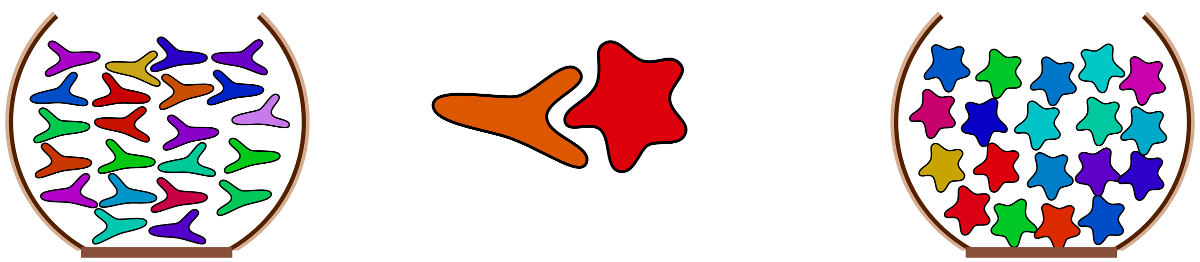
# Optimal immune systems



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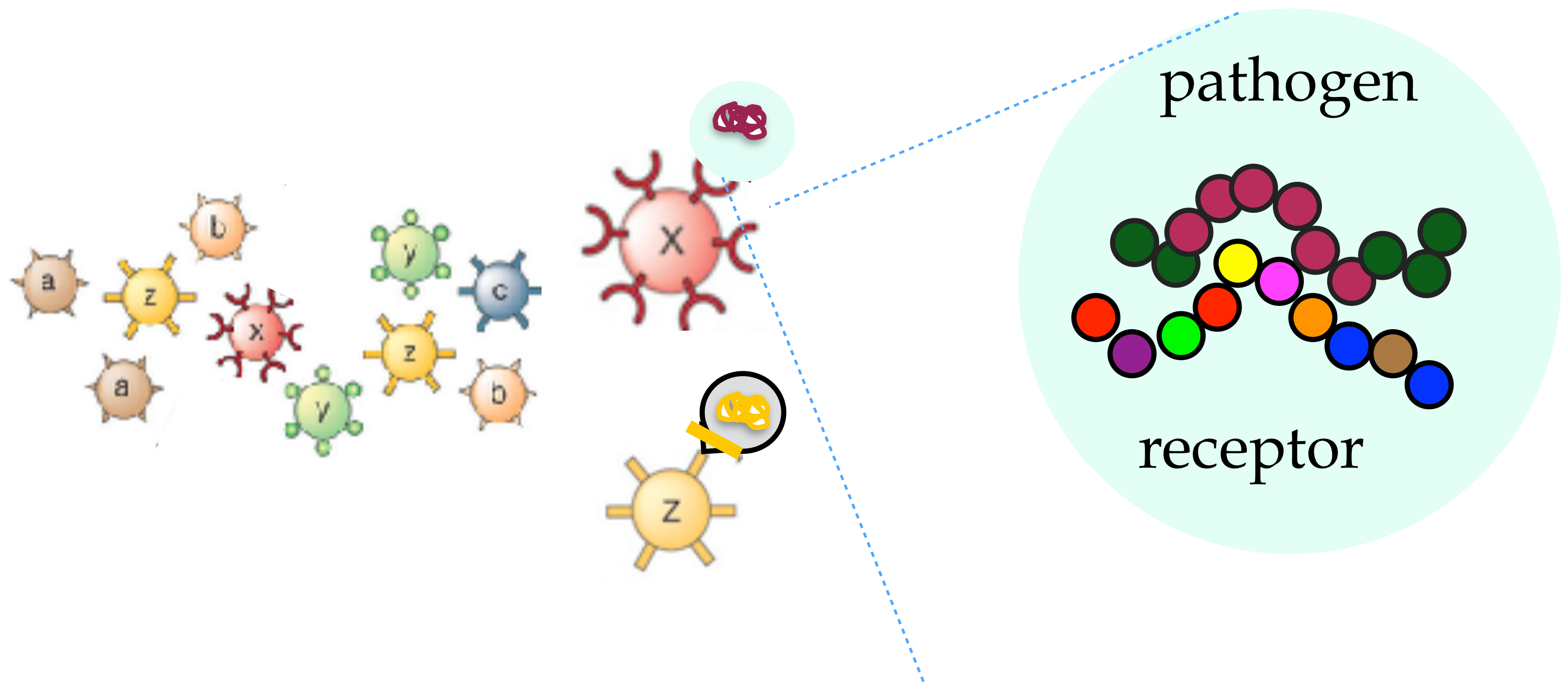
**U Penn**
Vijay Balasubramanian

**ENS Paris**
**Andreas Mayer**
Aleksandra Walczak

# Immune receptors

B - and T-cells important actors of immune system



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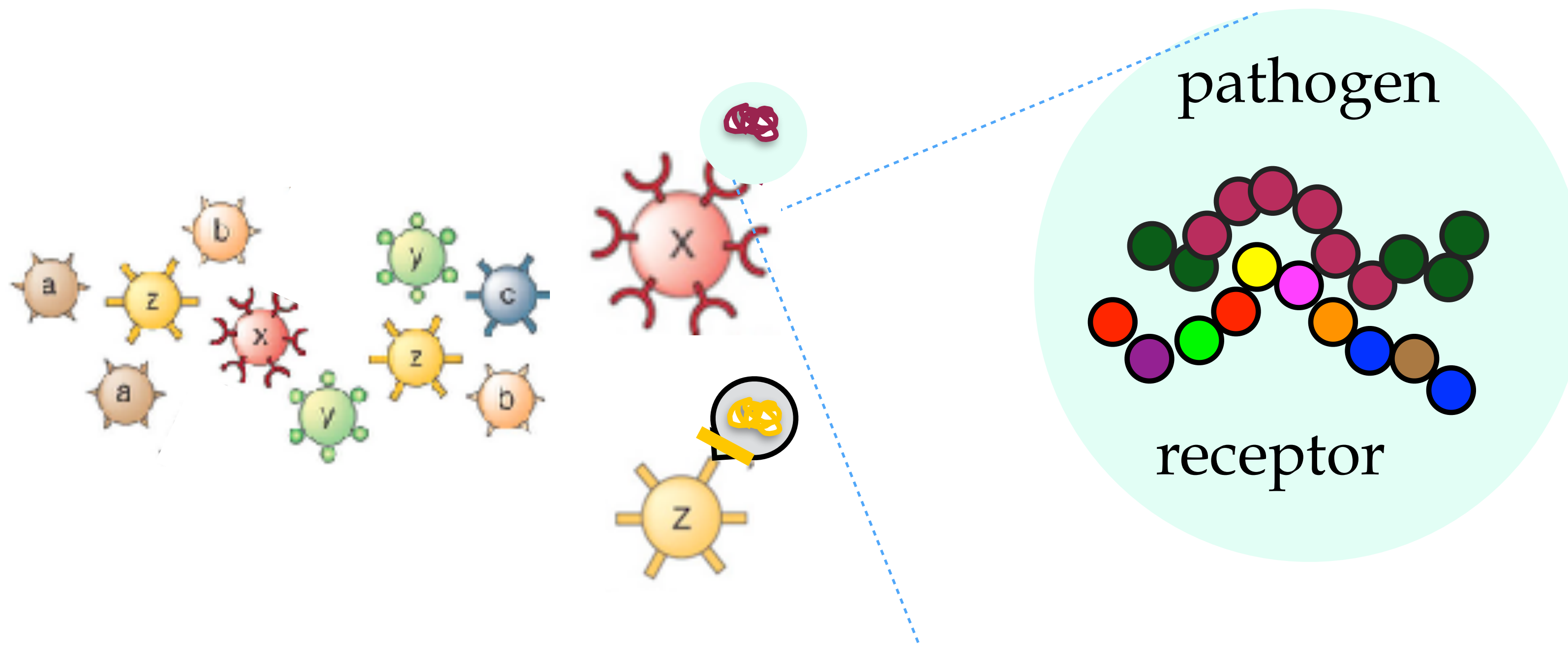


many unique receptors ⟷ many different pathogens (virus...)

# Immune receptors

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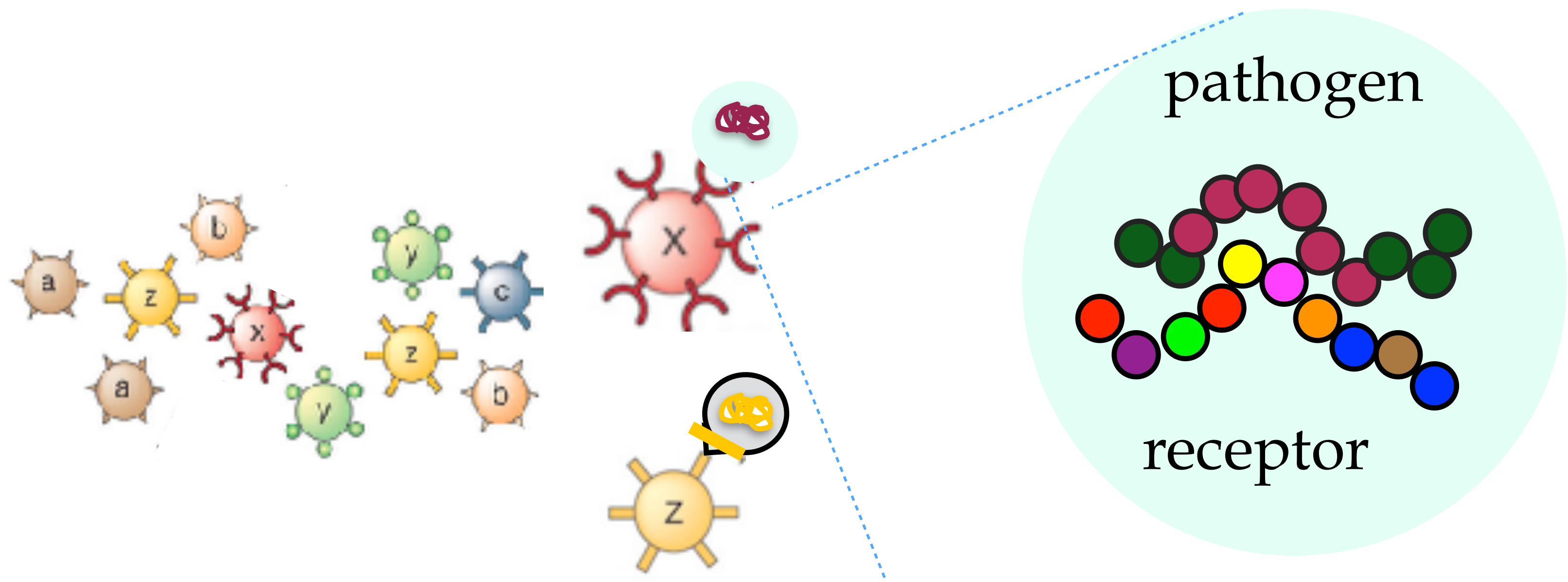


many unique receptors ⟷ many different pathogens (virus...)

how diverse is the repertoire of receptors?

# Immune receptors

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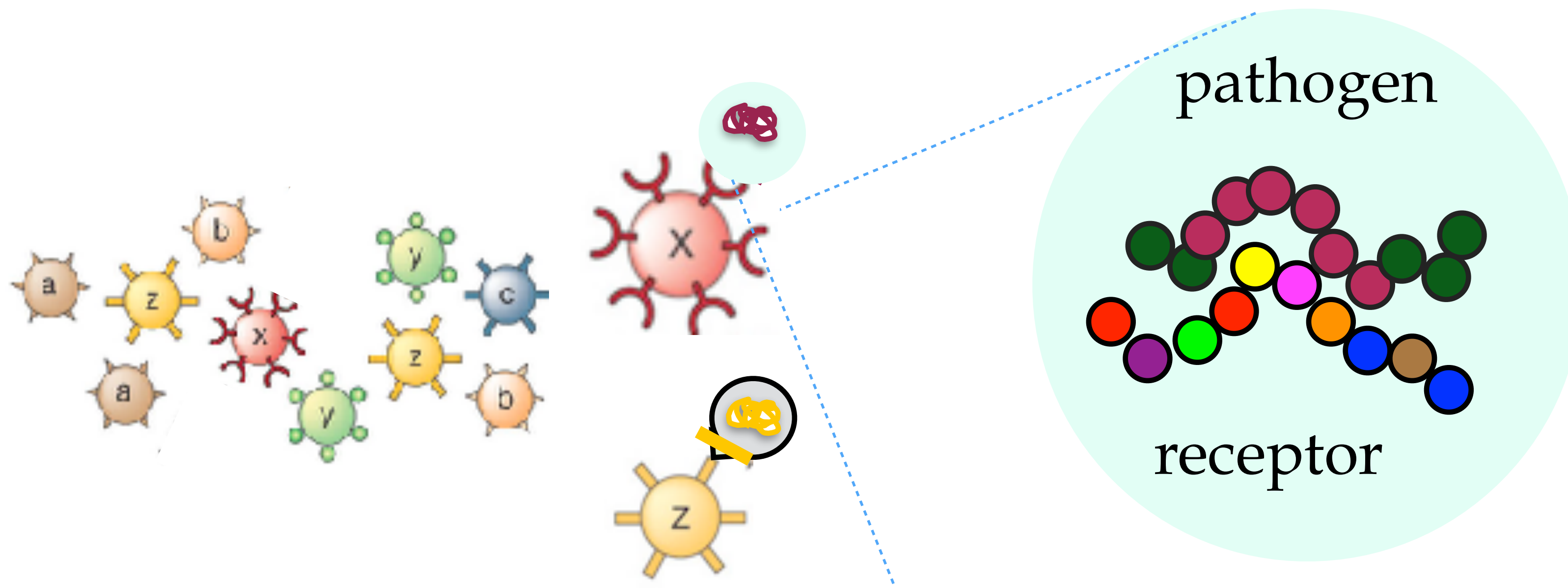


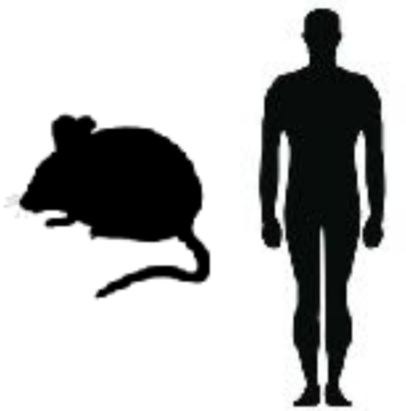

many unique receptors ⟷ many different pathogens (virus...)

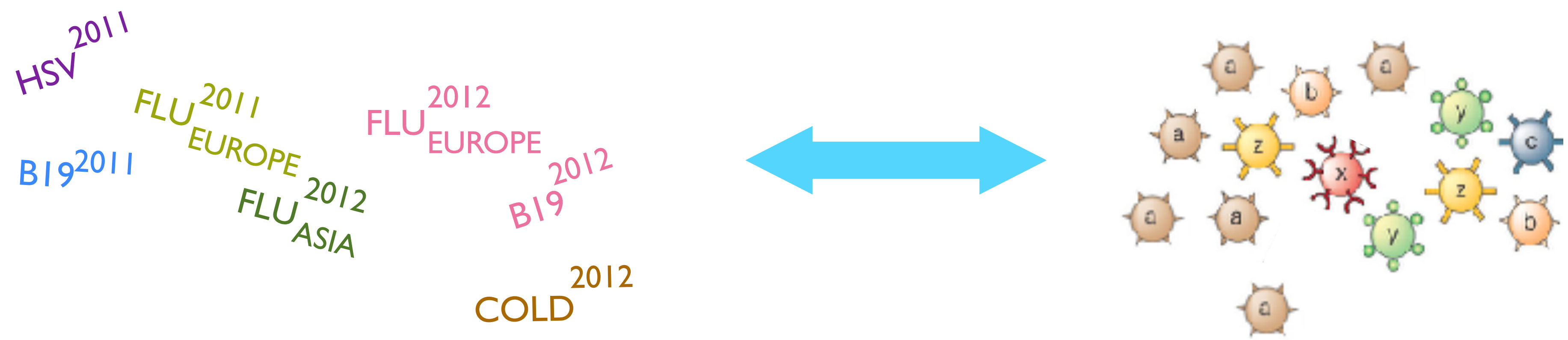
how diverse is the repertoire of receptors?

what principles of organisation?

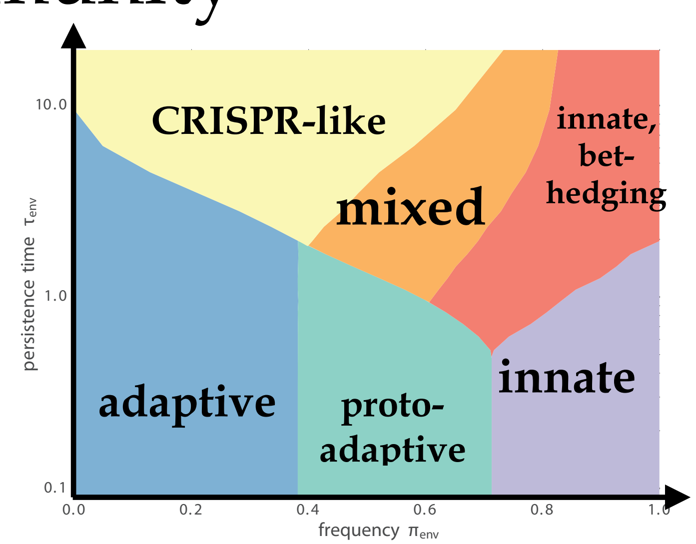
# Design principles?

## Repertoire level: diversity



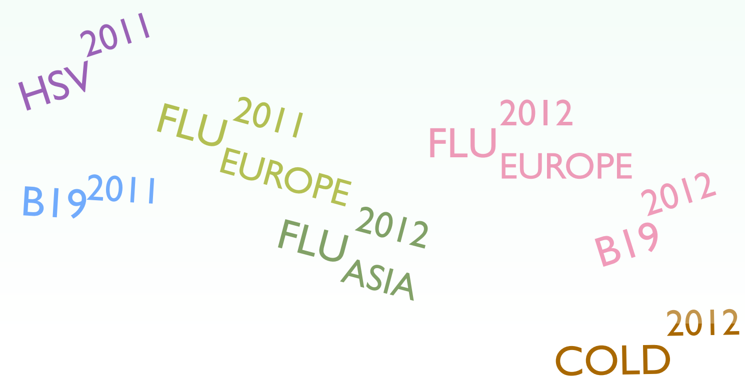


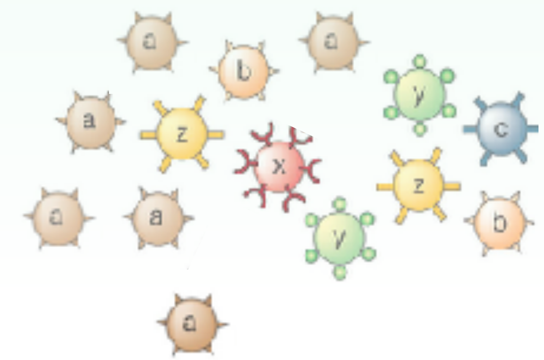

## Population level: modes of immunity



# Design principles?

## Repertoire level: diversity

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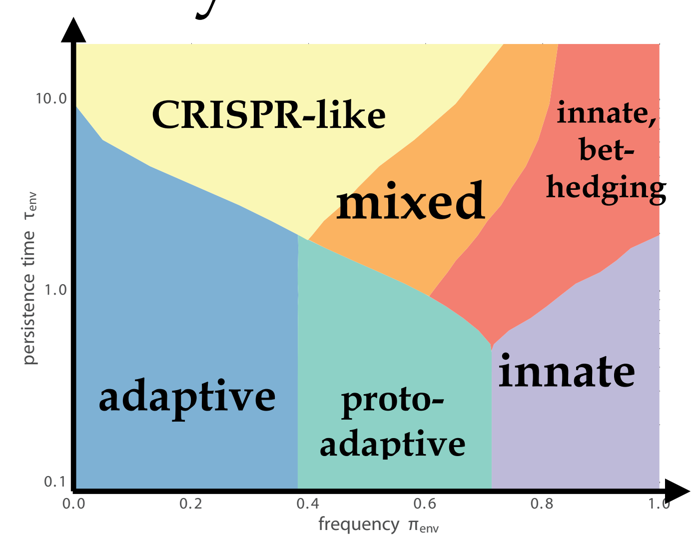
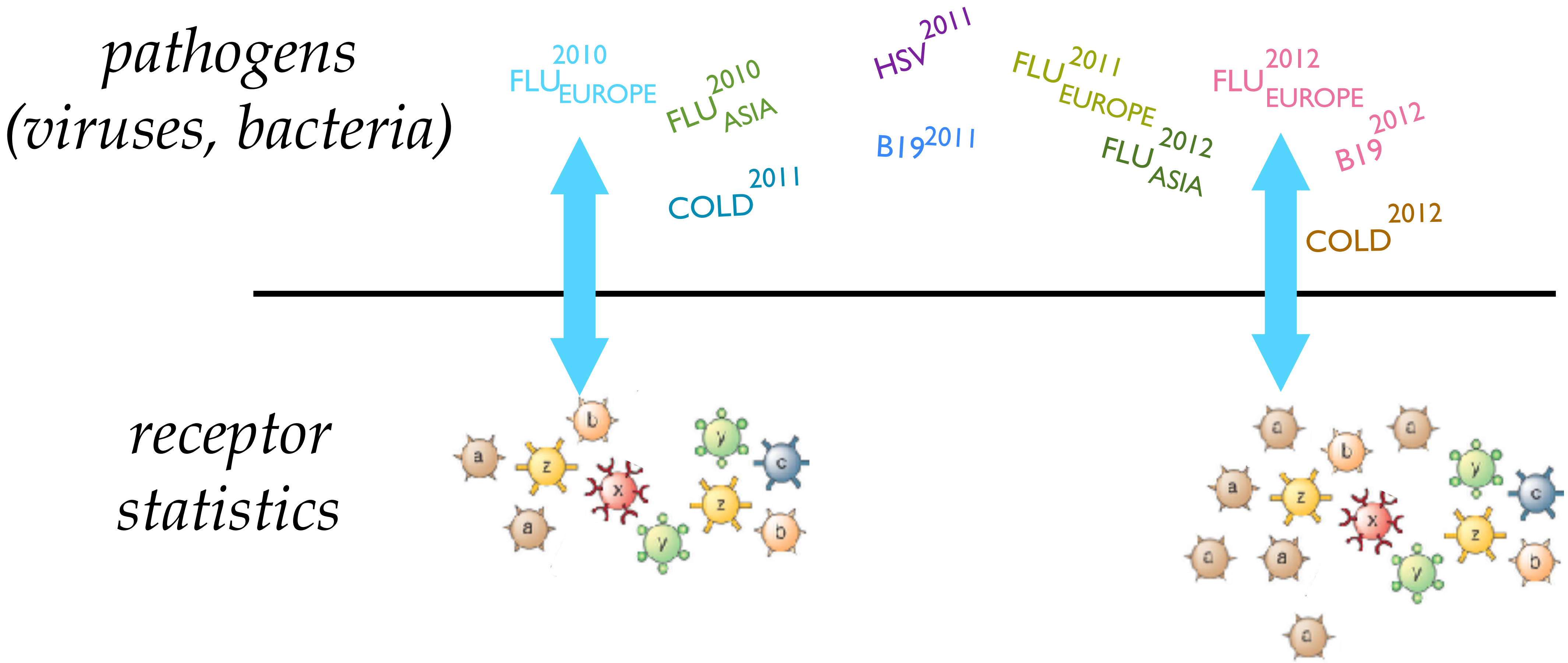


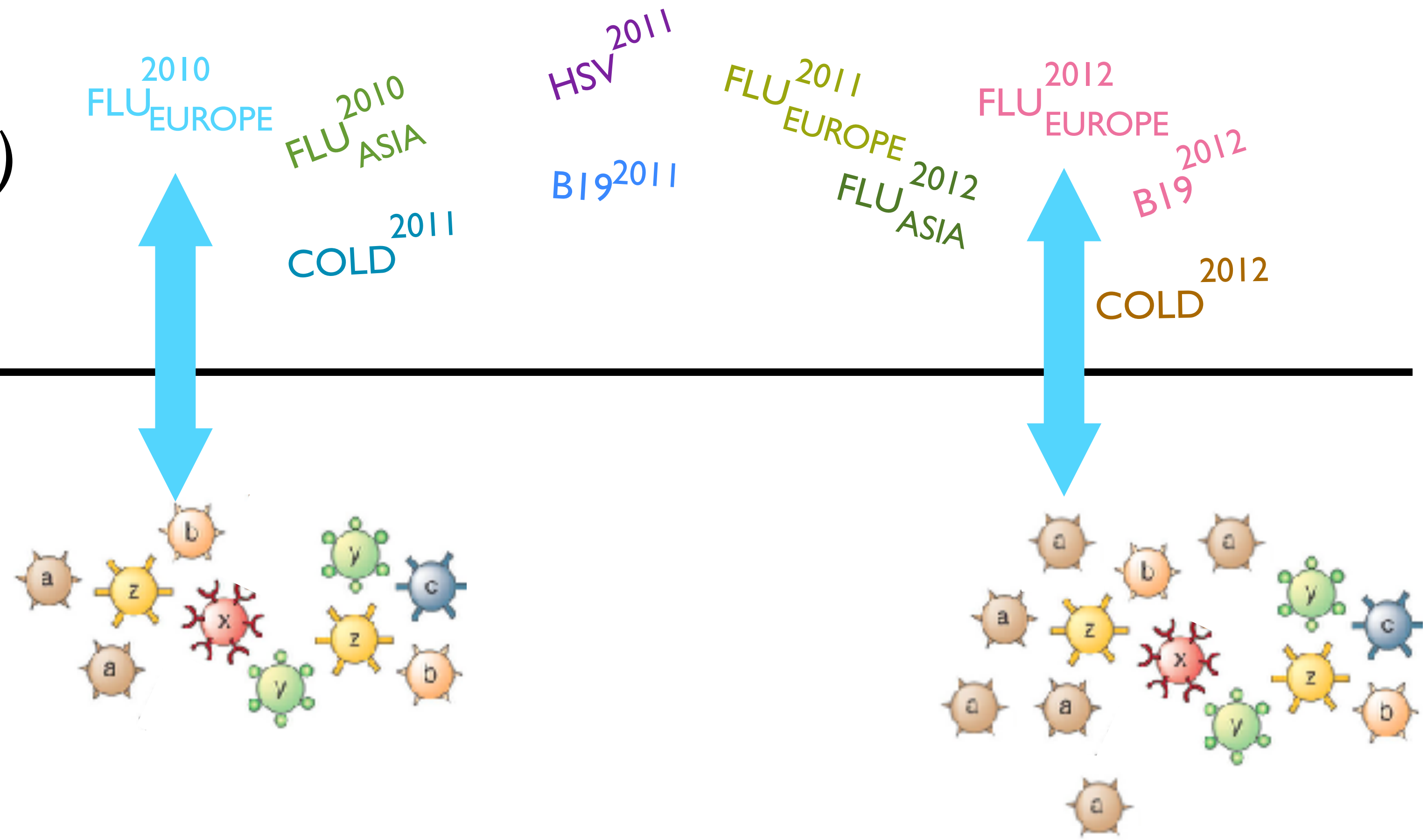
# Receptor distribution



# Receptor distribution

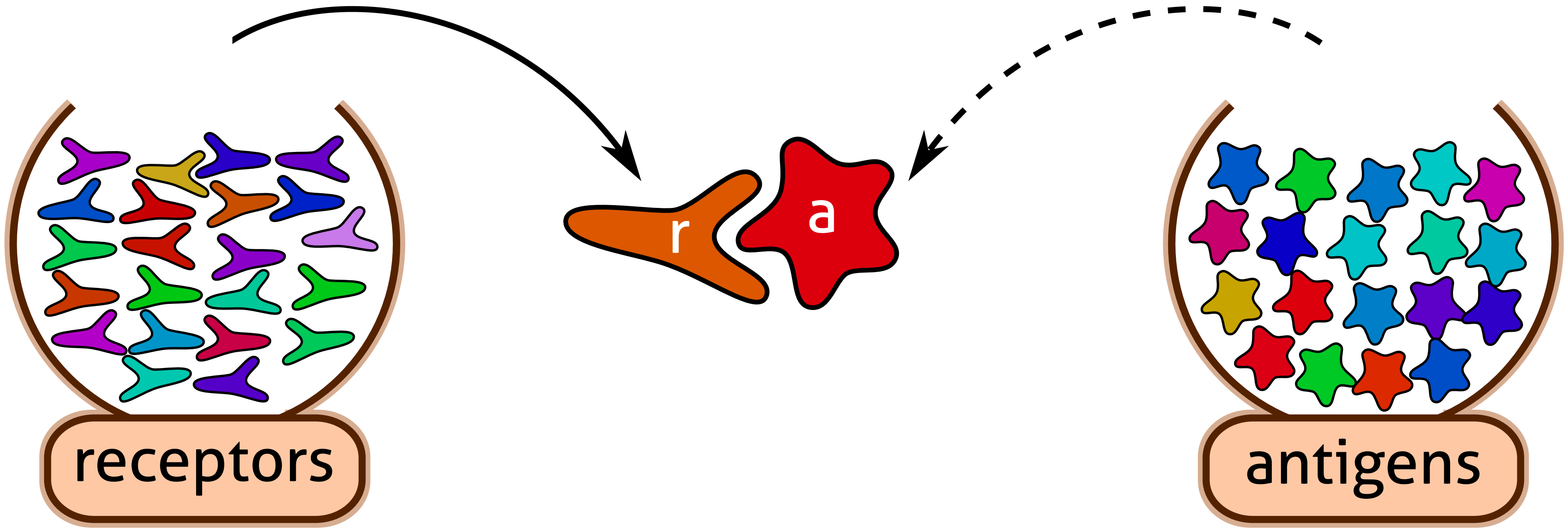
*pathogens (viruses, bacteria)*

*receptor statistics*



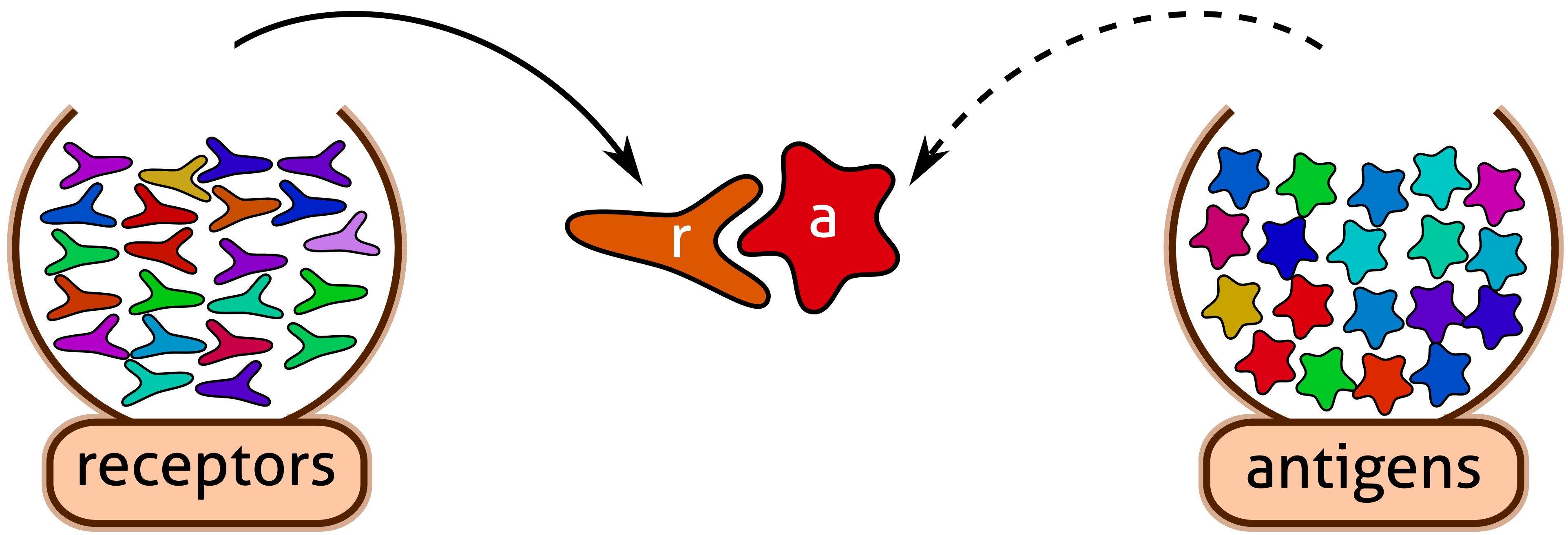

Question: how well is the receptor distribution adapted to the pathogen distribution?

# The trade-off




limited number of encounters

# The trade-off

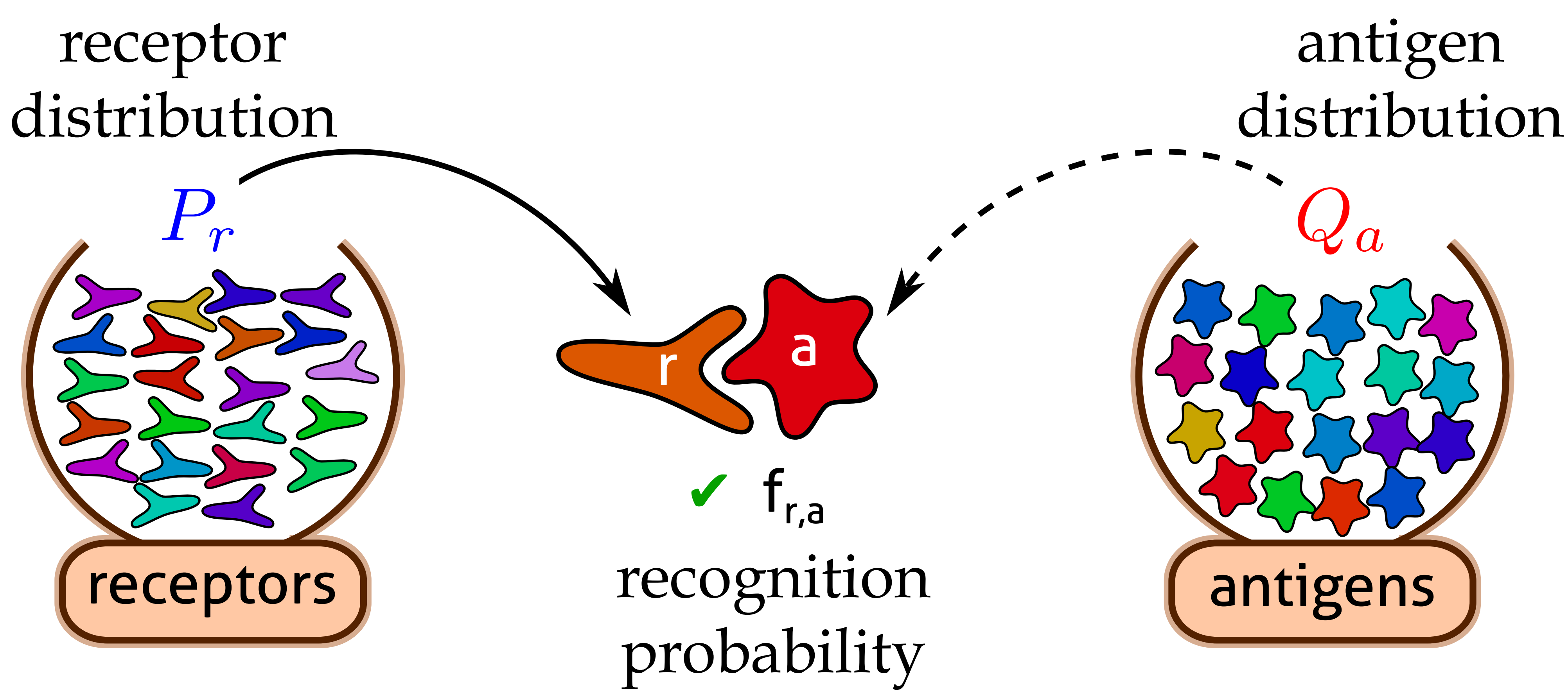



limited number of encounters

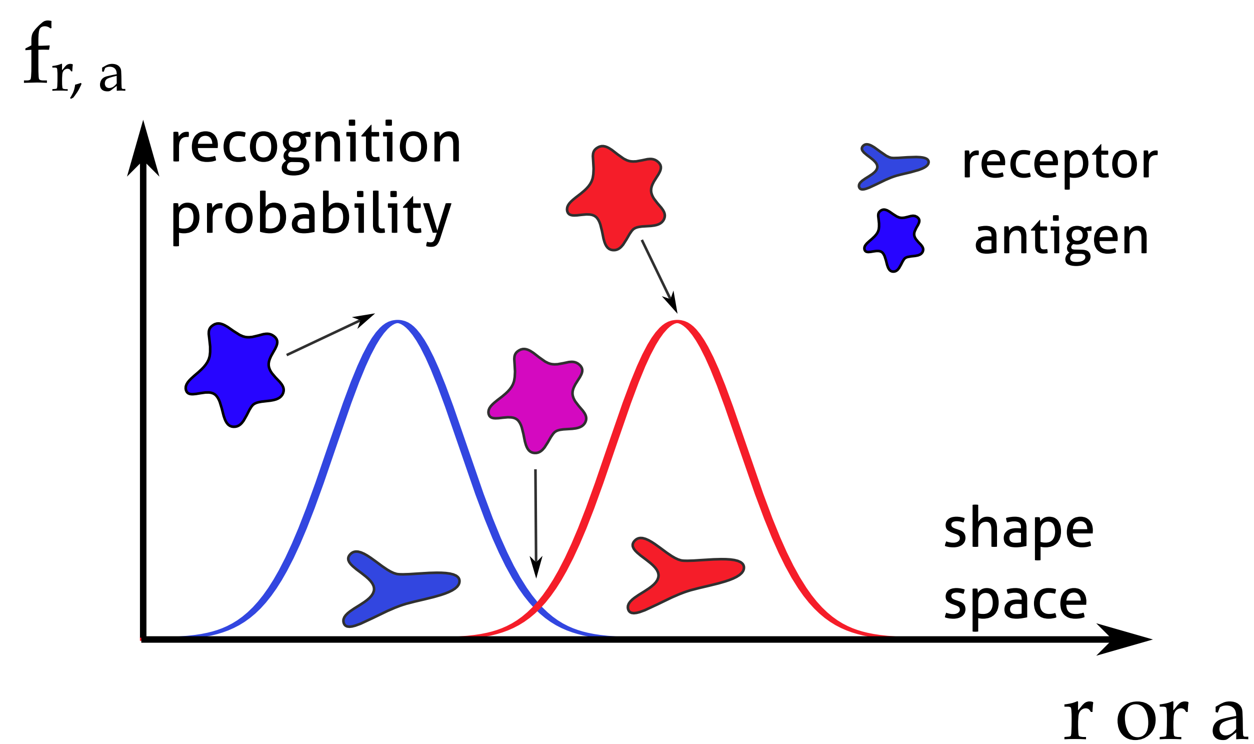
**How should immune receptors be distributed to minimize harm from infections?**

lymphocyte repertoire ⟷ antigenic environment

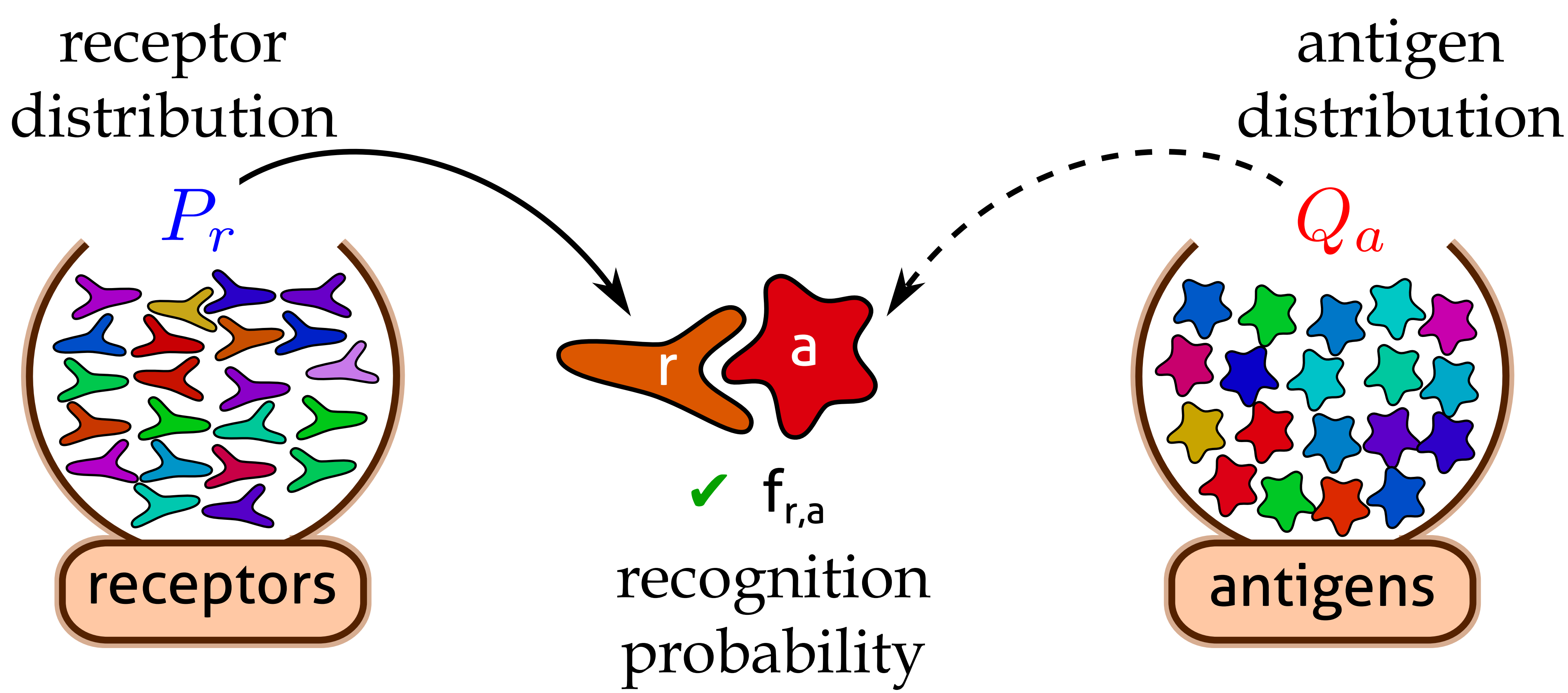
# Cross reactivity




- cross-reactivity
  - recognition probability

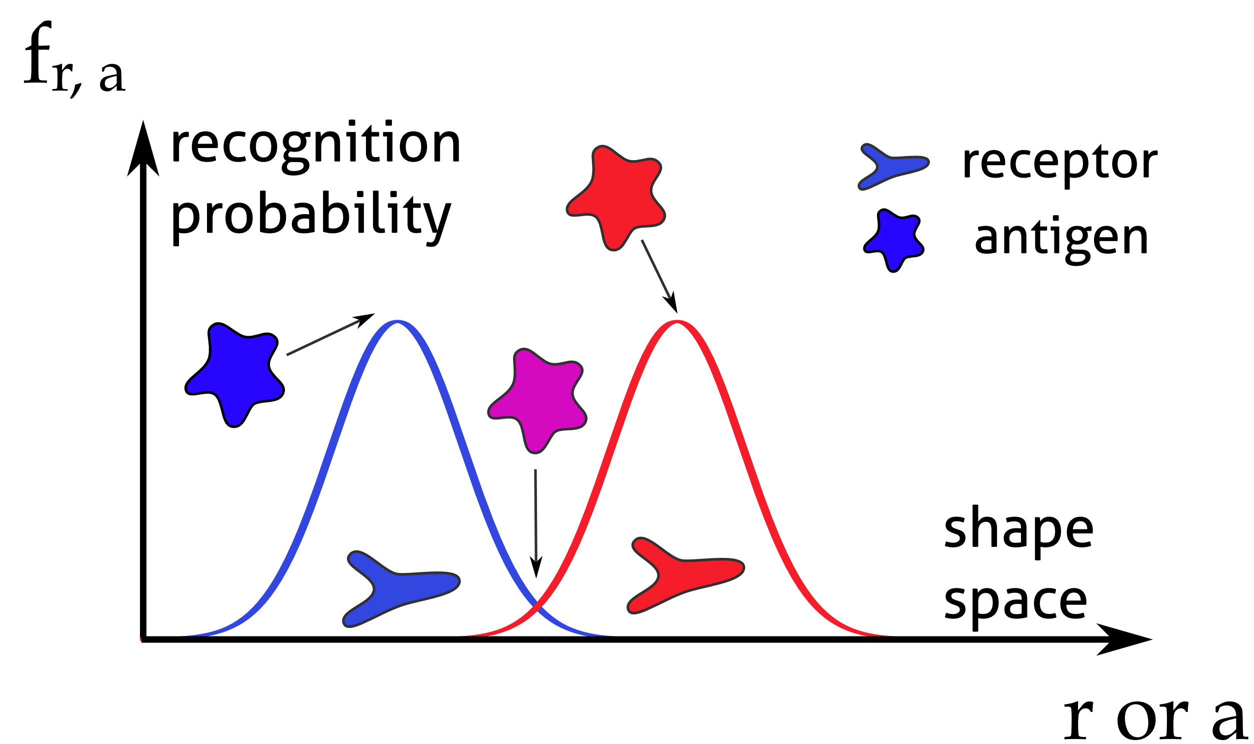


# Cross reactivity




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

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



# The harm of non-recognition

- probability of recognition
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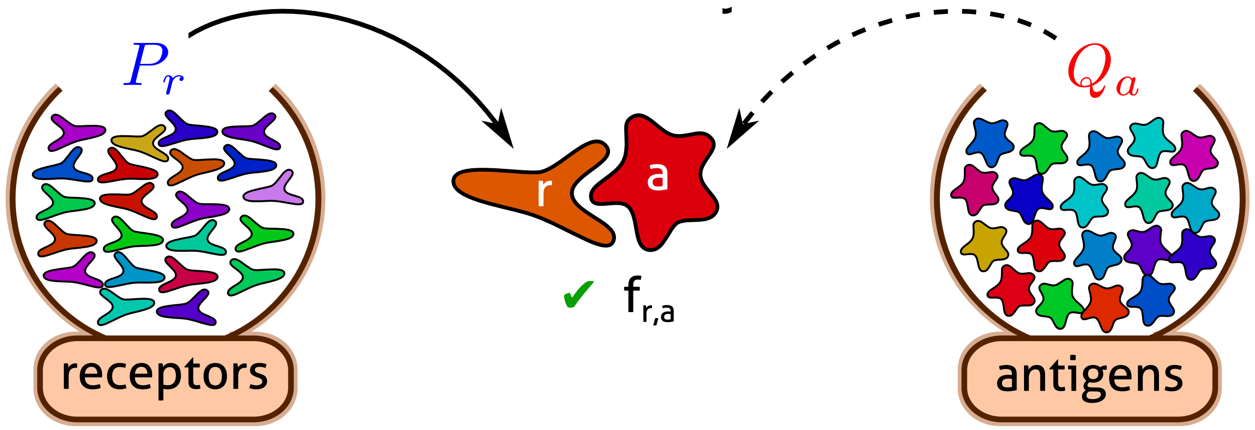

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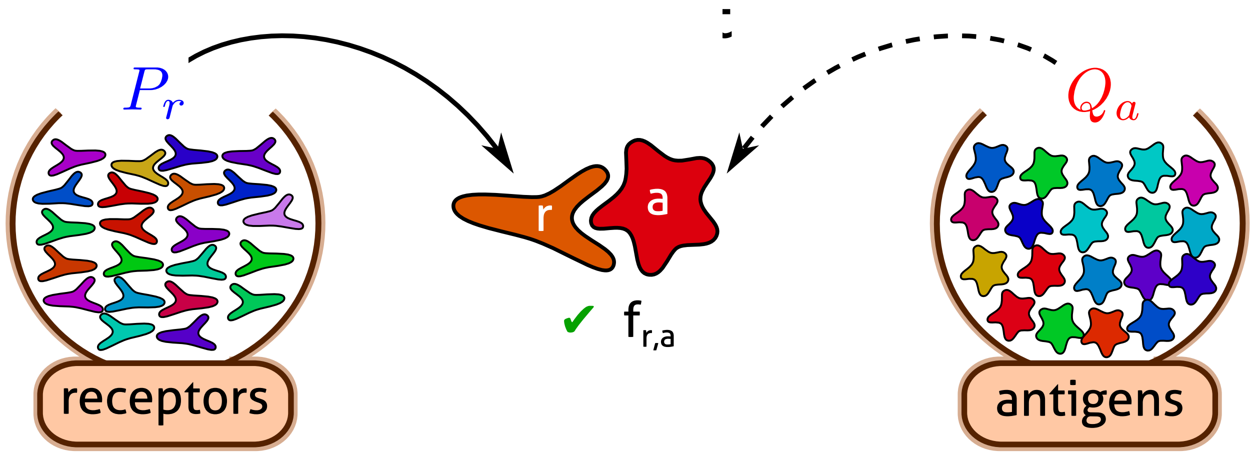


- time measured in
  mean number of encounters $m$

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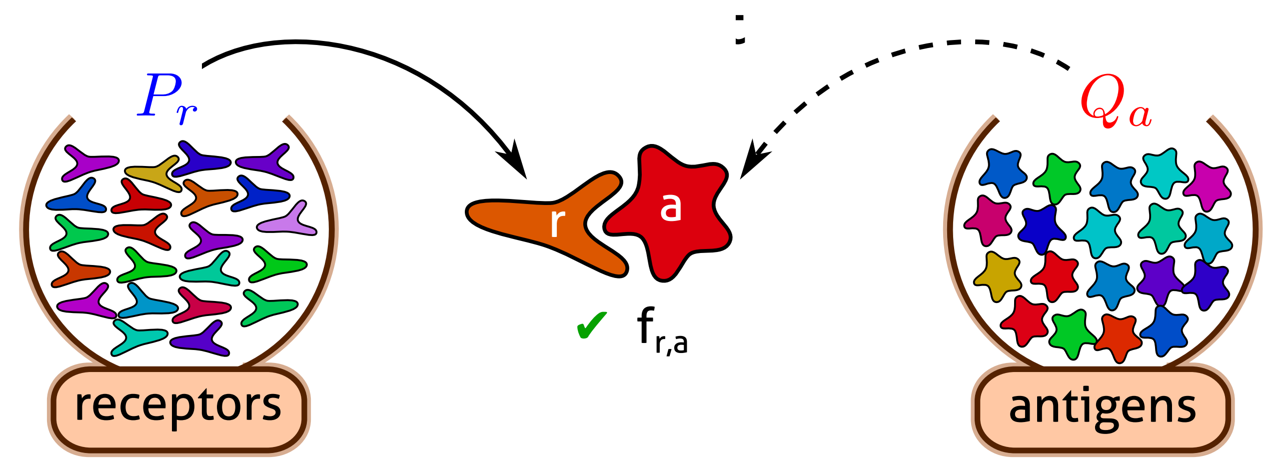


- time measured in
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- harm $\mu_a F_a(m)$ caused
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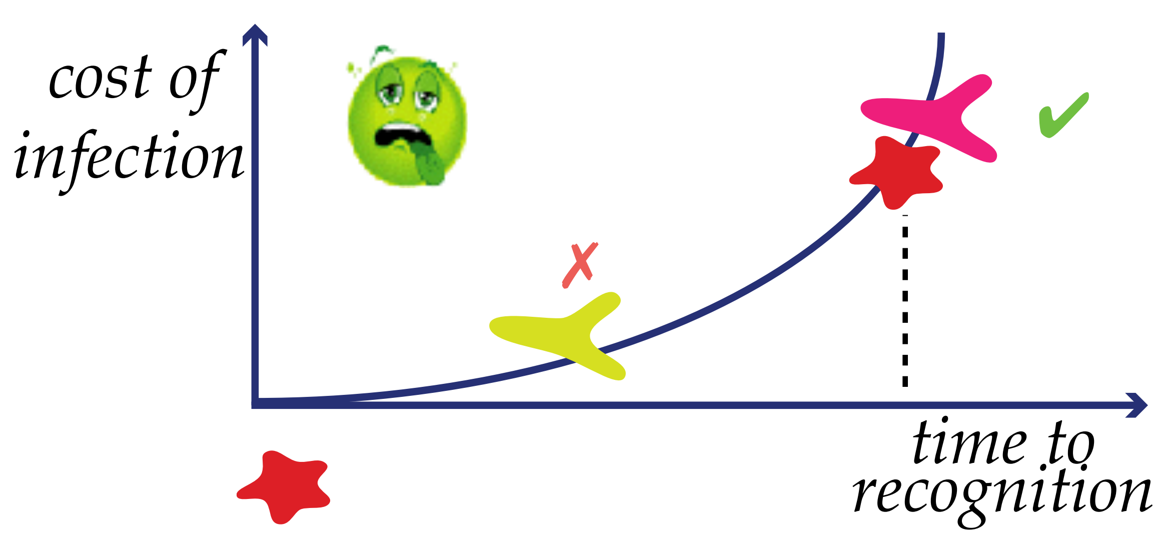
  with time $m$



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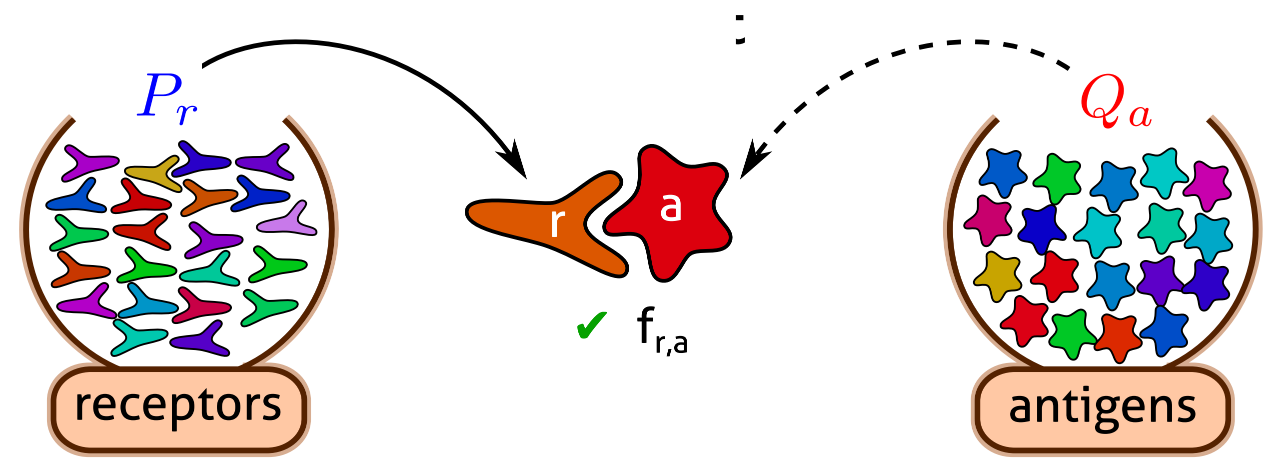


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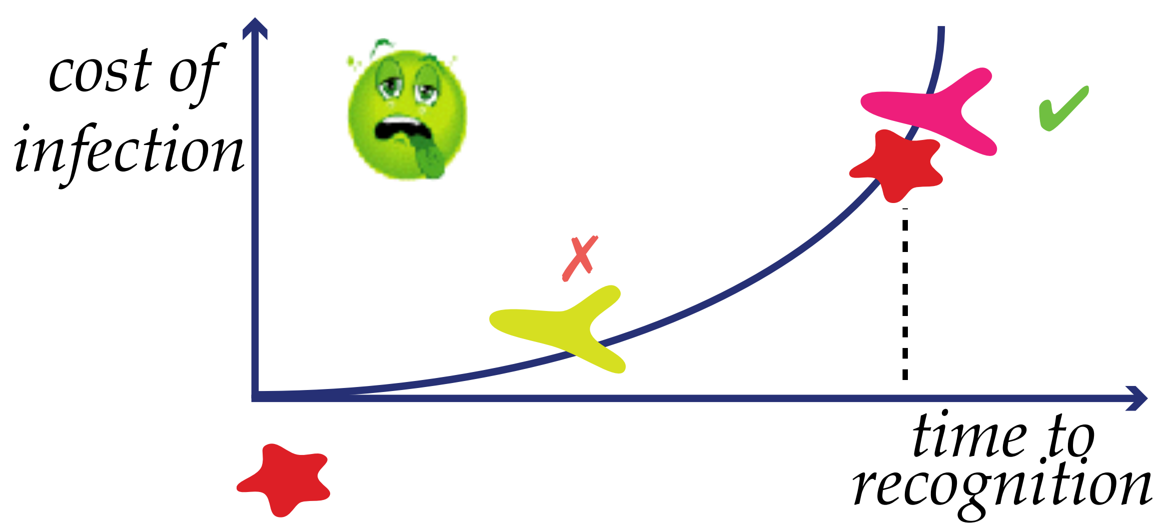
virulence ↓ ; effective harm of infection ↓

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

↑ Poisson distributed recognition time



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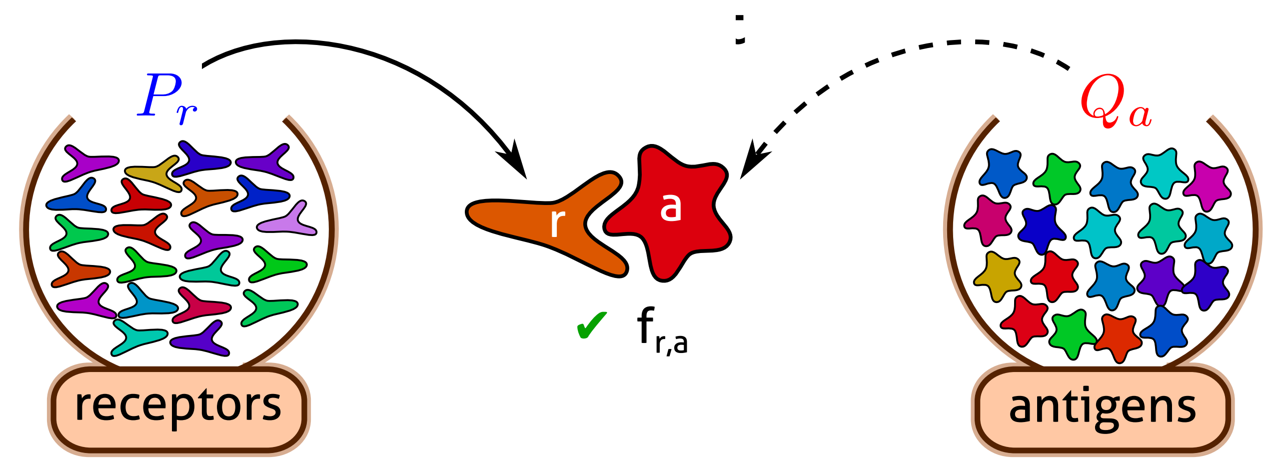


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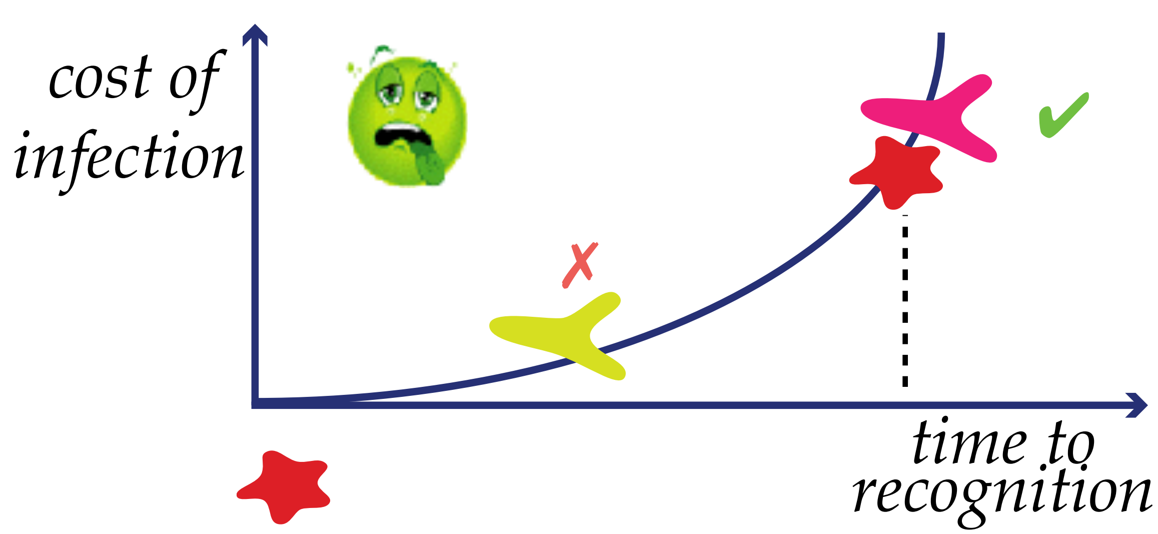
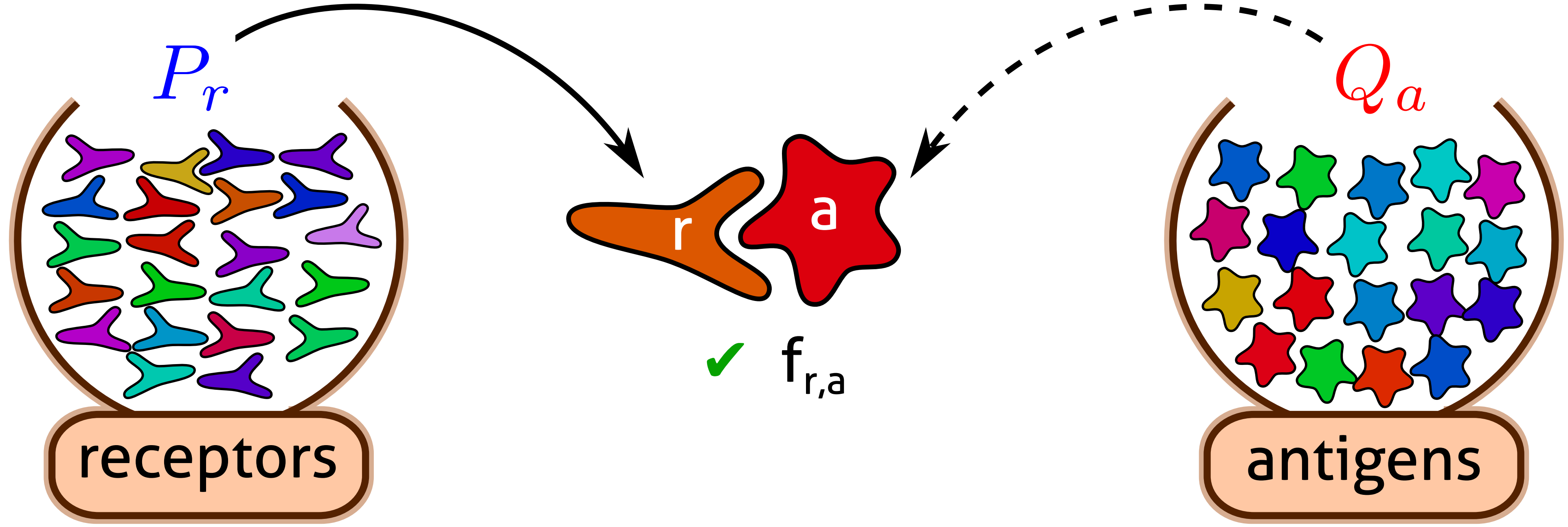



$$\mathrm{Cost}(\{P_r\}) = \sum_a Q_a \bar{F}_a(P_r)$$

# Cost function




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

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

**Optimal repertoire?**

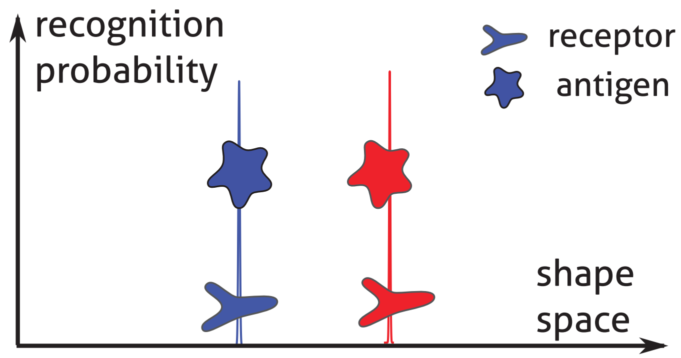
$\longrightarrow$ minimize cost over $P_r$ for a *given* antigen distribution $Q_a$

# Covering rare pathogens

How many resources aimed at common/rare antigen? (no cross-reactivity)

depends on cost of late recognition

$$\tilde{P}_r = P_r$$



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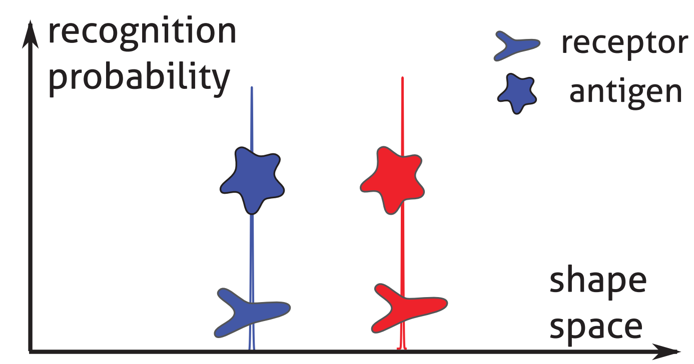
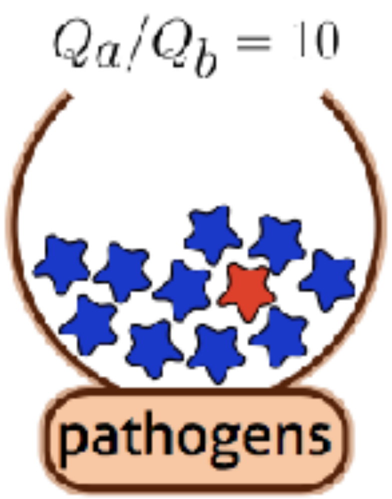


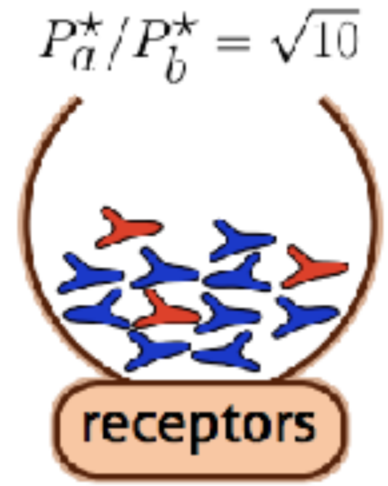

- exponentially expanding antigen population

$\longrightarrow \; F(m) = m$




optimal repertoire

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

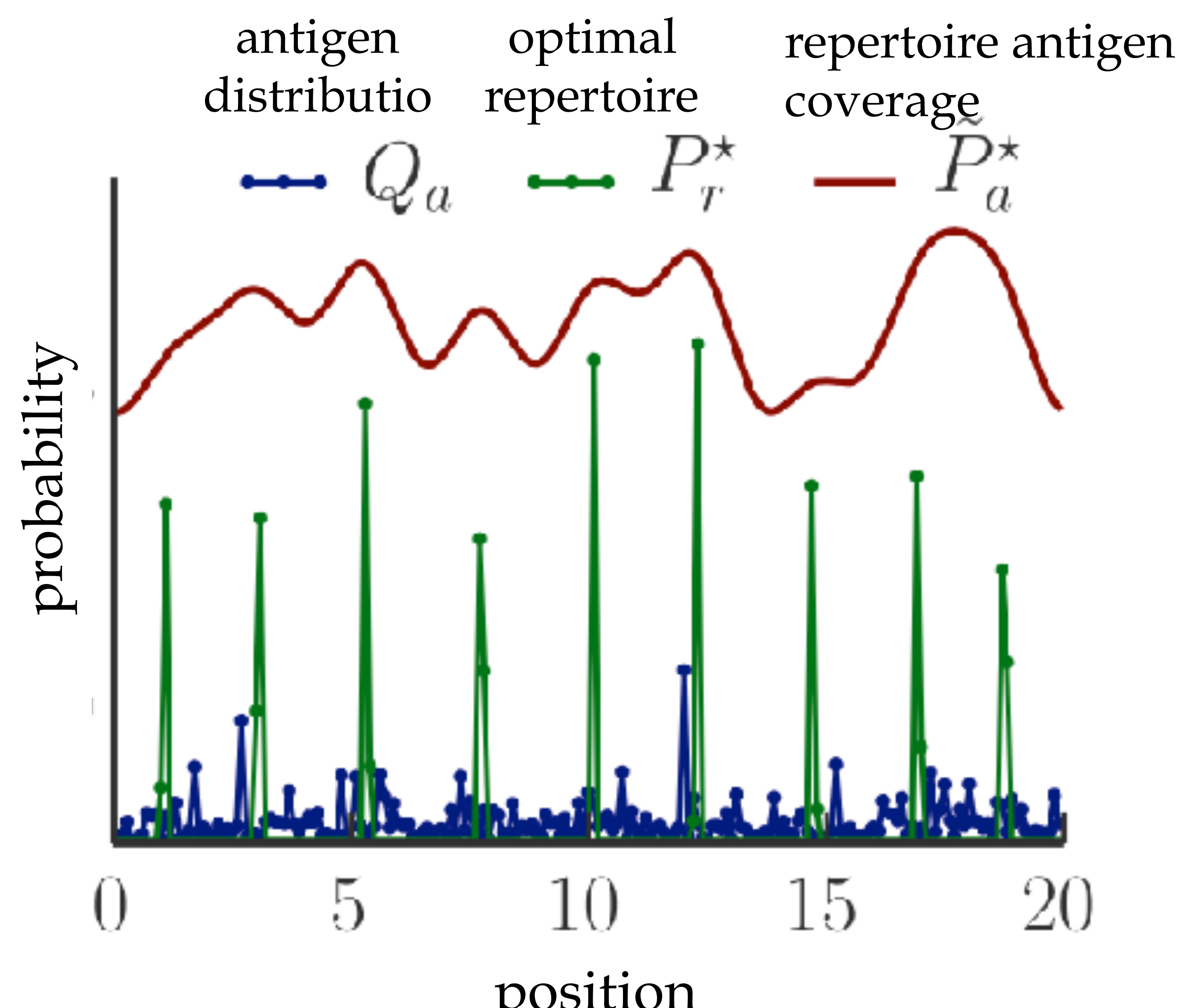



- $F(m) = m^\alpha \longrightarrow P_r^* \propto {Q_r}^{1/(1+\alpha)}$
- $F(m) \propto \ln m \longrightarrow P_r^* \propto Q_r$

# Peaked optimal distribution

- exponentially expanding antigen population $F(m) = m$

- peaked distributions
- tiles space

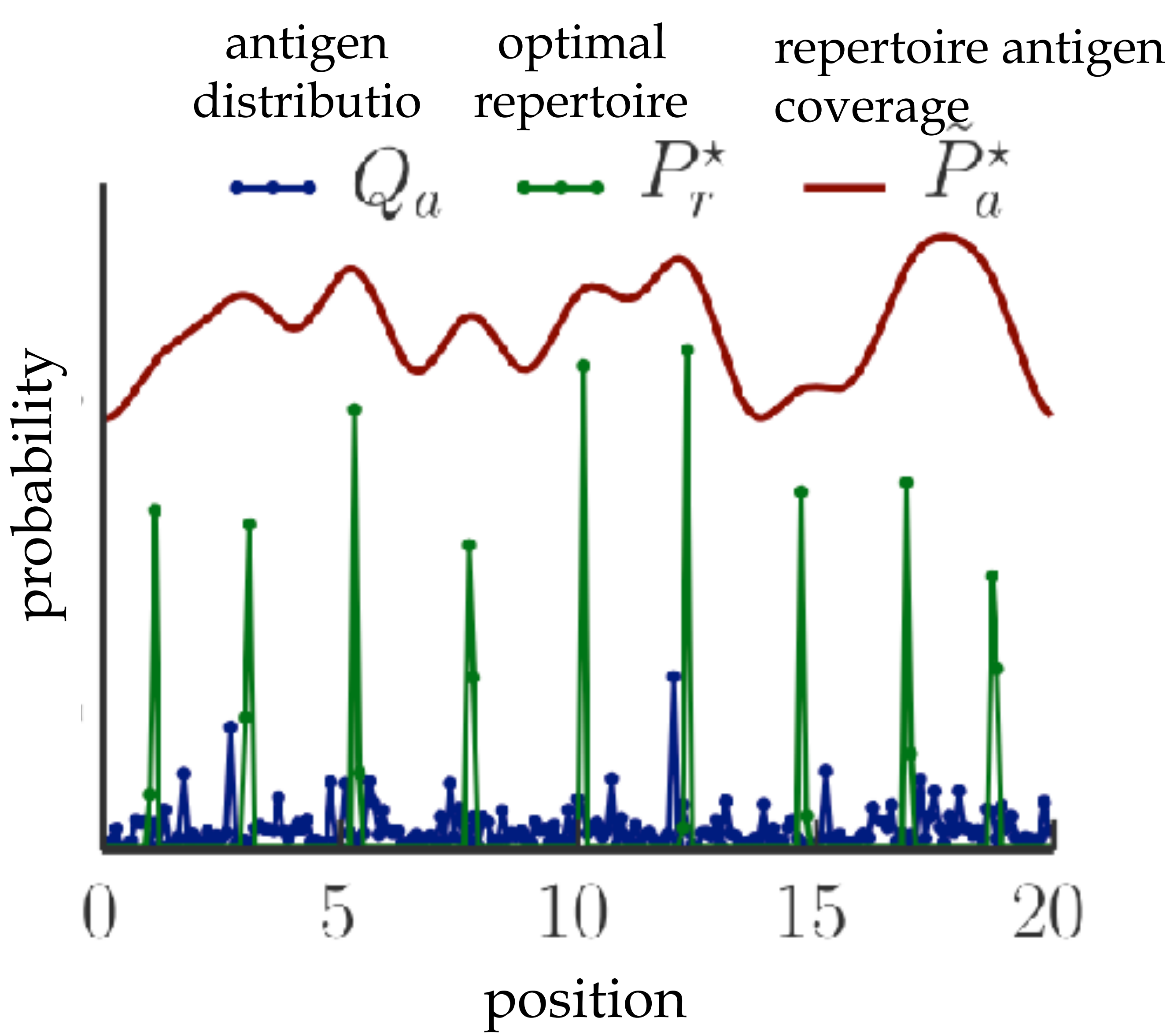


# Peaked optimal distribution

- exponentially expanding antigen population $F(m) = m$

- peaked distributions
- tiles space

- tracks antigen distribution
- but not exactly

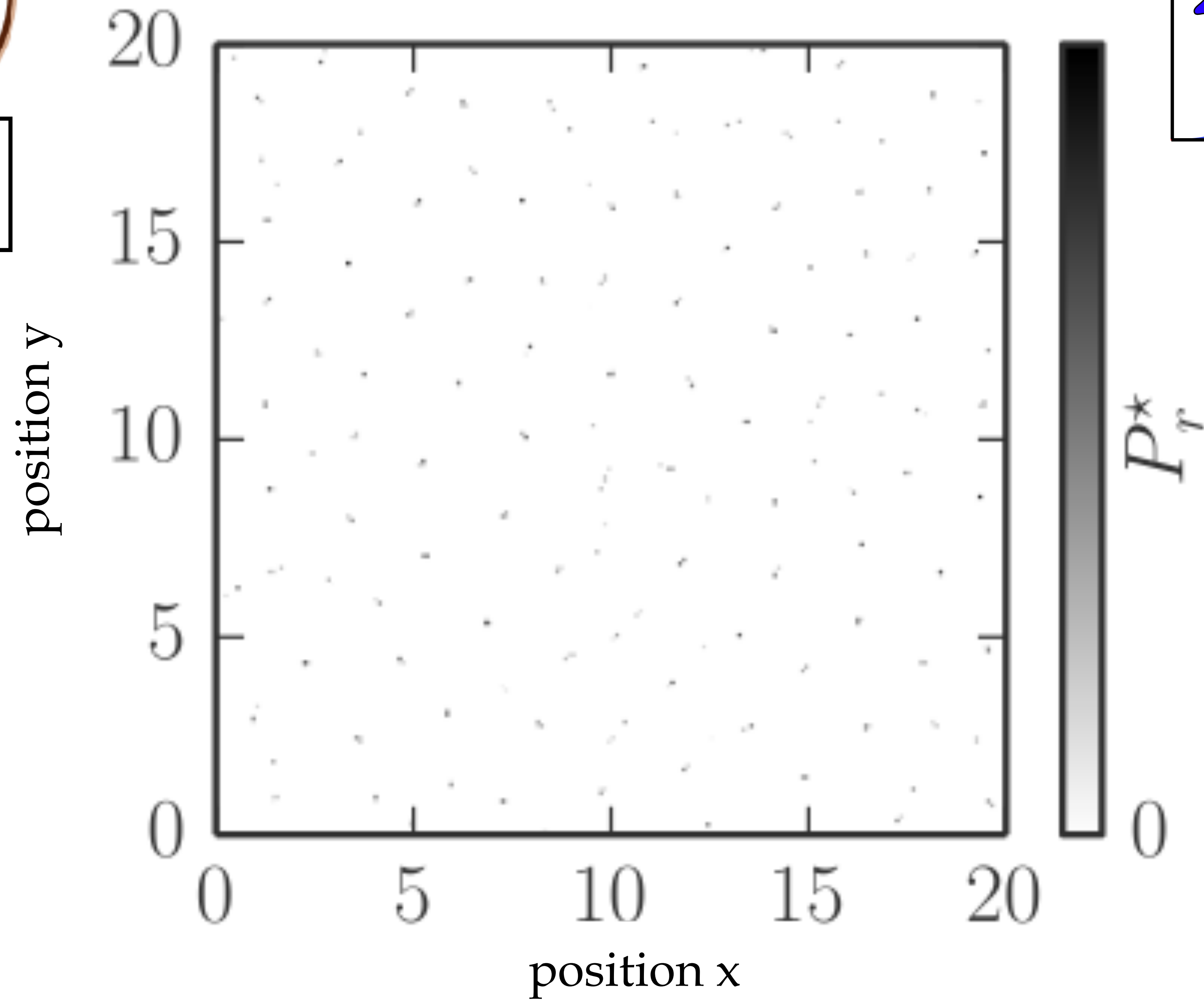


# Two conflicting effects

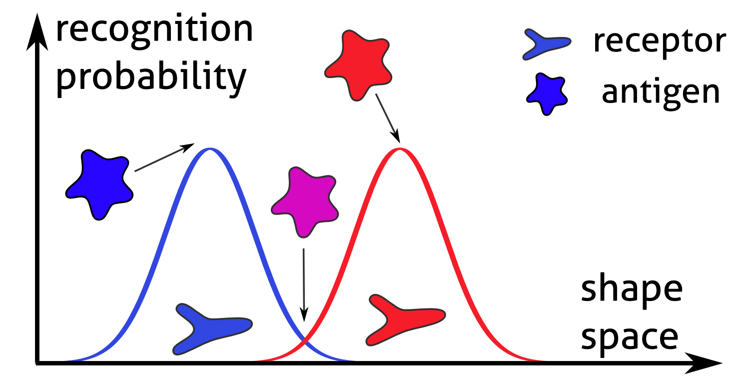
rare antigens

broaden distribution

in 2D



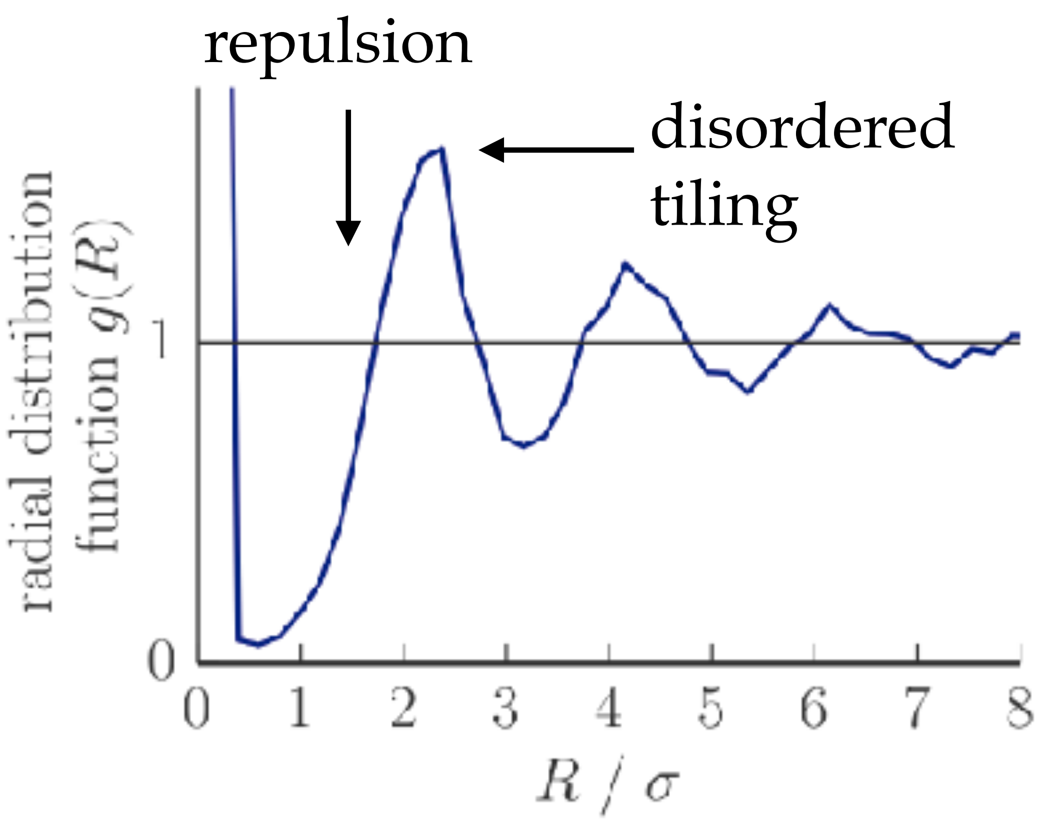

cross-reactivity

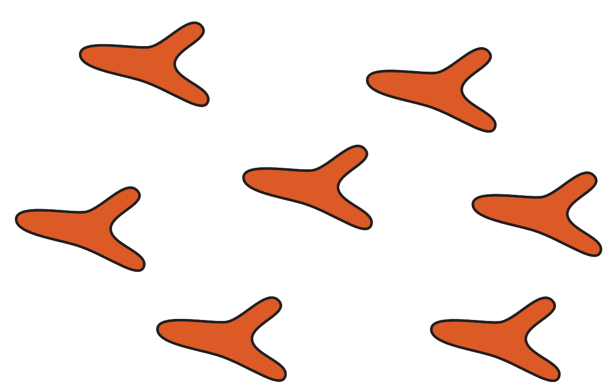



shrinks distribution

# Disordered hyperuniformity

*Torquato Stillinger PRE (2003)*



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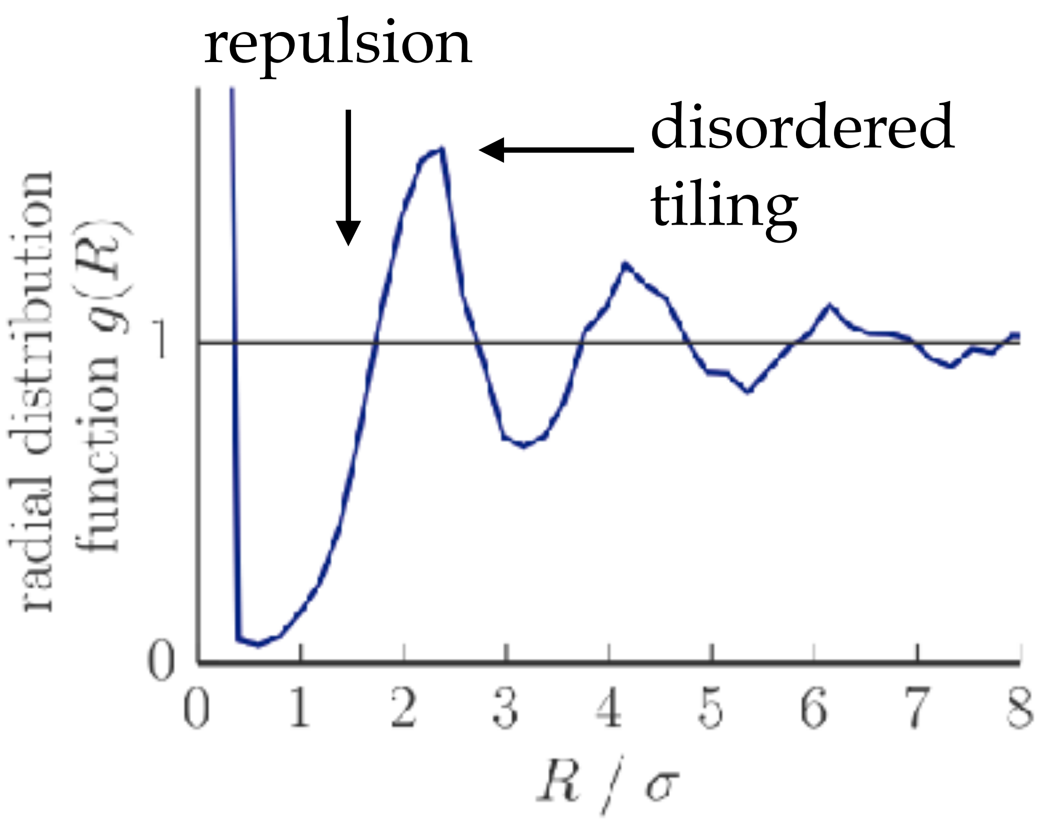


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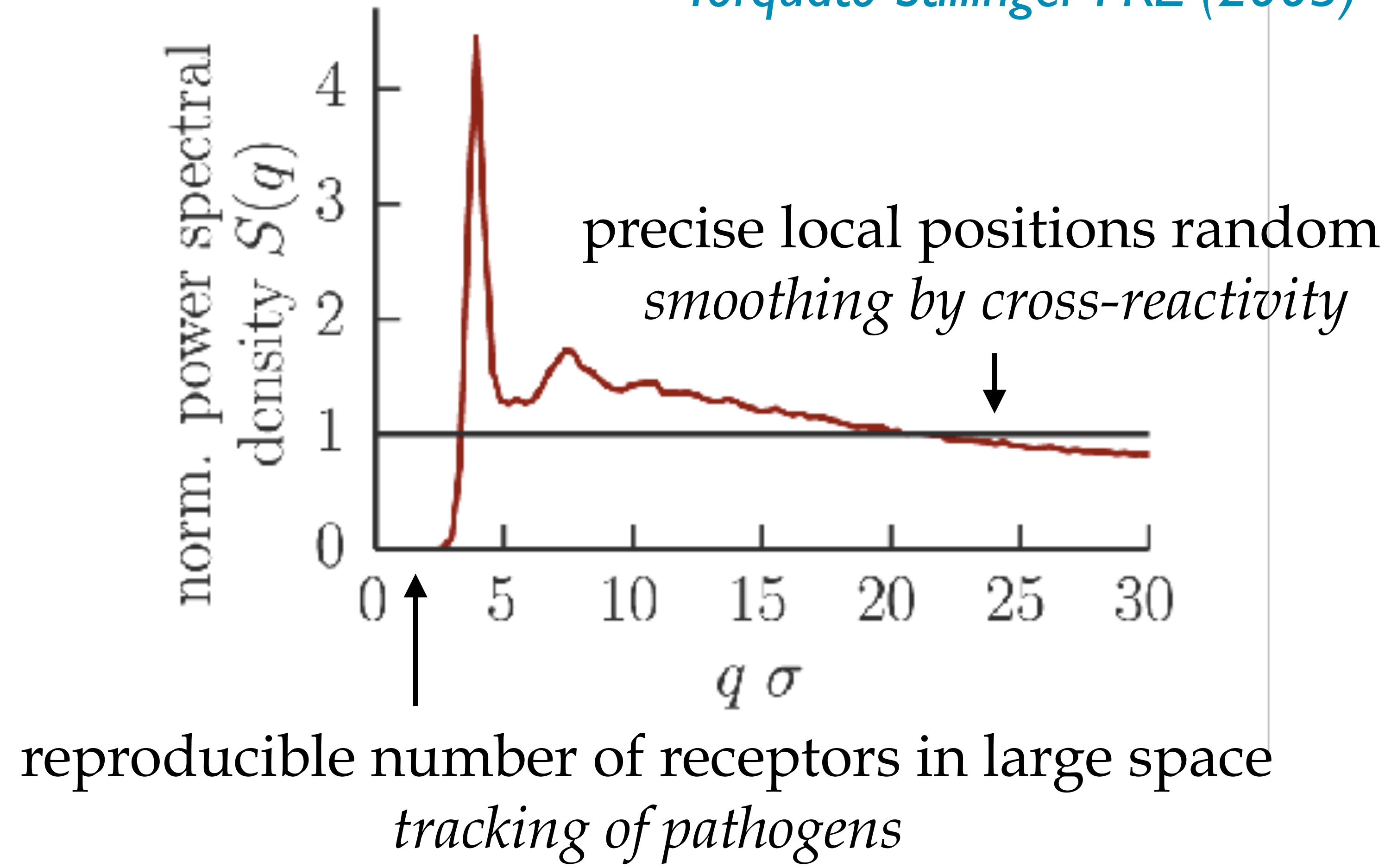
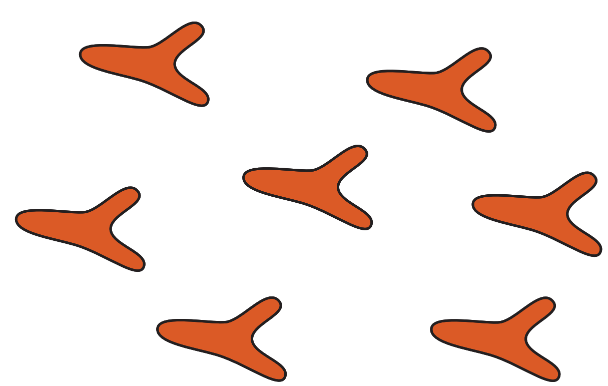
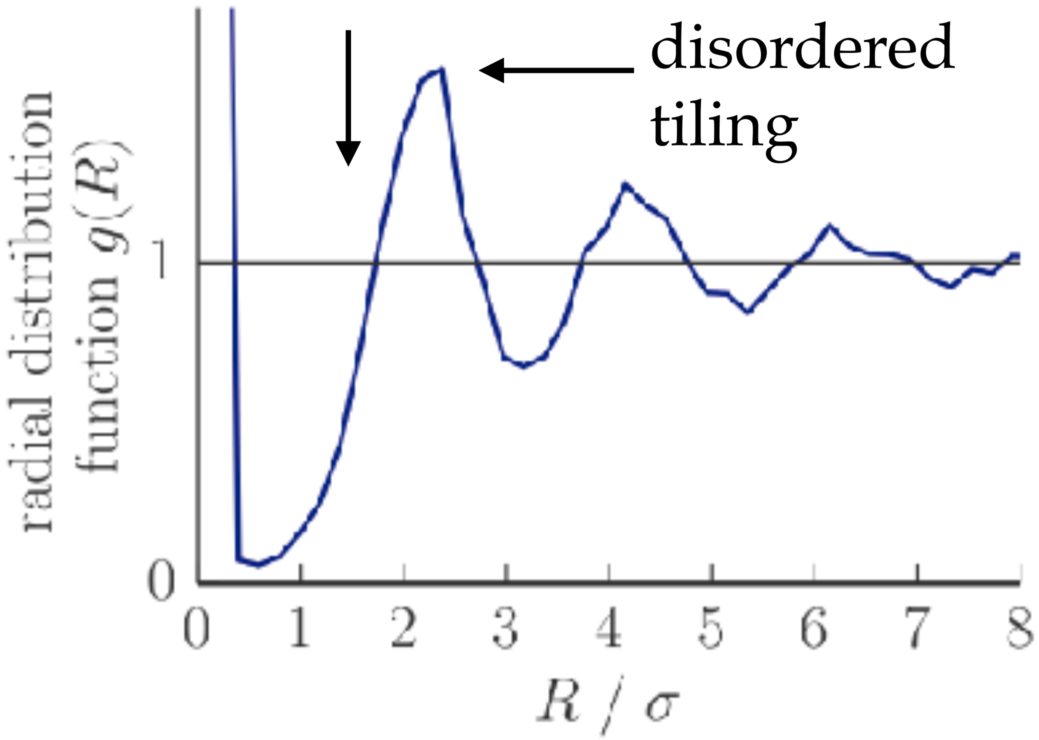


# Disordered hyperuniformity

repulsion

disordered tiling

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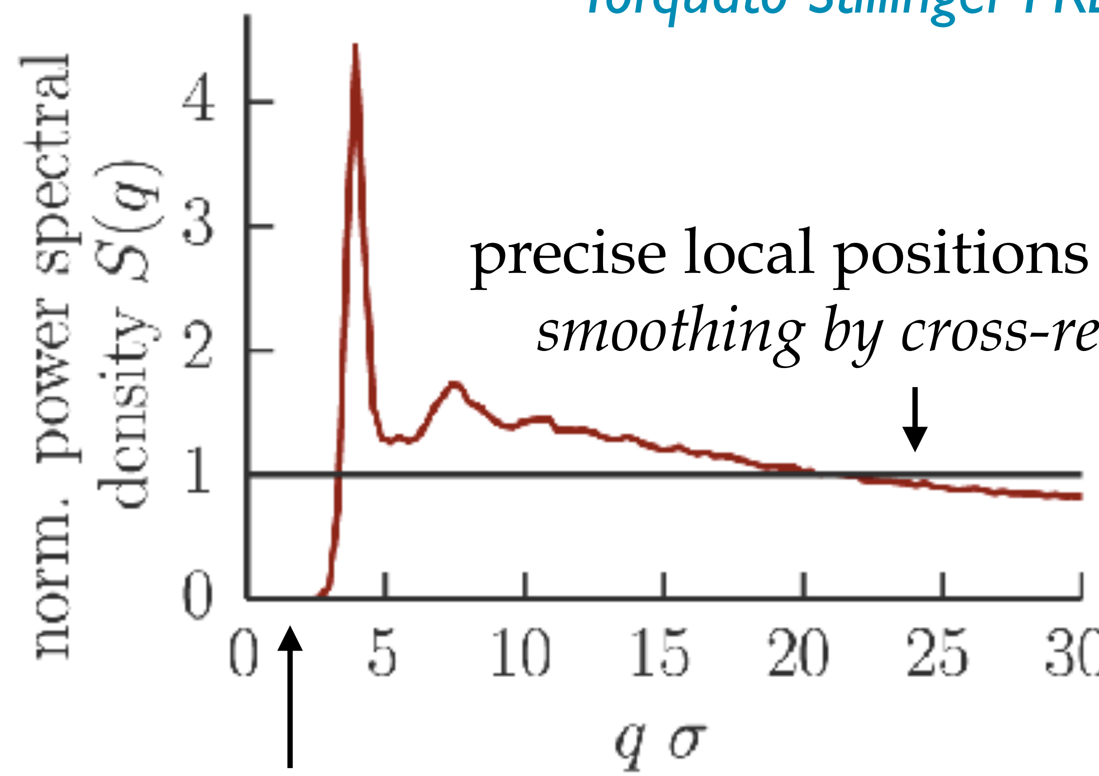
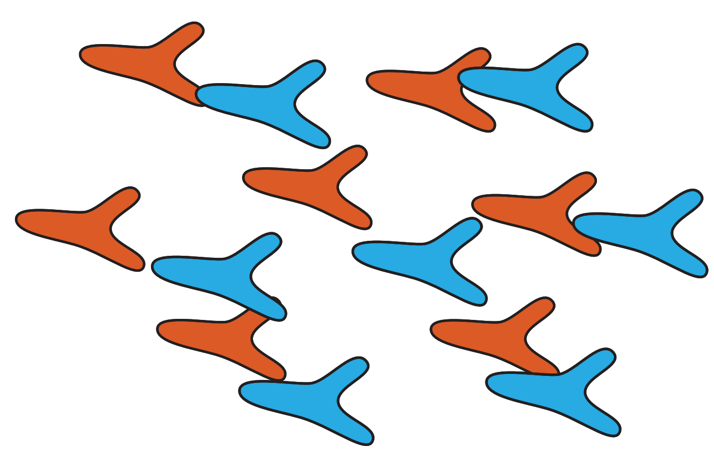



precise local positions random

*smoothing by cross-reactivity*

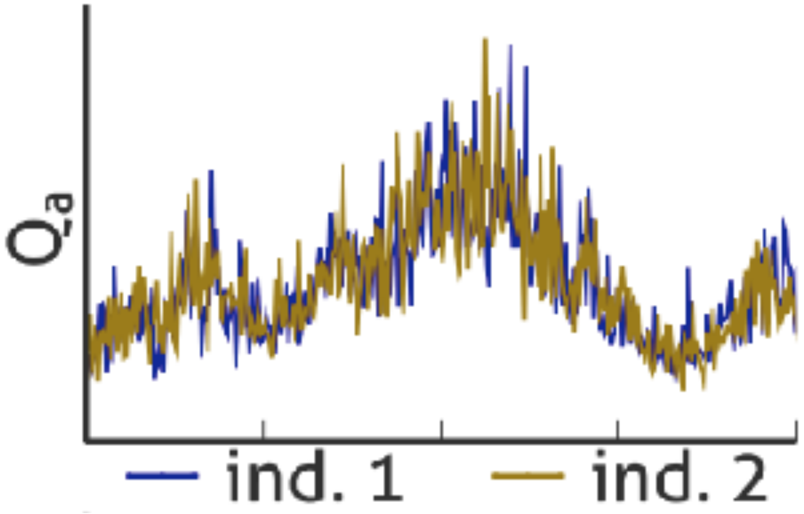
reproducible number of receptors in large space

*tracking of pathogens*



# Personalized response

two individuals see the environment slightly differently



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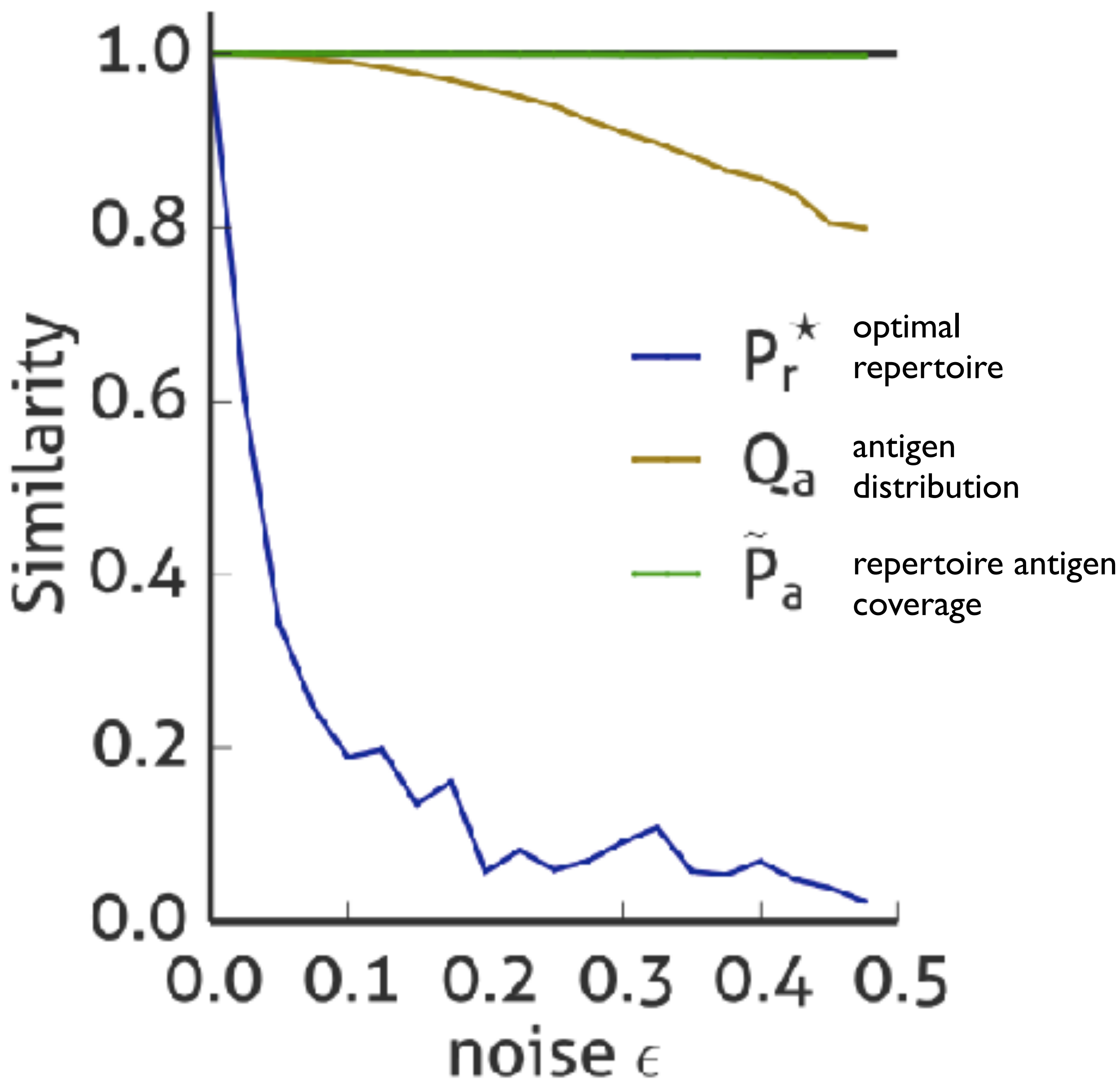
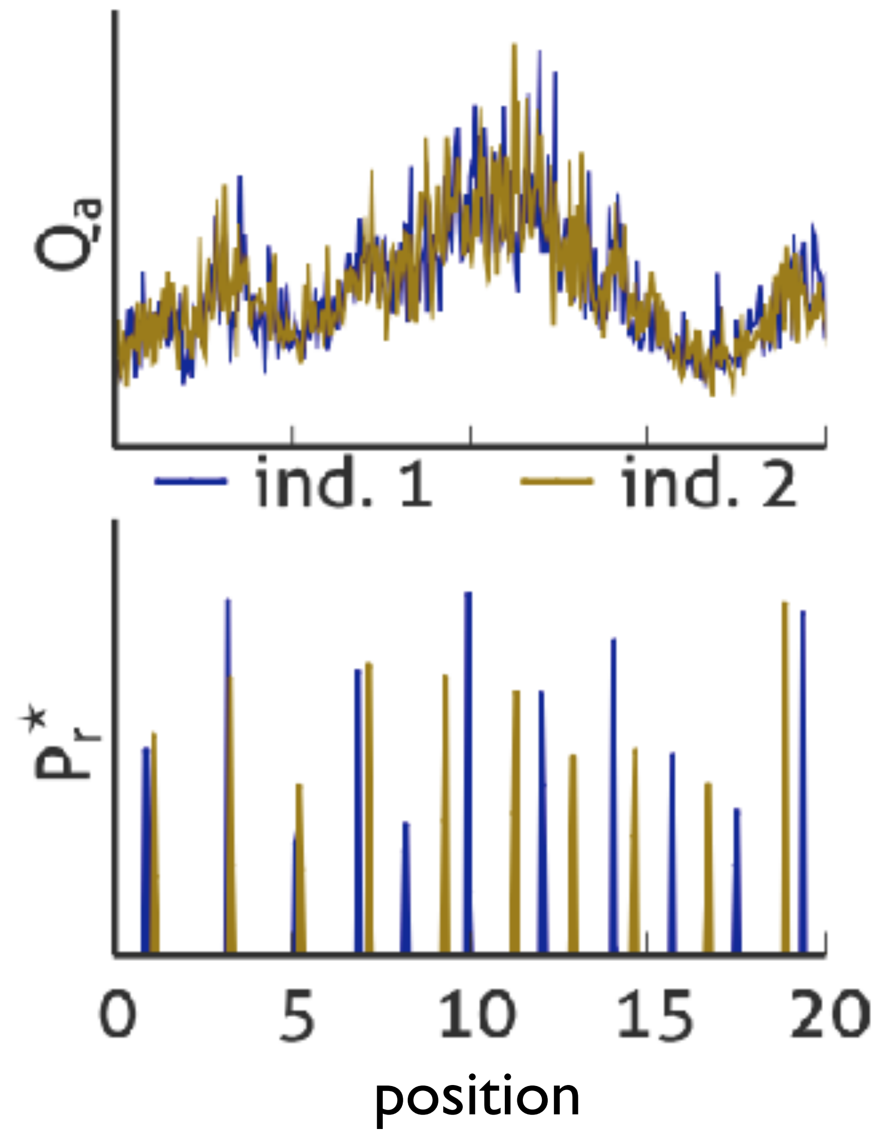
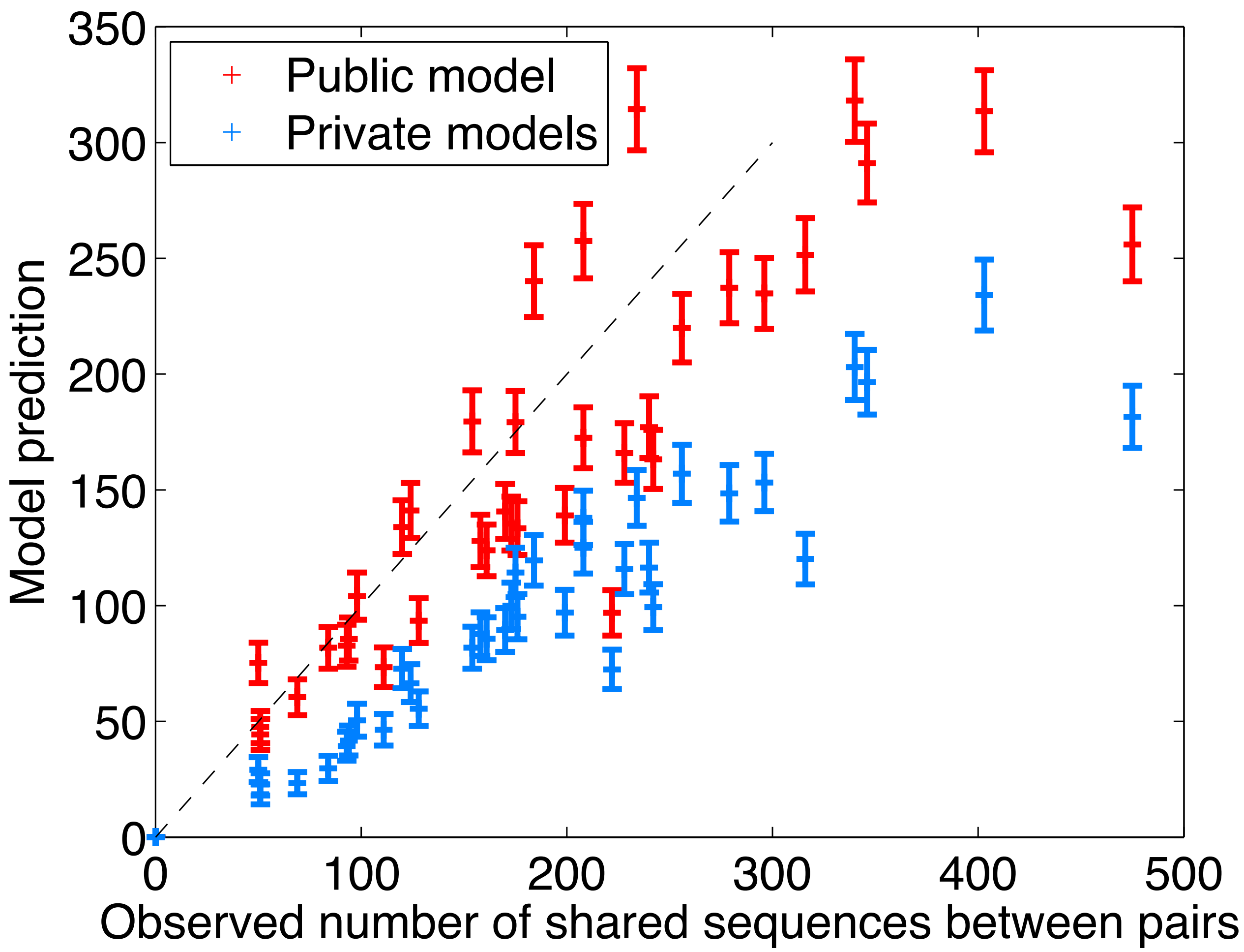



⟶ very different repertoires

# Personalized response

how many shared receptors
between 2 people?

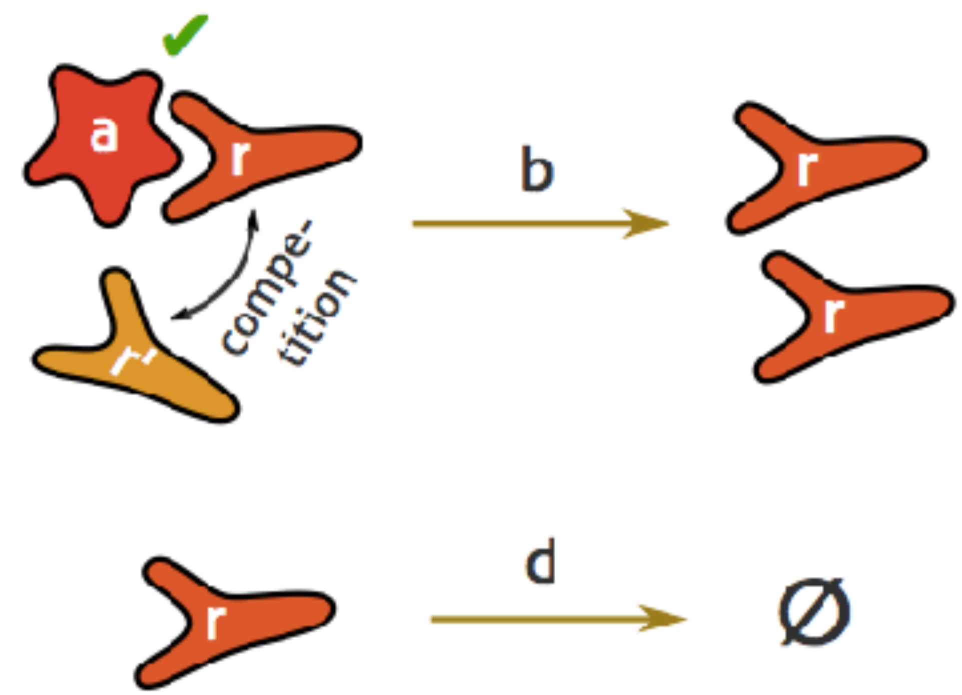



close to random expectations

*Elhanati Callan Mora Walczak PNAS 2014*

# Receptor dynamics

Can optimal repertoires be reached via dynamics?

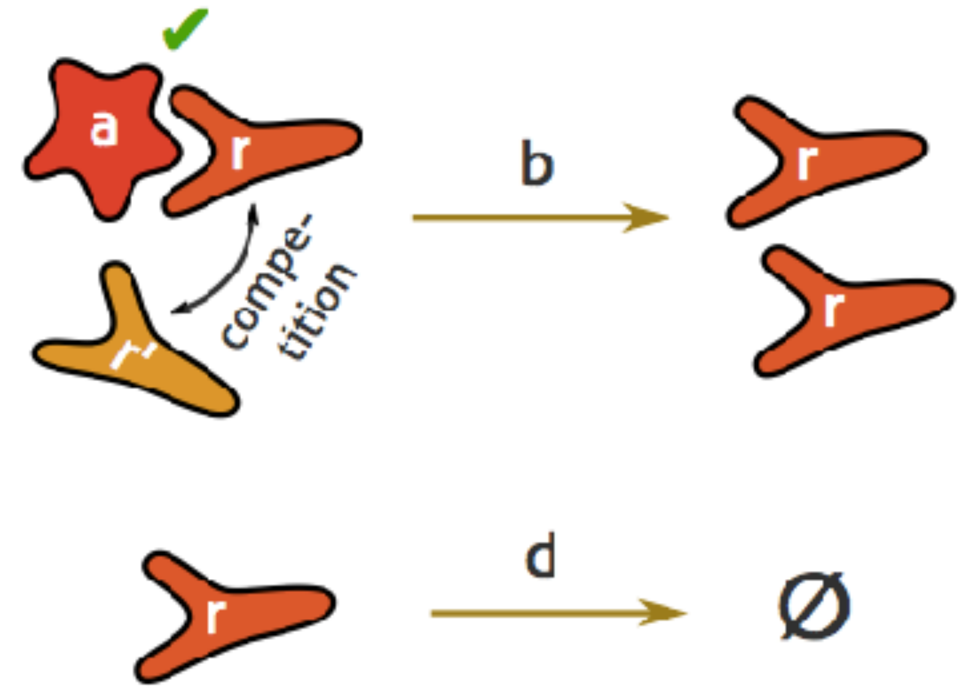


# Receptor dynamics

Can optimal repertoires be reached via dynamics?

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

- 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




(Lokta-Volterra equations
de Boer, Perelson ’95, ’97, ‘01)

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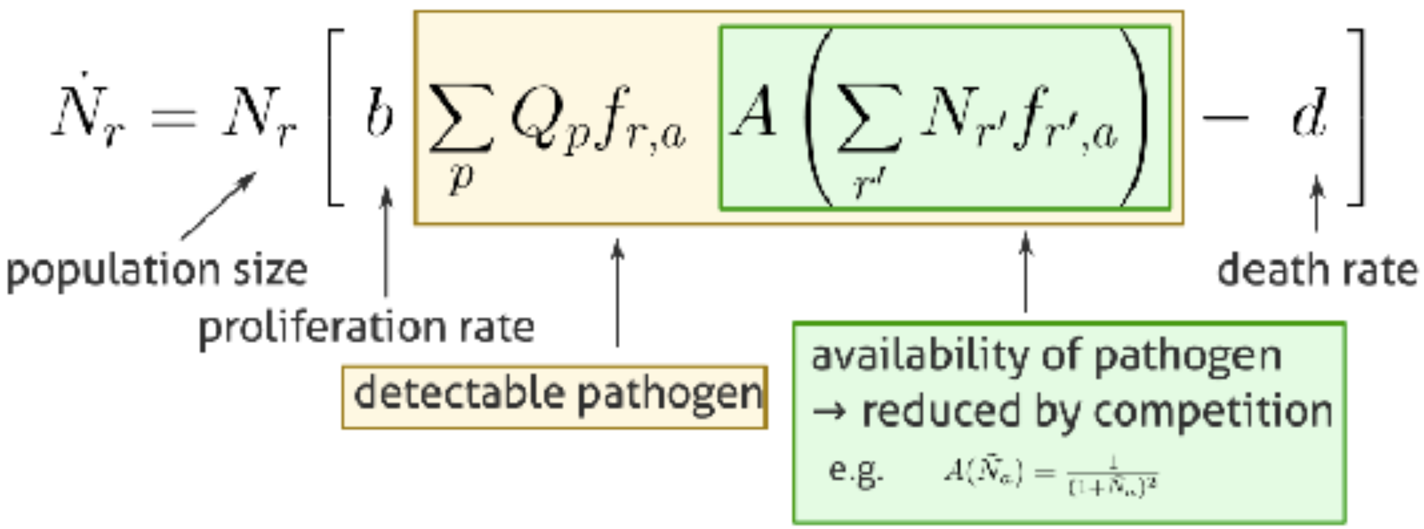


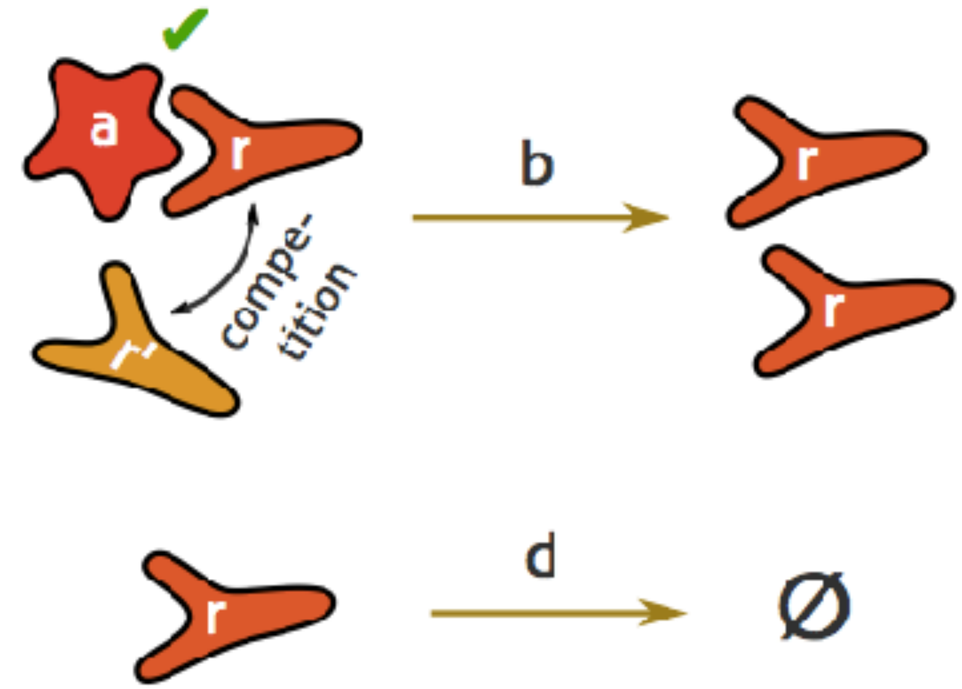


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optimal repertoire reached if

availability function $A\left(\tilde{N}_a\right) \sim -\bar{F}'\left(\tilde{N}_a\right)$ cost function steepness

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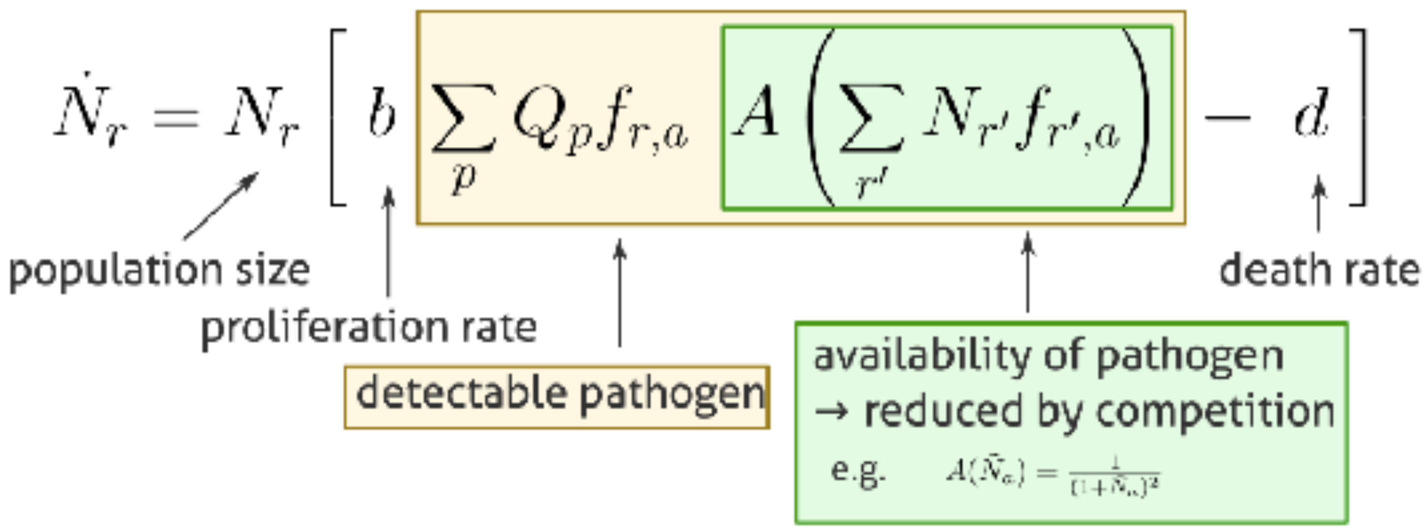


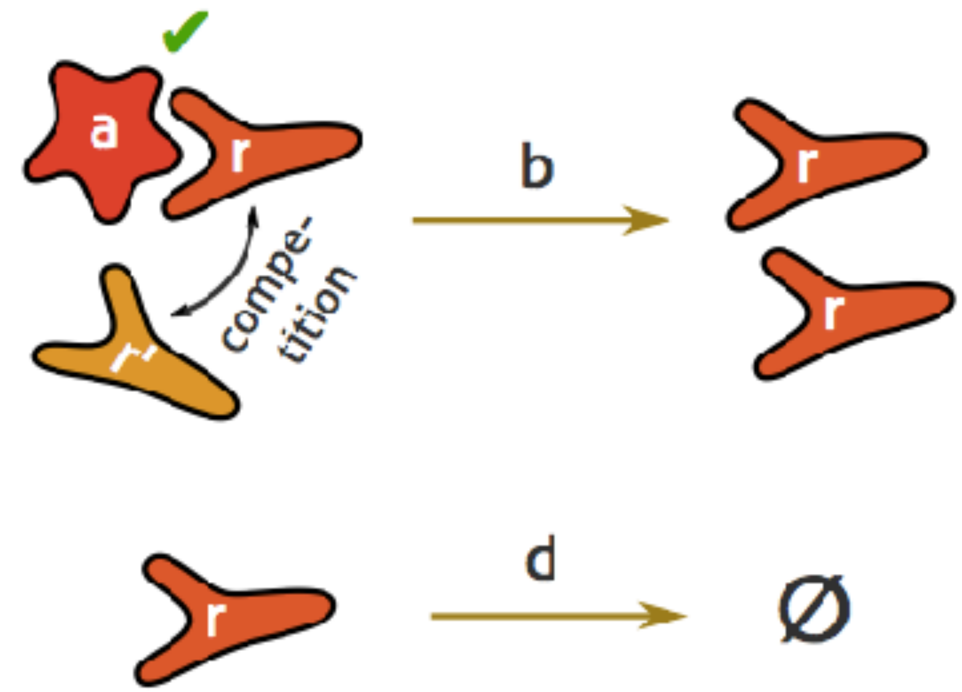


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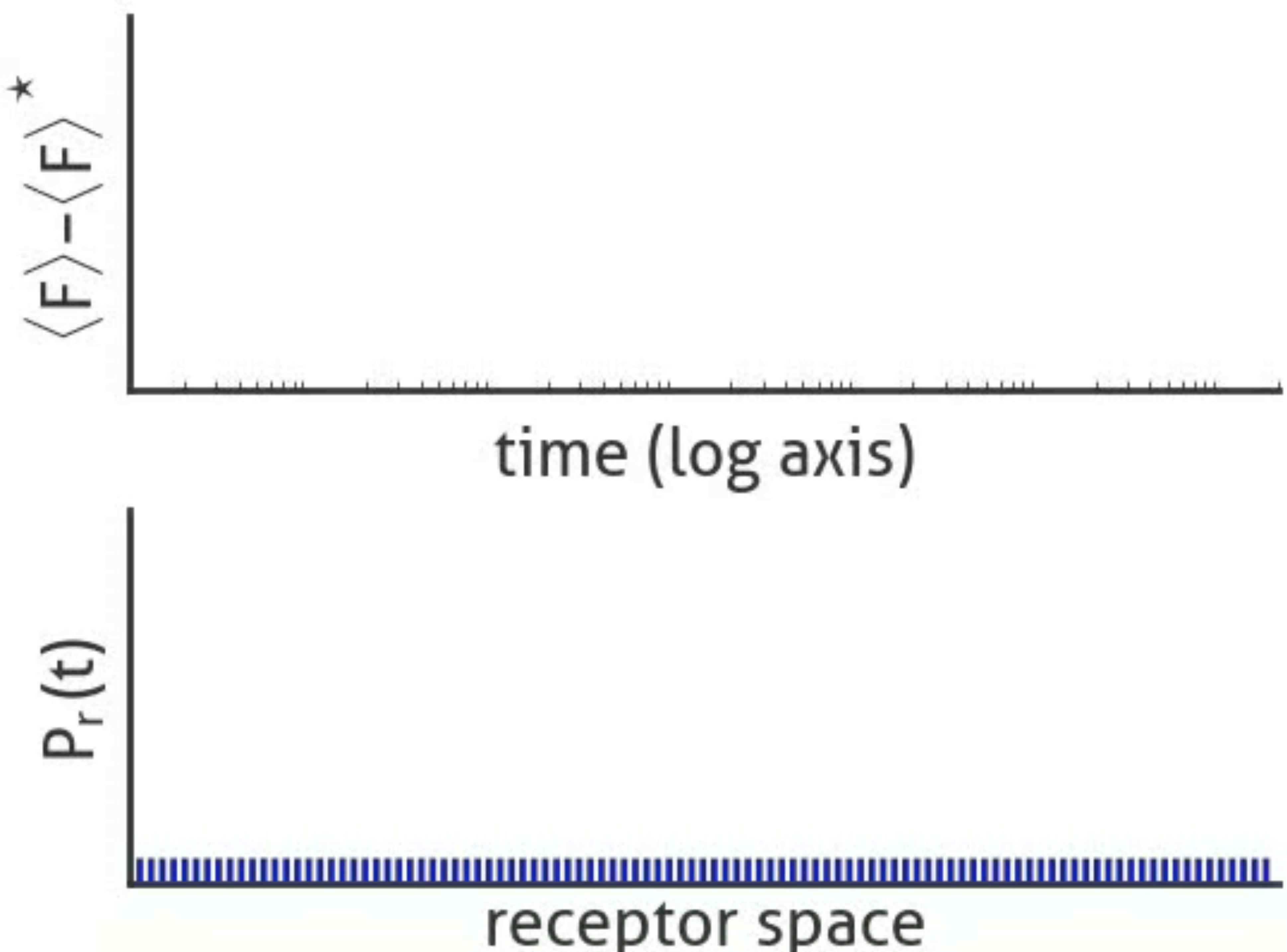
⟶ Through competition of receptors for antigens

# Self-organised dynamics



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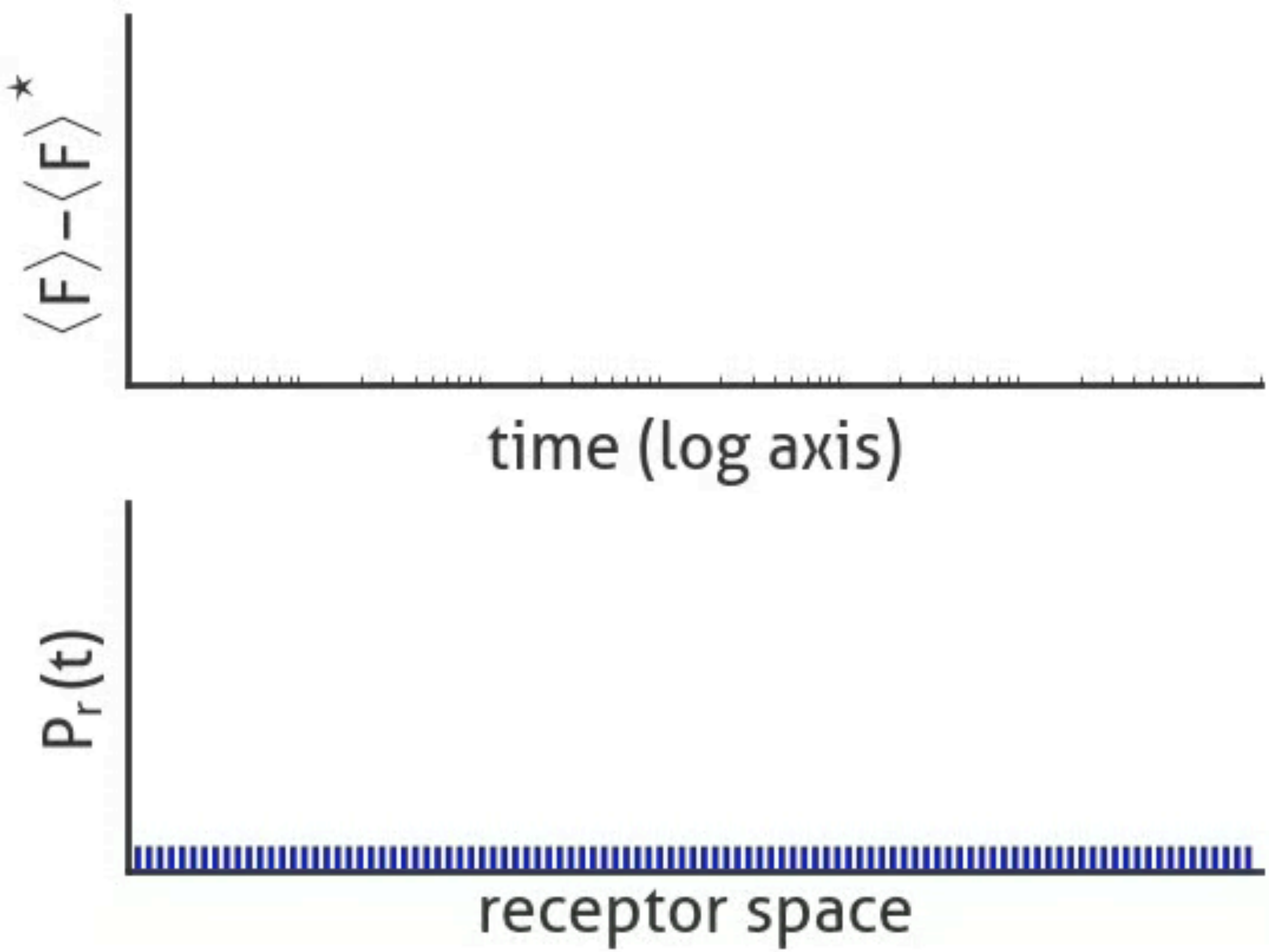

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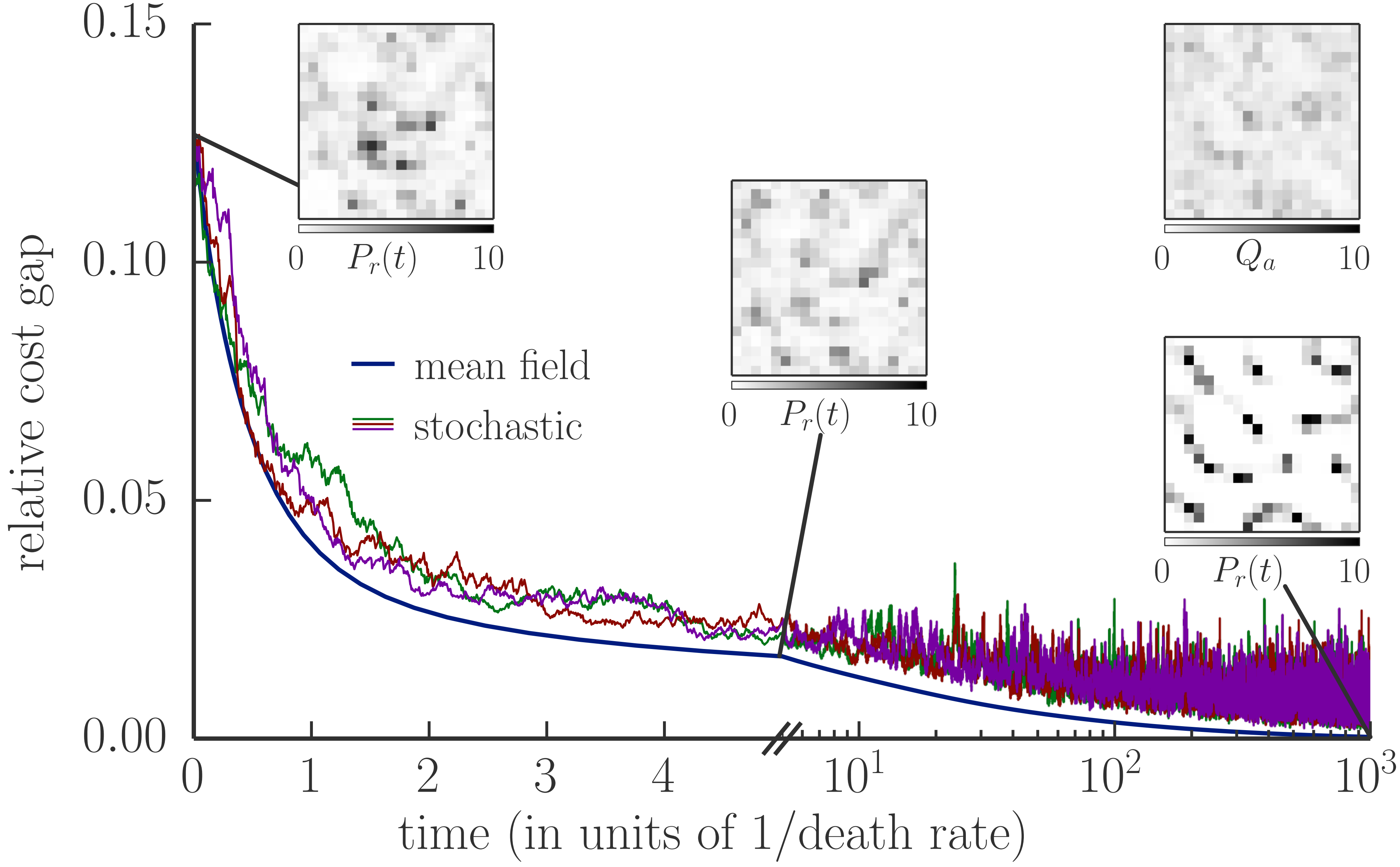
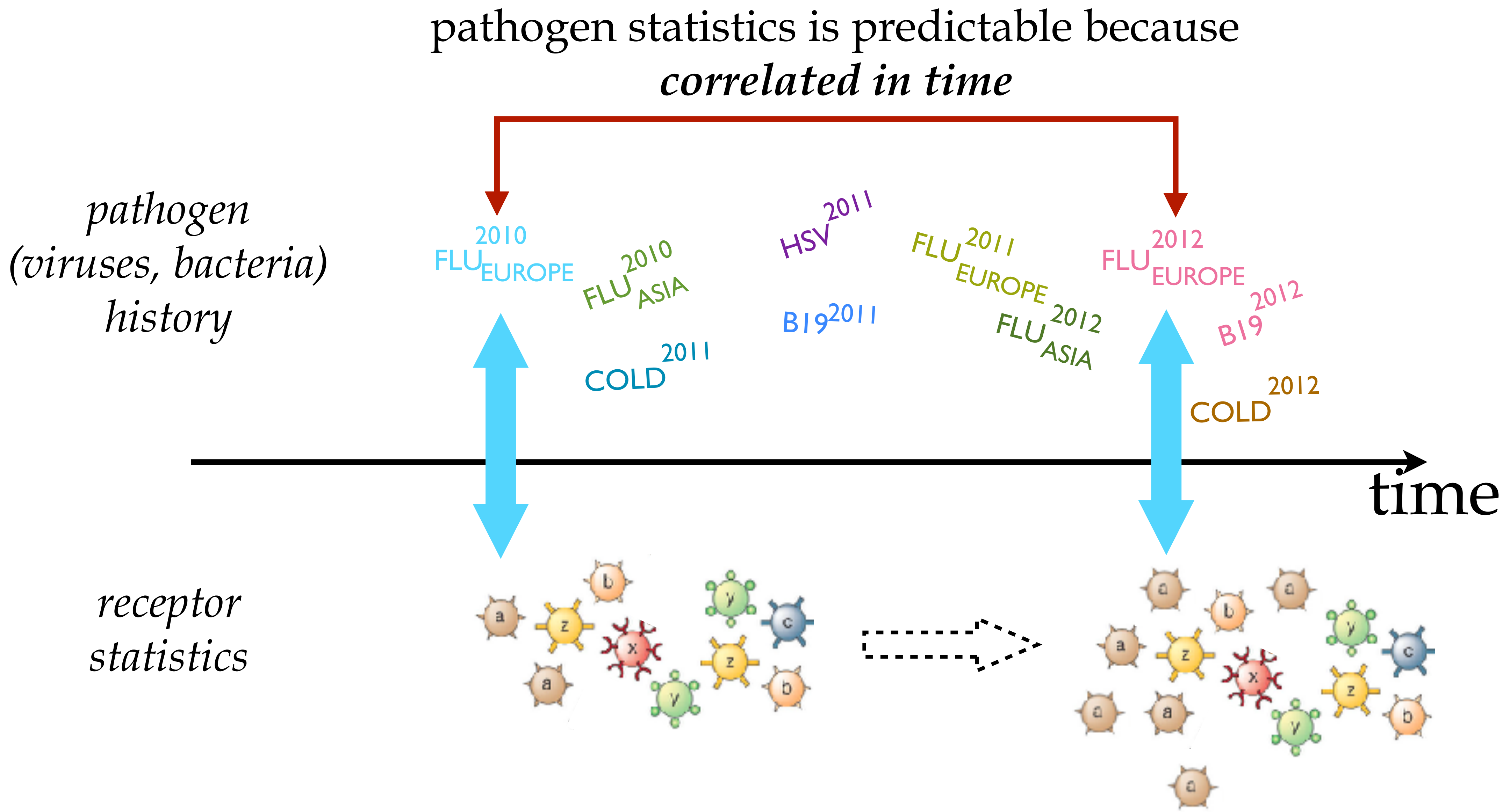


# Predicting the future



# Bayesian belief

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

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***belief*** of Q(t)

$$\downarrow$$

$$\langle \mathrm{Cost}\left(\mathrm{P(t)}, \mathrm{Q(t)}\right)\rangle = \int \mathrm{dQ}\ \mathrm{Cost}\left(\mathrm{P(t)}, \mathrm{Q}\right) \mathrm{B}\left(\mathrm{Q}, \mathrm{t}\right)$$

# Bayesian belief

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

***belief*** of Q(t)

↓

$$\langle \mathrm{Cost}\,(\mathrm{P}(\mathrm{t}), \mathrm{Q}(\mathrm{t}))\rangle = \int \mathrm{dQ}\ \mathrm{Cost}\,(\mathrm{P}(\mathrm{t}), \mathrm{Q})\ \mathrm{B}\,(\mathrm{Q}, \mathrm{t})$$

$$\langle \mathrm{Cost}\,(\mathrm{P}(\mathrm{t}), \mathrm{Q}(\mathrm{t}))\rangle = \sum_{\mathrm{a}} \langle \mathrm{Q}_{\mathrm{a}}(\mathrm{t})\rangle \bar{\mathrm{F}}_{\mathrm{a}}\,(\mathrm{P}_{\mathrm{r}}(\mathrm{t}))$$

only average
belief matters

$$\langle Q(t)\rangle = \int dQ\ Q\ B\,(Q, t)$$

# Belief dynamics

*unknown* — antigen frequencies **Q**(t)

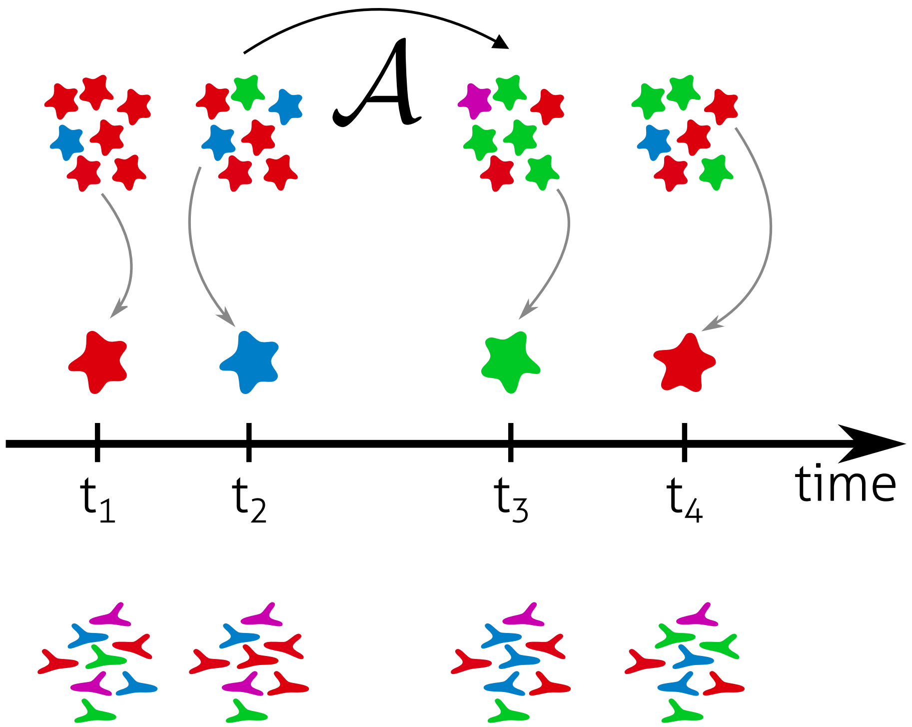
⇓

*what we see* — antigen encounters $\{t_i, \bigstar\}$

⇓

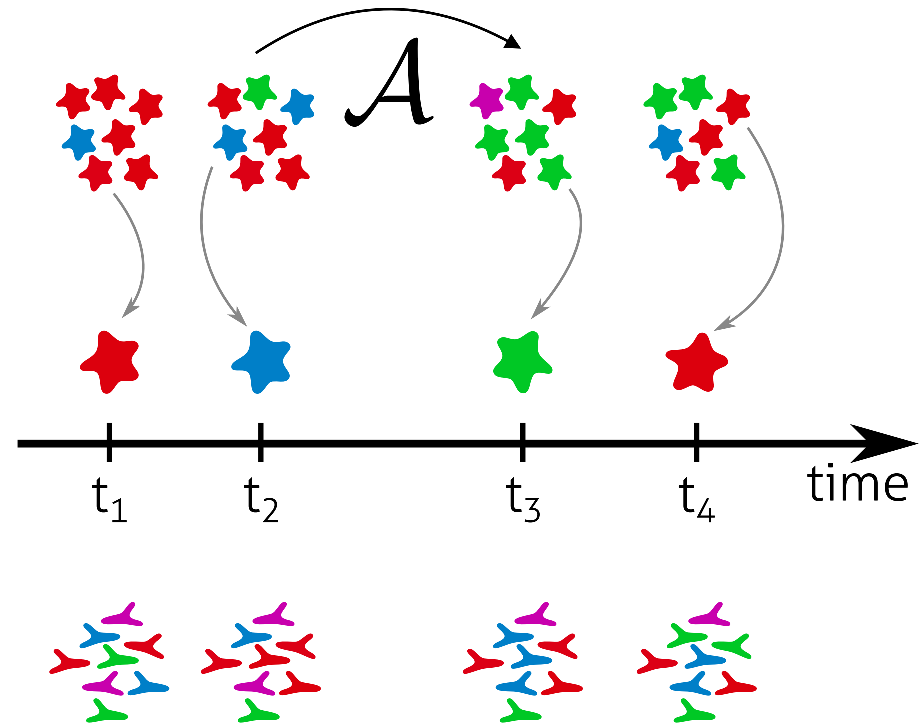
*get by minimizing* — receptor frequencies **P**(t)

$$\sum_a \langle Q_a(t) \rangle \bar{F}_a \left( P_r(t) \right)$$



# Belief dynamics

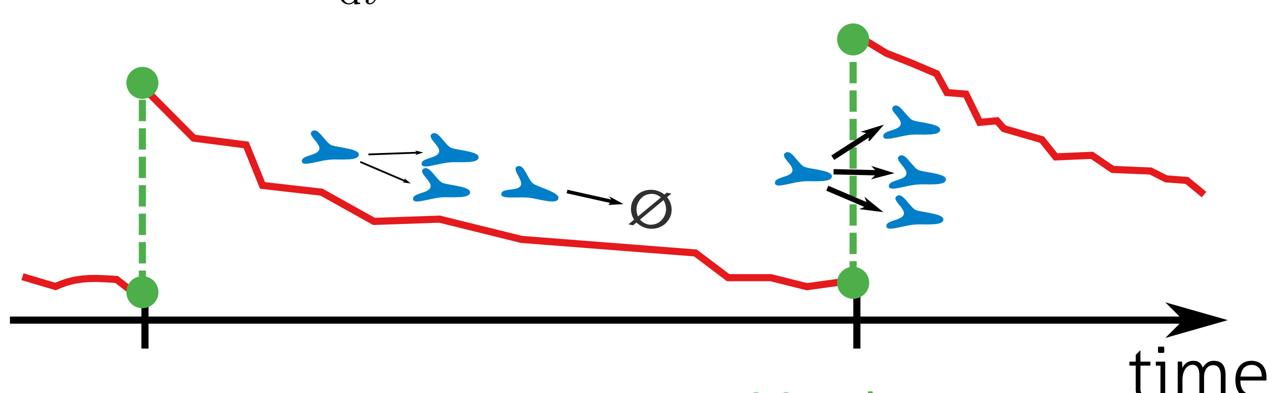
| | | |
|---|---|---|
| *unknown* | antigen frequencies **Q**(t) | |
| | ⇓ | |
| *what we see* | antigen encounters {$t_i$, ★} | |
| | ⇓ | |
| *get by minimizing* $\sum_a \langle Q_a(t) \rangle \bar{F}_a\left(P_r(t)\right)$ | receptor frequencies **P**(t) | |




## optimal (Bayesian strategy) update strategy

Prediction

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

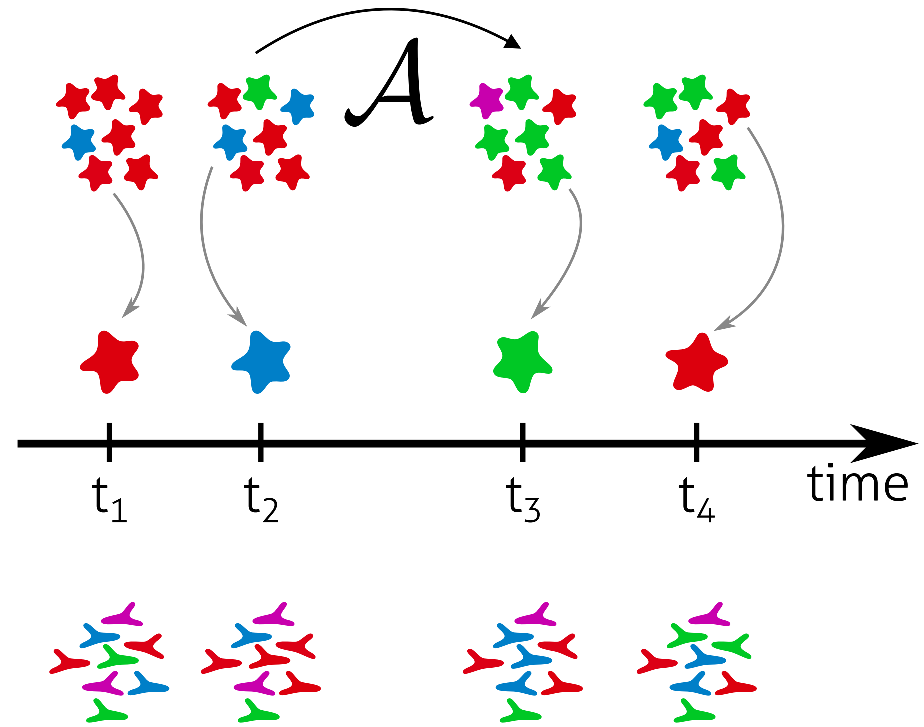



Update

$$B(\boldsymbol{Q},t^{+}) = Q_a B(\boldsymbol{Q},t^{-})/Z$$

# Belief dynamics

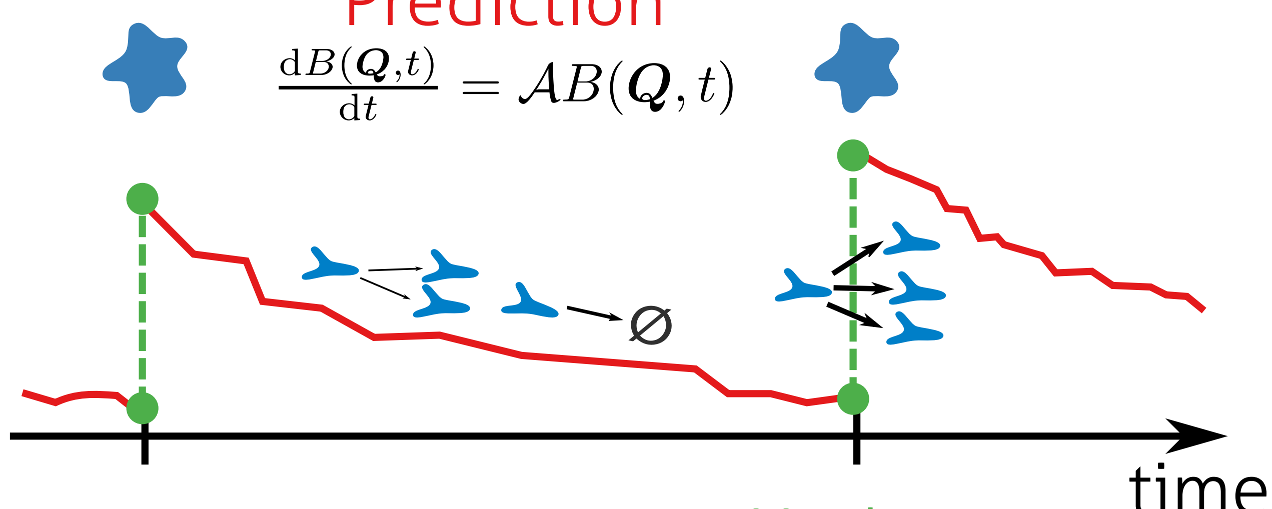
| | | |
|---|---|---|
| *unknown* | antigen frequencies **Q**(t) | |
| | ⇓ | |
| *what we see* | antigen encounters $\{t_i, \bigstar\}$ | |
| | ⇓ | |
| *get by minimizing* $\sum_a \langle Q_a(t) \rangle \bar{F}_a \left(P_r(t)\right)$ | receptor frequencies **P**(t) | |




## optimal (Bayesian strategy) update strategy

Prediction

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




Update

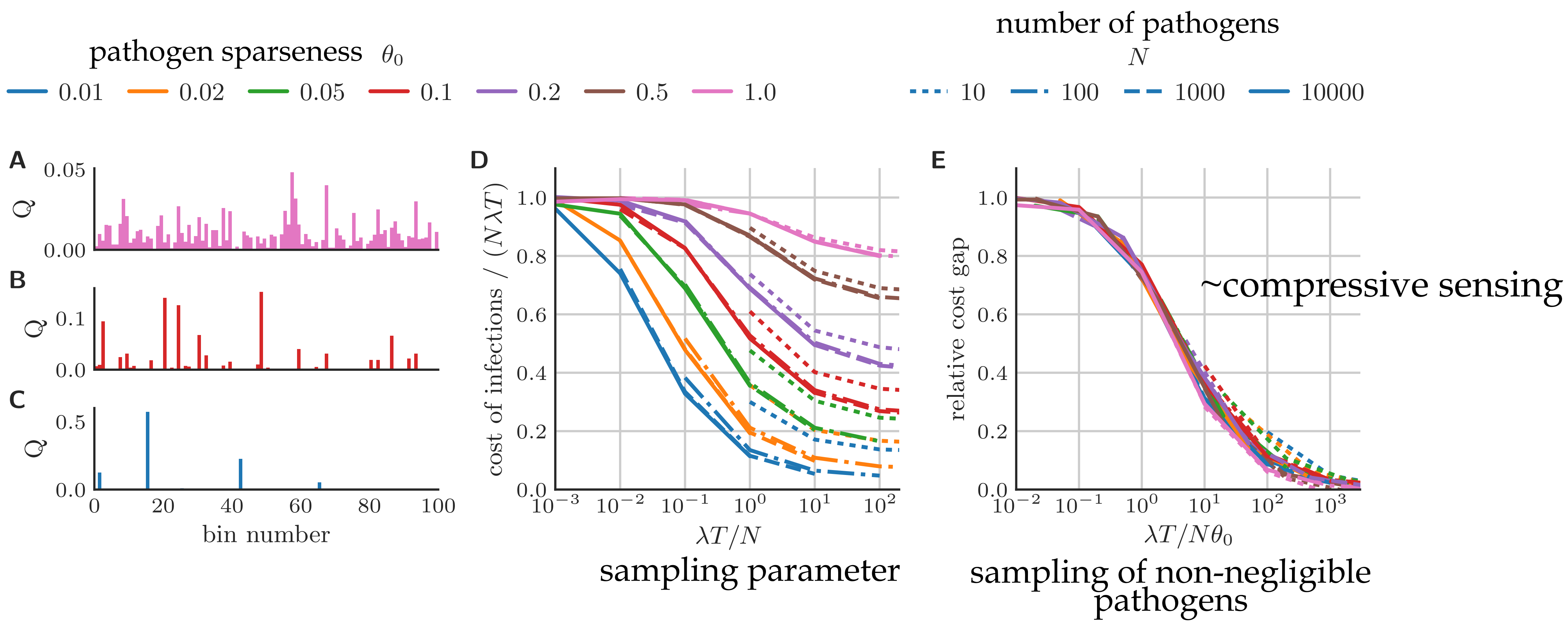
$$B(\boldsymbol{Q},t^{+}) = Q_a B(\boldsymbol{Q},t^{-})/Z$$

Burnet's clonal selection theory

# Sparseness helps

- memory helps in sparse environments

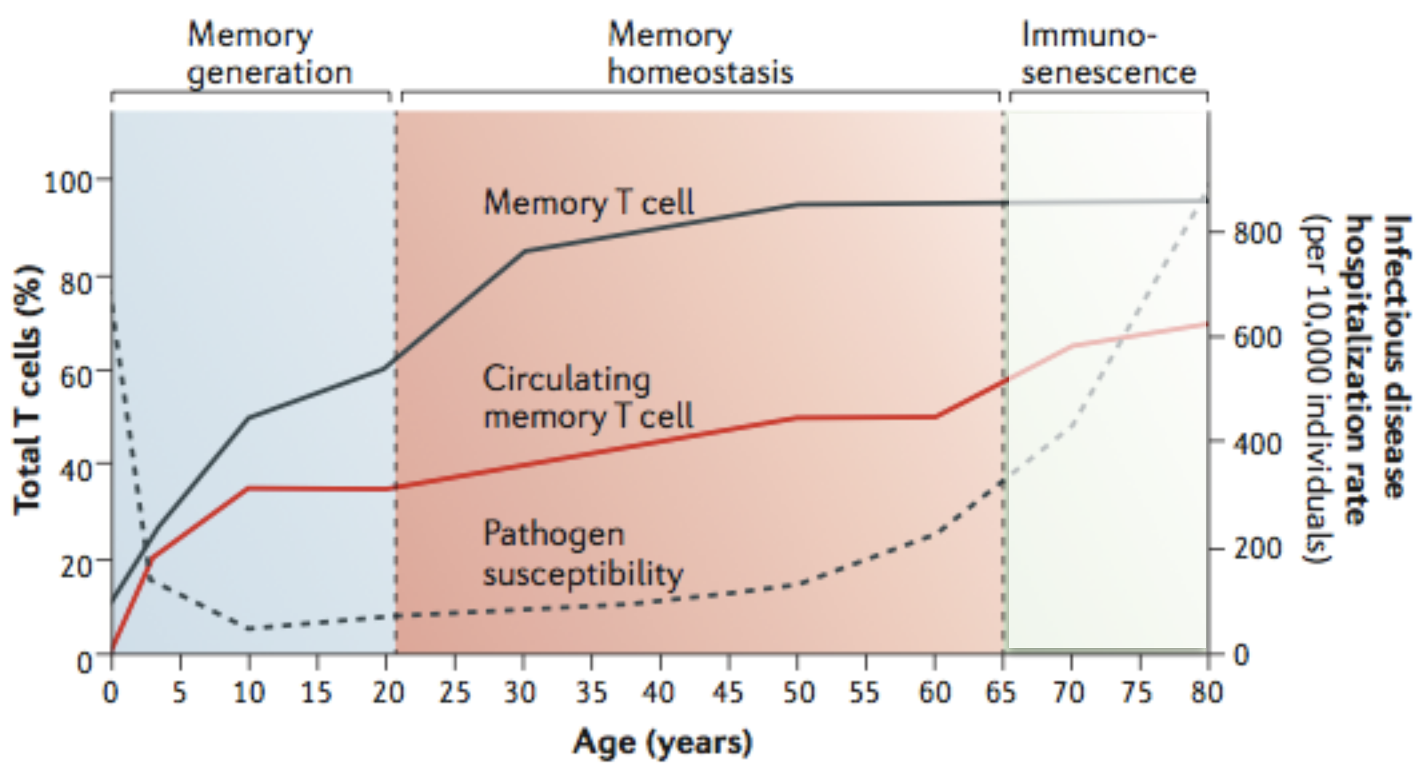
  → fast detection of few pathogens



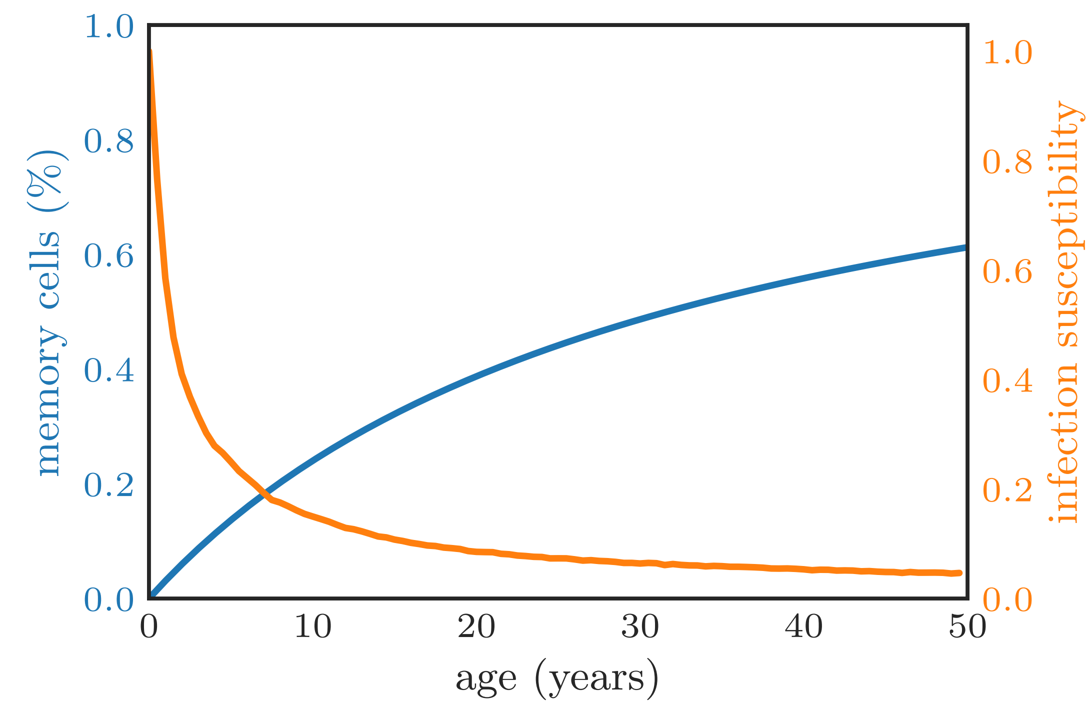

- advantage of memory - depends on sampling

# Memory management

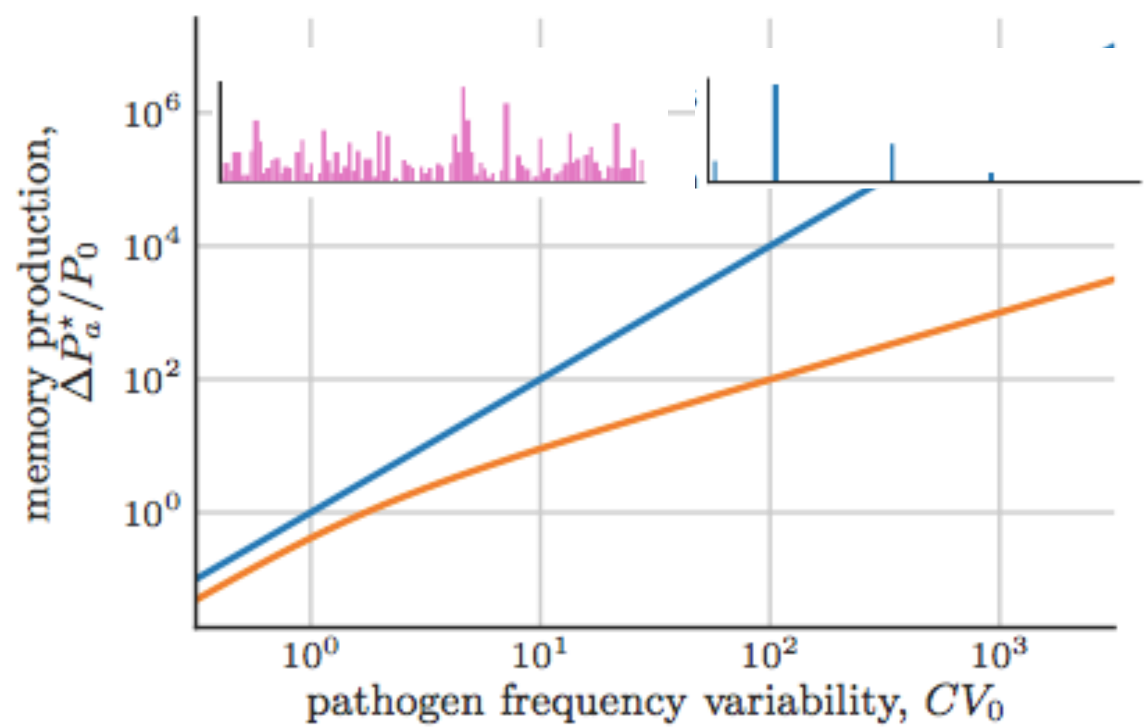
- infection susceptibility increases as memory increases




D. L. Farber, N. A. Yudanin, N. P. Restifo, Nat. Rev. Immunol. **2013**

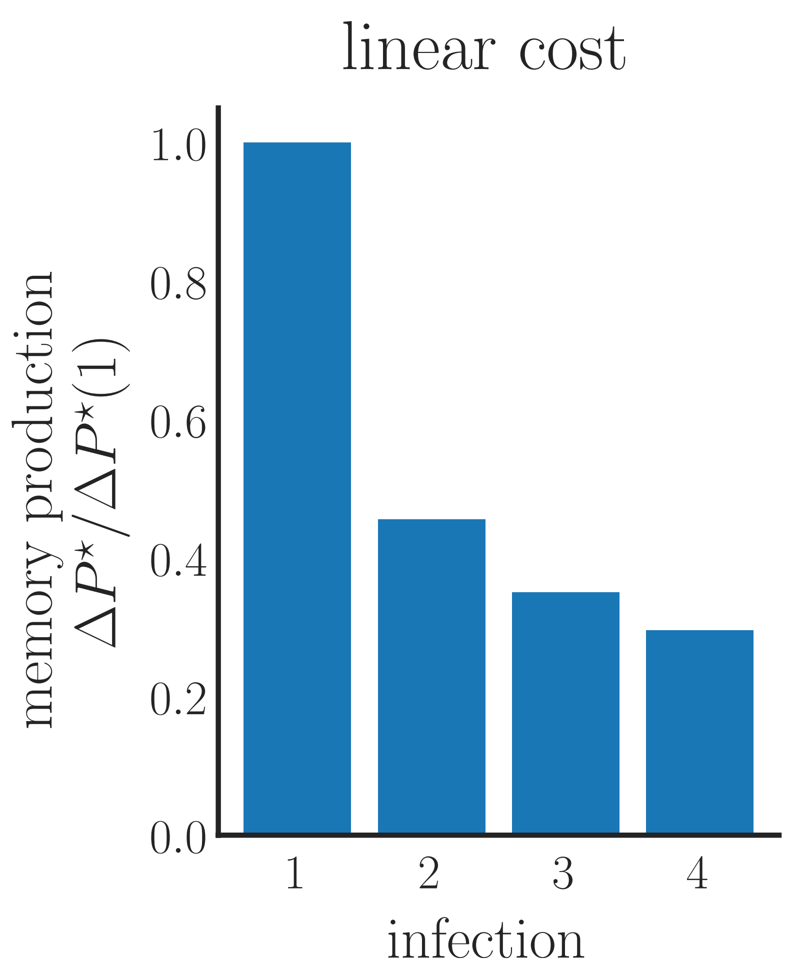



- sparse env. → strong response



# Memory management

- later encounters = less evidence




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