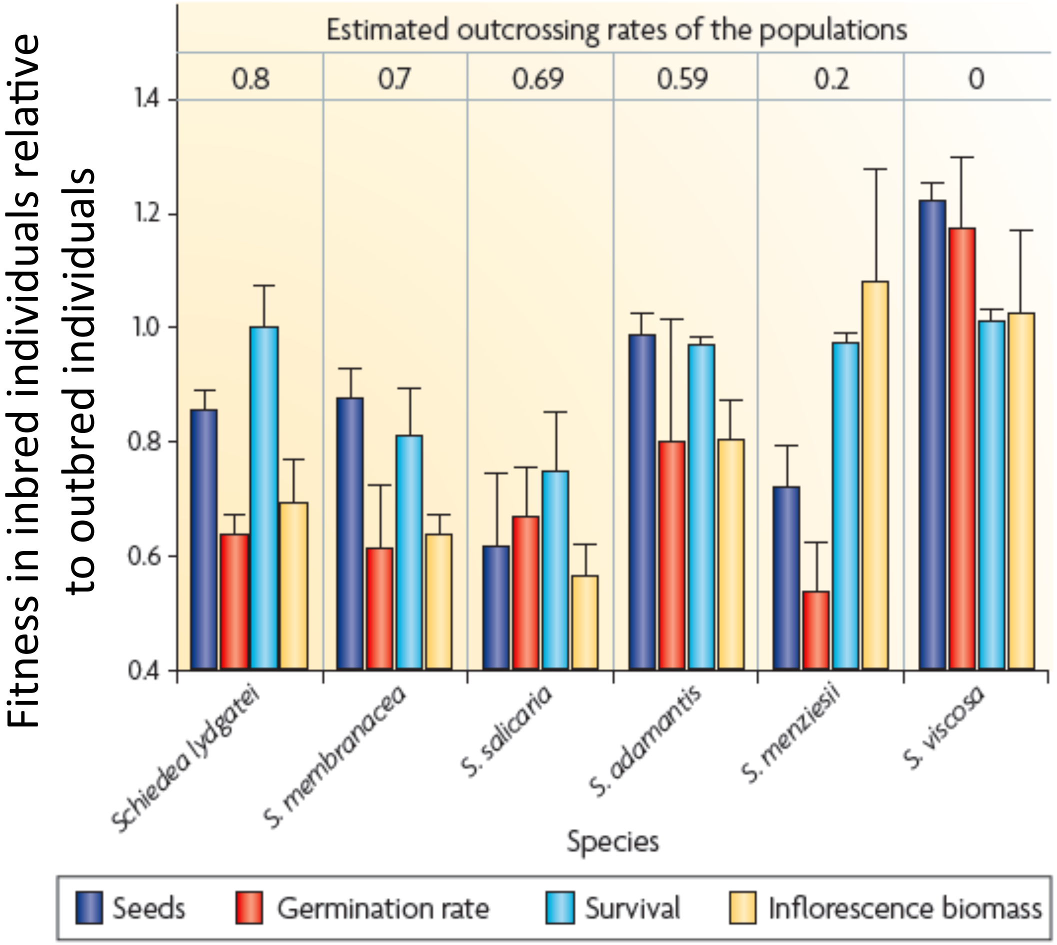
Purging of inbreeding load in partially selfing populations

Given an inbreeding coefficient of *f*, the equilibrium frequency is

$$q_e \approx \frac{\mu}{\left(h(1-f)+f\right)s}$$

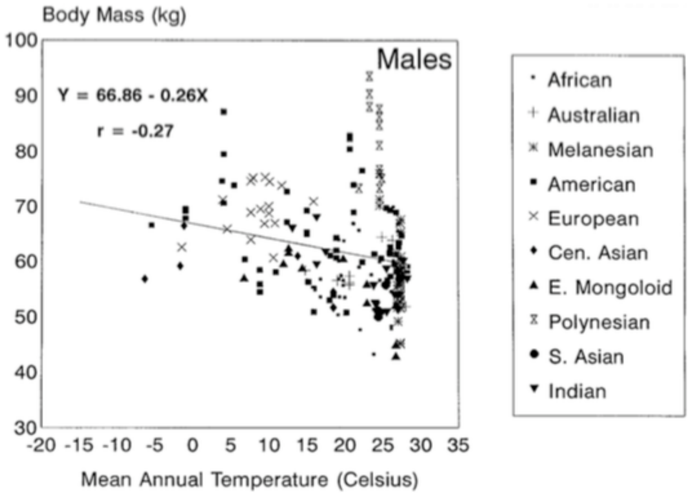


Data from various *Schiedea* species with different extent of inbreeding. From Charlesworth & Willis (2009) *Nat Rev Gen* (redrawn from Weller et al. 2005 *J Evol Bio*)

Spatially varying selection
and
migration–selection balance

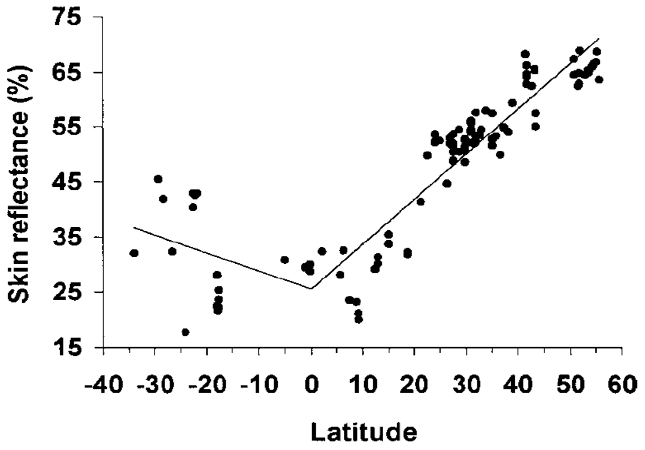
Clinal variation:
local adaptation on broad scales

Human body mass and mean annual temperature



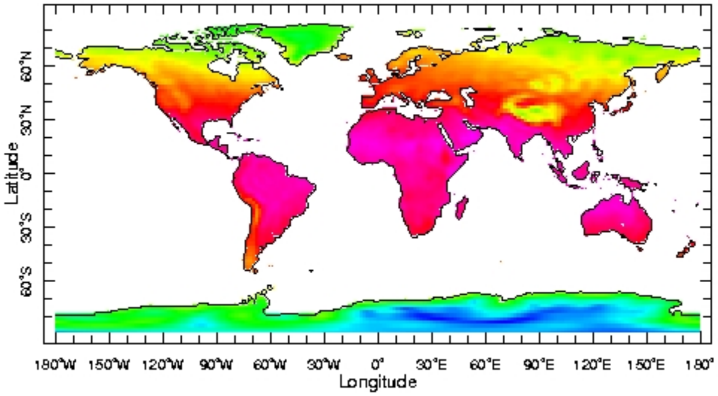
Katzmarzyk & Leonard (1998) *Am J Phys Anthropol*
previous study: Roberts (1953)

Skin reflectance and latitude

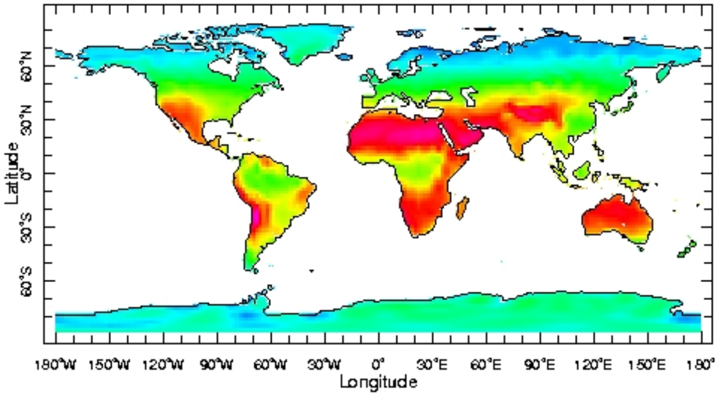


Relethford (1997) *Am J Phys Anthropol*

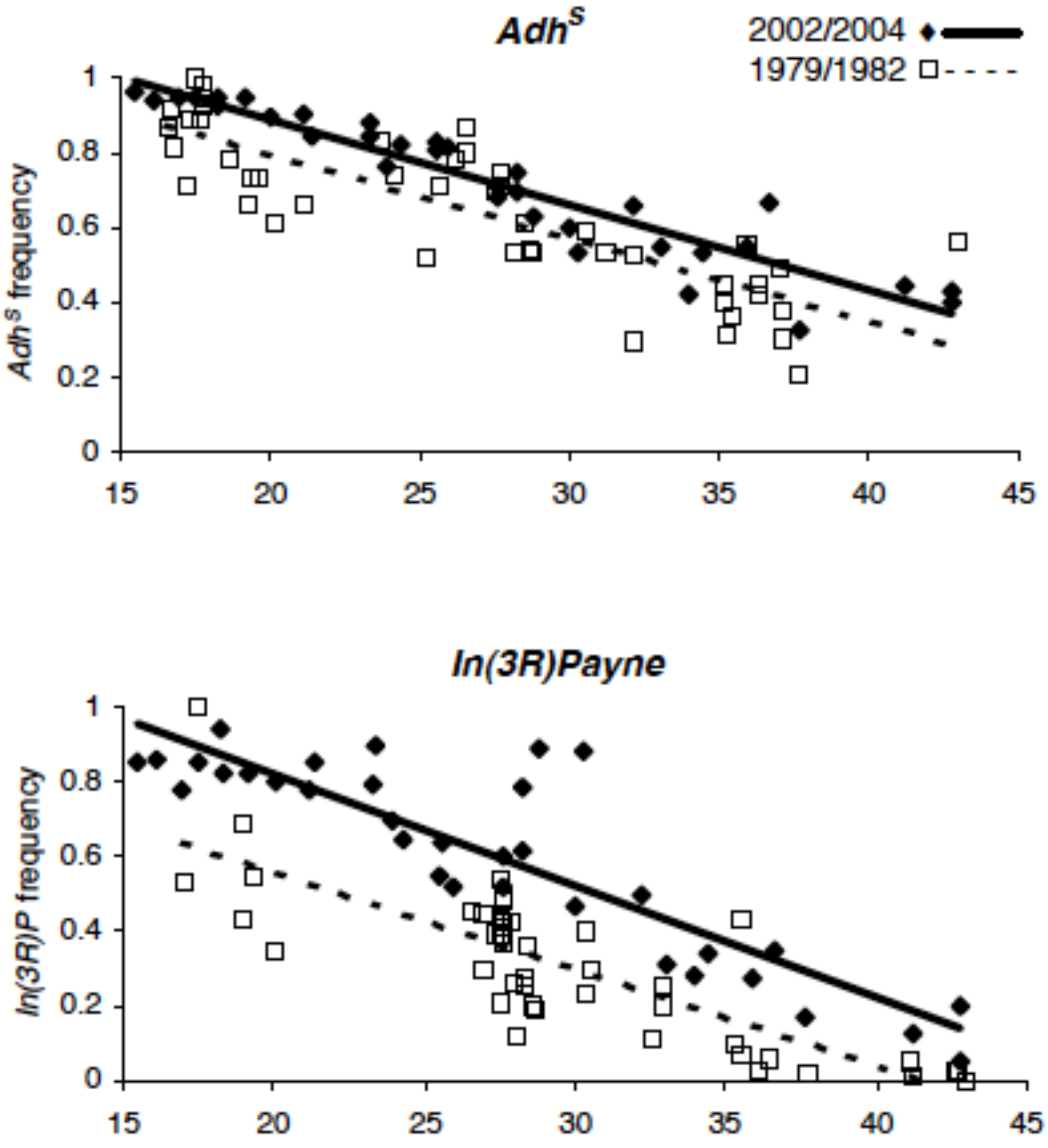
Mean temperature



Short-wave radiation



Clines in inversion frequencies in *Drosophila*



Latitude (degrees south)

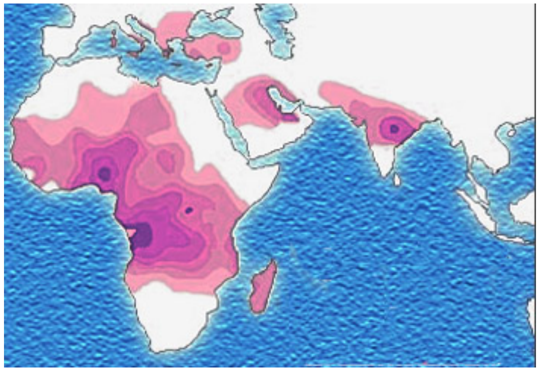
A Rapid Shift in a Classic Clinal Pattern in *Drosophila* Reflecting Climate Change

P. A. Umina,[1] A. R. Weeks,[2] M. R. Kearney,[2]
S. W. McKechnie,[1] A. A. Hoffmann[2]*

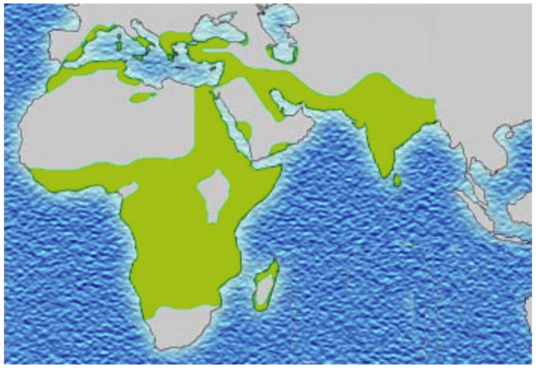
Geographical clines in genetic polymorphisms are widely used as evidence of climatic selection and are expected to shift with climate change. We show that the classic latitudinal cline in the alcohol dehydrogenase polymorphism of *Drosophila melanogaster* has shifted over 20 years in eastern coastal Australia. Southern high-latitude populations now have the genetic constitution of more northerly populations, equivalent to a shift of 4° in latitude. A similar shift was detected for a genetically independent inversion polymorphism, whereas two other linked polymorphisms exhibiting weaker clinal patterns have remained relatively stable. These genetic changes are likely to reflect increasingly warmer and drier conditions and may serve as sensitive biomarkers for climate change.

Allele-frequency clines

When selection pressures vary smoothly on a scale much greater than dispersal, and different alleles at the same locus are favoured in different environments, we observe clines in allele frequencies. These do not depend on migration.



Sickle allele distribution



Malaria distribution

Local adaptation can occur on very short geographic scales

- Mine tailing piles contain high concentrations of zinc, copper, lead, &/or arsenic that are toxic to intolerant plant genotypes.

- Old tailings in Great Britain are sparsely populated with two grass species:
  - *Agrostis tenuis*
  - *Anthoxanthum oderatum*.

RÖDVEN. AGROSTIS TENUIS SIBTH.

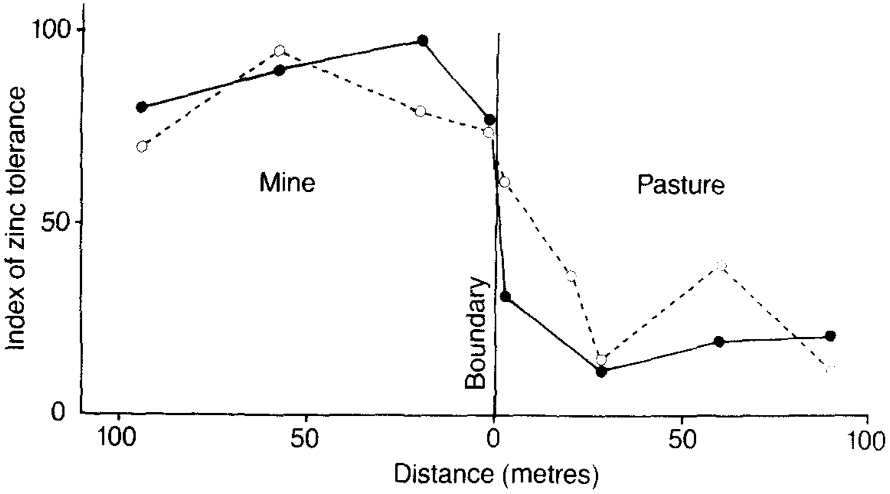
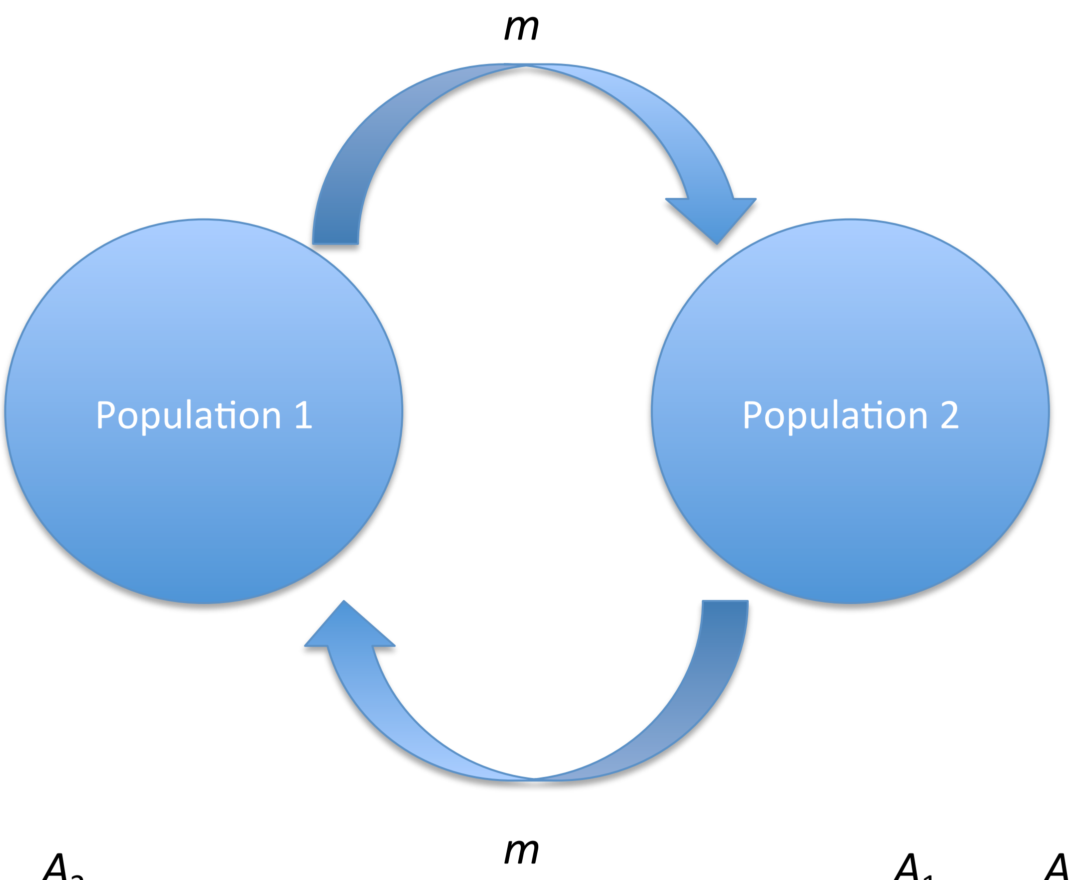


Fig. 2. The zinc tolerance of populations of *Anthoxanthum odoratum* (closed circles) and *Agrostis capillaris* (open circles) at the mine boundary at Trelogan, North Wales. All *A. capillaris* values have been multiplied by three. *Redrawn after Ref.* 10.

Macnair (1987) *TREE*

Modelling migration–selection balance

A simple haploid model



A_1	A_2
1	$1 - s$

A_1	A_2
$1 - s$	1

Example: Colour polymorphism in rock pocket mice (*Chaetodipus intermedius*) on and off black volcanic lava flows in southern Arizona (Hoekstra *et al.* 2004, *Evolution*)

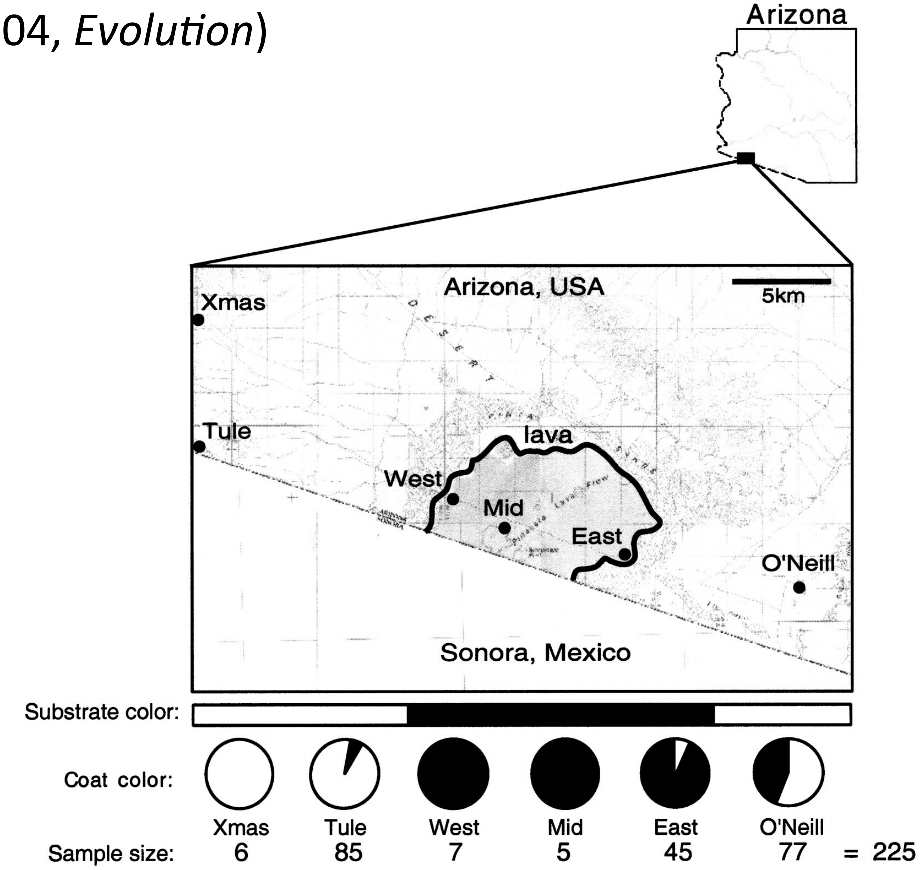
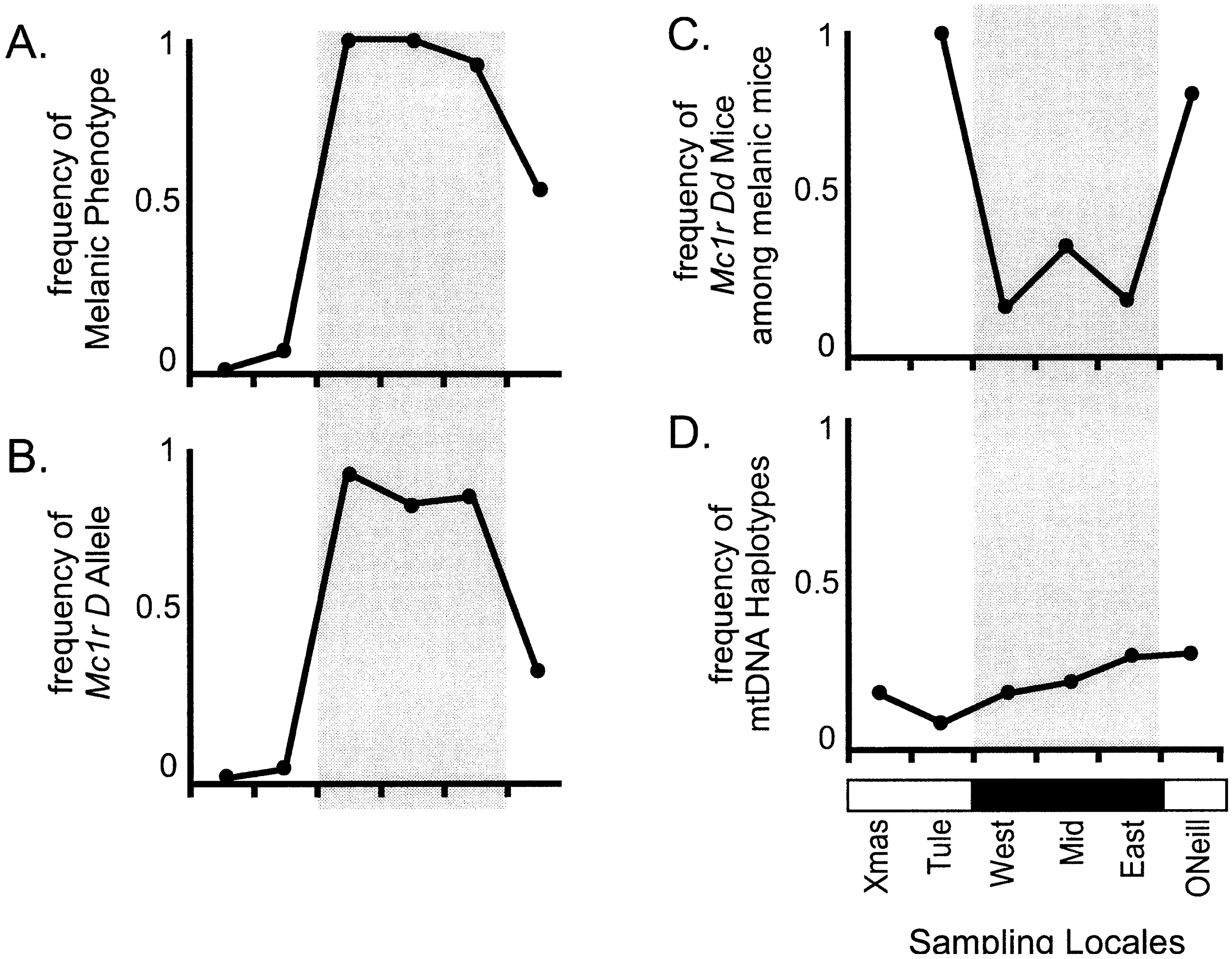


FIG. 1. Collecting sites, substrate color, and coat color frequencies on and neighboring the Pinacate lava flow in south central Arizona. Six sites were sampled: three on dark volcanic rock and three on light-colored substrate. The lava flow is surrounded by approximately 1 km of the Pinta Sands. Substrate color is indicated schematically below. Pie diagrams refer to the frequencies of light and melanic mice at each collecting site. Sample sizes are given.

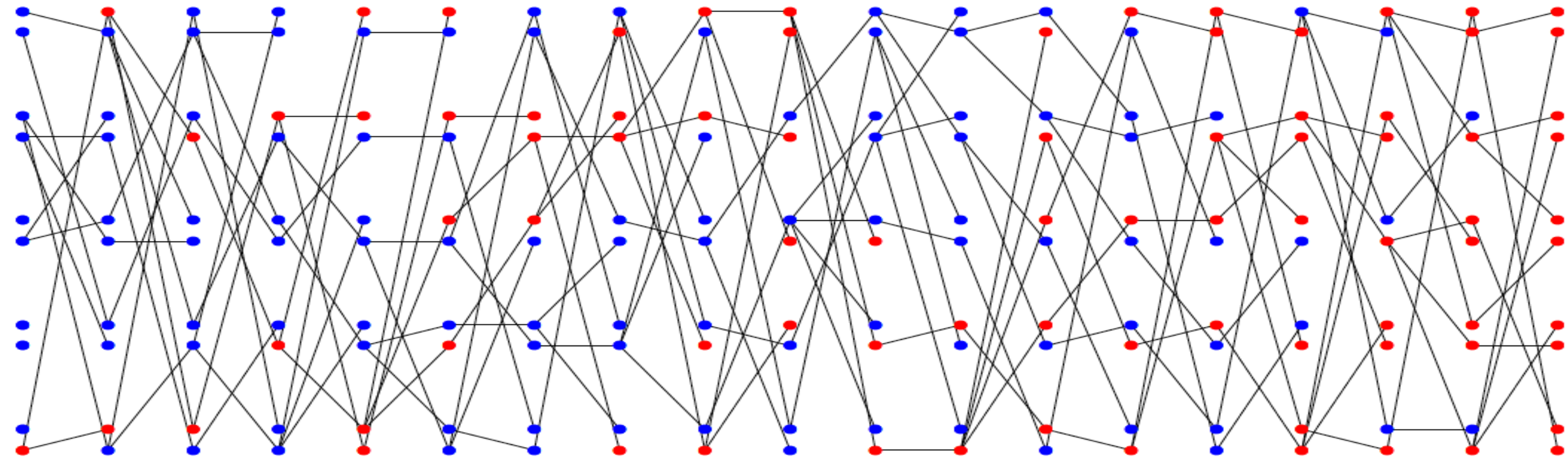
Here, dark colour is due to a change at the melanocortin-1 receptor (*Mc1r*) gene, and the agent of selection is most likely predation. The dark mutation is dominant.

Hoekstra et al. (2004) *Evolution*

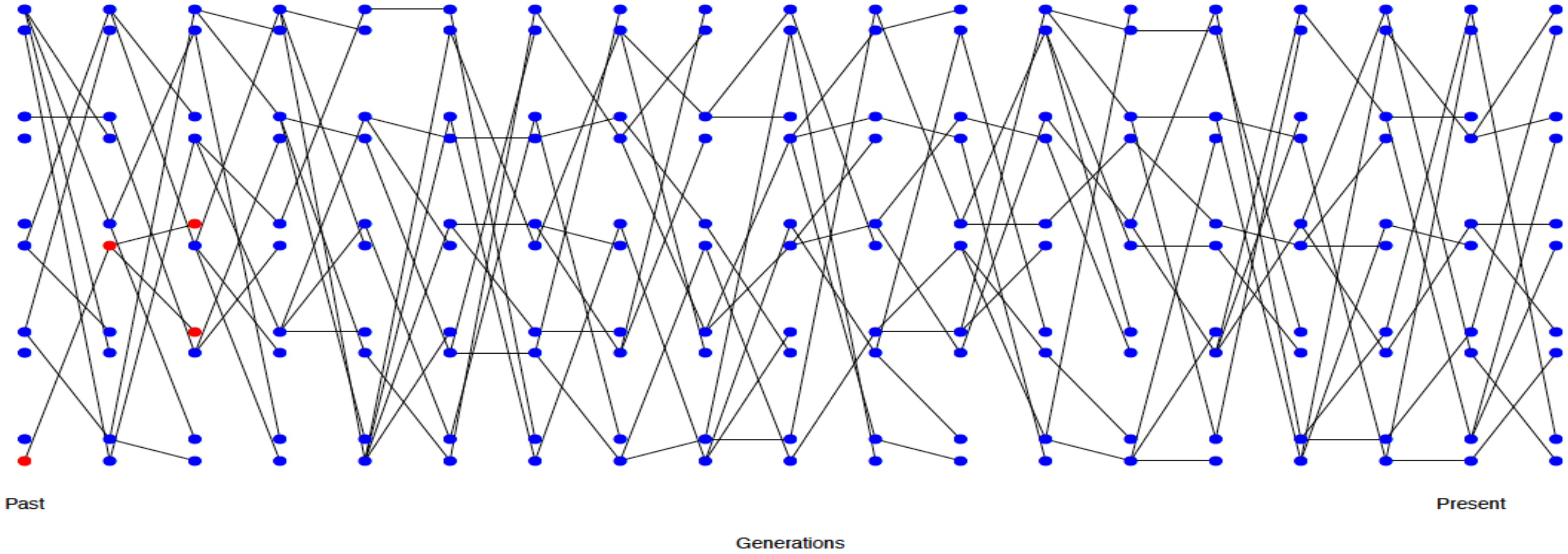


Tule Mountains $q_e = 0.029$

Selected mutation (e.g. from a G->T) spreads through population to become a substitution

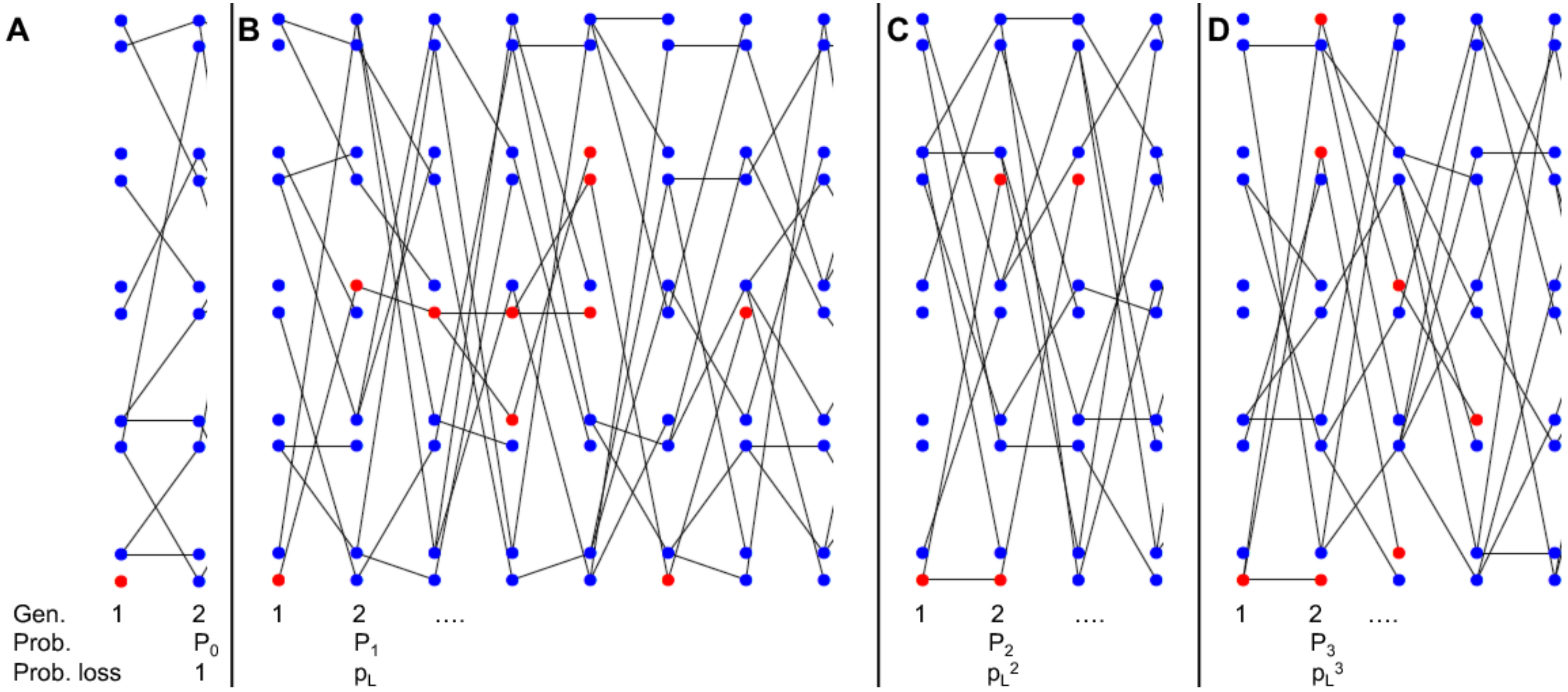


But even strongly beneficial mutations can be lost from the population when rare



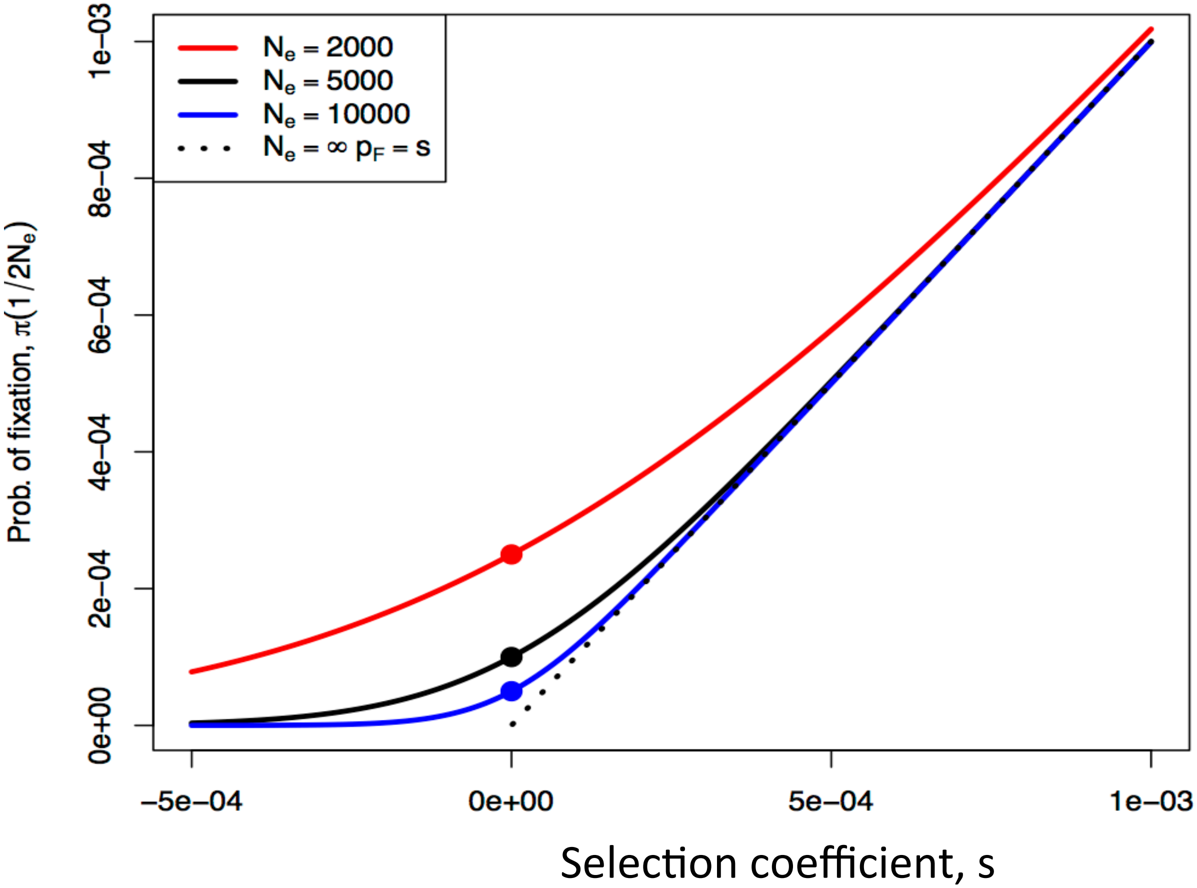
A selected allele which increases its bearer’s relative fitness by s has just been introduced by mutation

Strongly advantageous alleles $s \gg 1/(2N_e)$ have a probability s of fixing in population

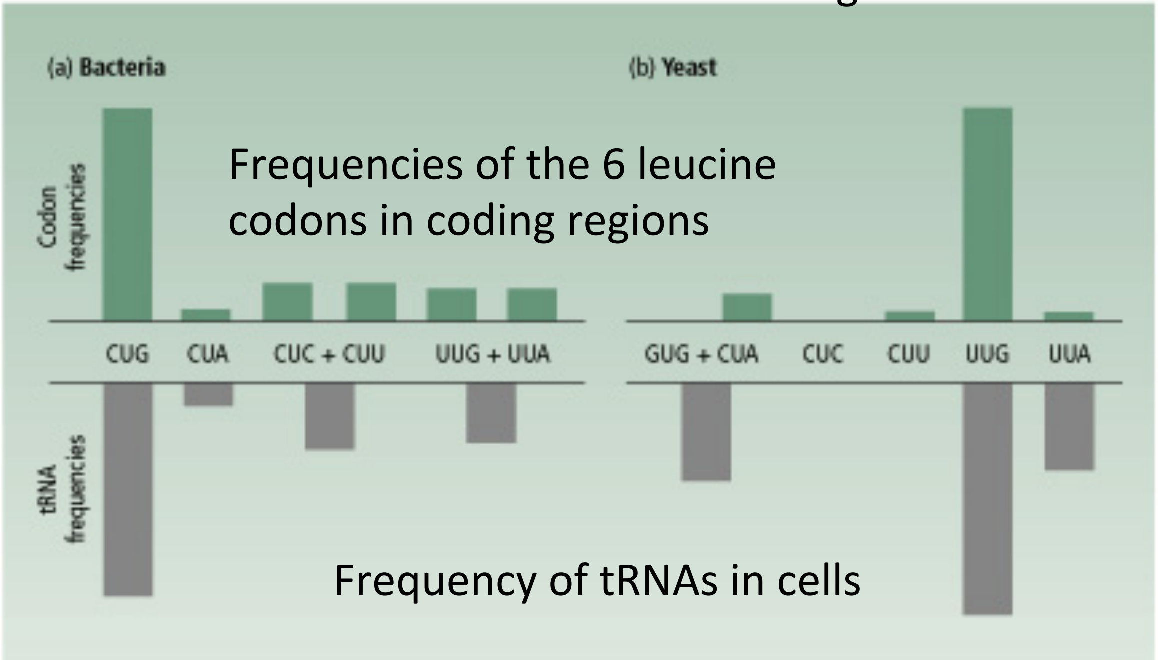


Chance (genetic drift) plays a role in the fate of all alleles.

- A selected allele which increases its bearer's relative fitness by s has just been introduced by mutation
- Strongly advantageous alleles $s>>1/(2N_e)$ have a probability s of fixing in population
- Very deleterious alleles $|s| >> 1/(2N_e)$ can never fix
- Alleles with $|s| < 1/(2N_e)$ are effectively neutral & have $1/(2N_e)$ fixing in population.

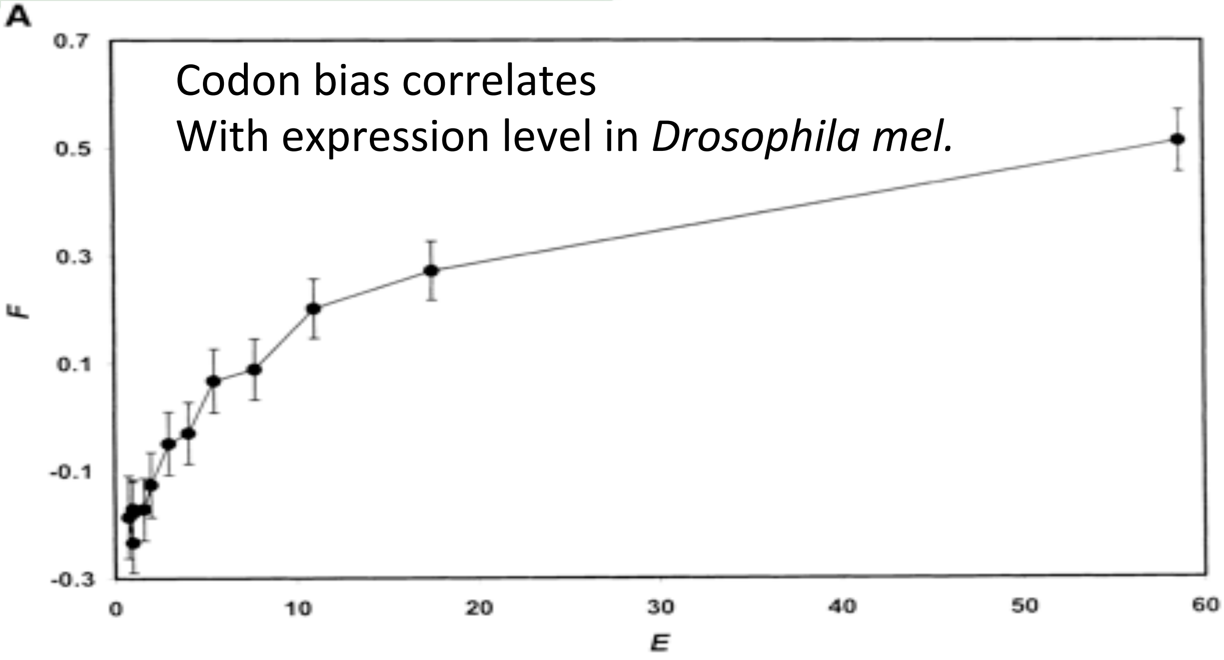


In large populations selection can act on very small fitness benefits
Codon-usage bias



Frequencies of the 6 leucine codons in coding regions

Frequency of tRNAs in cells



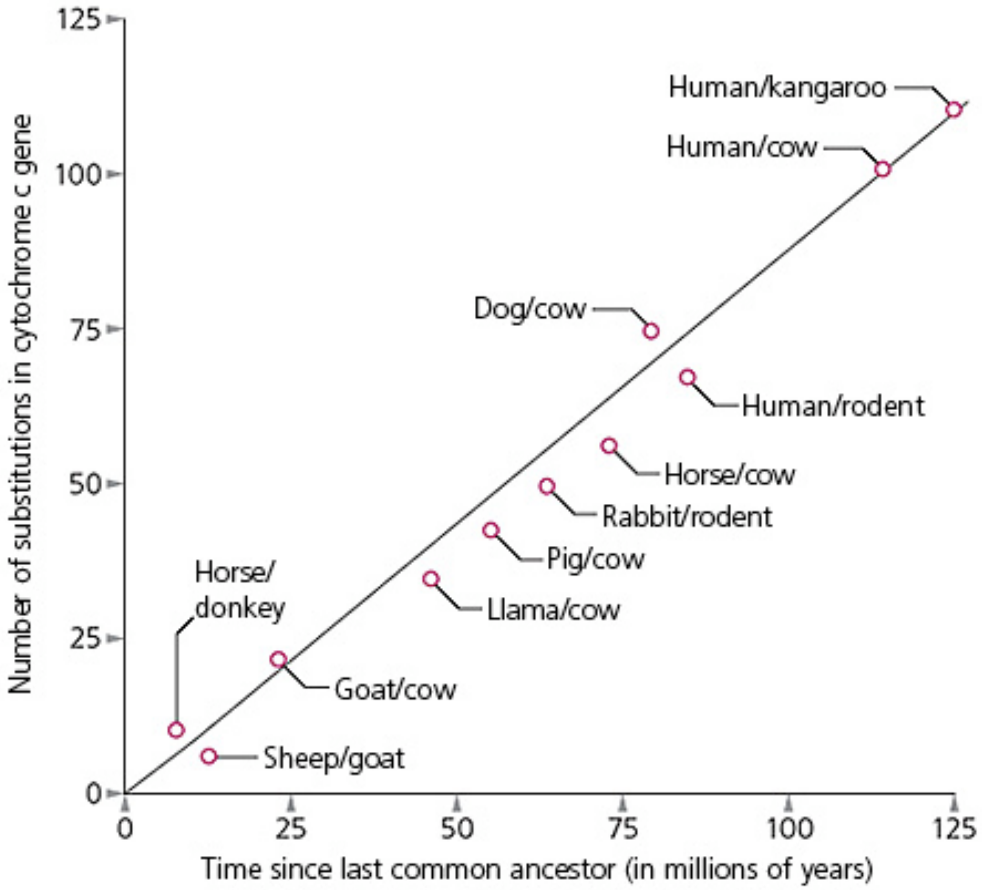
Codon bias correlates
With expression level in *Drosophila mel.*

This effect is not strongly seen in vertebrates

The Molecular Clock

Observation: Rate of **amino acid** substitution in many, but not all, proteins surprisingly constant over time, i.e. evolve in a clock-like manner.

- Neutral theory Claim: Due to most amino acid replacement substitutions between species being neutral

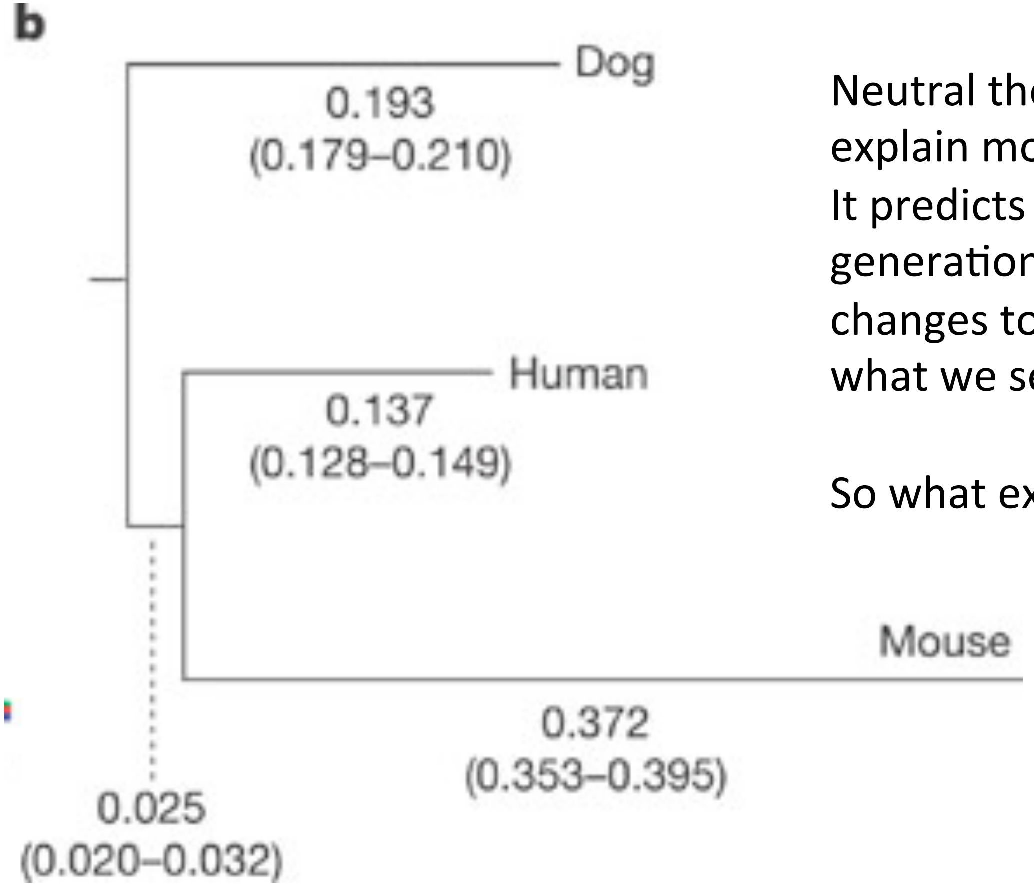


From fossil record

Zimmer book

Generation time effect

Strong generation time effect seen for least constrained sites.
i.e. the changes most likely to be neutral, do not show a molecular clock in years
Non-syn. substitutions show much less of a generation time effect.



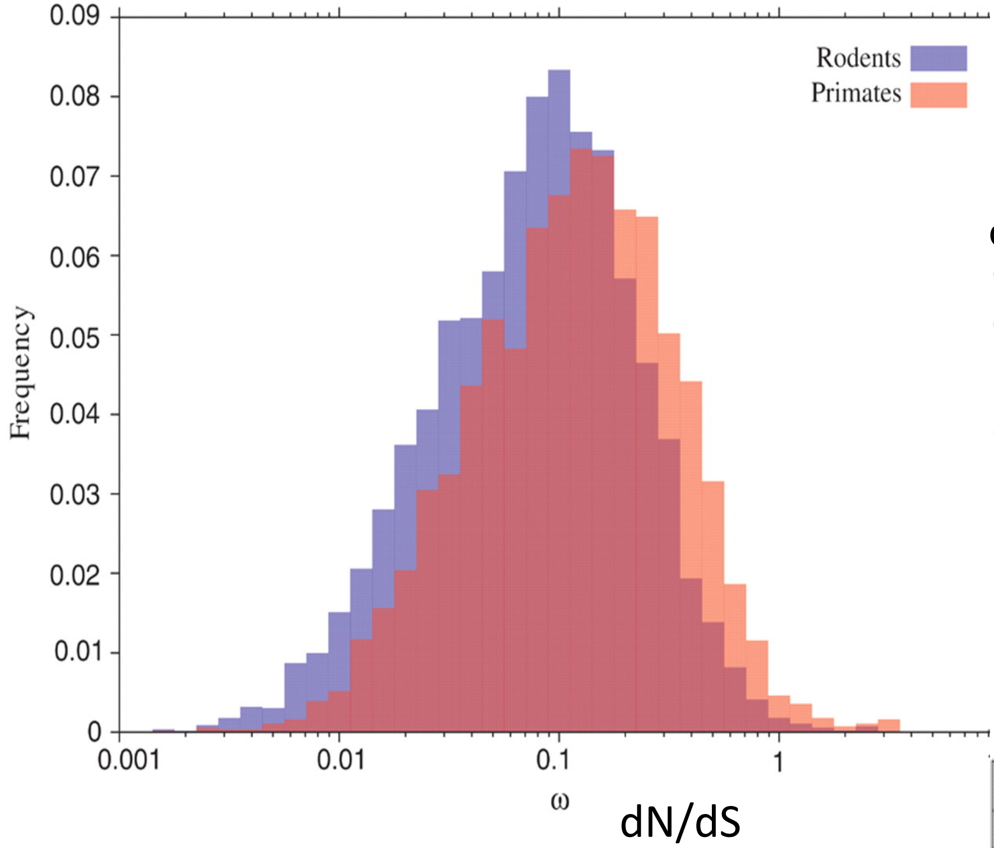
Neutral theory of molecular evolution can not explain molecular clock measured in years.
It predicts a molecular clock measured in generations, which is exactly what we see for changes to synonymous/non-coding sites but not what we see for changes to the protein.

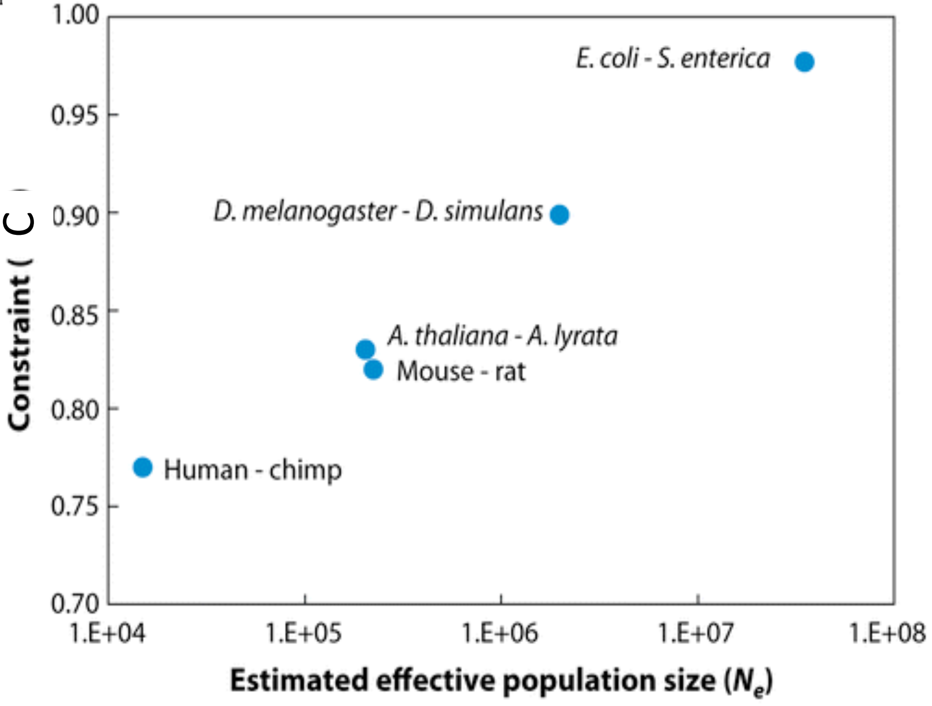
So what explains the protein molecular clock?

Phylogram from Dog genome paper (Nature 2005)
Using mostly non-coding sequence data

Nearly Neutral theory proposed by Ohta
Perhaps much of molecular evolution
due to substitutions with selection coefficients |s| ~$1/(2N_e)$
Much to commend this idea, including fact that it may explain the protein molecular clock.

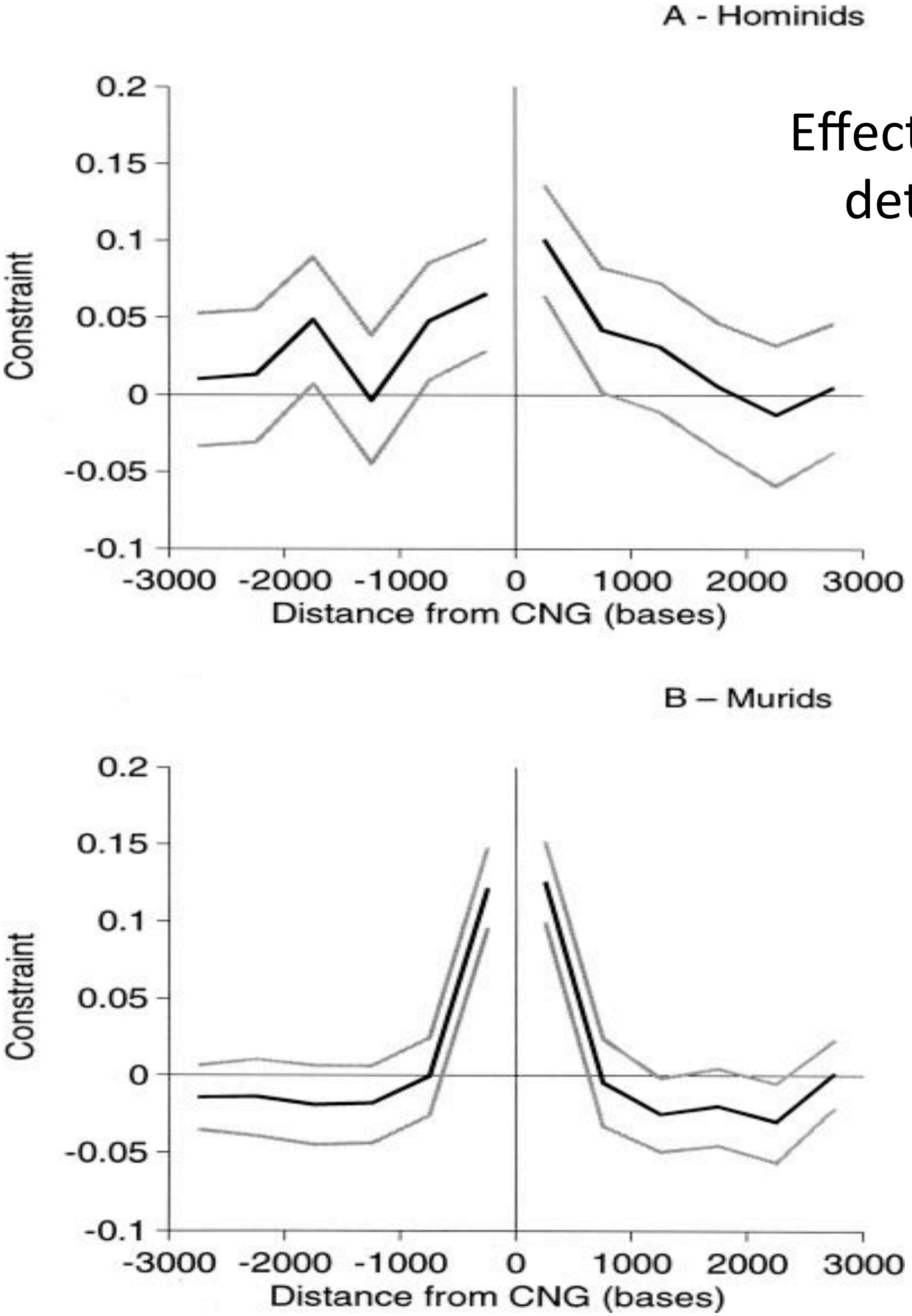
Effective Population size potentially determines levels of constraint





Wright SI, Andolfatto P. 2008.
Annu. Rev. Ecol. Evol. Syst. 39:193–213

Effective Population size potentially determines levels of constraint



Hominids show weaker conservation of
CNG (Conserved non-genic)
than rodents.

Keightley et al 2005

Current status of views on molecular evolution

Most* of the substitutions/polymorphism in non-coding DNA & synonymous changes in organisms with large genomes are likely neutral, as are a reasonable fraction of non-synonymous changes.

Weakly deleterious alleles likely make a significant contribution to substitution rates in species (such as our own) with small effective population sizes.

There is increasing evidence that a reasonable fraction (>10%) of non-synonymous changes are driven by selection in species with large effective population sizes. But the selection coefficients may be very small ~ $1/(2N_e)$. We have no clue what most of these do!

* --but not all