



Population Genetics and Evolution – II

The Mechanisms of Evolution: Mutation and Drift

Bengaluru / December 2017

SMRI (Italy)

luca@peliti.org

Mutations

Mutations and selection

Drift

Mutations

Hardy-Weinberg equilibrium

- Sexual reproduction, diploid genome
- Notation: A, a variant *alleles* at one *locus* (ultimately, DNA subsequences)
- Genotypes: AA & aa *homozygotes*, Aa *heterozygote* (same as aA)
- Population of size N , with genotype frequency vector (x_{AA}, x_{Aa}, x_{aa})
- Then $p = 2x_{AA} + x_{Aa}$ is the frequency of the A allele, and $q = 2x_{aa} + x_{Aa}$ that of the a allele

Hardy-Weinberg equilibrium

- **Hardy-Weinberg theorem:** Assume
 - Large population (fluctuations are neglected)
 - Neutral genotypes (fitness equal for everybody)
 - Mating is random (*panmictic* population)
- Then, *at the next generation*:

$$x_{AA} = p^2 \quad x_{Aa} = 2pq \quad x_{aa} = q^2$$

- Allele frequencies determine the genotype frequencies!

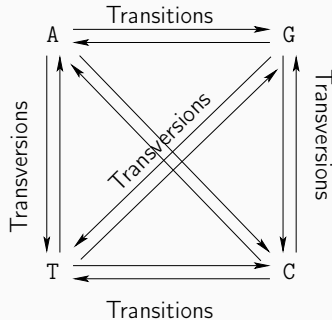
Nature of mutations

- Sequence mutations are changes in the offspring DNA wrt that of its parent(s)
- According to their *nature*, *small* (point) mutations are:

Transitions: $A \rightleftharpoons G$ or $C \rightleftharpoons T$

Transversions: $A \rightleftharpoons C, T$ or $G \rightleftharpoons C, T$

Indels: Insertion or deletion of a short nucleotide sequence



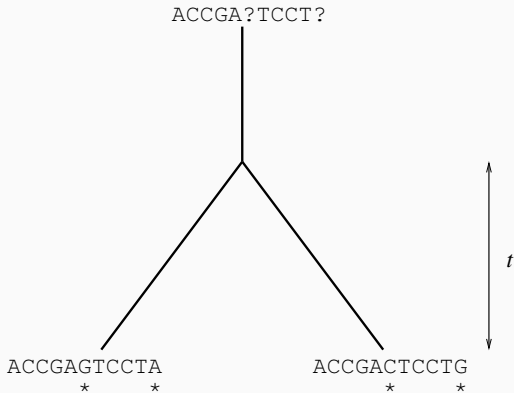
Mutations in coding sequences

- In *coding sequences* each nucleotide triplet codes for a codon
- According to their *effects* mutations are:
 - Synonymous or silent:** The mutated codon corresponds to the same amino acid (weakest effect)
 - Non-synonymous or missense:** The mutated codon corresponds to a *different* amino acid (stronger effect)
 - Nonsense:** The replacement changes the codon into one of the stop ones (*much* stronger effect)
- Indels with a length which is *not* a multiple of 3 produce **reading frame shifts**: all codons after the indel are affected (strongest effect)

Mutation rates

- Mutations are a *stochastic process*, due both to the effect of the environment and of the organism's internal workings
- Mutation rates can be estimated by comparing *orthologous* sequences in two related life forms and counting changes
- One assumes a simple mutation model and estimates its parameters by making the comparison

Mutation rates



Jukes' rule: the time separation between the two sequence is $2t$
Assumes that backward evolution is the same as forward evolution
(*reversibility*)

Mutation rates

- The comparison evaluates *substitution* rates, rather than *mutation* rates
- However, for *neutral* mutations the rates are equal (see later) (*Kimura*)
- The estimate is based on four general assumptions (all of them false!):
 1. The rates are uniform (do not depend on the position in the genome)
 2. They are constant in time
 3. They are the same for the two branches
 4. The equilibrium frequencies of the nucleotides are the same for the ancestral sequence and for the two “evolved” ones

Model for nucleotide substitution

- **Substitution matrix** $W = (\mu_{ji})$: rate of substitution $j \leftarrow i$, $i, j \in \{A, G, C, T\}$
- Frequency of base i : $f_i(t)$
- Evolution equation for f_i :

$$\frac{df_i}{dt} = \sum_{j (\neq i)}' [\mu_{ij} f_j - \mu_{ji} f_i]$$

- Equilibrium frequencies: f_i^{eq} : $\sum_{j (\neq i)} [\mu_{ij} f_j^{\text{eq}} - \mu_{ji} f_i^{\text{eq}}] = 0$
- **Evolution matrix** $P(t) = (p_{ji}(t))$: conditional probability to find nucleotide j at time t , given that nucleotide i was in that position at $t = 0$
- Observed data: **Divergence matrix** $X(t) = (x_{ji}(t))$: joint pdf to find nucleotide j in the first sequence and nucleotide i at the same position in the second sequence

Model for nucleotide substitution

- Equation for $P(t)$:

$$\frac{dp_{ij}}{dt} = \sum_{k (\neq i)}' [\mu_{ik}p_{kj} - \mu_{ki}p_{kj}] \quad p_{ij}(0) = \delta_{ij}$$

- Divergence matrix:

$$X(t) = P(t)X(0)P^T(t) \quad x_{ij}(0) = f_i^{\text{eq}}\delta_{ij}$$

- Symmetry: $X^T = X$, i.e., $x_{ji}(t) = x_{ij}(t)$ (not exactly satisfied due to sampling errors)
- Normalization constraint on the diagonal elements:
$$2x_{ii} = 2f_i - \sum_{i (\neq j)}' x_{ij} - \sum_{j (\neq i)}' x_{ji}$$
- Thus the divergence matrix X (16 entries) has only 6 independent parameters

Model for nucleotide substitution

Jukes-Cantor model

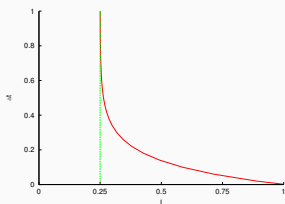
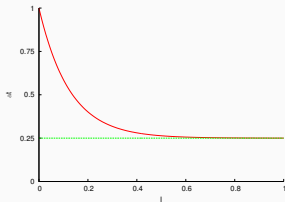
All substitutions are equally probable:

$$\mu_{ij} = \alpha, \forall (i \neq j)$$

- $f_i^{\text{eq}} = \frac{1}{4}, \forall i;$
 $p_{ij}(t) = \frac{1}{4} (1 - e^{-4\alpha t} + 4\delta_{ij}e^{-4\alpha t})$
- Probability of observing the *same* nucleotide in the two sequences:

$$\mathcal{I}(t) = \frac{1}{4} (1 + 3e^{-8\alpha t})$$

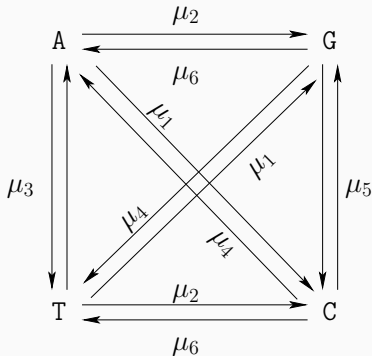
- Thus $\alpha t = -\frac{1}{8} \ln \left(\frac{4\mathcal{I}-1}{3} \right)$



Model for nucleotide substitution

General 6-parameter model

- A substitution $A \leftarrow C$ implies the corresponding substitution $T \leftarrow G$ in the opposite strand
- Thus $w_{AC} = w_{TG}$, ecc.
- Thus we have only 6 independent rates from *stable sequences*:



Reversibility vs. detailed balance

O. ZAGORDI AND J.-L. LOBRY, 2005

- Detailed balance: $\mu_{ij}f_j^{\text{ex}} = \mu_{ji}f_i^{\text{ex}}, \forall i \neq j$
- Reversibility: $P(-t) = P(t)$ (needed by Jukes' rule)
- Theorem: Reversibility \Leftrightarrow Detailed balance
- Problem: A model which fits the data is reversible?
- Answer: Chargaff rule: $f_A = f_T, f_G = f_C$ (*no strand bias*)
- There are only *five* independent observable quantities in \mathbf{X} !
- One can impose an additional constraint on the model, e.g., $\mu_1\mu_6 = \mu_2\mu_4$ (reversibility)

Infinite allele and infinite site model

- We often want to model mutations starting from a given wild type
- **Infinite allele model:** *Each mutation produces a wholly new genotype*
- No structure in the mutants: all mutants are as different from the wild type as from each other
- **Infinite site model:** *Each mutation hits a different site*
- Mutants can be binned in k -classes: Classes with k mutations wrt wild type

Mutations and selection

A simple model

(Cf. Kavita's lecture 1)

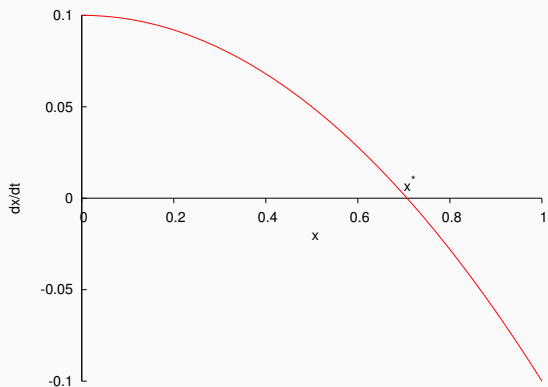
- Population with two types: A and B
- Selection coefficient $s = f_A - f_B$
- **Mutation:** $A \xrightleftharpoons{\mu} B$

Evolution equation:

$$\frac{dx}{dt} = sx(1-x) + \mu(1-x) - \mu x = sx(1-x) + \mu(1-2x)$$

A simple model

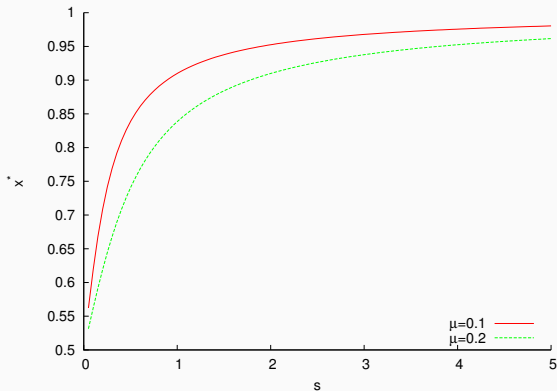
(Cf. Kavita's lecture 1)



A simple model

(Cf. Kavita's lecture 1) Fixed point x^* :

$$x^* = \frac{s - 2\mu + \sqrt{s^2 + 4\mu^2}}{2s}$$



Optimization?

- $\langle f \rangle_x = f_A x + f_B(1 - x)$ is not maximal at x^*
- But define

$$\Phi(x) = \underbrace{\langle f \rangle_x}_{\text{“energy”}} + \underbrace{\mu \log [x(1 - x)]}_{\text{“entropy”}}$$

- Then

$$\begin{aligned} \frac{d\Phi}{dt} &= s \frac{dx}{dt} + \mu \frac{1 - 2x}{x(1 - x)} \frac{dx}{dt} \\ &= x(1 - x) \left[s + \mu \frac{1 - 2x}{x(1 - x)} \right]^2 \geq 0 \end{aligned}$$

- Φ increases and reaches its maximum at the fixed point

Multiple alleles

- r alleles: $\alpha \xrightarrow{\mu} \beta \quad \alpha, \beta = 1, \dots, r \quad \mu(\alpha \rightarrow \beta) = \mu_{\beta}$
- Set $x_r = 1 - \sum_{j=1}^{r-1} x_j$
- Define:

$$s_j = f_j - f_r = \frac{\partial \langle f \rangle_{\mathbf{x}}}{\partial x_j}, \quad j = 1, \dots, r-1$$

$$\Gamma_{jk}(\mathbf{x}) = \begin{cases} -x_j x_k, & \text{if } j \neq k \\ x_j(1 - x_j), & \text{if } j = k \end{cases} \quad \Gamma \text{ positive definite}$$

- Evolution equation for $\mathbf{x} = (x_1, \dots, x_{r-1})$:

$$\frac{dx_j}{dt} = \sum_{k=1}^{r-1} \Gamma_{jk}(\mathbf{x}) s_k + \mu_j(1 - x_j) - x_j \sum_{\alpha(\neq j)}' \mu_{\alpha}$$

Optimization II

- Define

$$M(\mathbf{x}) = \sum_{\alpha} \mu_{\alpha} \log x_{\alpha}$$

- Then

$$\sum_k \Gamma_{jk}(\mathbf{x}) \frac{\partial M}{\partial x_k} = \mu_j(1 - x_j) - x_j \sum_{\alpha(\neq j)}' \mu_{\alpha} = \mu_j - x_j \sum_{\alpha} \mu_{\alpha}$$

and

$$\begin{aligned} \frac{dx_j}{dt} &= \sum_k \Gamma_{jk}(\mathbf{x}) \frac{\partial}{\partial x_k} [\langle f \rangle_{\mathbf{x}} + M(\mathbf{x})] = \sum_k \Gamma_{jk}(\mathbf{x}) \frac{\partial \Phi}{\partial x_k} \\ \Phi(\mathbf{x}) &= \langle f \rangle_{\mathbf{x}} + M(\mathbf{x}) \end{aligned}$$

- Thus

$$\frac{d\Phi}{dt} = \sum_{j,k} \frac{\partial \Phi}{\partial x_j} \Gamma_{jk}(\mathbf{x}) \frac{\partial \Phi}{\partial x_k} \geq 0$$

The quasispecies (QS) model

M. EIGEN, 1971

- Nonoverlapping generations; large number of alleles
- Mutation rate $k \xrightarrow{Q_{k\ell}} \ell$ depending on “distance” of alleles
- Evolution equation for $\mathbf{x} = (x_1, \dots, x_r)$:

$$x_j(t+1) = \frac{1}{\langle W \rangle_{\mathbf{x}}} \sum_{k=1}^r Q_{jk} W_k x_k(t)$$

where $\langle W \rangle_{\mathbf{x}} = \sum_j W_j x_j$

Asymptotic behavior of the QS model

- Define the unnormalized population vector $\mathbf{y}(t)$:

$$\begin{aligned}\mathbf{y}(0) &= \mathbf{x}(0) \\ y_j(t+1) &= \sum_{k=1}^r Q_{jk} W_k y_k(t) = \sum_{k=1}^r T_{jk} y_k(t)\end{aligned}$$

- Decompose \mathbf{y} according to the right eigenvectors of $\mathbb{T} = (Q_{jk} W_k)$:

$$\begin{aligned}\mathbf{y} &= \sum_{\kappa} c_{\kappa} \boldsymbol{\xi}^{(\kappa)} \\ \mathbb{T} \cdot \boldsymbol{\xi}^{(\kappa)} &= \lambda^{(\kappa)} \boldsymbol{\xi}^{(\kappa)}\end{aligned}$$

- **Perron-Frobenius theorem:** the largest eigenvalue $\lambda^{(0)}$ is positive and has a unique right eigenvector $\boldsymbol{\xi}^{(0)}$, $\xi_i^{(0)} > 0$, $\forall i$
- Thus, for $n \gg 1$

$$\mathbb{T}^n \cdot \mathbf{y} = \sum_{\kappa} \left(\lambda^{(\kappa)}\right)^n c_{\kappa} \boldsymbol{\xi}^{(\kappa)} \simeq \left(\lambda^{(0)}\right)^n c_0 \boldsymbol{\xi}^{(0)}$$

The composition vector \boldsymbol{x}

Since

$$\boldsymbol{x}(t) = \frac{\boldsymbol{y}(t)}{\sum_j y_j(t)}$$

we have

$$\lim_{t \rightarrow \infty} \boldsymbol{x}(t) = \boldsymbol{\xi}^{(0)}$$

independently of the initial condition

The error threshold

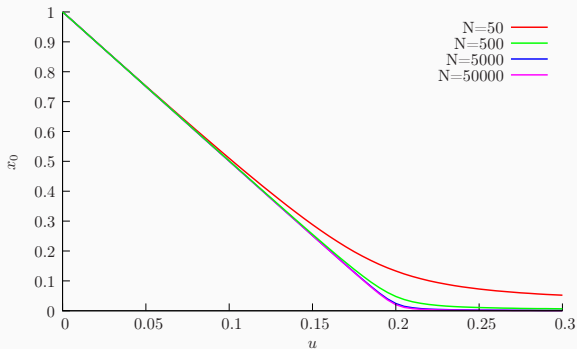
- One optimal genotype 0: $W_0 > W_k = W, \forall k \neq 0, r \gg 1$
- Mutation probability $\mu \rightarrow 0$: $\mu r = u$
- Define $W/W_0 = 1 - s$
- Then

$$x_0(t+1) = \frac{W_0(1-u)x_0}{W_0x + W(1-x_0)} = \frac{(1-u)x_0}{1-s+sx_0}$$

The error threshold

Fixed point:

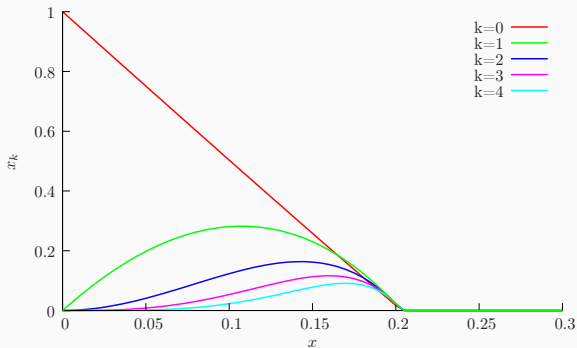
$$x_0^* = 1 - \frac{u}{s}$$



Selection factor $s = 0.2$

Error classes

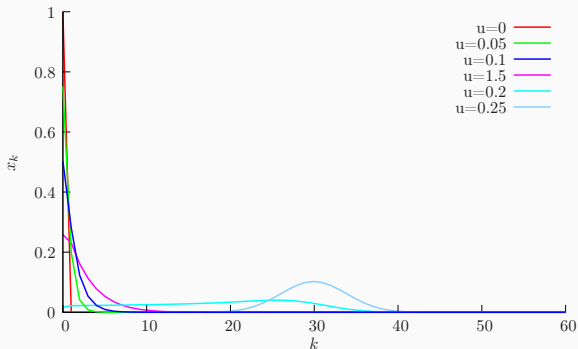
x_k : fraction of individuals with k "errors" with respect to selected type



$N = 60$ loci, two alleles, selection factor $s = 0.2$

Error classes

x_k : fraction of individuals with k “errors” with respect to selected type



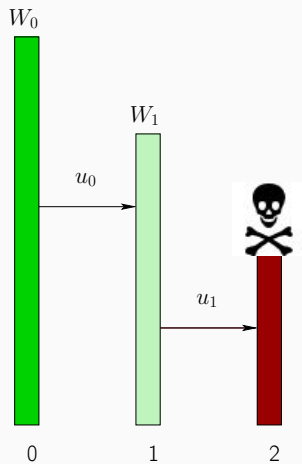
$N = 60$ loci, two alleles, selection factor $s = 0.2$

Error threshold vs. extinction

J. BULL ET AL., 2005; C. O. WILKE, 2005

- Simple model with three genotype classes:
 - Class 0: Fitness $W_0 > 1$, mutation probability u_0 to Class 1
 - Class 1: Fitness $W_1 < W_0$, mutation probability $u_1 < u_0$ to Class 2
 - Class 2: Fitness $W_2 = 0$ (does *not* reproduce)

Error threshold vs. extinction



Error threshold vs. extinction

Evolution equation for the population vector $\mathbf{n} = (n_0, n_1, n_2)$:

$$\mathbf{n}(t+1) = \mathsf{T}\mathbf{n}(t)$$
$$\mathsf{T} = \begin{pmatrix} (1-u_0)W_0 & 0 & 0 \\ u_0W_0 & (1-u_1)W_1 & 0 \\ 0 & u_1W_1 & 0 \end{pmatrix}$$

The total population is given by $N(t) = \sum_j n_j$

Error threshold vs. extinction

Eigenvalues and eigenvectors:

$$\lambda^{(0)} = W_0(1 - u_0)$$

$$\mathbf{n}^{(0)} = \left(\frac{(1 - u_0)(W_0(1 - u_0) - W_1(1 - u_1))}{W_0 u_0 u_1}, \frac{(1 - u_0)W_0}{W_1 u_1}, 1 \right)$$

$$\lambda^{(1)} = W_1(1 - u_1)$$

$$\mathbf{n}^{(1)} = \left(0, \frac{1 - u_1}{u_1}, 1 \right)$$

$N(t) \sim (\lambda^{\max})^t$: extinction if $\lambda^{\max} < 1$

Error threshold vs. extinction

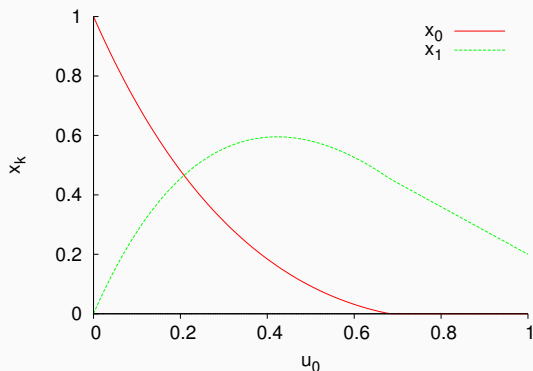
Error threshold:

$$(1 - u_0)W_0 = (1 - u_1)W_1$$

Extinction threshold:

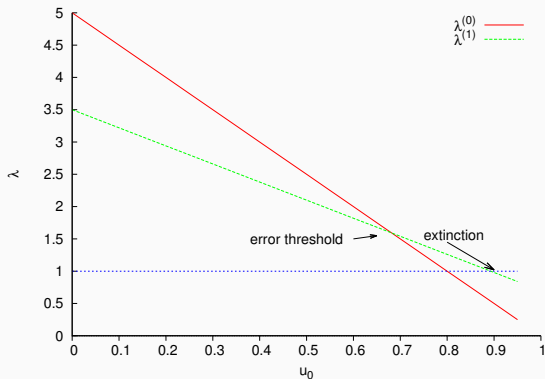
$$\lambda^{\max}(W_0, W_1, u_0, u_1) = 1$$

The transitions



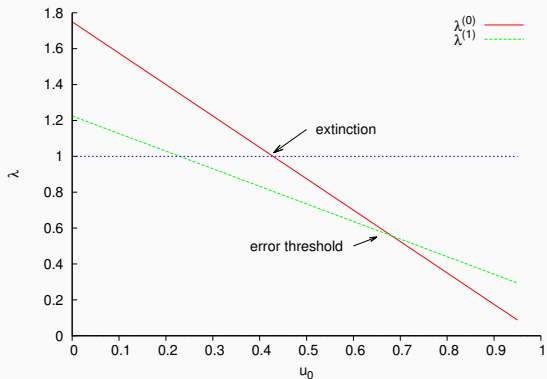
$W_1 = 0.7W_0$, $u_1 = 0.8u_0$: The error threshold is independent of W_0

The transitions



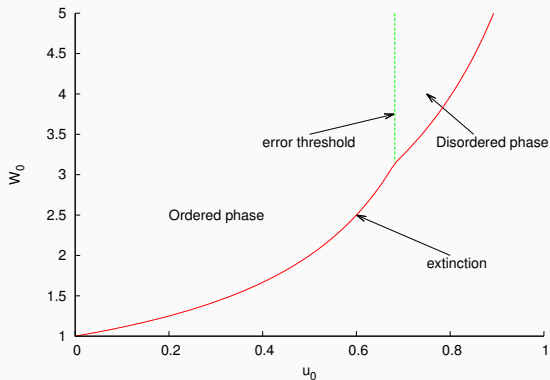
$W_0 = 5.0$: The error catastrophe *delays* the extinction

The transitions



$W_0 = 1.75$: Extinction *prevents* the error catastrophe

The transitions



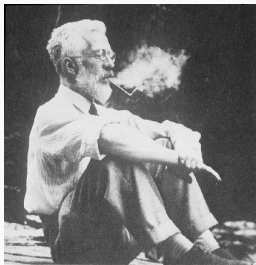
Phase diagram in the (u_0, W_0) plane

Drift

The Population Genetics Triad



Sewall Wright



Ronald A. Fisher



Motoo Kimura

Finite population

The Wright-Fisher model

- Population size N , number n_k of individuals of type k , $k = 1, \dots, r$, with fitness w_k
- Nonoverlapping generations
- Given the composition vector $\mathbf{x} = (x_i)$, $x_i = n_i/N$, the numbers n'_k in the next generation are distributed according to

$$\text{Prob}(n'_1, \dots, n'_r) = \frac{N!}{n'_1! \dots n'_r!} \xi_1^{n'_1} \dots \xi_r^{n'_r}$$

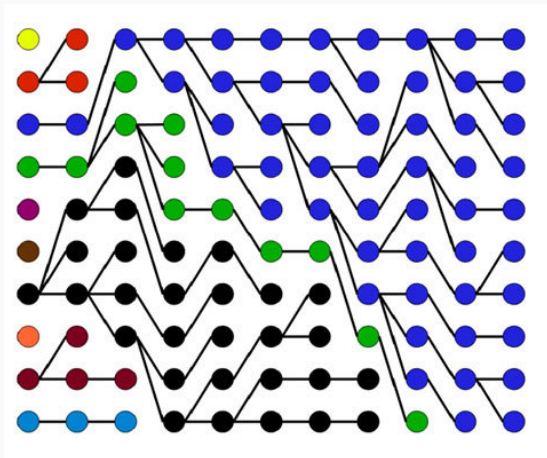
where

$$\xi_k = \frac{x_k w_k}{\sum_j x_j w_j}$$

- Thus n'_k is approximately distributed as a Gaussian with mean $N\xi_k$ and variance $N\xi_k(1 - \xi_k)$

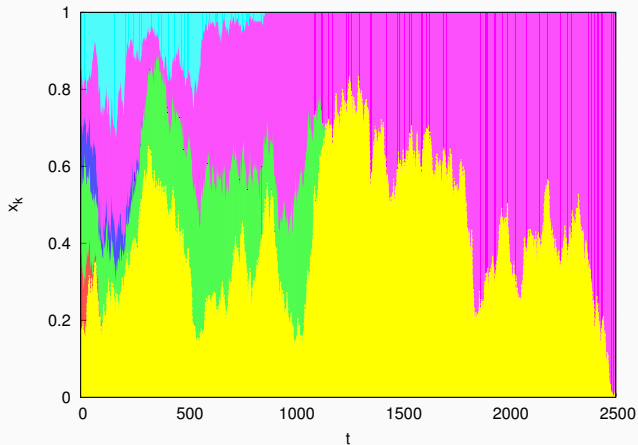
Finite population

The Wright-Fisher model



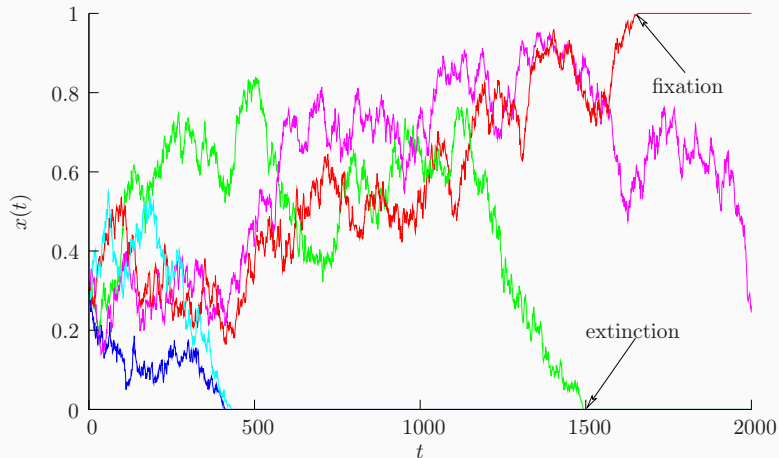
Finite population

The Wright-Fisher model: one realization (neutral)



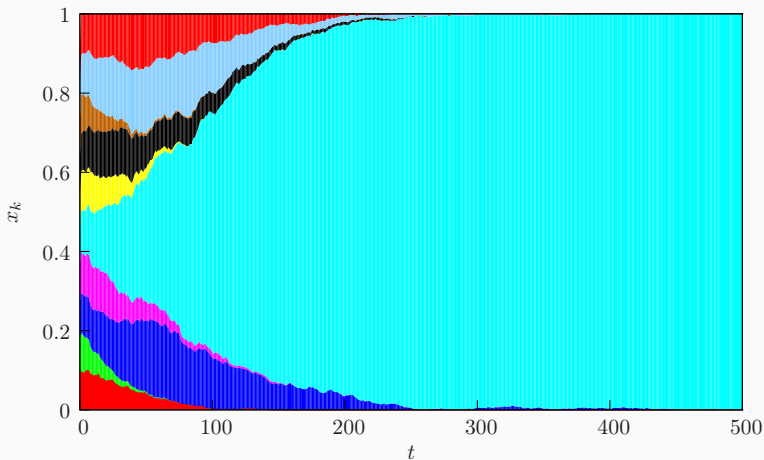
Finite population

The Wright-Fisher model: several realizations (neutral)



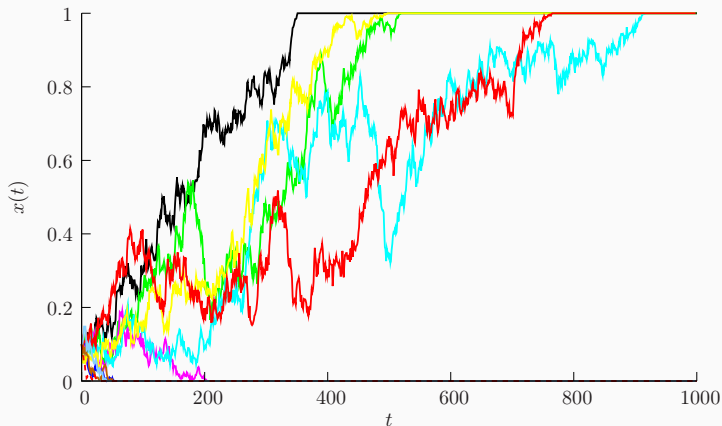
Finite population

The Wright-Fisher model: one realization (selective: $N = 10\,000$,
 $w_k \in \{1.0, 1.1\}$, $x_k(0) = 0.1$)



Finite population

The Wright-Fisher model: several realizations (selective: $N = 500$, $s = 0.01$, $x(0) = 0.1$)



Fixation in 5 cases out of 10

...it is often convenient to consider a natural population not so much as an aggregate of living individuals as an aggregate of gene ratios. Such a change of viewpoint is similar to that familiar in the theory of gases...

R. A. FISHER, 1953

We will start our discussion from the simplest situation where the gene frequency fluctuates from generation to generation because of the random sampling of gametes in a finite population. Since Wright's work, the term drift has become quite popular among biologists. However, in the mathematical theory of Brownian motion, the term drift originally connotes directional movement of the particle; therefore in our context the adjective random should be attached to it.

M. KIMURA, 1964 (ABRIDGED)

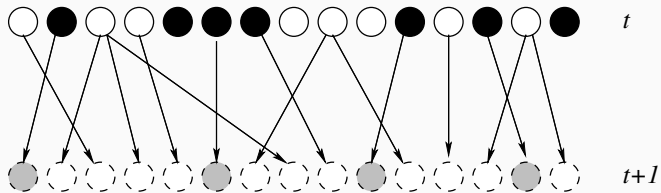
- Finite population implies different outcomes for different experiments in the same conditions (lack of *self-averaging*)
- Necessity to describe an *ensemble* of populations
- Use of the theory of Markov processes
- Simplification by means of *diffusion equations*

Random drift in the neutral case

- Population of N haploid individuals, 2 neutral alleles: A, a
- Frequency of the A allele: $x = n_A/N$
- Wright-Fisher model: At each time step, each individual i of the new generation picks up a parent at random and copies it

Random drift in the neutral case

The Wright-Fisher model



Random drift in the neutral case

- Probability that $n_A(t+1) = n$, given $n_A(t) = Nx(t)$:

$$p_n(t+1) = \binom{N}{n} (x(t))^n (1-x(t))^{N-n}$$

- Assume $N \gg 1$, $\frac{1}{N} \ll x \ll 1 - \frac{1}{N}$, then

$$\text{Prob}(x(t+1)=x) \propto \exp\left(-\frac{(x-x(t))^2}{2Nx(t)(1-x(t))}\right)$$

- $\Delta x(t) = x(t+1) - x(t)$:

$$\langle \Delta x(t) \rangle = 0 \quad \langle (\Delta x(t))^2 \rangle = \frac{x(t)(1-x(t))}{N}$$

The diffusion equation

Fokker-Planck equation:

$$\frac{\partial}{\partial t} p(x, t) = -\frac{\partial}{\partial x} (\langle \Delta x \rangle_x p(x, t)) + \frac{1}{2} \frac{\partial^2}{\partial x^2} (\langle \Delta x^2 \rangle_x p(x, t))$$

In our case

$$\frac{\partial p}{\partial t} = \frac{1}{2N} \frac{\partial^2}{\partial x^2} (x(1-x) p(x, t))$$

The solution in the neutral case

- Set $p(x, t | x_0, 0) = \sum_n c_n(x_0) \chi_n(x) e^{-\lambda_n t / (2N)}$
- Eigenvalue equation:

$$x(1-x)\chi_n''(x) + (1-2x)\chi_n'(x) + \lambda_n \chi_n(x) = 0$$

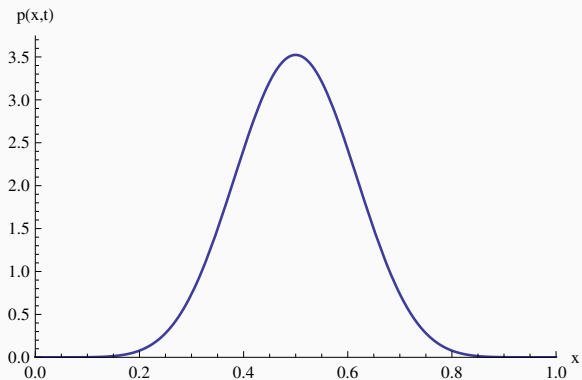
- Boundary conditions: $x = 0, 1$ are singular points; we require $\chi_n(0, 1)$ finite $\forall n$
- Initial condition:

$$p(x, 0 | x_0, 0) = \sum_n c_n(x_0) \chi_n(x) = \delta(x - x_0)$$

- Solution in terms of hypergeometric functions:

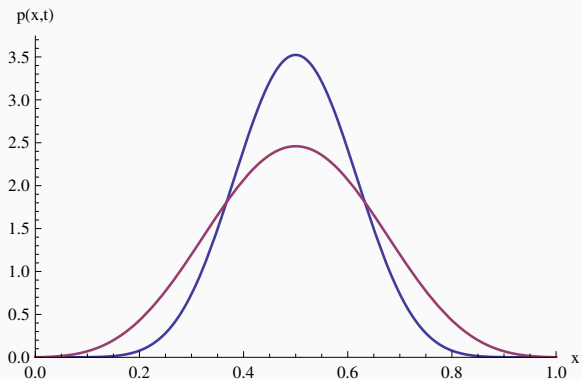
$$\chi_n(x) = F(1-n, n+2, 2, x) \quad \lambda_n = n(n+1)$$

The solution in the neutral case



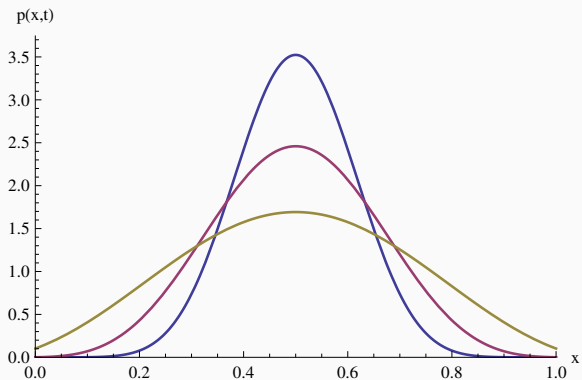
$$t = 0.05N$$

The solution in the neutral case



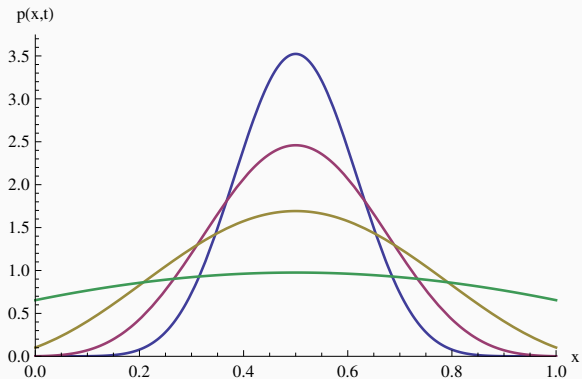
$$t = 0.1N$$

The solution in the neutral case



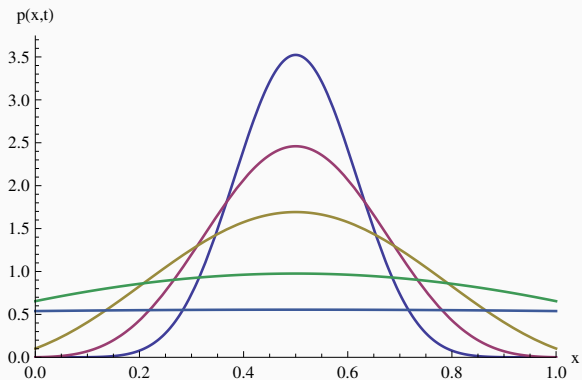
$$t = 0.2N$$

The solution in the neutral case



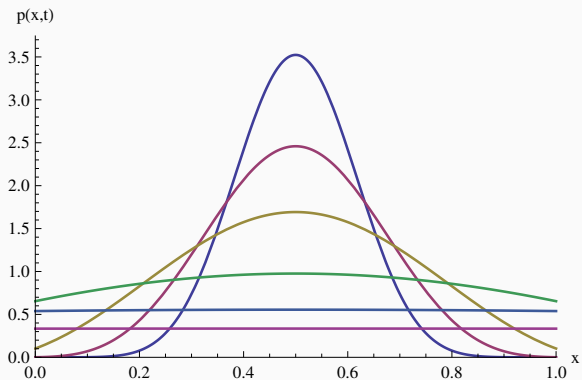
$$t = 0.5N$$

The solution in the neutral case



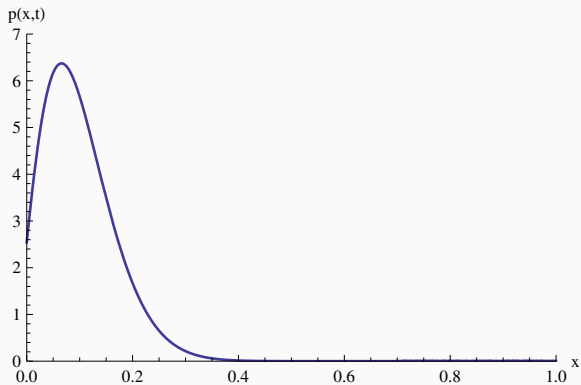
$$t = N$$

The solution in the neutral case



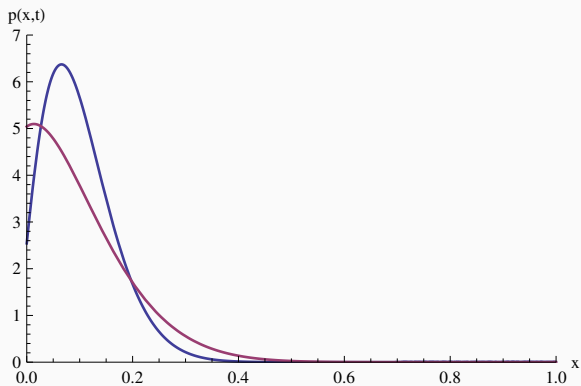
$$t = 1.5N$$

Initial condition $x(0) = 0.1$



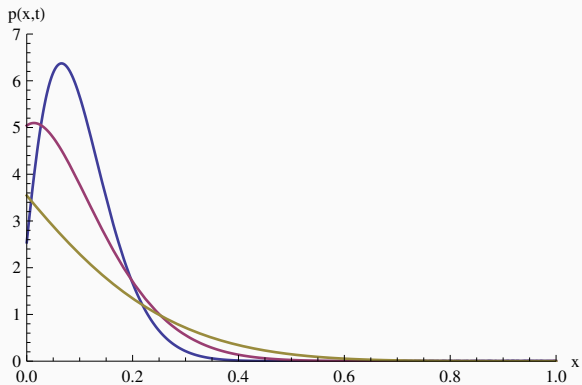
$$t = 0.05N$$

Initial condition $x(0) = 0.1$



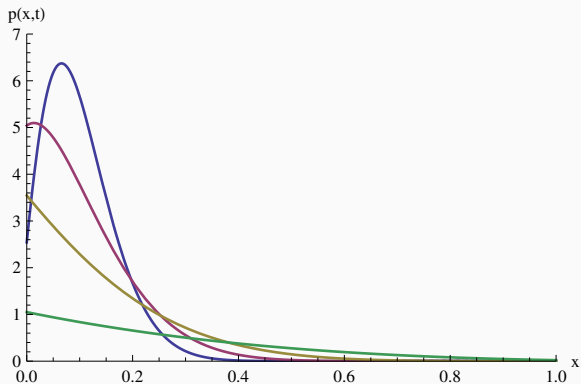
$t = 0.1N$

Initial condition $x(0) = 0.1$



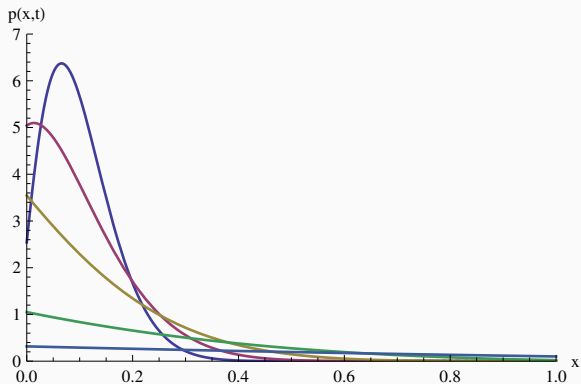
$t = 0.2N$

Initial condition $x(0) = 0.1$



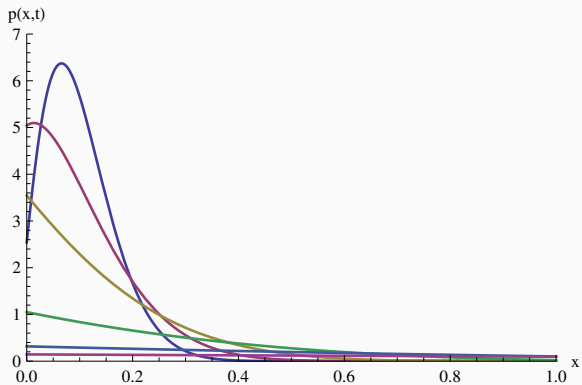
$t = 0.5N$

Initial condition $x(0) = 0.1$



$t = N$

Initial condition $x(0) = 0.1$



$t = 1.5N$

Results

- $p(x, t)$ decays exponentially: $p(x, t) \simeq 6x(0)(1 - x(0))e^{-t/N}$ for $t \gg N$
- Probability that A and a coexist at generation t :
 $\Omega(t) = \int_0^1 dx p(x, t)$ decays with the same rate ($p(x, t)$ is flat)
- However, $p(x, t)$ becomes flat later when $x(0) \neq \frac{1}{2}$
- What is the probability of fixation of allele A as a function of $x(0)$?

The backward equation

- $p(x, t | x_0, t_0)$: Conditional probability that $x(t) = x$ given that $x(t_0) = x_0$
- Consider the effect of a single-generation sampling near t_0 :
 $x(t_0 + 1) = x_0 + \Delta x_0$
- Equation for $p(x, t | x_0, t_0)$:

$$-\frac{\partial p}{\partial t_0} = \langle \Delta x_0 \rangle_{x_0} \frac{\partial p}{\partial x_0} + \frac{1}{2} \langle \Delta x_0^2 \rangle_{x_0} \frac{\partial^2 p}{\partial x_0^2}$$

- In our case

$$-\frac{\partial p}{\partial t_0} = \frac{x_0(1-x_0)}{2N} \frac{\partial^2 p}{\partial x_0^2}$$

The fixation probability

- $P(t, x_0, t_0) = p(1, t | x_0, t_0)$: probability of being fixed by time t
- “Ultimate” fixation probability: $p^{\text{fix}}(x_0) = \lim_{t \rightarrow \infty} P(t, x_0, t_0)$
- From the backward equation we obtain

$$\frac{d^2 p^{\text{fix}}}{dx_0^2} = 0 \quad x \in [0, 1]$$

- Boundary conditions: $p^{\text{fix}}(x_0=0) = 0$ and $p^{\text{fix}}(x_0=1) = 1$
- Solution:

$$p^{\text{fix}}(x_0) = x_0$$

Wright-Fisher model with selection

- Population of N haploid individuals, two alleles A and a
- Fitnesses: w_A, w_a
- Probability that an individual with allele A is chosen as a parent:

$$\xi_A = \frac{n_A w_A}{\sum_{j=1}^N w_j} = \frac{n_A w_A}{n_A w_A + n_a w_a} = \frac{x w_A}{x w_A + (1-x) w_a}$$

- Probability that $n_A(t+1) = n$:

$$p_n(t+1) = \binom{N}{n} \xi_A^n (1 - \xi_A)^{N-n}$$

- Average and variance:

$$\begin{aligned} \langle x_A(t+1) \rangle &= \xi_A \\ \langle (x_A(t+1) - \langle x_A(t+1) \rangle)^2 \rangle &= \xi_A (1 - \xi_A) / N \end{aligned}$$

If the first human infant with a gene for levitation were struck by lightning in its pram, this would not prove the new genotype to have low fitness, but only that the particular child was unlucky.

JOHN MAYNARD SMITH

Selection and drift

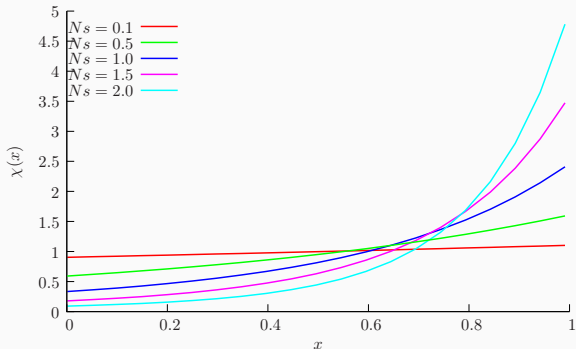
- Set $w_A = 1 + s$, $w_a = 1$, $s \ll 1$
- Then $\xi_A = xw_A/(xw_A + w_a(1 - x)) = (1 + s)x/(1 + sx)$
- Then $\langle \Delta x \rangle_x = \langle x(t + 1) \rangle - x = sx(1 - x)/(1 + sx) \simeq sx(1 - x)$
and $\langle \Delta x^2 \rangle \simeq (x(1 - x)/N)$
- Diffusion equation for $p(x, t)$:

$$\frac{\partial p}{\partial t} = -s \frac{\partial}{\partial x} (x(1 - x)p) + \frac{1}{2N} \frac{\partial^2}{\partial x^2} (x(1 - x)p)$$

- Solution in terms of spheroidal functions...
- Asymptotically $p(x, t) \propto \chi(x) e^{-\lambda t/N}$

Solution with selection

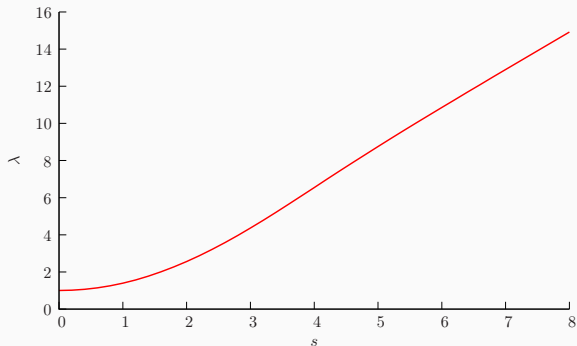
The long-living eigenfunction:



The leading eigenfunction $\chi(x)$ for several values of s

Solution with selection

The decay rate:



Leading eigenvalue λ as a function of Ns ; decay rate: λ/N

The fixation probability with selection

- The backward equation:

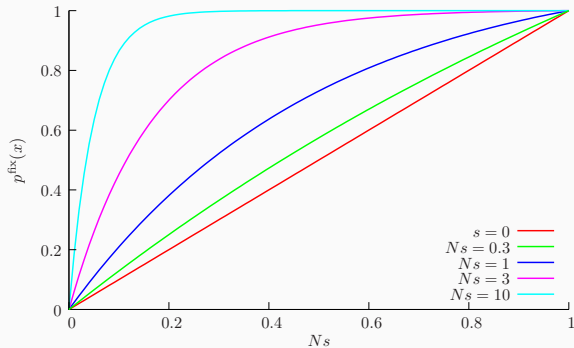
$$\frac{\partial p}{\partial t_0} = sx_0(1-x_0)\frac{\partial p}{\partial x_0} + \frac{x_0(1-x_0)}{2N}\frac{\partial^2 p}{\partial x_0^2}$$

- Stationary solution:

$$\begin{aligned}\frac{\partial p^{\text{fix}}}{\partial x_0} &= C_1 e^{-2Nsx_0} \\ p^{\text{fix}}(x_0) &= C_0 - C_1 e^{-2Nsx_0} \\ &= \frac{1 - e^{-2Nsx_0}}{1 - e^{-2Ns}}\end{aligned}$$

- In particular, for $s \rightarrow 0$, $p^{\text{fix}} \rightarrow x_0$

The fixation probability with selection



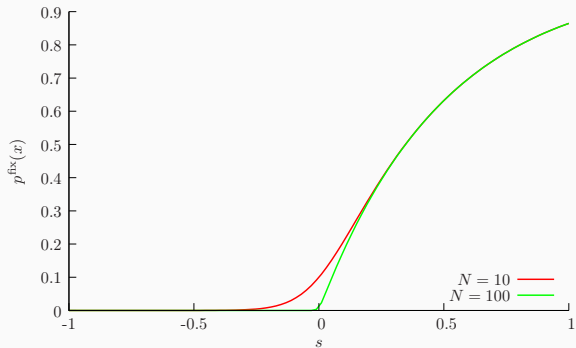
Fixation probability of a single mutant

- For a single mutant $x_0 = \frac{1}{N}$
- Thus

$$p^{\text{fix}} = \frac{1 - e^{-2s}}{1 - e^{-2Ns}}$$

- Limits:
 - $s > 0, Ns \gg 1$: $p^{\text{fix}} \simeq 1 - e^{-2s}$ (for $s \ll 1$, $p^{\text{fix}} \simeq 2s$)
 - $s < 0, |Ns| \gg 1$, $p^{\text{fix}} \simeq 0$
 - $|Ns| \lesssim 1$, $p^{\text{fix}} \simeq \frac{1}{N}$

Fixation probability of a single mutant



Frequency needed to obtain fixation

- How large must be x to be “almost sure” that a beneficial mutant fixes?
- Solve

$$p^{\text{fix}}(x^*) = 1 - \gamma$$

- For $Ns \gg 1$ we have $p^{\text{fix}}(x) \simeq 1 - e^{-2Nsx}$, thus

$$x^* = -\frac{\log \gamma}{2Ns} \quad \text{or} \quad n^* = -\frac{\log \gamma}{2s}$$

- The fate of the mutant is determined in its initial phase, where it undergoes a branching process—the size of N is irrelevant!

Substitution rate

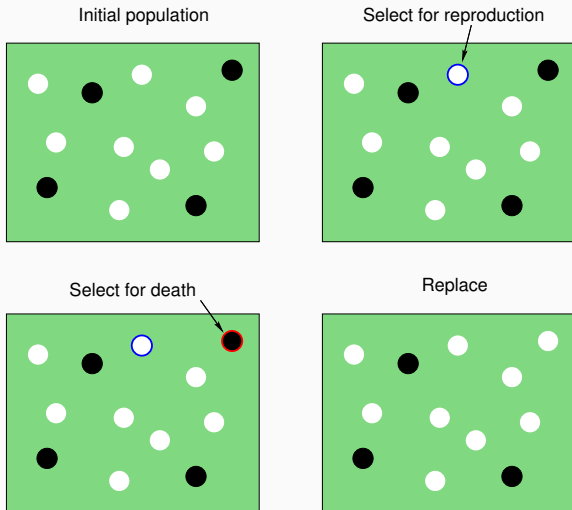
- For a new mutant, $x_0 = \frac{1}{N}$
- For a neutral mutant, $s = 0$, thus $p^{\text{fix}} = x_0 = \frac{1}{N}$
- If u is the mutation probability per genome and generation, the expected number of mutants per generations is uN
- Of these, only a fraction $\frac{1}{N}$ reaches fixation, i.e., produces a *substitution*
- Therefore the rate ν of *neutral* substitutions in a population with mutation rate u is equal to u :

$$\boxed{\text{substitution rate} = \text{mutation rate}}$$

independently of the population size N

The Moran model

Overlapping generations individual-based model:



The Moran model

- Selection: $p_{\text{kill}}(A) = 1 - s$, $p_{\text{kill}}(a) = 1$
- $\Delta t = \frac{1}{N}$; $\Delta n_A \in \{-1, 0, +1\}$
- Probabilities:

$$\begin{aligned}P_{-1} &= \underbrace{\frac{n_a}{N}}_{\text{Prob}_{\text{repr}}(a)} \underbrace{(1-s)\frac{n_A}{N}}_{\text{Prob}_{\text{kill}}(A)} \\ &= (1-s)x(1-x) \\ P_{+1} &= \frac{n_A}{N} \frac{n_a}{N} = x(1-x) \\ P_0 &= 1 - (P_{+1} + P_{-1})\end{aligned}$$

The Moran model

- Thus, for $\Delta t = \frac{1}{N}$, $s \ll 1$:

$$\begin{aligned}\langle \Delta n_A \rangle &= P_{+1} - P_{-1} = sx(1-x) \\ \langle (\Delta n_A)^2 \rangle &= P_{+1} + P_{-1} = (2-s)x(1-x) \simeq 2x(1-x)\end{aligned}$$

- The diffusion equation for the Moran model:

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x} (sx(1-x)p) + \underbrace{\frac{1}{N}}_{= 1/2N \text{ for WF}} \frac{\partial^2}{\partial x^2} (x(1-x)p)$$

- The devil (or God?) is in the details...

Finite population of size N , r alleles, Moran model. Effects of mutation and selection:

$$\frac{dx_j}{dt} = \sum_k \Gamma_{jk} \frac{\partial \Phi}{\partial x_k}; \quad \Phi = \langle f \rangle_x + \sum_{\alpha} \mu_{\alpha} \log x_{\alpha}$$
$$\Gamma_{jk}(\mathbf{x}) = \begin{cases} -x_j x_k, & \text{if } j \neq k \\ x_j(1 - x_j), & \text{if } j = k \end{cases} \quad \Gamma \text{ positive definite}$$

- Random drift: $\mathbf{x} \longrightarrow \mathbf{x} + \boldsymbol{\xi}$

$$\langle \xi^j \rangle_{\mathbf{x}} = 0; \quad \langle \xi^j \xi^k \rangle = 2 \frac{\Gamma_{jk}(\mathbf{x})}{N}$$

- Fokker-Planck equation for the pdf $P(\mathbf{x})$:

$$\begin{aligned} \frac{\partial P}{\partial t} &= \sum_{jk} \frac{\partial}{\partial x_j} \left[-\frac{\partial \Phi}{\partial x_k} (\Gamma_{jk} P) + \frac{1}{N} \frac{\partial}{\partial x_k} (\Gamma_{jk} P) \right] \\ &= \sum_{jk} \frac{\partial}{\partial x_j} \Gamma_{jk} \left(-\frac{\partial \tilde{\Phi}}{\partial x_k} P + \frac{1}{N} \frac{\partial P}{\partial x_k} \right) \end{aligned}$$

- $\tilde{\Phi} = \Phi - \frac{1}{N} \log \det \Gamma$; $\det \Gamma = \prod_{\alpha} x_{\alpha}$
- Stationary solution:

$$P^{\text{eq}}(\mathbf{x}) \propto e^{N\tilde{\Phi}} = (\det \Gamma)^{-1} e^{N\Phi} = P_0 e^{N\langle f \rangle_{\mathbf{x}}}$$
$$P_0(\mathbf{x}) \propto \prod_{\alpha} x^{-1+N\mu_{\alpha}}$$

- Thus, for a *static* fitness function f ,

$$[N \langle f \rangle_{\mathbf{x}}]_{\text{av}}^{\text{eq}} = \int d\mathbf{x} P^{\text{eq}}(\mathbf{x}) \log \frac{P^{\text{eq}}(\mathbf{x})}{P_0(\mathbf{x})} = \underbrace{D_{\text{KL}}(P^{\text{eq}} \| P_0)}_{\text{Kullback-Leibler divergence}}$$

$$D_{\text{KL}}(p \| q) = \sum_k p_k \log \frac{p_k}{q_k} \quad (1)$$

- Factor binding sites are *short* DNA sequences which bind activating factors
- Small mutation rates: $\mu N \ll 1 \Rightarrow$ Population becomes monomorphic ($\mathbf{x} = (x_\alpha) \rightarrow \delta_{\alpha\beta}$)

$$p_\beta = \text{Prob}(\mathbf{x} = \delta_{\alpha\beta}) \propto e^{Nf_\beta}$$

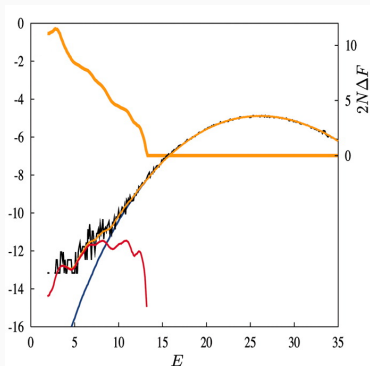
- It is reasonable to assume that their fitness depends on their binding energy E
- One can expect a *linear model* for $E(\sigma)$, $\sigma = (\sigma_1, \dots, \sigma_\ell)$, $\sigma_i \in \{\mathbf{A}, \mathbf{T}, \mathbf{G}, \mathbf{C}\}$

$$E(\sigma) = \sum_{i=1}^{\ell} \epsilon_i(\sigma_i) \quad \text{with } \epsilon_i(\sigma) = \epsilon_0 \log \frac{q_i(\sigma)}{p_0(\sigma)}$$

$p_0(\sigma)$: background nucleotide frequency

cAMP-response protein binding loci in *E. Coli*

MUSTONEN AND LÄSSIG, 2005



Log histogram $P(E)$ of binding energy E for 520 729 CRP-binding loci in *E. Coli*. Compared with $P(E) = (1 - \lambda)P_0(E) + \lambda P_0(E)e^{2NF(E)}$. The inferred form of $2NF(E)$ is also plotted. (W-F model)

Thank you!

- G. H. Hardy, Mendelian proportions in a mixed population, *Science* **28** 49–50 (1908)
- W. Weinberg, Über den Nachweis der Vererbung beim Menschen, *Jahreshefte des Vereins für vaterländische Naturkunde in Württemberg* **64** 368–382 (1908)
- B. de Finetti, Considerazioni matematiche sull'ereditarietà mendeliana, *Metron* **6** 29–37 (1926)
- John H. Gillespie, *Population Genetics: A Concise Guide* (2nd ed.) (Baltimore: Johns Hopkins Press, 2004)
- M. Eigen, Self-organization of matter and the evolution of biological macromolecules, *Naturwissenschaften* **58** 465–523 (1973)

References ii

- C. O. Wilke, Quasispecies theory in the context of population genetics, *BMC Evolutionary Biology* **5** 44 (2005)
- J. J. Bull and C. O. Wilke, Theory of Lethal Mutagenesis for Viruses, *Journal of Virology* **81** 2930–2939 (2006)
- J. J. Bull and C. O. Wilke, Lethal Mutagenesis of Bacteria, *Genetics* **180** 1061–1070 (2008)
- S. Crotty, C. E. Cameron and R. Andino, RNA virus error catastrophe: Direct molecular test by using ribavirin *Proc. Natl. Acad. Sci. USA* **98** 6895 (2001)
- M. Kimura, *The neutral theory of molecular evolution* (Cambridge: Cambridge U. P., 1983)
- R. A. Fisher, *The Genetical Theory of Natural Selection* (Oxford: Clarendon Press, 1930)

References iii

- R. A. Fisher, Population genetics, *Proc. Roy. Soc. London, Ser. B* **141** 510-523 (1953)
- S. Wright, Evolution in Mendelian populations, *Genetics* **16** 97-159 (1931)
- M. Kimura, Diffusion models in population genetics, *J. Appl. Prob.* **1** 177-232 (1964)
- J. Maynard Smith, *Evolutionary Genetics* (Oxford: Oxford U. P., 1989)
- P. A. P. Moran, Random processes in genetics, *Mathematical Proceedings of the Cambridge Philosophical Society* **54** 60-71 (1958)
- T. Ohta, Population size and rate of evolution, *J. Mol. Evol.* **1** 305-314 (1972)

- V. Mustonen and M. Lässig, From fitness landscapes to seascales: Non-equilibrium dynamics of selection and adaptation, *Trends Genet* **25** 111–119 (2009)
- V. Mustonen and M. Lässig, Fitness flux and ubiquity of adaptive evolution, *Proc. Natl. Acad. Sci. USA* **107** 4248–4253 (2010)