A Modelling Framework for the Effect of Nematode Resistance on MHC Diversity

D R Singleton, M J Stear, L Matthews
Boyd Orr Centre for Population and Ecosystem Health, Institute of Comparative Medicine, Faculty of Veterinary Medicine, University of Glasgow

Introduction

- Resistance to gastro-intestinal parasitism in sheep is a heritable trait.
- Selection for a particular trait may act to fix alleles in a population.
- The same MHC alleles that confer resistance to one disease could confer susceptibility to another disease.
- Selective breeding for nematode resistance that results in decreased allelic diversity could increase the susceptibility to other infections.
- However, heterozygote advantage can act to maintain diversity if differences in allelic effects are small.
- ***Will selective breeding for nematode resistance reduce allelic diversity in the MHC class II region and potentially increase the risk from other diseases?***

Modelling Nematode Infection in Sheep

- Bishop and Stear[1] describe a mathematical framework that can be used to model the response to selection for resistance to gastro-intestinal parasites in sheep.
- This uses six input parameters to estimate faecal egg count (FEC).

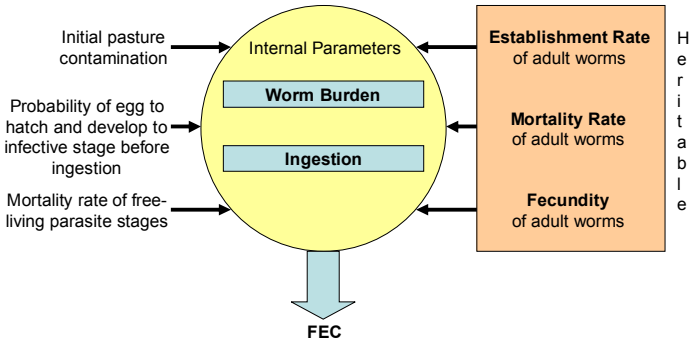

Figure 1. A schematic of the Bishop and Stear model, showing the six input parameters and two further internal parameters. The establishment, mortality and fecundity of adult worms have heritable components, and as such will be expected to vary over generations of a selective breeding program to reduce FEC.

- The parameters of establishment, mortality and fecundity of the adult worm have genetic and environmental components.
- Individual-based simulations of sheep populations model the inheritance of the genetic components.
- The existing framework has been modified to take account of developing immunity in sheep and its effect on establishment rate.
- Other modifications have been made to produce outputs that mimic empirical observations of FEC.[2]

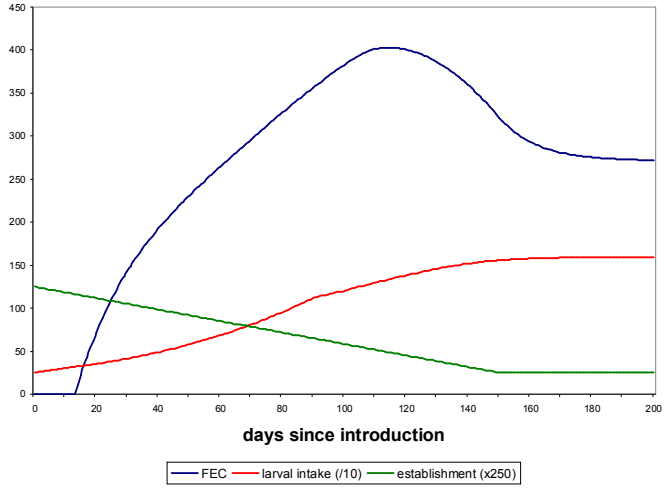

Figure 2. Showing how FEC and larval intake of lambs changes over time since introduction to a contaminated pasture. Also shown is the development of immunity reflected in decreasing establishment of parasites.

Heterozygote Advantage in Nematode Resistance

- Heterozygote advantage is observed in various systems, and is a mechanism of balancing selection through which genetic polymorphism is maintained in a population.

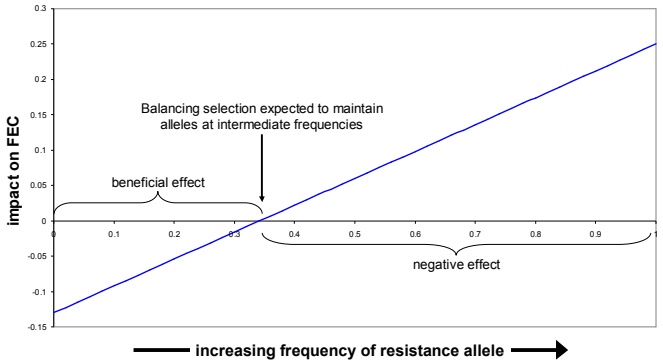

Figure 3. At lower frequencies a resistance allele can confer an advantage in terms of reduced FEC. However, at higher frequencies the benefits are lost as the probability of homozygosity increases.[3]

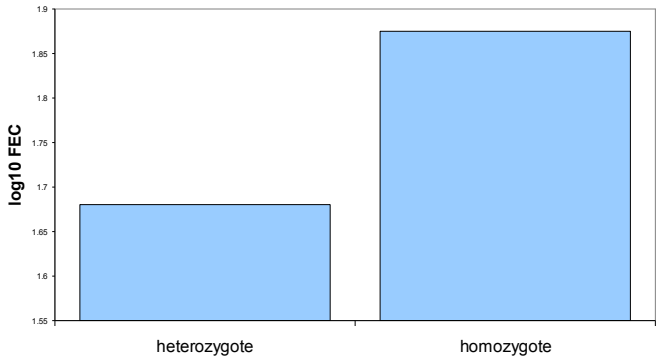

Figure 4. Sheep population studies show that heterozygotes have a lower mean FEC than homozygotes.[3]

- These observations suggest that a model of selection for nematode resistance should take account of heterozygote advantage effects.
- This could be achieved by expanding the original framework to model the MHC more realistically.

Modelling the MHC

- The original framework will be modified to include an individual-based genetic model.
- This differs from the original method, where heritable traits were simulated from a distribution of values.
- The updated model will simulate actual loci in the MHC.
- In this way, sheep can be assigned individual genotypes and allele frequencies can be tracked.
- Data will come from ongoing genotyping of the MHC class II region, focusing on six polymorphic loci.
- Both individual and combined effects of these loci on nematode resistance will be investigated.
- Selection will be based on FEC and FEC plus lamb growth rate.

Future Work

- Determine suitable breeding strategies for maintenance of diversity.
- Explore variations in selective breeding strategies, e.g. stringency of selection criteria.
- Investigation into non-selective effects such as population size, genetic drift and migration.

References:

1. Bishop, S. C. and Stear, M. J. 1997. Modelling responses to selection for resistance to gastro-intestinal parasites in sheep. *Animal Science* **64**, 469-478.
2. Stear, M. J., *et al.* 2006. Variation among faecal egg counts following natural nematode infection in Scottish Blackface lambs. *Parasitology* **132**, 275-280.
3. Stear, M. J., Innocent, G. T. and Buitkamp, J. 2005. The evolution and maintenance of polymorphism in the major histocompatibility complex. *Veterinary Immunology and Immunopathology* **108**, 53-57.