Interference of deleterious and beneficial mutations in spatial habitats

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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 \( f \rightarrow f' = (1 + s)^{-1} f, \quad s > 0 \)

- 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 \( N \rightarrow \infty \) 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
Benificial mutations

- Beneficial mutations occur at rate $U_b$ and increase fitness multiplicatively as $f \rightarrow f' = (1 + s) f$

- 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:

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

- $t_{\text{mut}} \gg t_{\text{fix}}$: Periodic selection, rate of adaptation $V_b \sim N$

- $t_{\text{mut}} \ll t_{\text{fix}}$: 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 $V_d \rightarrow 0$ for $N \rightarrow \infty$ suggests that the total rate of adaptation $V > 0$ for any $U_b > 0$ when $N$ is large

- This statement has been proven rigorously $\quad$ 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 developed in a variety of contexts:
  – Cancer
  – Microbial range expansions
  – Spatial microbial games

• 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 corresponds to infinite habitat size $L \rightarrow \infty$
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  
  \[ t_{\text{mut}} = \frac{1}{2sU_bN} = \frac{1}{2sU_bL^d} \]

- Boundaries of mutant clones spread at speed \( \sim s \)  
  \[ t_{\text{fix}} \sim L/s \]

- 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)
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 $U^c_d$.
- For $U_d > U^c_d$ 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

Boundaries of deleterious bubbles perform random walks with a small inward bias $\sim s$ ⇒ 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 $1 - \rho_0 \sim \mathcal{O}(1) \Rightarrow U_d^c \sim s^2$
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 its 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 $V_d \sim (U_d - U_d^c)^{v_\|}$ for $U_d > U_d^c$ where $v_\|$ 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: $U_d^c \sim s^2(c_1 + c_2s)$ in $D = 1$
Scaling theory I

- Consider rate of accumulation of beneficial or deleterious mutations $\mathcal{V}(t)$ and its long-time limit $V = \lim_{t \to \infty} \mathcal{V}(t)$

- Population undergoes adaptation (Muller's ratchet) when $V > 0$ ($V < 0$)

- For $U_d, U_b > 0$ we conjecture the scaling form

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

  where $\Delta_d = U_d - U_d^c$ and $\nu_b$ 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 $\eta$ 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 $t_d \sim |\Delta_d|^{-\nu_{||}}$ and $t_b \sim U_b^{-\nu_b}$

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

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

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

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

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 $U_b^c \approx (a_s\Delta_d)^\phi$
Phase diagram in the $\Delta_d - U_b$ plane

- $U_b^c$ vs. $\Delta_d$ for $s = 2.5$
- Full lines show $U_b^c \sim \Delta_d^\phi$
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
  \[
  U_d = 5 \cdot 10^{-3}, s = 0.03 \text{ for a mutator strain of } Escherichia \text{ coli}
  \Rightarrow U_d < U_d^c \text{ in two dimensions and } U_b^c \approx 0.25U_d \text{ in one dimension}
  \]

- 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