SOME MATHEMATICAL MODELS OF EVOLUTION

III: The infinitesimal model

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Thanks

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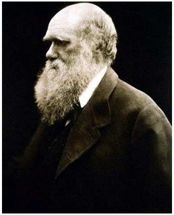
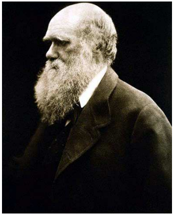
Traits and factors



Traits and factors

Darwin: Heritable traits that increase reproductive success will become more common in a population.



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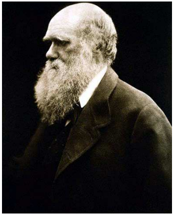

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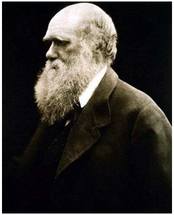

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Requires:

- Variation in population
- Offspring must be similar to parents

Mendel: Traits 'determined' by genes (factors).

- Genes occur in different types (alleles)
- Offspring inherit genes from parents

Complex traits?

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Toy example: M genes, each with 2 alleles, effects $\pm 1/\sqrt{M}$ on trait, say. Genetic component trait value

$$Z = z_0 + \sum_{l=1}^{M} \frac{\eta_l}{\sqrt{M}},$$

where $\eta_l = \pm 1$ with equal probability.

Fisher and natural selection

Fisher's infinitesimal model: the (genetic component of the) trait value of the offspring of two unrelated parents is the mean of the parental trait values plus a normally distributed error with mean zero and variance the *additive genetic variance*.

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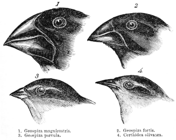
Fisher's fundamental theorem of natural selection: the rate of increase in mean fitness is proportional to the additive genetic variance in fitness.

"Natural selection is a mechanism for generating an exceedingly high degree of improbability."



The basic model

$$\text{Trait value} = \underbrace{\text{genetic}}_{Z} + \underbrace{\text{non-genetic}}_{E}$$

For today's purposes we ignore environmental component E.

Genetic component normally distributed; mean average of values in parents;

$$Z \sim \mathcal{N}\left(\frac{z_1 + z_2}{2}, V_0\right)$$

In a large outcrossing population, $V_0 =$ constant, otherwise decreases in proportion to relatedness.

The simplest case

Large outcrossing population. $Z \sim \mathcal{N}\left(\frac{z_1+z_2}{2}, V_0\right)$.

With purely random mating (neutral trait), the trait distribution in the population as a whole rapidly converges to a Gaussian with variance $2V_0$ (Bulmer, 1971).

If variance in parental population is V_1, that of offspring is

$$\frac{V_1}{2} + V_0,$$

At equilibrium, this is V_1, so $V_1 = 2V_0$.

Half variance is within families, half between.

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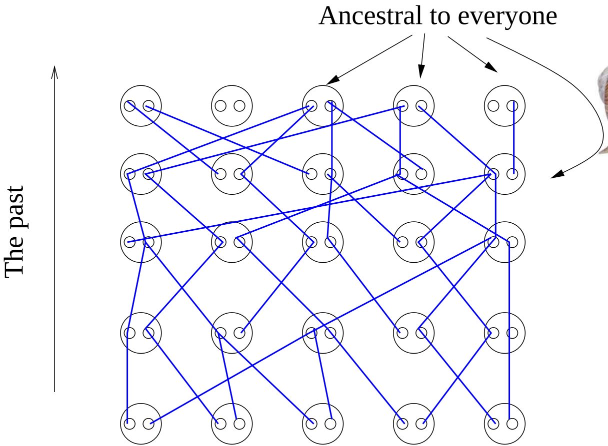
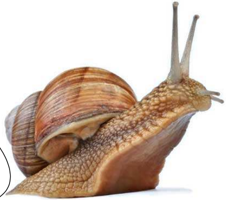
Trait distributions within families are normally distributed, with a variance-covariance matrix that is determined entirely by that in an ancestral population and the probabilities of identity determined by the pedigree.

As a result of the multivariate normality, conditioning on some trait values within the pedigree has predictable effects on the mean and variance within and between families.

A simple model of inheritance: the diploid Wright-Fisher model





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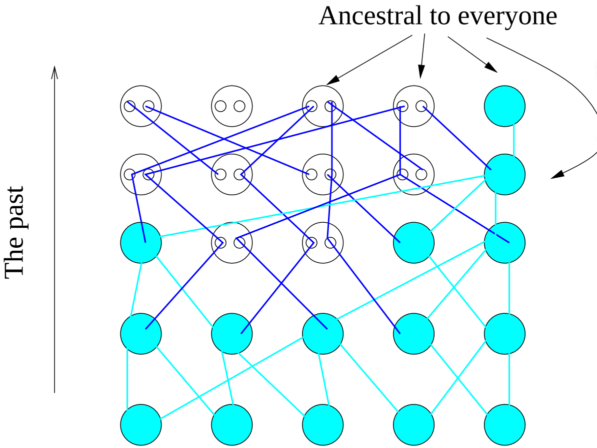
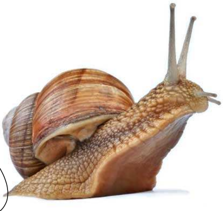


Ancestral to everyone

The past



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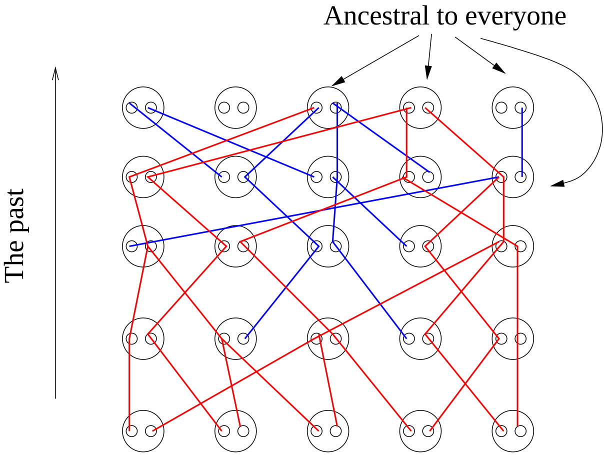

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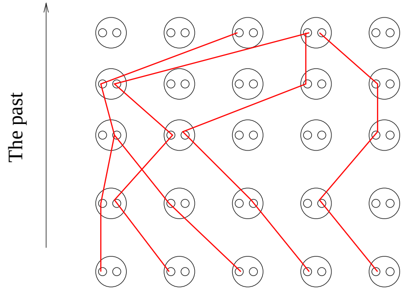

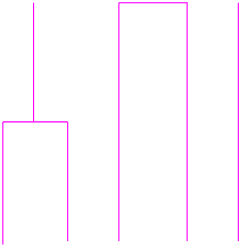

An aside on common ancestors

Theorem (Chang 1999)
Let τ_N be time to MRCA of population size N evolving according to diploid Wright-Fisher model (fixed population size, parents picked uniformly at random with replacement).

$$\frac{\tau_N}{\log_2 N} \xrightarrow{\mathbb{P}} 1 \quad \text{as } N \to \infty.$$

Theorem (Chang 1999)
Let $\mathcal{U}_N$ be time until all ancestors are either common to whole population or have no surviving progeny.

$$\frac{\mathcal{U}_N}{1.77 \log_2 N} \xrightarrow{\mathbb{P}} 1 \quad \text{as } N \to \infty.$$

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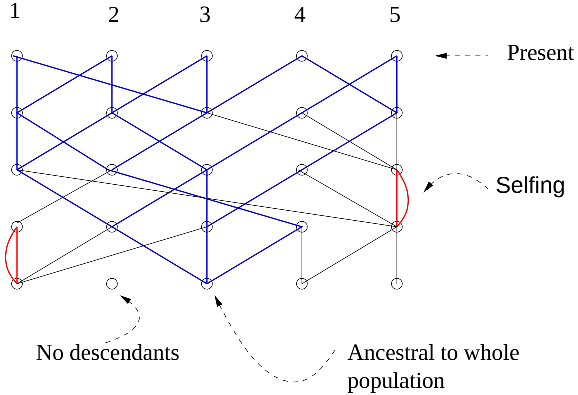
Contrast to timescales of N generations for Kingman's coalescent.

There are many routes through the pedigree.

Pedigrees and matrices

Time has turned around in these pictures!!!

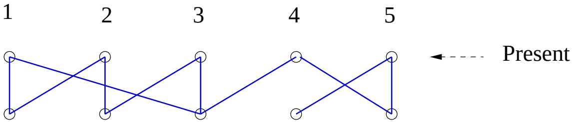
Each individual has *two* parents in the previous generation.



Pedigrees and matrices

Pedigree spanning t generations $\Leftrightarrow$ random matrices $M_0, \ldots, M_{t-1}$.

The ith row of M_t specifies parents of individual labelled i in generation t before the present.

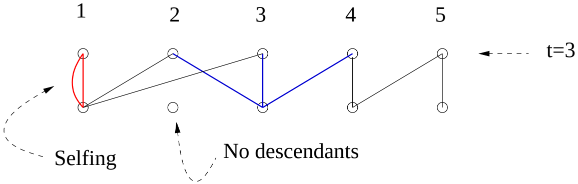


No need for constant population size

$$M_0 = \begin{pmatrix} \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ \frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & 0 & 0 & \frac{1}{2} & \frac{1}{2} \end{pmatrix}$$

Selfing

. . . or when there is selfing



$$M_3 = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & \frac{1}{2} & \frac{1}{2} & 0 \\ 0 & 0 & 0 & \frac{1}{2} & \frac{1}{2} \end{pmatrix}$$

Haploids versus diploids

Two models:

- Haploids $\rightsquigarrow$ mate to produce diploids $\rightsquigarrow$ immediate meiosis $\rightsquigarrow$ haploids;
- Diploids $\rightsquigarrow$ haploid gametes via meiosis $\rightsquigarrow$ immediately fuse $\rightsquigarrow$ diploids.

The distinction matters under selection on the trait; conditioning on the trait provides information about the whole genotype.

The probability of identity

Write $F_{ij}(t)$ for probability homologous genes in individuals labelled i, j in generation t descend from the same ancestral gene.

- Haploid case

$$F_{ij}(t) = \sum_{k,l} M_{ik}(t) M_{jl}(t) F_{kl}(t-1),$$

- Diploid case

$$F_{ij}(t) = \sum_{k,l} M_{ik}(t) M_{jl}(t) F^*_{kl}(t),$$

$$F^*_{kl} = F_{kl} \text{ if } k \neq l, \quad F^*_{kk} = \frac{1}{2}\left(1 + F_{kk}\right).$$

The infinitesimal model

Let

1. $\mathcal{P}^{(t)}$ denote the *pedigree* relationships between all individuals up to and including generation t;
2. $Z^{(t)}$ denote the *traits* of all individuals in the pedigree up to and including the tth generation.

Conditional on $\mathcal{P}^{(t)}$ and $Z^{(t-1)}$, ($[1]$, $[2]$ denote parents)

$$\left(Z_j - \frac{Z_j[1] + Z_j[2]}{2}\right)_{j=1,\ldots,N_t}$$

is (approximately) a mean zero multivariate normal with diagonal covariance matrix Σ_t.

$(\Sigma_t)_{jj}$ = *segregation variance* among offspring of the parents of individual j.

Why might it be a reasonable model?

Additive traits in haploids (no mutation)
M = number of (unlinked) loci affecting trait.

- Trait value in individual j:

$$Z_j = \bar{z}_0 + \sum_{l=1}^{M} \frac{1}{\sqrt{M}} \eta_{jl},$$

where $\bar{z}_0$ = average value in ancestral population.

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- Ancestral population. $\hat{\eta}_{jl}$ i.i.d (for different j), say.

Reproduction

$[1]$ and $[2]$ refer to the first and second parents of an individual.

- $\eta_{jl}[1]$ is the scaled allelic effect at locus l in the 'first parent' of the jth individual. Similarly, $Z_j[1]$ will denote the trait value of the 'first parent' of individual j.
- Write $X_{jl} = 1$ if the allelic type at locus l in the jth individual is inherited from the 'first parent' of that individual; otherwise it is zero. $\mathbb{P}[X_{jl} = 1] = 1/2 = \mathbb{P}[X_{jl} = 0]$.

$$
\begin{aligned}
Z_j &= \bar{z}_0 + \frac{1}{\sqrt{M}} \sum_{l=1}^{M} \{X_{jl}\eta_{jl}[1] + (1 - X_{jl})\eta_{jl}[2]\} \\
&= \frac{Z_j[1] + Z_j[2]}{2} + \frac{1}{\sqrt{M}} \sum_{l=1}^{M} \Big(\frac{1}{2} - X_{jl}\Big)\Big(\eta_{jl}[2] - \eta_{jl}[1]\Big).
\end{aligned}
$$

Conditioning

We would like to derive the distribution of trait values in generation t conditional on knowing $\mathcal{P}^{(t)}$ and $Z^{(t-1)}$.

$$Z_j = \frac{Z_j[1] + Z_j[2]}{2} + \frac{1}{\sqrt{M}} \sum_{l=1}^{M} \left(\frac{1}{2} - X_{jl}\right)\Big(\eta_{jl}[2] - \eta_{jl}[1]\Big).$$

Key: Need to be able to calculate the distribution of $\eta_{jl}[1]$ *conditional on* $Z^{(t-1)}$ and show that it is almost unaffected by the conditioning.

Then $\mathbb{E}[(\eta_{jl}^{[1]} - \eta_{jl}^{[2]})^2] \approx 2(1 - F_{[1][2]})\mathrm{var}(\hat{\eta}_l) \rightsquigarrow$ variance among offspring reduced proportional to probability of identity.

Back to our toy example

Suppose η_l are i.i.d. with $\eta_l = \pm 1$ with equal probability, $\bar{z}_0 = 0$.

$$Z = \frac{1}{\sqrt{M}} \sum_{l=1}^{M} \eta_l$$

Back to our toy example

Suppose η_l are i.i.d. with $\eta_l = \pm 1$ with equal probability, $\bar{z}_0 = 0$.

$$\begin{aligned}
\mathbb{P}[\eta_1 = 1 | Z = k/\sqrt{M}] &= \frac{\mathbb{P}\left[\sum_{l=1}^{M} \eta_l = k \middle| \eta_1 = 1\right]}{\mathbb{P}\left[\sum_{l=1}^{M} \eta_l = k\right]} \mathbb{P}\left[\eta_1 = 1\right] \\
&= \frac{\mathbb{P}\left[\sum_{l=2}^{M} \eta_l = (k-1)\right]}{\mathbb{P}\left[\sum_{l=1}^{M} \eta_l = k\right]} \mathbb{P}\left[\eta_1 = 1\right] \\
&= \frac{\frac{1}{2^{M-1}}}{\frac{1}{2^M}} \frac{\binom{M-1}{(M+k-2)/2}}{\binom{M}{(M+k)/2}} \mathbb{P}\left[\eta_1 = 1\right] \\
&= \left(1 + \frac{k}{M}\right) \mathbb{P}\left[\eta_1 = 1\right].
\end{aligned}$$

Toy example continued

If scaled allelic effects are i.i.d. Bernoulli,

$$\mathbb{P}\left[\eta_1 = 1 \middle| Z = \frac{k}{\sqrt{M}}\right] = \left(1 + \frac{k}{M}\right)\mathbb{P}\left[\eta_1 = 1\right].$$

For a 'typical' trait value, $k/M = \mathcal{O}(1/\sqrt{M})$.

For extreme values ($k = \pm M$), the trait gives complete information about the allelic effect at each locus.

For 'typical' k, the distribution of η_1 is almost unchanged because there are so many different configurations of allelic effects that correspond to the same trait value.

The infinitesimal model

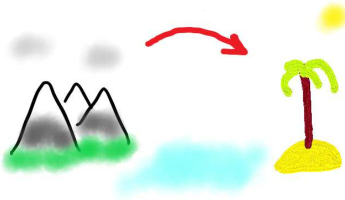
Conditional on $\mathcal{P}^{(t)}$ and $Z^{(t-1)}$,

$$\left(Z_j - \frac{Z_j[1] + Z_j[2]}{2}\right)_{j=1,\ldots,N_t}$$

converges (in distribution) to mean zero multivariate normal with diagonal covariance matrix Σ_t.

$(\Sigma_t)_{jj} =$ *segregation variance* among offspring of the parents of individual j.

Adapting to a new environment



- migration from a source population
- growth requires adaptation

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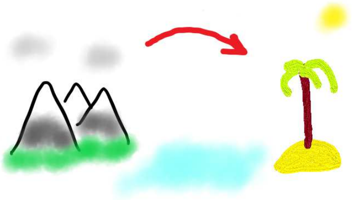

- migration from a source population
- growth requires adaptation

- chance that a single migrant establishes;
- time to establishment with steady migration;
- stationary distribution of trait and population size.

Adapting the infinitesimal model

Large source population, trait values $\sim \mathcal{N}(\bar{z}_s, 2V)$.

M (unrelated) migrants enter population in each generation.

$N(t)$ population size in generation t, $\overline{z}(t)$ mean trait value.

Before migrants arrive, number in next generation Poisson with expectation $N(t)\overline{W}$, where $\overline{W}$ mean fitness across offspring of random matings.

If $\overline{W} < 1$, then population only maintained by immigration.

Nick's model continued

Offspring of individuals i, j, have mean trait value given by the midparent value, variance:

- haploid parents $V_{ij} = V(1 - F_{ij})$,
- diploid parents $V_{ij} = V(1 - (F_{ii} + F_{jj})/2)$.

Assume the fitness of an individual with trait value z is $e^{\beta z}$.

$$N(t)\overline{W} = \frac{1}{N(t)} \sum_{i,j} \exp\left(\beta \frac{(z_i + z_j)}{2} + \frac{\beta^2}{2} V_{ij}\right).$$

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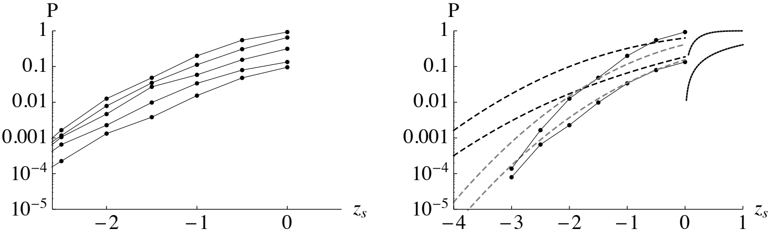
Expect density dependent fitness and stabilising selection to ultimately limit population size; assuming established before these are significant.

A single migrant, trait value z_0 (diploid)



Probability reach population size $\geq N = 100$. Source population $\mathcal{N}(\bar{z}_s, 1)$, $\beta = 0.125$, 0.25, 0.5, 1, 2 (bottom to top).

$\beta = 0.25$, 2. Solid curves, $z_0 = \bar{z}_s$. (Far right homozygous.) Black dashed curves, $z_0 \sim \mathcal{N}(\bar{z}_s, 1)$; grey dashed homozygous immigrant (population cannot evolve).

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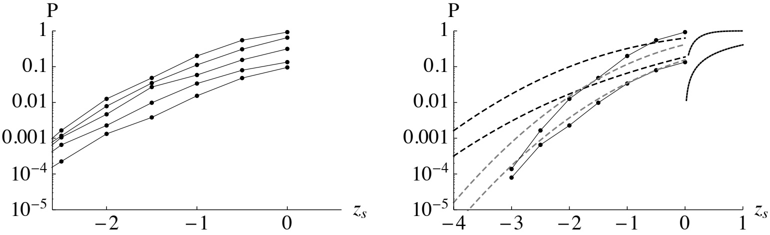

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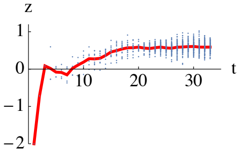
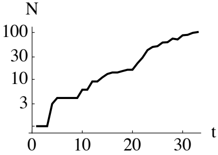
Establishment feasible from $\bar{z}_s$ 3 or 4 SD's below threshold for growth; necessary change in z contributed to similar degree by chance immigrant unusually fit,and subsequent evolution

Successful establishment

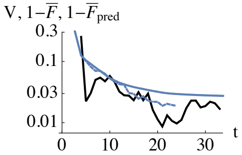
$z_0 = -2,\ \beta = 0.25.$



Trait values of each individual through time; red line = population mean.



Population size



Variance, $2V$, and heterozygosity, $1 - \overline{F}$ (solid, lower dashed).

Successful establishment

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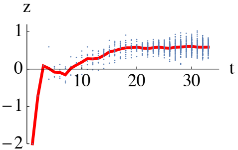

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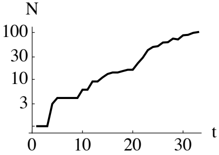

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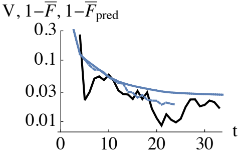

Variance, $2V$, and heterozygosity, $1 - \overline{F}$ (solid, lower dashed).

Upper curve on right shows the predicted heterozygosity if there were no selection, based on the population size: $\prod_t \left(1 - \frac{1}{2N_t}\right)$.

Steady migration: a 'deterministic' model

Assume that the trait distribution across the whole population is Gaussian. NOT a consequence of using the infinitesimal model.

First approximation: suppose population size and trait mean/variance evolve deterministically.

Each diploid migrant carrries half of the genetic variance in the source population, so modest rates of migration into a small 'sink' population can maintain high genetic variance.

Denote within family variance by V^*, assumed constant irrespective of origin of parents. (i.e. Assume $F = 0$, but can be a bit more sophisticated. Recall variance across population will then be $2V^*$.)

A recursion

The distribution of traits across the population $\sim \mathcal{N}(\bar{z}, 2V^*)$, so

$$\overline{W} = \exp\left(\beta \bar{z} + \beta^2 V^*\right),$$

After reproduction and the subsequent migration,

$$N(t+1) = M + N(t)\exp\left(\beta \bar{z}(t) + \beta^2 V^*\right);$$

$$\bar{z}(t+1) = \frac{1}{N(t+1)}\left(M \bar{z}_s + N(t)\mathbb{E}[z e^{\beta z}]\right),$$

(expectation is w.r.t. distribution of trait among offspring before selection, calculated by differentiating $\overline{W}$ w.r.t. β).

New coordinates

$$N(t+1) = M + N(t)\exp\left(\beta\bar{z}(t) + \beta^2 V^*\right);$$

$$\bar{z}(t+1) = \bar{z}(t) + 2\beta V^*\left(1 - \frac{M}{N(t+1)}\right) - \frac{M}{N(t+1)}\big(\bar{z}(t) - \bar{z}_s\big).$$

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$$N(t+1) = M + N(t)\exp\left(\beta \bar{z}(t) + \beta^2 V^*\right);$$

$$\bar{z}(t+1) = \bar{z}(t) + 2\beta V^* \left(1 - \frac{M}{N(t+1)}\right) - \frac{M}{N(t+1)}\left(\bar{z}(t) - \bar{z}_s\right).$$

Set $n = N/M$, $\alpha = \beta\sqrt{2V^*}$ and $y = (\bar{z} - \bar{z}_s)/\sqrt{2V^*}$.

New coordinates

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$$n(t+1) = 1 + n(t) W_s e^{\alpha y(t)}, \quad y(t+1) = (y(t) + \alpha)\left(1 - \frac{1}{n(t+1)}\right),$$

$$W_s = \exp\left(\beta \bar{z}_s + \beta^2 V^*\right)$$

(mean growth rate of the source population in the new conditions)

Critical behaviour

$$n(t+1) = 1 + n(t) W_s e^{\alpha y(t)}, \quad y(t+1) = (y(t) + \alpha)\left(1 - \frac{1}{n(t+1)}\right),$$

- If $W_s > W_{s,\mathrm{crit}}$, population size and trait increase together, regardless of M.
- If $W_s < W_{s,\mathrm{crit}}$, population may be unable to grow, regardless of how large is M; instead, it is maintained by migration as a poorly adapted ‘sink’.

The critical value

$$n(t+1) = 1 + n(t) W_s e^{\alpha y(t)}, \quad y(t+1) = (y(t) + \alpha)\left(1 - \frac{1}{n(t+1)}\right),$$

At equilibrium $y(t) = y(t+1) = \alpha(n-1)$, i.e., $y_{\text{crit}} = \alpha(n_{\text{crit}} - 1)$.

Writing $f(n) = 1 + n W_s e^{\alpha^2 (n-1)}$, must solve

$$n = f(n), \qquad 1 = f'(n).$$

Yields quadratic in n, whose positive solution is

$$n_{\text{crit}} = \frac{\alpha^2 + \sqrt{\alpha^4 + 4\alpha^2}}{2\alpha^2} = \frac{1}{2}\left(1 + \sqrt{1 + 4/\alpha^2}\right).$$

Back to original variables

$$N_{\text{crit}} = \frac{M}{2}\left(1 + \sqrt{1 + 2/(\beta^2 V^*)}\right),$$

$$W_{s,\text{crit}} = \frac{n_{\text{crit}} - 1}{n_{\text{crit}}} e^{-\alpha^2(n_{\text{crit}}-1)} = \left(1 - \frac{M}{N_{\text{crit}}}\right) e^{-\alpha^2(N_{\text{crit}}-M)/M},$$

$$\beta \bar{z}_{s,\text{crit}} = -\frac{1}{2}\alpha\left(\sqrt{4+\alpha^2}\right) - \log\left(\frac{\alpha + \sqrt{4+\alpha^2}}{-\alpha + \sqrt{4+\alpha^2}}\right).$$

For $\alpha = \beta\sqrt{2V^*} \ll 1$, $\beta \bar{z}_{s,\text{crit}} \sim -2\alpha$.

For $\alpha \gg 1$, $\beta \bar{z}_{s,\text{crit}} \approx -\alpha^2/2 - 2\log\alpha$.

A continuous time approximation

$$
\begin{aligned}
\frac{dN(t)}{dt} &= M + \beta \bar{z}(t) N(t); \\
\frac{d\bar{z}(t)}{dt} &= 2\beta V^{*} \left(1 - \frac{M}{2N(t)}\right) - \frac{M}{N(t)} (\bar{z}(t) - \bar{z}_s).
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Or, adding demographic stochasticity/ sampling drift,

$$\begin{aligned}dN(t) &= \Big\{M + \beta\bar{z}(t)N(t)\Big\}dt + \sqrt{N(t)}dW_t^1;\\ d\bar{z}(t) &= \left\{2\beta V^*\left(1-\frac{M}{2N(t)}\right)-\frac{M}{N(t)}(\bar{z}(t)-\bar{z}_s)\right\}dt\\ &\qquad\qquad + \sqrt{\frac{2V^*}{N(t)}}dW_t^2.\end{aligned}$$

Demographic stochasticity/sampling drift

Introduce the potential, U:

$$U = M \log N + \beta(N - \frac{M}{2})\bar{z} - \frac{M}{4V^*}\left(\bar{z} - \bar{z}_s\right)^2 .$$

$$\begin{aligned} dN &= \Big\{N \frac{\partial U}{\partial N}\Big\} dt + \sqrt{N} dW_t^1, \\ d\bar{z} &= \Big\{\frac{2V^*}{N} \frac{\partial U}{\partial \bar{z}}\Big\} dt + \sqrt{\frac{2V^*}{N}} dW_t^2 \end{aligned}$$

The ‘stationary distribution’

If there *were* a stationary distribution, it would satisfy

$$\psi \propto \frac{e^{2U}}{N} = N^{2M-1}\exp\left(\beta(2N-M)\bar{z} - \frac{M}{2V^*}\left(\bar{z}-\bar{z}_s\right)^2\right).$$

Diverges for large N, $\bar{z}$; should approximate the density near to a stable ‘sink’ equilibrium, when that exists.

- N^{2M-1}, migration that increases population size;
- $e^{\beta(2N-M)\bar{z}}$, directional selection on the trait;
- $e^{-M(\bar{z}-z_s)^2/2V^*}$, gene flow that pulls the trait mean towards the source.

More on the stationary distribution

For given N, the trait mean is normally distributed, with variance V^*/M, and mean

$$\mathbb{E}\left[\bar{z}\right] = \bar{z}_s + \beta V^*(2N - M)/M;$$

Deterministic equilibrium in which selection $2\beta V^*(1 - M/2N)$ increases the trait mean, but is opposed by gene flow at rate M/N.

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Integrating over $\bar{z}$, distribution of N proportional to

$$N^{2M-1} \exp\left(\beta^2 (2N - M)^2 \frac{V^*}{2M} + \beta(2N - M)\bar{z}_s\right).$$

If $M > 1/2$ and $\bar{z}_s < -2\sqrt{V^*(1 - 1/(2M))} + \beta V^*/2 \sim -2\sqrt{V^*}$, distribution has a peak at low density, and with $\bar{z} < 0$.
Metastable ‘sink’ population maintained by gene flow despite maladaptation.

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Work of Sacha Rybaltchenko on a string of colonies strengthens this last point, but note reduction in variance impedes ability to further adapt.