Within- and between-host modelling
Lessons from other diseases

Lorenzo **Pellis**

Sir Henry Dale Fellow, University of Manchester, UK
JUNIPER Consortium https://maths.org/juniper/
Alan Turing Institute, London, UK

Understanding the Generation Time for COVID-19
Isaac Newton Institute, 28-30 July 2021

Outline

- Introduction
  - Compartmental models
  - Time-since-infection models
- Why time-since-infection?
  - Arguments
  - Example 1: within-host HIV metapopulation model
  - Example 2: within- and between-host HIV model
- Open challenges:
  - Link between scales
  - Generation-time for complex models
  - Reinfection / superinfection

MANCHESTER 1824
The University of Manchester

Compartmental models
Time-since-infection models

INTRODUCTION

MANCHESTER 1824
The University of Manchester

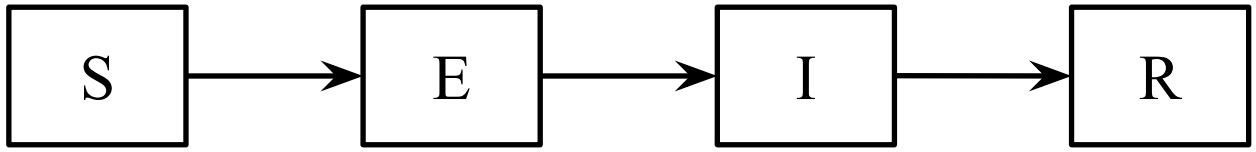
Compartmental models

Time-since-infection models

INTRODUCTION

State transitions

- The simplest form of within-host (WH) dynamics are transitions between states:



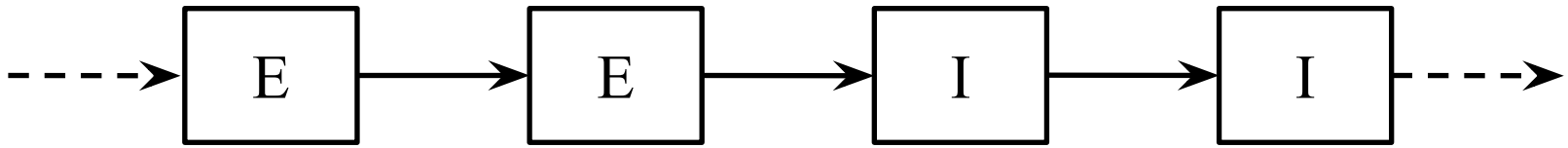
  - Traditionally modelled with ODEs

- Sensible starting point:
  - Simple
  - ODE numerical tools

- Limitations:
  - Constant rates
  - Exponential waiting times

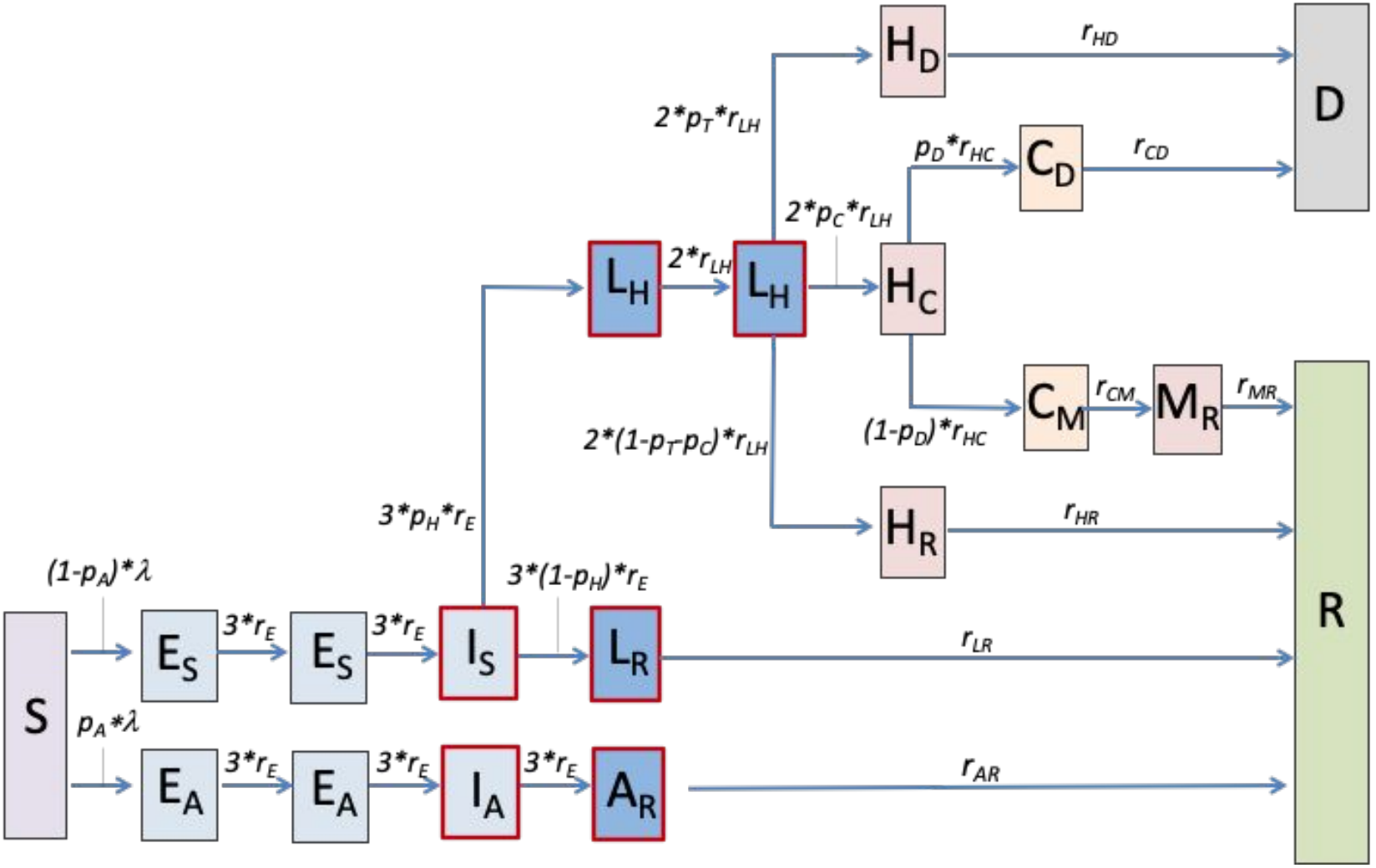
Extensions

- Gamma (Erlang) distributions, by adding multiple compartments:



- Phase-type distributions
- Different infectivities in different compartments
- Problems:
  - Number of compartments grows fast
  - In the limit of a constant duration, we need ∞ compartments

Our COVID-19 model



Overton*, Pellis* et al., *to be submitted soon*

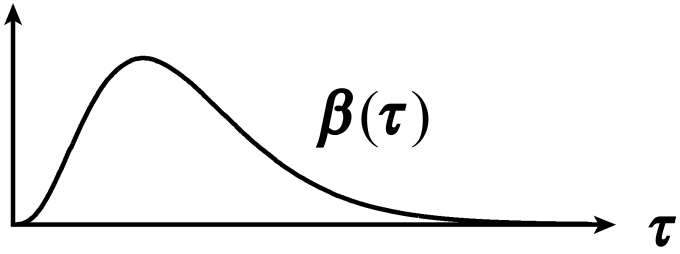
Compartmental models

Time-since-infection models

INTRODUCTION

Time-since-infection (TSI) models

- Function $\beta(\tau)$ to describe infectivity in terms of time-since-infection τ



Real-time growth rate

- Dynamics:

$$H(t) = \frac{S(t)}{N} \int_0^{+\infty} \beta(\tau) H(t-\tau)\, \mathrm{d}\tau$$

- Linearise:

$$S(t) \approx N \quad \Rightarrow \quad H(t) = \int_0^{+\infty} \beta(\tau) H(t-\tau)\, \mathrm{d}\tau$$

- Look for exponential solutions:

$$H(t) = k\mathrm{e}^{rt} \quad \Rightarrow \quad k\mathrm{e}^{rt} = \int_0^{\infty} \beta(\tau) k\mathrm{e}^{r(t-\tau)}\, \mathrm{d}\tau$$

- Euler-Lotka equation

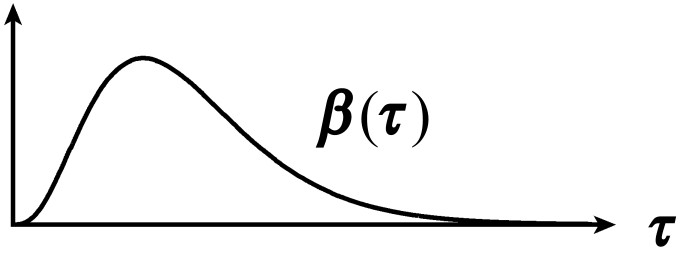
$$\int_0^{\infty} \beta(\tau)\mathrm{e}^{-r\tau}\, \mathrm{d}\tau = 1$$

- Given $R_0 = \int_0^{\infty} \beta(\tau)\mathrm{d}\tau$, it's easy to see that $r = 0 \quad \Leftrightarrow \quad R_0 = 1$

Diekmann & Heesterbeer (2000); **Diekmann, Heesterbeek & Britton** (2012)

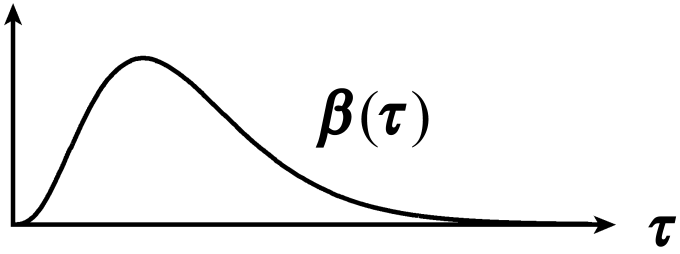
Time-since-infection (TSI) models

- Function $\beta(\tau)$ to describe infectivity in terms of time-since-infection τ

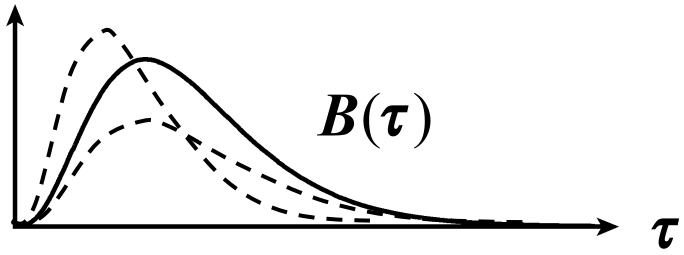


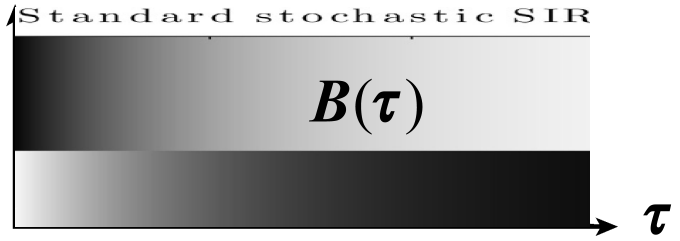
Time-since-infection (TSI) models

- Function $\beta(\tau)$ to describe infectivity in terms of time-since-infection τ



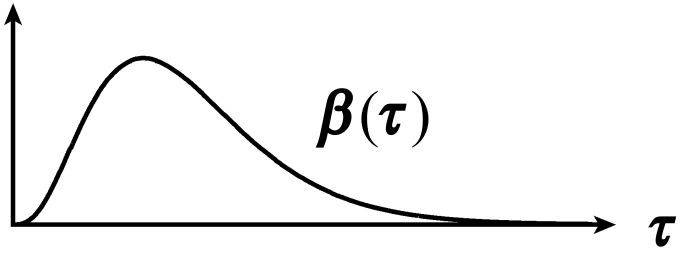
- We can also use a random version of it:
  - General enough to encompass all previous cases



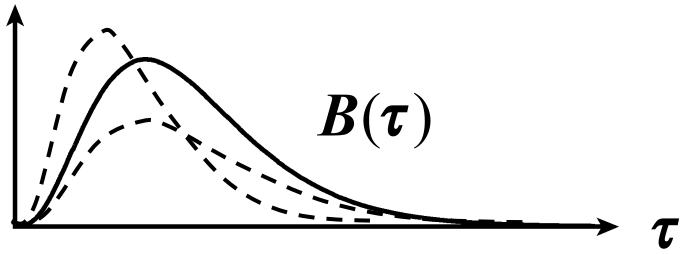


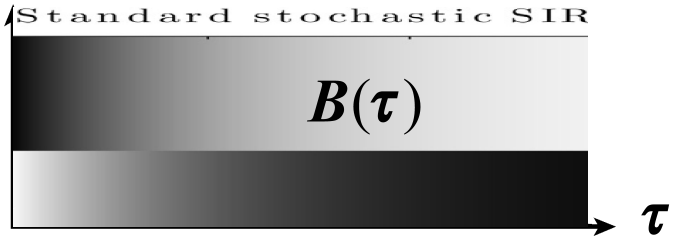
Time-since-infection models

- Function $\beta(\tau)$ to describe infectivity in terms of time-since-infection τ



- We can also use a random version of it:
  - General enough to encompass all previous cases





- Drawbacks:
  - Harder to study (PDEs or integral equations/DDEs)
  - Computationally intensive to integrate
  - Require initial conditions on an interval (the support of $\beta(\tau)$)

WHY TIME-SINCE-INFECTION?

Why using TSI?

- More general

Why using TSI?

MANCHESTER 1824
The University of Manchester

- More general

Why using TSI?

MANCHESTER 1824
The University of Manchester

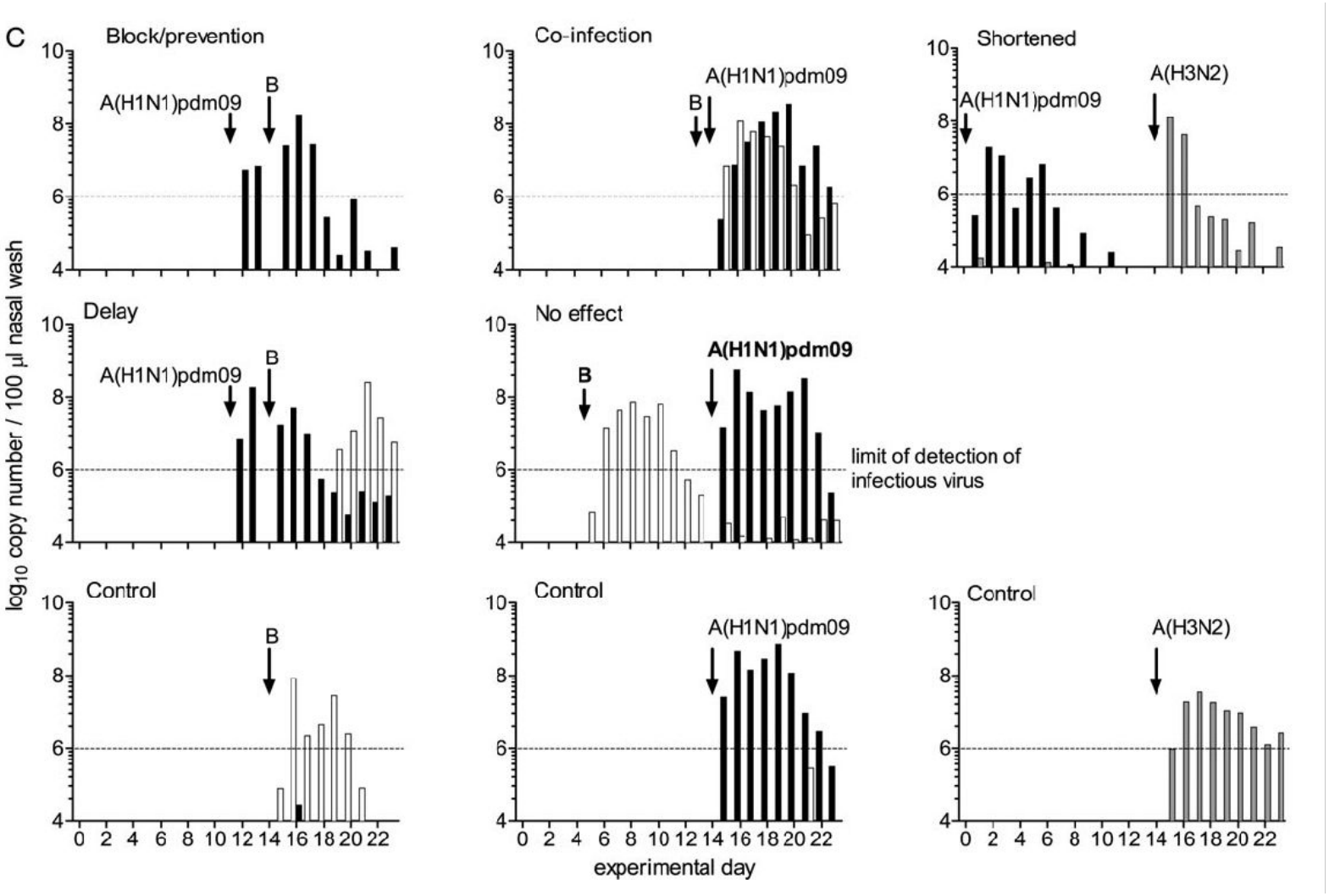
- More general
- Closer to biology / experiments:
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
  - Available data

Why using TSI?

MANCHESTER 1824
The University of Manchester

- More general
- Closer to biology / experiments:
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
  - Available data

Superinfection data



Laurie *et al* (2015), *JID*

Why using TSI?

The University of Manchester

- More general
- Closer to biology / experiments:
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
  - Available data
- Suitable to encapsulate complex within-host (WH) dynamics

Why using TSI?

MANCHESTER 1824
The University of Manchester

- More general
- Closer to biology / experiments:
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
  - Available data
- Suitable to encapsulate complex within-host (WH) dynamics

Examples (dengue)

- Model 1: Target cell limited

$$\begin{cases} \dot{S} = -\beta V S \\ \dot{I} = \beta V S - \delta I \\ \dot{V} = pI - cV \end{cases}$$

susceptible cells $S =$

infected cells $I =$

free virus $V =$

- Model 2: Innate immune response

$$\begin{cases} \dot{S} = -\beta \rho I S \\ \dot{I} = \beta \rho I S - \delta I - \kappa I N \\ \dot{N} = qI - dN \end{cases}$$

susceptible cells $S =$

infected cells $I =$

natural killer cells $N =$

$\rho = p / c$

Ben-Shachar & Koelle (2014), *Interface*

Examples (dengue)

- Model 3: Innate + adaptive cellular immune response

$$\begin{cases} \dot{S} = -\beta\rho IS \\ \dot{I} = \beta\rho IS - \kappa IN - \delta_T IT \\ \dot{N} = qI - d_N N \\ \dot{T} = q_T IT - d_T T \end{cases}$$

susceptible cells $S =$

infected cells $I =$

natural killer cells $N =$

T cells $T =$

$\rho = p / c$

Ben-Shachar & Koelle (2014), *Interface*

Gilchrist & Sasaki (2002)

- First example: *Gilchrist & Sasaki* (2002)
  - Within-host dynamics: $\begin{cases} \dot{P} = rP - \varepsilon BP \\ \dot{B} = aBP \end{cases}$ pathogen load $P =$ level immunity $B =$
  - Between-host dynamics:
  - Link: $\beta(\tau) = cP(\tau)$

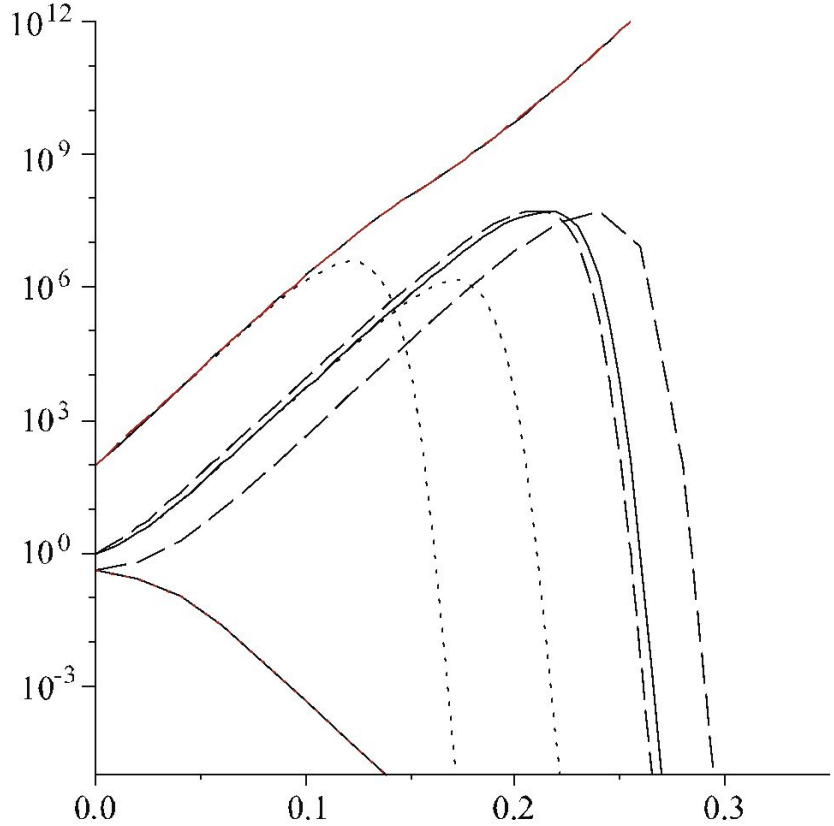
$$\begin{cases} \dfrac{dS}{dt} = bN(t) - S(t)\displaystyle\int_0^T \beta(\tau) I(t,\tau)\,d\tau - dS(t) \\ \dfrac{\partial I}{\partial t} + \dfrac{\partial I}{\partial \tau} = -\left(\alpha(\tau) - \iota(\tau) - d\right) I(t,\tau) \\ \dfrac{dR}{dt} = I(T,t) - dR(t) \\ N(t) = S(t) + \displaystyle\int_0^T I(t,\tau)\,d\tau + R(t) \end{cases}$$

Gilchrist & Sasaki (2002), *J Theor Biol*

Example

- Model: specific + aspecific immunity

$$\begin{cases} \dot{P} = rP - \dfrac{c_S P}{1 + a_S P} B - \dfrac{c_u P}{1 + a_u P} M \\ \dot{B} = \dfrac{kP}{1 + k_m P} B - \delta B + h \end{cases}$$



$P =$ pathogen load

$B =$ level of specific immuntity

$M =$ (constant) level of aspecific immunity

Pugliese & Gandolfi (2008), *Math Biosc*

Why using TSI?

MANCHESTER 1824
The University of Manchester

- More general
- Closer to biology / experiments:
  - Available data
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
- Suitable to encapsulate complex within-host (WH) dynamics
- Can enhance understanding of more complex models

Why using TSI?

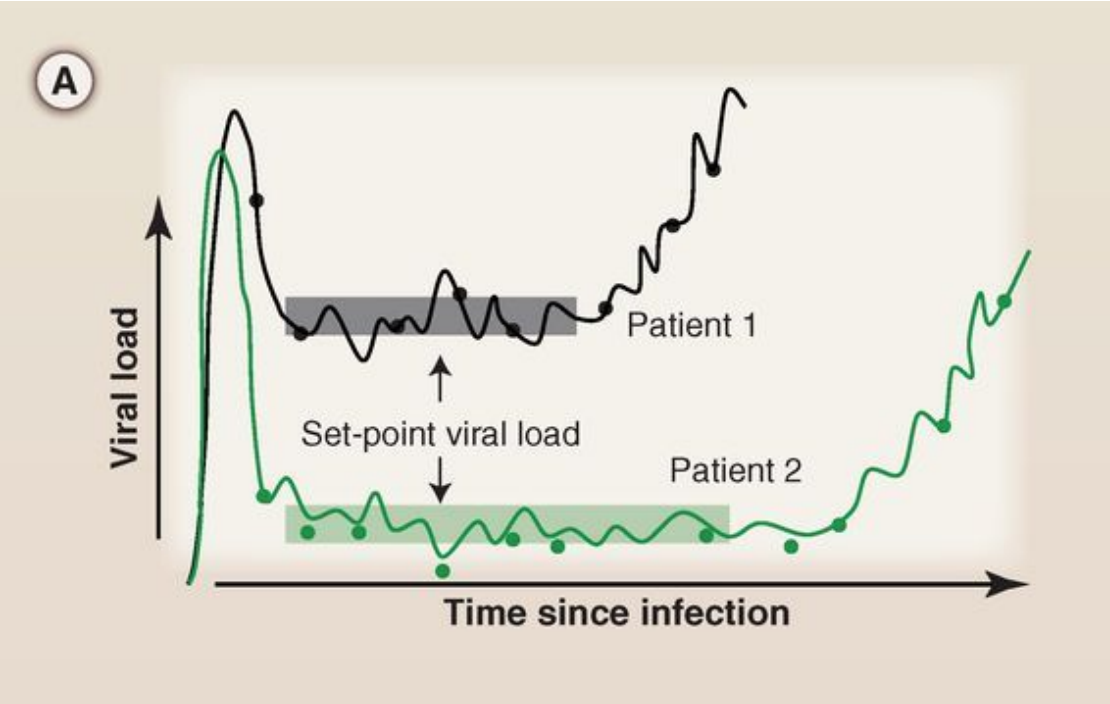
MANCHESTER 1824
The University of Manchester

- More general
- Closer to biology / experiments:
  - Available data
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
- Suitable to encapsulate complex within-host (WH) dynamics
- Can enhance understanding of more complex models

[**Lythgoe, Blanquart, Pellis & Fraser** (2016), *PLoS Biology*]

EXAMPLE 1: HIV WITHIN-HOST METAPOPULATION MODEL

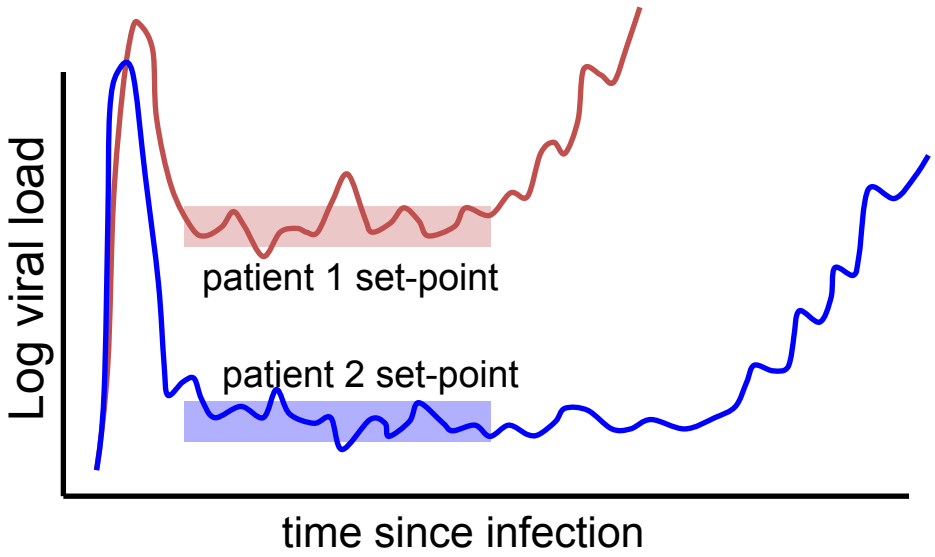
Set-point viral load

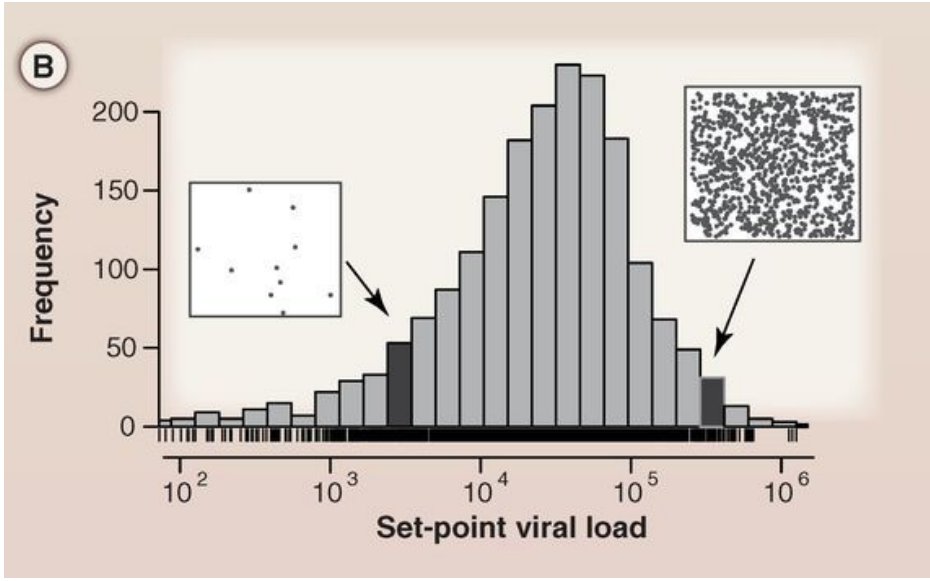


Fraser, **Lythgoe** *et al* (2014), *Science*

Motivation

- SPVL varies by at least 4 orders of magnitude between patients:



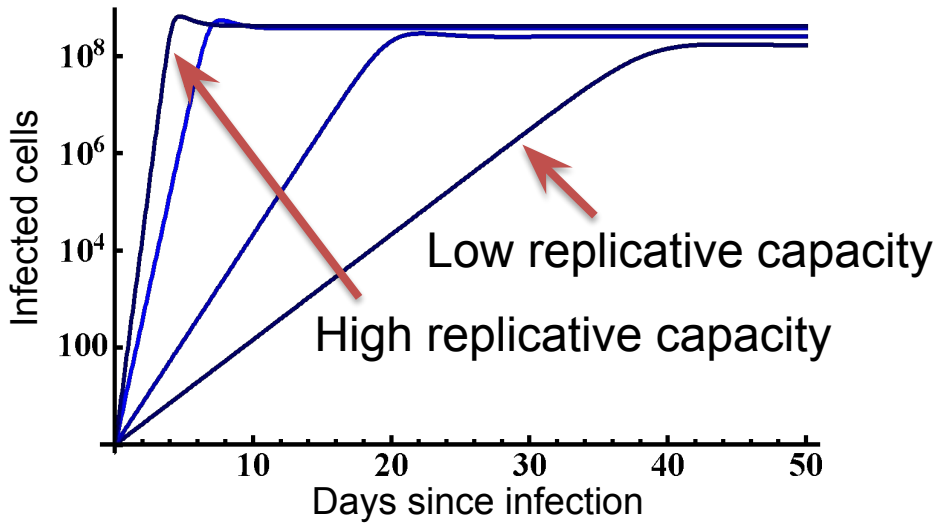


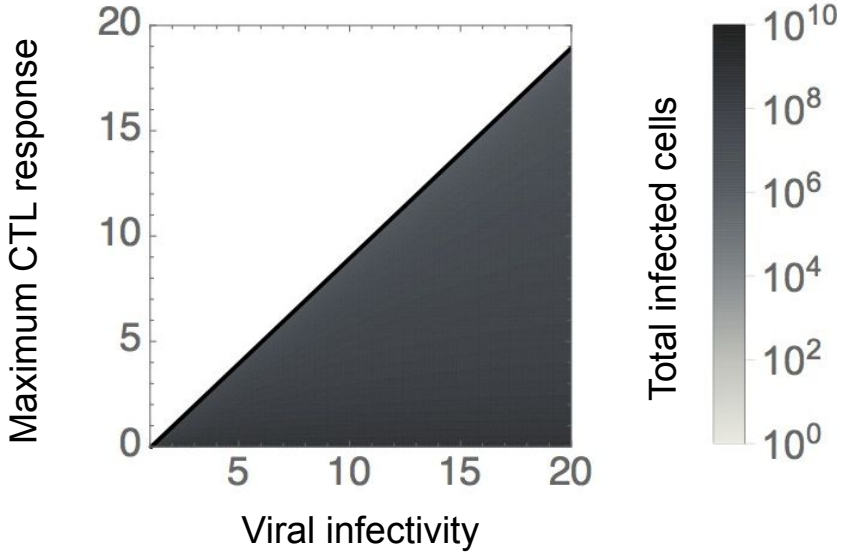
- What is causing this variation?

Factors determining SPVL

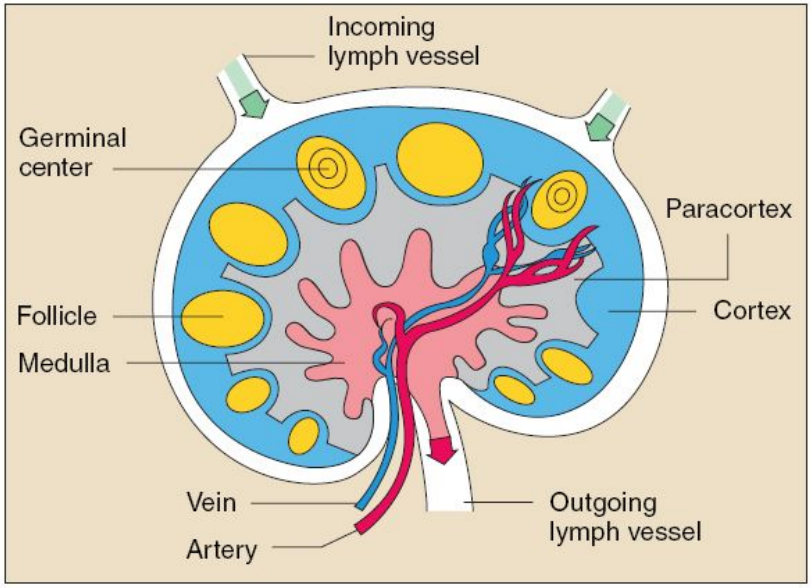
- Speed at which virus replicates and infects new cells
- Efficacy of CTL immune response
- …

However, in “well-mixed” models, these factors only mildly affect SPVL, unless we are close to the extinction threshold





But is HIV "well-mixed" within the host?

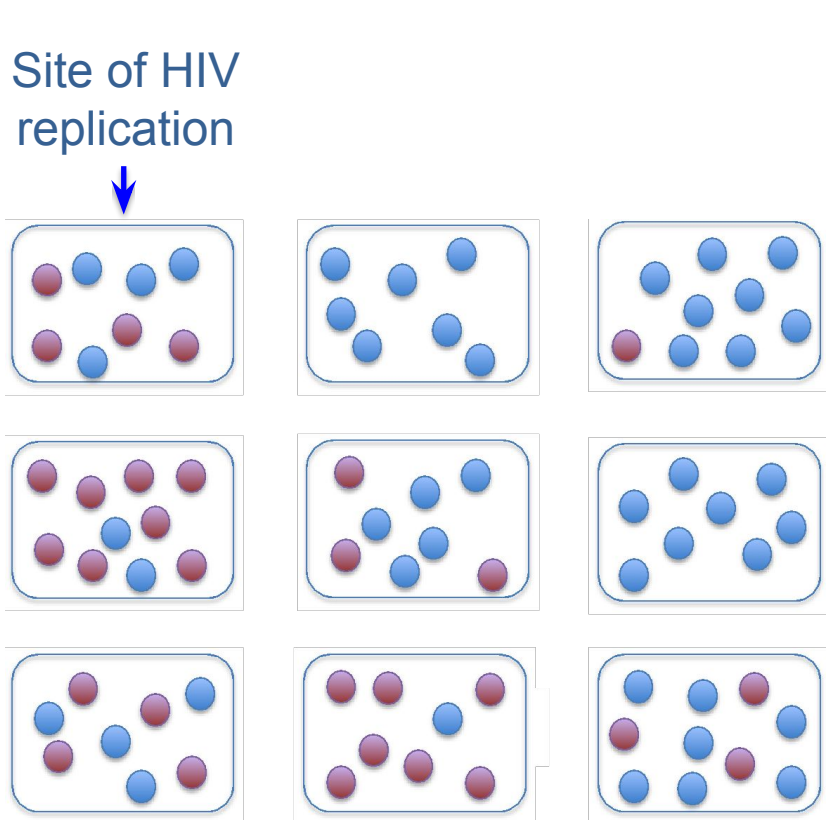


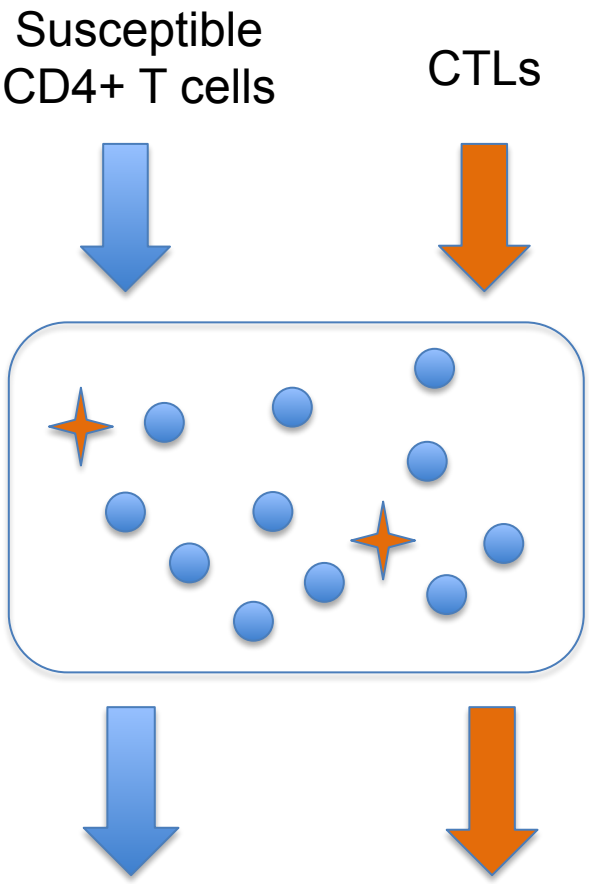
Probably not:

- Viral replication focused within specific regions of the body, e.g. lymph nodes
- We estimate there are between 1,000 and 10,000 of these sites of replication in the human body
- Viral populations genetically structured at a small spatial scale (though it might not persist over time)

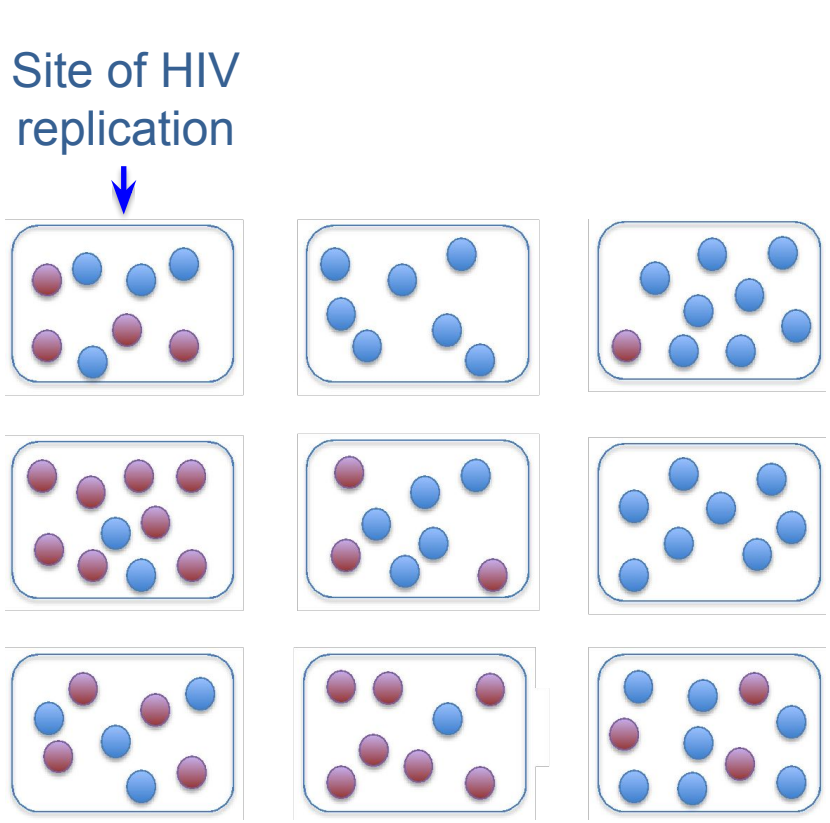
→ Within-host HIV dynamics are best described using a metapopulation model

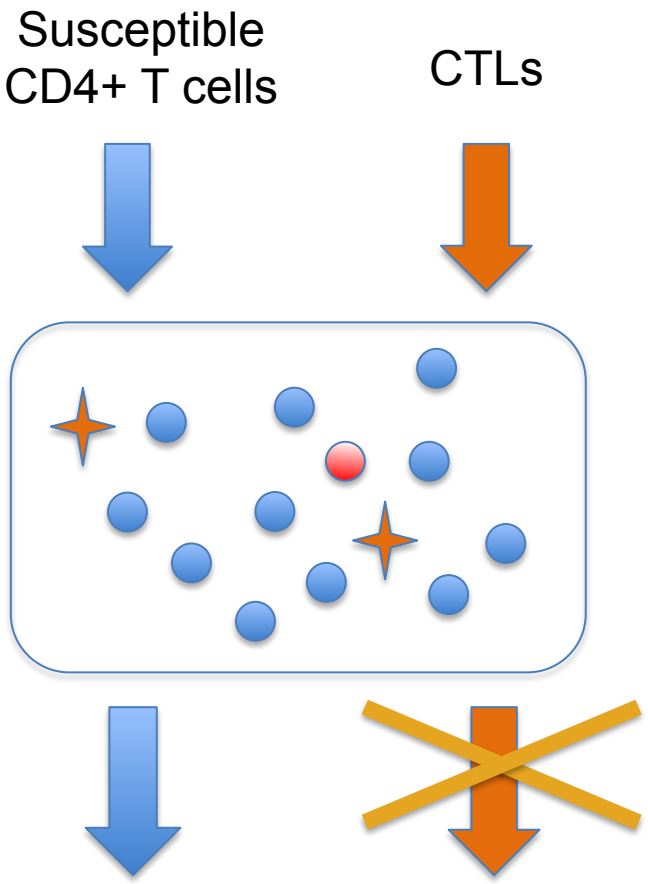
HIV metapopulation model



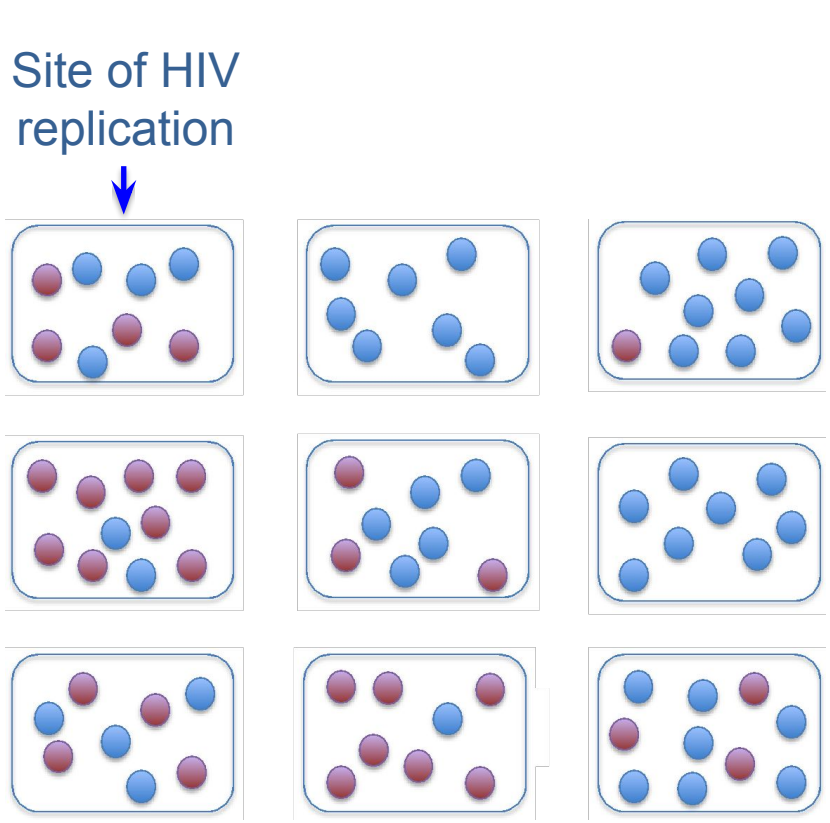


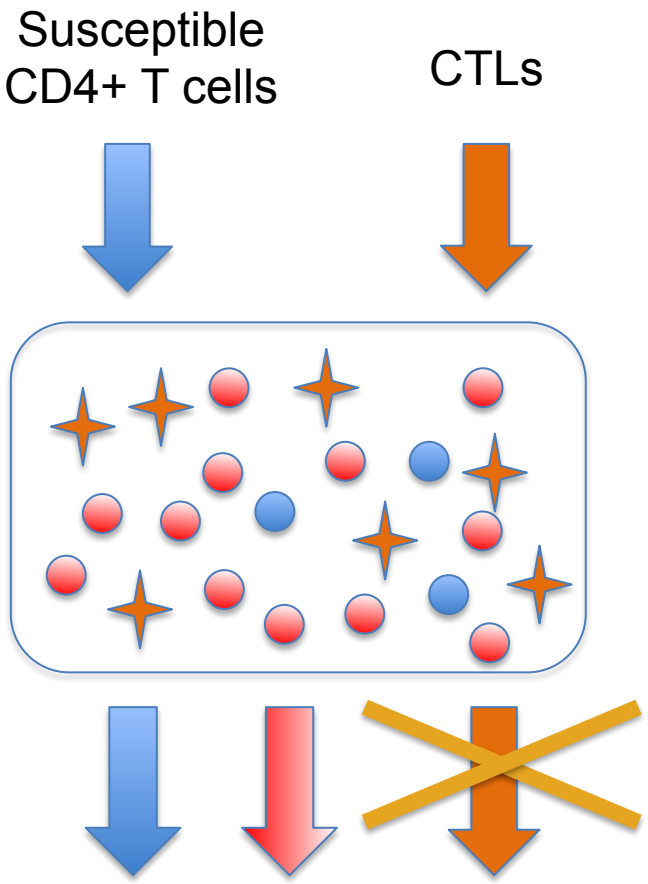
HIV metapopulation model



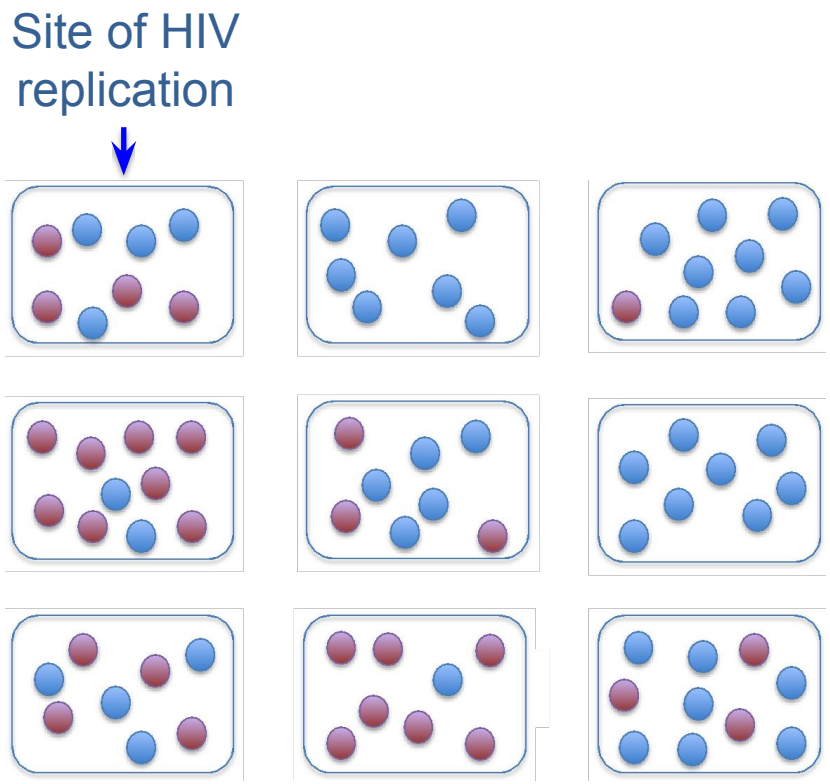


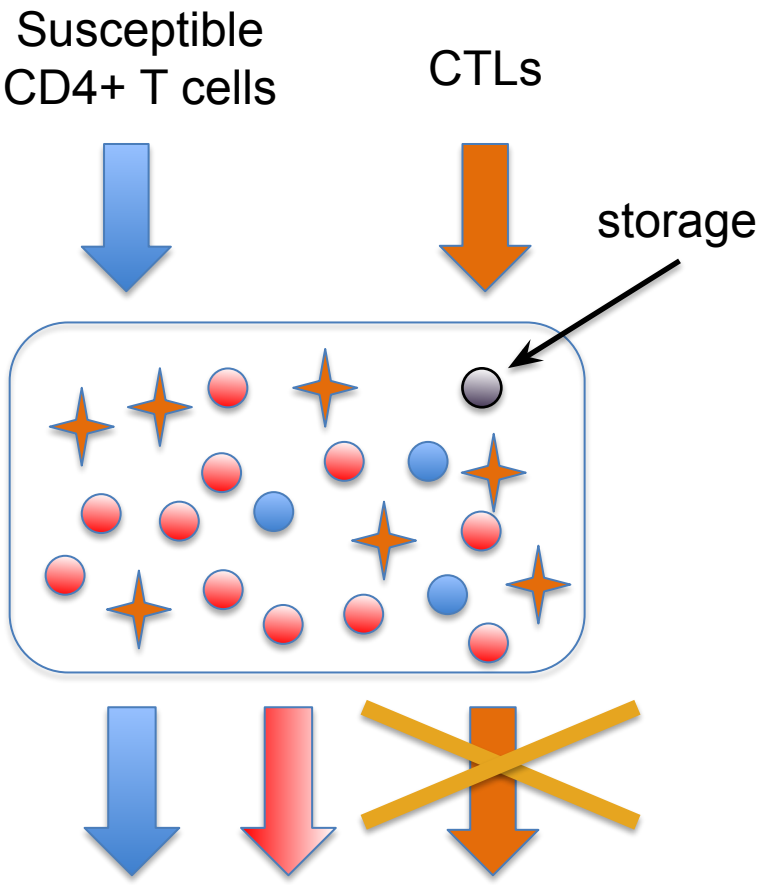
HIV metapopulation model





HIV metapopulation model





Full equations

$$\frac{d}{dt}x_i(t) = \gamma_i M x_B - \frac{x_i(t)}{x_i^{max}}\beta_i y_i(t) - \left[d + \varepsilon\right]x_i(t)$$

$$\frac{d}{dt}y_i(t) = \left(1-\lambda\right)\frac{x_i(t)}{x_i^{max}}\beta_i y_i(t) + \gamma_i\left[My_B(t) + \omega\,\rho S(t)\right] - \left[\delta + \varepsilon + k\frac{z_i}{z_i^{max}}\right]y_i(t)$$

$$\frac{d}{dt}y_B(t) = \sum_j \varepsilon y_j(t) - My_B(t) - \delta_B y_B(t)$$

$$\frac{d}{dt}z_i(t) = cz_i^{max}\left[1 - \frac{z_i}{z_i^{max}}\right] - \varepsilon z_i(t)\mathbb{I}_{y_i(t)=0}$$

$$\frac{d}{dt}S(t) = \sum_j \lambda\frac{x_j(t)}{x_j^{max}}\beta_j y_j(t) - \left(\rho + \delta_S\right)S(t)$$

Within-patch equations

$$\frac{d}{dt}x(t) = \gamma M x_B - \frac{x(t)}{x^{max}}\beta y(t) - \left[d + \varepsilon\right]x(t)$$

$$\frac{d}{dt}y(t) = \left(1-\lambda\right)\frac{x(t)}{x^{max}}\beta y(t) + \gamma\left[My_B(t) + \omega\rho S(t)\right] - \left[\delta + \varepsilon + k\frac{z}{z^{max}}\right]y(t)$$

$$\frac{d}{dt}z(t) = cz^{max}\left[1 - \frac{z}{z^{max}}\right] - \varepsilon z(t)\mathbb{I}_{y(t)=0}$$

Within-patch equations

$$\frac{d}{dt}x(t) = \gamma M x_B - \frac{x(t)}{x^{max}}\beta y(t) - \left[d + \varepsilon\right]x(t)$$

$$\frac{d}{dt}y(t) = \left(1-\lambda\right)\frac{x(t)}{x^{max}}\beta y(t) + \gamma\left[My_B(t) + \omega\rho S(t)\right] - \left[\delta + \varepsilon + k\frac{z}{z^{max}}\right]y(t)$$

$$\frac{d}{dt}z(t) = cz^{max}\left[1 - \frac{z}{z^{max}}\right] - \varepsilon z(t)\mathbb{I}_{y(t)=0}$$

Within-patch equations

$$\frac{d}{dt}x(t) = \gamma M x_B - \frac{x(t)}{x^{max}}\beta y(t) - \left[d + \varepsilon\right]x(t)$$

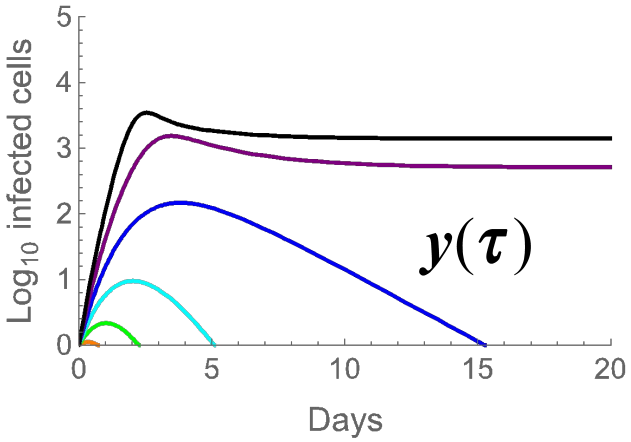
$$\frac{d}{dt}y(t) = \left(1-\lambda\right)\frac{x(t)}{x^{max}}\beta y(t) + \gamma\left[My_B(t) + \varpi\rho S(t)\right] - \left[\delta + \varepsilon + k\frac{z}{z^{max}}\right]y(t)$$

$$\frac{d}{dt}z(t) = cz^{max}\left[1-\frac{z}{z^{max}}\right] - \varepsilon z(t)\mathbb{I}_{y(t)=0}$$

Analytical approximation

If immigration of infected cells is negligible (after the first seeding):

- Within-patch dynamics



lead to a rate at which a patch infect other patches: $\beta_P(\tau) = \frac{M}{M+\delta_B}\varepsilon y(\tau)$

- Dynamics

$$H(t) = \frac{S(t)}{N}\int_0^{+\infty} H(t-\tau)\beta_P(\tau)\,\mathrm{d}\tau$$

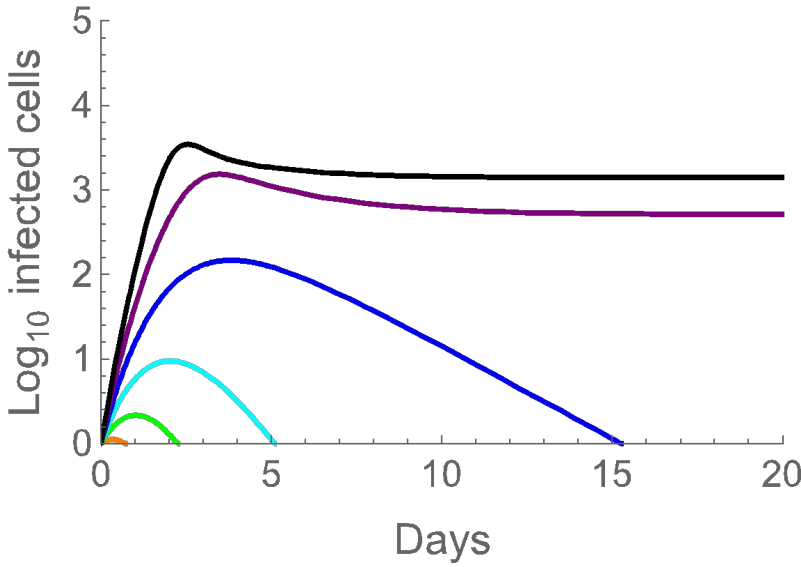
- Patch reproduction number: $R_P = \int_0^{+\infty} \beta_P(\tau)\,\mathrm{d}\tau$
- If $R_P \leq 1$ there is no infection

Within-patch dynamics

- 3 possible outcomes:

1. No or small burst of infection ($R_P \leq 1$)

   ➡ Disease-free equilibrium (DFE)

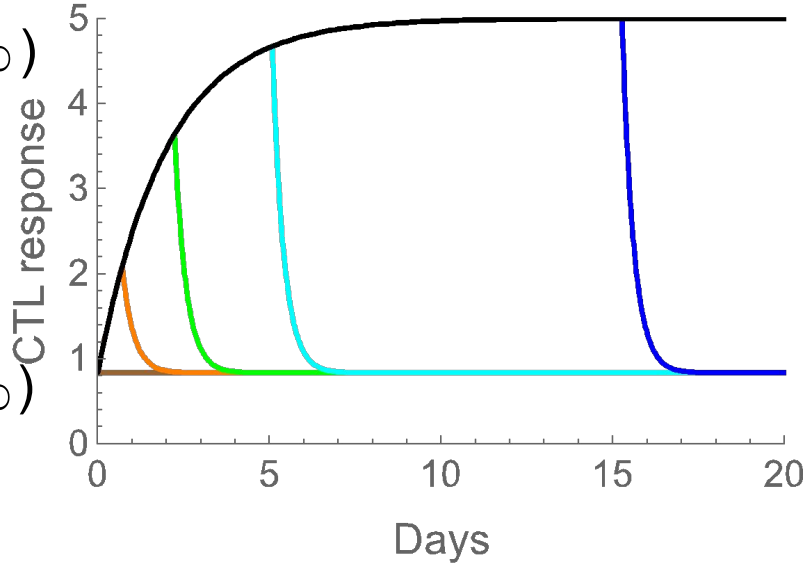


2. Short but big enough burst ($1 < R_P < \infty$)

   ➡ Shifting-mosaic steady state (SMSS)

3. Reaching endemic equilibrium ($R_P = \infty$)

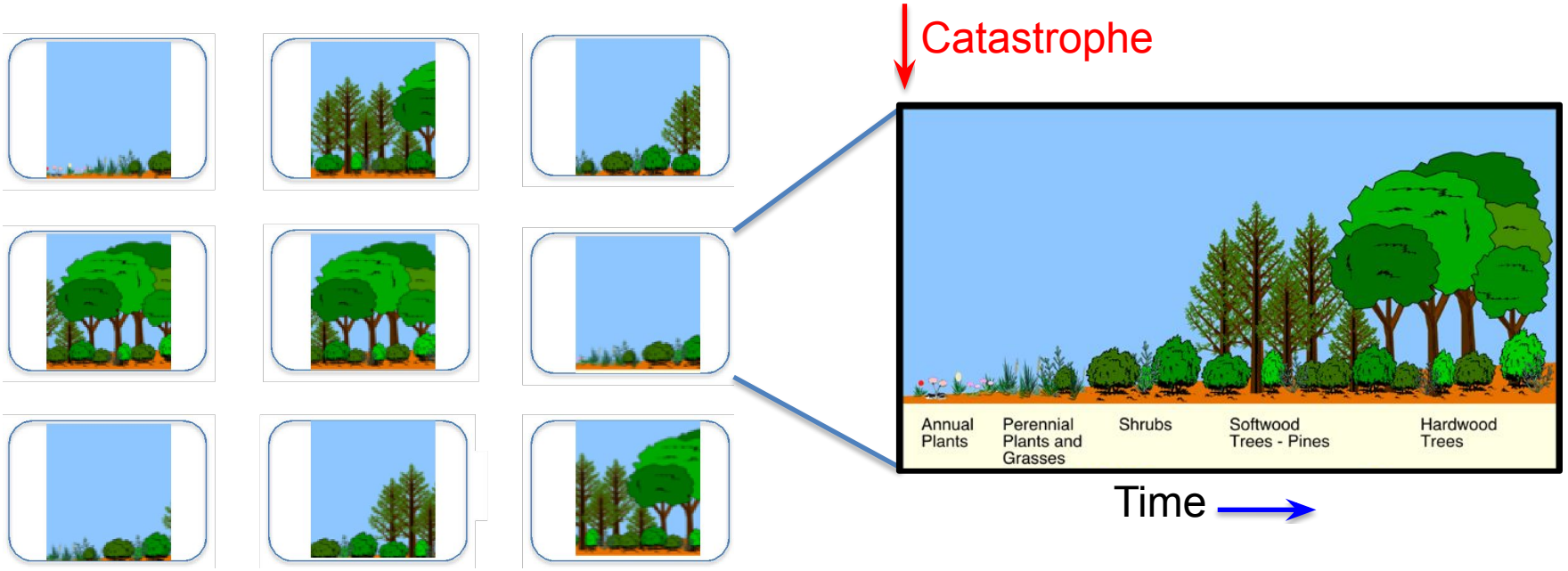
   ➡ Full equilibrium (FE)



‘Shifting mosaic’ steady state

The University of Manchester

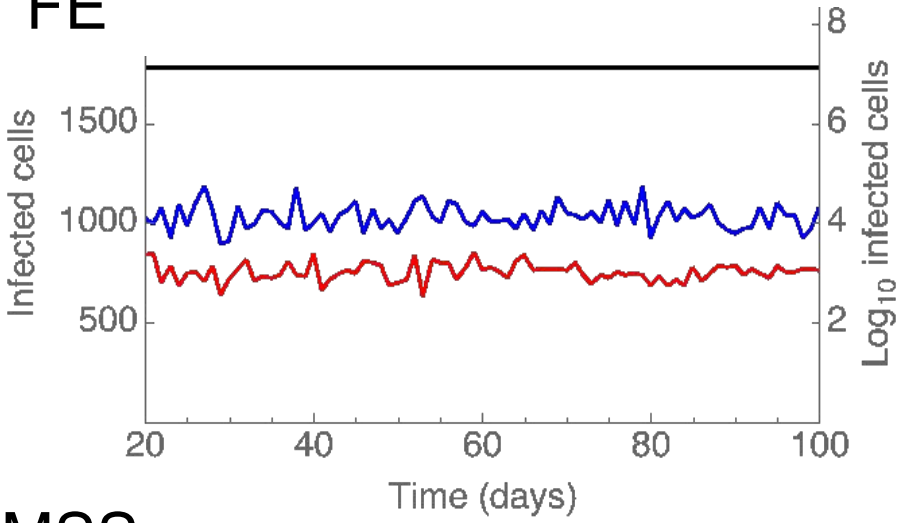
Bormann & Likens, 1979

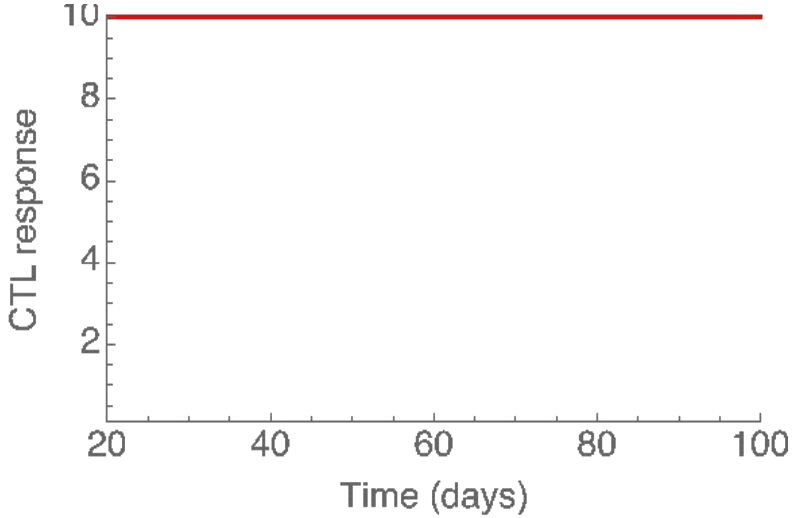


Although each patch is at a different phase,
the total biomass of the landscape is fairly constant

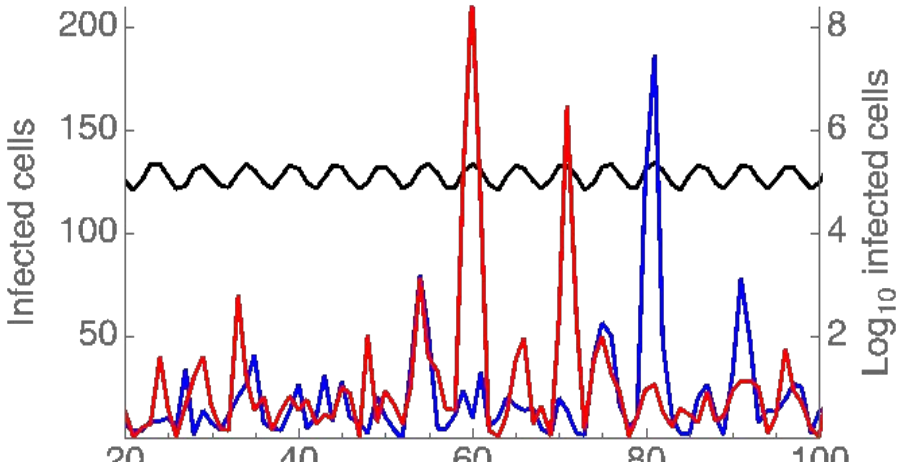
Full equilibrium VS SMSS

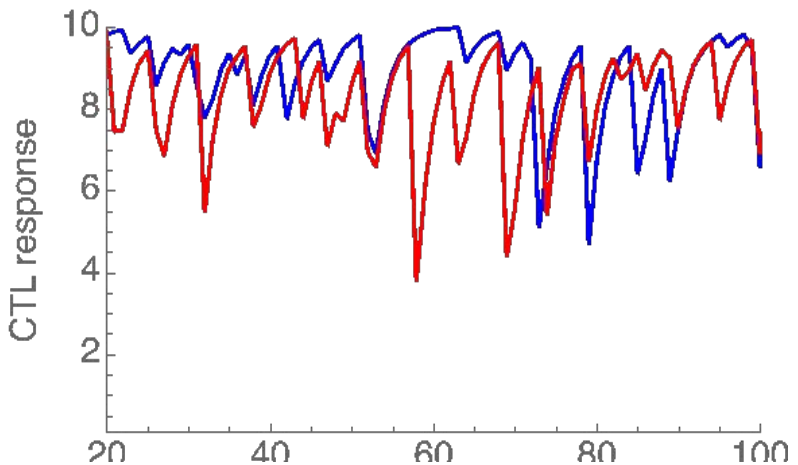
FE



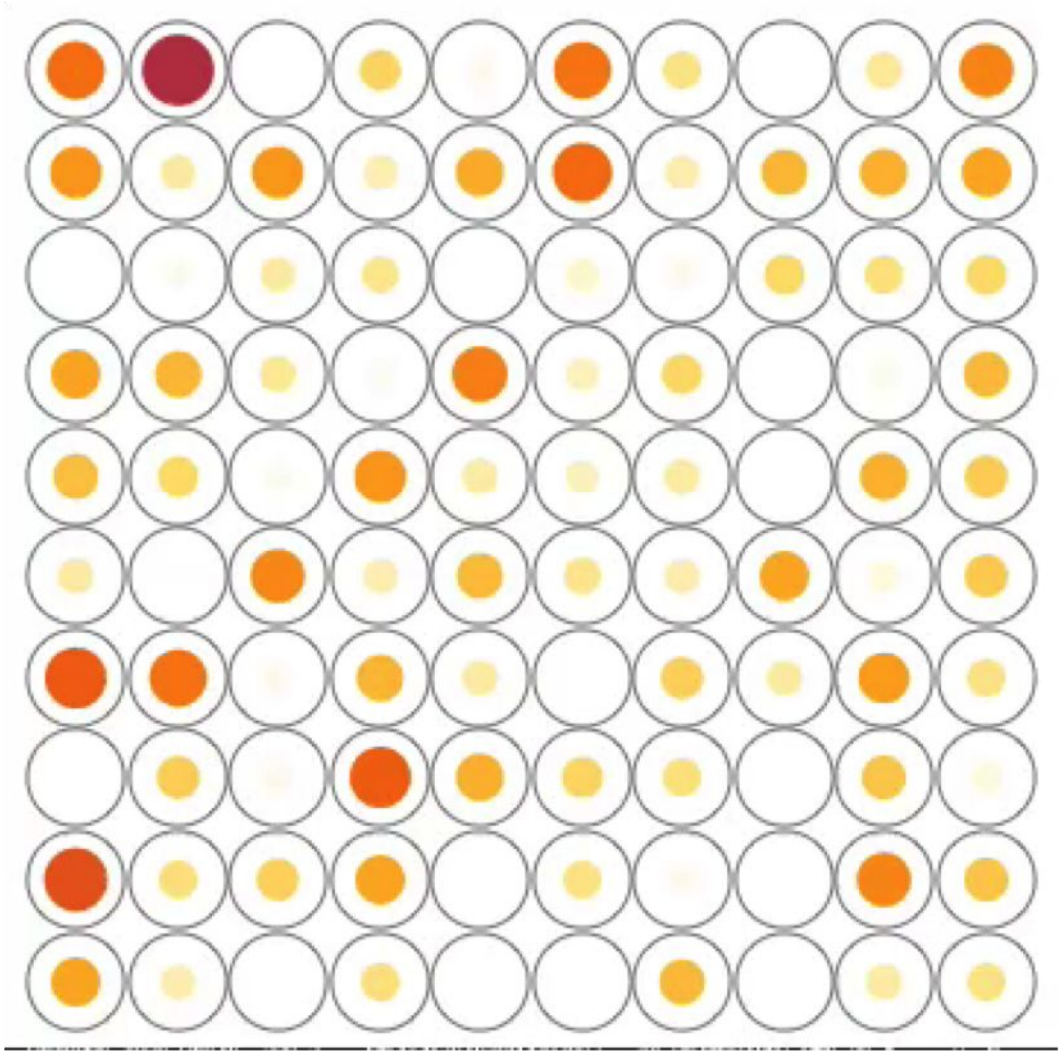


SMSS

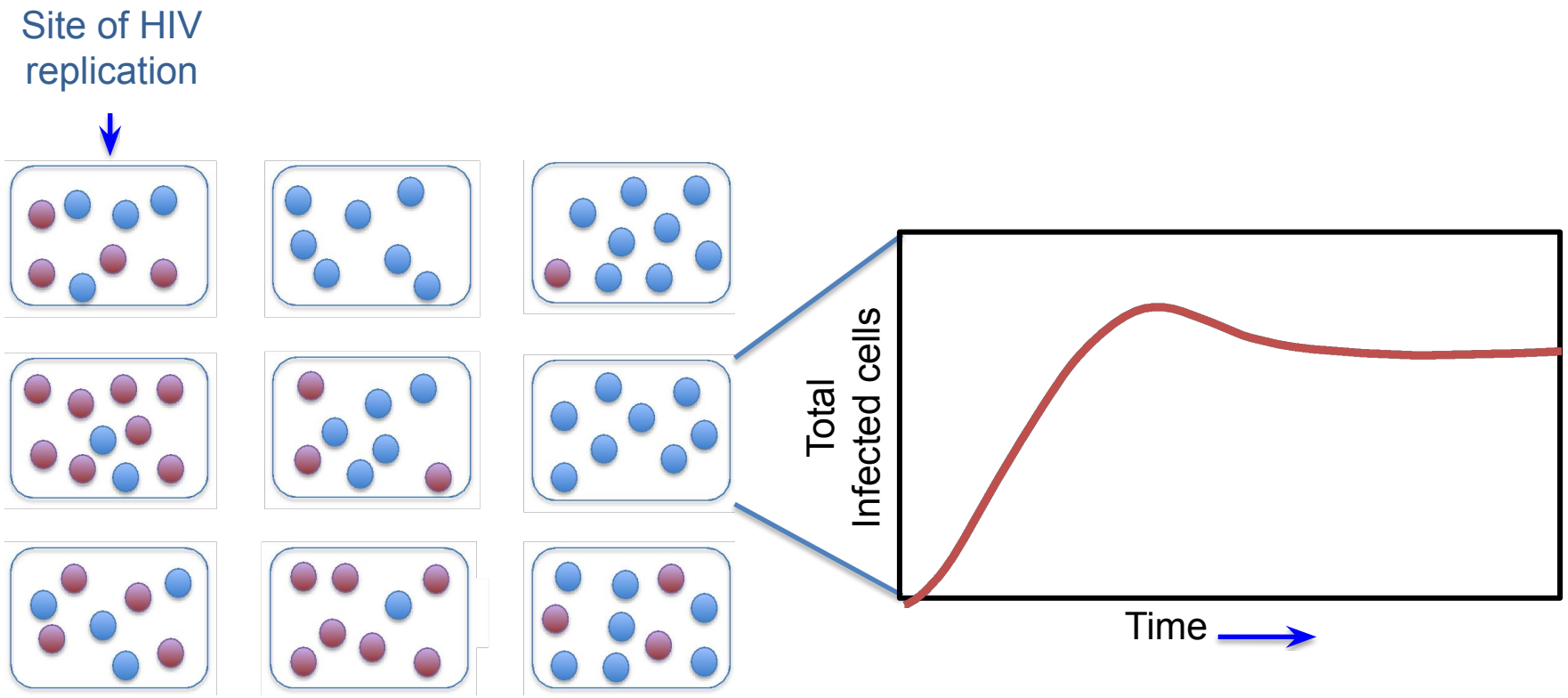




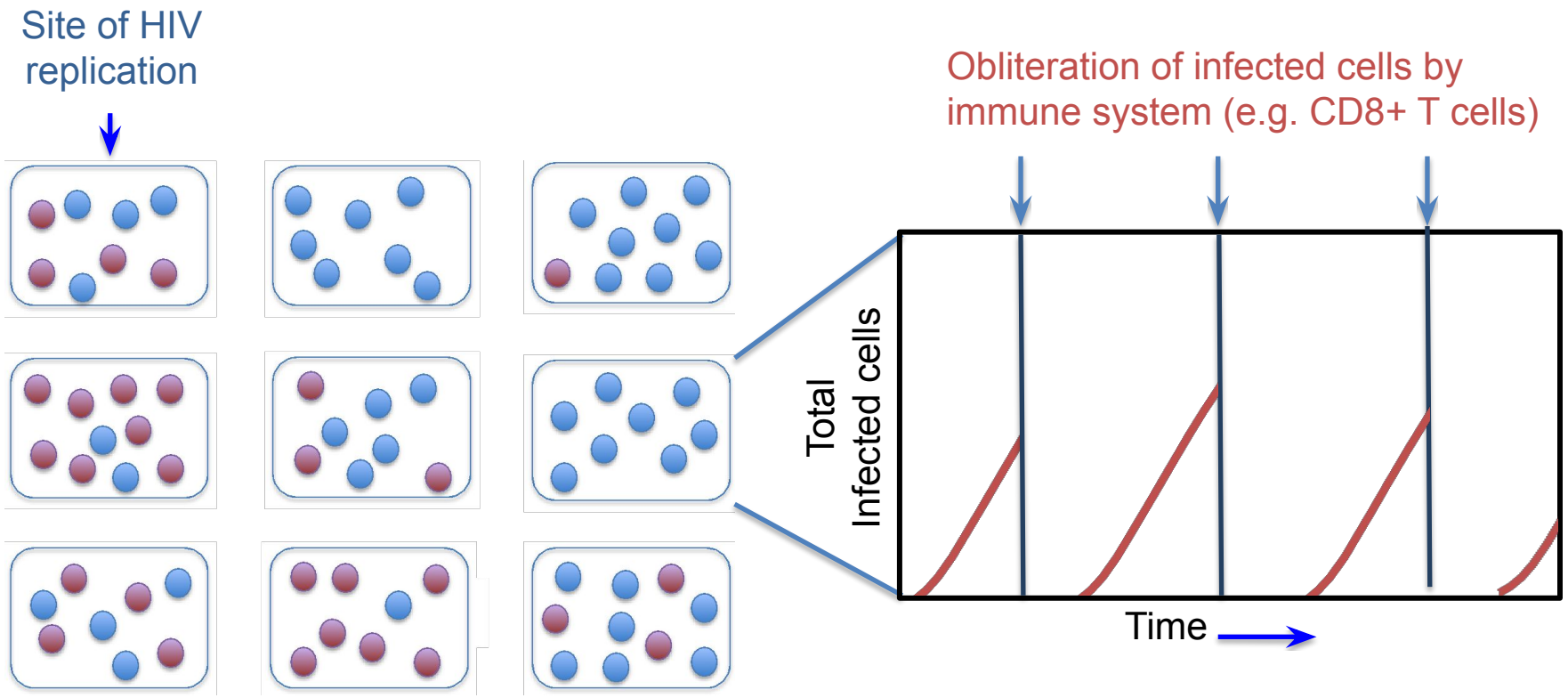
SMSS dynamics

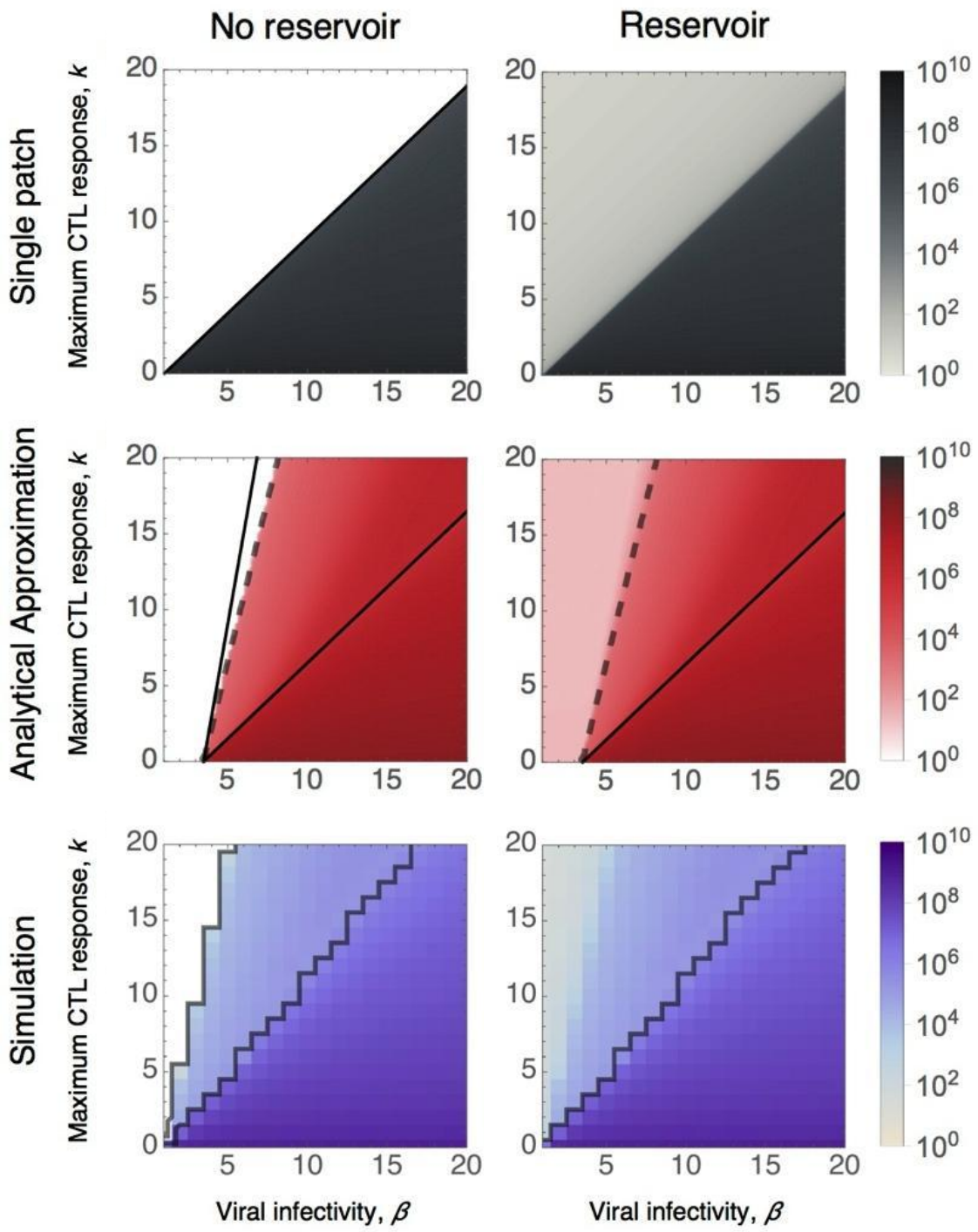


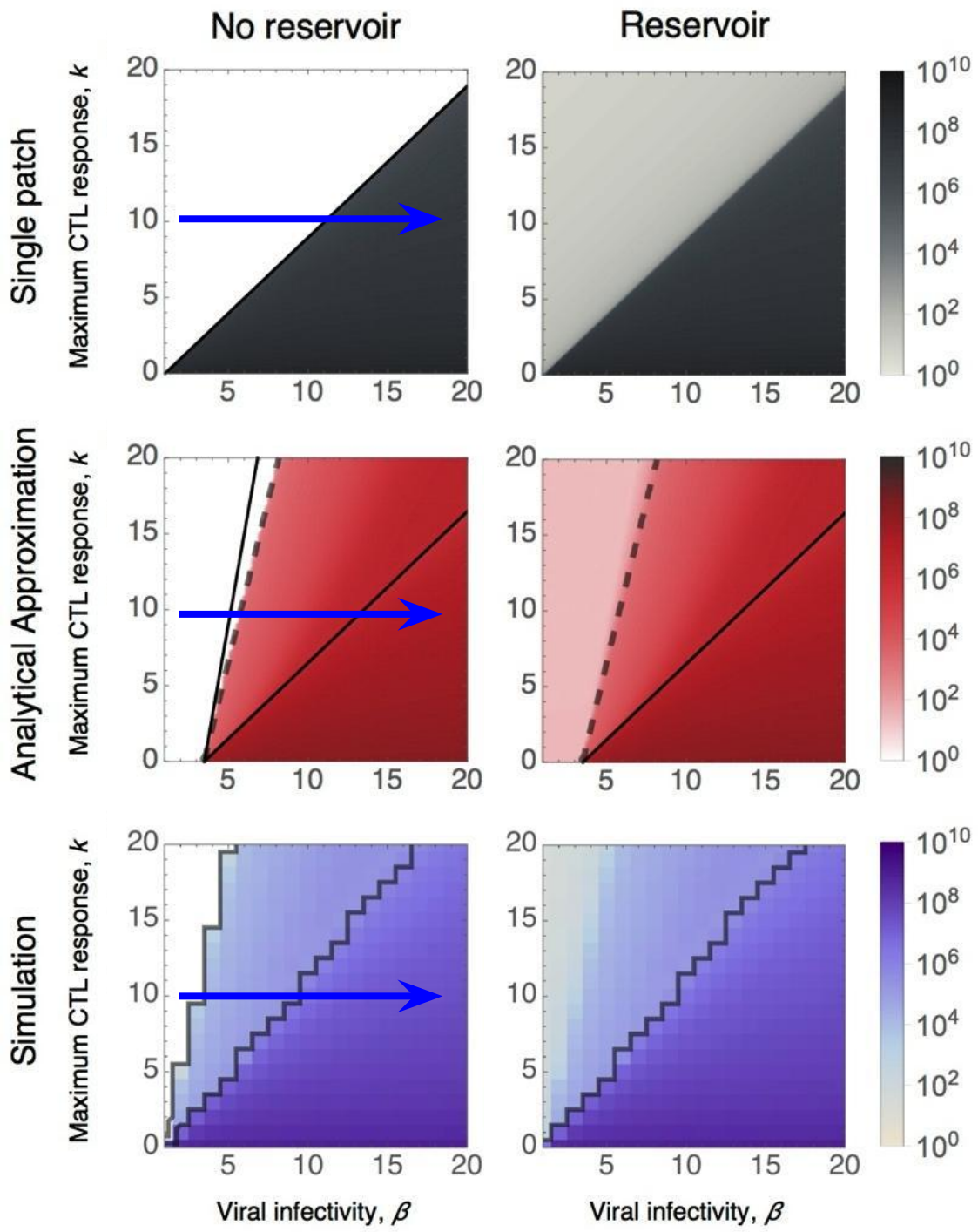
Sensitivity to parameters

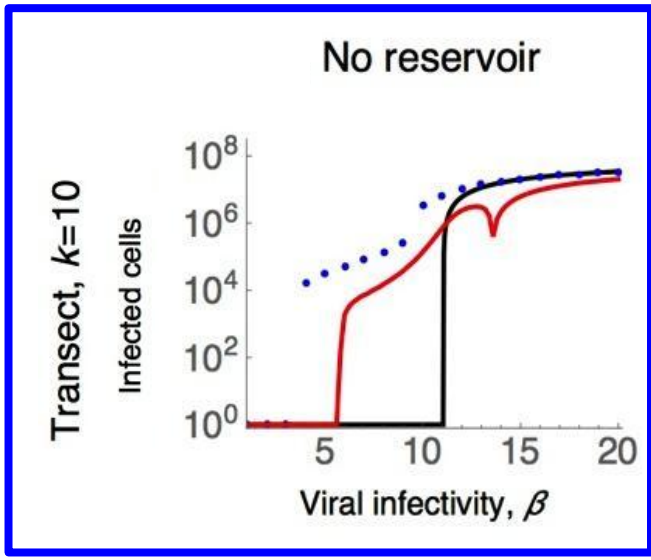


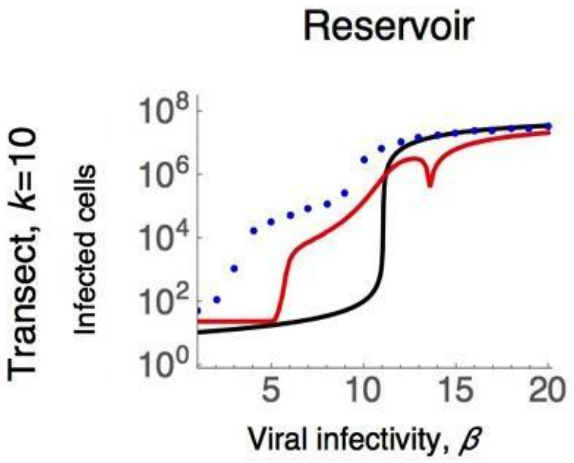
Sensitivity to parameters

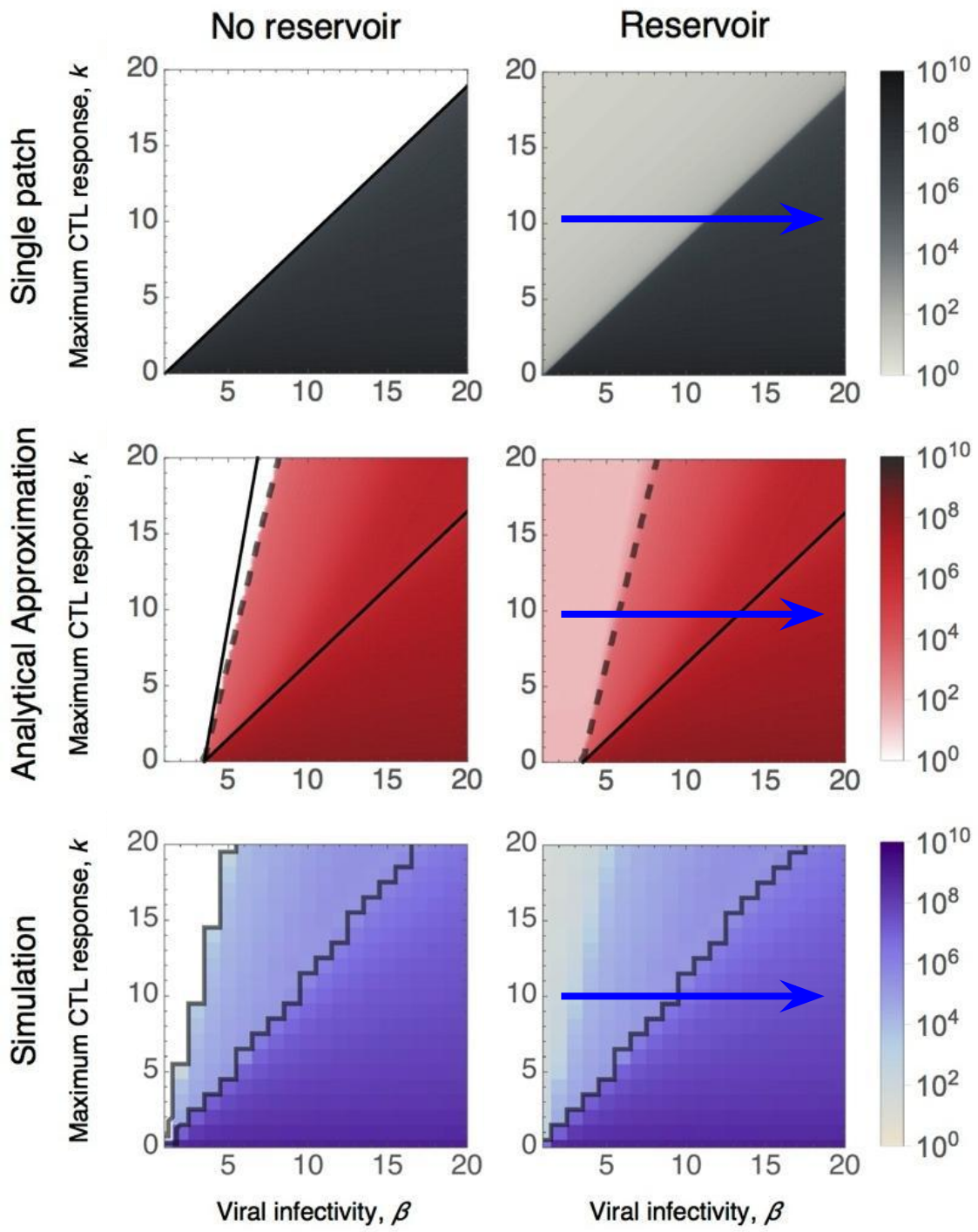


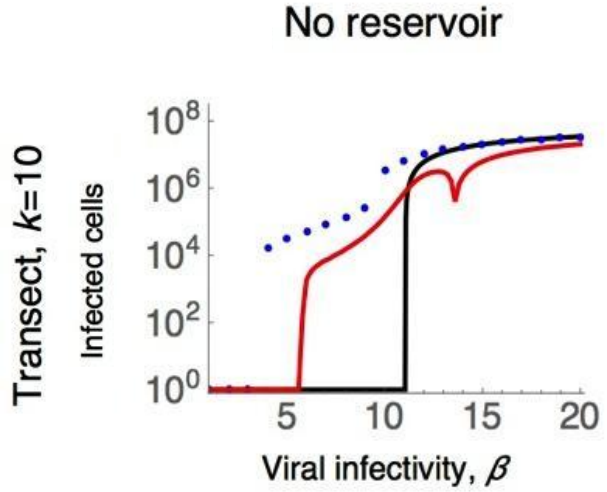

No reservoir
Reservoir
Single patch
Analytical Approximation
Simulation
Maximum CTL response, k
Viral infectivity, β
0
5
10
15
20
10^10
10^8
10^6
10^4
10^2
10^0

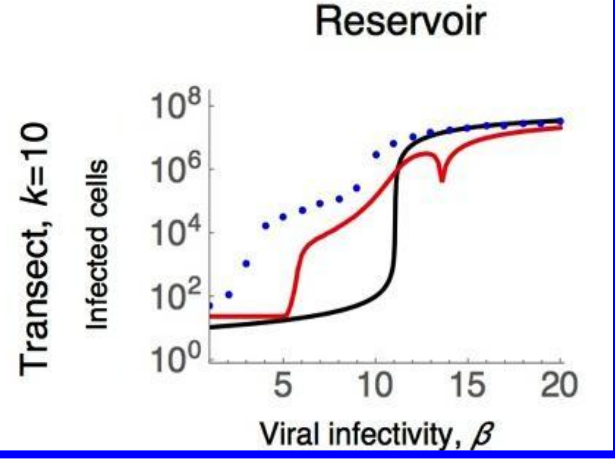

No reservoir
Reservoir
Single patch
Analytical Approximation
Simulation
Maximum CTL response, k
Viral infectivity, β
0
5
10
15
20
10^0
10^2
10^4
10^6
10^8
10^{10}


No reservoir
Transect, k=10
Infected cells
Viral infectivity, β
10^0
10^2
10^4
10^6
10^8
5
10
15
20


Reservoir
Transect, k=10
Infected cells
Viral infectivity, β
10^0
10^2
10^4
10^6
10^8
5
10
15
20


No reservoir
Reservoir
Single patch
Analytical Approximation
Simulation
Maximum CTL response, k
Viral infectivity, β
0
5
10
15
20
10^0
10^2
10^4
10^6
10^8
10^{10}


No reservoir
Transect, k=10
Infected cells
Viral infectivity, β
10^0
10^2
10^4
10^6
10^8
5
10
15
20


Reservoir
Transect, k=10
Infected cells
Viral infectivity, β
10^0
10^2
10^4
10^6
10^8
5
10
15
20

[**Lythgoe, Blanquart, Pellis & Fraser** (2016), *PLoS Biology*]

END OF EXAMPLE 1

Why using TSI?

MANCHESTER 1824
The University of Manchester

- More general
- Closer to biology / experiments:
  - Available data
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
- Suitable to encapsulate complex within-host (WH) dynamics
- Can enhance understanding of more complex models
- Harder to study, so it requires more thinking about which assumptions are really responsible for the results we see

Why using TSI?

MANCHESTER 1824
The University of Manchester

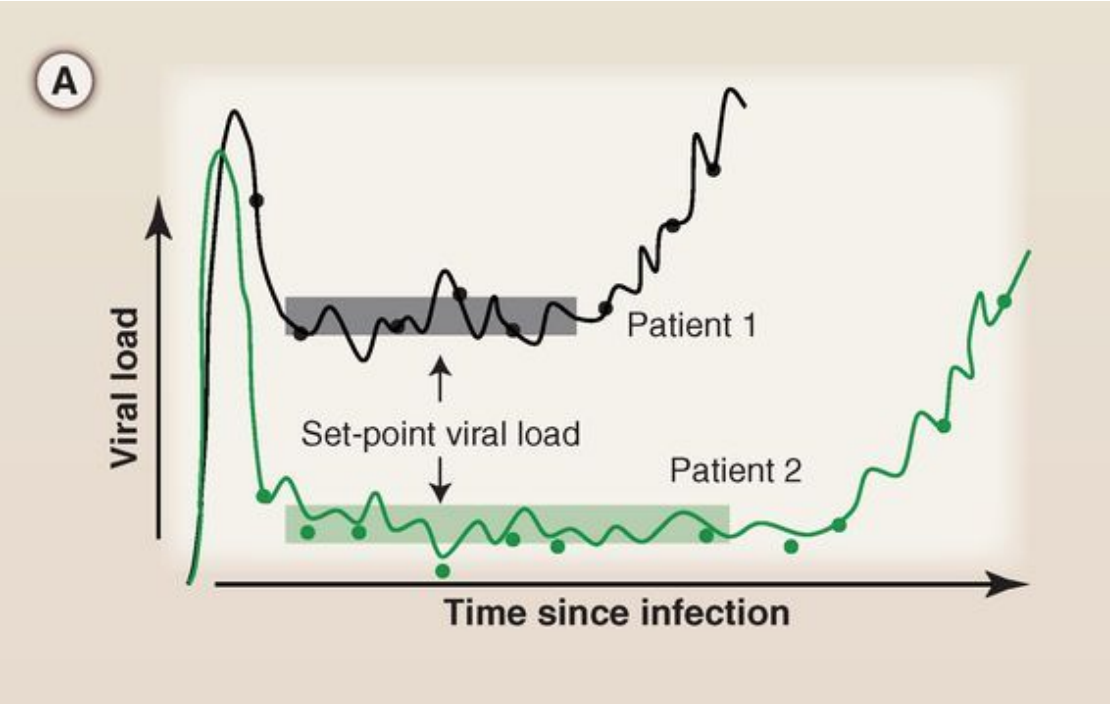
- More general
- Closer to biology / experiments:
  - Available data
  - Detailed time evolution of infection is deemed important
  - Complex / long infectivity profiles (e.g. HIV)
- Suitable to encapsulate complex within-host (WH) dynamics
- Can enhance understanding of more complex models
- Harder to study, so it requires more thinking about which assumptions are really responsible for the results we see

MANCHESTER 1824
The University of Manchester

[**Lythgoe, Pellis & Fraser** (2013), *Evolution*]

EXAMPLE 2: HIV WITHIN- & BETWEEN-HOST MODEL

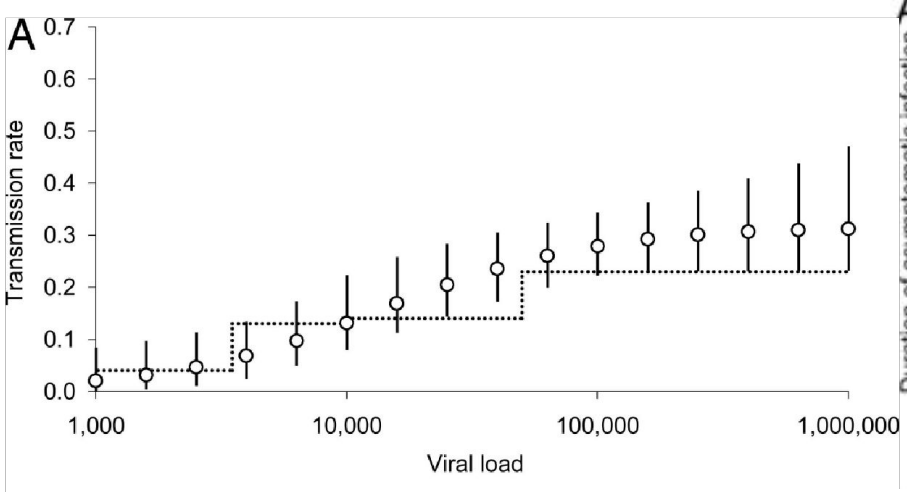
Set-point viral load



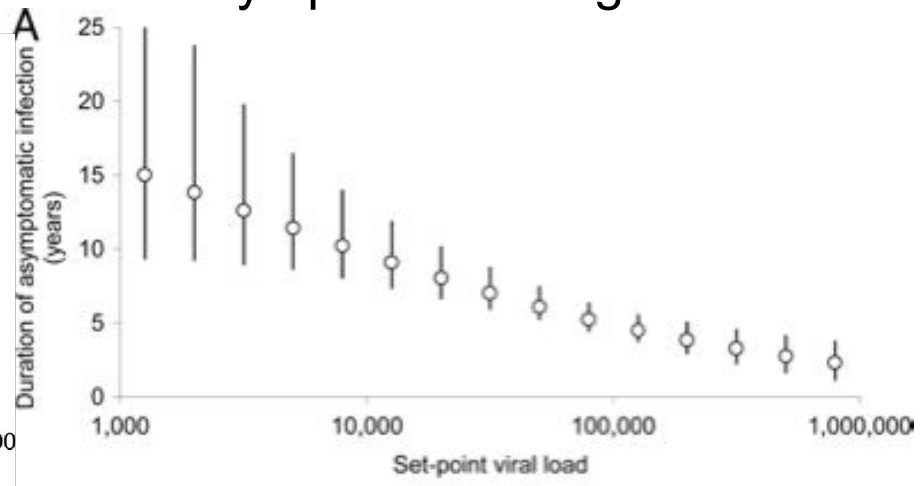
Fraser, **Lythgoe** *et al* (2014), *Science*

Set-point viral load (SPVL)

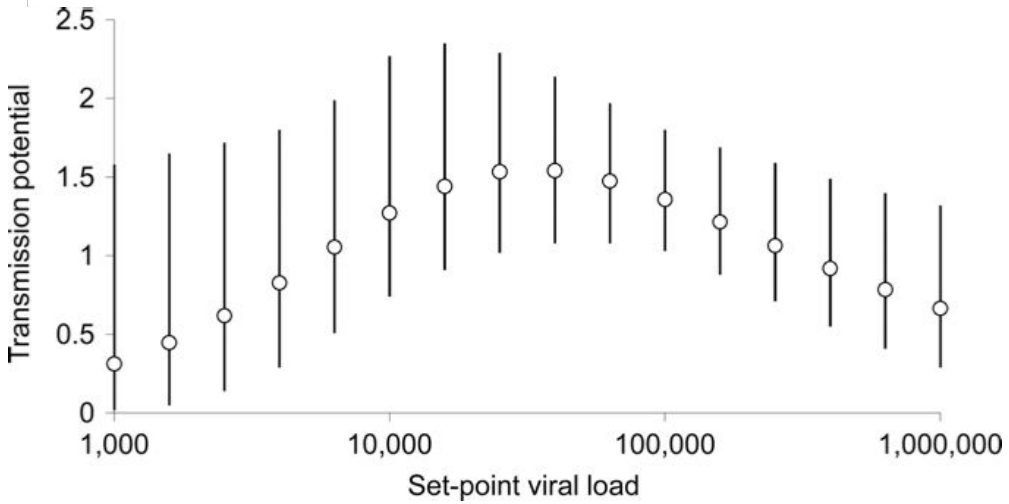
- Predicts infectiousness



- Predicts duration of asymptomatic stage



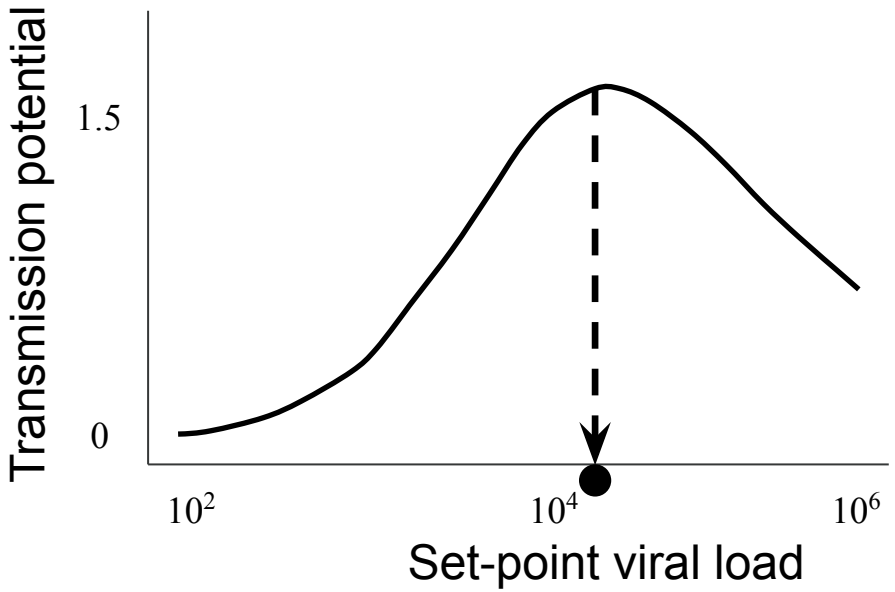
- Transmission potential = overall infectivity



Fraser *et al* (2007), *PNAS*

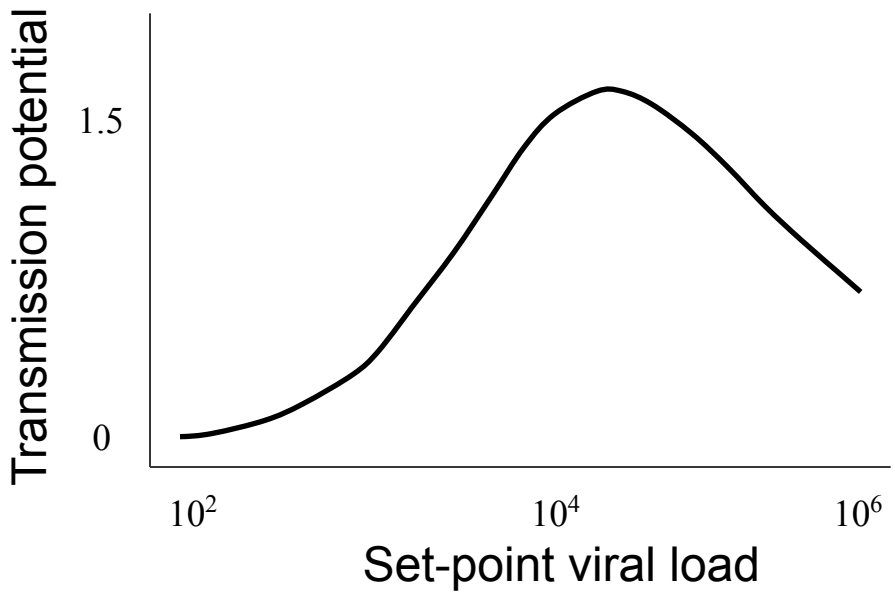
Evolution of SPVL

- SPVL is highly heritable
- Steadily increasing for 25 years
- Now seems to have plateaued
- The current mean value is very close to maximum transmission potential

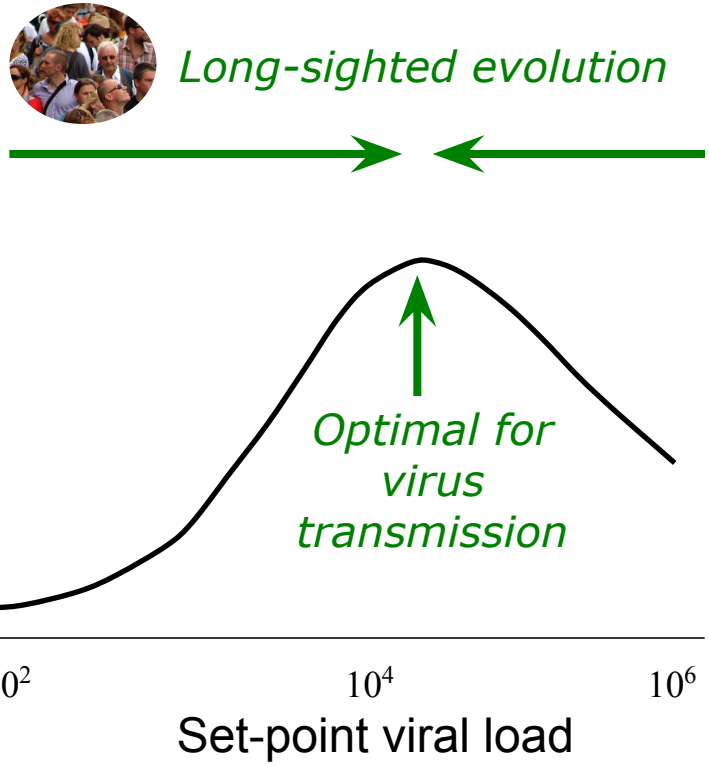


Fraser *et al* (2007), *PNAS*

HIV transmission potential

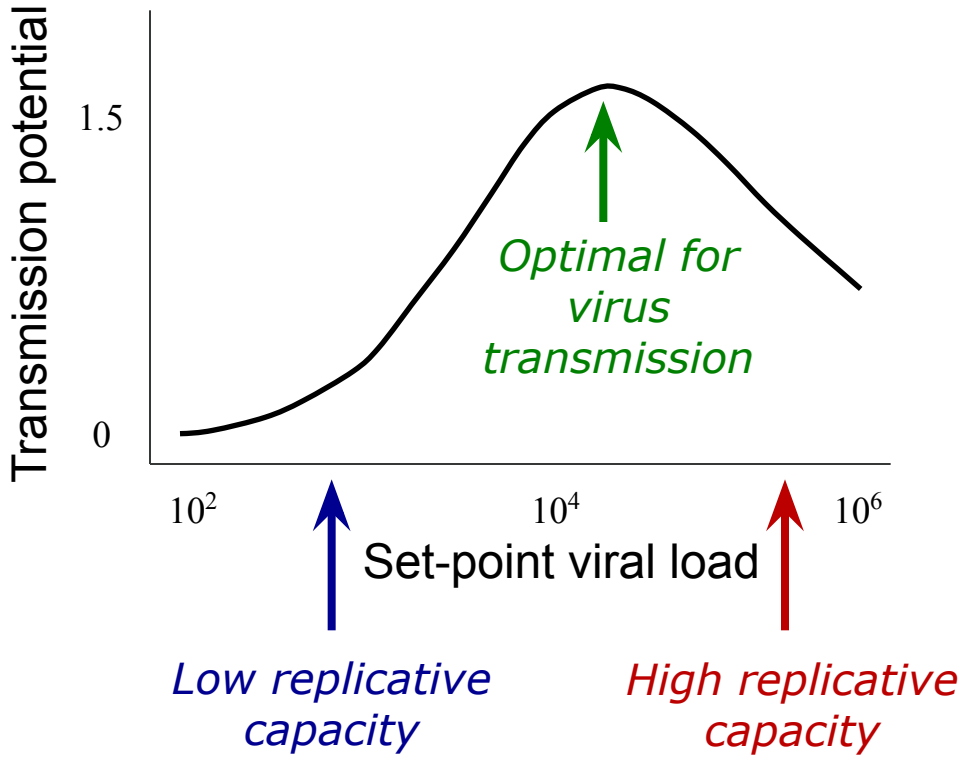


HIV transmission potential



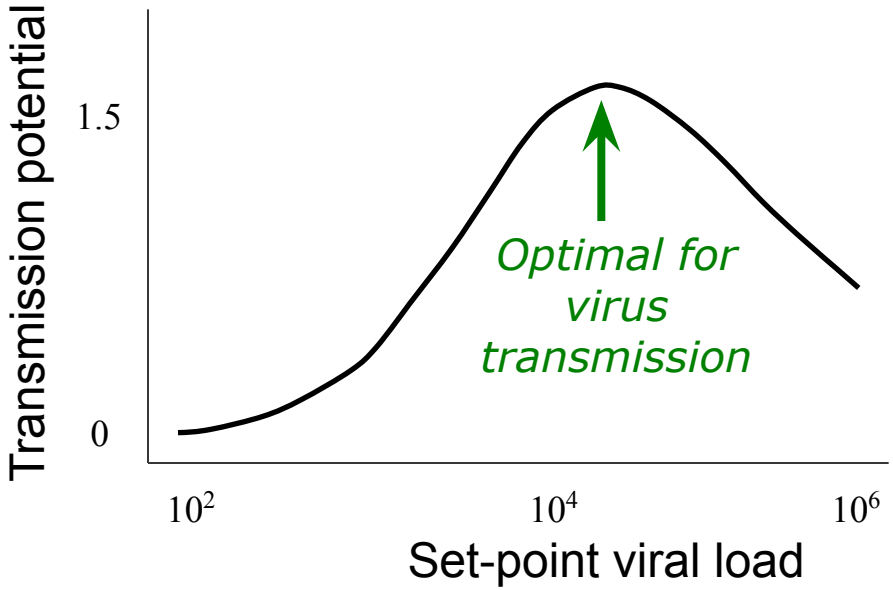
HIV transmission potential

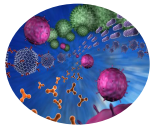
Long-sighted evolution



HIV transmission potential

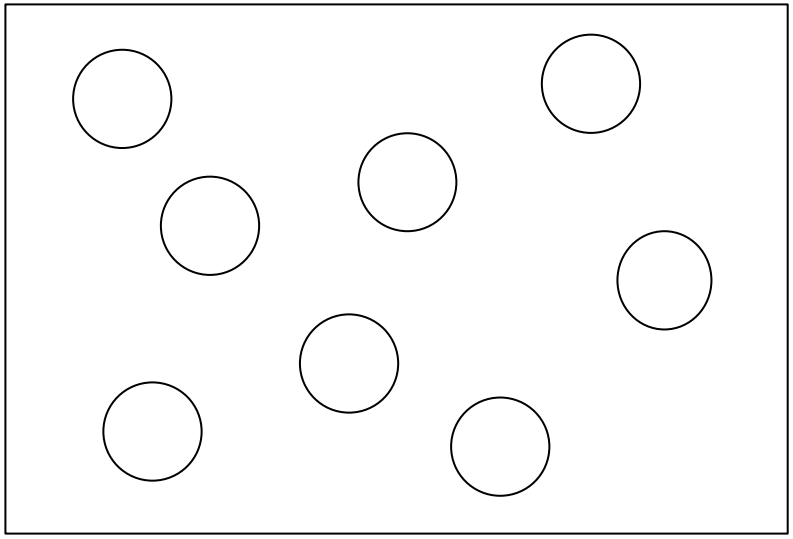
Long-sighted evolution





Short-sighted evolution

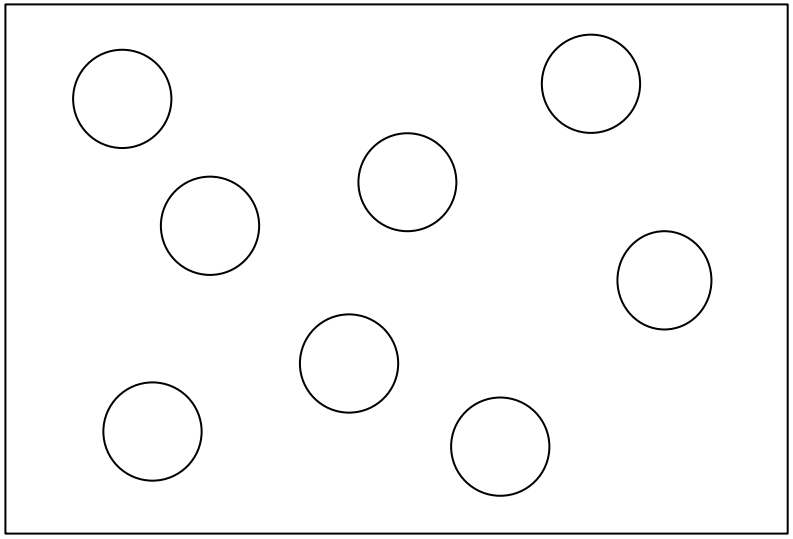
Population structure



- Deterministic model
- All susceptibles identical
- Homogeneous mixing
- Vital dynamics:

$$\frac{dN(t)}{dt} = B - \mu N(t)$$

Population structure

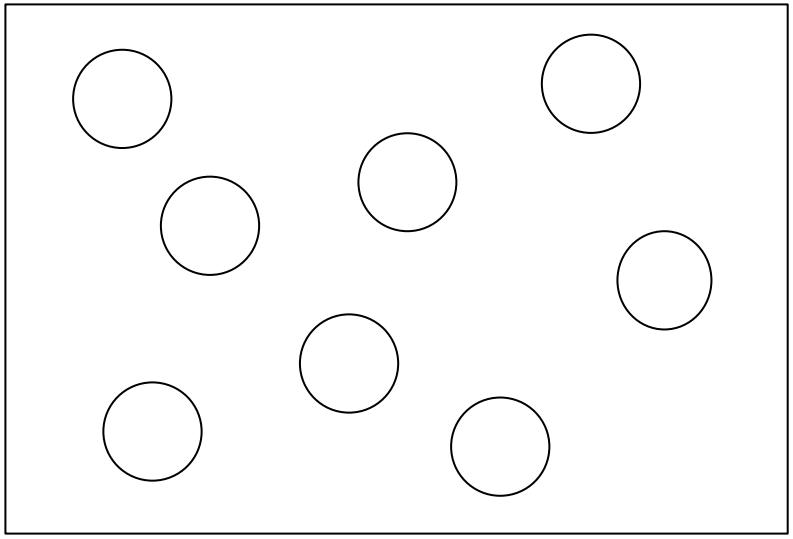


- Deterministic model
- All susceptibles identical
- Homogeneous mixing
- Vital dynamics:

$$\frac{dN(t)}{dt} = B - \mu N(t)$$

Total birth rate

Population structure



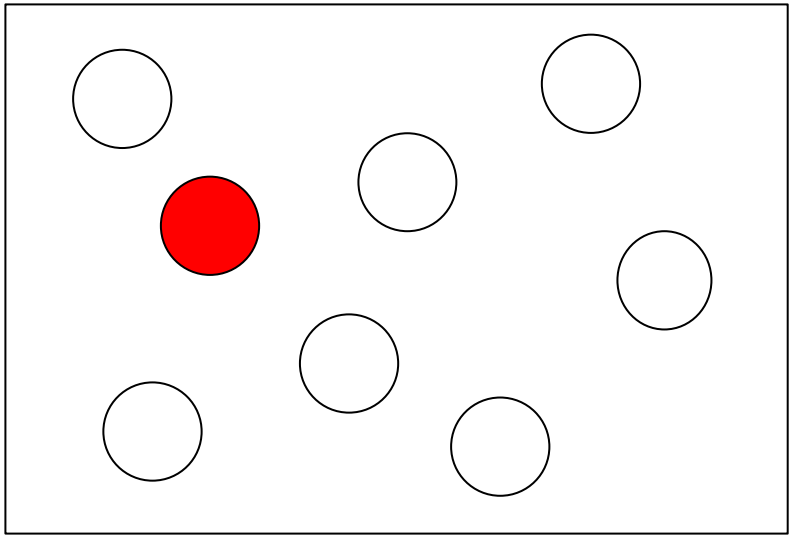
- Deterministic model
- All susceptibles identical
- Homogeneous mixing
- Vital dynamics:

$$\frac{dN(t)}{dt} = B - \mu N(t)$$

Total birth rate

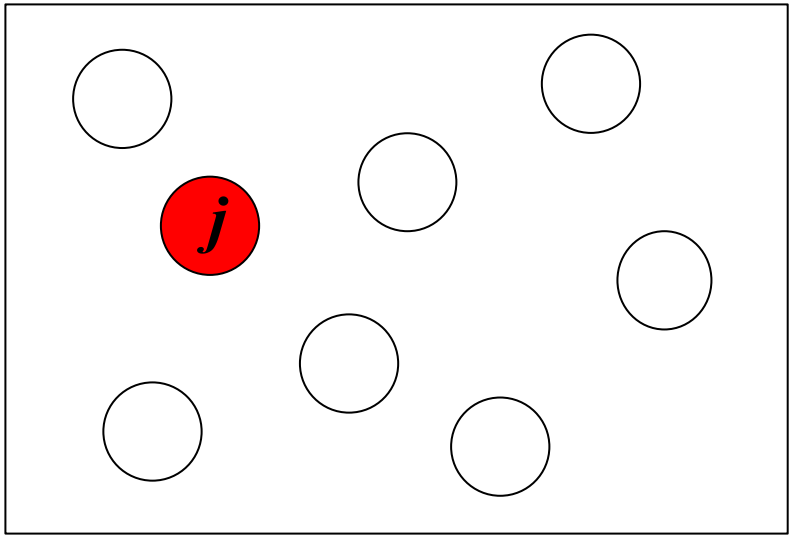
Per-capita death rate

Infection spread



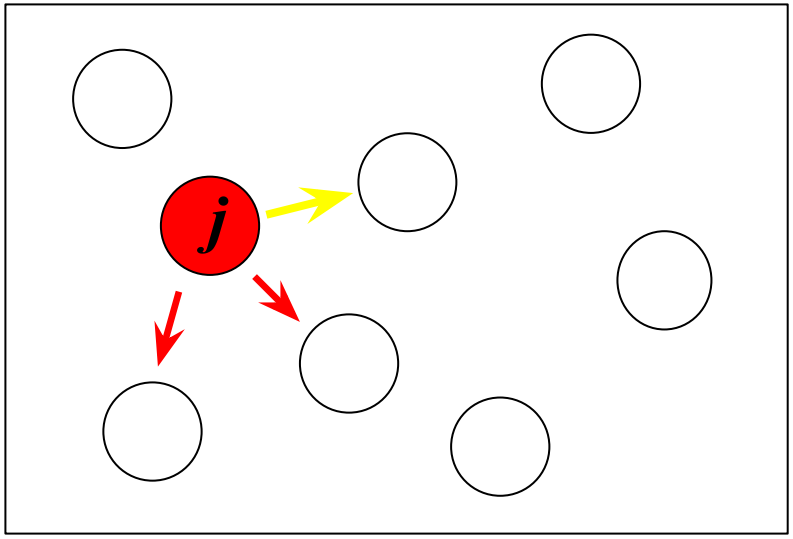
- SI model
- Infection caused by a single virion j
- Type-j case = infected with a virus of strain j
- Infector strain → SPVL → infectiousness and duration
- $\beta_{ij}(\tau) =$ rate at which type-j case transmit strain i

Infection spread



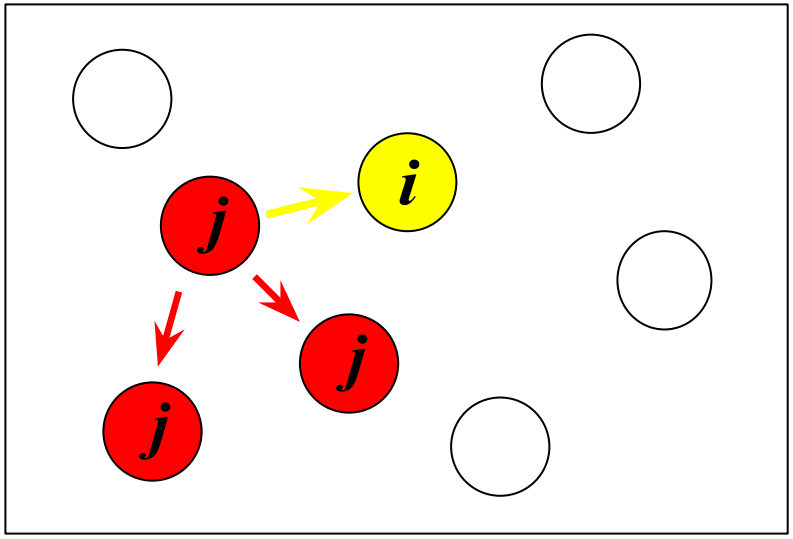
- SI model
- Infection caused by a single virion j
- Type-j case = infected with a virus of strain j
- Infector strain → SPVL → infectiousness and duration
- $\beta_{ij}(\tau) =$ rate at which type-j case transmit strain i

Infection spread



- SI model
- Infection caused by a single virion j
- Type-j case = infected with a virus of strain j
- Infector strain → SPVL → infectiousness and duration
- $\beta_{ij}(\tau) =$ rate at which type-j case transmit strain i

Infection spread



- SI model
- Infection caused by a single virion j
- Type-j case = infected with a virus of strain j
- Infector strain ⟹ SPVL ⟹ infectiousness and duration
- $\beta_{ij}(\tau) =$ rate at which type-j case transmit strain i

Equations

Dynamics:

$$H_i(t) = \frac{S(t)}{N(t)} \sum_{j=1}^{n} \int_0^{T_j} \beta_{ij}(\tau) H_j(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$S(t) = N(t) - \sum_{i=1}^{n} \int_0^{T_i} H_i(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = B - \mu N(t) - \sum_{i=1}^{n} H_i(t-T_i) \mathrm{e}^{-\mu T_i}$$

$H_i(t)$ = incidence of type-i cases

T_i = duration of life of type-i cases

Equilibrium:

$$\underline{H}^* = \left(H_i^*\right)$$

$$R_0 = \rho(K)$$

$$\Downarrow$$

$$\underline{H}^* = \frac{S^*}{N^*} K \underline{H}^*$$

$$\frac{S^*}{N^*} = \frac{1}{R_0}$$

$$\underline{H}^* = v(K)$$

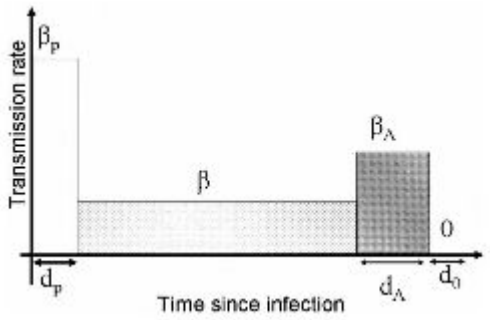
$$K = \left(k_{ij}\right) = \left(\int_0^{\infty} \beta_{ij}(\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau \right) = \text{Next-Generation Matrix}$$

Infectivity profiles

Ideally, we want a within-host model to construct the $\beta_{ij}(\tau)$

Two choices:

- Virus – immune system competition model:
  - Possible
  - Slow
  - No hope to get a non-unimodal infectivity profile
- Impose "artificially" a shape $\alpha_j(\tau)$ for the infectivity profile of type j and model changes in frequencies with the quasispecies equation
  - Very flexible
  - Fast
  - But requires many assumptions



The quasispecies equation

- Consider n strains and let

$\underline{\mathbf{y}}(t) = \left(y_i(t)\right)$ number of virions of strain i

$\underline{\mathbf{g}} = \left(g_i\right)$ vector of reproduction rates of strain i

$M = \left(m_{ij}\right)$ mutation matrix

$Q = \left(m_{ij} g_j\right)$ reproduction-mutation matrix

- Then the system for the unbounded growth is

$$\frac{\mathrm{d}\underline{\mathbf{y}}}{\mathrm{d}t} = Q\mathbf{y}$$

- Consider the frequencies

$$\underline{\mathbf{x}}(t) = \left(x_i(t)\right) = \left(\frac{y_i(t)}{\sum_j y_j(t)}\right)$$

- Quasispecies equation:

$$\frac{\mathrm{d}\underline{\mathbf{x}}}{\mathrm{d}t} = Q\underline{\mathbf{x}} - \bar{g}\underline{\mathbf{x}} \qquad \text{where} \qquad \bar{g}(t) = \sum_i g_i x_i(t)$$

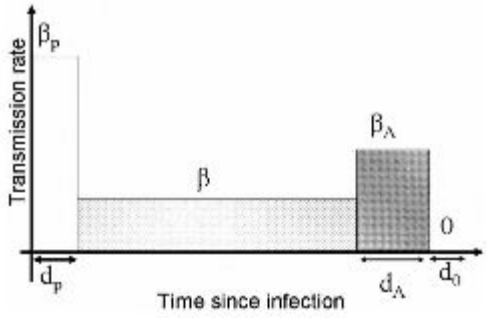
Linking within- and between-host

$$\beta_{ij}(\tau) = G_i \quad x_{ij}(\tau) \quad \alpha_j(\tau)$$

Linking within- and between-host

$$\beta_{ij}(\tau) = G_i \; x_{ij}(\tau) \; \alpha_j(\tau)$$

Infectivity profile of type-j case

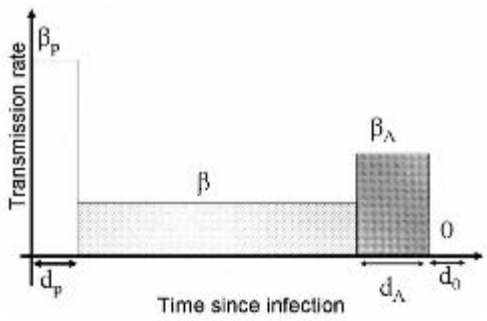


Linking within- and between-host

$$\beta_{ij}(\tau) = G_i \, x_{ij}(\tau) \, \alpha_j(\tau)$$

Frequency of strain i at time t after initial infection with strain j

Infectivity profile of type-j case



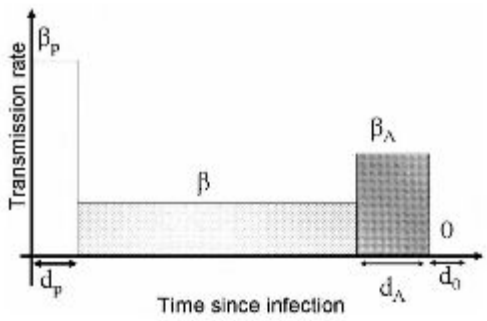
Linking within- and between-host

$$\beta_{ij}(\tau) = G_i \; x_{ij}(\tau) \; \alpha_j(\tau)$$

between-host transmissibility of strain-i virus

Frequency of strain i at time t after initial infection with strain j

Infectivity profile of type-j case



Within- and between-host fitness

Strain index:

$$\boldsymbol{i} = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad \boldsymbol{n}$$

Within- and between-host fitness

Strain index:

$$\boldsymbol{i} = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad \boldsymbol{n}$$

Within-host fitness:

$$\boldsymbol{g}_i =$$

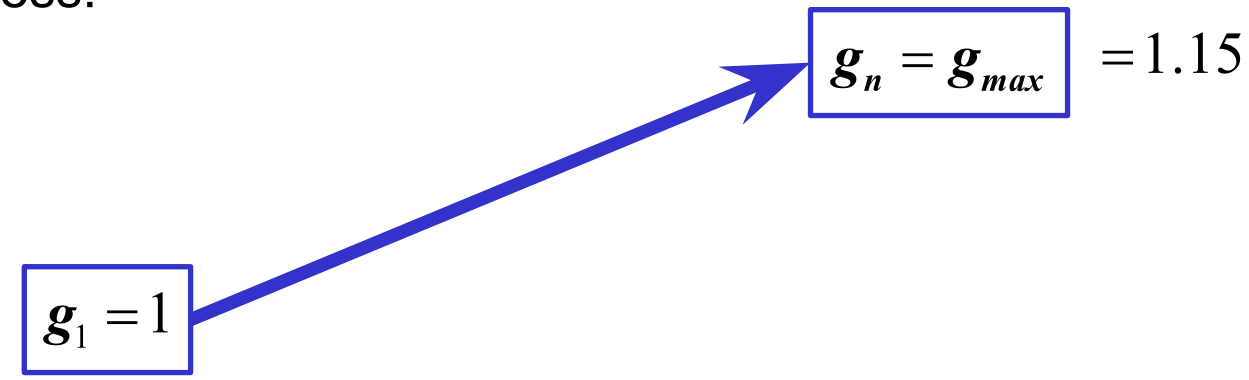
Within- and between-host fitness

Strain index:

$$i = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad n$$

Within-host fitness:

$$g_i =$$



Within- and between-host fitness

Strain index:

$$i = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad n$$

Within-host fitness:

$$g_i = \quad g_1 = 1 \rightarrow g_n = g_{max} = 1.15$$

Between-host fitness:

$$G_i = \quad G_1 \rightarrow \sum_i G_i = 1 \rightarrow G_n$$

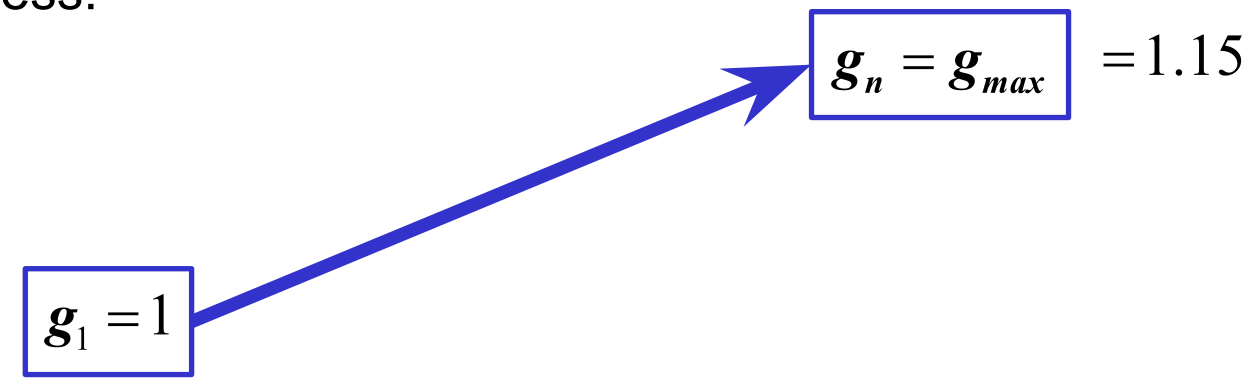
Within- and between-host fitness

Strain index:

$$i = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad n$$

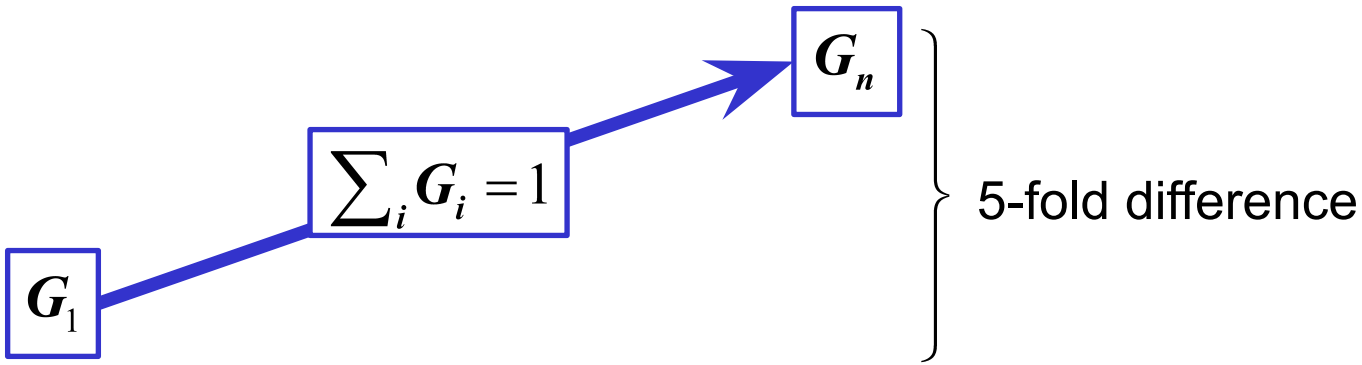
Within-host fitness:

$$g_i =$$



Between-host fitness:

$$G_i =$$



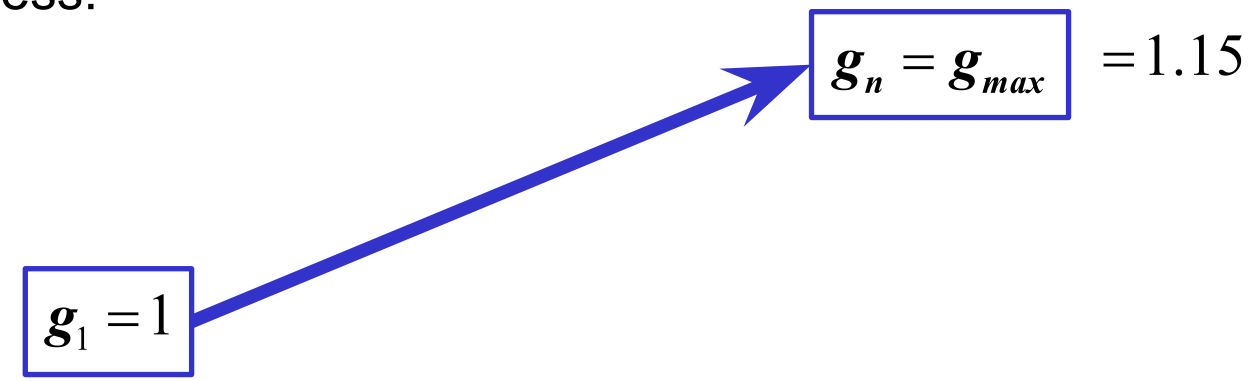
Within- and between-host fitness

Strain index:

$$i = \quad 1 \quad 2 \quad \ldots \quad \ldots \quad n$$

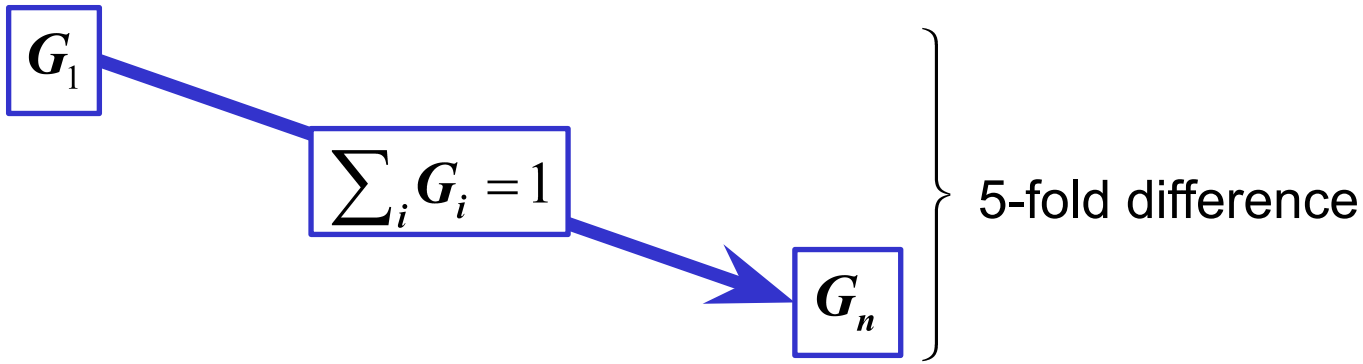
Within-host fitness:

$$g_i =$$



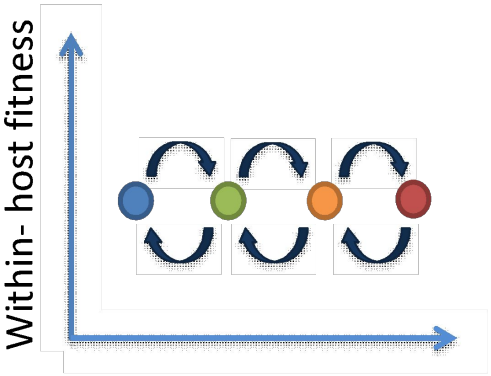
Between-host fitness:

$$G_i =$$



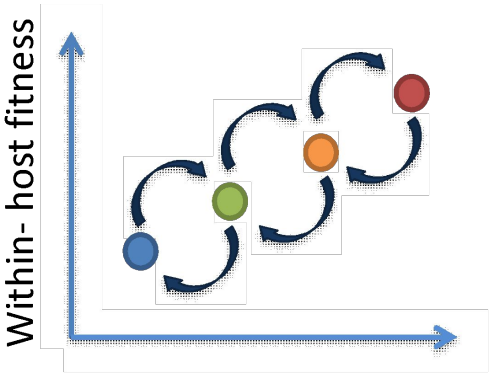
Reproduction-mutation matrix

- Flat:



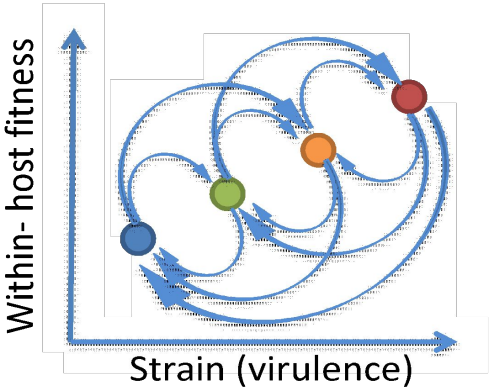
$$M = \begin{pmatrix} 1-\mu & \mu & & & & \\ \mu & 1-2\mu & \mu & & & \\ & \mu & 1-2\mu & \ddots & & \\ & & \ddots & \ddots & \mu & \\ & & & \mu & 1-2\mu & \mu \\ & & & & \mu & 1-\mu \end{pmatrix}$$

- Hill-climb:

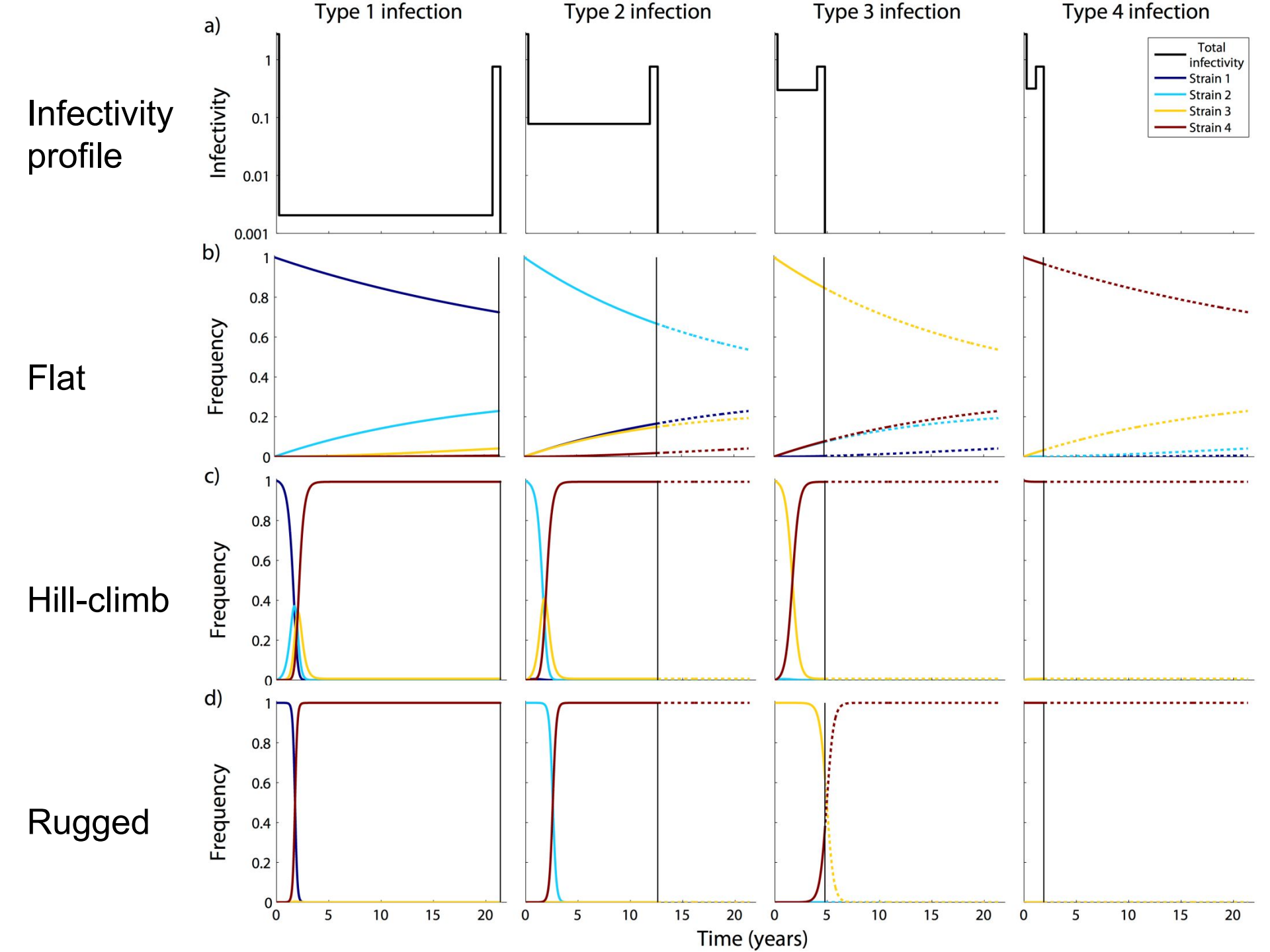


$$M = \begin{pmatrix} 1-\mu & \mu & & & & \\ \mu & 1-2\mu & \mu & & & \\ & \mu & 1-2\mu & \ddots & & \\ & & \ddots & \ddots & \mu & \\ & & & \mu & 1-2\mu & \mu \\ & & & & \mu & 1-\mu \end{pmatrix}$$

- Rugged:



$$M = \begin{pmatrix} (1-n\mu^2) & \mu^2 & \cdots & \mu^2 & \mu^2 \\ \mu^2 & (1-n\mu^2) & & \mu^2 & \mu^2 \\ \vdots & & \ddots & & \vdots \\ \mu^2 & \mu^2 & & (1-n\mu^2) & \mu^2 \\ \mu^2 & \mu^2 & \cdots & \mu^2 & (1-n\mu^2) \end{pmatrix}$$

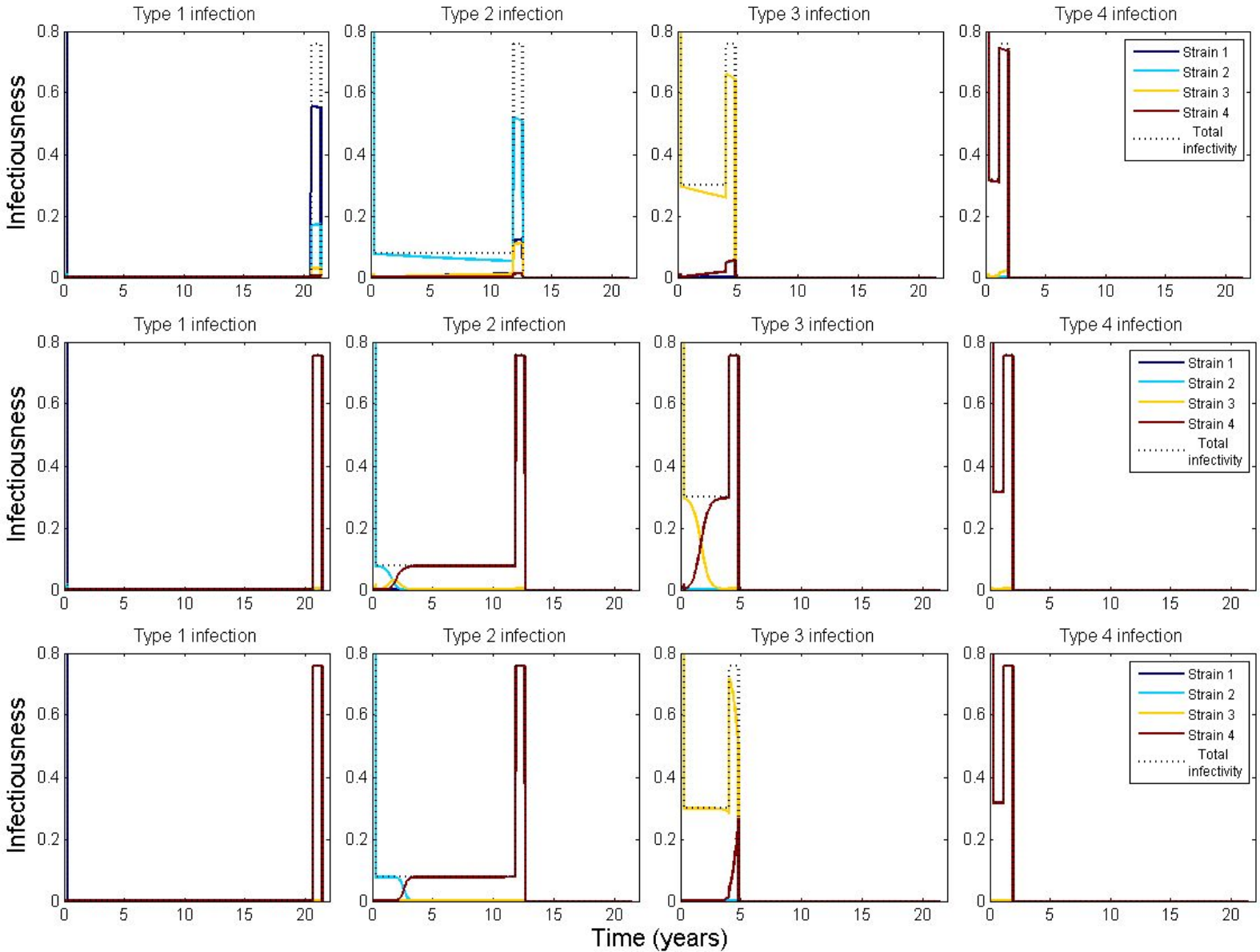

Infectivity profile
Flat
Hill-climb
Rugged
Type 1 infection
Type 2 infection
Type 3 infection
Type 4 infection
a)
b)
c)
d)
Infectivity
Frequency
Total infectivity
Strain 1
Strain 2
Strain 3
Strain 4
Time (years)

Infectivity profiles (4 strains)

Flat

Hill-climb

Rugged



Equations

Dynamics:

$$H_i(t) = \frac{S(t)}{N(t)} \sum_{j=1}^{n} \int_0^{T_j} \beta_{ij}(\tau) H_j(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$S(t) = N(t) - \sum_{i=1}^{n} \int_0^{T_i} H_i(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = B - \mu N(t) - \sum_{i=1}^{n} H_i(t-T_i) \mathrm{e}^{-\mu T_i}$$

$H_i(t)$ = incidence of type-i cases

T_i = duration of life of type-i cases

Equilibrium:

$$\underline{H}^* = \left(H_i^*\right)$$

$$R_0 = \rho(K)$$

$$\Downarrow$$

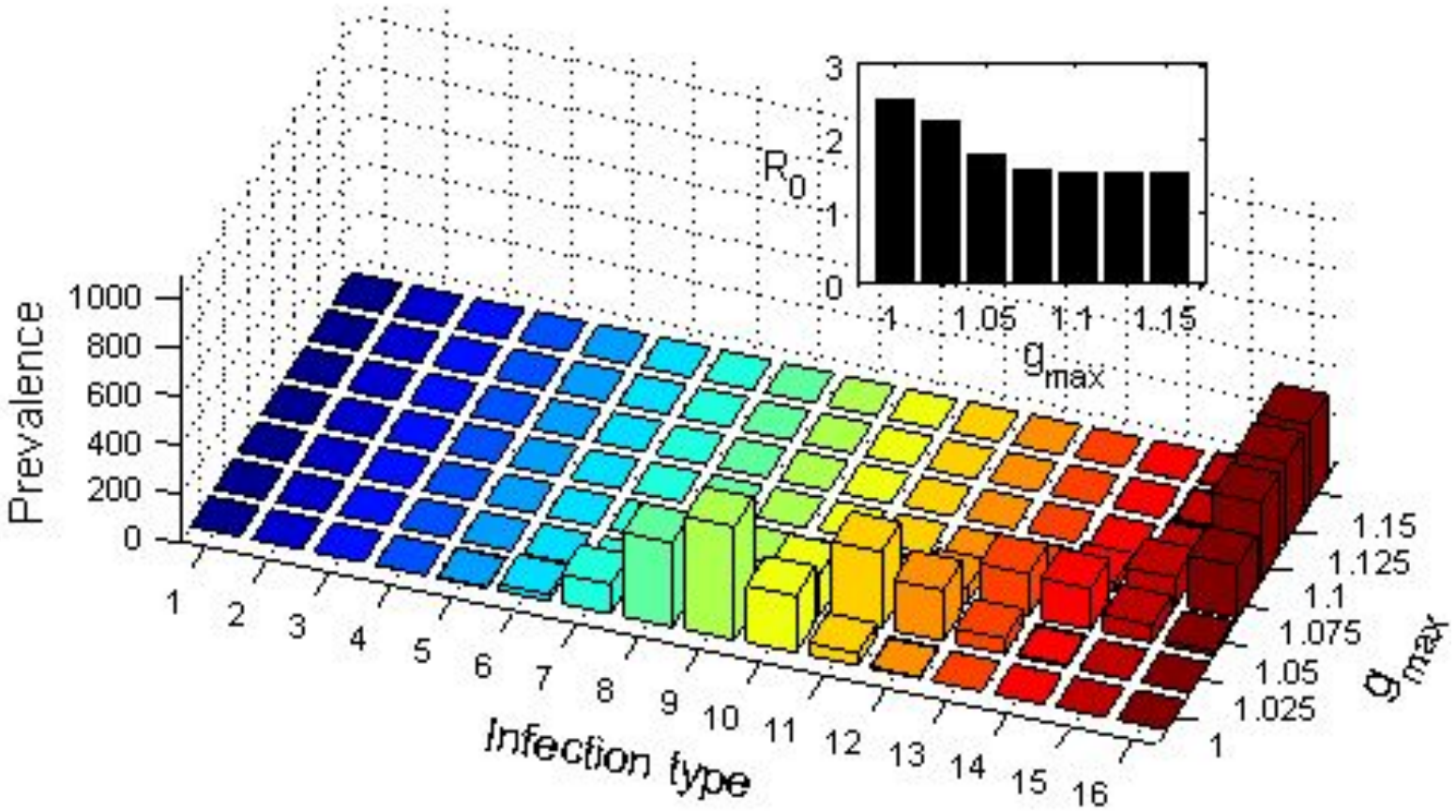
$$\underline{H}^* = \frac{S^*}{N^*} K \underline{H}^*$$

$$\frac{S^*}{N^*} = \frac{1}{R_0}$$

$$\underline{H}^* = v(K)$$

$$K = \left(k_{ij}\right) = \left(\int_0^{\infty} \beta_{ij}(\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau \right) = \text{Next-Generation Matrix}$$

Equilibria


Prevalence
1000
800
600
400
200
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Infection type
1.15
1.125
1.1
1.075
1.05
1.025
1
g_{max}
R_0
3
2
1
0
1
1.05
1.1
1.15
g_{max}

Overview of assumptions

MANCHESTER 1824
The University of Manchester

- Structural assumptions:
  - No external events
  - No superinfection

Equations of Example 2

Dynamics:

$$H_i(t) = \frac{S(t)}{N(t)} \sum_{j=1}^{n} \int_0^{T_j} \beta_{ij}(\tau) H_j(t-\tau) e^{-\mu\tau} \, d\tau$$

$$S(t) = N(t) - \sum_{i=1}^{n} \int_0^{T_i} H_i(t-\tau) e^{-\mu\tau} \, d\tau$$

$$\frac{dN(t)}{dt} = B - \mu N(t) - \sum_{i=1}^{n} H_i(t-T_i) e^{-\mu T_i}$$

$H_i(t) =$ incidence of type-i cases

$T_i =$ duration of life of type-i cases

Equilibrium:

$$\underline{H}^* = \left(H_i^*\right)$$

$$R_0 = \rho(K)$$

$$\Downarrow$$

$$\underline{H}^* = \frac{S^*}{N^*} K \underline{H}^*$$

$$\frac{S^*}{N^*} = \frac{1}{R_0}$$

$$\underline{H}^* = v(K)$$

$$K = \left(k_{ij}\right) = \left(\int_0^{\infty} \beta_{ij}(\tau) e^{-\mu\tau} \, d\tau \right) = \text{Next-Generation Matrix}$$

Lythgoe*, Pellis* & Fraser (2013), Evolution

Overview of assumptions

MANCHESTER 1824
The University of Manchester

- Structural assumptions:
  - No external events
  - No superinfection
- Implications:
  - Can use a time-since-infection framework
  - Can use a next-generation matrix (NGM) approach
  - Within- and between-host levels are linked
  - But no “full” feedback loop (no evolving population immunity)

Overview of assumptions

The University of Manchester

- Structural assumptions:
  - No external events
  - No superinfection
- Implications:
  - Can use a time-since-infection framework
  - Can use a next-generation matrix (NGM) approach
  - Within- and between-host levels are linked
  - But no “full” feedback loop (no evolving population immunity)
- Other assumptions that may be relaxed:
  - Single-virion infection (easy)
  - All-identical susceptibles (hard)

Equations of Example 2

Dynamics:

$$H_i(t) = \frac{S(t)}{N(t)} \sum_{j=1}^{n} \int_0^{T_j} \beta_{ij}(\tau) H_j(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$S(t) = N(t) - \sum_{i=1}^{n} \int_0^{T_i} H_i(t-\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau$$

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = B - \mu N(t) - \sum_{i=1}^{n} H_i(t-T_i) \mathrm{e}^{-\mu T_i}$$

$H_i(t) =$ incidence of type-i cases

$T_i =$ duration of life of type-i cases

$$K = \left(k_{ij}\right) = \left(\int_0^{\infty} \beta_{ij}(\tau) \mathrm{e}^{-\mu\tau} \, \mathrm{d}\tau \right) = \text{Next-Generation Matrix}$$

Equilibrium:

$$\underline{H}^* = \left(H_i^*\right)$$

$$R_0 = \rho(K)$$

$$\Downarrow$$

$$\underline{H}^* = \frac{S^*}{N^*} K \underline{H}^*$$

$$\frac{S^*}{N^*} = \frac{1}{R_0}$$

$$\underline{H}^* = v(K)$$

Lythgoe*, Pellis* & Fraser (2013), Evolution

OPEN CHALLENGES

Nested models

- Names: “nested”, “immuno-epidemiological”, “Within-between-host”
- Can always be constructed, as long as WH dynamics allow the construction of a between-host (BH) transmission rate $\beta(\tau)$
- They can be written as PDEs or DDEs/integral equations
- Caveat:
  - Most of the time they *assume* such the between-scale link (e.g., pathogen load and transmission rate)

- *Agreed terminology? Definition of “nested” model?*
- *Any benefit of using PDEs rather than DDEs?*
- *Experimental studies of between-scale links?*

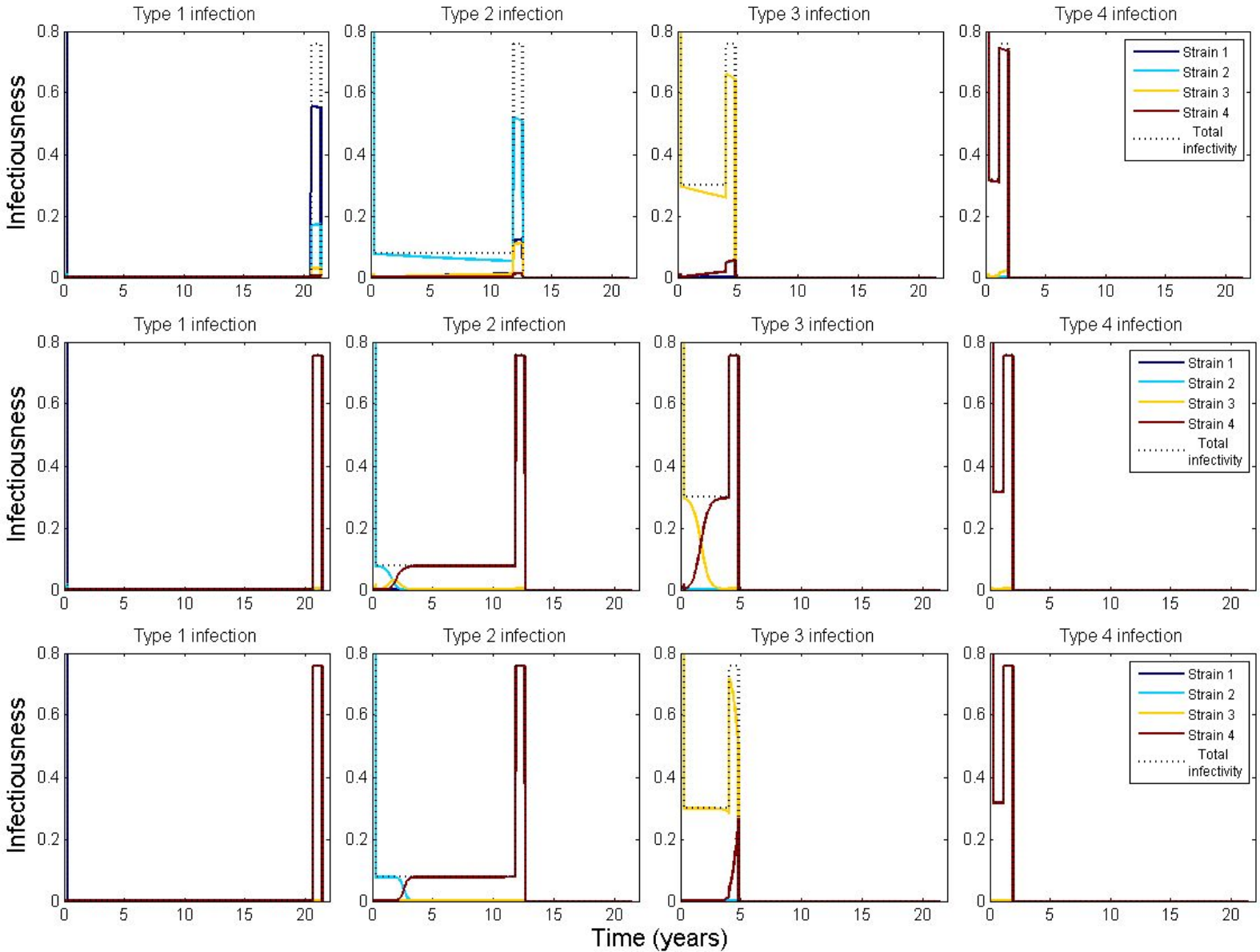
Generation time for complex models?

The University of Manchester

Flat

Hill-climb

Rugged



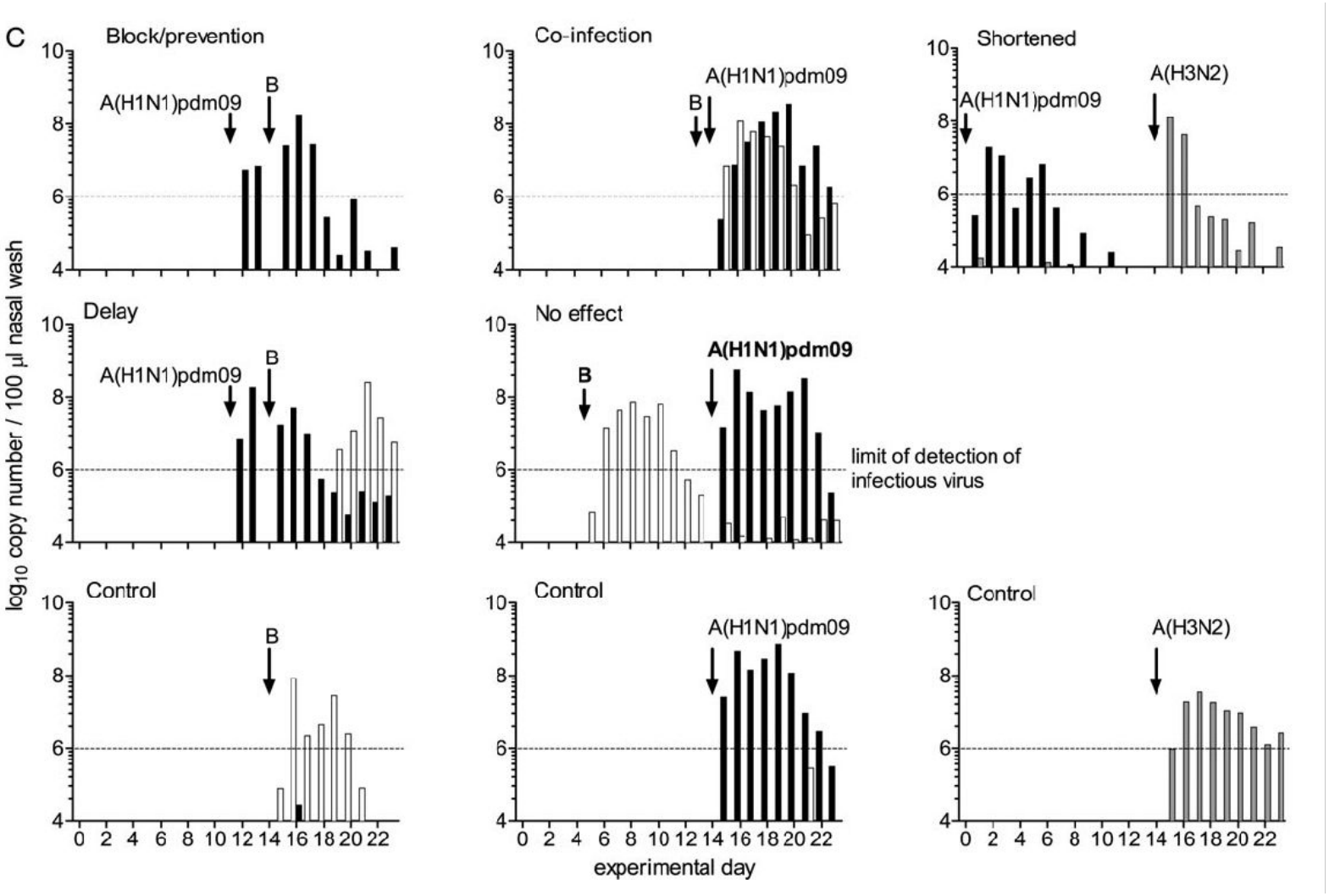
Reinfection

- Second infection after recovery, affected by past disease history
- Difficult: both population infectivity *and* susceptibility determine new cases
- Main reason: understanding the ecology of influenza:
  - Julia Gog
  - Viggo Andreasen
  - Adam Kucharski
- Problems:
  - With many strains, curse of dimensionality
  - Strong assumptions to reduce dimensions, e.g. past history does not reduce susceptiblity, or does not reduce infectivity
  - All ODE-based
  - Limited to acute infections

Superinfection

- A second infection before the first is “complete”
- Why do we need it?
  - Chronic infections (e.g. HIV, HCV)
  - HIV has high superinfection rates [**Redd** *et al.* (2014), *JID* and (2014), *AIDS*]
  - Data is becoming available [**Laurie** *et al.* (2015), *JID* and (2017), *JID*]
- Same problems as reinfection, but in addition:
  - Timing is probably very important
  - The TSI framework falls apart, i.e. WH evolution non-autonomous
  - Unclear usefulness of NGM, or even of R_0
  - All ODE-based
  - Limited to acute infections

Superinfection data



Laurie *et al* (2015), *JID*

Superinfection

- A second infection before the first is “complete”
- Why do we need it?
  - Chronic infections (e.g. HIV, HCV)
  - HIV has high superinfection rates [**Redd** *et al.* (2014), *JID* and (2014), *AIDS*]
  - Data is becoming available [**Laurie** *et al.* (2015), *JID* and (2017), *JID*]
- Same problems as reinfection, but in addition:
  - Timing is probably very important
  - The TSI framework falls apart, i.e. WH evolution non-autonomous
  - Unclear usefulness of NGM, or even of R_0
  - All ODE-based
  - Limited to acute infections

Summary

- The concept of generation time distribution is strongly linked with time-since-infection models

TSI harder than ODEs, but have some benefits:

- Useful for multi-scale / within- and between-host models
  - Probably more useful for chronic infections
- Useful when shape of infectivity profile is key. For COVID-19, e.g.
  - Contact tracing
  - Optimal timing of testing to keep infection out of closed settings
- Challenges:
  - The link between the two scales is almost always assumed
  - Concept of generation-time for complex models, e.g. multi-strain
  - TSI with reinfection / superinfection

Acknowledgements

KatrinaLythgoe Christophe Fraser Francois Blanquart Andrea Pugliese

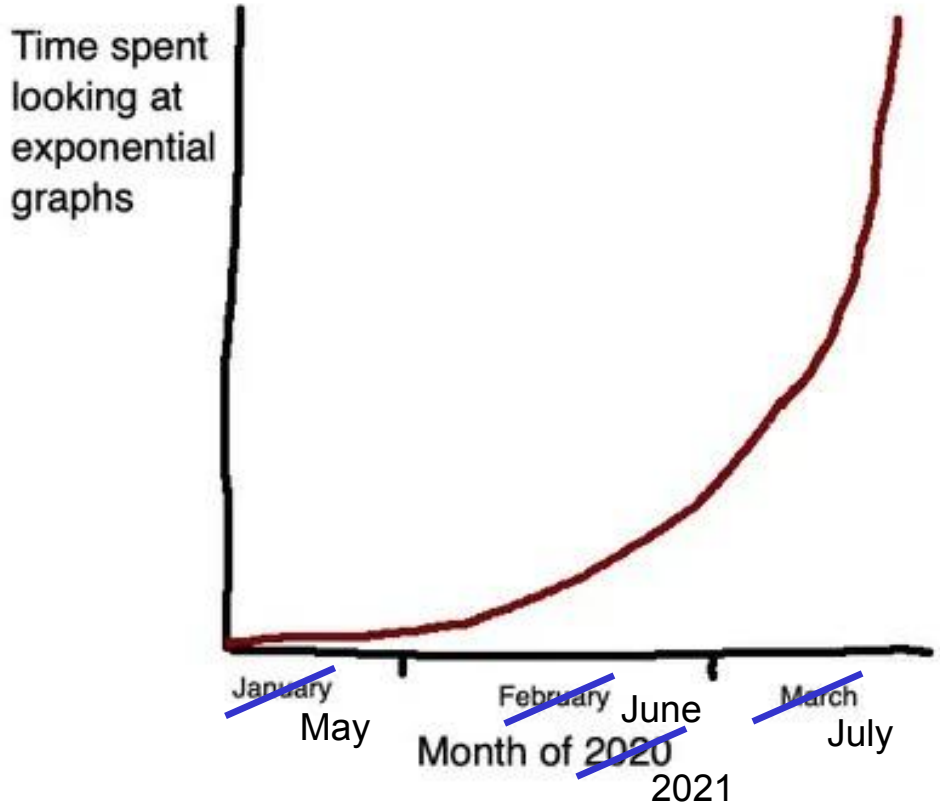



Helena Stage Chris Overton Francesca Scarabel



wellcome THE ROYAL SOCIETY MRC Medical Research Council EPSRC Engineering and Physical Sciences Research Council JUNIPER

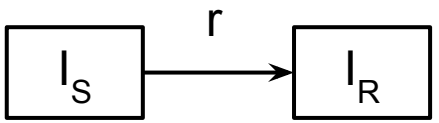
Acknowledgements



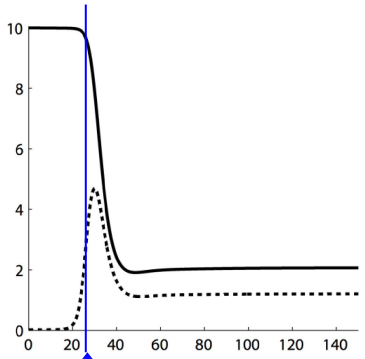
Thank you

Limitations of ODEs

- ODEs are extremely useful and easy to use
- But have many limitations:
  - Oversimplified emergence of resistance:



  - Time-scale separation argument:



  - Superinfection: