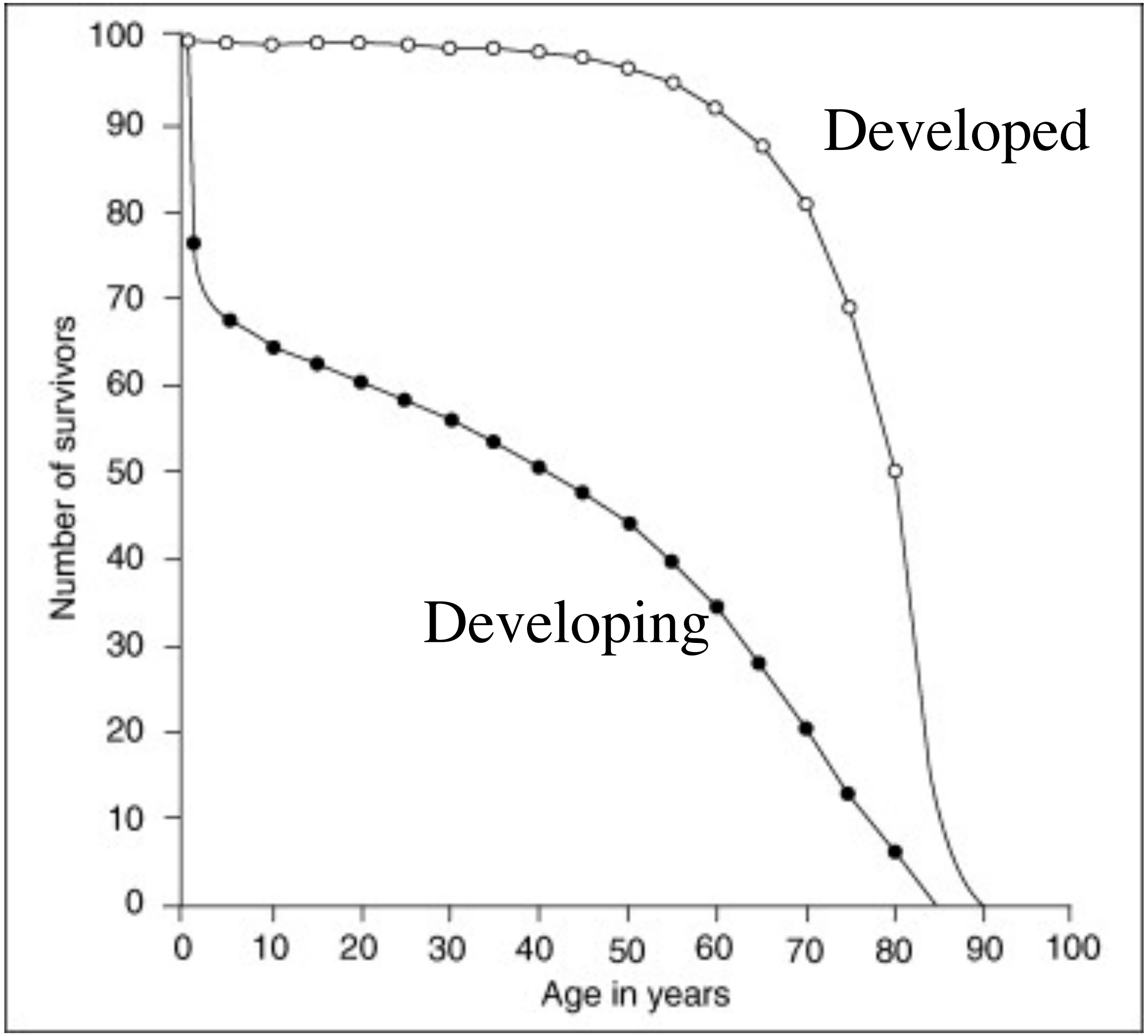
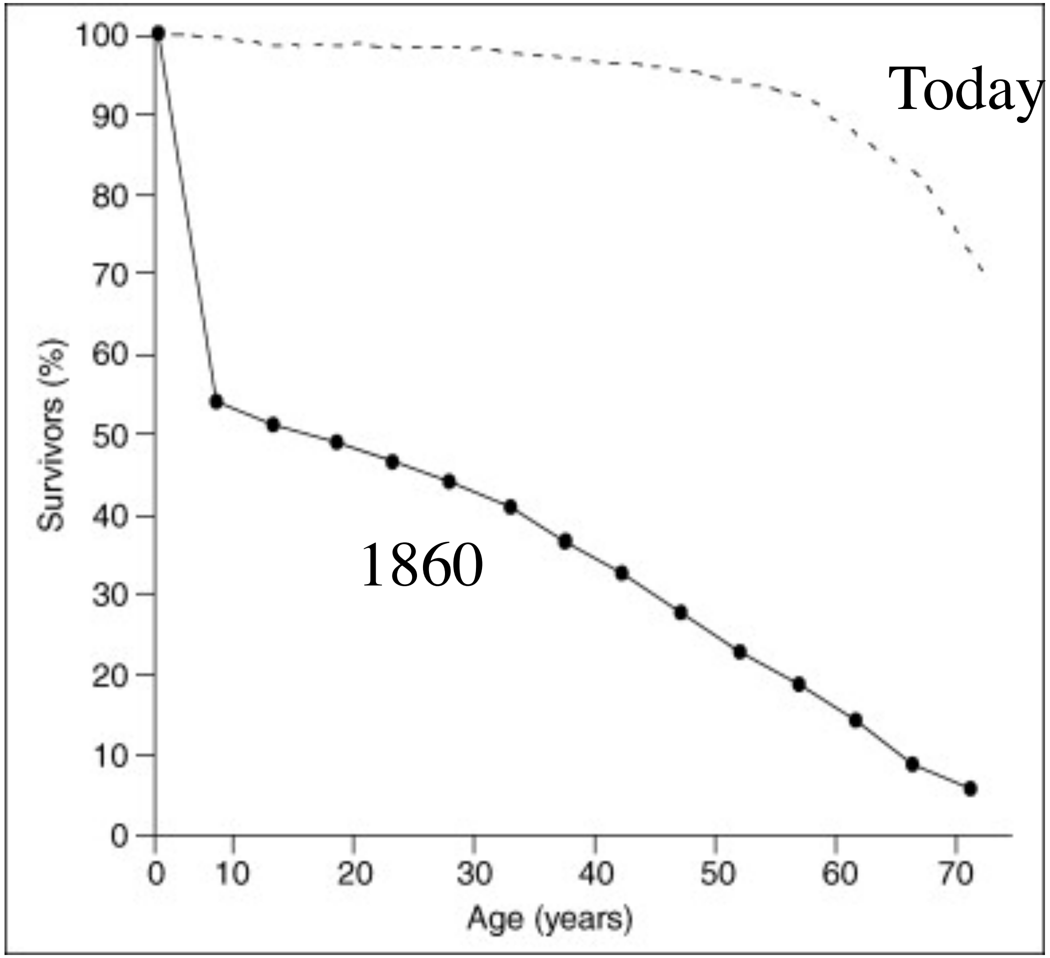
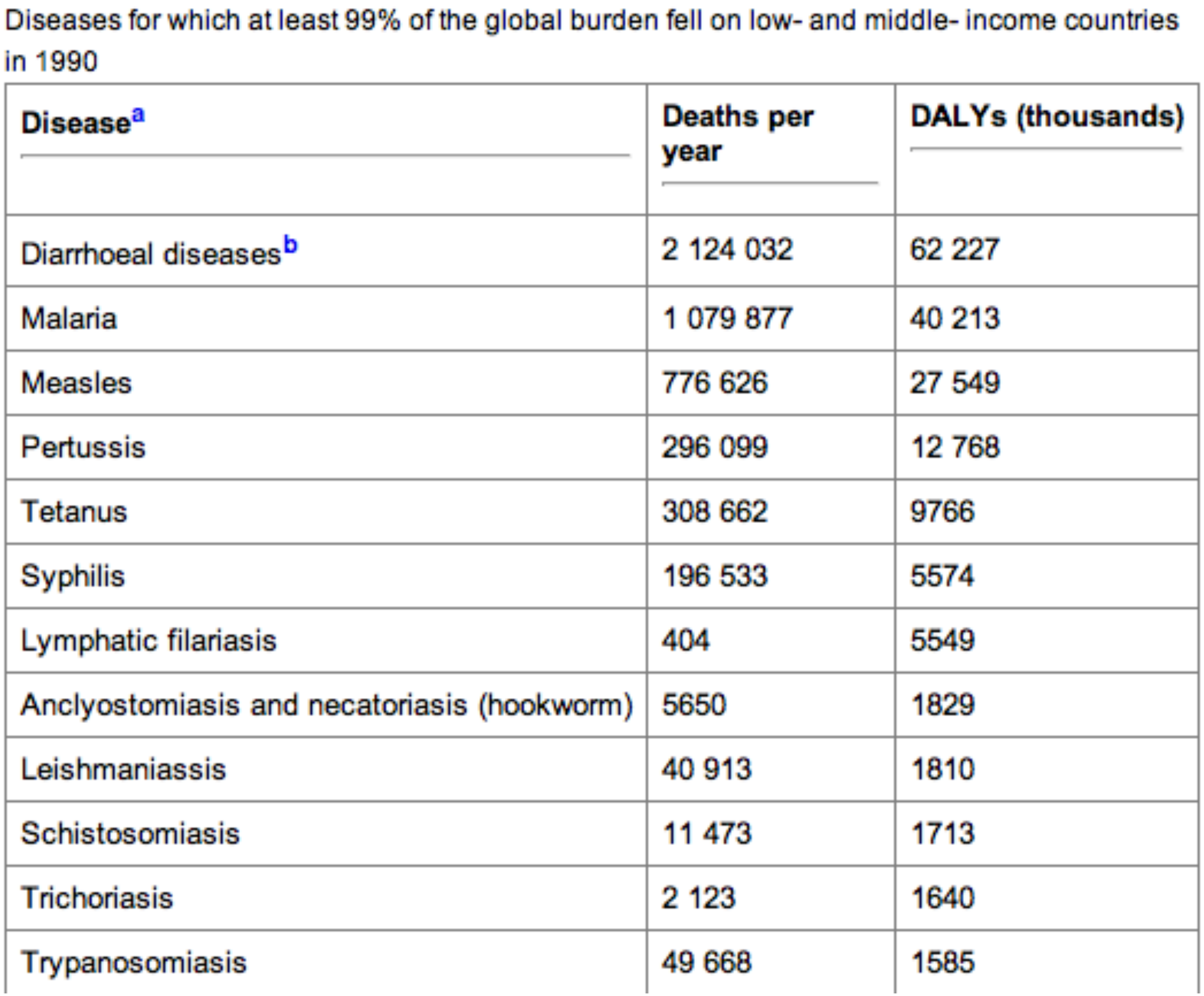
Human survivorship



Bob May (2007),
TREE 22: 497-503

Liverpool 150 years ago





Diseases for which at least 99% of the global burden fell on low- and middle- income countries in 1990

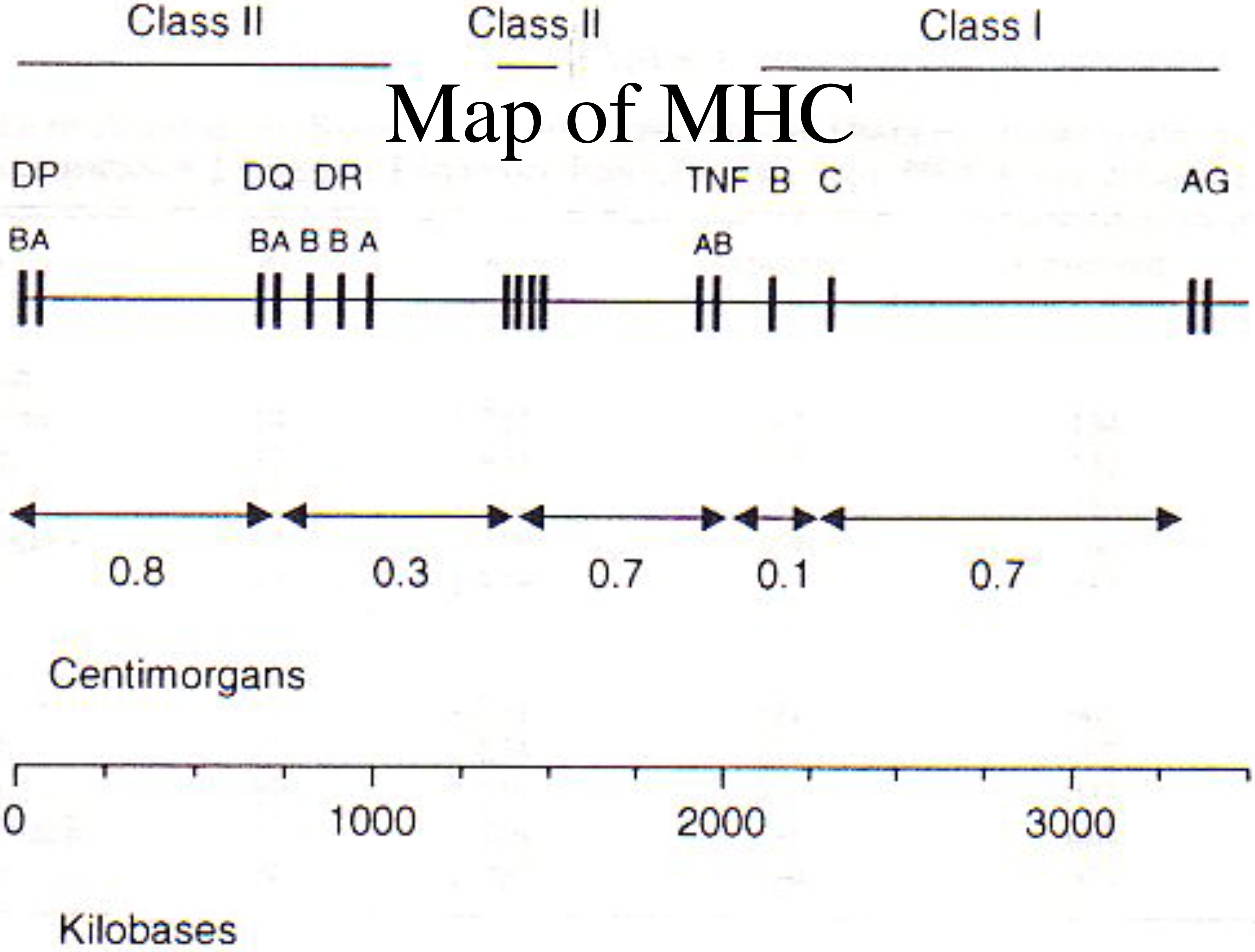
Disease[a]	**Deaths per year**	**DALYs (thousands)**
Diarrhoeal diseases[b]	2 124 032	62 227
Malaria	1 079 877	40 213
Measles	776 626	27 549
Pertussis	296 099	12 768
Tetanus	308 662	9766
Syphilis	196 533	5574
Lymphatic filariasis	404	5549
Anclyostomiasis and necatoriasis (hookworm)	5650	1829
Leishmaniassis	40 913	1810
Schistosomiasis	11 473	1713
Trichoriasis	2 123	1640
Trypanosomiasis	49 668	1585

Evolution of infectious disease
#1 Evolution of the MHC

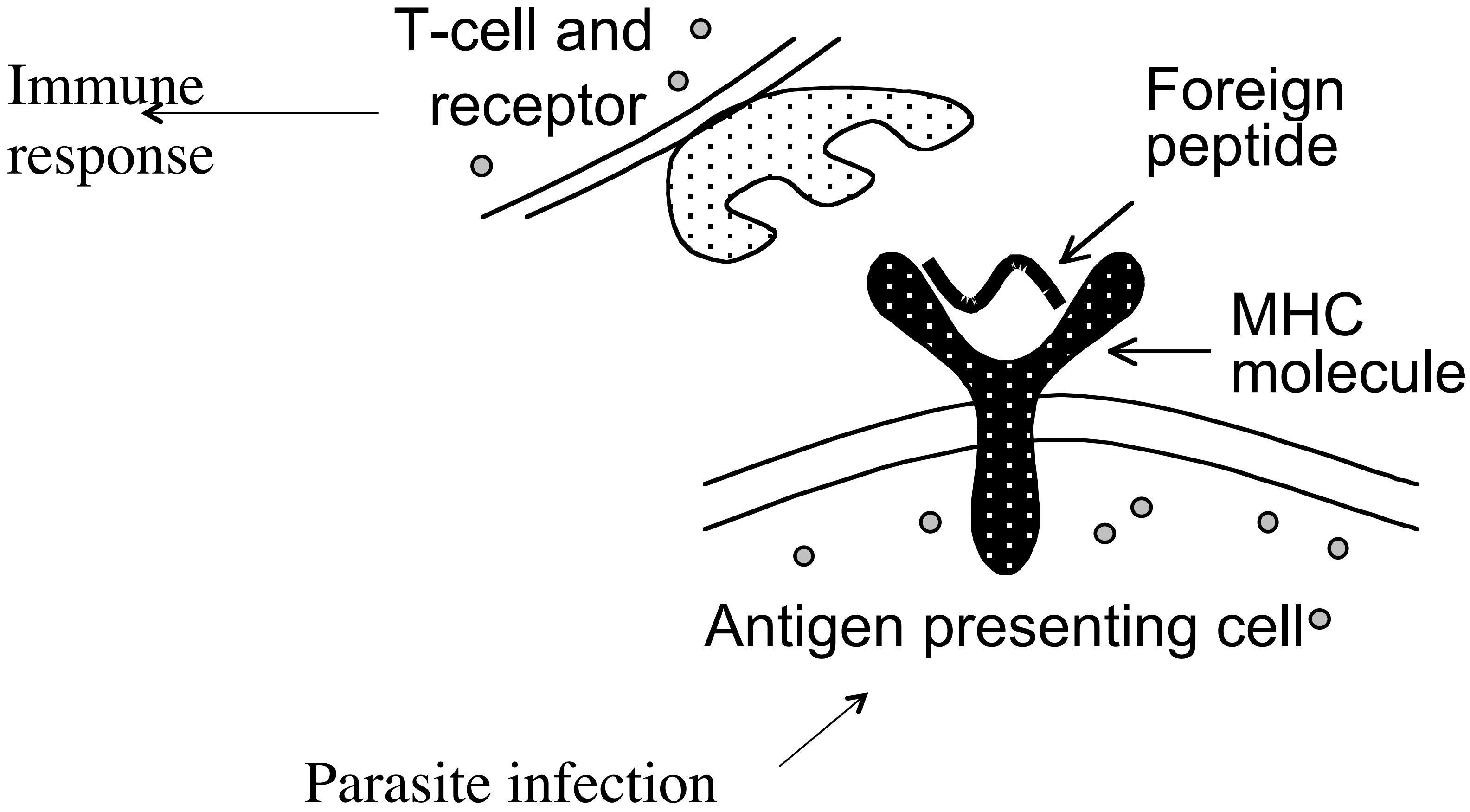
Steve Paterson
rm 202, s.paterson@liv.ac.uk

Map of MHC

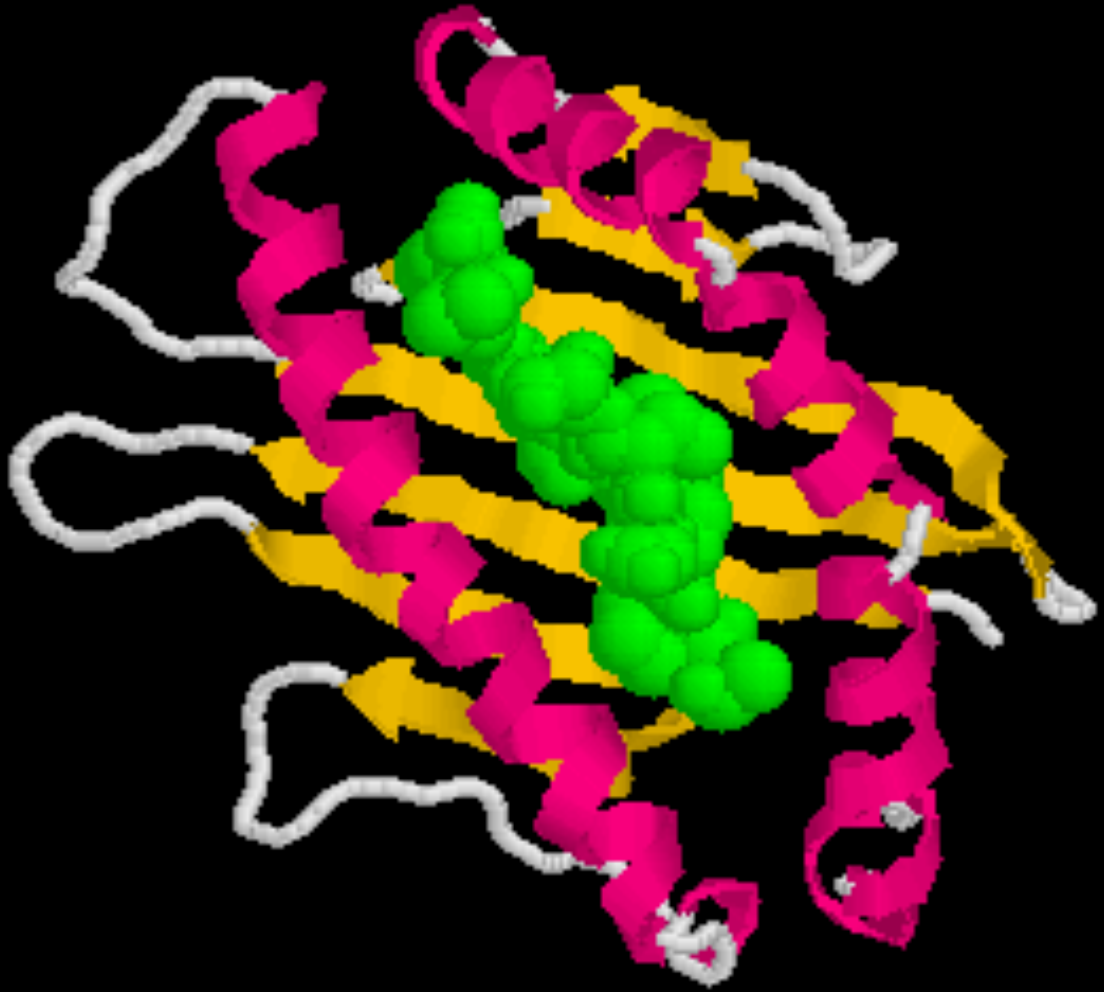
Map of MHC



presentation of peptides by MHC



MHC & peptide

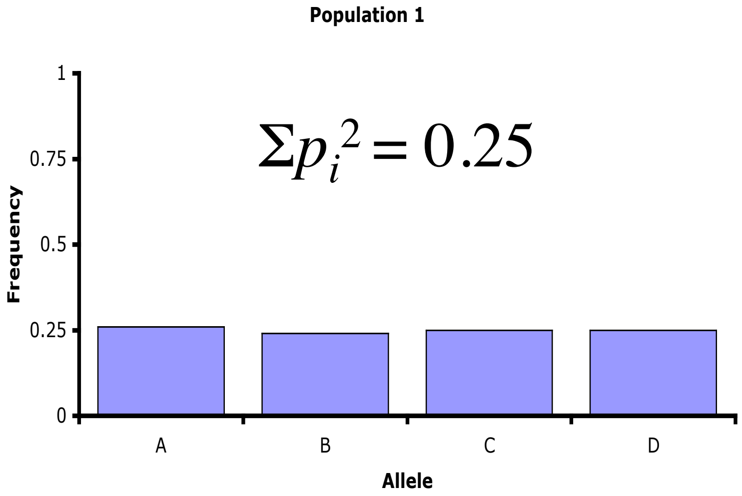


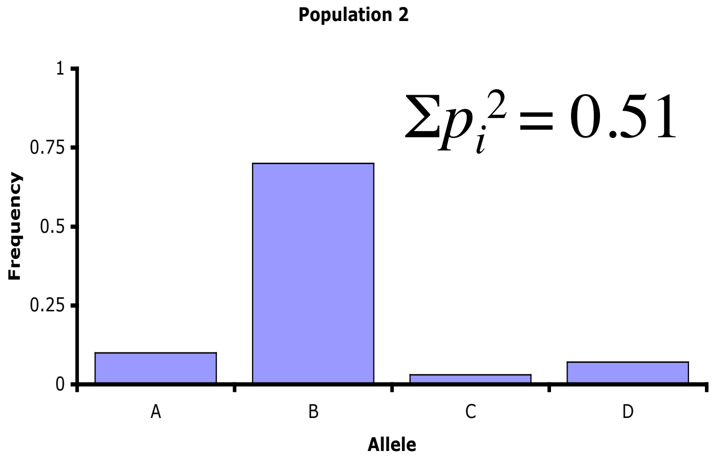
MHC polymorphism

- Most polymorphic region of vertebrate genome, >100 alleles at some loci
- Evidence for positive selection
  - Allele frequencies very even
  - Excess of coding substitution
  - Diversity maintained through speciation events

Allele frequencies

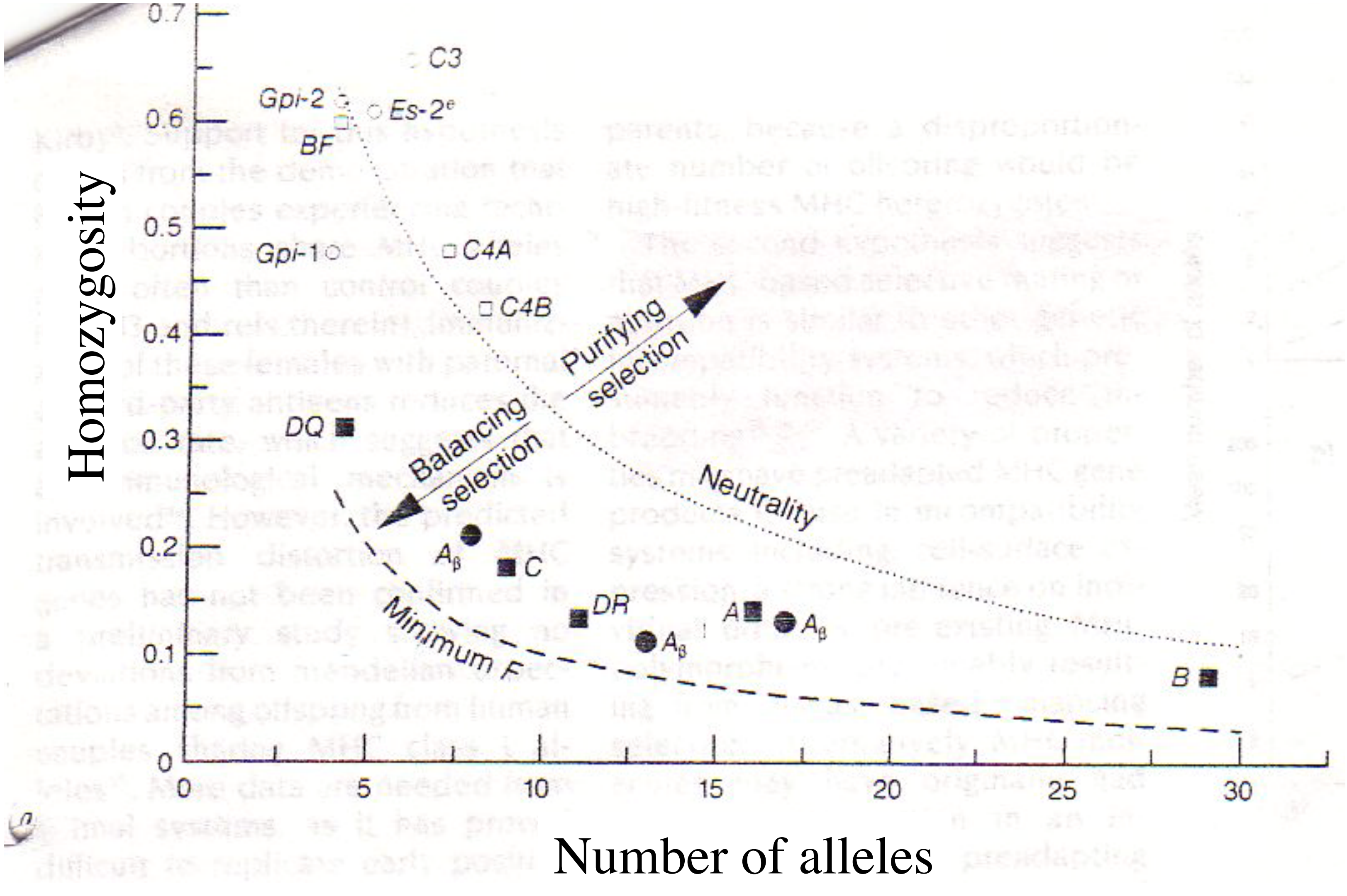
- Take a locus with 4 alleles, average allele frequency equals 0.25, but genetic drift makes it unlikely all alleles will have a frequency of 0.25, unless balancing selection





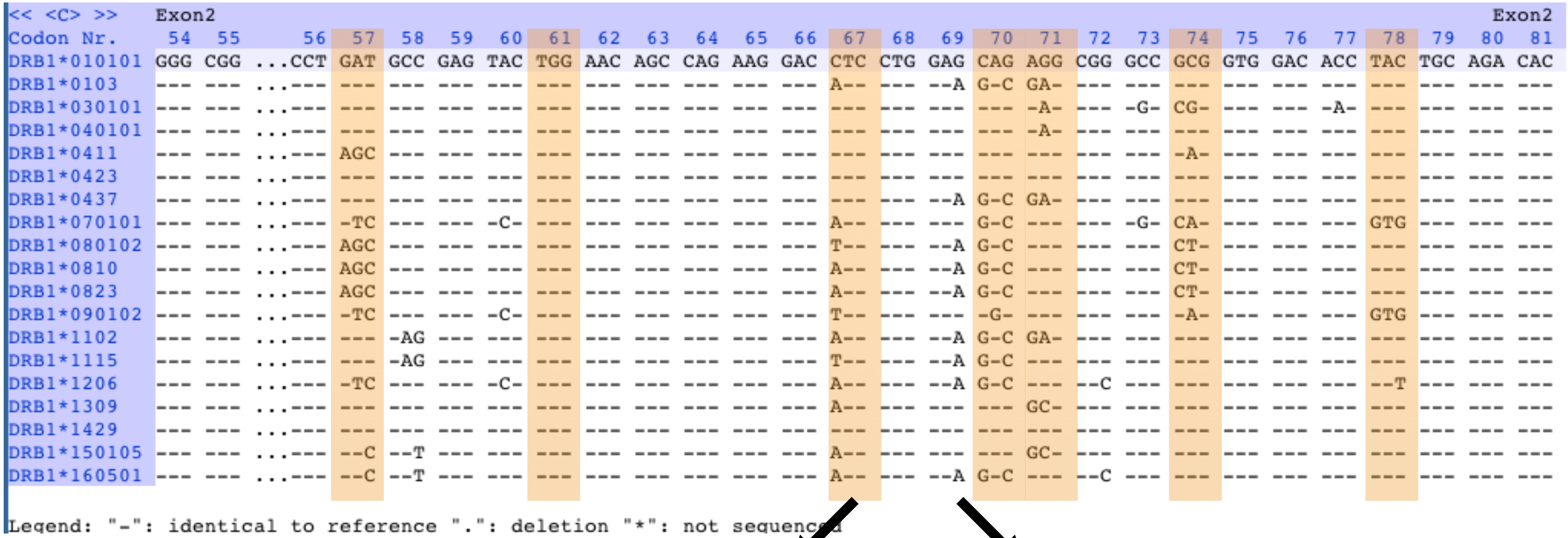
Allele frequencies, $\mathbf{p} = \{p_1, p_2, \ldots, p_i, \ldots, p_n\}$.
Expected homozygosity = Σp_i^2. Given number of alleles, one can calculate probability of allele frequency distribution.

MHC allele frequencies



Positive selective on gene sequence

Human DRB exon 2



<< <C> >>	Exon2																											Exon2
Codon Nr.	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81
DRB1*010101	GGG	CGG	...CCT	GAT	GCC	GAG	TAC	TGG	AAC	AGC	CAG	AAG	GAC	CTC	CTG	GAG	CAG	AGG	CGG	GCC	GCG	GTG	GAC	ACC	TAC	TGC	AGA	CAC
DRB1*0103	---	---	...---	---	---	---	---	---	---	---	---	---	---	A--	---	--A	G-C	GA-	---	---	---	---	---	---	---	---	---	---
DRB1*030101	---	---	...---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-A-	---	-G-	CG-	---	---	-A-	---	---	---	---
DRB1*040101	---	---	...---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-A-	---	---	---	---	---	---	---	---	---	---
DRB1*0411	---	---	...---	AGC	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	-A-	---	---	---	---	---	---	---
DRB1*0423	---	---	...---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
DRB1*0437	---	---	...---	---	---	---	---	---	---	---	---	---	---	---	---	--A	G-C	GA-	---	---	---	---	---	---	---	---	---	---
DRB1*070101	---	---	...---	-TC	---	---	-C-	---	---	---	---	---	---	A--	---	---	G-C	---	---	-G-	CA-	---	---	---	GTG	---	---	---
DRB1*080102	---	---	...---	AGC	---	---	---	---	---	---	---	---	---	T--	---	--A	G-C	---	---	---	CT-	---	---	---	---	---	---	---
DRB1*0810	---	---	...---	AGC	---	---	---	---	---	---	---	---	---	A--	---	--A	G-C	---	---	---	CT-	---	---	---	---	---	---	---
DRB1*0823	---	---	...---	AGC	---	---	---	---	---	---	---	---	---	A--	---	--A	G-C	---	---	---	CT-	---	---	---	---	---	---	---
DRB1*090102	---	---	...---	-TC	---	---	-C-	---	---	---	---	---	---	T--	---	---	-G-	---	---	---	-A-	---	---	---	GTG	---	---	---
DRB1*1102	---	---	...---	---	-AG	---	---	---	---	---	---	---	---	A--	---	--A	G-C	GA-	---	---	---	---	---	---	---	---	---	---
DRB1*1115	---	---	...---	---	-AG	---	---	---	---	---	---	---	---	T--	---	--A	G-C	---	---	---	---	---	---	---	---	---	---	---
DRB1*1206	---	---	...---	-TC	---	---	-C-	---	---	---	---	---	---	A--	---	--A	G-C	---	--C	---	---	---	---	---	--T	---	---	---
DRB1*1309	---	---	...---	---	---	---	---	---	---	---	---	---	---	A--	---	---	---	GC-	---	---	---	---	---	---	---	---	---	---
DRB1*1429	---	---	...---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
DRB1*150105	---	---	...---	--C	--T	---	---	---	---	---	---	---	---	A--	---	---	---	GC-	---	---	---	---	---	---	---	---	---	---
DRB1*160501	---	---	...---	--C	--T	---	---	---	---	---	---	---	---	A--	---	--A	G-C	---	--C	---	---	---	---	---	---	---	---	---

Legend: "-": identical to reference ".": deletion "*": not sequenced

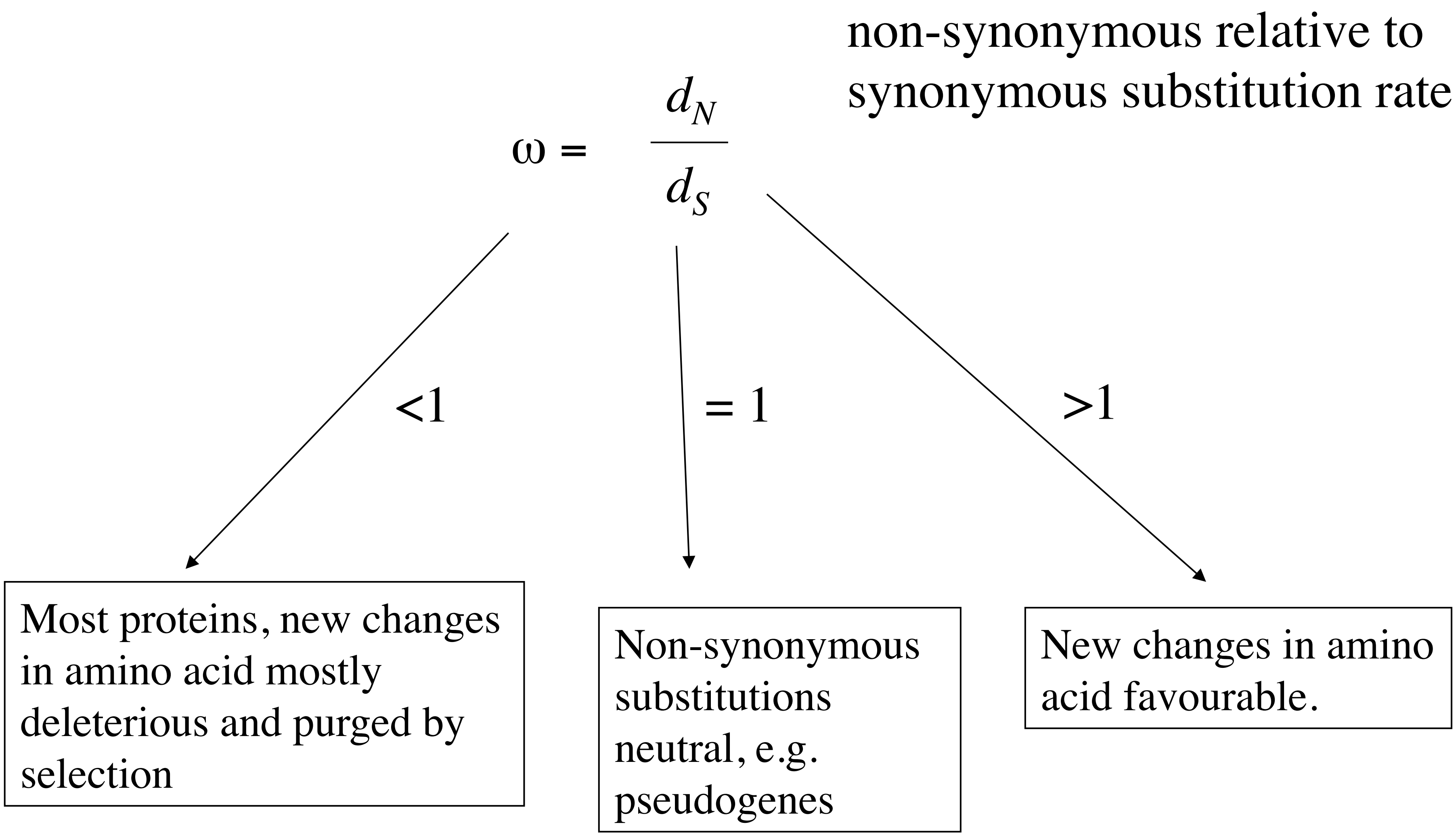
Substitution C <-> A
CTC = Leu
ATC = Ile
NON-SYNONYMOUS

Substitution G <-> A
GAG = Glu
GAA = Glu
SYNONYMOUS

🟧 Involved in antigen binding

Substitution rate

- Calculate synonymous substitution rate (d_S) from number of synonymous substitutions per synonymous site. (Ditto non-synonymous substitution rate, d_N.)
- We expect d_S to be dependent only on the mutation rate.
- We expect d_N to be dependent on the mutation rate and selection.



non-synonymous relative to synonymous substitution rate

$$\omega = \frac{d_N}{d_S}$$

<1

Most proteins, new changes in amino acid mostly deleterious and purged by selection

$= 1$

Non-synonymous substitutions neutral, e.g. pseudogenes

>1

New changes in amino acid favourable.

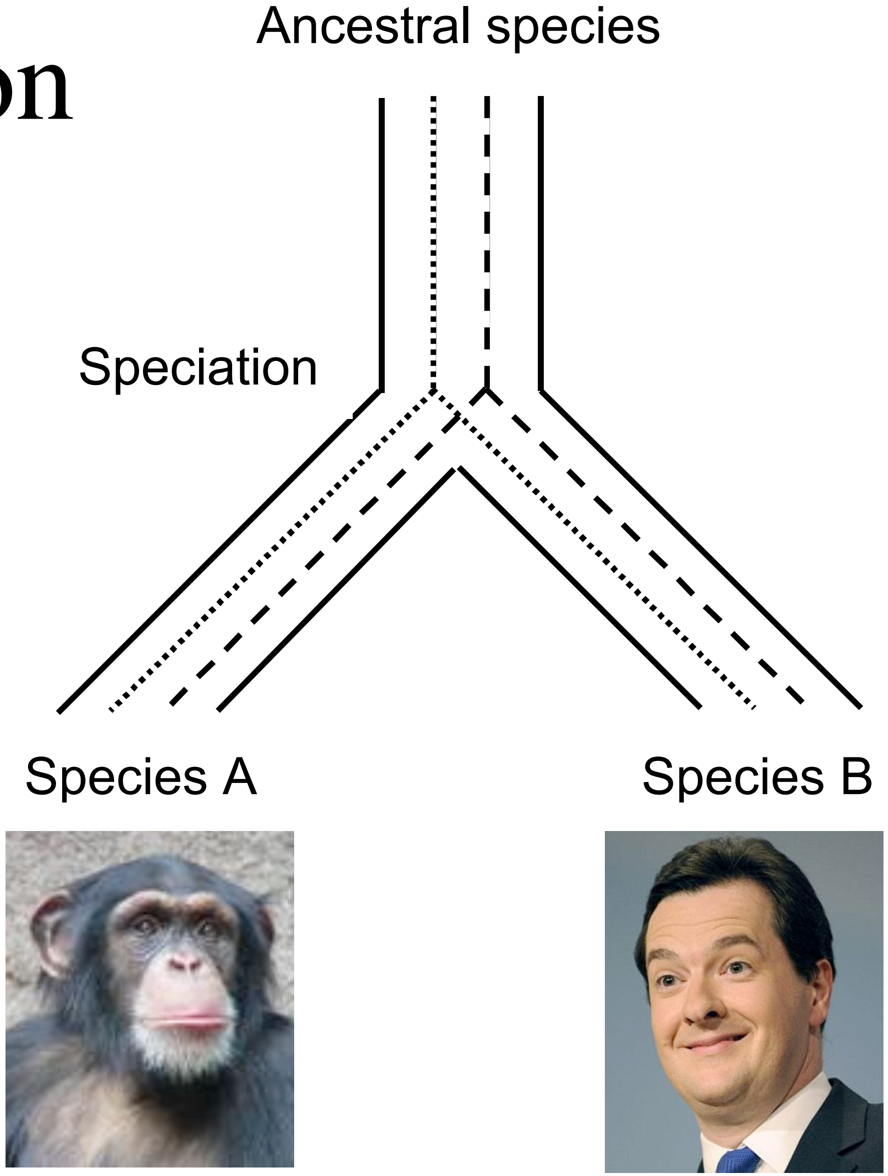
Positive selection at the MHC

	n	d_s (x100)	d_n (x100)	P
DPB1	6	1.7 ±2.4	9.8 ±3.0	<0.05
DQB1	9	7.3 ±4.2	19.3 ±3.6	<0.05
DRB1	23	6.1 ±3.9	24.7 ±3.5	<0.001
DRB3	4	4.5 ±4.5	10.3 ±3.3	n.s.
DRB5	4	4.3 ±4.4	10.8 ±3.7	n.s.

antigen presenting site only - Hughes et al (1994)

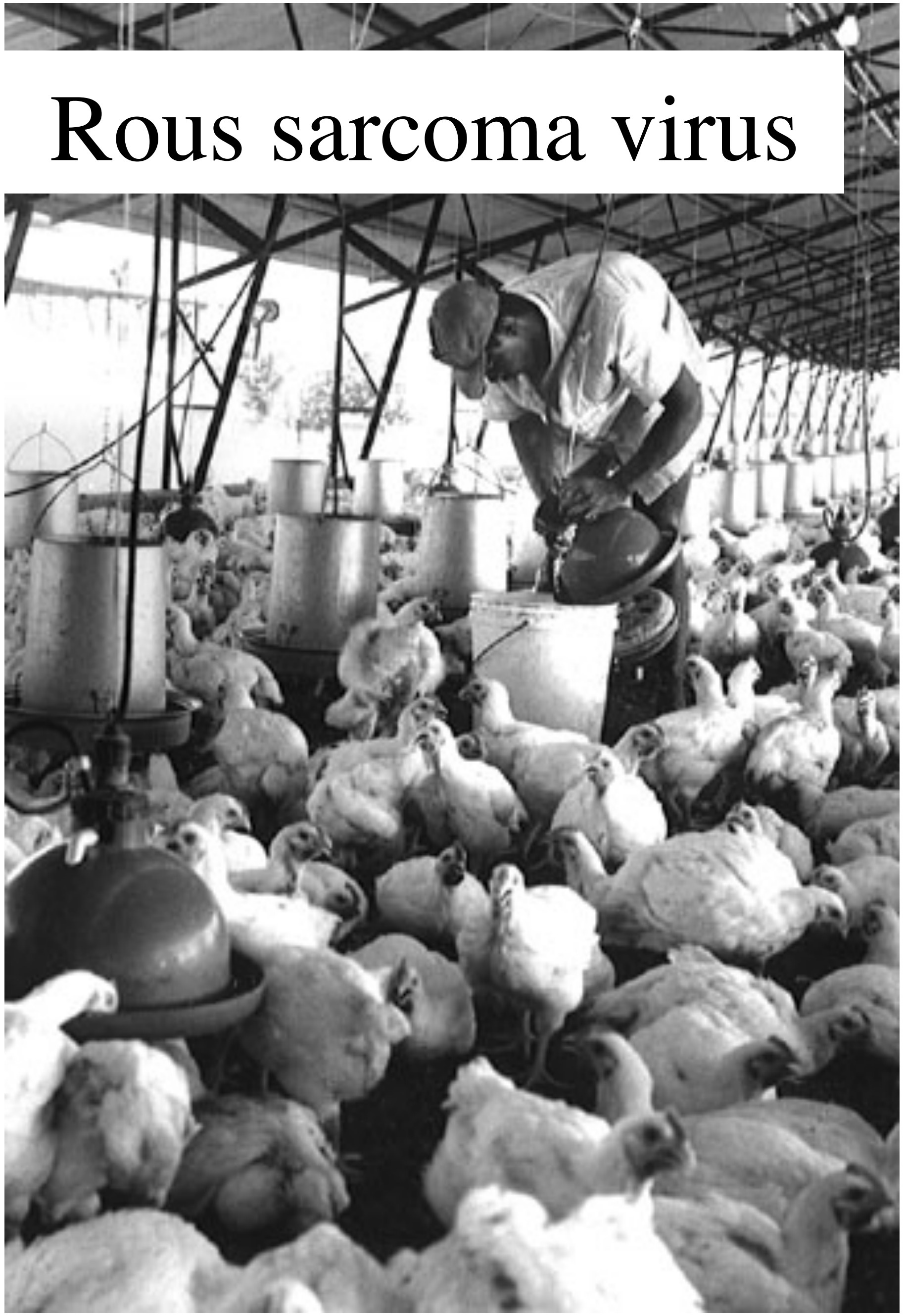
Trans-speciation

- In MHC, polymorphism is maintained through speciation events
- dotted and dashed, different allelic lineages



What is the selective force on the MHC?

Rous sarcoma virus



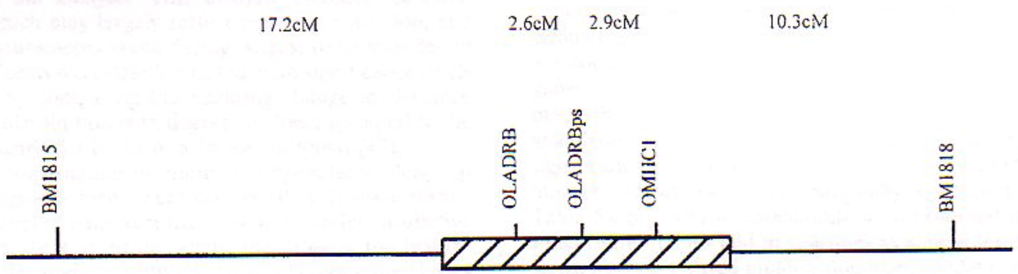
- causes uncontrollable tumours in chickens, eventually death
- caused by small RNA virus (retrovirus)
- 2 strains of chicken, different MHC types
  - CC susceptible
  - CB resistant
- anchor residues used by the MHC molecules in these different strains known

RSV & MHC

- RSV genome sequenced
- predict peptides in genome that can bind to MHC in 2 strains
- predicts that resistant CB strain can bind many more peptides than susceptible CC strain
- test by generating synthetic peptides and using as vaccines
- synthetic peptides provide protection in resistant CB strain but not susceptible CC strain

MHC in Soay sheep

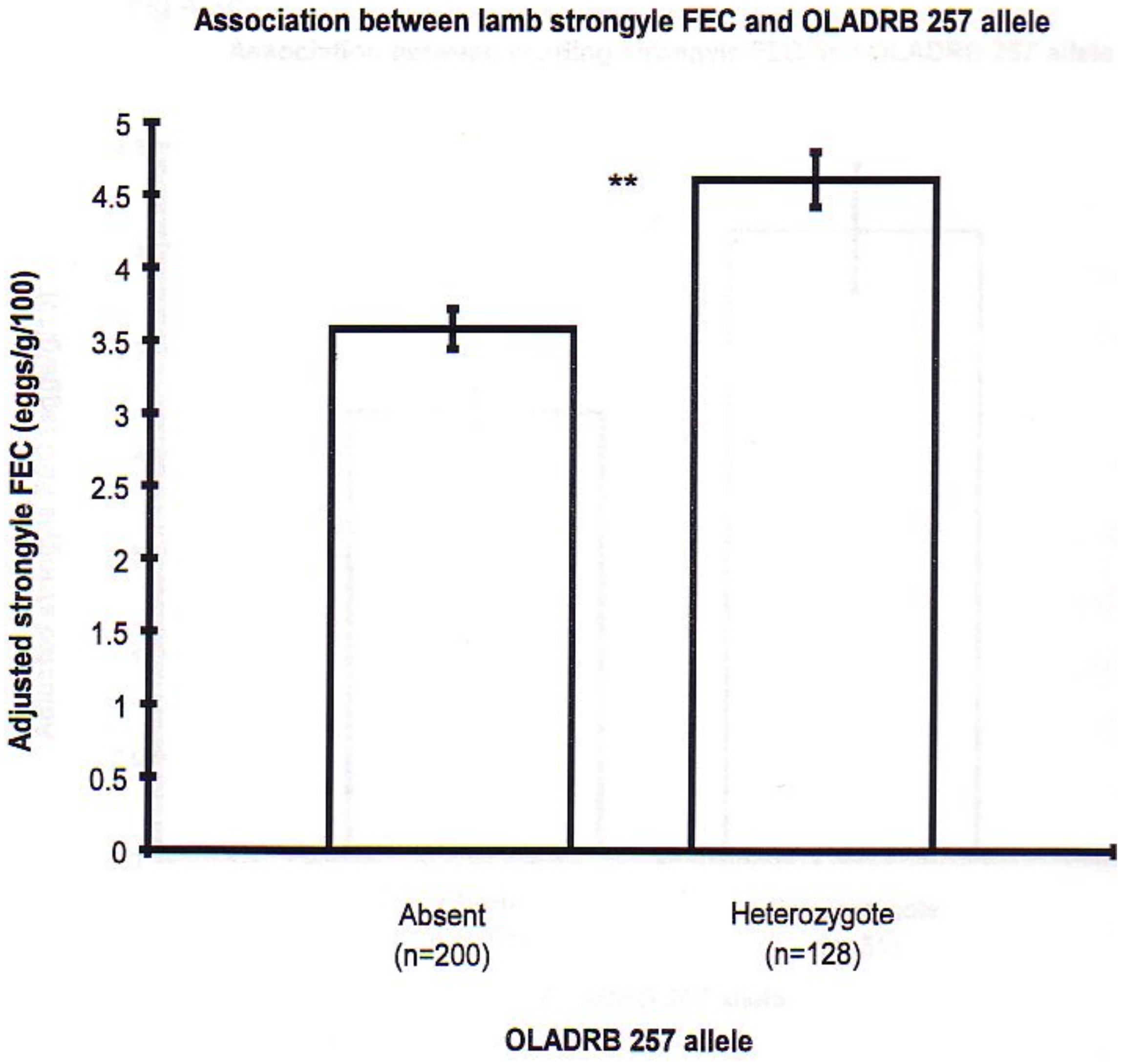
- show even allele frequency distribution
- increased rate of non-synonymous vs. synonymous substitution



MHC and worms in sheep

- population of feral Soay sheep on St. Kilda
- unmanaged, often high mortality in certain years
- nematode parasites contribute to this
  - if sheep are cleared of infection they survive better
- genotype microsatellite markers within MHC in linkage disequilibrium

MHC and parasite resistance



MHC and survivorship

DRB allele	lamb survivorship
205	0.026 (±0.310)
213	0.005 (±0.050)
257	-0.181 (±0.061)
263	0.085 (±0.053)
267	0.091 (±0.080)
276	-0.029 (±0.057)

Malaria

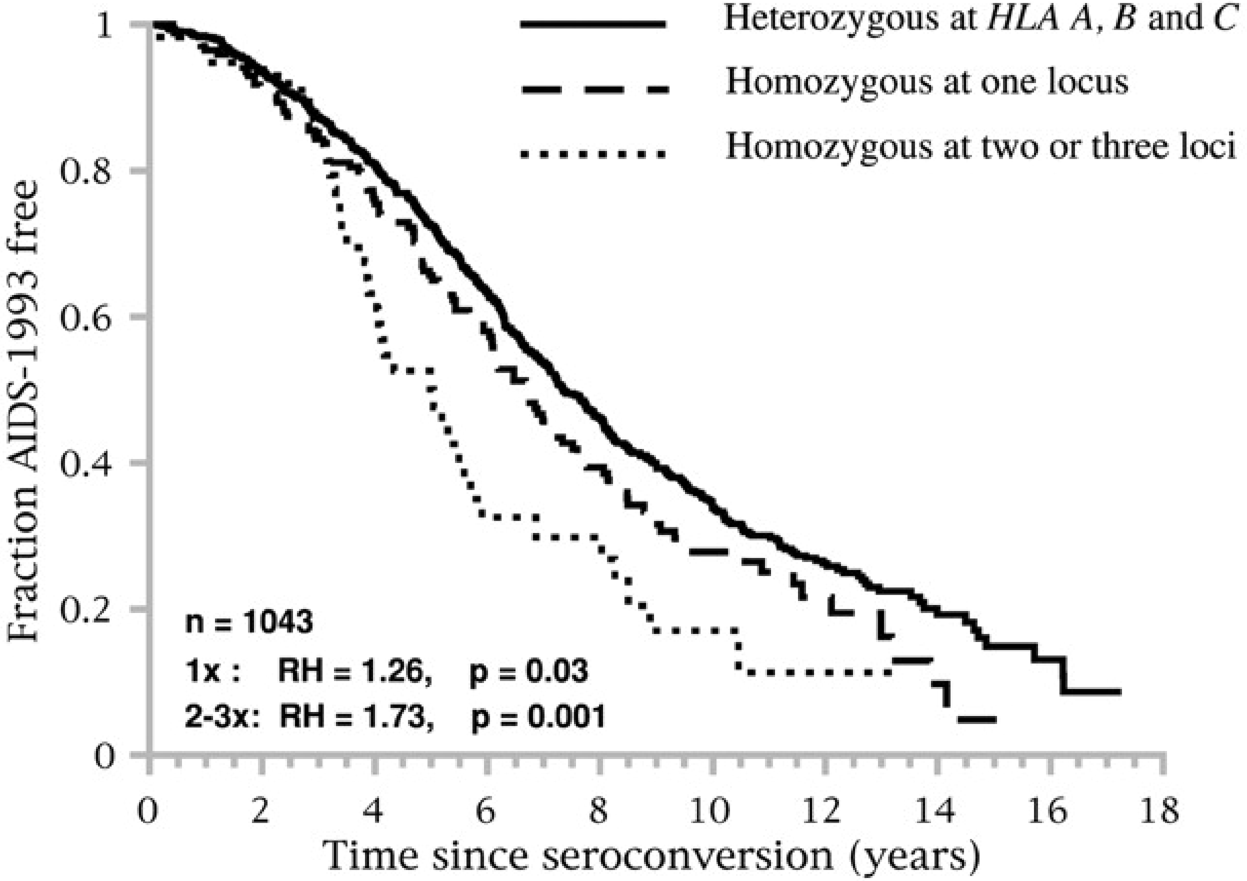
WHO/TDR

MHC and malaria

- malaria kills 1/20 of all children in sub-Saharan Africa before the age of 5
- Adrian Hill showed association between cerebral malaria and HLA-Bw53 (MHC type) Nature 352:595-600

	Serology	PCR
Severe malaria	15.7%	16.9%
Mild malaria	-	22.6%
controls	24.3%	25.4%

HIV/AIDS progression and MHC



Carrington and O'Brien, 2003 Annu. Rev. Med. 54; 535-51

Frequency-dependent selection

Host fitness

	H1	H2
P1	$1-v_1$	1
P2	1	$1-v_2$

Parasite fitness

	H1	H2
P1	1	$1-r_2$
P2	$1-r_1$	1