Explaining and Characterising MHC Diversity

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The Major Histocompatibility Complex (MHC)

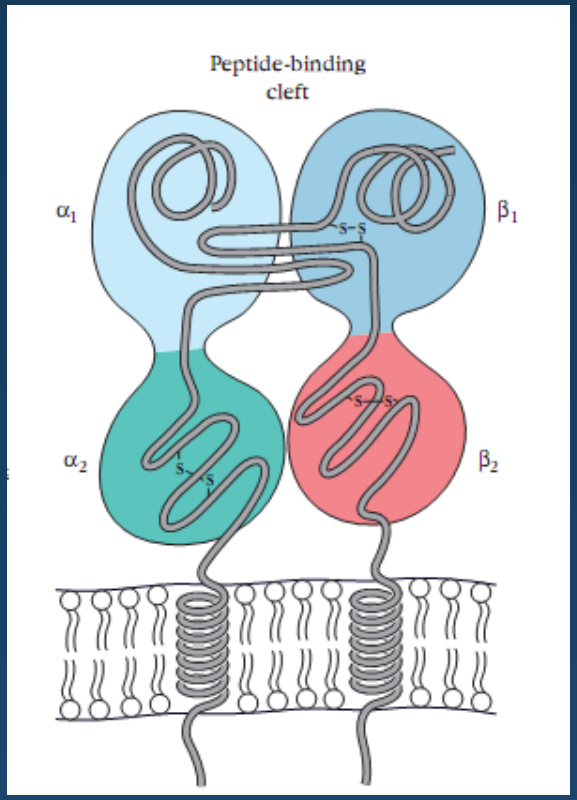
- **Genes encoding the MHC** are **most polymorphic loci** in vertebrates

➔ > 1000 alleles at class II HLA-DRB1 locus in humans

➔ BUT: Some species exhibit low diversity levels

The Major Histocompatibility Complex (MHC)

- MHC molecules play critical role in disease resistance of vertebrates
- Codominance in MHC genes
- Heterozygote advantage maintaining MHC diversity?



Can Heterozygote Advantage Explain MHC Diversity?

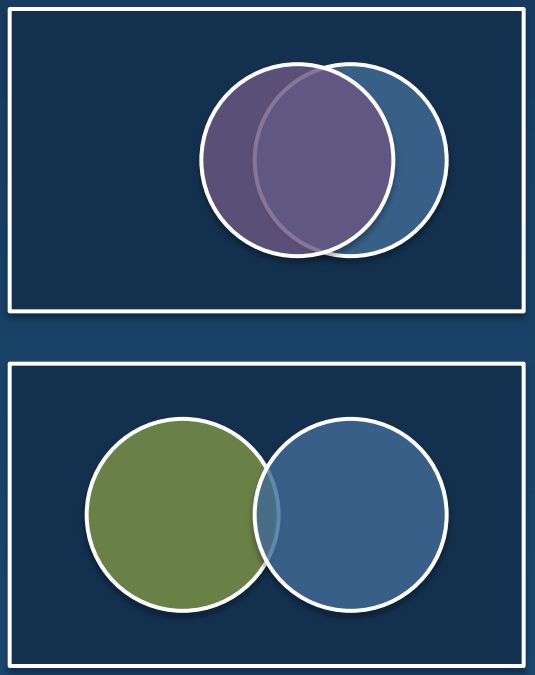
- This has been **controversial**
  - **Immunology**: heterozygotes will recognise a wider variety of parasite molecules
    - heterozygote advantage primary driving force maintaining MHC diversity
  - **Population Genetics**: (traditional) heterozygote advantage cannot maintain large numbers of alleles unless all alleles confer very similar fitness

A Special Form of Heterozygote Advantage

The Divergent Allele Advantage (DAA) Hypothesis

(Wakeland et al., 1990)

- MHC alleles with **highly divergent sequences** cover **unique segments** of the void
- **selection** will **favour highly divergent alleles**

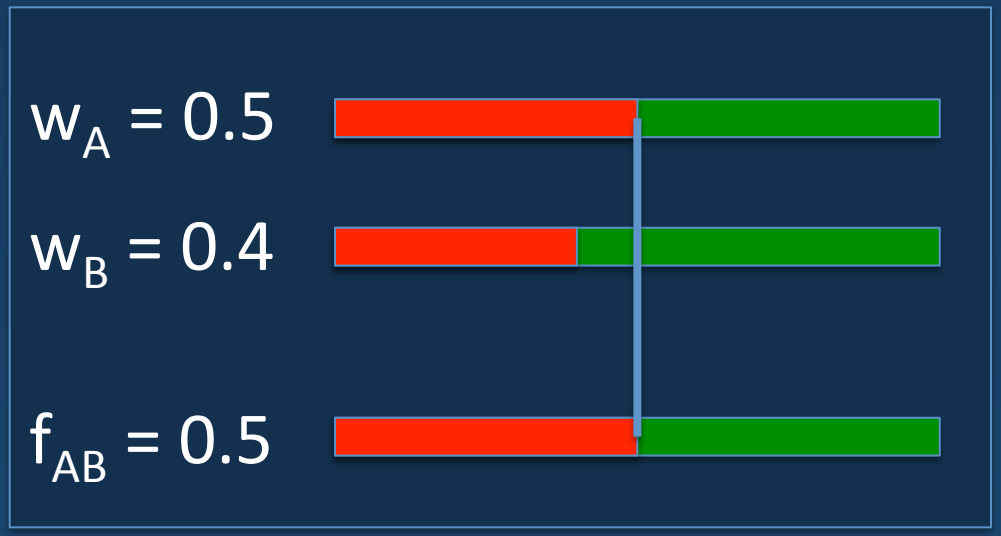


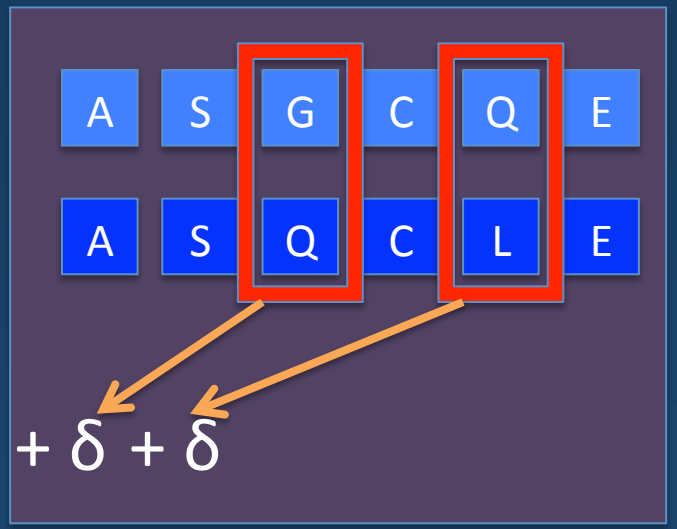
Divergent Allele Advantage in a Model of MHC Evolution

allele A (intrinsic merit $w_A = 0.5$)

allele B (intrinsic merit $w_B = 0.4$)

genotype fitness f_{AB} = dominance part + overdominance contribution





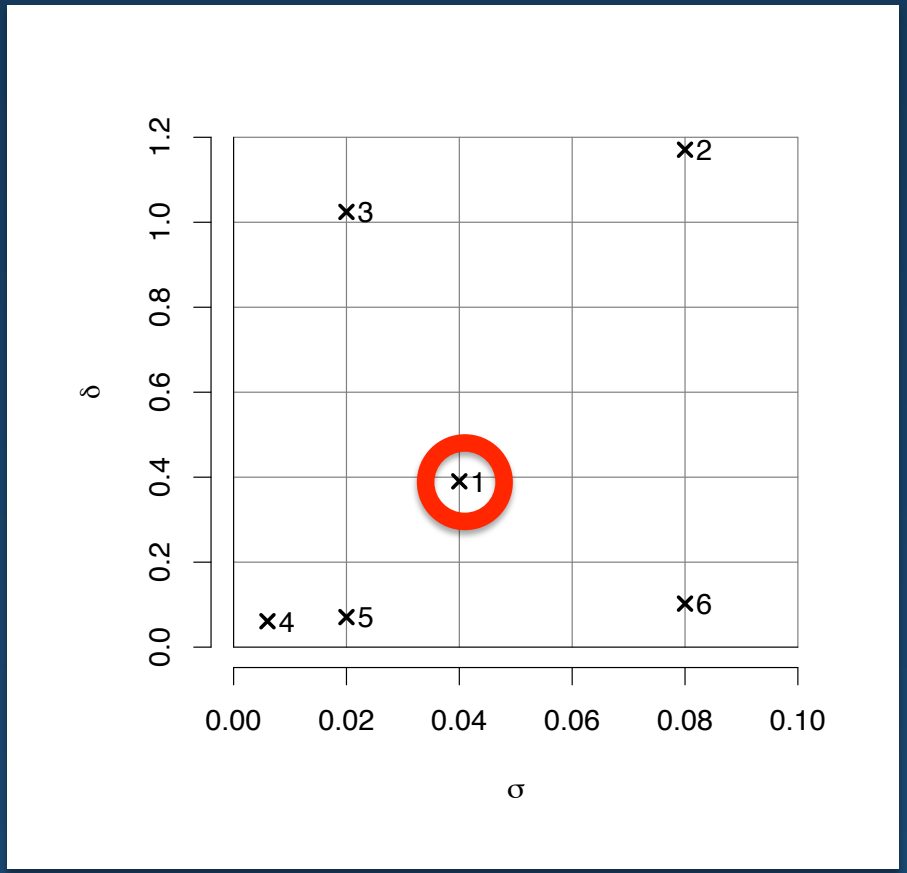
Divergent Allele Advantage in a Model of MHC Evolution

Simulations

- stochastic simulations over 40 million years (evolution of *bovidae*)
- starting with a single allele (all *bovid* species carry same inversion)

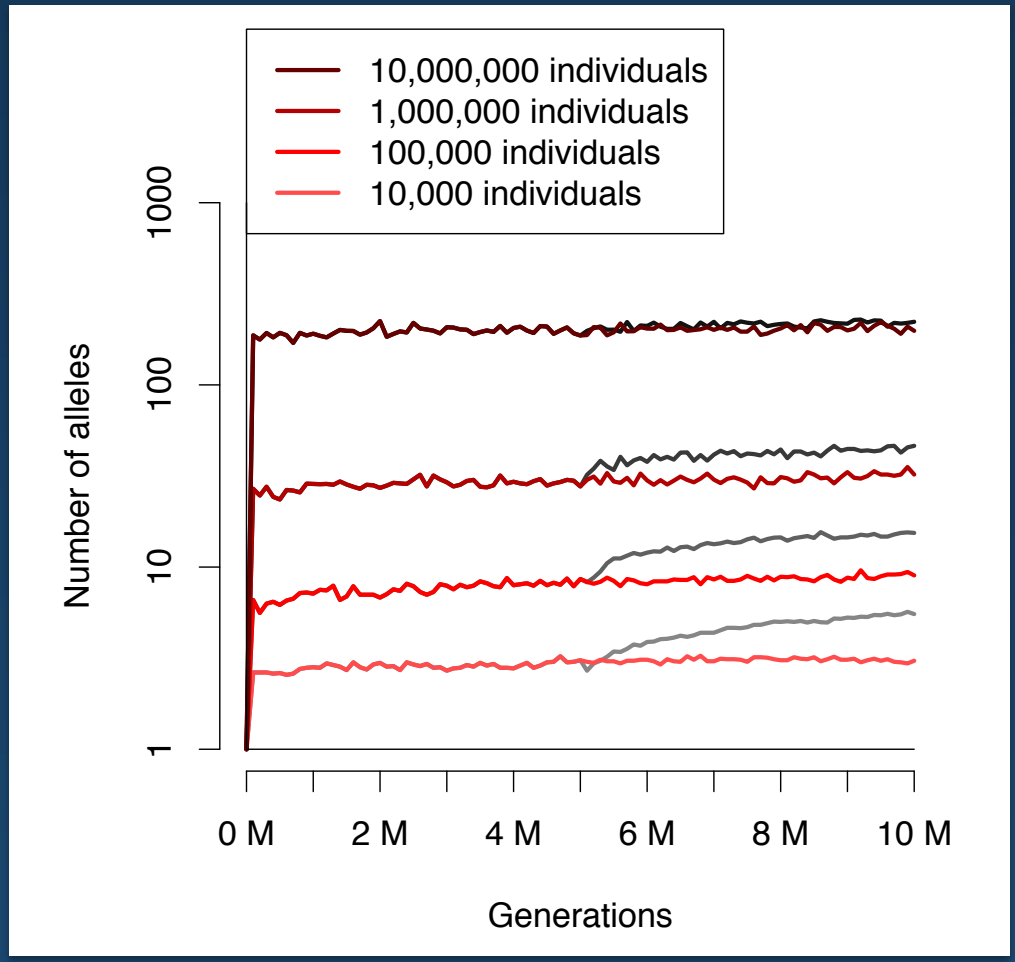
Parameters

- μ: mutation rate
- m: population size
- σ: variation in intrinsic merits
- δ: het. advantage



Results

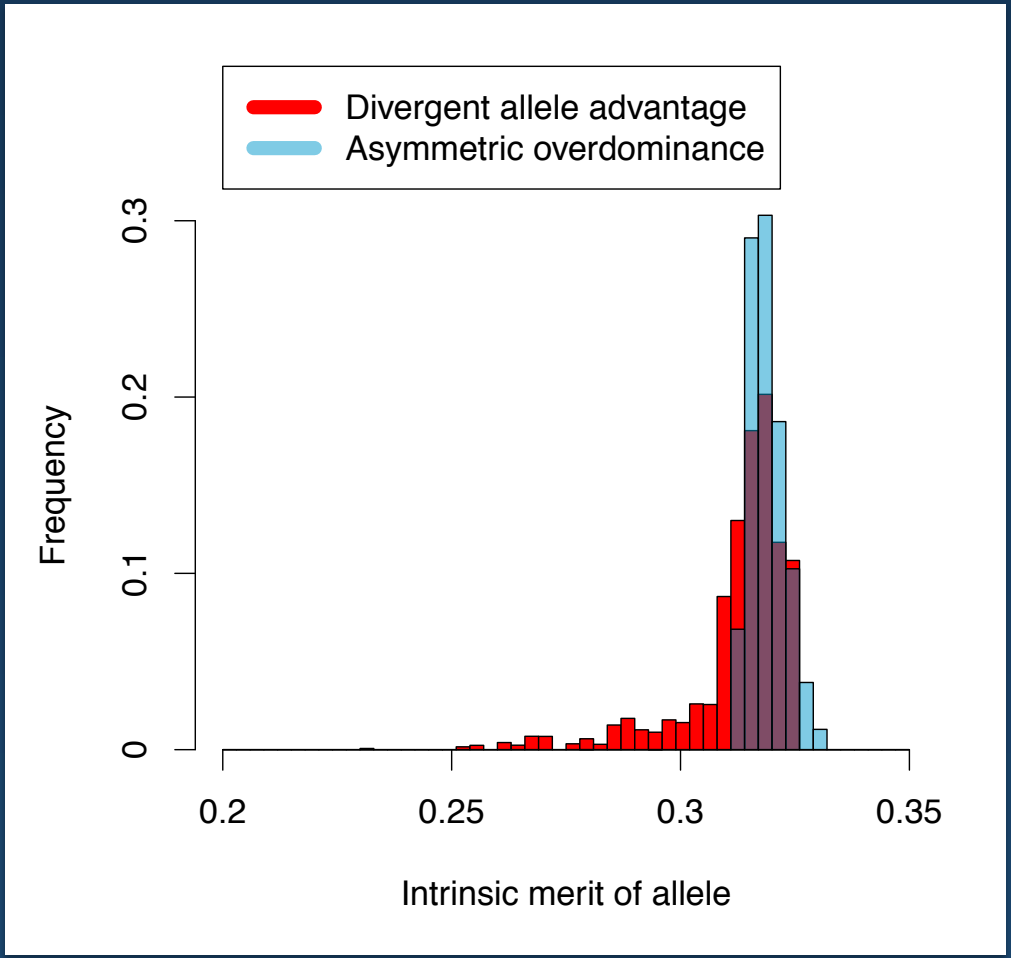
Number of alleles for a well-mixed and structured pop.



(well-mixed population in red, structured population in grey)

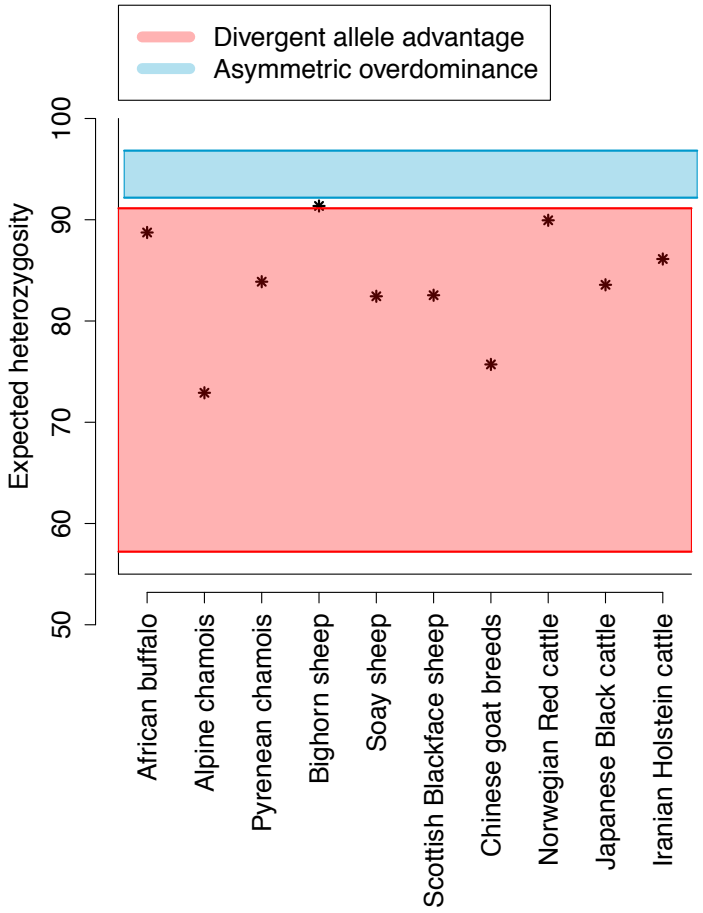
Results

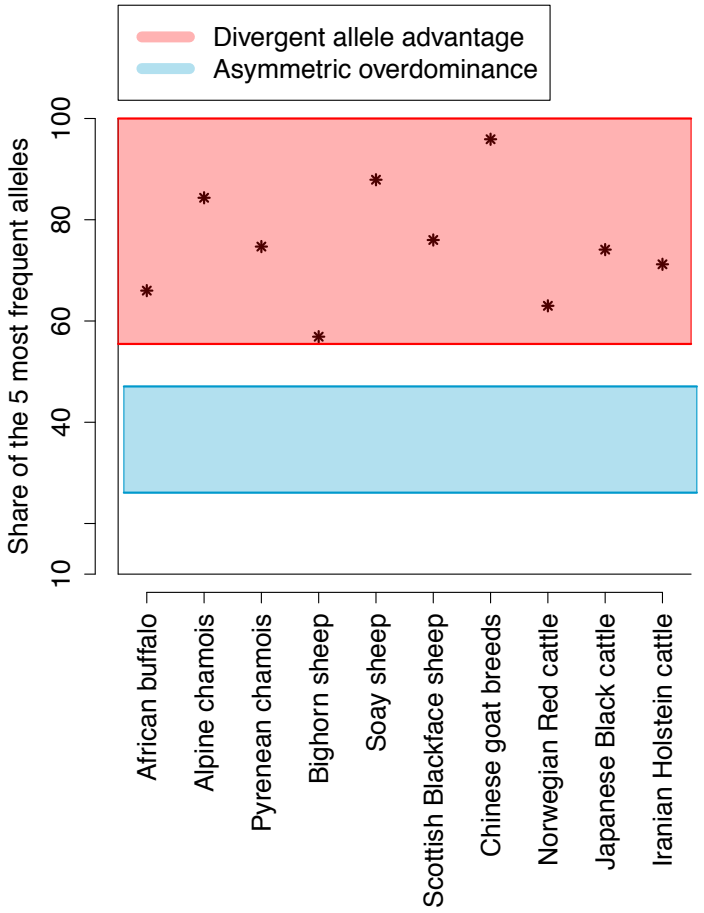
Distribution of intrinsic merits of alleles



Results

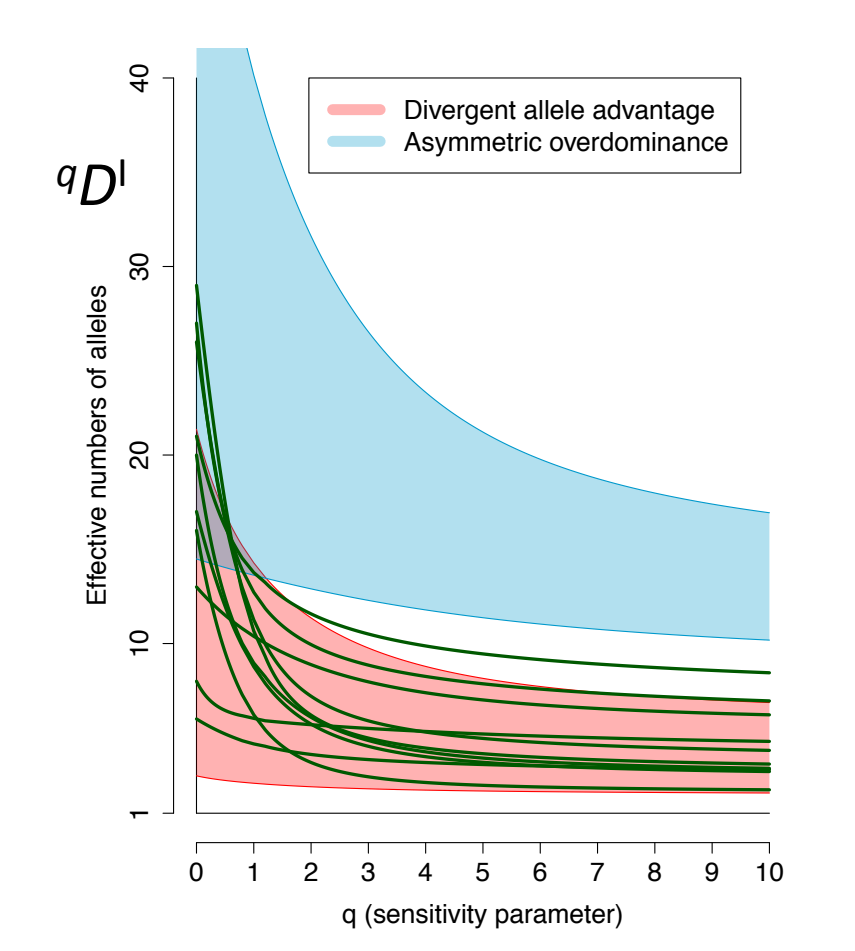
Comparisons to observed values





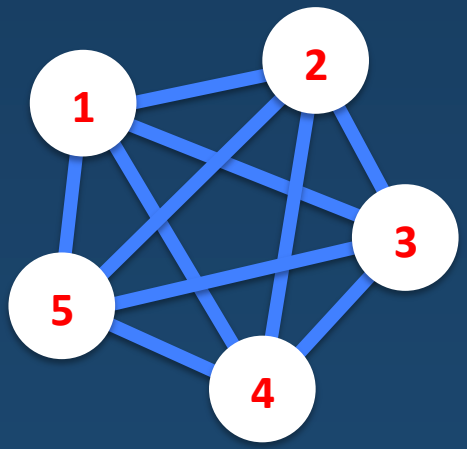
Results

Comparisons to observed values – Diversity profiles



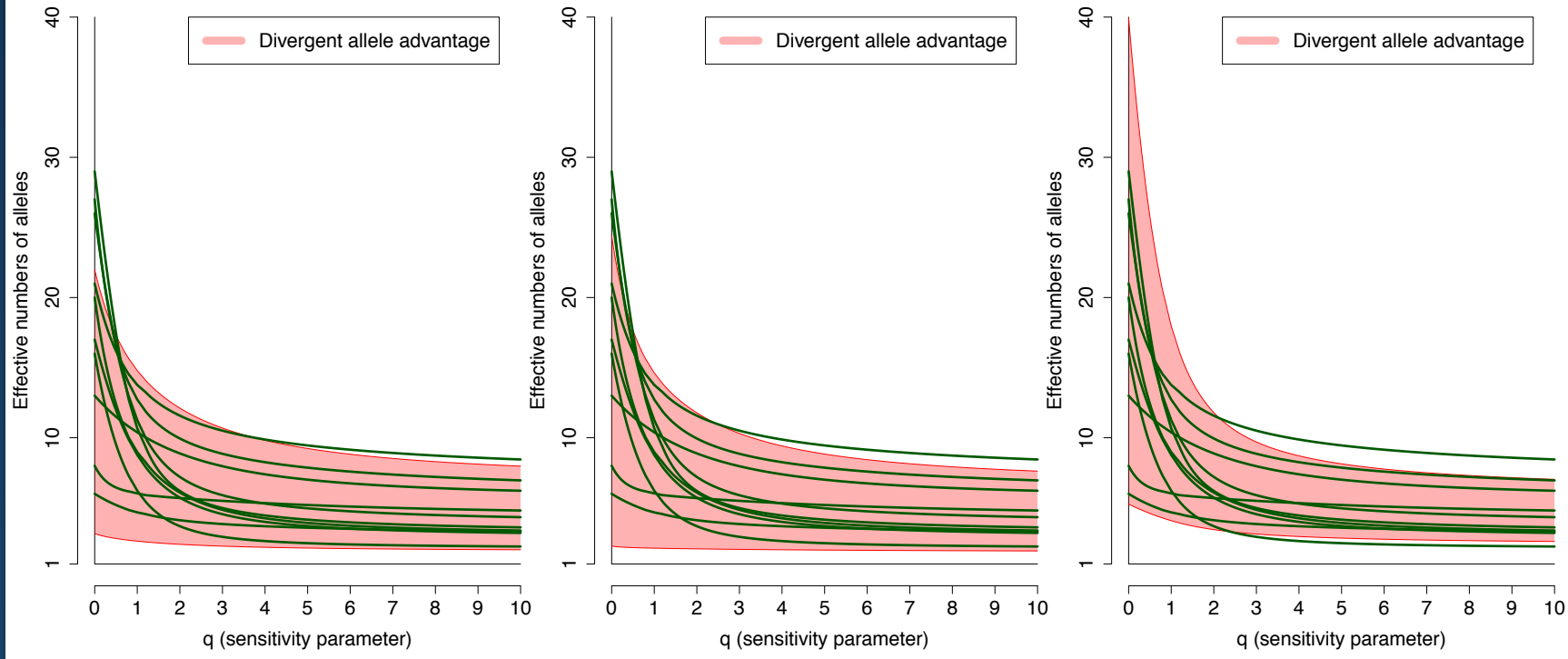
Extension – Metapopulation Dynamics

- Population is structured into subpopulations
  - migrations between the subpopulations
    - different frequencies and intensities of migration
    - different connectivity



Results

Well-mixed and structured populations



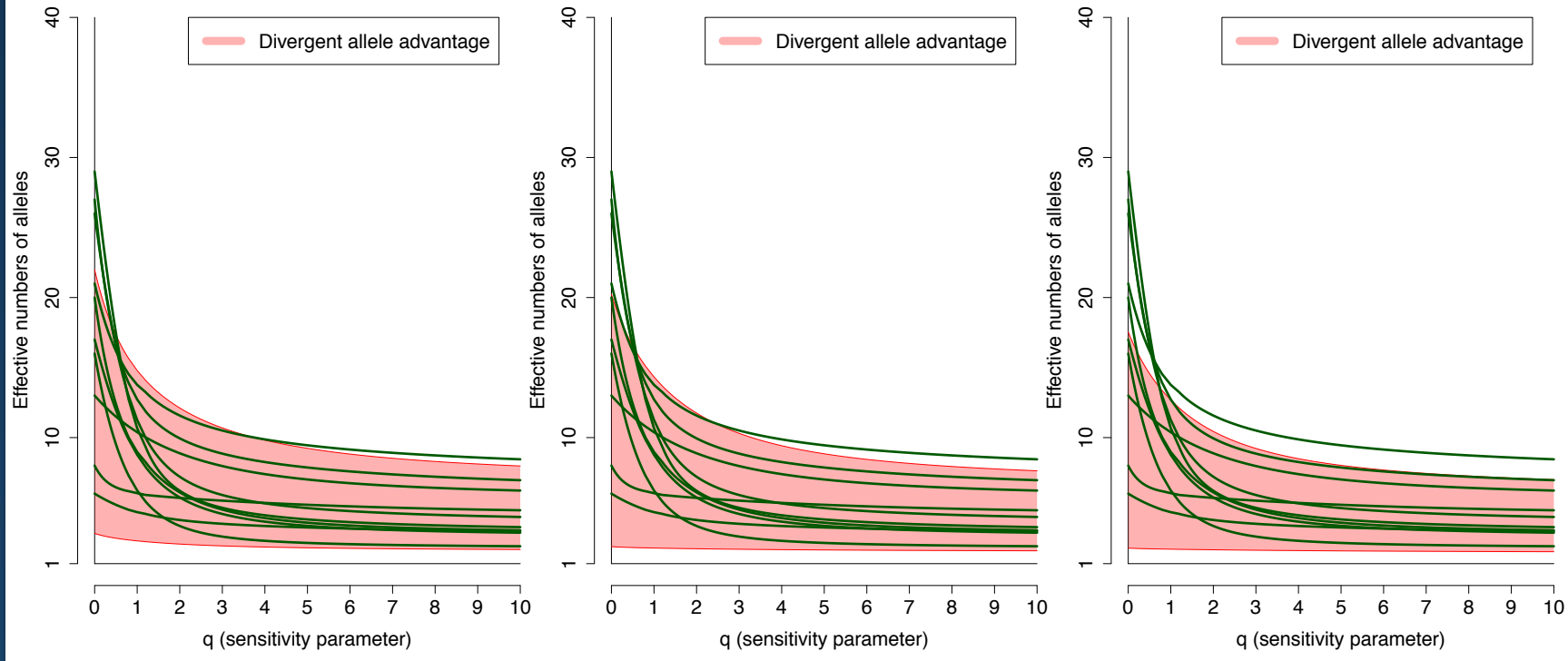
well-mixed single pop. 5 subpop., low migration 5 subpop., no migration

Sampling from entire population

$^{q}D^{I}$

Results

Well-mixed and structured populations



well-mixed single pop. 5 subpop., low migration 5 subpop., no migration

Sampling from one subpopulation

$^{q}D^{\mathrm{I}}$

Results

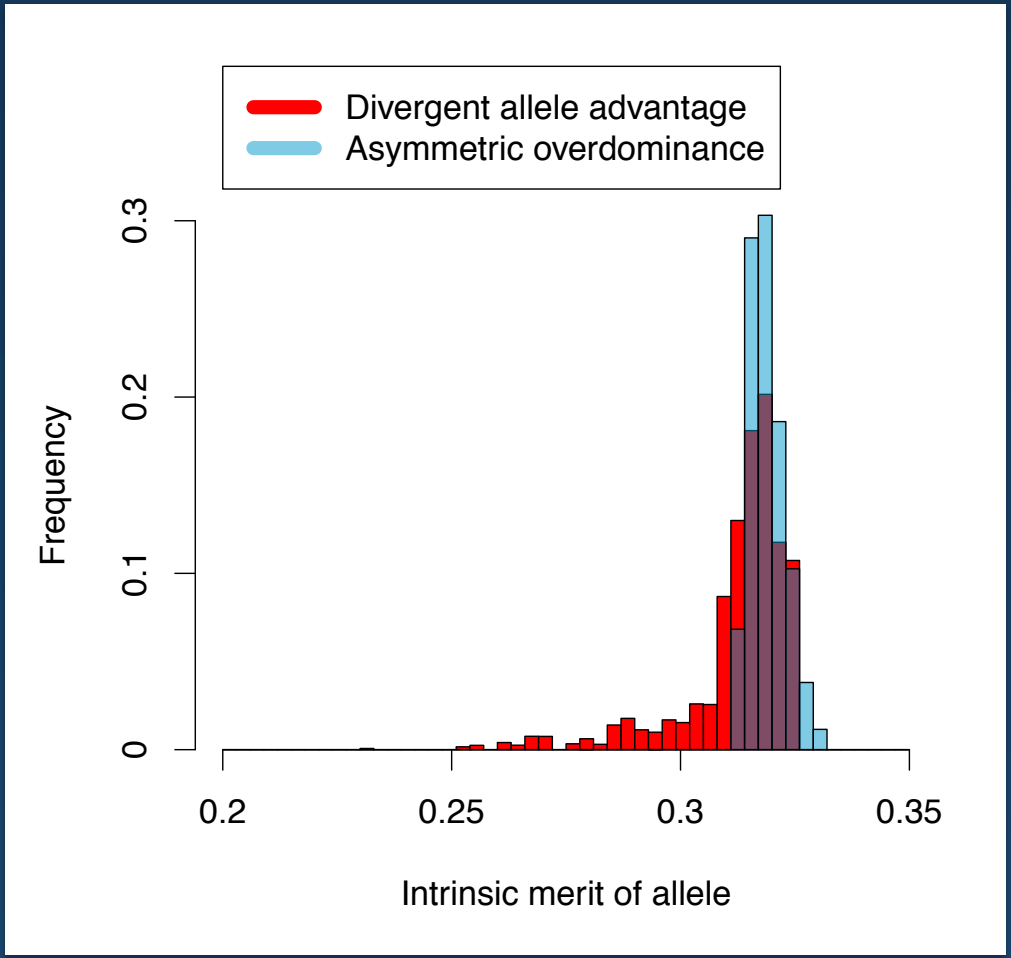
Using diversity profiles for model comparison

- Comparing naïve diversity to diversity that accounts for
  - differences in intrinsic merits between the alleles
  - differences in the amino acid sequences

- Models compared
  - divergent allele advantage
  - asymmetric overdominance

Results

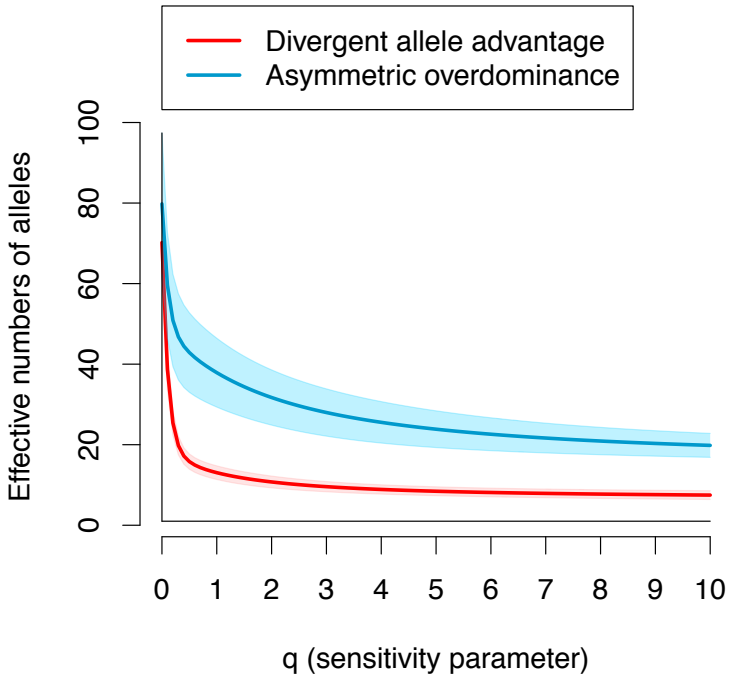
Distribution of intrinsic merits of alleles



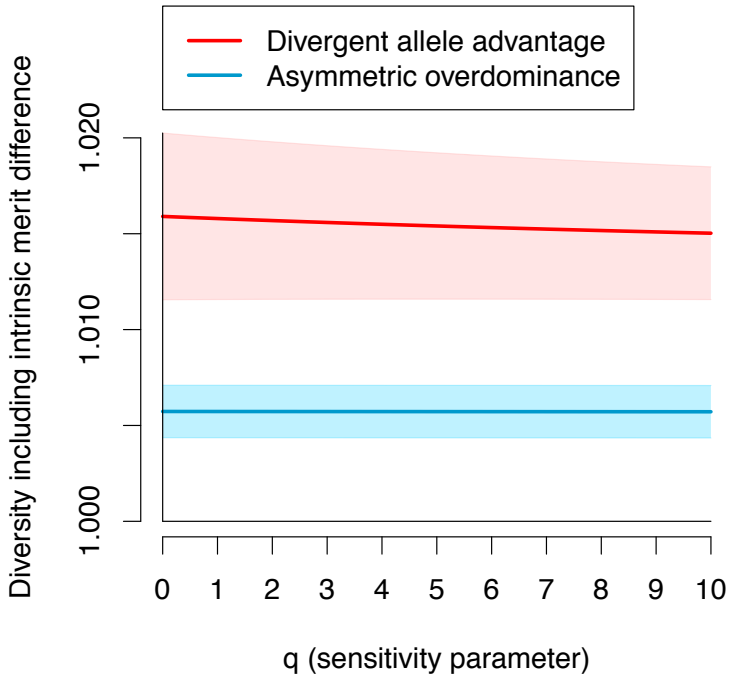
Results

Model comparison – Diversity with intrinsic merit difference

2,500,000 individuals



$^{q}D^{I}$



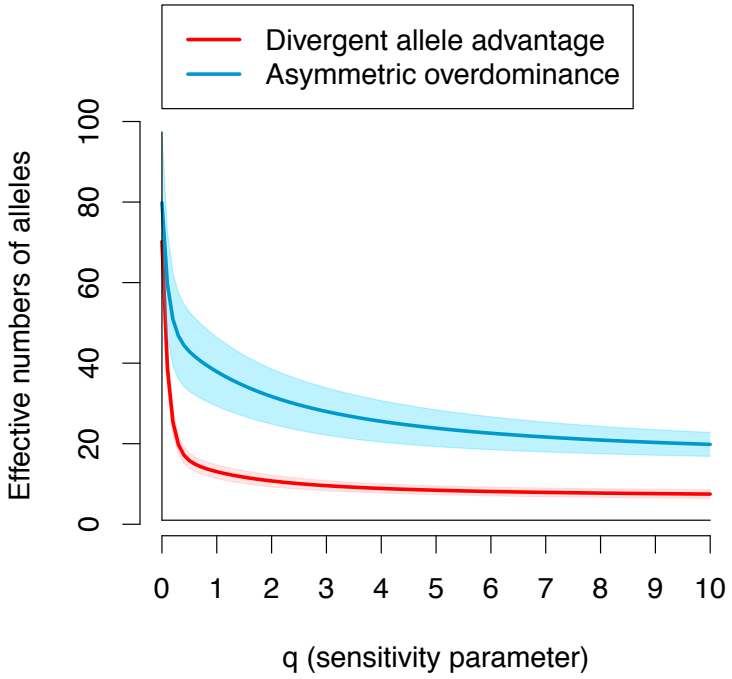
$^{q}D^{Z}$

$$z_{i,j} = \frac{w_{max} - w_{min} - |w_i - w_j|}{w_{max} - w_{min}}$$

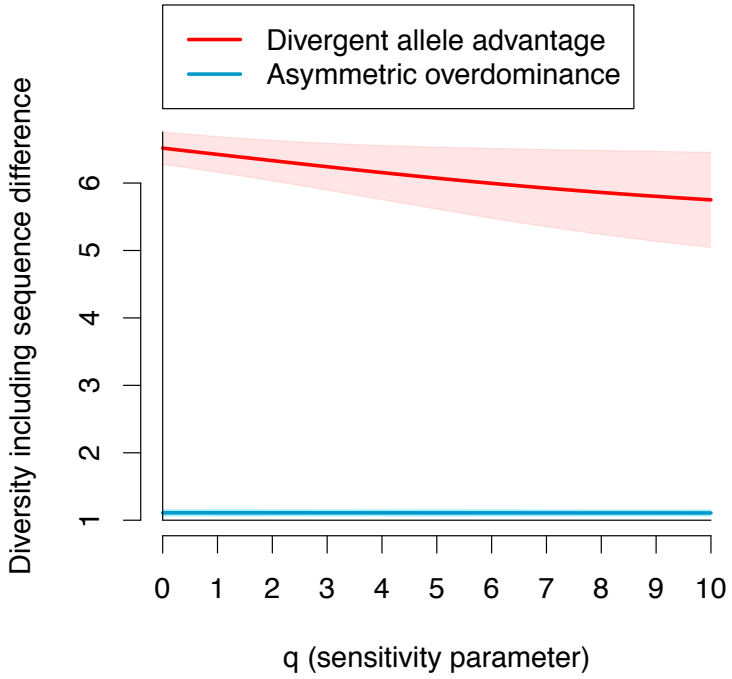
Results

Model comparison – Diversity with sequence difference

2,500,000 individuals



$^{q}D^{I}$



$^{q}D^{Z}$

$$z_{i,j} = \frac{d_{max} - d_{i,j}}{d_{max}}$$

Parameters

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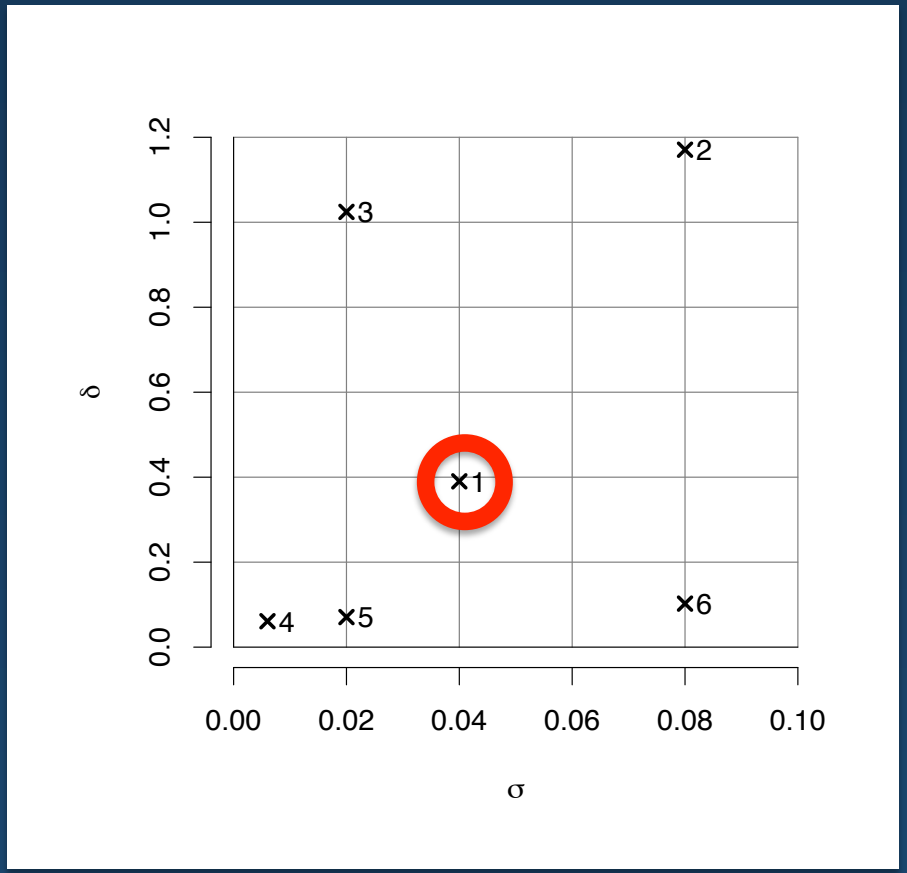


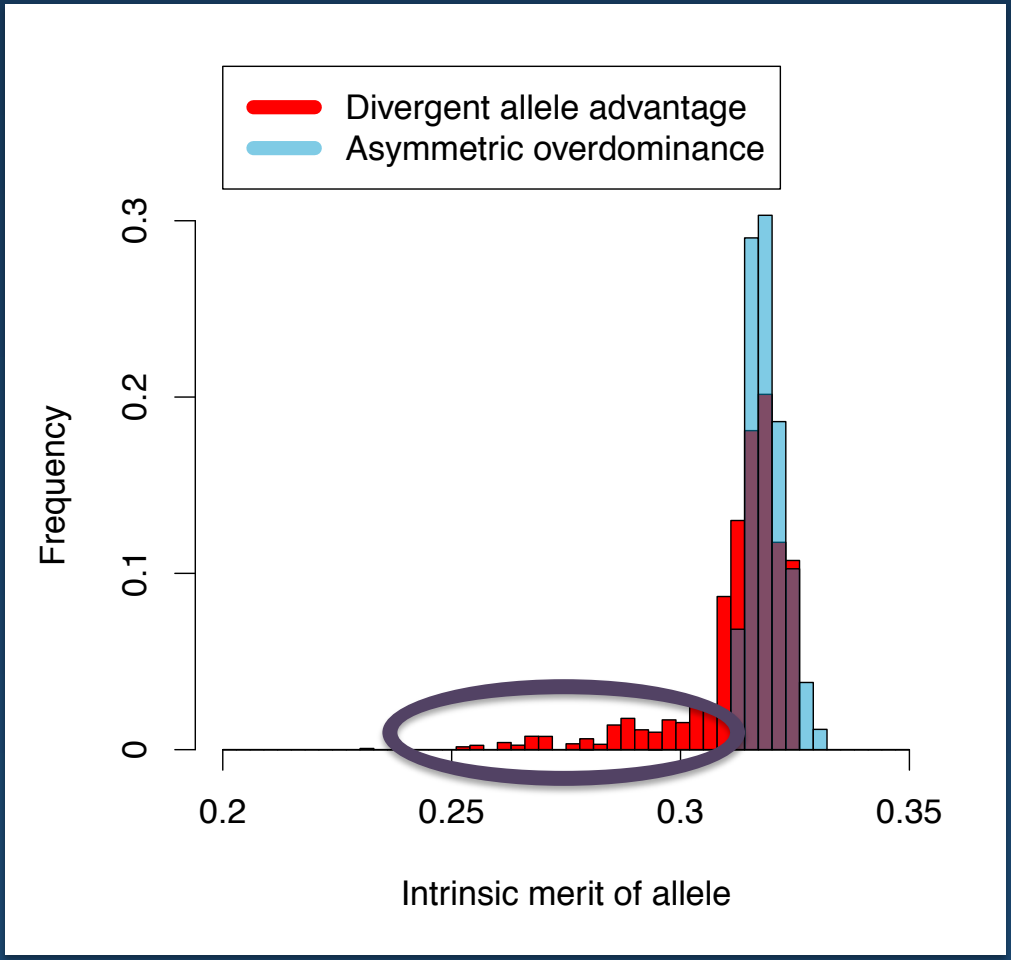
Conclusions

- Divergent allele advantage is the fundamental driver of MHC diversity
  - allelic diversity
    - number of alleles
    - other diversity measures
  - trans-species evolution
  - allows for variation in intrinsic merits of alleles

Applications
Divergent Allele Advantage Model

- Allele numbers in a population are less important than sequence diversity
  - a population with a large number of very similar alleles might be less fit than a population with a smaller number of very diverse alleles

Distribution of intrinsic merits of alleles



Applications
Divergent Allele Advantage Model

- Relatively unfit alleles may exist in a population at considerable frequencies
  - population may carry a high genetic load (homozygotes, heterozygotes with similar alleles)
  - identifying poor alleles and genotypes would help develop individualised human medicine
  - selecting a set of highly divergent alleles, or optimising the allele frequencies could improve disease resistance in managed populations

Acknowledgements

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