UNIVERSITY OF OXFORD

OXFORD ONLINE MATHS CLUB

Chaotic viruses

How could maths help us make new vaccines?

Francesca Lovell-Read

10th June 2021

About me

UNIVERSITY OF OXFORD

MERTON COLLEGE OXFORD

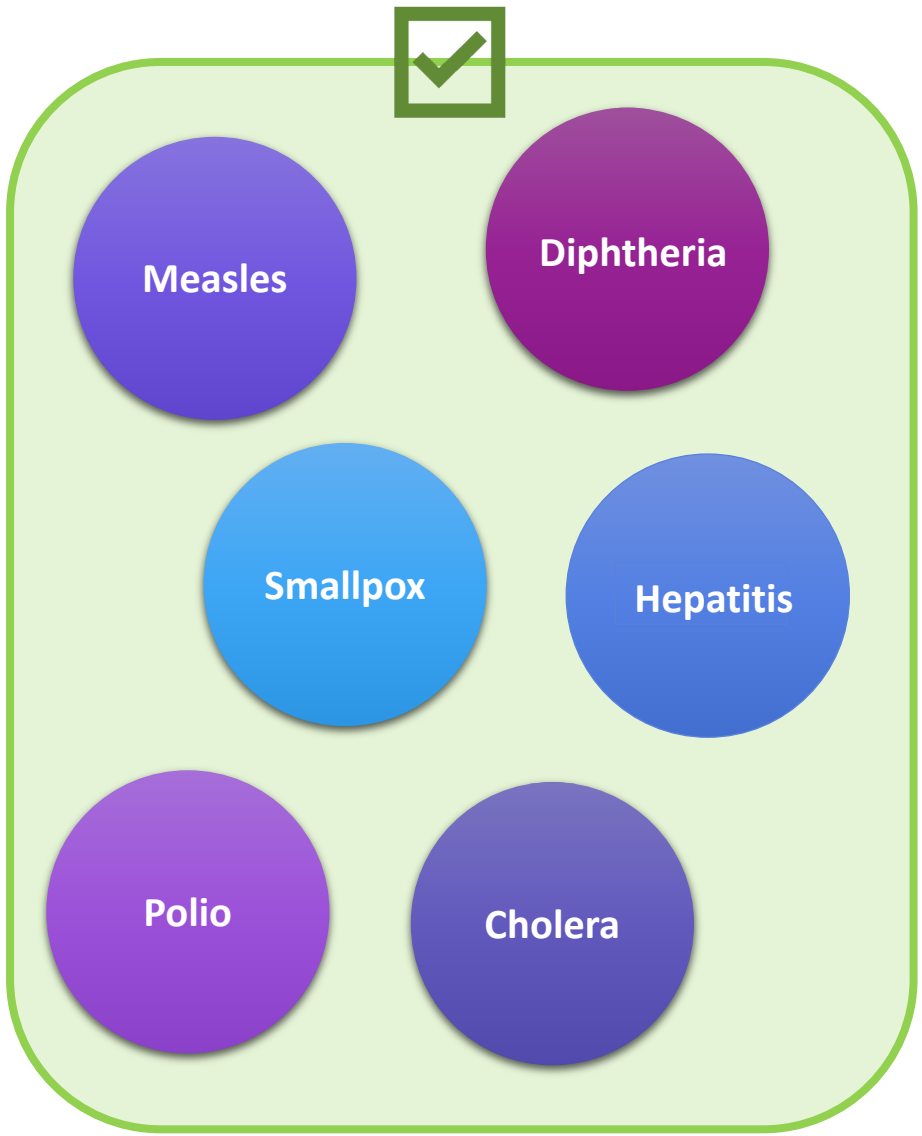
Wolfson Centre for Mathematical Biology

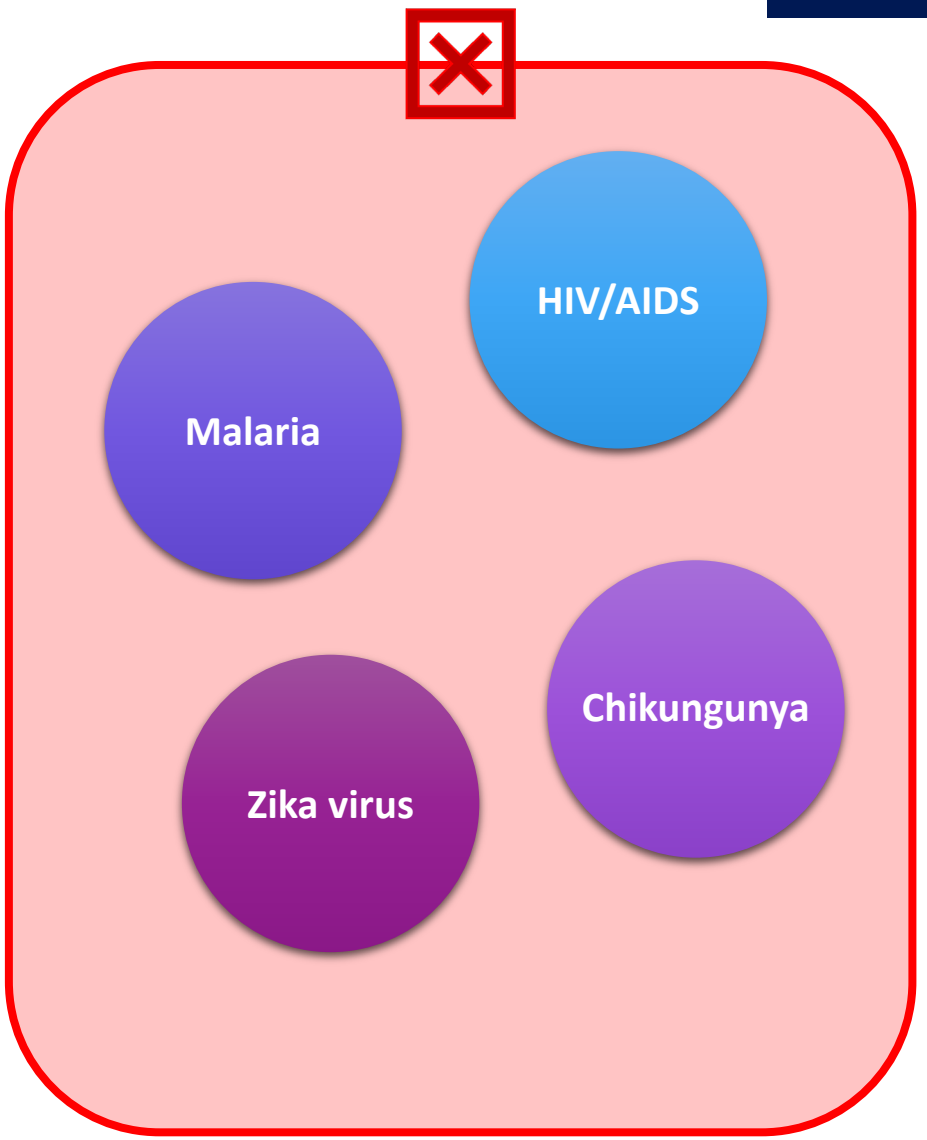
MATHEMATICAL INSTITUTE

OXFORD INTERDISCIPLINARY BIOSCIENCE DTP

Merton College

Which diseases do we have vaccines for?





All about measles

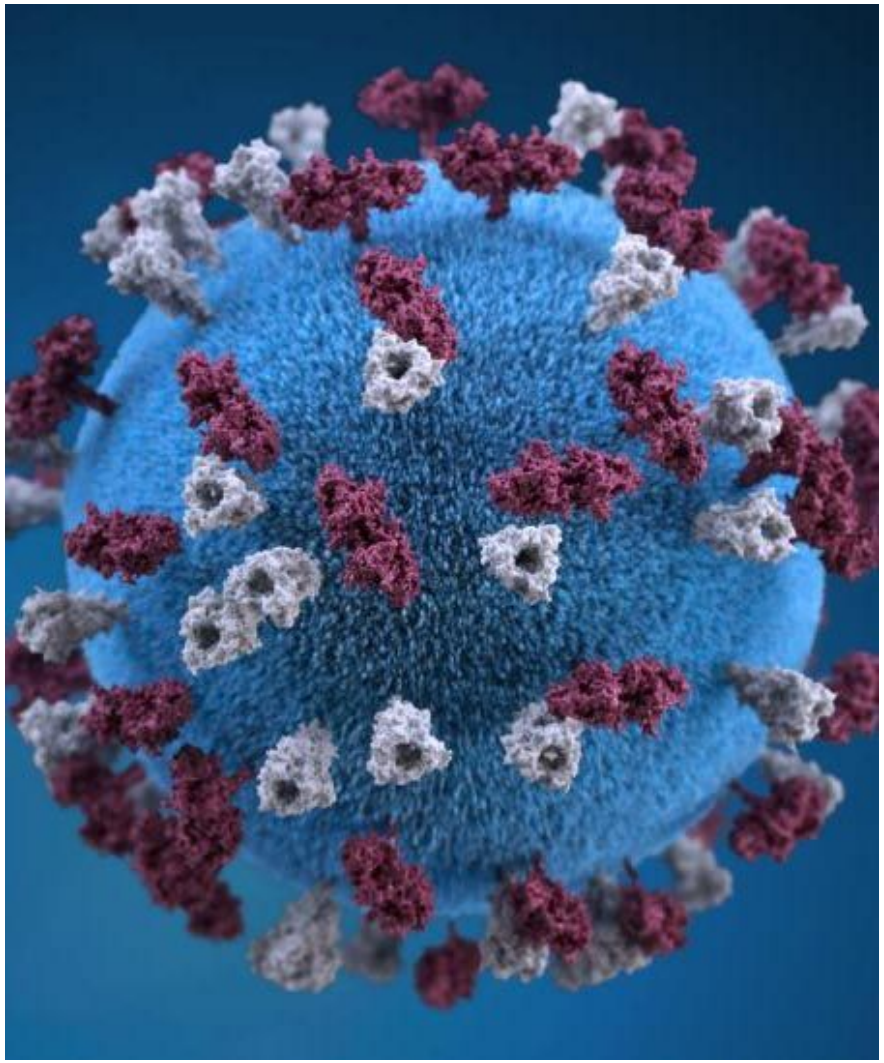


ILLUSTRATION BY ALISSA ECKERT/CDC (NATIONAL GEOGRAPHIC)

Why is the measles virus ideal for vaccinating against?

The immunogenic regions of the measles virus (the parts that trigger the immune response) are **conserved**

Lifelong immunity is conferred by a single infection or vaccination

The same vaccine developed in 1968 is still able to provide protection against measles half a century later!

What about flu?

UNIVERSITY OF OXFORD

So why do we have to get a new flu jab every year?

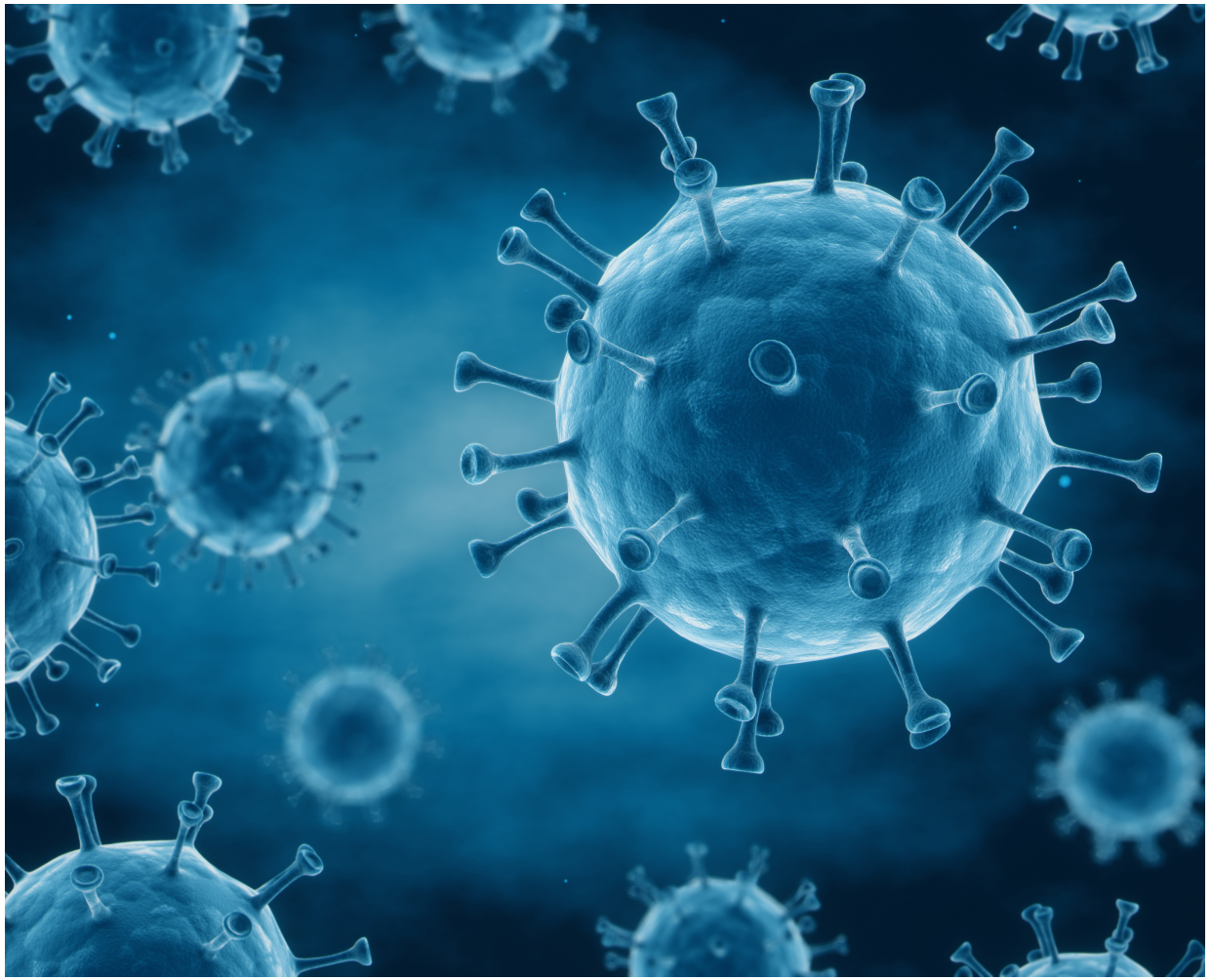
The influenza A virus is not like measles – its immunogenic regions are **NOT highly conserved**

Instead they are subject to a lot of variation, leading to new strains that can evade acquired host immunity

What we see with flu is different strains dominating in the population year on year in an unpredictable way

Classical theories can't explain this!

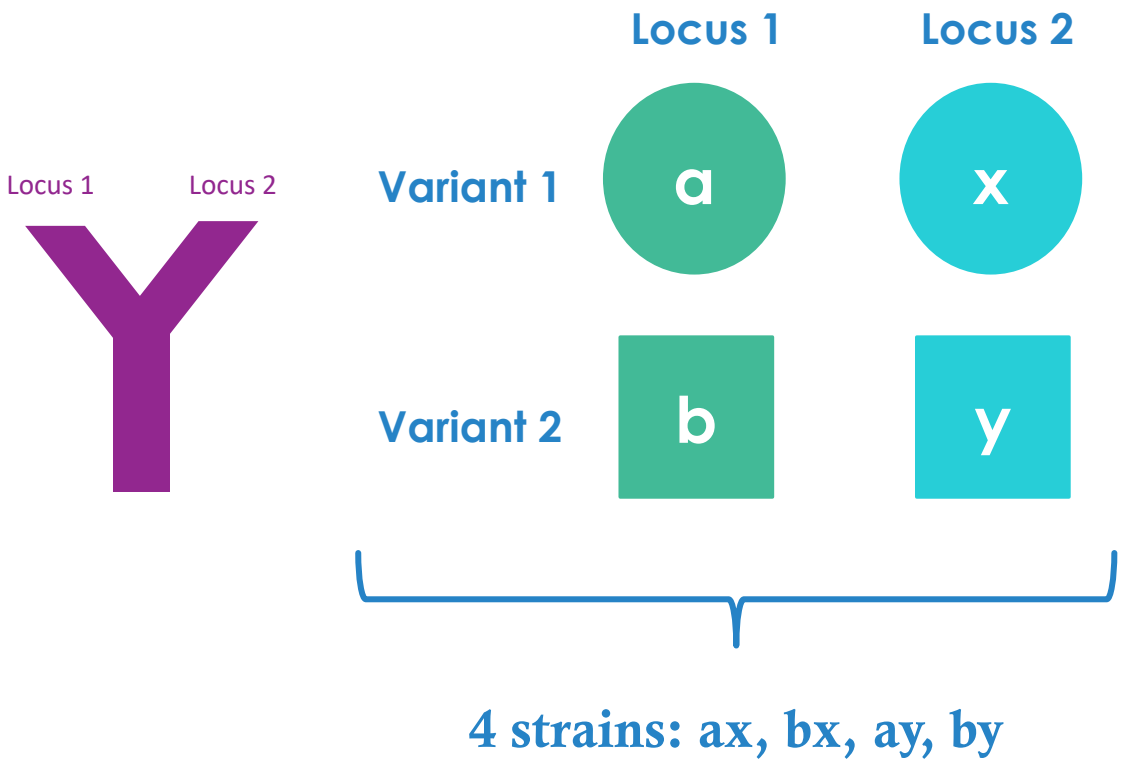
Can we build a mathematical model that can reproduce this behaviour?



The multi-locus model

- For a given antigen, there are k different immunogenic regions or *loci*
- Each locus i can display one of a choice of n_i different *alleles* or *variants*
- Any given combination of alleles defines a *strain*
- How many strains in total….? $N = n_1 n_2 \cdots n_k$

eg $k = 2, n_1 = n_2 = 2, N = 4$



How does transmission work?

- Everyone starts off totally susceptible to every strain
- If you are infected with strain ax, you are infectious for some time, and then recover and become immune to that strain
- If you have been infected with strain ax, you not only gain immunity to ax but also some partial 'cross protective' immunity to strains ay and bx

Mathematical model

We're going to build a differential equation model to understand how the different strains evolve in the population

Some notation:

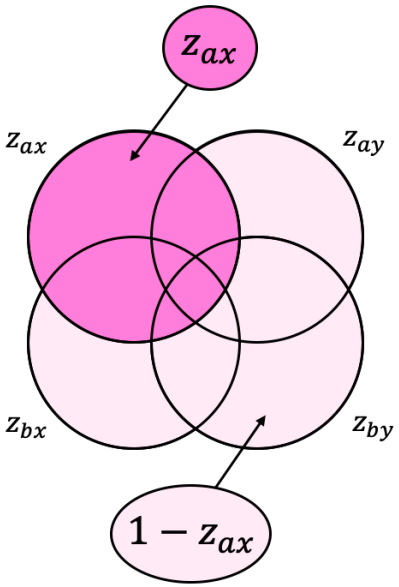
y_{ax} - proportion of population **currently infectious** with strain ax

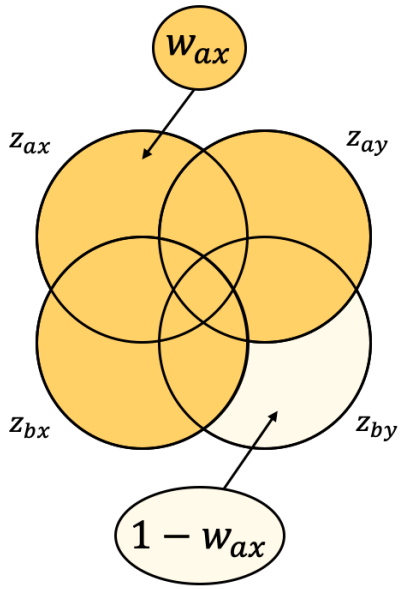
z_{ax} - proportion of population (completely) **immune** to strain ax

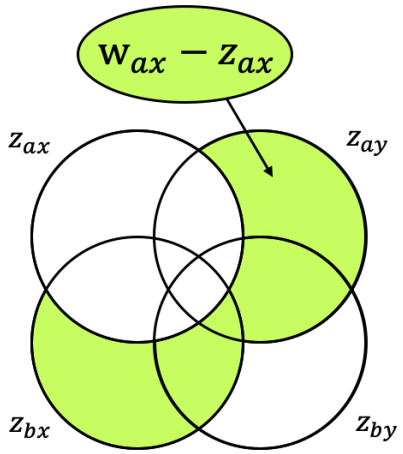
w_{ax} - proportion of population with **SOME (full or partial) immunity** to strain ax

have previously been infected with ax

have previously been infected with ax, ay or bx







And our parameters:

β: transmission coefficient

γ: strength of cross-protective response

$1/\mu$: life expectancy

$1/\sigma$: infectious period

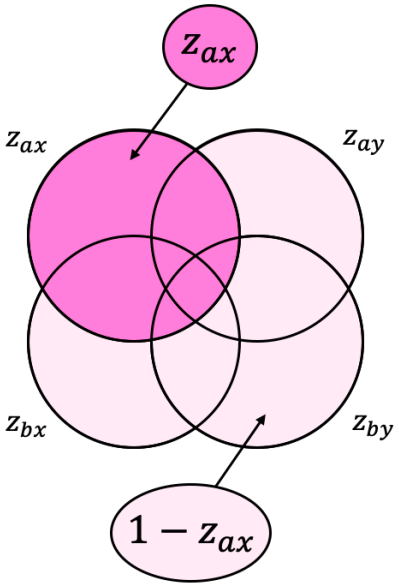
Mathematical model

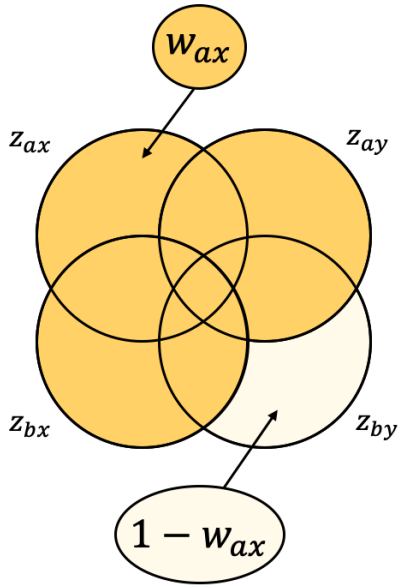
contact occurs between someone infectious with ax and someone not immune to ax…

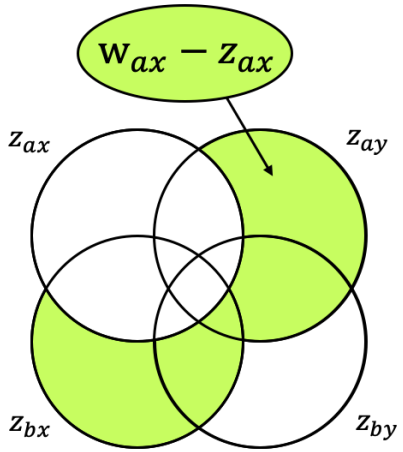
$$\frac{d}{dt} z_{ax} = \beta y_{ax}(1 - z_{ax}) - \mu z_{ax}$$

…and that contact leads to a transmission

people lose immunity when they die







Reminder of notation:

y_{ax} - proportion of population currently infectious with strain ax

z_{ax} - proportion of population (completely) immune to strain ax

w_{ax} - proportion of population with SOME (full or partial) immunity to strain ax

β: transmission coefficient

γ: strength of cross-protective response

$1/\mu$: life expectancy

$1/\sigma$: infectious period

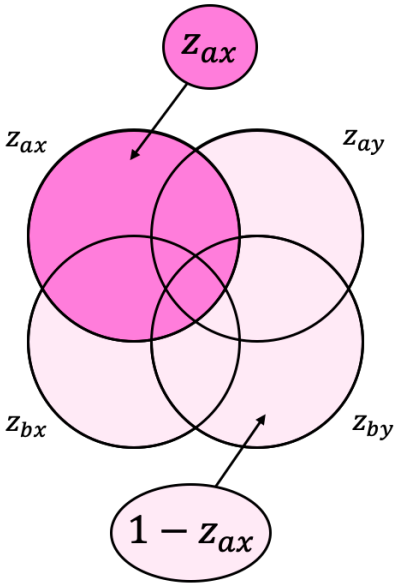
Mathematical model

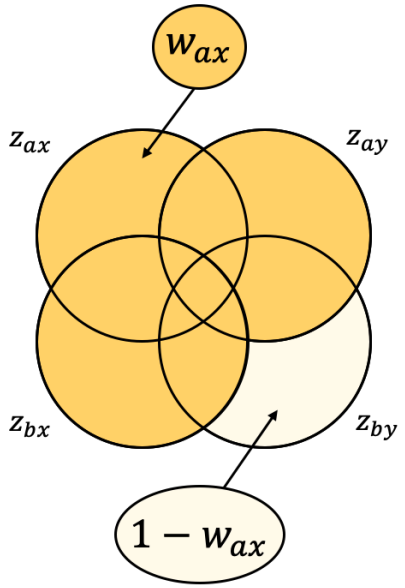
contact and transmission occurs between someone infectious with ax, ay or bx and someone not already partially immune to ax

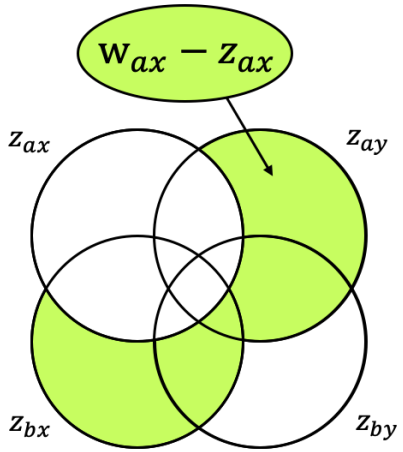
$$\frac{d}{dt}w_{ax} = \sum_{pq \sim ax} \beta y_{pq}(1 - w_{ax}) - \mu w_{ax}$$

summing over any strains sharing alleles with ax (i.e. pq=ax, ay or bx)

people lose partial immunity when they die







Reminder of notation:

y_{ax} - proportion of population currently infectious with strain ax

z_{ax} - proportion of population (completely) immune to strain ax

w_{ax} - proportion of population with SOME (full or partial) immunity to strain ax

β: transmission coefficient

γ: strength of cross-protective response

$1/\mu$: life expectancy

$1/\sigma$: infectious period

Mathematical model

contact and transmission occurs between someone infectious with ax, and…

EFFECT OF CROSS-PROTECTIVE RESPONSE

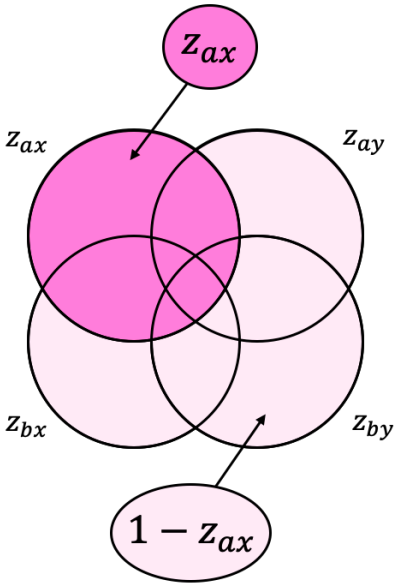
People lose infectiousness at the end of the infectious period

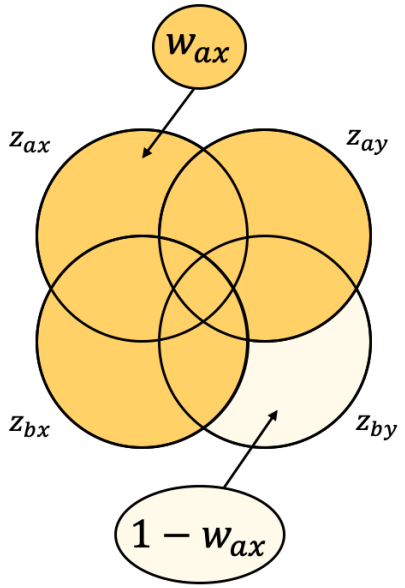
$$\frac{d}{dt}y_{ax} = \beta y_{ax}[(1 - w_{ax}) + (1 - \gamma)(w_{ax} - z_{ax})] - \sigma y_{ax}$$

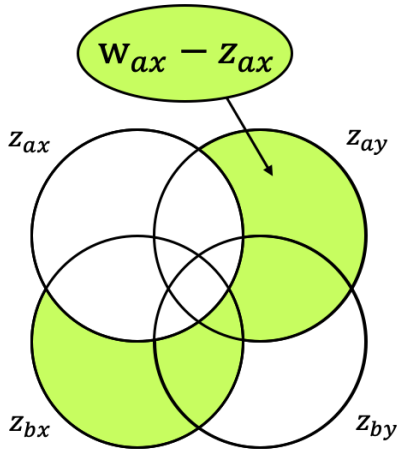
…someone with NO partial immunity to ax…

OR

someone with partial BUT NOT FULL immunity to ax







Reminder of notation:

y_{ax} - proportion of population currently infectious with strain ax

z_{ax} - proportion of population (completely) immune to strain ax

w_{ax} - proportion of population with SOME (full or partial) immunity to strain ax

β: transmission coefficient

γ: strength of cross-protective response

$1/\mu$: life expectancy

$1/\sigma$: infectious period

Mathematical model

So our model is:

For $i \in \{a, b\}$ and $j \in \{x, y\}$

$$\frac{d}{dt} z_{ij} = \beta y_{ij}(1 - z_{ij}) - \mu z_{ij}$$

$$\frac{d}{dt} w_{ij} = \sum_{pq \sim ij} \beta y_{pq}(1 - w_{ij}) - \mu w_{ij}$$

$$\frac{d}{dt} y_{ij} = \beta y_{ij}[(1 - w_{ij}) + (1 - \gamma)(w_{ij} - z_{ij})] - \sigma y_{ij}$$

Variables

Disease specific parameters (known)

Unknown! Let's vary it...

Solve numerically!

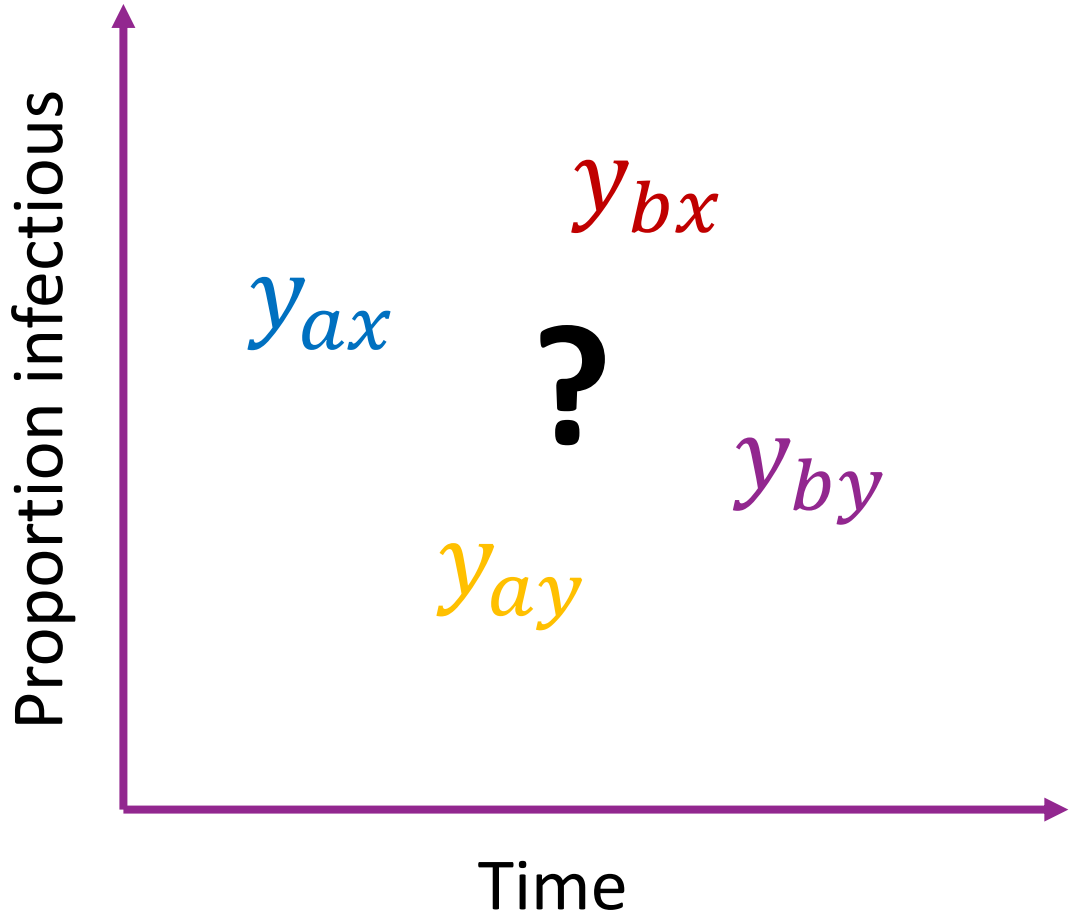
It's not very nice to solve analytically – so we'll get a computer to do it for us ☺

What we have to put in:

- The number of different loci and variants
- The system of differential equations we just wrote down
- Our choice of epidemiological parameters (β, μ, σ)
- Our choice of γ
- Some initial conditions
- Some other computational information eg how long do we want to run the simulation for

What we get out:

- Time series for each of our variables (information on how each of them changes over the whole period of time we've considered



Low cross protective response

If $\gamma = 0$, there is no partial immunity

→ you can only gain any immunity to strain ax by being infected with ax

→ Being infected with ax doesn't give you any immunity to anything else

→ **No competition between strains**

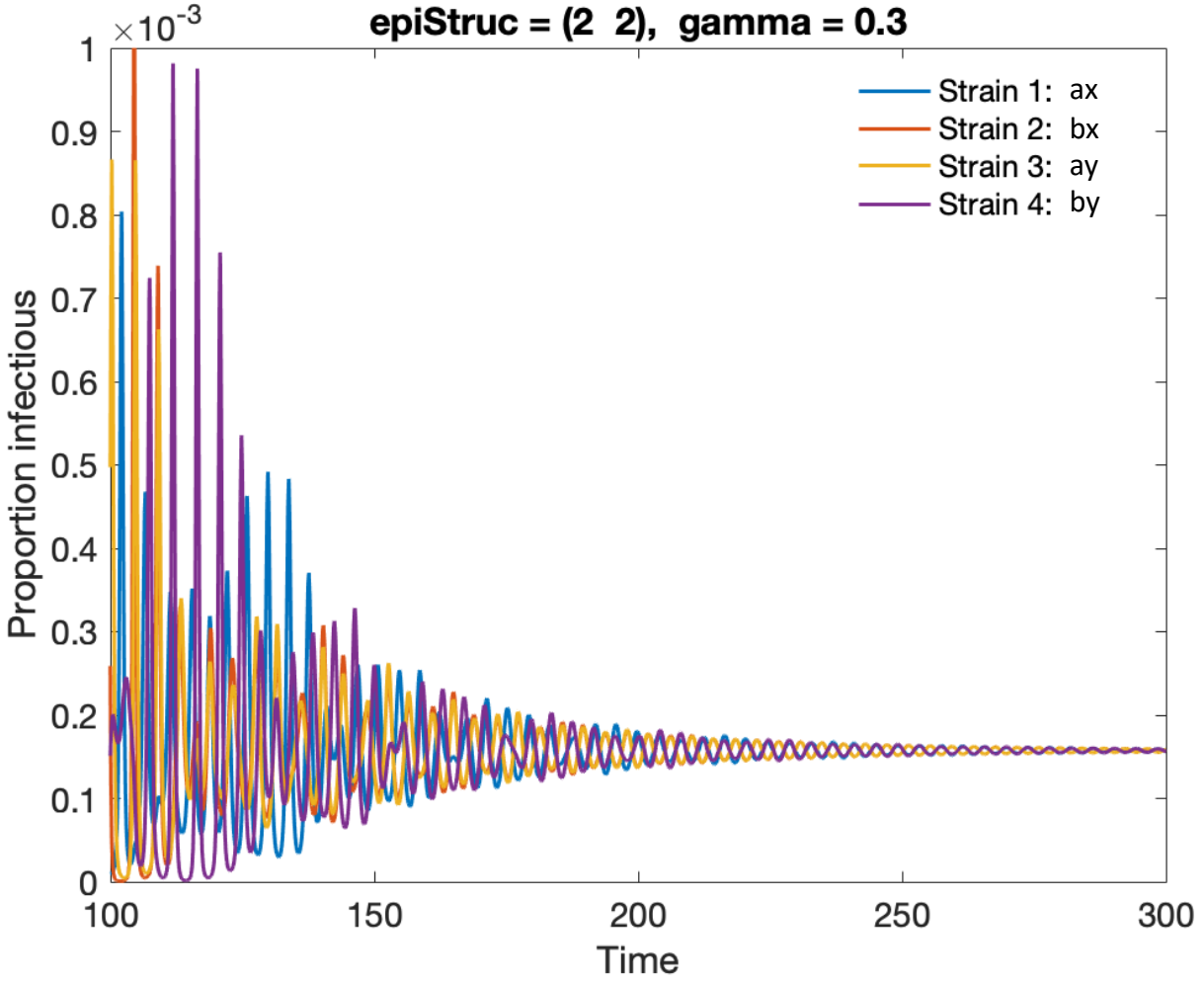
Same if γ is 'small enough' (what does this mean? We'll come back to that…)

→ Strains aren't competing with each other

→ They can all coexist happily! ☺

↓

'No Strain Structure' (NSS)



High cross protective response

If $\gamma = 1$, there is total cross-protection

→ Being infected by strain ax gives you total immunity not only to ax, but also to ay and bx

→ Being infected with ax doesn't give you any immunity to by because they don't share any alleles

→ **Strains segregate into 'discordant sets' that don't share any alleles (ax-by, and ay-bx)**

→ These sets compete with each other

Same if γ is 'large enough' (again, we'll come back to that…)

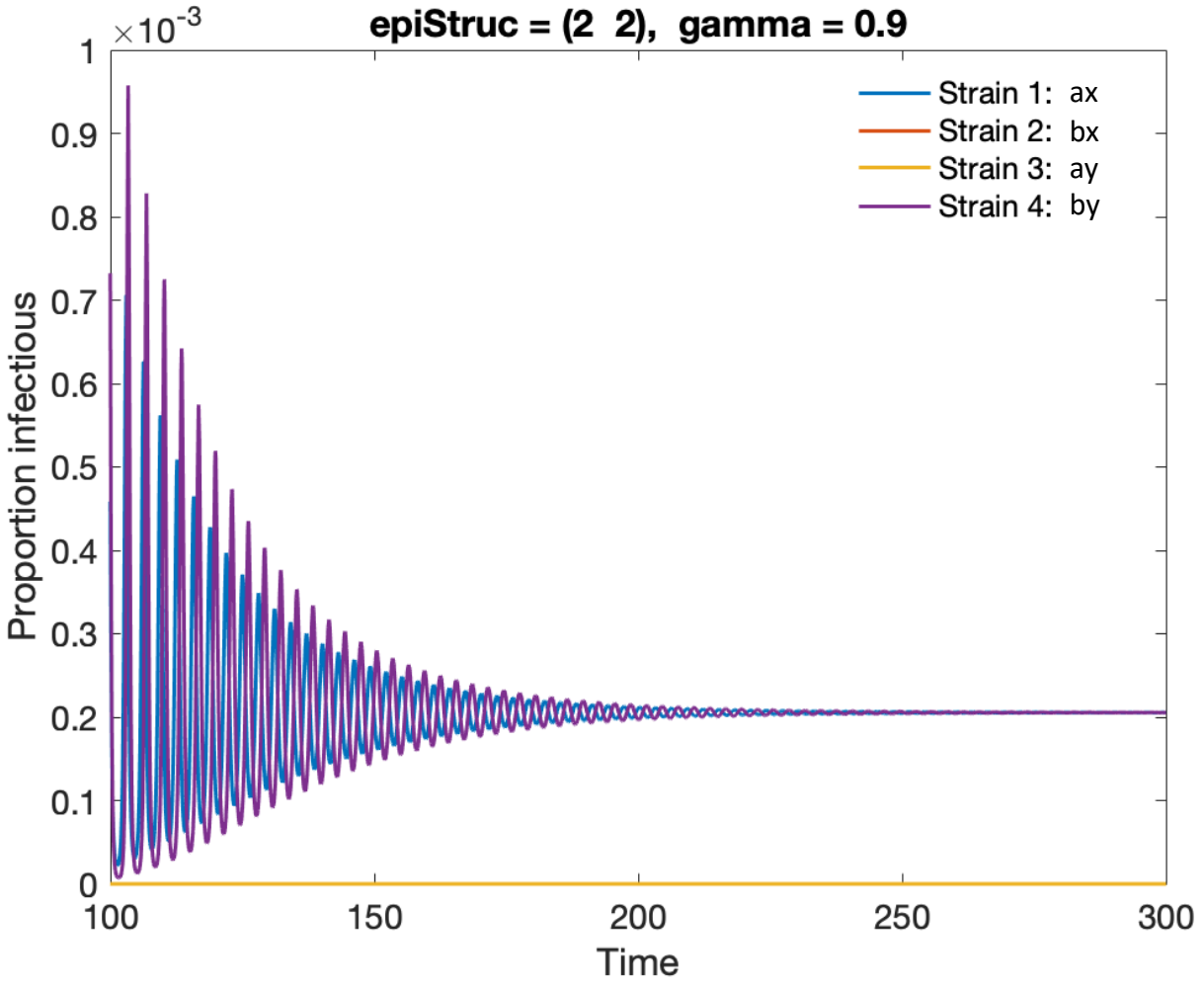
→ Discordant sets are competing with each other

→ They can't all coexist ☹

→ One set dominates, the other goes extinct

↓

'Discrete Strain Structure' (DSS)



Medium cross protective response

What if γ is somewhere in between?

→ Being infected by strain ax gives you total immunity to ax, and some partial immunity to ay and bx

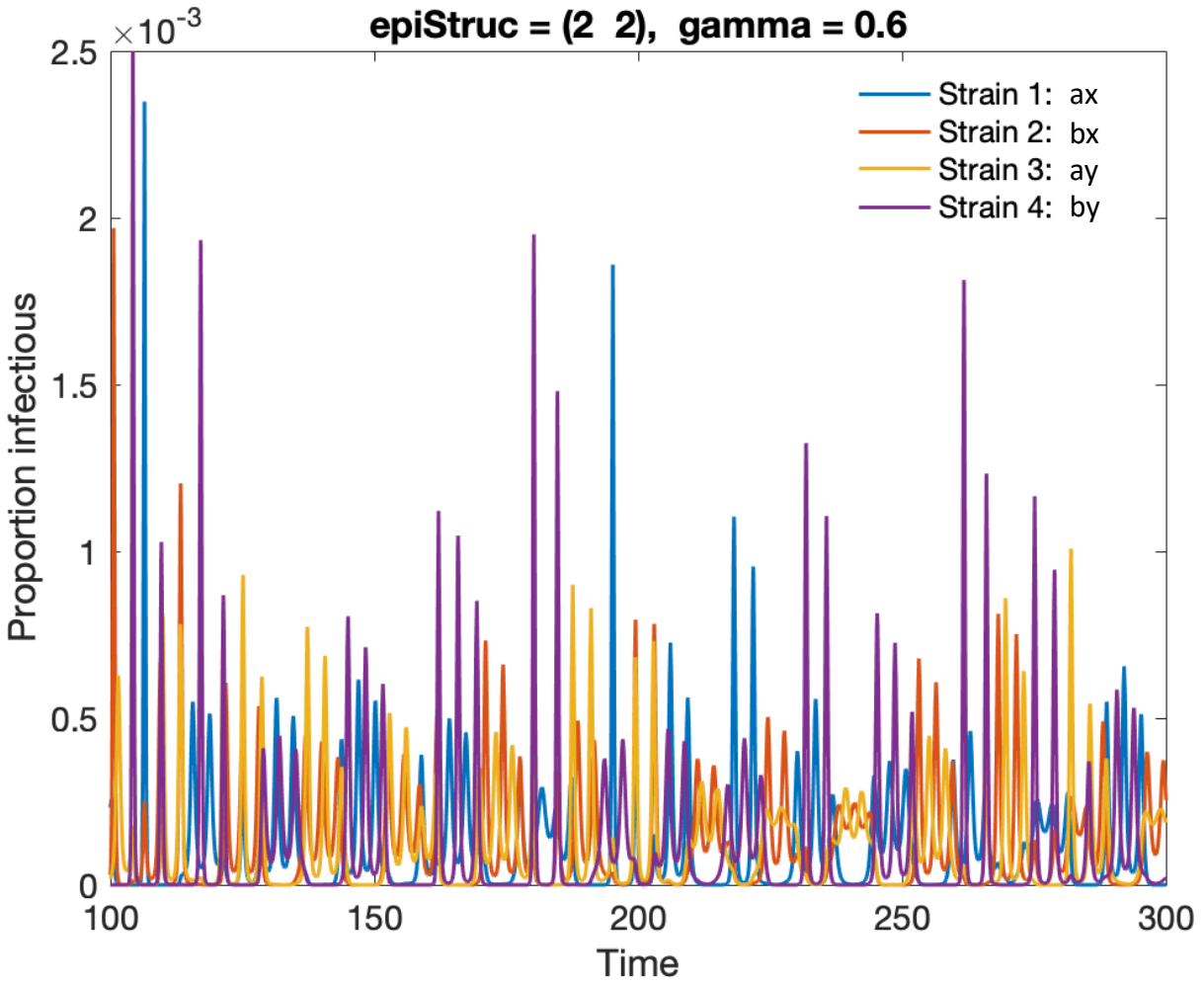
→ We observe **chaotic behaviour** in which individual strains sequentially dominate over the others

→ Immunological interference between strains means they cannot coexist and instead continually replace one another in an unpredictable sequence

↓

'Chaotic Strain Structure' (CSS)

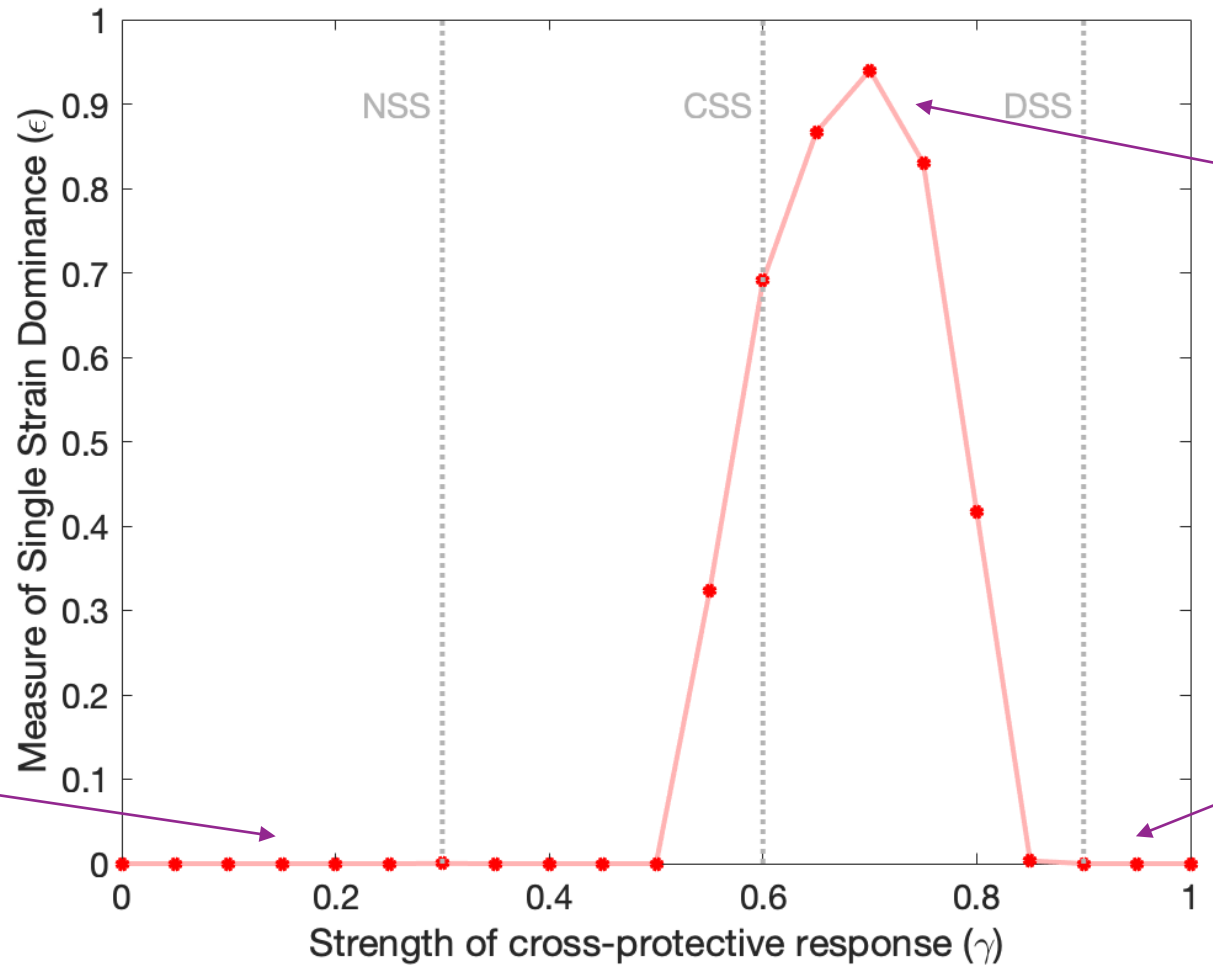
This is exactly what we observe with flu!!!

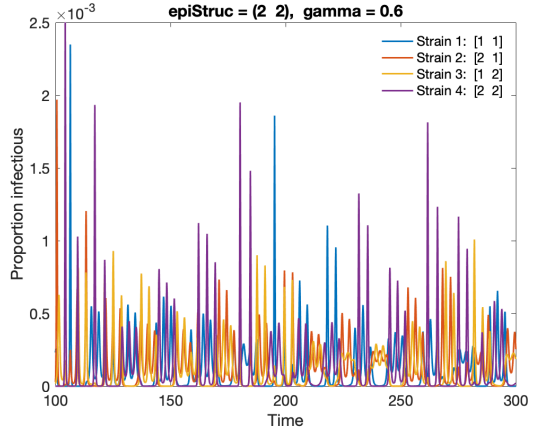


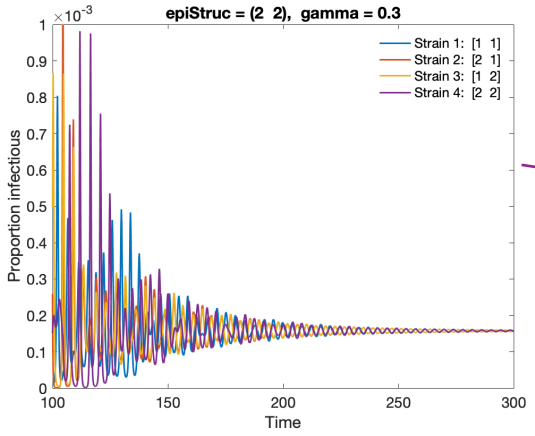
Single Strain Dominance (SSD)

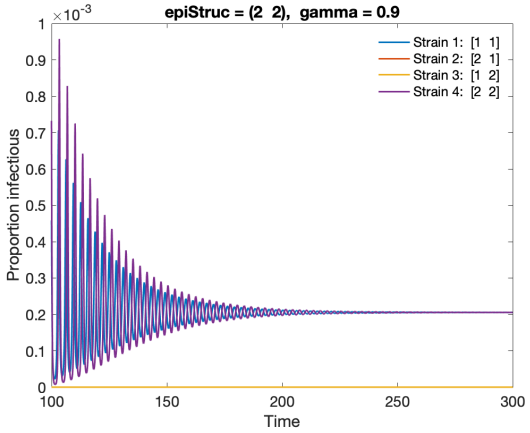
SSD:

$$\epsilon = \frac{1}{P}\sum_{i=1}^{P}\frac{y^i_{\max} - y^i_{\text{sub}}}{y^i_{\max}}$$





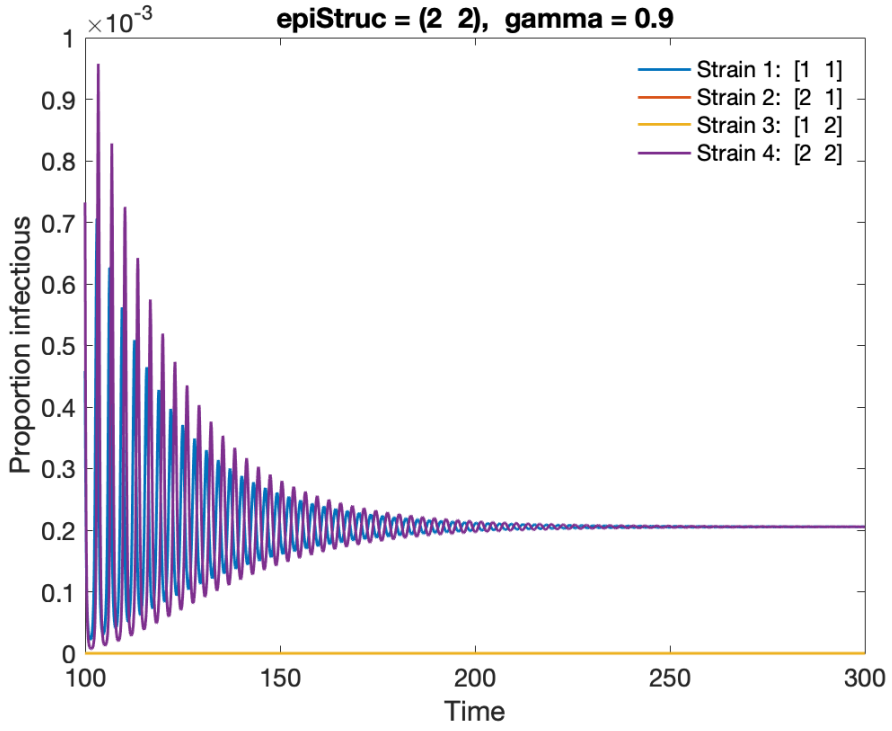




Very cool, but why is it important?

UNIVERSITY OF OXFORD

When designing a vaccine, you want to target regions that are strongly immunogenic, but have low variability – and this kind of modelling could help us find them!



We've seen that strong cross-protective responses can force strains to split into discordant sets

This shows up in the viral population as an imbalance in the frequency with which certain pairs of genes appear

Using genome sequencing methods and some cool techniques from statistics and information theory we can identify these sites

These loci provide potential targets for protective immunity!

UNIVERSITY OF OXFORD

Thanks for Listening!

Any questions?

UKRI Biotechnology and Biological Sciences Research Council