# Evolutionary selection between alternative modes of gene regulation

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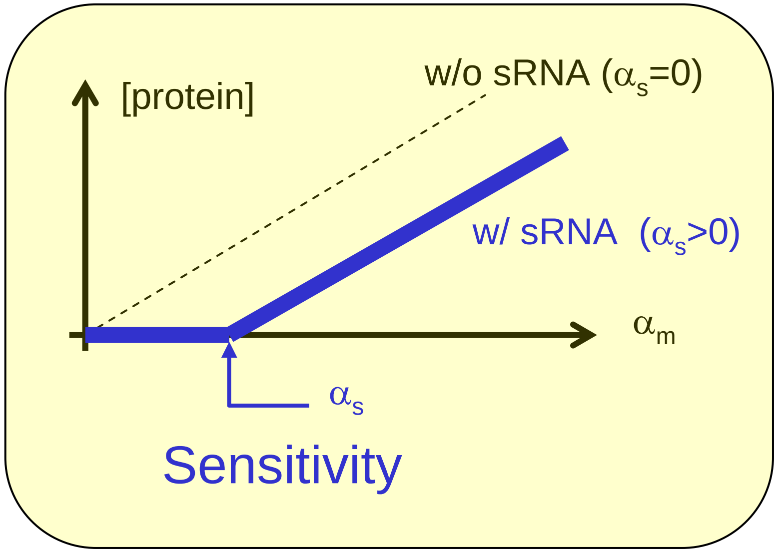
Fitness ~ Growth rate

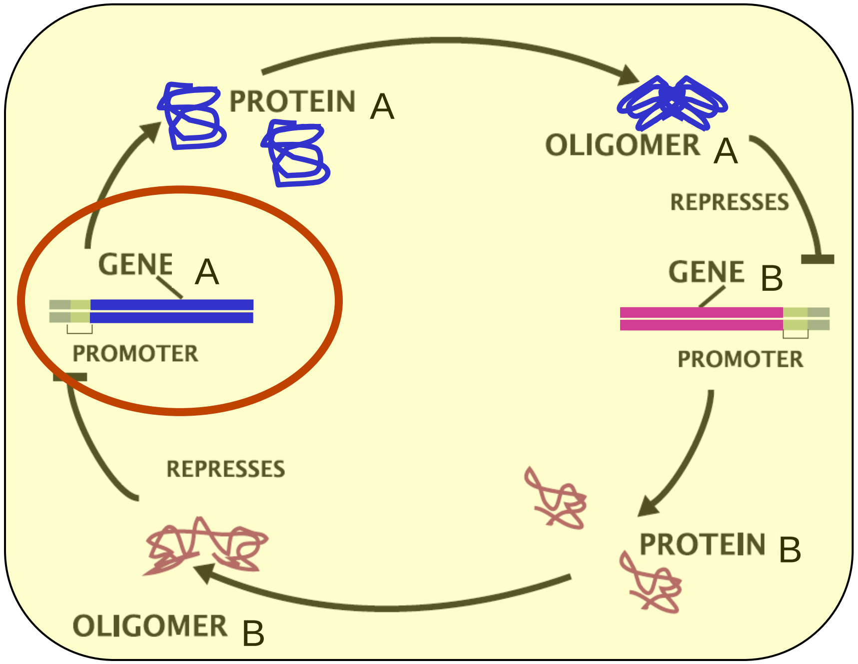
[ Cookies ]

# “Design principles“ of Regulatory Modules

Response function
of single node




Noisy dynamics of
linked nodes




All based on functional characteristics

# General Question

Given:
- 2 different designs
- perform (essentially) the same regulatory function

  (no fitness difference)

Choice is made by evolution …

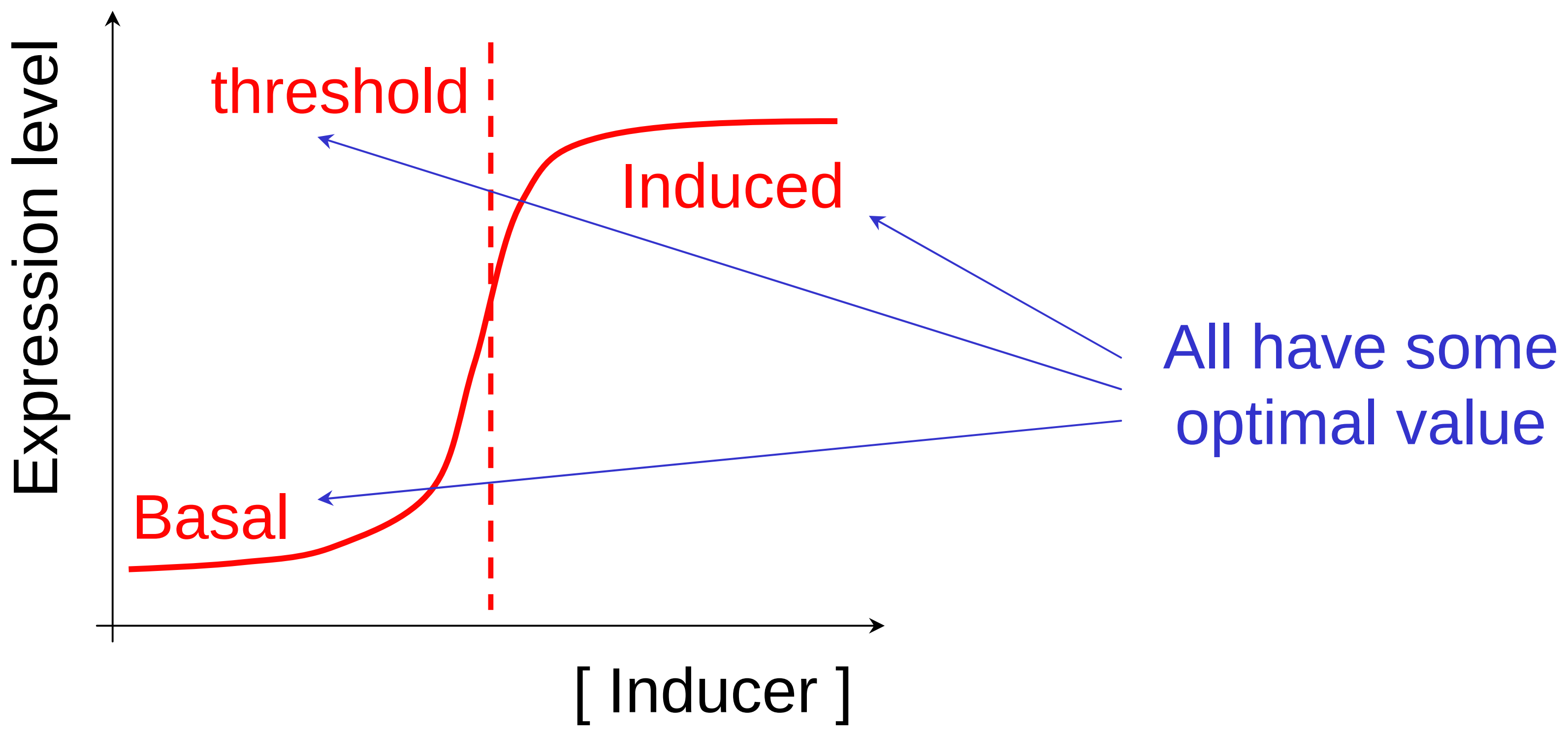
… at random?

… or is the choice biased?

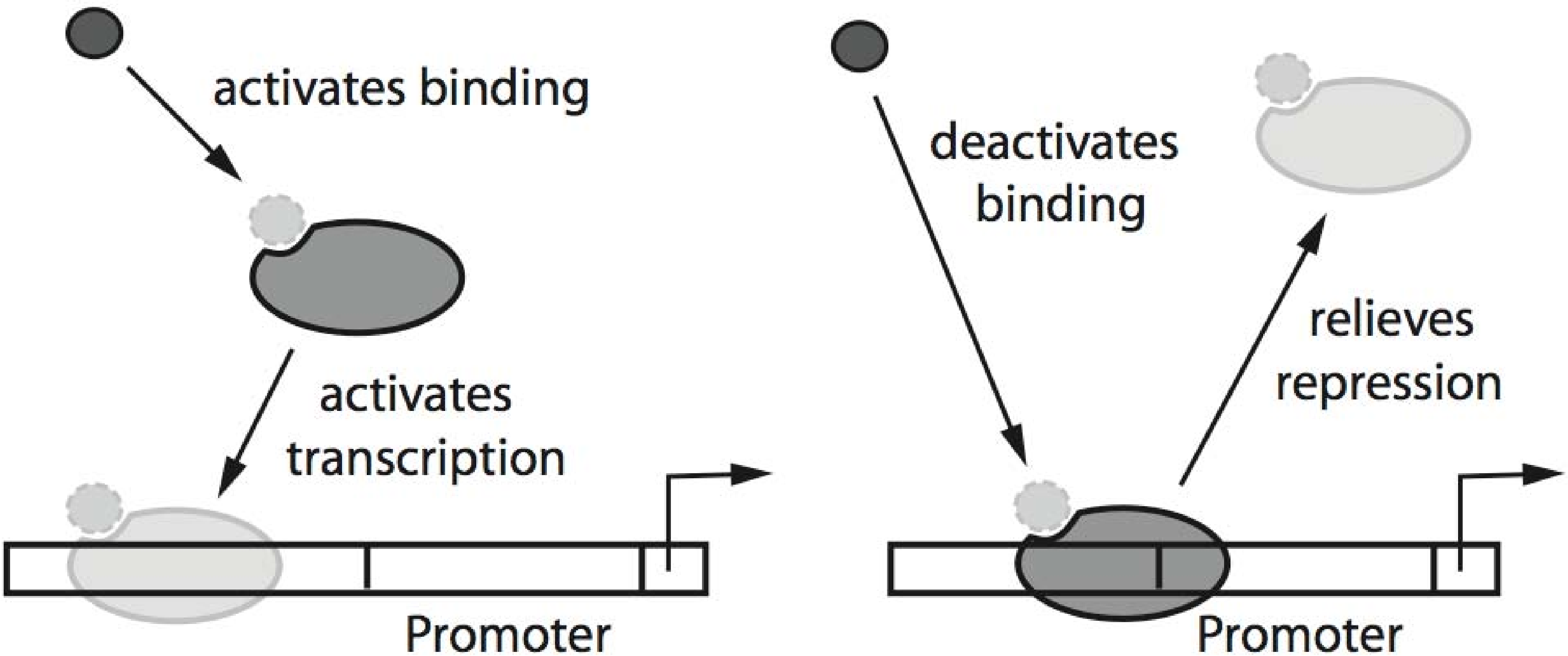
(→ population genetics problem)

# Case study: a simple genetic switch

Functional characteristic: Response function



# … can be obtained in two ways




“Double-positive control”

(e.g. arabinose)

“Double-negative control”

(e.g. lactose)

| System[a] | Nature of regulator: Observed[f] | Nature of regulator: Predicted | Demand for expression: Predicted | Demand for expression: Observed[f] |
|---|---|---|---|---|
| Inducible catabolic pathways | | | | |
| Arabinose | Activator | → | High | High |
| Galactose | Repressor | → | Low | Low |
| Glycerol | Repressor | → | Low | Low |
| Histidine | Repressor | → | Low | Low |
| Lactose | Repressor | → | Low | Low |
| Maltose | Activator | → | High | High |
| Rhamnose | Activator | → | High | High |
| Mannose | ? | Activator | ← | High |
| Tryptophan | ? | Activator | ← | High |
| Xylose | ? | Activator | ← | High |
| Repressible biosynthetic pathways | | | | |
| Arginine | Repressor | → | Low | Low |
| Cysteine | Activator | → | High | High |
| Isoleucine-valine[b] | Activator | → | High | High |
| Lysine | Repressor | → | Low | Low |
| Tryptophan | Repressor | → | Low | Low |
| Histidine | ? | Activator | ← | High |
| Isoleucine-valine | ? | Activator | ← | High |
| Inducible biosynthetic enzymes (within repressible biosynthetic pathways) | | | | |
| Isoleucine-valine | Activator | → | High | High |
| Tryptophan[c] | Repressor | → | Low | ? |
| Inducible drug resistance | | | | |
| Penicillin[d,e] | Repressor | → | Low | Low |
| Tetracycline | Repressor | → | Low | Low |
| Chloramphenicol[d] | ? | Repressor | ← | Low |
| Erythromycin[d] | ? | Repressor | ← | Low |
| Inducible prophages | | | | |
| λ | Repressor | → | Low | Low |
| P1 | Repressor | → | Low | Low |
| P2 | Repressor | → | Low | Low |
| P22 | Repressor | → | Low | Low |

# Empirical study

[ M. Savageau, PNAS (1977) ]

| Demand for gene product | Regulation |
|---|---|
| High (i.e. often) | Activator |
| Low (i.e. rarely) | Repressor |

Savageau suggests:

"Use-it-or-lose-it principle"

# Literature

Savageau, Genetics (1998)   “Demand theory”

- deterministic evolutionary analysis
  (different question)

Shinar, Dekel, Tlusty & Alon, *PNAS* (2006)

- hypothesize on a functional difference between
  the two modes of regulation
- if functional difference depends on demand
  $\rightarrow$ selection between the two modes

# Evolutionary design principle?

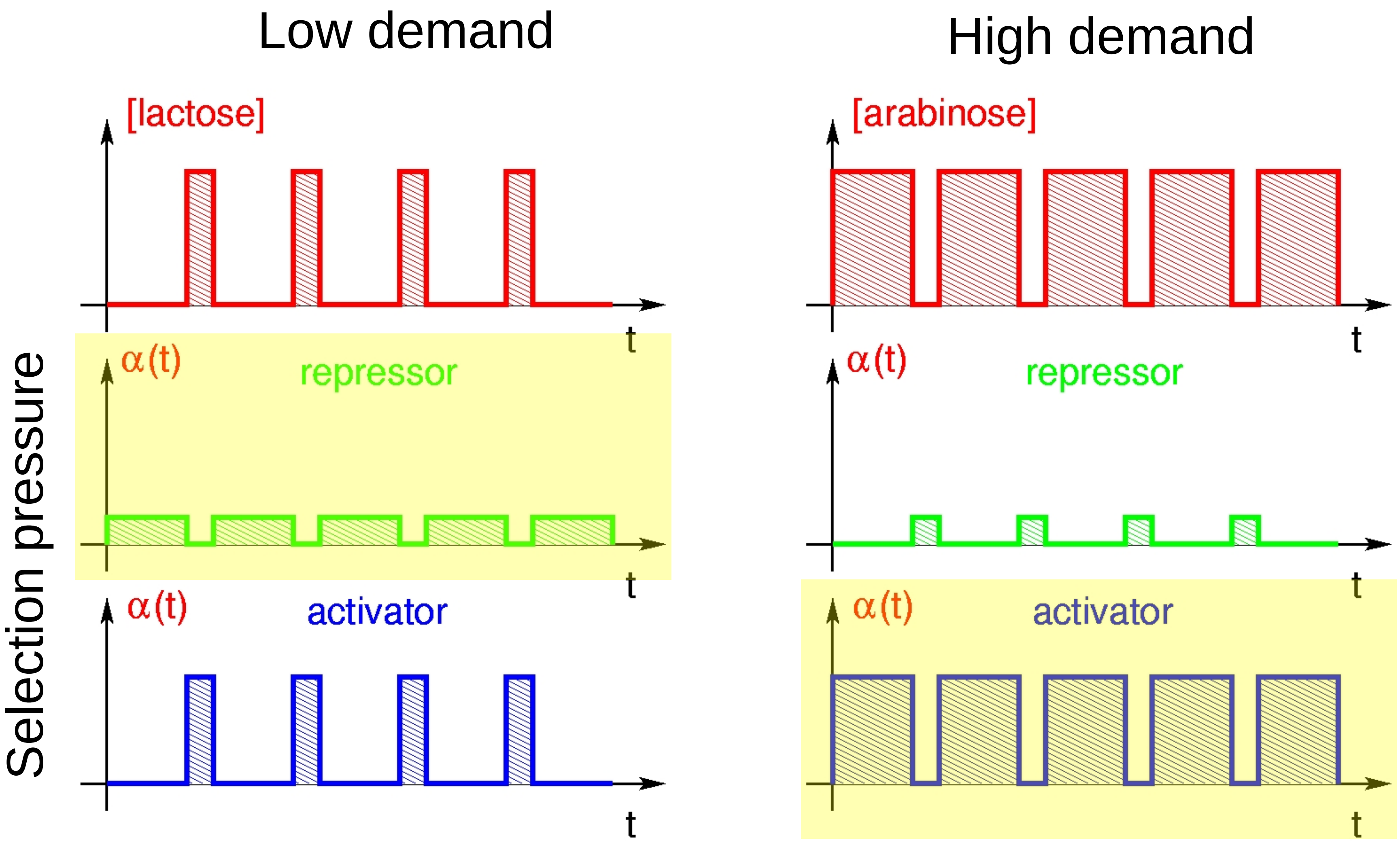
## Evolvability

- appears not to be a problem, both modes of gene regulation are ubiquitous

## Average growth rate of the population

- deleterious mutations reduce growth rate (a.k.a. mutational load)

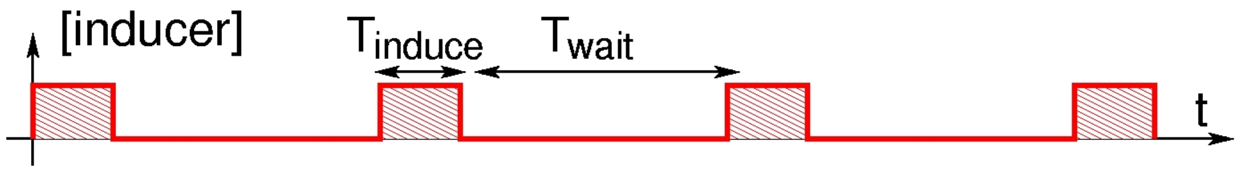
# Fluctuating environment - Time-dep. selection




Use-it-or-lose-it principle

# Evolution Model

Periodic selection pressure: $T = T_{induce} + T_{wait}$

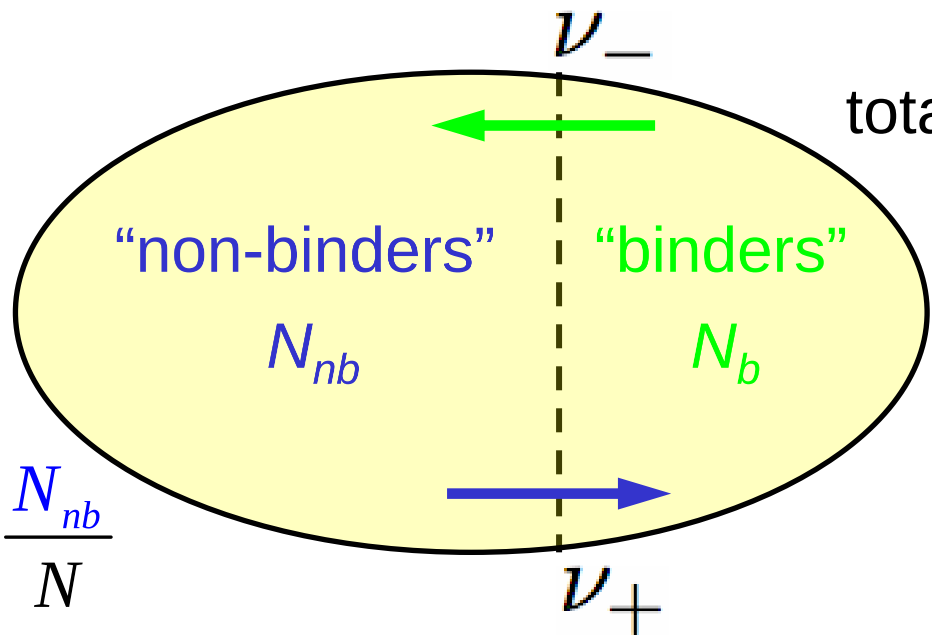



Demand:

$$\frac{T_{\text{induce}}}{T}$$

Population:

(mutation in operator or TF coding region)




total size $N$

(Functional TF-DNA interact.)

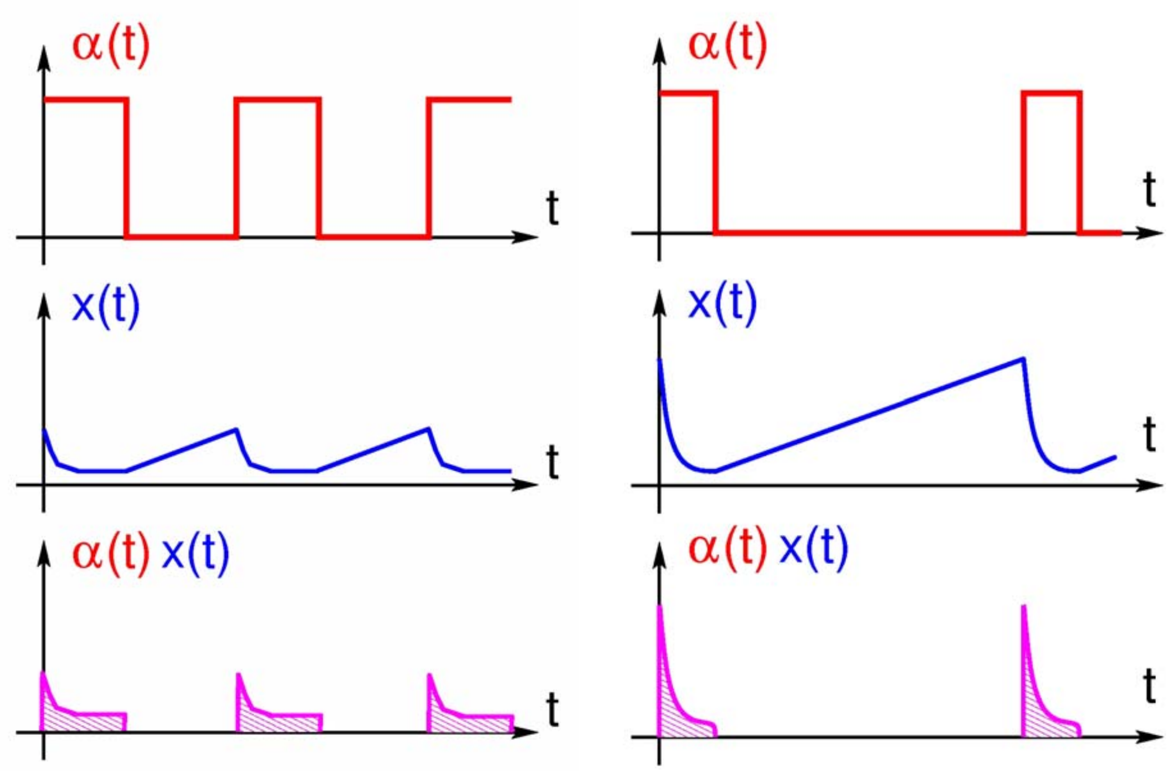
$$x(t) = \frac{N_{nb}}{N}$$

Time-evolution?

# Mutation-selection dynamics

Evolution equation: $$\frac{d}{dt}x = \nu_- - [\alpha(t) + \nu_- + \nu_+]\, x + \alpha(t)\, x^2$$

Instantaneous reduction of growth rate: $$\gamma = -\alpha(t) \cdot x(t)$$



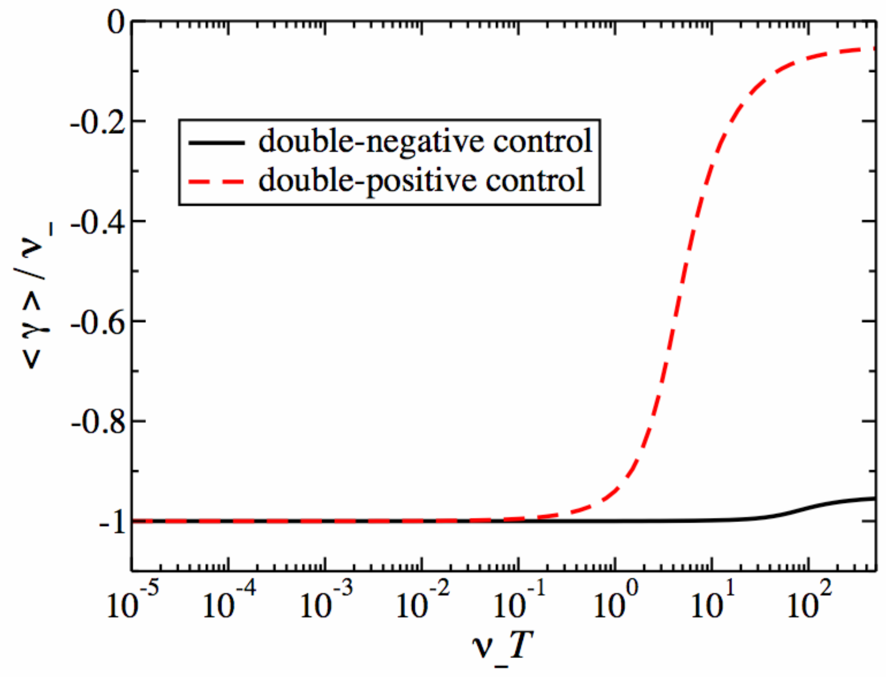

Time-averaged reduction:

$$\bar{\gamma} = -\nu_-$$

(independent of demand)

# Correction: $\bar{\gamma} = -\nu_- + \frac{(\nu_- T_{wait})(\nu_+ T_{wait})}{2T}$ + h. o.

Low demand:




So far:

~~Use-it-or-lose-it principle~~

"Wear and tear" principle

# Real life experience

# Real life experience

Work

Leisure

# Real life experience

Work

Leisure

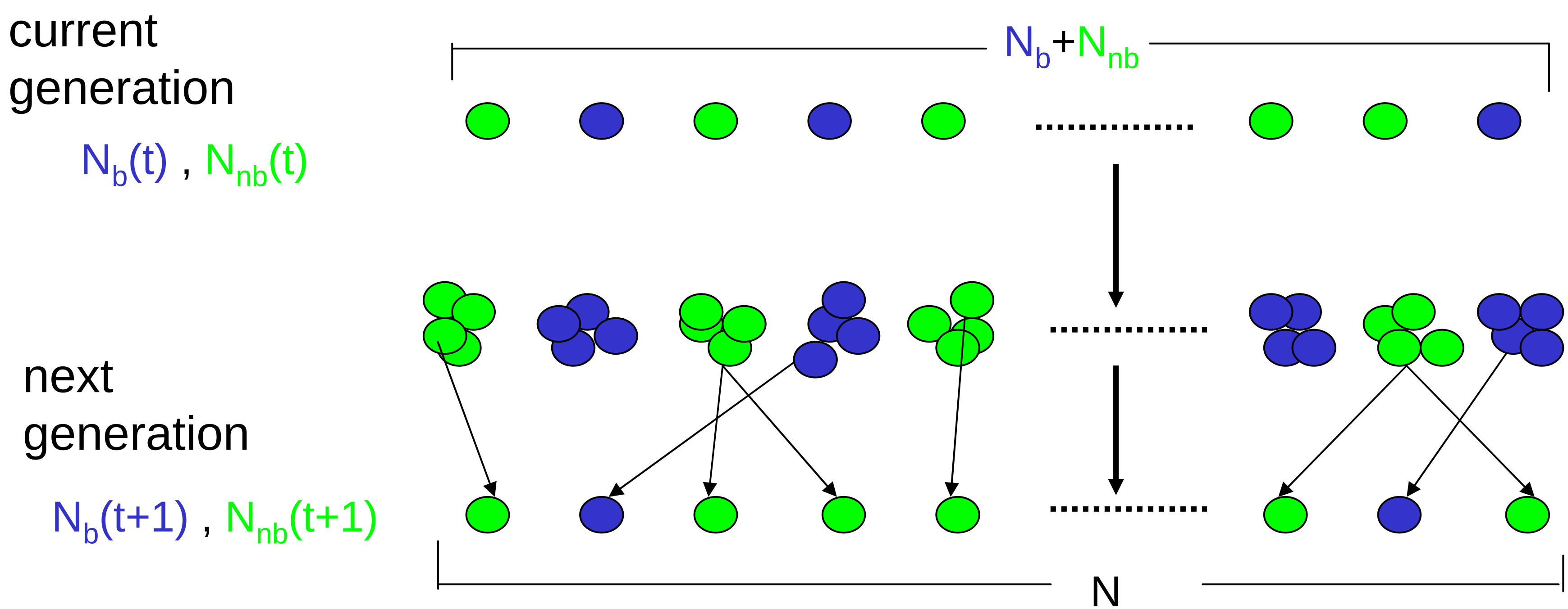

# Real life experience

Work

Leisure

# Finite Population: Fluctuation effects

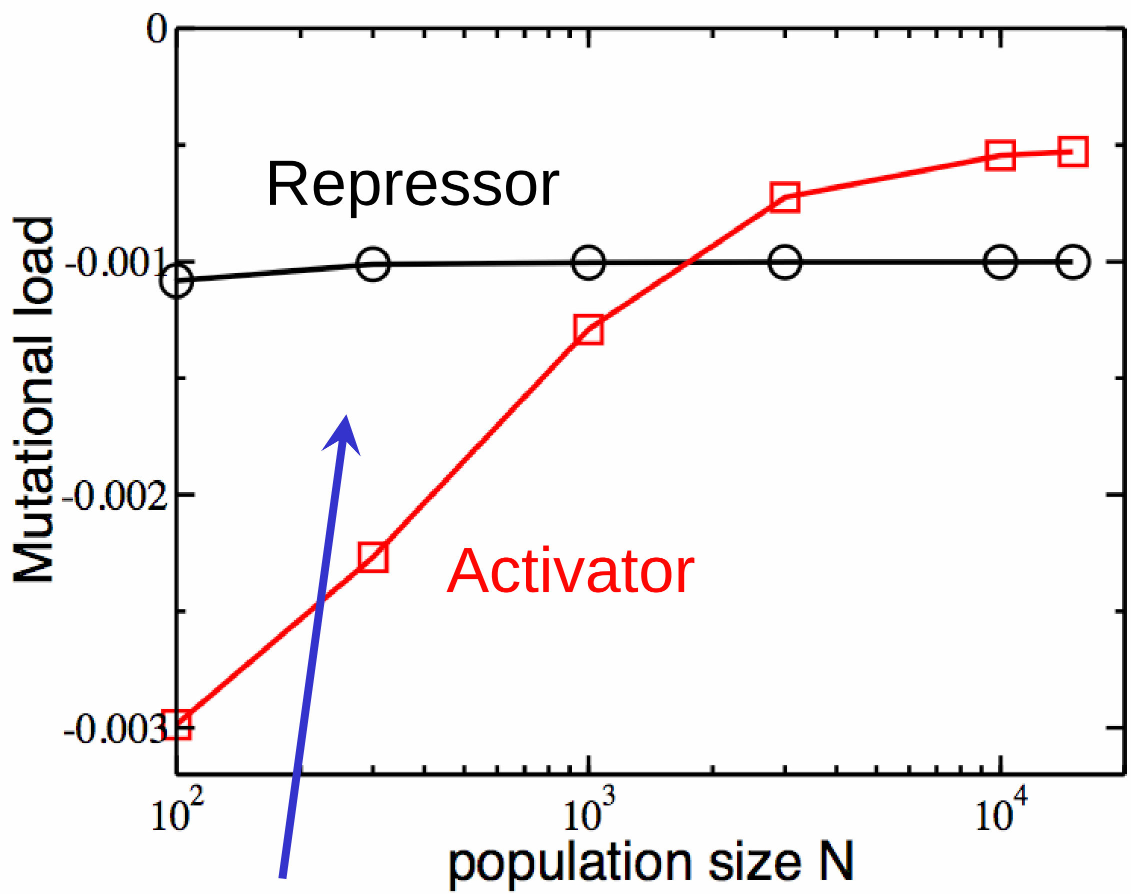
Wright Fisher model:




Genetic drift $$P(x',t+1\,|\,x,t)=\binom{N}{N\cdot x'}x^{N\cdot x'}(1-x)^{N(1-x')}$$

$N_b(t)$ changes without mutation or selection (sampling effect) !

# Dependence on population size



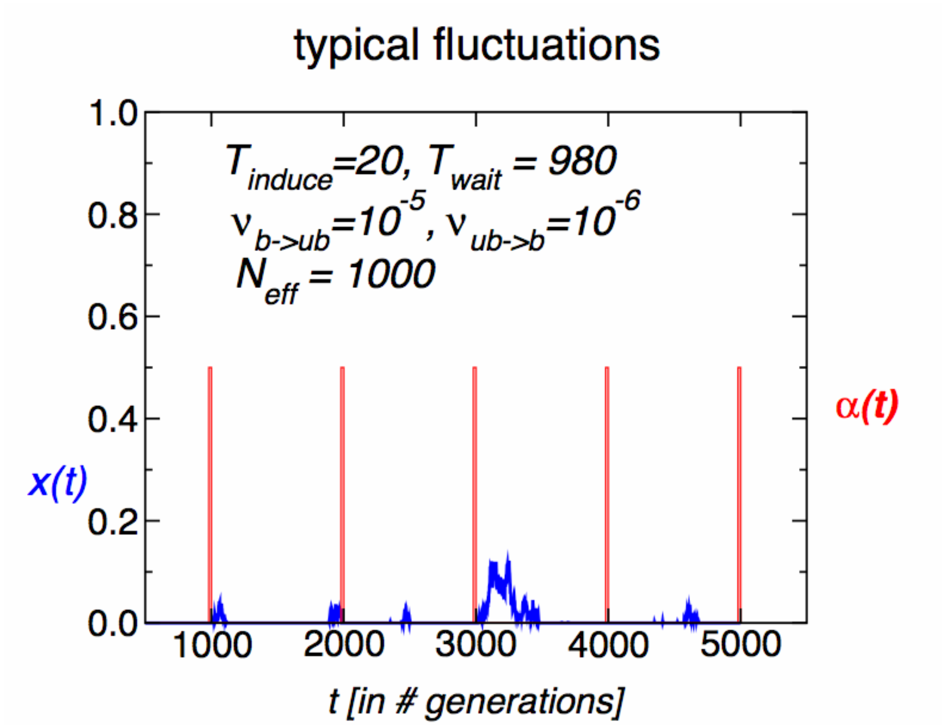

$$T_{induce} = 100$$
$$T_{wait} = 5000$$

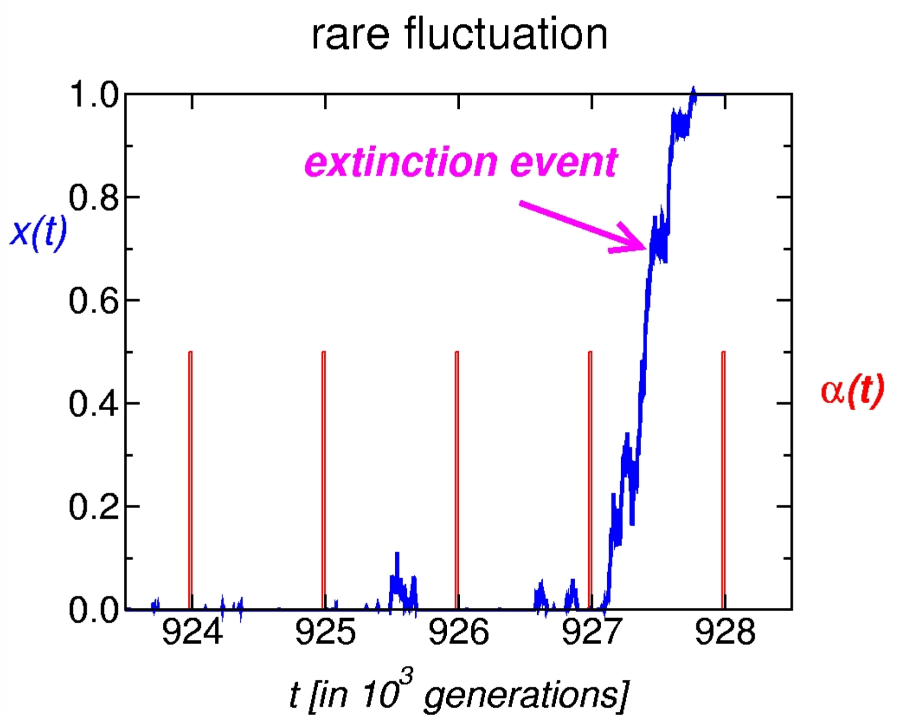
$$\nu_- = 10^{-3}$$
$$\nu_+ = 10^{-4}$$
$$s = 0.2$$

Use-it-or-lose-it principle

(for small populations)

# What is the new effect caused by genetic drift ?




How rare are these events ?

# "Extinction" probability

**Dynamics of nonbinders:**

**Inducer on:** nonbinders eliminated

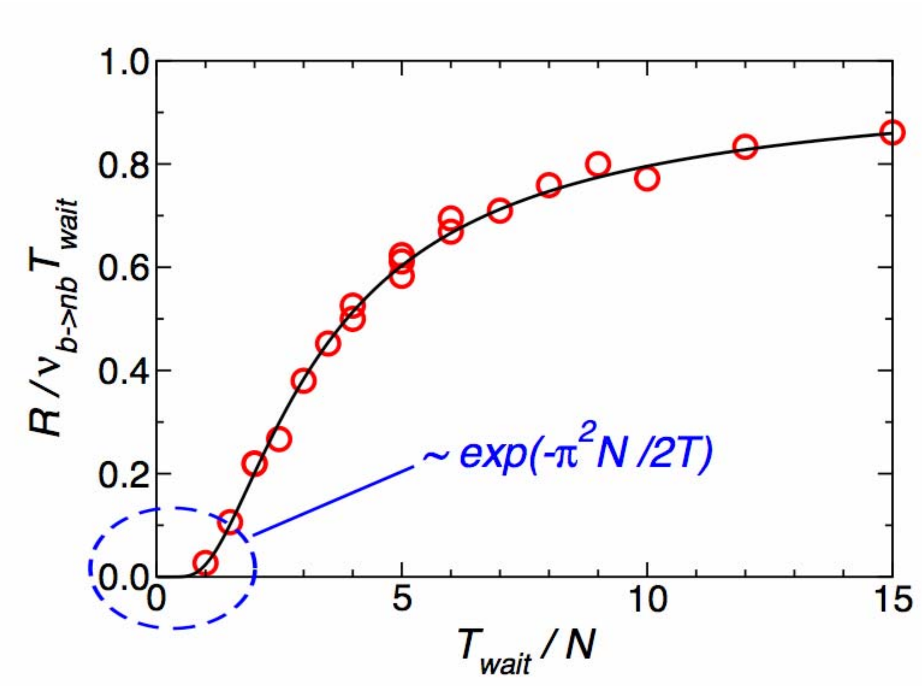
**Inducer off:** nonbinders generated

with prob. $p \sim \nu_{b \to nb} \cdot T_{wait} \cdot N$

fixation prob. $q \sim N^{-1} \cdot f(T_{wait} / N)$

**Extinction probability per cycle:**

$$R = p \cdot q = \nu_{b \to nb} \cdot T_{wait} \cdot f(T_{wait} / N)$$

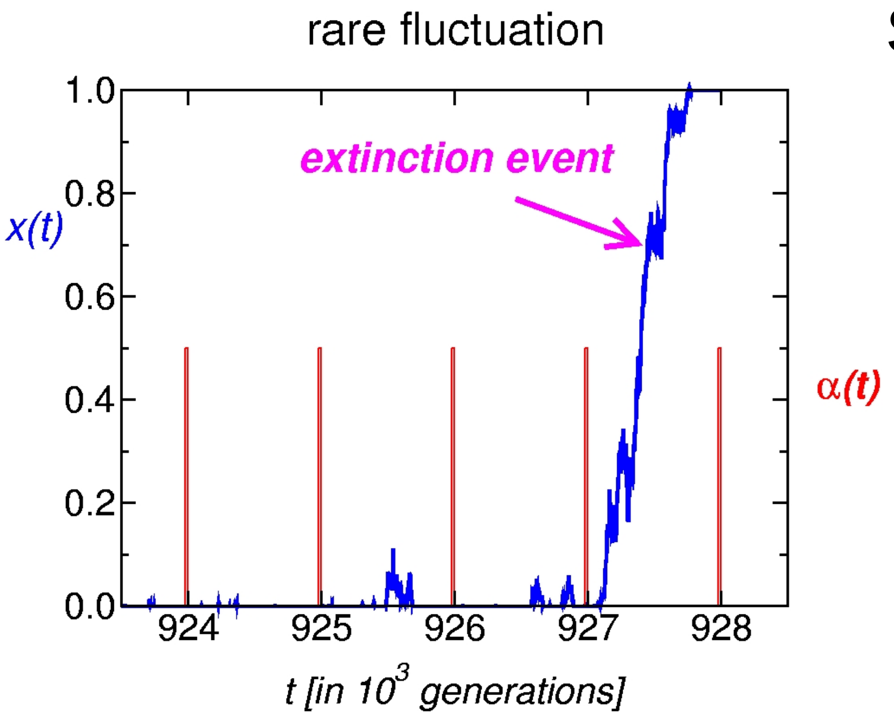



**Scaling function from (backward) Fokker-Planck equation:**

$$\frac{\partial}{\partial t} R(x_0, t) = \frac{x_0(1-x_0)}{2N} \frac{\partial^2}{\partial x_0^{\;2}} R(x_0, t) + \nu_{b \to nb}(1-x_0) \frac{\partial}{\partial x_0} R(x_0, t)$$

$R(x_0,t)$ = extinction probability given $x=x_0$ at $t=0$ $\qquad R \equiv R(x_0 = 0, t = T_{wait})$

# Two-state approximation




State where non-functional allele is fixated

$$\gamma \approx s\,\frac{T_\mathrm{s}}{T}$$

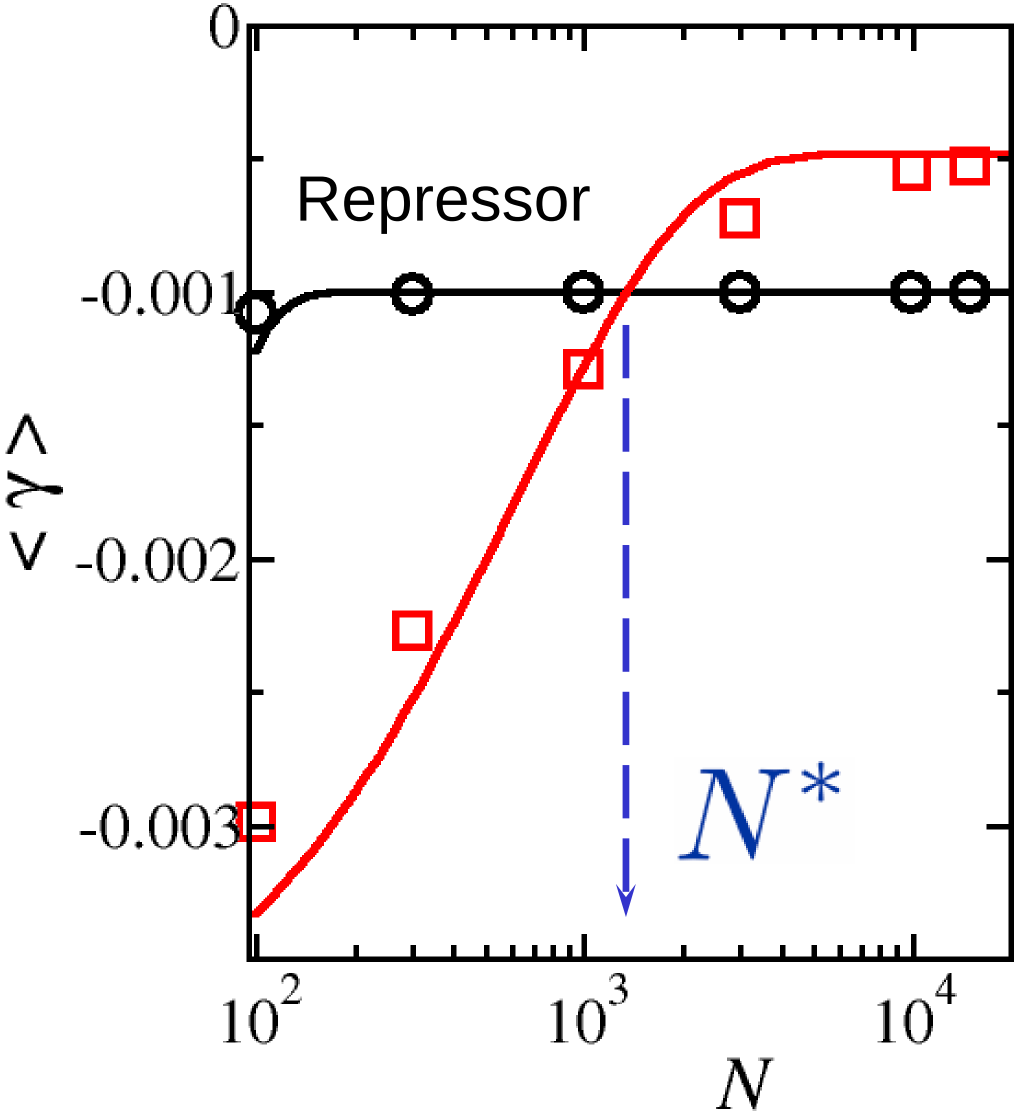
$$R_- \uparrow \quad \downarrow R_+$$

"normal state"

$$\gamma \approx \nu_-$$

$$R_- = \nu_- T_\mathrm{n} f(T_\mathrm{n}/N) \qquad R_+ = N\nu_+ T_\mathrm{s}$$

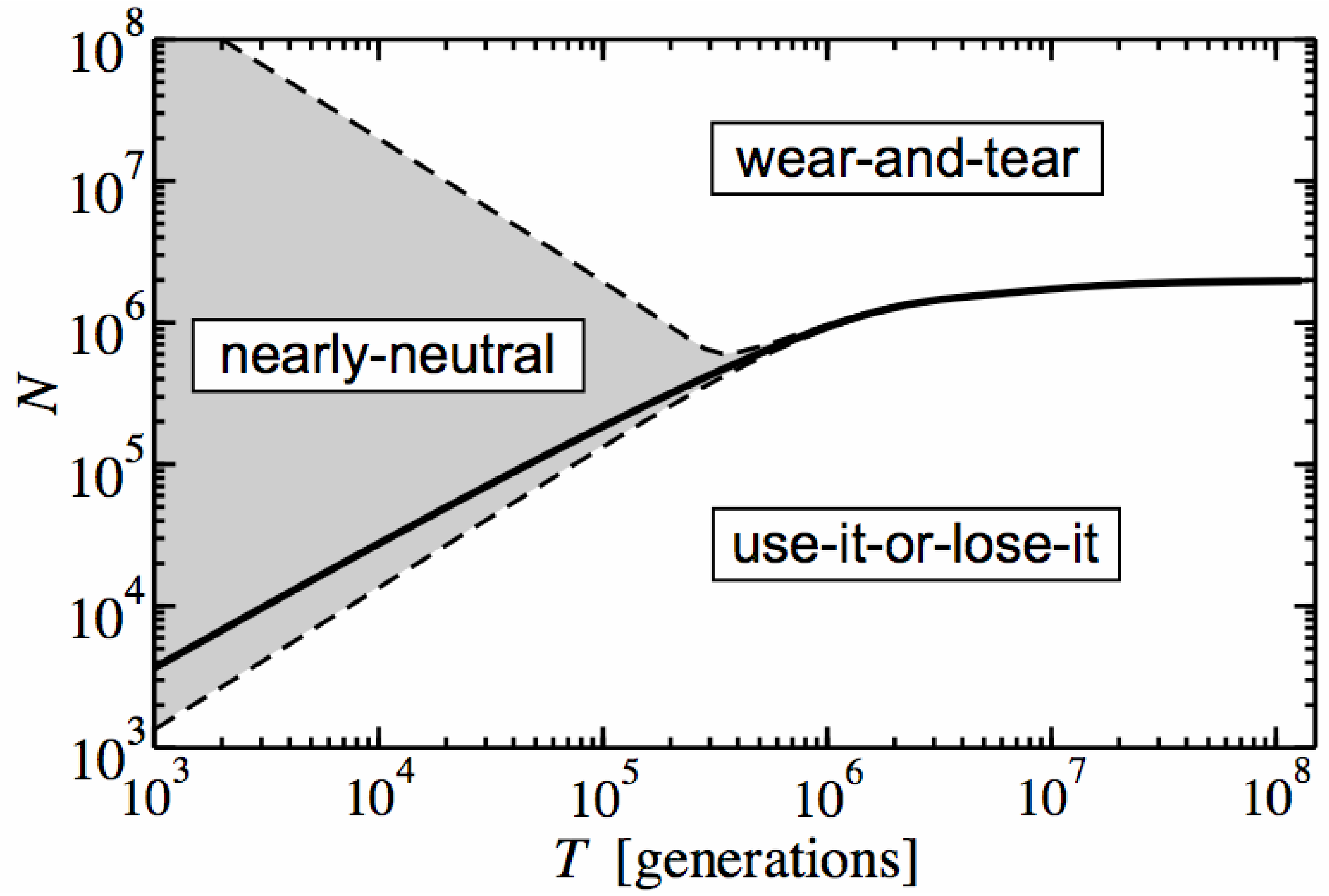
# Two-state approximation




$$\langle\gamma\rangle = \frac{R_+\gamma_0 + R_-\gamma_1}{R_+ + R_-}$$

"critical" population size

# Evolutionary design principle



# Effective population size

- typically smaller than census size
- E. coli: large range of estimates

$$10^5 < N_{eff} < 2 \cdot 10^8$$

[ Bulmer, Genetics (1991) ]        [ Hartl et al., Genetics (1994) ]

- pronounced population substructure

    (colonies inside our gut)

# Conclusions

- Population dynamics can lead to evolutionary design principle
- Two important parameters: Population size & Timescale of environmental fluctuations
- Quantitative description crucial: Balance between two opposing effects