COLLABORATIVE RESEARCH CENTER 1310

Predictability in Evolution

PROBABILISTIC STRUCTURES IN EVOLUTION

DFG SPP 1590

Interference of deleterious and beneficial mutations in spatial habitats

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"Stochastic models of evolving populations", ICMS Edinburgh, July 20, 2018

Deleterious and beneficial mutations

- Evolution of asexual populations is driven by novel mutations, most of which are deleterious

- In large populations deleterious mutations are efficiently purged by natural selection, and affect adaptation only through an overall mutational load

- In small populations deleterious mutations can fix by genetic drift, leading to fitness decline and mutational meltdown

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Message of this talk:

- In spatial populations deleterious mutations may dominate evolution even in the limit of infinite habitat size

Well-mixed populations

Muller's ratchet

However, a kind of irreversible ratchet mechanism exists in the non-recombining species (unlike the recombining ones) that prevents selection, even if intensified, from reducing the mutational loads below the lightest that were in existence when the intensified selection started, whereas, contrariwise, "drift" and what might be called "selective noise" must allow occasional slips of the lightest loads in the direction of increased weight.

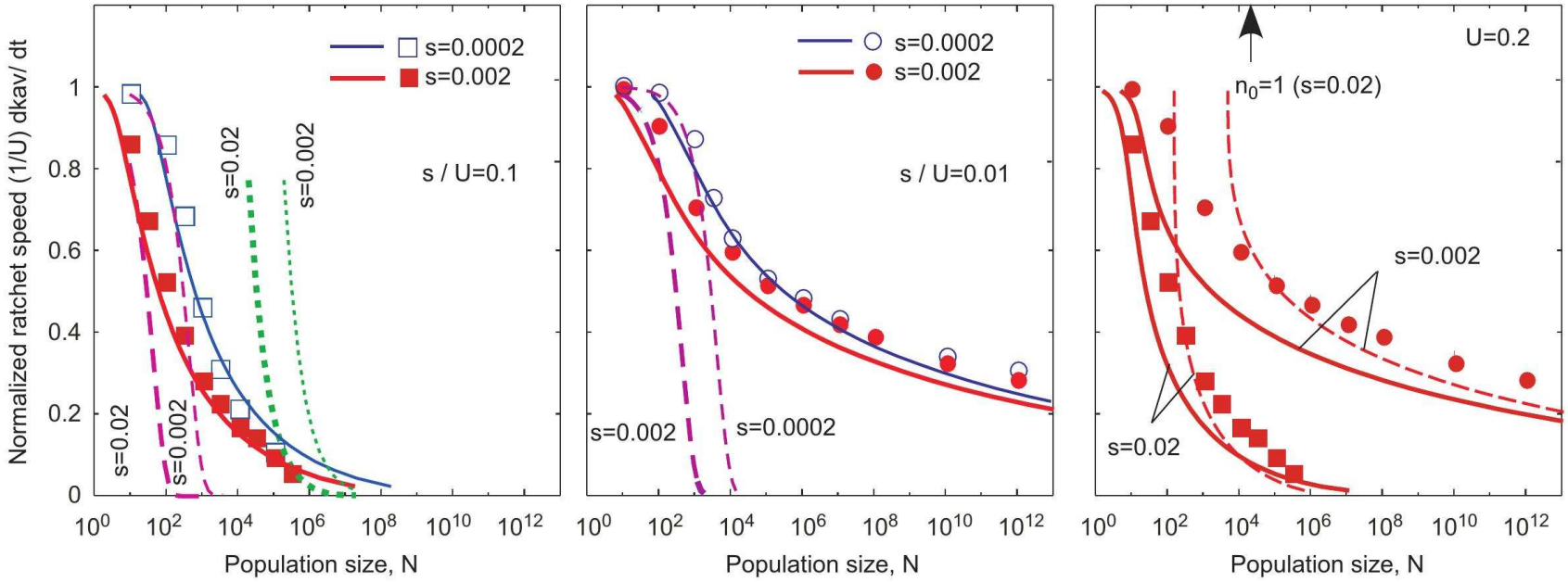
H.J. Muller, Mutation Research 1:2 (1964)

Muller's ratchet

- Population size N, infinite number of haploid loci
- Deleterious mutations occur at rate U_d per individual and generation, and reduce fitness multiplicatively as $f \to f' = (1+s)^{-1} f, \quad s > 0$
- Stationary frequency distribution of the number of mutations is Poisson with parameter U_d/s Haigh 1978
- The ratchet "clicks" when the number of mutations in the least loaded class increases by 1, i.e. when the current least loaded class is driven to extinction
- Ratchet regimes depend of the size of the least loaded class $n_0 = Ne^{-U_d/s}$:
  - $n_0 \gg 1$: Slow ratchet, click rate V_d decreases exponentially with N
  - $n_0 \ll 1$: Running ratchet, steady fitness decline
- For $N \to \infty$ the ratchet halts and the least loaded class has positive frequency $\rho_0 = e^{-U_d/s} > 0$

Speed of the running ratchet

Rouzine, Brunet, Wilke, TPB 2008



Squares: Simulations Full lines: Approximate theory

Beneficial mutations

Review: S.C. Park, D. Simon, JK, JSP 2010

- Beneficial mutations occur at rate U_b and increase fitness multiplicatively as $f \to f' = (1+s)\, f$
- In the absence of deleterious mutations $(U_b > 0,\ U_d = 0)$ dynamical regimes are governed by the time scales of mutation establishment and fixation:

$$t_{\rm mut} = \frac{1}{2sNU_b}, \qquad t_{\rm fix} = \frac{2\ln N}{s} \qquad \Rightarrow \qquad \frac{t_{\rm fix}}{t_{\rm mut}} = 4NU_b \ln N$$

- $t_{\rm mut} \gg t_{\rm fix}$: Periodic selection, rate of adaptation $V_b \sim N$
- $t_{\rm mut} \ll t_{\rm fix}$: Clonal interference, $V_b \sim \ln N$
- Assuming that the effects of deleterious and beneficial mutations combine roughly additively, the fact that $V_b \sim \ln N$ while $V_d \to 0$ for $N \to \infty$ suggests that the total rate of adaptation $V > 0$ for any $U_b > 0$ when N is large
- This statement has been proven rigorously Yu, Etheridge, Cuthbertson 2010

Spatial populations

The importance of being spatial

R. Durrett, S. Levin, TPB 1994

- Natural populations usually live in a spatial habitat and reproduce and compete locally

- The role of spatial structure has been recognized and spatial models have been delevoped in a variety of contexts:

  - Cancer — Komarova 2006; Waclaw et al. 2015
  - Microbial range expansions — Hallatschek et al. 2007
  - Spatial microbial games — Reichenbach et al. 2007

- Habitats of dimensions one, two and three can be realized:

  - $D = 1$: Edge of an expanding colony; colonic crypts
  - $D = 2$: Bacterial or fungal colonies; epithelial cells
  - $D = 3$: Biofilms; solid tumors

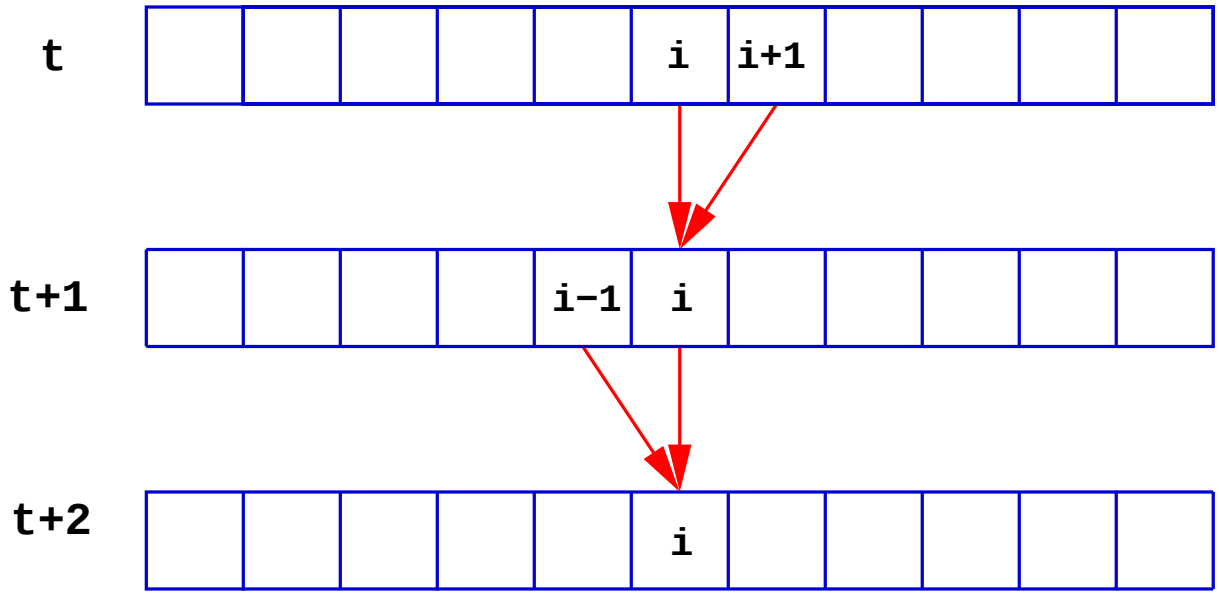
- Generally speaking, spatial structure increases diversity and reduces the strength of selection

Wright-Fisher model for spatial populations

- Discrete, non-overlapping generations; offspring picks ancestor with probability proportional to ancestral fitness

- Implementation on a D-dimensional lattice of length L with $N \sim L^D$: (here $D = 1$)

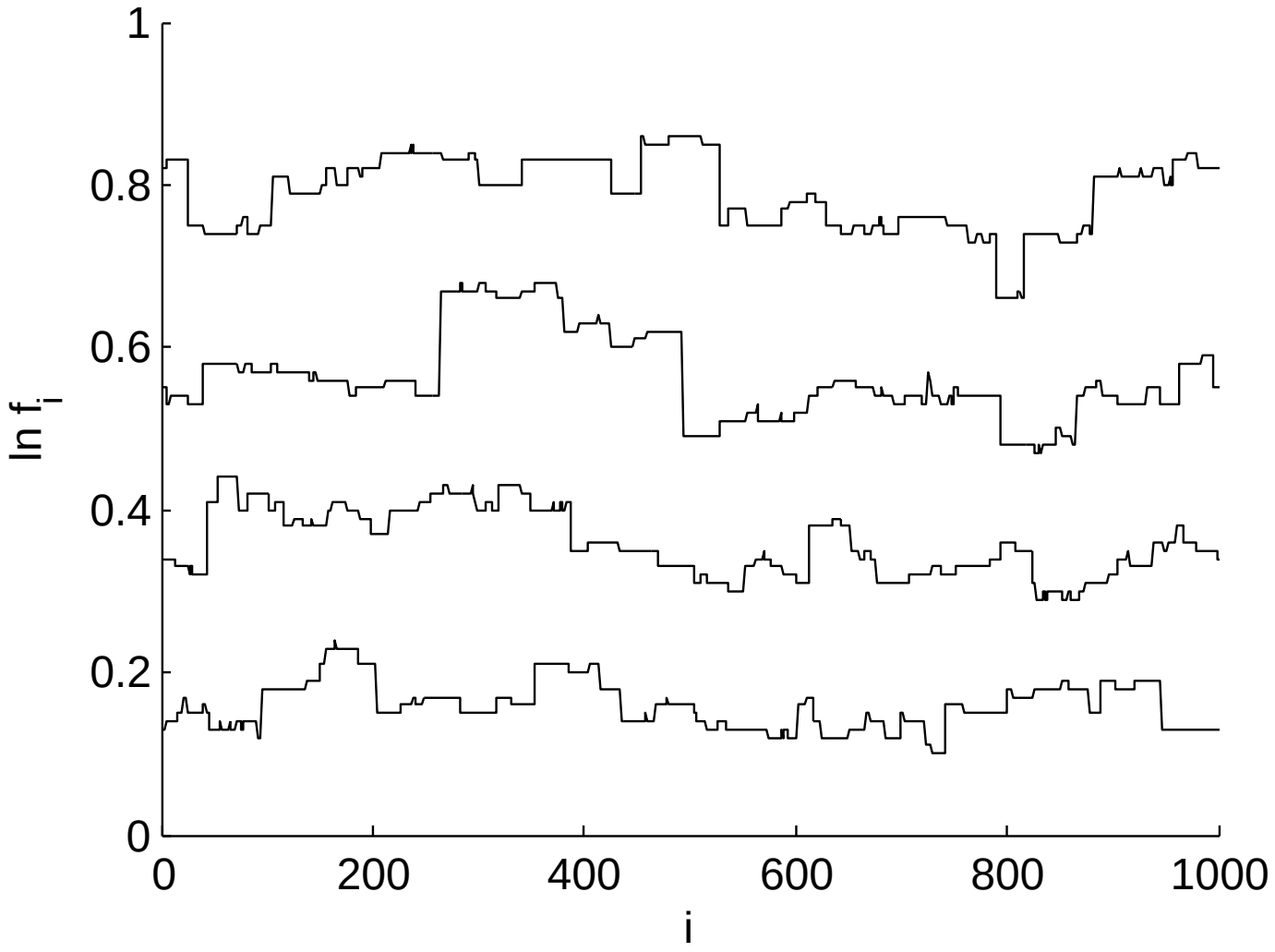
J. Otwinowski, S. Boettcher, PRE 84:011925 (2011)



- Infinite population size limit correponds to infinite habitat size $L \to \infty$

Adaptation $\equiv$ growth of the "fitness surface"

J. Otwinowski, S. Boettcher, PRE 84:011925 (2011)



$s = 0.01, U_b = 0.001$

Clonal interference in spatial populations

E.A. Martens, O. Hallatschek, Genetics 189:1049 (2011)

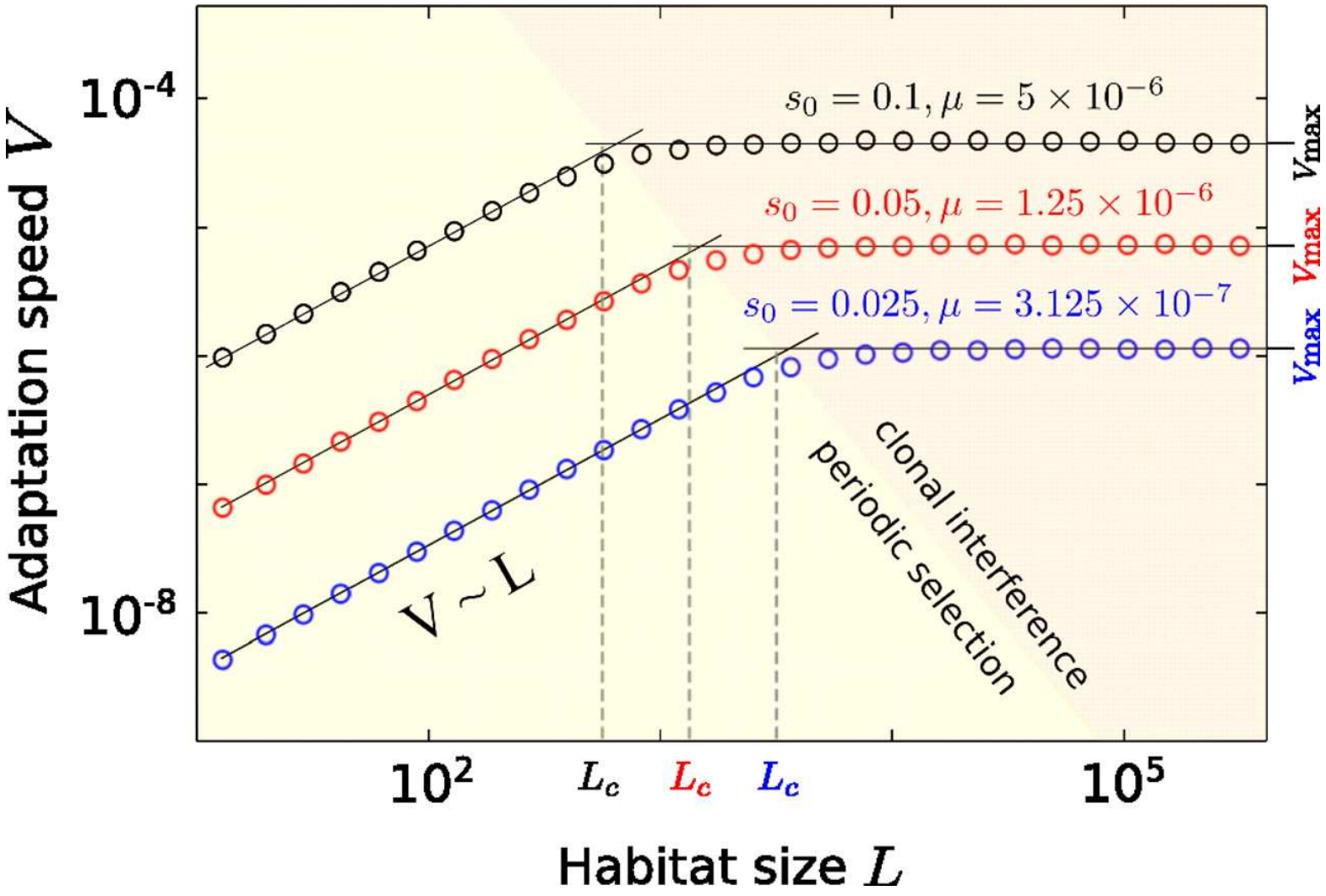
- Fixation probability is the same as in the well-mixed case Maruyama 1974

$$\Rightarrow \quad t_{\text{mut}} = \frac{1}{2sU_bN} = \frac{1}{2sU_bL^d}$$

- Boundaries of mutant clones spread at speed $\sim s \quad \Rightarrow \quad t_{\text{fix}} \sim L/s$
- Clonal interference sets in above the interference length $L_c \sim U_b^{-1/(D+1)}$
- For $L \ll L_c$ evolution occurs by periodic selection and the speed of adaptation is $V_b \sim 1/t_{\text{mut}} \sim U_bN$ as before
- For $L \gg L_c$ a speed limit given by $V_b^{\infty} \sim U_b^{1/(D+1)}$ is reached

Speed of evolution in linear habitats ($D = 1$)

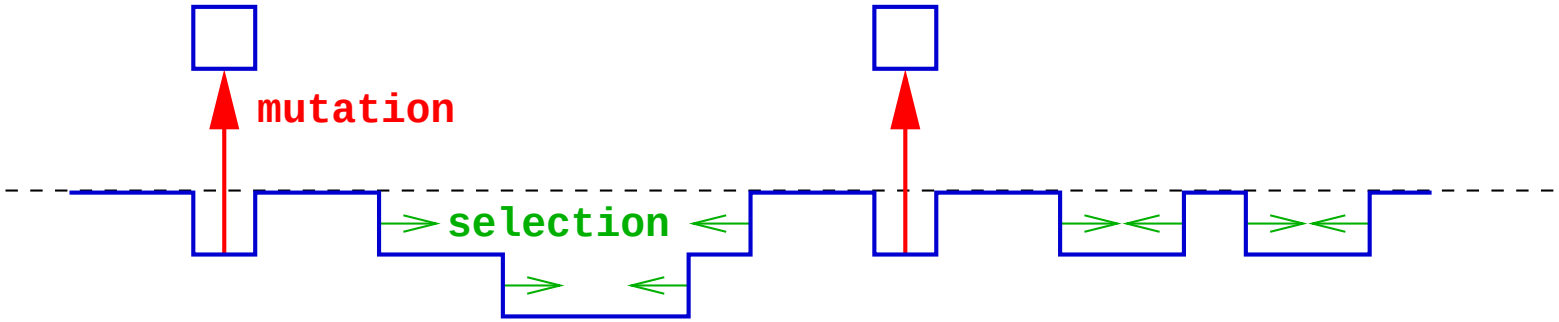
E.A. Martens, O. Hallatschek, Genetics 189:1049 (2011)



Spatial Muller's ratchet

J. Otwinowski, JK, Phys. Biol. 11:056003 (2014)

- Deleterious mutations punch holes into the fitness surface that are closed by selection:

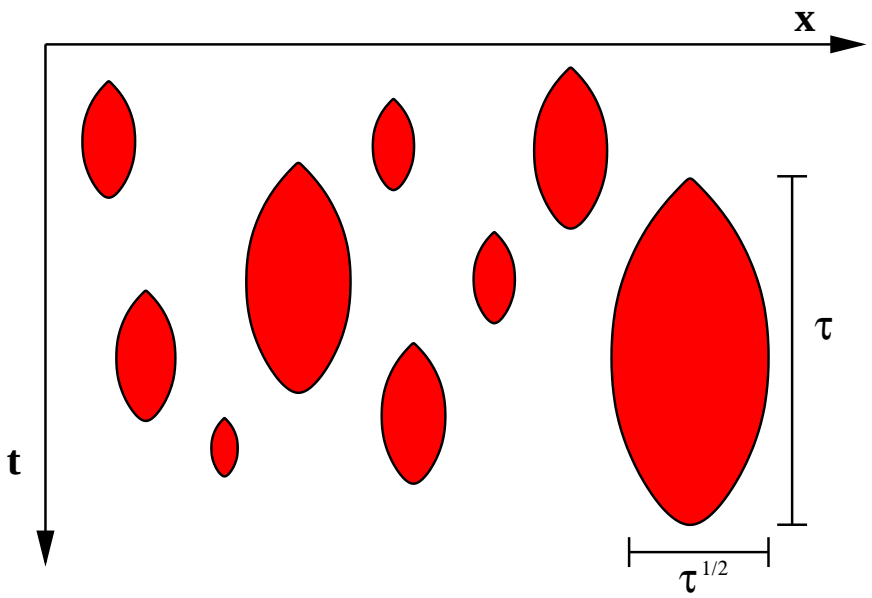


- For small U_d holes appear and heal independently
- With increasing U_d the holes start to merge and eventually percolate at a critical value U_d^c
- For $U_d > U_d^c$ the ratchet moves at a nonzero speed even for $L \to \infty$
- Phase transition is related to directed percolation and was previously observed in surface growth models

Kertész & Wolf 1989; Alon et al. 1996

Mutational load in one dimension

Hallatschek & Nelson 2010; Otwinowski & Krug 2014



- Boundaries of deleterious bubbles perform random walks with a small inward bias $\sim s \quad \Rightarrow \quad$ lifetime distribution $p(\tau) \sim \tau^{-3/2} \exp[-s^2 \tau]$
- Expected space-time extension of a bubble $\sim s^{-2}$, density of mutated sites $1 - \rho_0 \sim U_d / s^2$
- Percolation occurs when $1 - \rho_0 \sim \mathcal{O}(1) \quad \Rightarrow \quad U_d^c \sim s^2$

Spatial ratchet as a nonequilibrium phase transition

- $U_d = 0$, two fitness classes: Biased voter model/compact directed percolation (CDP) with critical point at $s = 0$

- $U_d > 0$, two fitness classes: Directed percolation transition at $s_c \sim U_d^{1/\phi}$ where the crossover exponent $\phi = \min[2/D, 1]$ in D dimensions

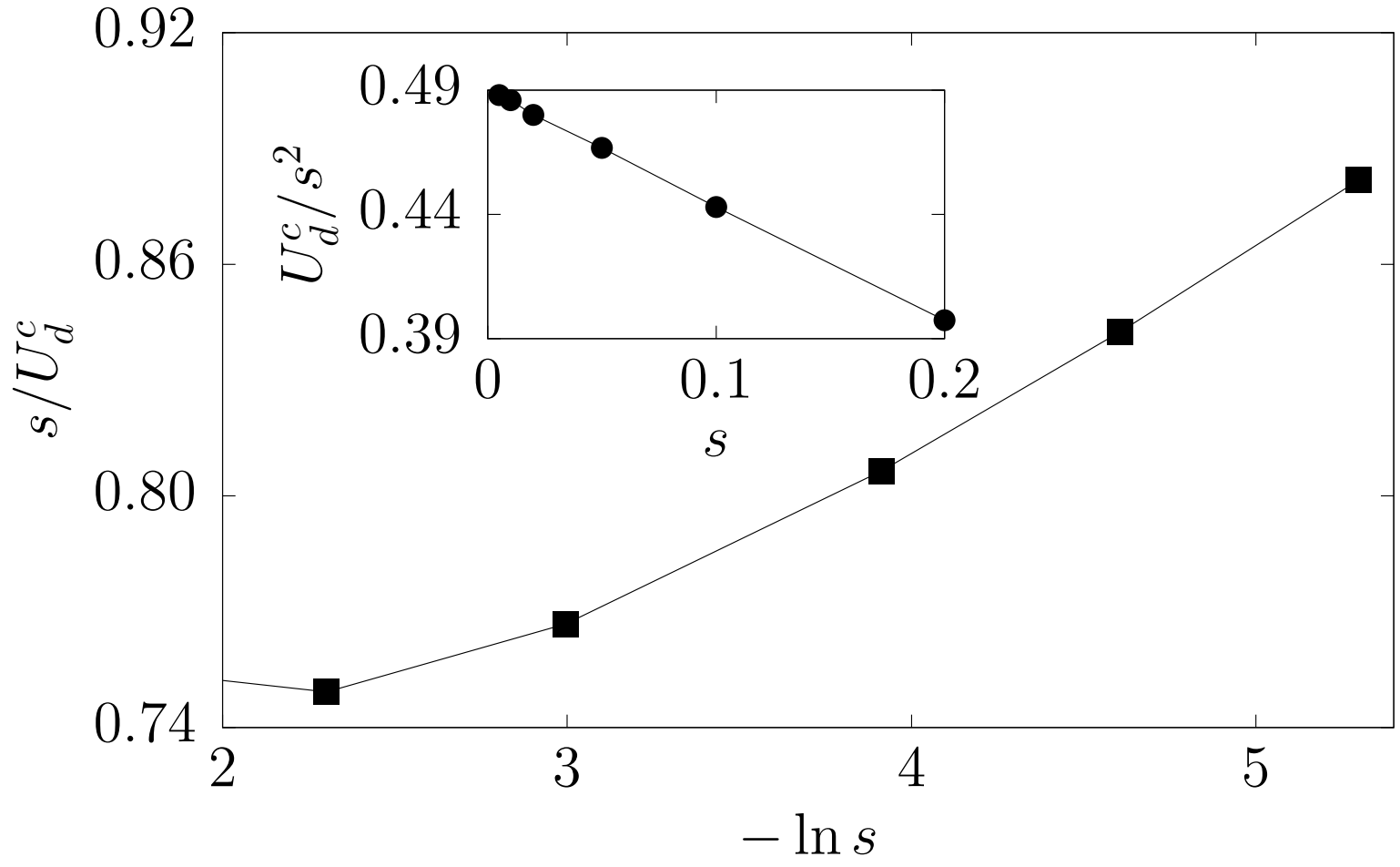
  Janssen 2005

- $U_d > 0$, unlimited number of fitness classes: Unidirectionally coupled directed percolation (UCDP) Goldschmidt et al. 1999

- In UCDP each fitness class $k \geq 1$ undergoes it own DP dynamics and is additionally fed from class $k-1$

- The dynamics of the least loaded class $k = 0$ is DP and the speed of the ratchet increases as $V_d \sim (U_d - U_d^c)^{\nu_\parallel}$ for $U_d > U_c^c$ where $\nu_\parallel$ is the DP correlation time exponent Otwinowski & Krug 2014

Critical deleterious mutation rate



Main figure: $U_d^c \sim s/\ln(s)$ in $D = 2$

Inset: $U_d^c \sim s^2(c_1 + c_2 s)$ in $D = 1$

Scaling theory I

- Consider rate of accumulation of beneficial or deleterious mutations $\mathscr{V}(t)$ and its long-time limit $V = \lim_{t\to\infty} \mathscr{V}(t)$
- Population undergoes adaptation (Muller's ratchet) when $V > 0$ ($V < 0$)
- For $U_d, U_b > 0$ we conjecture the scaling form

$$\mathscr{V}(t) = t^{-1} F(\Delta_d^{\nu_\parallel} t, U_b^{\nu_b} t)$$

  where $\Delta_d = U_d - U_d^c$ and ν_b is an unknown exponent
- At the DP critical point ($\Delta_d = 0$) this implies $V \sim U_b^{\nu_b}$
- Simulations yield the estimates $\nu_b = 0.76 \pm 0.03$ ($\nu_b = 0.81 \pm 0.03$) in one (two) dimensions
- Scaling arguments based on UCDP suggest that $\nu_b = 1/(1+\eta)$, where η is the DP initial slip exponent

Scaling theory II

- Competition between deleterious and beneficial mutations is quantified by the comparison of the corresponding time scales $t_d \sim |\Delta_d|^{-\nu_\parallel}$ and $t_b \sim U_b^{-\nu_b}$

- Crossover from ratchet behavior to adaptation occurs when $t_b \sim t_d$ or

$$U_b \sim |\Delta_d|^{\varphi} \quad \text{with} \quad \varphi = \nu_\parallel/\nu_b \approx 2.28 \quad (D=1) \quad \text{and} \quad \approx 1.59 \quad (D=2)$$

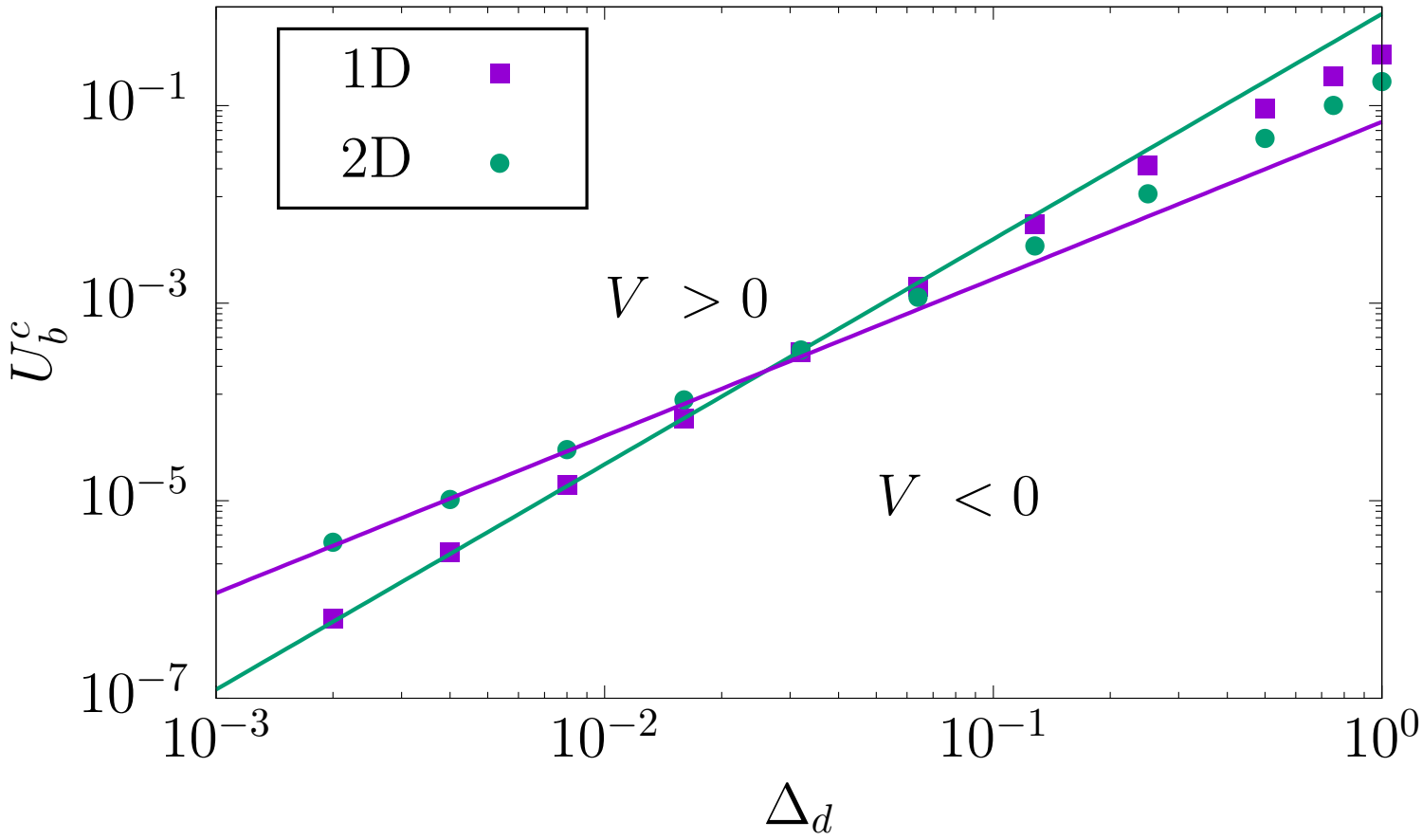
- The full scaling form of the asymptotic speed is expected to take the form

$$V = c_s^{-1} U_b^{\nu_b} H(a_s \Delta_d U_b^{-1/\varphi})$$

  with a two-branched scaling function H and s-dependent constants a_s, c_s

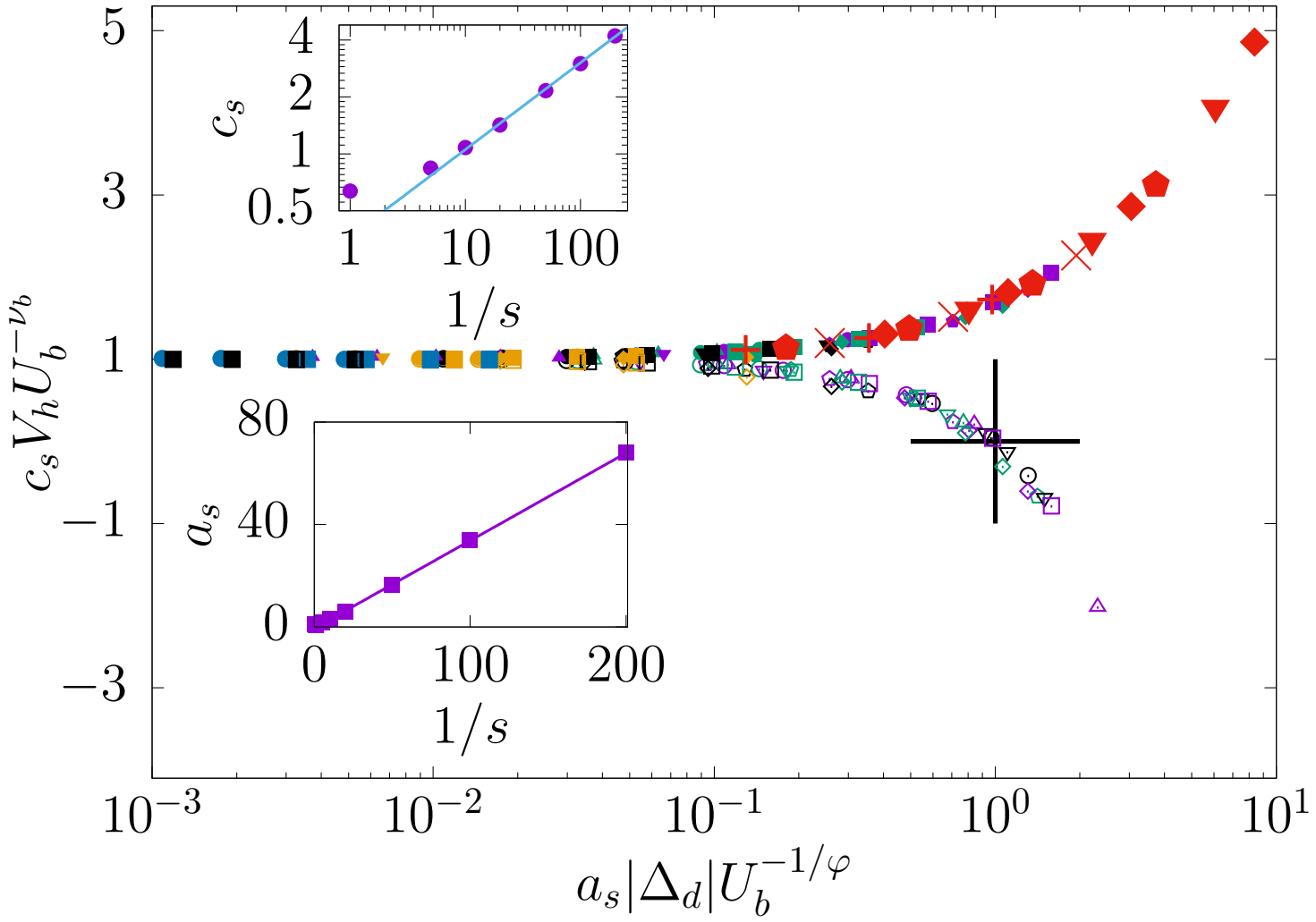
- The $\Delta_d > 0$-branch of the scaling function crosses zero at a beneficial mutation rate $U_b^c \approx (a_s \Delta_d)^{\varphi}$

Phase diagram in the $\Delta_d - U_b$ plane



- U_b^c vs. Δ_d for $s = 2.5$
- Full lines show $U_b^c \sim \Delta_d^{\varphi}$

Scaling collapse for $D = 1$



- Lower inset shows that $a_s \approx 0.34/s$
- Red symbols correspond to $U_d = 0$

Biological implications

Experiments on Muller's ratchet

- First experimental verification of the ratchet mechanism in bottlenecked serial transfers of RNA viruses Chao 1990, Elena & Moya 1999

- In these systems $U_d \sim 1$ and $s \ll 1$, which implies that the spatial ratchet cannot be halted by beneficial mutations

- Deleterious mutation rates in bacteria are much smaller and conditions where $U_d \sim U_d^c(s)$ appear to be realizable

- Example: Trindade et al. 2010
  $U_d = 5 \cdot 10^{-3}, s = 0.03$ for a mutator strain of *Escherichia coli*
  $\Rightarrow U_d < U_d^c$ in two dimensions and $U_b^c \approx 0.25 U_d$ in one dimension

- It has been suggested that bacteria have reduced their deleterious mutation rates in order to be able to form spatial biofilms Gralka et al. 2016

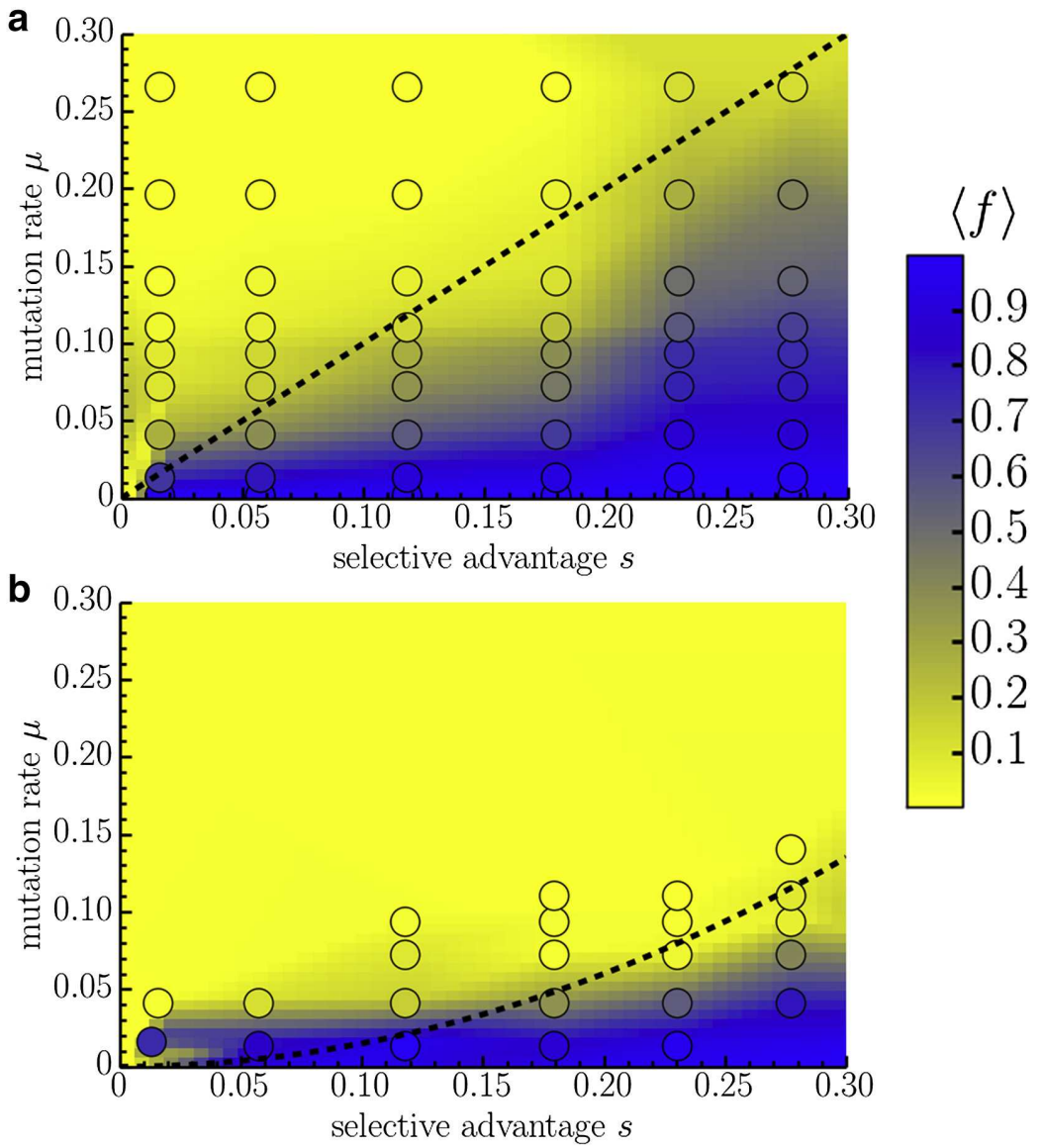
Conversional meltdown in yeast

Lavrentovich et al., Biophys. J. 110:2800 (2016)

- Engineered strain of *Saccharomyces cerevisiae* undergoes irreversible conversion to a cycloheximide-susceptible cell type at a tunable rate U_d
- The selective disadvantage s of the converted type can be tuned through the concentration of cycloheximide
- Conversional meltdown occurs when the non-converted cell type goes extinct
- Effectively one-dimensional geometry at the boundary of an expanding colony
- Experiments show a pronounced difference between well-mixed and spatial populations

Conversional meltdown in yeast

Lavrentovich et al. 2016



a. well mixed: $U_d^c \sim s$ **b.** one-dimensional: $U_d^c \sim s^2$

Summary and outlook

- Spatial Muller's ratchet undergoes a sharp phase transition that is governed solely by the mutational load, and not by the habitat size
- Underlying mechanism is a directed percolation phase transition
- At least for small U_b, the joint effect of beneficial and deleterious mutations is governed by the DP critical point and hence far from additive
- The phenomenon appears to be within reach of microbial experiments
- Open problems:
  - effect of the distribution of mutational effects
  - effect of spatial interaction structure
  - mutational meltdown in spatial populations