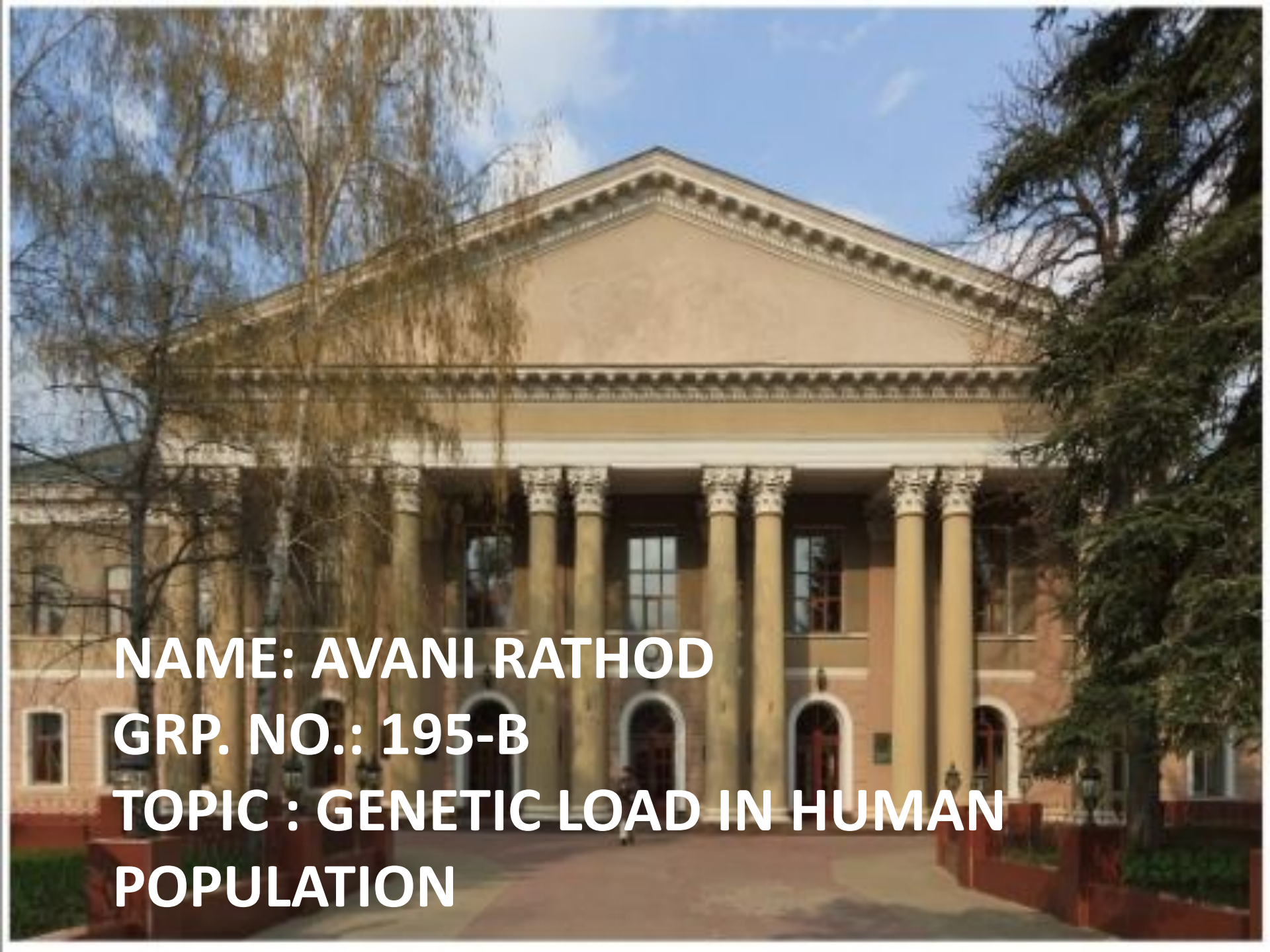

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TOPIC : GENETIC LOAD IN HUMAN POPULATION

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.**
- Genetic load : The average number of lethal mutations per individual in a population. Such mutations result in the premature death of the organisms carrying them.

- 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 (***L***) is defined as the reduction in the mean fitness of a population relative to a population composed entirely of individuals having the maximal fitness.

$$L = \frac{w_{\max} \quad \bar{w}}{w_{\max}}$$

mean fitness of the actual population

fitness of the fittest possible genotype (given the alleles in the population)

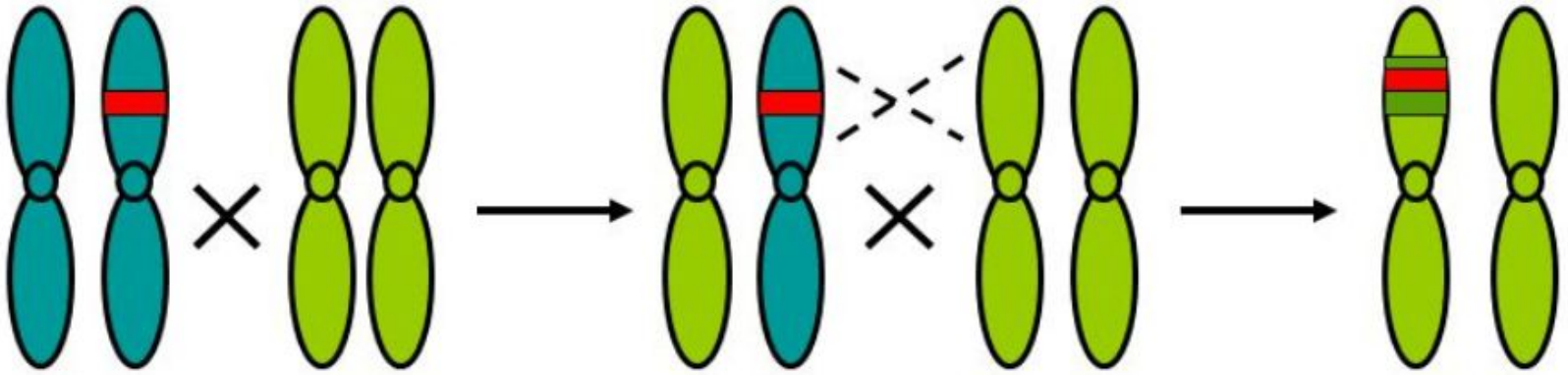
Types of Genetic Load

- Three main kinds of genetic load may be recognized:
- **A.Input Load:** in which inferior alleles are introduced into the gene pool of a population either by mutation or immigration;
- **B. Balanced Load:** which is created by selection favouring allelic or genetic combinations that, by segregation and recombination, form inferior genotypes every generation; and

- **C. Substitutional Load:** Which is generated by selection favouring the replacement of an existing allele by a new allele.
- Originally called the **'cost of natural selection' b**y the geneticist J. B. S. Haldane, substitutional load is the genetic load associated with transient polymorphism.
- The term 'genetic load' was originally coined by **H. J. Muller** in 1950

Genetic Load

- Negative effects of genetic load may hinder a hybrid's ability to compete and survive
- Negative epistatic effects of genetic load could trump any fitness benefits conferred by a fitness enhancing transgene



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.]*

Causes of Genetic Load

- 1.Deleterious mutation
- 2.Beneficial mutation
- 3.Inbreeding
- 4.Recombination/segregation load

DELETERIOUS MUTATIONS

- Deleterious mutation load is the main contributing factor to genetic load overall.
- Most mutations are neutral or slightly deleterious, and occur at a constant rate.
- The Haldane-Muller theorem of mutation–selection balance says that the load depends only on the deleterious mutation rate and not on the selection coefficient.
- Specifically, relative to an ideal genotype of fitness 1, the mean population fitness is exp(-U) where U is the total deleterious mutation rate summed over many independent sites.

- High load can lead to a small population size, which in turn increases the accumulation of mutation load, culminating in extinction via mutational meltdown.
- The accumulation of deleterious mutations in humans has been of concern to many geneticists, including Hermann Joseph Muller, James F. Crow, Alexey Kondrashov,W. D. Hamilton,and Michael Lynch.

Beneficial mutation

- New beneficial mutations create fitter genotypes than those previously present in the population.
- When load is calculated as the difference between the fittest genotype present and the average, this creates a substitutional load.
- The difference between the theoretical maximum (which may not actually be present) and the average is known as the "lag load.

- Motoo Kimura's original argument for the neutral theory of molecular evolution was that if most differences between species were adaptive, this would exceed the speed limit to adaptation set by the substitutional load.
- However, Kimura's argument confused the lag load with the substitutional load, using the former when it is the latter that in fact sets the maximal rate of evolution by natural selection.
- More recent "travelling wave" models of rapid adaptation derive a term called the "lead" that is equivalent to the substitutional load, and find that it is a critical determinant of the rate of adaptive evolution.

"IF WE DIDN'T HAVE GENETIC MUTATIONS, WE WOULDN'T HAVE US. YOU NEED ERROR TO OPEN THE DOOR TO THE ADJACENT POSSIBLE."

STEVEN JOHNSON

Inbreeding

- Inbreeding increases homozygosity.
- In the short run, an increase in inbreeding increases the probability with which offspring get two copies of a recessive deleterious alleles, lowering fitnesses via inbreeding depression.
- In a species that habitually inbreeds, e.g. through self-fertilization, recessive deleterious alleles are purged.

Recombination/segregation load

- Combinations of alleles that have evolved to work well together may not work when recombined with a different suite of coevolved alleles, leading to outbreeding depression.
- Segregation load is the presence of underdominant heterozygotes (i.e. heterozygotes that are less fit than either homozygote).

- Recombination load arises through unfavorable combinations across multiple loci that appear when favorable linkage disequilibria are broken down.

- Recombination load can also arise by combining deleterious alleles subject to synergistic epistasis, i.e. whose damage in combination is greater than that predicted from considering them in isolation.

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).

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	$1 - s_2$

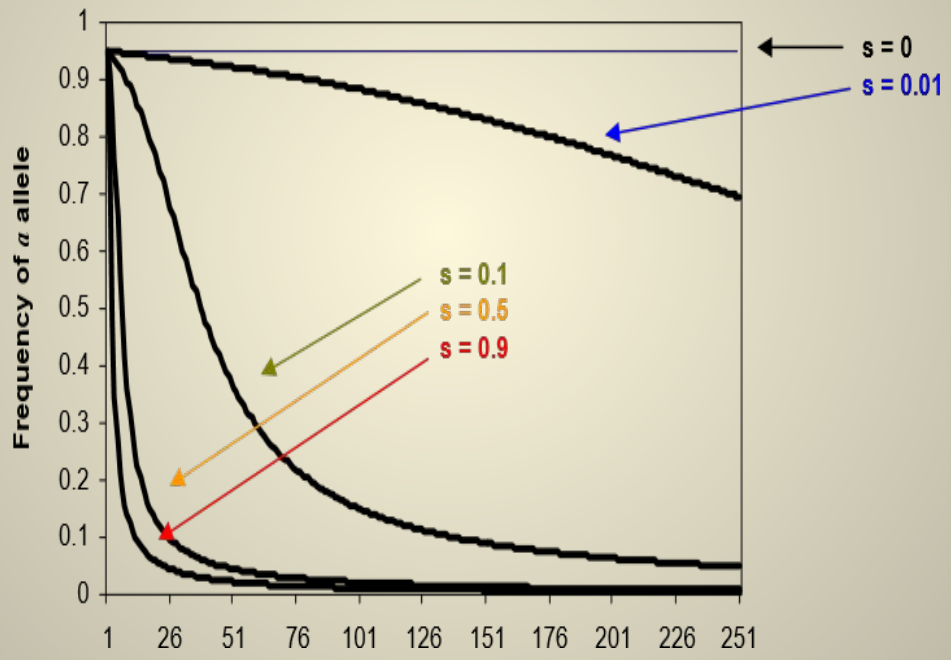
Well known examples exist; Haemoglobin, MHC locus, etc.

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

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

Migration load

- Migration load is the result of nonnative organisms that aren’t adapted to a particular environment coming into that environment.
- If they breed with individuals who are adapted to that environment, their offspring will not be as fit as they would have been if both of their parents had been adapted to that particular environment.

"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

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.

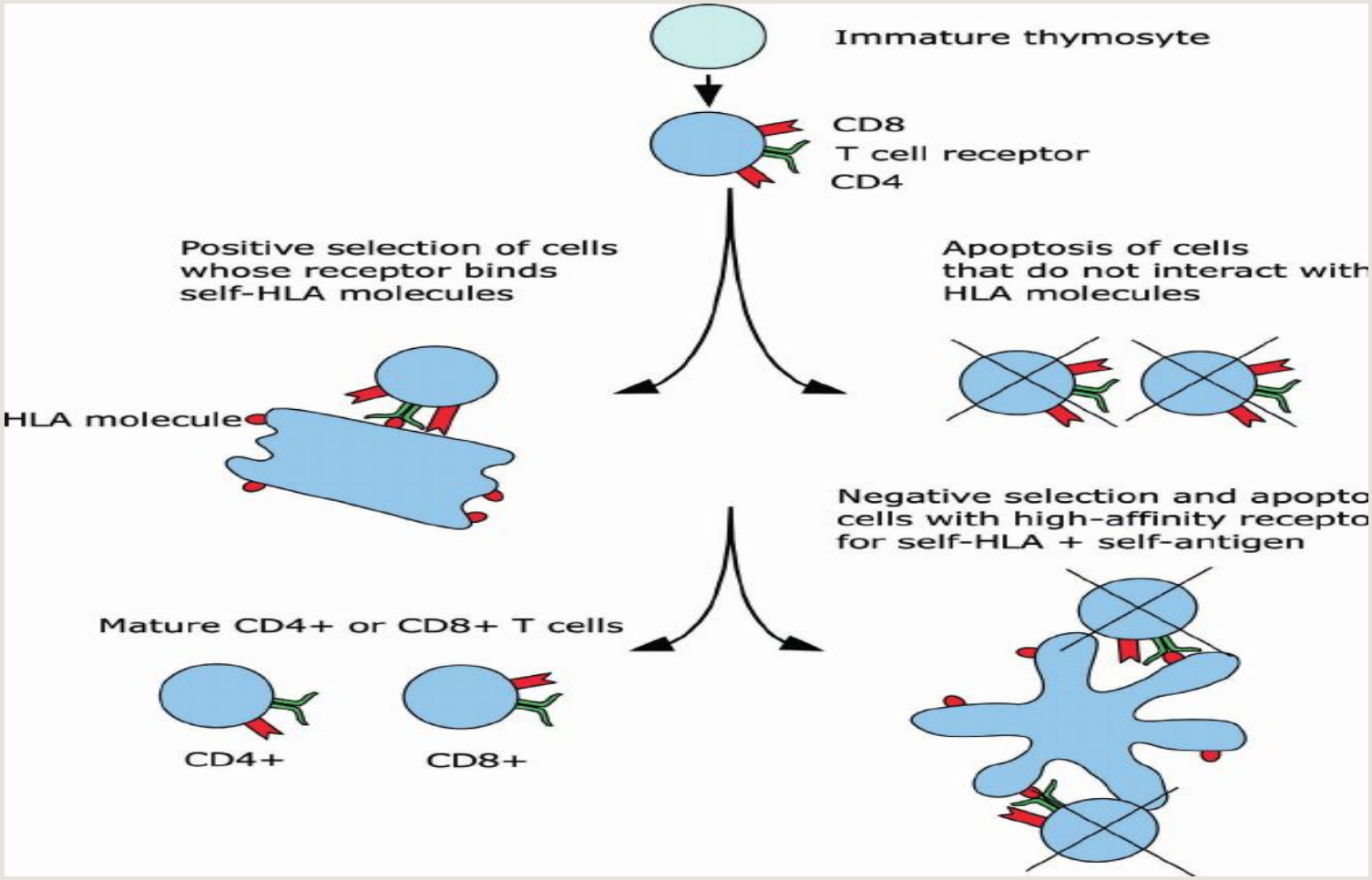
1. Positive Darwinian selection
2. Negative Darwinian selection

Defining two types directional selection

Type 1:

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

<u>Positive selection</u>: Same as above. [*Note that the above term is also shortened to "Darwinian selection".*



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.

Genes load the gun
but environment
pulls the trigger.
~Bruce Lipton

Epigenetic Labs


G
engin E ering
DNA
cur E s
trea T ments
I nformation
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THANK YOU