Model of Cross Immunity in Malaria Endemics

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Outline

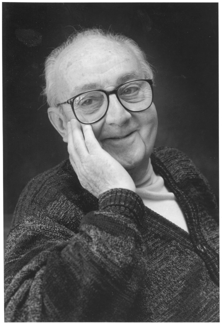
1. Epidemiological models
2. Malaria
3. The model of this thesis
4. Three questions to answer
5. Vaccine injection

Epidemiological models

Epidemiological models describe disease. Two important distinctions:

- Epidemic: Widespread disease for a short time.
- Endemic: Permanent disease in an area.

"All models are approximations. Essentially, all models are wrong, but some are useful. However, the approximate nature of the model must always be borne in mind." - George Box



Model example: SIR

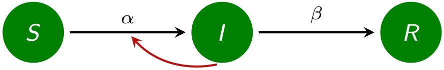
The SIR model describes epidemics using fundamental rules of disease transmissions.

SIR model rules:

- Transmission occurs when infected individuals meet susceptible individuals.
- Infected individuals recover over time.
- Recovered individuals are immune to infection.

SIR compartments

- The model puts each individual in compartments represented by a node.
- Black lines: Transitions.
- Red line: More infected individuals increases the infection rate.



Compartment notations:

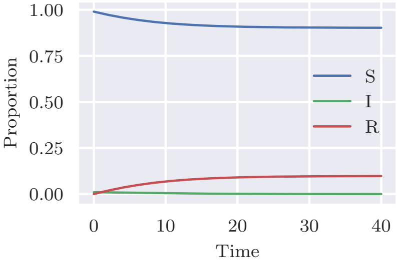
- Susceptible: S
- Infected: I
- Recovered: R

SIR equations

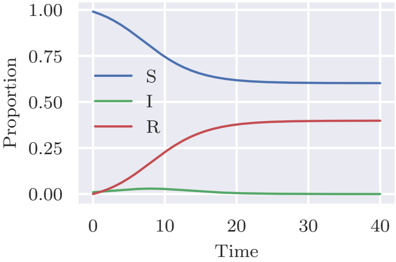
$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha I(t)S(t),$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha I(t)S(t) - \beta I(t),$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \beta I(t).$$

- α: Governs transmission rate
- β: Governs recovery rate

SIR model plots



$\alpha = 0.95$ and $\beta = 1.0$

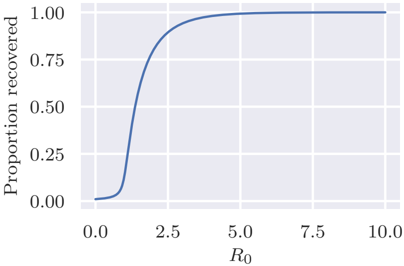


$\alpha = 1.25$ and $\beta = 1.0$

Basic reproduction number R_0

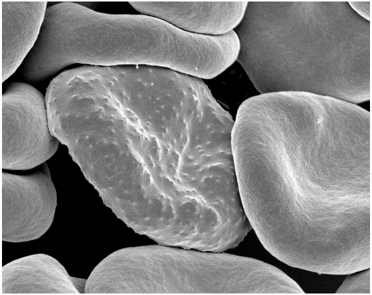
A metric describing the infectiousness of the disease:

$$R_0 = \frac{\alpha}{\beta}.$$



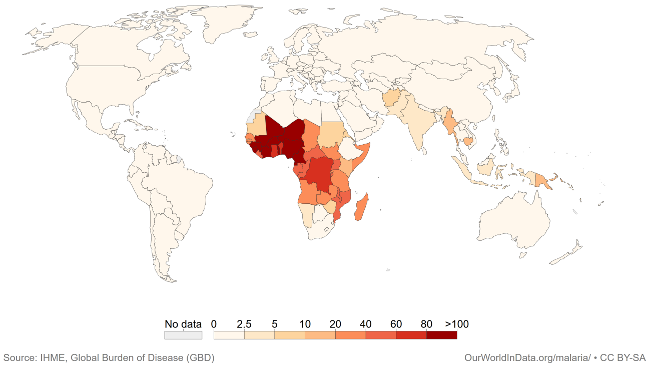
Malaria

- Endemic parasitic disease.
- Attacks red blood cells.
- No consistent medicine or vaccines.
- Symptoms include fever, headache, anaemia, and vomit.



Malaria prevalence

- $\approx 200,000,000$ infections per year.
- $\approx 400,000$ deaths per year.



Deaths per $100,000$ individuals in 2016

Malaria transmission

- Transmitted by mosquitoes
- Discovered by Sir Ronald Ross in 1894

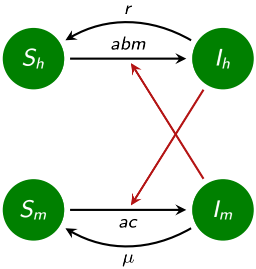
Sir Ronald Ross, Nobel prize winner

Anopheles mosquito

Ross' model

Ross' model has two classes: Humans and mosquitoes.

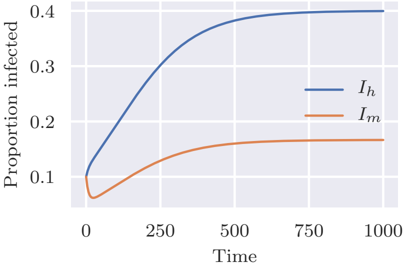
Unlike the SIR model, Ross' model describes endemics.



- S_h: Susceptible humans
- I_h: Infected humans
- S_m: Susceptible mosquitoes
- I_m: Infected mosquitoes

R_0 in Ross' model

Ross' model can be simulated.



Time-series of Ross' model.

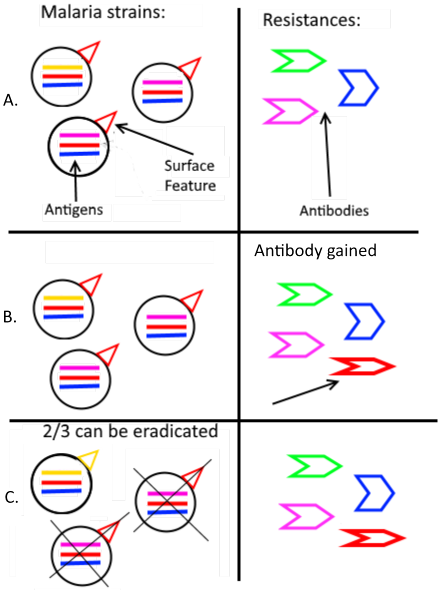
Basic reproduction number:

$$R_0 = \frac{a^2 bmc}{r\mu}. \tag{1}$$

- The mosquito biting rate a is squared.
- Most efficient prevention methods reduce the biting rate a.
- Example of an approximate model giving useful insights.

Human immune response against malaria

- Pathogens contain antigens.
- The immune system builds specific antibodies against specific antigens.
- After doing so, the body becomes resistant to that particular pathogen.
- A pathogen can come in varying strains, which have different antigens.
- Malaria has many antigens and produces new ones over time.
- Shared antigens between strains result in cross immunity.



The model of this thesis

The model takes antigenic diversity into account and is able to simulate cross immunity.

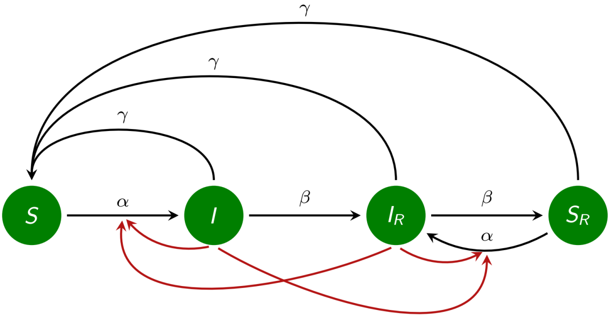
Thus, the following design decisions are made:

- Agent based with individual antibody memory.
- Stochastic and event based.
- No mosquito class (unlike Ross' model).
- SIR transmission dynamics.

The model of this thesis: Core components

Differences from SIR:

- Two events for complete recovery, $I \to I_R \to S_R$.
- Recovered individuals can be infected, but have reduced recovery time.
- Individuals are replaced, thereby losing their resistance (γ).



Compartments:

- S: Susceptible
- I: Infected
- I_R: Infected and resistant
- S_R: Susceptible and resistant

Parameters:

- α: Infection rate
- β: Recovery rate
- γ: Replacement rate

The model of this thesis: Strains and antigens

To model antigenic diversity, multiple strains exist, each with their own set of antigens.

- Individuals can be infected by different strains at the same time.
- To recover, individuals need to have antibodies for every antigen in a strain.

Example of a system with one strains and four antigens:

$$\text{Strain } 1 : [3, 4]$$
$$\text{Strain } 2 : [4, 5]$$

In the brackets, a number represents one antigen.

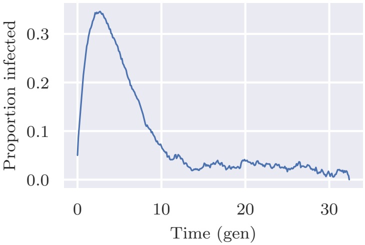
- Strains can spontaneously switch to avoid strain extinction with a rate proportional to a parameter.
- There can be any number of strains and antigens in a system.

Three questions to answer

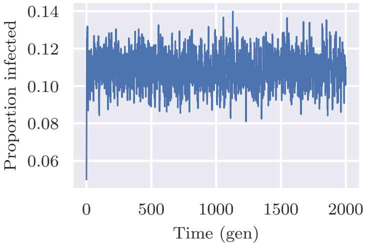
1. Are non-resistant individuals necessary for malaria's survival?
2. What are the effects of increased antigenic diversity?
3. Can strains co-exist when they share antigens?

Time-series plots for a system for a single strain and one antigen.

Difference between left and right plots due to positive γ (replacement rate).



$\alpha = 1.02, \beta = 1.0, \gamma = 0.0$



$\alpha = 0.8, \beta = 1.0, \gamma = 0.17$

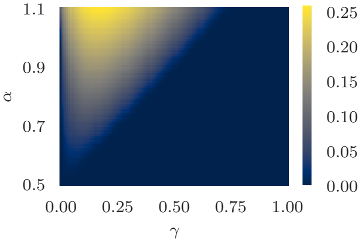
Time is measured in generations which equal $10,000$ iterations. $10,000$ is also the number of hosts.

Results 1.2: Parameter sweep

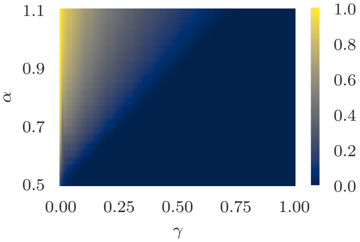
Are non-resistant individuals necessary for malaria's survival?

Plots indicate:

- Vulnerable individuals are an important part of malaria's competitiveness.
- Deaths of individuals should be avoided.
- An optimal γ exists and increases as a function α.



Proportion infected



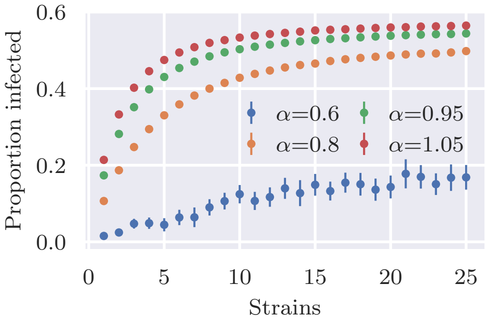
Proportion resistant

Results 2.1: Additional strains

What are the effects of increased antigenic diversity?

Additional strains are advantageous for malaria because:

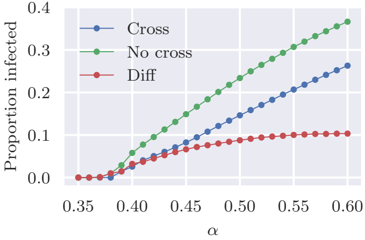
- More antigens
- Super-infection

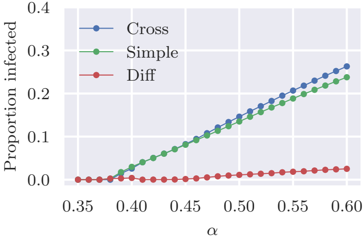


Results 2.2: Antigens matter

What are the effects of increased antigenic diversity?

The total number of unique antigens is a significant parameter for malaria's infectiousness compared to the number of strains.





Systems:

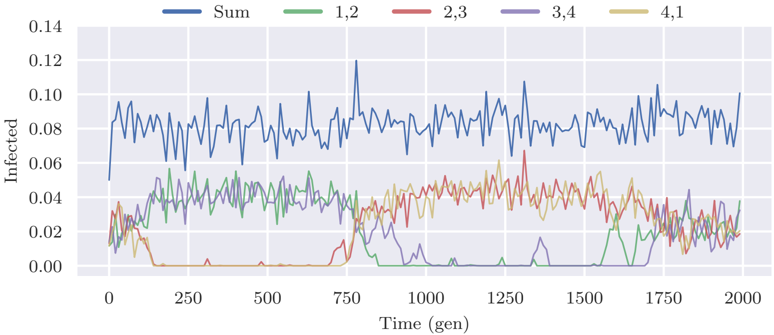
- *Cross*: $[1, 2]$, $[2, 3]$, $[3, 4]$, $[4, 1]$
- *No cross*: $[1, 2]$, $[3, 4]$, $[5, 6]$, $[7, 8]$
- *Simple*: $[1, 2]$, $[3, 4]$

Results 3.1: Domination

Can strains co-exist when they share antigens?

Time series plot for a system with cross immunity.

- Pairs of dominating strains.
- Dominating strains always maximise the number of unique antigens.

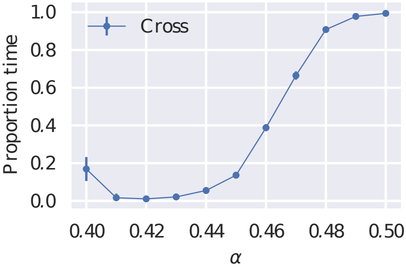


Each coloured line denotes the proportion of infected individuals for a single strain. The blue upper line is the total number of infected indivudals. $\alpha = 0.45$ and $\beta = 1.0$.

Results 3.2: Region of occurrence

Can strains co-exist when they share antigens?

Only a limited region in parameter space where strains cannot co-exist.



Time with no dominating strains

Vaccine injections 1

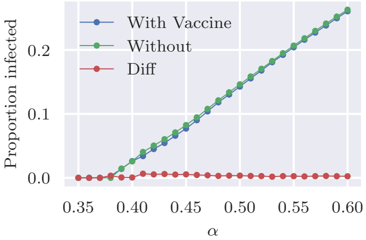
This model can simulate vaccines.

- Done by injecting antibodies in all individuals.
- The injected antibodies against antigens in the most dominant strain.
- Vaccines were not investigated in the thesis.

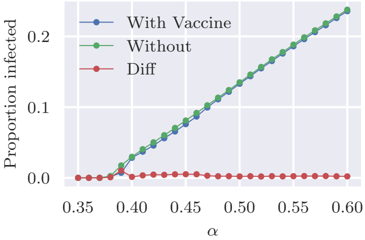
Vaccine injections 2

Vaccine injection every 250'th generation

Insignificant difference in the proportion of infected individuals if vaccines are given rarely.



Cross
$[1, 2],\ [2, 3],\ [3, 4],\ [4, 1]$

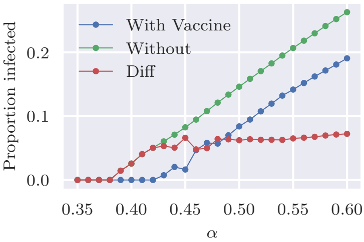


Simple
$[1, 2],\ [3, 4]$

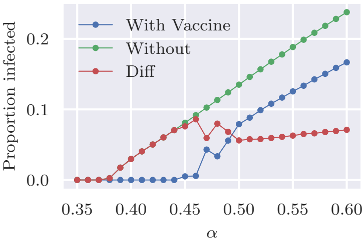
Vaccine injections 3

Vaccine injection every 10'th generation

Significant difference in the proportion of infected individuals if vaccines are given often.



Cross
[1, 2], [2, 3], [3, 4], [4, 1]



Simple
[1, 2], [3, 4]

Conclusion

Insights gained from the model:

- Non-resistant individuals may be necessary for malaria's survival.
- Antigenic diversity is advantageous for malaria.
- In systems with cross immunity, strains can only co-exist in severe regions.
- Vaccines in severe regions may have to be injected regularly.

References

George photo: https://upload.wikimedia.org/wikipedia/commons/a/a2/GeorgeEPBox.jpg

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World map: Seattle, United States: Institute for Health Metrics and Evaluation (IHME) 2017. Global Burden of Disease Collaborative Network. Global Burden of Dis- ease Study 2016 (GBD 2016) Results. http://ghdx.healthdata.org/gbd-results-tool

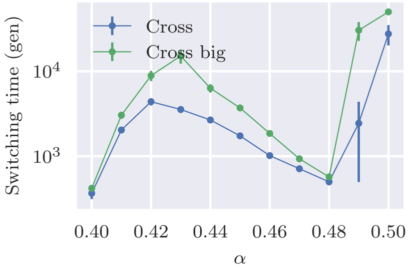
Ross photo: http://www.ivcc.com/news-and-media/blog/o-million-murdering-death-i-know-this-little-thing-a-myriad-men-will-save-sir

Mosquito photo: By Jim Gathany - This media comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #5814.Note: Not all PHIL images are public domain; be sure to check copyright status and credit authors and content providers., Public Domain, https://commons.wikimedia.org/w/index.php?curid=799284

Antigens and antibodies sketch: Fvasconcellos and National Human Genome Research Institute. Antibody.https://commons.wikimedia.org/wiki/File:Antibody.svg. May 2007.

Bonus slide 1

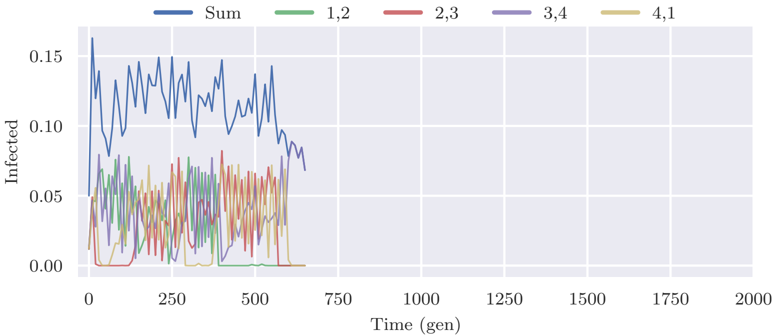
Switching time



Mean time to switch

Bonus Slide 2

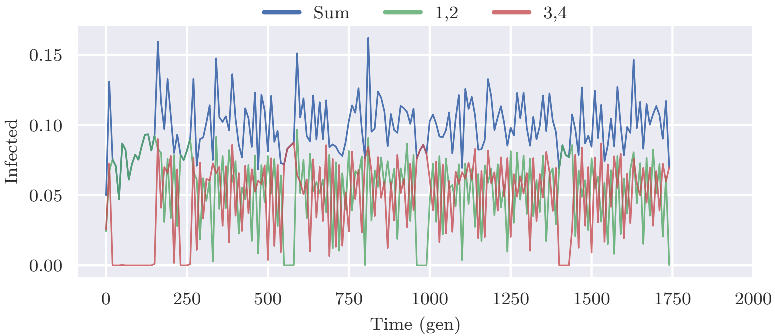
Vaccine time-series



$\alpha = 0.5$

Bonus Slide 3

Vaccine time-series



$\alpha = 0.5$