Investigating the impact of antagonistic selection in vector-transmitted parasitic diseases

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Pathogens and transmission

- A pathogen may be transmitted in a few different ways
  - Air: sneezing, coughing, the spread of dust – aerosolized particles
  - Water: contamination, pollution, poor sanitation
  - Organisms: rats, fleas, mosquitoes
- Disease-carrying organisms are called vectors

Vector-borne diseases

- Well-known vector-borne diseases include Lyme disease (ticks), bubonic plague (rats), and typhus (lice)
- Many are parasitic – microorganisms that live inside both vectors and hosts
- Parasites come in a variety of forms, but we are interested in eukaryotic protozoans
    - Leishmaniasis
    - Chagas disease
    - Malaria

Malaria

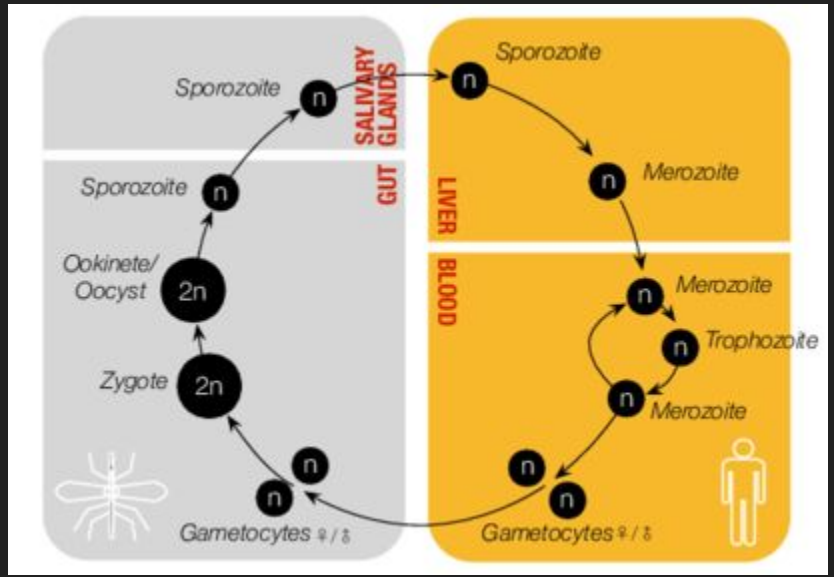
- Caused by organisms of the genus *Plasmodium*
- Transmitted by female *Anopheles* mosquitoes
- 2022: 249 million cases, 608 thousand deaths

Protozoan parasites: life cycle

- Differs between hosts and vectors
- *Plasmodium*: inside human hosts
  - Transmitted as sporozoites
  - Replicate inside liver as merozoites
  - Spread into bloodstream, cause malaria symptoms
  - Produce gametocytes, which get transmitted to mosquitoes

Protozoan parasites: life cycle

- Enter into midgut, develop into ookinetes
- Develop further into oocysts
- Travel to salivary glands, transition into sporozoites
- May now infect hosts



Selection & life cycle

- Different traits influence its behavior during the internal & transmission stages for both hosts and vectors
- Advantageous traits may spread across a parasite population
  - Fitness
  - Transmission probabilities
- Antagonistic traits: advantageous in one population, disadvantageous in the other

Mutations and fitness

- The parasite’s genes determine its behavior, and mutations can influence that
- If a mutated strain has a higher fitness than the wild-type strain, natural selection may make it more prevalent

$$p' = \frac{pW_1}{pW_1 + qW_2}$$

Genetic drift

- Evolution is not inherently deterministic
- An individual with higher fitness may die before producing offspring
- Inversely correlated with population size
  - Hosts: ~10^8 parasites, very small effect
  - Vectors: <100, much more significant effect
- Wright-Fisher model: discrete-time Markov chain, binomial sampling

$$P_{ij} = \binom{N}{j} \left(\frac{i}{N}\right)^j \left(1 - \frac{i}{N}\right)^{N-j}, \qquad i, j \in [0, N]$$

Transmission probabilities

- Contacts do not always result in transmission
- Analogous to fitness within hosts and vectors
- Antagonistic transmission probabilities may produce interesting behavior

Macroscopic model

- SIR model: “susceptible, infected, recovered”
  - SIRS – waning immunity
- Simplified somewhat
- Typically employ continuous-time Markov chains, but ours is a discrete-time approximation
  - Exponential random variables are computationally expensive
  - Interfaces better with microscopic model

Events and transition rates

Host population

Rate meaning	**Expression**	ΔS	ΔI	ΔR
Recovery	γI	0	-1	$+1$
Waning immunity	ωR	$+1$	0	-1
Infected contact	$\kappa S_v I_h / N_v$	-1^*	$+1^*$	0

Vector population

Rate meaning	**Expression**	ΔS	ΔI
Susceptible death	μS	-1	0
Infected death	μI	0	-1
Birth	μN	$+1$	0
Infected contact	$\kappa S_h I_v / N_h$	-1^*	$+1^*$

Weighted infected count

- Complicated by the microscopic side, where multiple strains might be present in an individual
- Infected counts had to be weighted accordingly

Host population

Rate meaning	Expression	ΔS	ΔI	ΔR
Recovery	γI	0	-1	$+1$
Waning immunity	ωR	$+1$	0	-1
Infected contact	$\kappa S_v I_h / N_v$	-1^*	$+1^*$	0

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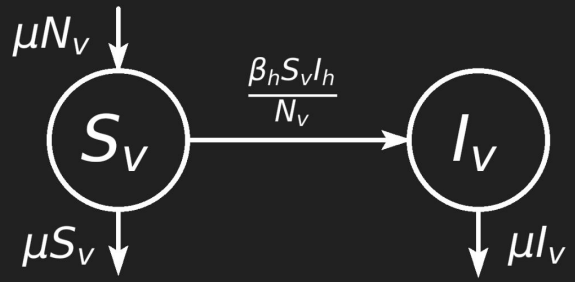
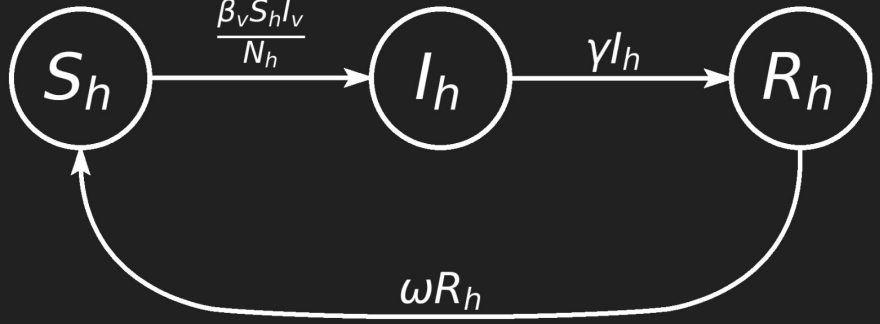
Birth	μN	$+1$	0
Infected contact	$\kappa S_h I_v / N_h$	-1^*	$+1^*$

Compartment diagram

VECTOR:



HOST:



Microscopic model

- Haploid in the host, diploid in the vector
- Two main algorithms: mutation, genetic drift
- Mutations only happen in the host
- Wright-Fisher model only used in the vector
- Simulated on a discrete basis

Algorithms

- Mutations per allele are Poisson-distributed
- Genetic drift uses binomial sampling instead of a transition probability matrix
  - Much faster
- For vectors, alleles are multinomially distributed across genotypes

$$\begin{bmatrix} P_{dd}, & P_{Dd}, & P_{DD} \end{bmatrix} = \begin{bmatrix} q^2, & 2pq, & p^2 \end{bmatrix}$$

Implementation

- Python: object-oriented, wide variety of useful packages
- Readable code, semantically clear methods and properties
- Efficient without meaningfully compromising accuracy

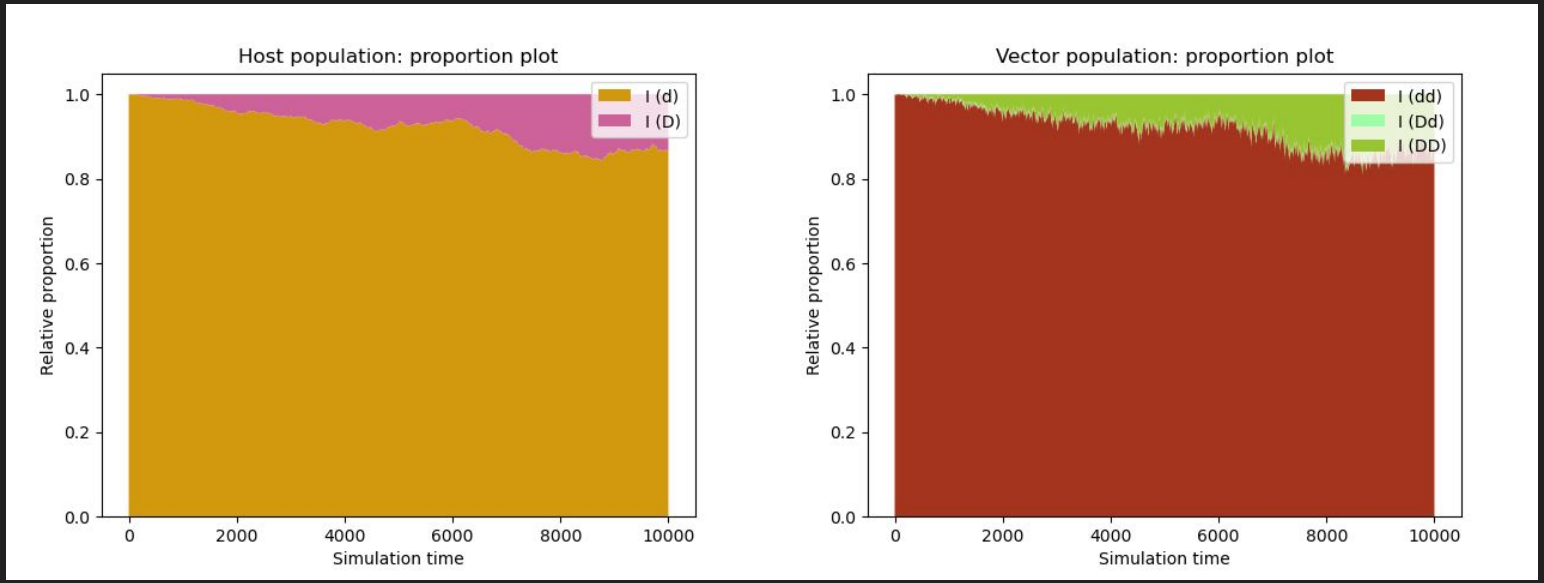
```
def getAlleleFreqs(self):
    '''
    Gets the frequency of the mutated allele in the individual's parasite population. Used primarily in `genDrift`.
    '''
    if self.is_hap: return self.genotype_freqs[self.main_all_char]
    else:
        mac = self.main_all_char
        return 2*self.genotype_freqs[mac+mac] + self.genotype_freqs[mac+self.scnd_all_char]

def getGenotypes(self):
    '''
    Returns all present genotypes as a list.
    '''
    return [gt for gt in self.genotype_freqs if self.genotype_freqs[gt]]
```

Numerical experiments

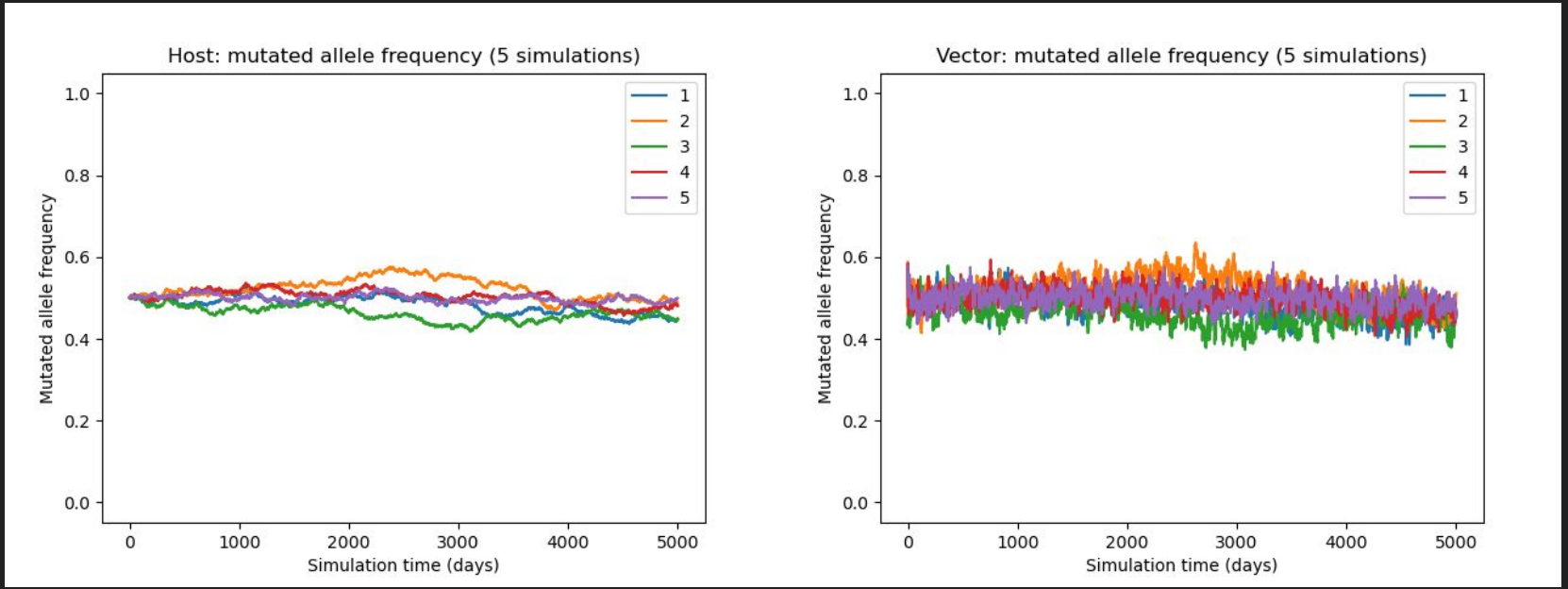
- Experiments were performed for both selection and transmission parameters
- Control: no advantages
- Host advantage only
- Vector advantage only
- Antagonistic advantages

Control


Host population: proportion plot
I (d)
I (D)
Relative proportion
Simulation time
0.0
0.2
0.4
0.6
0.8
1.0
0
2000
4000
6000
8000
10000
Vector population: proportion plot
I (dd)
I (Dd)
I (DD)
Relative proportion
Simulation time

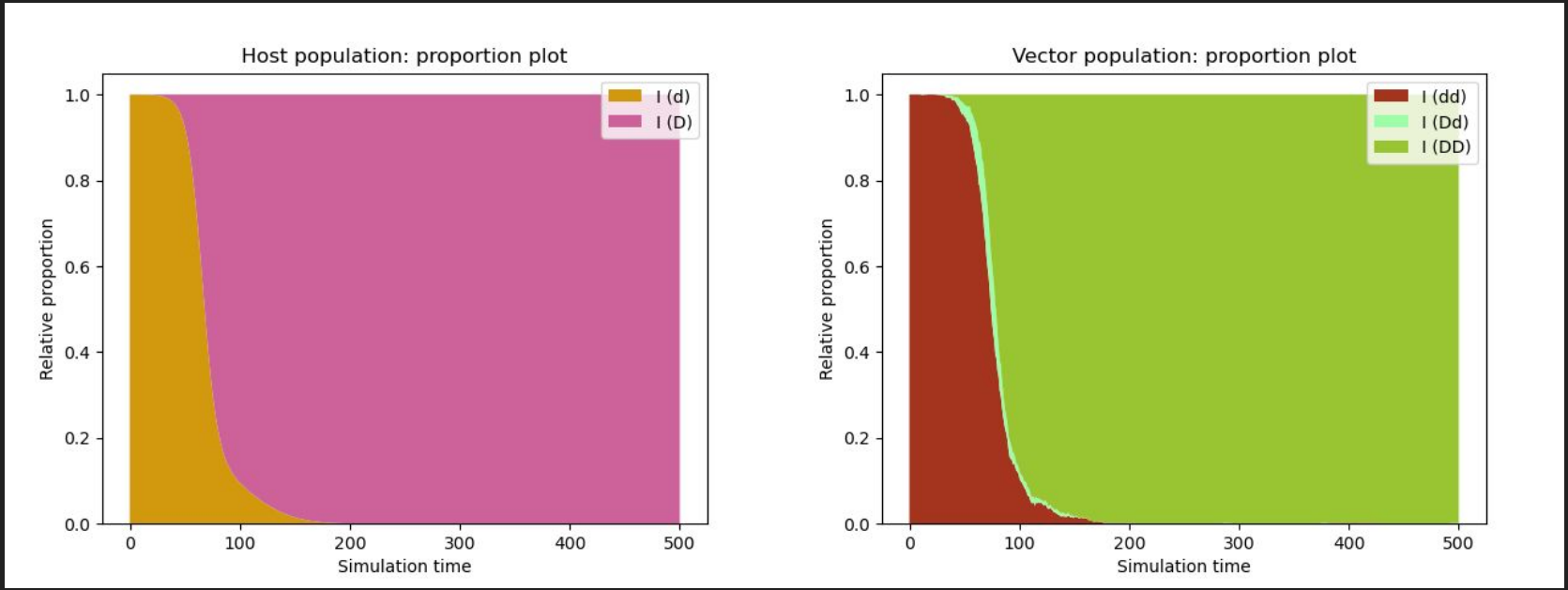
Control

Five simulations, 5000 days each



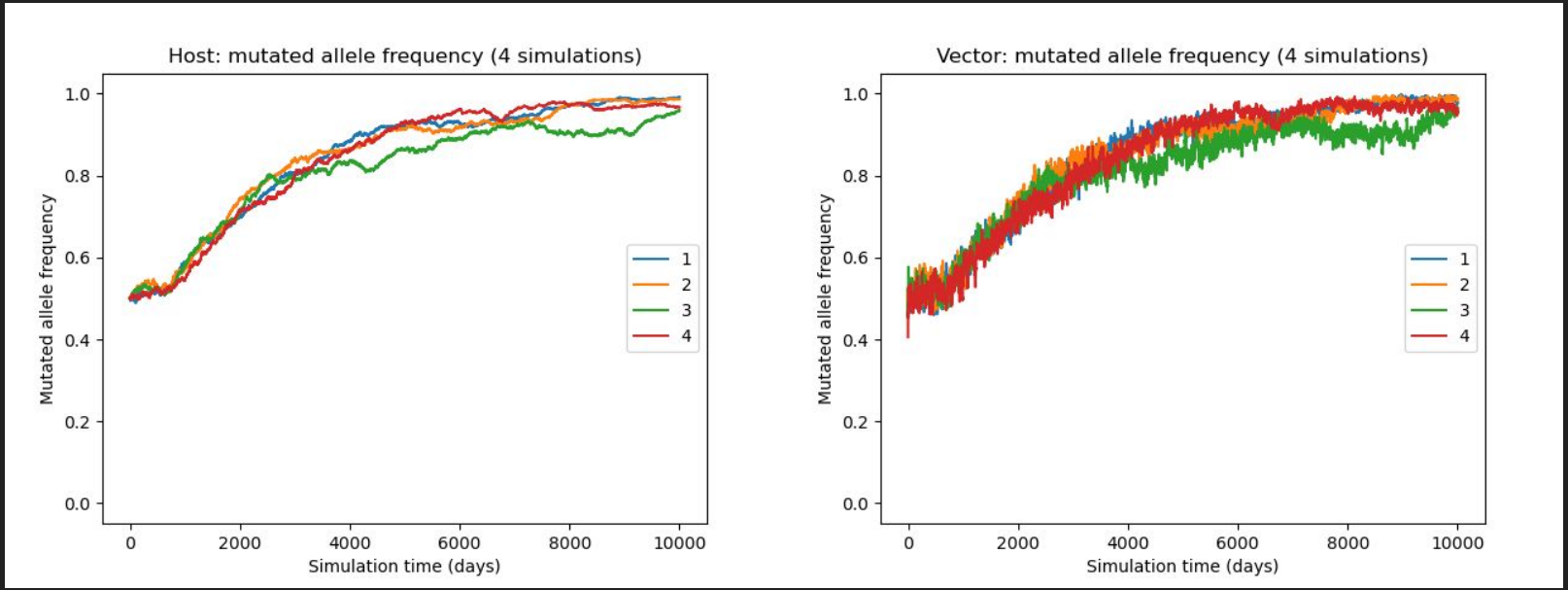
Host selection advantage

Relative fitness of 1.05 (mutated allele)



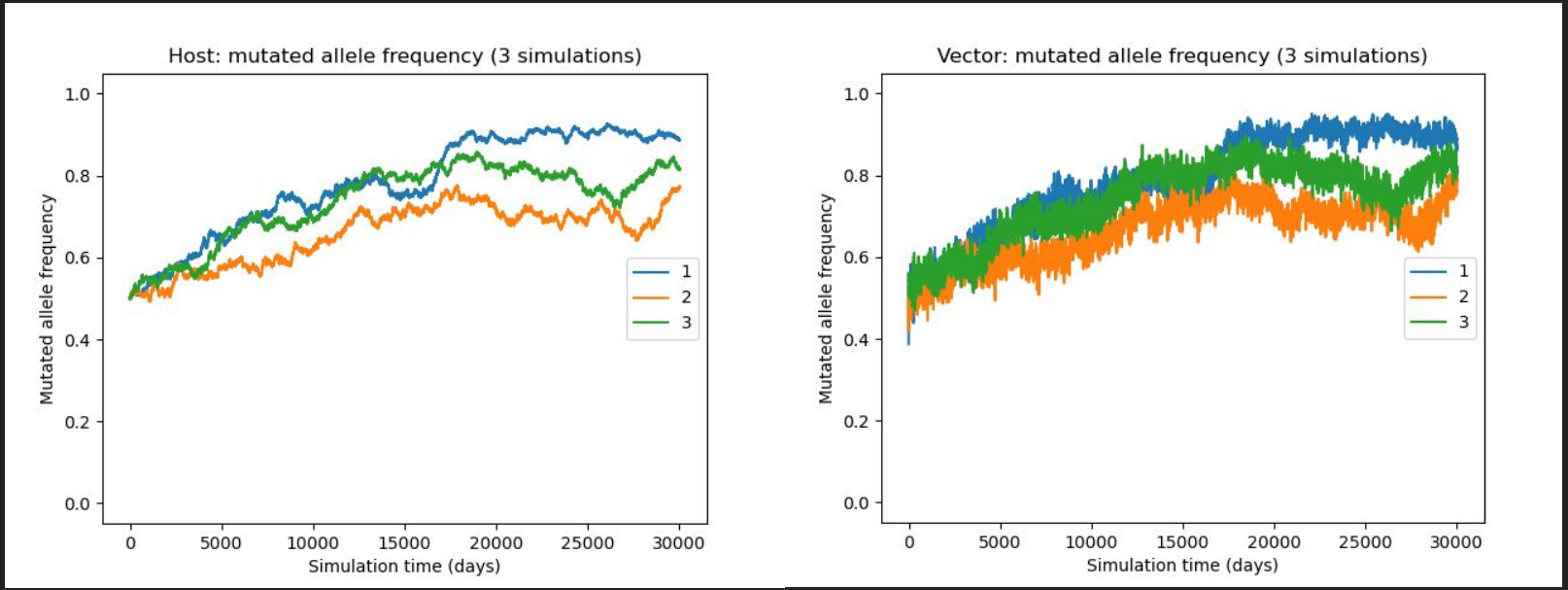
Host selection advantage

Relative fitness of 1.002 (mutated allele)



Vector selection advantage

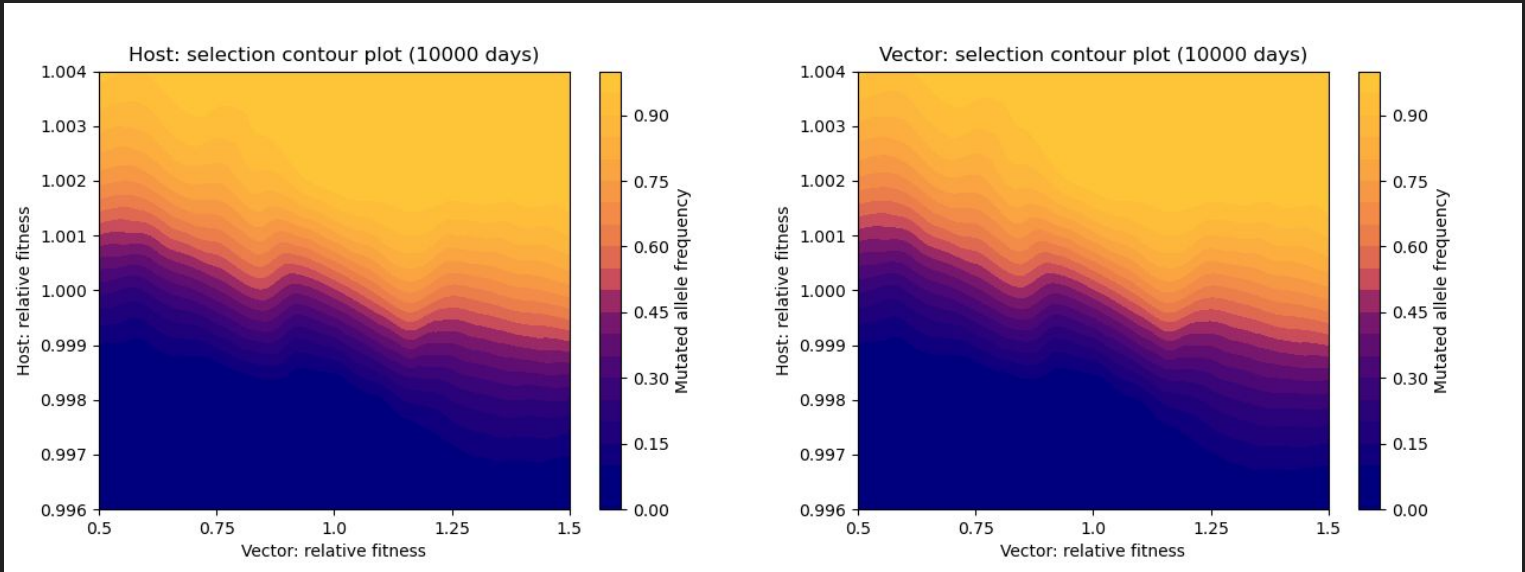
Relative fitness of 1.5 (mutated allele)



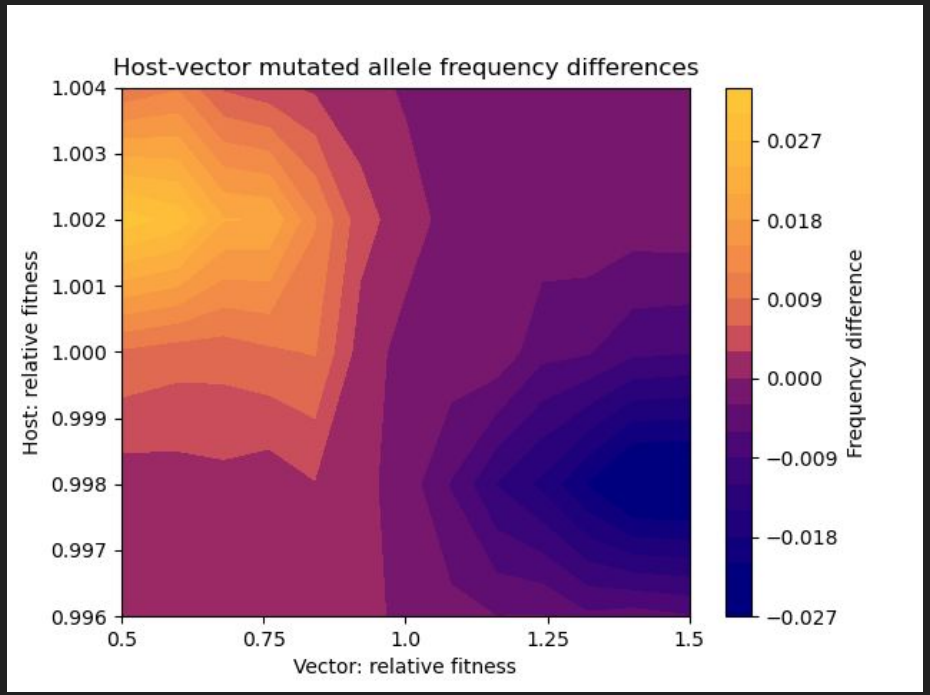
Antagonistic selection: contour plots

5 y-axis points (host), 13 x-axis points (vector)

2 simulations, 10000 days per point

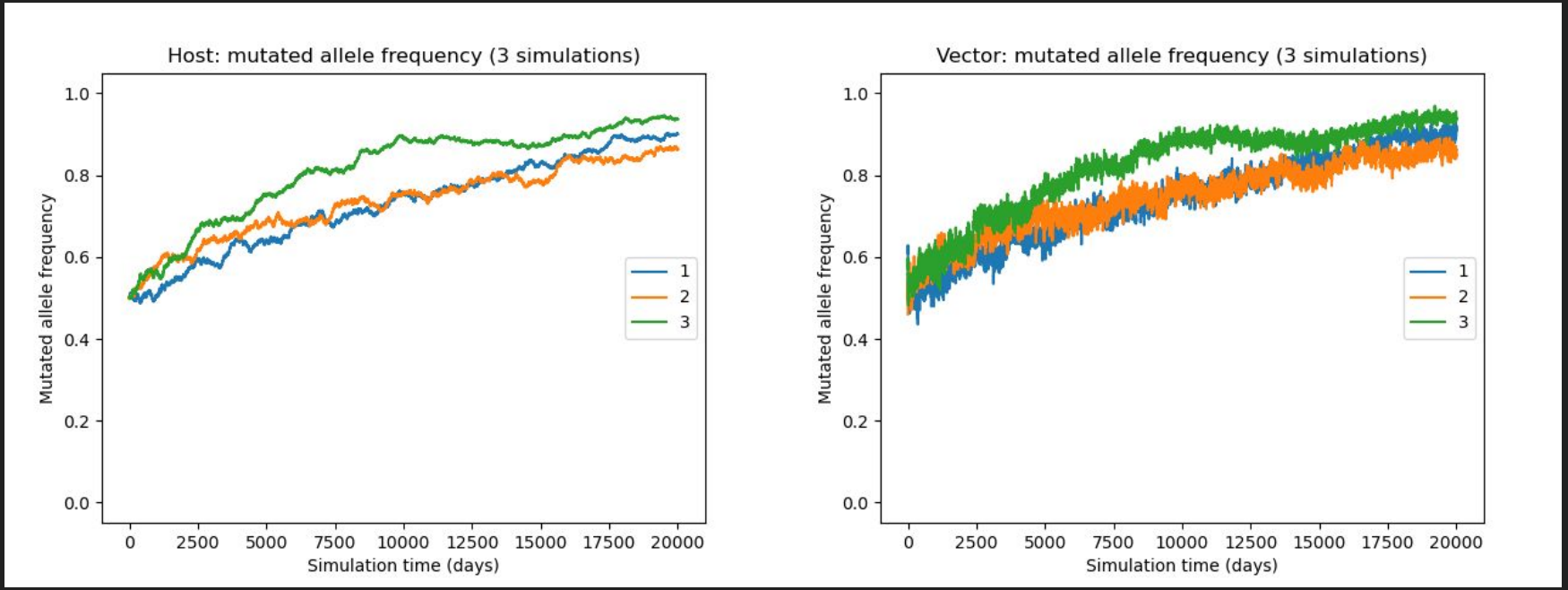


Antagonistic selection: difference plot



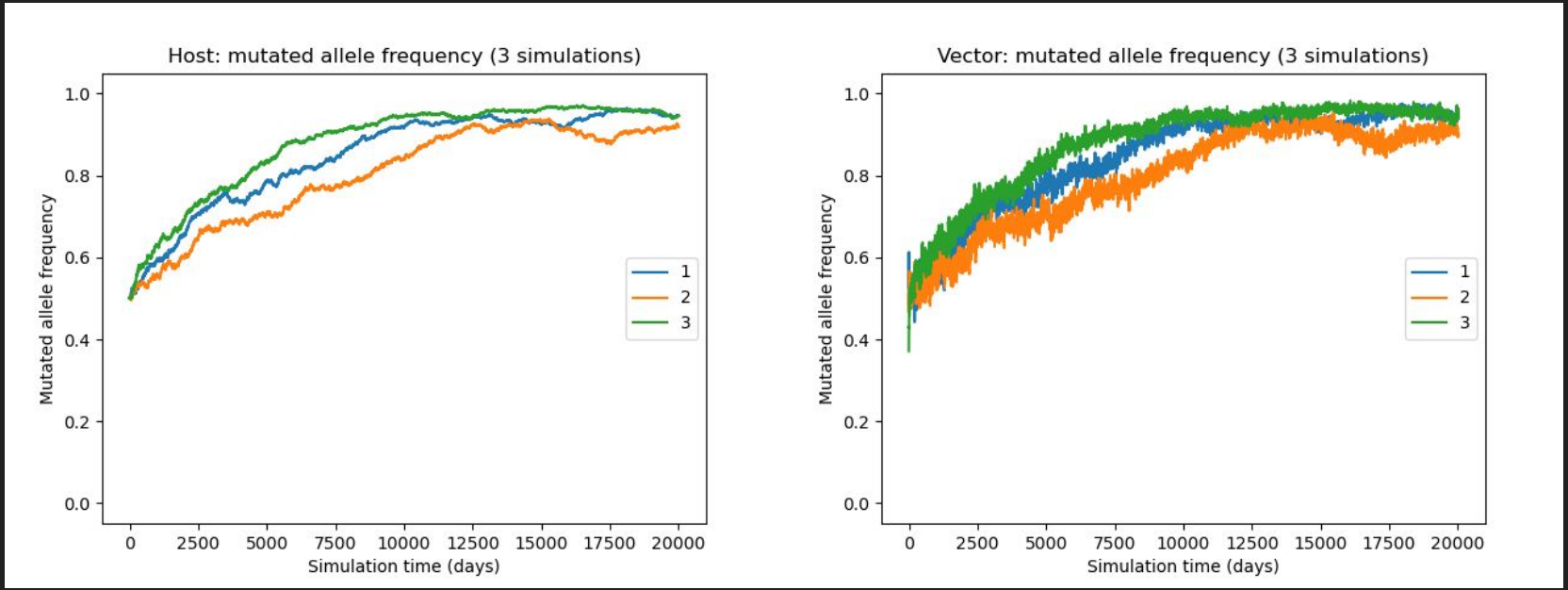
Host transmission advantage

Mutated allele: transmission probability 0.12 (wild-type: 0.11), hosts → vectors



Vector transmission advantage

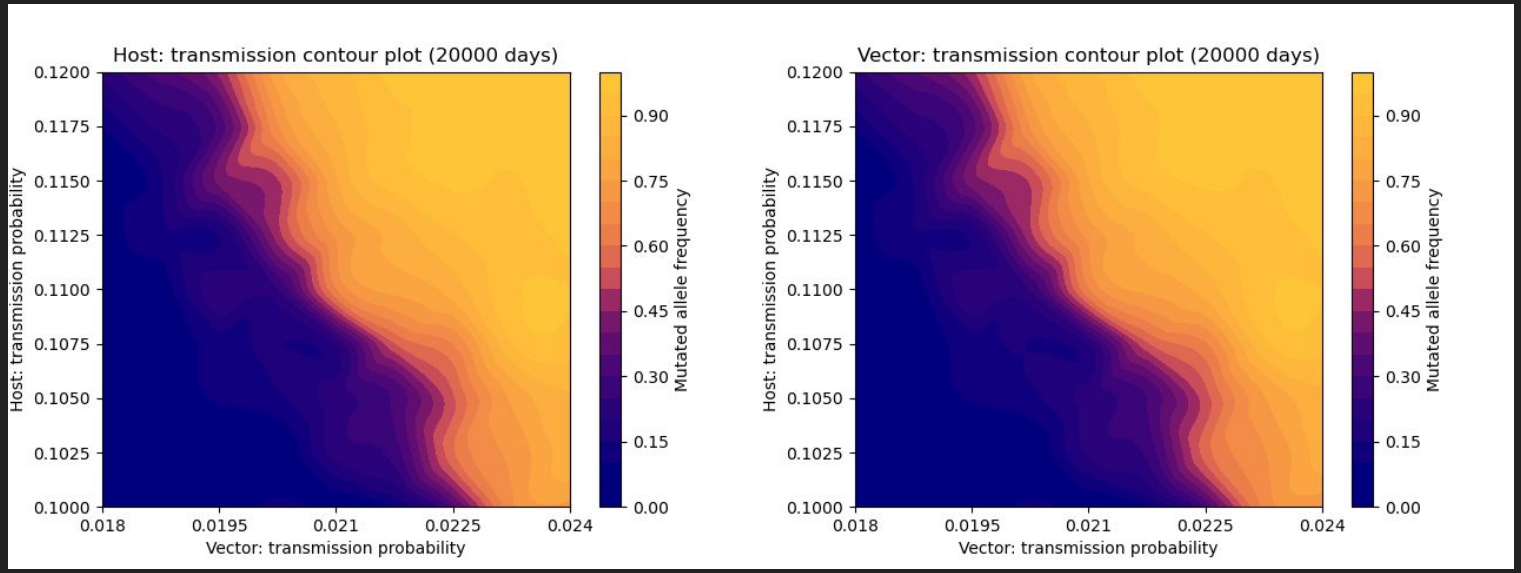
Mutated allele: transmission probability 0.024 (wild-type: 0.021), vectors → hosts



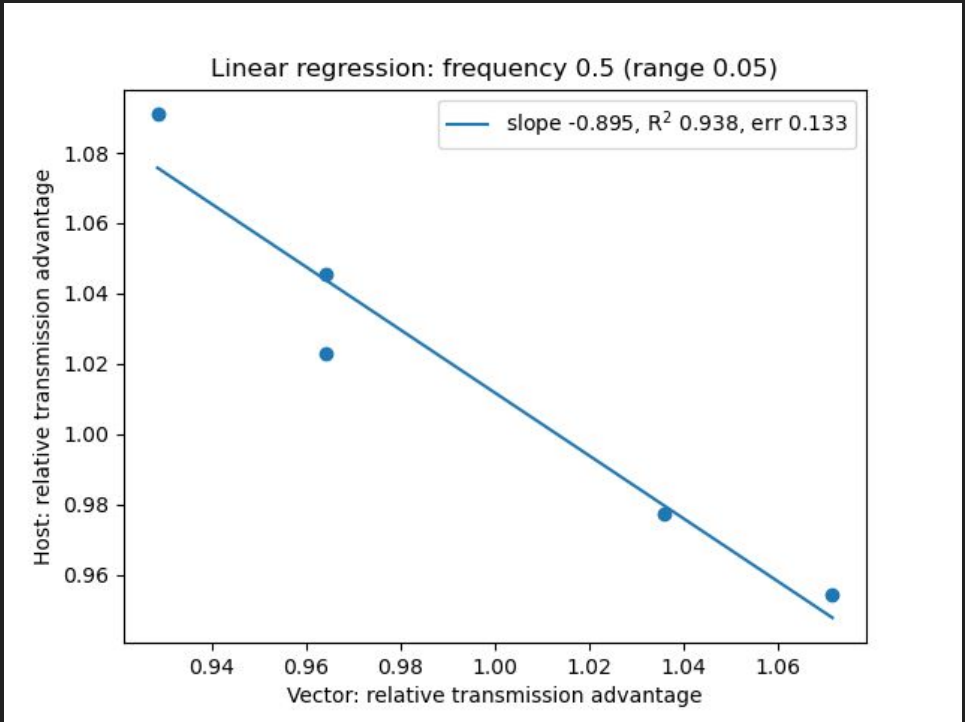
Antagonistic transmission: contour plots

9 y-axis points (host → vector), 9 x-axis points (vector → host)

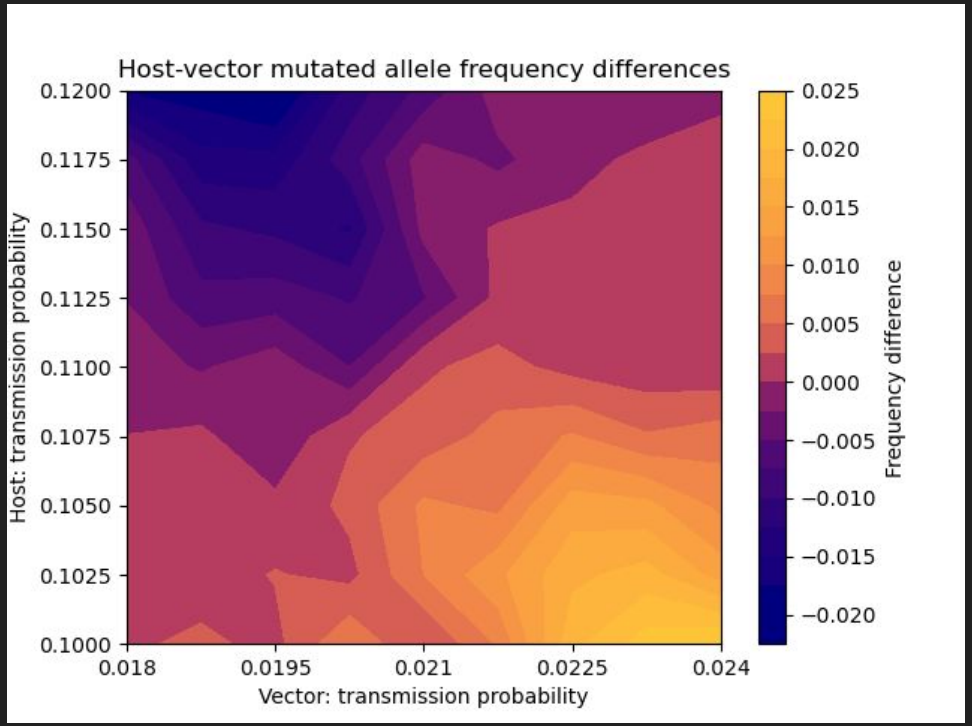
1 simulation, 20000 days per point



Transmission advantages: linear regression



Antagonistic transmission: difference plot



Conclusions

- Host and vector selection advantages differ greatly in strength: the former are much stronger, while the latter are limited by small vector parasite populations
- Transmission advantages, by contrast, showed no significant strength difference between hosts and vectors
- Antagonistic quadrants featured the greatest differences, but the contour curvature suggests the behavior is not purely quadrant-dependent
- Consistent behavior between antagonistic selection and transmission

Conclusions

- Limited by computational cost
- Areas of further interest
  - Multiple loci – comparing numerous competing alleles would have been interesting
  - Higher-resolution contour plots
  - Longer simulations – equilibrium frequencies
  - Larger populations
  - Antagonism between selection and transmission parameters

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All the code for the model can be found on Github: https://github.com/aclewis242/paramodel.git.