Modelling the spread of resistance to anthelmintic drugs in sheep nematodes

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Background

- Helminth infections (e.g. *Haemonchus contortus* or *Telgadorsagia circumcincta*) are widespread problem for livestock
- Anthelmintic drugs such as Ivermectin and Levamisole exist, but there is a growing problem of anthelmintic resistance (AHR), which complicates disease control, and the mechanisms of resistance are poorly understood
- Some resistance traits appear recessive, while others are dominant
- We wish to better understand how resistance genes spread throughout a population, but **most models to date** have assumed only a single locus and recessive resistance, which may fail to capture the correct transmission dynamics
- We explore the effects of both the number of loci associated with resistance, and the effects of dominance

Alleles, genotypes, and fitness

- All possible genotypes are identified and labelled with a unique number, so the numbers of each genotype can be tracked within the population
  - Example, for two loci each with two alleles, this would be $A_{11}B_{11}$, $A_{11}B_{12}$, $A_{11}B_{22}$, $A_{12}B_{11}$, $A_{12}B_{12}$, $A_{12}B_{22}$, $A_{22}B_{11}$, $A_{22}B_{12}$, $A_{22}B_{22}$, ($3\times3 = 9$ genotypes), labelled 1-9
- Each allele a has fitness values f_a^- and f_a^+, which are the fitnesses of the allele in the presence (+) and absence (-) of an anthelmintic drug
  - Fitnesses of alleles in different loci are additive (and scaled by the number of loci, to ensure a maximum possible fitness of 1)
- Each genotype g has fitness values f_g^- and f_g^+
  - Alleles with a lower number are dominant to alleles with a higher number at the same locus, so a genotype $A_{12}B_{12}$ has fitnesses $f^-_{A_{12}B_{12}} = f^-_{A_1} + f^-_{B_1}$ and $f^+_{A_{11}B_{22}} = f^+_{A_1} + f^+_{B_2}$

Model assumptions

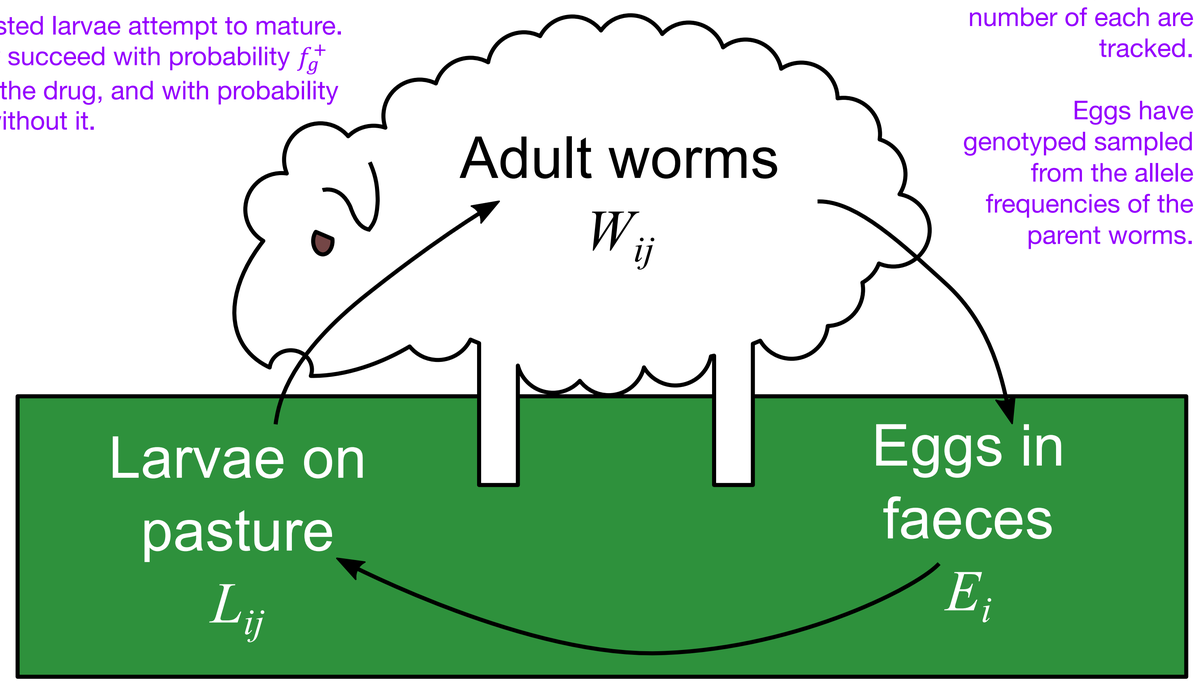
- Worms live in the hosts, a flock of n sheep, and produce eggs via sexual reproduction
- Eggs are excreted onto pasture, and hatch into larvae
- Larvae are consumed by (and in the process re-infect) the sheep
- A drug is administered for 3 months a year, which is assumed to kill larvae at the point of infection
- The model tracks the number of worms and larvae with each genotype in each sheep, and the number of eggs with each type
- The change in allele frequencies over time is recorded

Resistant worms are more likely to survive treatment

Ingested larvae attempt to mature. They succeed with probability f_g^+ with the drug, and with probability f_g^- without it.

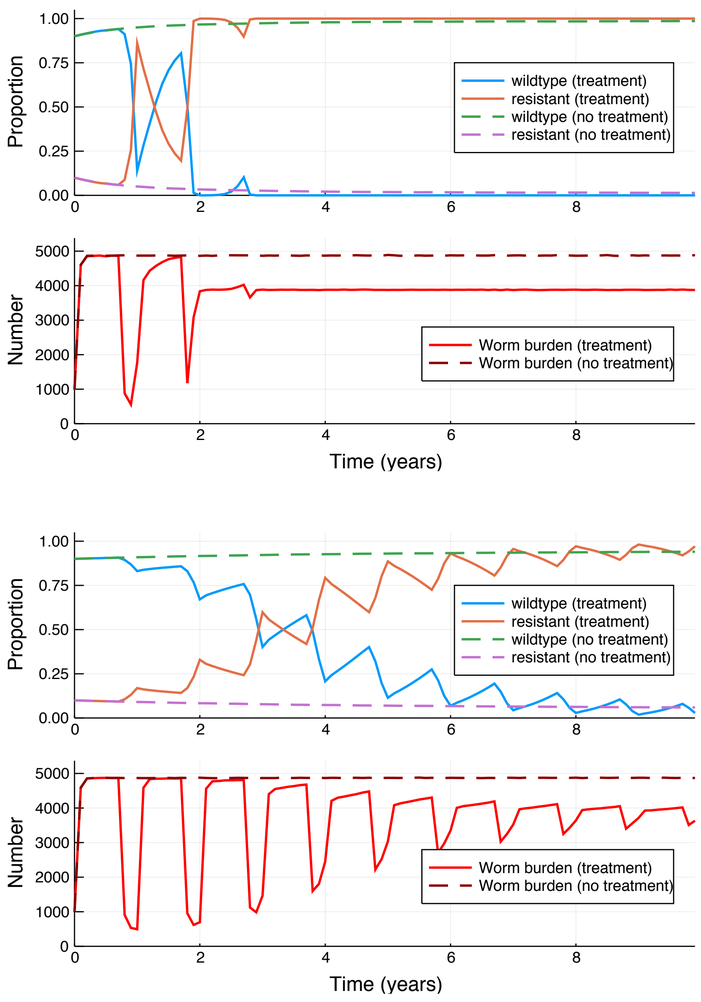
All possible genotypes are enumerated, and the number of each are tracked.

Eggs have genotyped sampled from the allele frequencies of the parent worms.



Impact of number of loci and dominant vs recessive alleles

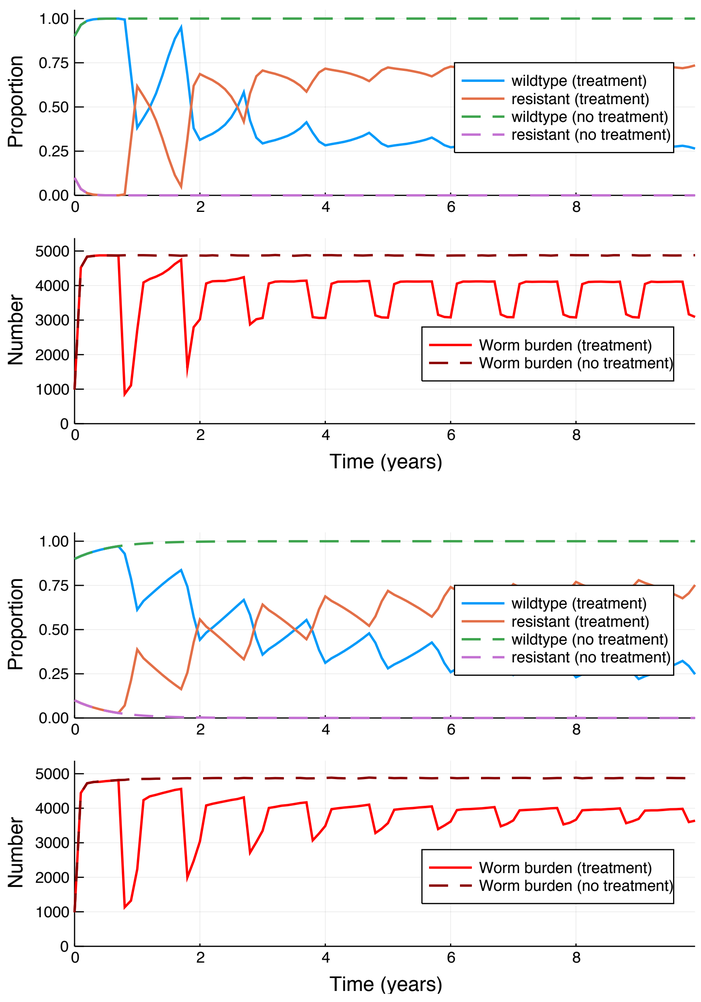
- Treatment is administered for 3 months out of the year (solid lines), and compared with no treatment (dashed lines)
- To clearly expose the dynamics, we examine an extreme scenario where resistant alleles are only 80% as fit as the wildtype
- In the absence of treatment, the fitnesses of wildtype alleles w and resistant alleles r are $f_w^- = 1.0/L$ and $f_r^- = 0.8/L$ (dividing by the number of loci L)
- In the presence of treatment, the fitnesses of wildtype alleles w and resistant alleles r are $f_w^+ = 0.1/L$ and $f_r^+ = 0.8/L$ (i.e. no loss of fitness for the resistant alleles)



1 locus
resistant allele is **recessive**

Time to fixation increases with the number of loci

5 loci
resistant allele is **recessive**



1 locus
resistant allele is **dominant**

Dominant alleles may not reach as high a level of fixation

5 loci
resistant allele is **dominant**

Key observations

- Dominant alleles may fail to reach the same fixation as resistant alleles
- Resistance spreads more quickly when resistance is a single locus trait, and more slowly when it is a multilocus trait

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