Introduction to Bioinformatics for Computer Scientists

Lecture 10

Outline

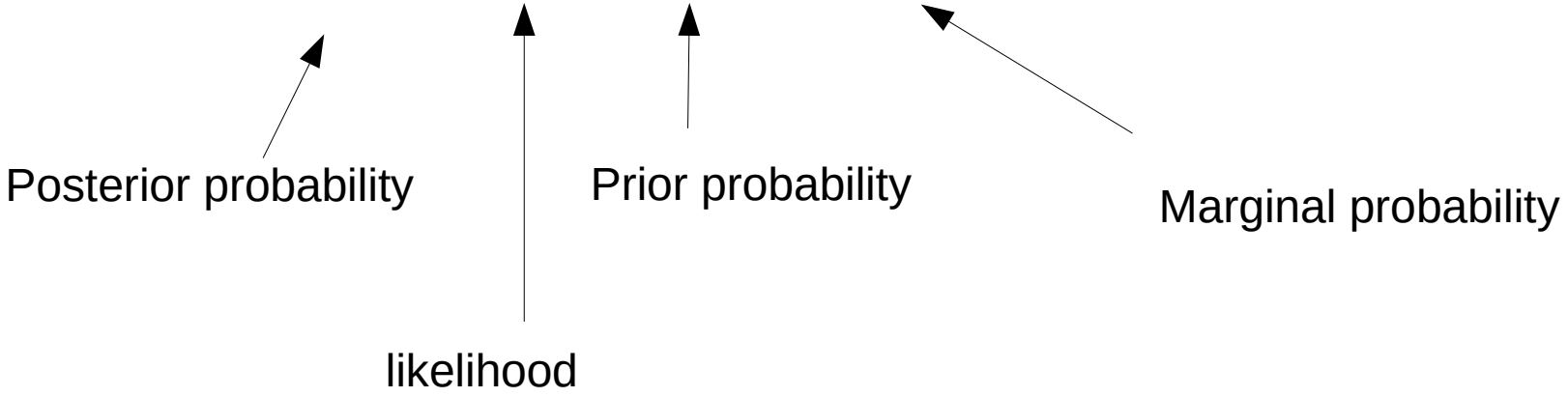
- Last Time
  - Bayesian statistics
  - Monte-Carlo simulation & integration
  - Markov-Chain Monte-Carlo methods
  - Metropolis-coupled MCMC-methods

Outline

- Last Time
  - Bayesian statistics
  - Monte-Carlo simulation & integration
  - Markov-Chain Monte-Carlo methods
  - Metropolis-coupled MCMC-methods
- Today
  - Bayesian Inference
    - **The curse of priors**
    - Some phylogenetic proposals
    - Reversible jump MCMC
  - Introduction to Population Genetics

Bayes Theorem

$$Pr(B|A) = Pr(A|B)\ Pr(B) / Pr(A)$$



A few words about priors

- Prior probabilities convey the scientist's beliefs, before having seen the data
- Using uninformative prior probability distributions (e.g., uniform priors, also called flat priors)

  → differences between prior and posterior distribution are attributable to likelihood differences **only**
- Priors can bias an analysis !
- For instance, we could chose an arbitrary prior distribution for branch lengths in the range [1.0,20.0]

  → what happens if branch lengths are much shorter?

An Analysis from Last Week

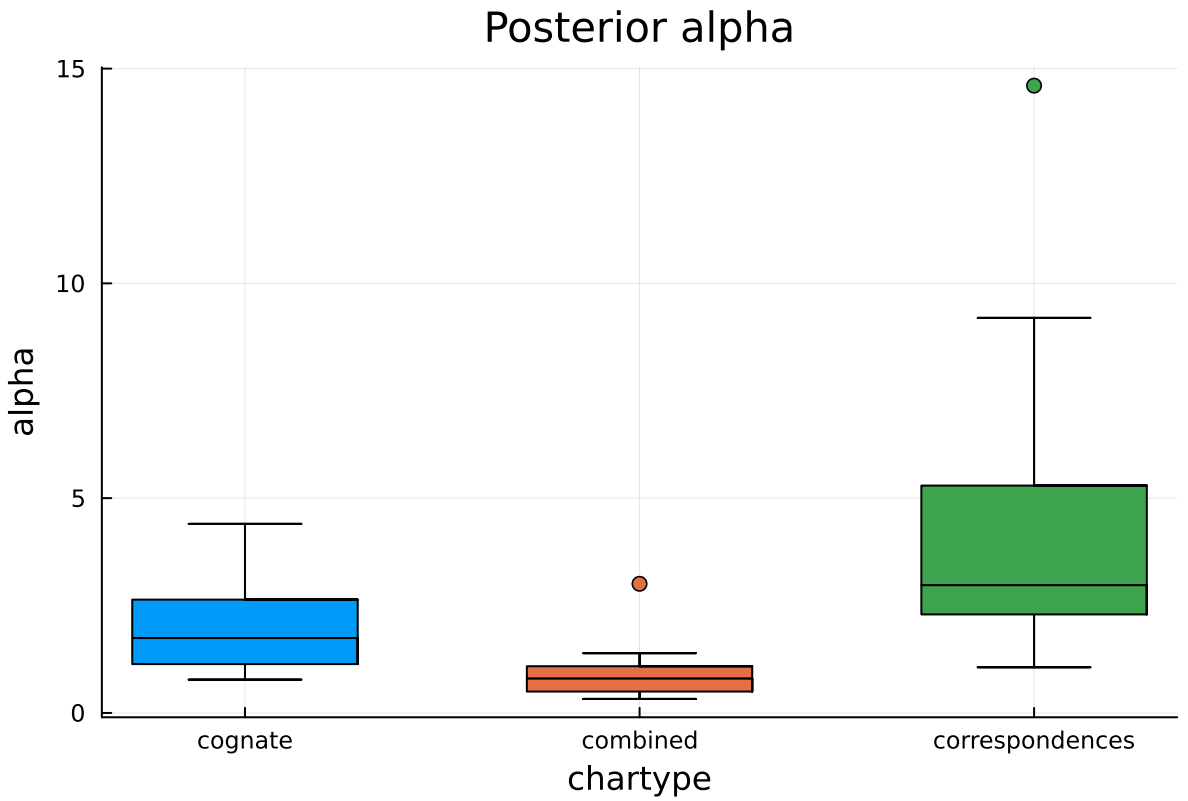
- We analyzed a couple of natural language datasets
- Under ML we found a very weird bi-modal distribution of the α-shape parameter for the Γ model of rate heterogeneity

dataset	cognate classes	sound correspondences	combined
constenlachibchan	0.592	**99.871**	4.178
crossandean	1.243	6.334	1.154
dravlex	0.702	4.301	2.234
felekesemitic	1.062	7.430	2.693
hattorijaponic	**99.848**	**99.897**	**99.890**
houchinese	2.357	6.120	4.195
leekoreanic	8.316	8.420	3.284
robinsonap	**99.869**	15.269	3.486
walworthpolynesian	1.333	4.233	1.624
zhivlovobugrian	**99.850**	4.244	3.134

Table 1: Alphas, Values indicating a very low rate heterogeneity are highlighted in bold

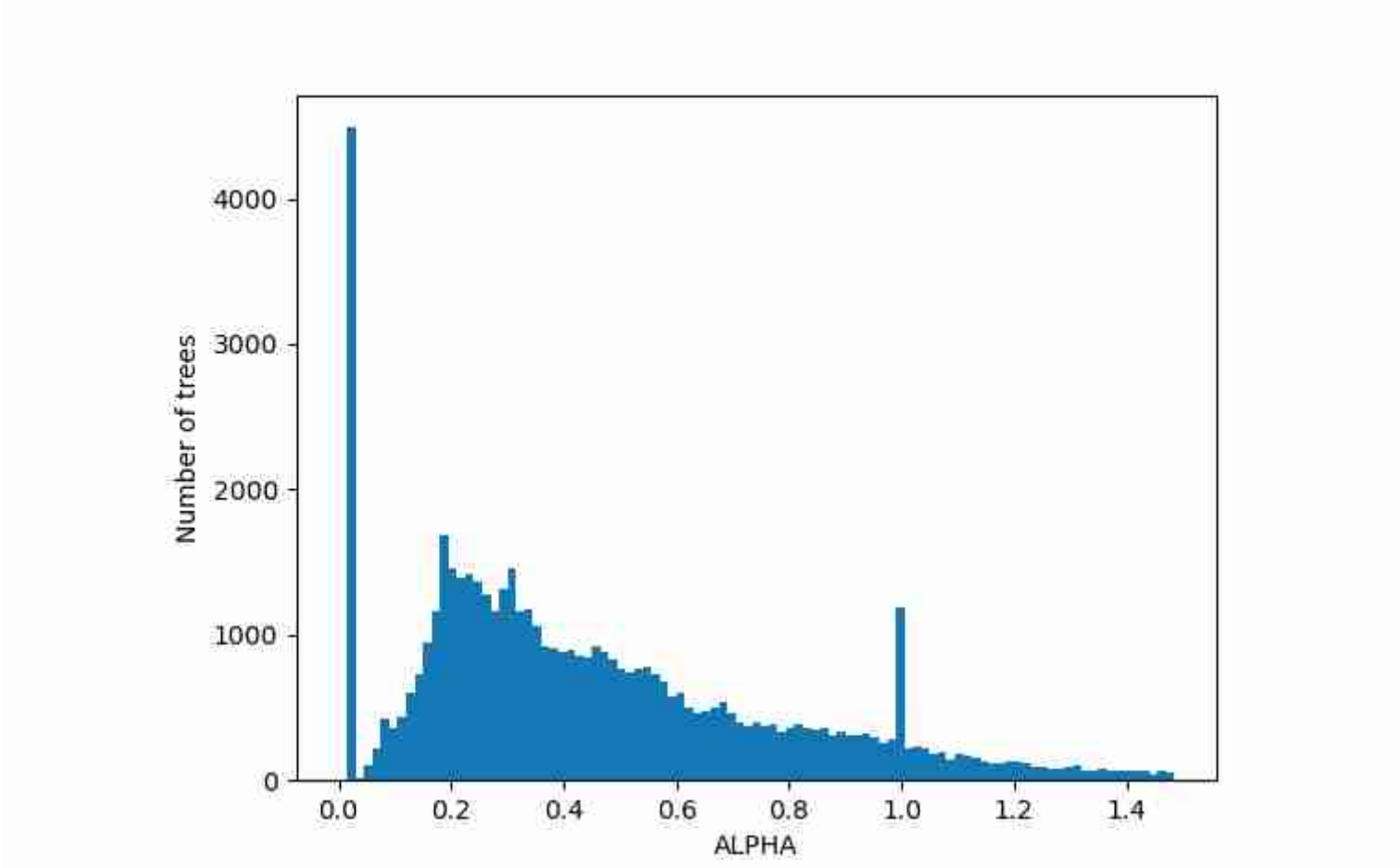
What did the Bayesian Inference yield?

- With the default prior used for molecular Sequence Datasets

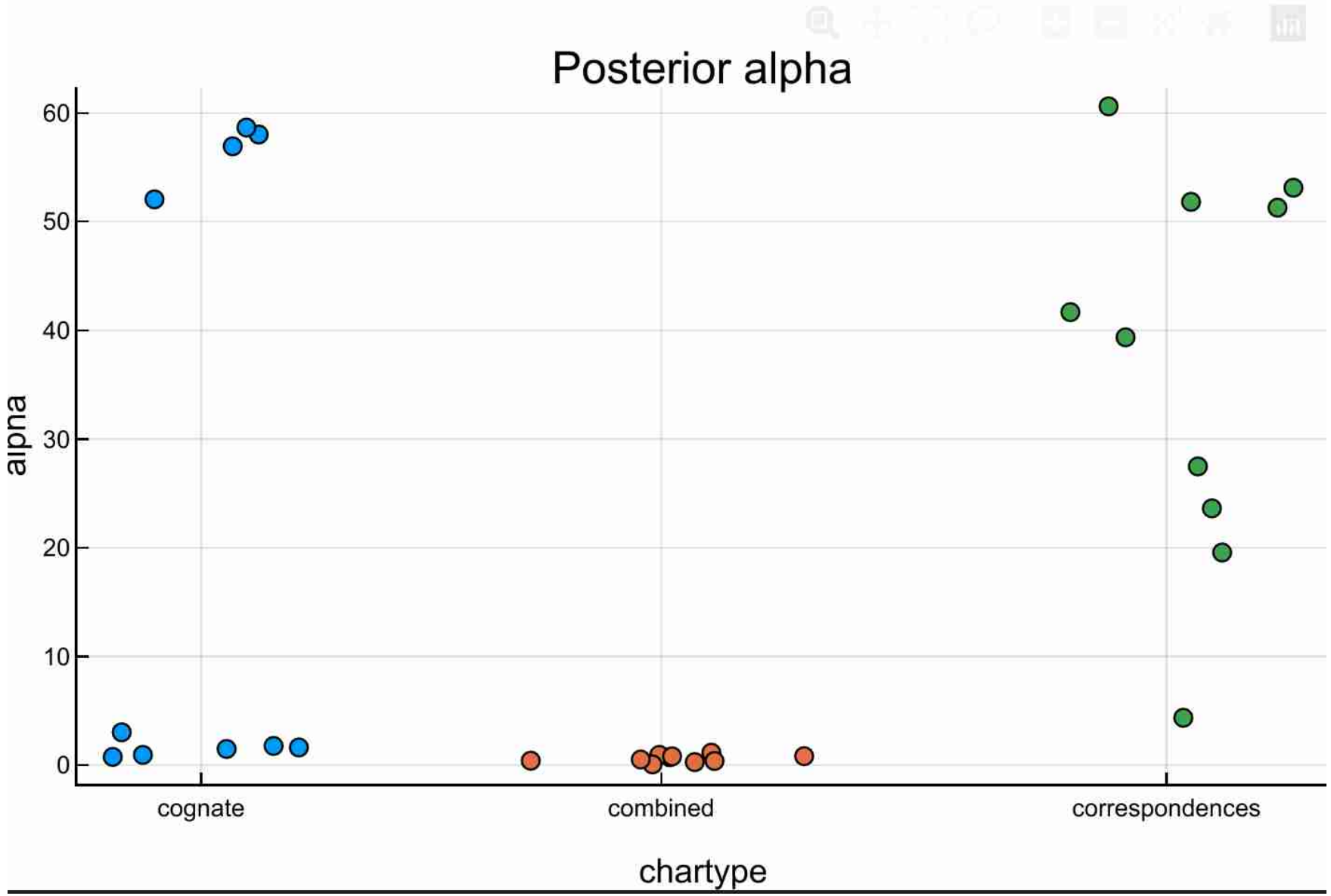


Empirical Distribution of α

- For tens of thousands of empirical molecular datasets this is how the ML estimate of α is distributed



When specifying a uniform prior



Outline

- Last Time
  - Bayesian statistics
  - Monte-Carlo simulation & integration
  - Markov-Chain Monte-Carlo methods
  - Metropolis-coupled MCMC-methods
- Today
  - Bayesian Inference
    - The curse of priors
    - **Some phylogenetic proposals**
    - Reversible jump MCMC
  - Introduction to Population Genetics

Some Phylogenetic Proposal Mechanisms

- Branch Lengths
  - Sliding Window Proposal
  - Multiplier Proposal
- Topologies
  - Local Proposal (the one with the bug in the Hastings ratio)
  - Extending TBR (Tree Bisection Reconnection) Proposal
- Remember: We need to design proposals for which
  - We either *don't need to* calculate the Hastings ratio
  - Or for which we *can* calculate it
  - That have a 'good' acceptance rate

    → all sorts of tricks being used, e.g., parsimony-biased topological proposals

Some Phylogenetic Proposal Mechanisms

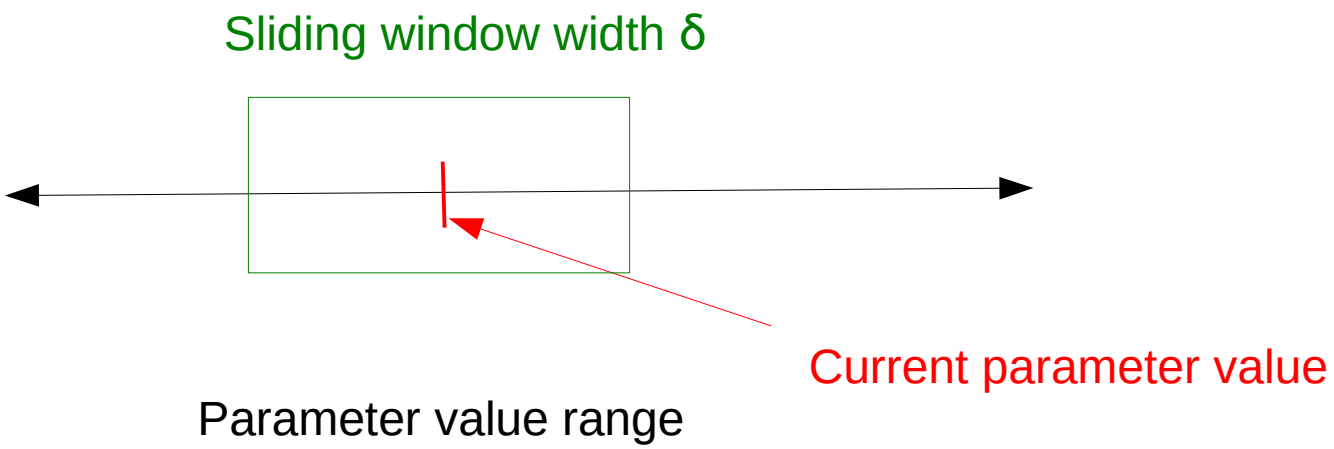
- Univariate parameters & branch lengths
  - Sliding Window Proposal
- Branch lengths
  - Node slider proposal
- Topologies
  - Local Proposal (the one with the bug in the Hastings ratio!)
- Remember: We need to design proposals for which
  - We either *don't need to* calculate the Hastings ratio
  - Or for which we *can* calculate it
  - That have an appropriate acceptance rate

    → all sorts of tricks being used, e.g., parsimony-biased topological proposals

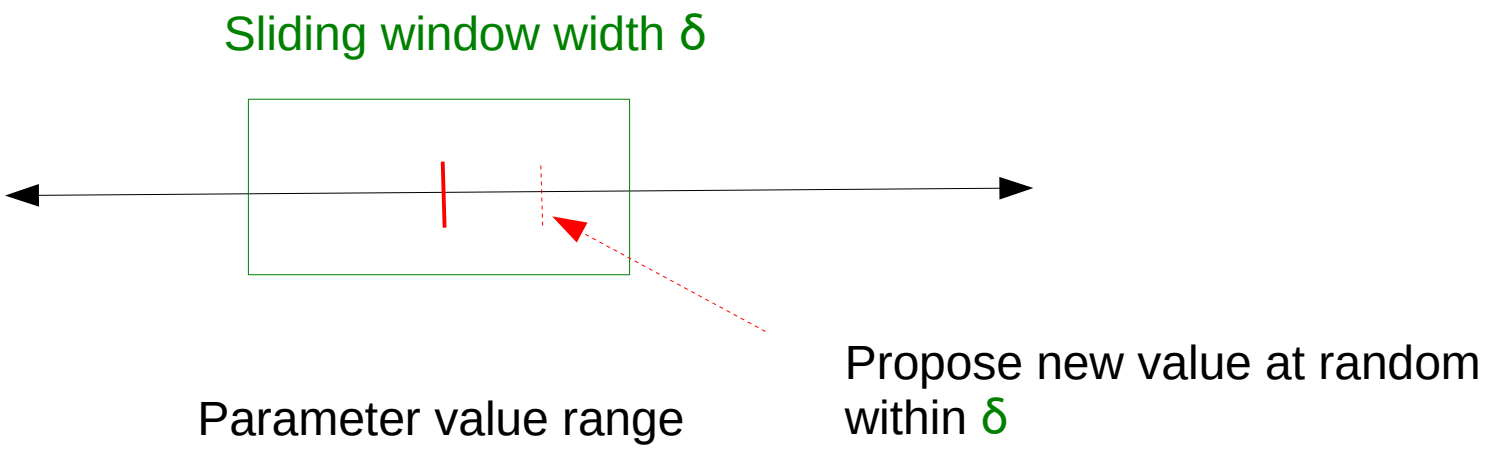
    → acceptance rate should be around 25% (empirical observation)

    → for sampling from a multivariate normal distribution it has been formally shown that an acceptance rate of 23.4% is optimal

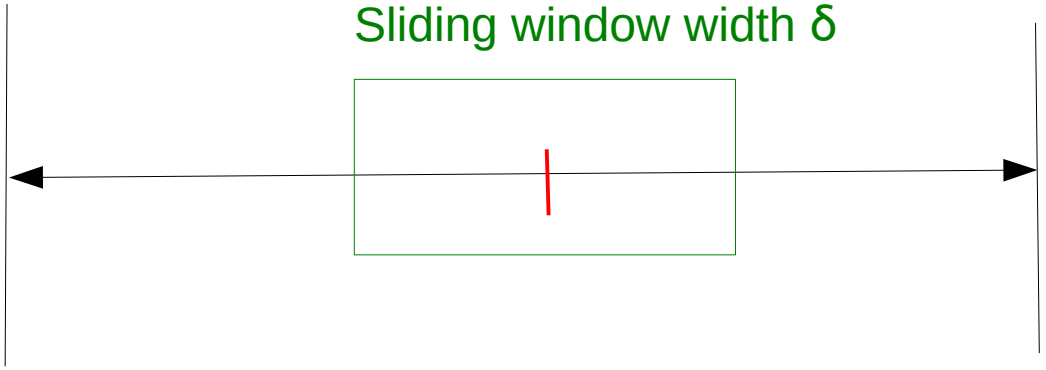
Sliding Window Proposal



Sliding Window Proposal

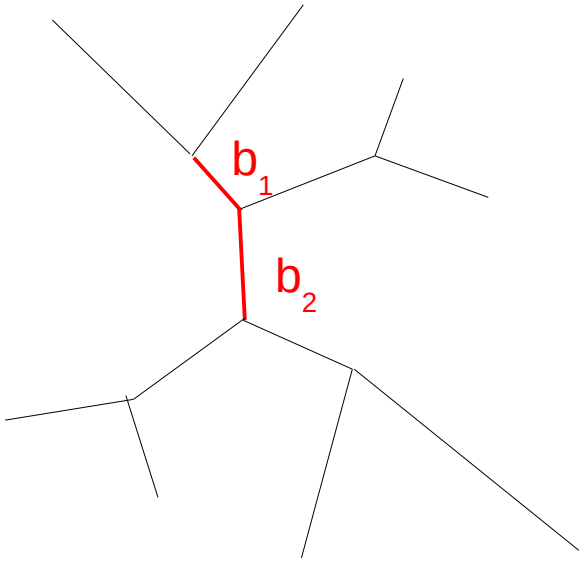


Sliding Window Proposal



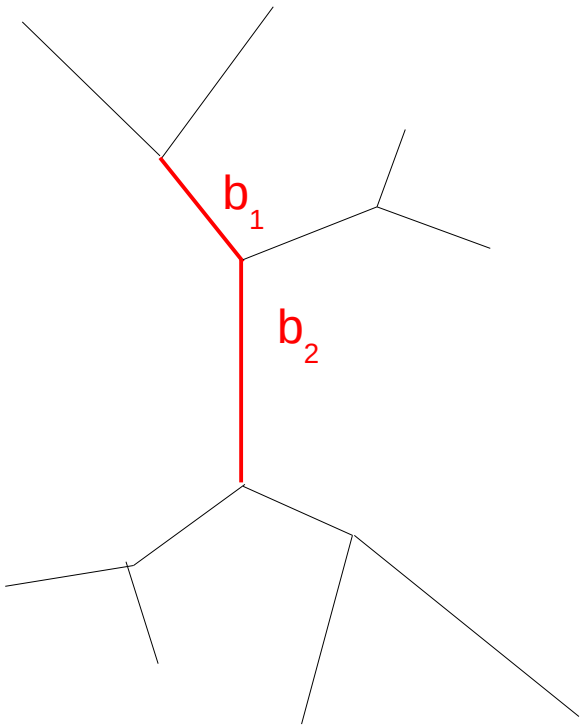
Notes:
1. The hastings ratio of this move is *1*
2. The edge cases can be handled by back-projection
3. The window size δ can be tuned itself (auto-tuning) to obtain an acceptance rate of ≈ ¼
4. This proposal can be used, e.g., for the *α*-shape parameter of the *Γ* function in rate heterogeneity models

The Node Slider Proposal



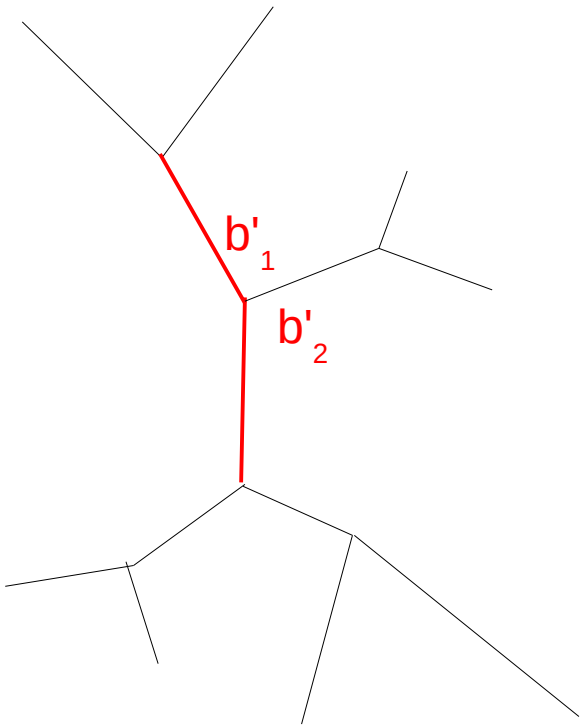
1. Pick *2* contiguous branches at random

The Node Slider Proposal



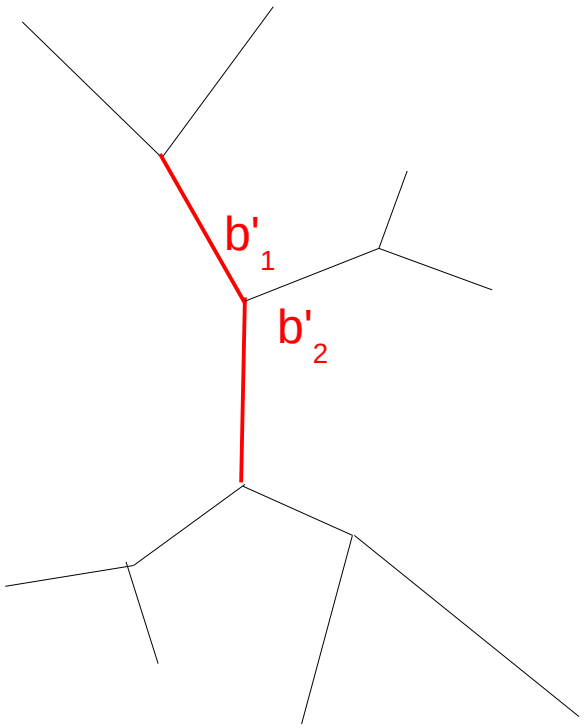
1. Pick *2* contiguous branches at random
2. Multiply the *2* branches by the same random number

The Node Slider Proposal



1. Pick *2* contiguous branches at random
2. Multiply the *2* branches by the same random number
3. Propose a new branch ratio b_1/b_2 at random

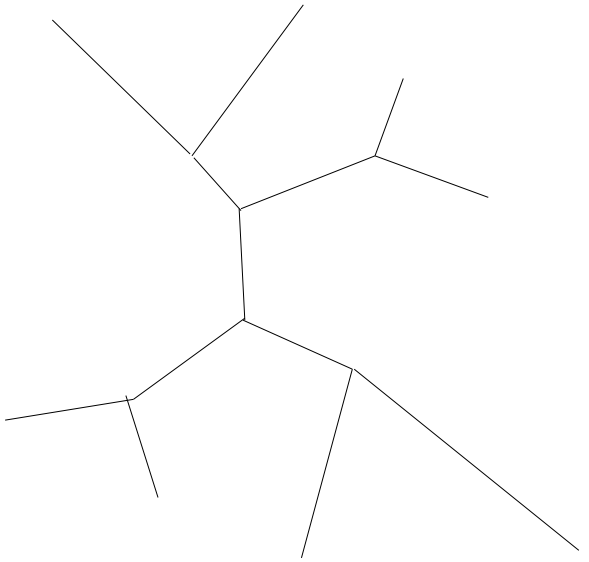
The Node Slider Proposal



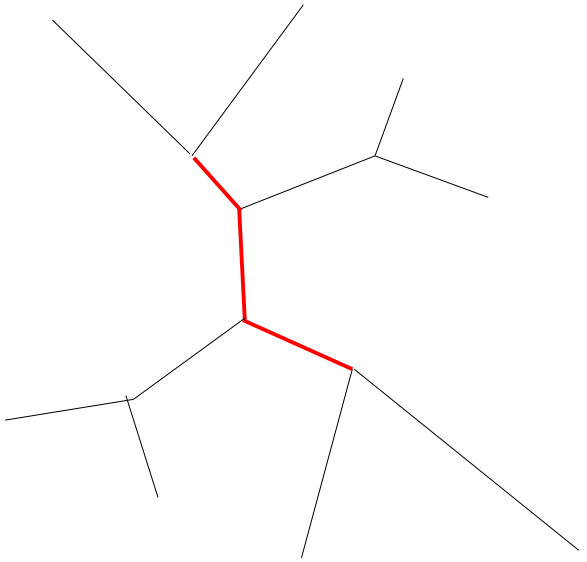
1. Pick *2* contiguous branches at random
2. Multiply the *2* branches by the same random number
3. Propose a new branch ratio b_1/b_2 at random

The Hastings ratio of this move is not *1*!

Moving through Tree Space

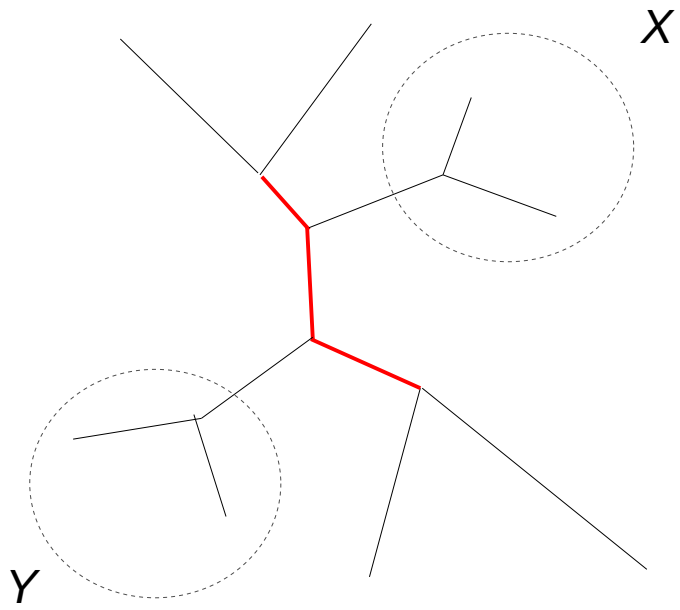


Moving through Tree Space



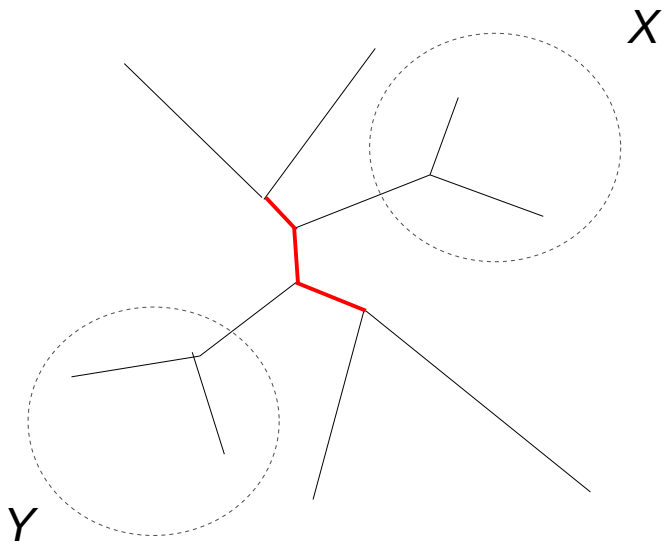
1. Pick *3* contiguous branches at random

Moving through Tree Space



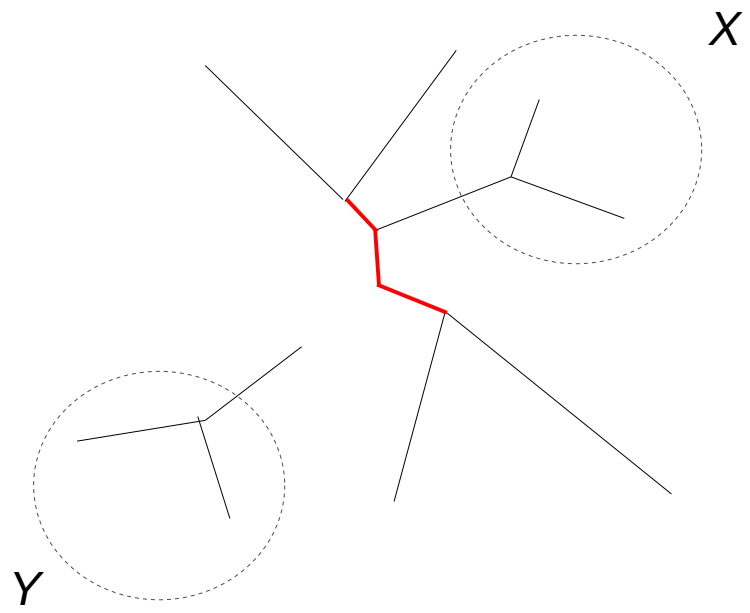
1. Pick *3* contiguous branches at random that define *2* Subtrees *X* and *Y*

Moving through Tree Space



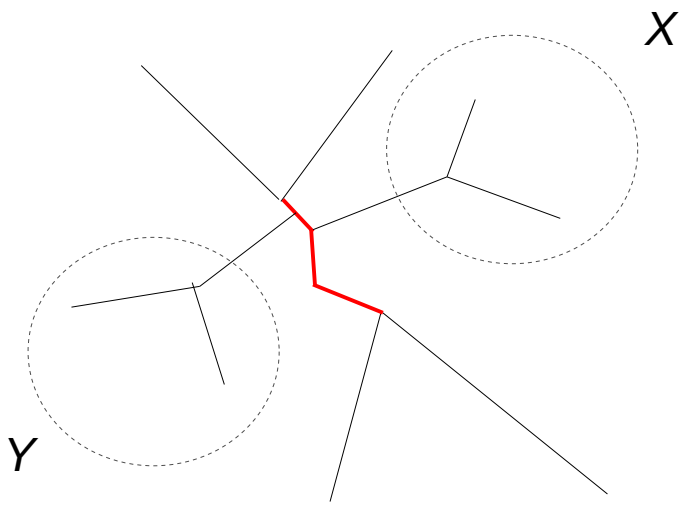
1. Pick *3* contiguous branches at random that define *2* Subtrees *X* and *Y*
2. shrink or grow selected *3* branch segment by a random amount

Moving through Tree Space



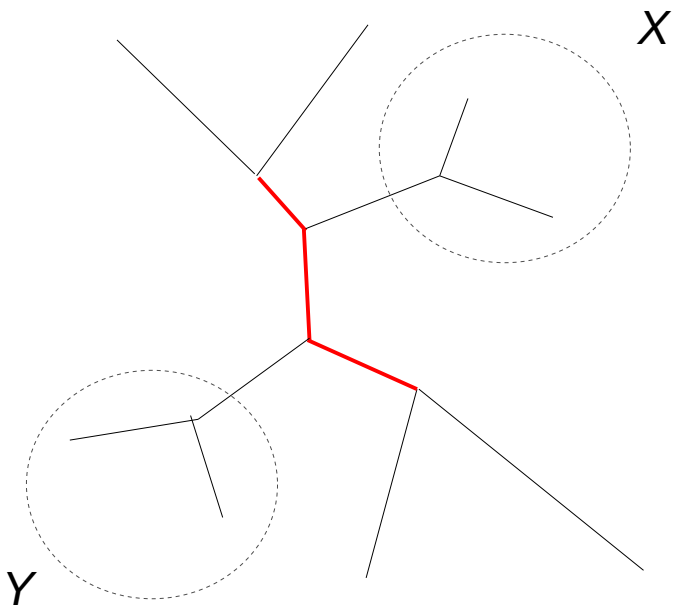
1. Pick *3* contiguous branches at random that define *2* Subtrees *X* and *Y*
2. shrink or grow selected *3* branch segment by a random Amount
3. Chose either *X* or *Y* at random and prune it from the tree

Moving through Tree Space

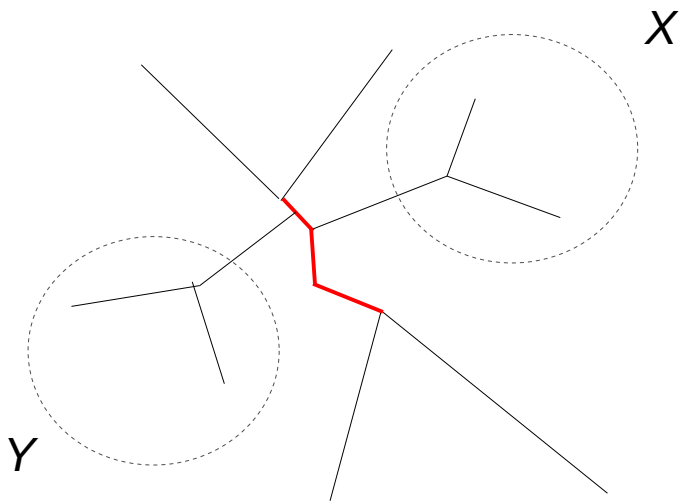


1. Pick *3* contiguous branches at random that define *2* Subtrees *X* and *Y*
2. shrink or grow selected *3* branch segment by a random Amount
3. Chose either *X* or *Y* at random And prune it from the tree
4. Re-insert *Y* at random into The *3* branch segment

Moving through Tree Space



Initial tree t_i

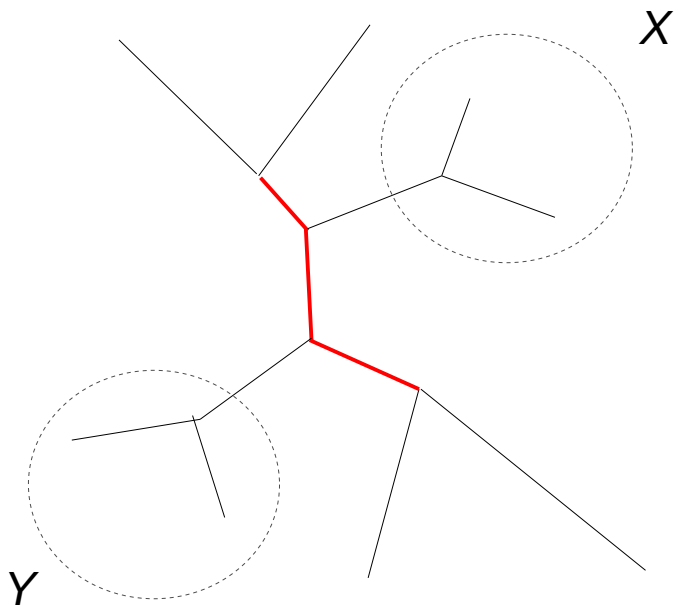


Proposed tree t_{i+1}

Proposed tree: *3* branch lengths changed and one NNI (Nearest Neighbor Interchange) move applied

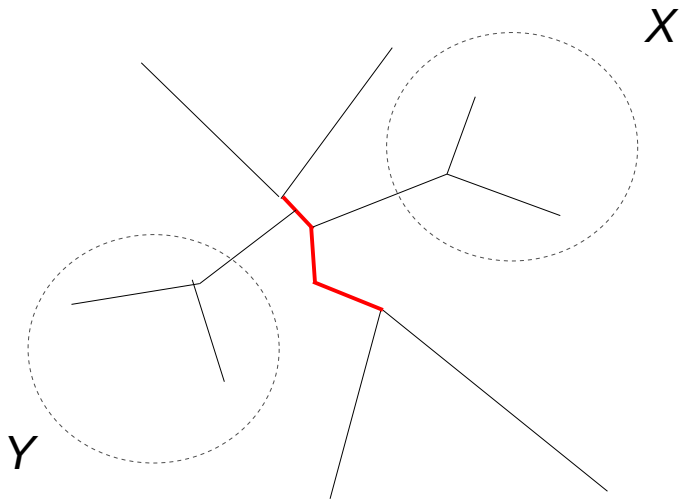
Moving through Tree Space

LnL = -3000



Initial tree t_i

LnL = -2900

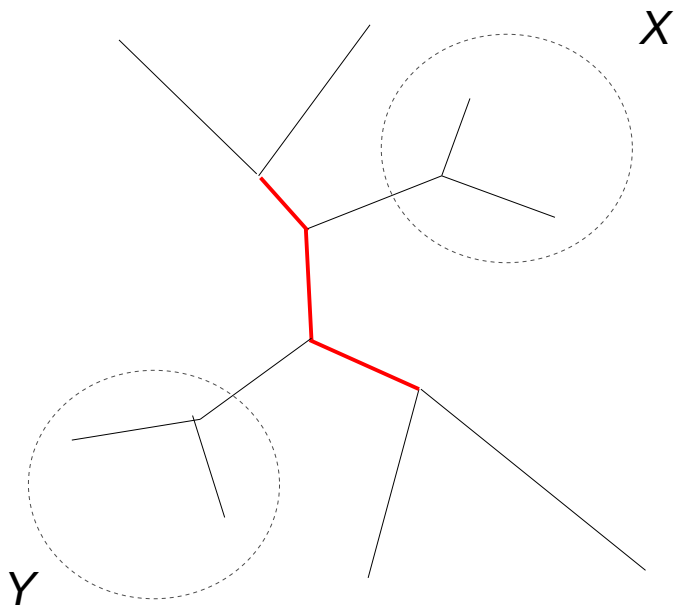


Proposed tree t_{i+1}

The proposed tree has a better likelihood!
Will the proposed tree always be accepted?

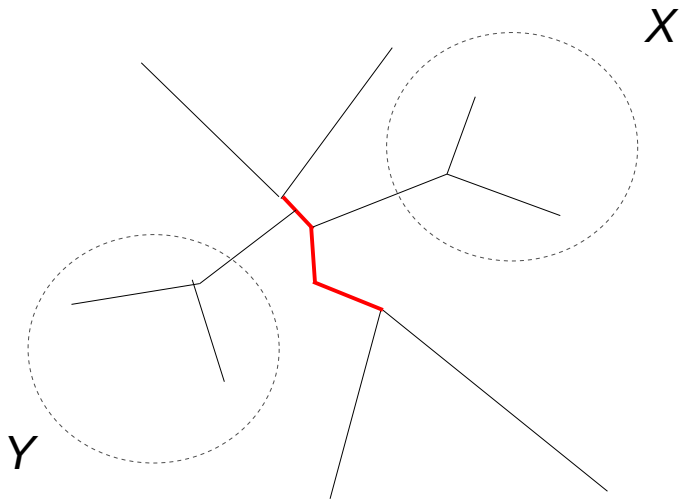
Moving through Tree Space

LnL = -3000



Initial tree t_i

LnL = -2900



Proposed tree t_{i+1}

The proposed tree has a better likelihood!
Will the proposed tree always be accepted?
→ think about Priors and Hastings ratio!

Outline

- Last Time
  - Bayesian statistics
  - Monte-Carlo simulation & integration
  - Markov-Chain Monte-Carlo methods
  - Metropolis-coupled MCMC-methods
- Today
  - Bayesian Inference
    - The curse of priors
    - Some phylogenetic proposals
    - **Reversible jump MCMC**
  - Introduction to Population Genetics

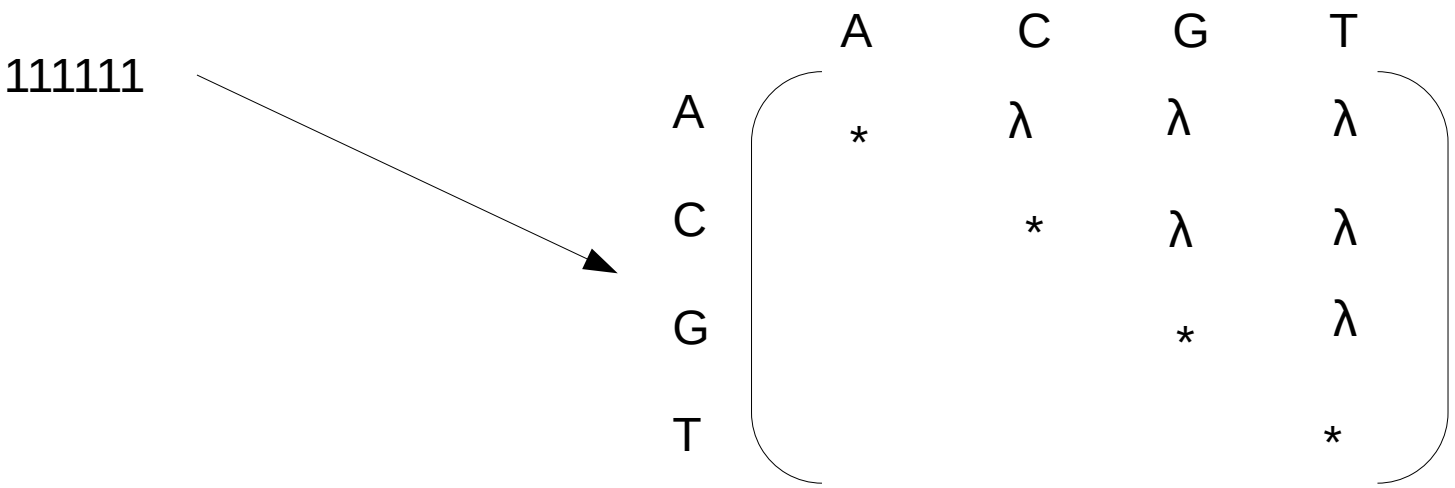
How do we select models using MCMC?

- **Example:** Consider all possible time-reversible nucleotide substitution models ranging from Jukes Cantor (JC, 1 rate) to the General Time Reversible Model (GTR, 6 rates)
- We will denote rate configurations by strings, e.g.,
  - 111111 is the JC model
  - ...
  - 123456 is the GTR model
- Let me explain this further ...

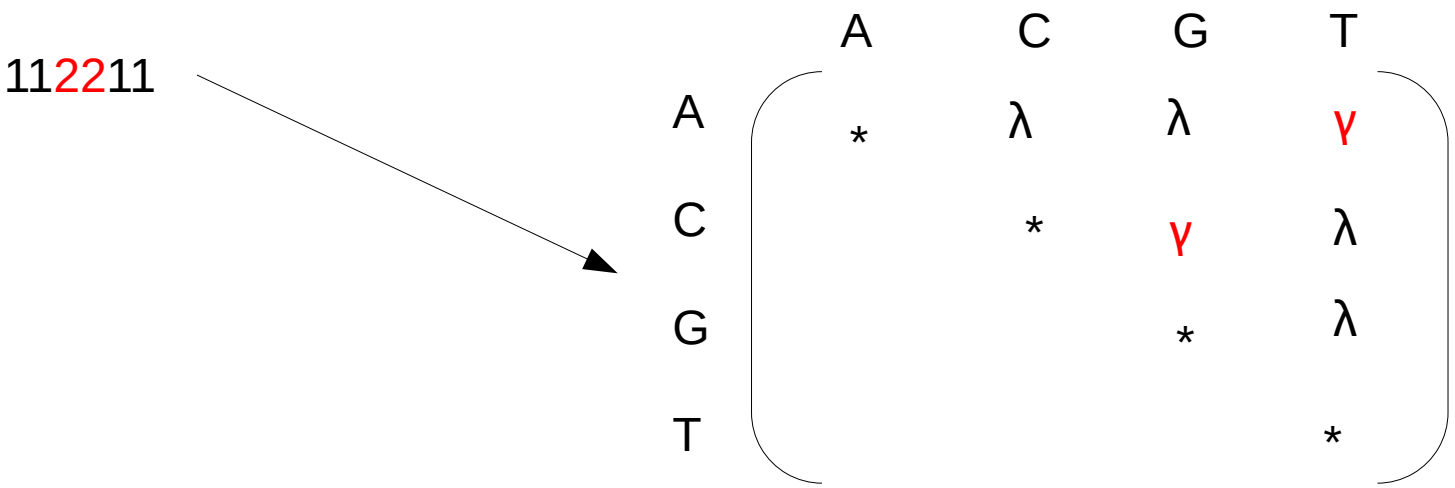
Model Strings

111111

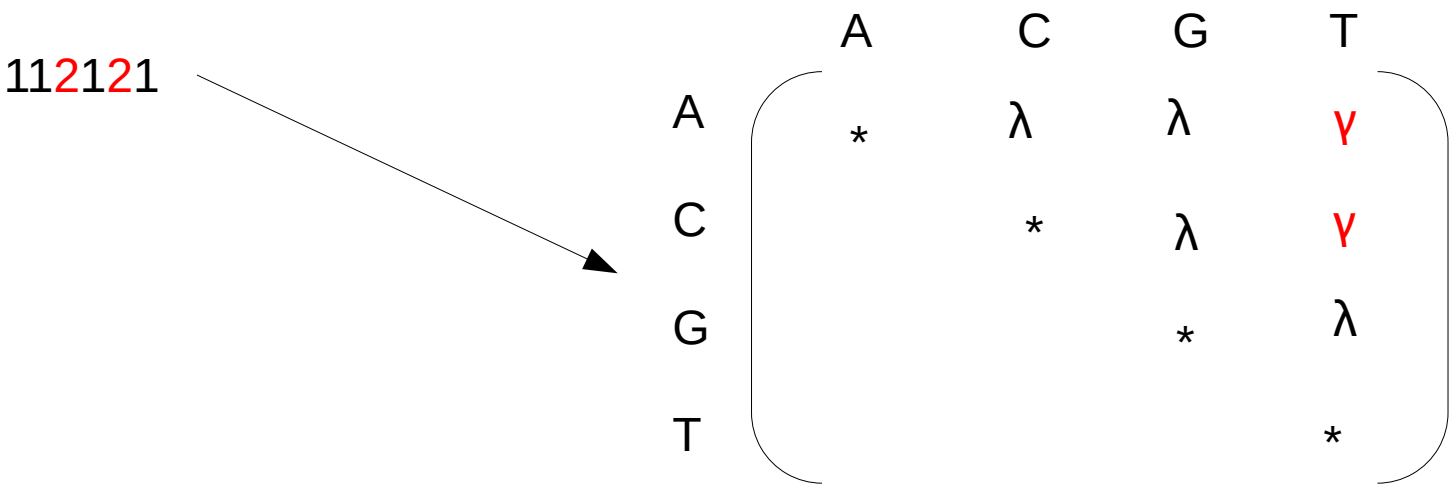
Model Strings



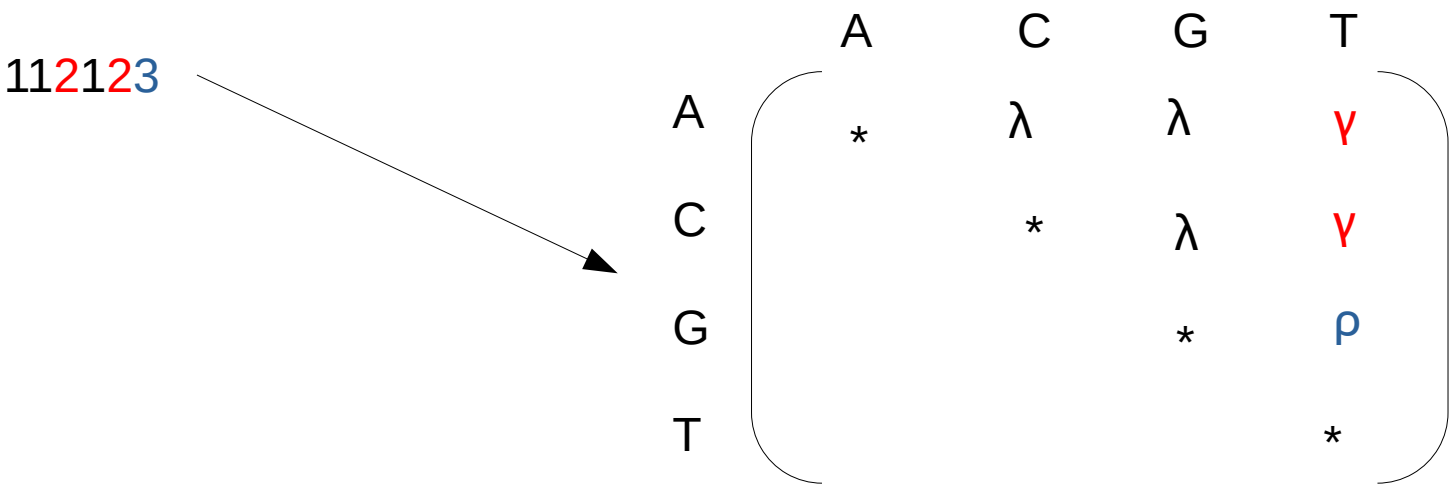
Model Strings



Model Strings



Model Strings



How many time-reversible DNA models are there?

- Number of ways a set with *n* objects can be partitioned into disjoint non-empty sets
- **Example:** the set *{a,b,c}* can be partitioned as follows:

  { {a}, {b}, {c} }

  { {a}, {b, c} }

  { {b}, {a, c} }

  { {c}, {a, b} }

  { {a, b, c} }

- The number of combinations for *n* (*3* in our example) is given by the so-called *Bell* number, for details see https://en.wikipedia.org/wiki/Bell_number

The Bell Numbers

- *n:= 1 → 1*
- *n:= 2 → 2*
- *n:=3 → 5*
- *n:= 4 → 15*
- *n:= 5 → 52*
- *n:= 6 → 203*
- *n:= 7 → 877*
- etc...

What do we need?

- Apart from our usual suspect parameters (tree topology, branch lengths, stationary frequencies, substitution rates, α), we also want to integrate over different models now …
- What are the problems we need to solve?

What do we need?

- Apart from our usual suspect parameters (tree topology, branch lengths, stationary frequencies, substitution rates, α), we also want to integrate over different models now …
- What are the problems we need to solve?
  - Problem #1: we need to design proposals for moving between different models
  - Problem #2: those models have different numbers of parameters, we can not directly compare likelihoods
- Here we use MCMC to not only sample model parameters, but also models

Problem #1
Model Proposals

- Any ideas?

Problem #1
Model Proposals

- Split move

  Chose a set of substitution rates with > *1* member at random

  111222 (two-parameter model)

  and split it randomly into two rates

  111223 (three-parameter model)

- Merge move

  Chose two substitution rate sets at random

  111223

  and merge them into one substitution rate set

  111222

Problem #1
Model Proposals

- Split move

  Chose a set of substitution rates with > *1* member at random

  111222 (two-parameter model)

  and split it randomly in

  111223 (three-param

- Merge move

  Chose two substi[illegible]ion rate sets at random

  111223

  and merge them into one substitution rate set

  111222

Clear to everyone what the respective rate matrix looks like?

Problem #2
Sampling Different Models

- Use reversible jump MCMC (rjMCMC) to jump between models (posterior probability distributions) with different number of parameters (posterior distributions with different dimensions)
- The model proposal moves we designed are reversible jump moves!
- Evidently, we need to somehow modify our proposal ratio calculation …
- In general terms, the acceptance ratio is calculated as:

  r = likelihood ratio * prior ratio * proposal ratio * Jacobian

A Jacobian defines
a linear map from $R^n \rightarrow R^m$
at point *x*, if function *f(x)*
is differentiable at *x*

Problem #2
Sampling Different Models

- Use reversible jump MCMC (rjMCMC) to jump between models (posterior probability distributions) with different number of parameters (posterior distributions with different dimensions)
- The model proposal moves we designed are reversible jump moves!
- Evidently, we need to somehow modify our proposal ratio calculation …
- In general terms, the acceptance ratio is calculated as:

  r = likelihood ratio * prior ratio * proposal ratio * Jacobian

I will not provide further Details; see work by Peter Green (1995, 2003) who developed the rjMCMC methods

rjMCMC - summary

- Need to design moves that can jump back and forth between models of different dimensions (parameter counts)
- Need to extend acceptance ratio calculation to account for jumps between different models
- The posterior probability of a specific model (e.g., *JC* or *GTR*) is calculated as the fraction of time (fraction of samples) the MCMC chain visited/spent time/generations sampling within that model ...

Outline

- Last Time
  - Bayesian statistics
  - Monte-Carlo simulation & integration
  - Markov-Chain Monte-Carlo methods
  - Metropolis-coupled MCMC-methods
- Today
  - Bayesian Inference
    - The curse of priors
    - Some phylogenetic proposals
    - Reversible jump MCMC
  - **Introduction to Population Genetics**

Outline: Population Genetics

- What is biological evolution?
- Units & Types of Evolution
- Good old G. Mendel (phenotypes)
- Alleles & SNPs (genotypes)
- Models of evolution for infinite populations (Hardy)
- Models of evolution for finite populations (Wright-Fisher)

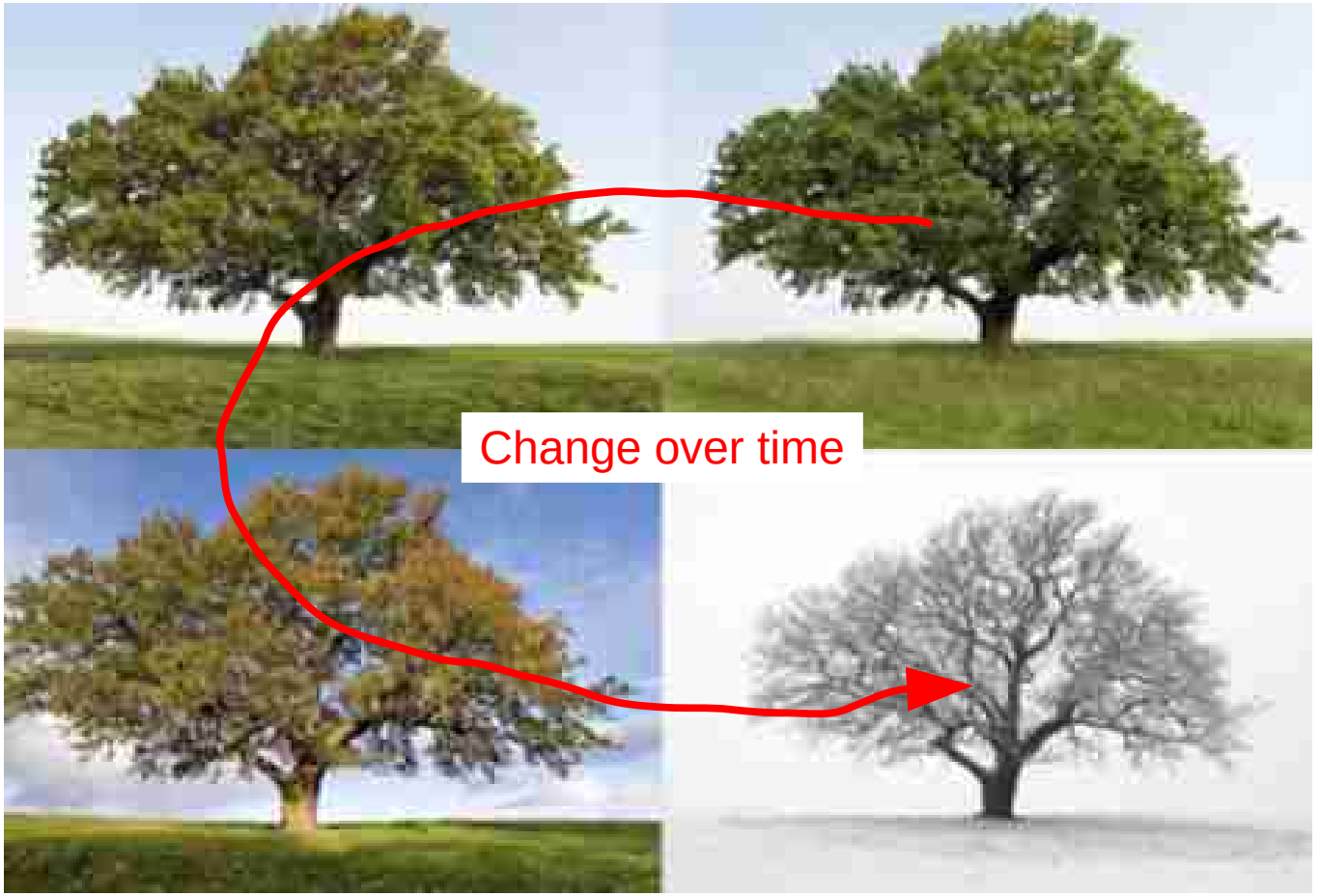
What is Evolution?

- Change over time
- Languages evolve → languages change
- Galaxies evolve → galaxies change
- Political systems change → political systems evolve

Biological Evolution

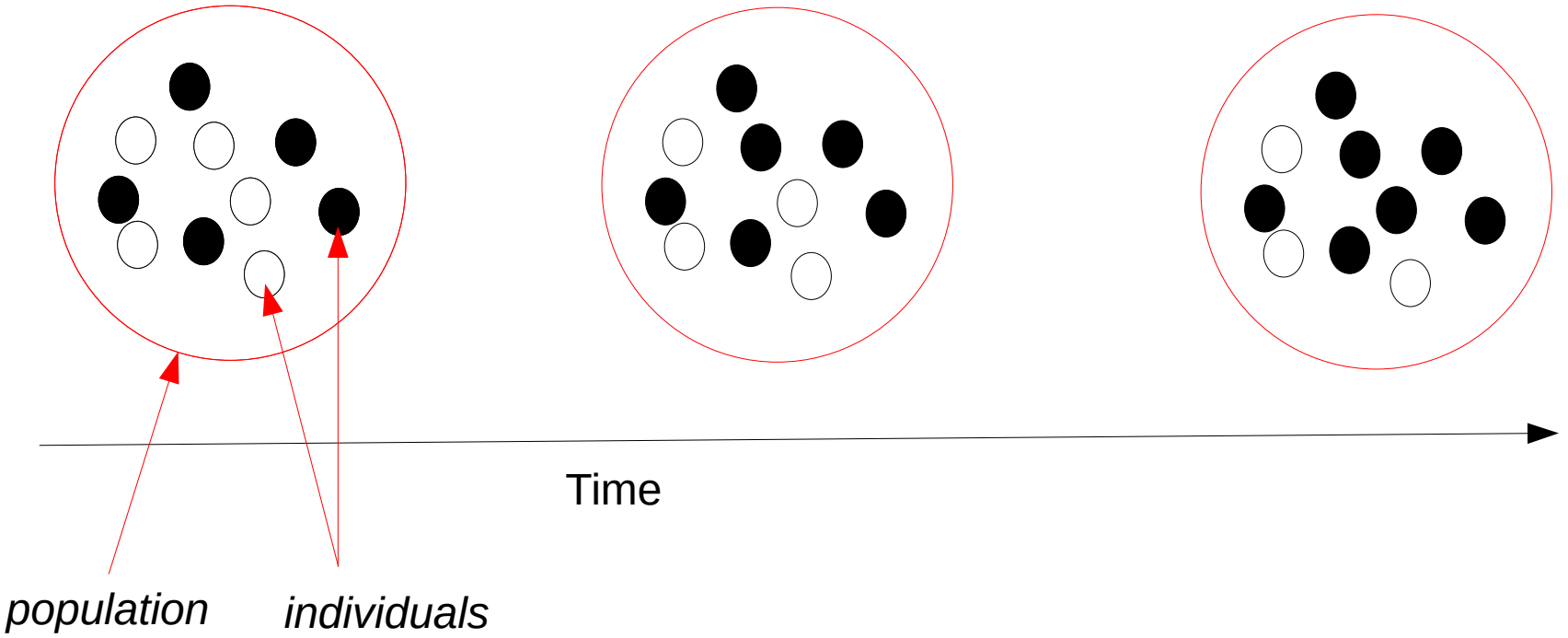
- In Biology one more condition, except for change, is required to characterize evolution
- Do you know which one?

Biological Evolution

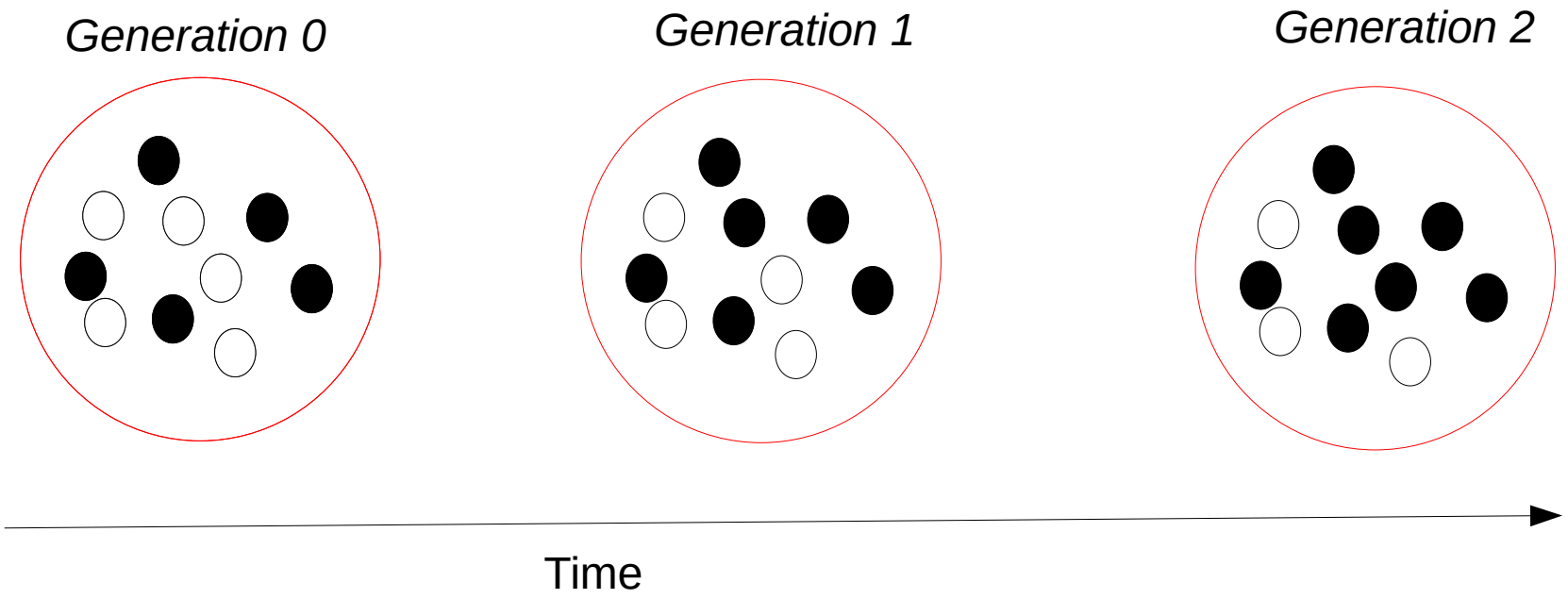


Is this evolution?

Biological Evolution



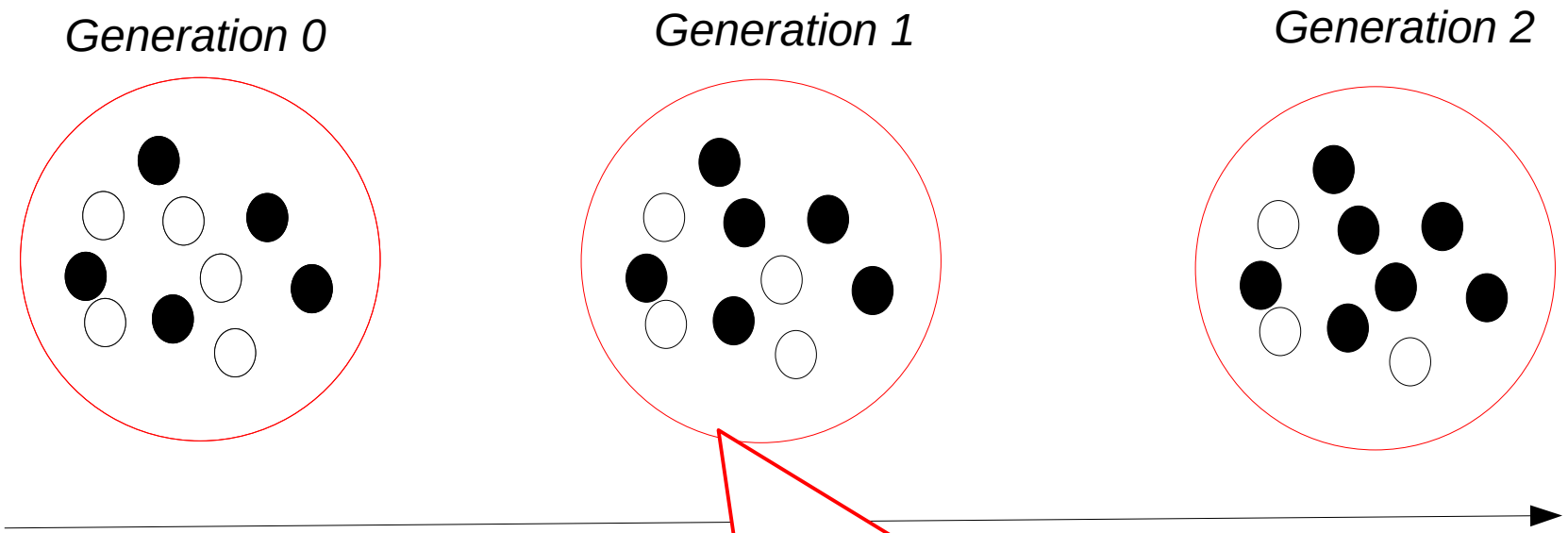
Biological Evolution



The frequency of black and white *individuals* in the *population* changes over time.

Is this evolution?

Biological Evolution

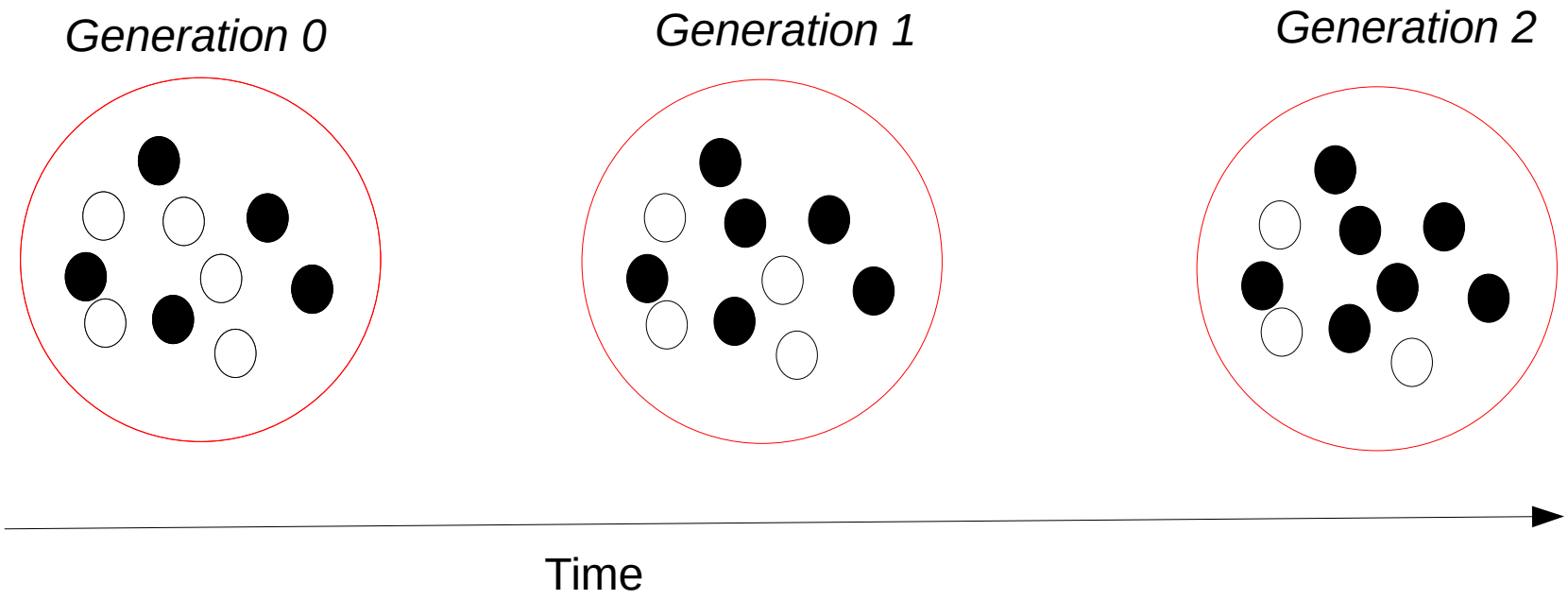


Note that the number of *individuals* remains constant here!
We refer to this as *constant population* size

The frequency of black a *on* changes over time.

Is this evolution?

Biological Evolution



In population genetics, we are interested in how characteristics (e.g., ratio of black versus white individuals) of populations change over time.

Another Example

- Population of 5 white and 5 black individuals
  - *frequency(white) = 0.5*
  - *frequency(black) = 0.5*
- Suddenly 7 out of 10 individuals die → 2 white and 1 black left
  - *frequency(white) = 2/3*
  - *frequency(black) = 1/3*
- The population has changed!
- Is this evolution?

Yet Another Example

- Population of 5 white and 5 black individuals
  - *frequency(white) = 0.5*
  - *frequency(black) = 0.5*
- 3 individuals (2 white & 1 black) decide to leave and form a new colony
  - *frequency(white) = 2/3*
  - *frequency(black) = 1/3*
- The population of the new colony is different!
- Is this evolution?

Biological Evolution

- The phenomenon of change is not sufficient for defining biological change/evolution
- For talking about biological evolution, change needs to be inherited
- The reasons for the change are not important for the definition of biological evolution
- … but we are of course interested in them!

Biological Evolution

- Given these examples, by biological evolution we refer to
  - Change of the frequency of occurrence of features of individuals in the population
  - Features can be, for instance, resistance to antibiotics, color, etc.
- These features should be inherited from generation to generation
- Key question: What are the mechanisms of feature inheritance?
- We distinguish between *phenotype* and *genotype*!

The basic Unit of Biological Evolution

- Based on the previous examples, what is the biological unit of evolution:
  - An individual?
  - A population?
  - Something else?

Units of Evolution

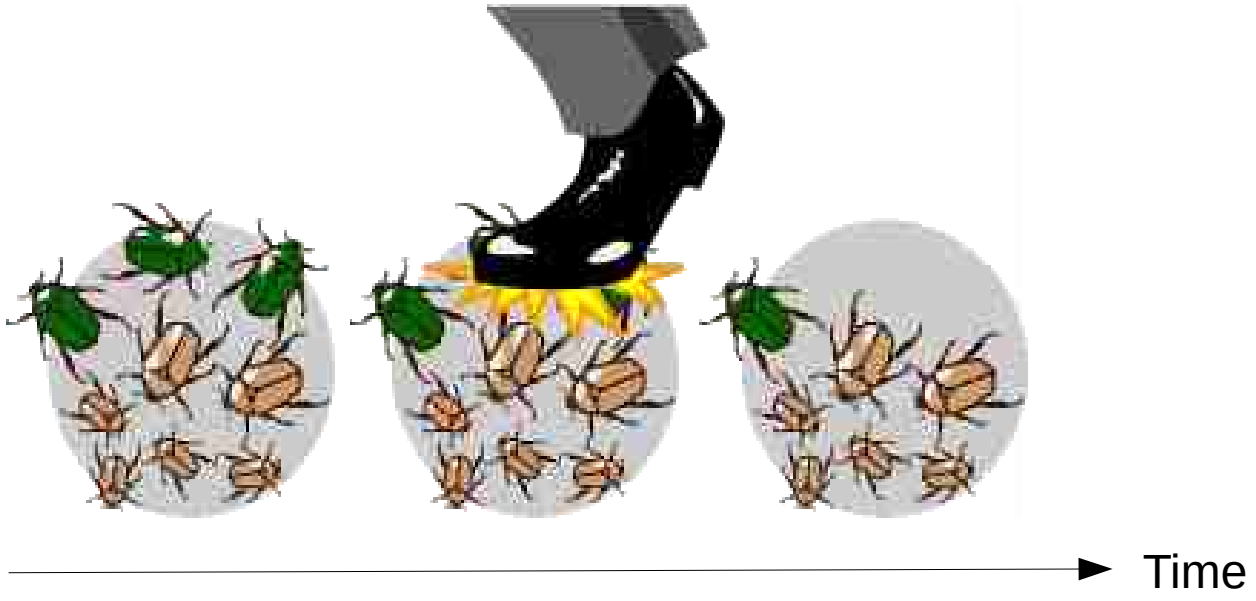
- The population
- A gene
- The genome of an individual
- One needs to define first at which level evolutionary forces act

  → what competes with what?

Units of Evolution: The Population

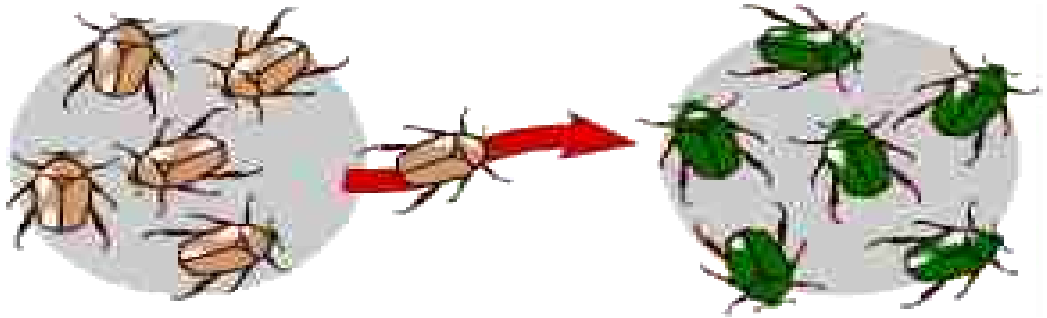
- A Population evolves because the *frequency* of the features of its individuals changes
- Features frequency can change due to
  1. *Genetic Drift*: Chance (other than a random mutation)
  2. *Migration*
  3. *Mutation*
  4. *Natural Selection*: Response to some pressure (e.g., antibiotics, climate change)
- Features can be:
  - *Genotype*
  - *Phenotype*

Genetic Drift



Composition of population changes by some random event

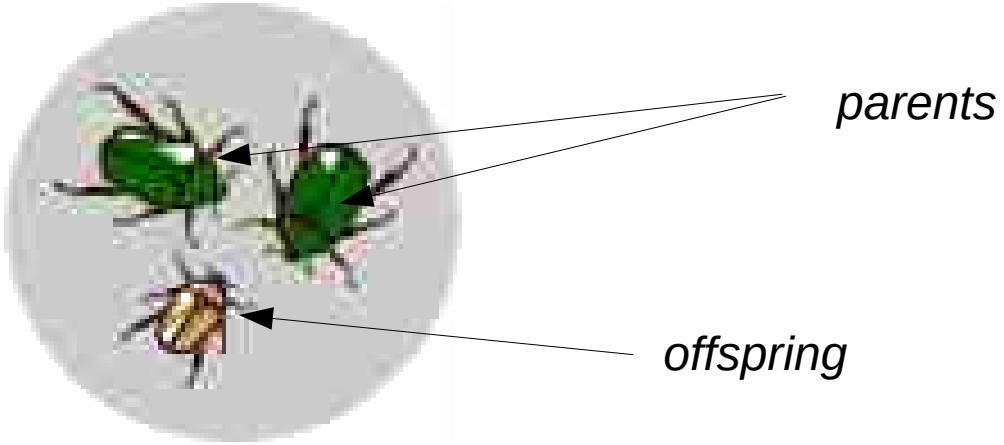
Migration



Population 1

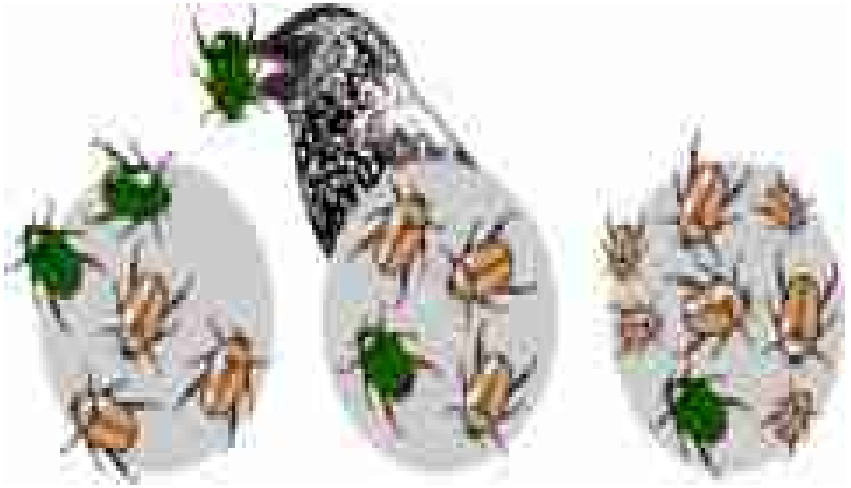
Population 2

Mutation



A random mutation may occur that changes the color of the offspring and hence the frequency of brown beetles in the population

Natural Selection



Time

Green Beetles may be easier to spot for birds → they will have less offsprings in the following generations

Units of Evolution: The Gene

- Genes encode information
- Assume that gene **A** encodes eye color
  - In reality a total of about 15 genes encode eye color
- If **A** has the *form* A → color = blue
- If **A** has the *form* a → color = brown
- What does *form* mean?

Units of Evolution: The Gene

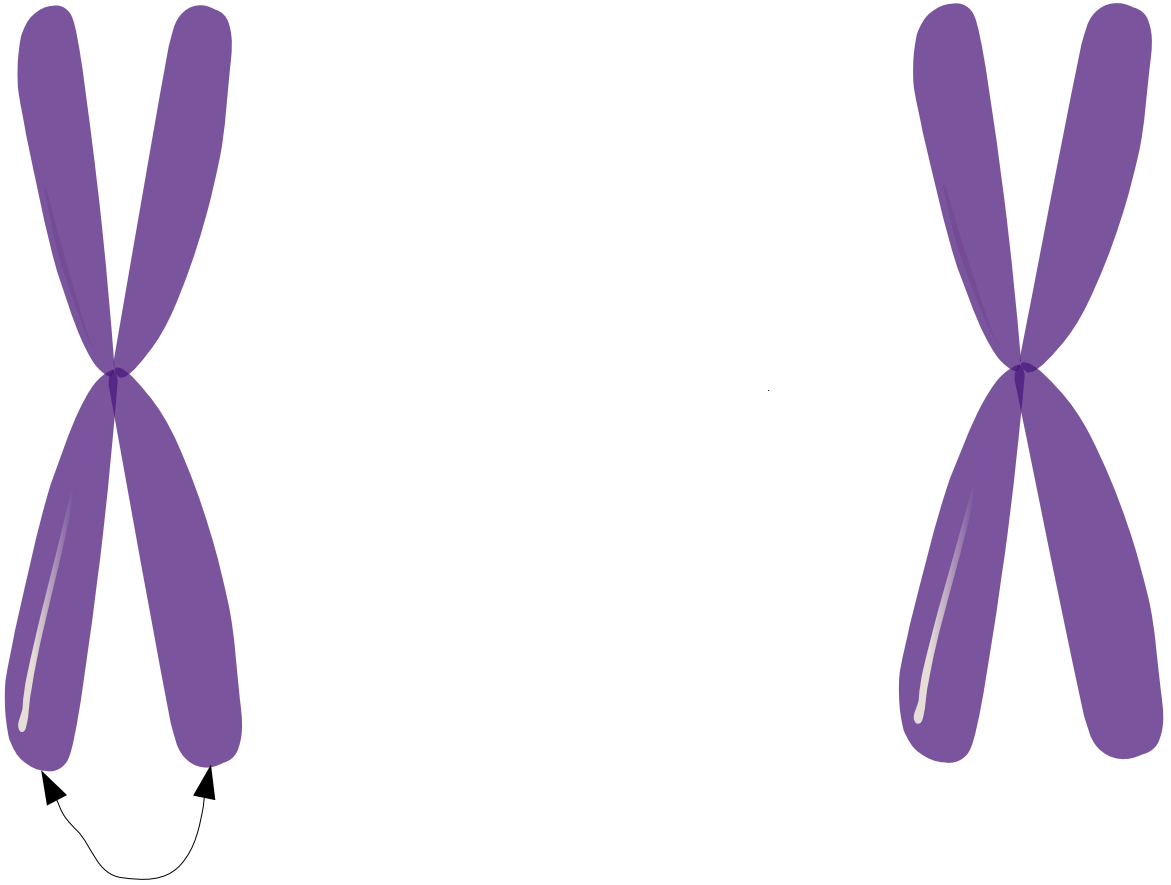
- Genes are inherited from generation → generation
- Inheritance take places via *Alleles*
- An *Allele* is a specific form (slightly different DNA sequence): a or A of gene **A**
- Most multi-cellular organisms are *diploid* → they have two sets of corresponding chromosomes that are called *homologous*
- Diploid organisms have one copy of each gene/allele in each of the homologous chromosome pairs
- If the Allele sequences in the two chromosomes are identical:

  homozygous
- If the Allele sequences in the two chromosomes are different:

  heterozygous

Units of Evolution: The Gene

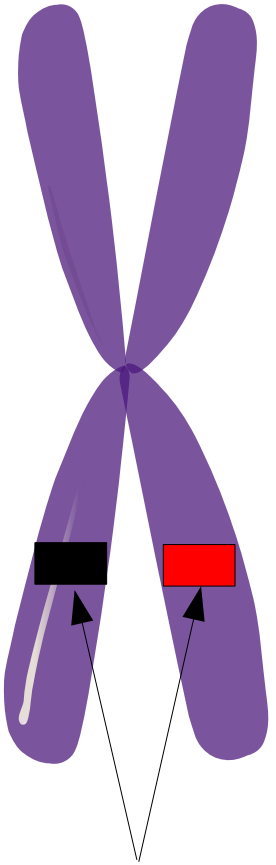
Diploid Chromosome



Homologous pair of chromosomes

Units of Evolution: The Gene

Homozygous Allele → identical DNA



Heterozygous Allele → different DNA sequence

Fraction of heterozygous Alleles

Ancient DNA Siberia
http://en.wikipedia.org/wiki/Denisova_Cave

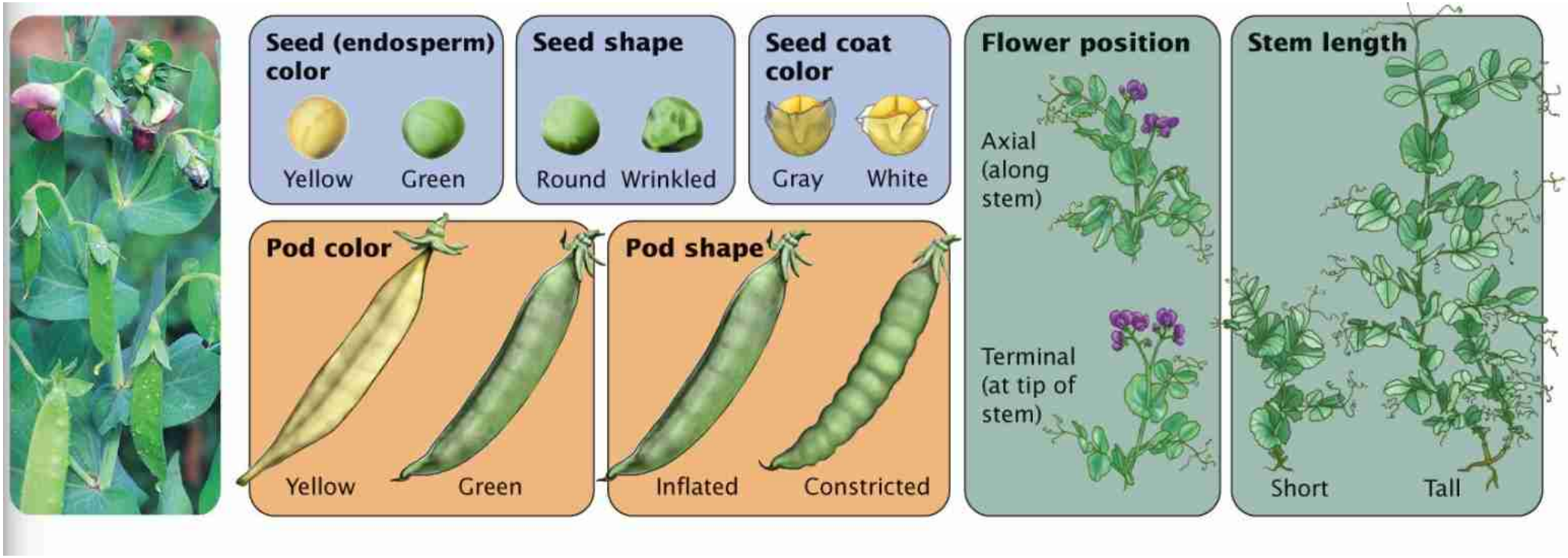
Individual	Heterozygosity estimate (%)
Denisova	0.0165
San	0.0721
Mandenka	0.0686
Yoruba	0.0649
Mbuti	0.0657
Dinka	0.0635
Sardinian	0.0490
French	0.0473
Dai	0.0465
Han	0.0454
Papuan	0.0386
Karitiana	0.0353

Table from:
http://genetics.med.harvard.edu/reich/Reich_Lab/Welcome_files/2013_Bryc_Genetics.pdf

Units of Evolution: The Gene

- Why are we interested in *heterozygous* versus *homozygous* Alleles?
- Inheritance → Humans inherit one allele from the father and one from the mother
- Some more terminology:
  - *Genotype* of a gene: the set of corresponding alleles in a diploid organism
  - *Phenotype* of a gene: observation for the trait/property that the gene controls (e.g. brown eye color) → in reality more complex genes interact on traits

Mendelian Inheritance



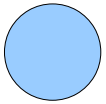
Pea plant traits (phenotype!) studied by G. Mendel

Dominance

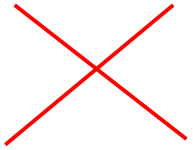
- In Mendel's experiment
  - An individual with the **R**ound-**W**rinkled *genotype* had the **R**ound *phenotype, i.e.,* ***RW → R***
  - We say that the round allele is *dominant* and the wrinkled allele is *recessive*
- What are the phenotypes of:
  - ***RR → ?***
  - ***RW → ?***
  - ***WR → ?***
  - ***WW → ?***
- If there is no dominance-recession relationship the phenotype is intermediate!

Mendel

Homozygous round seed: RR



cross

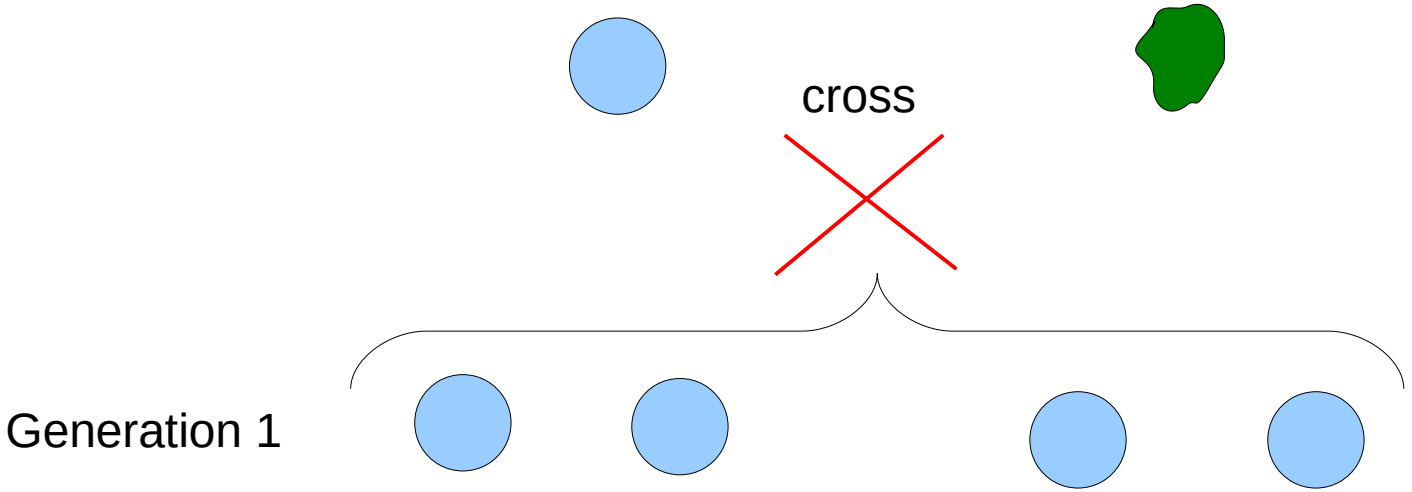


Homozygous wrinkled seed: WW

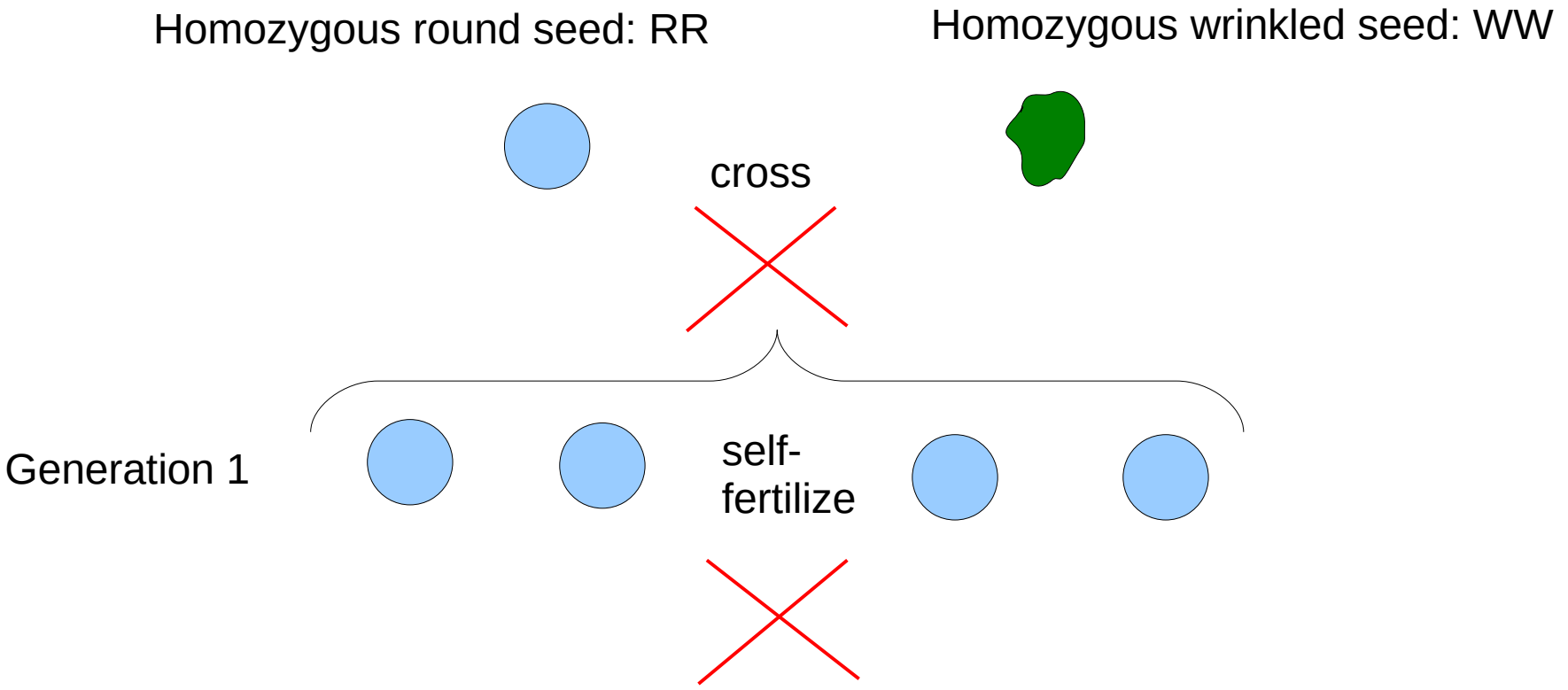
Mendel

Homozygous round seed: RR

Homozygous wrinkled seed: WW



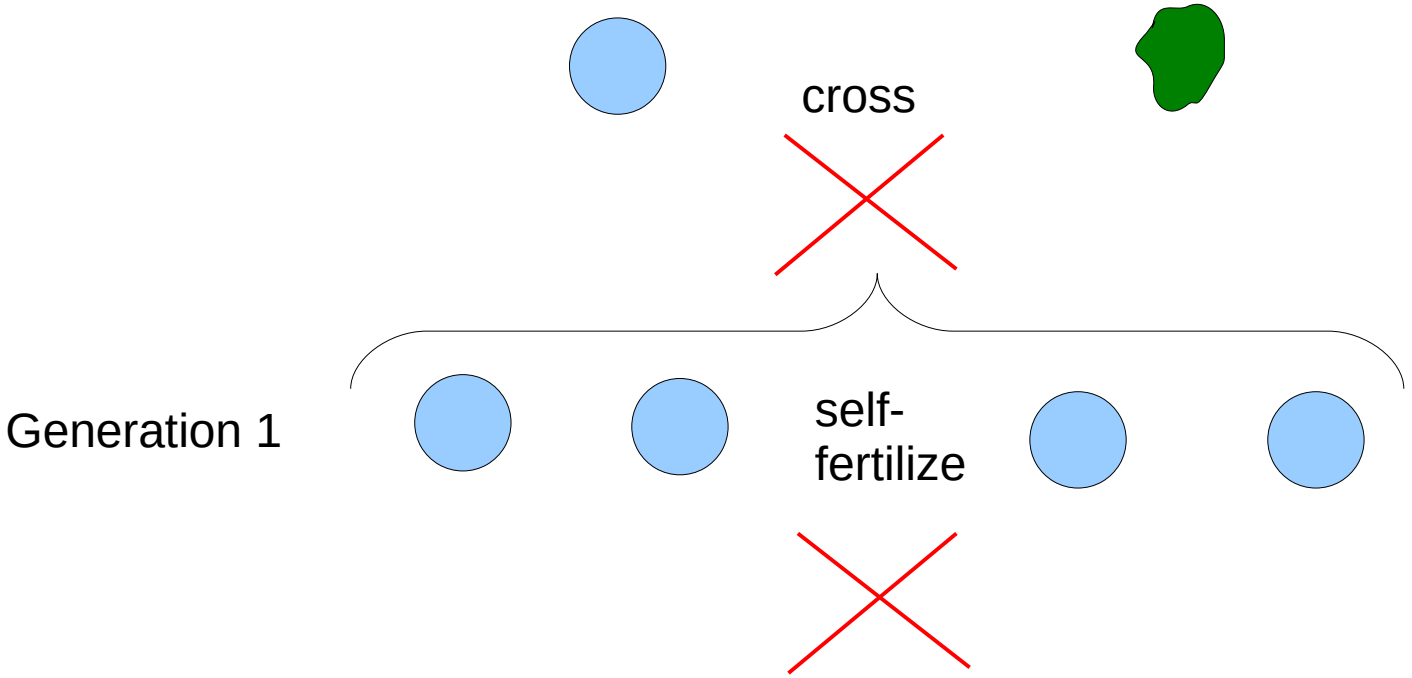
Mendel


Homozygous round seed: RR
Homozygous wrinkled seed: WW
cross
Generation 1
self-
fertilize

Mendel

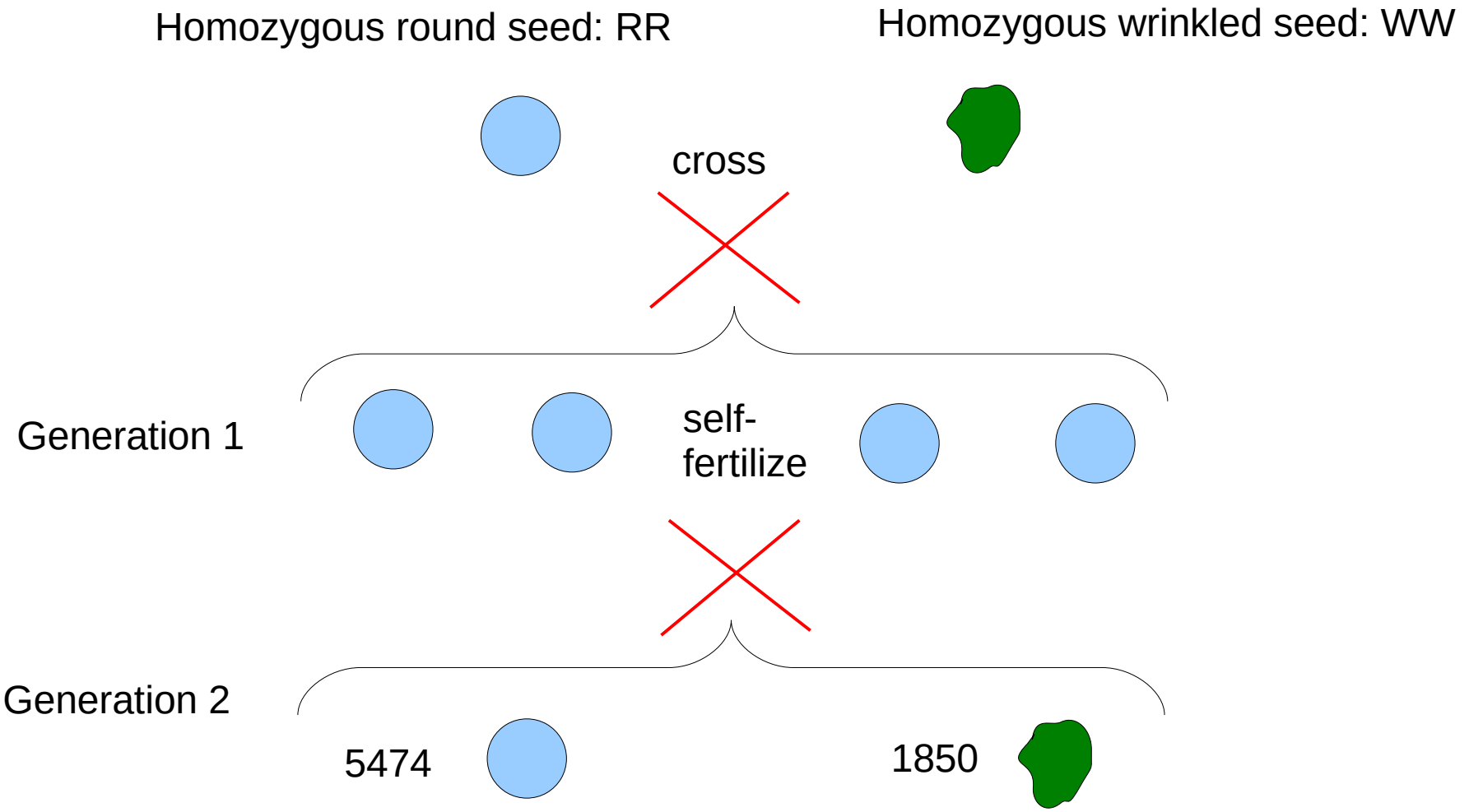
Homozygous round seed: RR

Homozygous wrinkled seed: WW

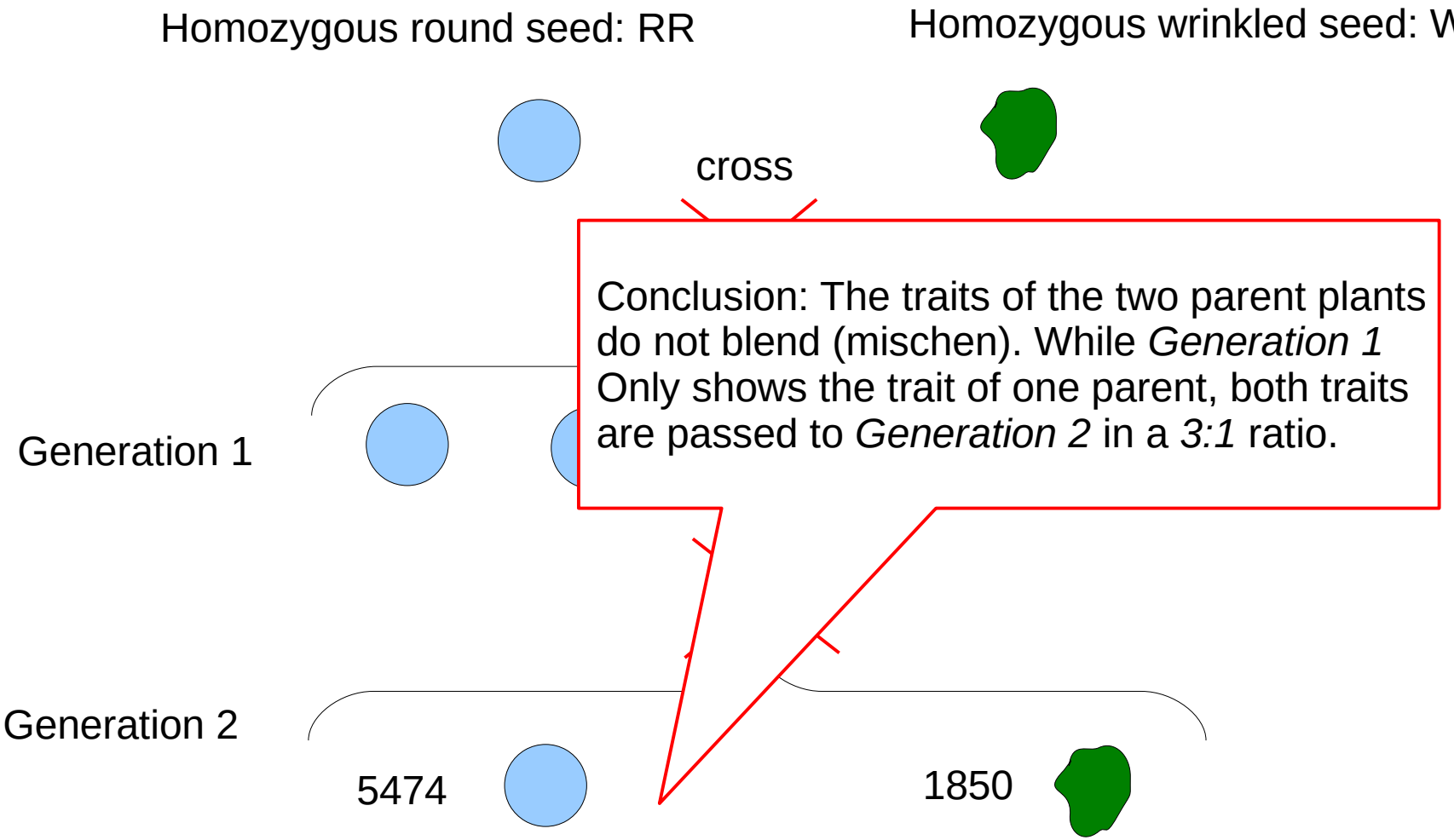


What do you expect?

Mendel


Homozygous round seed: RR
Homozygous wrinkled seed: WW
cross
Generation 1
self-
fertilize
Generation 2
5474
1850

Mendel


Homozygous round seed: RR
Homozygous wrinkled seed: WW
cross
Conclusion: The traits of the two parent plants do not blend (mischen). While *Generation 1* Only shows the trait of one parent, both traits are passed to *Generation 2* in a *3:1* ratio.
Generation 1
Generation 2
5474
1850

Mendel's 1st law
The principle of *Segregation*

Each physical trait of a diploid organism is determined by two factors (alleles). These two factors separate between the generations and re-unite in the next generation.

- **Observation**: the *2nd* generation shows all traits from the initial generation *0* even though the parents in generation *1* do not show all traits.
- **Conclusion**: Generation *1* must receive some information that causes this “hidden” trait to be revealed in generation *2*, in addition to the traits of generation *1*.

Allele Inheritance

- As we know, a diploid organism has *2* alleles per gene
- Alleles can either be *heterozygous* or *homozygous*
- One allele is inherited from the mother and one from the father

  → each parent will pass only one of his – possibly heterozygous – alleles to the offspring
- For a certain, single allele, there is a 50 % chance to have obtained it either from the mother or from the father

Allele Inheritance Terminology

- We denote a gene with the capital bold-font letter **A**
- We denote corresponding Alleles by *A* and *a* if two alleles exist or as A_1, A_2, A_3, … if more than two alleles exist
- *A* denotes both, an allele, and the corresponding gene which may sometimes lead to confusion
- I use bold font **A** to denote the gene and italic a, *A* to denote the corresponding Allele

Why do we care about Alleles?

- In population genetics we study the evolution of populations, that is:
  - How does the frequency of alleles change over time?
  - Why does the frequency change?
- As a consequence we are interested in the evolution of so-called *Polymorphisms*
- Polymorphism (Greek): many shapes

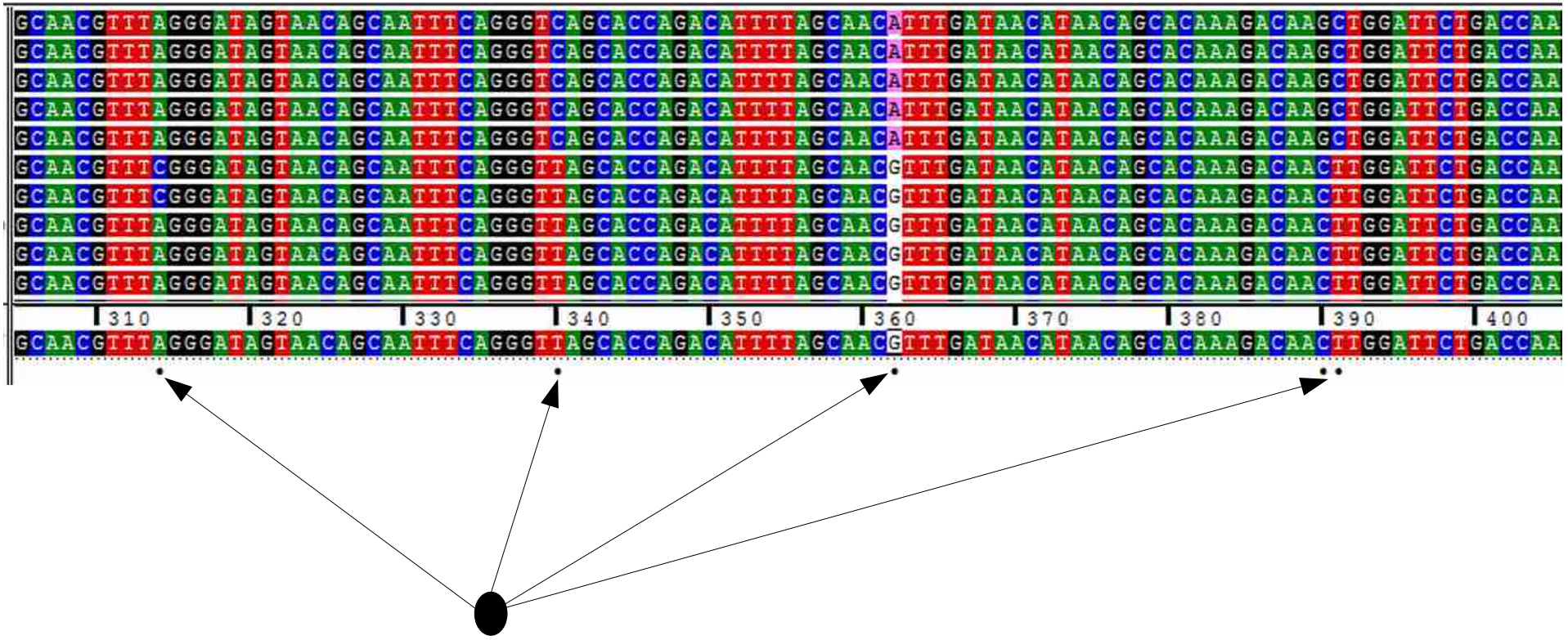
Polymorphism

- *Polymorphic* gene
  - A gene **A** in the population is polymorphic when there exist multiple alleles (e.g. *A, a*)
- *Polymorphic* site
  - Today, we can sequence the entire DNA of several individuals of a population
  - After multiple sequence alignment we can observe sites in certain genes with more than one state
  - Such sites are called *polymorphic*!

Population genetics versus Phylogenetics

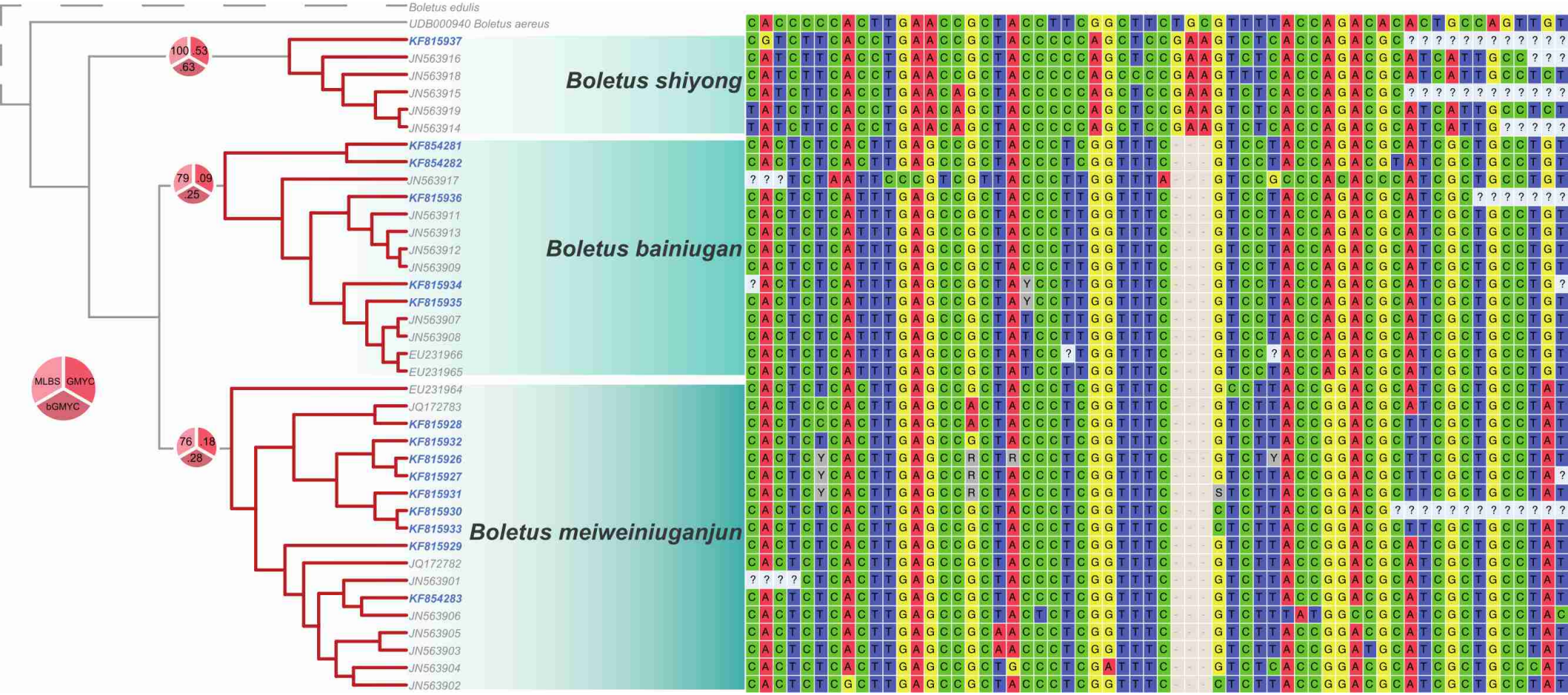
- Evolution at very different scales
- In an alignment of individuals of a single population (species) there will be far less mutations than in the phylogeny of mammals, for instance!
- Since in population genetics there are so few mutations and each mutation is much more important we need to absolutely get the alignment right!

An Alignment Of Individuals



Polymorphic sites

An Alignment of Species



Boletus is a Fungus

Polymorphic Sites – SNPs

- In the MSA of the individuals, we observe some sites, that have more than one nucleotide state
- Such sites are called *Polymorphic* sites or more commonly *SNPs = Single Nucleotide Polymorphisms*
- SNPs is pronounced: Snips
- Modern population genetic analyses mostly operate on SNPs

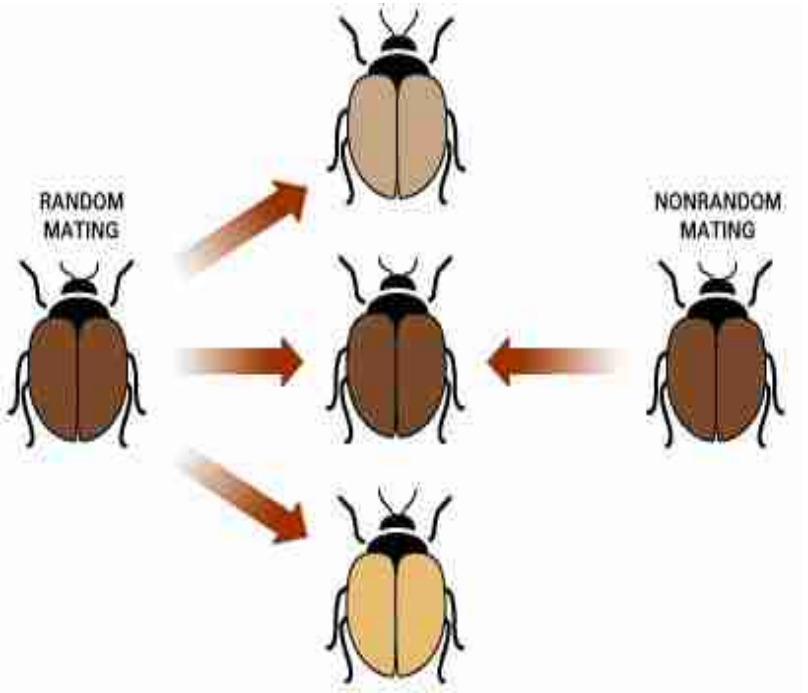
Modern Population Genetics

- Study of polymorphisms in a population
  - Which processes introduce polymorphisms into the population?
  - If a polymorphisms exists in a population will it be there for ever?
  - Is there some process that removes polymorphisms from the population?
  - Do polymorphisms exhibit patterns?
  - …

A simple Hypothesis & Model

- Question: Does dominance affect the frequency of alleles?
  - First tested by the famous mathematician G. Hardy at the beginning of the 20th century
  - Assume
    - infinite *population size*
    - *random mating*

Random Mating



A simple Hypothesis & Model

- Question: Does dominance affect the frequency of alleles?
  - First tested by the famous mathematician G. Hardy at the beginning of the 20th century
  - Assume
    - infinite *population size*
    - *random mating*
    - A gene **A** with 2 alleles: *A* and *a*
    - Current frequencies (at *generation 0*) of *allele* pairs defining the *genotype*
      - $f_0(A) = p$
      - $f_0(a) = q$
      - Evidently, $p + q = 1$
  - Does the frequency of occurrence of *A* change over generations?
  - Does the proportion of genotypes *AA:Aa:aa* change over generations?

Hardy-Weinberg Equilibrium

- What happens to the frequencies of two alleles at a single gene when the four evolutionary forces (*Natural selection, mutation, migration, genetic drift*) are not acting on a population, and where mating is random?
- If allele frequencies are the same between a parental and offspring generation → no evolution has occurred at that gene
- Serves as null hypothesis in evolutionary biology & population genetics

Hardy Weinberg – the Maths

- Assumptions/Definitions (again):
  - Population with *2* alleles: *A*, *a*
  - *A* is dominant and *a* is recessive
  - Mating is random
  - Population is infinitely large
  - Sexes are evenly distributed between 3 genotypes *AA*, *aa* and [*Aa* or *aA*]
  - The ratio of frequencies for the three genotypes

    $f(AA) : f(Aa) : f(aa) = x : 2y : z$

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA			
Aa			
aa			

$f(AA) : f(Aa) : f(aa) = x : 2y : z$

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2		
Aa			
aa			

$f(AA) : f(Aa) : f(aa) = x : 2y : z$

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

*f(AA) * f(AA) = x * x*

	AA	*Aa*	*aa*
AA	x^2		
Aa			
aa			

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2		
Aa	2xy		
aa			

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2		
Aa	2xy		
aa	zx		

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	
Aa	2xy		
aa	zx		

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	
Aa	2xy	$4y^2$	
aa	zx		

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	
Aa	2xy	$4y^2$	
aa	zx	2yz	

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	
aa	zx	2yz	

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	2yz
aa	zx	2yz	

f(AA) : f(Aa) : f(aa) = x : 2y : z

Hardy Weinberg – the Maths

- We want to find out how the frequencies of the genotypes and the gametes (individual alleles) evolve
- Let's start with the mating behavior assuming random mating via the Punnett square

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	2yz
aa	zx	2yz	z^2

f(AA) : f(Aa) : f(aa) = x : 2y : z

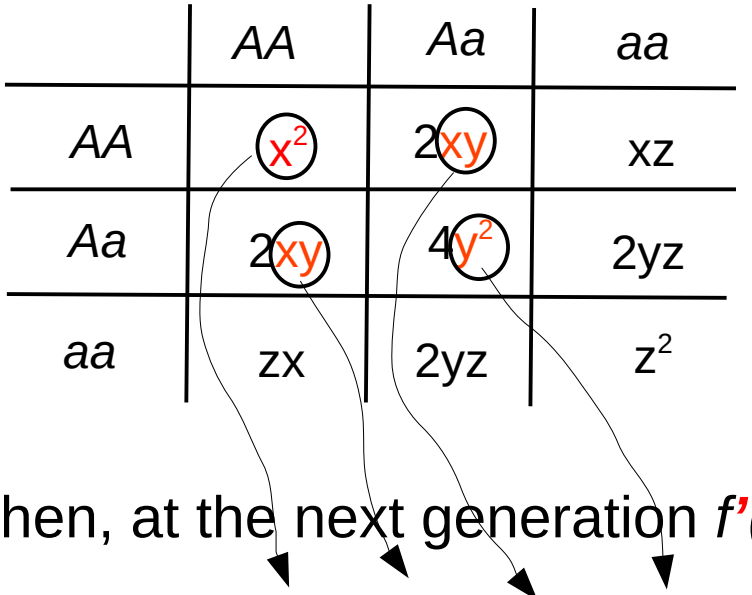
Hardy Weinberg – the Maths

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	2yz
aa	zx	2yz	z^2

- Then, at the next generation *f'()*

$$f'(AA) = x^2 + xy + xy + y^2$$

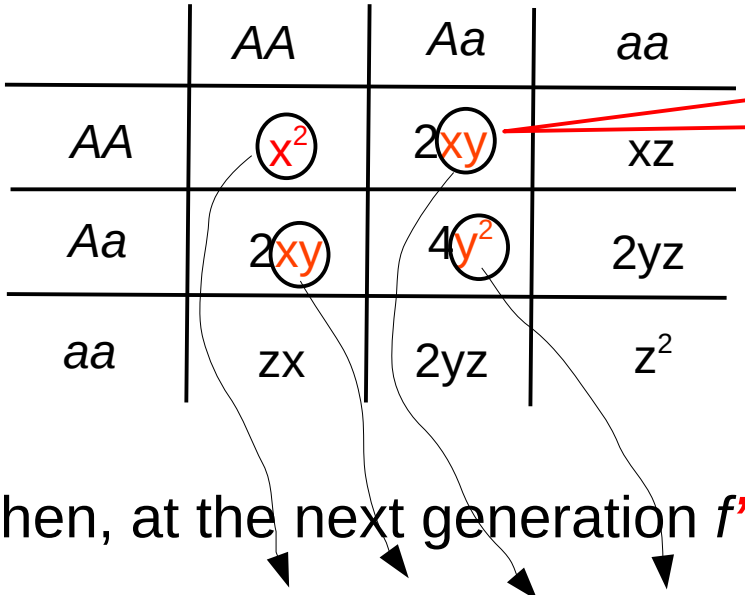
Hardy Weinberg – the Maths



- Then, at the next generation *f'()*

$f'(AA) = x^2 + xy + xy + y^2$

Hardy Weinberg – the Maths

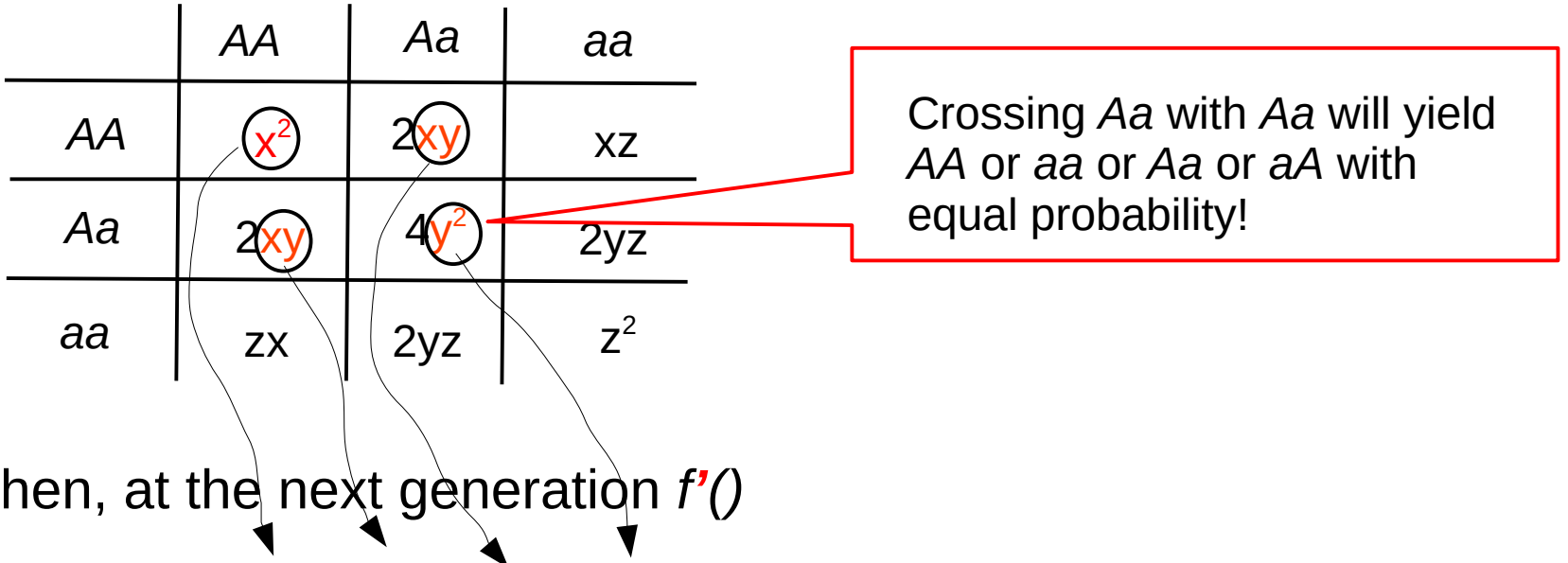


Crossing *AA* with *Aa* will yield *AA* or *Aa* with equal probability!

- Then, at the next generation ***f'()***

$$f'(AA) = x^2 + xy + xy + y^2$$

Hardy Weinberg – the Maths



- Then, at the next generation *f'()*

$$f'(AA) = x^2 + xy + xy + y^2$$

Hardy Weinberg – the Maths

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	2yz
aa	zx	2yz	z^2

- Then, at the next generation *f'()*

  $f'(AA) = x^2 + xy + xy + y^2$

  $f'(Aa) = \ldots = 2(y+z)(x+y)$

  $f'(aa) = \ldots = (y+z)^2$

Hardy Weinberg – the Maths

	AA	*Aa*	*aa*
AA	x^2	2xy	xz
Aa	2xy	$4y^2$	2yz
aa	zx	2yz	z^2

- Then, at the next generation ***f'()***

  $f'(AA) = x^2 + xy + xy + y^2$

  $f'(Aa) = \ldots = 2(y+z)(x+y)$

  $f'(aa) = \ldots = (y+z)^2$

- *Thus, the ratio now is:*

  $f'(AA) : f'(Aa) : f'(aa) = (x+y)^2 : 2(x+y)(y+z) : (y+z)^2 = x_1 : 2y_1 : z_1$

Hardy Weinberg – the Maths

- Then, at the next generation *f'()*

  $f'(AA) = x^2 + xy + xy + y^2$

  $f'(Aa) = \ldots = 2(y+z)(x+y)$

  $f'(aa) = \ldots = (y+z)^2$

- *Thus, the ratio now is:*

  $f'(AA) : f'(Aa) : f'(aa) = (x+y)^2 : 2(x+y)(y+z) : (y+z)^2 = x_1 : 2y_1 : z_1$

- *The ratio between the genotypes remains unaltered between generations when the following holds:*
  - $(x+y)^2 = x$ **and** $2(x+y)(y+z) = 2y$
  - Remember that the original ratio at generation *0* was defined as

    $x : 2y : z$

    and that the equality of *z to* $(y+z)^2$ follows because $x + 2y + z = 1$ *!*

Hardy Weinberg – the Maths

- Let's look at deducing $(x+y)^2 = x$

  $x^2 + 2xy + y^2 = x \rightarrow x(x + y) + y(x + y) = x \rightarrow y(x + y) = x(1 - x - y)$

  $\rightarrow y(x + y) = x(y + z)$ [remember $x+2y+z = 1$!]

Hardy Weinberg – the Maths

- Let's look at deducing $(x+y)^2 = x$

  $x^2 + 2xy + y^2 = x \rightarrow x(x + y) + y(x + y) = x \rightarrow y(x + y) = x(1 – x - y)$

  $\rightarrow y(x + y) = x(y + z)$ [remember $x+2y+z = 1$!] $\rightarrow$

  $xy + y^2 = xy + xz$

Hardy Weinberg – the Maths

- Let's look at deducing $(x+y)^2 = x$

$x^2 + 2xy + y^2 = x \rightarrow x(x + y) + y(x + y) = x \rightarrow y(x + y) = x(1 - x - y)$

$\rightarrow y(x + y) = x(y + z)$ [remember $x+2y+z = 1$!] $\rightarrow$

$xy + y^2 = xy + xz \rightarrow \boxed{y^2 = xz}$

Hardy Weinberg – the Maths

- Let's look at deducing $(x+y)^2 = x$

  $x^2 + 2xy + y^2 = x \rightarrow x(x + y) + y(x + y) = x \rightarrow y(x + y) = x(1 - x - y)$

  $\rightarrow y(x + y) = x(y + z)$ [remember $x+2y+z = 1$!] $\rightarrow$

  ~~xy~~ + y^2 = ~~xy~~ + xz $\rightarrow$ $y^2 = xz$

- Obviously, this holds for the frequencies after the first generation.

  Remember

  $f'(AA) = (x+y)^2$ ← this is our x above

  $f'(Aa) = 2(y+z)(x+y)$ ← this is our y above

  $f'(aa) = (y+z)^2$ ← this is our z above

- Thus, genotypic frequencies will remain constant FROM the first generation.

Hardy Weinberg – the Maths

- Let's look at the **gametic** frequencies now
- At generation *0* (remember: $f(AA) : f(Aa) : f(aa) = x : 2y : z$) they are:

  $f(A) = x + y$

  $f(a) = y + z$

- At generation *1* they are:

  $f'(A) = (x+y)^2 + (x+y)(y+z) = x + y$

  $f'(a) = \ldots = y + z$

remember

$f'(AA) = x^2 + xy + xy + y^2$

$f'(Aa) = \ldots = 2(y+z)(x+y)$

$f'(aa) = \ldots = (y+z)^2$

Hardy Weinberg – the Maths

- Let's look at the **gametic** frequencies now
- At generation *0* (remember: $f(AA) : f(Aa) : f(aa) = x : 2y : z$) they are:

  $f(A) = x + y$

  $f(a) = y + z$
- At generation *1* they are:

  $f'(A) = (x+y)^2 + (x+y)(y+z) = x + y$

  $f'(a) = \ldots = y + z$
- Thus, allelic frequencies will remain constant even from generation *0* onwards!

Effects of finite Population Size Random Genetic Drift

- Populations are of finite size!
  - Does this affect the evolution of allele frequencies over generations?
  - Assume:
    - there are *N* individuals in a diploid population → *2N* chromosomes
    - Frequency of *A* allele is *p*
- What will be the frequency of *A* in the next generation?

Random Genetic Drift

- Definition:

  *Genetic drift is a random process that causes changes in allele frequencies from one generation to the next. Some alleles will be passed on to the next generation disproportionally without being advantageous or harmful. Especially in **small** populations genetic drift is strong due to sampling errors. Alleles can be fixed or get lost by chance.*

The Wright-Fisher Model for finite populations

- Assume a diploid population:
  - *Population size*: *N* (*2N* chromosomes)
  - *Random mating*
  - *Non-overlapping generations* → something like discrete time steps from generation to generation (e.g., annual plants)
  - No *natural selection*
  - *Equal distribution of sexes*
- The *Wright-Fisher* model is the simplest model of evolution for a population of **finite** size

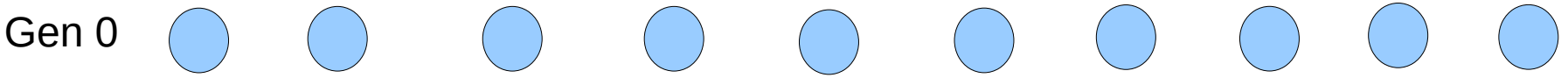
Wright-Fisher Rules/Simulation Example

- We assume a constant population → say 10 individuals (or 5 diploid individuals) per generation
- Each individual from the offspring generation picks a parent at random from the previous generation

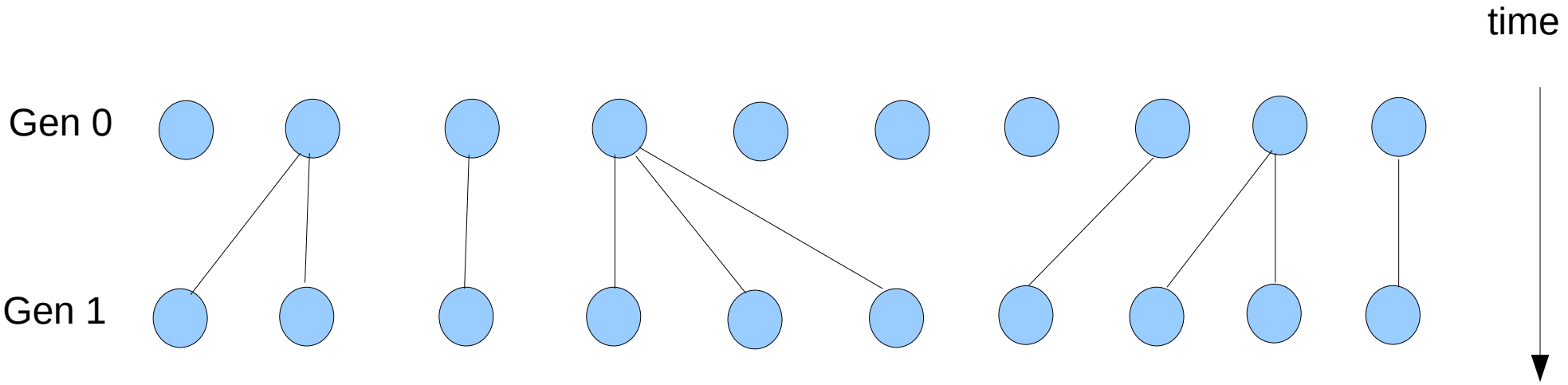
  → all parents have equal probability to be picked

  → a parent can be picked more than once
- Each offspring inherits the genetic information of the parent
- The process and maths are easier to understand if we forget about alleles for a second and just think about individuals

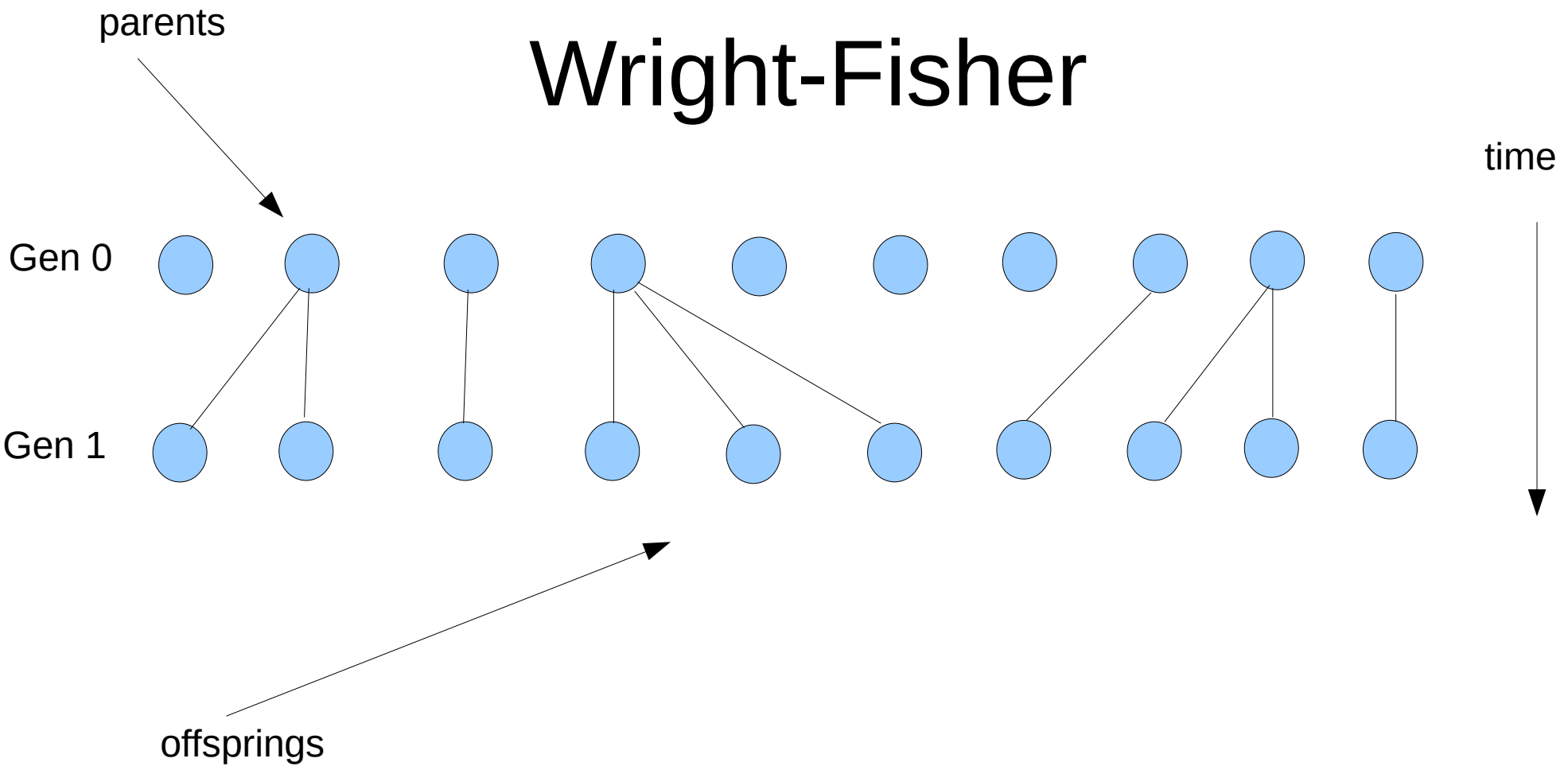
Wright-Fisher



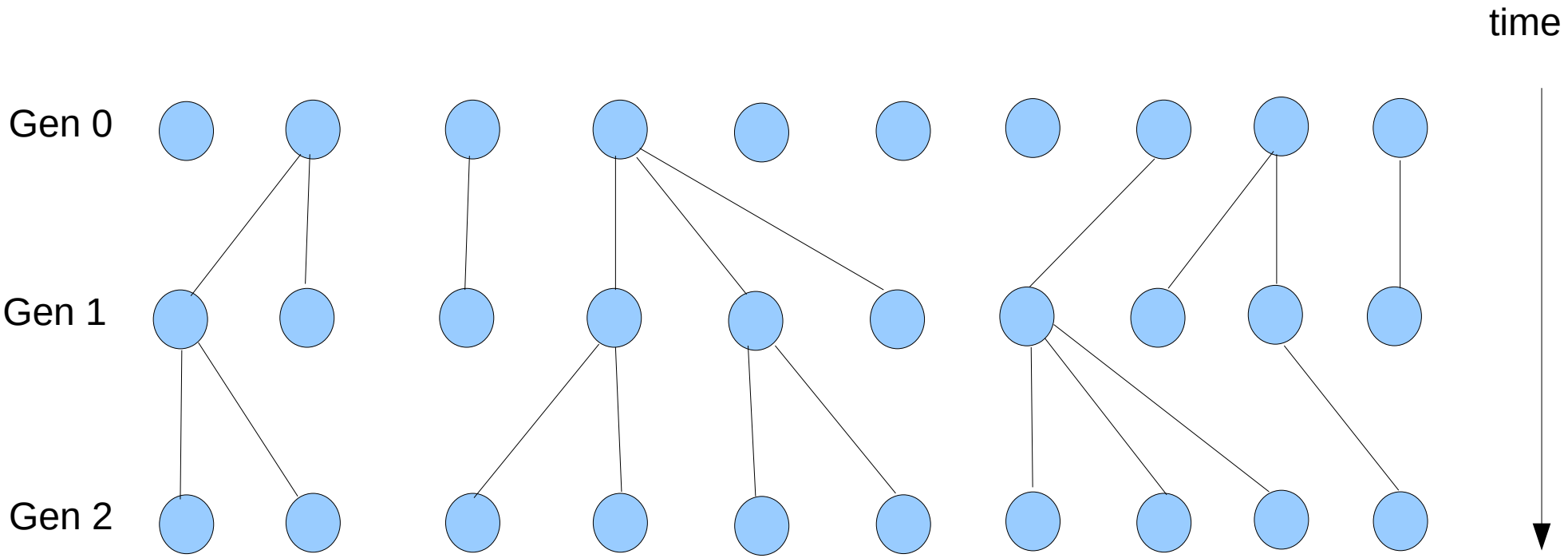
Wright-Fisher



Wright-Fisher



Wright-Fisher



Wright-Fisher Binomial Random Sampling

- The probability to pick an individual *X* as ancestor of an individual in the next generation is *p = 1/2N*
- If the population remains constant then you have to sample *2N* (*2N = 10* in our example) times from the current generation to construct the next generation with *2N* offsprings
- For every sample, the probability to pick *X* remains constant at *p* → by definition of our model
- The number of offsprings for *X* follows a binomial distribution, thus the probability to pick *X* as an ancestor *k* times is

$$\mathbf{P}[X = k] = \binom{n}{k} p^k (1-p)^{n-k}$$

- Where *p := 1/2N* and *n := 2N*

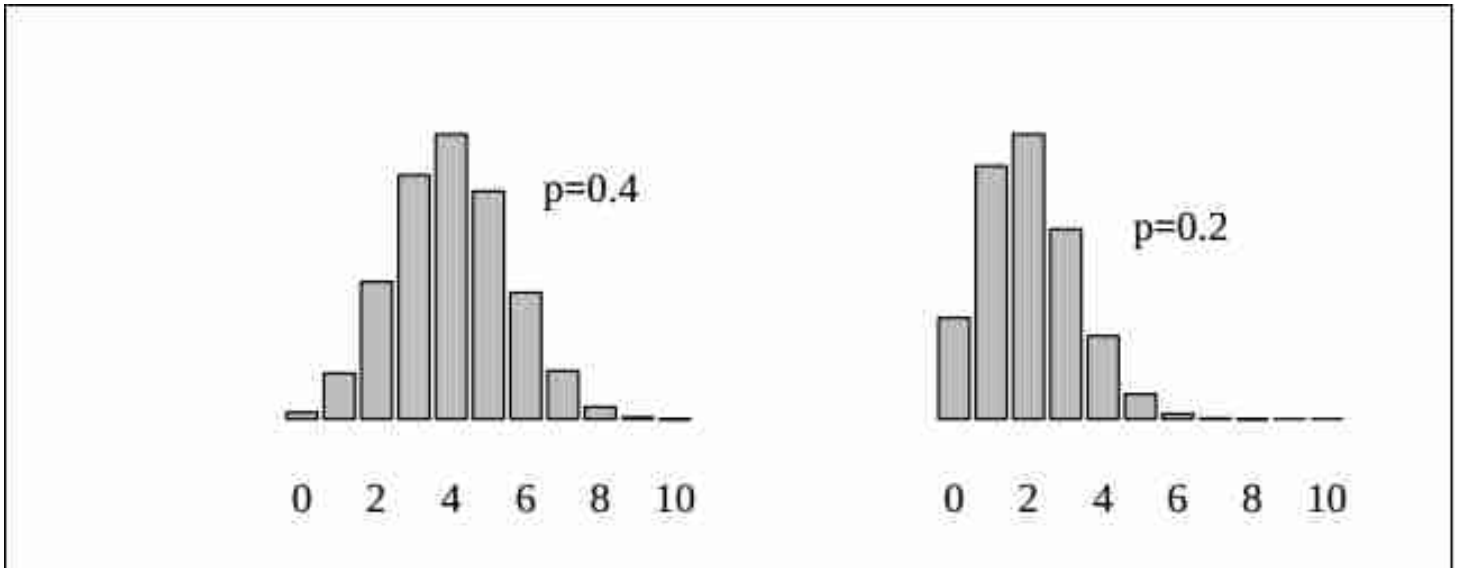
Binomial Random Sampling

- The probability to pick an allele *A* as ancestor of an individual in the next generation is *p = #A/2N*
- If the population remains constant then you have to sample *2N* (*2N = 10* in our example) times from the current generation to construct the next generation with *2N* offsprings
- For every sample, the probability to pick *A* remains constant at *p* → by definition of our model
- The number of offsprings for *A* follows a binomial distribution, thus the probability to pick A as an ancestor *k* times is

$$\mathbf{P}[X = k] = \binom{n}{k} p^k (1-p)^{n-k}$$

- Where *p := #A/2N* and *n := 2N*

Binomial Sampling of Alleles



Binomial distributions for frequency of allele *A* in the next generation for *p=f(A)=0.4* and *p=f(A)=0.2* and a population size of *2N = 10*

Mean and Variance of Allelic Frequency due to drift

- From the properties of the binomial distribution we obtain
  - $E(\#A) = 2N * p$
  - $Var(\#A) = 2N * p * (1 - p)$

The evolution of the frequency of *A* as a Markov Chain

- The evolution of the frequency of *A* over generations is a stochastic process!
- Even if we know everything about the population we cannot predict the state at the next generation with certainty
- One important property of the process: the next state depends only on the current state

  → The process can be modeled as a Markov Chain

Transition Probabilities Wright-Fisher

Frequency in next generation *t+1*

Frequency in current generation *t*

Probability of changing from *i alleles* in generation *t* to *j* alleles in generation *t+1*

$$\text{Prob}\{X(t+1) = j \mid X(t) = i\}$$

$$= p_{ij} = \binom{2N}{j} \left\{\frac{i}{2N}\right\}^{j} \left\{1 - \left(\frac{i}{2N}\right)\right\}^{2N-j}$$

$$i, j = 0, 1, 2, \ldots, 2N$$

Population size *2N* haploid or *N* diploid organisms

Example

- Prob of change from $i = 4 \rightarrow j = 8$ Alleles of same type for a population of size $2N := 10$ from one generation to the next

$$p_{4,8} = \binom{10}{8}(\frac{4}{10})^8(1-(\frac{4}{10}))^{10-8} = 0.0106168$$

Wright-Fisher Model

- A state of a Markov process is called *absorbing* when the probability to exit this state once we have entered it is 0.
- Are there absorbing states in the Wright-Fisher model?

Probability to enter an absorbing state

- Useful to study the evolution in a Wright-Fisher model as a Markov Chain because you can answer a lot of questions via standard Markov Chain theory.
- For instance: What is the probability that the population will end up (after how many generations?) in the absorbing state where *f(A)=1?*

  → this is also called *fixation*
- Given that the frequency of *A* is *#A/2N,* the probability that *A* will become fixed is *#A/2N*
- For details, see: http://people.sc.fsu.edu/~pbeerli/isc5317-notes/pdfs/01-populationmodels.pdf

Random genetic Drift

- The change in allele frequencies over generations in finite populations due to stochasticity (re-sampling) is called *random genetic drift*
- What is the effect of random genetic drift on the polymorphism level?
- Since our human population is finite, why do we still observe polymorphisms?

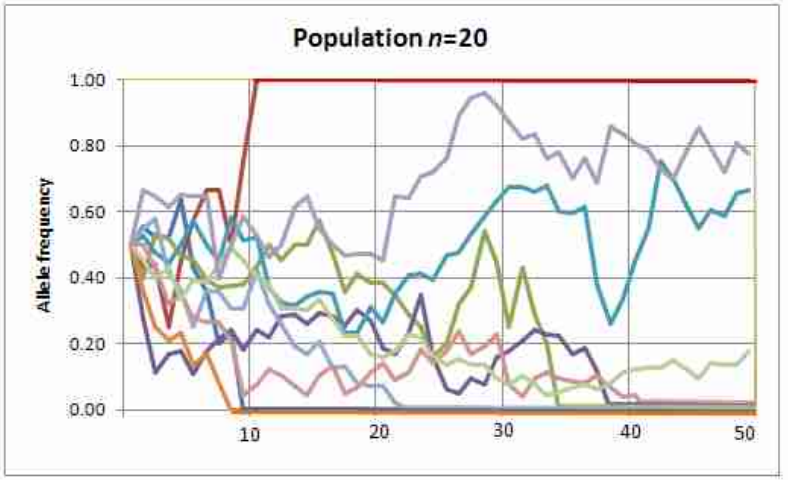
Heterozygosity and Genetic Drift

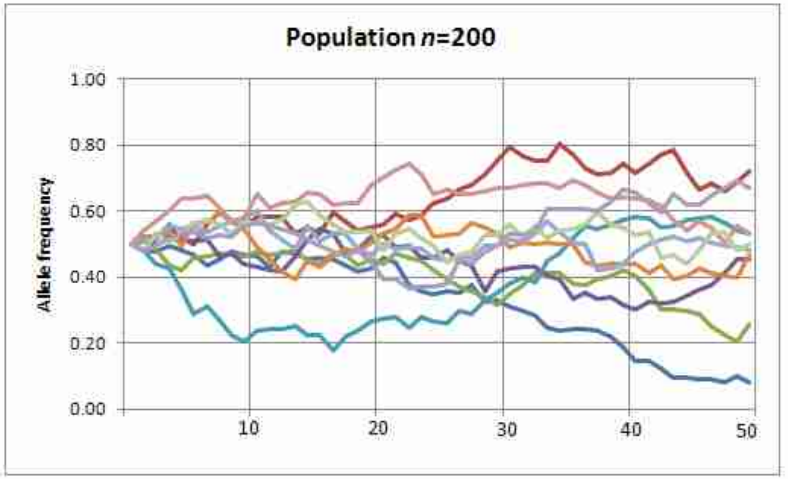
- Reduction of polymorphism is quantified by the degree of homozygosity → The probability that two alleles are identical

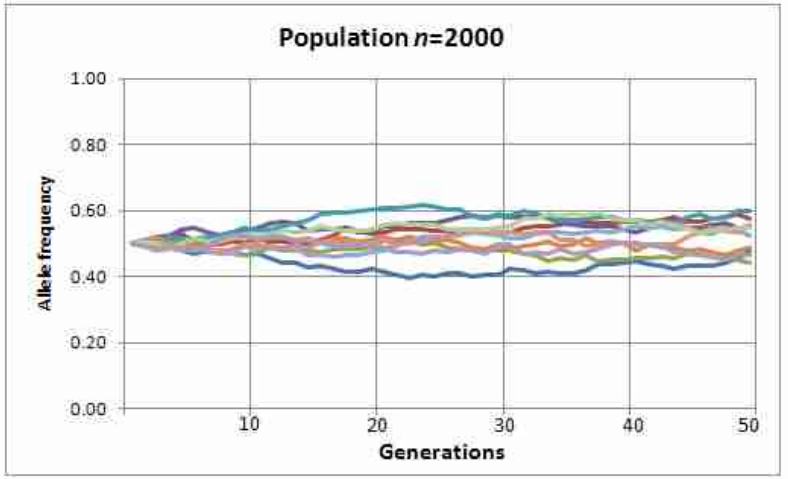
  → *heterozygosity = (1 – homozigosity)* at generation *t* is defined as: Het_t

- Assume a population of size *2N*
- We can define the heterozygosity recursively as $Het_t = Het_{(t-1)} (1 – 1/2N)$
- Thereby we obtain: $Het_t = Het_0 (1 - 1/2N)^t$

Probability that two randomly chosen Alleles are different







Initial allele frequency
f(A) = 0.5

Mutation-Drift Balance

- Genetic drift removes polymorphisms (SNPs) from the population
- Mutations introduce polymorphism (SNPs) into the population
- Is there some balance?

Heterozygosity at mutation – drift balance

- *Define:*
  - *Het*: heterozygosity
  - *-1/2N * Het*: Loss of heterozygosity **per generation** due to genetic drift
  - *μ:* mutation rate **per gene** (remember two alleles per gene!) and **per generation**
  - *2μ(1 – Het)*: gain of heterozygosity due to mutation
- Pick two alleles
- Consider transition from generation $t \rightarrow t + 1$
- The probability that they are identical is: *(1-Het)*
- If they are identical, the probability that one out of the two will mutate is *2μ*

  $\rightarrow$ *2μ(1 – Het) gain in* heterozygosity due to mutation
- Overall: $Het_{t+1} = Het_t - 1/2N * Het_t + 2\mu\ (1-Het_t)$

  $\Delta Het = -1/2N * Het_t + 2\mu(1-Het_t)$
- $\Delta Het = 0 \rightarrow Het = (4\mu N) / (1 + 4\mu N)$

Rate of Evolution by mutation and genetic drift

- Rate of Evolution = The probability of a new mutation to arise in the population and to eventually become fixed
- Assume
  - μ is the probability of mutation *per* generation and *per* individual
  - $2N$ individuals $\rightarrow$ $2N\mu$ mutations per generation
- The probability that a particular mutation will be fixed is $1/2N$
- Thus, the rate at which a mutation will arise and fix in the population is $1/2N * 2N\mu = \mu$
- Why is this result remarkable?

Natural Selection

- So far, we have assumed that the probabilities of *fitness* and *reproduction* are the same for each individual, independently of its genotype
- Consequently, a random individual at generation $t+1$ descends from any individual in generation t, with the same probability
- We denote the ability of an individual “to survive and reproduce” as *fitness*
- We assume that *fitness* depends on the genotype

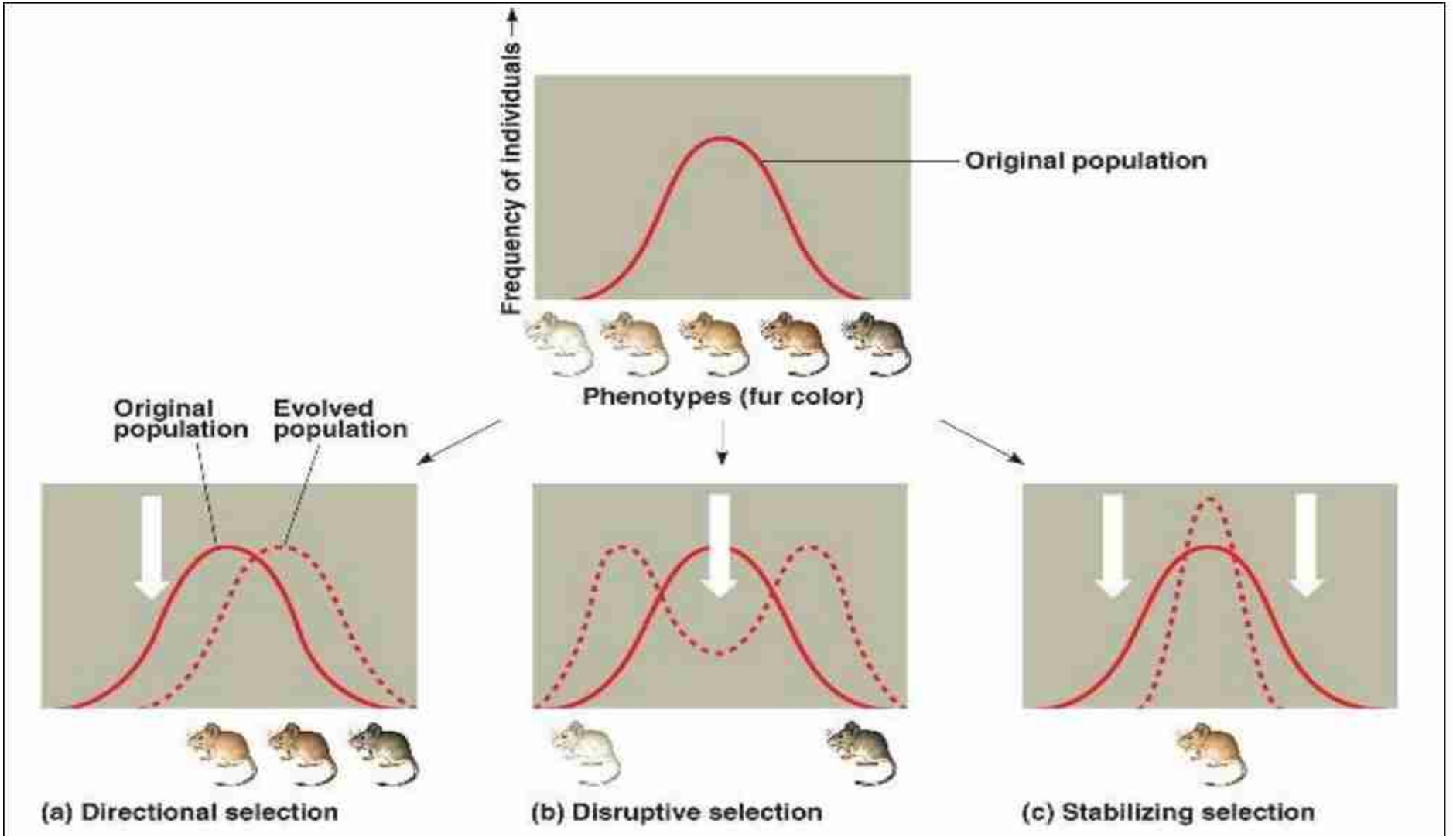
Natural Selection

- The term *selection* means that a genotype reproduces more frequently than others
- If a certain genotype, e.g., *AA* has better/higher fitness

  → it will fix in the population after several generations

  → consequently, the allele *A* will also fix
- We say: *Natural selection* has favored allele *A*
- In this case, the *natural selection* on *A* is termed *Positive Selection*

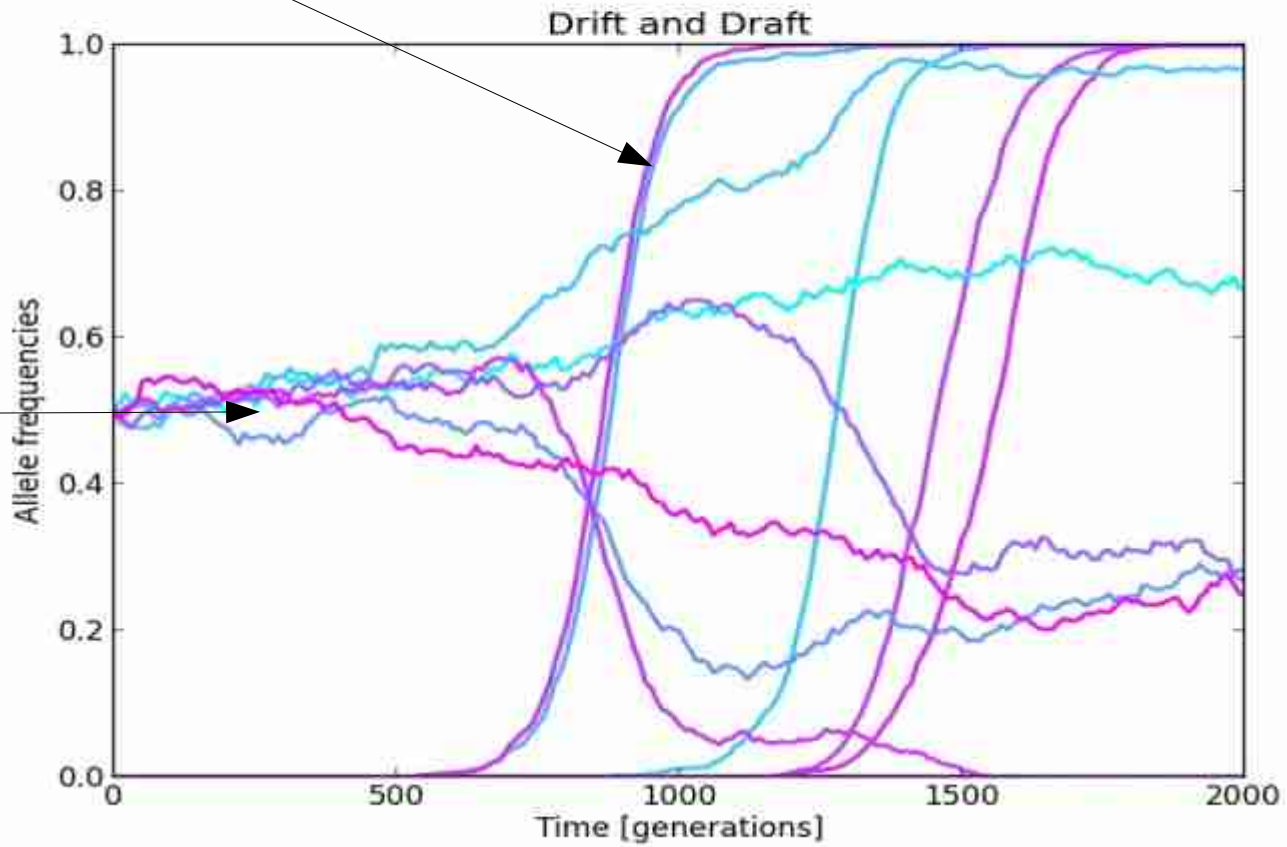
Different Modes of Selection



The Frequency Evolution of *A* under Positive Selection

Positive selection

Random genetic drift



Summary Statistics

- Summary statistics provide a summarized description of the dataset, e.g., the number of polymorphic sites
- Summary statistics are important because:
  - They allow to estimate parameters of the population
  - They help us to assess if positive selection occurred
- Differences to phylogenetics
  - Given the data (MSA of individuals)
  - We don't reconstruct a population tree for the individuals
  - We simulate evolution under different scenarios (including more complex models with changing population sizes etc)
  - Then we compare if one of the scenarios fits the summary statistics (e.g. # SNPs) of our empirical dataset