Adaptive walks in changing environments

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EBM

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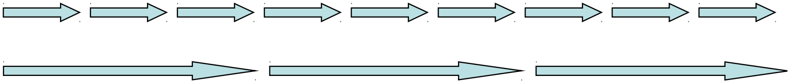
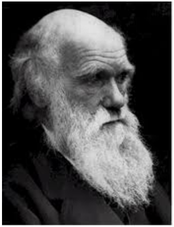
The genetic basis of adaptation



Does evolution proceed in small or large steps?

The genetic basis of adaptation

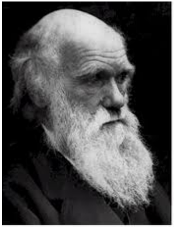
Darwin



"*Natural selection uses everyday variation and evolution proceeds in many small steps*"

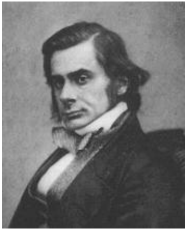
The genetic basis of adaptation

Darwin



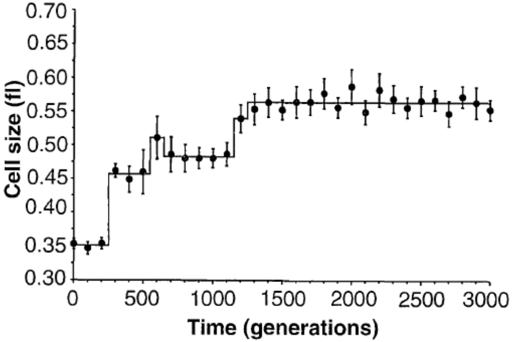
"*Natural selection uses everyday variation and evolution proceeds in many small steps*"

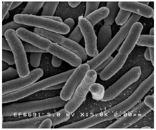
Huxley



"*Small variants will get lost. Selection uses occasional larger mutations*"

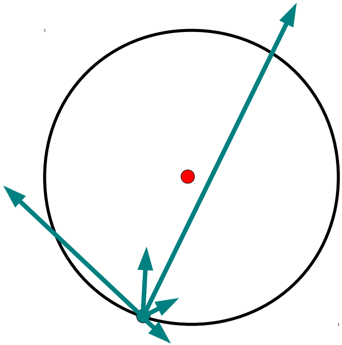
Evidence for large mutations: experimental evolution





From Elena (1996)

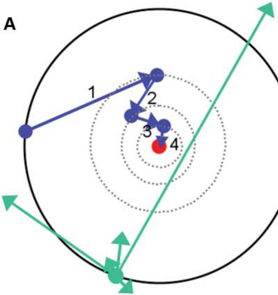
Fisher’s geometric model



From Farrell (2004)

Large mutations are likely to be deleterious.

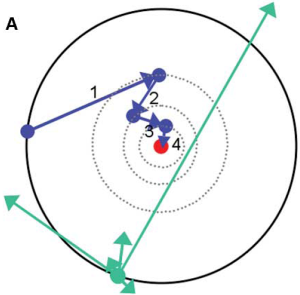
Models of “adaptive walks”



From Farrell (2004)

- **Fisher** (1930): Most large mutations are deleterious.

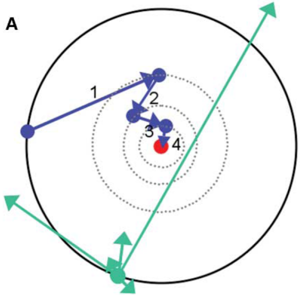
Models of “adaptive walks”



From Farrell (2004)

- **Fisher** (1930): Most large mutations are deleterious.
- **Kimura** (1983): But large beneficial mutations have high fixation probability.

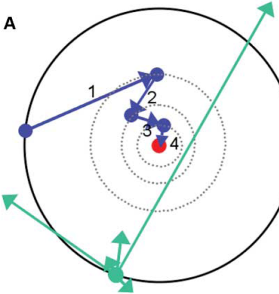
Models of "adaptive walks"



From Farrell (2004)

- **Fisher** (1930): Most large mutations are deleterious.
- **Kimura** (1983): But large beneficial mutations have high fixation probability.
- **Orr** (1998): Need to consider entire sequence.

Models of “adaptive walks”

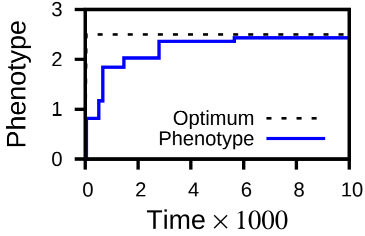


From Farrell (2004)

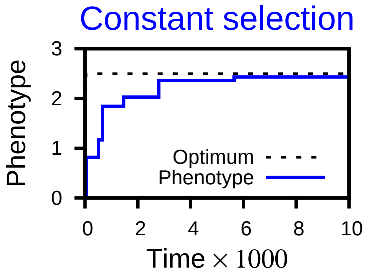
Key predictions:

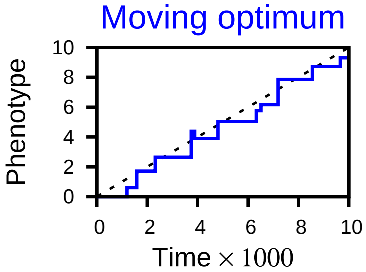
- **First steps are largest.**
- **Distribution of step sizes is exponential.**
- **Small overall number of steps**

Constant selection



Population approaches the optimum with diminishing returns.





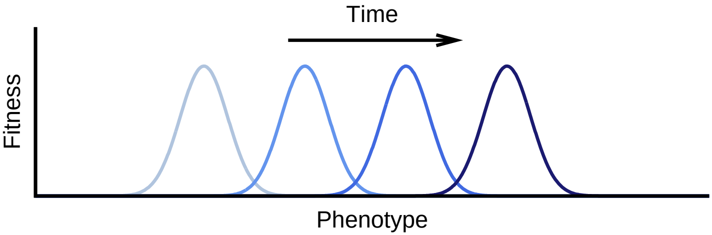
Population approaches the optimum with diminishing returns.

Population follows the optimum in a quasi-steady state.

Structure

- Part 1: Adaptation of a single trait
- Part 2: Adaptation of multiple traits (Fisher)

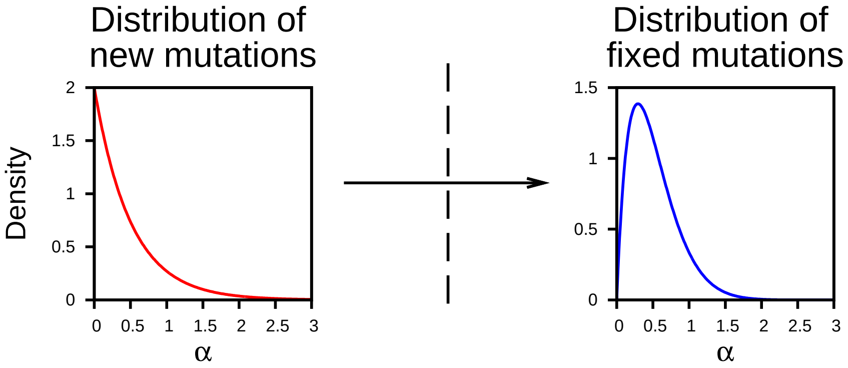
Single-trait model



- Optimal phenotype moves at speed v

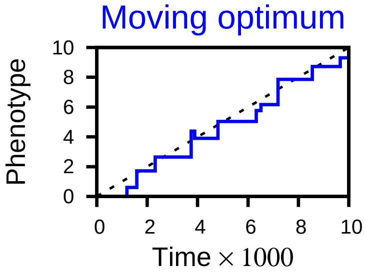
$$w(z,t) = \exp\left[-\sigma^{-1}(z - vt)^2\right].$$

- Recurrent mutations at rate μ
- Constant, finite population size N



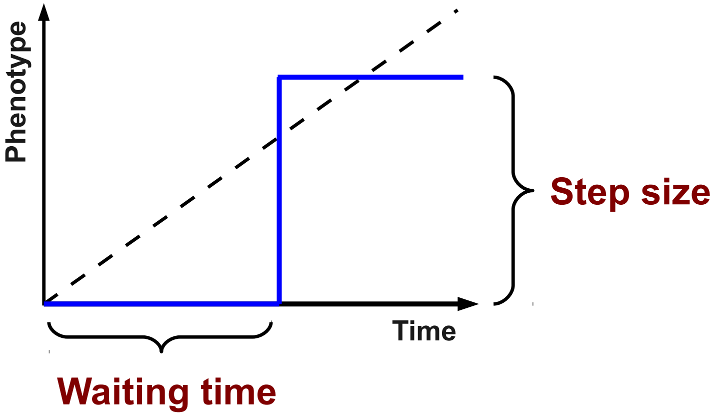
The selective environment acts as a **sieve**.

The adaptive walk approximation



- Neglect genetic details
- Assume instantaneous fixation
- $\Rightarrow$ Adaptation can be treated as a stochastic process.

Deriving the distribution of the first step



- Selection coefficient for a single beneficial mutation of size α

$$s_\alpha(t) = \frac{w(\alpha, t)}{w(0, t)} - 1 \approx \lambda_\alpha(t - \tau_\alpha)$$

with $\lambda_\alpha = 2\sigma^{-1}\alpha v, \tau_\alpha = \frac{\alpha}{2v}$ (lag time)

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- Rate of appearance: $N\mu p(\alpha) = \frac{\Theta p(\alpha)}{2}$
- Fixation probability: $2s_\alpha(t) \approx 2\lambda_\alpha(t - \tau_\alpha)$

Waiting time $T_{w,\alpha}$ for a *successful* mutation follows **inhomogenous Poisson process** with rate $2\Theta p(\alpha)\lambda_\alpha(t-\tau_\alpha)$ [for $t>\tau_\alpha$].

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Probability that mutation of size α has not yet fixed by time t:

$$F_\alpha(t) = \exp\left(-\frac{\Theta}{2}\lambda_\alpha(t-\tau_\alpha)^2\right).$$

Probability that no mutation of any size has fixed by time t:

$$F(t) = \prod_{\alpha < 2vt} \exp\left(-\frac{\Theta p(\alpha)}{2} \lambda_\alpha (t - \tau_\alpha)^2 \right)$$
$$= \exp\left(- \int_{\alpha < 2vt} \frac{\Theta p(\alpha)}{2} \lambda_\alpha (t - \tau_\alpha)^2 d\alpha \right)$$

Distribution of step size, given the step happens at time t:

$$\pi(\alpha|t) = \frac{s(\alpha, t)p(\alpha)}{\int_{\beta<2vt} s(\beta, t)p(\beta)d\beta}$$

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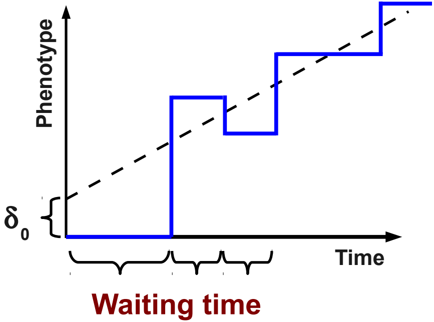
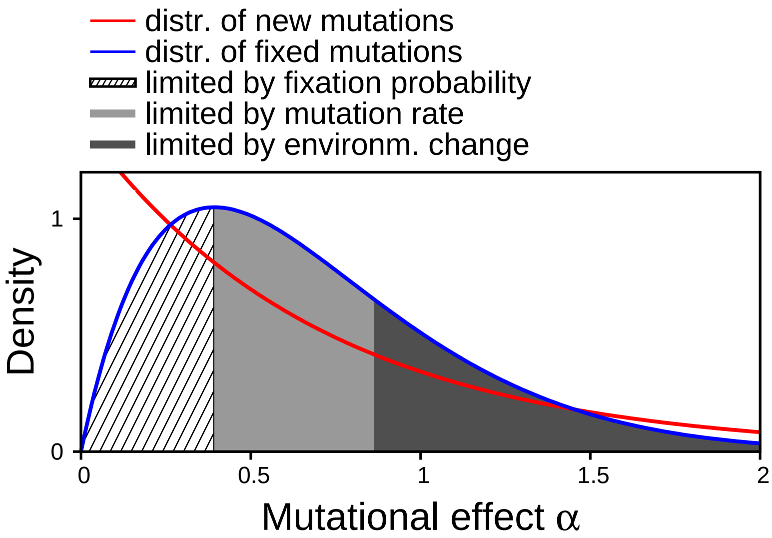
Unconditional distribution of first step

$$\pi(\alpha) = \int_{t=0}^{\infty} \frac{\Theta p(\alpha)}{2} 2s(\alpha, t)F(t)dt$$

Waiting time for an arbitrary next step



$$F(t|\delta_0) = \frac{\text{sign}(\delta_0 + vt)F\left(t + \frac{\delta_0}{v}|0\right)}{\text{sign}(\delta_0)F\left(\frac{\delta_0}{v}|0\right)}$$

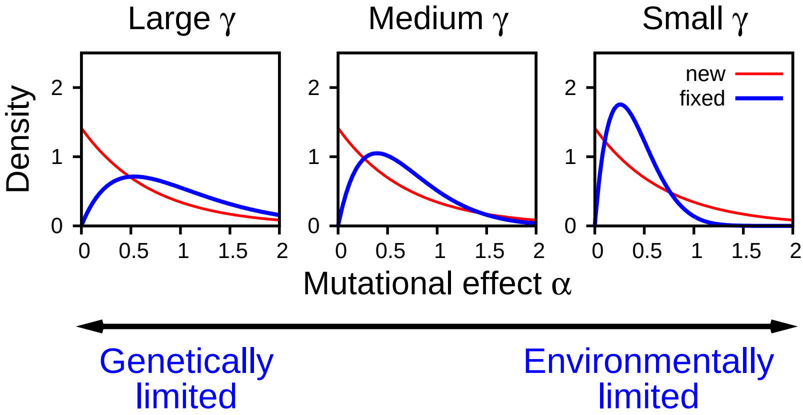

distr. of new mutations
distr. of fixed mutations
limited by fixation probability
limited by mutation rate
limited by environm. change
Density
1
0
0
0.5
1
1.5
2
Mutational effect α

A key composite parameter

$$\gamma = \frac{v}{\Theta\omega^3\sigma^{-1}} = \frac{\text{speed of optimum}}{\text{“adaptive potential”}}$$

- v = speed of optimum
- Θ = population-wide mutation rate
- ω = standard deviation of new mutations
- σ^{-1} = strength of stabilizing selection

$$\gamma = \frac{v}{\Theta\omega^3\sigma^{-1}} = \frac{\text{speed of optimum}}{\text{“adaptive potential”}}$$



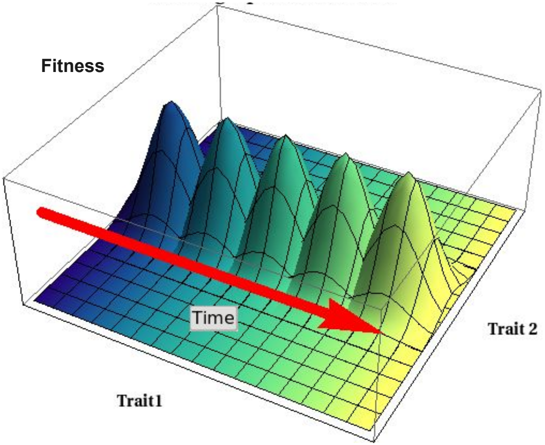
Explicit solution for first step in environmentally-limited case

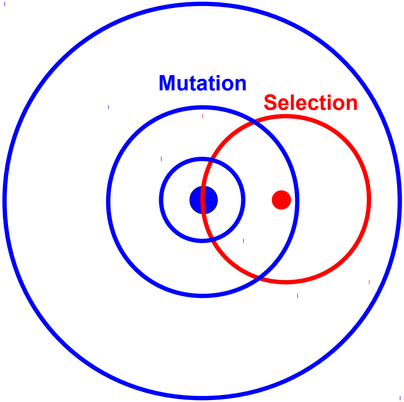
- Approximate $p(\alpha)$ by uniform $p(\alpha) = p_0$
- Waiting time distribution becomes

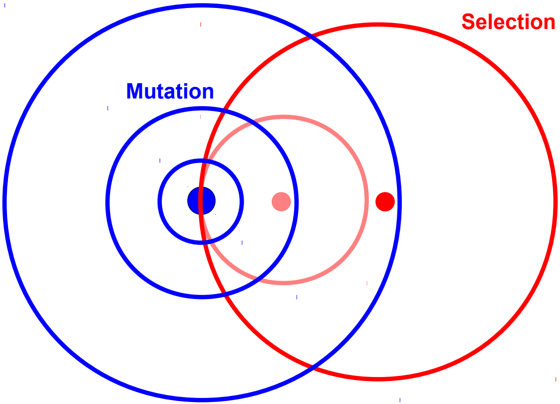
$$F(t) = \exp\left(-\frac{p_0(vt)^4}{3\gamma}\right)$$

- Mean waiting time: $\bar{t} = \frac{\Gamma(5/4)}{v}\left(\frac{3\gamma}{p_0}\right)^{1/4}$
- Mean step size: $\bar{\alpha} = v\bar{t}$.

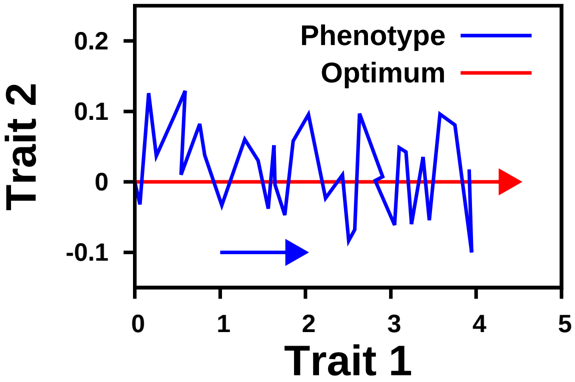
Fisher's model with a moving optimum




Mutation
Selection


Selection
Mutation

Adaptive walks



Fitness function

$$w(z,t) = \exp(-(z - vt)'\Sigma^{-1}(z - vt))$$

Selection coefficient

$$s_\alpha(t) = \frac{w(\alpha,t)}{w(0,t)} - 1 \approx \lambda_\alpha(t - \tau_\alpha)$$

with

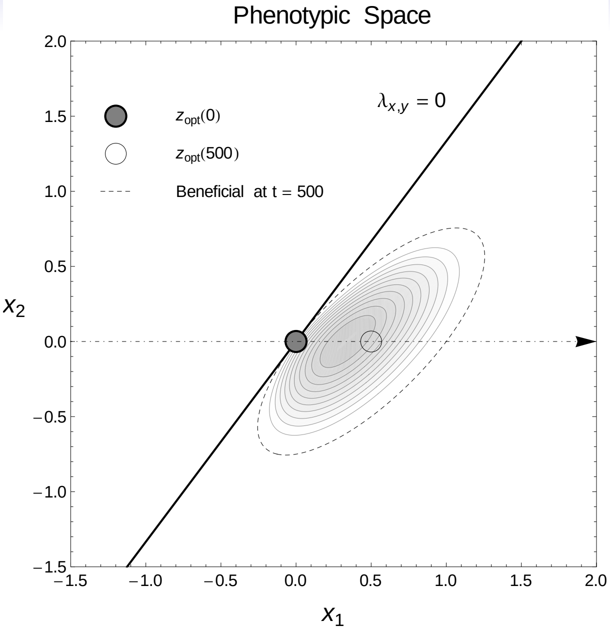
$$\lambda_\alpha = 2\alpha'\Sigma^{-1}v, \quad \tau_\alpha = \frac{\alpha'\Sigma^{-1}\alpha}{2\alpha\Sigma^{-1}v}$$

Waiting time to first step

Probability that no mutation of any size has fixed by time t is again:

$$F(t) = \exp\left(-\int_{s(\alpha,t)>0} \frac{\Theta p(\alpha)}{2} \lambda_\alpha (t-\tau_\alpha)^2 d\alpha\right)$$

The integral is over all mutations that have a positive selection coefficient at time t (ellipsoid around the current optimum).


Phenotypic Space
$\lambda_{x,y} = 0$
$z_{opt}(0)$
$z_{opt}(500)$
Beneficial at t = 500
x_2
x_1
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−1.5
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0

Assume that the distribution of new mutations, $p(\alpha)$ is multivariate normal.

In the environmentally-limited case, we approximate it by a uniform distribution $p(\alpha) = (2\pi)^{-T/2}$.

Then, the integral in $F(t)$ can be solved to

$$\kappa(t) = t^{T+3} \left(\sqrt{v' \Sigma^{-1} v}\right)^{T+2} \sqrt{\det(\Sigma)}\, \eta(T)\, \theta$$

with

$$\eta(T) = \frac{2^{-T/2}}{(T+3)\Gamma(2+T/2)} \tag{1}$$

To make further progress, we again consider the environmentally-limited case.

Assume the distribution of new mutations is multivariate normal, and is approximated by a uniform distribution, $p(\alpha) = (2\pi)^{-1/T}$.

Then, after some calculations, the mean size of the first step is

$$\bar{\alpha} = \frac{v}{||v||}\gamma^{\frac{1}{T+3}}\Gamma\left(\frac{T+4}{T+3}\right)$$

Composite parameter γ

$$\gamma = \frac{||v||}{p_0 \Theta \hat{\sigma}^{-1} \eta(T) \sqrt{|\Sigma_v|}}$$

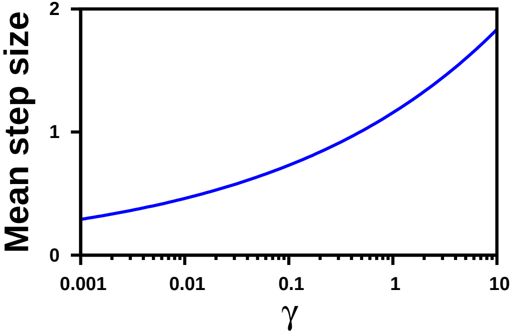
with

$$\eta(T) = \frac{\pi^{T/2}}{(T+3)\Gamma(2+T/2)}$$

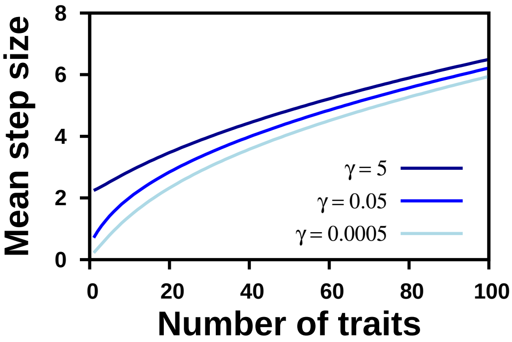
$$\hat{\sigma}^{-1} = \frac{v'\Sigma^{-1}v}{v'v} \text{ (selection in movement direction)}$$

$$\Sigma_v = \Sigma\hat{\sigma}^{-1}$$

The mean step size increases with γ



The mean step size increases with the number of traits



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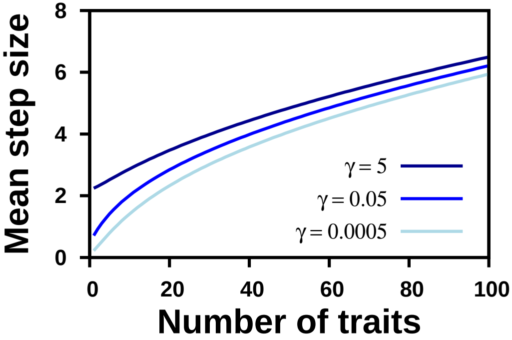
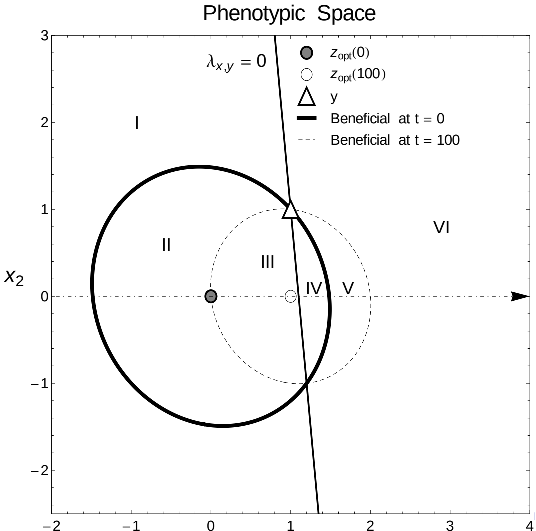
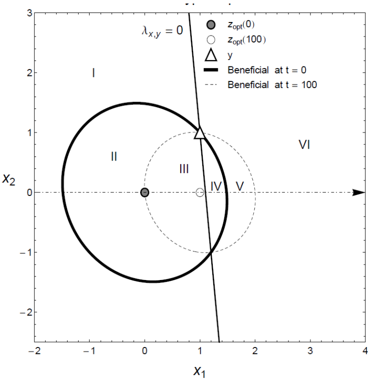


More traits ⇒ Fewer beneficial mutations ⇒ Longer waiting time between steps ⇒ Optimum moves farther away ⇒ Selection for larger mutations.

Wild-type different from initial optimum



1 minus waiting time



$$F_x(t) = \begin{cases} 1 & \text{Sector I} \\ \dfrac{1}{exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta\tau_{x,y}^2]} & \text{Sector II} \\ \dfrac{exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta(t-\tau_{x,y})^2]}{exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta\tau_{x,y}^2]} & \text{Sector III} \\ \dfrac{exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta(t-\tau_{x,y})^2]}{exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta\tau_{x,y}^2]} & \text{Sector IV} \\ exp[-\frac{1}{2}p(\boldsymbol{\alpha})\lambda_{x,y}\Theta(t-\tau_{x,y})^2] & \text{Sector V} \\ 1 & \text{Sector VI} \end{cases}$$