INTRODUCTION TO POPULATION GENETICS

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1 Brief history

1859 *On the origin of species by means of natural selection* by Charles Darwin is published

- in a population, individual differences exist (variation)
- this variation is (partially) inherited so that offspring are also different
- those variants that are better suited to the environment are selected, i.e. produce more offspring / have higher chances of survival etc.

Some major questions

- mode : does evolution proceed gradually or in jumps? monotonically increasing fitness?

  Population passes through intermediates each of which is fitter than the previous one (Darwin, Fisher) but Wright proposed passing through low fitness valleys also

- tempo : slow or fast

  Infinitesimally slow (Darwin) but earth has a finite age (Lord Kelvin)

  Recent works have shown that adaptation can occur very rapidly

  e.g., microbes to fishes to finches

- what is the mechanism of heredity?

  - Darwin assumed that new variation is created in every generation so that natural selection can act on it

    To keep the variability in check, hypothesised blending inheritance

    Idea: genetic material in the offspring is a blend of that of the parents' (e.g., tall parent and short parent to give moderately tall offspring (not giant/dwarf) - produced new variation but not too much of it)

  - Blending inheritance hypothesis was accepted but natural selection hypothesis was not !

    Fleeming Jenkin argues against natural selection given blending inheritance (1867) "Suppose a white man to have been wrecked on an island inhabited by negroes.... Our shipwrecked hero would probably become king; he would kill a great many

blacks in the struggle for existence; he would have a great many wives and children, while many of his subjects would live and die as bachelors....In the first generation there will be some dozens of intelligent young mulattoes [blend], much superior [natural selection] in average intelligence to the negroes. We might expect the throne for some generations to be occupied by a more or less yellow king; but can any one believe that the whole island will gradually acquire a white, or even a yellow population...? Here is a case in which a variety was introduced, with far greater advantages than any sport every heard of, advantages tending to its preservation, and yet powerless to perpetuate the new variety."

1865 Mendel's experiments

- Experimented with pea plant for seven phenotypic traits (flower color, pod, leaves ...)
  - established pure lines [1] for flower colors (purple/white)

$$w \text{ X } w \rightarrow w \ , \ p \text{ X } p \rightarrow p$$

  - crossed pure white and pure purple line (F_1 gen)

$$w \text{ X } p \rightarrow p_2$$

    obtained only purple flowers (not a blend !!)
  - selfed the plants in previous generation

$$p_2 \text{ X } p_2 \rightarrow w, p$$

    obtained both white and purple plants in 1:3 ratio

- Importance of Mendel's work
  - Similar experiments on pea plant were carried out by Darwin also but Mendel came up with a model to understand his results
    * hypothesised that the inherited material is particulate in nature
    * Mendel's model (I will use modern jargon)
      Denote the 'phenotype' white/purple by 'genotypes' A_1/A_1 and A_2/A_2 resp. A_1/A_1 stands for the two copies[2] of genetic material at a 'locus' [3] that carries genes for color. Since there are two 'alleles' [4] here, we also have A_2/A_2.

[1] A population in which all offspring produced by selfing or crossing within the population are identical for this character under study.

[2] A/A means first copy is from one parent and second copy from other parent

[3] location in the genome

[4] variant at a locus

pure lines: A_1/A_1 (white), A_2/A_2 (purple)
crossed lines: A_1/A_1 X $A_2/A_2 \to A_1/A_2$ (purple) [5]
selfed lines: A_1/A_2 X $A_1/A_2 \to A_1/A_1(1)$ and $A_2/A_2, A_1/A_2$ (3)

– particulate inheritance also creates variation (some p, some w) as Darwin needed for natural selection to work

1900 de Vries rediscovers Mendel's results and coins the term 'pangenes' for hereditary material

Early 1900s: Birth of population genetics

Just as in physics, basic evolutionary processes ('forces') have been identified

- Natural selection (s): some genotypes are fitter than the others
- Mutation (μ): genotypes undergo random changes during reproduction
- Random genetic drift (N):

  - Deterministic ($N \to \infty$) and stochastic models (finite N)

  - stochastic models are more realistic, but deterministic models help in setting up problem and gain intuition

- Population structure (age structure, mating system, ploidy, geographical structure, ...)

Population genetics is a framework to understand evolution of a population under the action of the above forces

[5] A_1 recessive, A_2 dominant

2 One locus models

Below we consider one or more of the forces, and ask how the genotypic or allele frequency changes.

2.1 Hardy-Weinberg law **(Weinberg 1908; Hardy 1908)**

Blending inheritance depletes variation (recall Jenkin's argument). But we need variation for natural selection. Does Mendelian inheritance preserve variability in a population?

- Simplest model: no selection (all equally good), no mutation, no stochasticity

Genotypes	Female frequency	Male frequency
A_1/A_1	X	X
A_1/A_2	2 Y	2 Y
A_2/A_2	Z	Z

where, $X + 2Y + Z = 1$. What are the frequencies if Mendel's rules are obeyed?

- Frequency of A_1/A_1 in next generation,

$$X' = 1(X.X) + \frac{1}{2}.2.(X.2Y) + \frac{1}{4}(2Y.2Y)$$

Mom X Dad	Offspring	Probability
A_1/A_1 X A_1/A_1	A_1/A_1	1
A_1/A_1 X A_1/A_2	A_1/A_1	1/2
A_1/A_2 X A_1/A_1	A_1/A_1	1/2
A_1/A_2 X A_1/A_2	A_1/A_1	1/4

$$X' = (X + Y)^2$$

Exercise: Frequency of A_1A_2 in next generation,

$$2Y' = 1.2.(X.Z) + \frac{1}{2}.2.(X.2Y) + \frac{1}{2}.(2Y.2Y) + \frac{1}{2}.2.(2Y.Z)$$

$$2Y' = 2(X + Y)(Y + Z)$$

Mom X Dad	Offspring	Probability
A_1/A_1 X A_2/A_2	A_1/A_2	1
A_1/A_2 X A_1/A_1	A_1/A_2	1/2
A_1/A_2 X A_1/A_2	A_1/A_2	1/2
A_1/A_2 X A_2/A_2	A_1/A_2	1/2

In one generation, frequencies $(X, 2Y, Z)$ have changed to $(X', 2Y', Z')$

$$X' = (X+Y)^2 \quad (1)$$
$$2Y' = 2(X+Y)(Y+Z) \quad (2)$$
$$Z' = (Y+Z)^2 \quad (3)$$

After one more generation,

$$X'' = (X'+Y')^2 = X' \quad (4)$$
$$2Y'' = 2(X'+Y')(Y'+Z') = 2Y' \quad (5)$$
$$Z'' = (Y'+Z')^2 = Z' \quad (6)$$

- Equilibrium reached in just one generation !!

  Biological Importance: Mendelian rules preserve variability (after one generation) provided there is no selection, no mutation etc... Blending inheritance out !

  Theoretical Importance: Simplifies the work with diploids

- Equilibrium frequencies obey: $Y^2 = XZ$ (Hardy-Weinberg equil) [use (1)-(3)]

- **Exercise:** Show that variability is not preserved under b.i. (Fisher, Chap. 1).

  Hint: Let the average height in a population be a. The height of a couple is a random variable denoted by $a + \Delta_M$ and $a + \Delta_D$. Then the variance in the parent generation is

  $$V_t = \langle (\Delta_M^2 + \Delta_D^2)/2 \rangle$$

  Assuming both parents contribute equally under b.i., the height of the offspring is

  $$a + (1/2)(\Delta_M + \Delta_D)$$

  What is the variance V_{t+1} in the offspring generation?

  Solution: Using $\langle \Delta_{M,D} \rangle = 0$, we have

  $$V_{t+1} = \langle (a + \frac{\Delta_M + \Delta_D}{2})^2 \rangle - a^2 = \frac{V_t}{2} \left(1 + \frac{\langle \Delta_M \Delta_D \rangle}{V_t} \right)$$

Also,

$$\frac{\langle(\Delta_M - \Delta_D)^2\rangle}{\langle\Delta_M^2\rangle + \langle\Delta_D^2\rangle} = 1 - \frac{\langle\Delta_M\Delta_D\rangle}{V_t} \geq 0$$

Thus the variance decreases exponentially with time!

2.2 Effect of selection (Punnett/Norton 1915; Haldane 1924)

As the purpose here it to demonstrate some basic concepts, for simplicity, I will assume asexual [6] and haploid [7] individuals.

- Some individuals are fitter than the others. Intuitive expectation is that the fitter one will survive.
- Model

Genotypes	(Wrightian) Fitness	Frequency
A_1	1	x_1
A_2	$1-s$	$x_2 = 1 - x_1$

Expect frequency of the fitter to be higher in next generation,

$$x_1' \propto F_1 x_1 \ , \ x_2' \propto F_2 x_2$$

Since $x_1 + x_2 = 1$ at all times,

$$x_1' = \frac{F_1 x_1}{F_1 x_1 + F_2 x_2}$$

  - only relative fitnesses matter

    (experimental measurements w.r.t. wild type; allows to set one of fitnesses to be 1 as done above)
  - nonlinear in x

- Equilbria ($x' = x$ as in HWE)?

  How many? multiple equilibria are possible - $x_1^* = 0/1$

  Exercise: How many are stable?

$$x' = f(x) = f(x^*) + (x - x^*)f'(x^*) \implies \delta x' = f'(x^*)\delta x$$

Thus, $\delta x_t = (f'(x^*))^t \delta x_0$: Stable if $f'(x*) < 1$ since perturbation decays

[6] Y chromosome, mitochondria

[7] they exist: e.g., fungi, algae, germ cells...

Here, since

$$f'(x_1) = (1-s)/(1-x_2 s)^2$$

the equilibrium at $x_1^* = 1$ is stable, at $x_1^* = 0$ is unstable

Intuitively: expected since A_1 is fitter

- Dynamics? Start with freq $x_1(0)$, at large times, $x_1(t)$ will go to one (as shown)

  But, in how much time? Use computer/ devise simple approx

  - Approx: If the fitness disadvantage is small (empirically $s \ll 0.1$), expect freq changes to be small in one gen. Allows one to approximate discrete time equation by a continuous time one ($x' - x \ll 1$ so derivative)

$$\frac{dx_1}{dt} \approx x_1 x_2 (F_1 - F_2) = s x_1 (1 - x_1)$$

    * Meaning of continuous time equation: growth term + death term

$$\frac{dx_1}{dt} \approx F_1 x_1 - \overset{avg}{(F_1 x_1 + F_2 x_2)}\, x_1$$

    * Check: $x_1^* = 0, 1$ (as already seen)

  - In how much time?

$$x_1(t) = \frac{x_1(0)}{x_1(0) + x_2(0) e^{-st}}$$

  - Time taken for x_1 to be close to unity $\propto 1/s$ as in e^{-st}
  - intuitively okay : takes longer to displace if fitness difference is small

- Favorable type does get selected in reasonable times ($\ll$ age of earth; recall Kelvin)

2.3 Effect of mutation

Selection destroys variation since p^* is trivial (although it does so slowly). How are new variants created?

- Model: Let A_1 change into A_2 with probability $\mu_{1\to 2}$ and A_2 change into A_1 with probability $\mu_{2\to 1}$. Assume that both A_1 and A_2 are equally fit.

Genotypes	Fitness	Frequency
A_1	1	x_1
A_2	1	x_2

A_1 contributes if it does not mutate away; A_2 also contributes if it mutates

$$x_1' = (1 - \mu_{1\to 2})x_1 + \mu_{2\to 1}x_2$$

Linear equation obtained

- In equilibrium, both types are present !

$$x_1^* = \frac{\mu_{2\to 1}}{\mu_{2\to 1} + \mu_{1\to 2}}$$

For later reference: note that $x_1^* = 1/2$ when the two mutation rates are equal

- Dynamics? work out the same way as before if mutation rates are small

$$x_1(t) = x_1^* + (x_1(0) - x_1^*)e^{-(\mu_{12}+\mu_{21})t}$$

Time scale $\sim (\mu_{12} + \mu_{21})^{-1}$. But as mutation rates are very small ($\mu < 10^{-6}$ except for RNA viruses), mutations alone will take a long time to increase variation in a population.

- Mutations create new variation on which selection can act but the process is very slow

2.4 Effect of selection and mutation

Selection removes variation, mutation creates it. What will happen when both are present?

- **Exercise:** Model

Genotypes	Fitness	Mutation	Frequency
A_1	1	μ	x_1
A_2	$1 - s$	μ	x_2

Would only the better one survive?

$$x_1' = \frac{(1-\mu)F_1x_1 + \mu F_2x_2}{F_1x_1 + F_2x_2}$$

As before, relative fitnesses matter and equation is nonlinear

– Equilibria: Turns out only one stable equilibrium

For simplicity, $\mu_{1\to 2} = \mu_{2\to 1} = \mu$ and work out the quadratic eqn for x_1:

$$x_1^2 + x_1\left(\frac{2\mu}{s} - (1+\mu)\right) - \frac{\mu}{s}(1-s) = 0$$

– Plot x_1^* as a function of μ

- Useful to consider the limiting cases

  for $\mu \ll s$ (recall $\mu = 0$): expect $x_1 \approx 1$ $[x_1 = 1 - (\mu/s)]$

  for small enough mutation rates, fitter has a high frequency

  for $\mu \gg s$ (recall $s = 0$), expect $x_1 = 1/2$

  for large enough mutation rates, selection is not effective

- Biological meaning: 'phase transition' in the behavior !

  biologically: $\mu \ll s$ so the transition point is not realistic but in more complex models, such transition occurs at reasonable values

  also, some empirical evidence for 'error threshold' transition[8]

2.5 Modeling stochasticity

We have implicitly assumed that resources (food) are infinite. But that's not realistic ! A finite food supply can support a finite number of individuals. E.g., a petri dish with enough glucose for 5 bacteria. Each of them replicates, but half of the population must die.

A_1	A_1	A_2	A_1	A_2	
A_1A_1	A_1A_1	A_2A_2	A_1A_1	A_2A_2	reproduction step
A_1	A_1	A_2	A_1	A_1	selection step

Which ones? Expect the fitter has higher chances of survival. Pick 5 individuals with

$$\text{prob} \propto \text{its fitness}$$

- A_2 also stays !
- new generation created by stochastic sampling

- Wright-Fisher process (Eliminate the intermediate step, implement N conservation)

  Each offspring chooses a parent with prob $\propto$ parent's fitness

  e.g., let fitness of A_1 be F_1, A_2 be F_2. Then the first A_2 is chosen to be parent with prob $= \frac{F_2}{3F_1+2F_2}$

[8] reviewed in Jain & Krug, arXiv:q-bio/0508008

$$\begin{array}{ccccc} A_1 & A_1 & A_2 & A_1 & A_2 \\ \nearrow & \uparrow & \uparrow & \uparrow & \nwarrow \\ A_1 & A_1 & A_2 & A_1 & A_1 \end{array}$$

- Can also introduce mutations

$$\begin{array}{ccccc} A_1 & A_1 & A_2 & A_1 & A_2 \\ \nearrow & \uparrow & \uparrow & \uparrow & \nwarrow \\ A_1 & A_1 & A_2 & A_1 & A_1 \\ A_2 & A_1 & A_2 & A_2 & A_1 \end{array} \quad \text{mutation step}$$

- Simulate it !
  - wiped out a generation completely (annual plants, e.g., peas) but models with overlapping generation also studied
  - assumed pop size exactly fixed, but models with fluctuating number with constt average can also be studied

- Relationship between deterministic and stochastic models

  Let A_1 is chosen to be a parent with prob p_1 and A_2 with prob $p_2 = 1 - p_1$. Then the probability of j successes is given by

$$P(jA_1, t+1 | iA_1, t) = \binom{N}{j} p_1^j (1-p_1)^{N-j}$$

  [prefactor to take care of $A_1A_1A_2$ and its permutations]

  - Binomial distribution but with a difference : here the "heads" prob p_1 depends on the number of A_1s in the previous generation,

$$p_1 = \frac{F_1 i}{F_1 i + F_2(N-i)} = \frac{F_1 x_1}{F_1 x_1 + F_2(1-x_1)}$$

  - Since mean of a binomial distribution equals Np_1, the average frequency of A_1 in generation $t+1$ is given by

$$\langle x_1(t+1) \rangle = p_1(t) = \frac{F_1 x_1}{F_1 x_1 + F_2(1-x_1)}$$

as already seen in the deterministic model. Expected as deterministic theory is about means, ignores fluctuations

– Variance of a binomial distribution, $Np_1(1-p_1)$

Thus, variance in frequency

$$\sigma^2(t+1) = \frac{p_1(1-p_1)}{N} \overset{N\to\infty}{\to} 0$$

In infinitely large populations, fluctuations can be ignored while finite populations evolve stochastically

– Above discussion is useful to set up PDEs (Fokker-Planck/Kolmogorov eqns).

2.6 Effect of random genetic drift

- Ignore mutations and selection in Wright-Fisher process. For neutral case,

$$\langle x_1(t+1)\rangle = x_1(t)$$

Due to stochastic sampling, eventually, all the population consists of either all A_1s or all A_2s:

$$P(0A_1, t+1|iA_1, t) = (1-x_1)^N$$

(similarly, for all A_1's)

What is the chance that all are A_1s (fixation probability), starting from $x_1(0)$?

From above, we have

$$\langle x_1(t+1)\rangle = x_1(t)$$

If we start with $x_1(0)$, then averaging over all stochastic trajectories, we get

$$\langle x_1(t+1)\rangle = \langle x_1(t)\rangle = ... = x_1(0)$$

Imagine doing E numerical experiments out of which E_1 leads to fixation of A_1. Then, as the average frequency of A_1 must be $x_1(0)$, we get

$$\frac{1E_1 + 0E_0}{E} = x_1(0)$$

but the LHS is precisely the fixation probability. Thus, we have

$$\pi_{neu} = x_1(0)$$

- Genetic drift destroys variability (all A_1s/A_2s) and therefore counter its effect via mutations. How much diversity/variability is maintained?

– Consider a gene with $l = 500$ nucleotides. Then number of possible states $4^l \sim 10^{300}$. If we now think of each state as an allele, each mutation produces a new allele (infinite alleles model). Now the chance that a mutated site is mutated back to original is $1/l$ which is zero if $l \to \infty$ (infinite sites model). Thus every mutation occurs at a distinct site with a probability μ.

  Imagine picking two individuals at random in a population of size N at time t. G_t =Prob(two random individuals have identical sequence at time t) ?

  (i) Both of them have same parent in previous generation and none of them have mutated (because if they mutated, they would be different sequence in infinite alleles model).

  (ii) Have different parents in the previous generation and these parents are identical. As before, none of the offspring should mutate.

  Thus, we have the following recursion relation,

$$G_{t+1} = (1-u)^2 \cdot N \cdot (1/N^2) + (1-u)^2 \left(1 - \frac{1}{N}\right) G_t$$

– At large times, diversity $H = 1 - G$ is nonzero due to mutation-drift balance

$$H^* = \frac{N\mu(2-\mu)}{(N-1)\mu(2-\mu)+1} \approx \frac{2N\mu}{2N\mu+1}$$

  Note that diversity depends on a composite parameter $\theta = 2N\mu$

  * $\theta \gg 1$: $H^* = 1 - \theta^{-1}$: variation in a large population as fluctuations are small
  * $\theta \ll 1$: $H^* = 2N\mu < 1$ - drift more important, destroys variability

– Useful expression since LHS is measurable from data - (parameters determined/neutral selection hypothesis can be tested).

  Exercise: For e.g., we have 5 individuals with 500 sites (here only different loci shown)

1 : ... 0 ... 0 ... 0 ... 0...

2 : ... 1 ... 0 ... 0 ... 0...

3 : ... 0 ... 1 ... 0 ... 0...

4 : ... 0 ... 1 ... 1 ... 0...

5 : ... 0 ... 0 ... 0 ... 1...

  The chance that sequence 1 and 4 are different is 2/500. Find the average nucleotide diversity using all this data.

Solution:

$$\frac{1}{500 \times 10}((1+1+2+1)+(2+3+2)+(1+2)+(3)) = 0.0036$$

- Back to biallelic model: Frequency of A_1 is a random variable. What is the distribution of the fraction of A_1s in a population of size N when A_1 and A_2 mutate between each other with probability μ? Let's guess the shape of the equilibrium distribution from what we learnt.
  - Expect that answer depends on $2N\mu$
  - if $2N\mu \gg 1$(think of large population): deterministic approx. good, expect distribution to be narrowly peaked around deterministic value 1/2
  - if $2N\mu \ll 1$ (think of negligible mutation): A_1 can get fixed / go extinct (U-shaped function)
  - Diffusion theory shows that x_1 distributed according to a beta distribution,

$$P(x_1) \propto [x_1(1-x_1)]^{2Nu-1} \ , \ \langle x_1 \rangle = 1/2 \ , \ \sigma^2 \sim 1/N$$

- Drift and selection: Let the fitness of A_1 and A_2 be $1+s$ and 1, respectively. Start with $x_1(0)$ fraction of A_1. Then in the absence of mutations, one of the alleles eventually fixes. Would the fitter one take over with probability one?

  An analysis based on Fokker-Planck equation shows that (Kimura, 1962)

$$\pi(A_1) = \frac{1-e^{-2Nsx_1(0)}}{1-e^{-2Ns}}$$

  Here the fixation probability depends on the composite parameter Ns.

  - neutral ($N|s| \ll 1$): take limit (same for $s \to 0+$ or $0-$); recover $\pi = 1/N$
  - when A_1 is fitter ($Ns \gg 1$)
    - decreases as N increases (easier to fight off the lone better mutant)
    - saturates to $\approx 1 - e^{-2s}$, not one ! (fitter mutant even in a large but finite pop does not spread for sure unless it is infinitely better)
  - when A_2 is fitter ($s < 0, N|s| \gg 1$) : expo decrease in $\pi(A_1)$ but it can get fixed !

- Recall the deterministic evolution,

$$x_1(t) = \frac{x_1(0)}{x_1(0) + x_2(0)e^{-st}}$$

Starting from $x_1(0) = 1/N$, the time taken to reach a finite fraction (say, $x_1(T) = 1 - (1/N)$) is given by

$$T = (2/s) \ln N$$

However, we have seen that a rare mutant is not definitely fixed. Thus the initial frequency required that would escape loss due to drift equals $1/(Ns)$ (from expression of $\pi \approx 2Nsx_1(0), Ns \gg 1$ which is of order one when $x_1(0) \sim 1/(2Ns)$). This yields a better estimate, $T \sim \ln(Ns)/s$.

3 Multilocus genetics

Earlier we considered biallelic one locus models and we now consider more than one locus (2-loci then ℓ loci[9]).

3.1 Recombination

Ignore selection, mutation, drift. For 2 loci, we have alleles A and B at first and second locus, respectively.

Genotypes	Frequency	Recombining gametes
A_1B_1	x_1	A_1B_2, A_2B_1
A_1B_2	x_2	A_1B_1, A_2B_2
A_2B_1	x_3	A_1B_1, A_2B_2
A_2B_2	x_4	A_1B_2, A_2B_1

If c is the probability of recombination,

$$x_1' = x_1 + c(x_2x_3 - x_1x_4) \quad (7)$$
$$x_2' = x_2 - c(x_2x_3 - x_1x_4) \quad (8)$$
$$x_3' = x_3 - c(x_2x_3 - x_1x_4) \quad (9)$$
$$x_4' = x_4 + c(x_2x_3 - x_1x_4) \quad (10)$$

where, $x_1 + x_2 + x_3 + x_4 = 1$.

Define linkage disequilibrium (Lewontin & Kojima, 1960)

$$D = x_2x_3 - x_1x_4$$

[9]see Lecture 3 video

Using the conservation of frequencies,

$$\begin{aligned} D &= x_2(1 - x_1 - x_2 - x_4) - x_1 x_4 && (11)\\ &= x_1 - (x_1 x_2 + x_1 x_4 + x_2 x_2 + x_2 x_4) && (12)\\ &= x_1 - (x_1 + x_2)(x_2 + x_4) && (13)\\ &= f(A_1 B_2) - f(A_1) f(B_2) && (14) \end{aligned}$$

- Measure of 'linkage'[10]. When $D = 0$, freq of two locus genotype=freq(first locus) times freq (second).
- So, when is D zero?

  $$D' = x_2' x_3' - x_1' x_4' = (1 - c)D$$

  Thus LD decays exponentially fast, $D(t) \approx e^{-ct}$ and is negligible when $t \gg 1/c$. When c is small (asexuals), associations remain for a long time while for large c (sexuals), they decay rapidly and may be neglected ("linkage equilibrium").

4 References

- *Elements of Evolutionary Genetics*, Charlesworth & Charlesworth
- *Evolution*, Barton et al.
- *Mathematical Population Genetics*, Ewens
- *Probability Models for DNA Sequence Evolution*, Durrett
- *The Mathematical Theory of Selection, Recombination and Mutation*, Bürger
- *Origins of Theoretical Population Genetics*, Provine

[10] reminiscent of correlation function in physics