Modelling of infections at within- and between-host levels

Cameron Smith

April 16th, 2025

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What can we do?

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Seven challenges in modeling pathogen dynamics within-host and across scales
Gog *et al.* (2015)

Introduction

In general we cannot (or do not wish to) model multi-scale processes in full mechanistic detail, and even simulating such models becomes computationally intractable. Can we come up with ways of extracting the essence of lower-scale models so that they can be embedded into higher-scale models efficiently (Mideo *et al.*, 2008)?

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Infection

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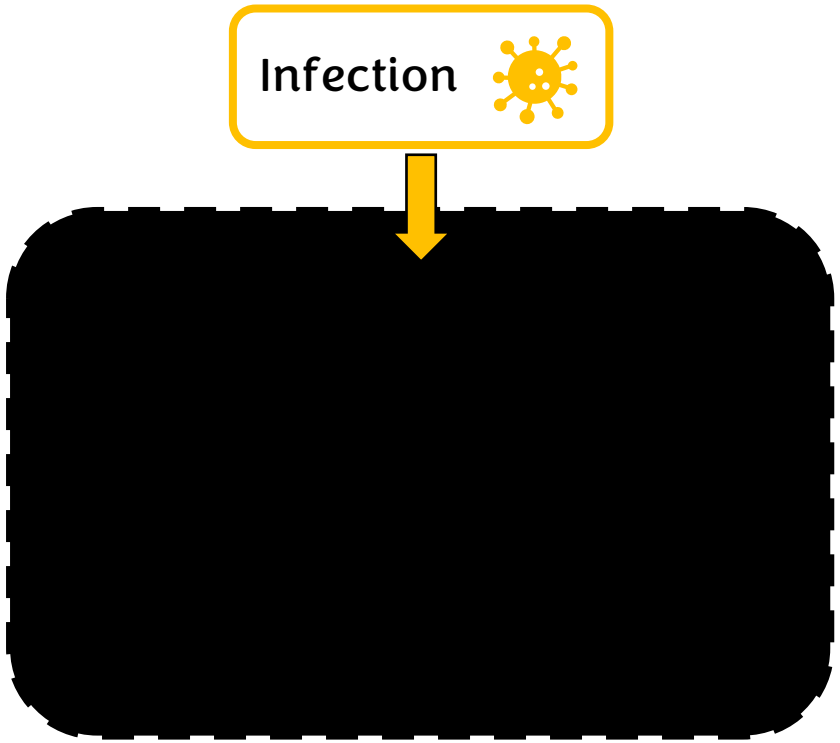

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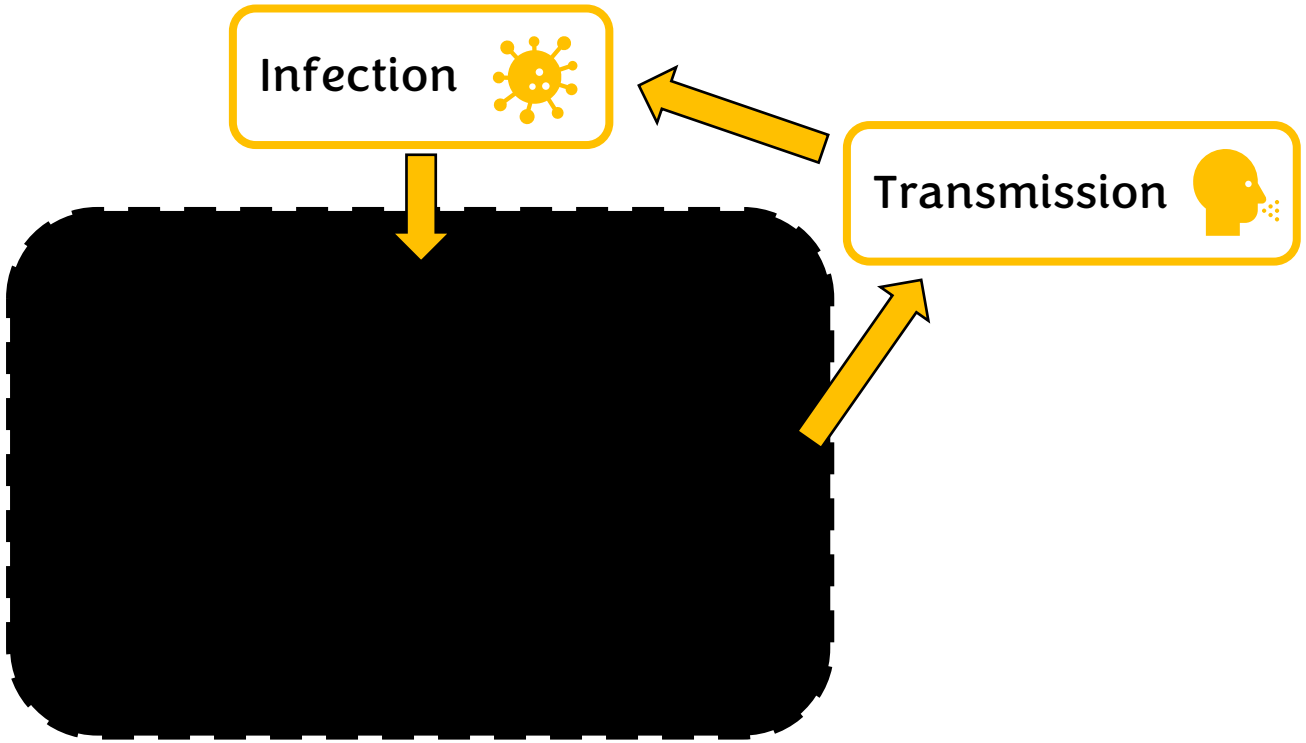

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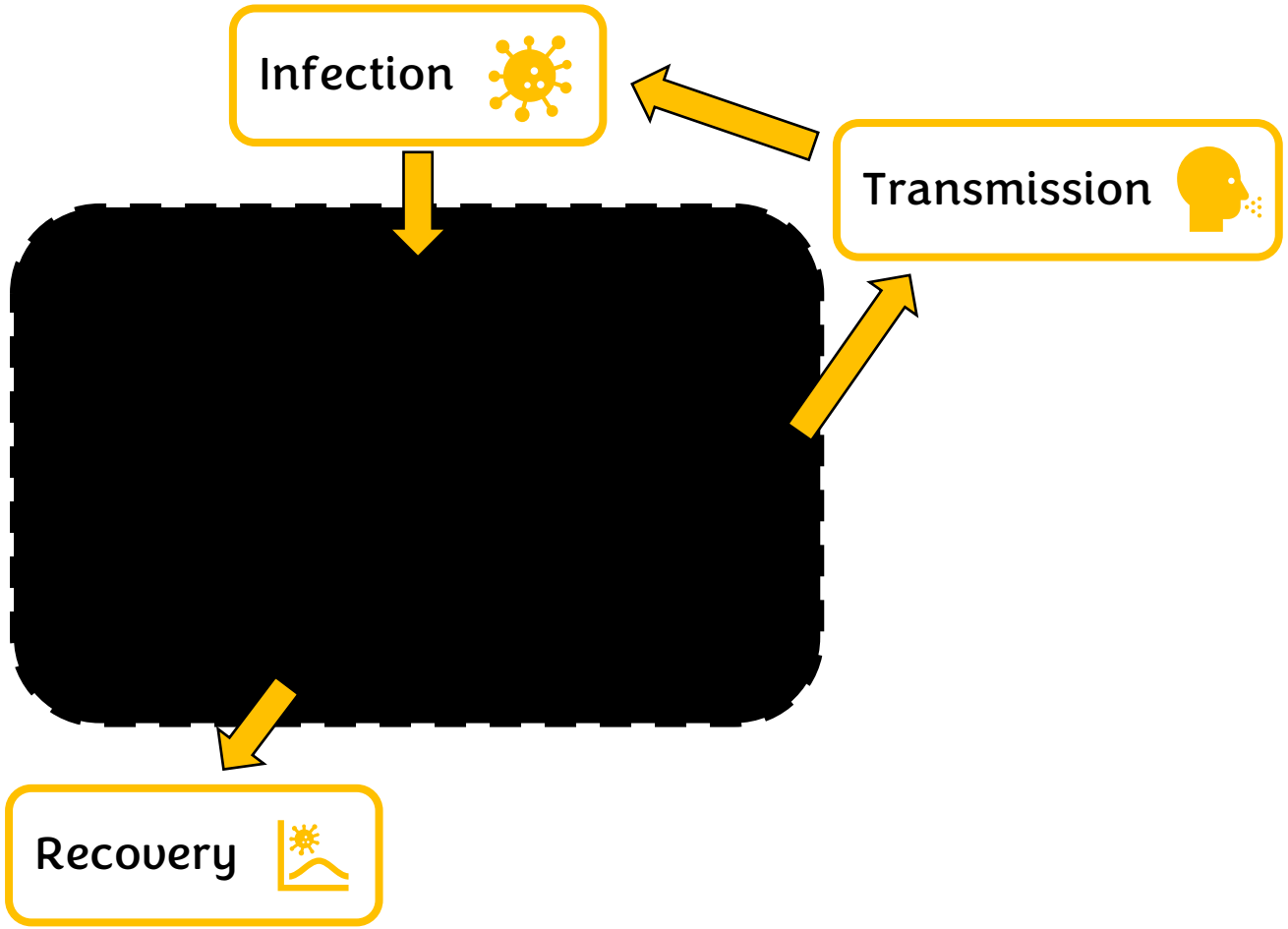

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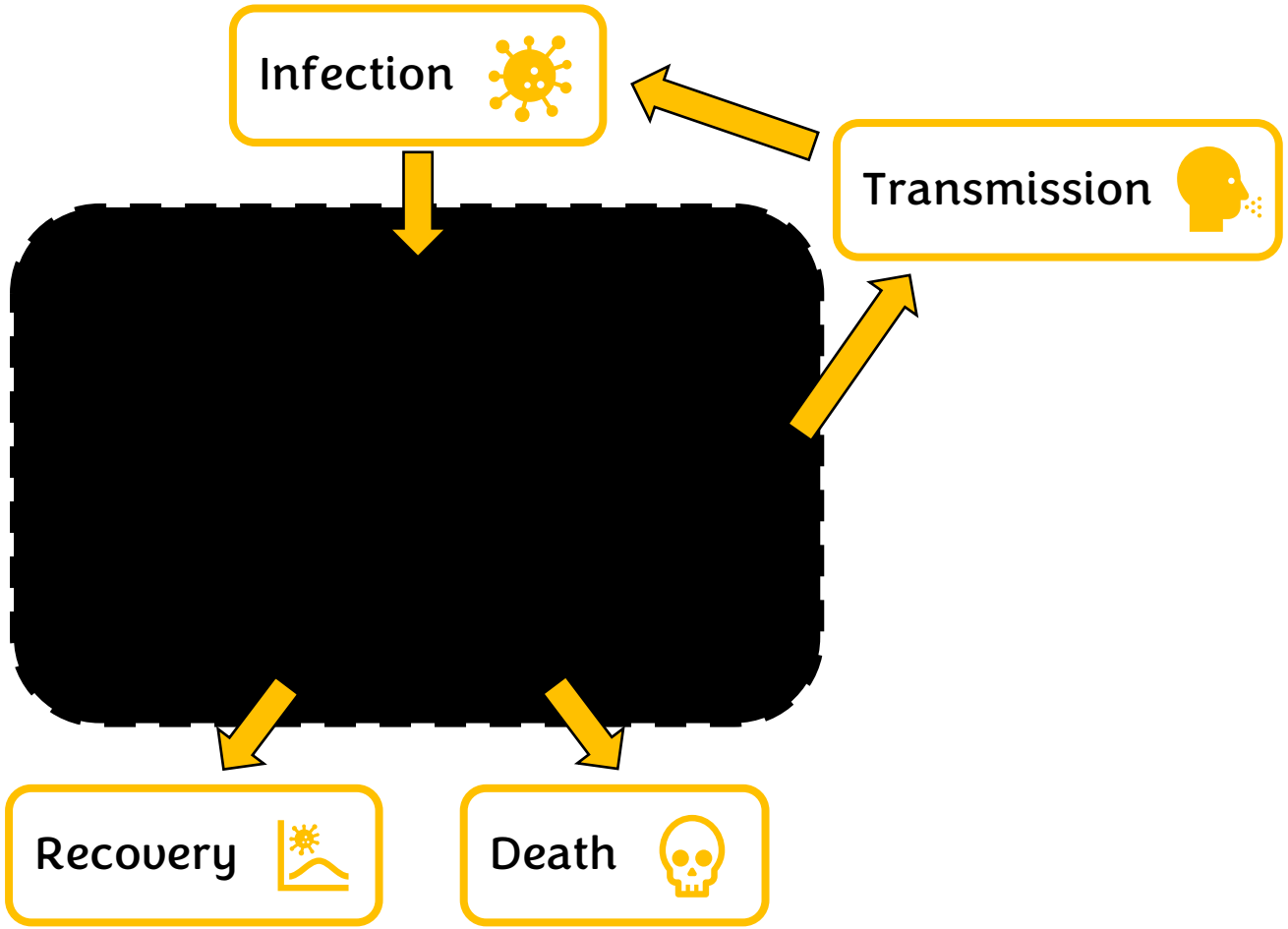

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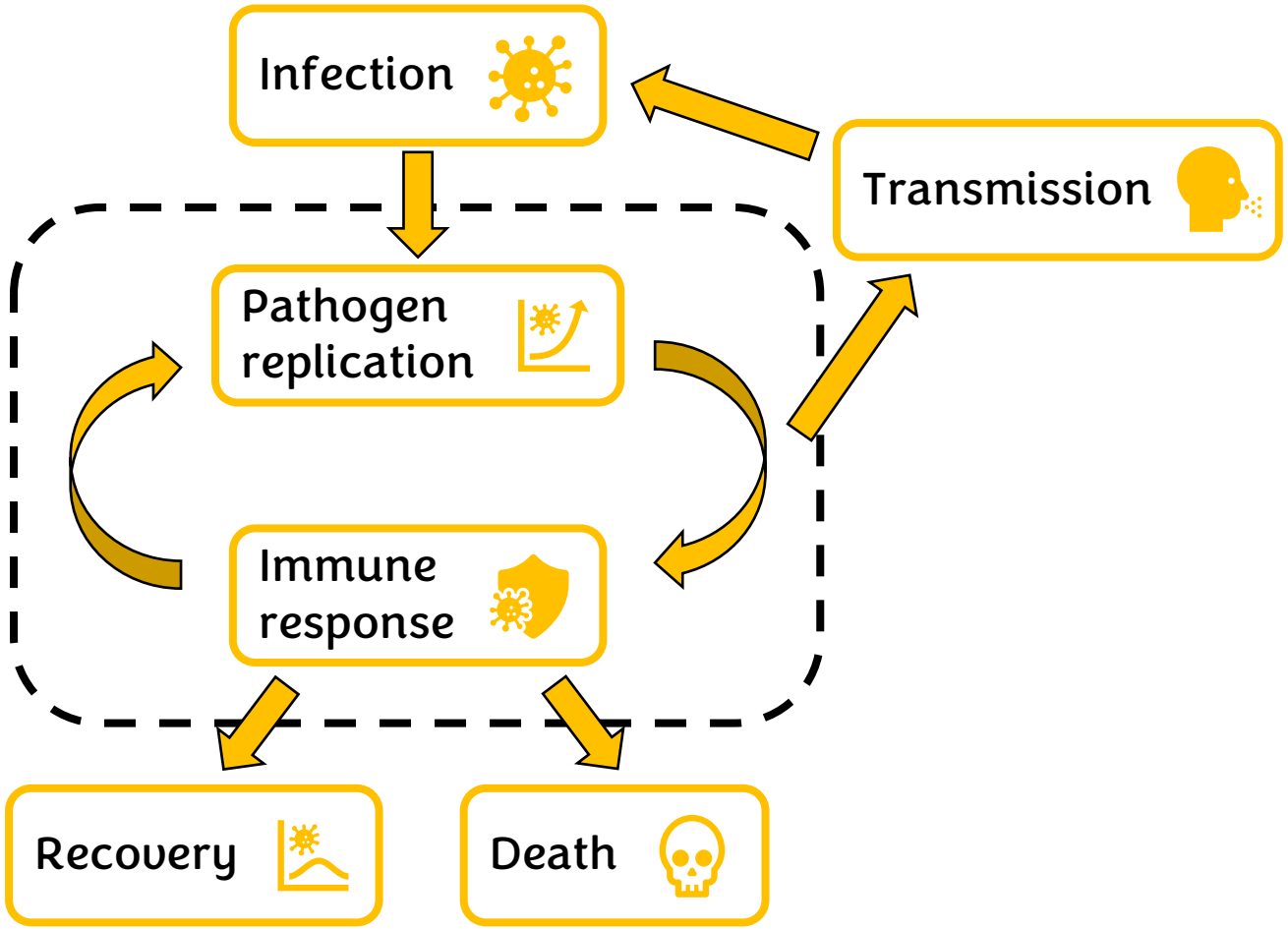

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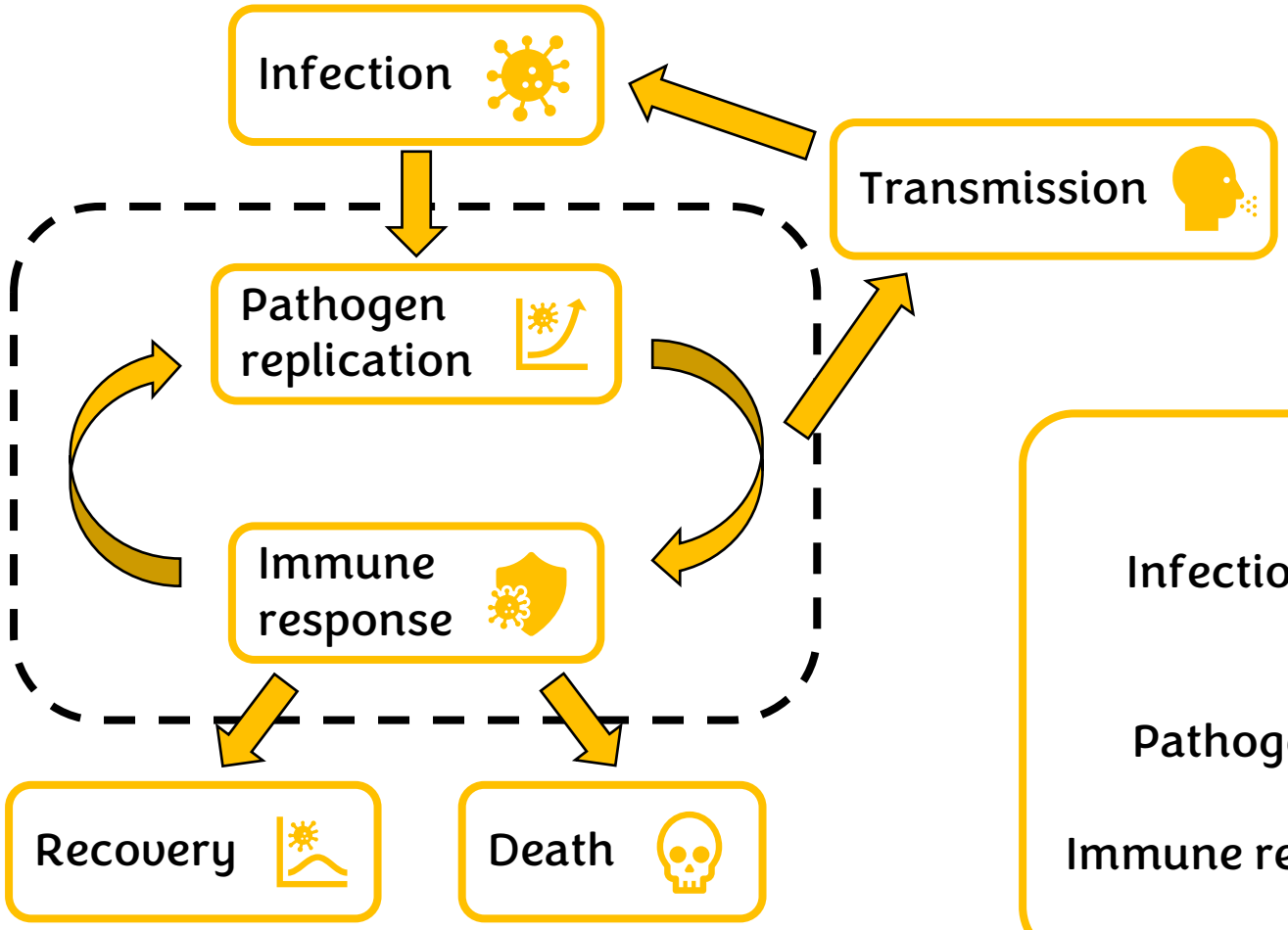

<u>The infection process is individual</u>

Infection: Depends on transmission bottlenecks, how infectious was the infector.

Pathogen replication: Multiple strains, initial dosage.

Immune response: Cross-immunity, vaccination, immuno-compromised.

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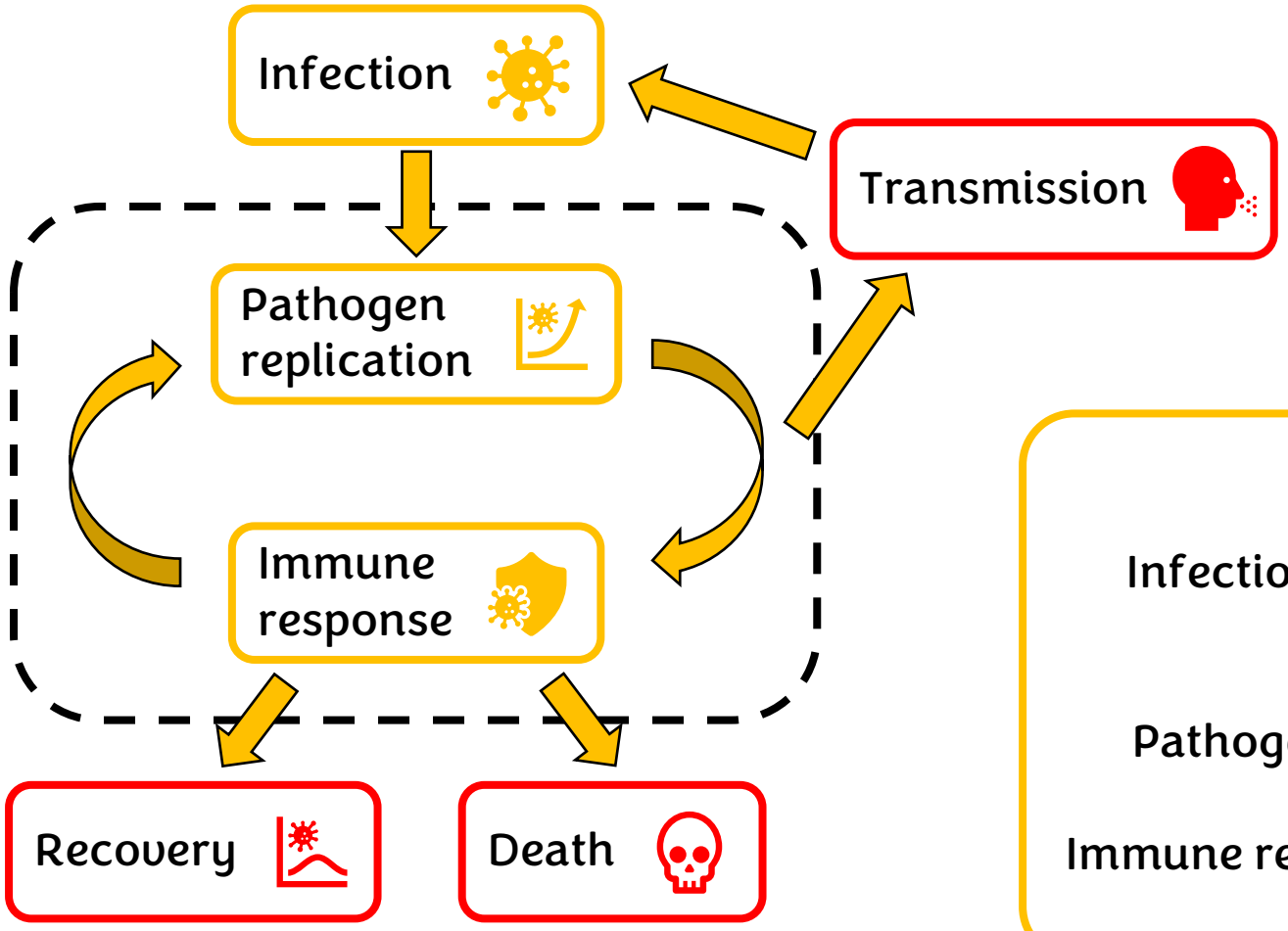

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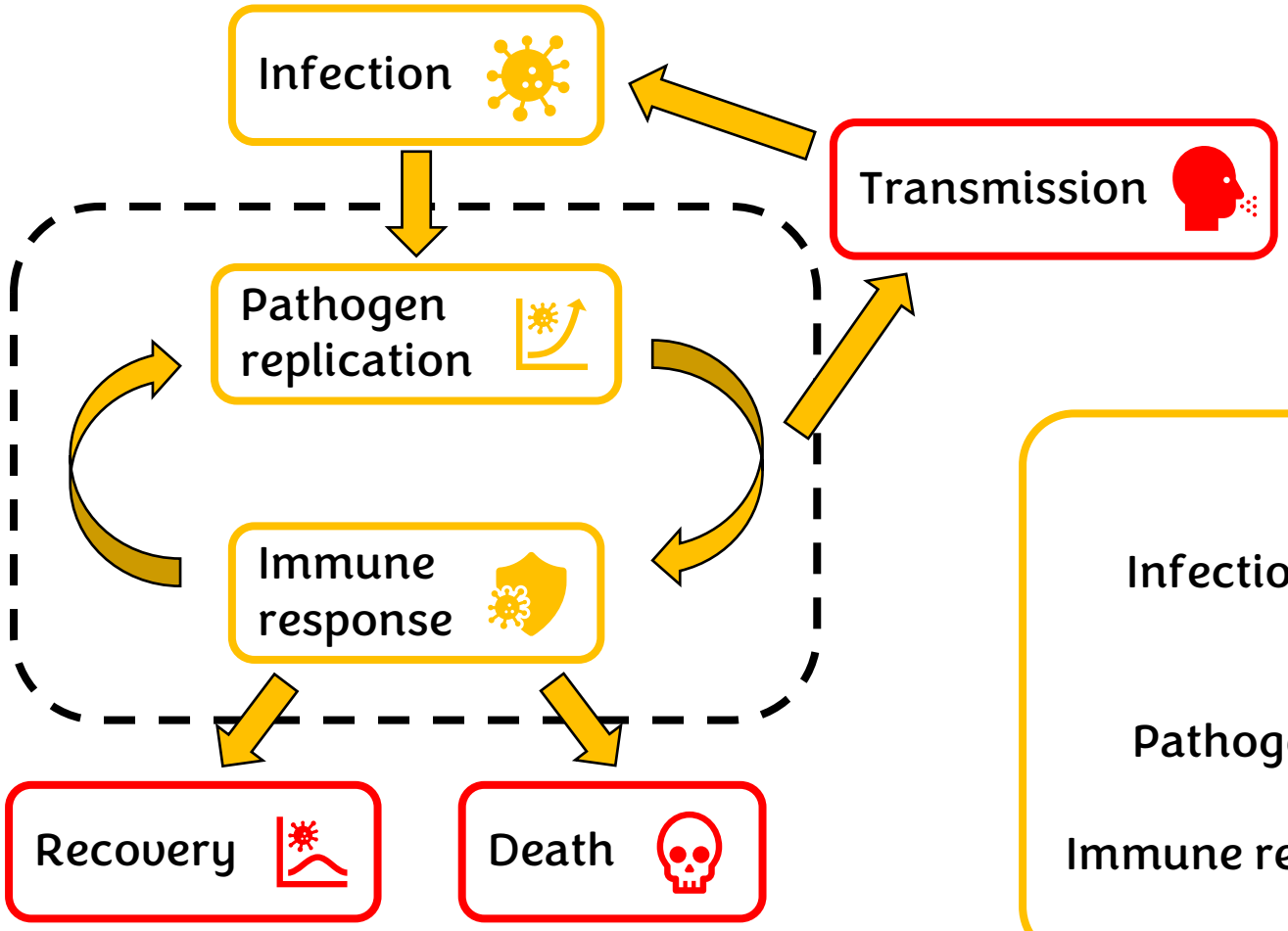

<u>These are "outcomes"</u>

They are functions of an individual, not a universal measure of everyone.

They impact population level dynamics and will be different for each individual.

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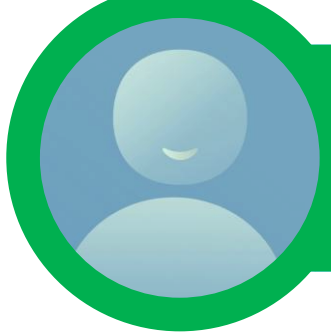

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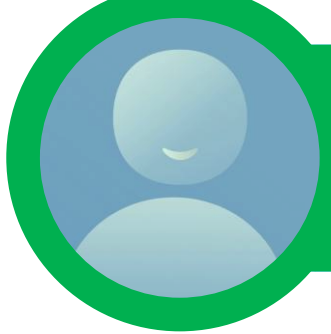

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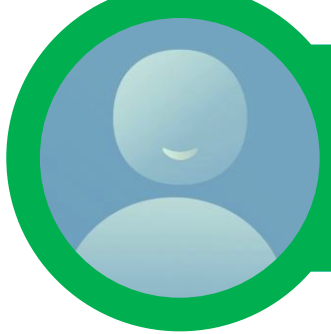

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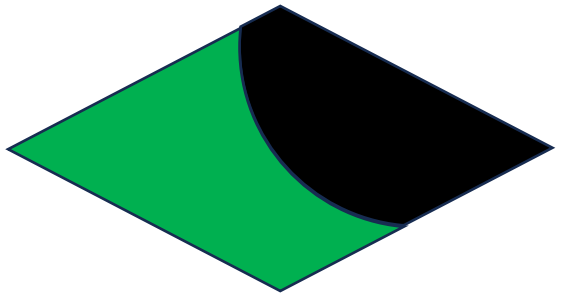

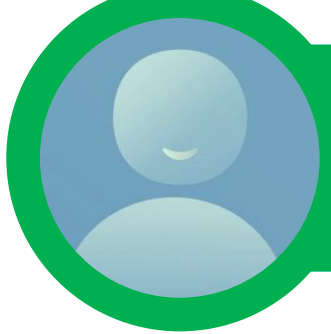

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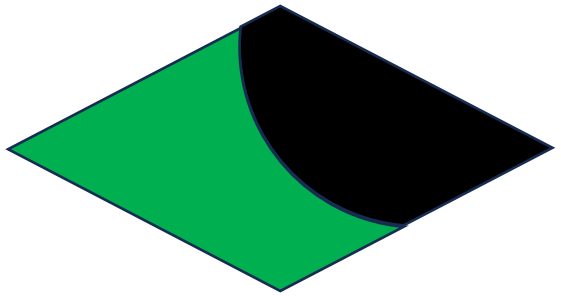

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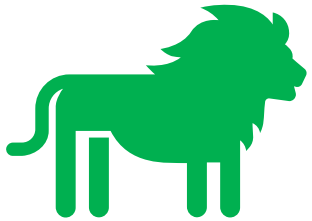

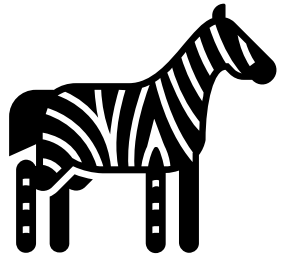

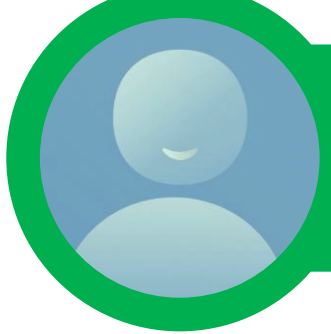

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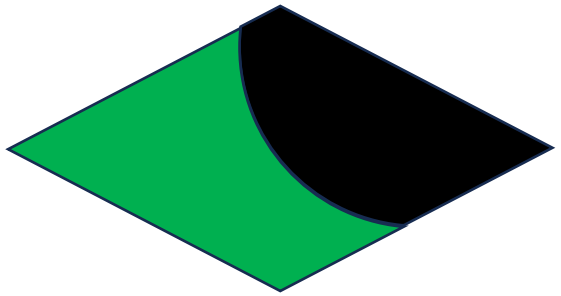

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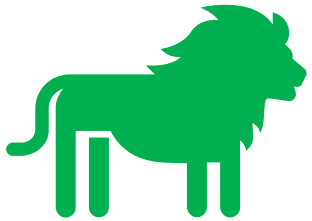
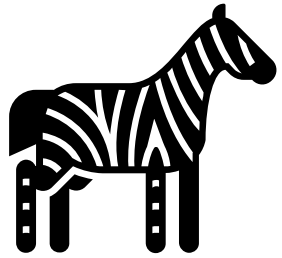
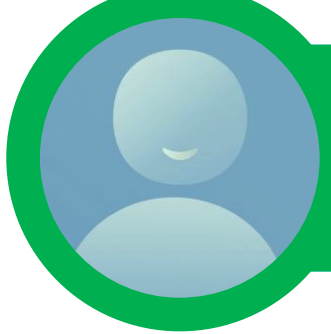




Operators

DIFFUSION

REACTIONS



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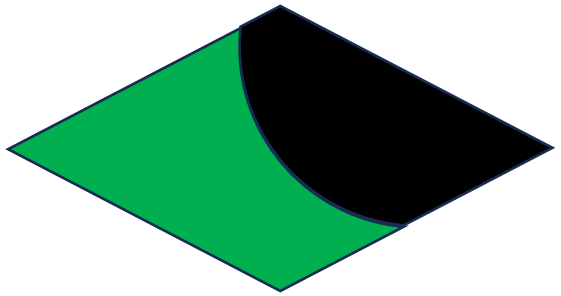

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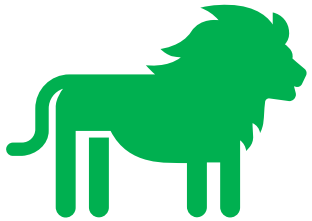

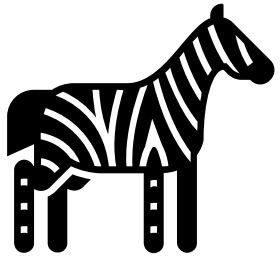

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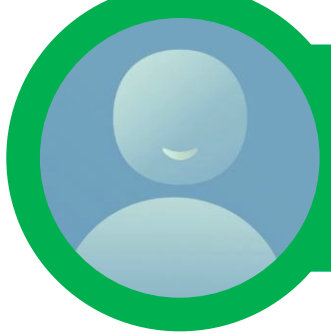

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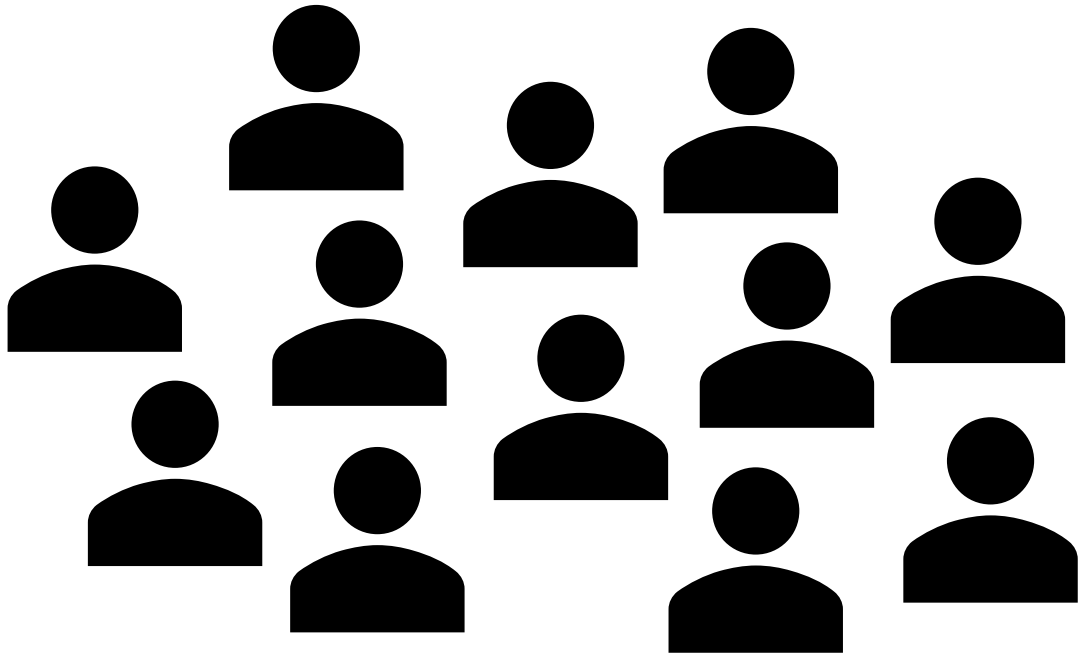

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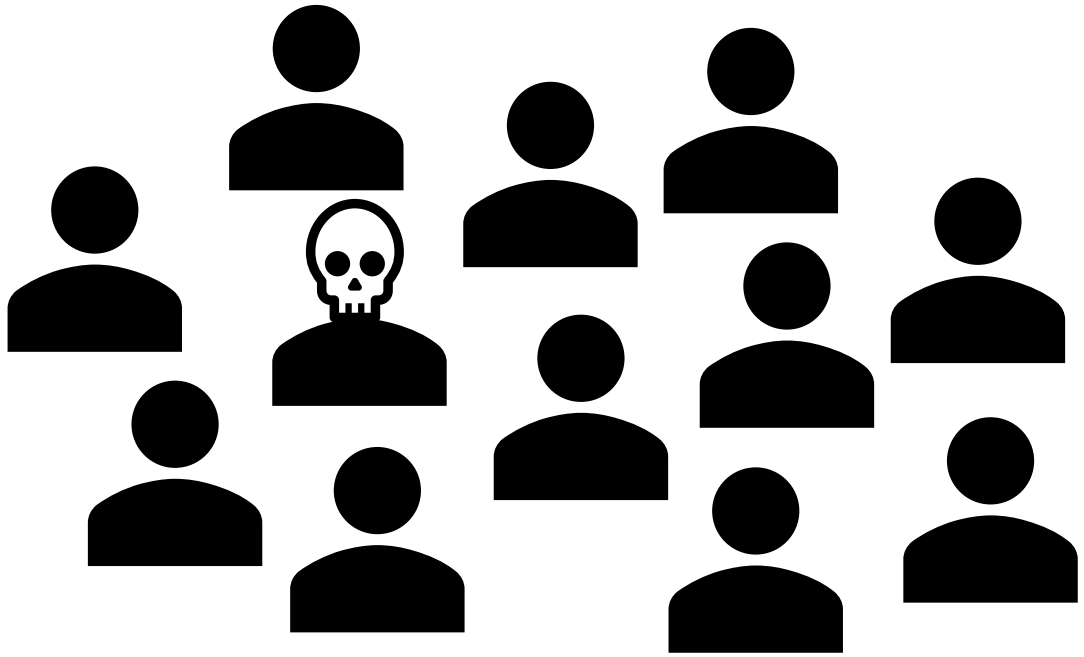

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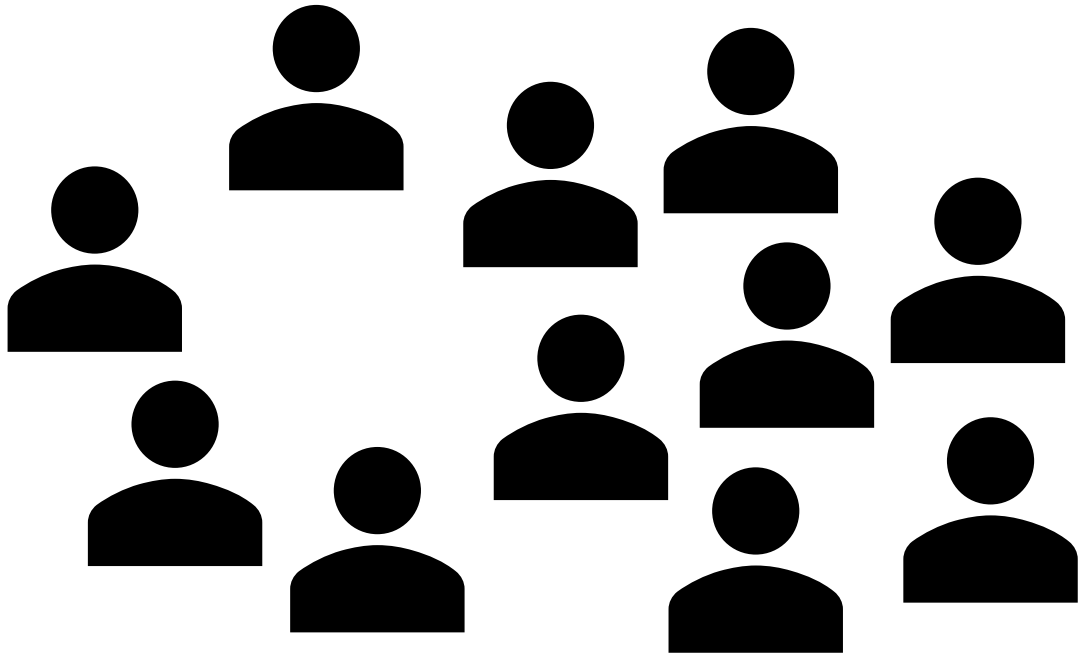

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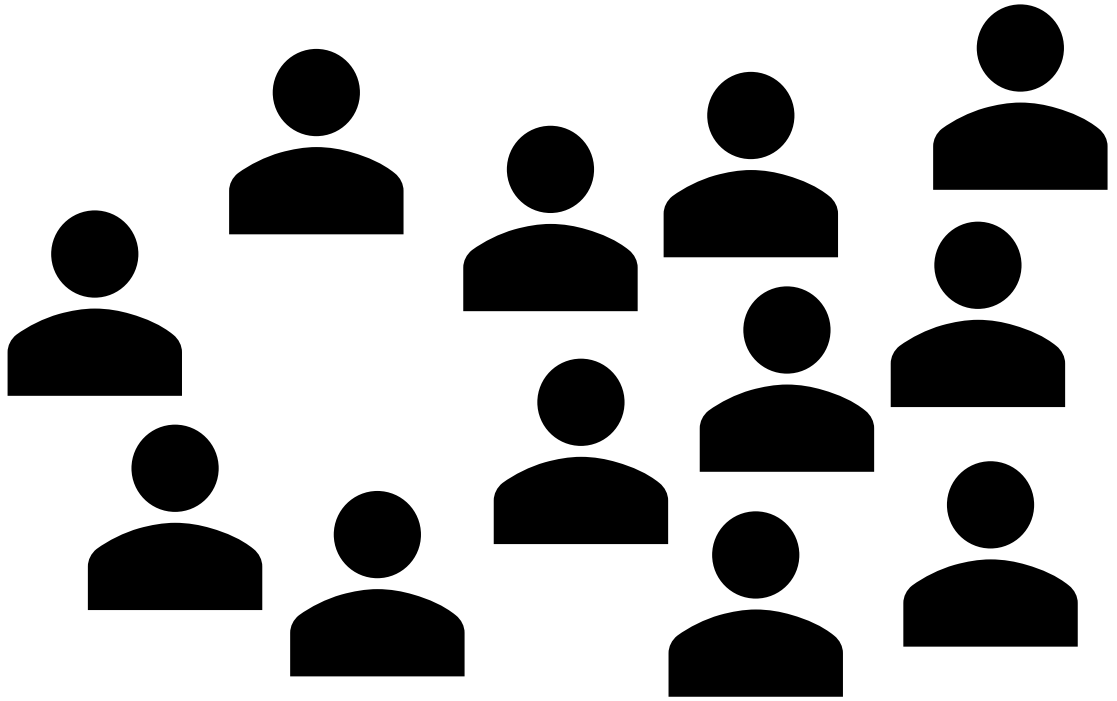

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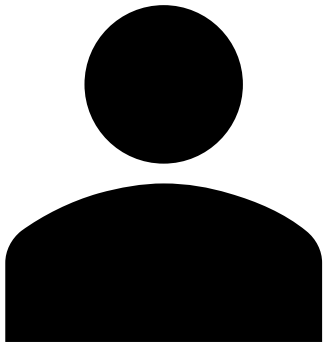

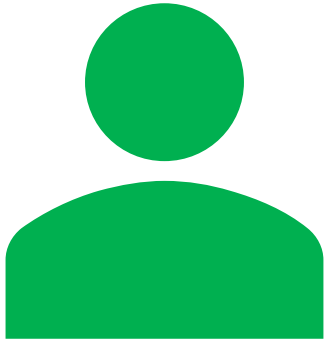

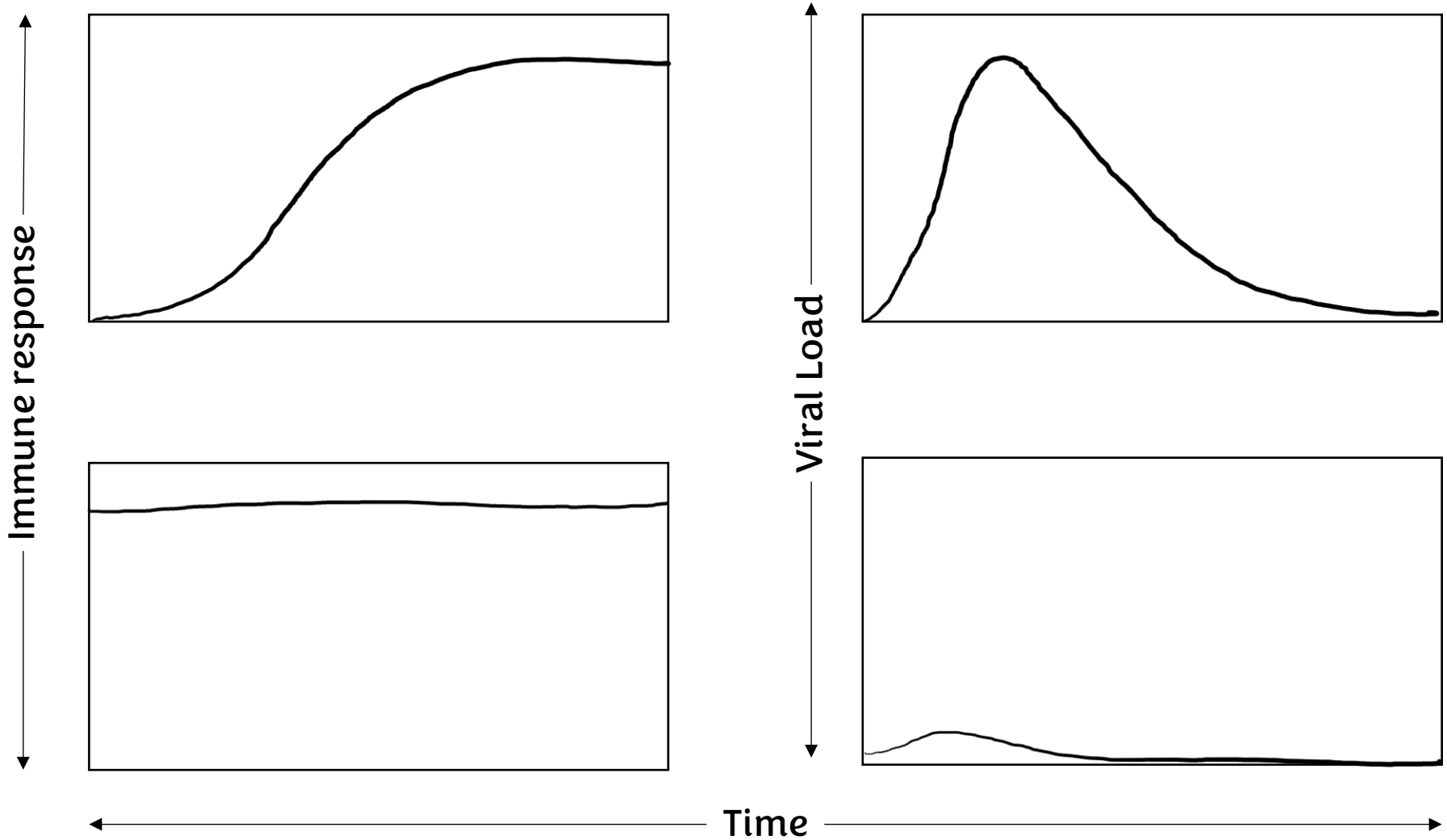

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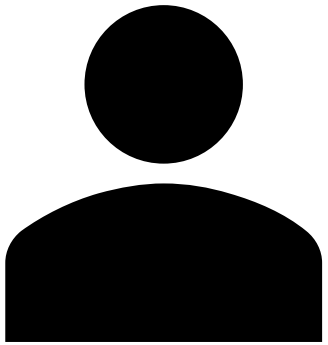

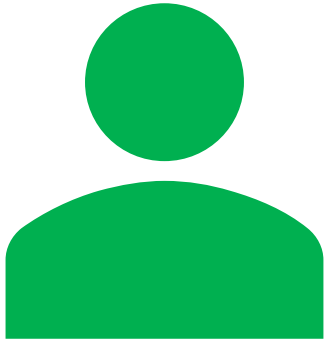

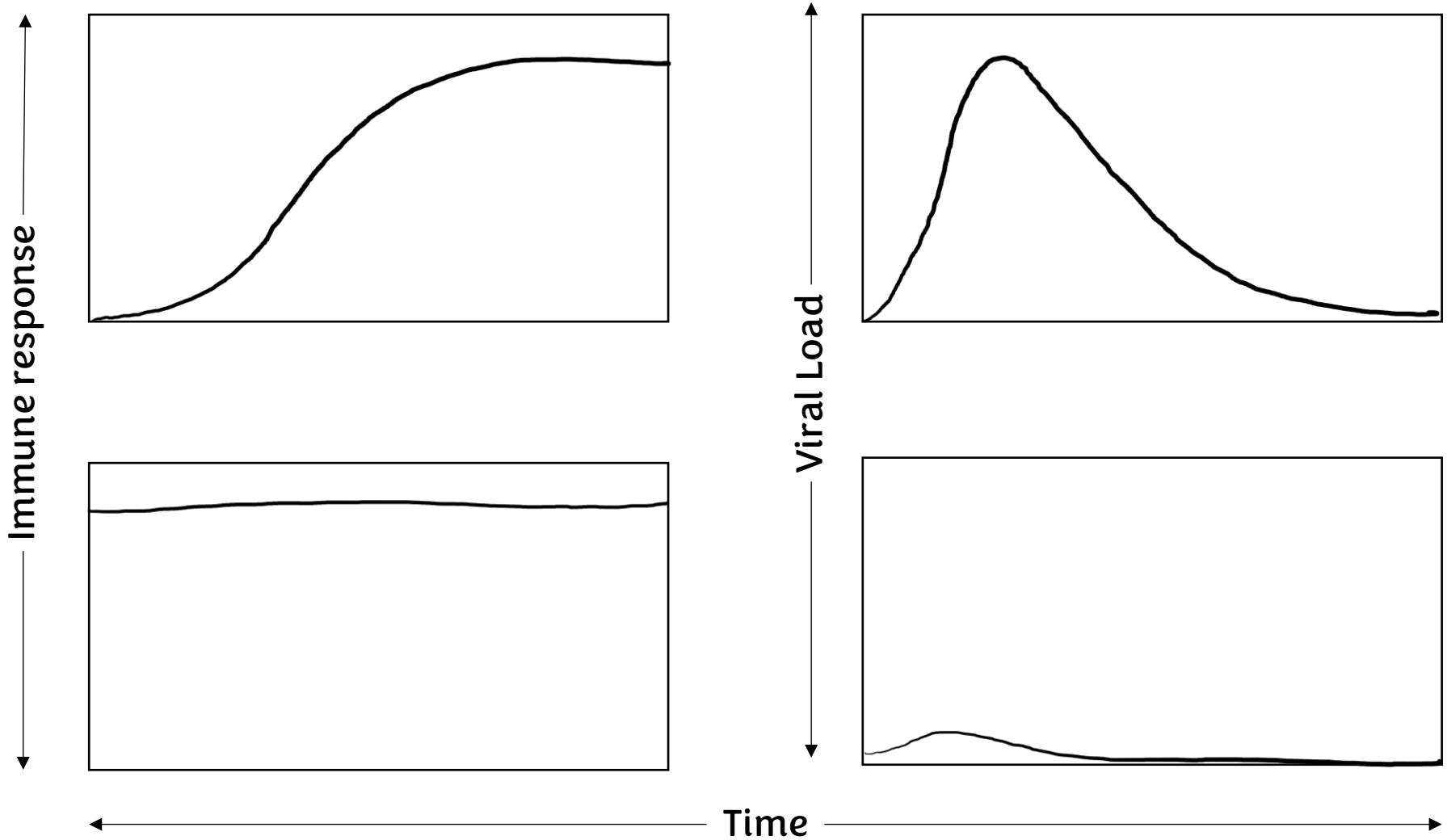

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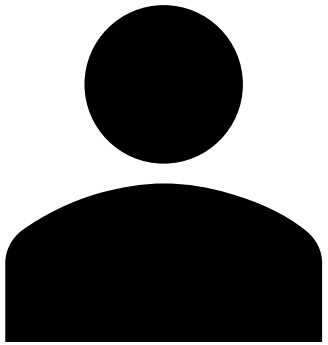

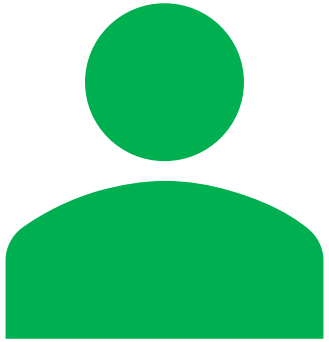

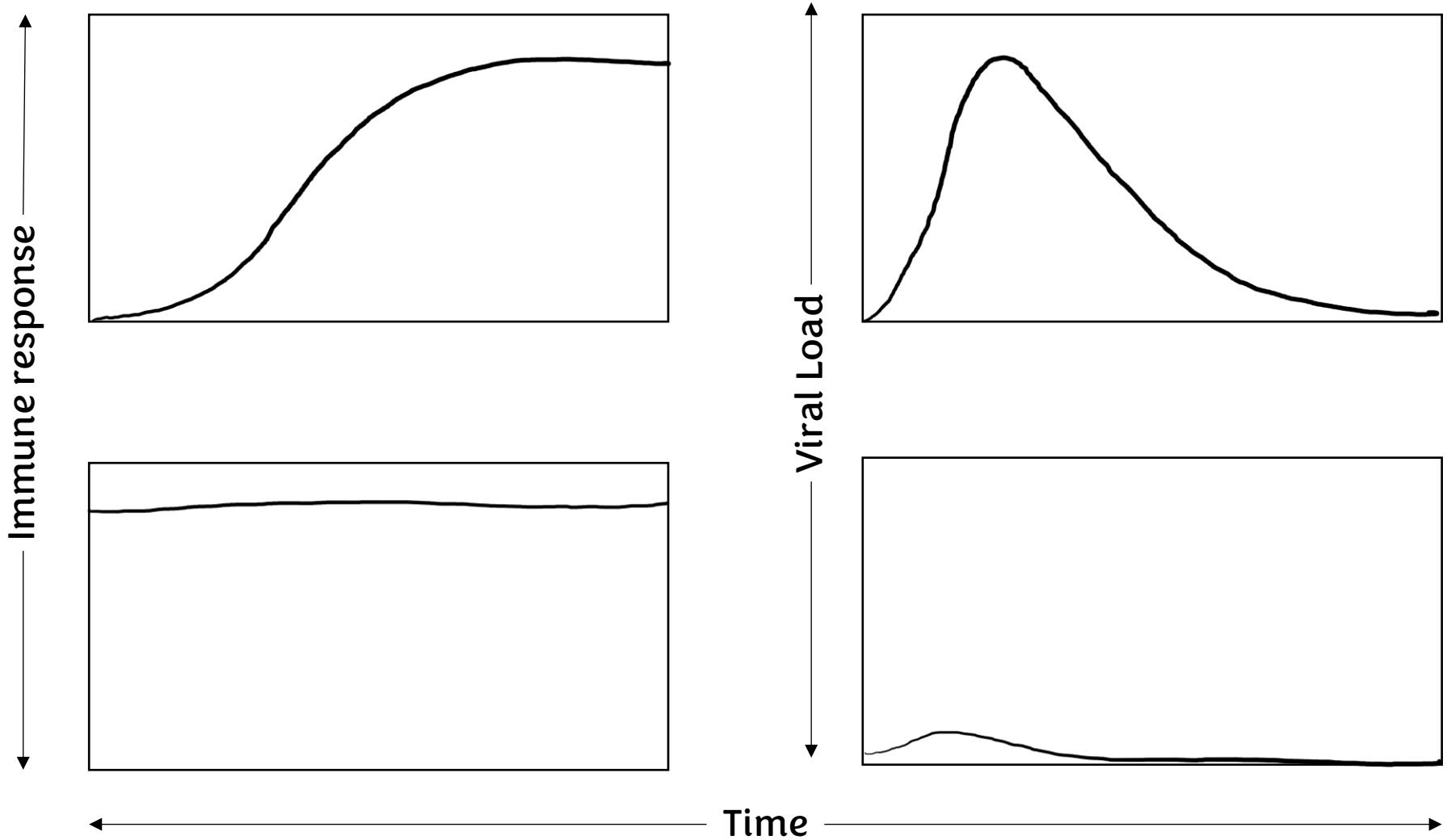

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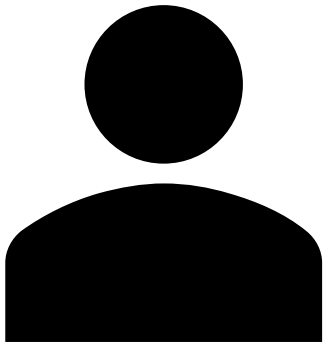

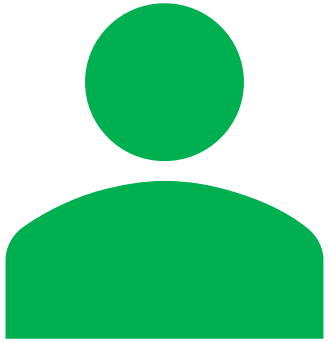

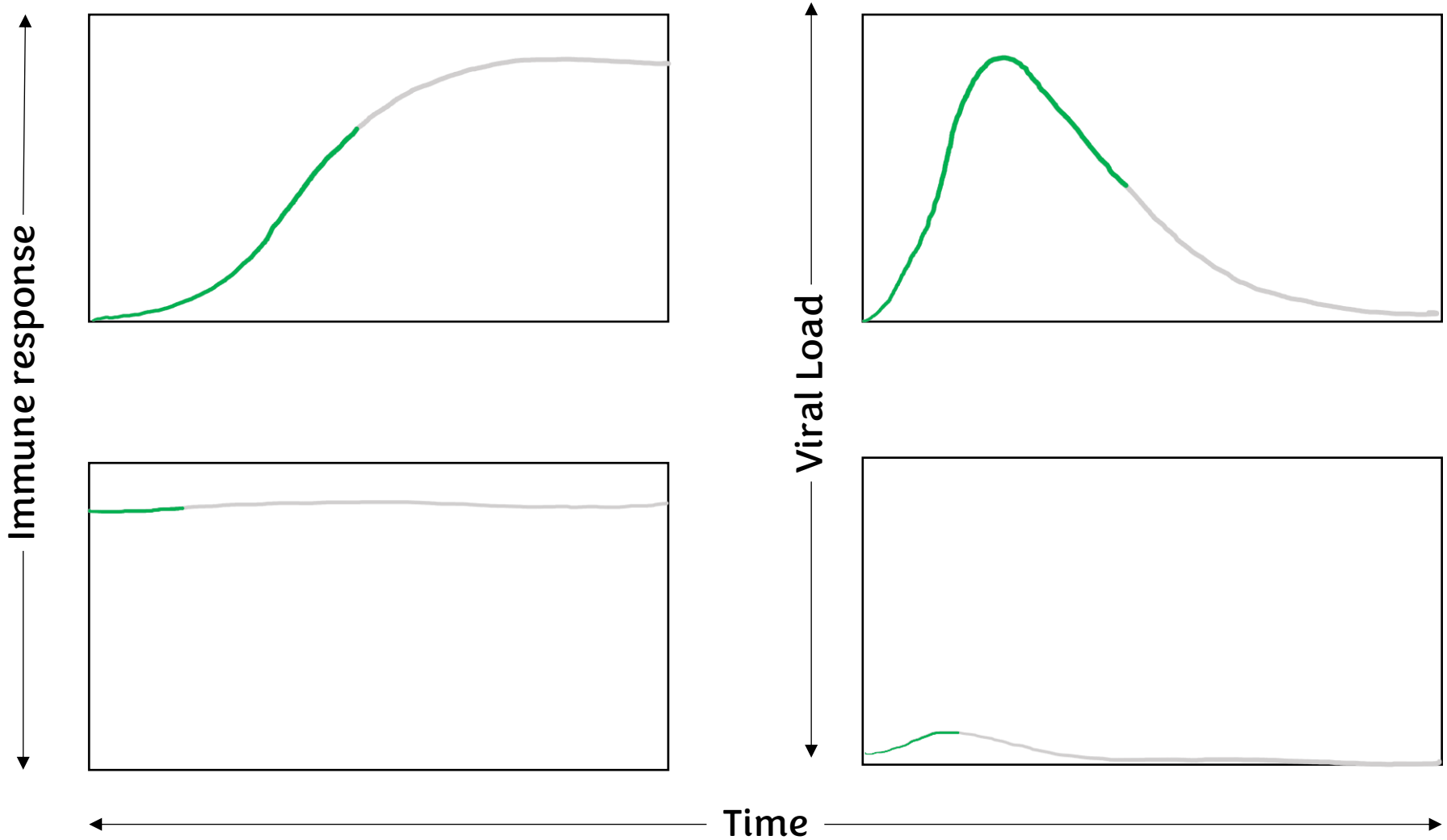

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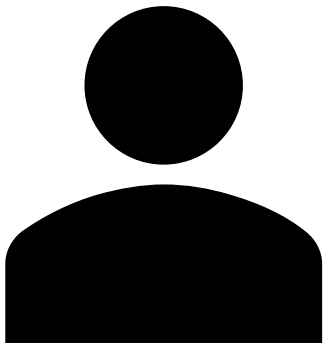

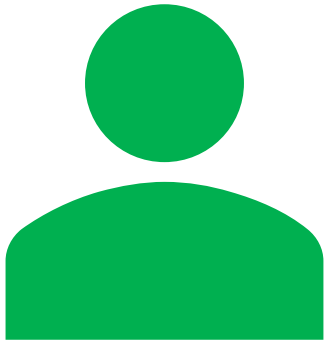

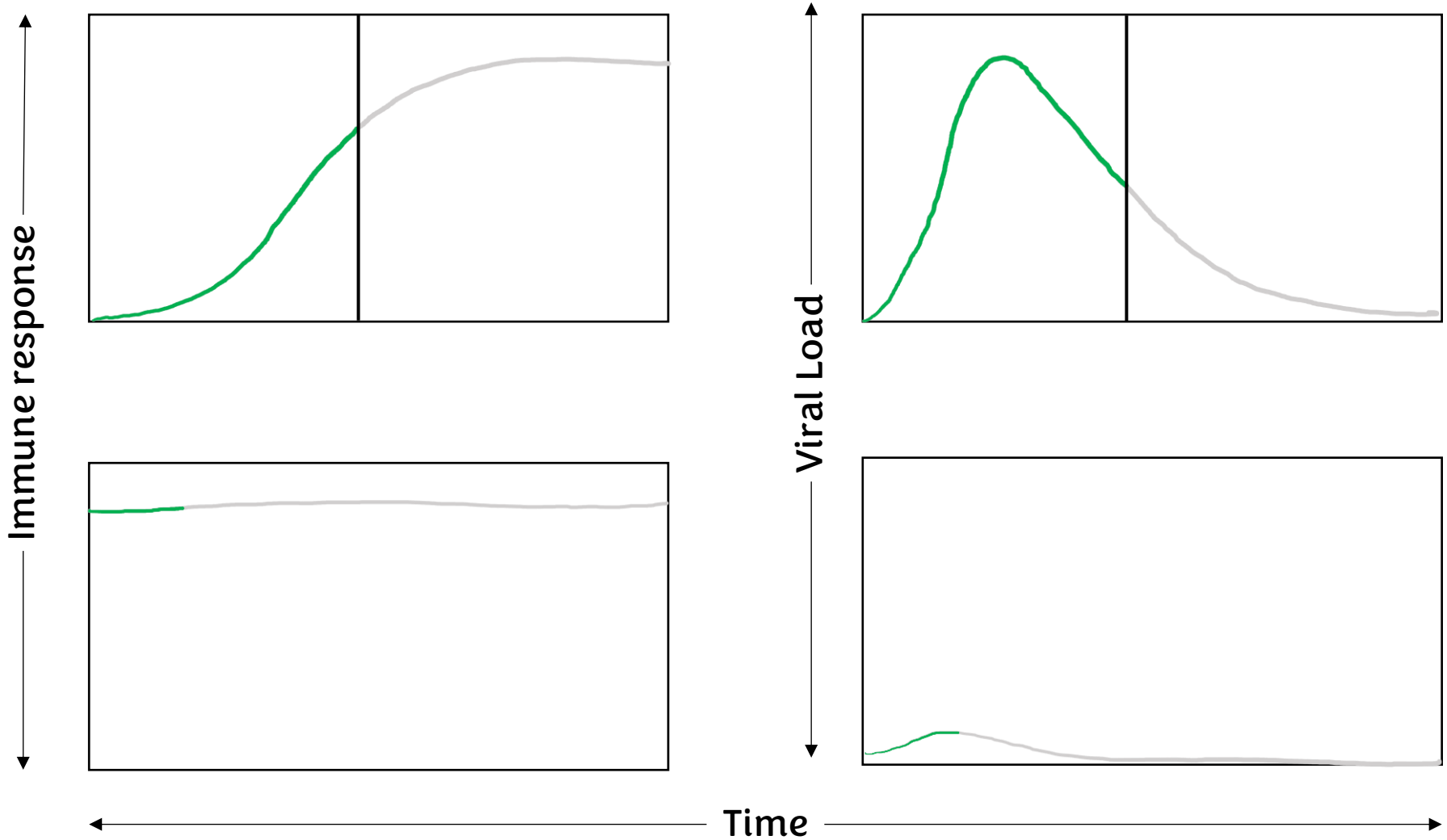

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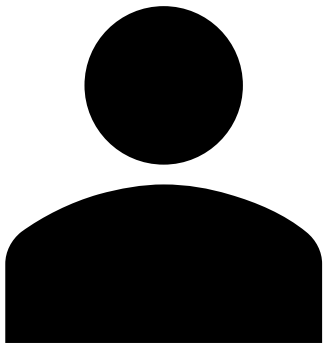

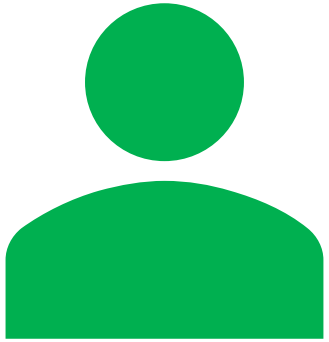

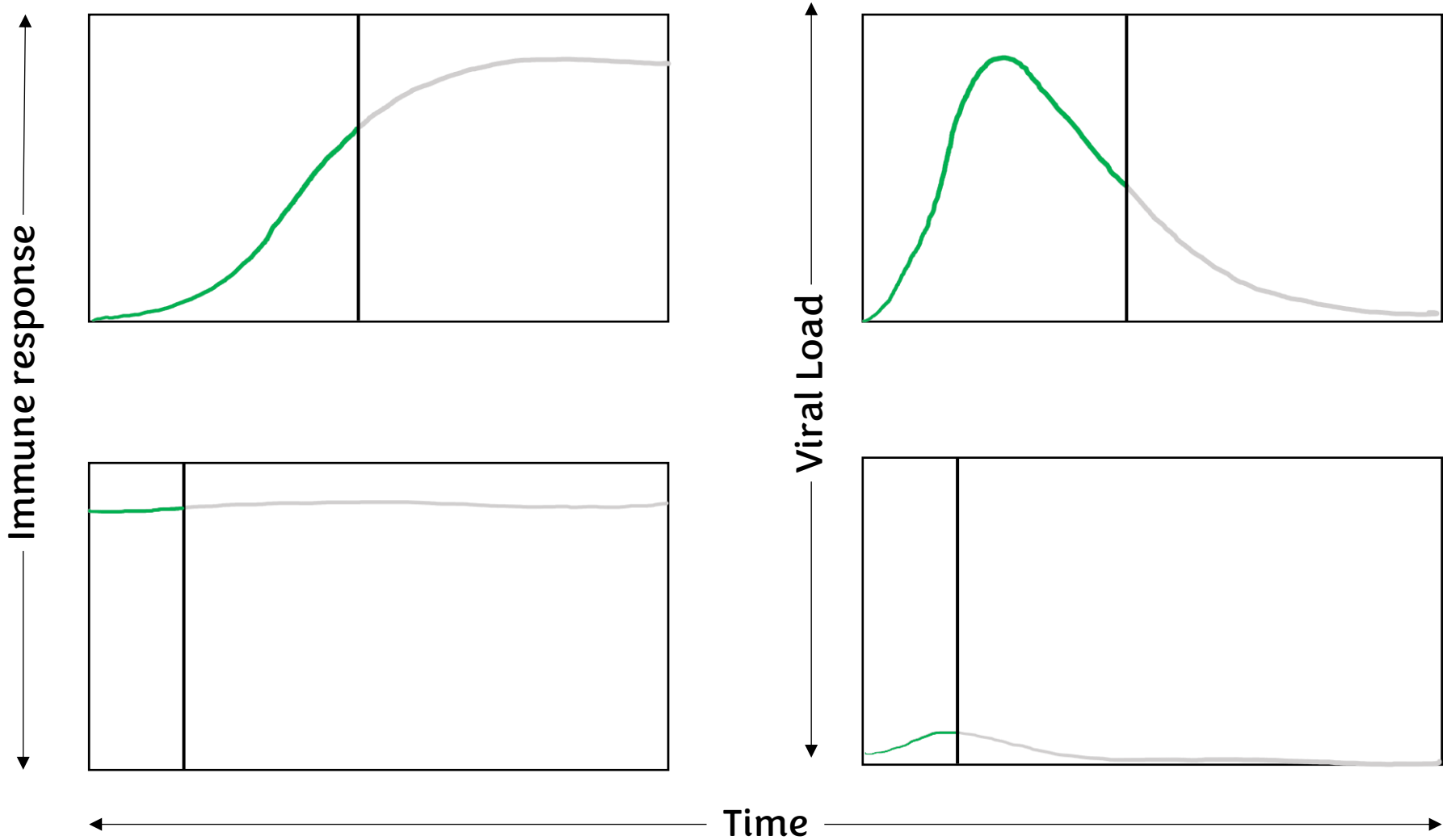

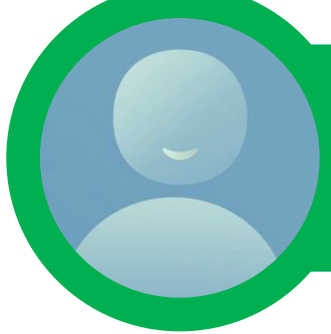

Hybrid methodology

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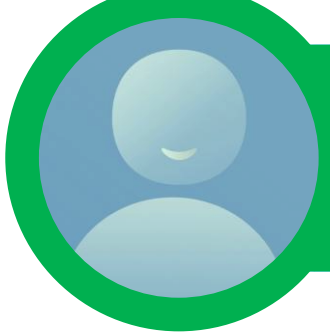
Host demographics

All host demographics calculated here;

At their simplest, they might be:

$$\dot{S} = N(a - qN) - bS,$$
$$\dot{I} = -bI,$$
$$\dot{R} = -bR.$$

ODEs



Hybrid methodology

Within-host dynamics

Each individual has their own ODE system;

Internal state determines transmission, recovery, virulence;

$$\frac{d\boldsymbol{W}_i}{dT_i} = \boldsymbol{f}_W(\boldsymbol{W}_i, \boldsymbol{\theta}_W, T_i)$$

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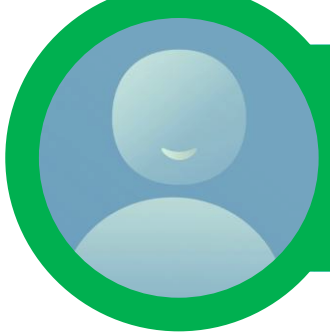

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ODEs

Transmission

$\beta(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

Recovery

$\gamma(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

Virulence

$\alpha(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

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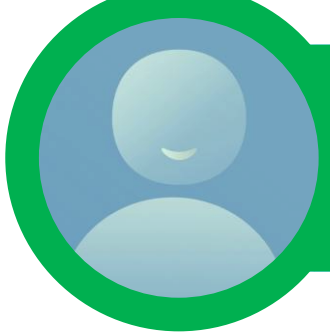

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$$\frac{d\boldsymbol{W}_i}{dT_i} = \boldsymbol{f}_W(\boldsymbol{W}_i, \boldsymbol{\theta}_W, T_i)$$

ODEs

Transmission

$\beta(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

Recovery

$\gamma(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

Virulence

$\alpha(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)$

Natural mortality

SSA

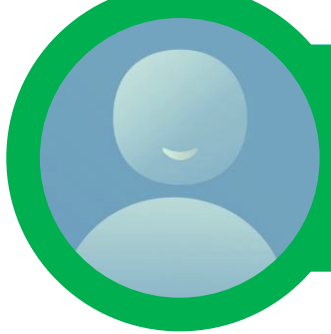
Host demographics

All host demographics calculated here;

At their simplest, they might be:

$$\dot{S} = N(a - qN) - bS,$$
$$\dot{I} = -bI,$$
$$\dot{R} = -bR.$$

ODEs



Hybrid methodology

Within-host dynamics

Let $P_i(T_i)$ be the pathogen count of individual i for an infection of age T_i. Then:

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ODEs

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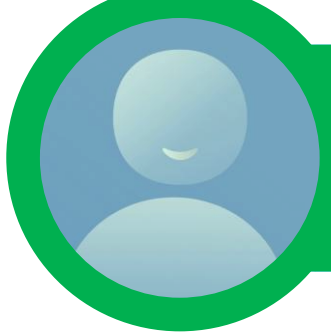

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ODEs

Transmission

$$\beta(P_i) = \beta_1 P_i$$

Recovery

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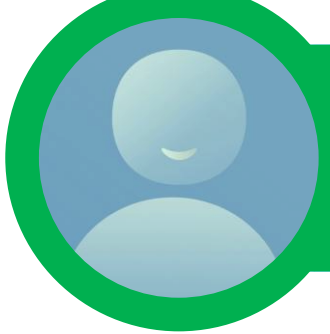

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ODEs

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Recovery

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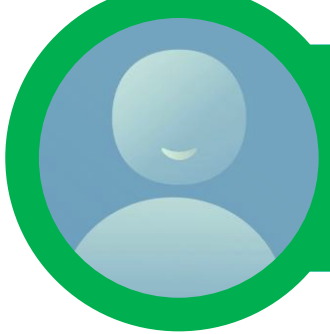

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ODEs

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$$\alpha(P_i) = \alpha_1 P_i^2$$

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ODEs

Example

Hybrid methodology

Within-host dynamics

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ODEs

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Recovery

$$\gamma(P_i) = 0$$

Virulence

$$\alpha(P_i) = \alpha_1 P_i^2$$

Natural mortality

SSA

Host demographics

Let $S(t)$ and $I(t)$ be the density of susceptible and infected individuals respectively, t days after the initial infection. Then:

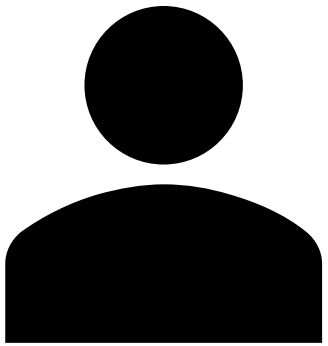
$$\frac{dS}{dt} = N(a - qN) - bS$$

$$\frac{dI}{dt} = -bI$$

ODEs

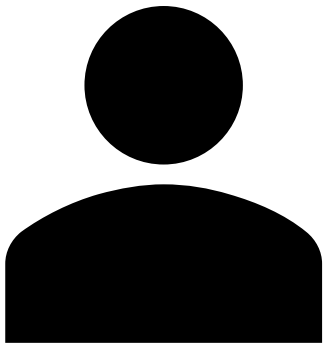
Example

Hybrid methodology



What can we track for each individual?

Hybrid methodology



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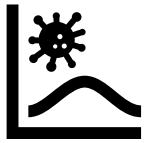
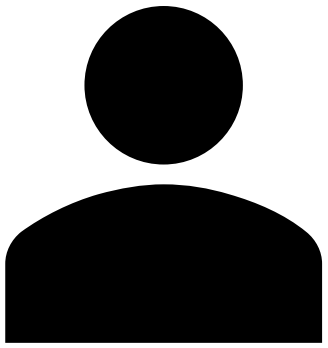


Within-host state

Hybrid methodology



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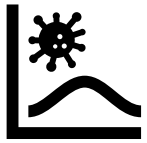

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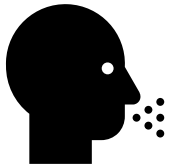
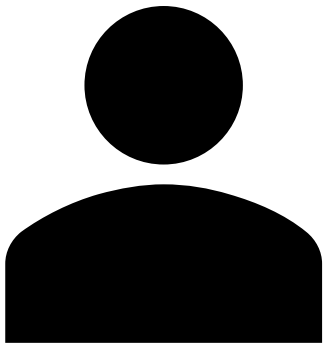


Infection history

Hybrid methodology



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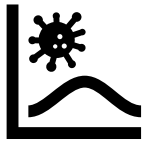

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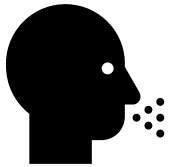
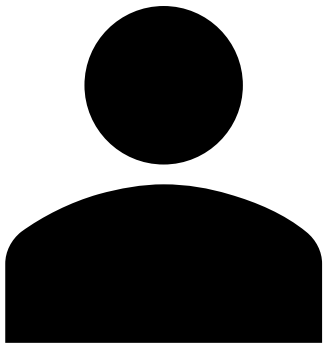


Infection history

Who infects who?

Hybrid methodology



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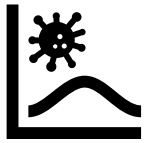

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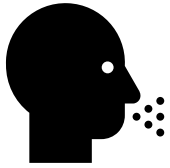
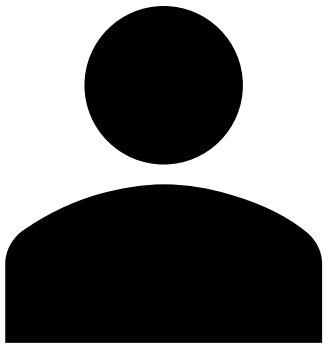


Infection history

Who infects who?

Timings of infection

Hybrid methodology



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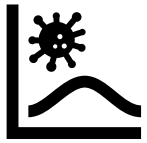

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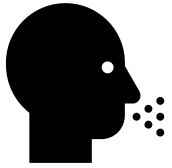


Infection history

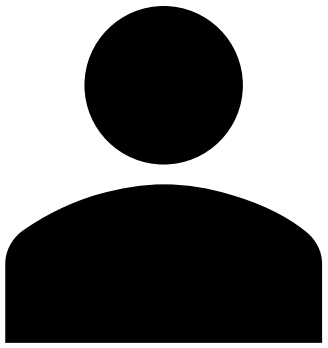
ACGTCAA
ACGTGAA

Mutation history

Who infects who?

Timings of infection

Hybrid methodology



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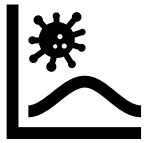

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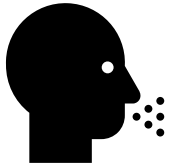

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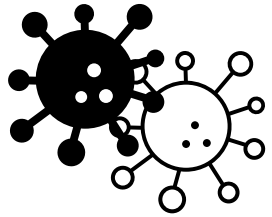
Who infects who?

Timings of infection

Which variant?



Outline

Introduction

Hybrid methodology

What can we do?

Outline

What can we do?

Applications

<u>CASE STUDY 1:</u> Slow clearing pathogen

Prevalence

$$\frac{dP_i}{dT_i} = rP_i\left(1 - \frac{P_i}{K}\right)$$

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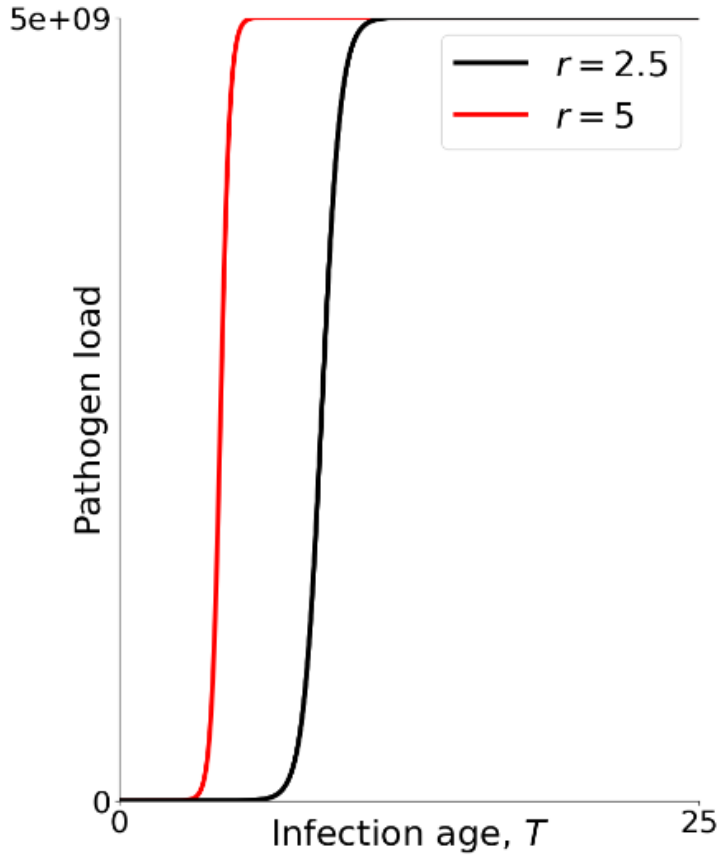

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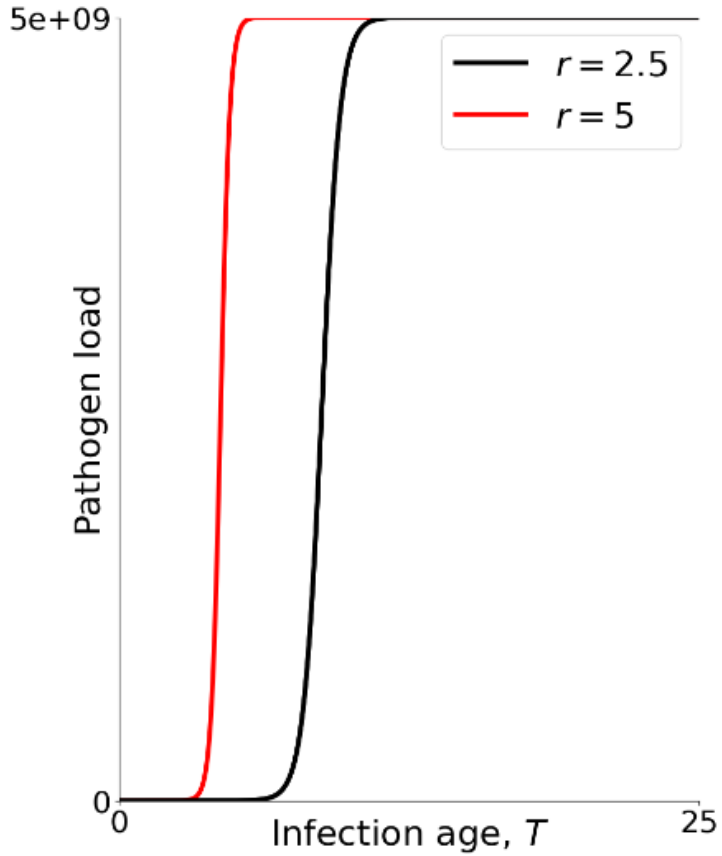

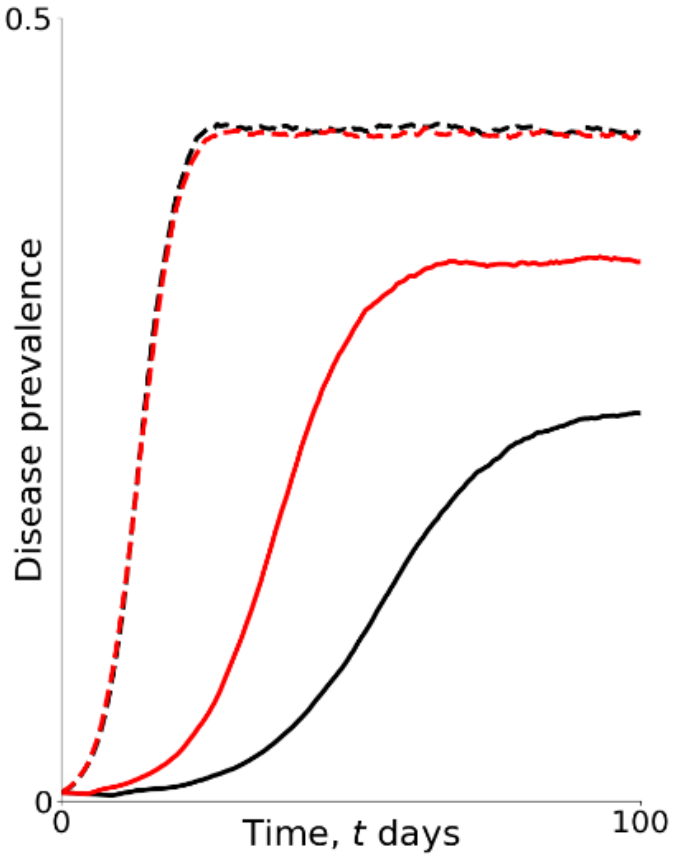

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CASE STUDY 1: Slow clearing pathogen

Within-host evolution

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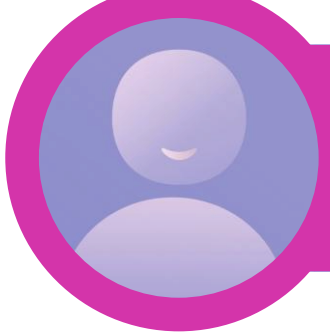

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<u>CASE STUDY 1:</u> Slow clearing pathogen

Within-host evolution

Evolve the growth rate, r

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Within-host evolution

Evolve the growth rate, r

At equilibrium, $P^* = K$, independent of r – (A)

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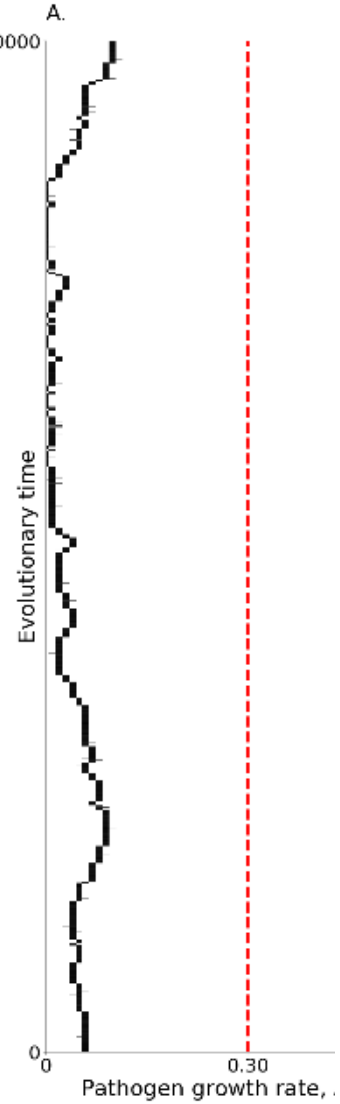

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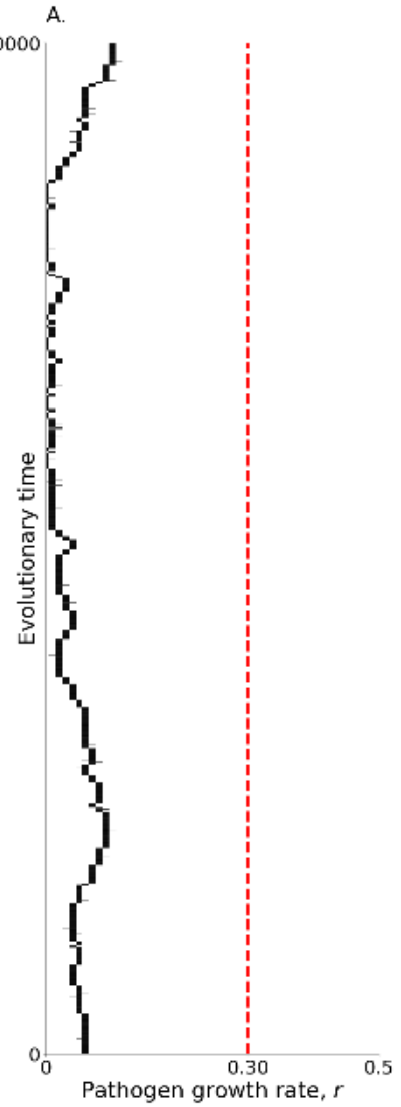
Full transient dynamics – (B)



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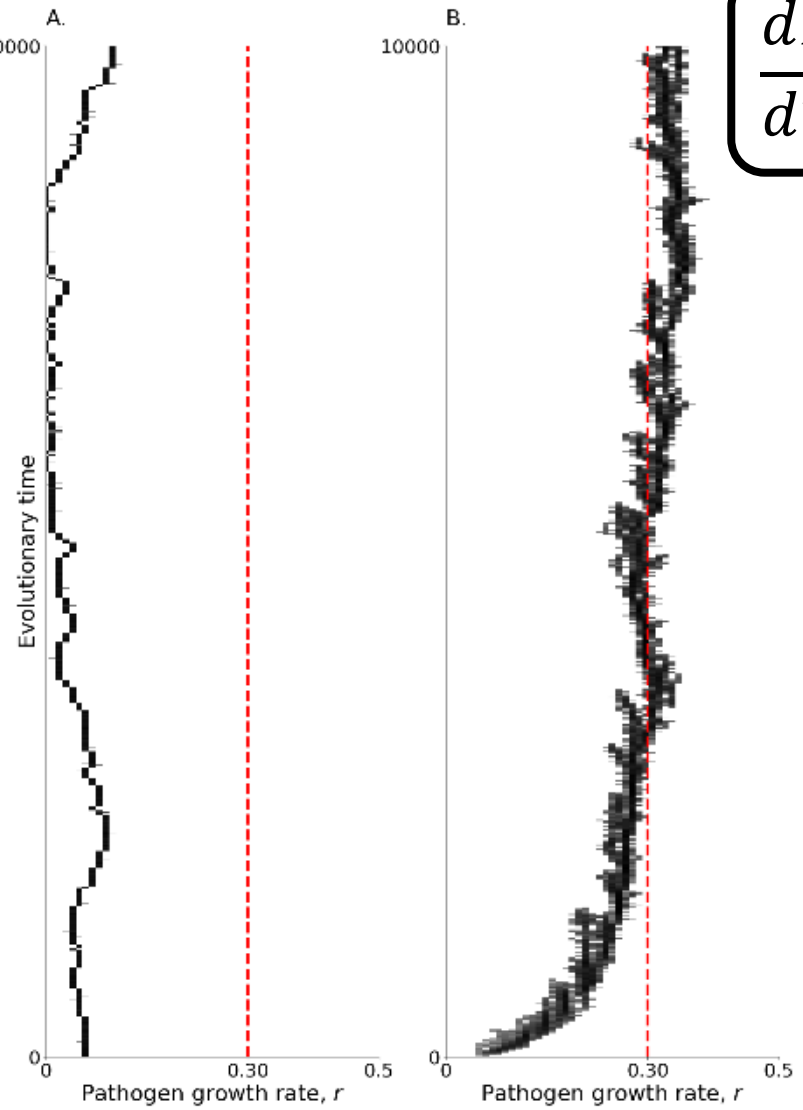
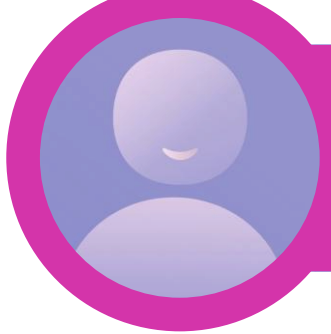
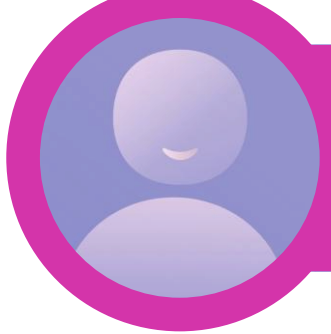




Applications

<u>CASE STUDY 2:</u> Possible recovery

Prevalence



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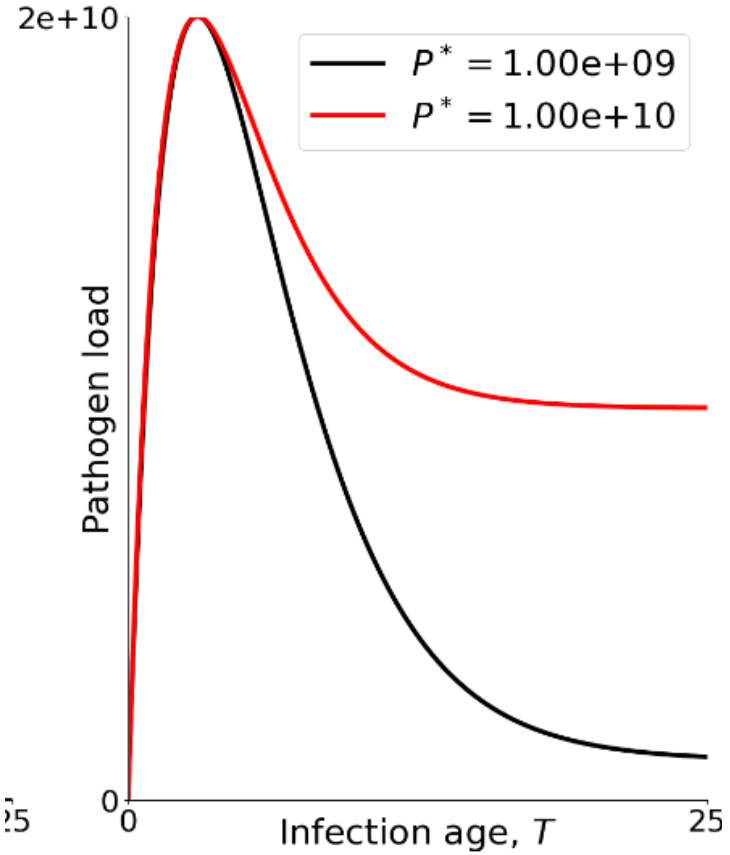

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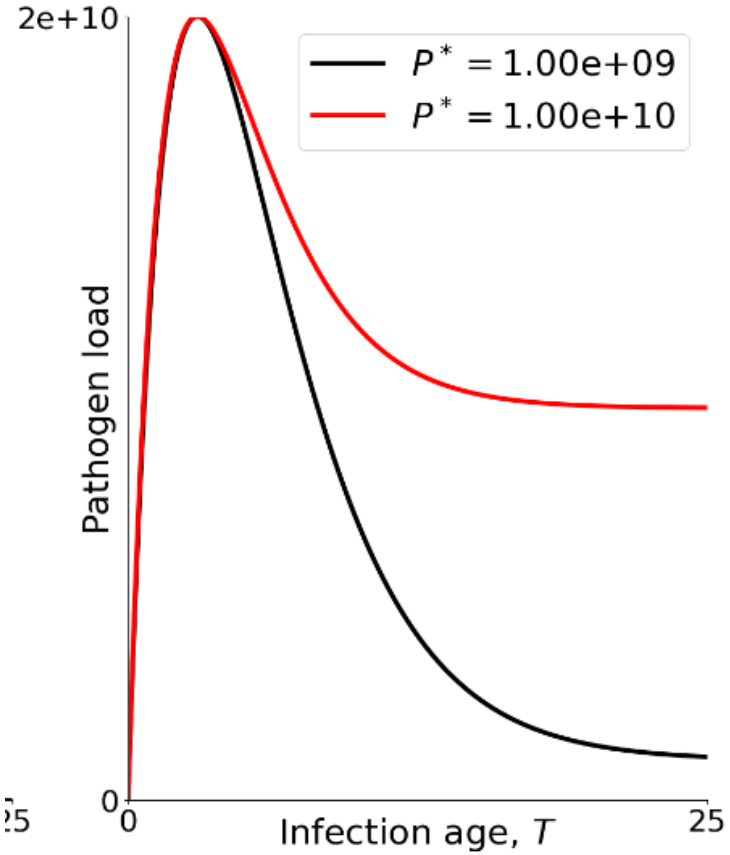

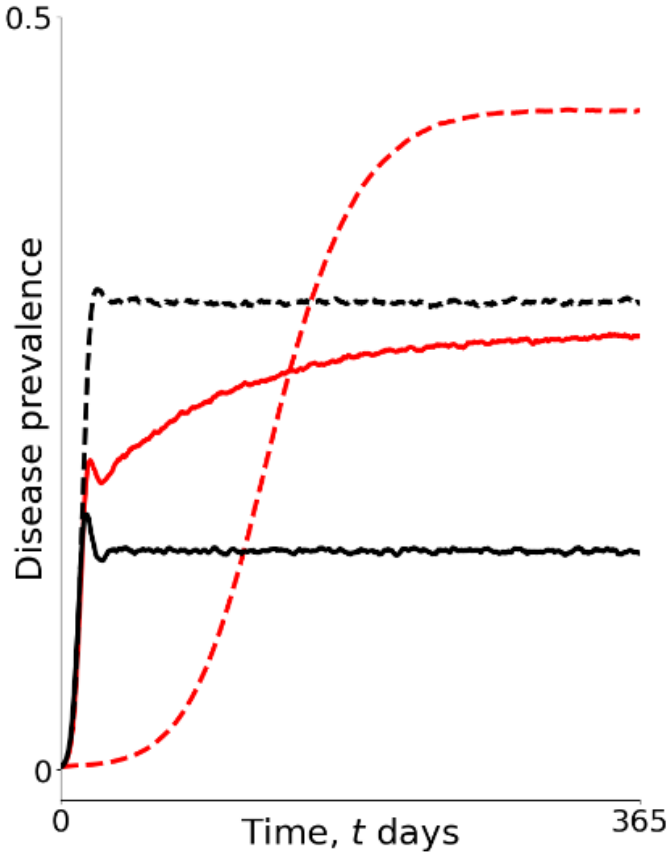

Applications

<u>CASE STUDY 2:</u> Possible recovery
Phylogeny

$$\frac{dP}{dT_i} = re^{-\eta T_i} + \eta(P^* - P_i)$$

150 base genotype

Neutral mutation

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$$\frac{dP}{dT_i} = re^{-\eta T_i} + \eta(P^* - P_i)$$

<u>CASE STUDY 2:</u> Possible recovery

Phylogeny

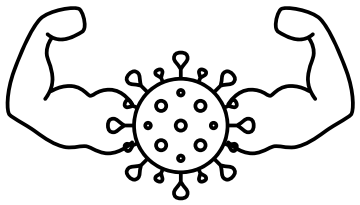
150 base genotype

Neutral mutation

To the future...

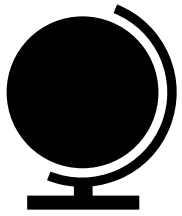
Complex behaviour

Additional host classes (exposed etc.).
Interactions between pathogen and microbiome.
Fitness to phylogeny.



Super infection

Can multiple pathogens exist within a host?
Transmission bottlenecks?
Selection at multiple scales.



Spatial components

Phylogeny and space.
Do we get different clusters?
Can we trace backwards?

...and beyond

...and beyond

Random mutations.

...and beyond

Random mutations.

Comparison of results with implicit WHDs – parasite/symbiont.

...and beyond

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Comparison of results with implicit WHDs – parasite/symbiont.

Python package/GUI to easily simulate epidemics.

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Python package/GUI to easily simulate epidemics.

Comparisons with experimental data.

Tools for phylogenetics/tree reconstruction – TransPhylo package in R.

Theoretical results – R_0, fitness functions...

Recap

Recap

In general we cannot (or do not wish to) model multi-scale processes in full mechanistic detail, and even simulating such models becomes computationally intractable. **Can we come up with ways of extracting the essence of lower-scale models so that they can be embedded into higher-scale models efficiently** (Mideo et al., 2008)?

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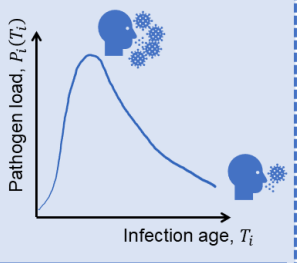
Within-host dynamics (WHD)



$$\frac{\mathrm{d}\boldsymbol{W}_i}{\mathrm{d}T_i} = \boldsymbol{f}_W(\boldsymbol{W}_i, \boldsymbol{\theta}_W, T_i)$$

Note: $P_i(T_i)$ is a component of the state vector $\boldsymbol{W}_i(T_i)$

Coupling

$N_I(t) \xrightarrow{\beta(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)} N_I(t)+1$ Transmission

$N_I(t) \xrightarrow{\alpha(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)} N_I(t)-1$ Virulence

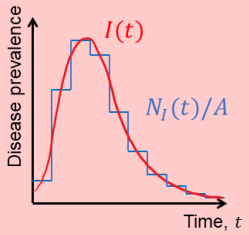
$N_I(t) \xrightarrow{\gamma(\boldsymbol{W}_i, \boldsymbol{\theta}_C, T_i)} N_I(t)-1$ Recovery

$N_I(t) \xleftarrow{} N_I(t)-\kappa(t)$ Natural mortality

$\kappa(t) \sim \mathrm{Poisson}(|\delta I(t)|)$

$\delta I(t) = AI(t) - N_I(t)$

Host demographic dynamics (HDD)



$$\frac{\mathrm{d}\boldsymbol{D}}{\mathrm{d}t} = \boldsymbol{f}_D(\boldsymbol{D}, \boldsymbol{\theta}_D, t)$$

Note: $I(t)$ is a component of the state vector $\boldsymbol{D}(t)$

Recap

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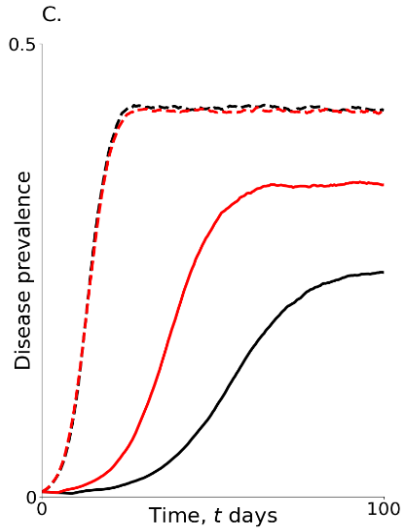

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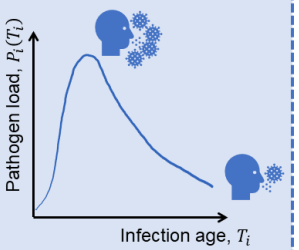

$$\frac{\mathrm{d}\boldsymbol{W}_i}{\mathrm{d}T_i} = \boldsymbol{f}_W(\boldsymbol{W}_i, \boldsymbol{\theta}_W, T_i)$$

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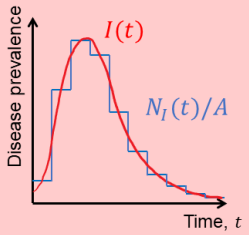

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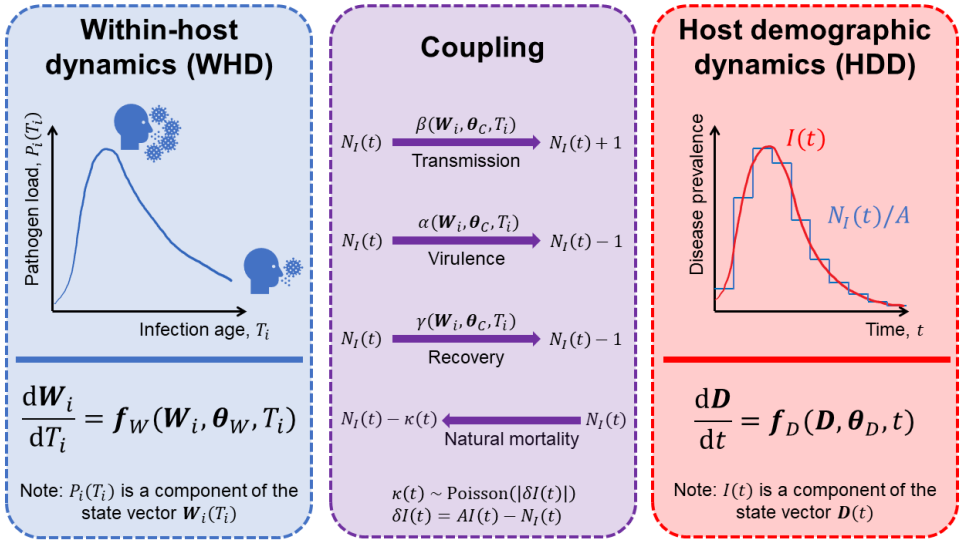

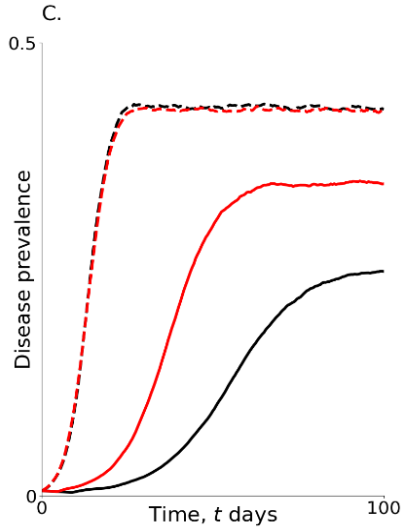

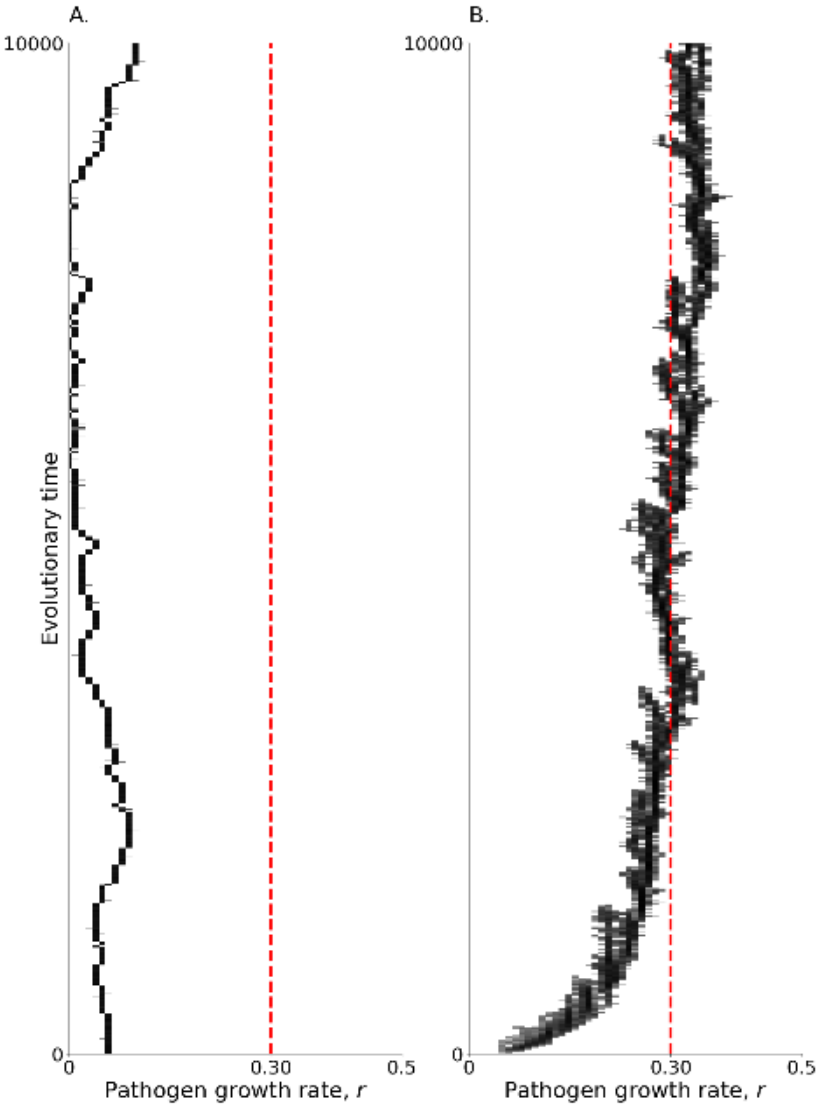

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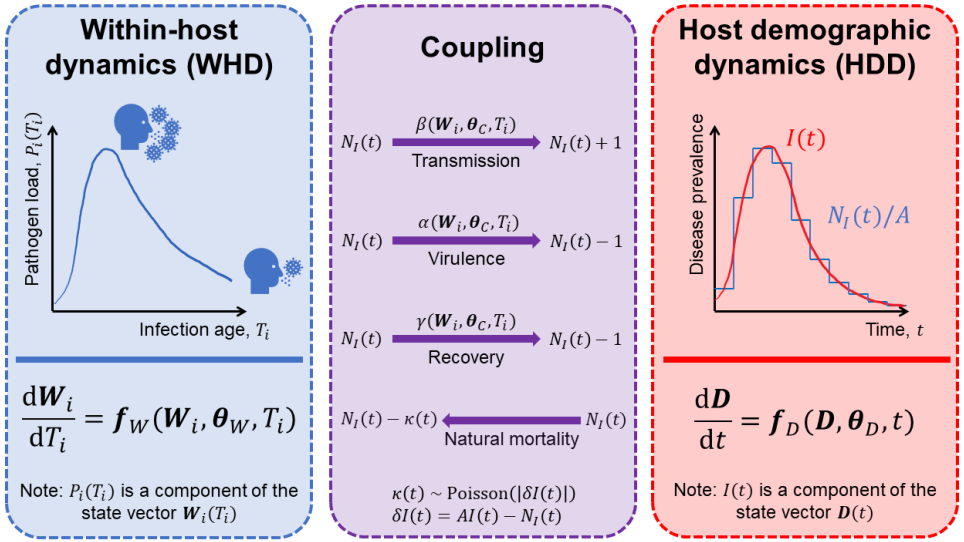
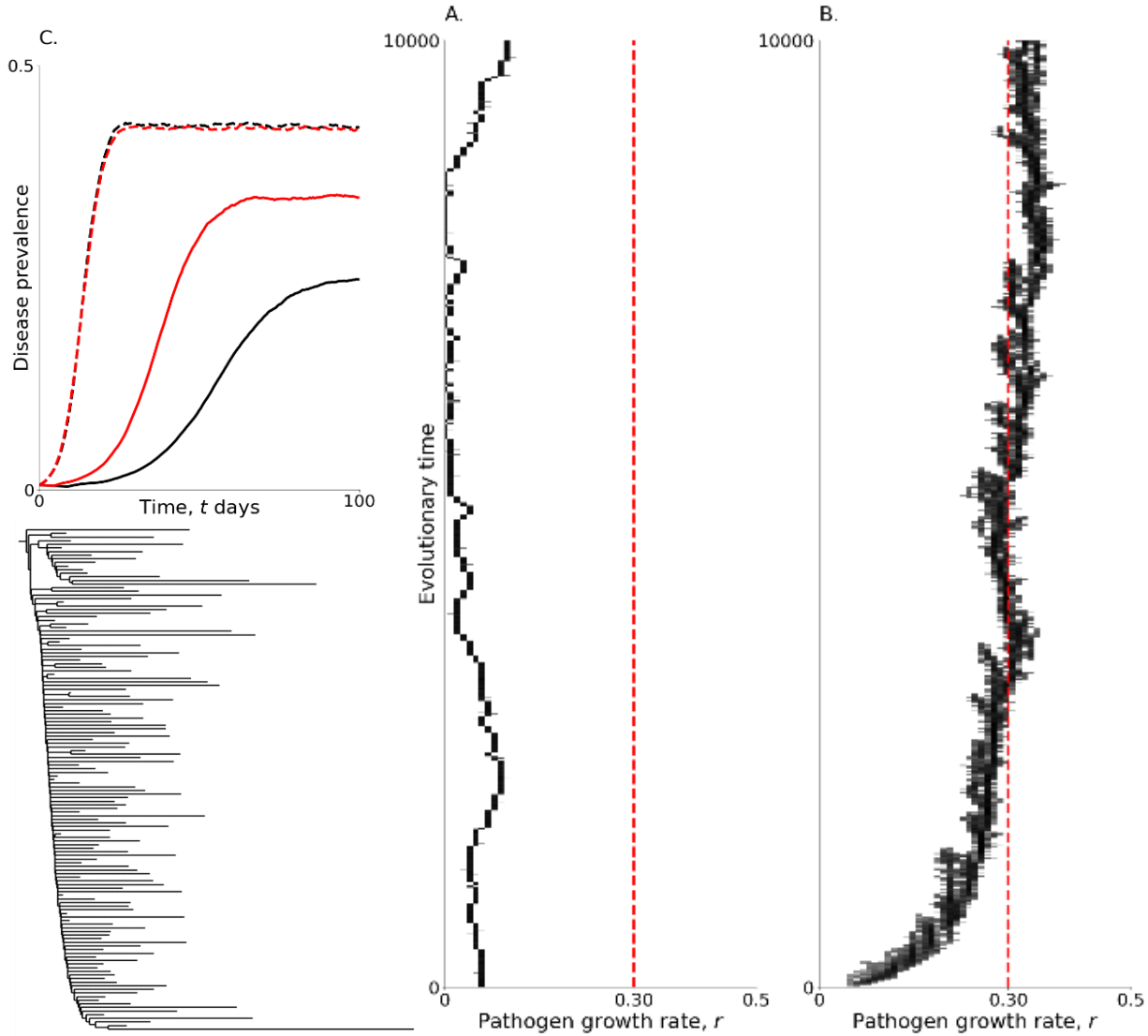




Thank you!

Efficient coupling of within- and between-host infectious disease dynamics
C.A. Smith and B. Ashby
Journal of Theoretical Biology

Ben Ashby

Simon Fraser University

eco-evo theory

Kayla King

University of British Columbia

KING LAB

Get in touch!

cs640@bath.ac.uk
(live from next week!)

cameronsmith50.github.io

Funders/affiliations

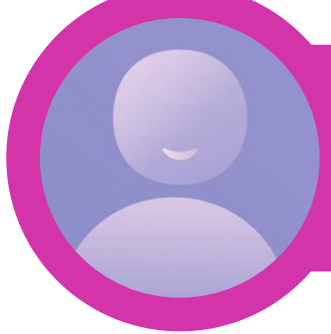
erc

UKRI Natural Environment Research Council

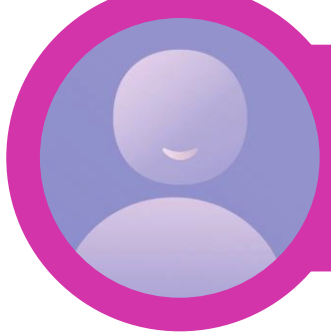
UNIVERSITY OF BATH

Department of BIOLOGY

UNIVERSITY OF OXFORD



Ecology



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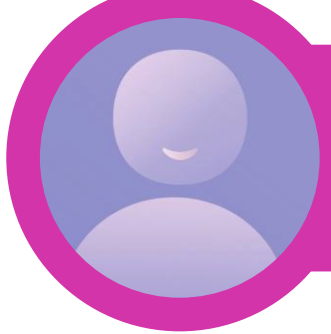
Questions to answer:



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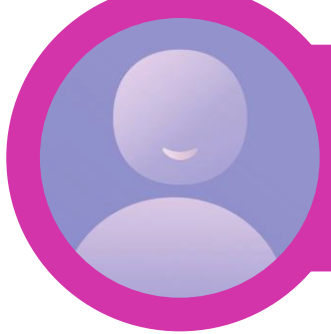

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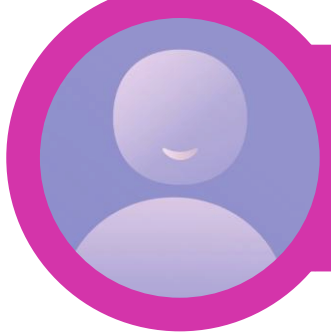

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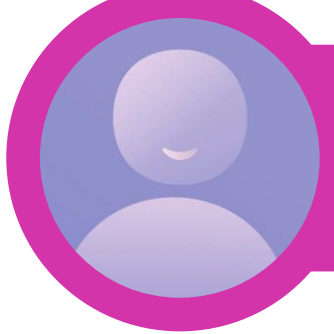

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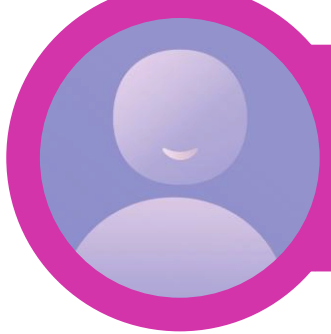
Infection trees



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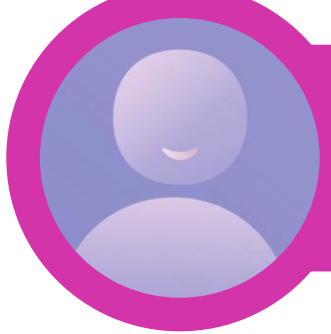

Ecology

Reminder: Logistic pathogen growth

$$\frac{dP_i}{dt} = rP_i\left(1 - \frac{P_i}{K}\right)$$

Proxy for an infection which cannot be recovered from.

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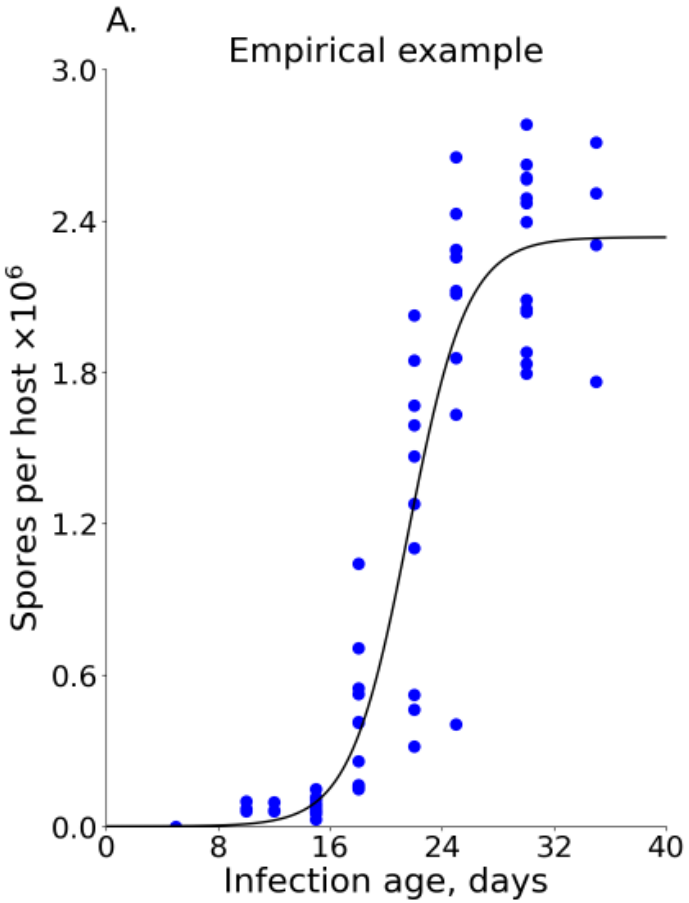

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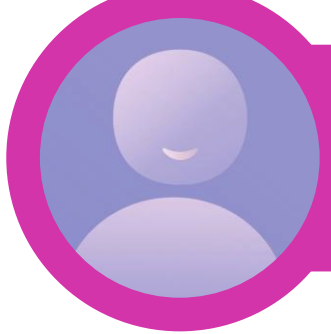

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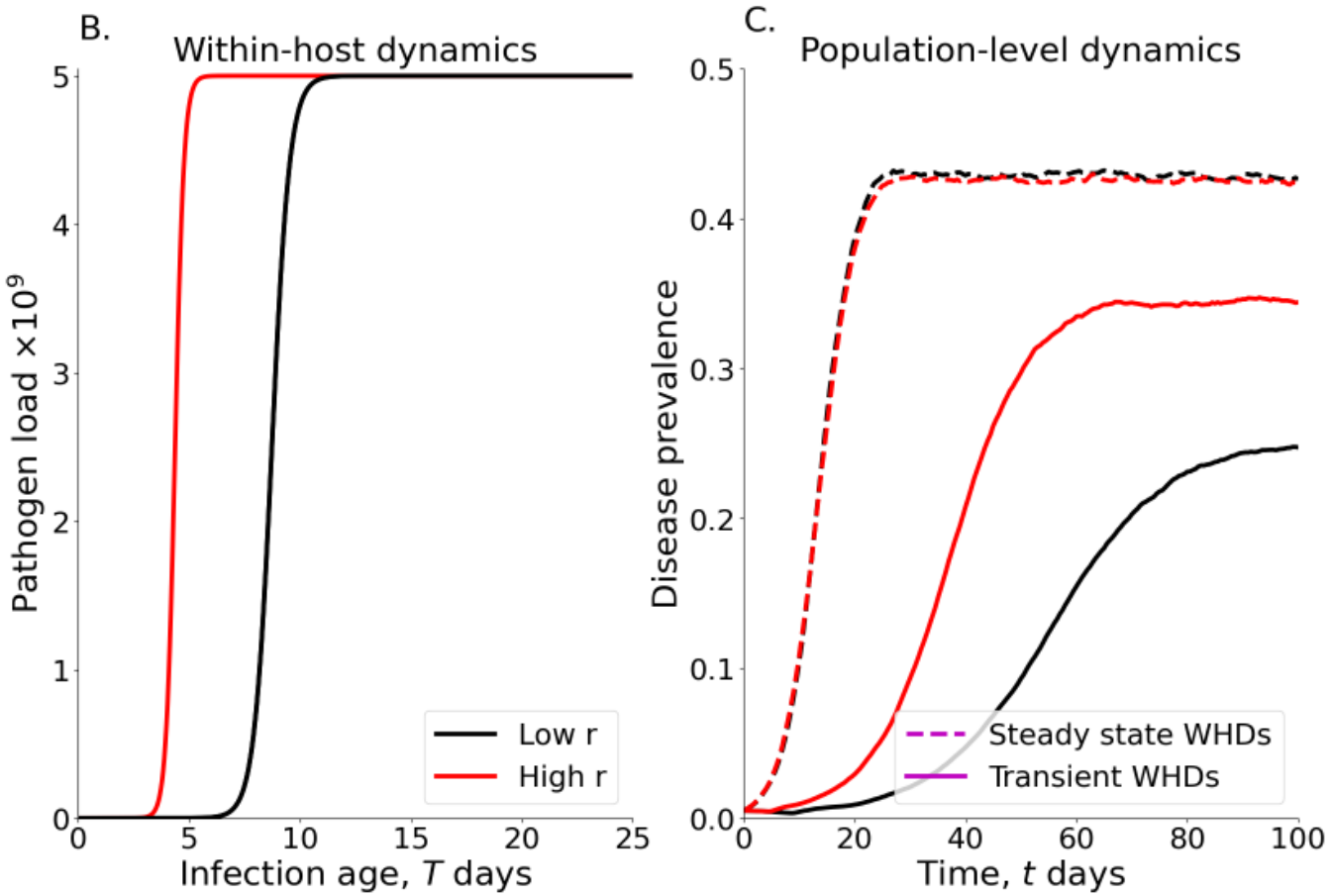

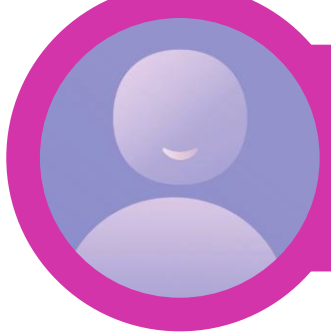

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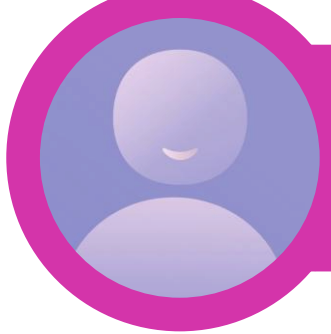

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Start M identical simulations with one infected individual until they die/recover;

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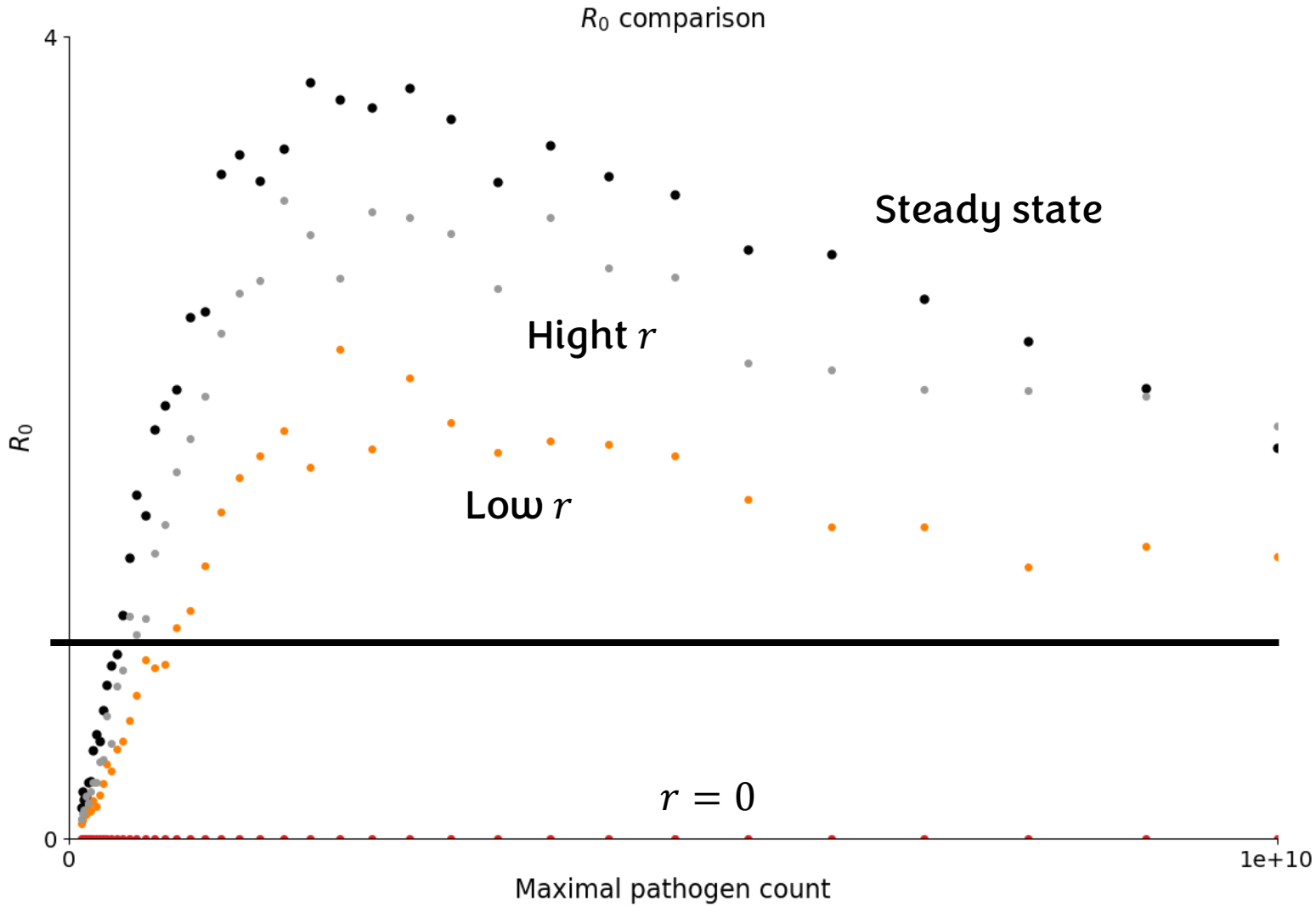

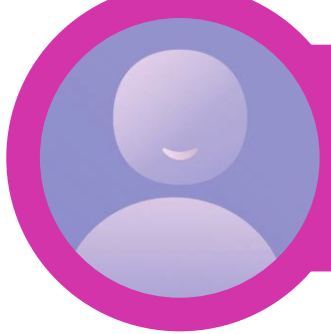

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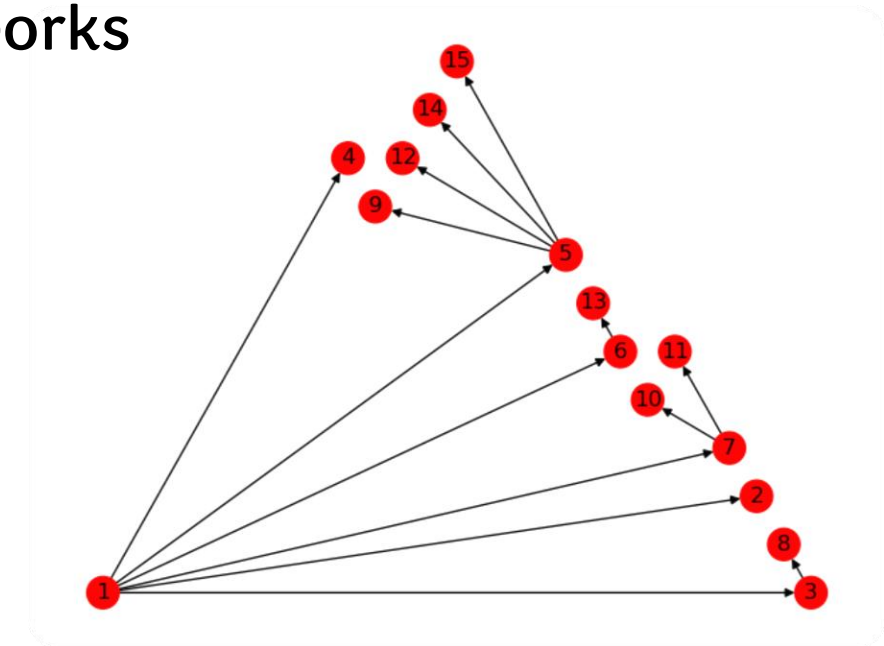

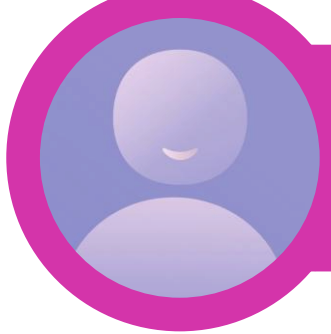

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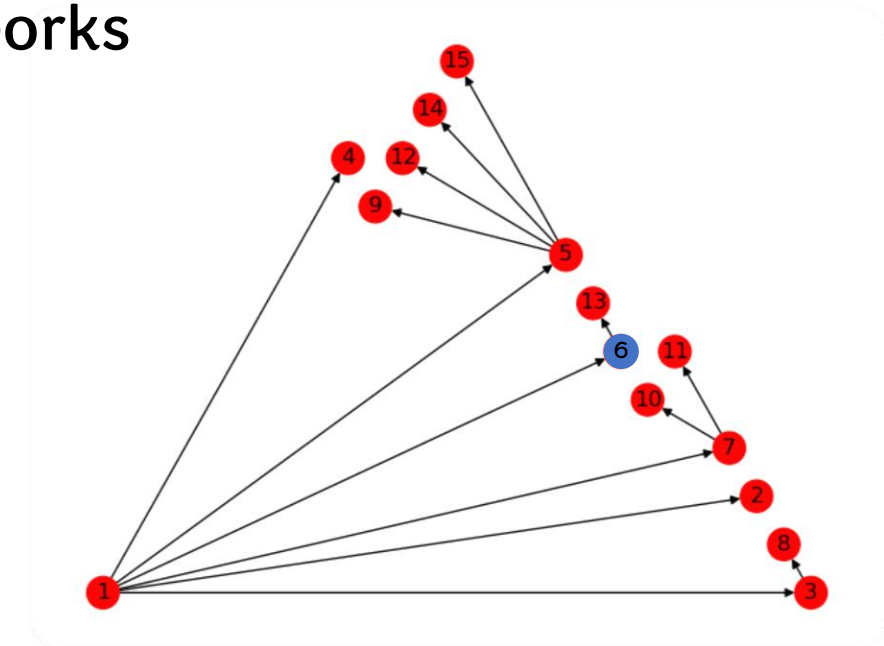

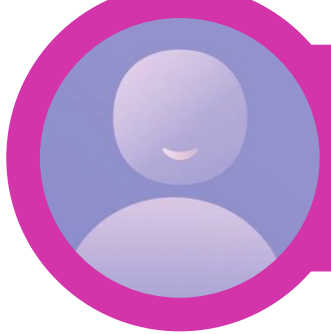

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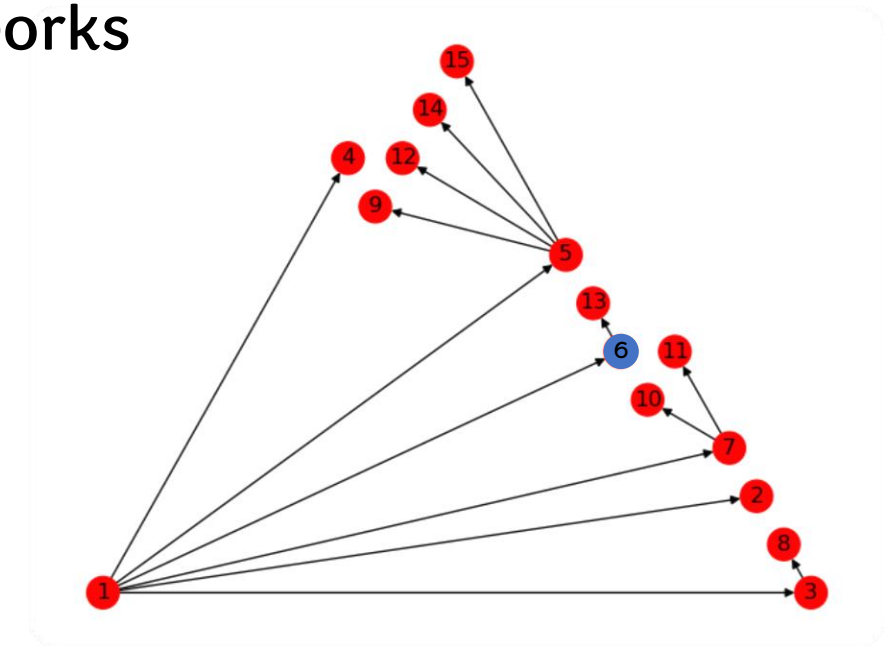

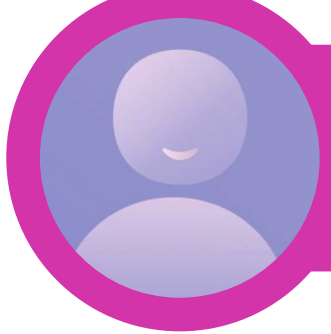

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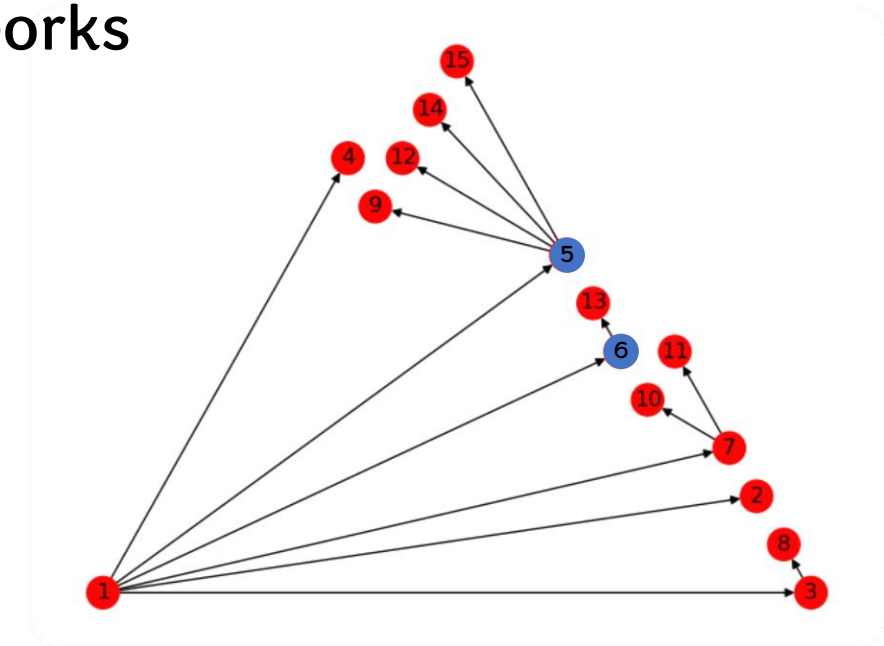

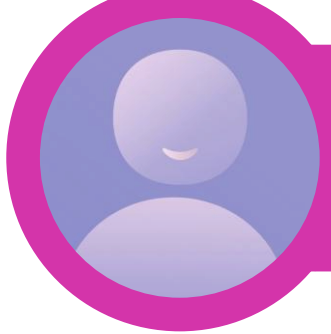

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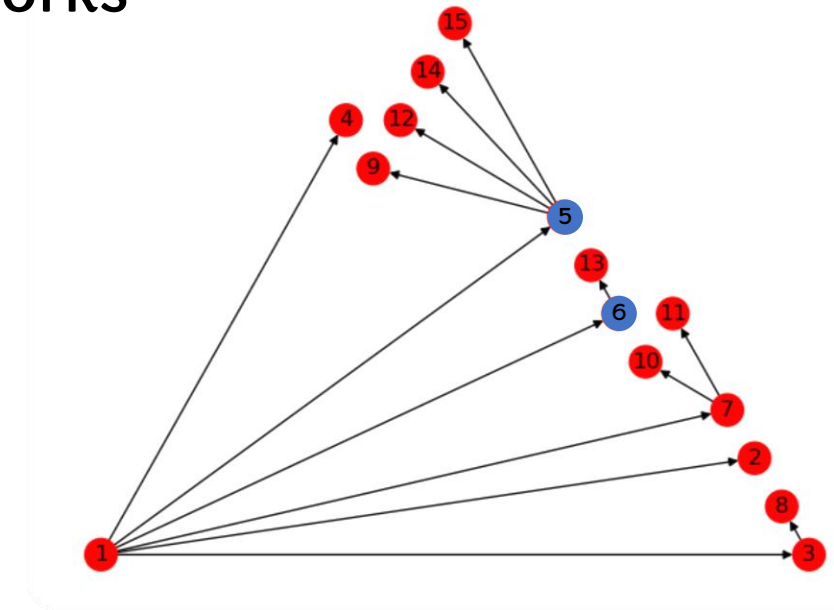

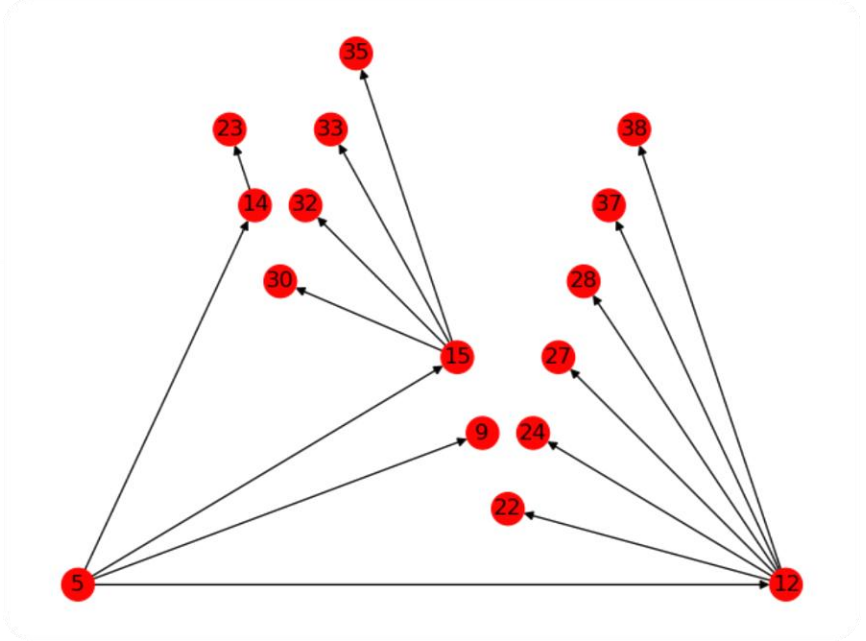

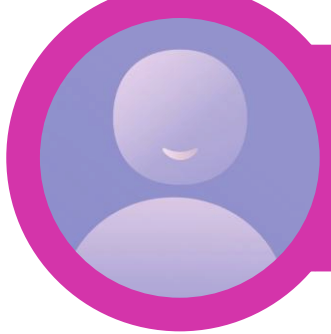

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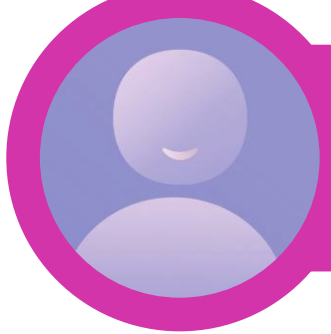

Evolution

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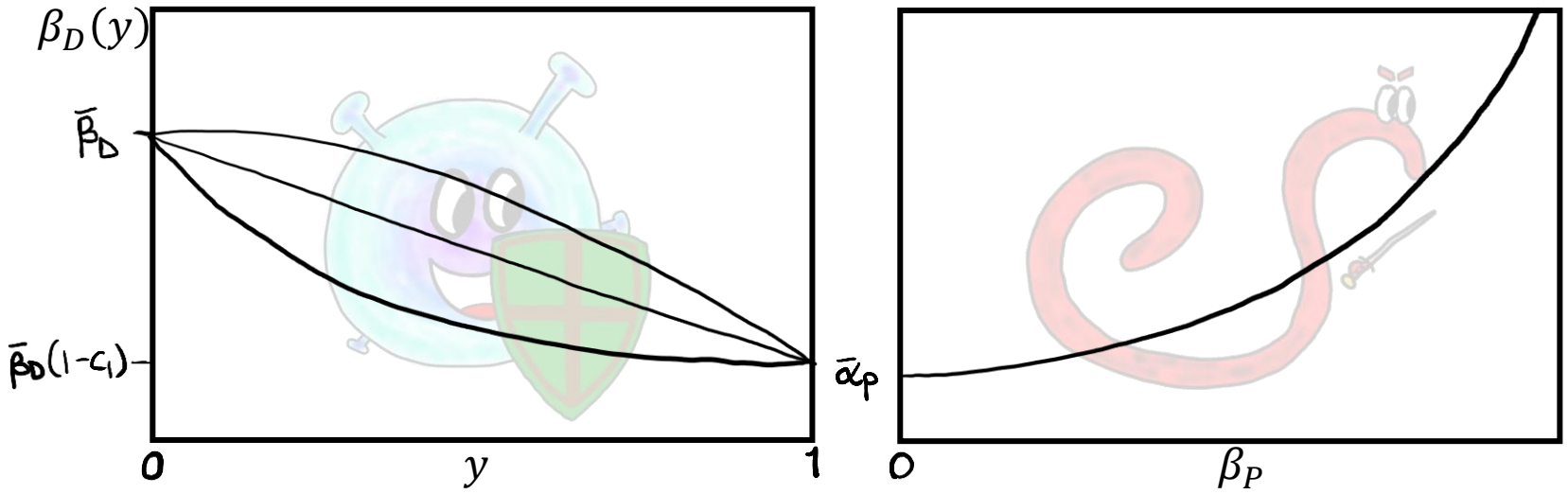

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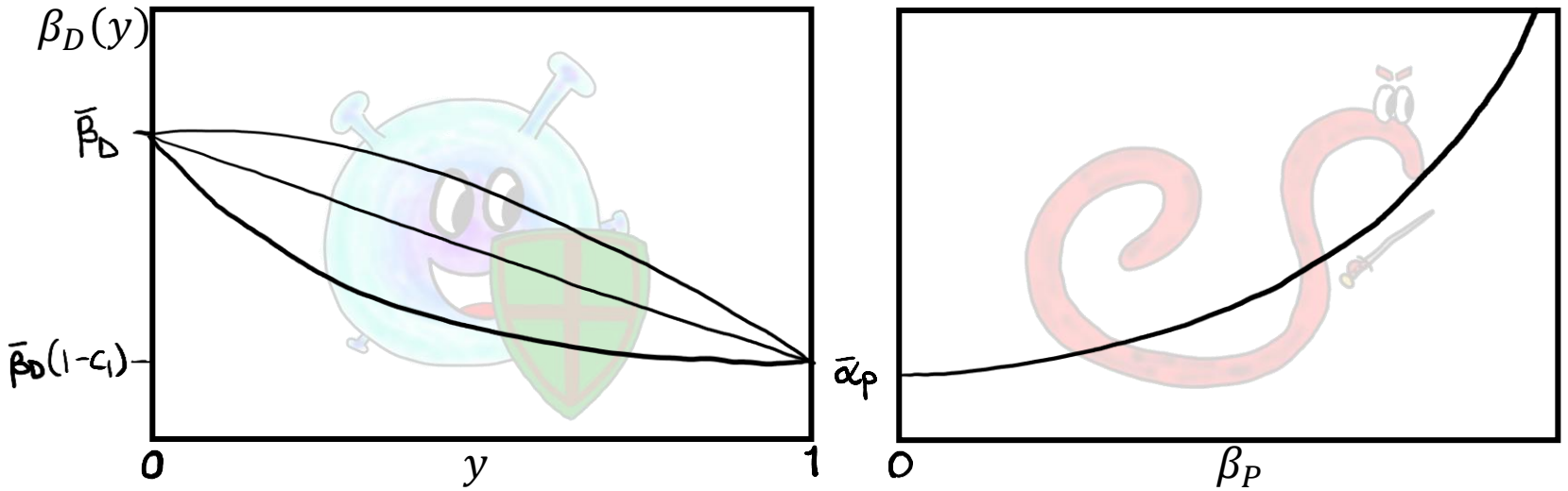

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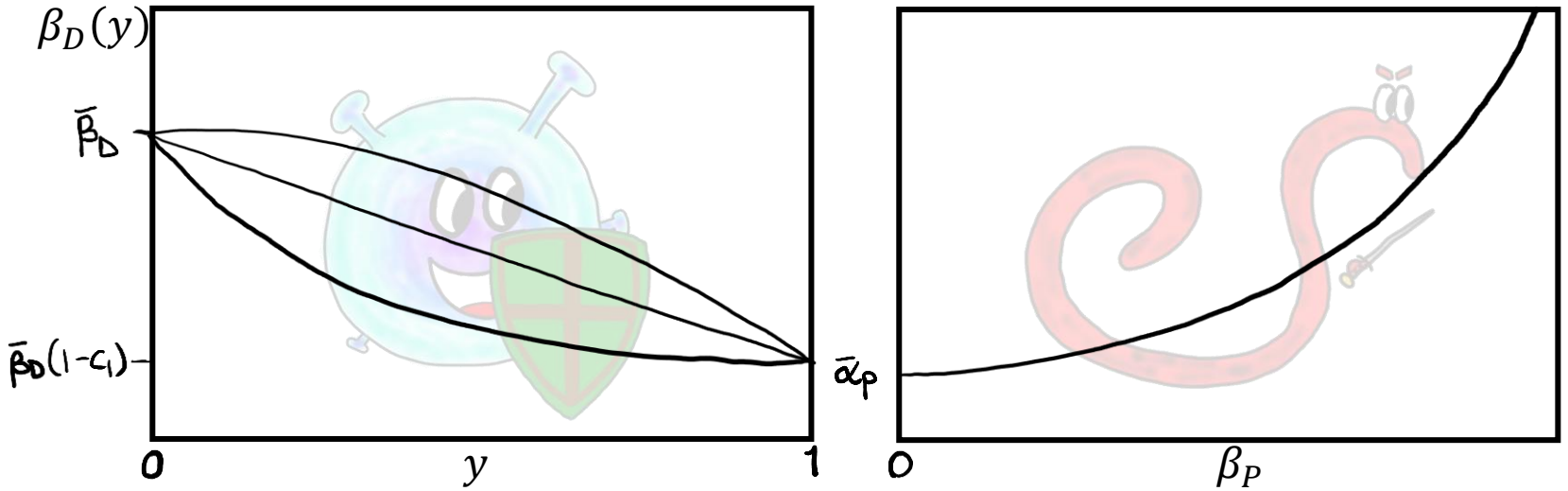

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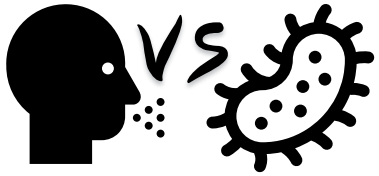

Conflicting selection

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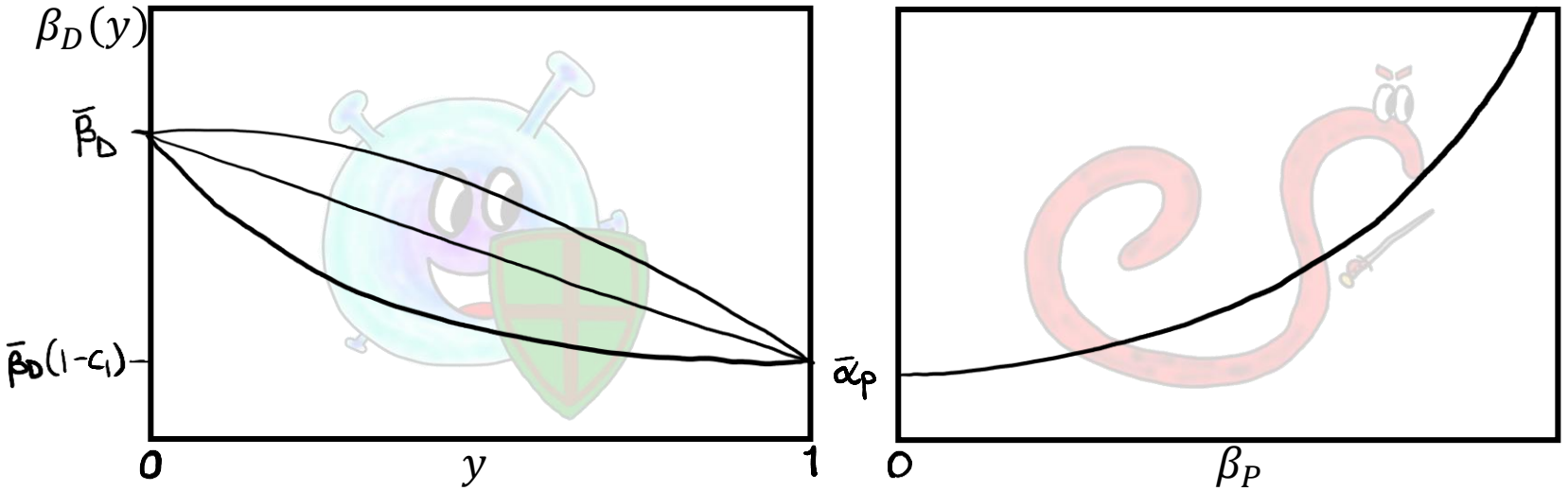

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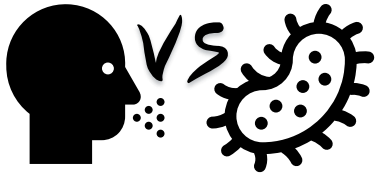

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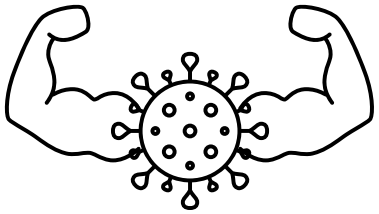

Super infection

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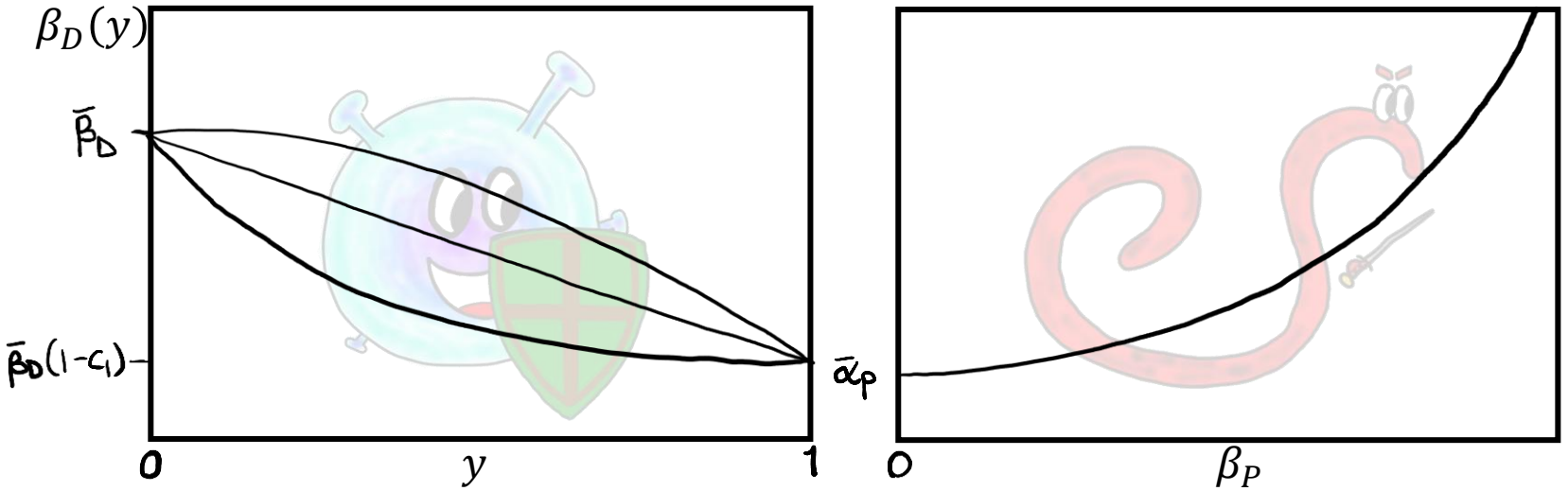

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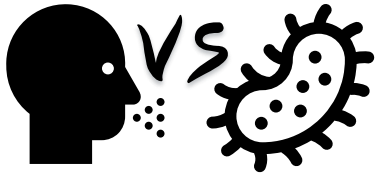
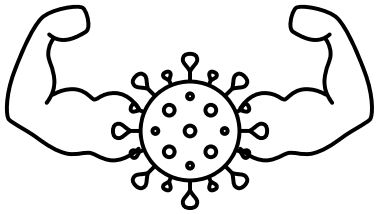
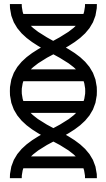


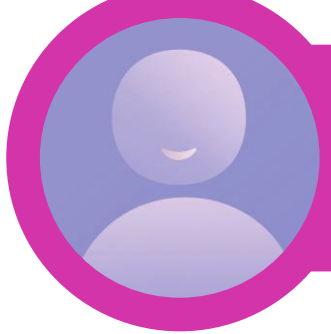
Conflicting selection



Super infection



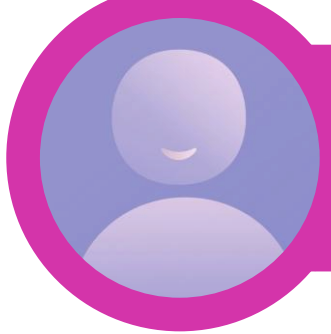
Individual mutations



Evolution

What effects can we incorporate with explicit WHDs?

$$\frac{dP_{ij}}{dT_i} = r_j P_{ij}\left(1 - \frac{P_{ij}}{K}\right)$$



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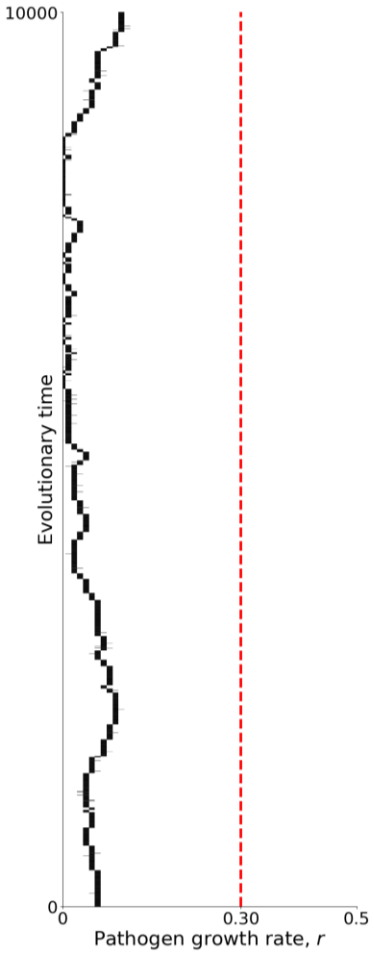
Note that $P^*_{ij} = K$ is not a function of r_j. Therefore, should be no selection at steady state.

Evolution



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Steady state

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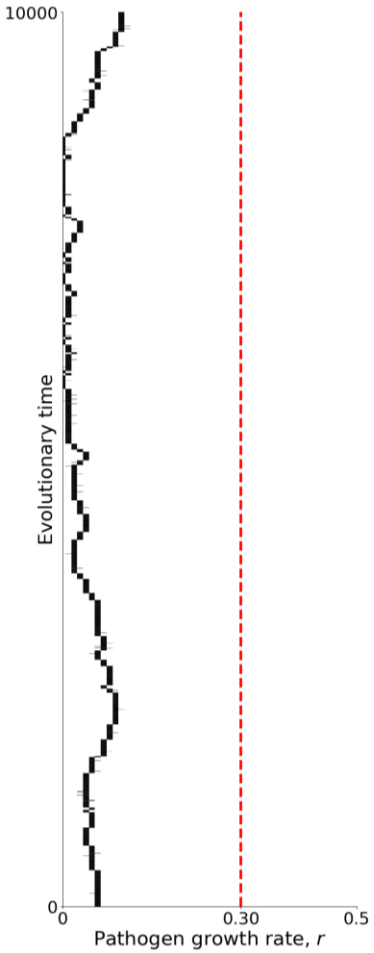
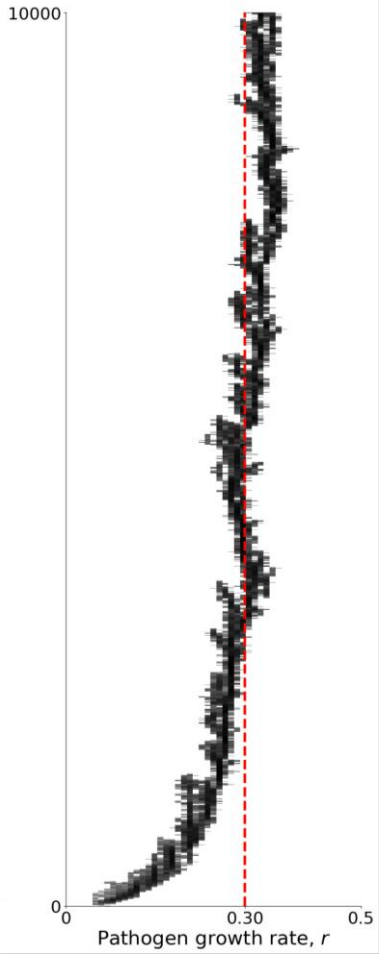
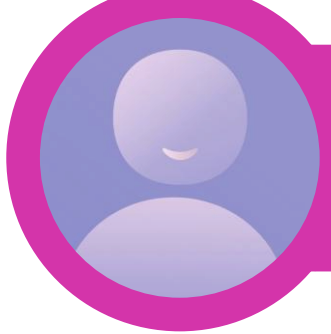


Steady state

Full dynamics





Evolution

Since we have individuals, we can track genetic data and trace an exact phylogeny.

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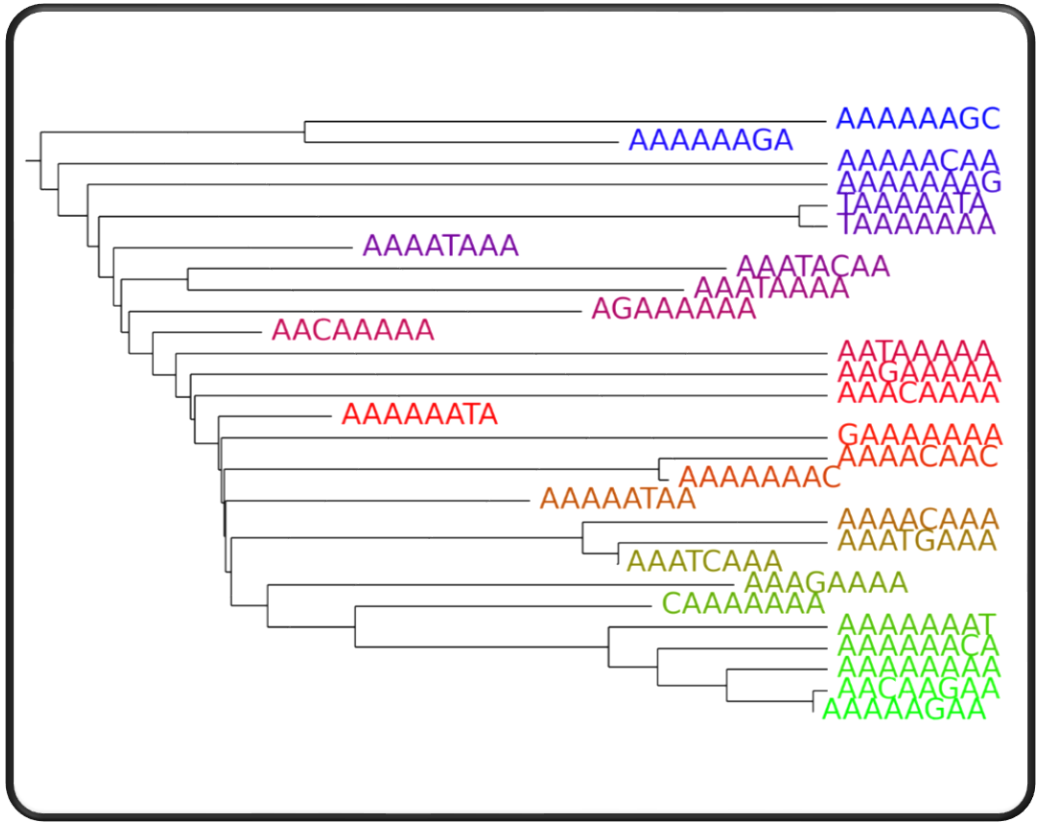

500 individuals, 8b genome, 10^{-4} mutation rate.

Evolution

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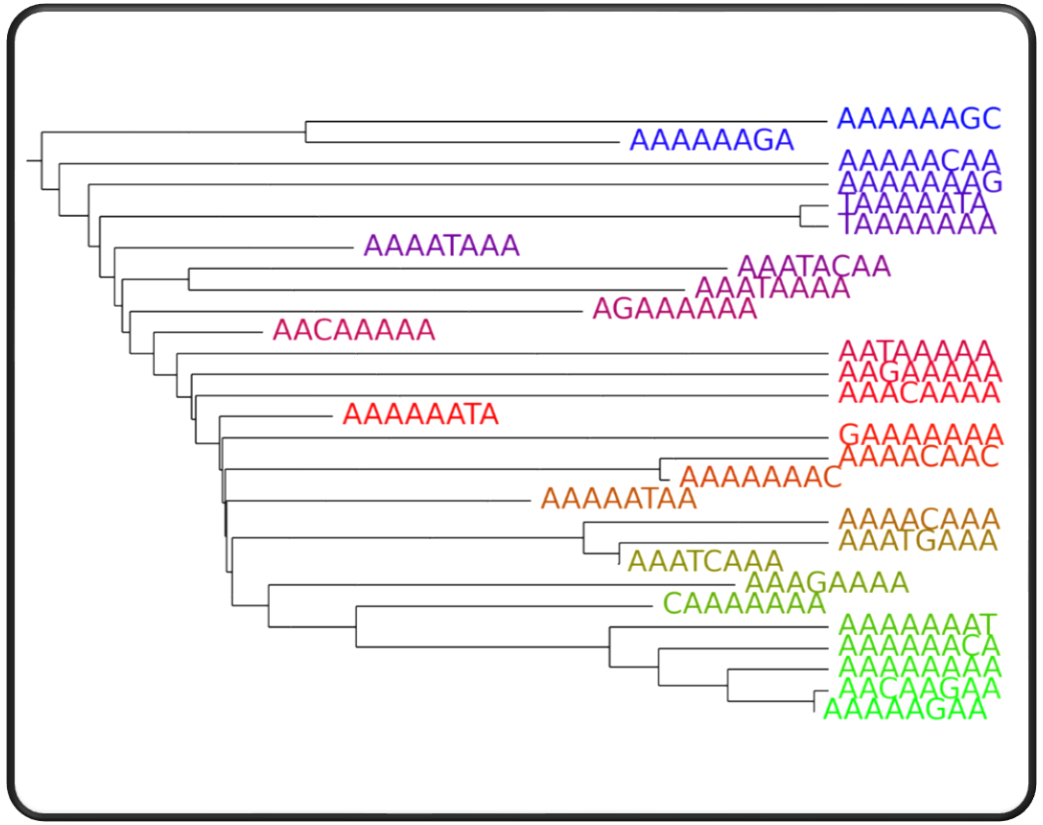

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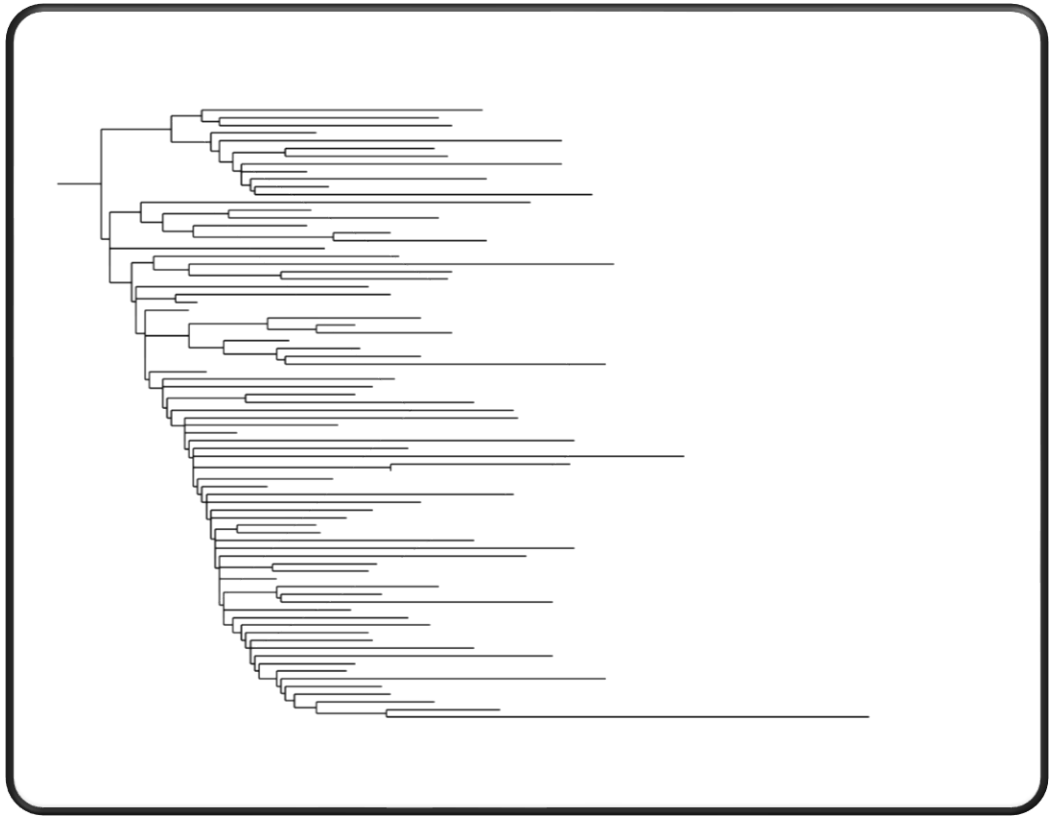
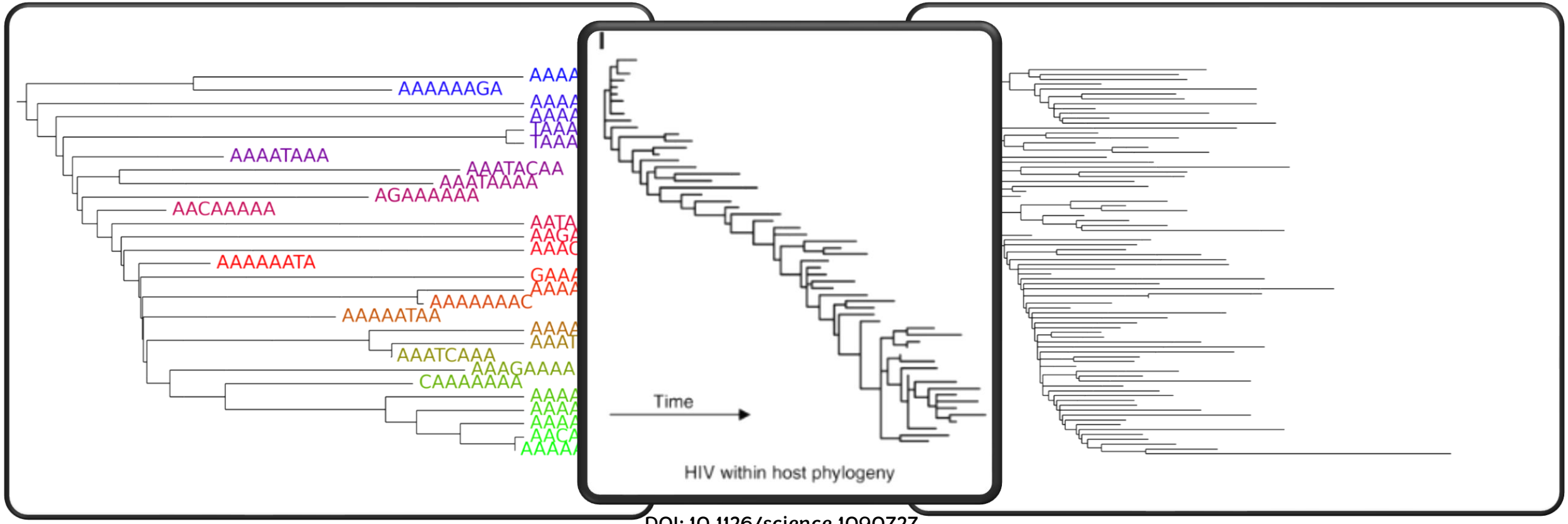


5000 individuals, 150b genome, 5×10^{-4} mutation rate.

Evolution

Since we have individuals, we can track genetic data and trace an exact phylogeny.



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500 individuals, 8b genome, 10^{-4} mutation rate.

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