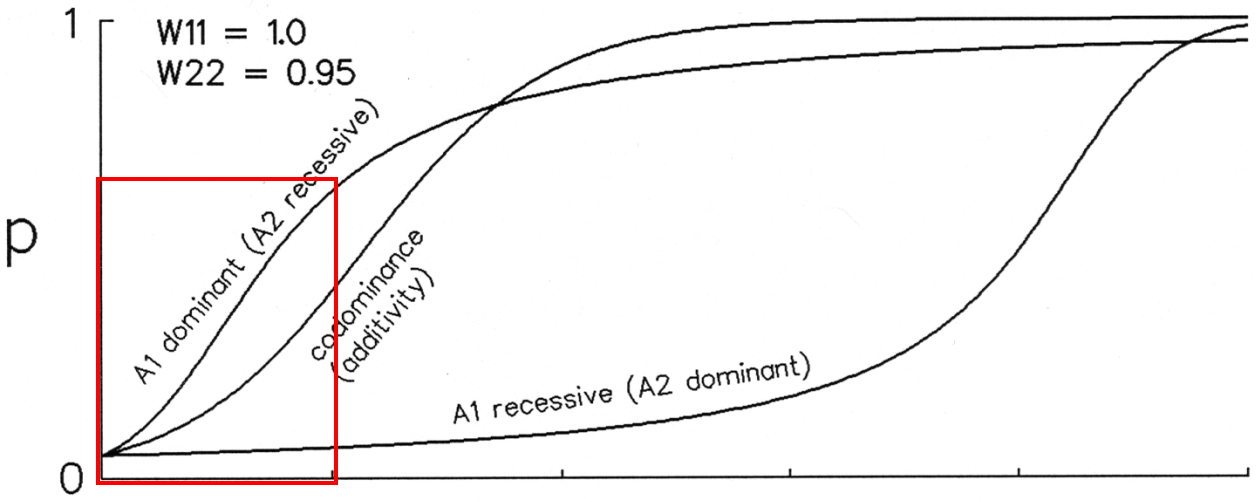
Allele-frequency histories ("trajectories") can easily be calculated by *iterating* the recurrence equation:

$$p' = p[\bar{W}_1]/\bar{W}$$

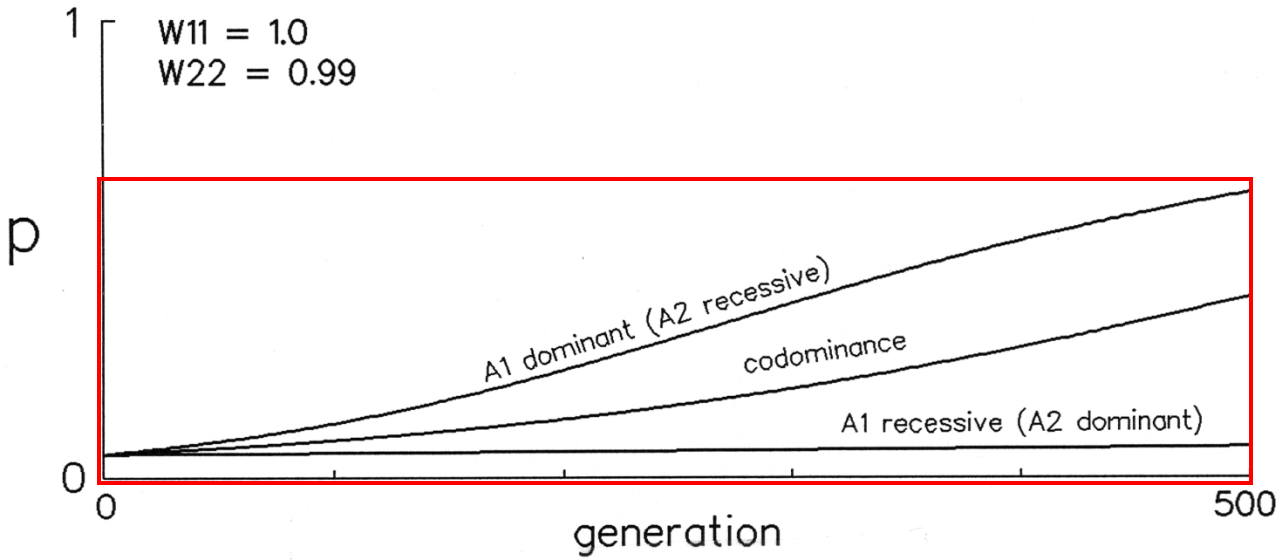
$$p' = f(p)$$



(1) The rate of allele-frequency change is fastest at intermediate allele frequencies (when *pq* is greatest).

(2) Rare recessive alleles (whether advantageous or harmful) are almost "invisible" to selection.

(3) Smaller fitness differences lead to proportionally slower rates of allele-frequency change.



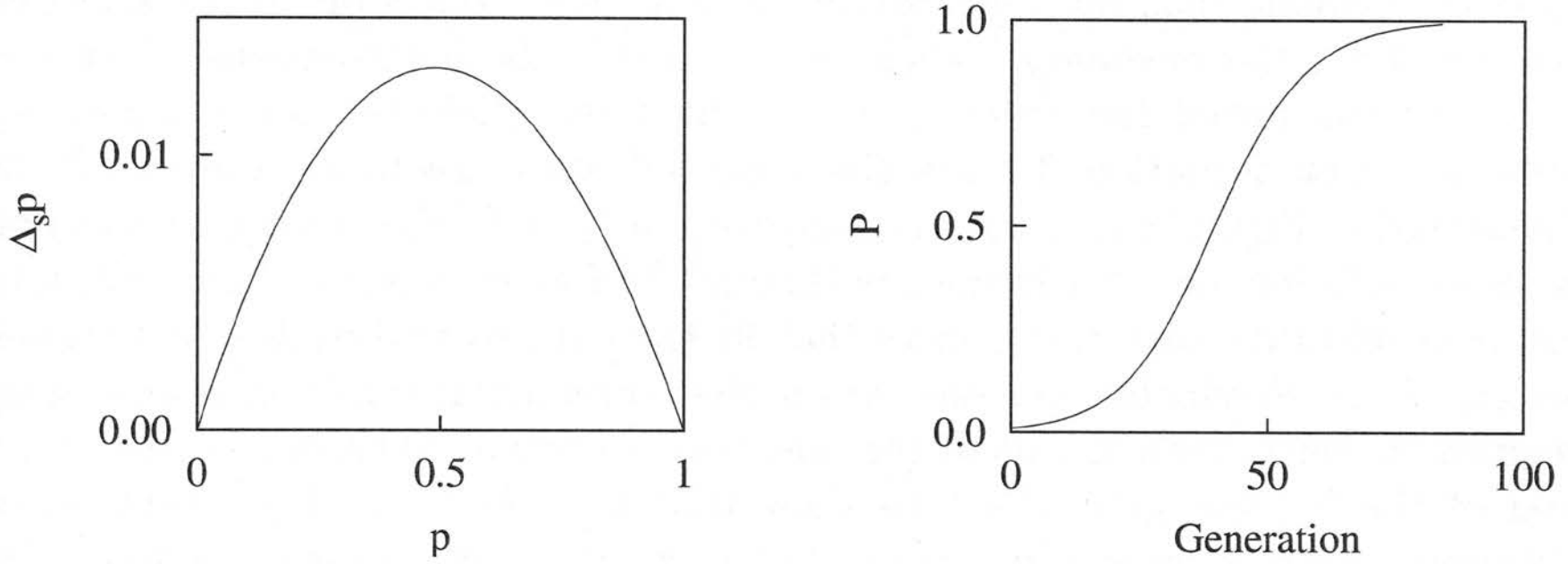


Figure 3.3: Properties of directional selection with $h = 0.5$ and $s = 0.1$. The left-hand graph shows the change in the allele frequency in a single generation. The right-hand graph shows the evolution of the allele frequency over 100 generations.

How and when do typical genes contribute to fitness?

A major puzzle: Most genes appear to be *unnecessary!*

Half or more can be "knocked out" (fully disabled) in yeast, worms, flies and even mice, without any obvious phenotypic effects (in the lab, anyway).

But these genes are maintained in evolution, so they must be useful. *How?*

Two hypotheses:

(1) Most are "special-purpose" genes needed only under certain circumstances (stresses that occur in nature but not in the lab).

(2) Most are "fine-tuning" genes that increase the efficiency or accuracy of some physiological or developmental process in most environments.

Experimental test devised by Joe Dickinson:

Compete "no-phenotype knockouts" against genotypes that are identical except for the knockout, and let natural selection measure their relative fitnesses.

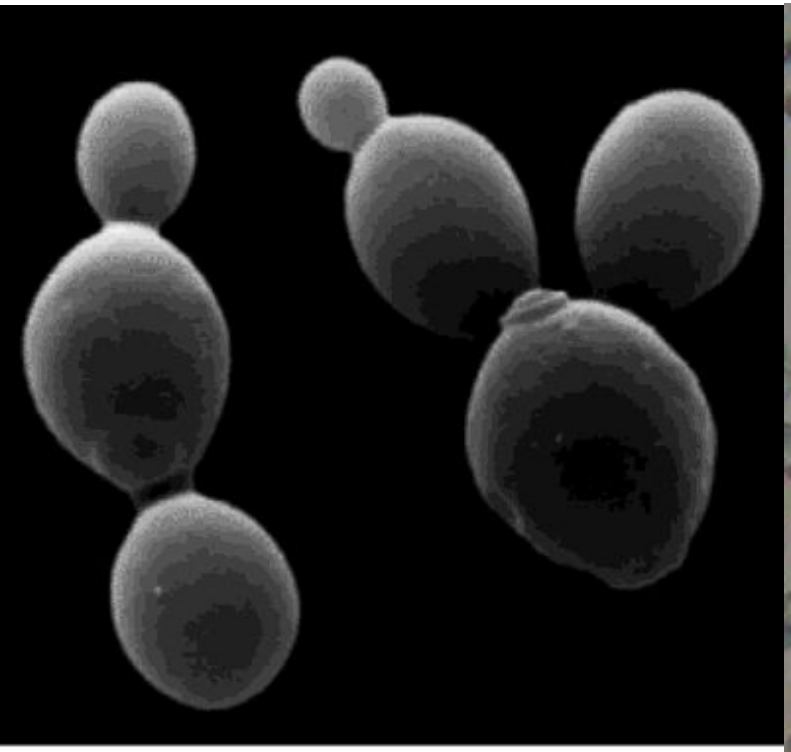
Dickinson talked Janet Shaw (a yeast cell biologist) and John Thatcher (an undergraduate) into helping him try to do this with yeast.

How to ask cells if they miss a (random) gene

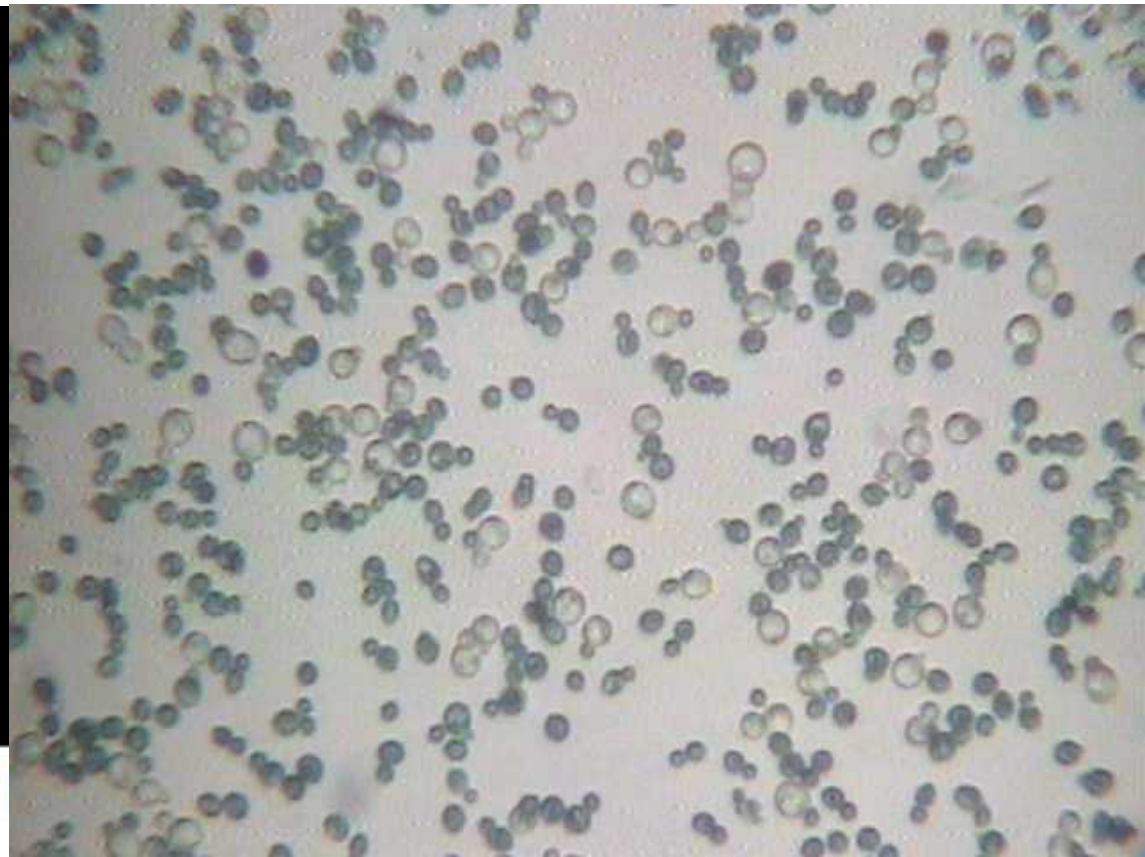
Mark either the random, "no-phenotype" knockout, or the wild-type parent, with *lacZ* so that you can score their relative numbers on indicator plates.

Start populations with equal numbers of wild-type and knockout cells; grow them for many generations in complete (rich) liquid media.

Sample the populations every 10-20 generations and score the relative numbers of marked and unmarked cells.

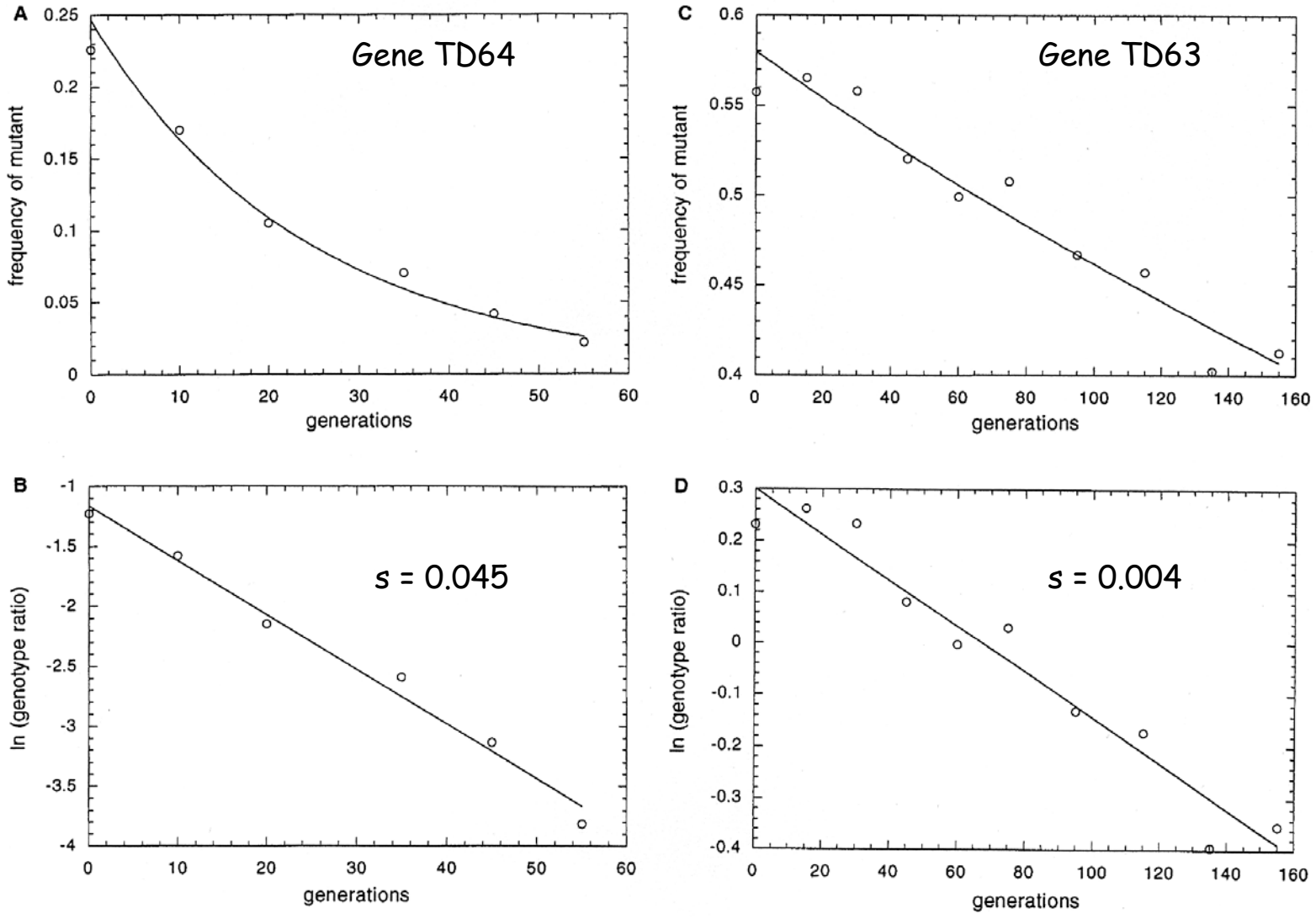


Yeast (*Saccharomyces cerevisiae*)



Plot the frequency of the knockout as a function of generations (A, C)

Also plot the log of the ratio of the allele frequencies [ln(*q*/*p*)] versus generation (B, D). The slope of this (straight) line is an estimate of the selection coefficient (-*s*).



Summary of results for 27 "no-phenotype" knockouts

Nineteen mutations (70%) showed statistically significant fitness defects ranging from 0.3% (s = 0.003) to 23% (s = 0.23).

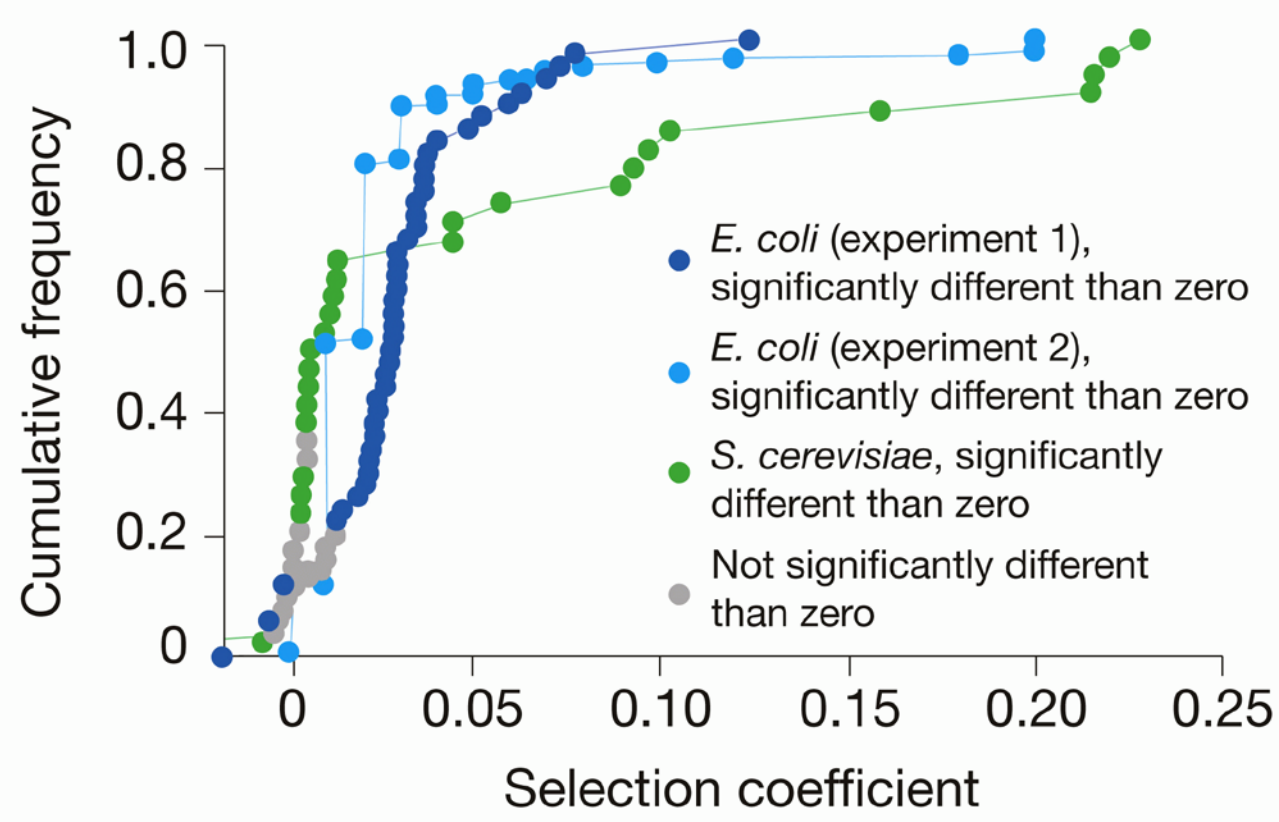
Among these, the typical (median) selection coefficient was 1-2%.

Six mutations (22%) were not statistically distinguishable from neutral. (Five of the six appeared to be weakly deleterious, and one appeared to be beneficial.)

A more sensitive experimental design (with larger populations and allele-frequency assays) would probably show most of these to be significant, raising the fraction of deleterious no-phenotype knockouts to 85-90%.

Two of the 27 knockouts (7%) were significantly *advantageous*, with "negative" coefficients of s = -0.005 and s = -0.007.

Conclusion: Most genes make *modest* contributions to fitness



This finding (in bacteria, too) supports the "fine-tuning" hypothesis.

Such small effects *could not be detected except by natural selection.*

Read the paper: Thatcher, Shaw & Dickinson, *PNAS* **95**, 253-257 (1998).