CSMU

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*"It is altogether unlikely that two genes would have identical selective values under all the conditions under which they may coexist in a population. … cases of neutral polymorphism do not exist … it appears probable that random fixation is of negligible evolutionary importance"*

-Ernst Mayr

**Neo-Darwinism**

1930's:

—no way to test the predictions of different schools

—arguments centered on mathematical models

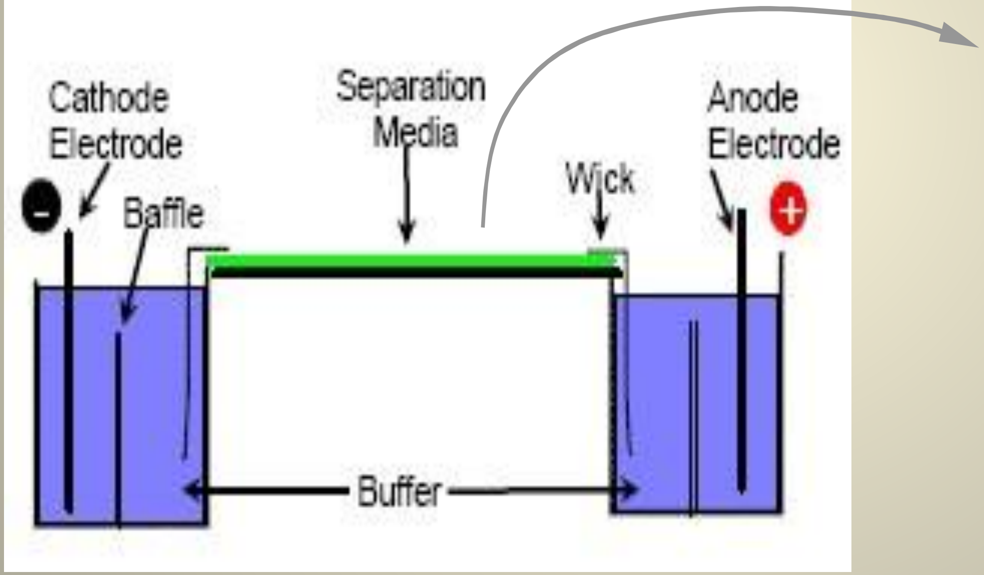
1950's and 1960's:

—protein sequencing (slow and painful)

—protein gel electrophoresis (fast and cheap

# Protein electrophoresis: big changes in the 1960's

A) Diagram of a protein gel electrophoresis apparatus, and (B) a photograph of a "stained" protein gel, the blue "blotches" are the proteins, their position indicates how far they migrated in the electric field.



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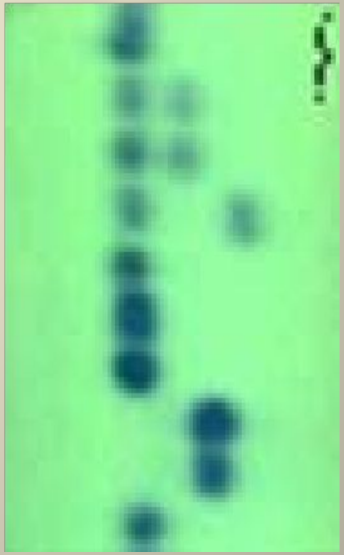

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# Protein electrophoresis: the results are in …

**Lewontin and Hubby (1966):**

- 5 natural populations of Drosophila
- 18 loci
- 30% of loci (27 over the 5 popn.s) were polymorphic
- Fruitfly heterozygosity: 11%

**Harris (1966):**

- Humans
- 71 loci
- 28% (20) were polymorphic
- Human heterozygosity: 7% (2-53%)

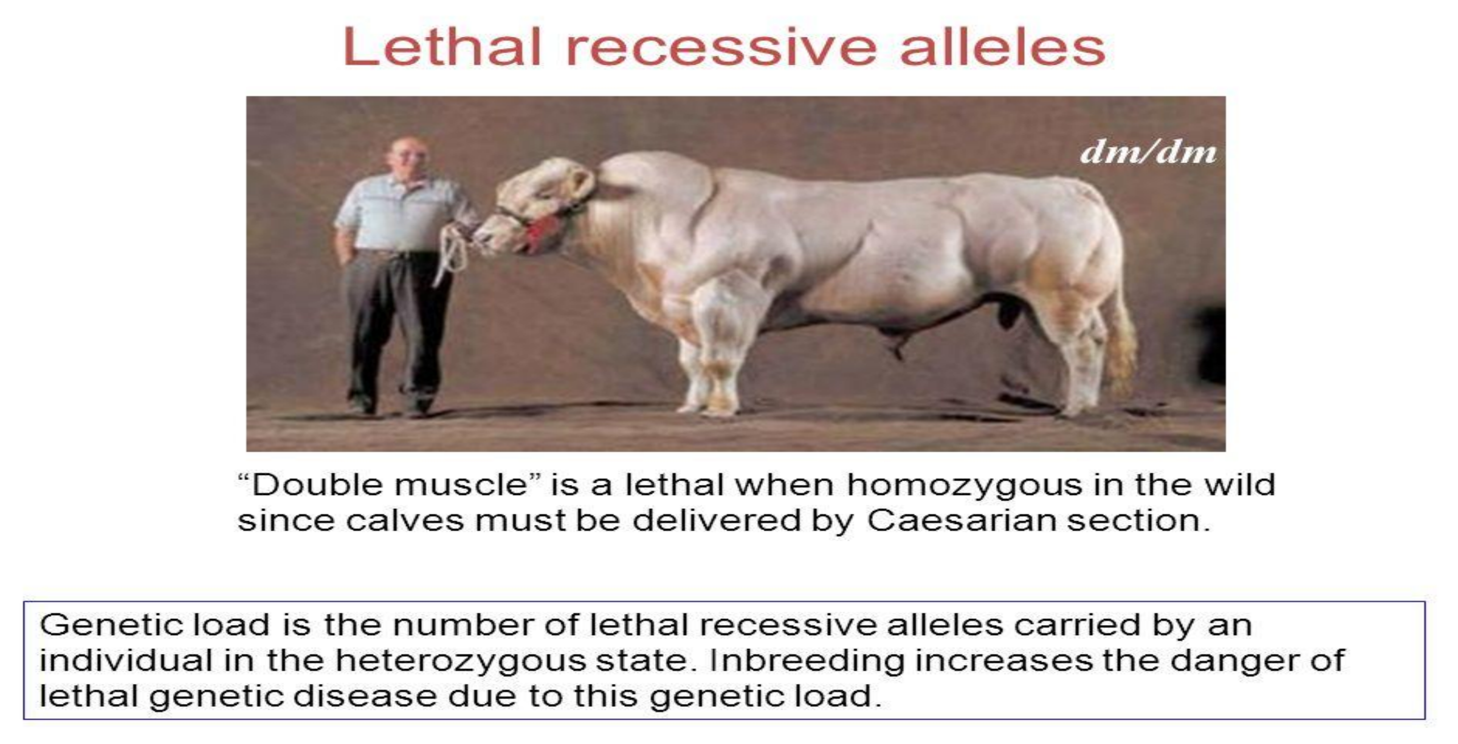
*Balance school: predictions correct !*

*Classical school: predictions wrong (But, what about load!)*

*Lewontin and Hubby (1966) suggested that some of the polymorphism must be neutral*

# Genetic load

- Genetic load: the extent to which the fitness of an individual is below the optimum for the population as a whole due to the deleterious alleles that the individual carries in its genome.



## Lethal recessive alleles

"Double muscle" is a lethal when homozygous in the wild since calves must be delivered by Caesarian section.

Genetic load is the number of lethal recessive alleles carried by an individual in the heterozygous state. Inbreeding increases the danger of lethal genetic disease due to this genetic load.

Genetic load

- Selection can cause the death of some individuals or make them unable to reproduce
- This cost is called a genetic load

Belgian Blue cattle

- Genetic load: the difference between the average fitness of the population and the fitness of the best genotype. It measures the probability of selective death of an individual in a population.
- *W* = average fitness
- Genetic load (L) = 1 - *W*

# Genetic load an Example…

Selective death (or genetic death): the chance that an individual will die without reproducing as a consequence of natural selection. [*e.g.,15% of offspring in above*]

**Two alleles (*A* and a) with frequencies *p* = *q* = 0.5:**

**Survival to reproduce:**
**AA = 40% Aa = 50% aa = 30%**

**The relative fitness values are:**
**AA = 0.8 Aa = 1 aa = 0.6**

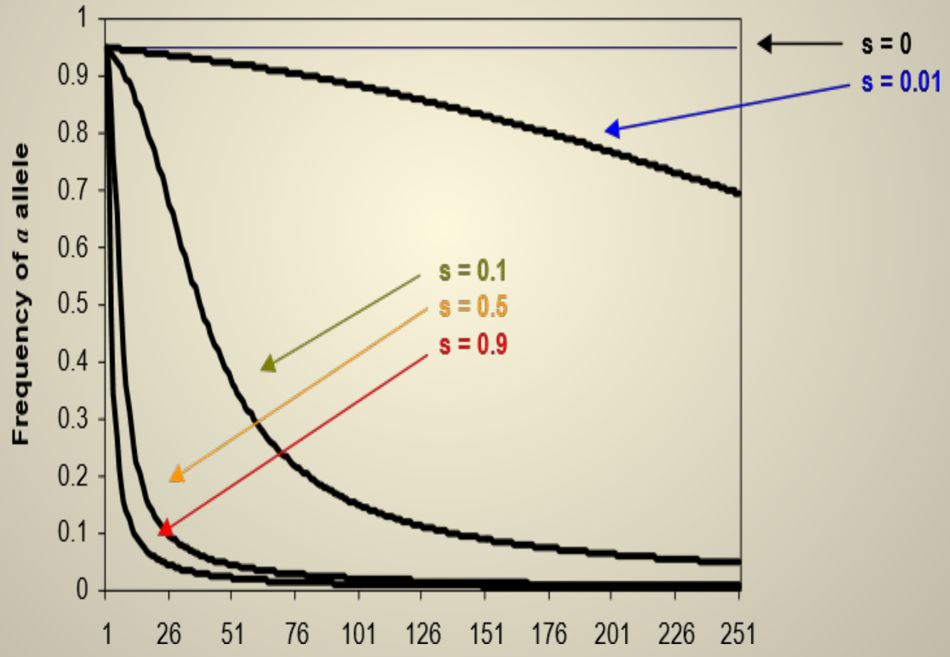
**The mean fitness of the population = 0.25(0.8) + 0.5(1) + 0.25(0.6) = 0.85**

**The load of this population (L) = 1 – 0.85 = 0.15**

***[Note that if every member of the population had the same genotype the average fitnes would equal 1 and the load on the population would be zero.]***

Genetic load has implications for the long term fate of a population.

Haldane: the total load tolerated by a population is bounded by its excess reproductive capacity.



There is a cost to selection, in genetic death, during this time period

# Genetic load : Sources

1. Mutational load
2. Substitutional load [Haldane’s load]
3. Segregational load

# Genetic load : Mutation

**Let’s assume: (i) new mutations are deleterious alleles, and (ii) recessive.**

**Remember the approximation of the equilibrium frequency of deleterious alleles [See population genetics, Topic 5 for a review]:**

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

**Remember that population load is:**

$$L = 1 - W$$

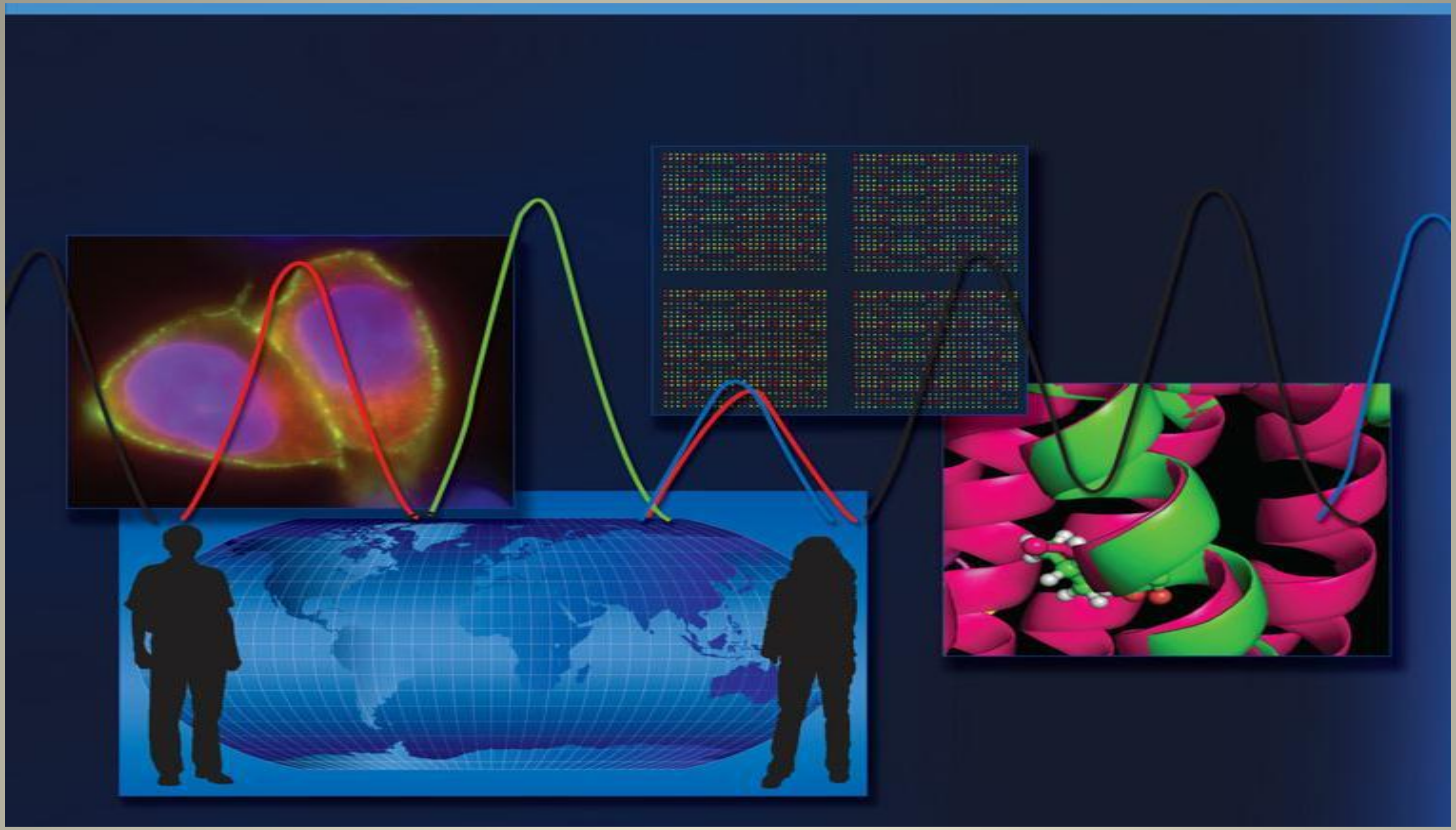
**And remember that the average fitness under these assumptions was:**

$$W = 1 – sq^2$$

**We can make substitutions:**

$$L = 1 - {}^{W}$$
$$L = 1 – (1 – sq^2)$$
$$L = 1 – (1 – s(\mu/s))$$
$$L = 1 – (1 – \mu)$$
$$L = \mu$$

**It is interesting that we estimate that the load is equal to the mutation rate. Because it suggests that the load is approximately independent of the reduction in fitness caused by the mutant (*s*).**



- Mutational load is minor:
- Equilibrium yields a polymorphism involving an allele that is very rare in the population
- The load is trivial for the population, as the required excess reproductive capacity is not large

# Defining Directional Section

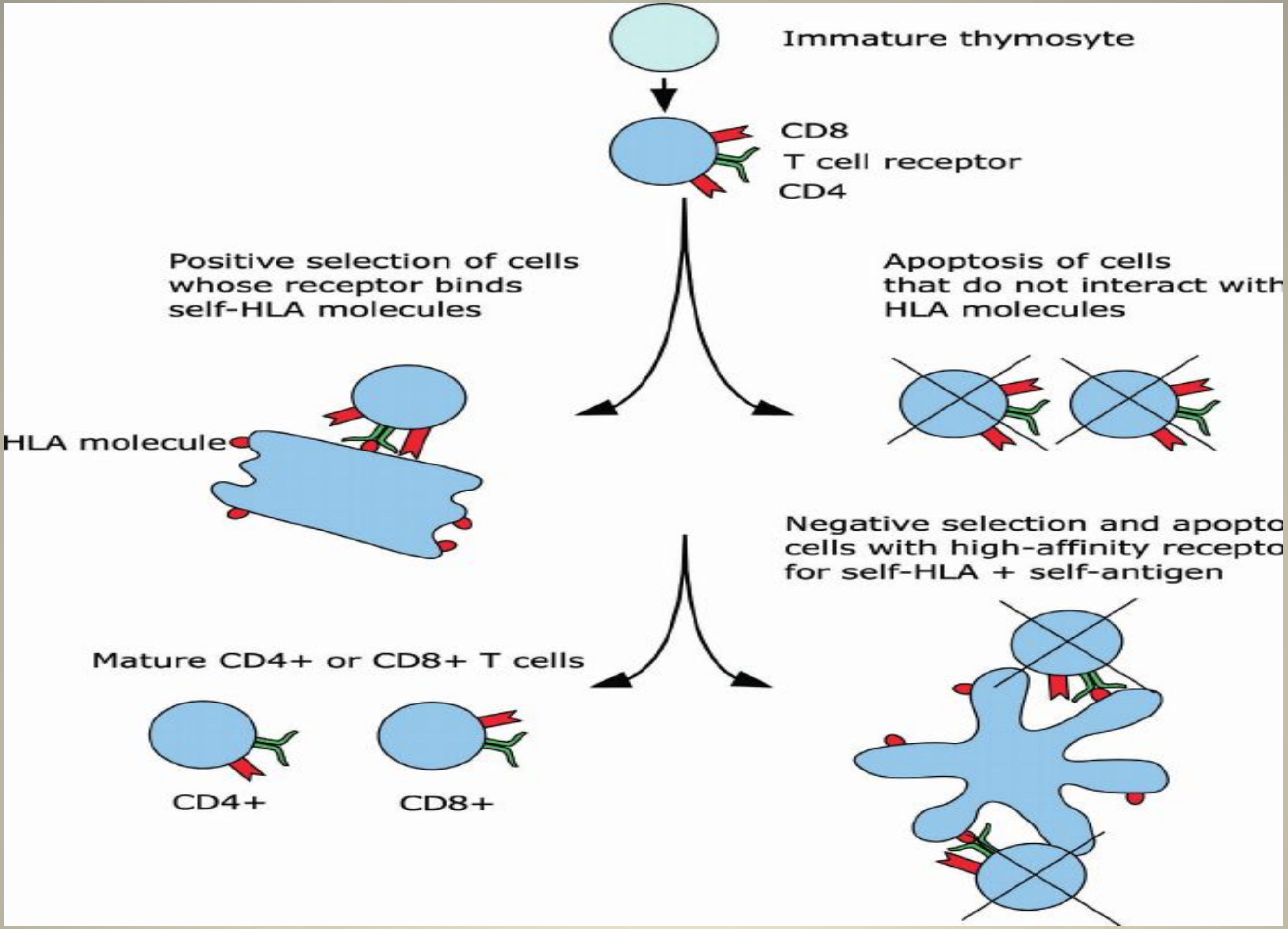
- Directional selection: selection that favours the phenotype at an extreme of the range of phenotypes

- Directional selection: can be subdivided into two broad categories. These subtypes have been given different names, leading to a possible point of confusion. The next page is an attempt to clarify this issue

# Defining two types directional selection

**Type 1:**

Positive Darwinian selection: directional selection for *fixation* of a **new** and beneficial mutation in a population.



**Positive selection:** Same as above. [*Note that the above term is also shortened to "Darwinian selection"; this is a bad habit of which I am very guilty*.

## Type 2:

Negative Darwinian selection: directional selection for *removal* of a **new** and deleterious mutation from a population.

Negative selection: same as “negative Darwinian selection”.

Purifying election: same as negative selection.

# Genetic load: segregational

- Segregational load is a big problem for the balance school:

| **The model** | | | |
|---|---|---|---|
| Genotype | AA | Aa | aa |
| Frequency | $p_0 2$ | $2p0q0$ | $q_0 2$ |
| $w$ | $1 - s_1$ | 1 | $1 - s_2$ |

*Well known examples exist; Haemoglobin, MHC locus, etc.*
*Balance school would extend this to most polymorphic loci in the genome.*
*Let’s see if this will work*

Humans:

30% of loci are polymorphic (from Harris 1966)

30,000 genes (from recent genome projects), so 9000 are polymorphic

Let’s assume a very small load on average: L = 0.001

Let’s assume that only half are under balancing selection (4500) [remember the balance school predicted a majority would be under balancing selection]

Fitness of an individual locus = 0.999

Fitness over whole genome = $0.999^{4500} = 0.011$

Load = 1- 0.011 = 0.989 [That is huge!!!]

Cost = 0.989/0.011 = 89  [Do you know of any humans with families that big?

# Genetic Load: Other

1. Recombinational Load
2. Incompatibility Load
3. Lag Load

***Note: all load arguments tend to be based on overly-simplistic models.***

# Neutral Theory of Molecular Evolution

**Motoo Kimura**:
troubled by cost Haldane's dilemma:
1 substitution every 300 generations
troubled by Zukerkandl and Pauling's (1965) molecular clock:
1 substitution every 2 years
Published a model of neutral evolution in 1968

Jack King and Thomas Jukes:
Independently arrived at same conclusion as Kimura
Published (1969) under the provocative title "Non-Darwinian evolution"

**I cannot over emphasize how radical this idea was at that time.**

# THANK YOU