# Modelling the Generation and Maintenance of Diversity at the MHC

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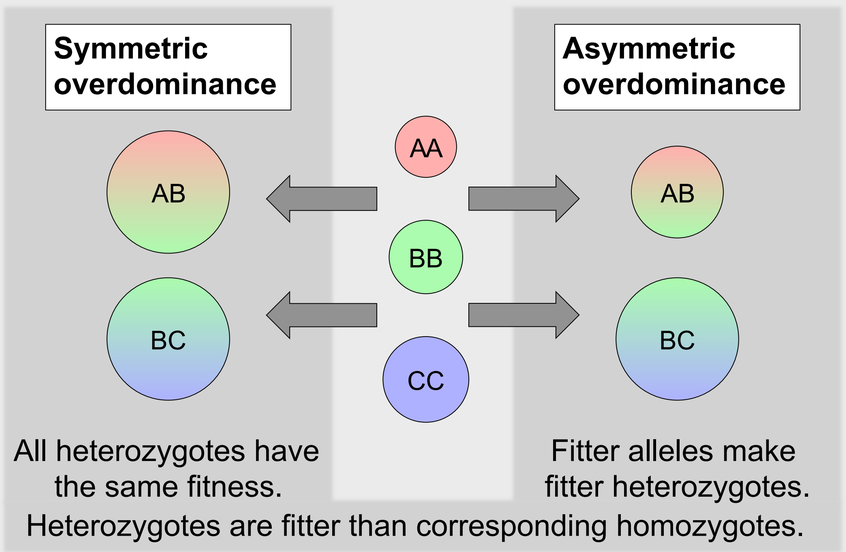
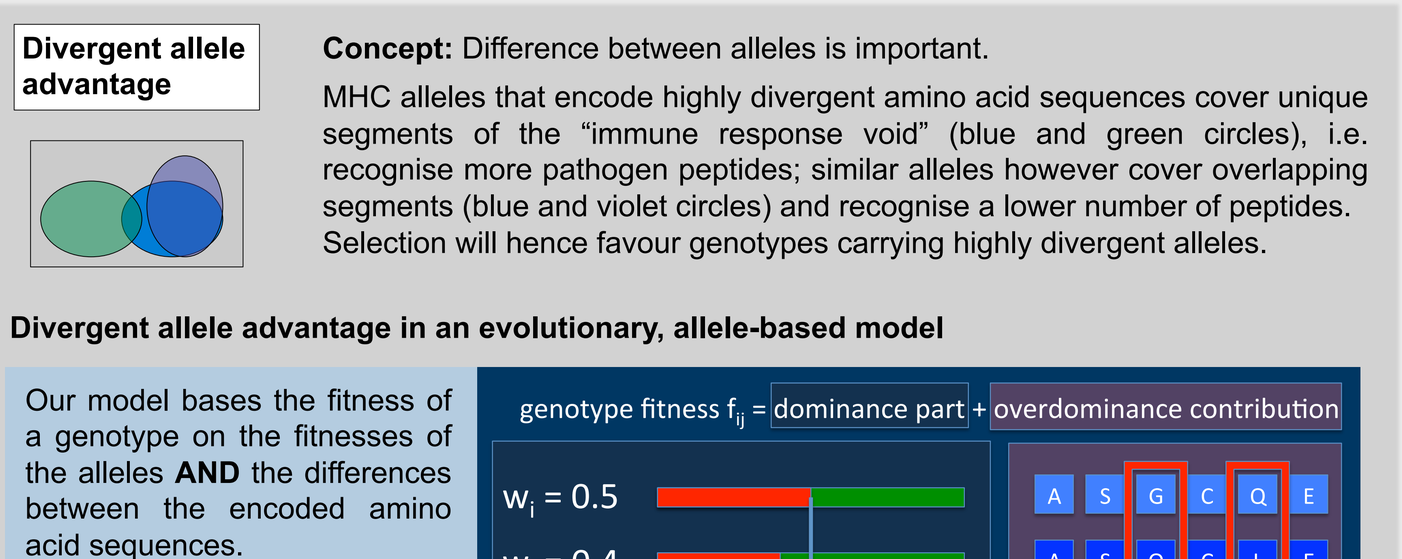
## Introduction

Genes encoding the major histocompatibility complex (MHC) are the most polymorphic loci in vertebrates. As MHC molecules play a central role in the immune system of vertebrates, pathogen-driven selection is assumed to be a main factor in maintaining diversity at MHC loci. Heterozygote advantage (also referred to as overdominance) is one of the popular explanations of how balancing selection forces act on MHC genes.

We develop a novel model based on the divergent allele advantage hypothesis of Wakeland et al[1], compare it to other popular models of heterozygote advantage, examine how well this new model reflects specific features of the MHC genes, and examine the implications. Finally, we discuss how using this model to deliberately select suitable animals can help in practical problems like breeding for increased disease resistance.

## Heterozygote advantage: explanations of its mode of operation



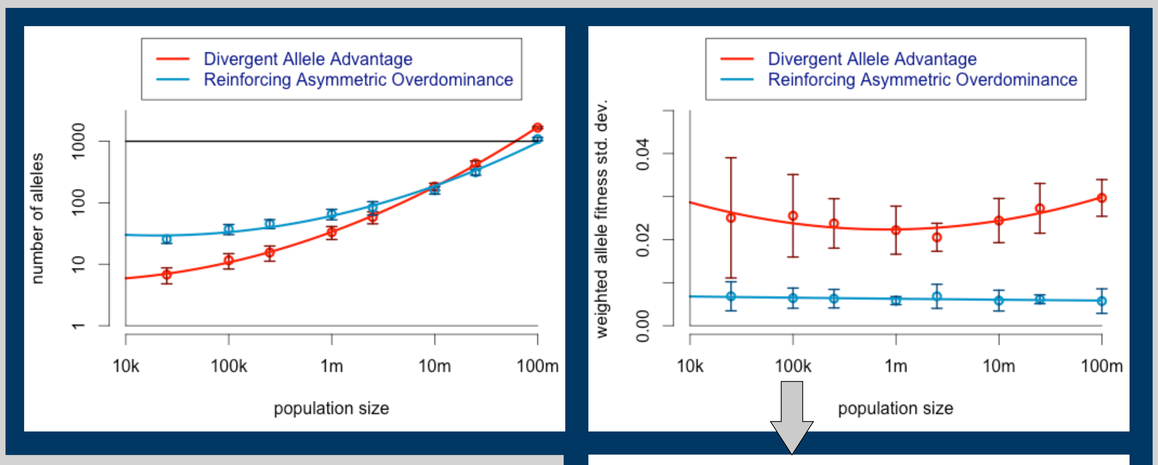




## Methods

Using these allele-based models, we performed stochastic simulations over evolutionary time scales covering millions of years, starting with a single allele and allowing for mutations as well as frequency changes based on fitness differences between alleles.

## Results and Discussion

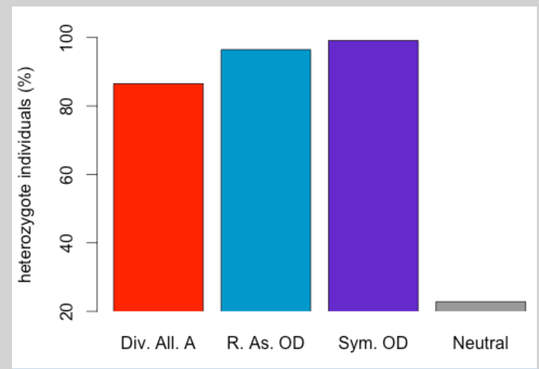
### Model comparison: the divergent allele advantage model characterises MHC features best




Both the asymmetric overdominance model and the divergent allele advantage model predict **large** enough **numbers of alleles** in the final gene pool for wide ranges of parameter values. Only the latter model, however, also maintains a **realistic range of allele fitness values**. Alleles present in the asymmetric overdominance model fall in a tight fitness range, but a considerably broader one is seen in the divergent allele advantage model. Relatively **unfit alleles** may **exist** in this model at **considerable frequencies**.

Fitness ranges for the final sets of alleles for the asymmetric overdominance model (blue) and the divergent allele advantage model (red) for 100,000 individuals.

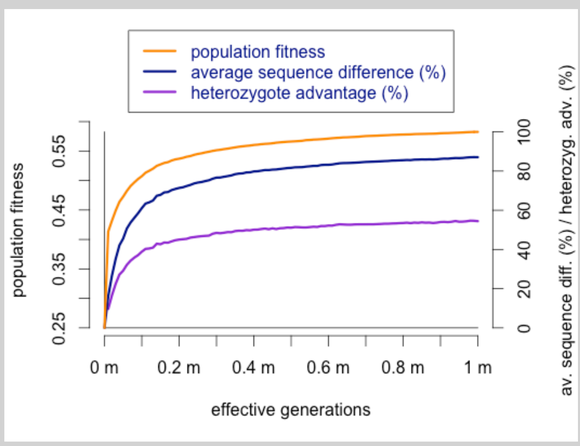
The symmetric overdominance model is known to allow for the generation and maintenance of a large number of alleles, however, our simulations show that allele frequencies are too even in this model. For that reason, it over-estimates **heterozygosity**. The **divergent allele advantage model** on the other hand predicts **realistic** percentages, while heterozygosity still clearly remains above neutral levels.




Heterozygosity levels for populations of 100,000 individuals

### Consequences for populations under the divergent allele advantage model

In the divergent allele advantage model, **population fitness** comes close to **equilibrium** values only after **millions of years**, even for large population sizes (pictured: 10 million individuals). This is because heterozygote advantage is linked to sequence divergence in the gene pool. Population crashes strongly degrade this highly evolved system, and regeneration in terms of fitness can take a long time after numbers of individuals have recovered.




## Conclusions

Heterozygote advantage acting through a divergent allele advantage model can explain observed properties of MHC alleles in our simple stochastic evolutionary model. It does not exhibit shortcomings of other models of heterozygote advantage. There is therefore a strong case to include sequence divergence in theoretical models of MHC genes.

## Applications

Knowledge of the way the MHC operates can help in selective breeding programmes by attaching importance to maintaining allelic diversity - both in terms of heterozygosity and sequence difference - as opposed to selecting for the fittest allele.

**References**
Wakeland, E.K., Boehme, S., She, J.X., Lu, C., McIndoe, R.A., Cheng, I., Ye, Y., and Potts, W.K. 1990. Immunological Research. 9, 115-122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