The fate of beneficial mutations in a range expansion

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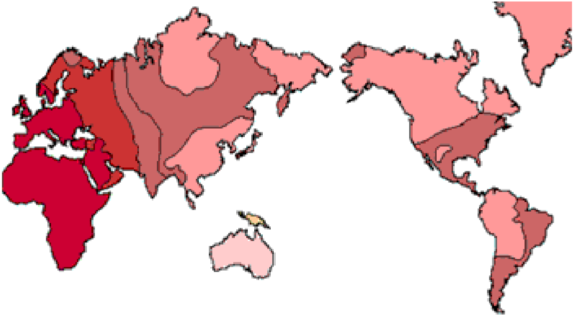
Outline

Range expansion reduces genetic diversity

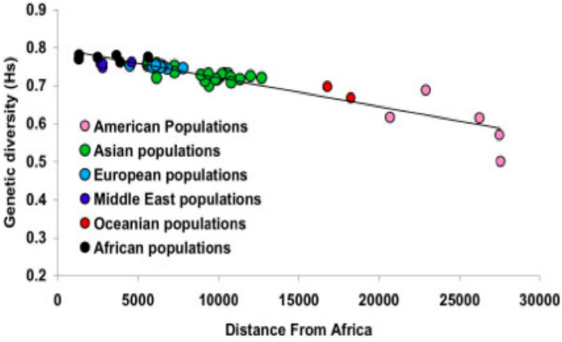
Out of Africa:



Cavalli-Sforza *et al.*, 1994

Range expansion reduces genetic diversity

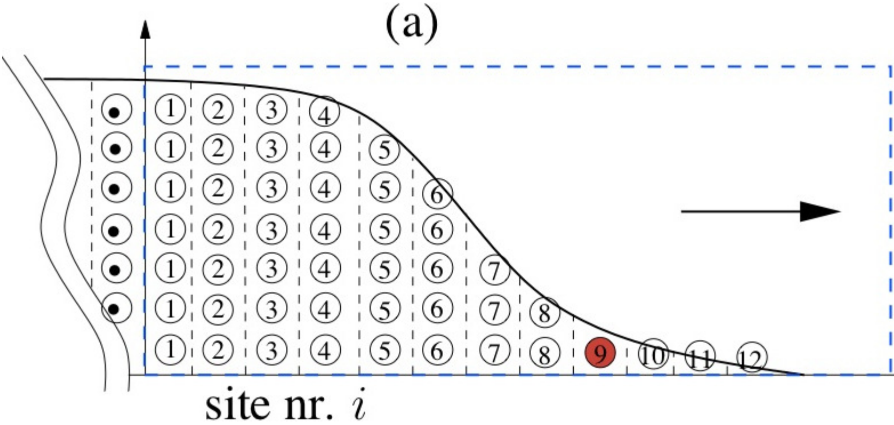
Out of Africa:



Prugnolle *et al.*, 2005

Gene surfing

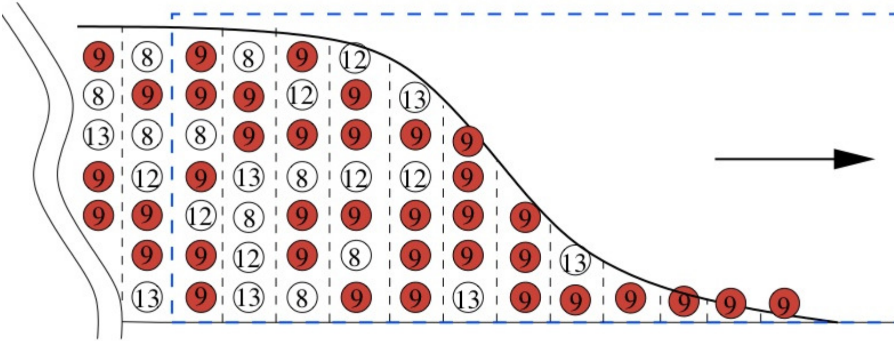
Hallatschek and Nelson, 2007



Gene surfing

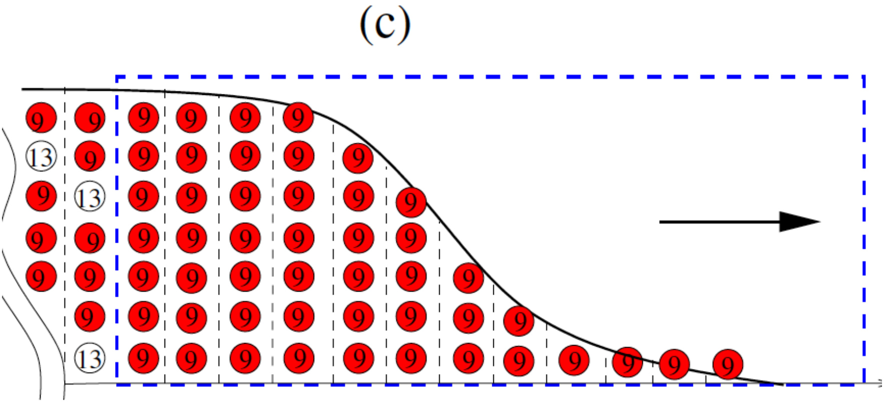
Hallatschek and Nelson, 2007

(b)

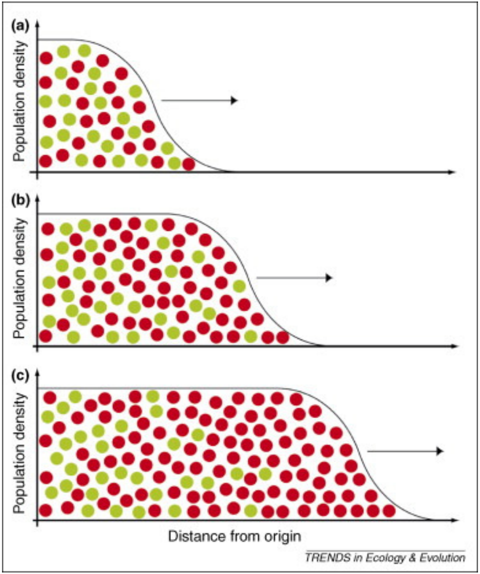


Gene surfing

Hallatschek and Nelson, 2007



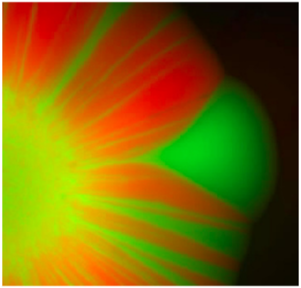
Gene surfing

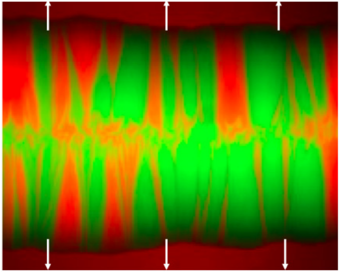


Excoffier and Ray, 2008

Experiments on a Petri dish

Haploid CFP and RFP-marked *S. Cerevisiae*





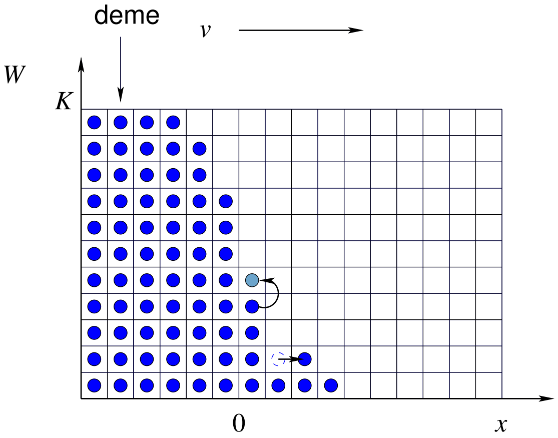
Hallatschek and Nelson, 2007

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

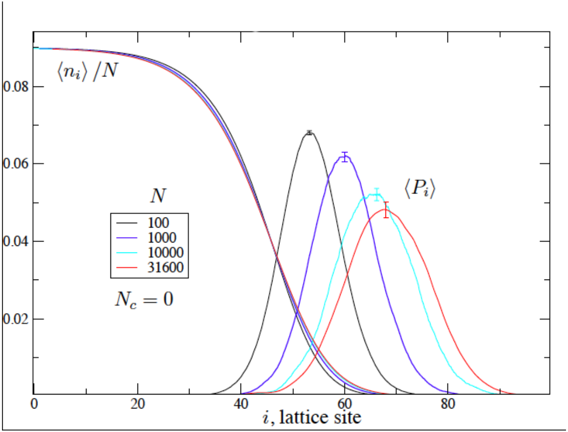


At each step:

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

The ancestor location in the neutral case

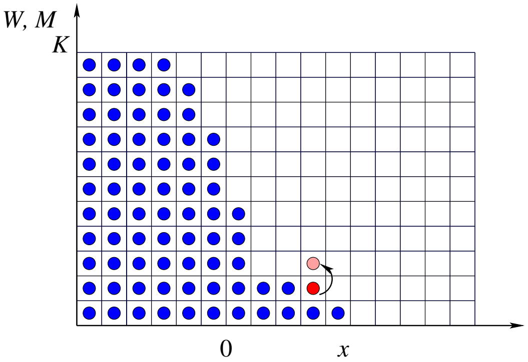
Hallatschek and Nelson, 2007



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: $p_{\mathrm{rep}} \propto K - (W + M)$
- Death: $p_{\mathrm{death}} \propto (1 - r_{\mathrm{m}}) p_{\mathrm{rep}}$ (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 (but they disappear from the window)

A stochastic reaction-diffusion system

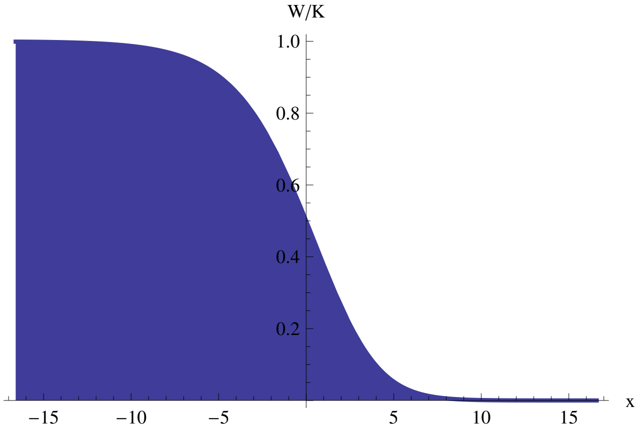
$$w = W/K \qquad m = M/K \qquad r_{\mathrm{w,m}} \ll 1$$

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

Can be made adimensional (depending only on $K_{\mathrm{e}} = K\sqrt{r_{\mathrm{w}}}$ and $\alpha = r_{\mathrm{m}}/r_{\mathrm{w}}$) by setting

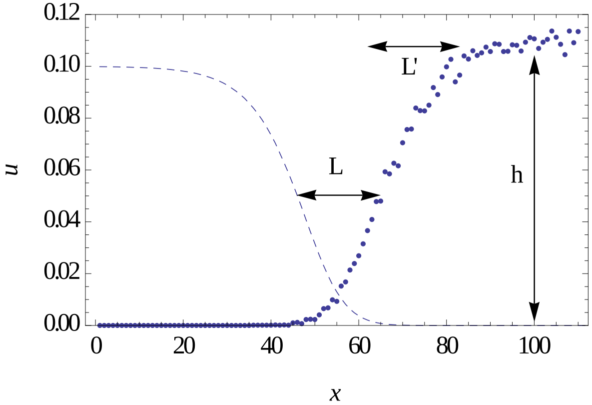
$$X = \sqrt{r_{\mathrm{w}}}\,x \qquad T = r_{\mathrm{w}} t$$

The Fisher wave



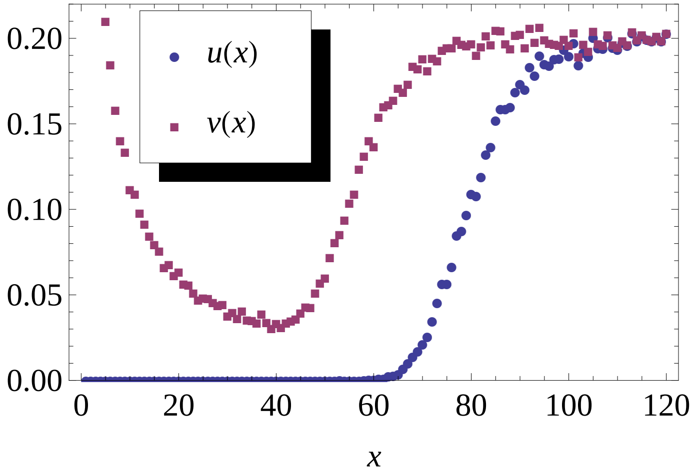
$v = 2\sqrt{Dr}$ (Fisher, 1937)

The fixation probability $u(x)$



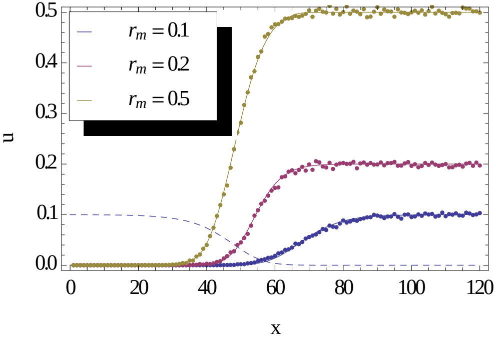
N.B.: Data for $r_w = 0.1$, $r_m = 0.11$

Fixation and failure



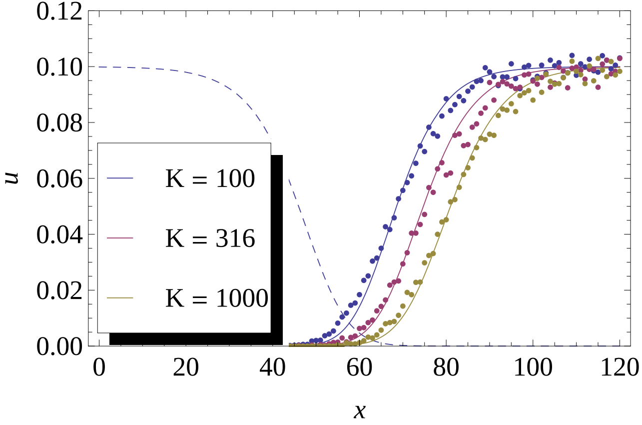
- $u(x)$: probability of fixation
- $v(x)$: probability of failure

Limit behavior of $u(x)$

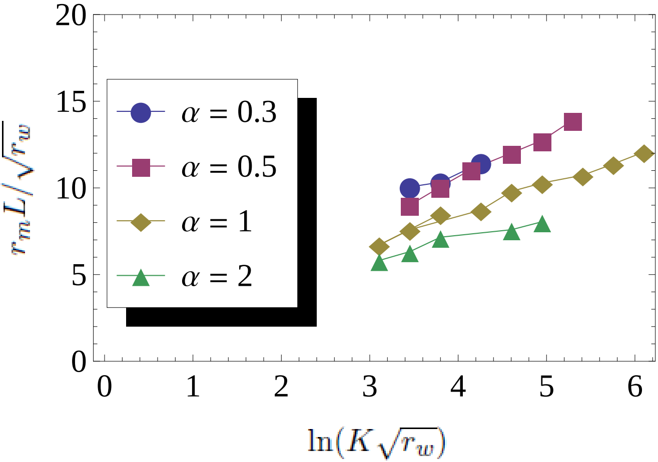


- For $x \to -\infty$, $u(x) \to 0$: neutral dynamics “against” an infinite population
- For $x \to +\infty$, $u(x) \to r_\mathrm{m}$: fixation *provided* the mutant survives sampling fluctuations

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 $m > m_{\mathrm{c}}(K_{\mathrm{e}}, \alpha)$
- 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 $x \to +\infty$

The large-x limit

- For $x \to +\infty$, 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 $(1 - r_{\text{m}})$ less likely than birth events
- Thus the survival probability $P_{m_{\text{tot}}}$ satisfies

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

  with boundary conditions

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

- Thus

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

  and

$$P_1 = r_{\text{m}}$$

The length L

Can we estimate the behavior of L?

- Speed of the advancing wildtype wave: $v \simeq 2\sqrt{r_\mathrm{w}}$ (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: $\langle N_\mathrm{m} \rangle \simeq \mathrm{e}^{r_\mathrm{m} t}$
- Thus $\langle \bar{N}_\mathrm{m} \rangle = \exp(r_\mathrm{m} t)/r_\mathrm{m}$
- Success requires $N_m(t_0) \geq m_\mathrm{c} K/\sqrt{r_\mathrm{m}}$
- Thus survival may take place if

$$x_0 > L \simeq \frac{v}{r_\mathrm{m}} \ln(m_\mathrm{c} K \sqrt{r_\mathrm{m}}) \approx \frac{\sqrt{r_\mathrm{w}}}{r_\mathrm{m}} \ln(K\sqrt{r_\mathrm{m}})\, f(\alpha, K_\mathrm{e})$$

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

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

The survival probability $u(x)$ apparently satisfies

$$\frac{\partial^2 u}{\partial x^2} - v_\mathrm{w}\frac{\partial u}{\partial x} + r_\mathrm{m}(1 - \langle w \rangle)u - u^2 = 0$$

with the boundary conditions

$$\lim_{x\to-\infty} u(x) = 0 \qquad \lim_{x\to+\infty} u(x) = r_\mathrm{m}$$

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 $r_{\mathrm{m}}(1 - \langle w(x) \rangle)$

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 $w(x, t) \simeq w(x, \tau) = w_{\mathrm{init}}(x)$
- Then $u(x)$ is the probability that the mutant in x fixes
- If all events are independent, $u(x)$ satisfies

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

- Differentiating wrt t we obtain

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

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

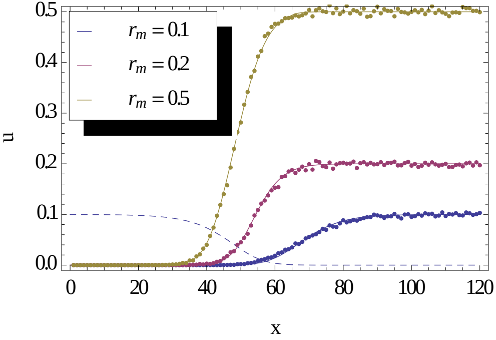
$$\frac{\partial p}{\partial t} = r_m \left(1 - \langle w \rangle_{init}\right) p + v \frac{\partial p}{\partial x} + \frac{\partial^2 p}{\partial x^2}$$

- Thus

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

  valid for $u \ll 1$
- The $-u^2$ term imposes $\lim_{x \to +\infty} u(x) = r_{\mathrm{m}}$

Comparison with the data



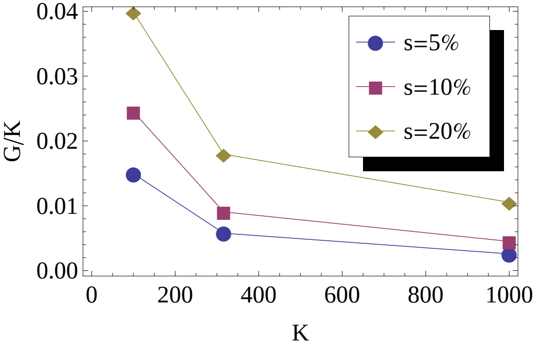
The lines correspond to the solution of the differential equation
The differential equation “correctly” evaluates L

The substitution rate

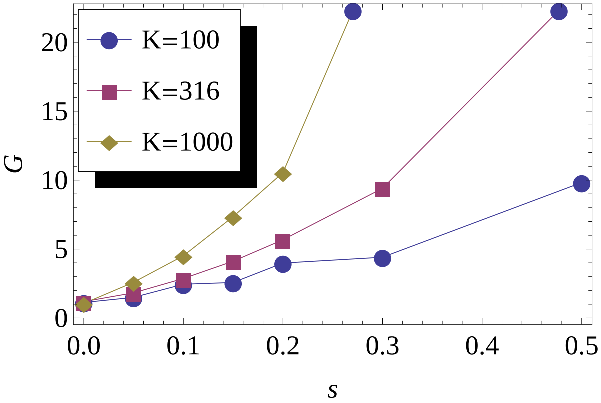
- Substitution rate R vs. the beneficial mutation rate U_b:

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

- 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 $G \propto K$



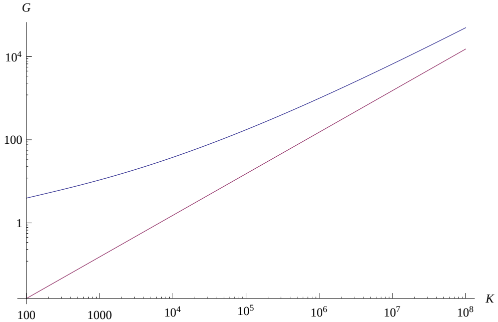
Results for G



Effects of finite density

By exploiting the analogy with travelling waves ($s = r_{\rm m}/r_{\rm w} - 1$)

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



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
- A similar phenomenon favors individuals with larger D (but equal fitness) (Pigolotti and Benzi, 2014)

- The moral:
  Rather than the “fittest” or “most deserving”
  Evolution favors those who are in the right place at the right moment!!