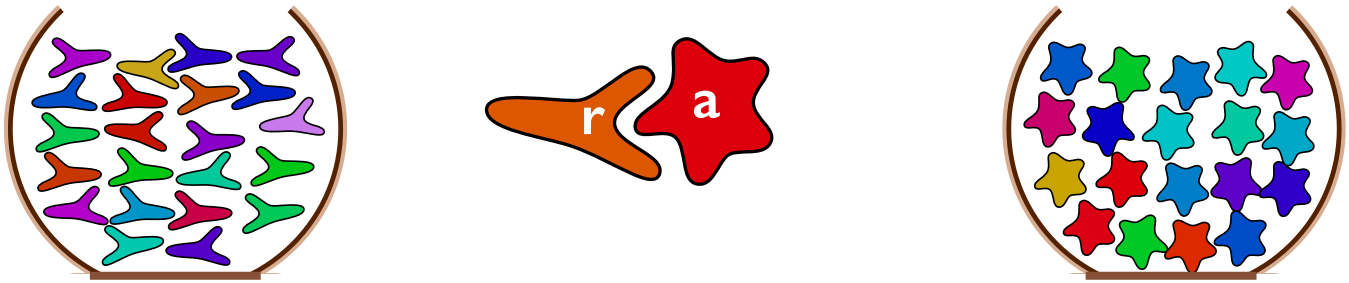


Analysis of immune receptor repertoires
Part 2

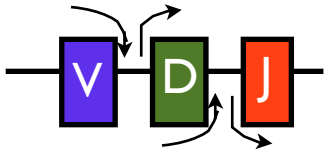
Aleksandra M Walczak
Laboratoire de Physique Théorique - ENS, CNRS

work with
Rhys Adams, ENS
Yuval Elhanati, ENS
Quentin Marcou, ENS
Maximilian Puelma Touzel, ENS
Andreas Mayer, ENS
Zachary Sethna, Princeton
Justin Kinney, CSHL
Olivier Rivoire, UJF
Anand Murugan, Princeton
Curt Callan, Princeton
Thierry Mora, ENS

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

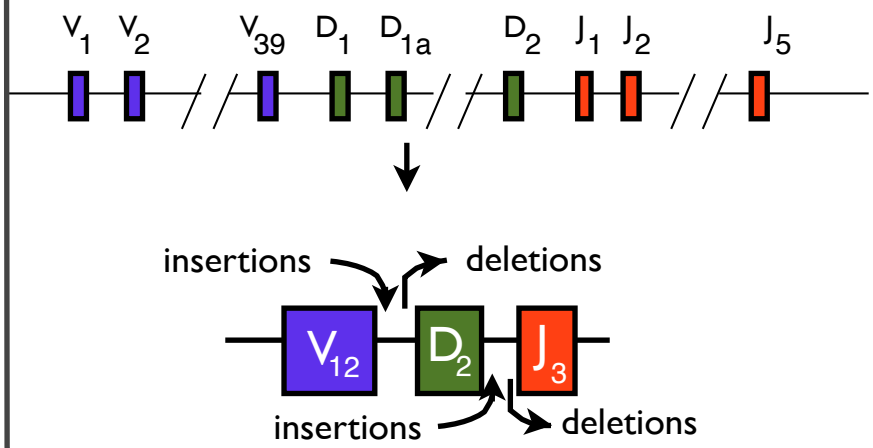
erc
European Research Council
Established by the European Commission

Probabilistic VDJ recombination annotation



sequence generation:

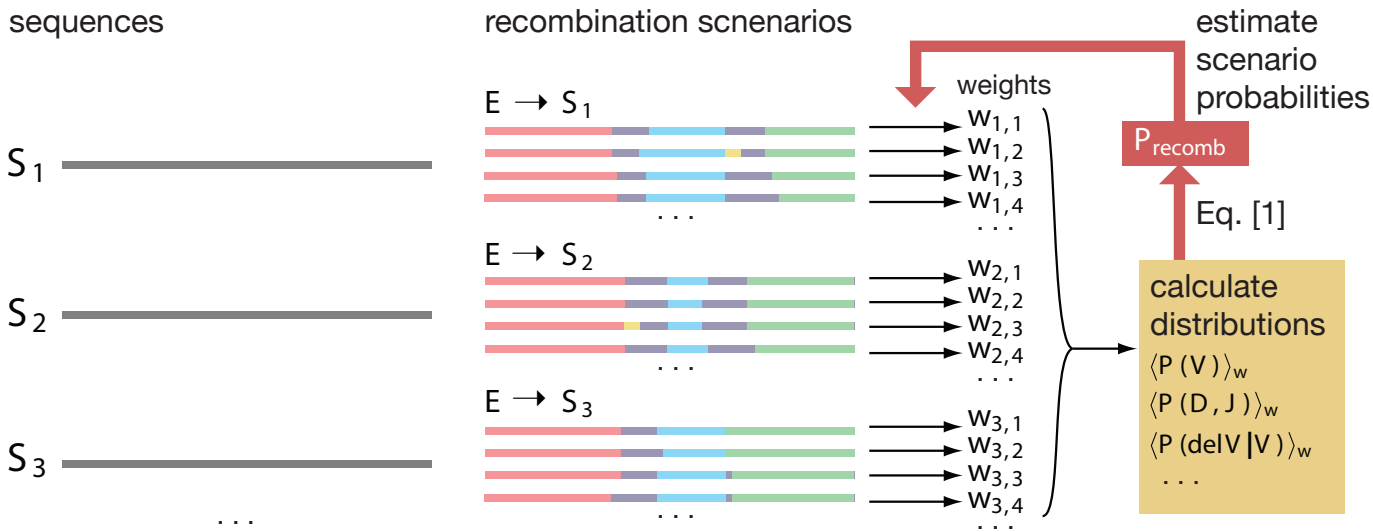
combinatorics + *randomness* → diversity



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

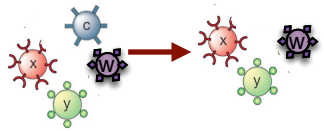
```
TAGGACCTCGGAAACCTCTTCTGCTGGCGCAGAGATACAGGGCTGAGTCTTCTT
TATCTGCCGATGTCGCGAAGGCCCTCCCGCTAAGATCACTGGTGGCACAGAAGT
TAGGGAGAGGTGCCTAACTGCTGGCACAGAAGTACAGAGAGGTCTGGTTGGGGT
TCCGCCGCTAGTCCCTGAAACTACTGGCACAGAGATAGAAAGCTGTCGGGTTCT
CGAAACTGCTGGCACAGAAGTACACAGATGTTTGGGAGGGAGCAGCCGACTCCA
TCTTGGCCGCTAGTCCGAGAAACTGCTGGCACAGAAGTACACAGATGTTTGGGA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

- probabilistic assignment of:

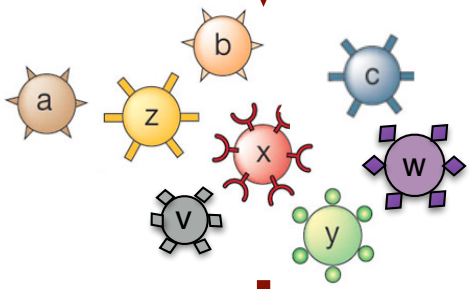


$$\mathrm{P}^{\mathrm{recomb}}(\mathrm{scenario}) = P(V)P(D,J)P(\mathrm{deletions}V|V)P(\mathrm{insertions}DJ)\ldots$$ [1]

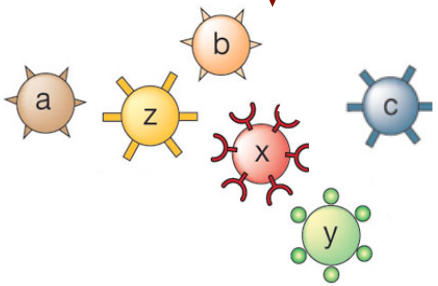
Receptor sharing

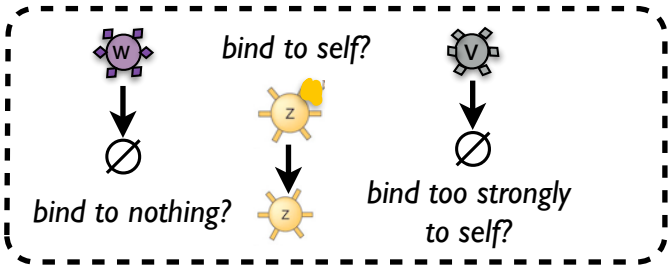


RECEPTOR GENERATION



THYMIC SELECTION

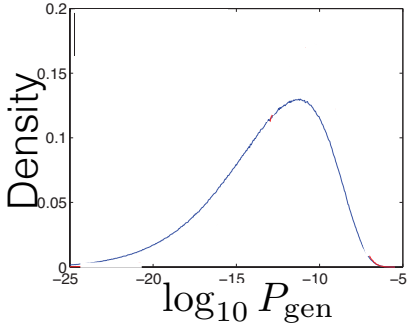




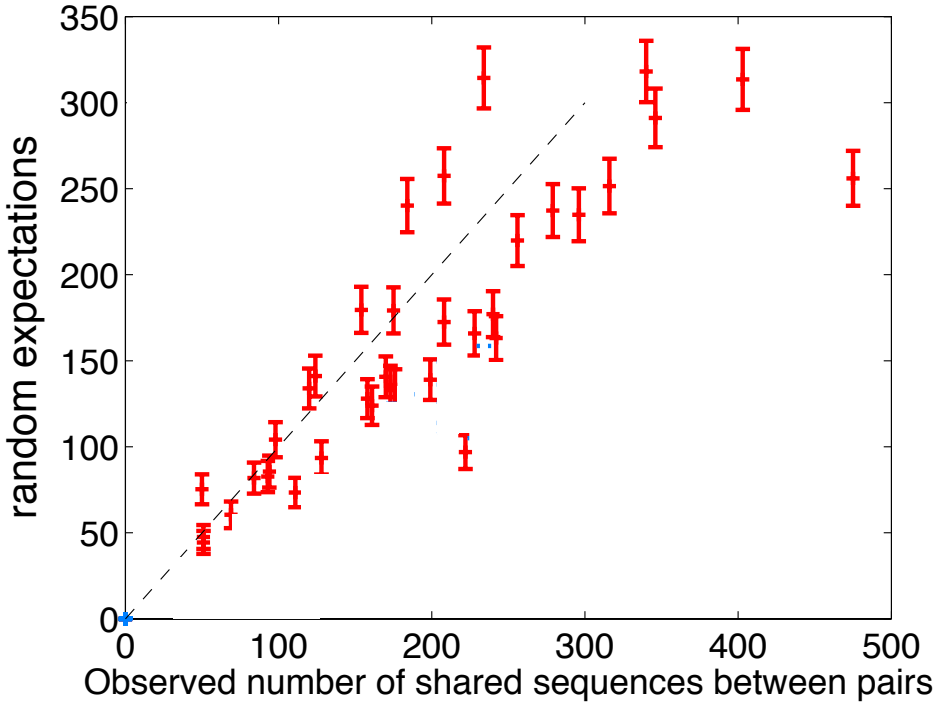
human beta TCR data from Robins lab

- 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

Condition specific TCRs

- clonotypes can be shared
  - for functional reasons (common antigen)
  - by chance (convergent recombination)

- large cohort association studies to find condition-specific TCRs

- can we tell the difference using the m

SCIENTIFIC REPORTS

OPEN

CD8+ T cells specific for the islet autoantigen IGRP are restricted in their T cell receptor chain usage

Received: 07 November 2016
Accepted: 13 February 2017
Published: 16 March 2017

Yannick F. Fuchs[1,2,3,*], Anne Eugster[1,*], Sevina Dietz[1,2,3], Christian Sebelefsky[4], Denise Kühn[1], Carmen Wilhelm[1], Annett Lindner[1,2,3], Anita Gavrisan[5], Jan Knoop[4,5], Andreas Dahl[6], Anette-G. Ziegler[4,5,7] & Ezio Bonifacio[1,2,3,5]

nature genetics

Immunosequencing identifies signatures of cytomegalovirus exposure history and HLA-mediated effects on the T cell repertoire

Ryan O Emerson[1,4], William S DeWitt[1,2,4], Marissa Vignali[1], Jenna Gravley[3], Joyce K Hu[1], Edward J Osborne[1], Cindy Desmarais[1], Mark Klinger[1], Christopher S Carlson[3], John A Hansen[3], Mark Rieder[1,5] & Harlan S Robins[1,2,5]

The Journal of Immunology

Preferential Use of Public TCR during Autoimmune Encephalomyelitis

Yunqian Zhao,*,[1] Phuong Nguyen,*,[1] Jing Ma,* Tianhua Wu,* Lindsay L. Jones,* eqing Pei,† Cheng Cheng,† and Terrence L. Geiger*

JCI insight

RESEARCH ARTICLE

Tissue distribution and clonal diversity of the T and B cell repertoire in type 1 diabetes

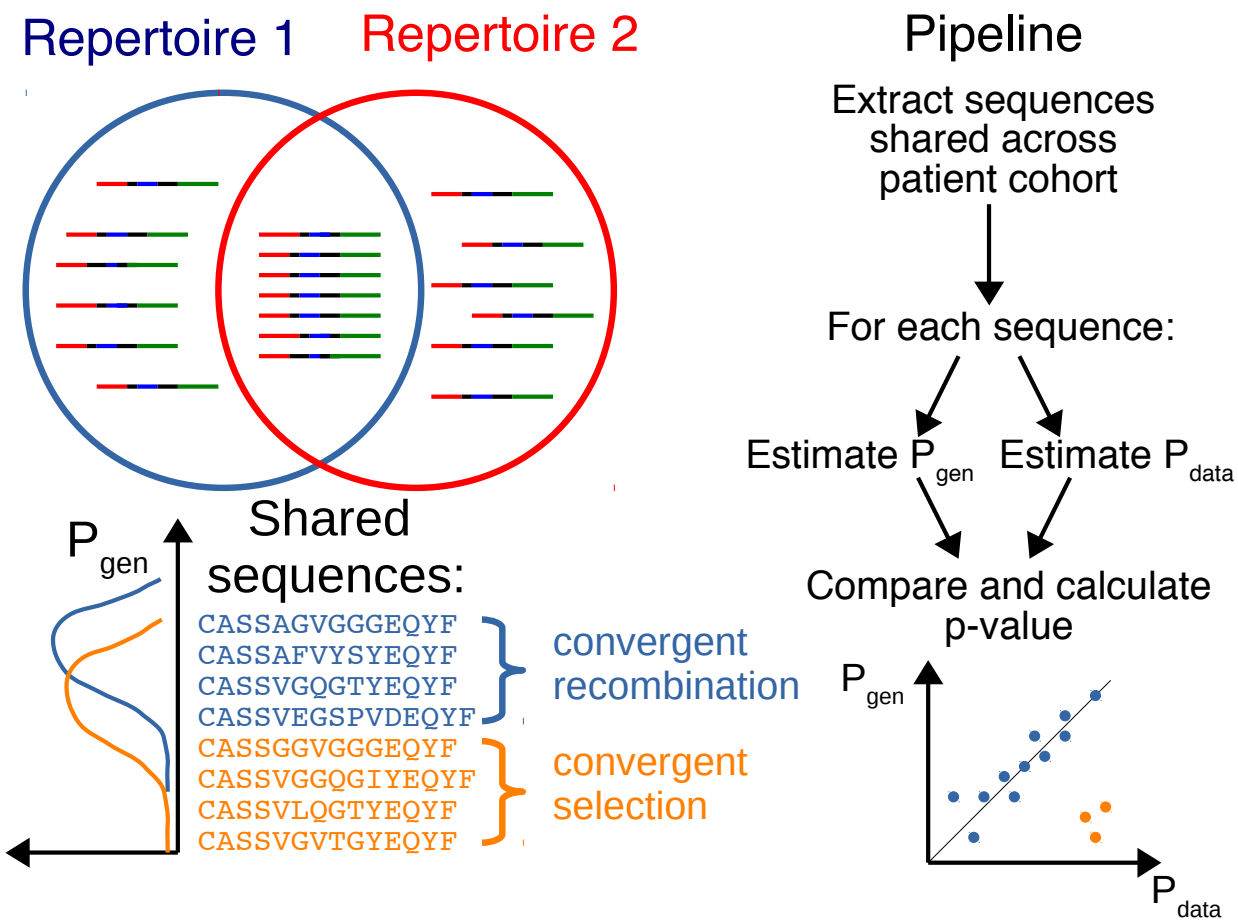
Howard R. Seay,[1] Erik Yusko,[2] Stephanie J. Rothweiler,[1] Lin Zhang,[1] Amanda L. Posgai,[1] Martha Campbell-Thompson,[1] Marissa Vignali,[2] Ryan O. Emerson,[2] John S. Kaddis,[3] Dave Ko,[3] Maki Nakayama,[4] Mia J. Smith,[5] John C. Cambier,[5] Alberto Pugliese,[6] Mark A. Atkinson,[1] Harlan S. Robins,[2,7] and Todd M. Brusko[1]

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 4, April 2017, pp 774–784
DOI 10.1002/art.40028

Discovery of T Cell Receptor β Motifs Specific to HLA–B27–Positive Ankylosing Spondylitis by Deep Repertoire Sequence Analysis

Malek Faham,[1] Victoria Carlton,[1] Martin Moorhead,[1] Jianbiao Zheng,[1] Mark Klinger,[1] Francois Pepin,[1] Thomas Asbury,[1] Marissa Vignali,[1] Ryan O. Emerson,[1] Harlan S. Robins,[2] James Ireland,[3] Emily Baechler-Gillespie,[4] and Robert D. Inman[5]

Condition specific TCRs



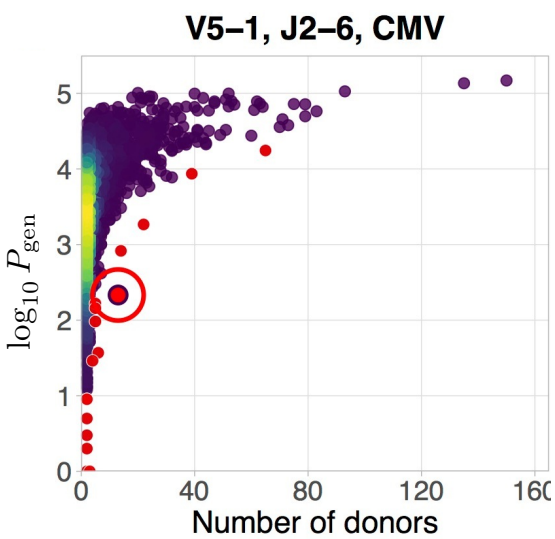
Condition specific TCRs

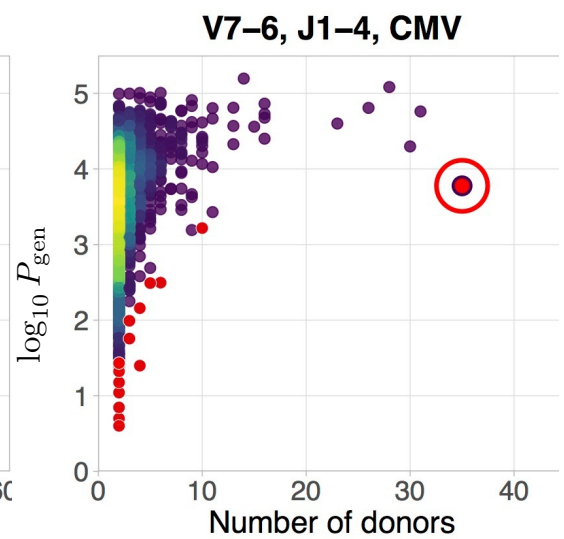
- clonotypes can be shared
  - for functional reasons (common antigen)
  - by chance (convergent recombination)

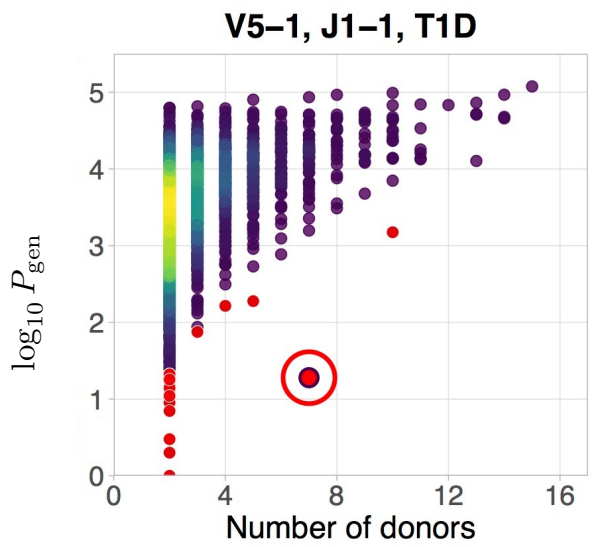
- large cohort association studies to find condition-specific TCRs

- can we tell the difference using the model?

- re-analysis ***without negative cohort***





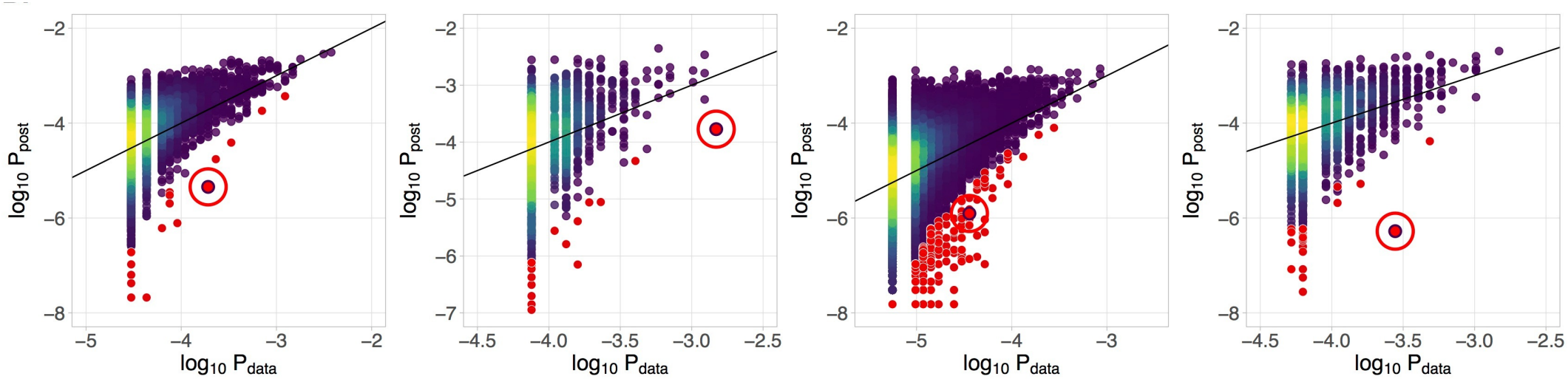


Emerson,…, Robins, Nat. Gen. 2017

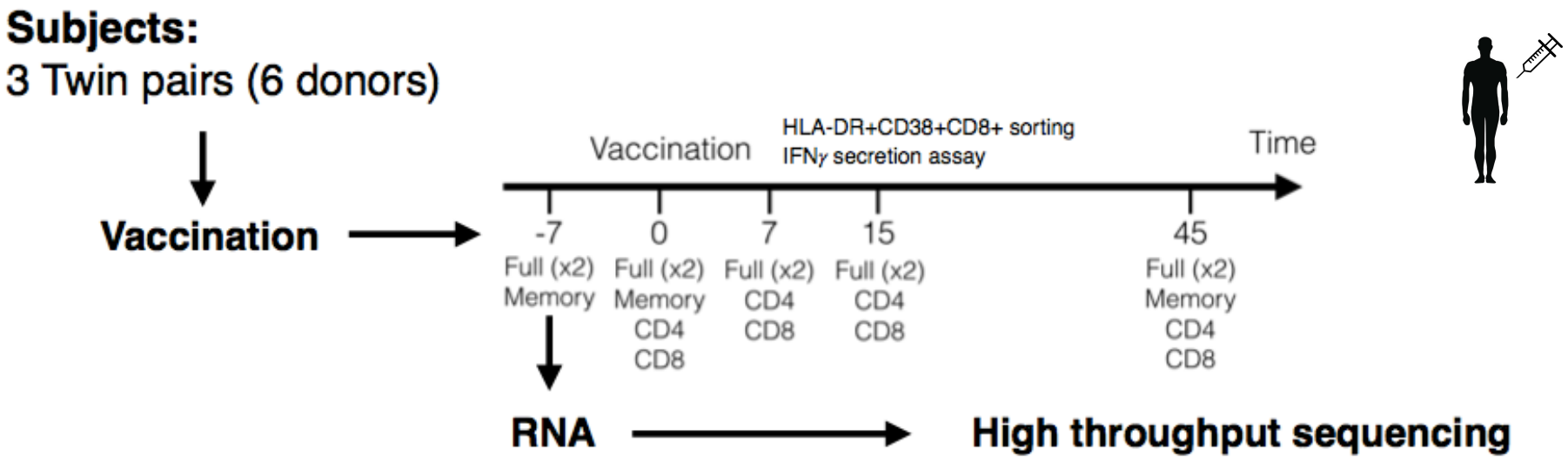
Seay ,…, Brusko, JCI Insight 2016

Condition specific TCRs

$$P_{\text{data}} \approx \frac{\text{number of donors with condition}}{\sum_{\text{donors}} \text{number of clonotypes}}$$



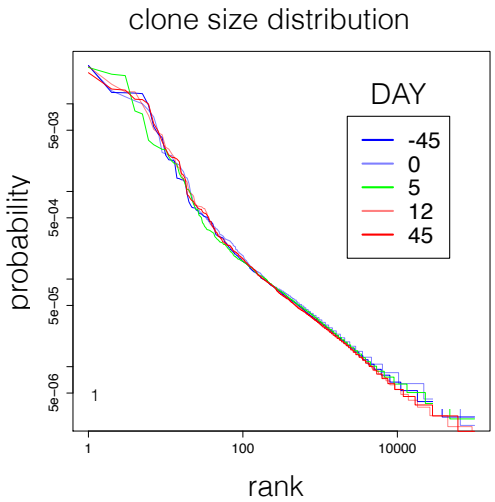
Vaccine response

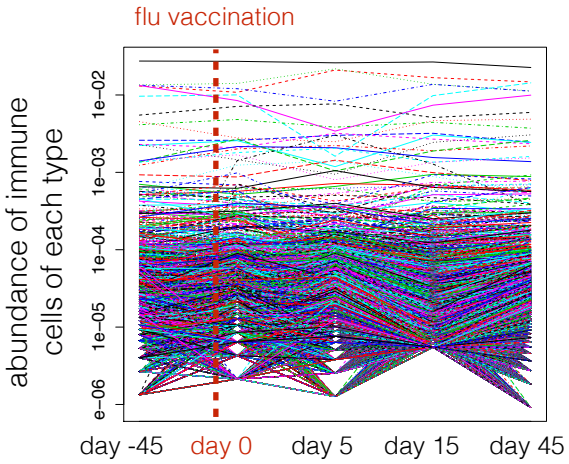


- flu vaccine
- yellow fever vaccine

Vaccine response

T-cell flu vaccine response:





→ characterize noise model

→ probabilistic inference of *response*

- experimental noise → calibrate noise model at same time point

Noise model

for each clone, (unknown) frequency *f*

number of cells $m \sim \mathrm{NegBinom}(fM, \beta(fM)^{\alpha})$ M cells total

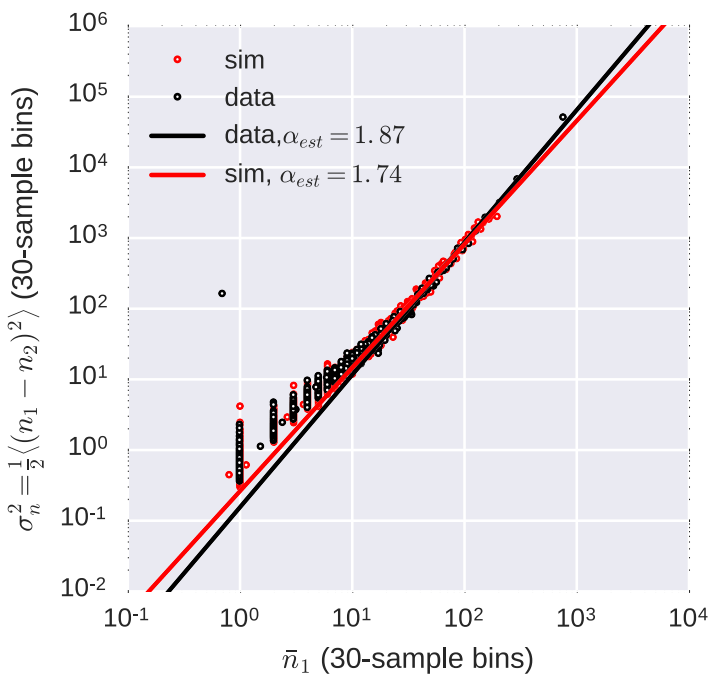
number of reads $n \sim \mathrm{Poisson}(rm)$ rM reads total

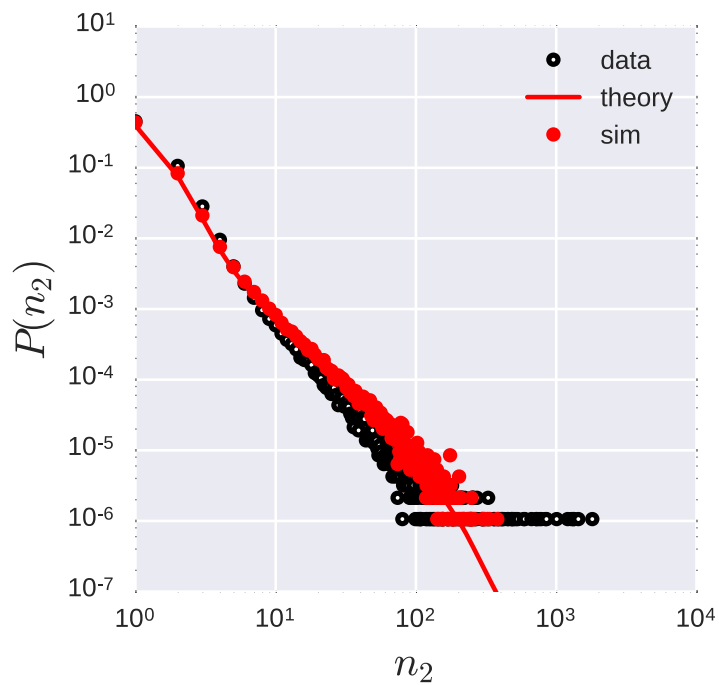
Likelihood

1st replicate ↓ 2nd replicate ↓ power law ↓

$$\mathcal{L}(\mathrm{data}) = \prod_{a=1}^{K} \int_0^1 df\, P(n_{1a}|f) P(n_{2a}|f) \rho(f)$$

$$P(n|f) = \sum_m P(n|m) P(m|f)$$





Expansion model

expansion by s

$$f_1 = f_2 \exp(s)$$

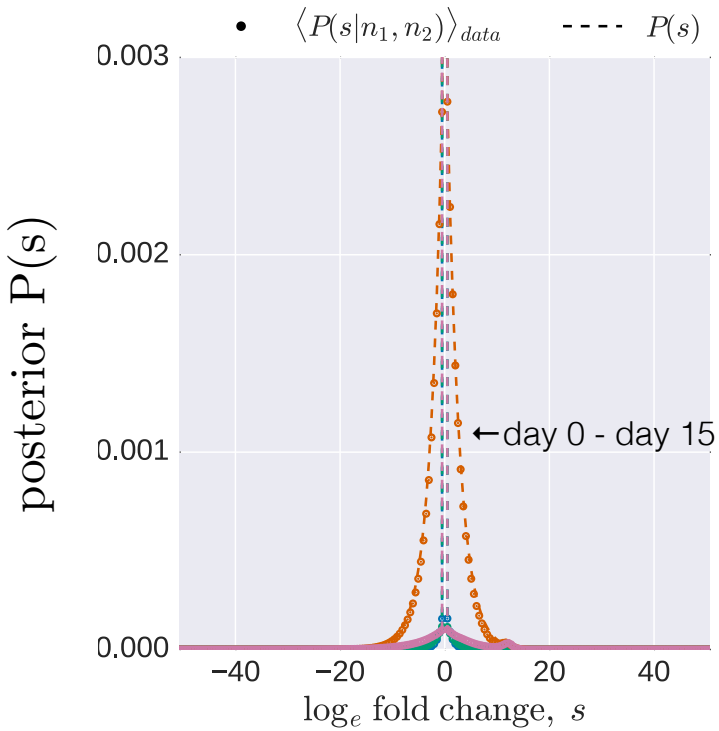
prior: a fraction α of clones expands by typical effect $\bar{s}$

$$P_{\text{prior}}(s) = (1-\alpha)\delta(s) + \frac{\alpha}{2\bar{s}} \exp(-|s|/\bar{s})$$

$$P(s|n_1, n_2) \propto \int_0^1 df\, P_{\text{prior}}(s) P(n_1, f) P(n_2|fe^s)$$

→ identify expanded clones

e.g. $P(s > 0|n_1, n_2) > 0.95$

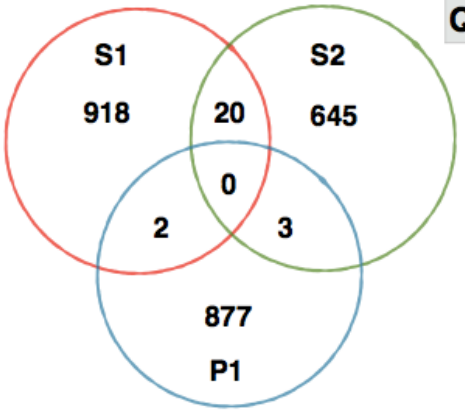


Yellow fever vaccine response

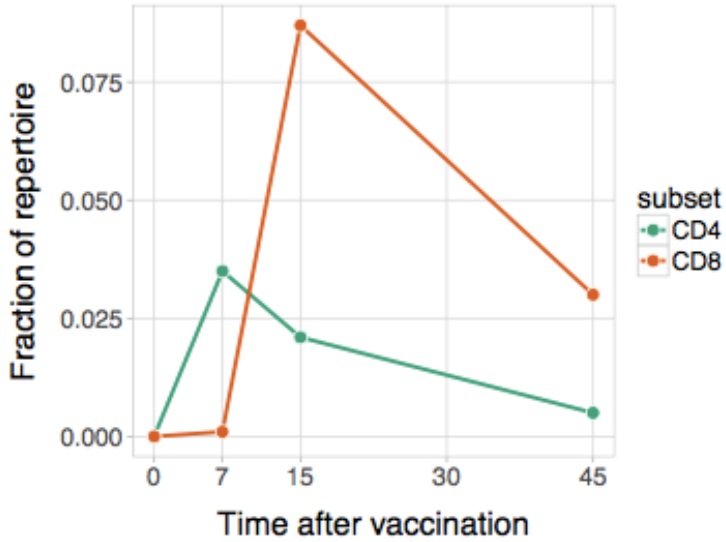
- identify expanding clonotypes above background

donor	-7	7	15	45
S1	2	42	940	409
S2	4	7	668	373
P1	18	63	882	112
P2	160	75	834	197
Q1	25	26	264	41
Q2	21	77	993	270

- twins share more expanded clonotypes

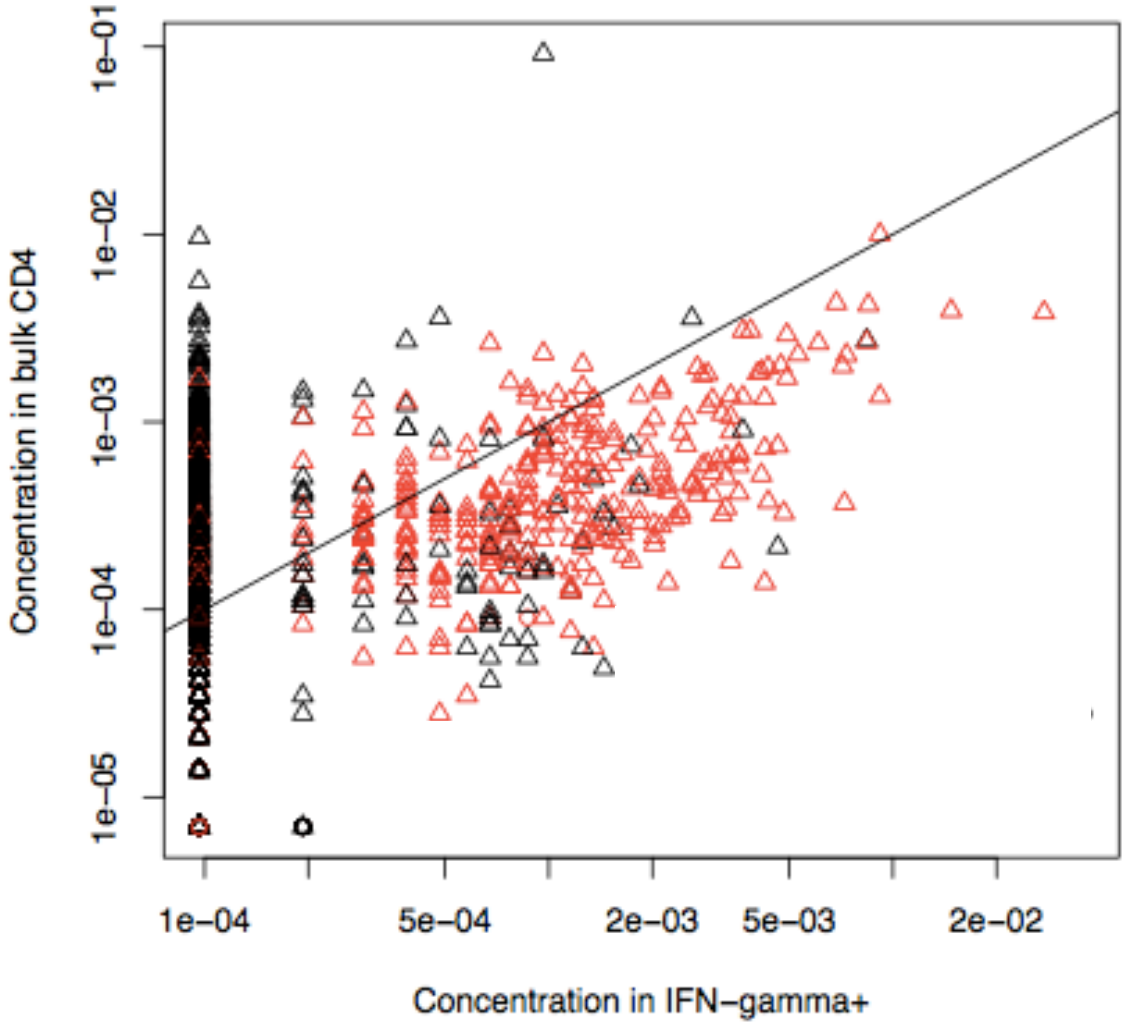


- large CD4 and CD8 expansion but different dynamics



Yellow fever vaccine response

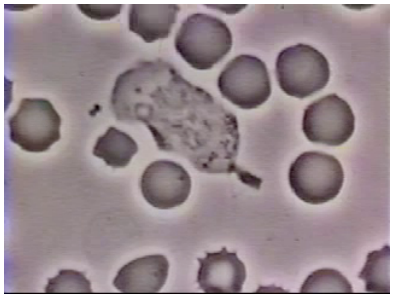
- validation with IFNγ secretion assay (CD4 stimulation)



Different immune strategies

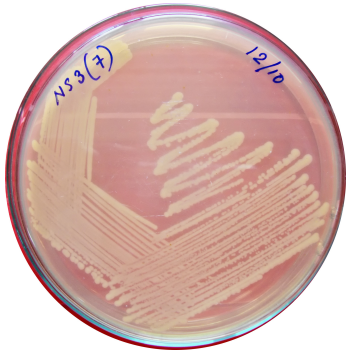
adaptive immunity

Other immune strategies



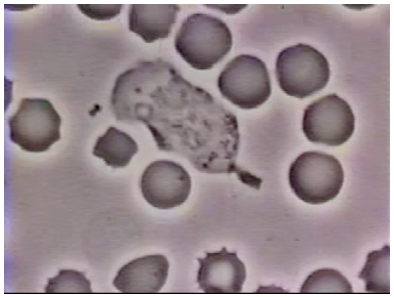
innate immunity

adaptive immunity



CRISPR immunity

Common strategic choices



innate immunity

adaptive immunity

randomly acquired

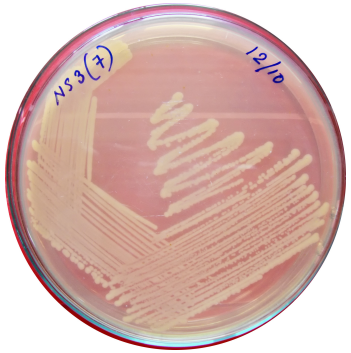
regulated

heritable

non-heritable

constitutive

actively acquired

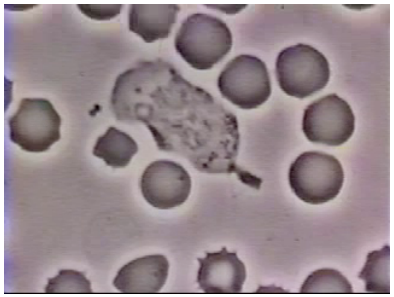


CRISPR immunity

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

Response during **organism** lifetime

Common strategic choices



randomly acquired

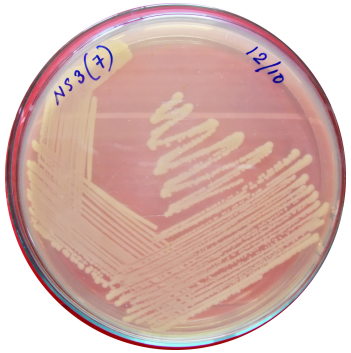
regulate

in

optimal immunity?

ty

constitutive



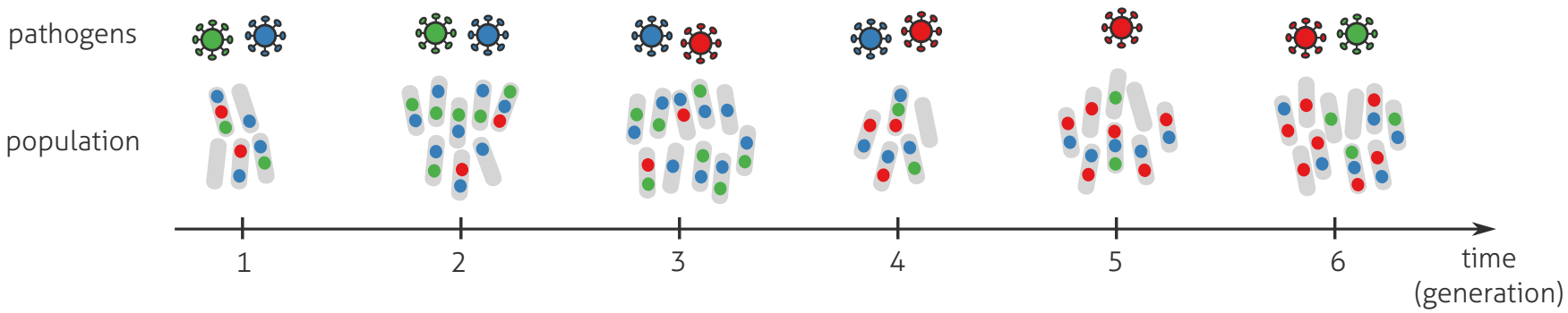
CRISPR immunity

actively acquired

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

Response during **organism** lifetime

Optimal immunity

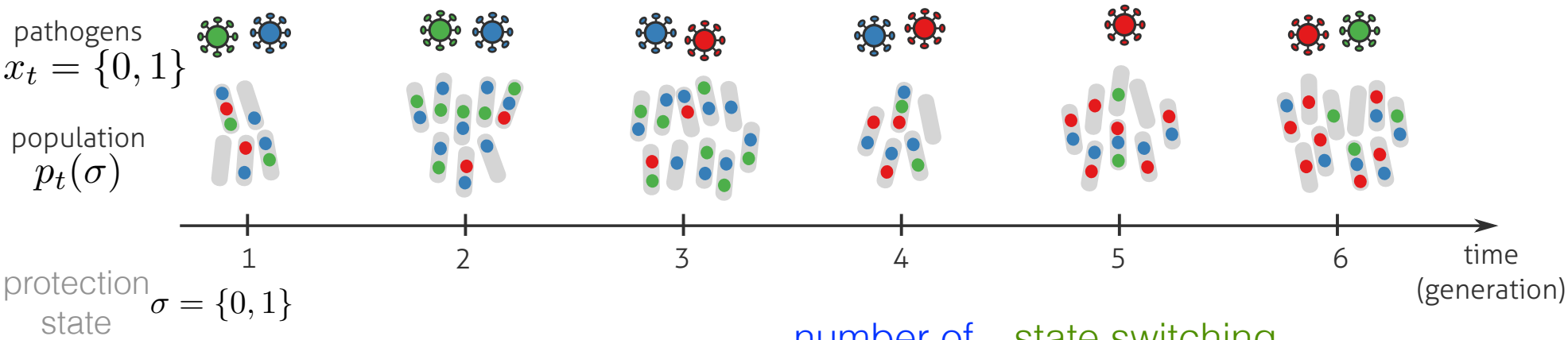


- match environment statistics
- ensure long term population growth

→ immunity as adaptation to pathogen statistics

- consider different strategies
- optimize long term population growth

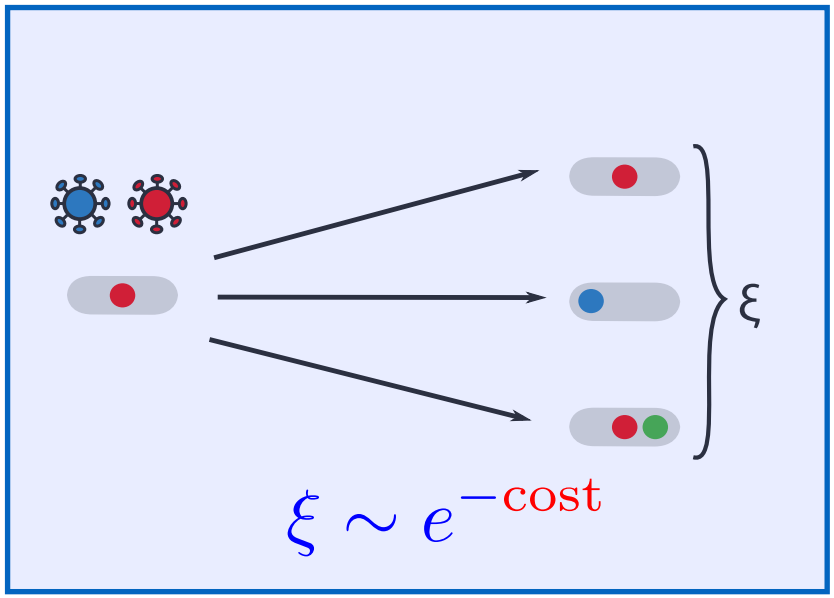
Population growth



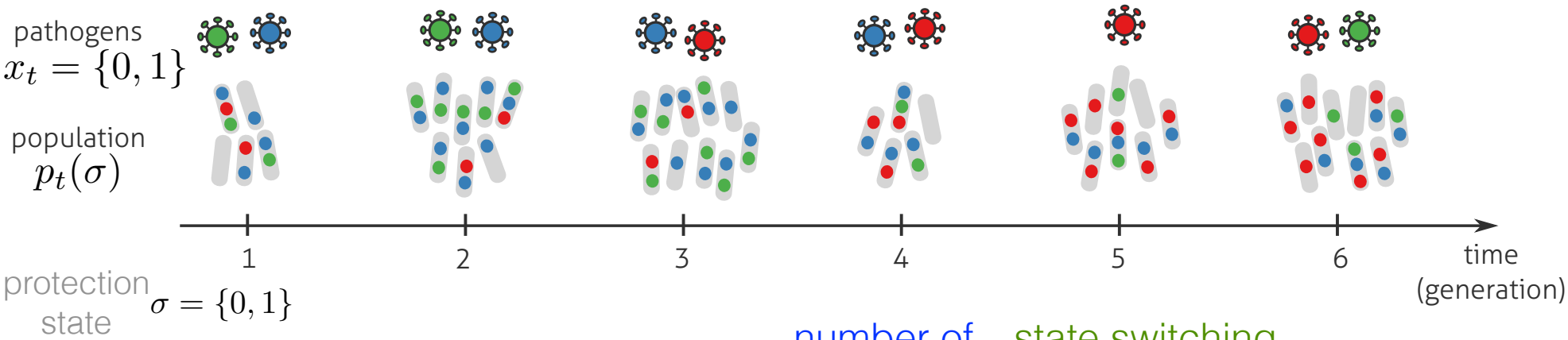
number of offspring

state switching probability

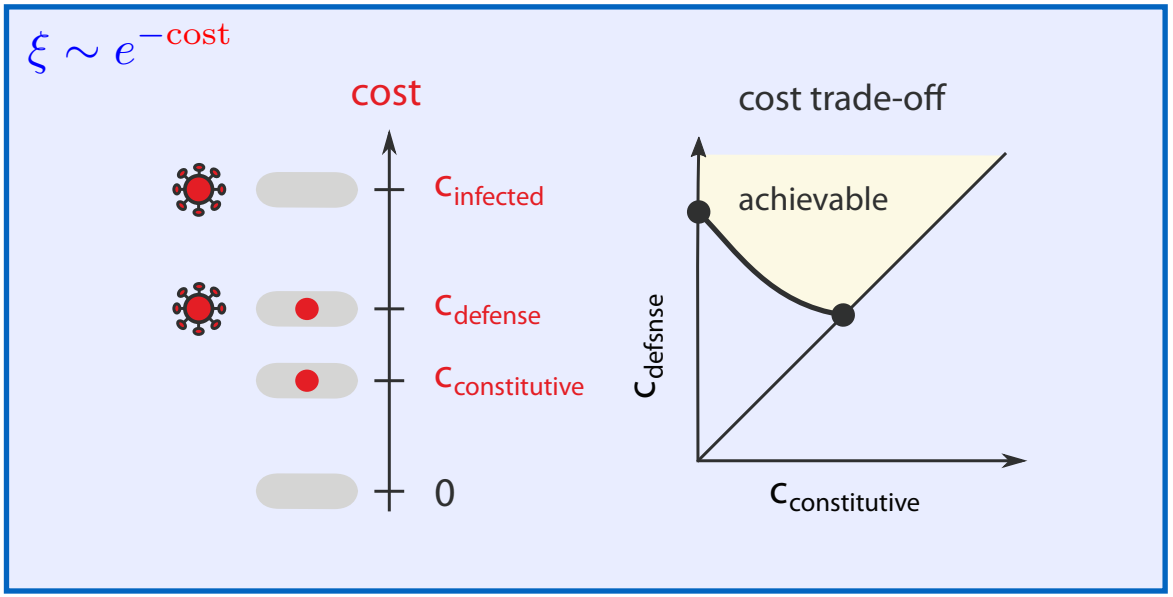
$$p_{t+1}(\sigma) = \frac{1}{Z_t} \sum_{\sigma'} \xi(\sigma', x_t)\, \pi(\sigma|\sigma', x_t)\, p_t(\sigma')$$

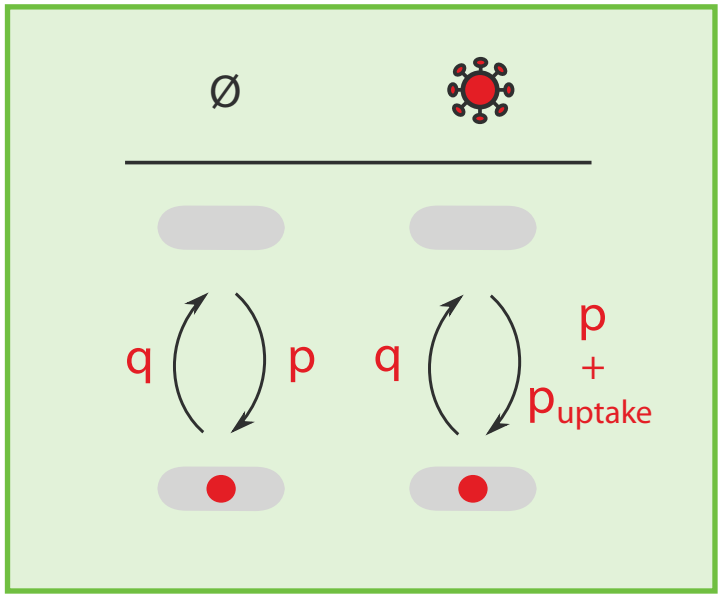


Population growth

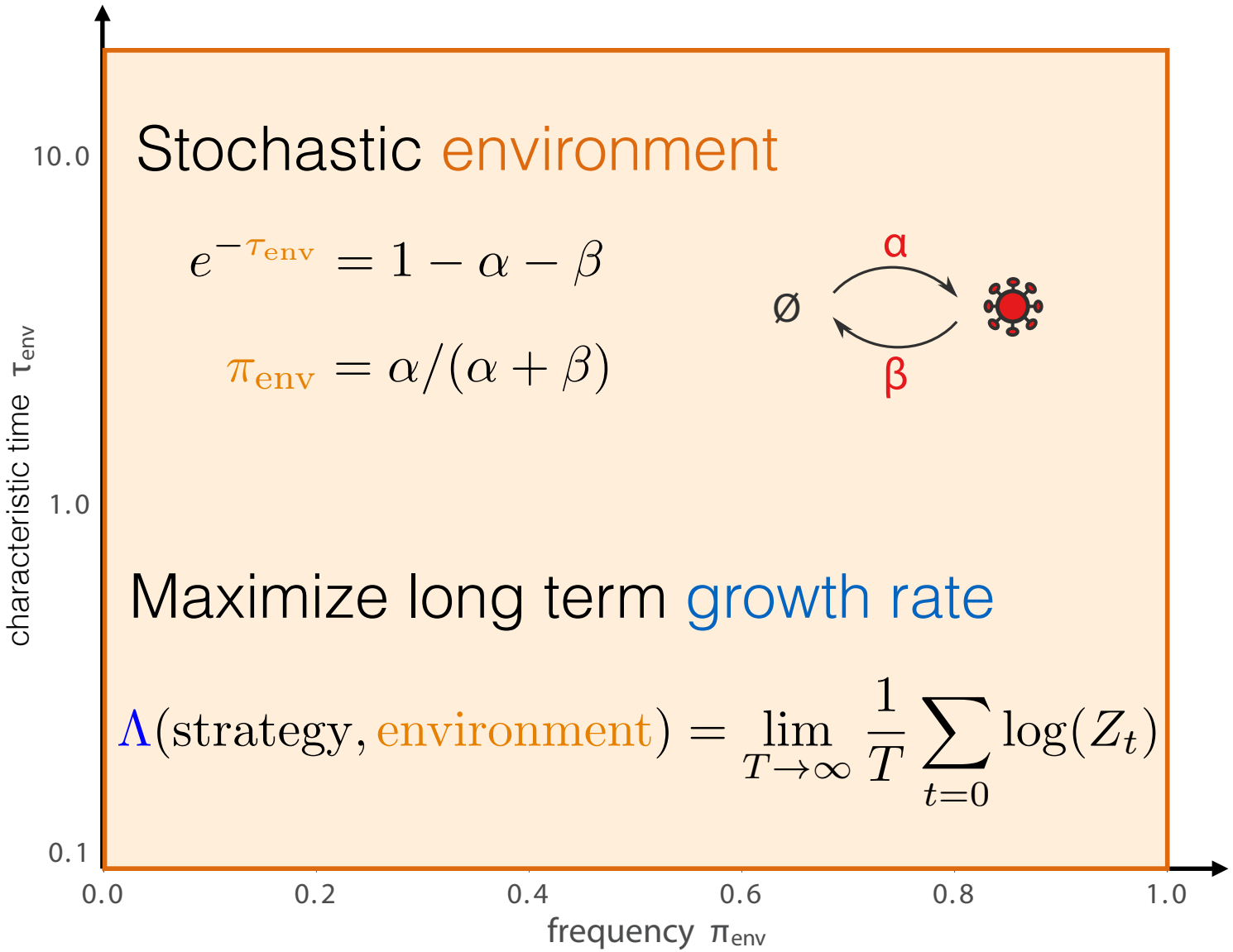


$$p_{t+1}(\sigma) = \frac{1}{Z_t} \sum_{\sigma'} \underbrace{\xi(\sigma', x_t)}_{\text{number of offspring}} \underbrace{\pi(\sigma|\sigma', x_t)}_{\text{state switching probability}} p_t(\sigma')$$





The environment



Stochastic environment

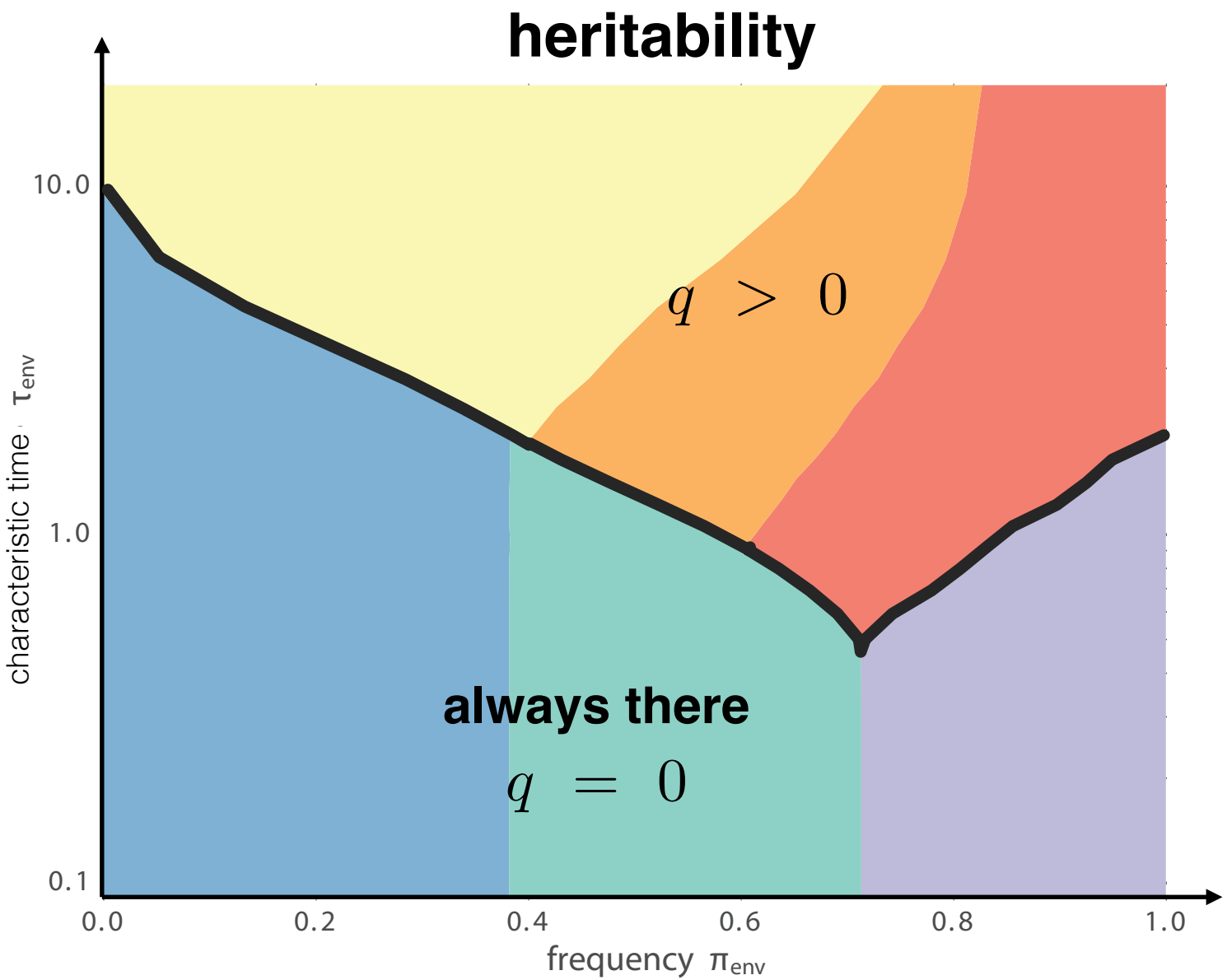
$$e^{-\tau_{\text{env}}} = 1 - \alpha - \beta$$

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

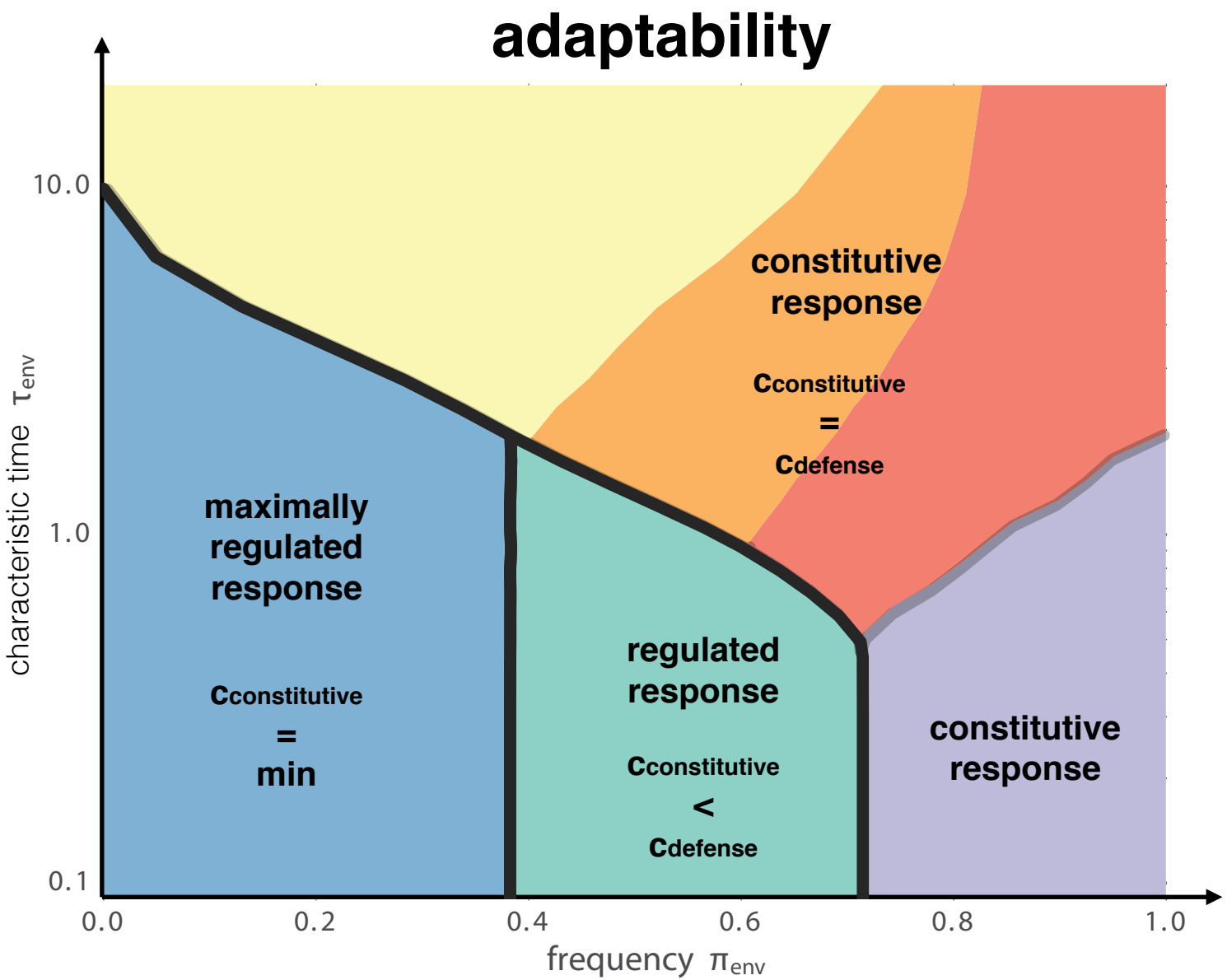
Maximize long term growth rate

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

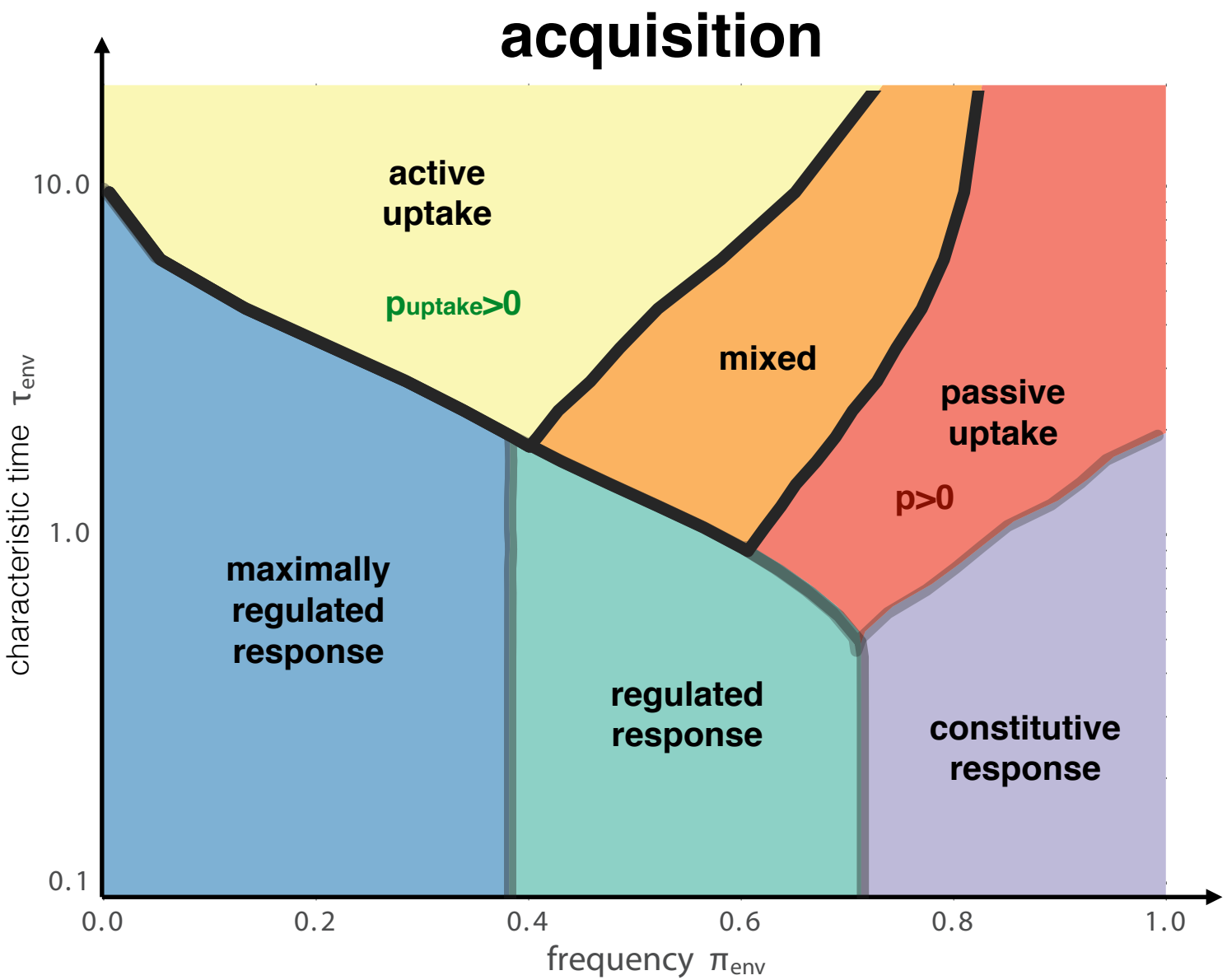
Optimal strategies



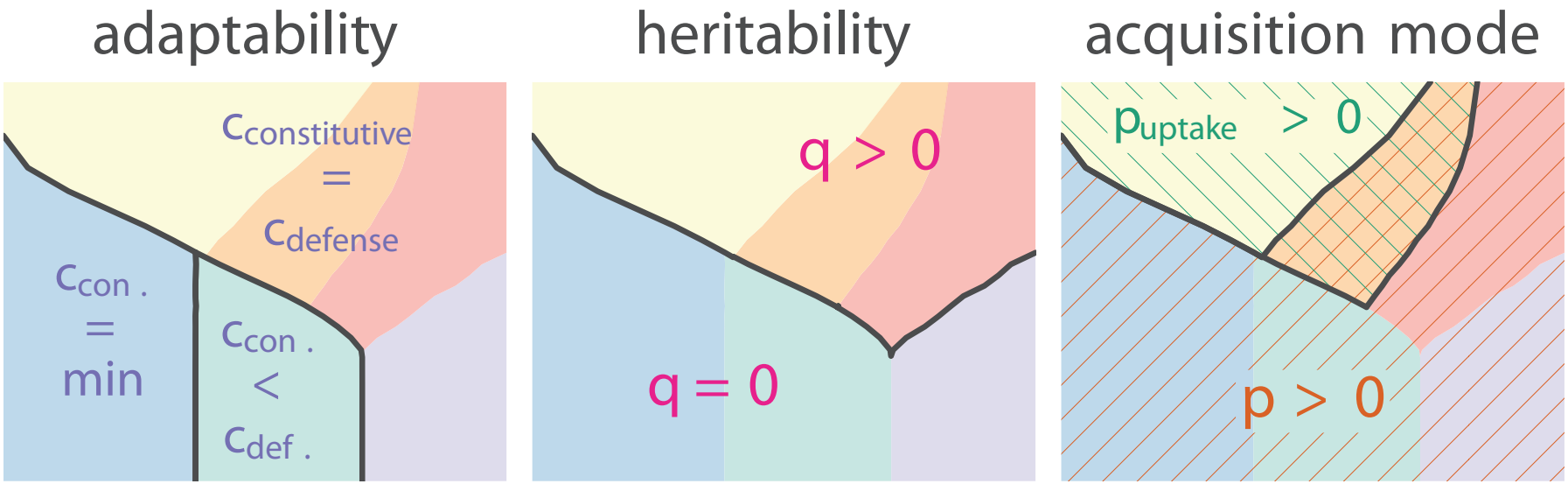
Optimal strategies



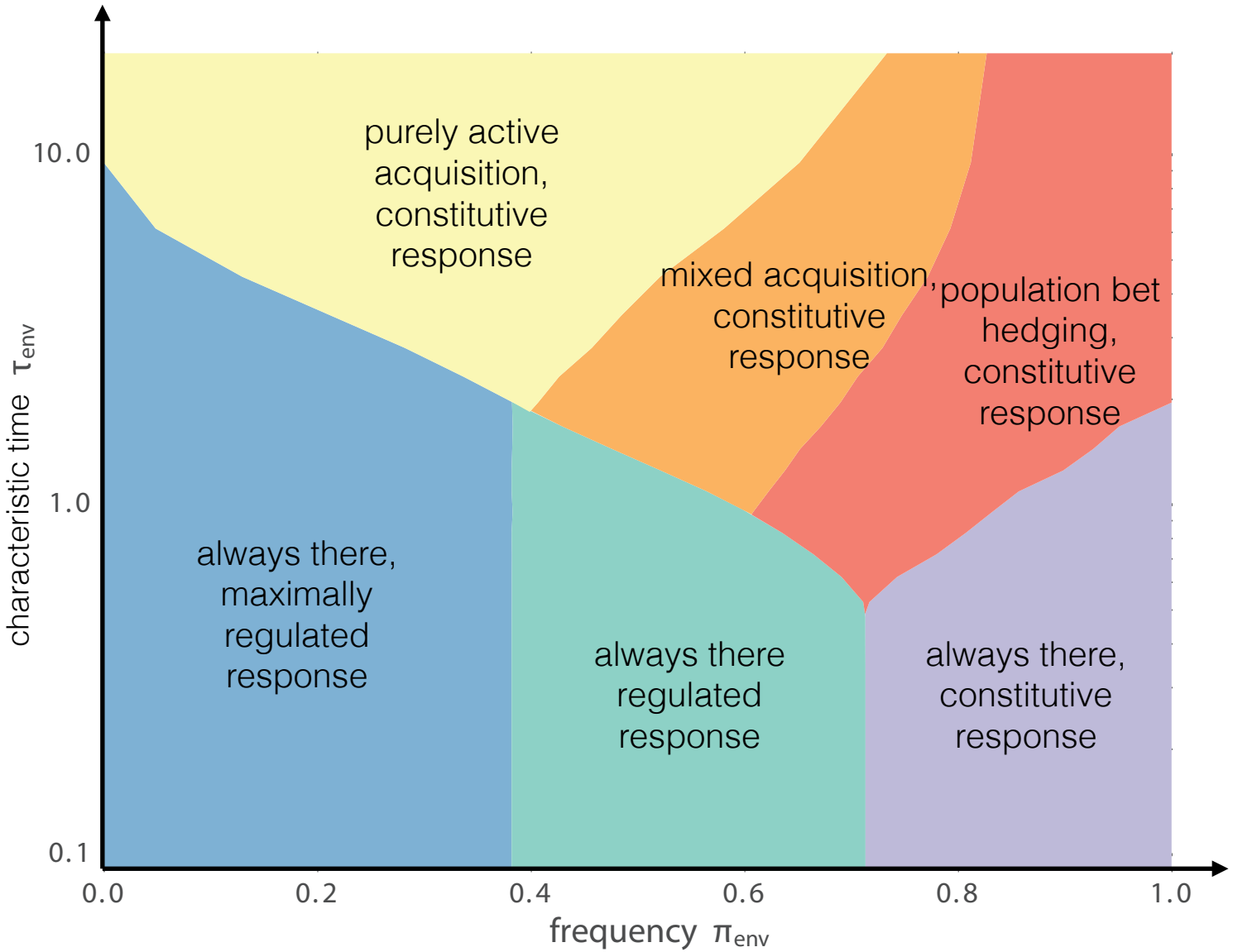
Optimal strategies



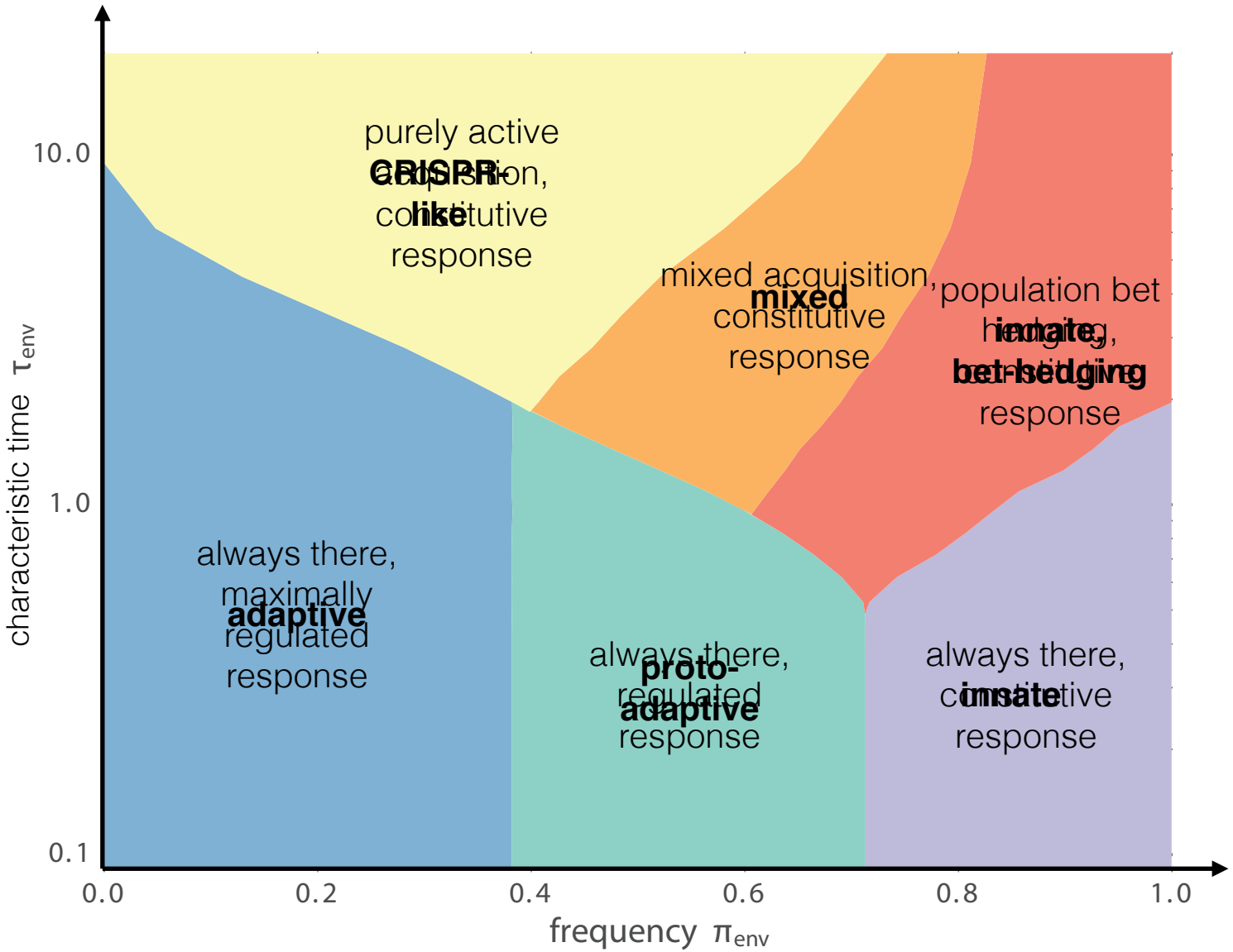
Three strategy axes



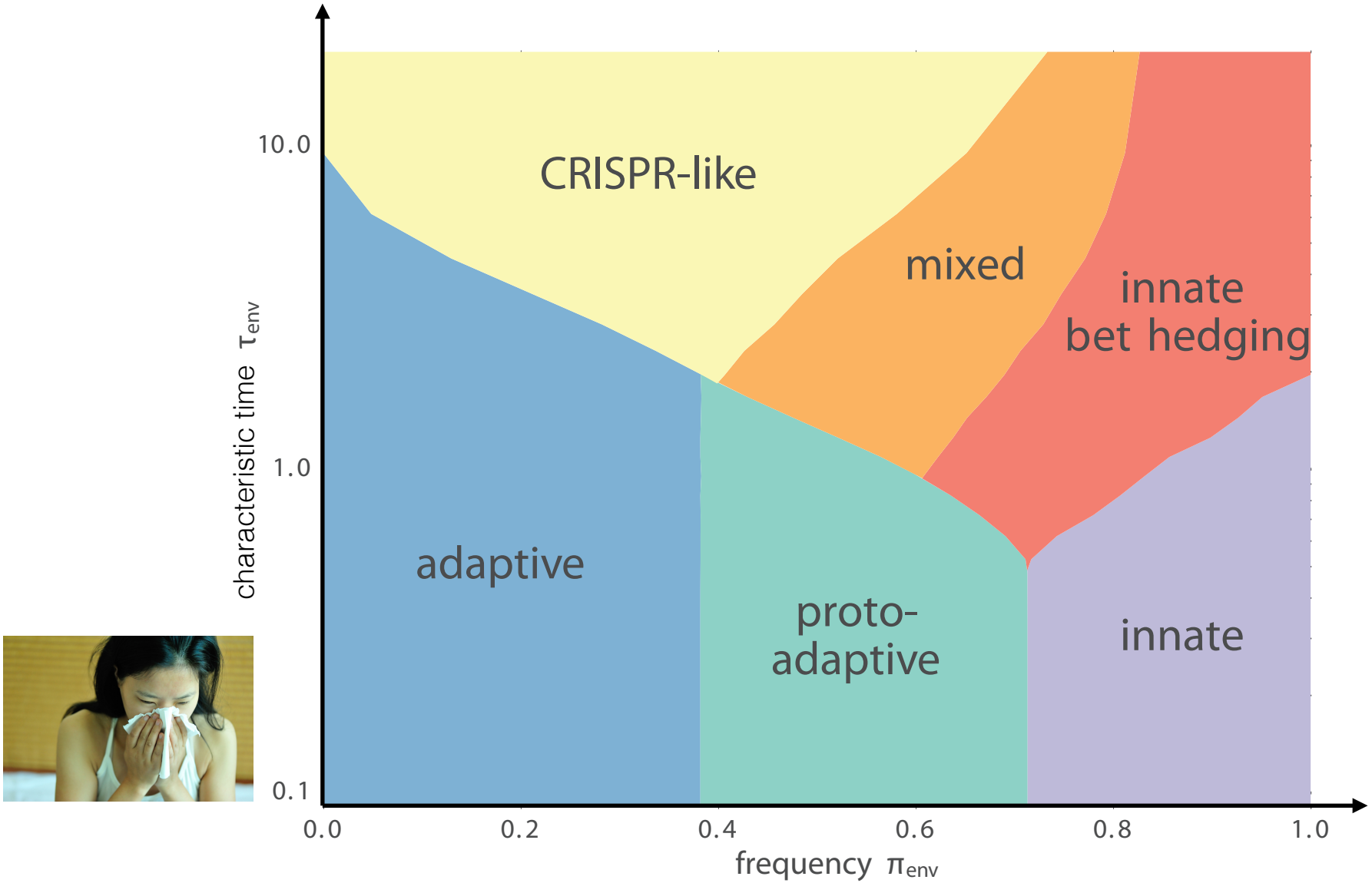
Optimal strategies



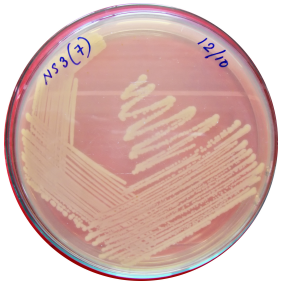
Optimal immune systems

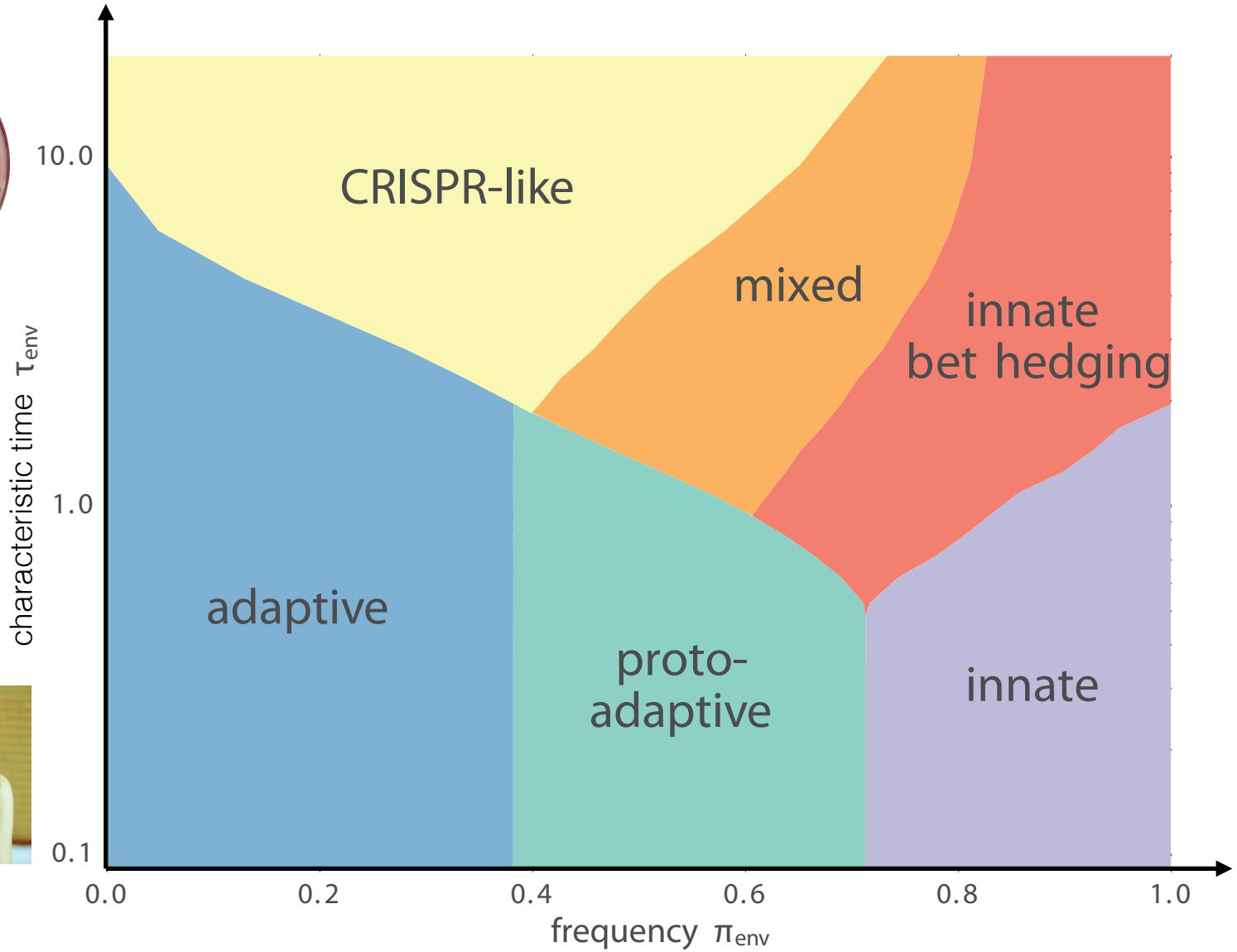


Optimal immune systems



Optimal immune systems





Conclusions

response:

- identify responding clonotypes
- observe selection on standing variation

optimal immunity:

- known immunity from evolutionary constraints
- depends on environment statistic

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