

The fate and rate of beneficial mutations surfing on the wave of a range expansion

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May 29, 2012 / Anacapri

Outline

Introduction

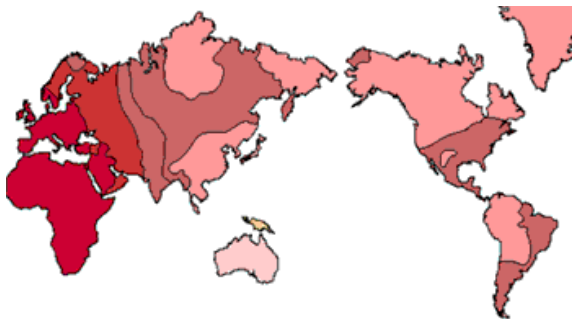
The model

Results

Analysis

Range expansion reduces genetic diversity

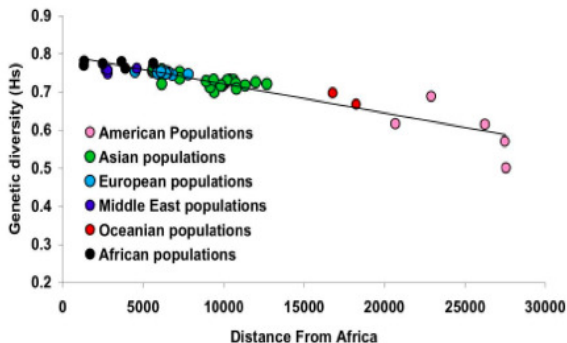
Out of Africa:



Cavalli-Sforza *et al.*, 1994

Range expansion reduces genetic diversity

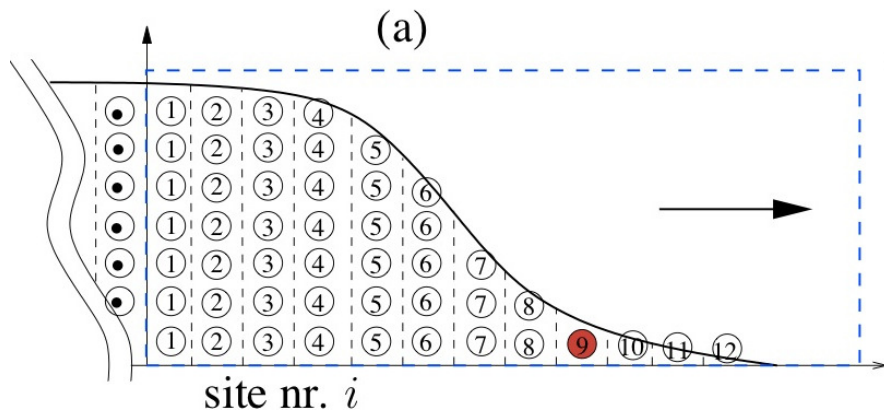
Out of Africa:



Prugnolle *et al.*, 2005

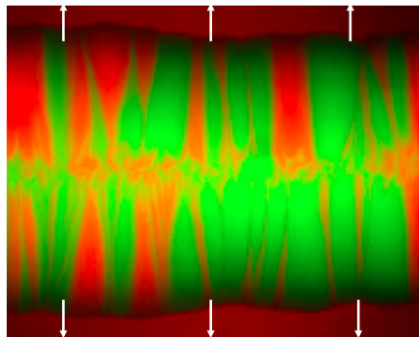
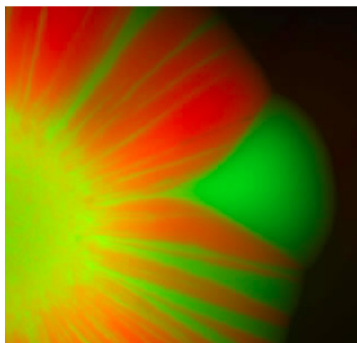
Gene surfing

Hallatschek and Nelson, 2007



Experiments on a Petri dish

Haploid CFP and RFP-marked *S. Cerevisiae*



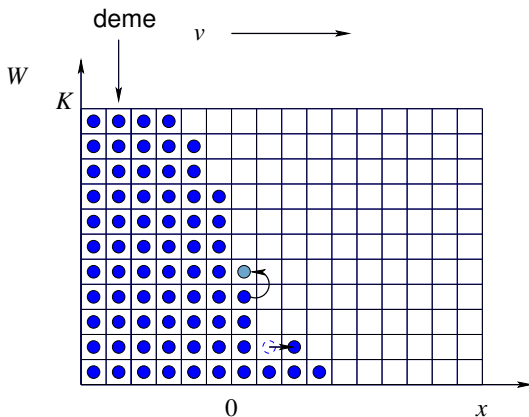
Hallatschek and Nelson, 2007

The question

- How does range expansion interfere with selection?
- If a mutant arises with an offset x wrt an advancing Fisher wave, what is the probability $u(x)$ that it eventually fixes?
- How does $u(x)$ depend on the growth rate r_m of the mutant and on the local carrying capacity of the environment?

The stepping-stone model

Kimura and Weiss, 1964

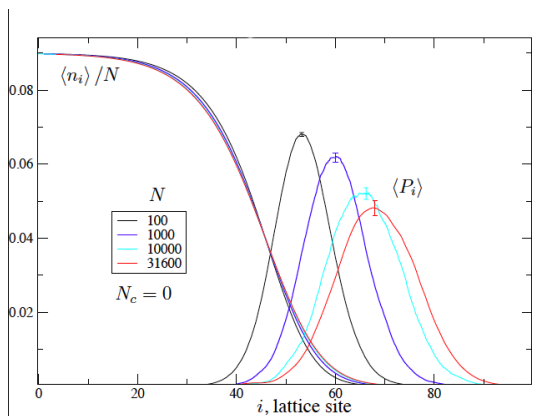


At each step:

- Replication in a deme: $p_{\text{rep}} \propto K - W$
- Death: $p_{\text{death}} \propto (1 - r_w)p_{\text{rep}}$
- Diffusion

The ancestor location in the neutral case

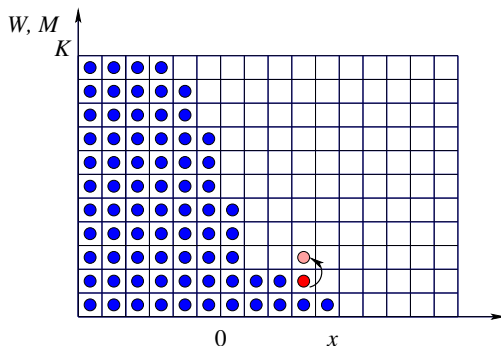
Hallatschek and Nelson, 2007



Two competing effects:

- The *fixation probability* $u(x)$ increases as x increases
- The *population density* $n(x)$ decreases as x increases

Introducing the mutants



A single mutant is *added* at location x wrt the center of the wave
 W : number of wildtypes, M number of mutants

- Replication in a deme: $p_{\text{rep}} \propto K - (W + M)$
- Death: $p_{\text{death}} \propto (1 - r_m)p_{\text{rep}}$ (no advantage in a full deme)

Possible outcomes

N.B.: The window is placed so that the total number of individuals is kept roughly constant

Fixation: The window is filled by mutants

Extinction: All the mutants die off in the window

Failure: At least one mutant crosses the left boundary

A stochastic reaction-diffusion system

$$w = W/K \quad m = M/K \quad r_{w,m} \ll 1$$

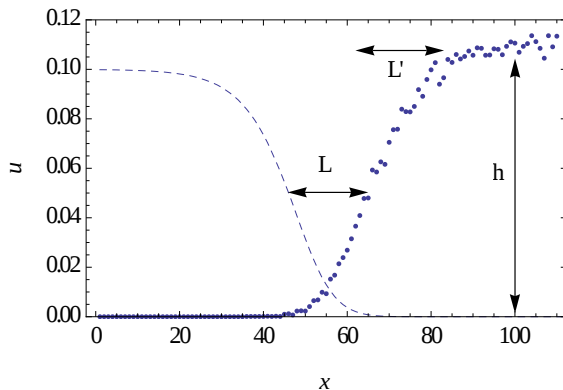
$$\begin{aligned} \frac{\partial w}{\partial t} = & r_w w(1 - m - w) + \frac{\partial^2 w}{\partial x^2} \\ & + \sqrt{2 \frac{w(1 - m - w)}{K}} \eta^w(x, t) - \sqrt{2 \frac{mw}{K}} \eta^{w,m}(x, t) \end{aligned}$$

$$\begin{aligned} \frac{\partial m}{\partial t} = & r_m m(1 - m - w) + \frac{\partial^2 m}{\partial x^2} \\ & + \sqrt{2 \frac{m(1 - m - w)}{K}} \eta^m(x, t) + \sqrt{2 \frac{mw}{K}} \eta^{w,m}(x, t) \end{aligned}$$

Can be made adimensional (depending only on $K_e = K\sqrt{r_w}$ and $\alpha = r_m/r_w$) by setting

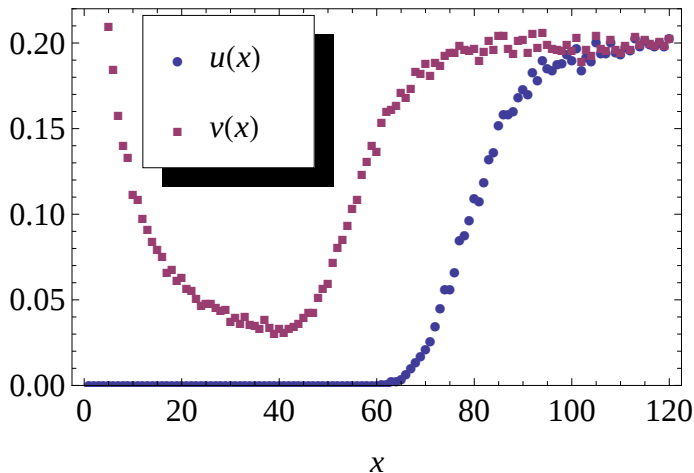
$$X = \sqrt{r_w} x \quad T = r_w t$$

The fixation probability $u(x)$



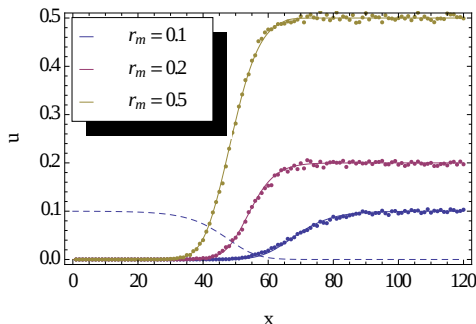
N.B.: Data for $r_w = 0.1$, $r_m = 0.11$

Fixation and failure



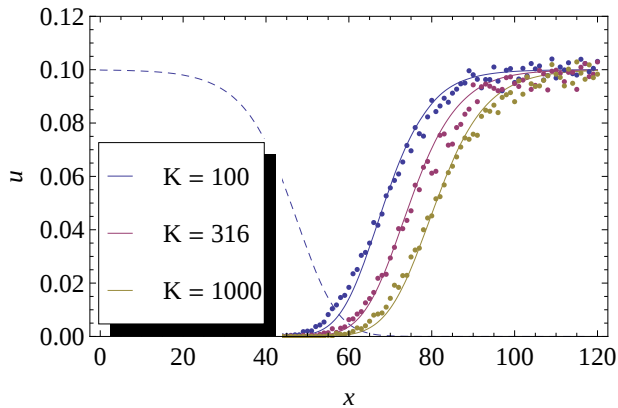
- $u(x)$: probability of fixation
- $v(x)$: probability of failure

Limit behavior of $u(x)$

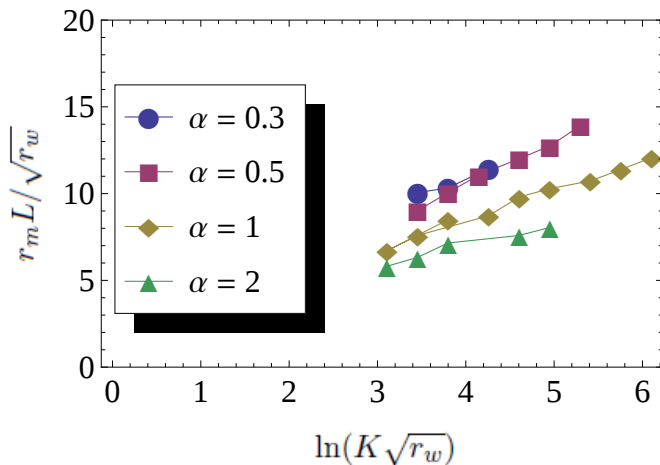


- For $x \rightarrow -\infty$, $u(x) \rightarrow 0$: neutral dynamics “against” an infinite population
- For $x \rightarrow +\infty$, $u(x) \rightarrow r_m$: fixation *provided* the mutant survives sampling fluctuations

Dependence on K



Dependence of L on K and α



The basic scenario

- Mutants are **established** when their population is large enough for its advantage to be felt
- In an *empty* deme, this requires $m > m_c(K_e, \alpha)$
- In a full deme, the mutant's offspring undergoes neutral “drift” against an “infinite” wild-type population: fixation probability vanishes $u(x) \simeq 0$ for $x < 0$
- For $x \simeq 0$ the mutant population can get established, but is rapidly surrounded by the wild-types: it will disappear on a much longer time scale: thus $u(x) \simeq 0$, but $v(x) > 0$
- For $x > L$, the mutant population can get established *before* the wildtype population reaches it: thus $u(x) > 0$ for $x \rightarrow +\infty$

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The large- x limit

- For $x \rightarrow +\infty$, it only matters if the mutant population avoids stochastic death at the beginning, and the wave of advancing wildtypes is irrelevant
- In a well-mixed population with growth rate r_m , this probability equals r_m (Moran model)
- This also holds true in our model with spatial structure and local logistic growth

The argument

- The only relevant dynamical variable is $m_{\text{tot}} = \sum_i m_i$
- Diffusion events do not change m_{tot}
- Death events are $(1 - r_m)$ less likely than birth events
- Thus the survival probability $P_{m_{\text{tot}}}$ satisfies

$$P_{m_{\text{tot}}} = \frac{1 - r_m}{2 - r_m} P_{m_{\text{tot}}-1} + \frac{1}{2 - r_m} P_{m_{\text{tot}}+1}$$

with boundary conditions

$$P_0 = 0 \quad P_\infty = 1$$

- Thus

$$P_{m_{\text{tot}}} = 1 - (1 - r_m)^{m_{\text{tot}}}$$

and

$$P_1 = r_m$$

The length L

Can we estimate the behavior of L ?

- Speed of the advancing wildtype wave: $v \simeq 2\sqrt{r_w}$ (diffusion constant $D = 1$)
- Time available for a mutant to grow: $t_0 = x_0/v$
- Assume free exponential growth *on average* for the mutant population: $\langle N_m \rangle \simeq e^{r_m t}$
- Thus $\langle \bar{N}_m \rangle = \exp(r_m t)/r_m$
- Success requires $N_m(t_0) \geq m_c K / \sqrt{r_m}$
- Thus survival may take place if

$$x_0 > L \simeq \frac{v}{r_m} \ln(m_c K \sqrt{r_m}) \approx \frac{\sqrt{r_w}}{r_m} \ln(K \sqrt{r_m}) \quad f(\alpha, K_e)$$

- Actually this is just an upper bound (one can check that $\lim_{K \rightarrow \infty} L < \infty$)

A differential equation for the survival probability $u(x)$?

The survival probability $u(x)$ apparently satisfies

$$\frac{\partial^2 u}{\partial x^2} - v_w \frac{\partial u}{\partial x} + r_m(1 - \langle w \rangle)u - u^2 = 0$$

with the boundary conditions

$$\lim_{x \rightarrow -\infty} u(x) = 0 \qquad \lim_{x \rightarrow +\infty} u(x) = r_m$$

where $\langle w(x) \rangle$ is the average profile of the wildtype wave

A heuristic derivation

Assumptions:

- The fate of the mutant population is settled when m is still very small (does not hold for nearly neutral, neutral, or disadvantageous mutations)
- We consider a local average growth rate $r_m(1 - \langle w(x) \rangle)$

Define $p(x, t|\xi, \tau)$ as the probability to find a mutant at x at time t , given that one was introduced at ξ at time τ

- Assume $t > \tau$, but very close: then
 $w(x, t) \simeq w(x, \tau) = w_{\text{init}}(x)$
- Then $u(x)$ is the probability that the mutant in x fixates
- If all events are independent, $u(x)$ satisfies

$$u(\xi) = \int_{-\infty}^{+\infty} dx u(x) p(x, t|\xi, \tau)$$

- Differentiating wrt t we obtain

$$\int_{-\infty}^{+\infty} dx \, u(x) \frac{\partial}{\partial t} p(x, t | \xi, \tau) = 0$$

- Setting $-r_m m w \simeq -r_m m \langle w \rangle_{init}$:

$$\frac{\partial p}{\partial t} = r_m (1 - \langle w \rangle_{init}) p + v \frac{\partial p}{\partial x} + \frac{\partial^2 p}{\partial x^2}$$

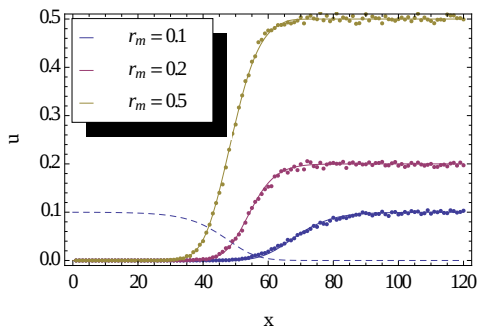
- Thus

$$r_m (1 - \langle w \rangle_{init}) u - v \frac{\partial u}{\partial x} + \frac{\partial^2 u}{\partial x^2} = 0$$

valid for $u \ll 1$

- The $-u^2$ term imposes $\lim_{x \rightarrow +\infty} u(x) = r_m$

Comparison with the data



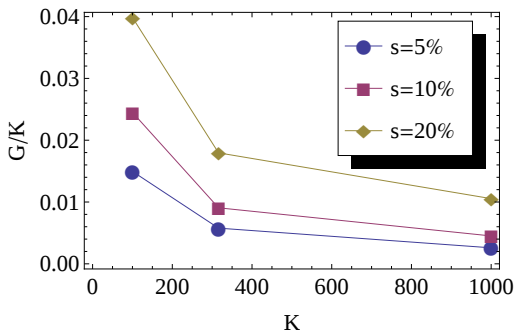
The lines correspond to the solution of the differential equation
The differential equation “correctly” evaluates L

The substitution rate

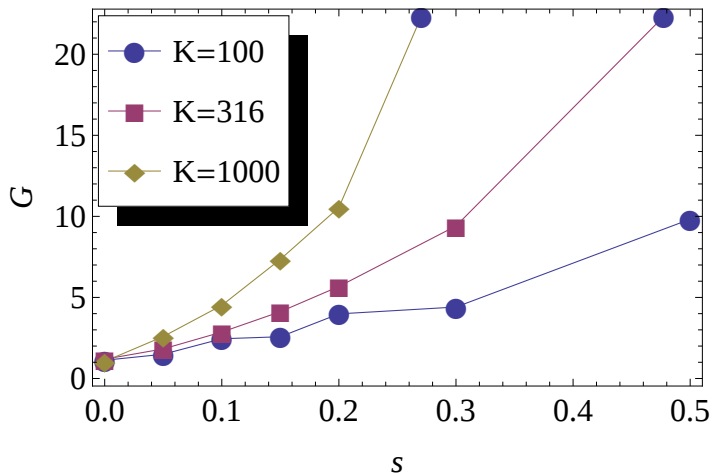
- Substitution rate R vs. the beneficial mutation rate U_b :

$$R = U_b \int dx \langle u(x) W(x) \rangle = U_b G$$

- For $K \gg 1$, $\langle u(x) W(x) \rangle \simeq \langle u(x) \rangle \langle W(x) \rangle$
- Since $W(x) = Kw(x)$, we expect $G \propto K$



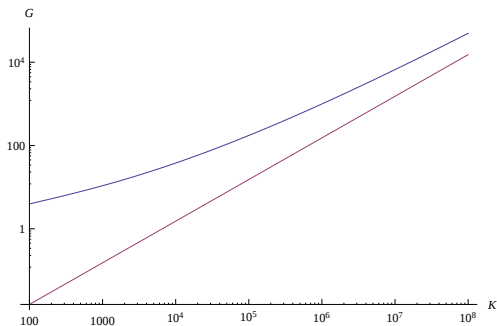
Results for G



Effects of finite density

By exploiting the analogy with travelling waves ($s = r_m/r_w - 1$)

$$G \approx \frac{2\pi K_e^{1-\pi/\sqrt{s \ln^2 K_e + \pi^2}}}{\sqrt{\left(\pi^2 / \ln^2 K_e\right) + s}}.$$



Asymptotics is reached *very* slowly!

Summary

- Range expansion “suffocates” beneficial mutations, unless they arise enough far ahead of the expanding waves
- The substitution rate is strongly decreased for weakly beneficial mutations
- However, even a small amount of drift substantially increases the substitution rate
- Outlook
 - More satisfactory analysis of the substitution rate
 - Generalization to 2D
 - Inferring selection strength from sector shapes

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