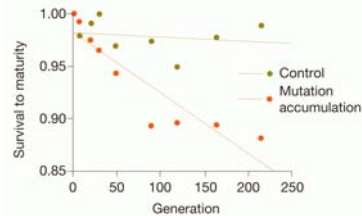


When bad things happen to good genes: the balance between mutation and selection

Most mutations are expected to be harmful. Why? Many random changes are expected to destroy a gene or degrade its product or its regulation. Very few mutations will *improve* a gene's performance. These expectations are strongly confirmed by mutation-accumulation experiments like that of Vassilieva and colleagues.

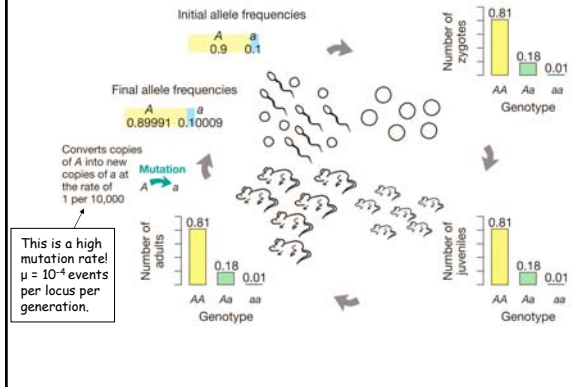
Questions:

How common are deleterious (harmful) mutations expected to be, at equilibrium between mutation and selection? What are the implications for natural populations?



Biol 3410, 6 Feb 09

By itself, mutation is an extremely weak (slow) evolutionary force



But selection can also be slow and weak, if mutations are recessive

Let q be the frequency of allele A_2 and assume it is recessive and deleterious.

The marginal fitness of the "normal" allele A_1 will be $W_1 = 1$, because that is the fitness of both genotypes in which it occurs.

The marginal fitness of A_2 will be $W_2 = pW_{12} + qW_{22} = p + qW_{22}$.

But q is close to 0 (because A_2 is deleterious), so W_2 is close to 1.

Thus the mean fitness $\bar{W} = pW_1 + qW_2$ is very close to 1.

We can therefore simplify the selection equation by eliminating \bar{W} .

Thus to a good approximation,

$$q' = qW_2,$$

and the allele-frequency change in a single generation is

$$\Delta q = q' - q = qW_2 - q = q(W_2 - 1).$$

The equilibrium is a balance of two weak forces

The slow change in allele frequency caused by selection is negative:

$$\Delta q_s = q' - q = qW_2 - q = q(W_2 - 1).$$

But the slow change caused by mutation from A_1 to A_2 is positive:

$$\Delta q_m = p\mu = (1-q)\mu \approx \mu \text{ (because } q \text{ is close to 0).}$$

At equilibrium these must balance: $\Delta q_s + \Delta q_m = 0$.

A little algebra gives the equilibrium frequency of A_2 , which is

$$q = (\mu/s)^{1/2}$$

where $s = 1 - W_{22}$ is the fitness loss suffered by A_2A_2 homozygotes.

(Differences between fitnesses are called selection coefficients.)

In words, the equilibrium frequency of a purely deleterious recessive allele is the square root of the ratio of (1) the mutation rate and (2) the selection coefficient against homozygotes.

Deleterious mutation rates can be very high

Spinal muscular atrophy is caused by homozygosity for recessive mutations of the telomeric survival motor neuron gene (*telSMN*).

Seven of 340 patients were found to carry new mutations not present in either of their parents.

This implies a mutation rate of around 1×10^{-4} (see page 214 and Box 6.11).

The selection coefficient (s) for homozygotes is estimated to be around 0.9.

The predicted allele frequency at mutation-selection equilibrium is therefore $q = (0.0001/0.9)^{1/2} \approx 0.01$.

In Caucasian populations, roughly 1 in 10,000 infants is affected.

This implies $q^2 = 1/10,000 = 0.0001$, or $q = 0.01$, in excellent agreement with the mutation rate estimated directly from pedigrees and our simple model of mutation-selection equilibrium!

But equilibrium deleterious allele frequencies can be high even with low mutation rates

Suppose $\mu = 10^{-6}$.

What's the equilibrium frequency of a lethal recessive?

$$q = (10^{-6}/1)^{1/2} = 10^{-3} = 0.001.$$

That's still 1 in 1000 copies of the gene.

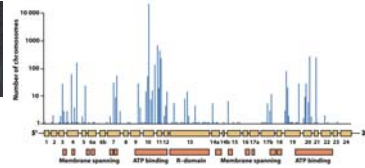
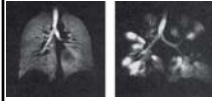
And 1 in 500 individuals are heterozygous carriers! (2pg, remember?)

But only 1 in 1,000,000 are affected homozygotes, among the offspring of unrelated parents.

Homework problem: Work out the expected allele and genotype frequencies for mutation rates of 10^{-5} , 10^{-6} , and 10^{-7} , with selection coefficients of 0.01, 0.1, and 1. Then think about the implications for outbreeding species, on the assumption that many genetic loci have only minor "fine tuning" functions, as suggested by the experiment of Thatcher, Shaw and Dickinson.

But are all "deleterious" alleles really (just) deleterious?

Cystic fibrosis is caused by homozygosity for broken alleles at the CFTR locus.



There are many such alleles; most are rare, but a few are common.

Roughly 1 in 2500 newborns are affected in populations of European descent. Thus the combined loss-of-function allele frequency is $(0.0004)^2 = 0.02$.

Assuming lethality (probably true in the past), this would require $\mu = 4 \times 10^{-4}$.

But pedigree studies imply that the mutation rate at CFTR is only 7×10^{-7} .

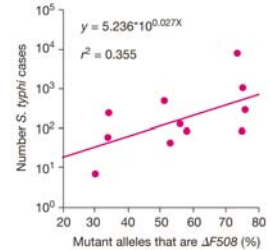
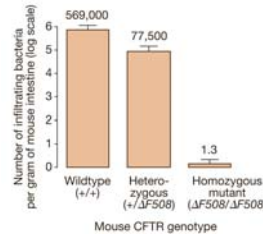
Our model fails. What's going on?

Maybe heterozygotes sometimes have an advantage, as with hemoglobin S. Possible mechanism: resistance to typhoid fever (*Salmonella enterica typhi*).

Evidence in support of the typhoid-fever hypothesis

Cultured mouse cells resist infiltration by *Salmonella typhi* if they are heterozygous (or homozygous) for the most common human CFTR mutation.

European countries with larger numbers of *S. typhi* outbreaks have higher relative proportions of the most common CFTR mutation ($\Delta F508$).



In an outbreeding species, every individual carries many serious deleterious (even lethal) recessive alleles.

We showed earlier that 1 in 500 individuals is expected to be heterozygous for a lethal deleterious allele at any locus where the mutation rate to such alleles is 1×10^{-6} per generation (a low estimate).

How many such loci are there?

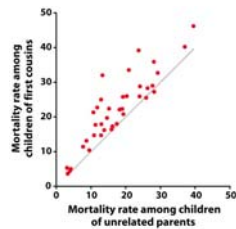
Mammals have around 25,000 genes.

Suppose just 10% (2,500) are subject to lethal deleterious mutations.

Then a typical individual would be heterozygous for a lethal recessive mutation at $2500/500 = 5$ loci.

Inbreeding would greatly increase the (low) level of homozygosity at such loci.

The offspring of cousin matings suffer increased childhood mortality, consistent with this prediction.



Would "eugenics" work, even in principle?

In the early 20th century, many scientists and policy makers proposed that individuals expressing genetic "defects" should be sterilized.

But most such defects are recessive.

If they harm fitness, then they're rare.

And if they're rare, then most carriers are heterozygotes.

That means that most of the alleles are in (unaffected) heterozygotes.

So sterilizing (or even killing) the afflicted homozygotes will do very little to reduce the frequencies of the deleterious recessive alleles.

Next generation, there will be almost as many sufferers as there were this generation, and the bad allele will be nearly as frequent.

