Selection and Mutation

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GE02: day 2 part 3

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Selection

Acts trough differential reproduction

Fitness of genotype *g*

- probability of reproductive success of an individual having this genotype

- r(g): "**r**eproductive success" or "survival"
- s(g): "**S**election pressure" or "mortality"

- r(g) = 1 – s(g)

Differential reproduction

Can occur because of different mechanisms

- Survival, e.g. a mutation may lead to death before reproductive age
- Damaged reproductive system, e.g. complete sterility or lowered fertility
- Distorted sexual behavior
- ...

Problem: dominant lethal allele

- Two alleles are present in population, **N** and **D**
- Initial frequency of **D** is q_0
- Survival in **NN** is not affected (normal fitness), while carriers of **D** have absolute mortality (all dead at early development):

  s(**NN**) = 0, s(**ND**) = s(**DD**) = 1
- What will happen to the allele **D** after some time?

Solution

- It will be immediately eliminated!

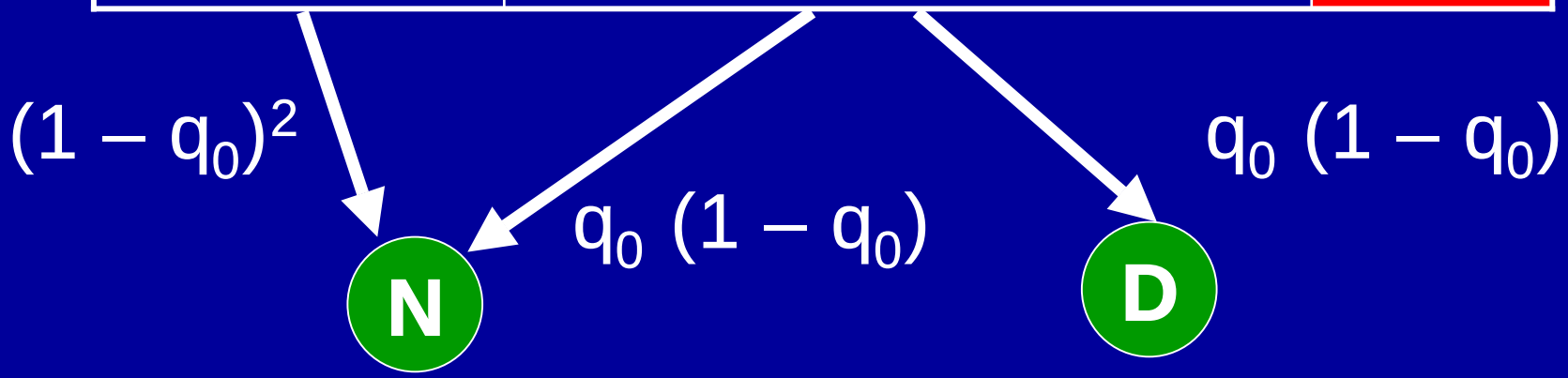
Problem: recessive mutation

- Two alleles, **N** and **D**
- Initial frequency of **D** is q_0
- Population is large and mating is random
- Individuals of genotype **DD** are sterile, while fitness of other genotypes is not distorted:

  s(**NN**) = s(**ND**) = 0; s(**DD**)=1
- What will happen to the allele **D** after some time?

Solution

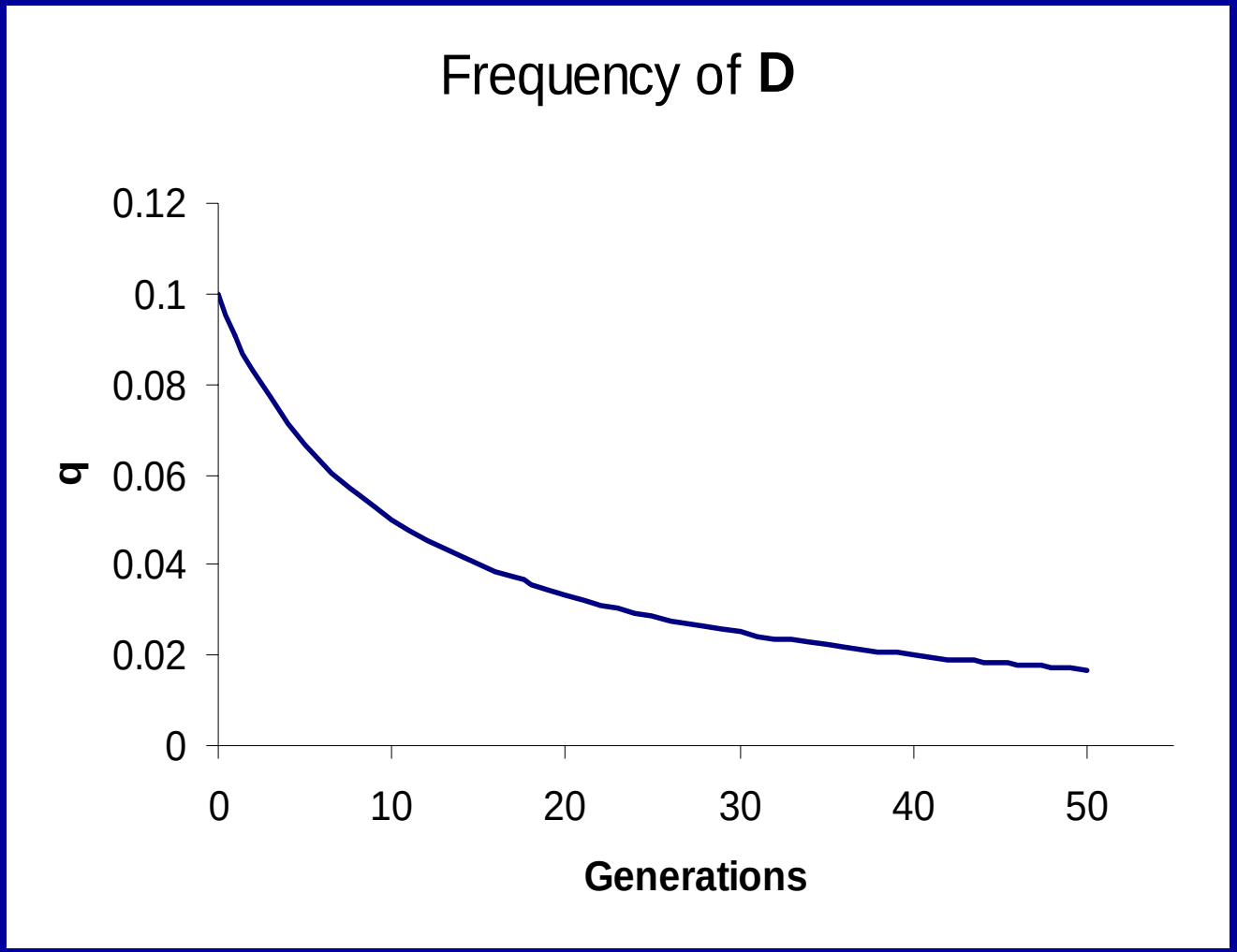
NN	ND	DD
$(1 - q_0)^2$	$2\ q_0\ (1 - q_0)$	q_0^2



$$q_1 = \frac{q_0(1-q_0)}{(1-q_0)^2 + 2q_0(1-q_0)} =$$

$$\frac{q_0}{(1-q_0)+2q_0} = \frac{q_0}{1+q_0}$$

Elimination of mutant



Generalisation to arbitrary s

- Two alleles, **D** (deleterious) and **N** (normal)
- Survival in **DD** is decreased by some **s**:
  - only (1 – **s**) survive and reproduce

Solution

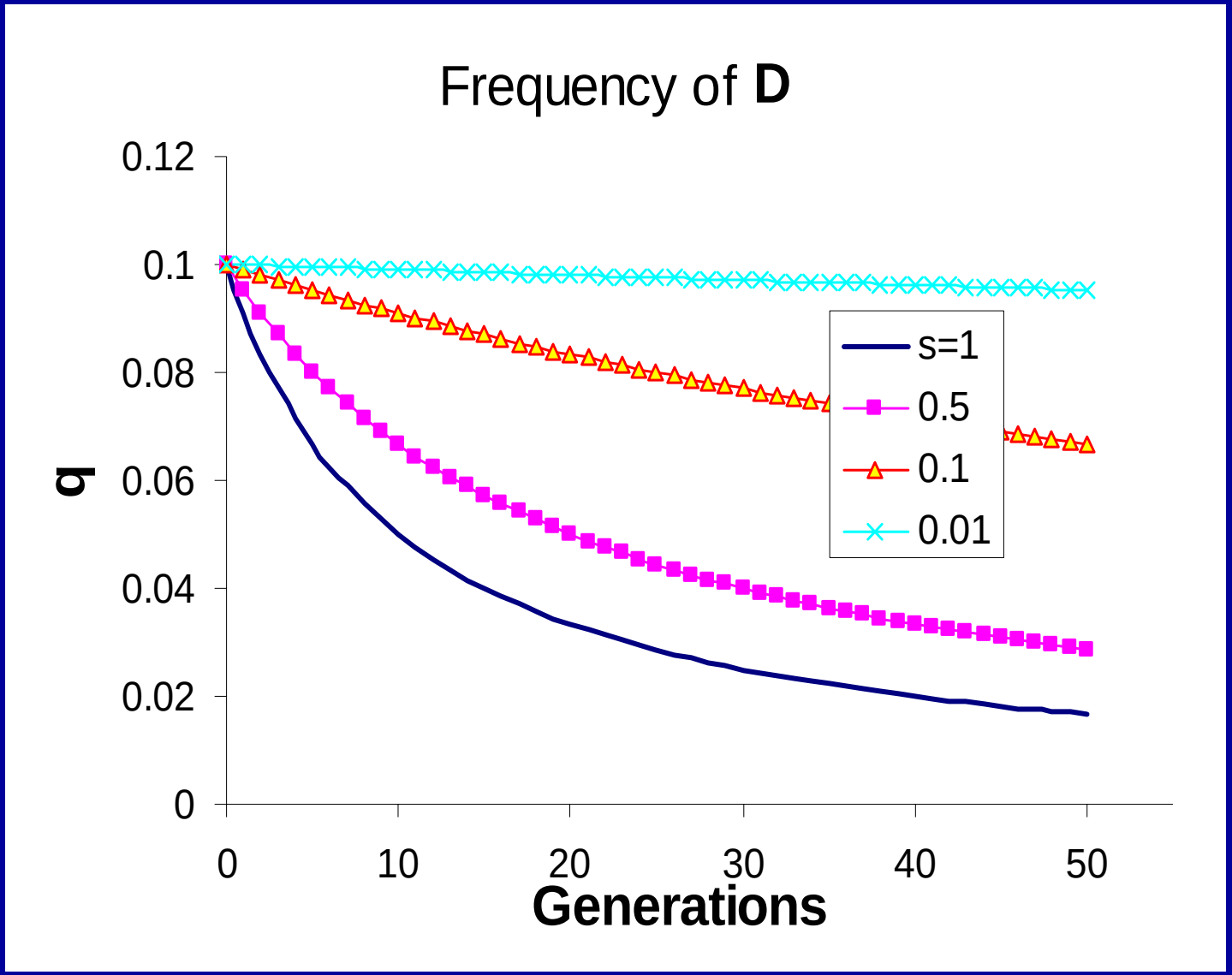
NN	ND	DD
$(1 - q_0)^2$	$2\ q_0\ (1 - q_0)$	$(1\text{-}s)\ q_0^2$

- It is easy to show that

$$q_1 = \frac{q_0(1-q_0) + q_0^2(1-s)}{(1-q_0)^2 + 2q_0(1-q_0) + q^2(1-s)} =$$

$$\frac{q_0(1-q_0 s)}{1-sq_0^2} = \frac{q_0}{1+sq_0}$$

Elimination at different s



Mutation and selection

- Two alleles, **D** (deleterious) and **N** (normal)
- Survival in **DD** is decreased by some **s**:
  - only (1 – **s**) survive and reproduce
- Thus selection eliminates **D** from population

- Opposing force: mutation changes **N** to **D** with probability μ (per gamete generated)
- There must be a mutation / selection balance (equilibrium point)

Fate of a rare recessive mutation

- At the equilibrium point, the frequency of **N** in next generation must be the same as in previous generation

$$p = \frac{(p^2 + pq)\cdot(1-\mu)}{1-sq^2}$$

$$p = \frac{p\cdot(1-\mu)}{1-sq^2}$$

$$p\cdot(1-sq^2) = p\cdot(1-\mu)$$

$$sq^2 = \mu$$

$$q = \sqrt{\frac{\mu}{s}}$$

Problem: cystic fibrosis

- Mutation in CFTR gene
- Recessive monogenic model
- Homozygous carriers ha(ve)(d) ¼ chance to die before reproduction age
- Carrier frequency is 1/30

- Assuming mutation/selection balance model, what is mutation rate, μ*?*

Solution

- $P(\mathbf{D})^2 = \boldsymbol{\mu} / \mathbf{s}$
- $\boldsymbol{\mu} = \mathbf{s}\, P(\mathbf{D})^2$

- $\mathbf{s} = ¼$
- $P(\mathbf{D}) = 1/(2*30) = 1/60$

- $\boldsymbol{\mu} = ¼\ 1/3600 = 10^{-5}$
- A bit too high...

Balancing selection

Genotype	AA	Aa	aa
Success	$1 - s_1$	1	$1 - s_2$
Sel. press.	s_1	0	s_2

- Idea: because of heterozygous advantage, both A and a must be present in population

Solution

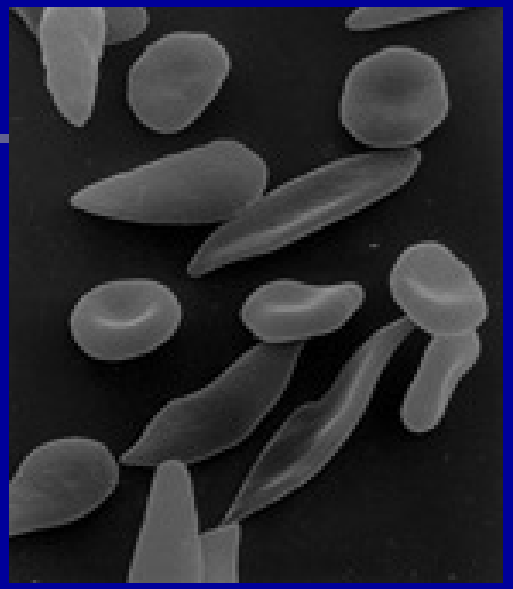
- Let us denote frequency of “A” as **q**
- Equation:

  $q' = [q^2 (1 - s_1) + pq]/[1 - s_1 p^2 - s_2 q^2]$
- At equilibrium point:

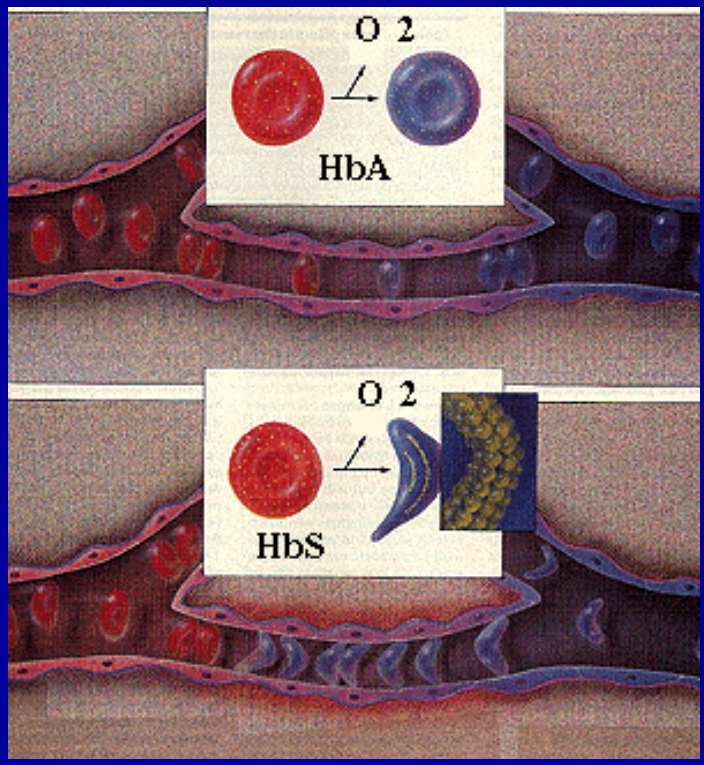
  $q' = q$
- Solution:

  $q = s_1 /(s_1 + s_2)$

Sickle-cell anemia (SCA)

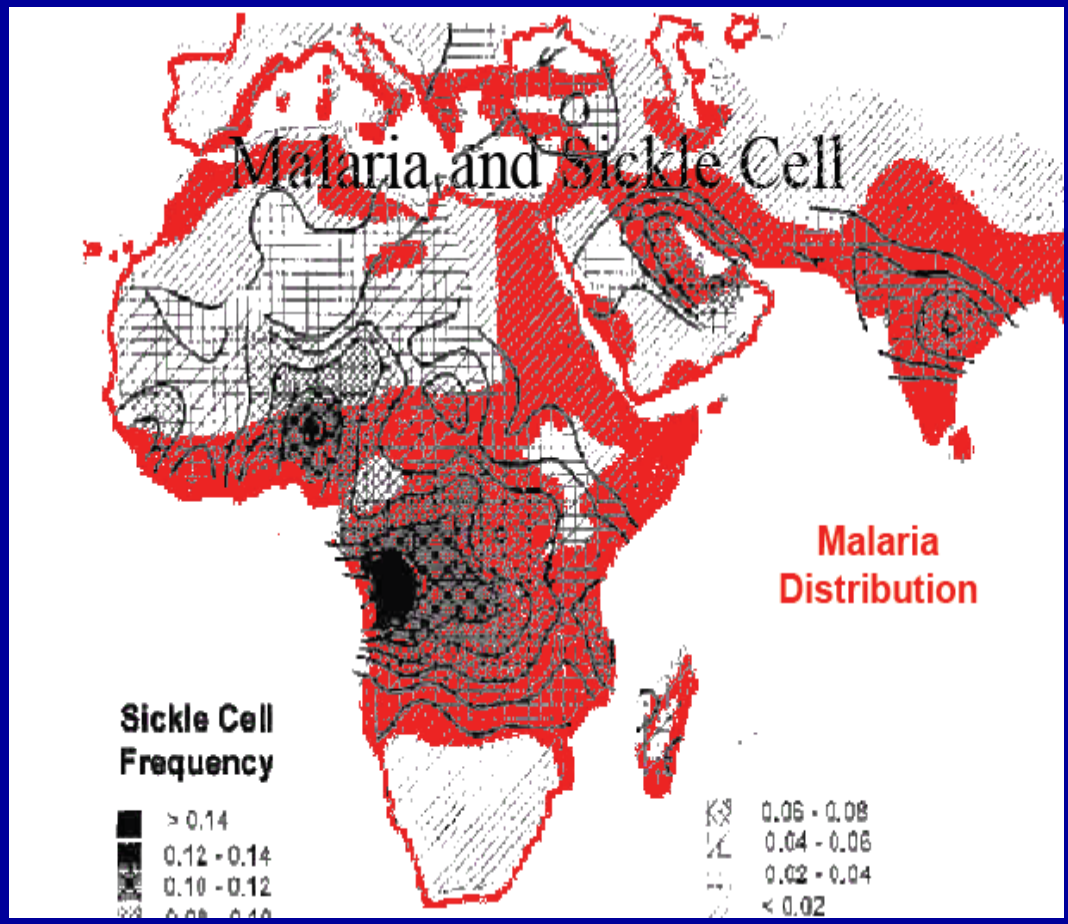


- HbS allele of human beta-globin
  - Hb/Hb ⇒ normal
  - HbS/Hb ⇒ normal
  - HbS/HbS ⇒ SCA
- SCA
  - sickle cells are “sticky” ⇒ vasooclusion and local hypoxia ⇒ vascular damage, organ infarcts, painful crises
  - High risk of death before 3 y.o.
  - Shorter life expectancy in adult



High HbS frequency ⇔ malaria

- Hb/Hb
  - malaria
- HbS/Hb
  - Malaria less frequent, lower parasite level ⇒ 30% more survive to adulthood
- HbS/HbS
  - SCA
  - Malaria less frequent, lower parasite level



Application to SCA

- Assume
  - Malaria is endemic

Genotype	Hb/Hb	Hb/HbS	HbS/HbS
Survival	0.77	1	0.1
Sel. press.	0.23	0	0.9

- Equilibrium frequency

  $q = 0.23/(0.23 + 0.9) = 0.20$

Fitness is context-dependent

A “harmful” allele may

- ... have been favorable or neutral in the past
- ... may be harmful in homo- but favorable in heterozygous form
- ... may have opposite effect at different ages
- ... may have opposite effect on different traits
- ...
- If population is/was small, it also could attain high frequency just by chance (drift)