Selection
Mutation & selection balance

24.10.2005
GE02: day 2 part 1

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Selection

- Acts trough differential reproduction of individuals having different genotypes
- It is assumed that some genotypes are less "fit" then others
- Fitness of some genotype, *g*, is expressed as probability of reproductive success of an individual having this genotype

  $r(g) = 1 - s(g)$

  where $s(g)$ is probability that a person with genotype *g* will fail to reproduce

  $r(g)$ is some times termed "***r***eproductive success" or "survival"

  $s(g)$ is some times termed "***S***election pressure" or "mortality"

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, **A** and **a**
- Initial frequency of **a** is p_0
- AA have normal fitness while carriers of **a** have high mortality (are dead before birth):

  $s(\mathbf{AA}) = 1$, $s(\mathbf{Aa}) = s(\mathbf{aa}) = 0$
- What will happen to the **a** allele after some time?

Solution

- It will be immediately eliminated!

Problem: recessive model

- Two alleles are present in population, **A** and **a**
- Initial frequency of **a** is p_0
- Population is large and mating is random
- Individuals of genotype **aa** are sterile (do not mate):

  $s(\mathbf{AA}) = s(\mathbf{Aa}) = 0$; $s(\mathbf{aa})=1$
- What will happen to the **a** allele after some time?

Solution

- Genotypic frequencies in 1st generation:

$$(1 - p_0)^2 : 2\, p_0\, (1 - p_0) : p_0^2$$

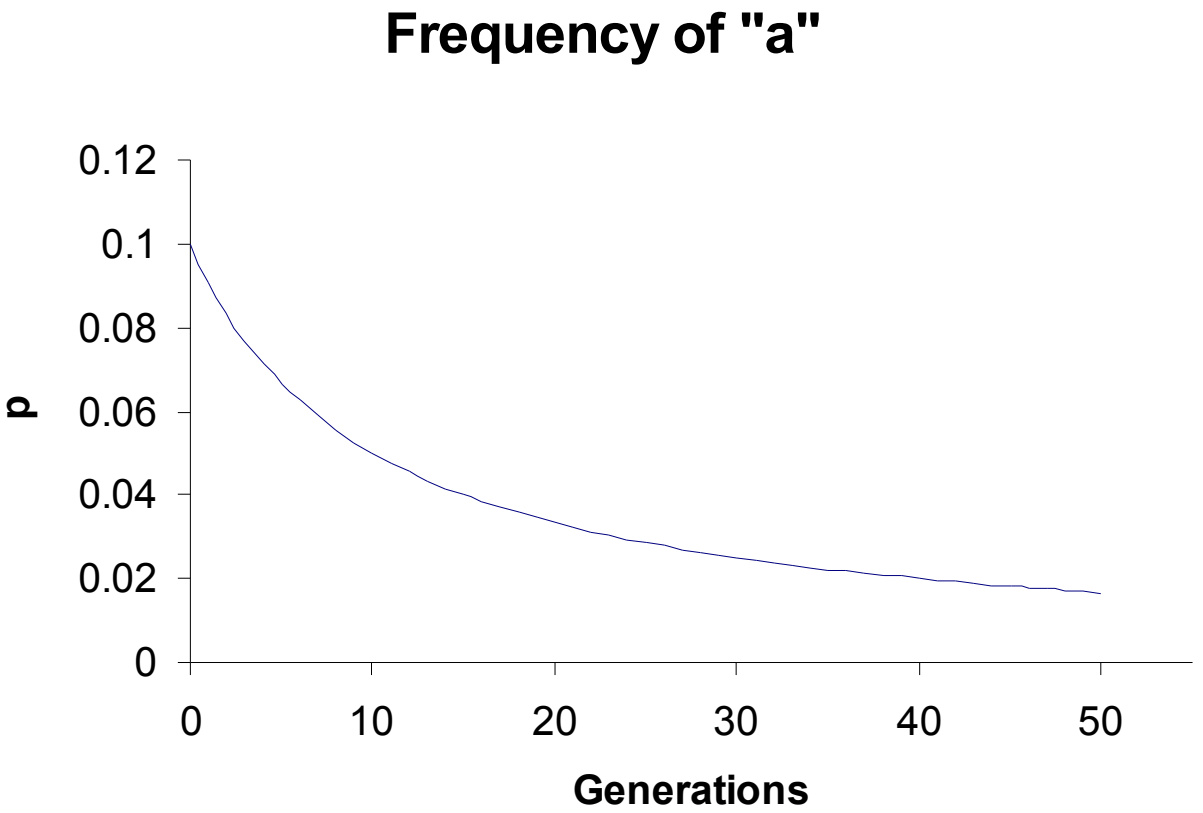
- Only **AA** and **Aa** contribute to the next generation
- New frequency will be

$$p_1 = p_0\, (1 - p_0) / (1 - p_0^2)$$

- Next generation

$$p_2 = p_1\, (1 - p_1) / (1 - p_1^2)$$

Elimination of mutant



Fate of a rare recessive mutation

- Two alleles, M (deleterious) and N (normal)
- Mutation changes N to M with probability μ
- Survival in MM is affected, say only $(1 - s)$ survive and reproduce (for previous example, s was 1)
- There must be mutation / selection balance

Fate of a rare recessive mutation

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

$$P(N) = \frac{(P(N)\cdot P(M) + P(N)^2)\cdot(1-\mu)}{1 - s\,P(M)^2} = \frac{P(N)\cdot(1-\mu)}{1 - s\,P(M)^2}$$

- This gives the equilibrium solution

$P(M)^2 = \mu/s$

Example: cystic fibrosis

- Mutation in CFTR gene
- Recessive monogenic mode
- Homozygous carriers has ¼ chance to die before reproduction age
- Carrier frequency is 1/30

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

Solution

- $P(M)^2 = \mu/s$
- $\mu = s\ P(M)^2$

- $s = ¼$
- $P(M) = 1/(2*30) = 1/60$

- $\mu = ¼\ 1/3600 = 10^{-5}$ (a bit too high...)

Balancing selection

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

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

Solution

- Equation:

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

- At equilibrium point:

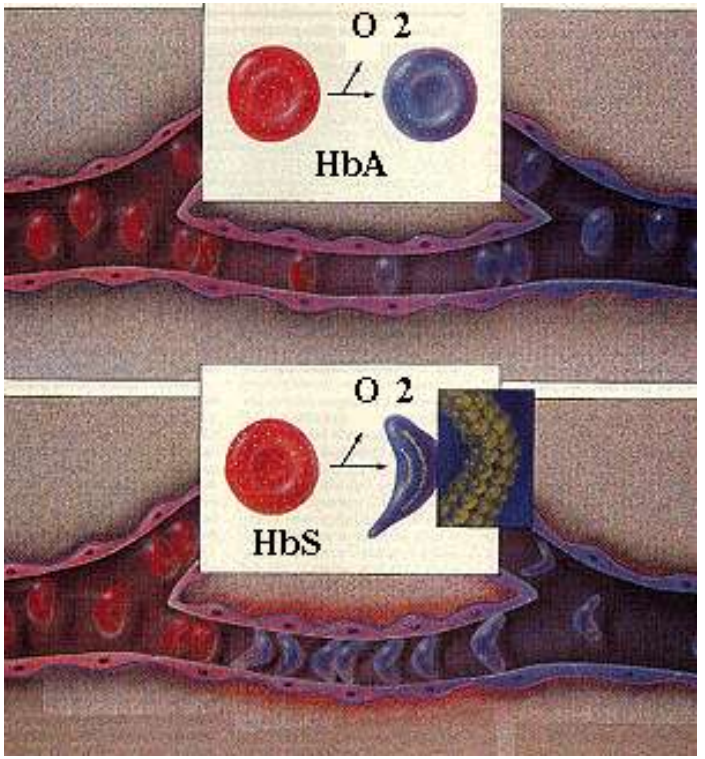
$$q' = q$$

- Solution:

$$q = s_1 /(s_1 + s_2)$$

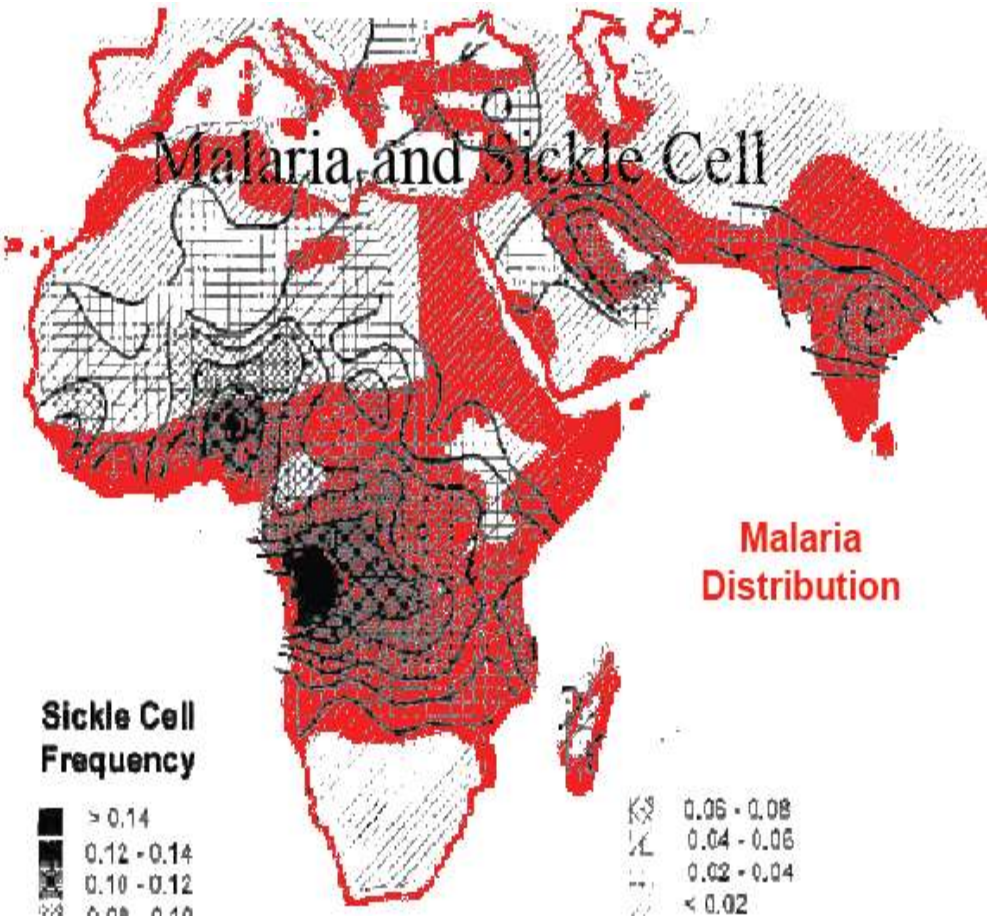
Sickle-cell anemia (SCA)

- HbS allele of human beta-globin
  - Hb/Hb => normal
  - HbS/Hb => normal
  - HbS/HbS => SCA
- SCA
  - sickle cells are “sticky” => vaso-oclusion 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 => 29% more survive to adulthood
- HbS/HbS
  - SCA
  - Malaria less frequent, lower parasite level



Application to SCA

- Assume
  - Malaria is endemic

Genotype	AA	Aa	aa
Survival	0.78	1	0.2 (?)
Sel. press.	0.22	1	0.8

- Equilibrium frequency

  $q = 0.22/(0.22 + 0.8) = 0.216$

The lesson to learn

- Fitness of a genotype 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
  - … because of stochastic processes (drift, to be considered later)