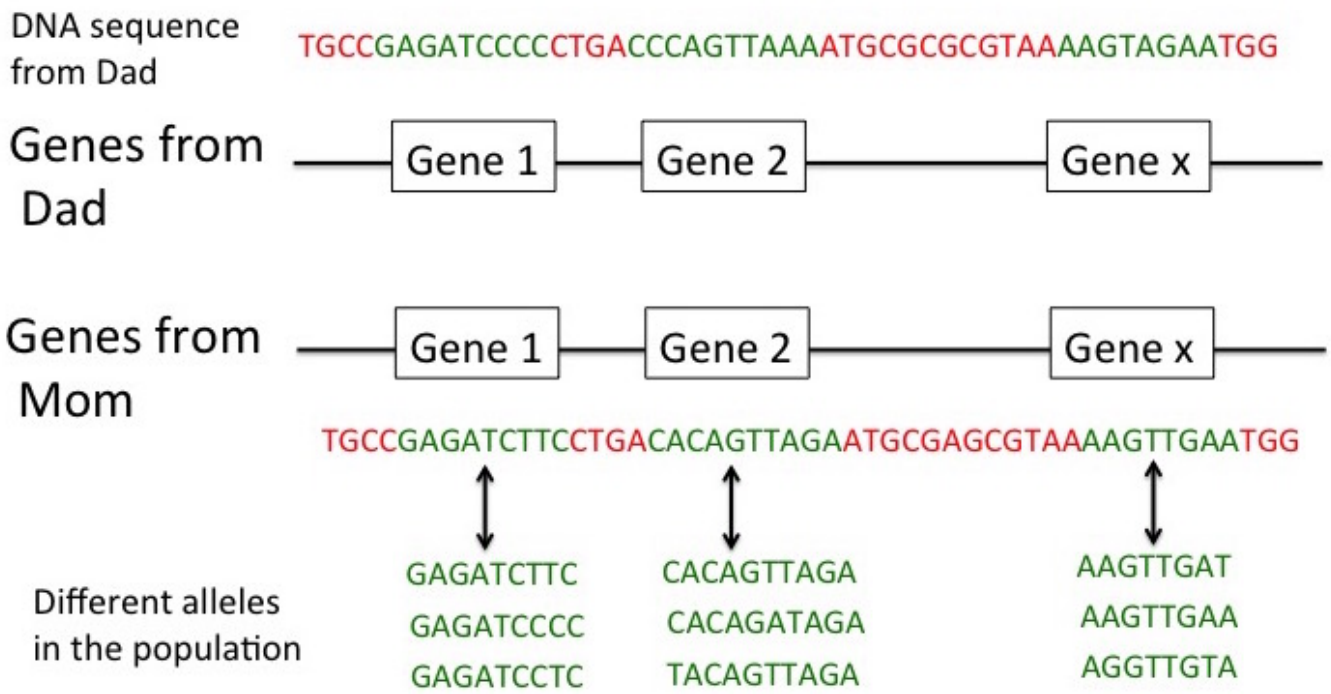
Mutation

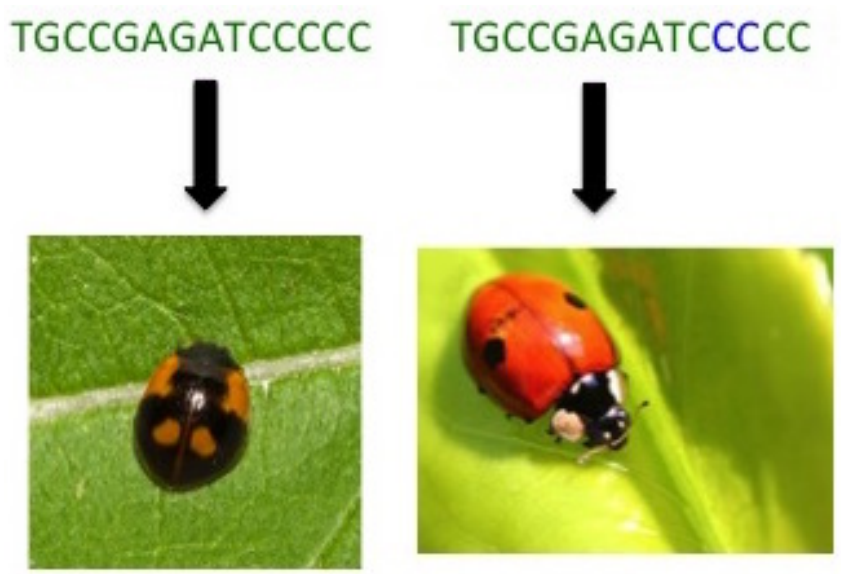
Allelic variation in a population



Different alleles causes differences in eye color, differences in resistance to pathogens, differences in abilities to digest milk, differences in tallness, differences in any conceivable phenotype.

Populations tend to be polymorphic and this depends (not exclusively) on individuals having different allelels

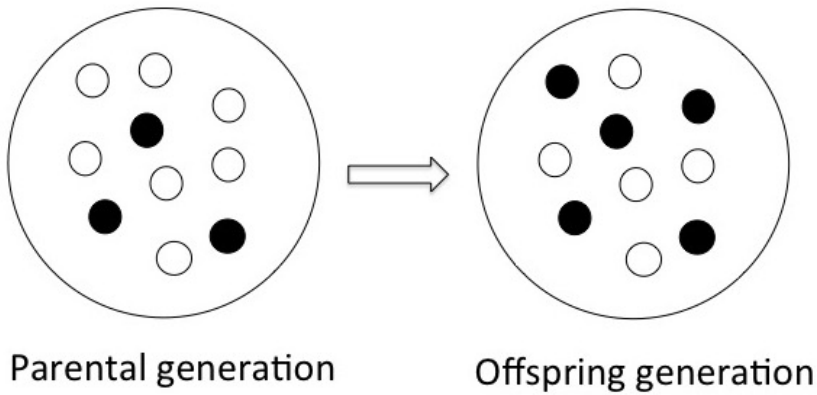
Usually populations are polymorphic and the biological differences are partly heritable and thus encoded in the DNA.



Change in allele frequency

In a two allele system, say allele A and B, the change in the average frequency of allele A over one demographic time period (from some parental to offspring generation) is

$$\Delta p = p' - p$$



Natural selection is fueled by allelic variation

Given allelic variation, the change in the frequency of allele A in an asexual reproducing population is

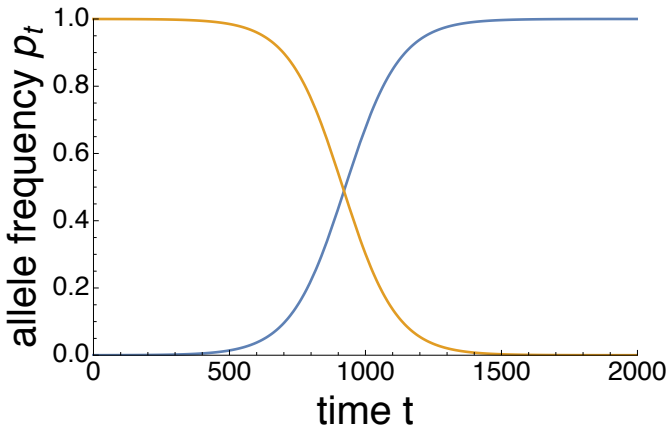
$$\Delta p = \frac{p(1-p)s}{\bar{w}} \qquad \text{with} \qquad s = w_{\mathrm{A}} - w_{\mathrm{B}}$$

1. Replication.
2. Variation.
3. Faithful heredity.

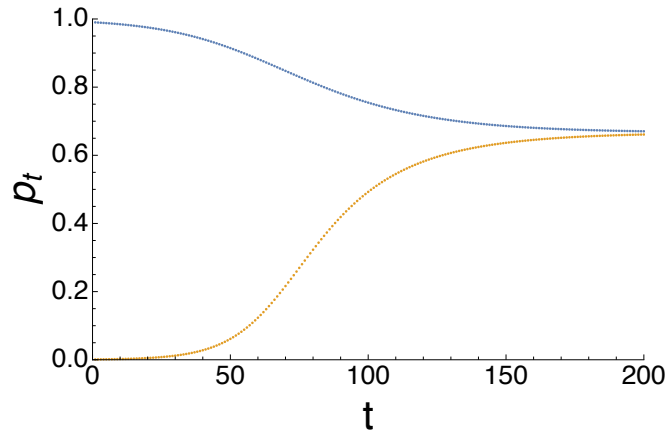
This underlies the idea of the "survival of the fittest".

Natural selection tends to eliminate or maintain variation

Different modes of natural selection.



Constant selection regime.
Parameters: $p_0 = 10^{-4}$ and $s = 0.01$ (blue), $p_0 = 1 - 10^{-4}$ and $s = -0.01$ (yellow).

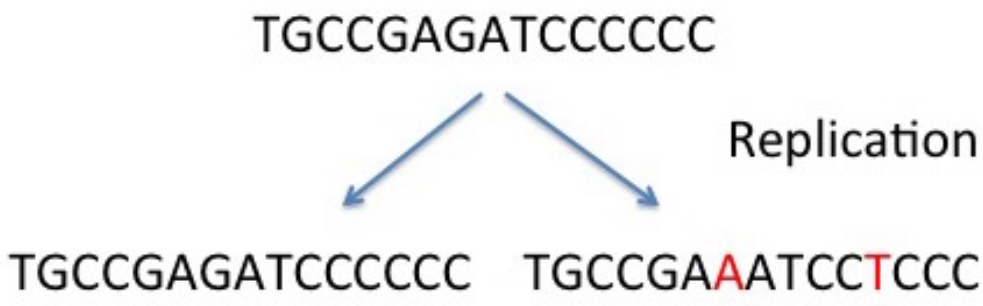


Frequency-dependent selection under Hawk-Dove game.
Parameters: $V = 0.2$ and $C = 0.15$, and $p_0 = 0.001$ (blue) and $p_0 = 0.99$ (blue).

This applies to any form of inheritance. It underlies the phrase "survival of the fittest".

Mutations generate allelic variation

Mutation: Spontaneous production of heritable changes in the DNA sequence of an individual. It can results in the creation of new alleles during cell replication.



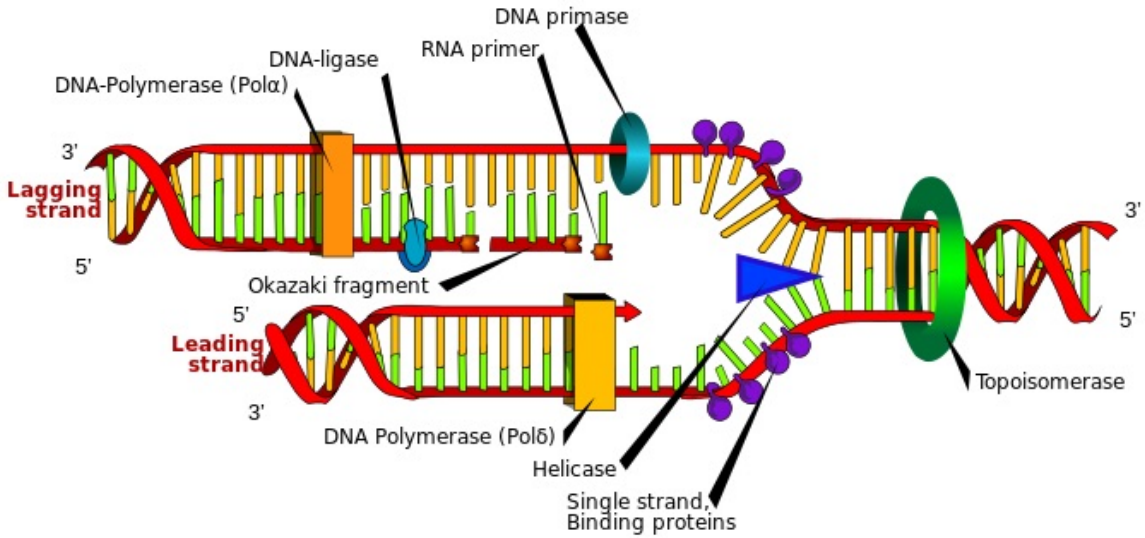
Replication of DNA occurs when cell division occurs. This happens

1. During reproduction (formation of offspring, germ line mutation)
2. During an individual's lifespan (somatic mutation)[1].

[1] Sperm and egg (germ line cells) are formed by meiosis while somatic cells are formed by mitosis.

DNA replication is a complicated process

Mutations are essentially unavoidable during replication as this involves a very complicated cellular machinery to do.



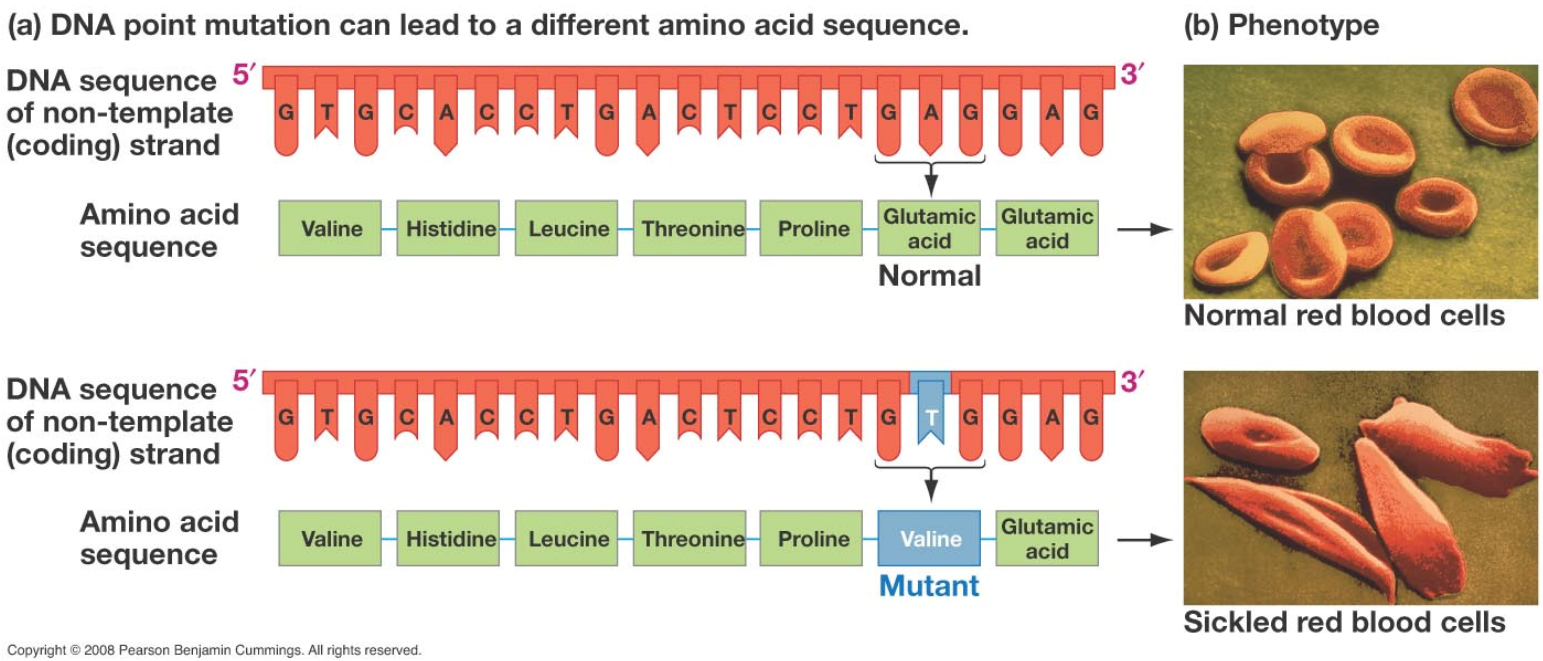
The machinery involved in replication involves many enzymes (proteins catalyzing chemical reactions) and is part of an individual's phenotype that is subject to natural selection.

Mutations have actually different origins

- Errors in the process of replication, these are often nucleobase specific.
- Can be caused by radiation or exposition to chemical mutagens (e.g., exposition to the sun, tobacco).
- Lateral DNA transfer such as insertion or deletion of mobile genetic elements.
- Large DNA rearrangements, such as insertion or deletion of parts of the genome.

Small DNA change can have large effects on phenotype

The change in a single nucleotide of DNA can have a drastic effect on the phenotype of an individual.



Mutations are often observed in natural populations

Mutation in a tomato

Mutation resulting in albinism

- Phenotypic effects of mutations are likely to result in survival and fecundity differences.
- **Caution**: only two third of mutations can have a phenotypic effect, this is because there is some redundancy in the genetic code. And most mutations have small effects so we don't really see them.

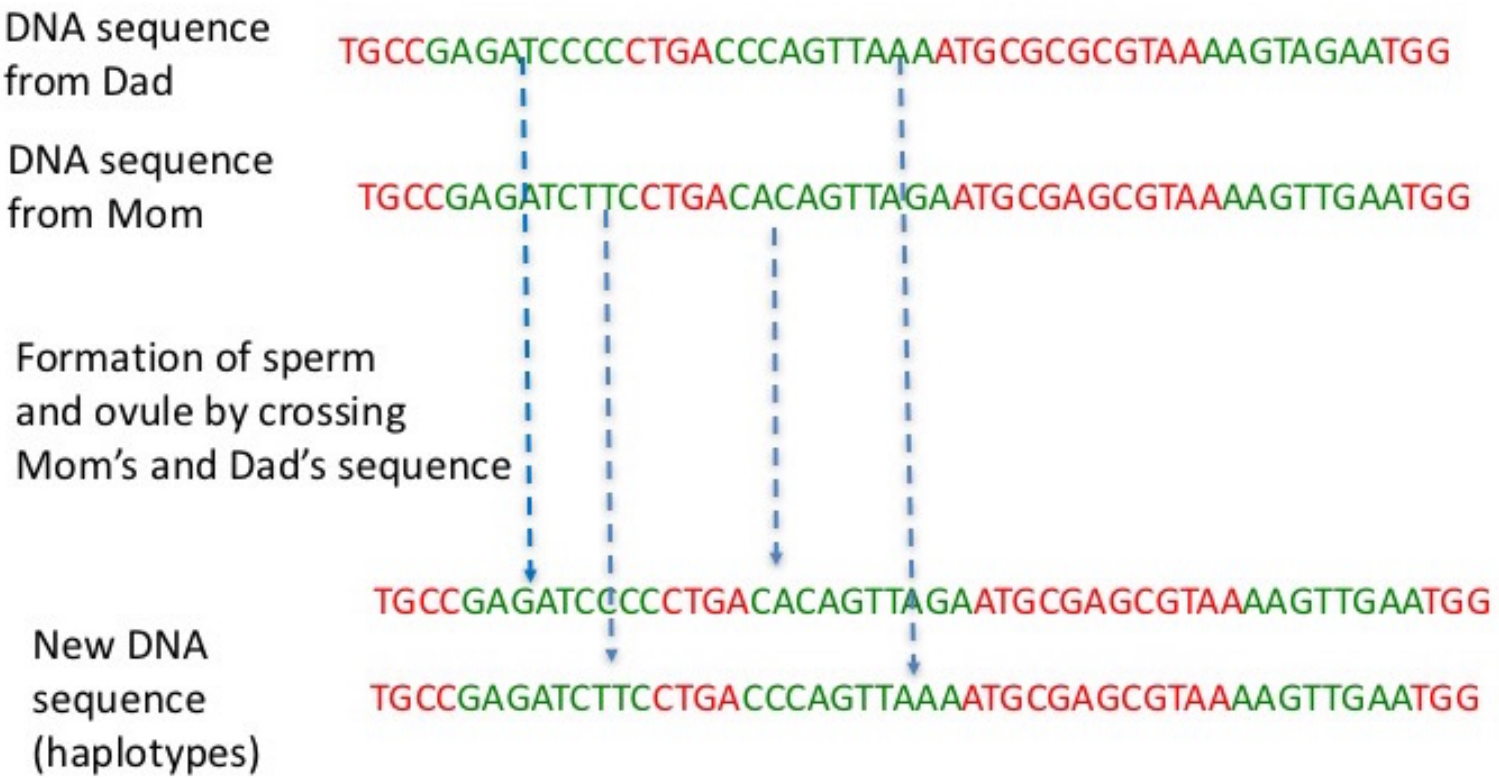
Mutations rates

Mutation rates are generally low but not negligibly low.

- Some viruses have a mutation rate of the order of 10^{-3} to 10^{-5} per nucleobase site per replication unit.
- Humans have approximatively a mutation rate of the order of 10^{-8} per nucleobase site per generation. The human genome is of the order 10^{-9} sites ($\approx 3 \times 10^{-9}$ sites from Mom and nearly same from Dad).
- Taking together single site mutations and DNA sequence rearrangements (insertions and deletions), an average human newborn contains about 100 de novo mutations. We are all mutants!

Recombination also generates genetic variation

Recombination: production of changes in the DNA sequence due to the reshuffling (recombination) of alleles inherited from Mom and Dad during the formation of gametes (sperm and egg) in sexually reproducing organisms.



Recombination also generates variation

- Recombination generates variability, but (in general) maintains allele frequencies at each gene in the population: recombination does not result in allele frequency change.

- Hence, the ultimate source of variability is mutation, which introduces new alleles in a population. In this course, we will not investigate the very complicated dynamics induced by recombination, and only focus on mutation.

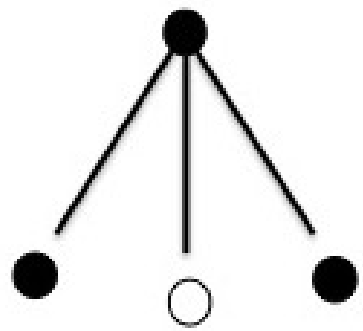
Questions

- How do mutations affect the evolutionary dynamics?
- How does the interaction between selection and mutation work out?

The mutation rate

We again consider a population where only two alleles segregate, allele A and allele B. Suppose we focus on an individual carrying allele A.

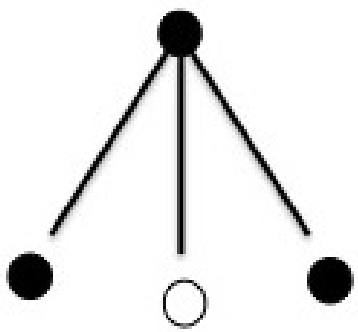
In order to describe quantitatively mutations from parent to offspring we denote by μ_{A} the probability that, during reproduction, a A carrier produces an offspring carrying allele B.



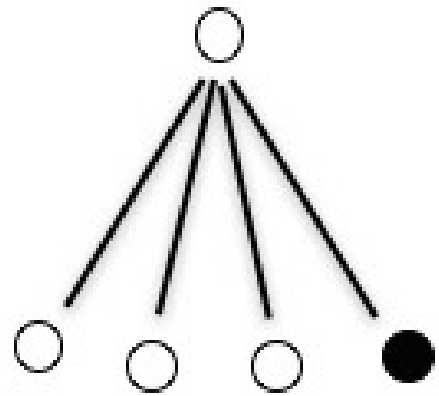
We here have $\mu_{\mathrm{A}}=1/3$. The quantity μ_{A} is the mutation rate of allele A.

The mutation rate

In a two-allele system, with allele A mutating to B at rate μ_{A} and allele B mutating to A at rate μ_{B} we have.



The mutation rate is $\mu_{\mathrm{A}}=1/3$

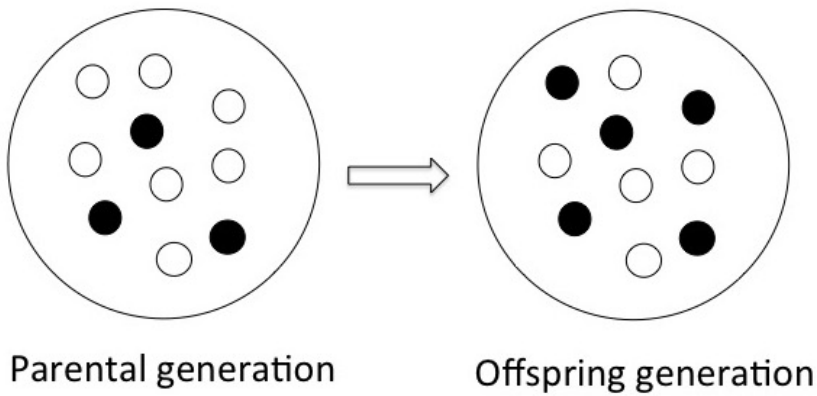


The mutation rate is $\mu_{\mathrm{B}}=1/4$

Change in allele frequency

The change in the average frequency of A over one demographic time period (from some parental to offspring generation) is

$$\Delta p = p' - p$$



We are now going to evaluate this change by allowing for mutation only (no fitness differences so that every individual in the population has same fitness w.

Mutation as an evolutionary force

In the absence of natural selection, the change in A frequency is

$$\Delta p = \mu_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} p$$

This can be understood as follows.

1. A proportion $1-p$ of individuals in the offspring generation descend from parents having allele B, which have produced offspring that have mutated into A with probability μ_{B}. This increases the frequency of allele A in amount $\mu_{\mathrm{B}}(1-p)$.
2. A proportion p of individuals in the offspring generation descend from parents with allele A, which have produced offspring that have mutated into B with probability μ_{A}. This decreases the frequency of A in amount $\mu_{\mathrm{A}} p$.

Mutation as an evolutionary force

The change in the frequency of allele A is

$$\Delta p = \mu_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} p$$

implies that mutation is a diversifying force.

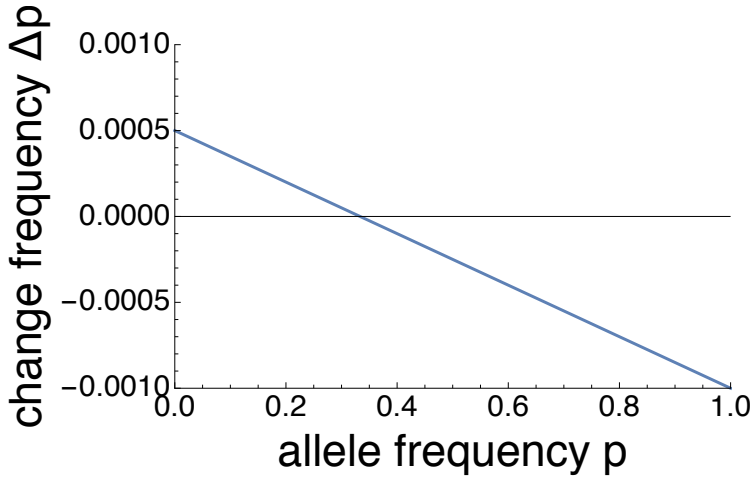
- If $p \approx 0$, $\Delta p \geq 0$, since $\mu_{\mathrm{B}} \geq 0$.
- If $p \approx 1$, $\Delta p \leq 0$, since $\mu_{\mathrm{A}} \geq 0$.

Hence, mutation tends to increase the genetic variance, $v = p(1-p)$, among the individuals in the population.

Mutation alone: change of allele frequency

The change in the frequency of A is

$$\Delta p = \mu_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} p$$



Parameters $\mu_{\mathrm{A}} = 0.001$ and $\mu_{\mathrm{B}} = 0.0005$

Frequency change is zero at some intermediate frequency.

Mutation alone: equilibrium points

No change when $\Delta p = 0$ (the population is in equilibrium). Hence an equilibrium point p^* satisfies

$$\mu_{\mathrm{B}}(1 - p^*) - \mu_{\mathrm{A}} p^* = 0$$

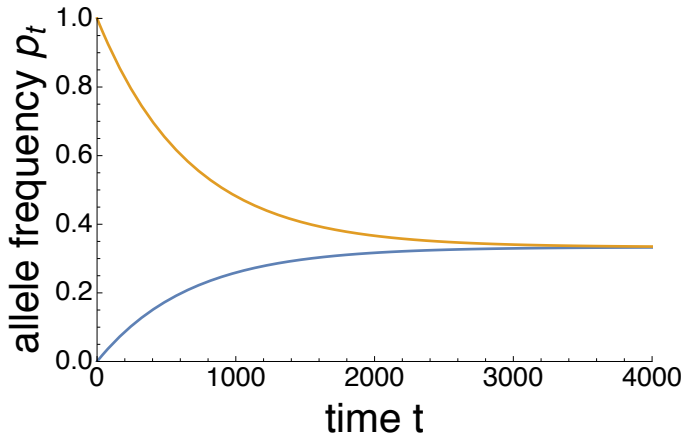
The equilibrium frequency is

$$p^* = \frac{\mu_{\mathrm{B}}}{\mu_{\mathrm{A}} + \mu_{\mathrm{B}}}$$

The equilibrium frequency is the ratio of the mutation rate towards A to the total mutation rate.

Mutation alone: time dynamics

Given initial frequency p_0 at time $t = 0$, the frequency p_t can be solved explicitly as a function of time.



Parameters values are $\mu_{\mathrm{A}} = 0.001$ and $\mu_{\mathrm{B}} = 0.0005$; further $p_0 = 0$ (blue) and $p_0 = 1$ (yellow).

For any initial frequency, the dynamics converges in the long run towards the equilibrium $p^* = \mu_{\mathrm{B}}/(\mu_{\mathrm{A}} + \mu_{\mathrm{B}})$.

Mutation alone: summary

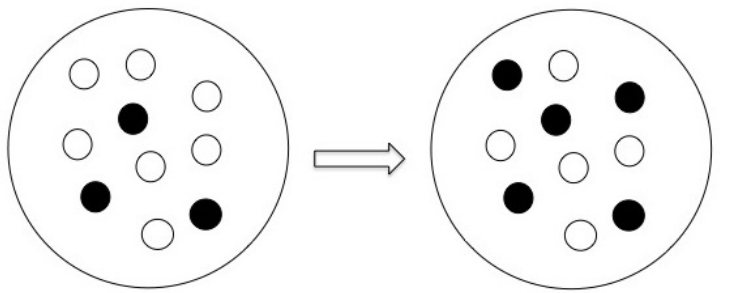
- Mutation is an evolutionary force.
- Mutation is a "linear force". The change in allele frequency is linear in the frequency of the different alleles in the population [e.g., $\Delta p = \mu_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} p$].
- There is usually a global stable equilibrium frequency.
- Mutation thus favors diversity.

But how does the introduction of mutation affects selection?

Change in allele frequency

The change in the average frequency of A is

$$\Delta p = p' - p$$



- We are now going to evaluate this change by allowing for natural selection and mutation.
- Individuals bearing allele A have fitness w_{A} while individuals bearing allele B have fitness w_{B}.

Interaction between natural selection and mutation

In the presence of natural selection and mutation, the change in the frequency of A can be decomposed into two terms as

$$\Delta p = \Delta p_{\mathrm{s}} + \Delta p_{\mu}$$

where

1. Δp_{s} is the change in allele frequency due to natural selection on faithfully transmitted alleles.
2. Δp_{μ} is the change in allele frequency due to mutation.

Interaction between natural selection and mutation

We have evaluated before the change due to selection and it is

$$\Delta p_{\mathrm{s}} = \frac{p(1-p)s}{\bar{w}}$$

The change due to mutation is[2]

$$\Delta p_{\mu} = \mu_{\mathrm{B}} \frac{w_{\mathrm{B}}(1-p)}{\bar{w}} - \mu_{\mathrm{A}} \frac{w_{\mathrm{A}} p}{\bar{w}}$$

- $w_{\mathrm{B}}(1-p)/\bar{w}$ is the proportion of individuals in the offspring generation that descend from B parents.
- $w_{\mathrm{A}} p/\bar{w}$ is the proportion of individuals in the offspring generation that descend from A parents.

[2] When there is no selection this reduced to $\Delta p = \mu_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} p$.

Interaction between natural selection and mutation

We can now write the change in the frequency of A as

$$\Delta p = \frac{p(1-p)s}{\bar{w}} + \frac{\mu}{\bar{w}}$$

where $s = w_{\mathrm{A}} - w_{\mathrm{B}}$ is the *selection coefficient* and

$$\mu = \mu_{\mathrm{B}} w_{\mathrm{B}}(1-p) - \mu_{\mathrm{A}} w_{\mathrm{A}} p$$

is the mutation flow rate of A: the difference between the number of individual of type A that are created by mutation and those that are annihilated (because they mutate to allele B). This is either positive, negative, or zero. When it is positive it means more A individuals are "created" than "annihilated" by mutation.

Change in average allele frequency

The change in the frequency of A is

$$\Delta p = \frac{p(1-p)s}{\bar{w}} + \frac{\mu}{\bar{w}}$$

Three things should be noted about this equation.

1. Mutation is a diversifying force (brings in variation).
2. The change due to selection can be swamped by the effect of mutation.
3. It describes the evolutionary dynamics of any replicator, which is defined as any entity displaying: (1) multiplication, (2) heredity ("like begets like"), and (3) variation.

We now work out a number of consequences of this.

Mutation-selection interaction: model assumptions

Let's make the following assumptions:

1. Constant selection where allele A is favored over allele B and let the fitnesses of A and B be

$$w_{\mathrm{A}} = 1 \qquad\qquad w_{\mathrm{B}} = 1 - s$$

2. Only one way mutation from A to B but not the reverse event ($\mu_{\mathrm{A}} > 0$ and $\mu_{\mathrm{B}} = \mu_{\mathrm{B}} = 0$).

Mutation-selection interaction: deleterious alleles

- We can think that A is an allele resulting in the optimal fit to the environment and B is a so-called deleterious allele.
- The majority of mutations are actually (mildly) deleterious, this is a very well documented result in (evolutionary) biology.
- This is so because there are much more ways to do things wrong than to do them right.

An average human newborn contains ≈ 100 *de novo* mutations. Among them about 10 are deleterious and the other's do not have any appreciable effect on the phenotype.

Males as they age produce sperm with more mutations and thus more deleterious mutations. Autism and schizophrenia have been correlated to Dad's age.

Mutation-selection interaction: change in allele frequency

For this situation $\mu = -p\mu_{\mathrm{A}}$ and the change Δp in the frequency of A is given by

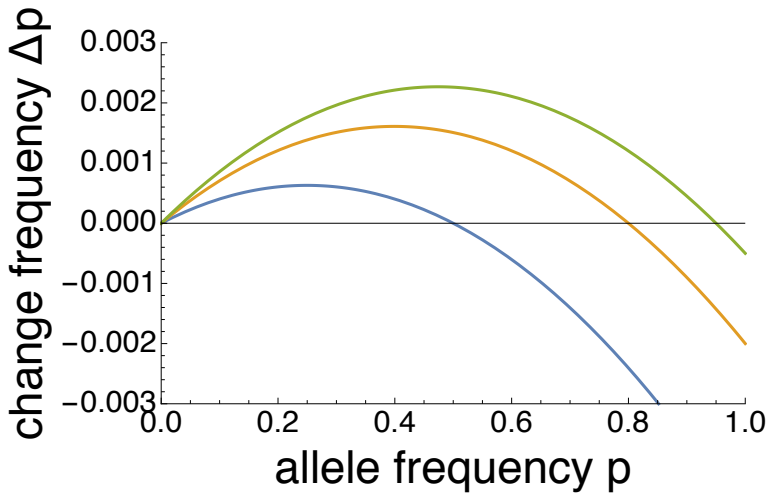
$$\Delta p = \frac{p(1-p)s}{\bar{w}} - \frac{p\mu_{\mathrm{A}}}{\bar{w}}$$

Two opposing forces:

1. Selection favors A, this increases the A frequency, $\Delta p > 0$.
2. Mutation favors B, this decreases the A frequency, $\Delta p < 0$.

Mutation-selection interaction: change in allele frequency

The change Δp in the frequency of A as a function of p is



Parameters: $s = 0.01$ and $\mu_{\mathrm{A}} = 0.005$ (blue), $\mu_{\mathrm{A}} = 0.002$ (yellow) and $\mu_{\mathrm{A}} = 0.0005$ (green).

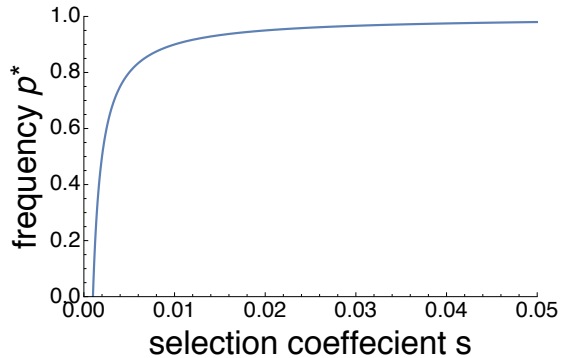
This model displays two equilibria:

1. The boundary equilibrium $p = 0$, which is unstable.
2. An internal equilibrium that is stable where the two forces of selection and mutation balance each other out.

Mutation-selection balance

The interior equilibrium satisfies $\Delta p = 0$. The equilibrium frequency thus satisfies $p^*(1-p^*)s - p^*\mu_{\mathrm{A}} = 0$ for p^*, which gives

$$p^* = 1 - \frac{\mu_{\mathrm{A}}}{s}$$

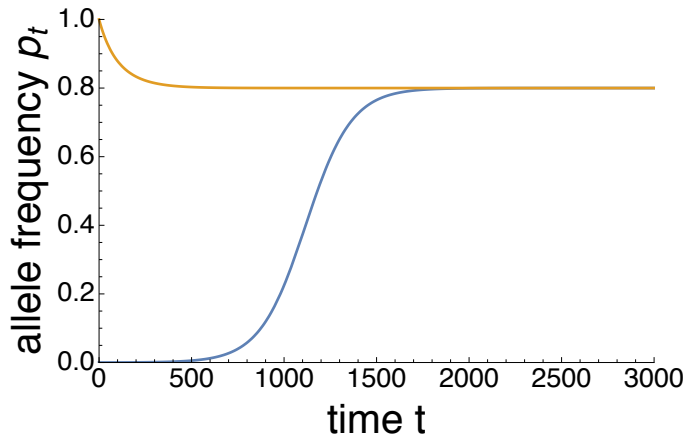


Parameters $\mu_{\mathrm{A}} = 0.001$.

- This is the frequency of A at the mutation-selection equilibrium.
- Selection must be stronger than mutation ($s > \mu_{\mathrm{A}}$) for A to be maintained in the population at equilibrium.

Mutation-selection balance: time dynamics

The frequency p_t of A as a function of time is



Parameters: $s = 0.01$ and $\mu_{\mathrm{A}} = 0.002$; further $p_0 = 10^{-4}$ (blue) and $p_0 = 1$ (yellow).

For any initial frequency, the dynamics converges in the long run towards $p^* = 1 - \mu_{\mathrm{A}}/s = 0.8$.

Genetic load

The genetic load of a population is defined as

$$L = \frac{w_{\max} - \bar{w}}{w_{\max}}$$

We have

- $w_{\max}$ is the fitness of an individual carrying the allele that has the largest fitness in the population and mean fitness, $\bar{w}$, is evaluated at the mutation-selection equilibrium p^*.
- The genetic load thus measures the decrease in mean fitness in the population relative to the reference allele, the allele resulting in the largest fitness.

Genetic load

For our two allele model under mutation selection balance $w_{\max} = w_{\mathrm{A}}$. Using $p^* = 1 - \mu_{\mathrm{A}}/s$ then yields the load

$$L = \mu_{\mathrm{A}}$$

- The genetic load is exactly equal to the mutation rate away from the optimal allele.
- This holds generally approximately also for sexual reproduction and multiple alleles.

Genetic load: the human exceptionalism

Humans have a (low) mutation rate as is seen in many other species. But there is one thing exceptional about the human genetic load:

- There is an overall relaxed selection pressure on essentially every part of the genome, since with the advent of medicine we have a strong inclination towards minimizing the fitness consequences of mutations with small effects.[3]
- That means there is a relaxed selection pressure on the mutational rate itself, which is an evolving phenotype.

[3] Mutation with large effects are likely to be counter-selected, pre-natal tests are nowadays used routinely to screen genetic defects.

Genetic load: the human exceptionalism

- The majority of people reaching their thirties have suffered of at least one chronic disease or some handicapp.
- These are mostly due to genetic effects and about 20000 thousand deleterious alleles have been identified.

Disease	Frequency
Neoplasms (benign and cancerous tumors)	0.01
Diseases of the blood and blood-forming organs	0.03
Endocrine, nutritional, and metabolic diseases	0.05
Mental, behavioral, and neurodevelopmental disorders	0.4
Intellectual disability, severe	0.005
Intellectual disability, moderate	0.01
Schizophrenia	0.005
Autism spectrum disorders	0.01
Bipolar disorder	0.01
Major depression	0.10
Anxiety disorders	0.15
Behavioral disorders	0.10
Diseases of the nervous system	0.15
Diseases of the eye	0.01
Diseases of the ear	0.02
Diseases of the circulatory system	0.01
Diseases of the respiratory system	0.10
Diseases of the digestive system	0.04
Diseases of the skin and subcutaneous tissue	0.12
Diseases of the musculoskeletal system and connective tissue	0.01
Diseases of the genitourinary system	0.02

Genetic load: the human exceptionalism

- Hence, the genetic load should increase: there is an accumulation of deleterious mutations magnifying the mutation rate.
- It is has been suggested that human fitness (measured as fecundity and survival) is currently dragged down by 1% per generation ($\approx$ 25-30 years, Lynch 2016, Kondrashov 2017).[4]
- Reduction of baseline physical and mental performance in populations with the resources to minimize the fitness consequences of mutations with small effects (the "richer" the "weaker").

[4] This idea was already proposed in 1950, but now more data are available to confirm the trend.

Genetic load: the human exceptionalism

- In the optimistic scenario, selection-mutation balance will reach a novel equilibrium. In the pessimistic scenario, we should observe a slow but steady mutational meltdown of the human condition over centuries.

- This raises the fundamental socio-political problem of whether anything can or should be done about it.

- This also raises a fundamental economic problem as to whether biomedical innovations will emerge at a sufficiently high rate to solve both short- and long-term challenges associated with the increased genetic load.

Summary

- “In short, mutations are accidents, and accidents will happen”. Alfred Sturtevant
- Mutation is an evolutionary force. It introduces allelic variation and provide the raw material for evolution.
- Both mutation and natural selection interact.
- The balance between selection and mutation is captured by the genetic load that is increasing in human populations.