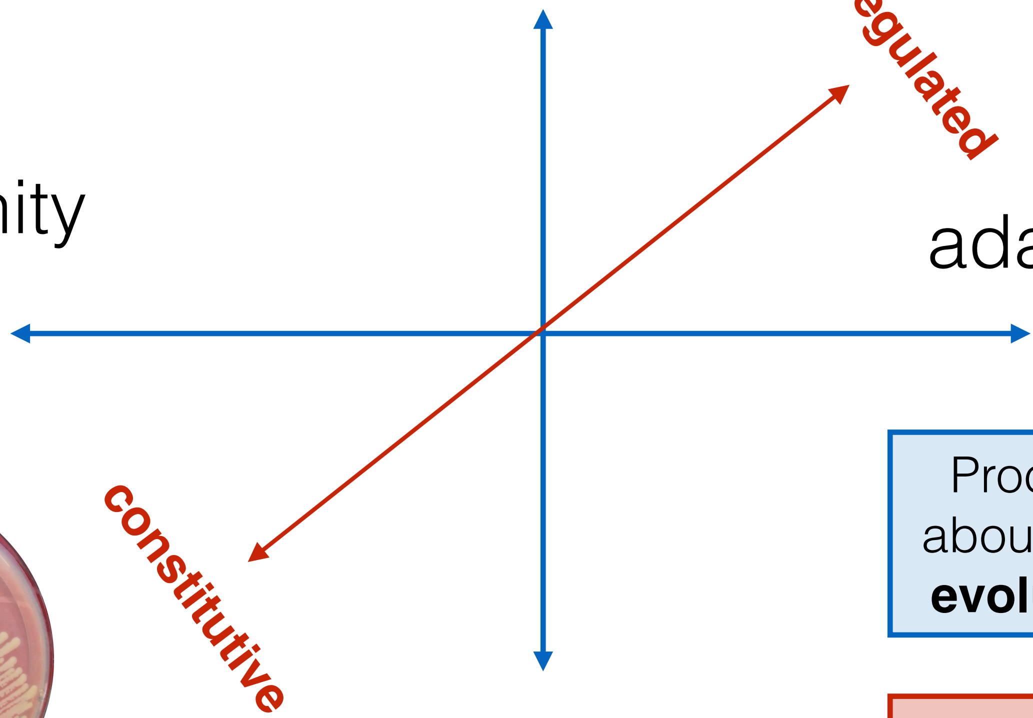
CRISPR immunity

Common strategic choices



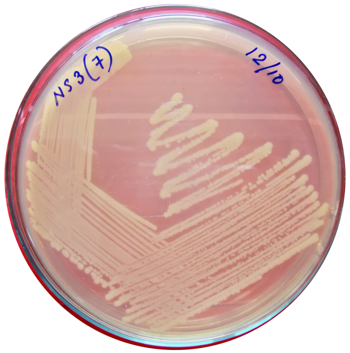
innate immunity

adaptive immunity



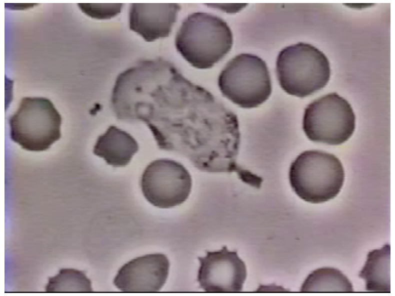
Processing information about the environment on **evolutionary** timescales

Response during **organism** lifetime



CRISPR immunity

Common strategic choices



randomly acquired

regulate

in

optimal immunity?

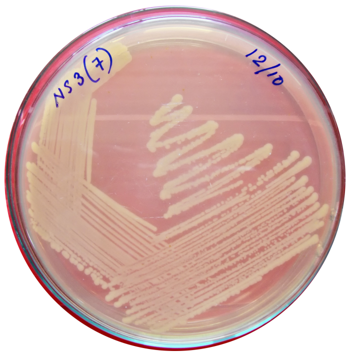
ty

constitutive

actively acquired

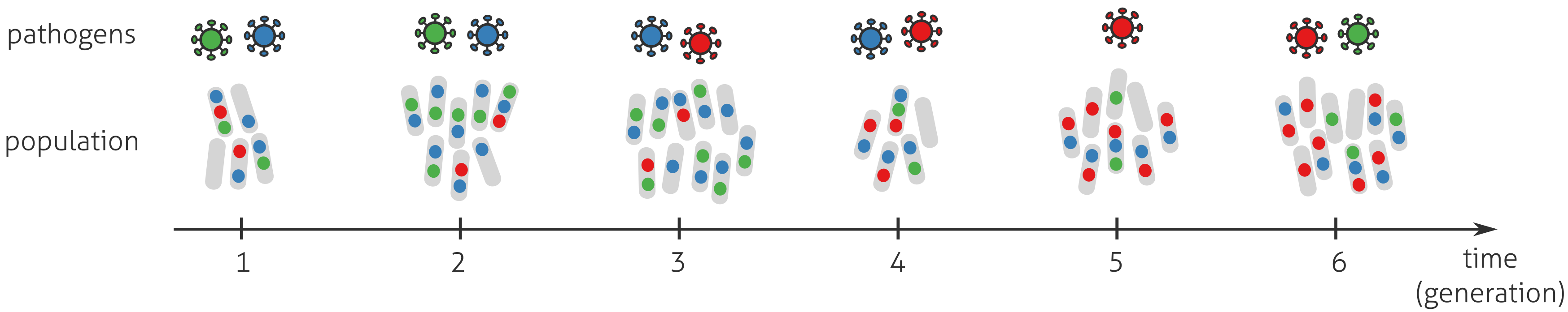
Processing information about the environment on **evolutionary** timescales

Response during **organism** lifetime



CRISPR immunity

Optimal immunity

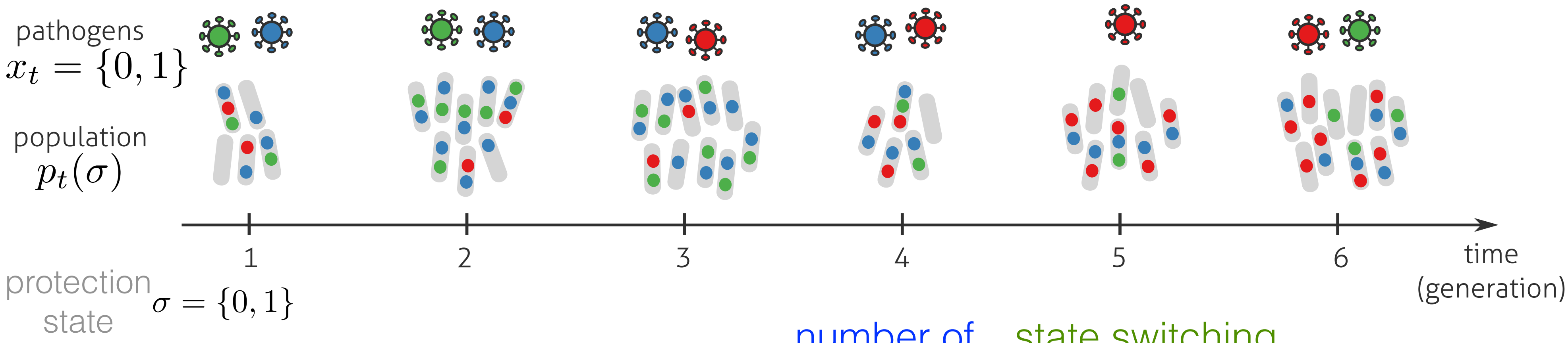


- match environment statistics
- ensure long term population growth

→ immunity as adaptation to pathogen statistics

- consider different strategies
- optimize long term population growth

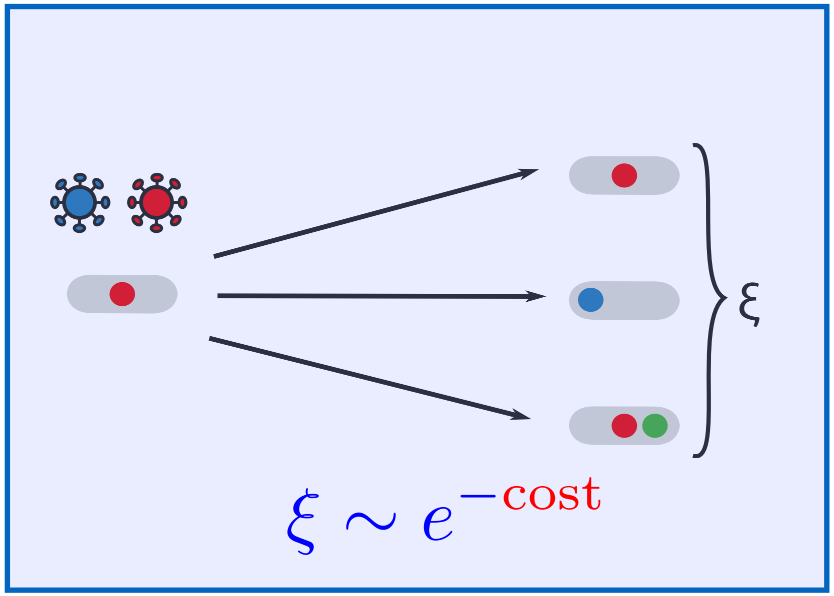
Population growth



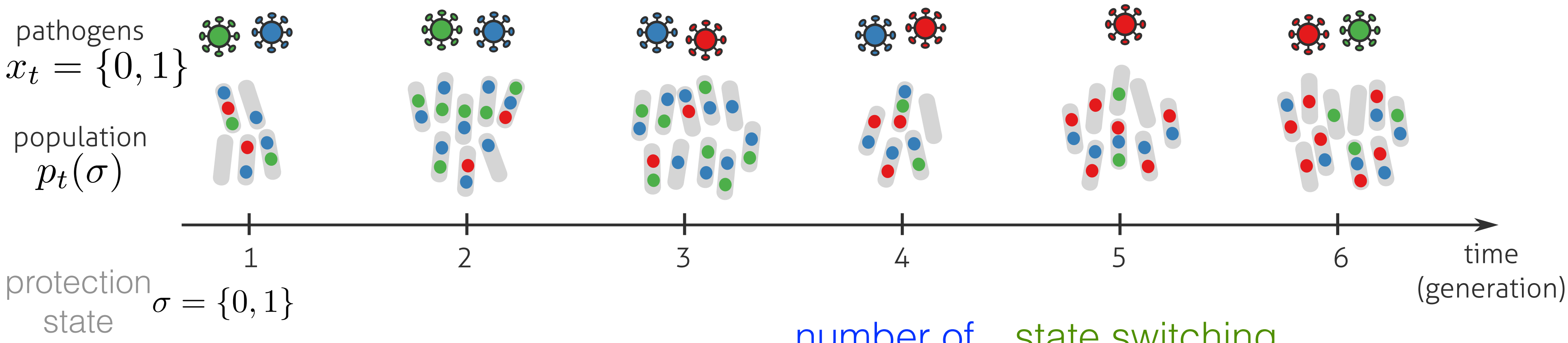
number of offspring

state switching probability

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

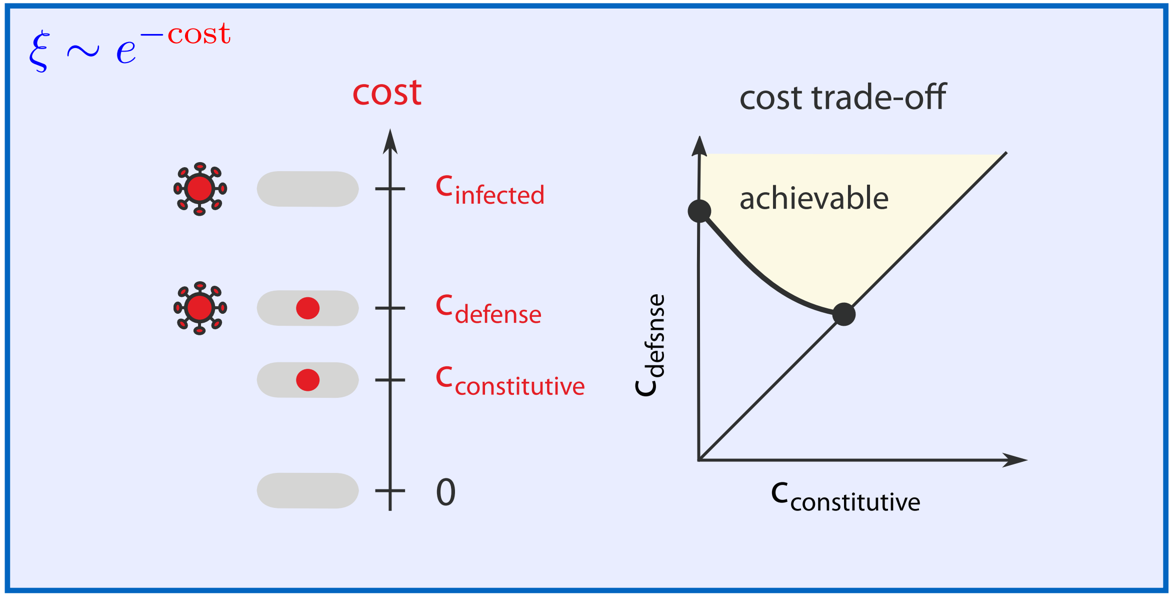


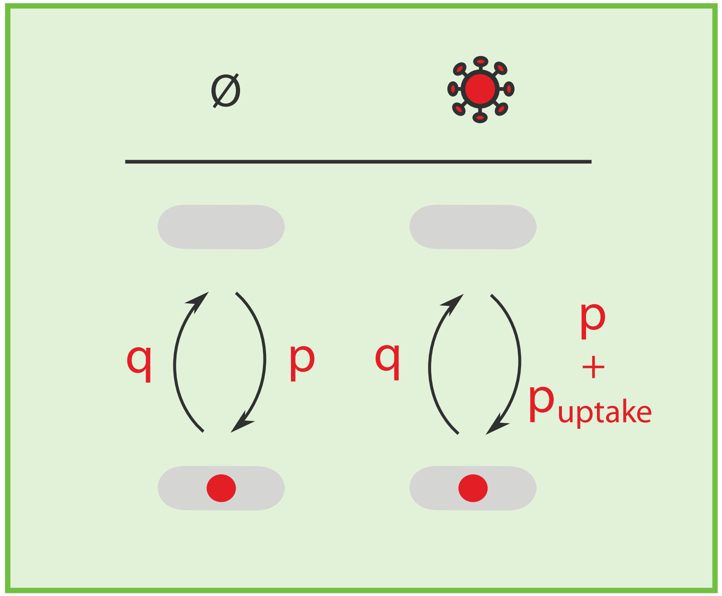
Population growth



number of offspring — state switching probability

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



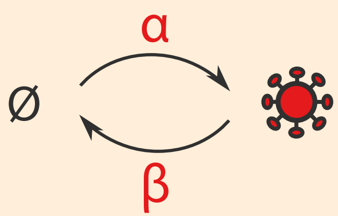


The environment

Stochastic environment

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

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



Maximize long term growth rate

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

characteristic time τ_{env}

10.0

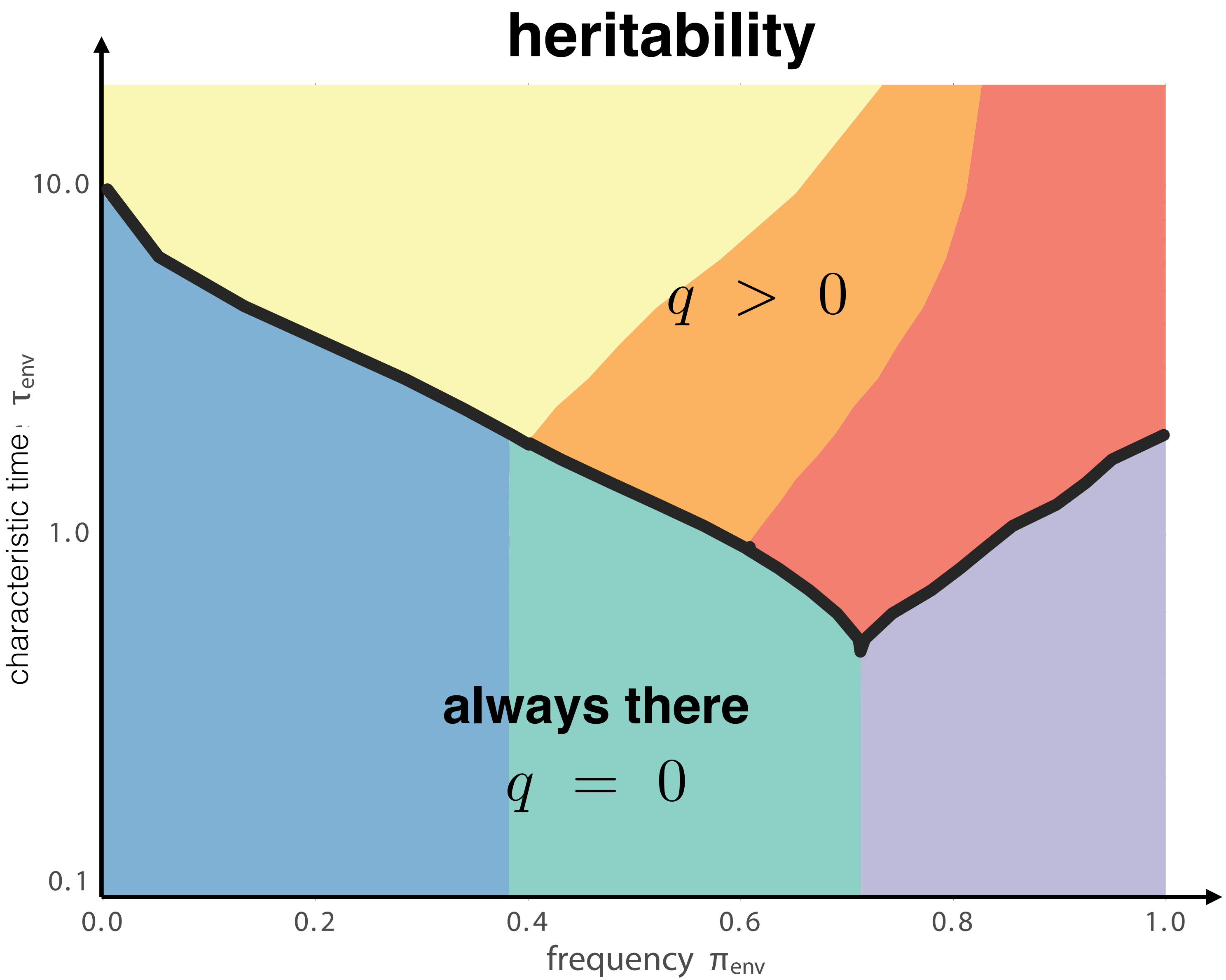
1.0

0.1

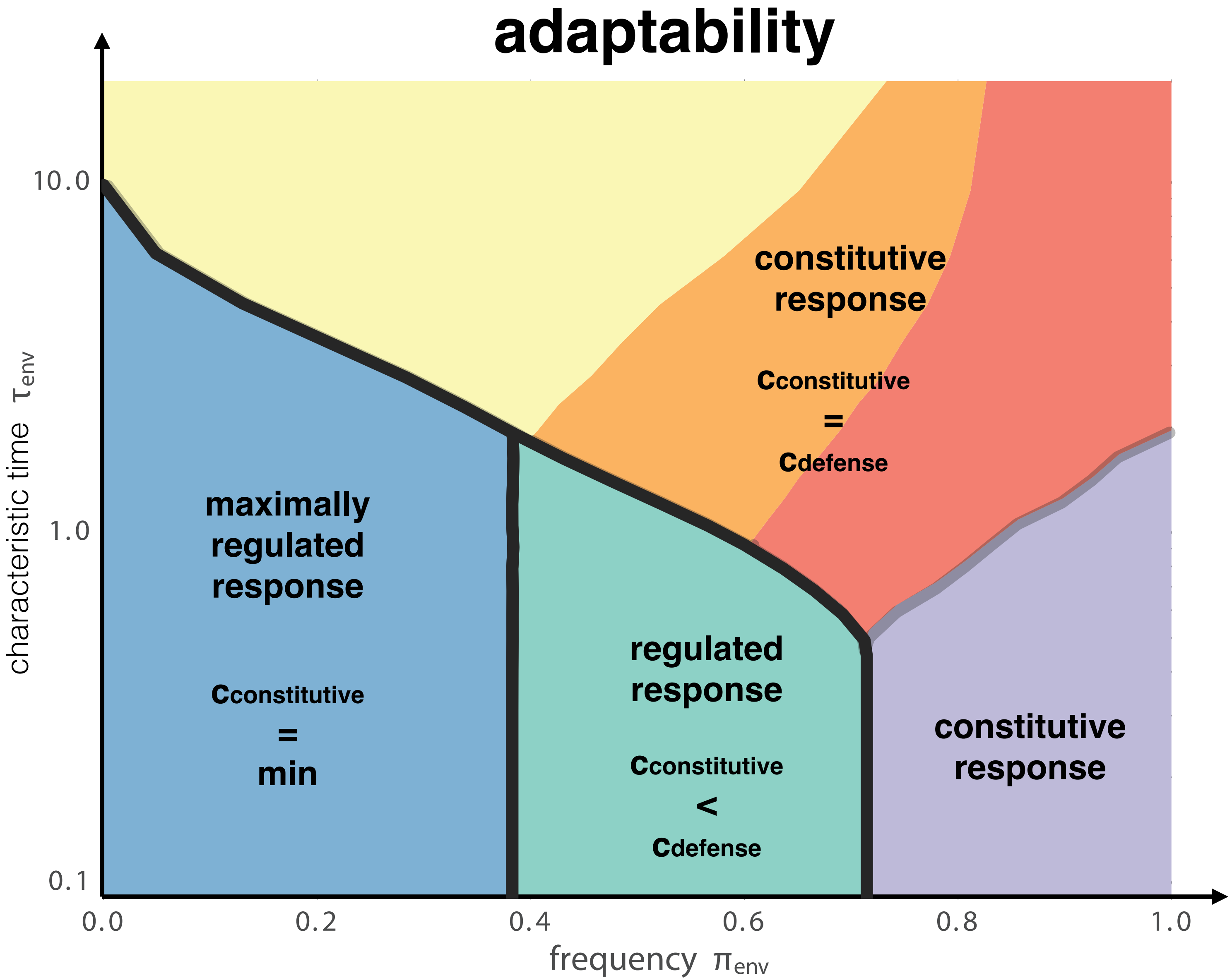
0.0 0.2 0.4 0.6 0.8 1.0

frequency π_{env}

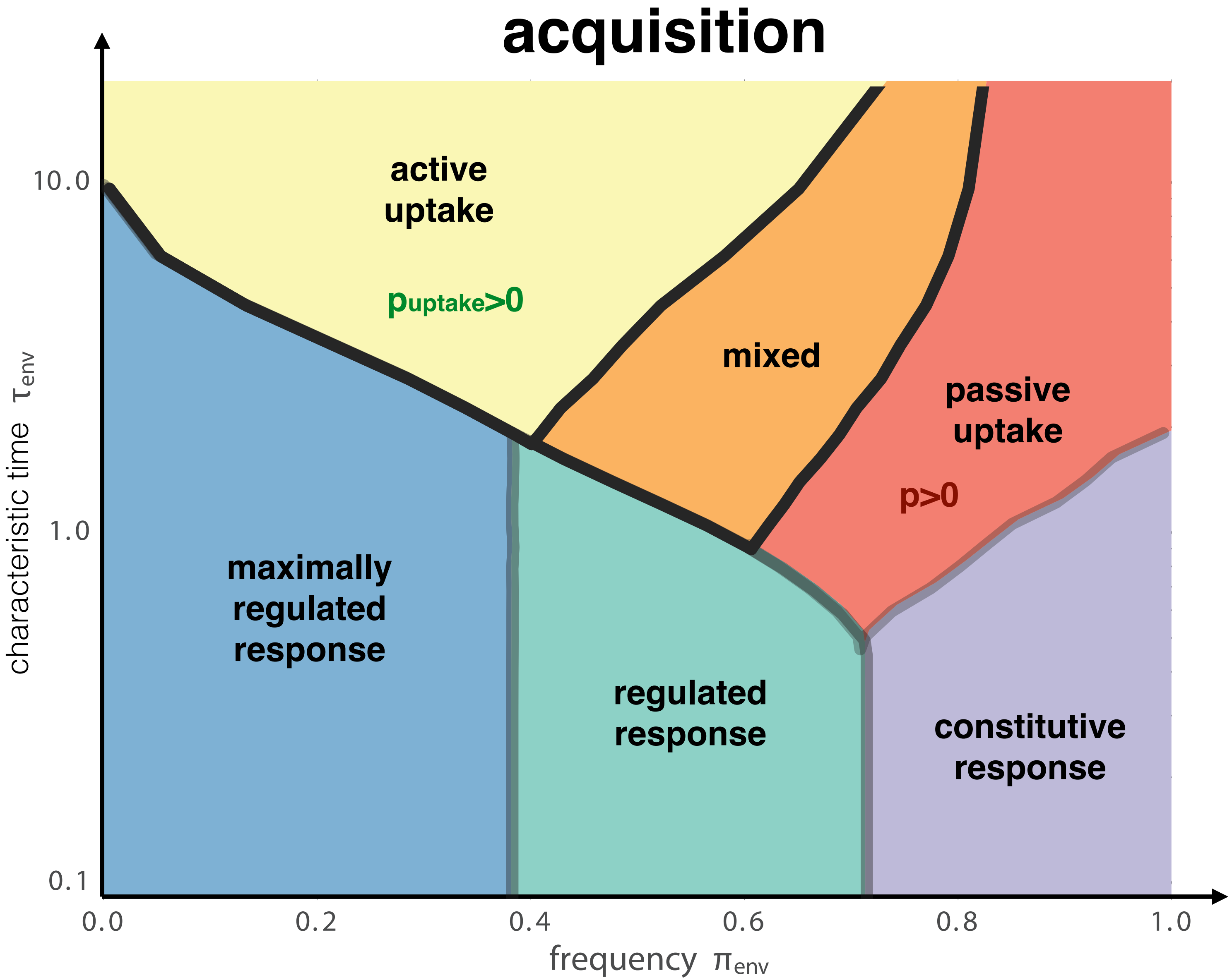
Optimal strategies



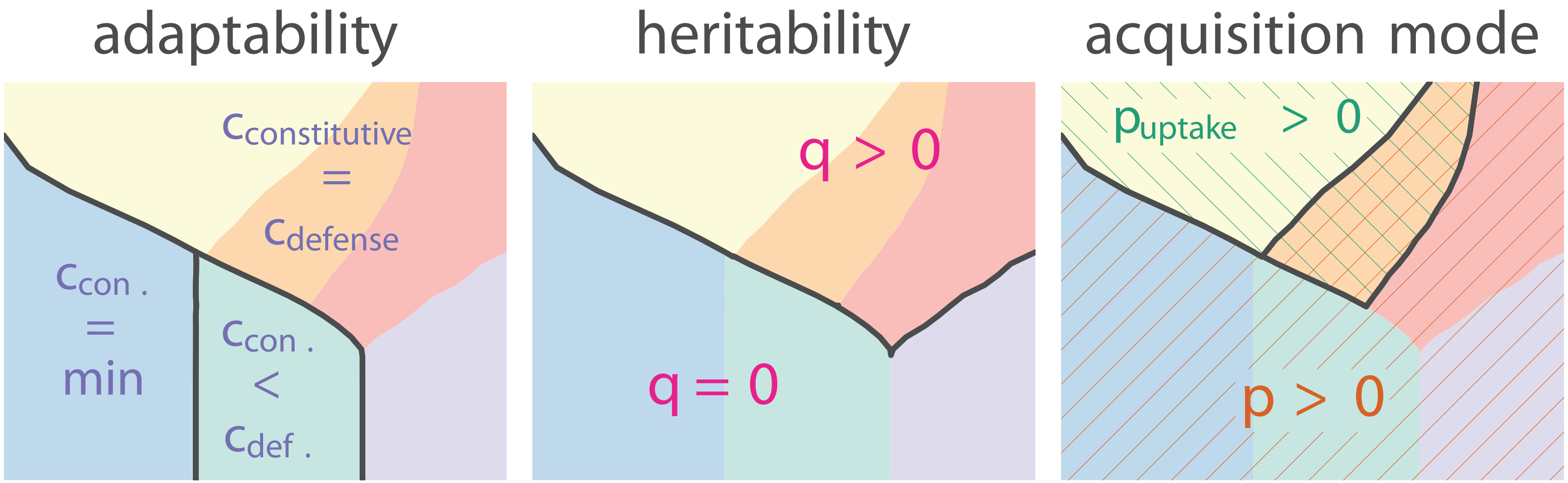
Optimal strategies



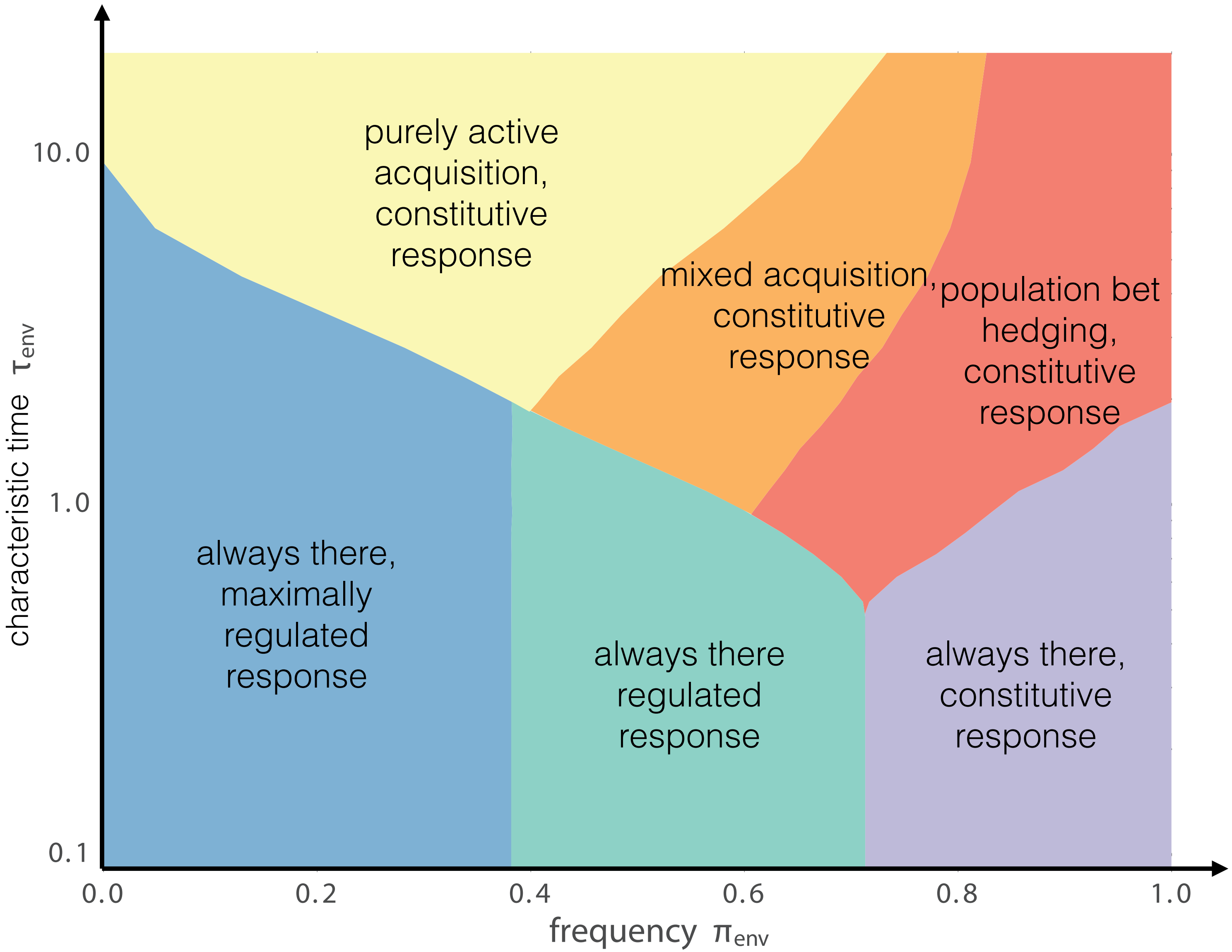
Optimal strategies



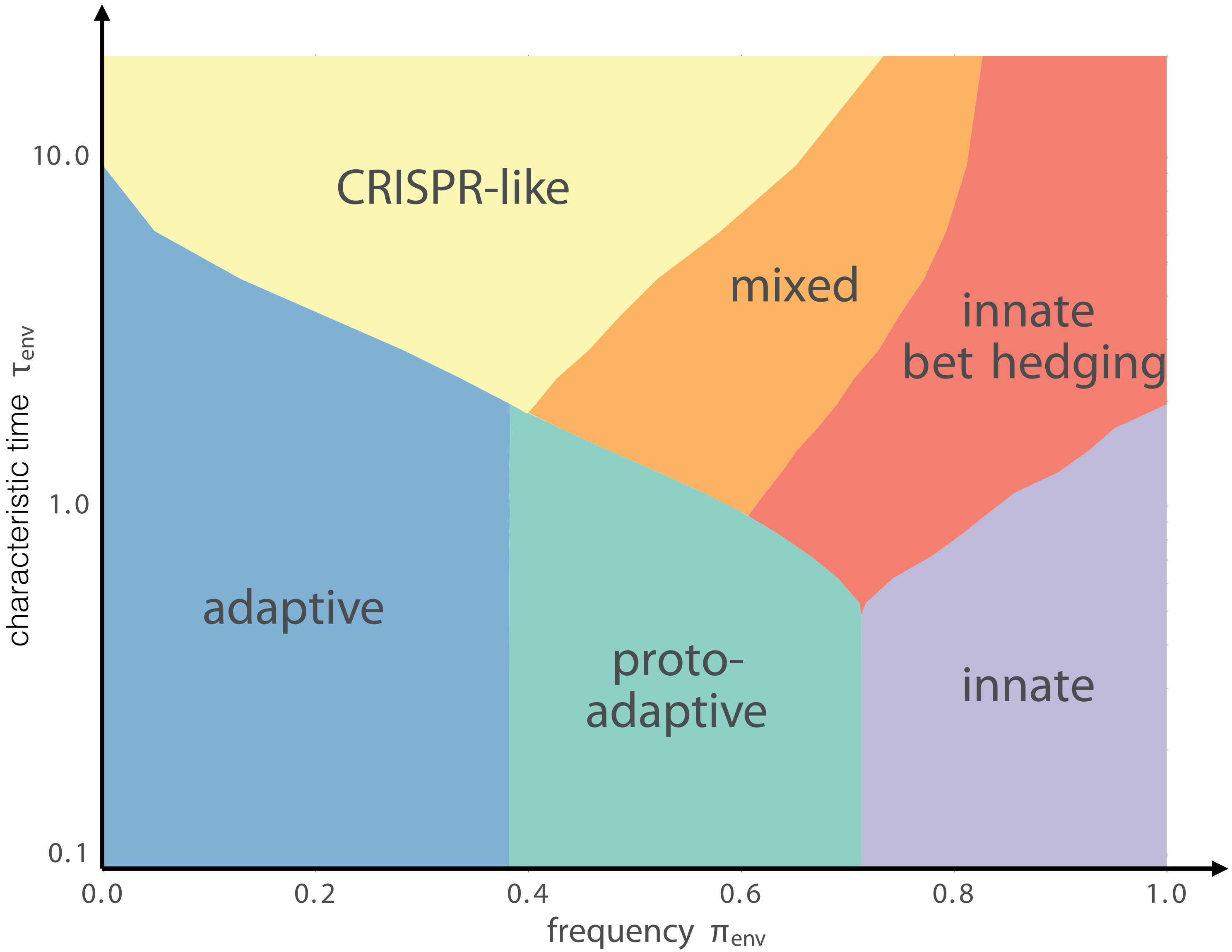
Three strategy axes



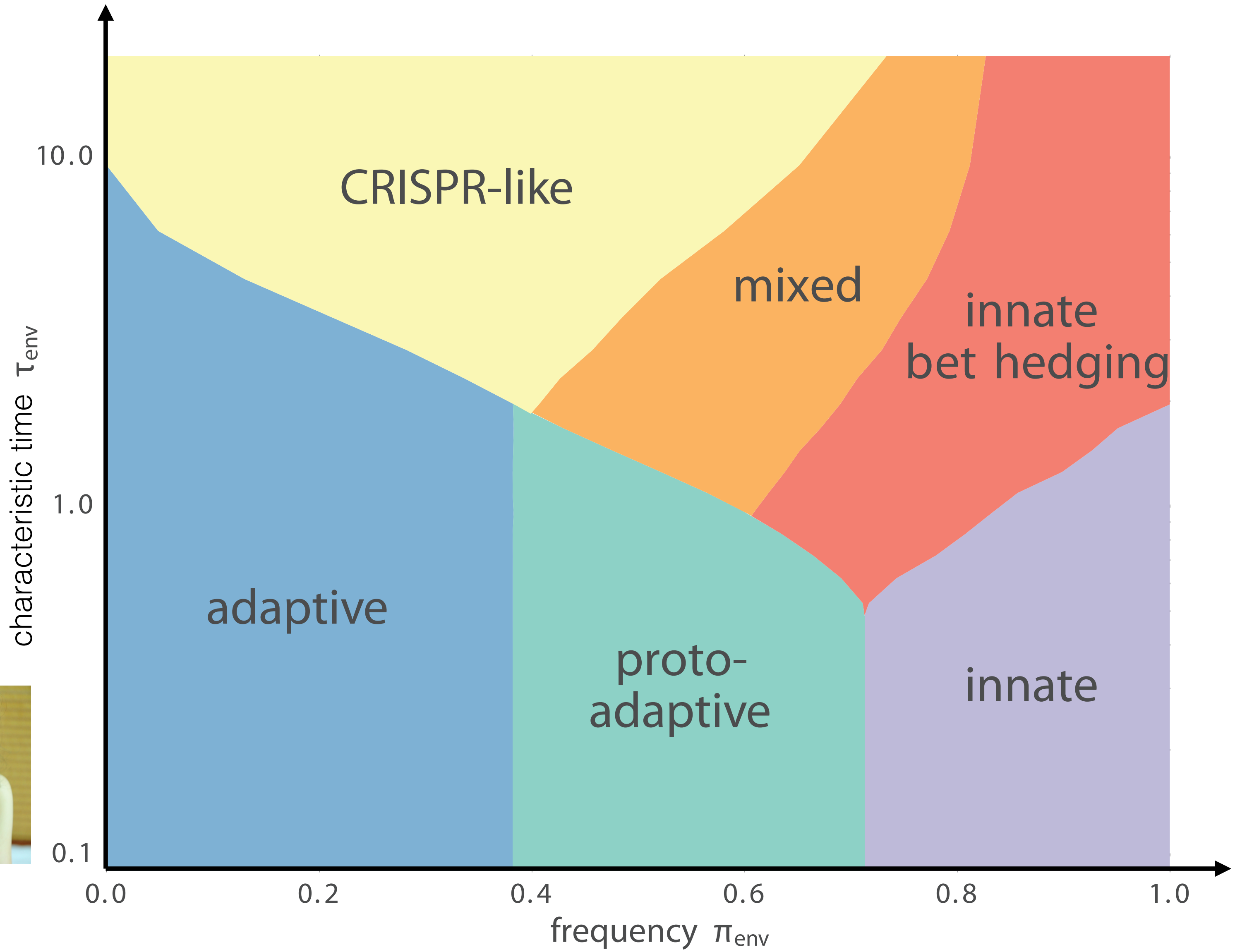
Optimal strategies



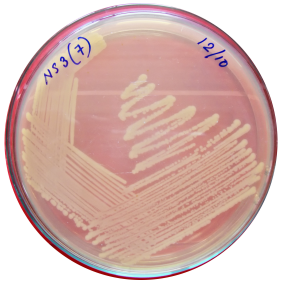
Optimal immune systems

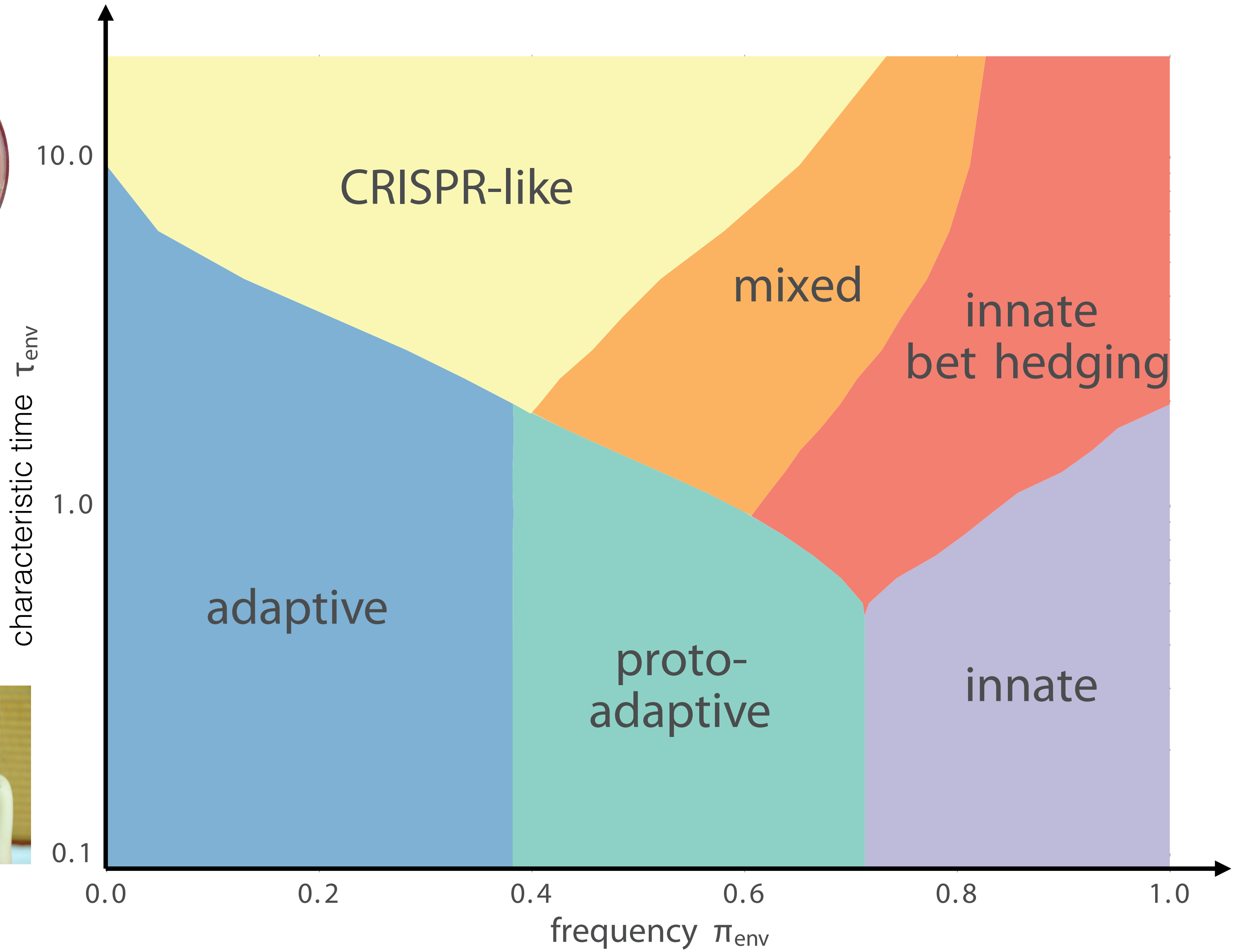


Optimal immune systems



Optimal immune systems





Conclusions

optimal repertoires:

- cover space but are random
- differ in two individuals
- result from competitive receptor dynamics

optimal immunity:

- known immunity from evolutionary constraints
- depends on environment statistic
- reproduces human vs bacterial types of immunity

A Murugan, T Mora, AM Walczak, CG Callan, PNAS (2012)
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