MαMoδ Africa

AIMS

Swiss TPH

Advanced infectious disease modeling

March 17 - March 26

lecture: 2-4 PM, problem session: 6-8PM

AIMS-Rwanda, Kigali

Christian Selinger, Swiss TPH

Christian's Agenda:

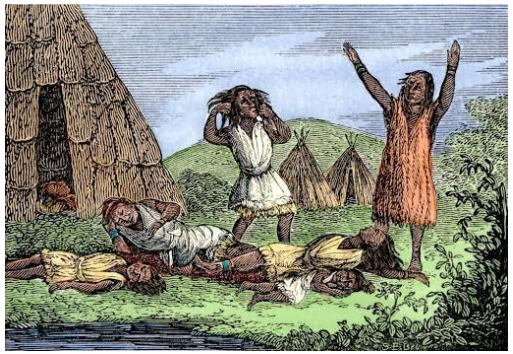
DATE	TITLE	CONTENT
Monday March 17, 2025	Malaria model parameters	Parameterizing and simulating ODE models of malaria in R
Tuesday March 18, 2025	R0	Basic reproduction number theory and examples
Wednesday March 19, 2025	R0	Sensitivity analysis for infectious disease models: gradients, Sobol index
Thursday March 20, 2025 (T,$)	Sensitivity analysis	Sensitivity analysis for infectious disease models: gradients, Sobol index
Friday March 21, 2025 (*)	Model fitting	Fitting model output curves to data using optimisation algorithms
WEEKEND BREAK		
Monday March 24, 2025	Statistical inference	Concepts of statistical inference (frequentist, Bayesian, maximum likelihood)
Tuesday March 25, 2025	Statistical inference	Bayesian updating, Monte Carlo integration
Wednesday March 26, 2025	Statistical inference	Monte Carlo integration
Wednesday March 26, 2025	Resistance modeling	bioinformatics meets disease modeling

(*) Quiz
($) Assignment

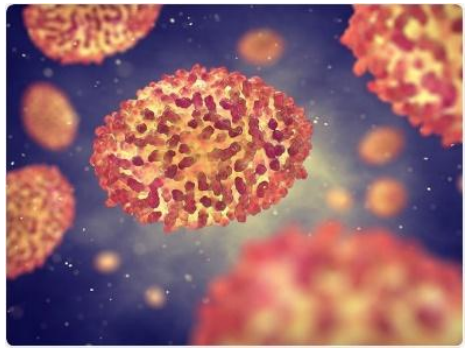
(T) Tutorial

Phenomenology – describing the invisible

Find the name of the pathogen!



Native populations in the Americas



220-450 nm

Acute infectious disease that begins with a high **fever**, headache, and back pain and then proceeds to an **eruption on the skin** that leaves the face and limbs covered with cratered marks.

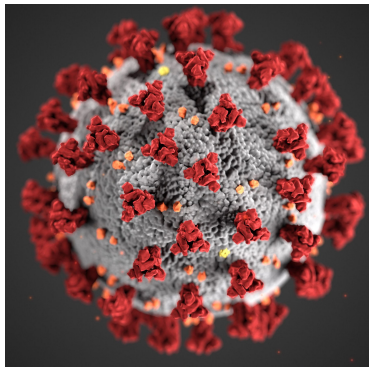
Encyclopedia Britannica

Smallpox virus

Phenomenology – describing the invisible

Find the name of the pathogen!

Manu Dibango



50-140 nm

Acute viral infection characterized primarily by fever and respiratory symptoms.

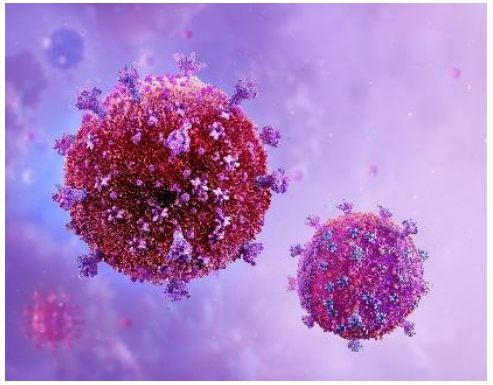
Encyclopedia Britannica

Severe Acute Respiratory Syndrome Coronavirus 2

Phenomenology – describing the invisible

Find the name of the pathogen!

Ervin Johnson



120 nm

Transmissible disease of the **immune system** caused by a virus that **slowly** attacks and destroys the immune system, the body's defense against infection, leaving an **individual vulnerable** to a variety of other infections and certain malignancies that eventually cause death.

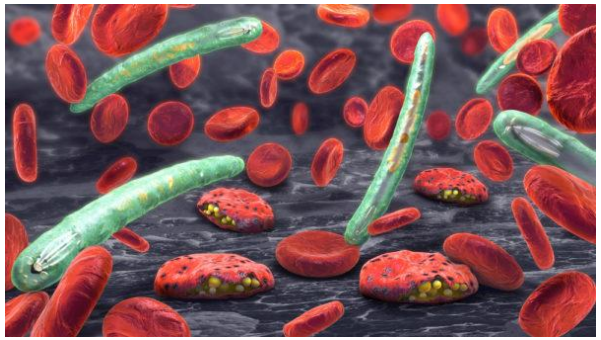
Encyclopedia Britannica

Human Immuno-deficiency Virus

Phenomenology – describing the invisible

Find the name of the pathogen!

Alexander the Great



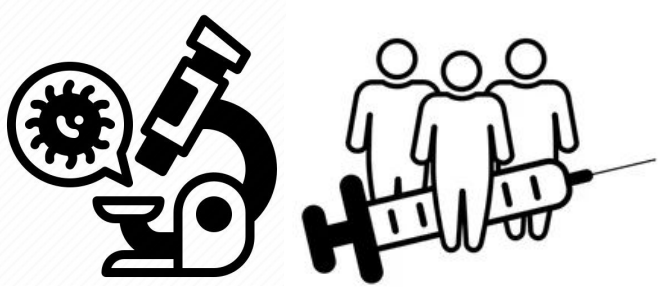
10000-15000 nm

Many of the early Greeks thought the disease was contracted by drinking swamp water; later, the Romans attributed it to **breathing vapours**, arising from bodies of stagnant water.

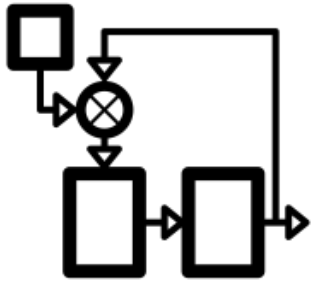
Encyclopedia Britannica

Plasmodium falciparum sporozoites
(and Red Blood Cells)

Modeling = a process where people from different worlds meet on a common ground

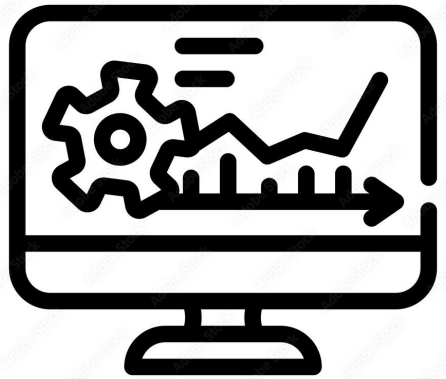


***biologist/epidemiologist/malaria program**:*
translate biological and population-level observations into flow diagrams



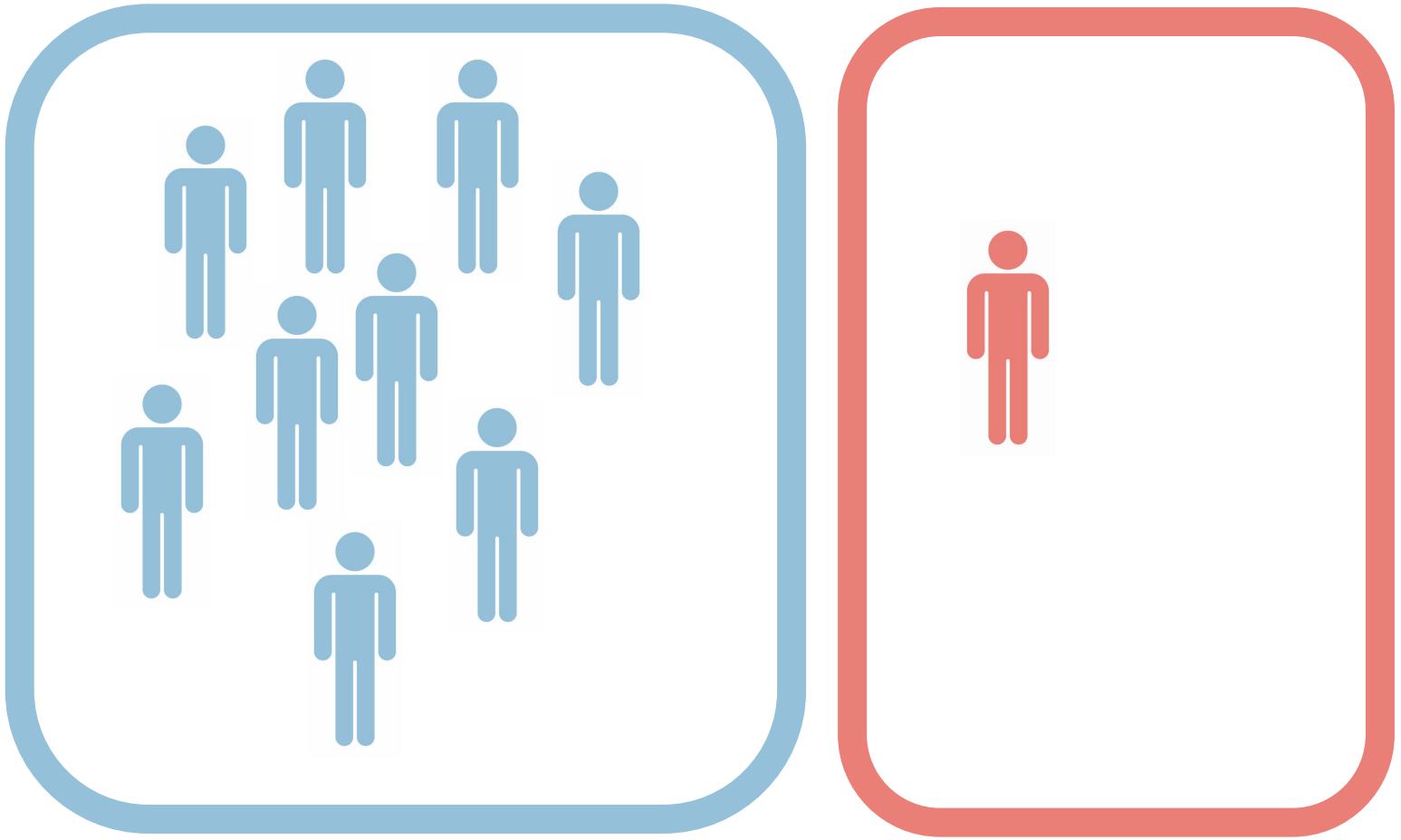
mathematician:
translates flow diagrams into equations

software engineer/computer science:
translates equations into computer code



Putting people into boxes - compartments

Contagion process - simplified



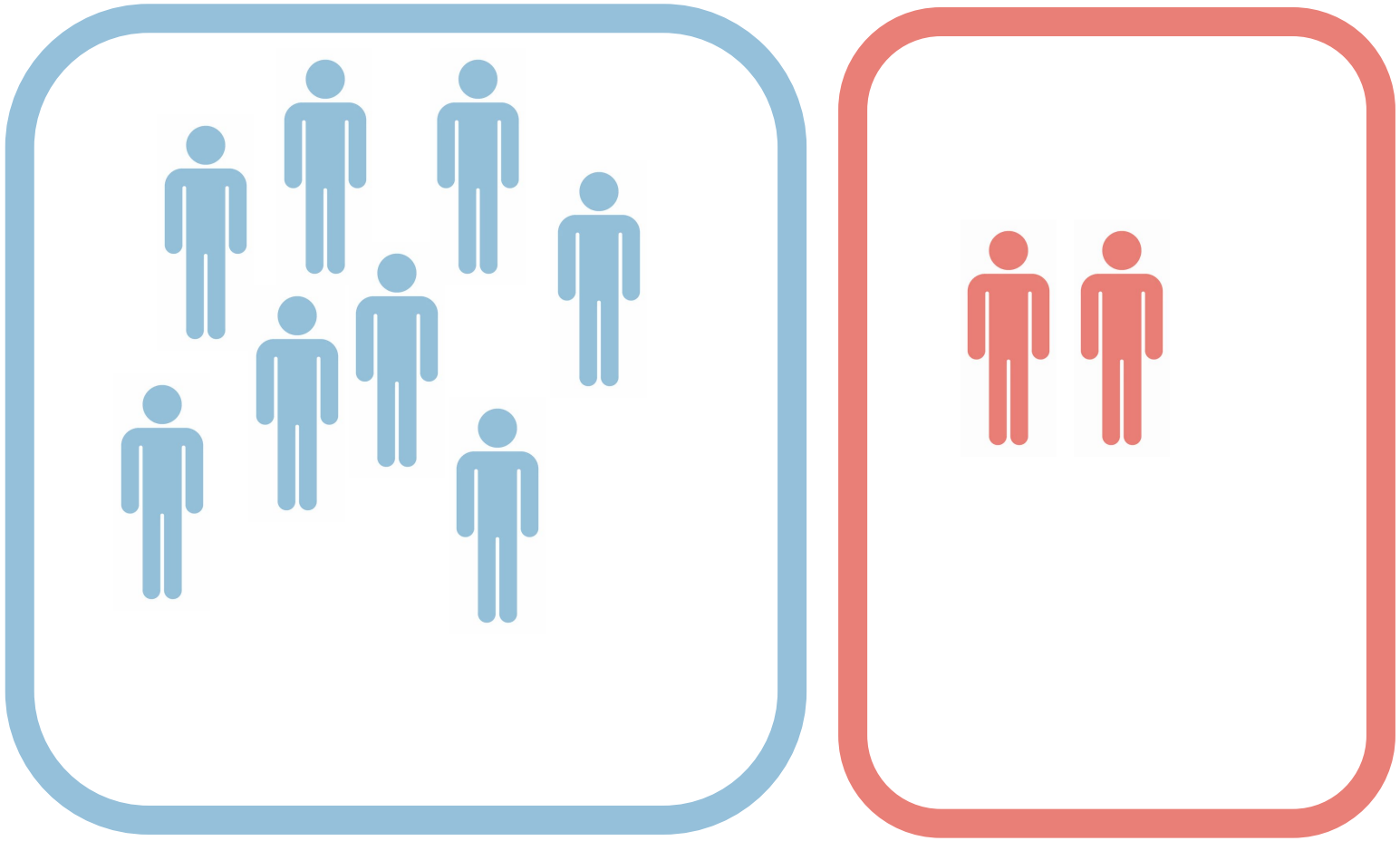
healthy: 9

sick: 1

day: 0

Putting people into boxes - compartments

Contagion process - simplified



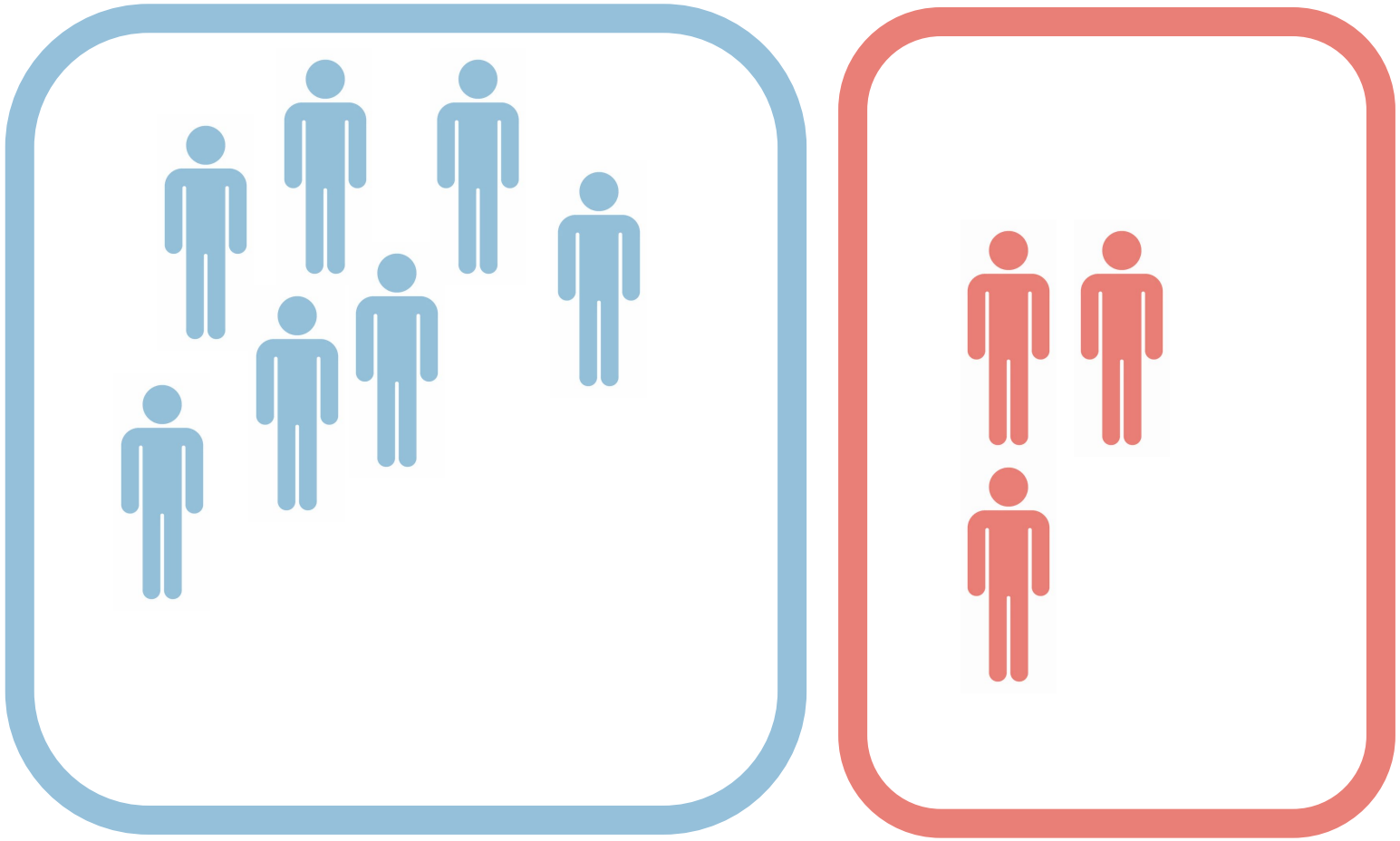
healthy: 8

sick: 2

day: 1

Putting people into boxes - compartments

Contagion process - simplified



healthy: 7

sick: 3

day: 2

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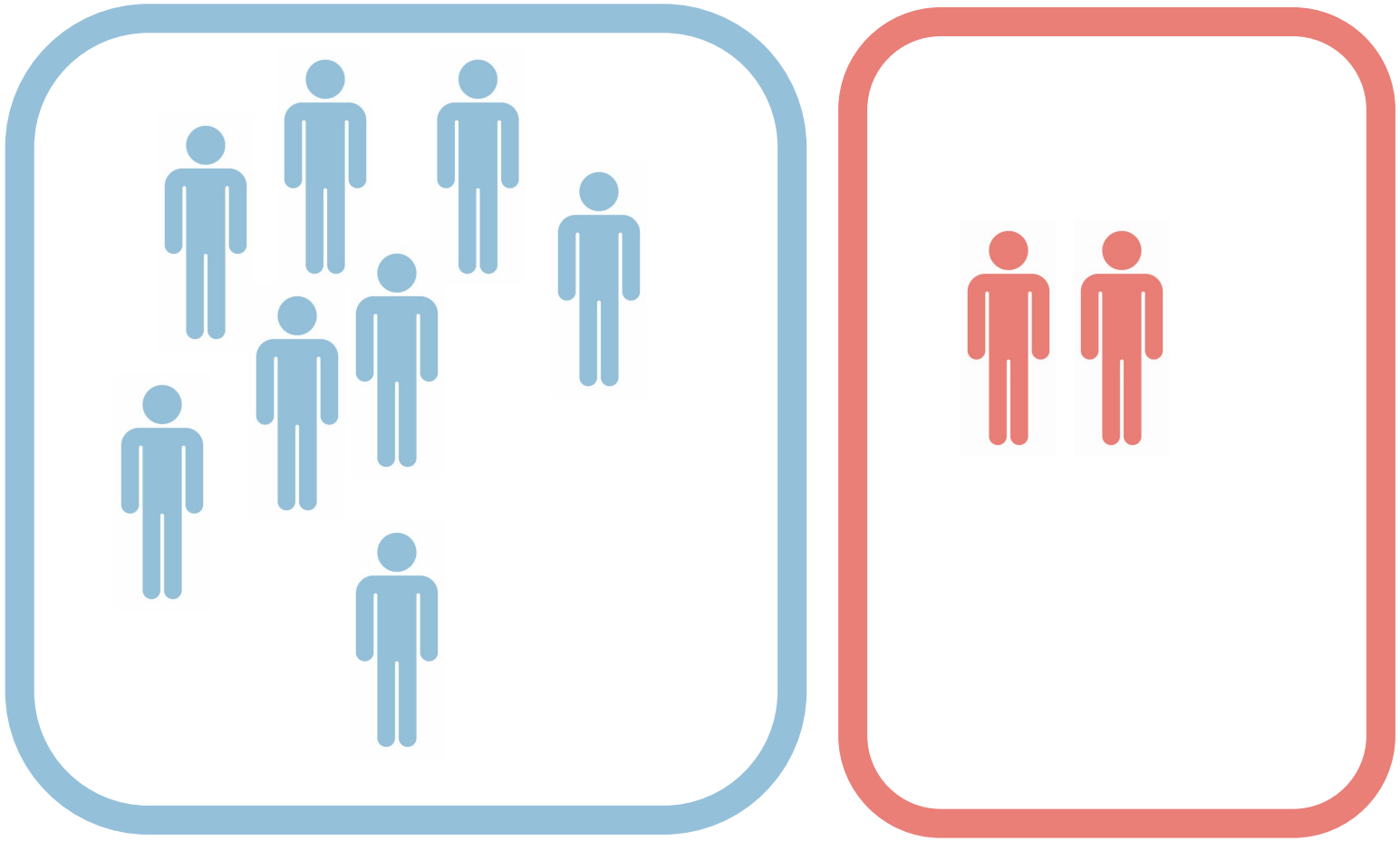

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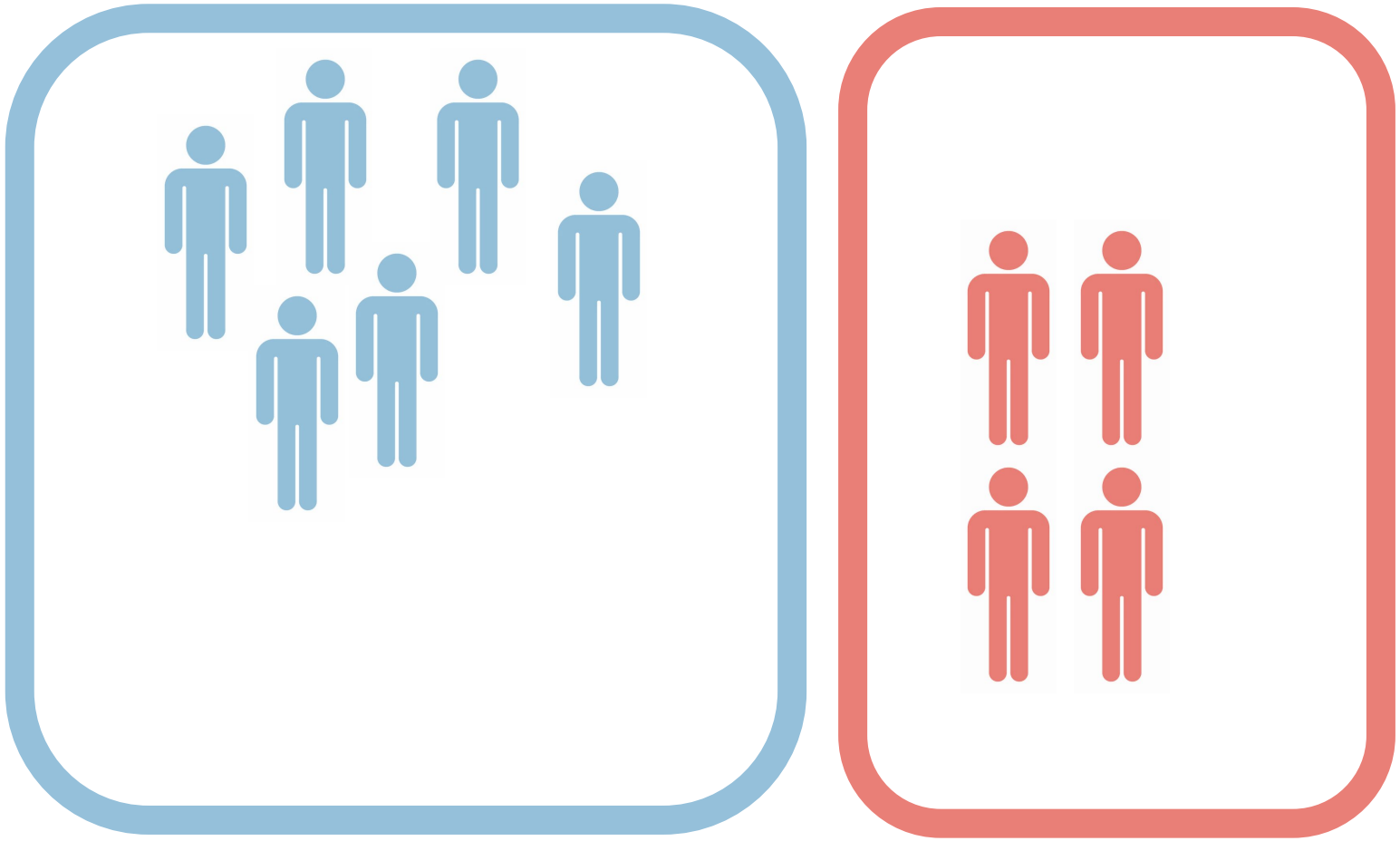


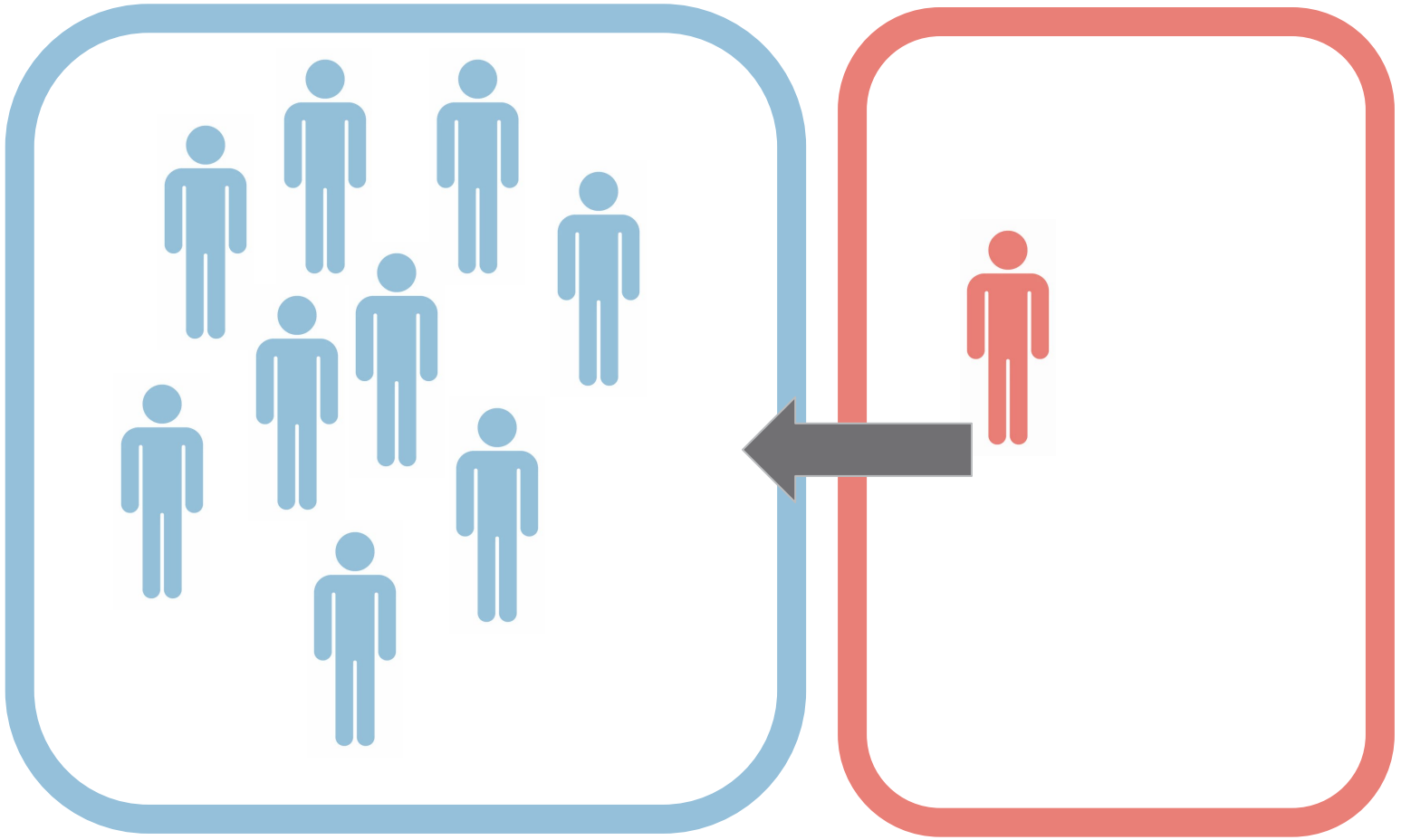
healthy: 6

sick: 4

day: 4

Transferring people between boxes - transitions

Contagion process - simplified



from sick to healthy
RECOVERY

depends **only** on **sick individual**

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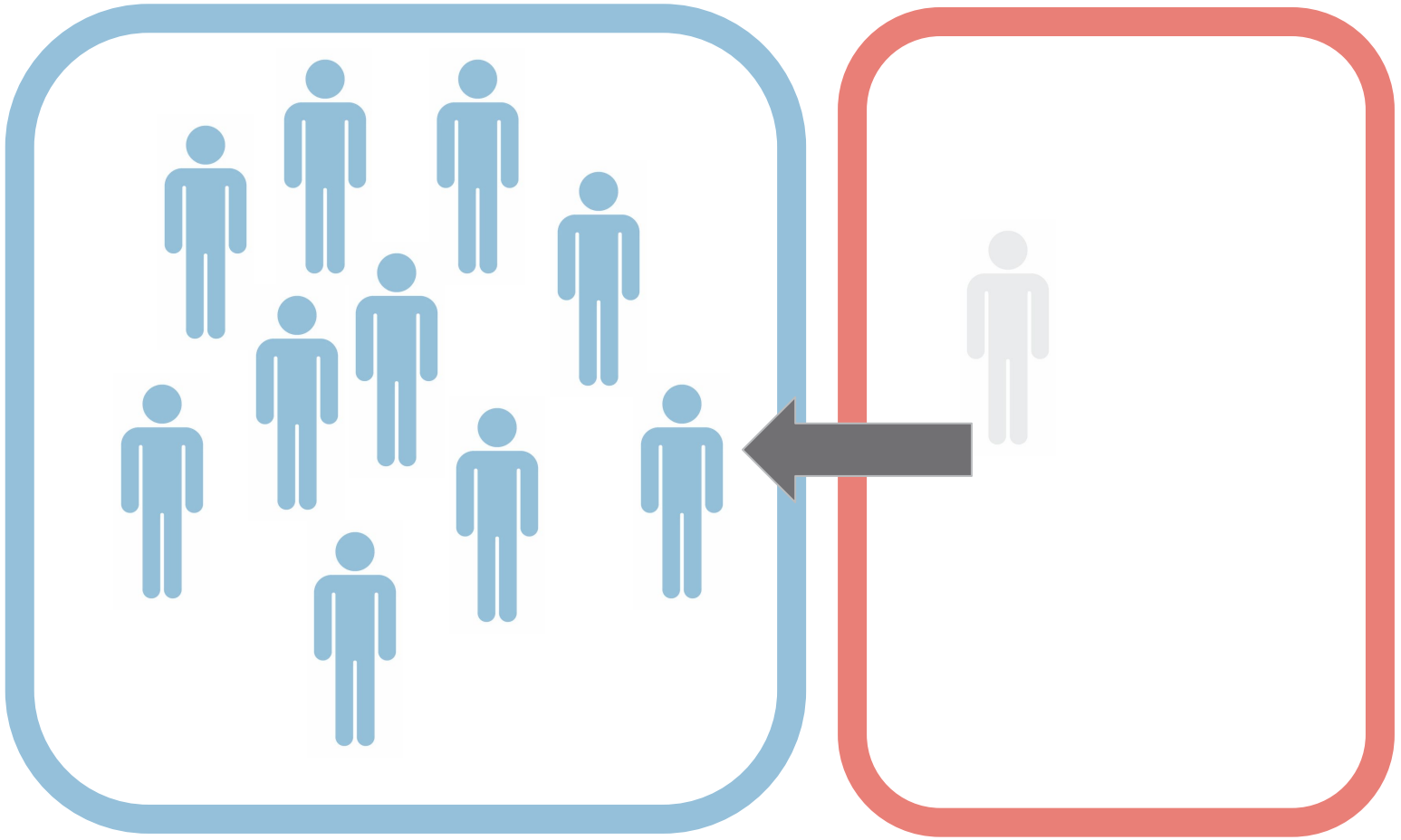
Transferring people between boxes - transitions

Contagion process - simplified



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Transferring people between boxes - transitions

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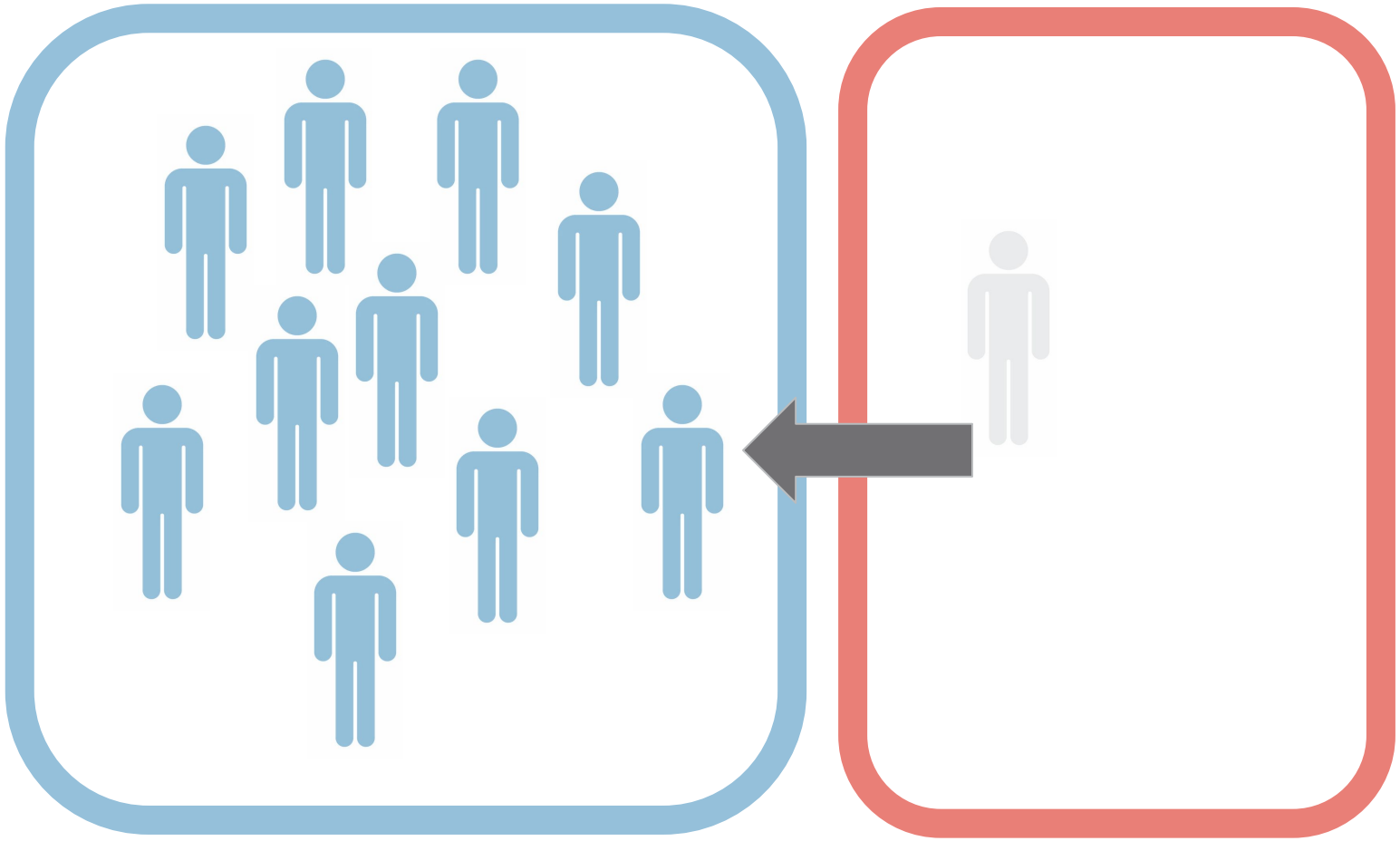

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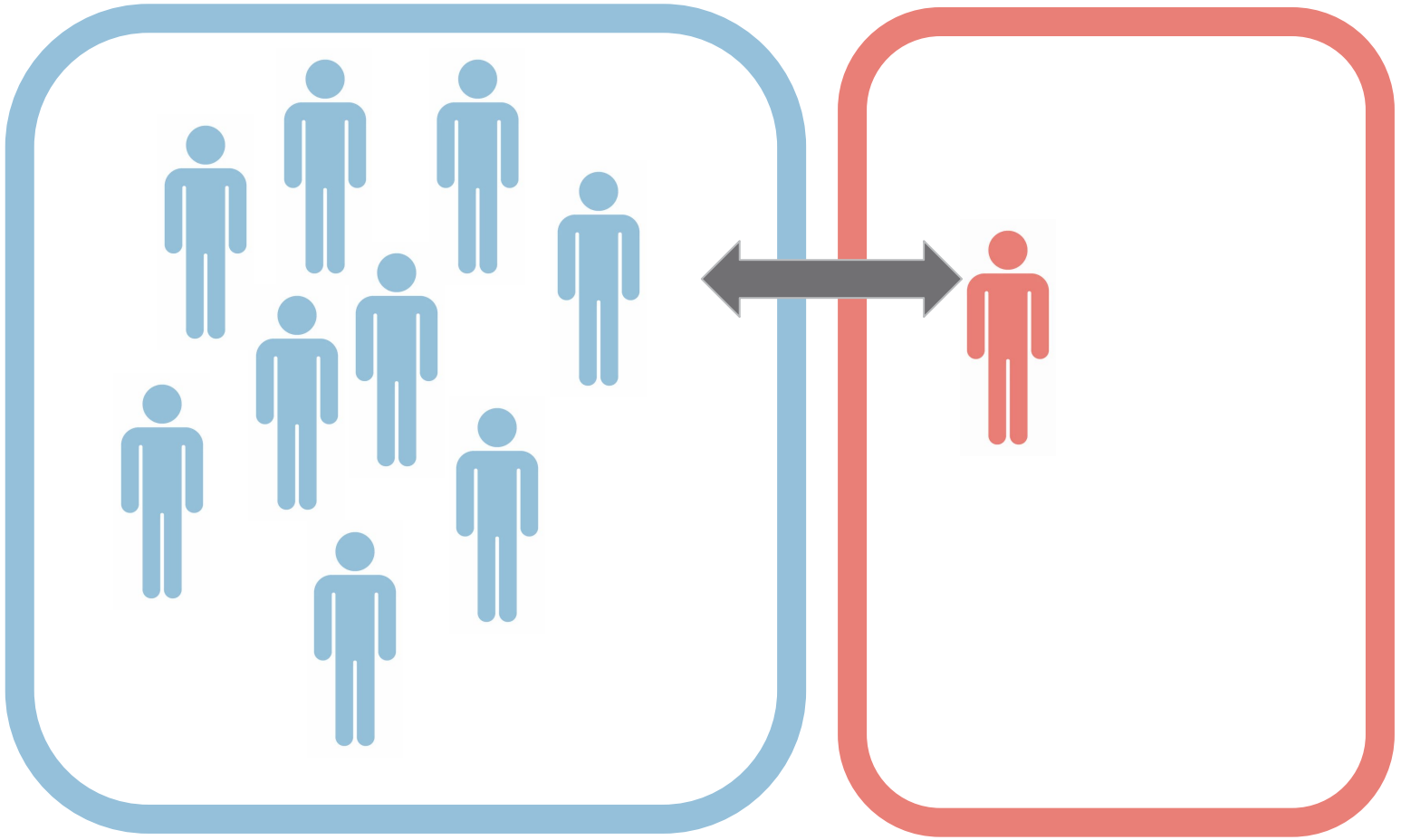
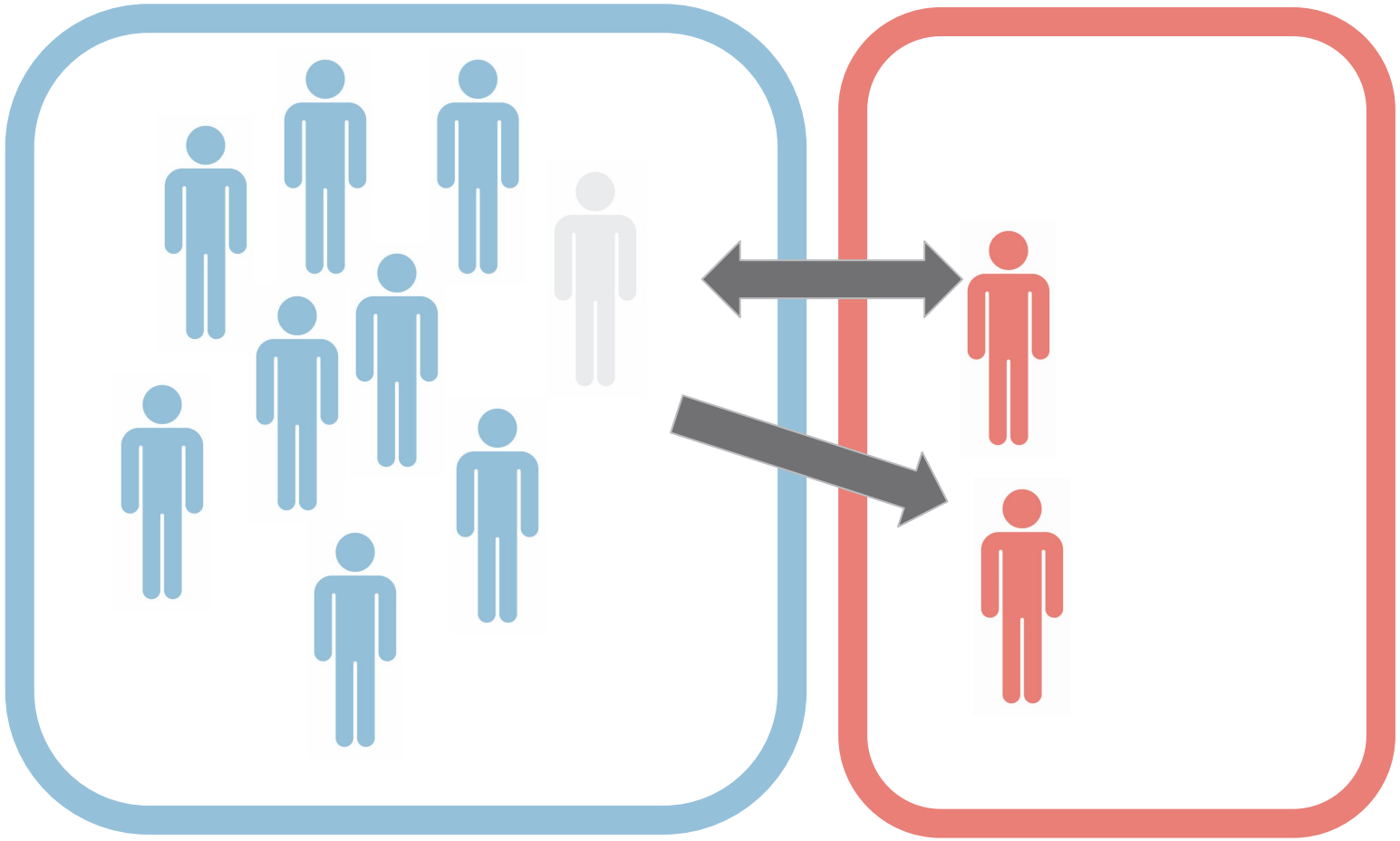


from healthy to sick
TRANSMISSION

depends on **encounter** between sick and healthy individual

Transferring people between boxes - transitions

Contagion process - simplified



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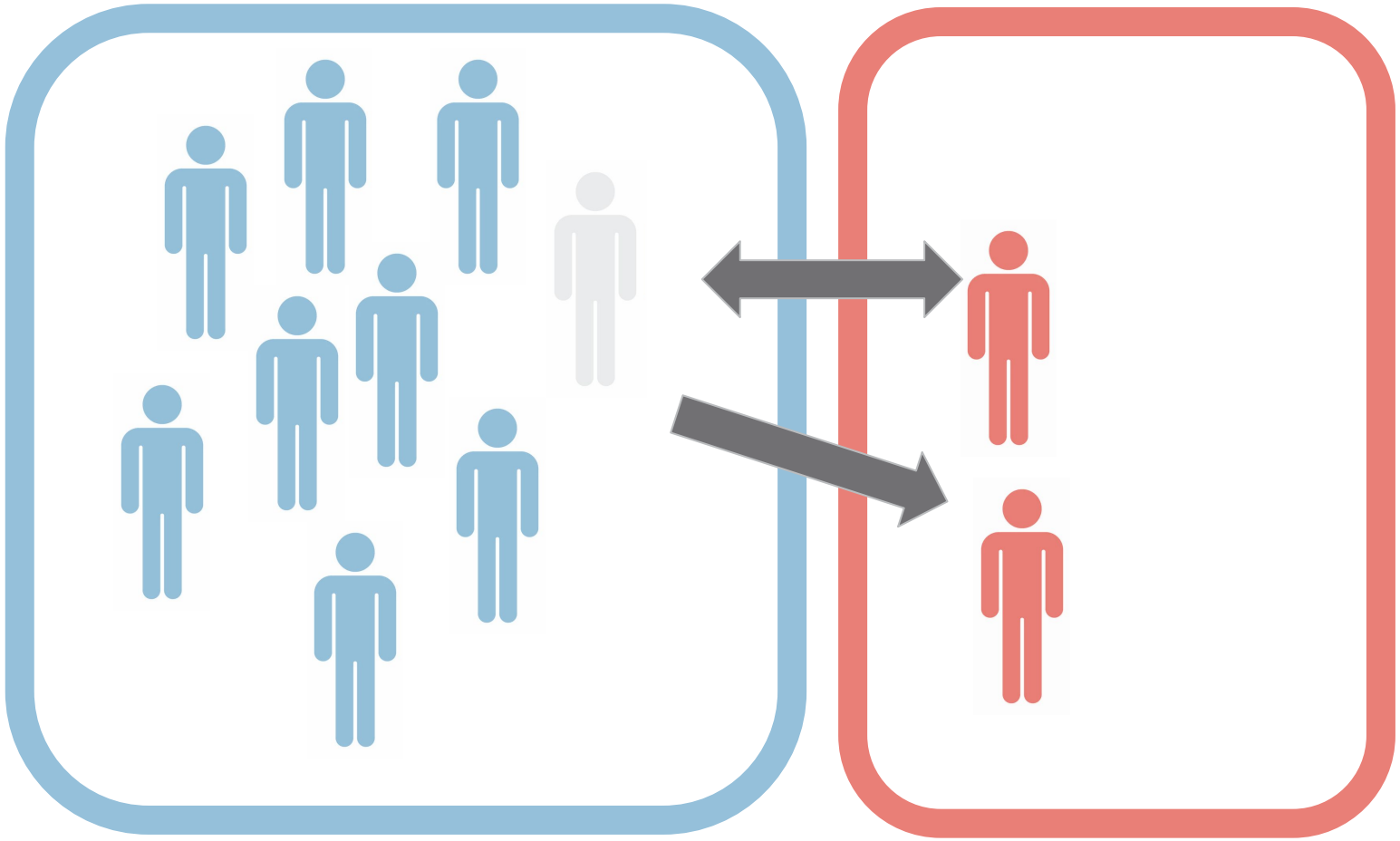

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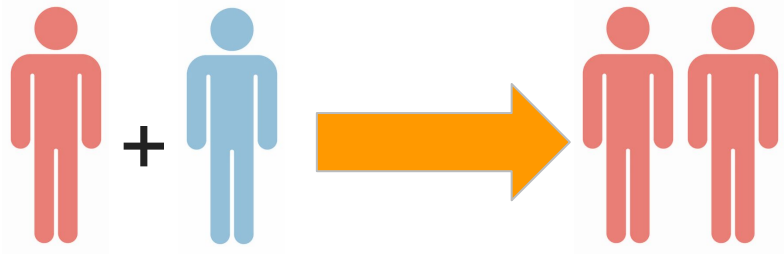
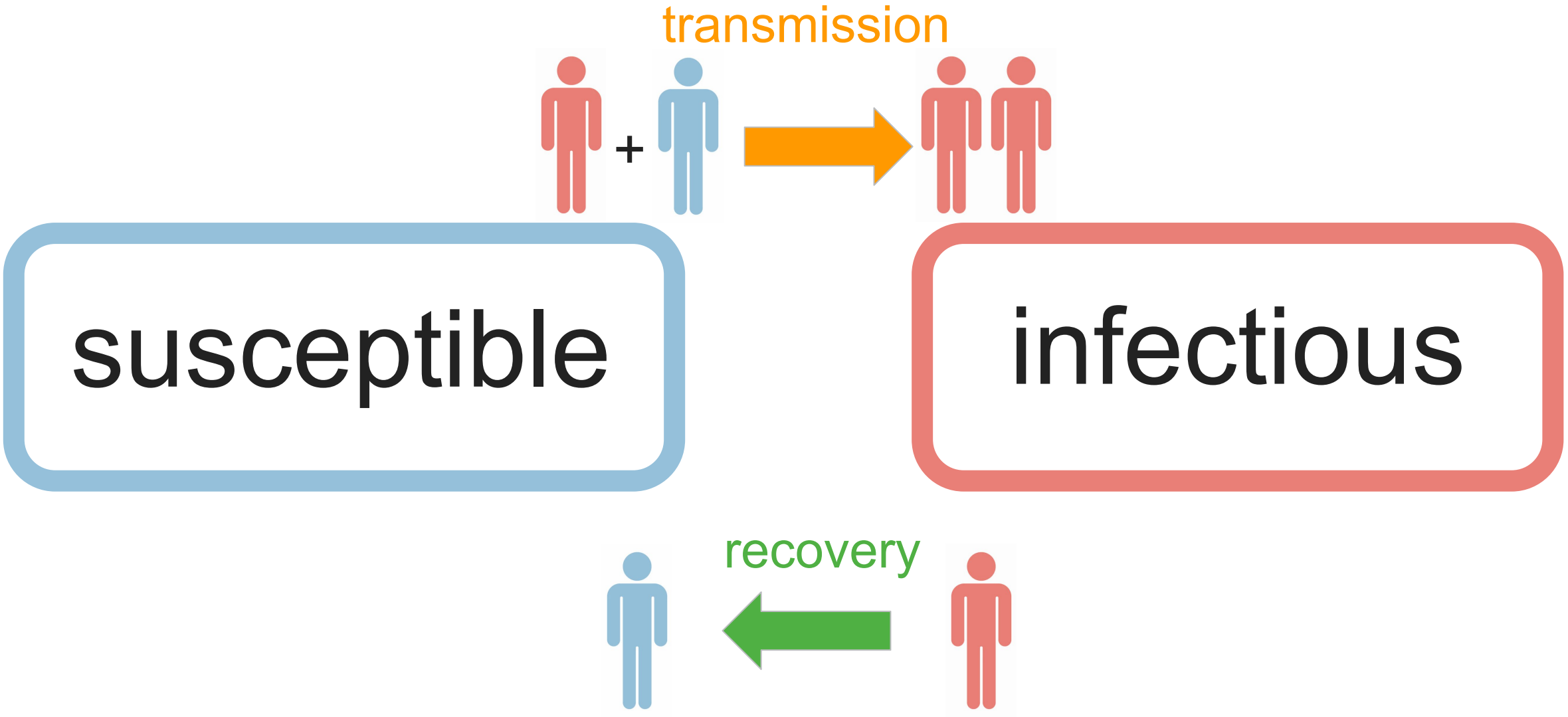


“transmission kernel”

Flow diagrams for disease transmission



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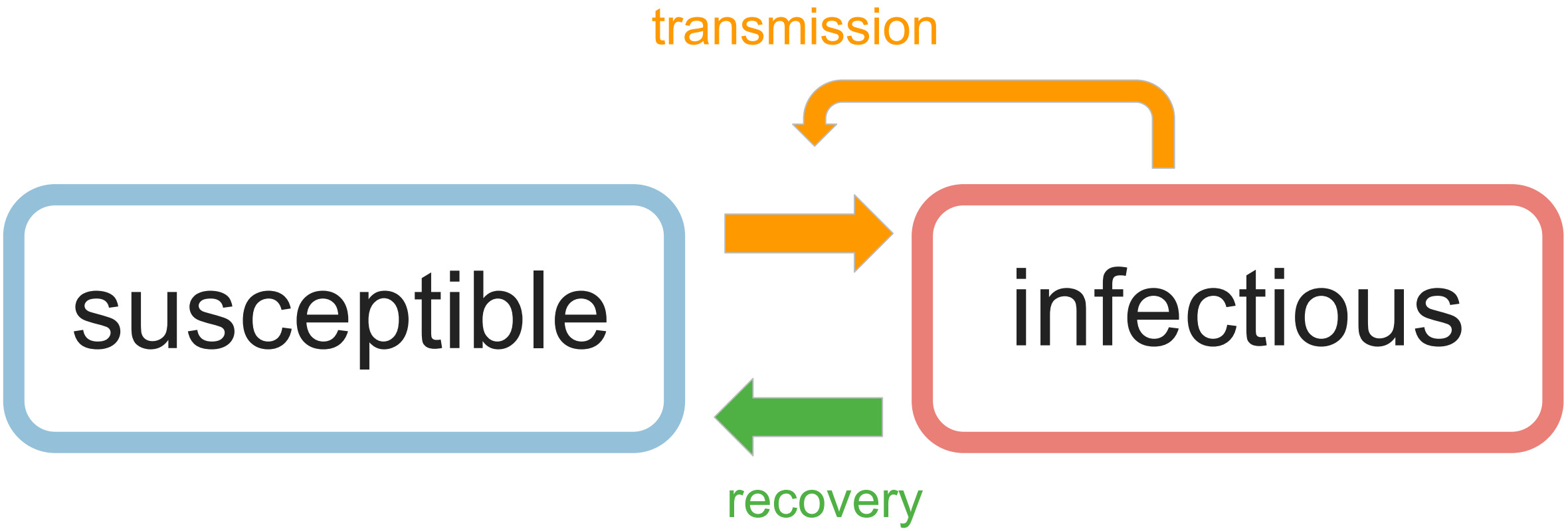

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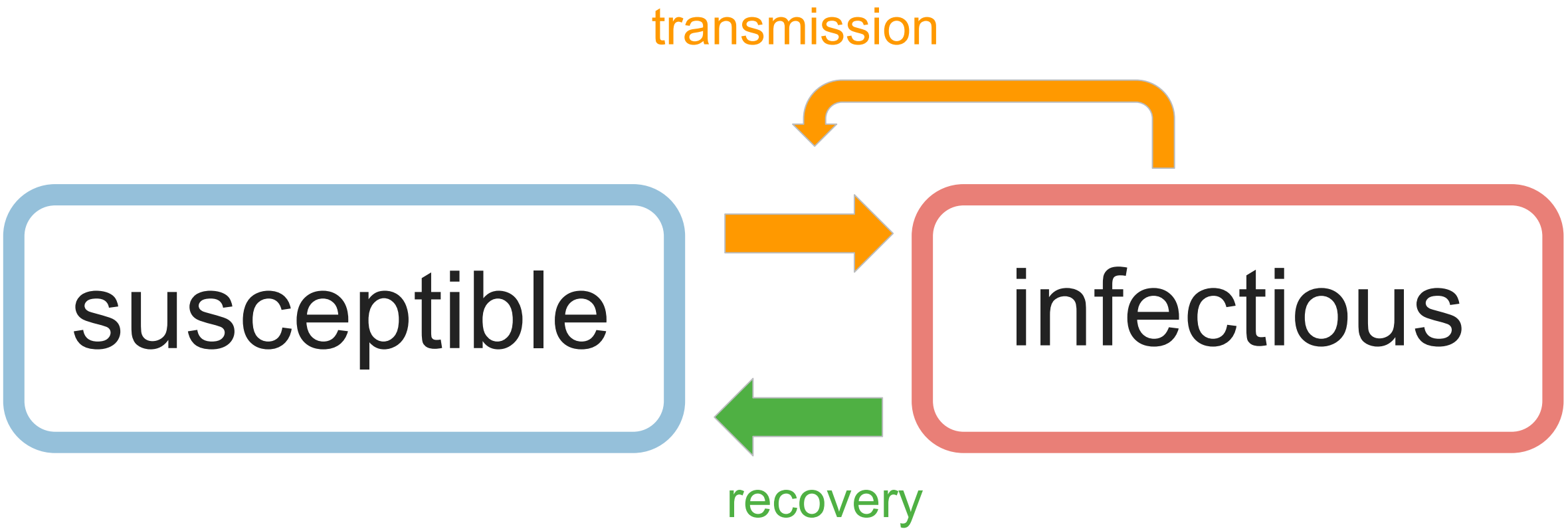

SIS model

Flow diagrams for disease transmission: assumptions!

We need to be clear about the underlying assumptions:

Hypothesis A: Individuals become immediately also infectious upon infection

Hypothesis B: There are no births or deaths in the population, there is no migration.

Hypothesis C: Once an individual recovers, it will become immediately susceptible again.

Hypothesis D: All susceptible hosts are equally likely to meet an infected host.

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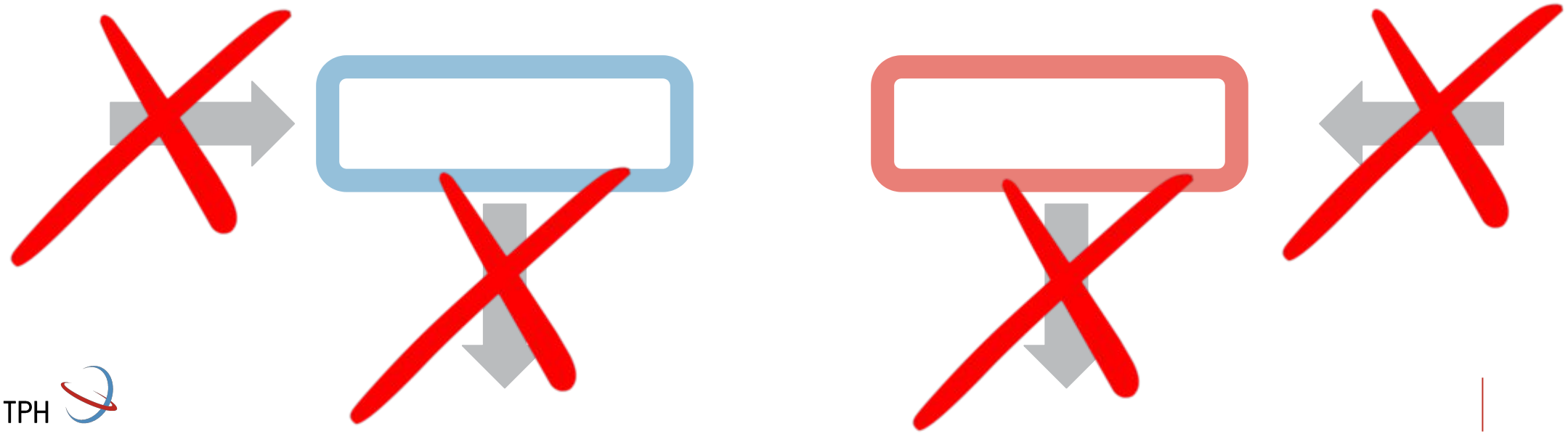

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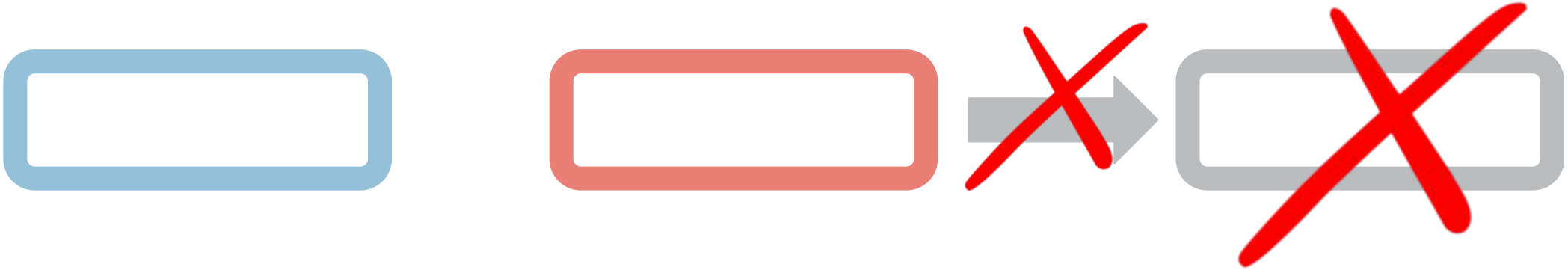

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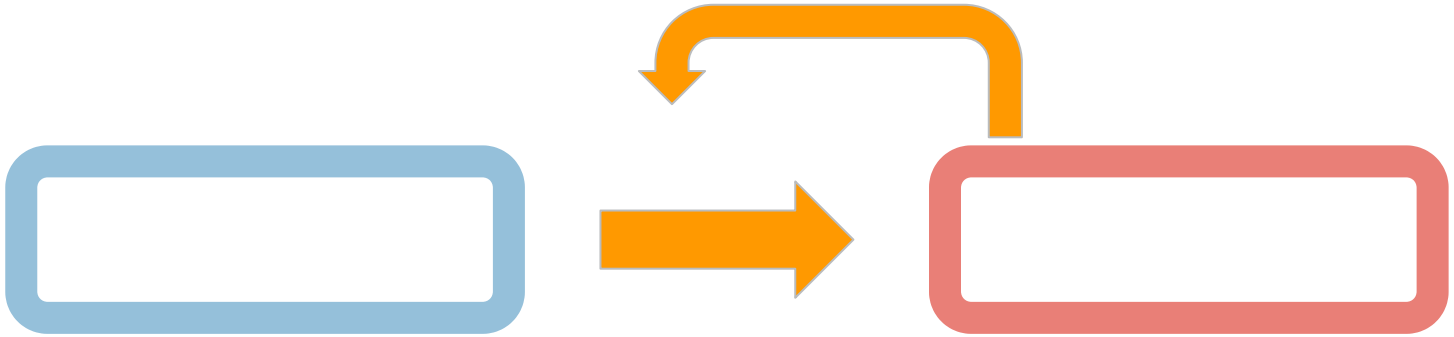
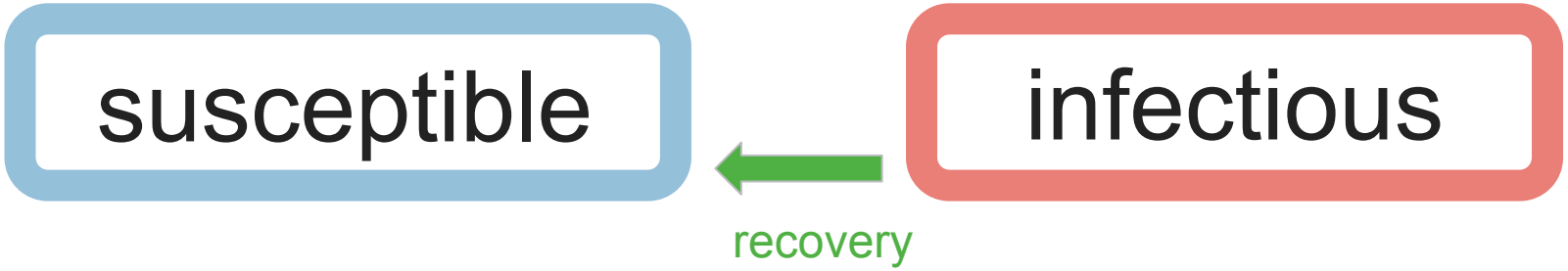
rate for new infection depends on relative proportion of infectious individuals



Flow diagrams as differential equations



inflow **into** susceptible

$$S(t+1) - S(t) = \gamma\, I(t)$$

outflow **from** infectious

$$I(t+1) - I(t) = -\gamma\, I(t)$$

What is γ ?

rate =expected number of events per time unit

Flow diagrams as differential equations

susceptible ← recovery — infectious

inflow **into** susceptible

$$S(t+1) - S(t) = \gamma\, I(t)$$

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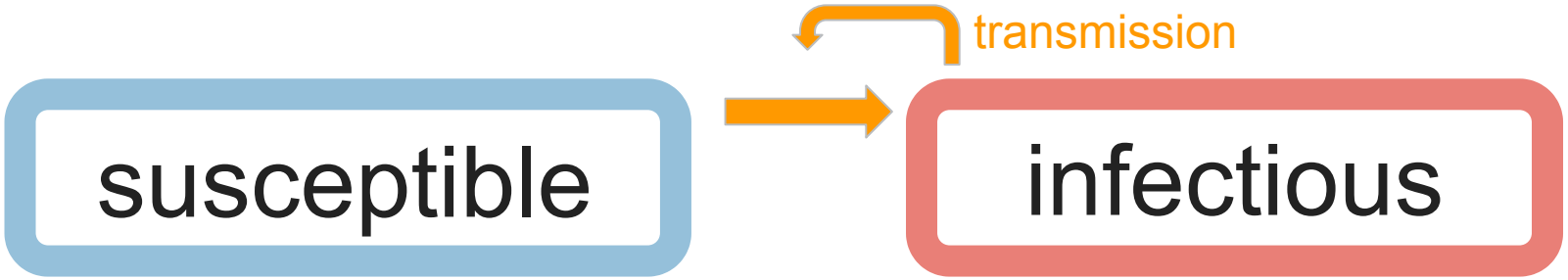


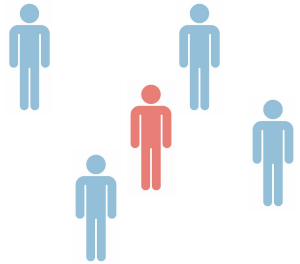
outflow **from** susceptible

$$S(t+1) - S(t) = -\beta \underbrace{\frac{I(t)}{S(t)+I(t)}} S(t)$$

probability of finding an infectious individual in the population

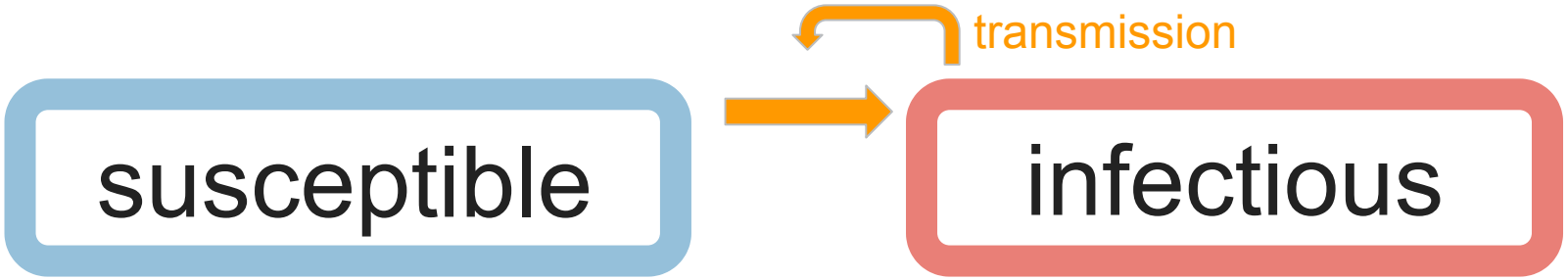
inflow **into** infectious

$$I(t+1) - I(t) = \beta \frac{I(t)}{S(t)+I(t)} S(t)$$



assumption: all individuals are well mixed

Flow diagrams as differential equations



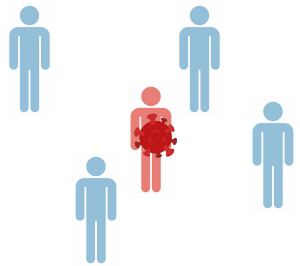
outflow **from** susceptible

$$S(t+1) - S(t) = -\beta \frac{I(t)}{S(t)+I(t)} S(t)$$

transmission rate

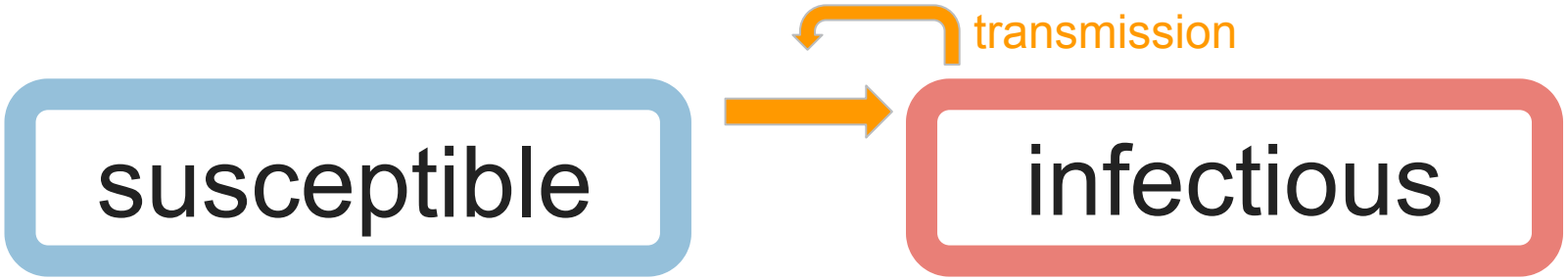
inflow **into** infectious

$$I(t+1) - I(t) = \beta \frac{I(t)}{S(t)+I(t)} S(t)$$



assumption: transmission is constant in time and across infectious individuals

Flow diagrams as differential equations



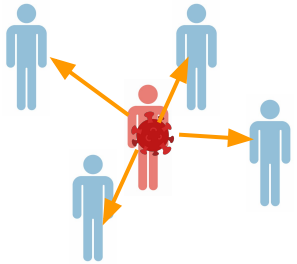
outflow **from** susceptible

$$S(t+1) - S(t) = -\beta \frac{I(t)}{S(t)+I(t)} S(t)$$

inflow **into** infectious

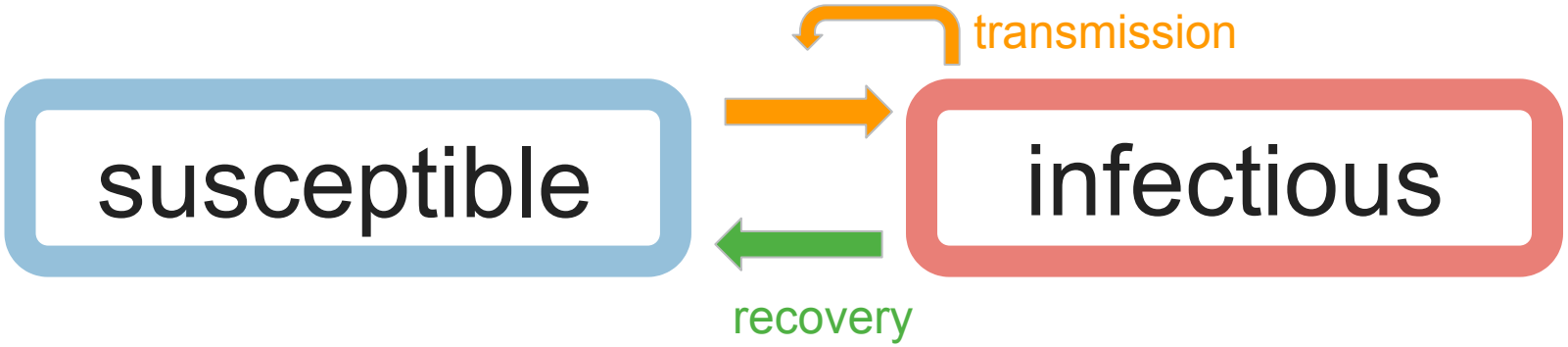
$$I(t+1) - I(t) = \beta \frac{I(t)}{S(t)+I(t)} S(t)$$

currently susceptible individuals

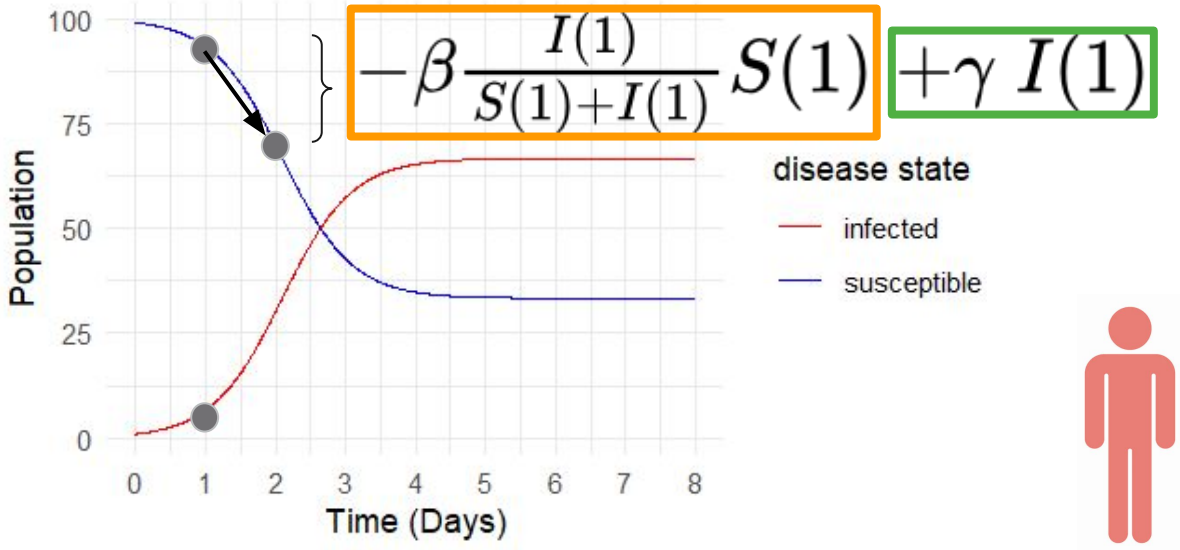


assumption: new infection happens **independently** and with **same probability** to each susceptible individual

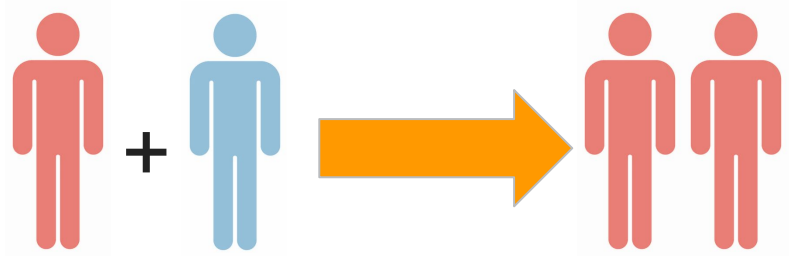
Flow diagrams as differential equations



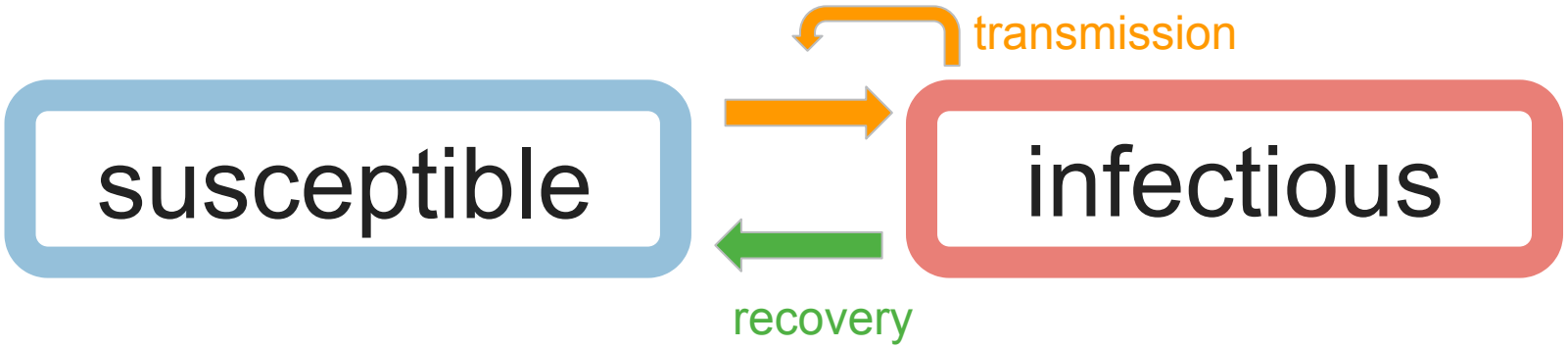
$$S(t+1) - S(t) = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t)$$



"coupled system"



Flow diagrams as differential equations



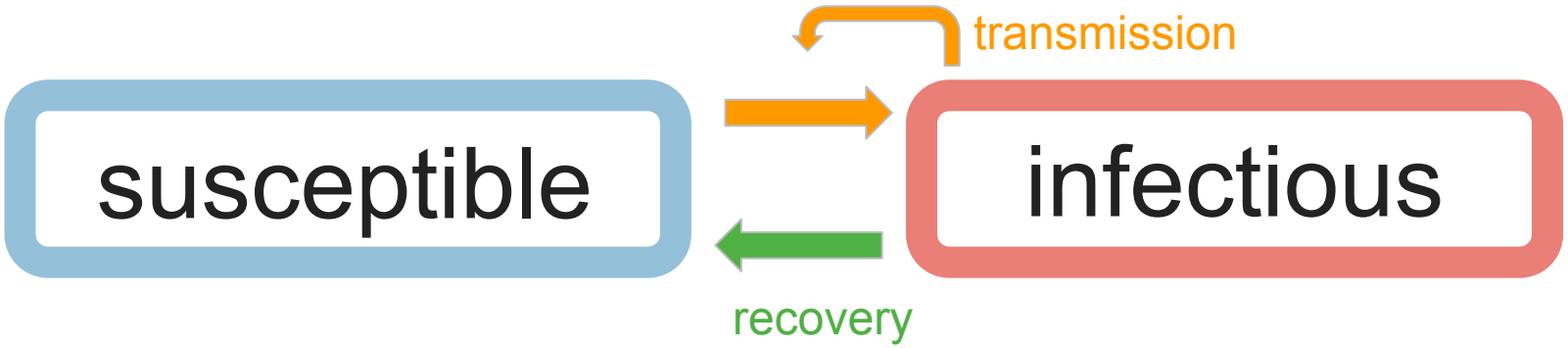
$$\begin{cases} \frac{S(t+\Delta)-S(t)}{\Delta} = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t) \\ \frac{I(t+\Delta)-I(t)}{\Delta} = \beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma\, I(t) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N$$

$$\Delta \to 0$$

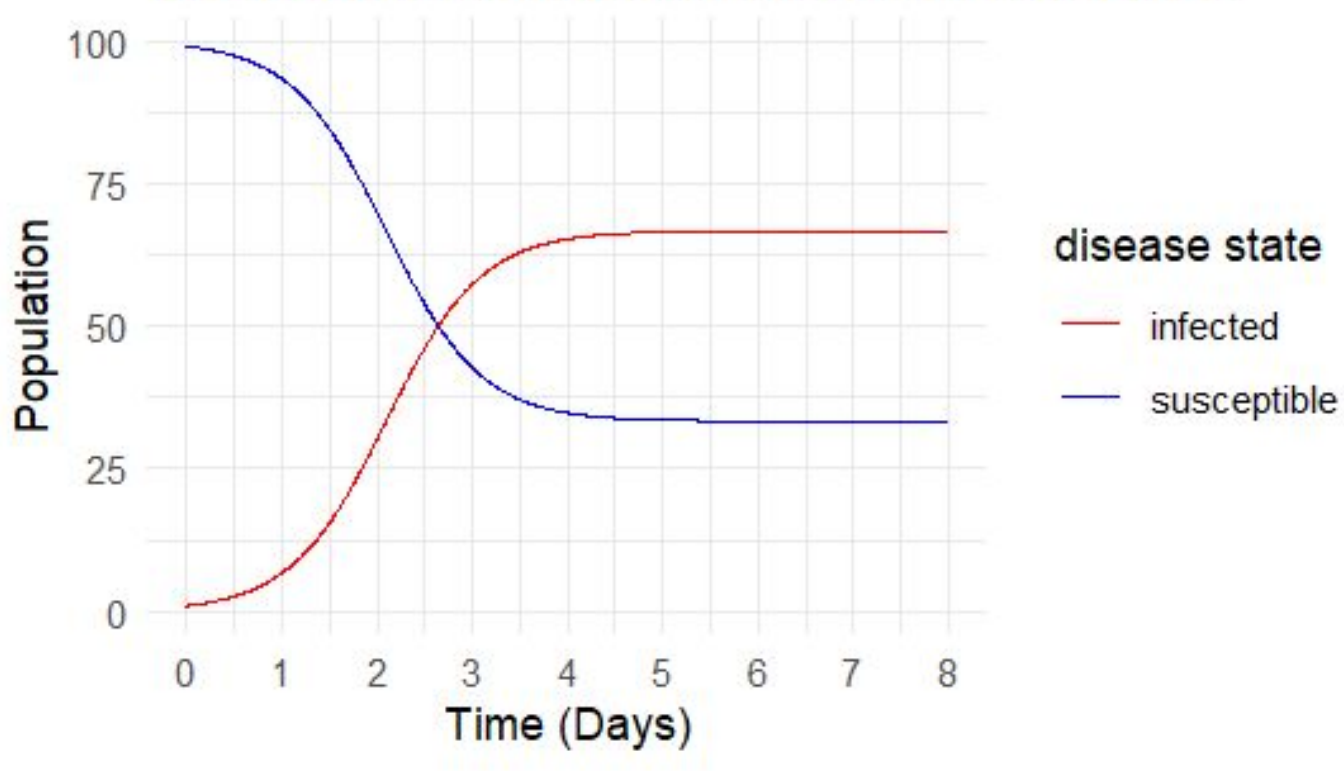
SIS differential equation system

Flow diagrams as differential equations



transmission kernel:

- **depletion** of susceptibles: as there are fewer susceptible individuals in the population, infections also stall
- **non-linearity**: new infections are generally **not proportional** to current infections



Solving differential equations with computers

- many **nonlinear differential equations** require advanced mathematical methods to be solved explicitly (e.g. characteristic polynomial, monodromy matrix, variation of parameters, special functions)

- certain **qualitative** properties of SIS differential equations can be obtained by **linearizing** the system (e.g. basic reproduction number)

- we will use **computers** to calculate **numerical solution** curves that approximate exact solution to SIS differential equations

Solving differential equations with computers

$$\begin{cases} \frac{S(t+\Delta)-S(t)}{\Delta} = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t) \\ \frac{I(t+\Delta)-I(t)}{\Delta} = \beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma\, I(t) \end{cases}$$

Initial condition

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$

$$\Delta \to 0$$

Solving differential equations with computers

$$\begin{cases} \frac{S(t+\Delta)-S(t)}{\Delta} = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t) \\ \frac{I(t+\Delta)-I(t)}{\Delta} = \beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma\, I(t) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$

Constant population size

$$\Delta \to 0$$

Solving differential equations with computers

$$\begin{cases} \frac{S(t+\Delta)-S(t)}{\Delta} = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t) \\ \frac{I(t+\Delta)-I(t)}{\Delta} = \beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma\, I(t) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$

Step size

$$\Delta \to 0$$

Solving differential equations with computers

$$\begin{cases} \frac{S(t+\Delta)-S(t)}{\Delta} = -\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma\, I(t) \\ \frac{I(t+\Delta)-I(t)}{\Delta} = \beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma\, I(t) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$

Rewrite the equation system:

recurrence

$$\begin{cases} S(t+\Delta) = S(t) + \Delta \left(-\beta \frac{I(t)}{S(t)+I(t)} + \gamma I(t) \right) \\ I(t+\Delta) = I(t) + \Delta \left(\beta \frac{I(t)}{S(t)+I(t)} - \gamma I(t) \right) \end{cases}$$

$$0 < \Delta \ll 1$$

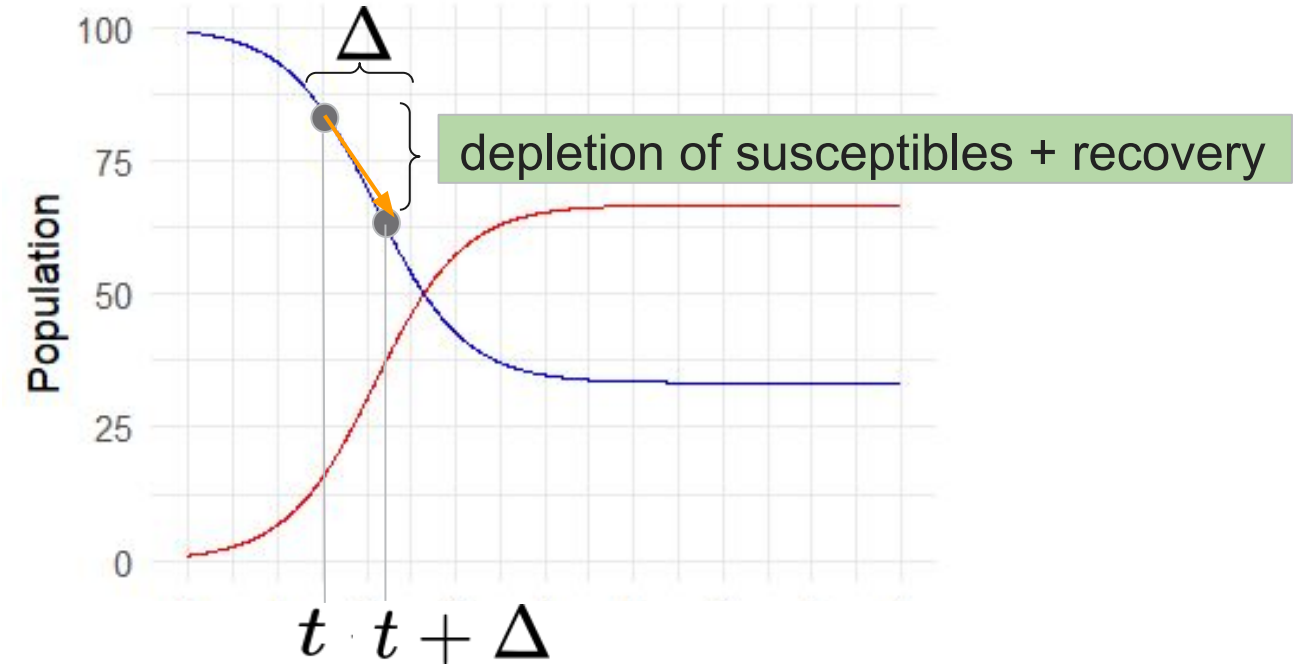
Solving differential equations with computers

Recurrence:

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$



$$0 < \Delta \ll 1$$

Solving differential equations with computers

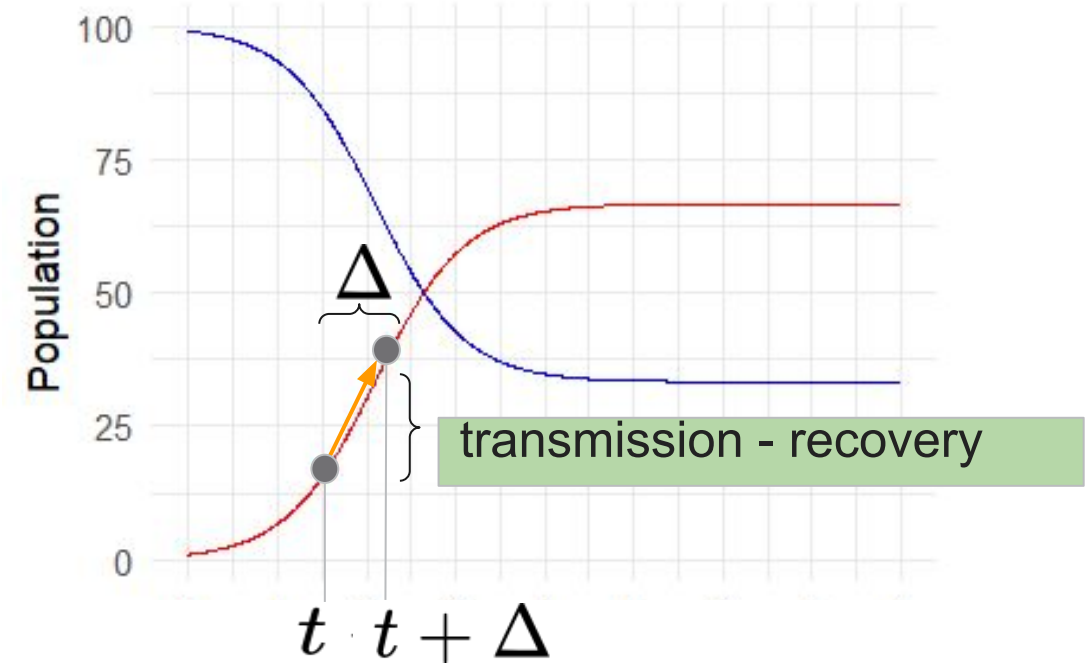
Recurrence:

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$

$$0 < \Delta \ll 1$$



Solving differential equations with computers

Recurrence:

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

$$S(0) = S_0$$
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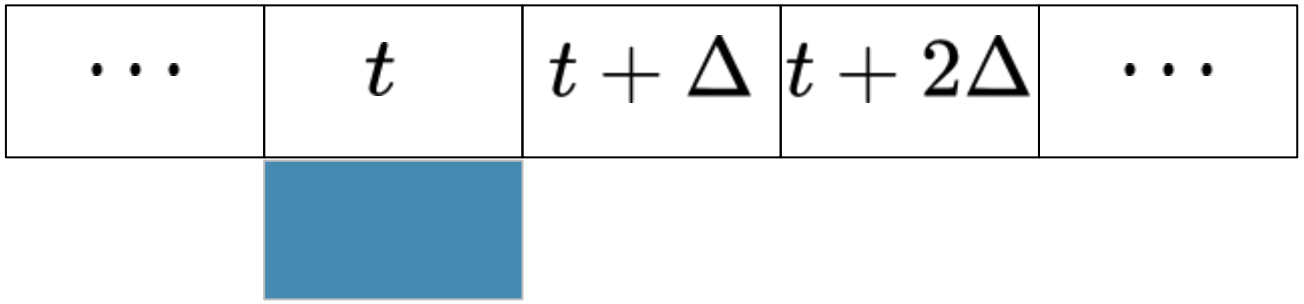
$$S(t) + I(t) = N;\ t \geq 0$$



$$0 < \Delta \ll 1$$

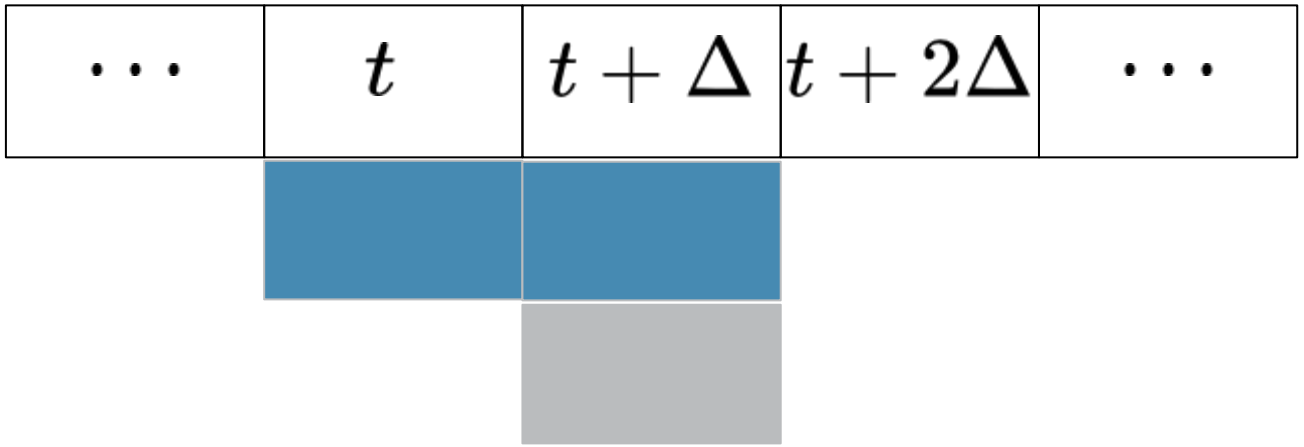
Solving differential equations with computers

Recurrence:

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

$$S(0) = S_0$$
$$I(0) = I_0$$

$$S(t) + I(t) = N;\ t \geq 0$$



$$0 < \Delta \ll 1$$

Solving differential equations with computers

Simulation setup

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

Solving differential equations with computers

Simulation setup

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

```
Delta=0.01
timeHorizon=100
timesteps<-seq(0,timeHorizon,Delta)

S=I=rep(0,length(timesteps))
N=500
I0=1
S[1]=N-I0
I[1]=I0
```

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

Solving differential equations with computers

Simulation setup

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

```
Delta=0.01
timeHorizon=100
timesteps<-seq(0,timeHorizon,Delta)

S=I=rep(0,length(timesteps))
N=500
I0=1
S[1]=N-I0
I[1]=I0
```

$$\{0, \Delta, 2\Delta, \ldots, 100\}$$

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)} + \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)} - \gamma I(t)\right) \end{cases}$$

Solving differential equations with computers

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

infectivity parameter

recovery parameter

$$\begin{cases} S(t+\Delta) = S(t) + \Delta\left(-\beta \frac{I(t)}{S(t)+I(t)} S(t) - \gamma I(t)\right) \\ I(t+\Delta) = I(t) + \Delta\left(\beta \frac{I(t)}{S(t)+I(t)} S(t) + \gamma I(t)\right) \end{cases}$$

Solving differential equations with computers

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

```
beta=0.3
gamma=0.1
```

infectivity parameter

recovery parameter

$$S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)}S(t) - \gamma I(t)\right)$$

$$I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)}S(t) + \gamma I(t)\right)$$

Solving differential equations with computers

$$0 < \Delta \ll 1$$
$$S(0) = S_0$$
$$I(0) = I_0$$
$$S(t) + I(t) = N;\ t \geq 0$$

Update next time step

$$S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)}S(t) - \gamma I(t)\right)$$
$$I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)}S(t) + \gamma I(t)\right)$$

Solving differential equations with computers

loop over time steps index set

```
for (i in c(1:(length(timesteps)-1))){

  S[i+1] = S[i] + Delta*(-beta*I[i]/N*S[i] + gamma*I[i])
  I[i+1] = I[i] + Delta*(beta*I[i]/N*S[i] - gamma*I[i])

}
```

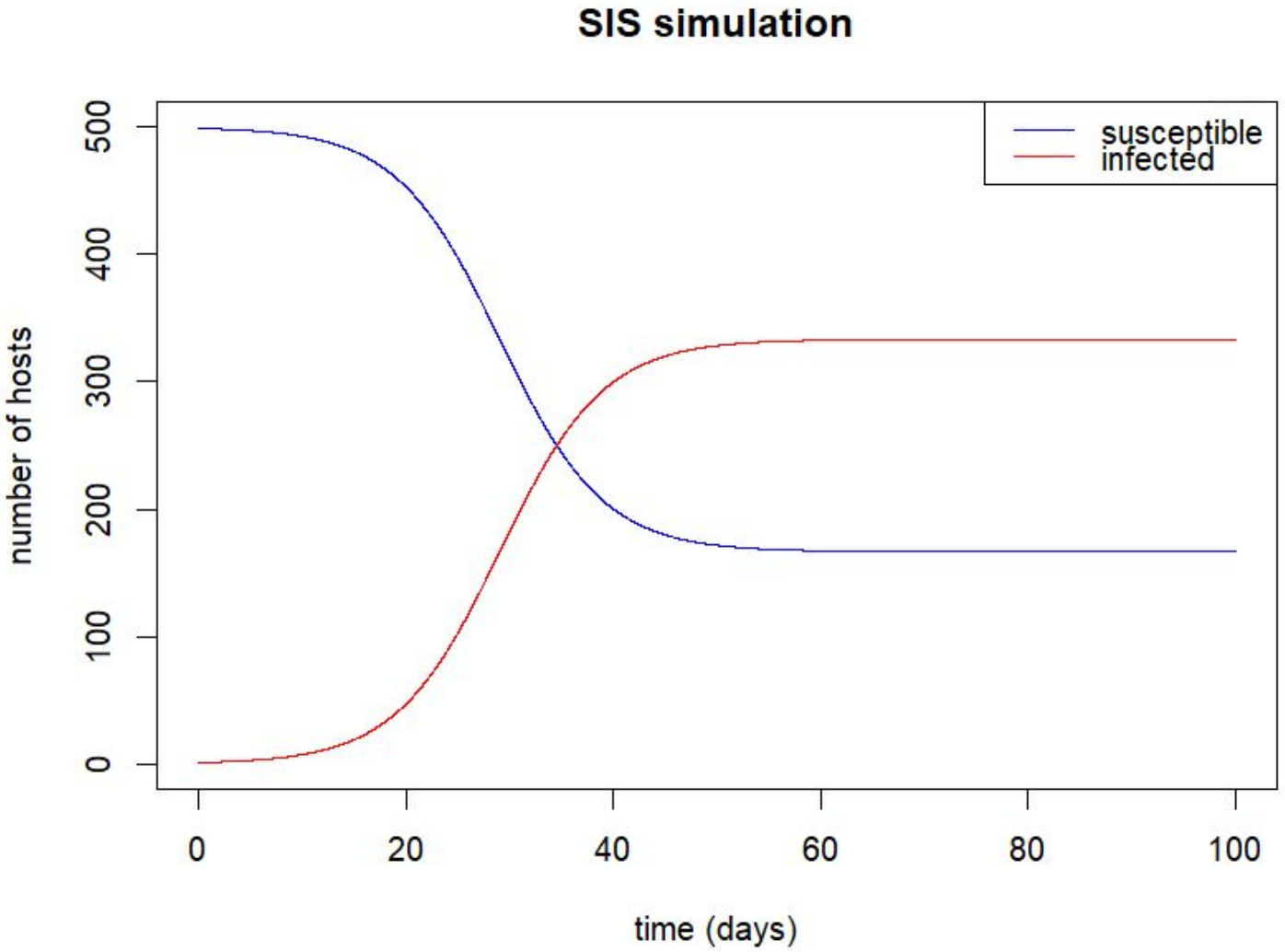
$$S(t+\Delta) = S(t) + \Delta\left(-\beta\frac{I(t)}{S(t)+I(t)}S(t) - \gamma I(t)\right)$$

$$I(t+\Delta) = I(t) + \Delta\left(\beta\frac{I(t)}{S(t)+I(t)}S(t) + \gamma I(t)\right)$$

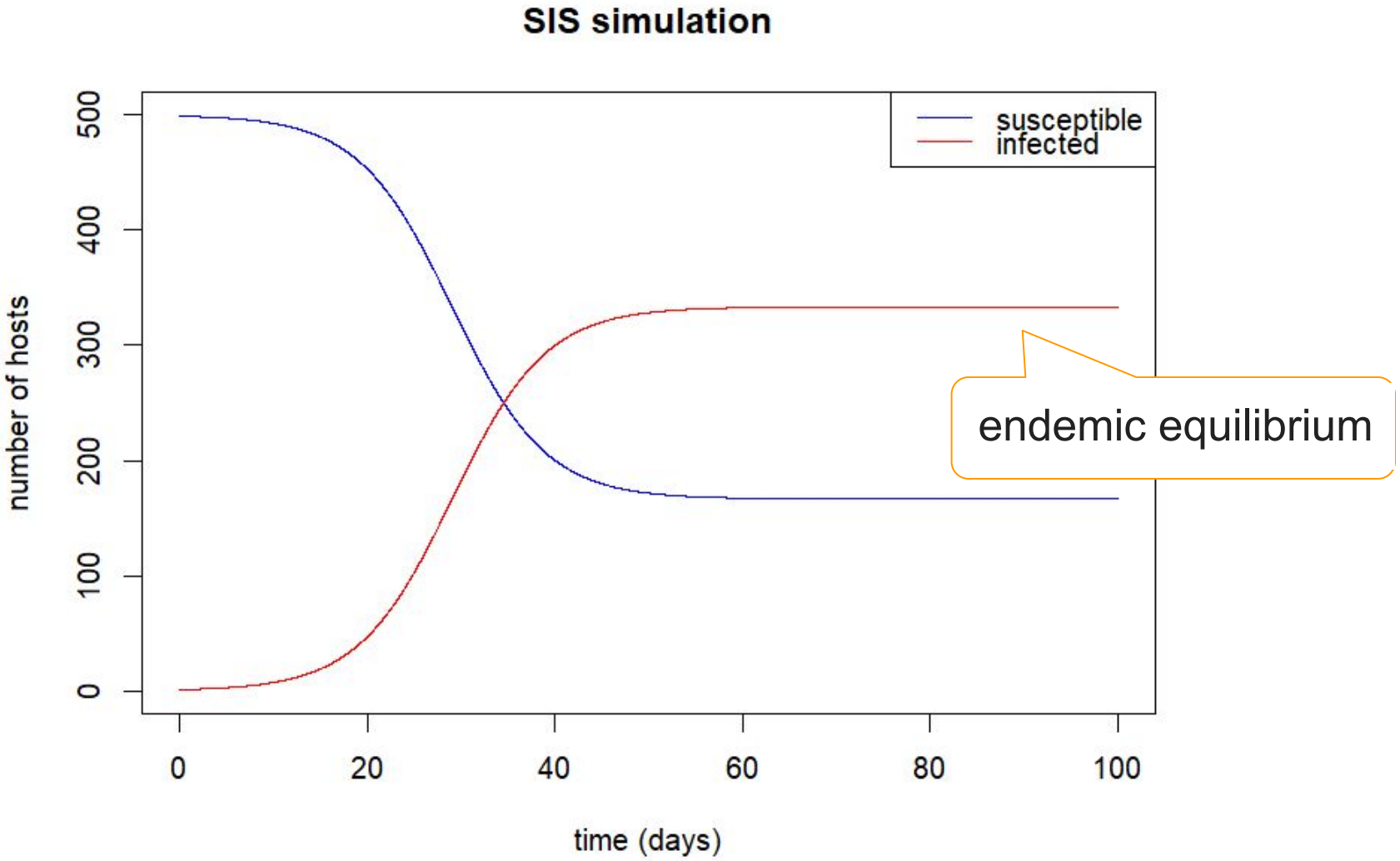
Solving differential equations with computers

```
plot(timesteps,S,col="blue",type="l",
     xlab="time steps (days)",ylab="number of hosts",
     main="SIS simulation",ylim = c(0, N))

lines(timesteps,I,col="red")

legend( x="topright",
        legend=c("susceptible","infected"),
        col=c("blue","red"),lwd=1)
```

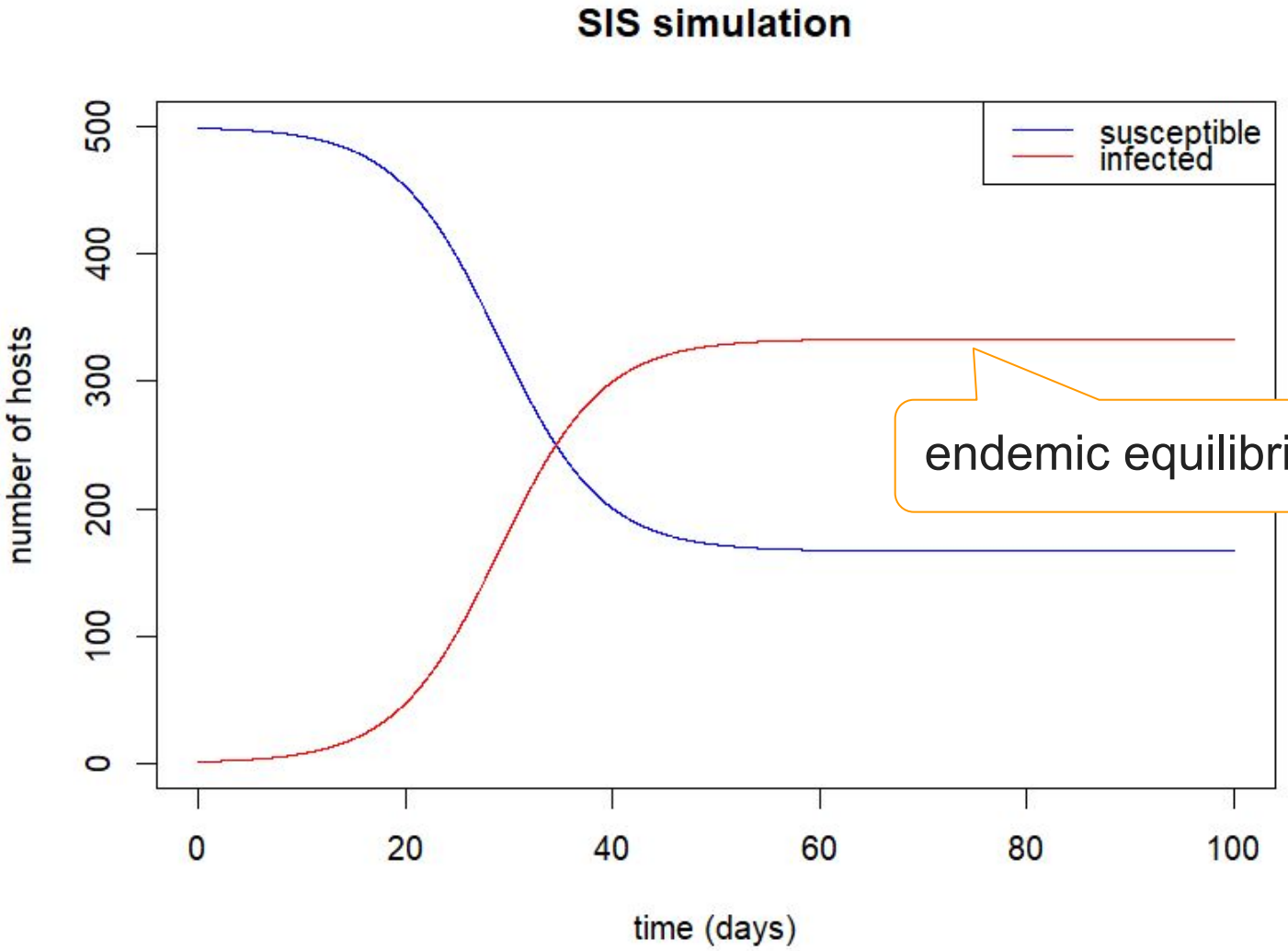
Solving differential equations with computers



Solving differential equations with computers



Solving differential equations with computers



endemic equilibrium

equilibrium = no change between time points !

$$0 = \frac{S^*(t+\Delta) - S^*(t)}{\Delta}$$

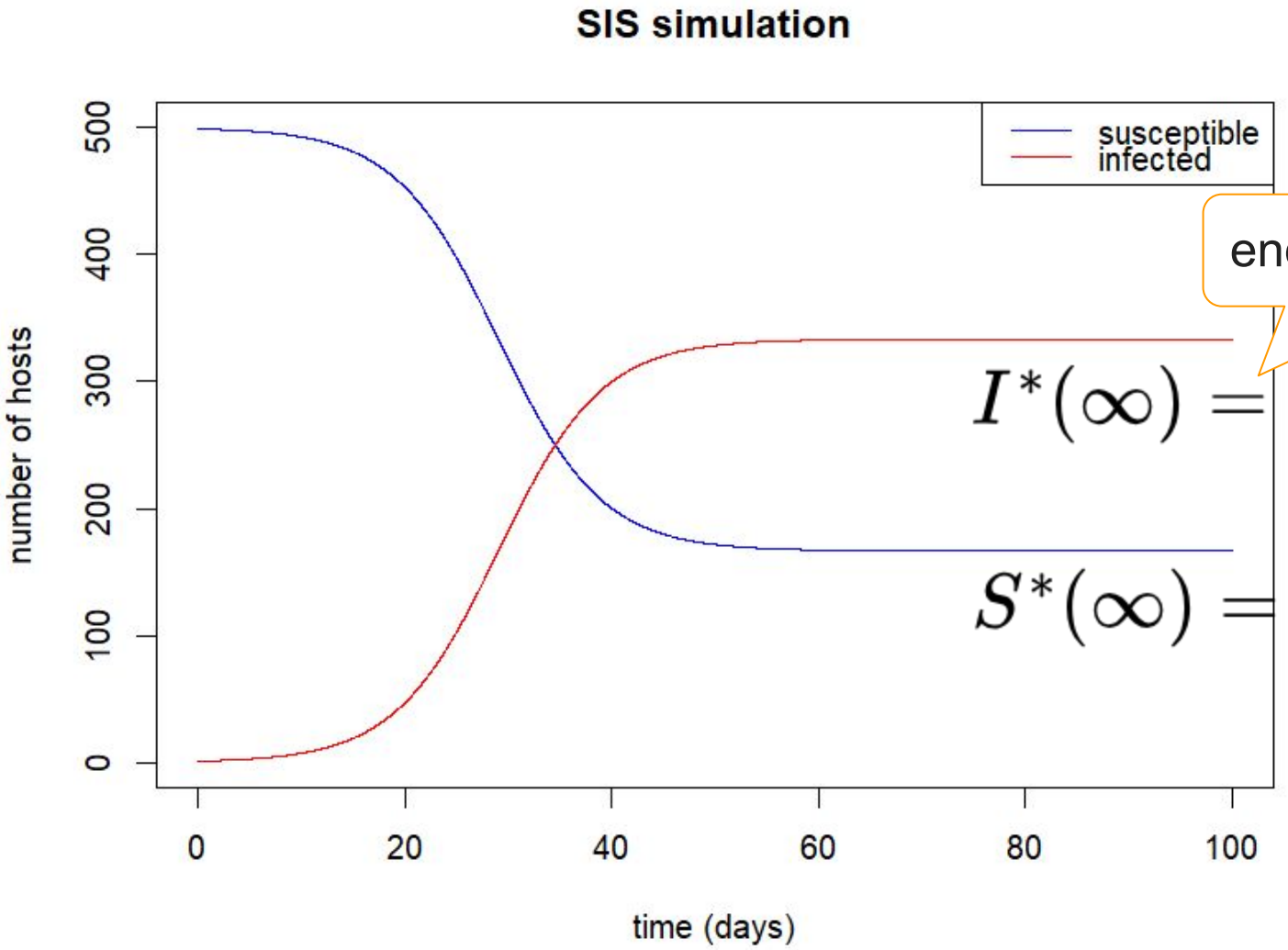
$$= -\beta \frac{I^*(t)}{N} S^*(t) + \gamma I^*(t)$$

$$= I^*(t)\left(-\beta \frac{S^*(t)}{N} + \gamma\right)$$

$$\Leftrightarrow -\beta \frac{S^*(t)}{N} + \gamma = 0$$

$$\Leftrightarrow S^*(\infty) = \frac{\gamma}{\beta} N$$

Solving differential equations with computers



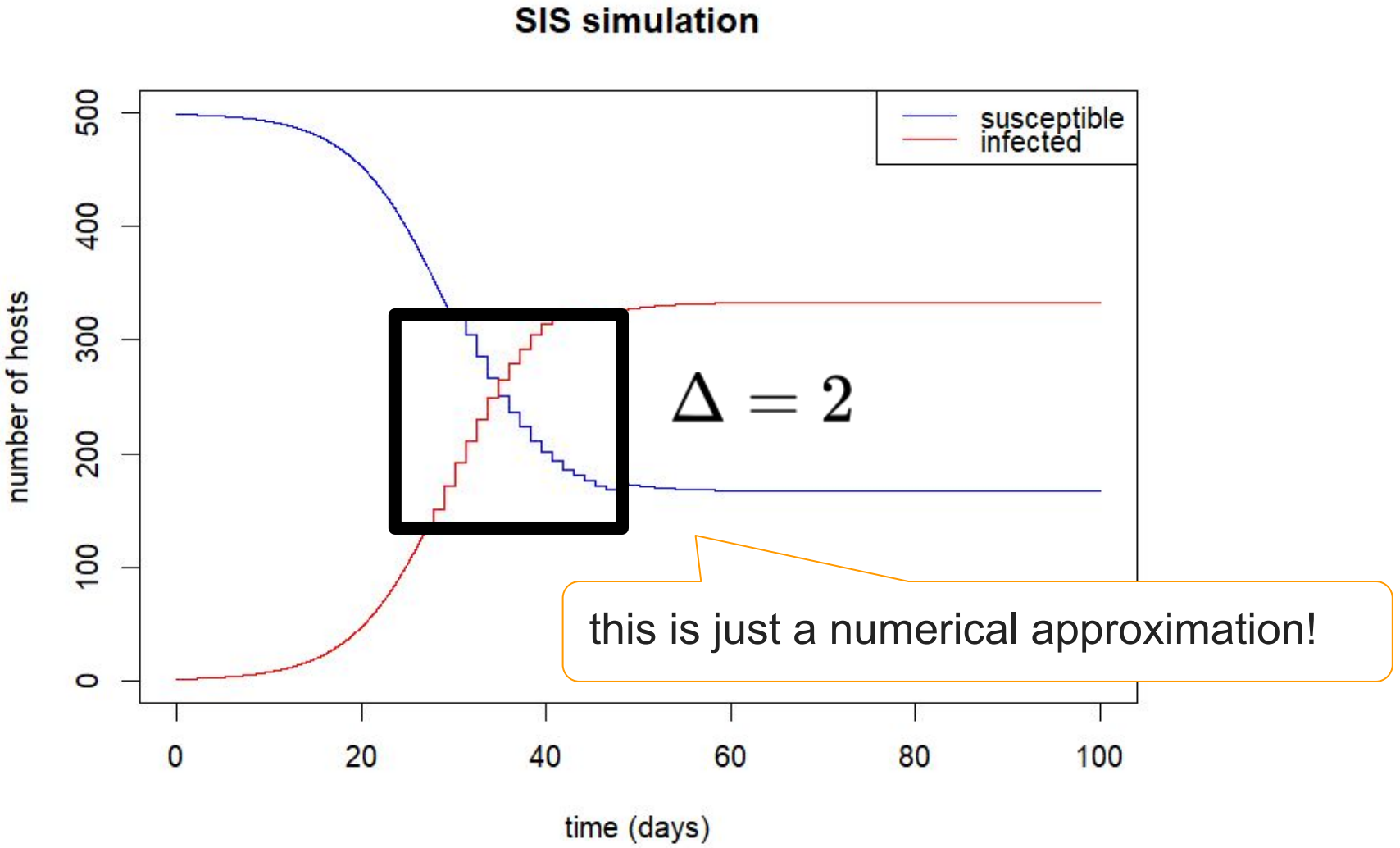
endemic equilibrium

disease prevalence

$$I^*(\infty) = N - S^*(\infty) = \frac{2}{3}500$$

$$S^*(\infty) = \frac{\gamma}{\beta}N = \frac{1}{3}500$$

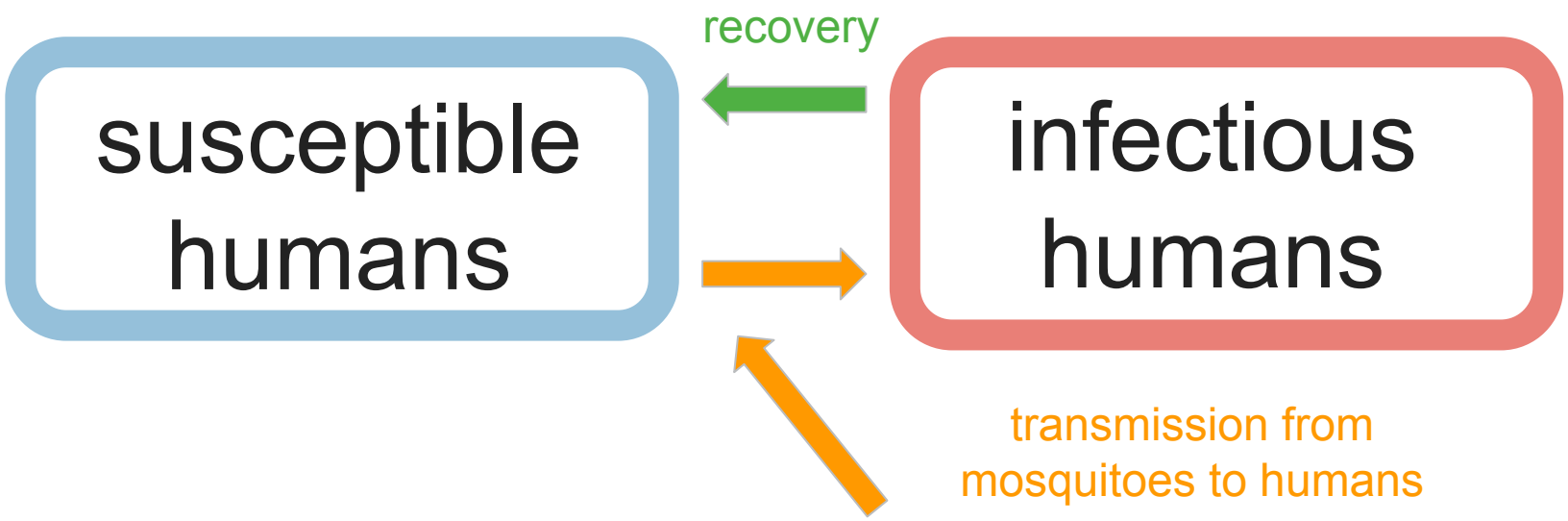
Solving differential equations with computers



Swiss TPH

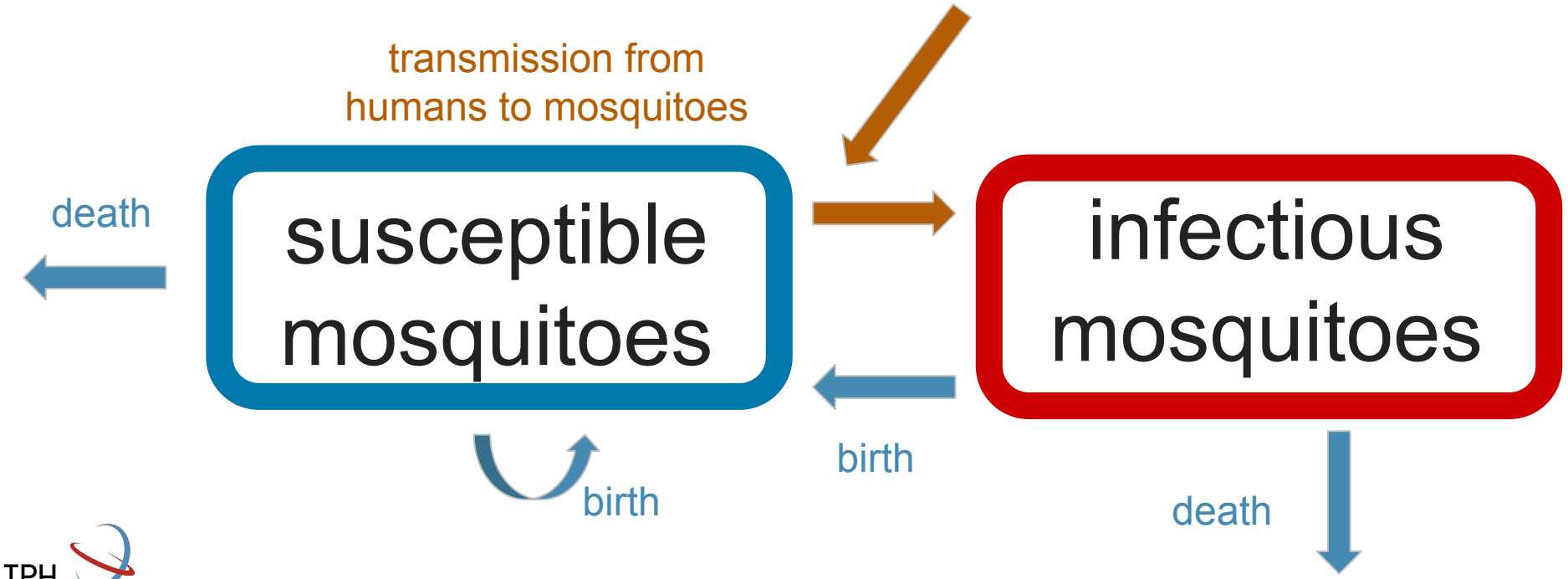
1 - Malaria model parameters

Malaria transmission between host and vector



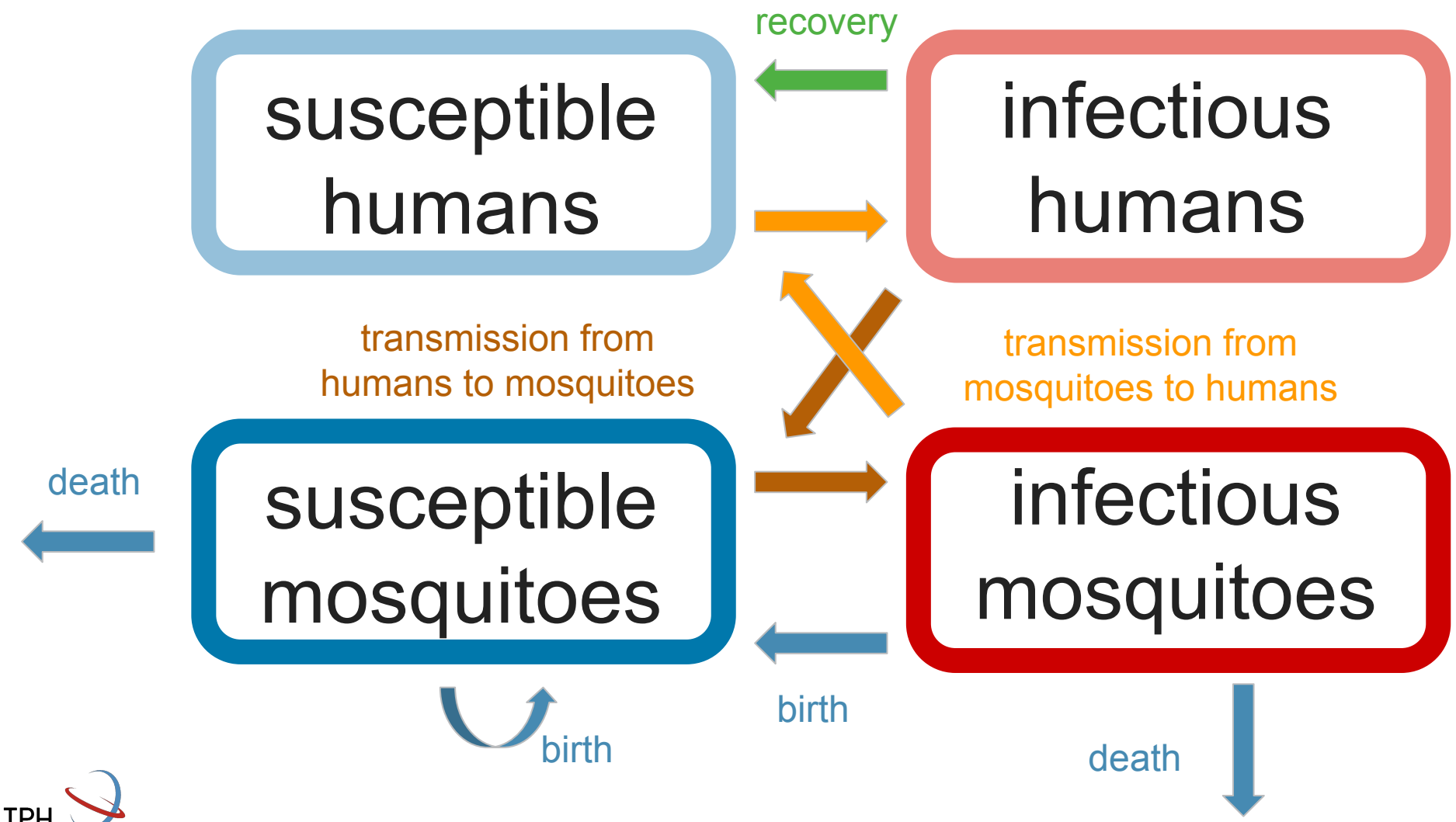
SIS

Malaria transmission between host and vector



SI

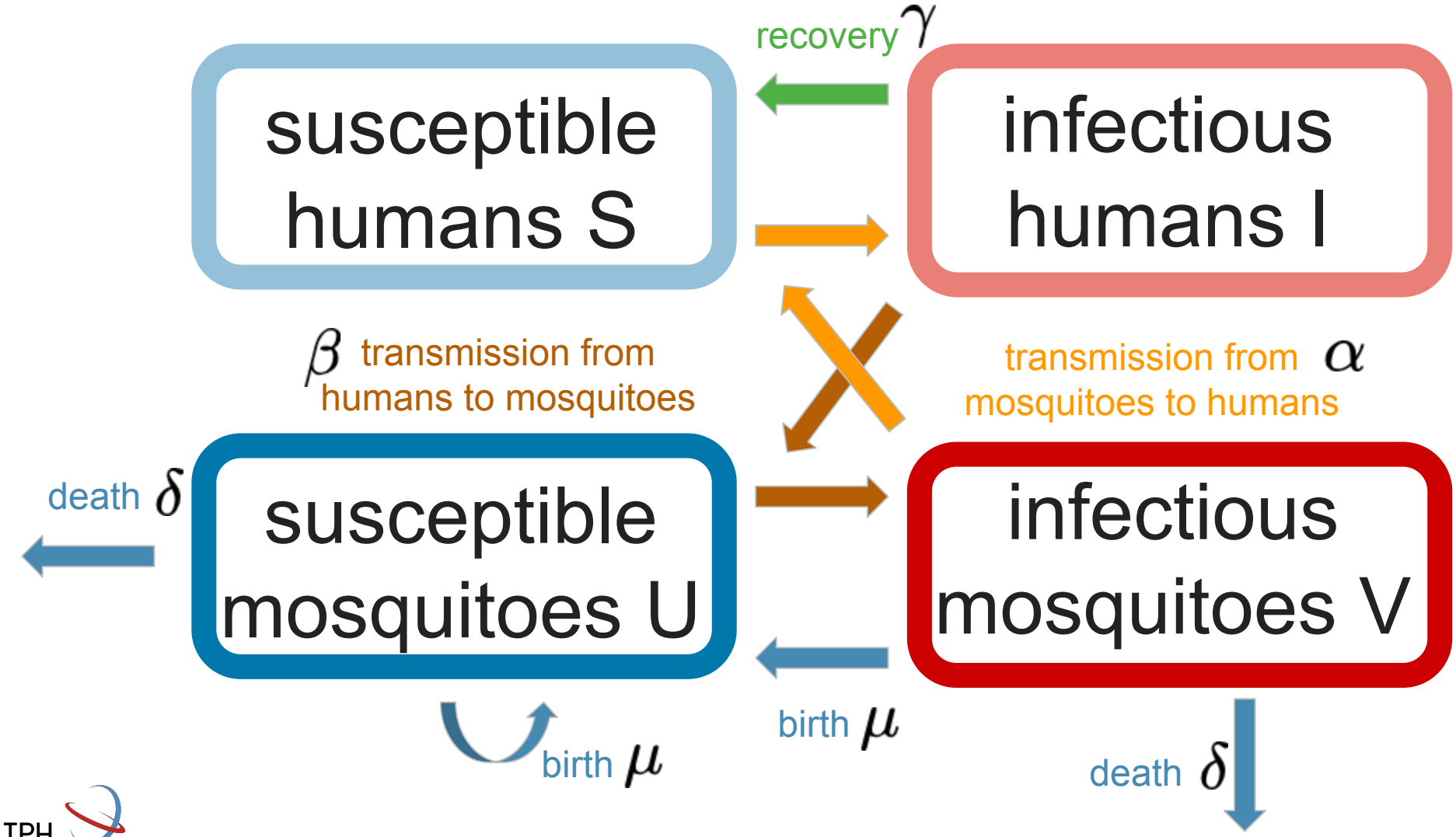
Malaria transmission between host and vector



SIS

SI

Malaria transmission between host and vector



Where can we get parameter values from?

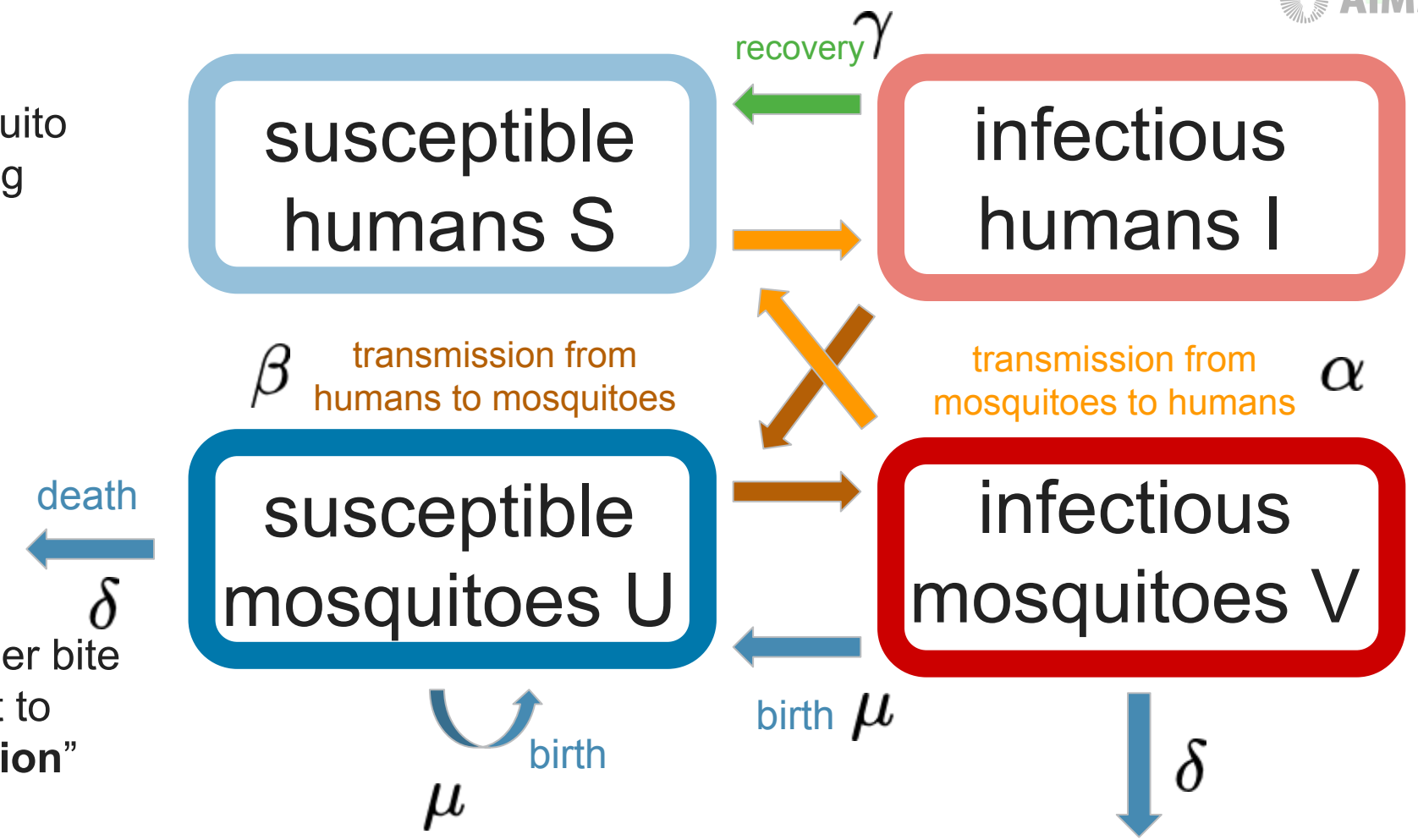
$\frac{1}{\mu}$ time span from ovipositing to emergence of adult female mosquito from pupa stage, given ovipositing

$\frac{1}{\delta}$ life span of adult female mosquito

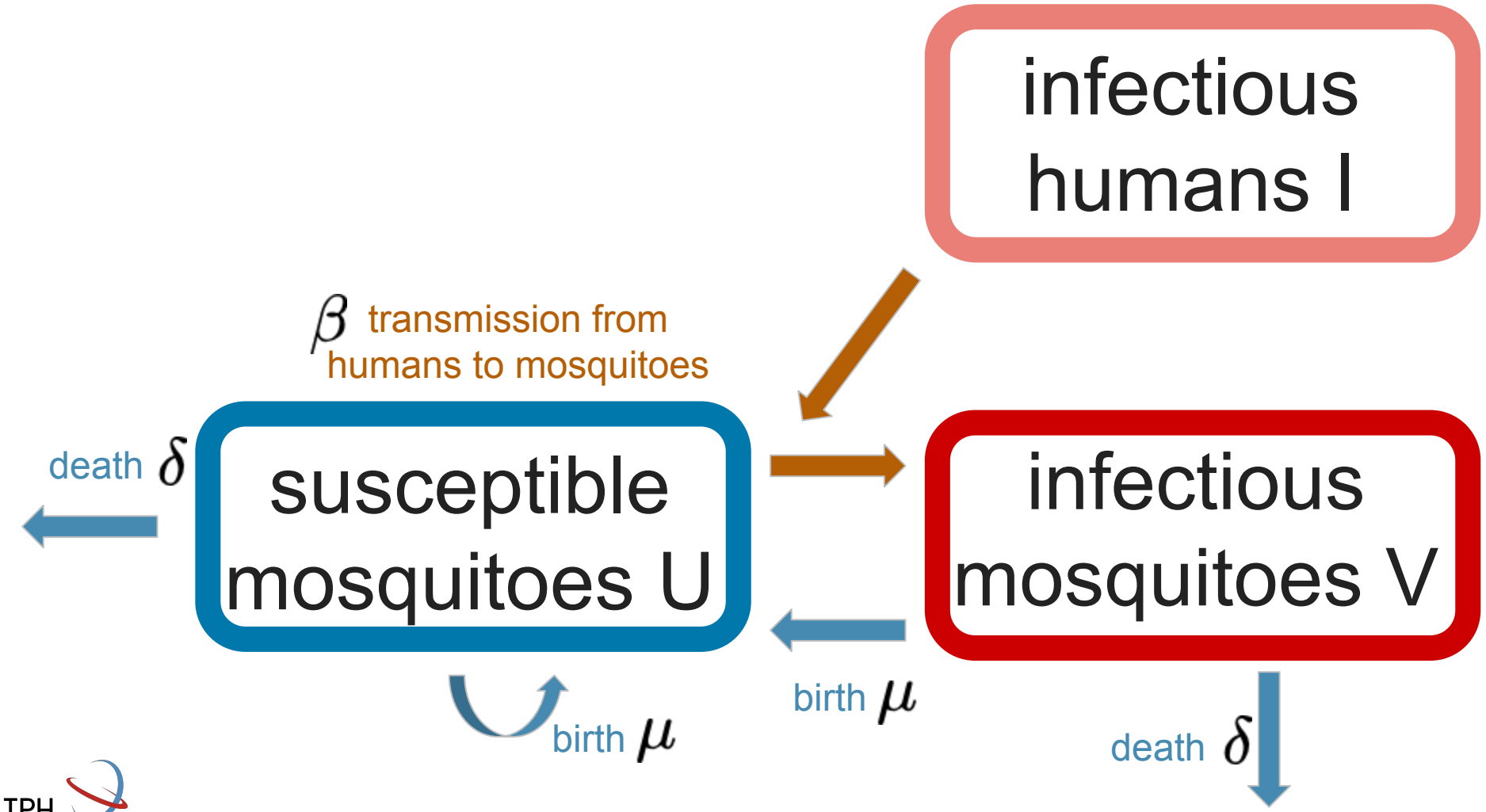
$\frac{1}{\gamma}$ duration of infection in human

α host seeking/biting X probability per bite for infectious mosquito to transmit to human: "**entomological inoculation**"

β host seeking/biting X acquisition rate from infectious human with gametocytemia to mosquito



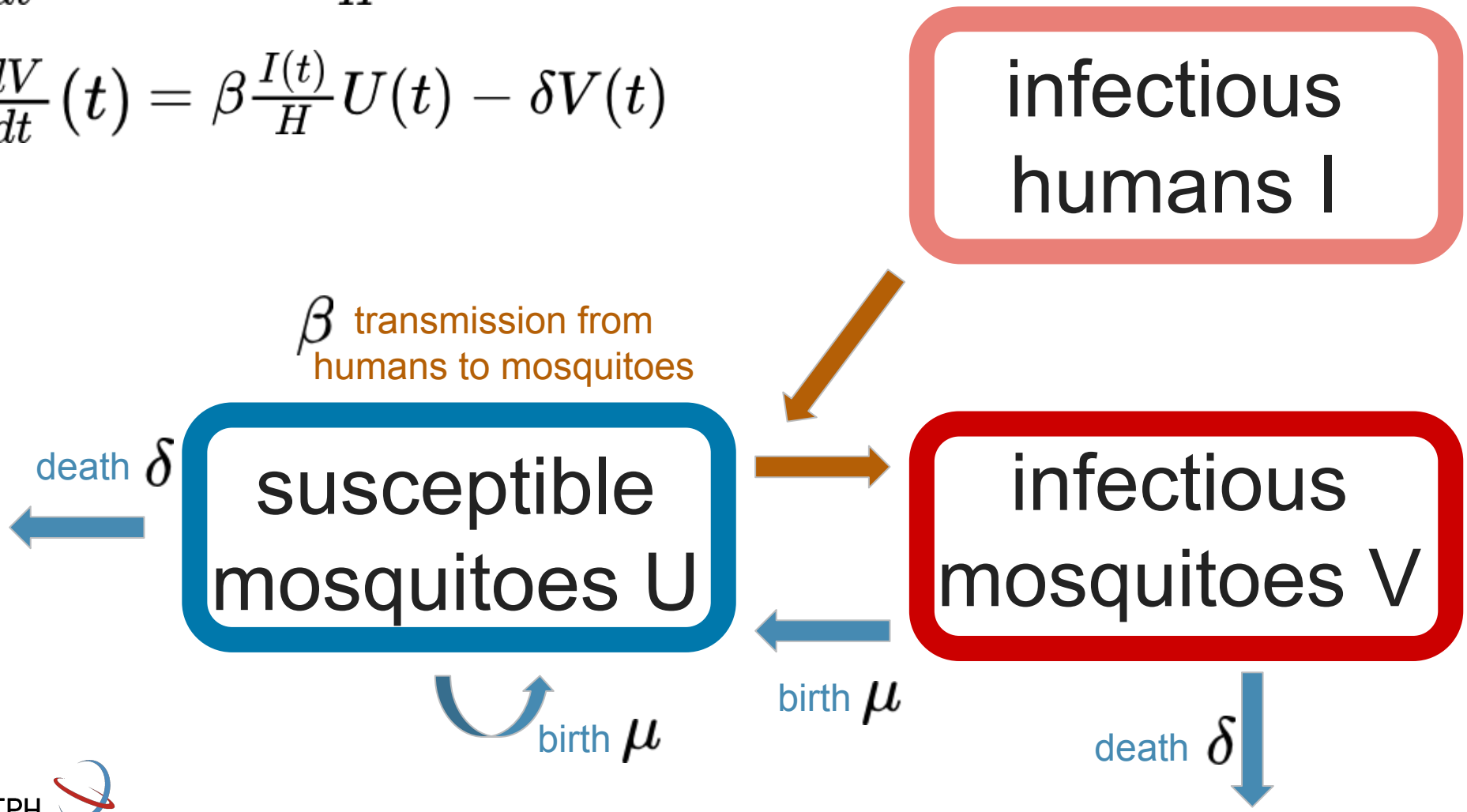
Malaria transmission between host and vector



Malaria transmission between host and vector

$$\frac{dU}{dt}(t) = -\beta \frac{I(t)}{H} U(t) + \mu M - \delta U(t)$$

$$\frac{dV}{dt}(t) = \beta \frac{I(t)}{H} U(t) - \delta V(t)$$



Malaria transmission between host and vector

$$\frac{dU}{dt}(t) = -\beta\frac{I(t)}{H}U(t) + \mu M - \delta U(t)$$

$$\frac{dV}{dt}(t) = \beta\frac{I(t)}{H}U(t) - \delta V(t)$$

$M = U(0) + V(0)$ constant mosquito population size

at equilibrium $\mu = \delta$

infectious humans I

β transmission from humans to mosquitoes

death δ

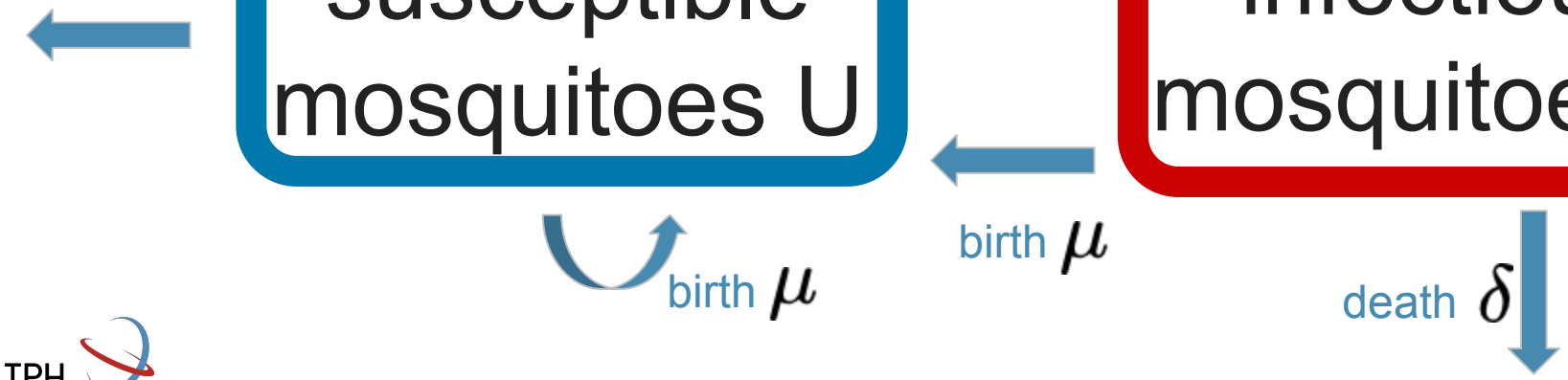
susceptible mosquitoes U

infectious mosquitoes V

birth μ

birth μ

death δ



Swiss TPH

Malaria transmission between host and vector

$$\frac{dU}{dt}(t) = -\beta \frac{I(t)}{H} U(t) + \mu M - \delta U(t)$$

$$\frac{dV}{dt}(t) = \beta \frac{I(t)}{H} U(t) - \delta V(t)$$

$H = S(0) + I(0)$ constant human populations size

$\frac{I(t)}{H}$ infectious human density

infectious humans I

β transmission from humans to mosquitoes

death δ

susceptible mosquitoes U

infectious mosquitoes V

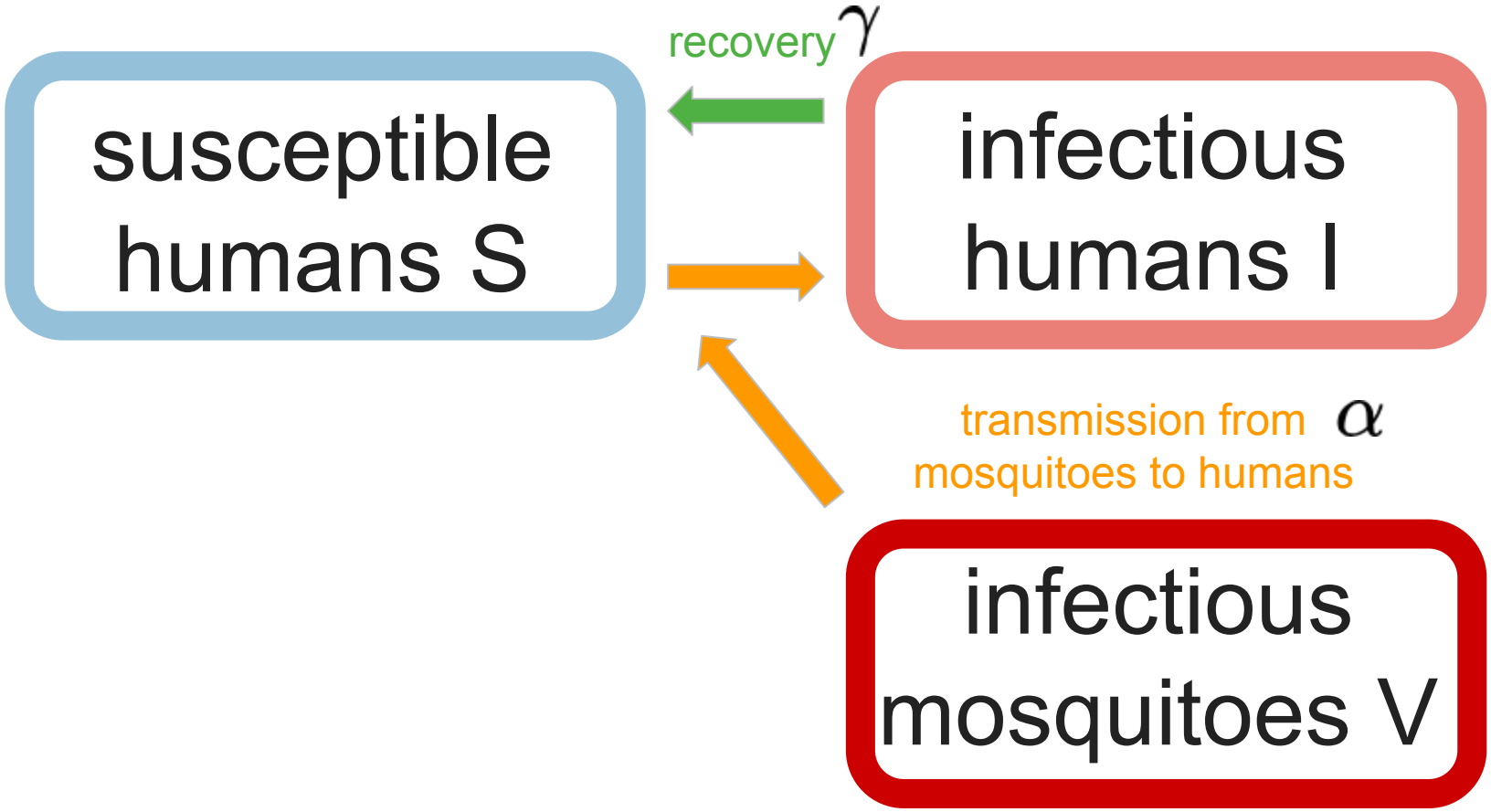
birth μ

birth μ

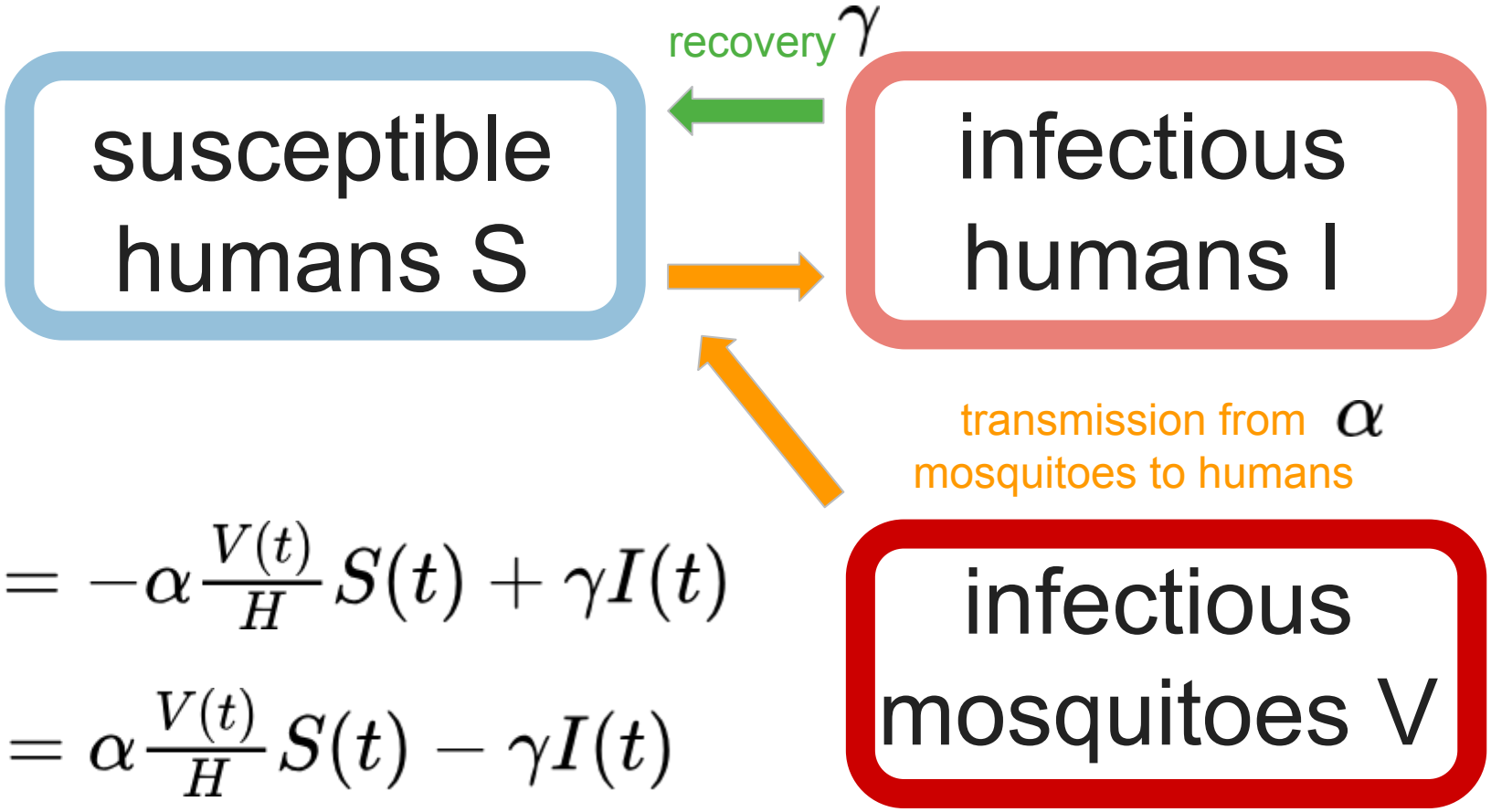
death δ

Swiss TPH

Malaria transmission between host and vector



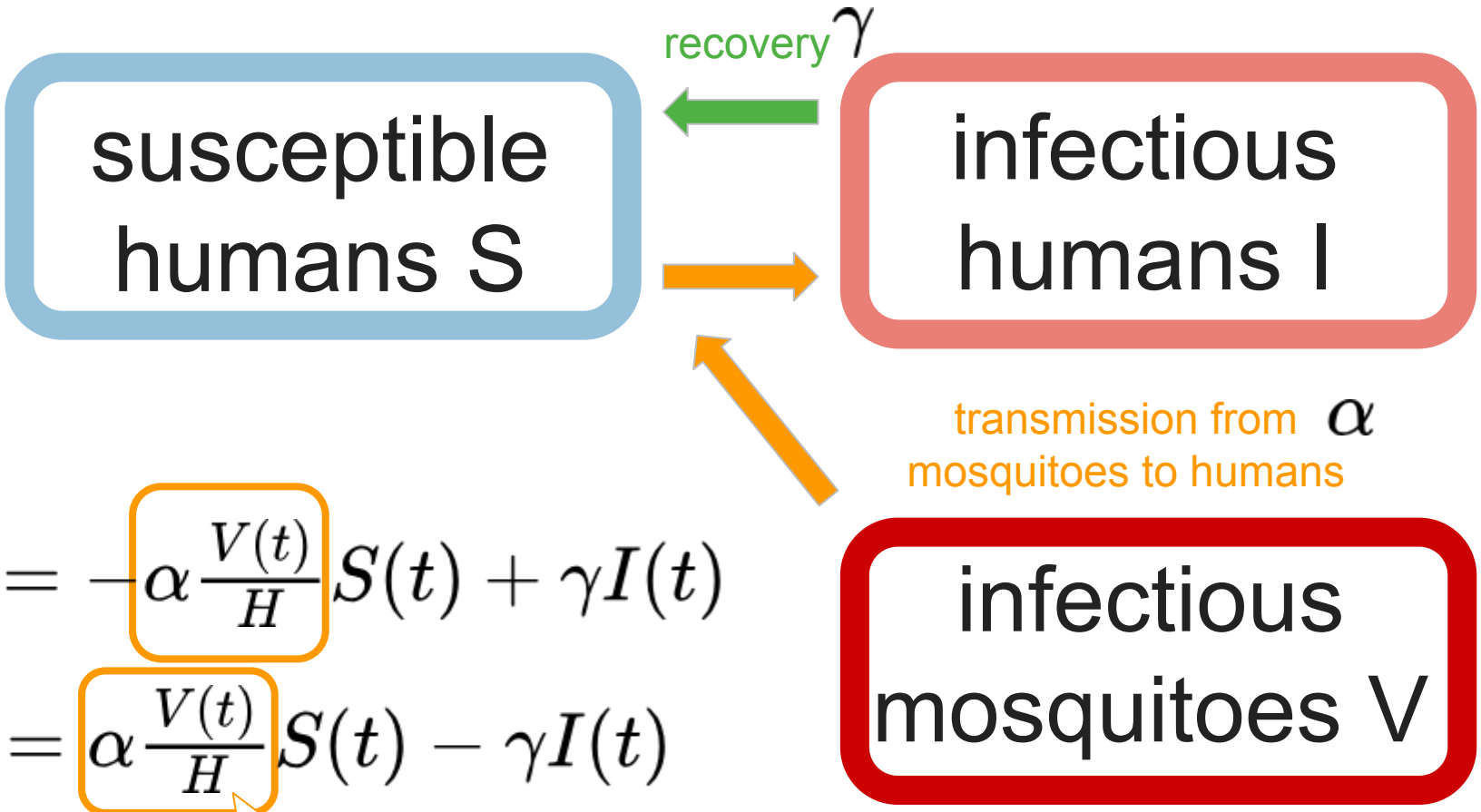
Malaria transmission between host and vector



$$\frac{dS}{dt}(t) = -\alpha \frac{V(t)}{H} S(t) + \gamma I(t)$$

$$\frac{dI}{dt}(t) = \alpha \frac{V(t)}{H} S(t) - \gamma I(t)$$

Malaria transmission between host and vector

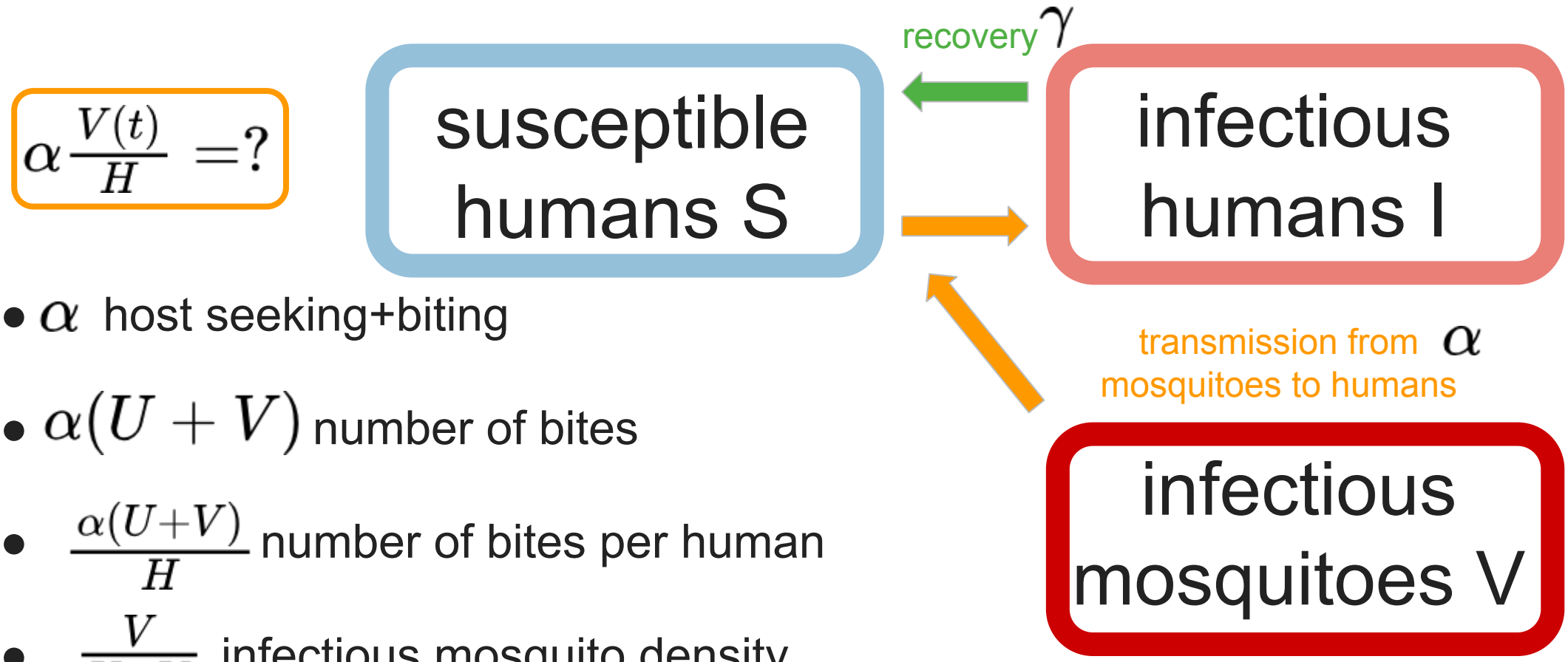


$$\frac{dS}{dt}(t) = -\alpha \frac{V(t)}{H} S(t) + \gamma I(t)$$

$$\frac{dI}{dt}(t) = \alpha \frac{V(t)}{H} S(t) - \gamma I(t)$$

unintuitive!

Malaria transmission between host and vector



- α host seeking+biting
- $\alpha(U+V)$ number of bites
- $\frac{\alpha(U+V)}{H}$ number of bites per human
- $\frac{V}{U+V}$ infectious mosquito density
- $\frac{V}{U+V}\alpha\frac{U+V}{H} = \alpha\frac{V}{H}$

Malaria transmission between host and vector

```
###SIS-SI host-vector model
Delta=0.01 #step size
timeHorizon=200 #maximum number of days/weeks/months to simulate
timesteps<-seq(0,timeHorizon,Delta)#time points to simulate

S=I=U=V=rep(0,length(timesteps))
H=1000
K=5 #VectorHumanRatio
M=H*K
I0=1
V0=8
S[1]=H-I0
I[1]=I0
U[1]=N*K-V0
V[1]=V0
```

setup & initial conditions

Malaria transmission between host and vector

```
###SIS-SI host-vector model
Delta=0.01 #step size
timeHorizon=200 #maximum number of days/weeks/months to simulate
timesteps<-seq(0,timeHorizon,Delta)#time points to simulate

S=
H=
K=5 #VectorHumanRatio
M=H*K
I0=1
V0=8
S[1]=H-I0
I[1]=I0
U[1]=N*K-V0
V[1]=V0
```

We have 5 times as many mosquitoes as human hosts!

Malaria transmission between host and vector

$$\frac{S(t+\Delta)-S(t)}{\Delta} = -\alpha \frac{V(t)}{H} S(t) + \gamma I(t)$$

$$\frac{I(t+\Delta)-I(t)}{\Delta} = \alpha \frac{V(t)}{H} S(t) - \gamma I(t)$$

```
alpha=0.05
gamma=1/20
beta=0.08
delta=1/10
mu=delta

for (i in c(1:(length(timesteps)-1))){

  S[i+1] = S[i] + Delta*(- alpha*V[i]*S[i]/H + gamma*I[i])
  I[i+1] = I[i] + Delta*( alpha*V[i]*S[i]/H - gamma*I[i])
  U[i+1] = U[i] + Delta*(- beta*U[i]*I[i]/H + mu*M - delta*U[i])
  V[i+1] = V[i] + Delta*( beta*U[i]*I[i]/H - delta*V[i])

}
```

Malaria transmission between host and vector

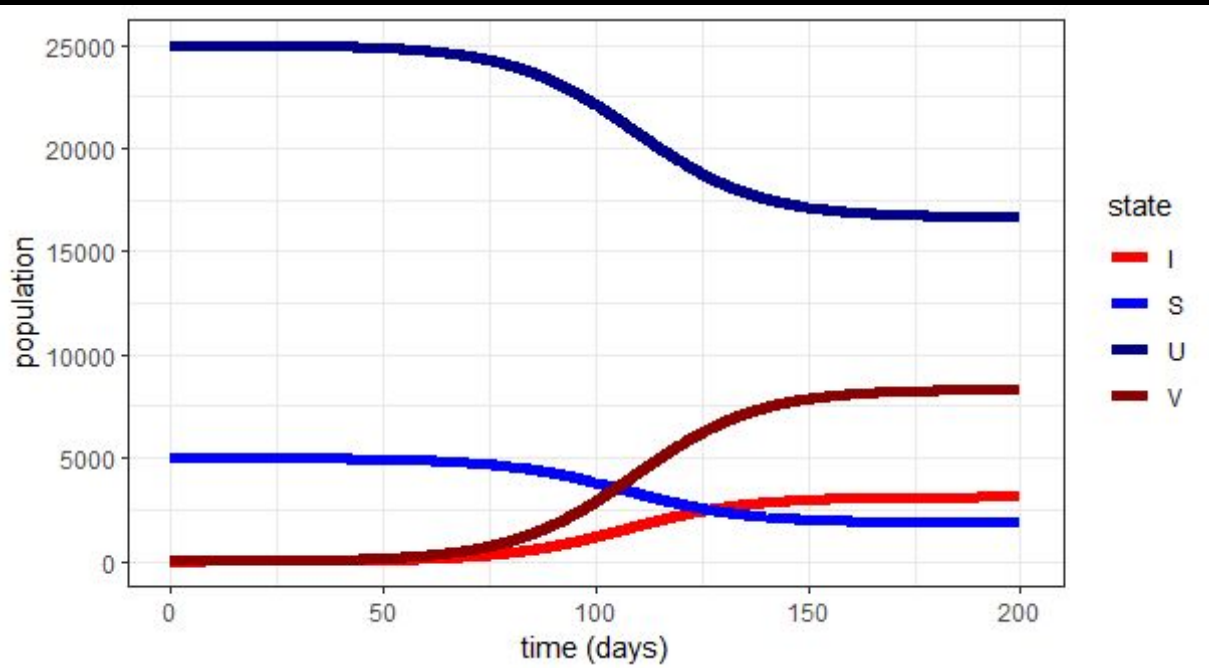
$$\frac{U(t+\Delta)-Ut()}{\Delta} = -\beta\frac{I(t)}{H}U(t) + \mu M - \delta U(t)$$

$$\frac{V(t+\Delta)-V(t)}{\Delta} = \beta\frac{I(t)}{H}U(t) - \delta V(t)$$

```
alpha=0.05
gamma=1/20
beta=0.08
delta=1/10
mu=delta

for (i in c(1:(length(timesteps)-1))){

  S[i+1] = S[i] + Delta*(- alpha*V[i]*S[i]/H + gamma*I[i])
  I[i+1] = I[i] + Delta*( alpha*V[i]*S[i]/H - gamma*I[i])
  U[i+1] = U[i] + Delta*(- beta*U[i]*I[i]/H + mu*M - delta*U[i])
  V[i+1] = V[i] + Delta*( beta*U[i]*I[i]/H - delta*V[i])

}
```

Malaria transmission between host and vector

```
cbind(timesteps,S,I,U,V)%>%
  as.data.frame%>%
  pivot_longer(cols = -timesteps)%>%
  ggplot()+
  geom_line(aes(x=timesteps,y=value,color=name),linewidth=2)+
  scale_color_manual(values=c("red","blue","darkblue","darkred"),name="state")+
  scale_y_continuous(name="population")+
  scale_x_continuous(name="time (days)")+
  theme_bw()
```



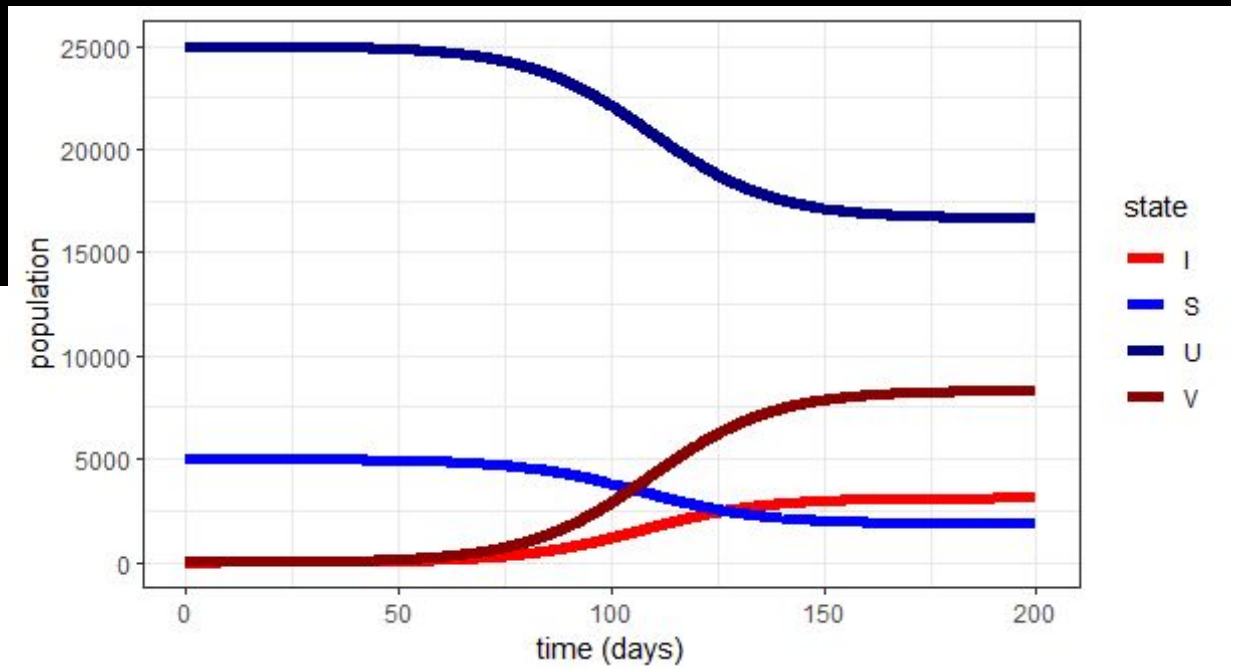
Malaria transmission between host and vector

For more complex models, use the `deSolve` R package!

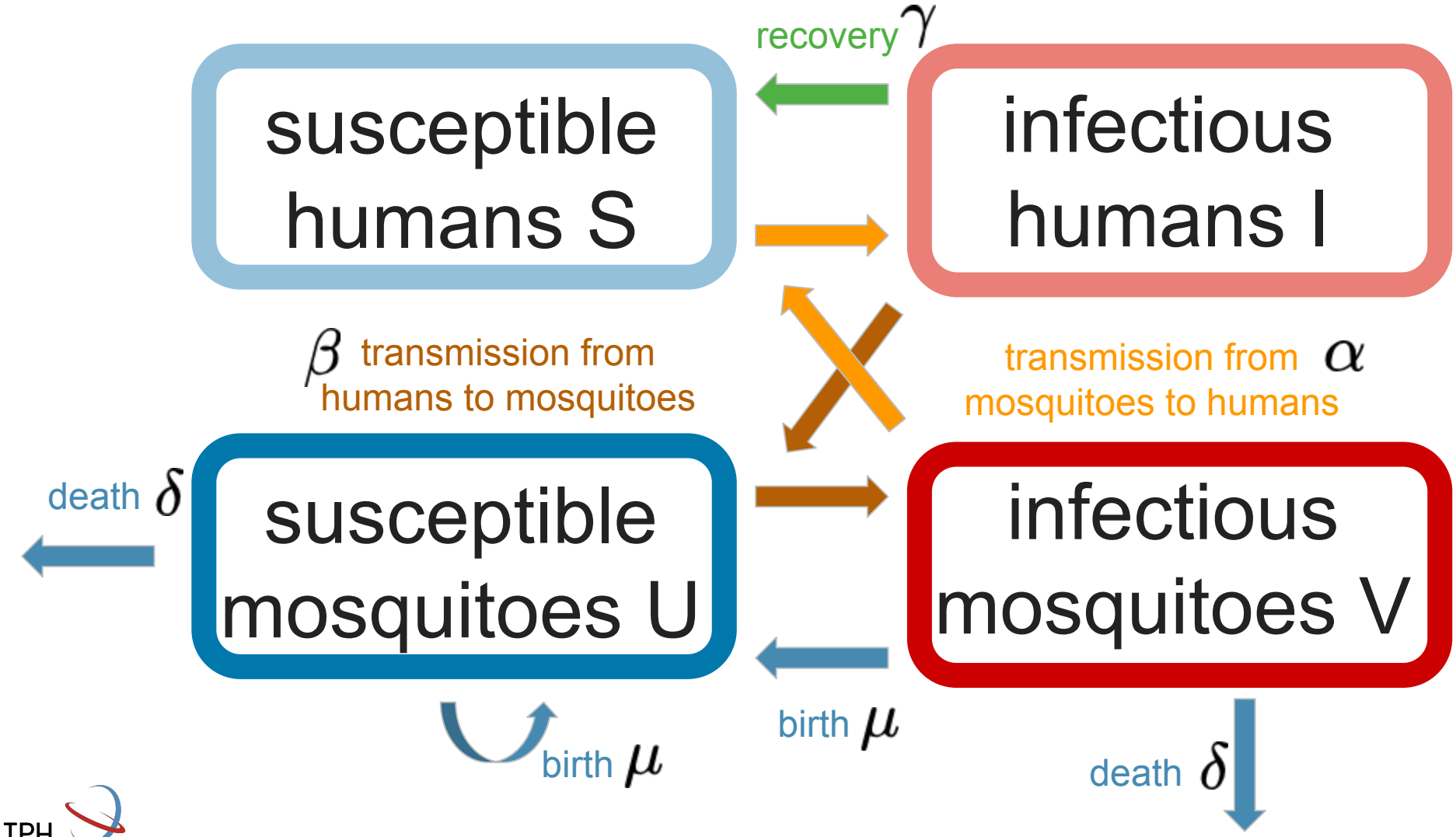
```
###Use R package deSolve for ODEs
  library("deSolve")
  RossMcDonald.model<-function(time,state,parms){
    with(as.list(c(state,parms)), {

      alpha=parms[1]; gamma=parms[2]; beta=parms[3]; mu=parms[4]; delta=parms[5]
      S=state[1]; I=state[2]; U=state[3]; V=state[4];
      H=5000; K=5; M=H*K

      dS= - alpha*V*S/H + gamma*I
      dI= alpha*V*S/H - gamma*I
      dU= -beta*U*I/H + mu*M-delta*U
      dV= beta*U*I/H-delta*V

      return(list(c(dS,dI,dU,dV)))
    })
  }
  K<-5
  x0 <- c(S=H-I0,I=I0,U=H*K-V0,V=V0)##initial condition
  timesteps<-seq(0,200,1)##time unit in days
  parms <- c(alpha=0.05, gamma=1/20, beta=0.08, mu=1/10,delta=1/10)#parameters
  output<-ode(x0,timesteps,RossMcDonald.model,parms)
```

Malaria transmission between host and vector

```
output%>%
  as.data.frame%>%
  pivot_longer(cols = -timesteps)%>%
  ggplot()+
  geom_line(aes(x=timesteps,y=value,color=name),linewidth=2)+
  scale_color_manual(values=c("red","blue","darkblue","darkred"),name="disease
state")+
  scale_y_continuous(name="population")+
  theme_bw()
```



Malaria transmission model with vector control



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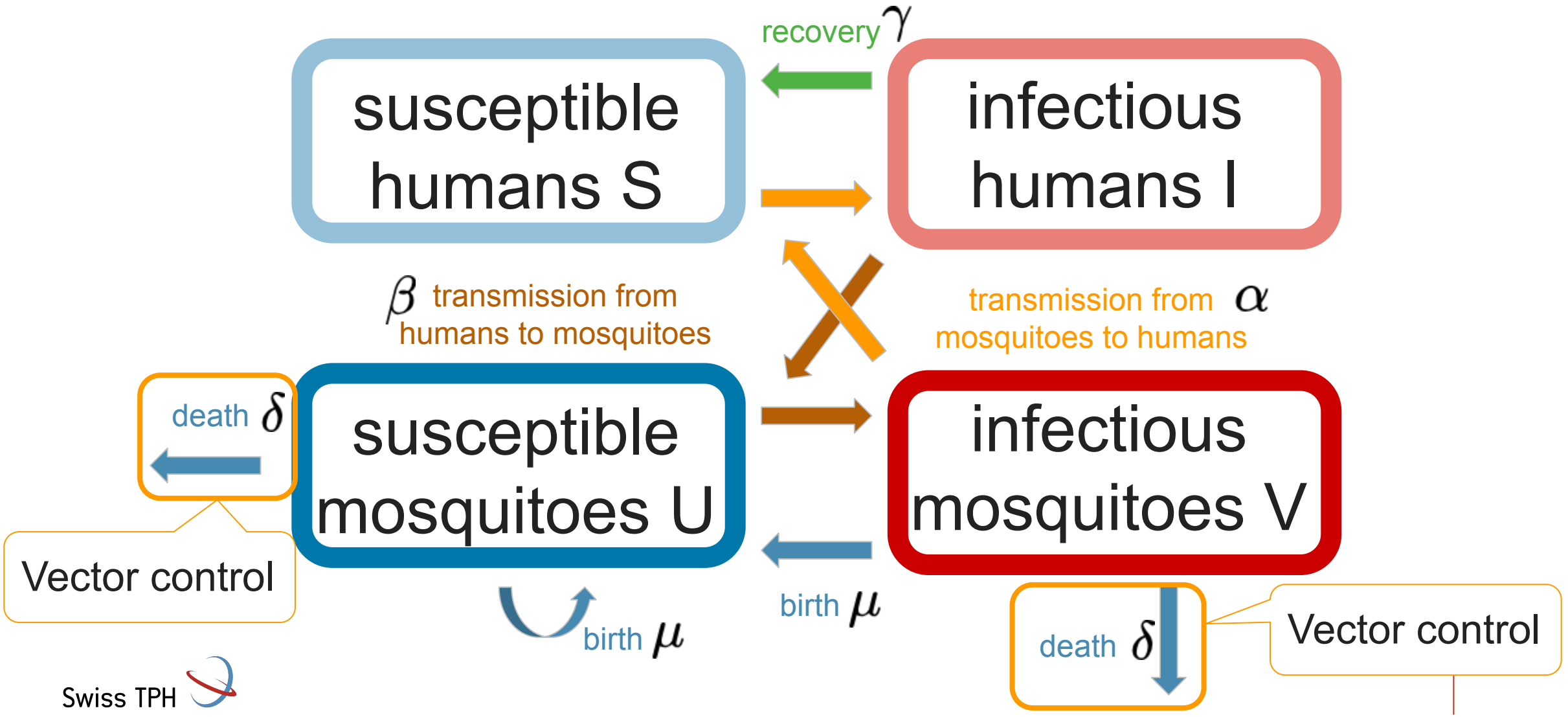

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Practical

SIS-SI host-vector model with vector control

We want to run and **compare** two simulations in R:

- simulation 1 as in the slides
- simulation 2 starts from simulation 1, but adds vector control as an 20% increase in the default mosquito mortality rate $\delta = \frac{1}{10}$, all other parameters are kept the same
- **compare** the endemic equilibrium of infected hosts between simulation 1 & 2

Practical

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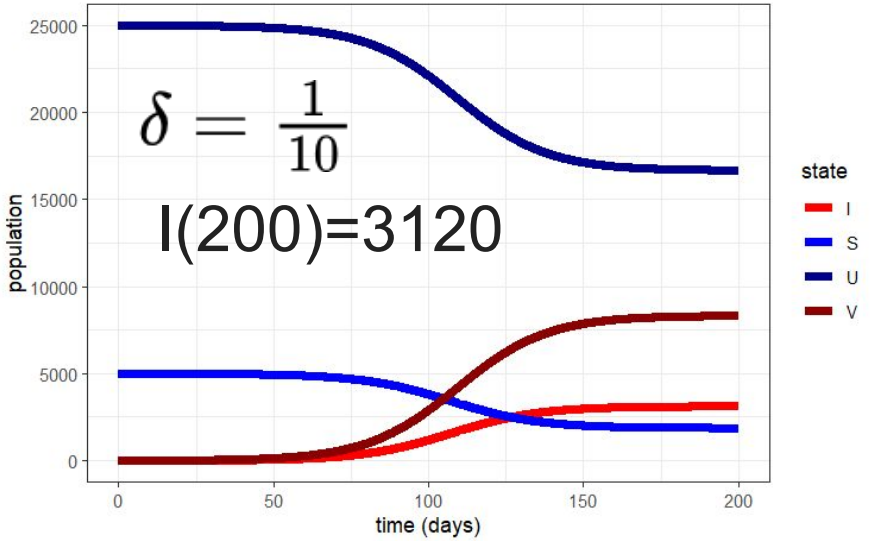

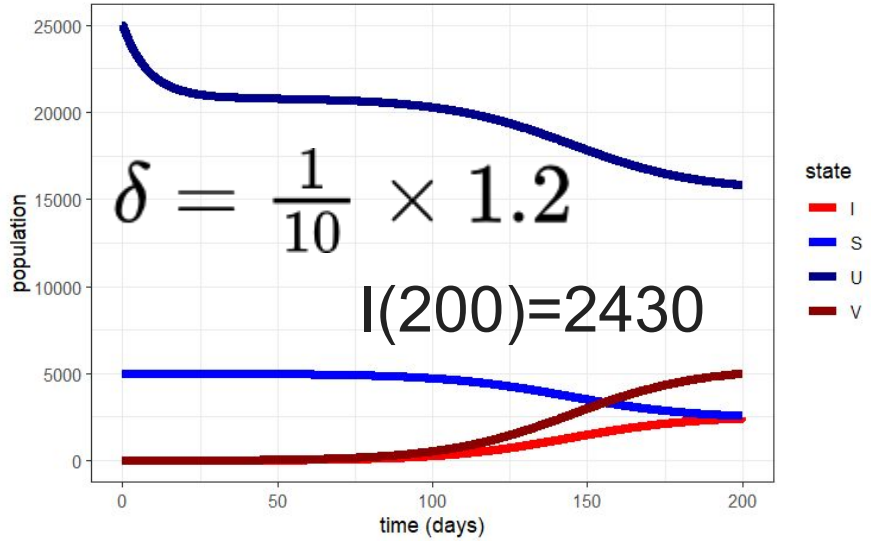

Practical

SIS-SI host-vector model with vector control

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- simulations 2&3 start from simulation 1, but add vector control as 3 times and 5 times the default mosquito mortality rate $\delta = \frac{1}{10} \quad \mu = \delta$
- **compare** the solution curves for infections in humans! discuss!

Practical

SIS-SI host-vector model with vector control

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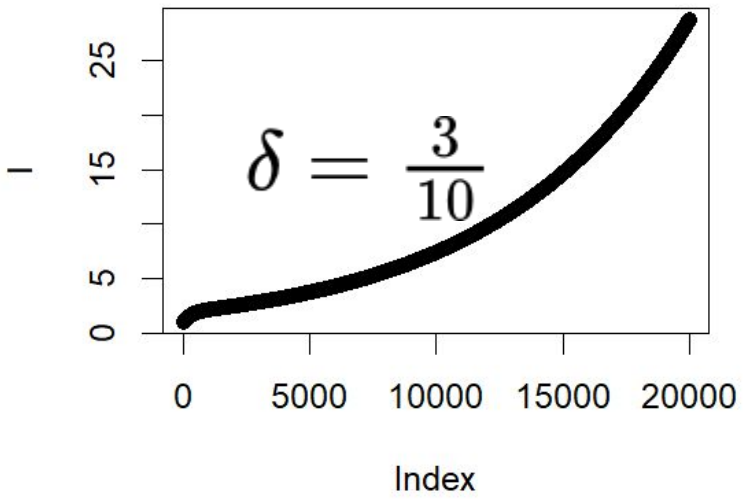

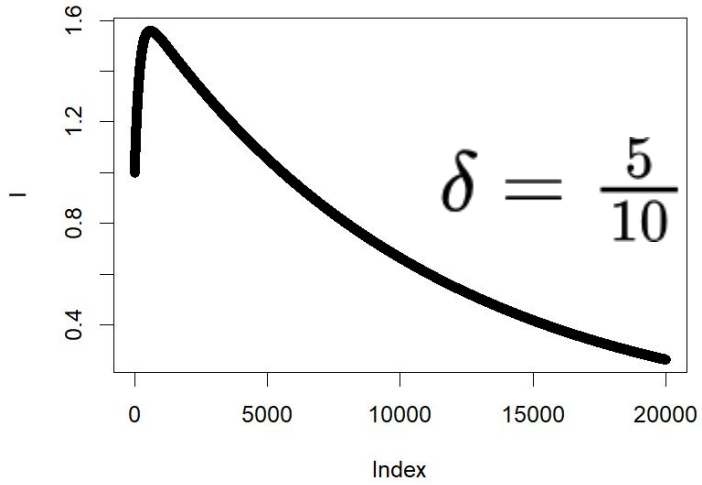

Practical

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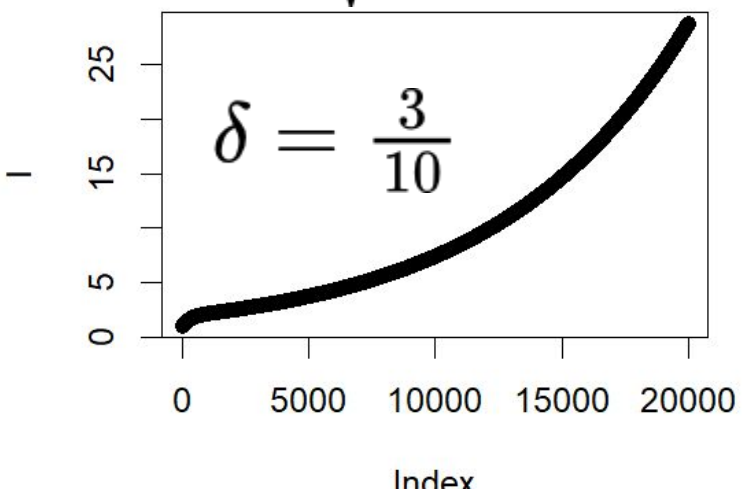

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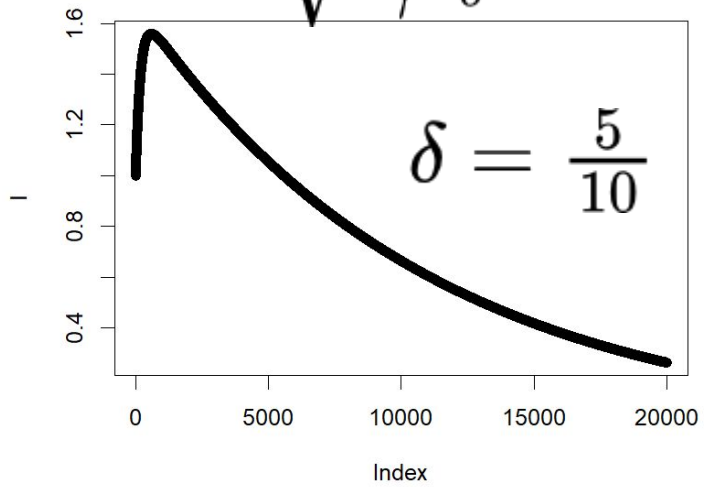

Practical

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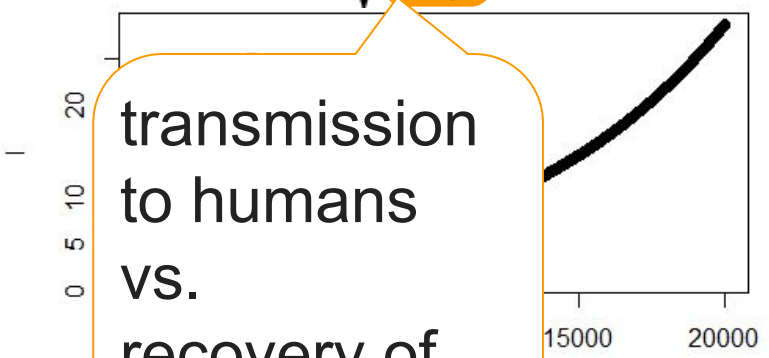

transmission to humans vs. recovery of humans

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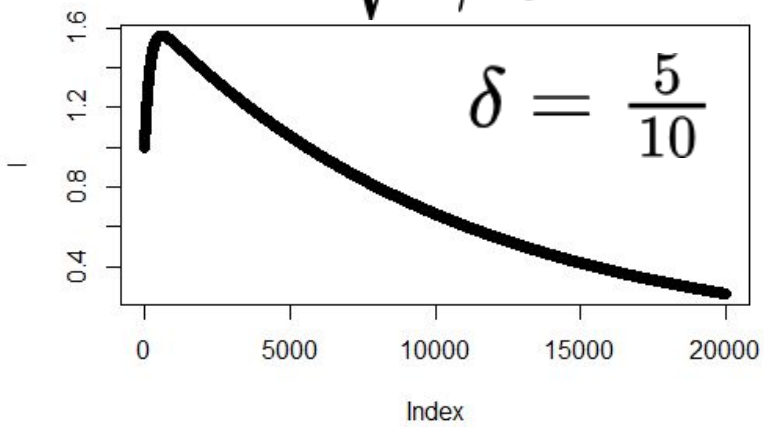

Practical

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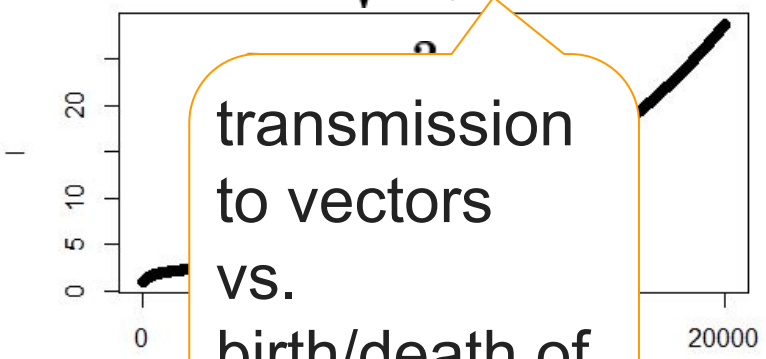
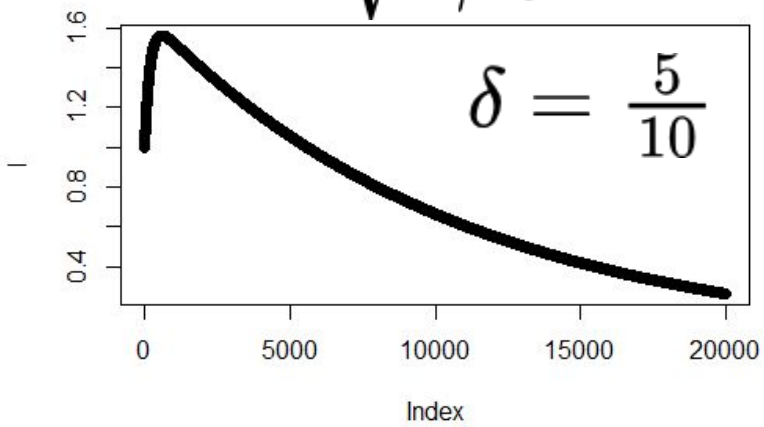


transmission to vectors vs. birth/death of vectors

$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}K} < 1$$



Practical

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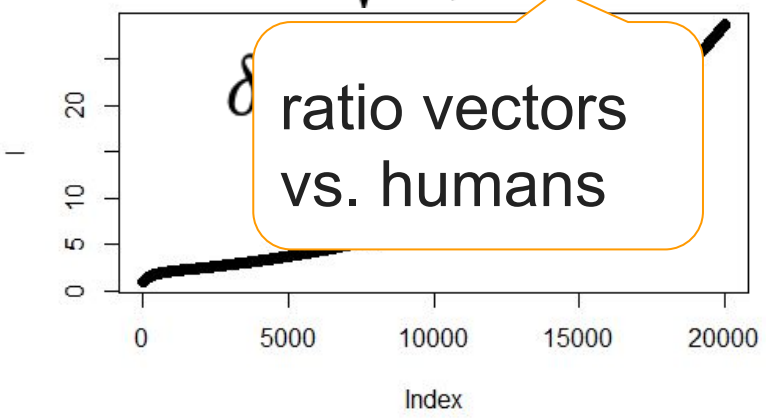

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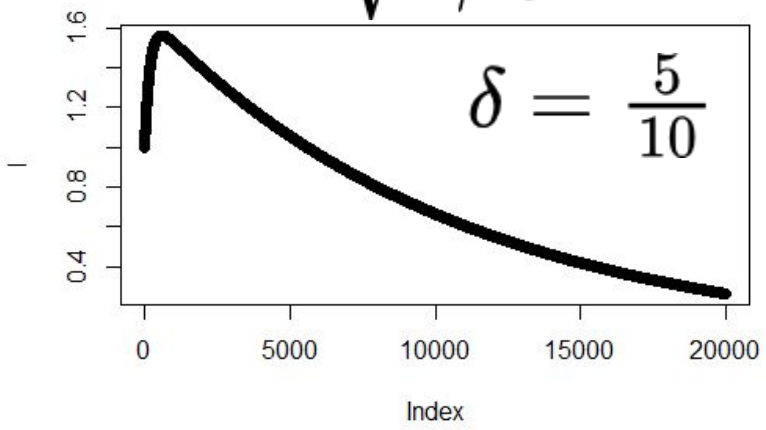
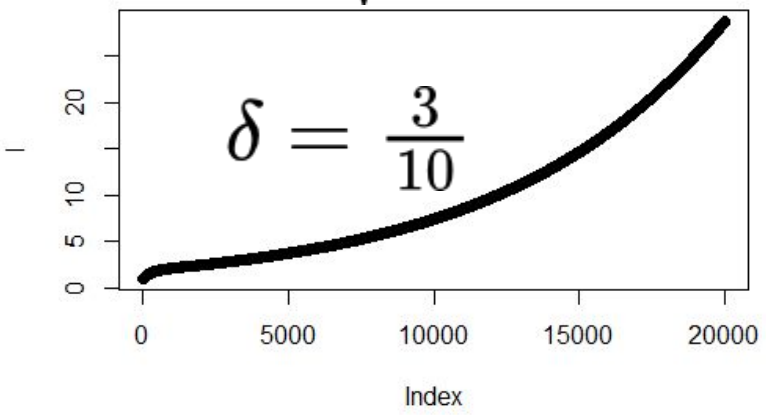


Practical

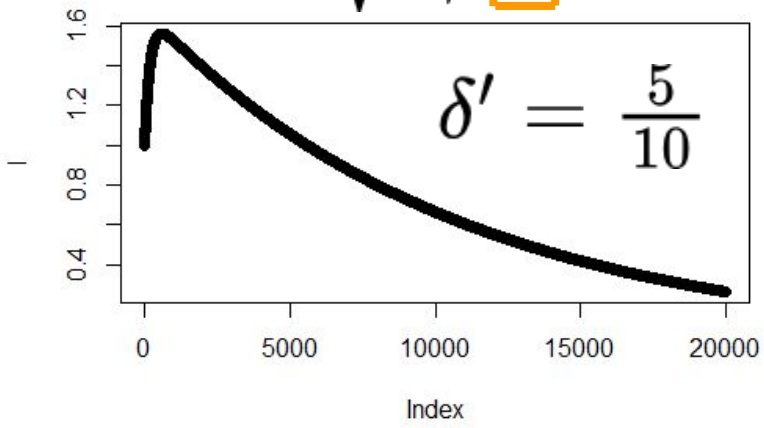
SIS-SI host-vector model with vector control

Mosquito Theorem:
vector control is a sufficient condition for malaria elimination in humans

$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}K} > 1$$



$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta'}K} < 1$$



$$\frac{K}{\delta'} = \frac{K}{\delta}\frac{3}{5} < \frac{K}{\delta}$$

Practical

SIS-SI host-vector model with vector control

We want to run and **compare** two simulations in R:

- Sweep through 20, 40, …, 300% increase in mosquito mortality $\delta = \frac{1}{10}$.
- Visualize the relationship between mosquito mortality and prevalence at the endemic equilibrium!
- **Hint**: write a function in R with δ as input parameter and **prevalence** at the endemic equilibrium as output

```
prevalence_EE<-function(delta){
   mu<-delta
   delta<-delta
#… all the simulation code goes here!
   prev_EE=tail(I,1)/H
   output=data.frame(delta=delta,EE=prev_EE)
return(output)
}
```

Practical

SIS-SI host-vector model with vector control

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- Visualize the relationship between mosquito mortality and prevalence at the endemic equilibrium!
- **Hint**: write a function in R with δ as input parameter and **prevalence** at the endemic equilibrium as output

```
delta_increase<-seq(1,5,0.2)

lapply(1/10*delta_increase,prevalence_EE)%>%
  bind_rows()->df

df%>%
  ggplot()+geom_line(aes(x=delta,y=EE))+
  scale_x_continuous(name="mosquito mortality rate")+
  scale_y_continuous(name="prevalence at equilibrium")+
  theme_bw()
```

Practical

SIS-SI host-vector model with vector control

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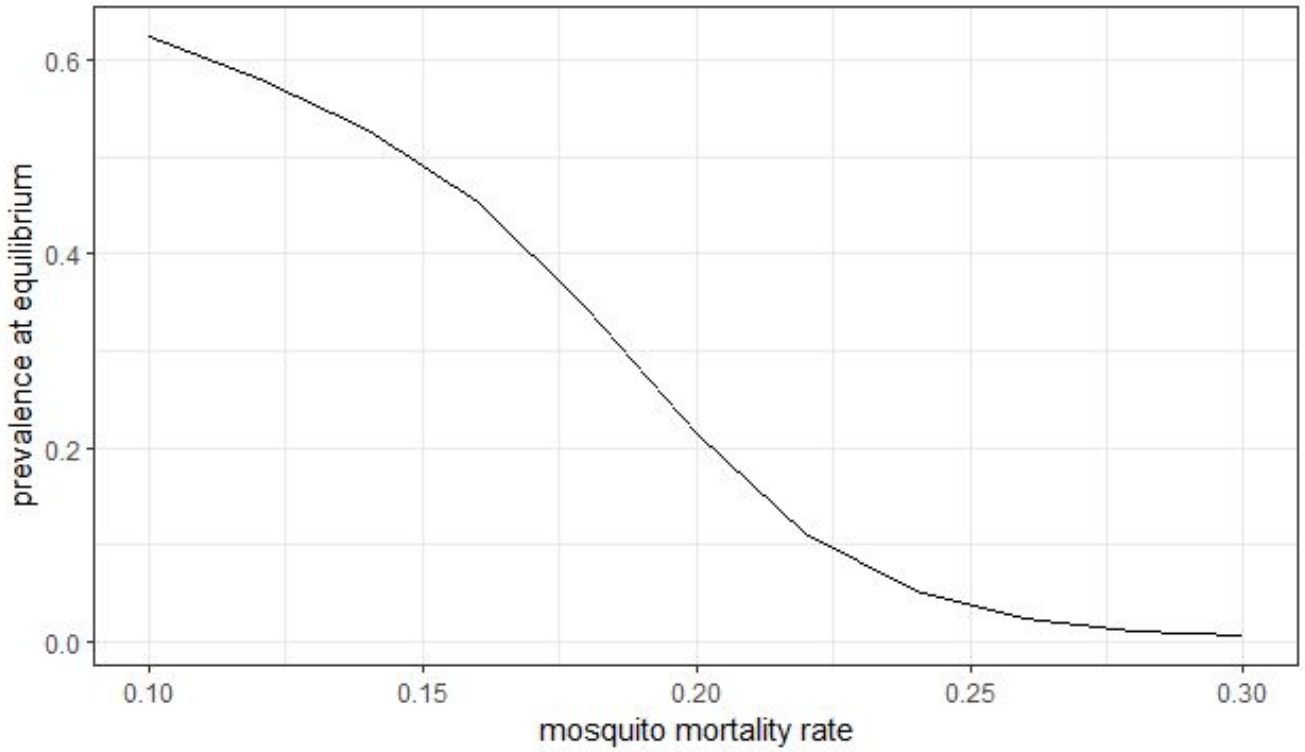
- Sweep through 20, 40, …, 300% increase in mosquito mortality $\delta = \frac{1}{10}$.
- Visualize the relationship between mosquito mortality and prevalence at the endemic equilibrium!



Ramifications of our vector-host model

What mechanisms should be included and how should those be implemented numerically?

mechanism	**model ramification**	**numerical considerations**
seasonality	transmission to humans is not constant	time-dependent coefficients from periodic function
immunity	number of past episodes influences rate for productive infection	exposed compartments for human hosts
climate	vector birth/death parameters are not constant	monotone functions from calendar time to climate variable to vector parameters
health system	compartments for humans in various stages of treatment cascade	multi-stage Markov model on top of disease transmission model

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Israel's course!

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Israel's course!

Swiss TPH

Key takeaway points:

- **host-vector** models take into account vector population dynamics and biting

- **ratio between vector and host population** can switch between two distinct quantitative infection dynamics (extinction vs endemicity)

- vector control modeled as increased vector mortality allows to **link entomological** parameters to **infection** outcomes in humans

Where can we get parameter values from?

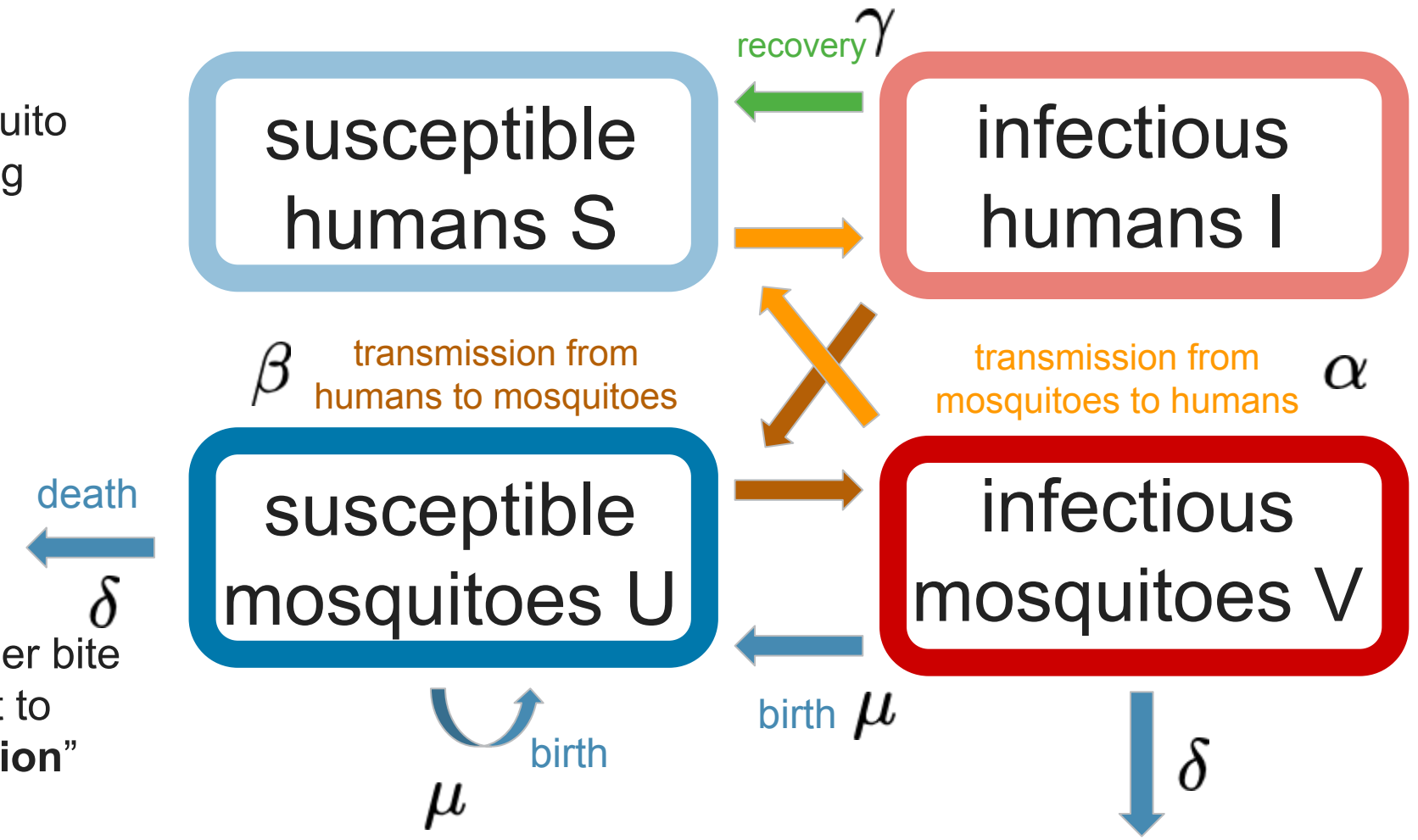
$\frac{1}{\mu}$ time span from ovipositing to emergence of adult female mosquito from pupa stage, given ovipositing

$\frac{1}{\delta}$ life span of adult female mosquito

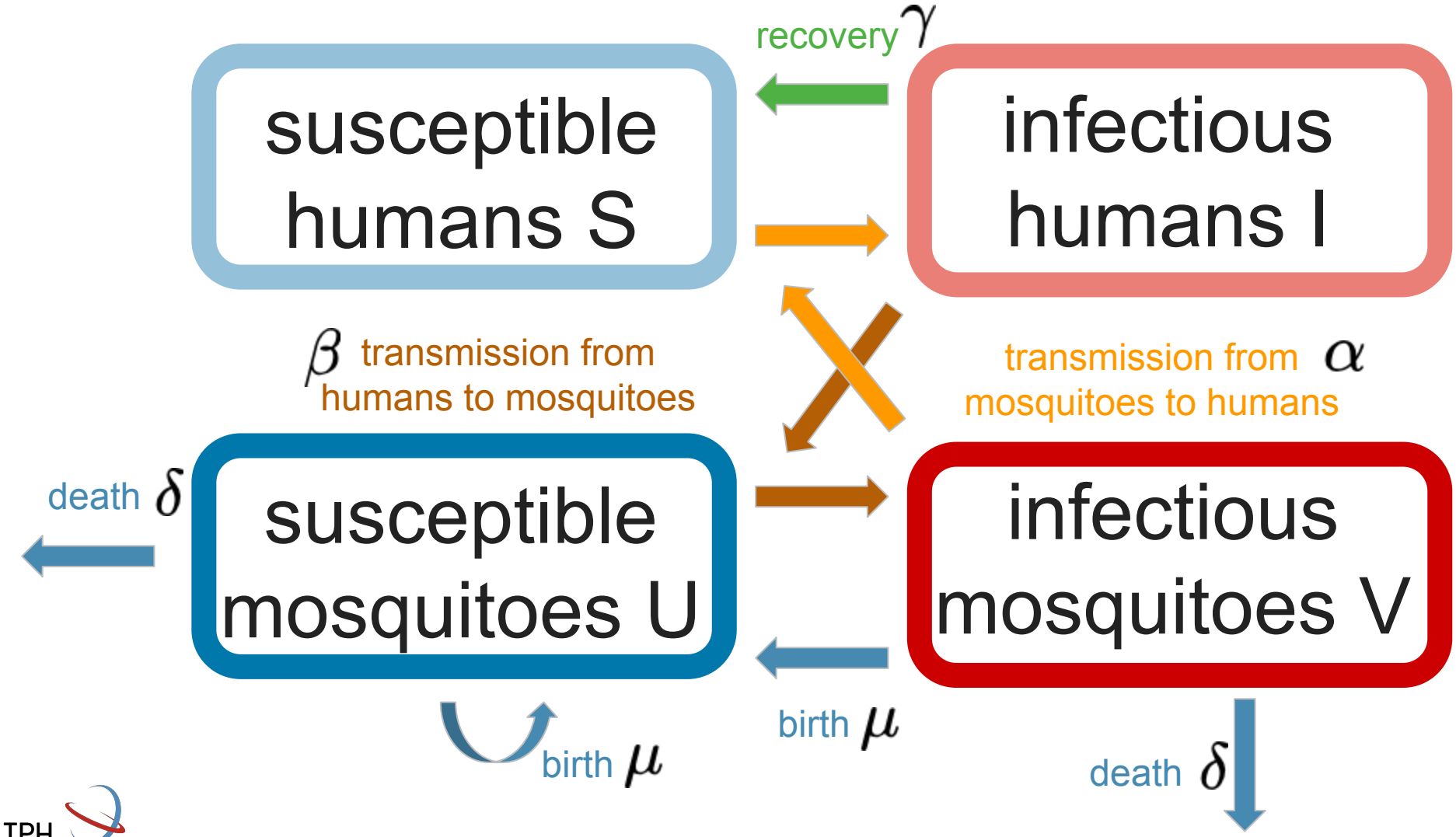
$\frac{1}{\gamma}$ duration of infection in human

α host seeking/biting X probability per bite for infectious mosquito to transmit to human: "**entomological inoculation**"

β host seeking/biting X acquisition rate from infectious human with gametocytemia to mosquito



Malaria transmission model with vector control



From infection duration to recovery rates

recovery γ

susceptible humans S

infectious humans I

$$\frac{I(t+\Delta)-I(t)}{\Delta} = -\gamma I(t)$$

$$\Delta \ll 1$$

rate γ = expected number of recovery events between time t and $t+\Delta$

From infection duration to recovery rates

recovery γ

susceptible humans S

infectious humans I

$$\frac{I(t+\Delta)-I(t)}{\Delta} = -\gamma I(t) = -\underbrace{(\gamma + \cdots + \gamma)}_{I(t) \text{ times}}$$

$\Delta \ll 1$

rate γ = expected number of recovery events between time t and $t + \Delta$

recovery events in individuals are independent from each other

From infection duration to recovery rates

recovery γ

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R random variable: **time to recovery** for infected hosts

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R random variable: time to recovery for infected hosts

Assumption: time to recovery R is **memory-less**

$$\mathbb{P}(R > t + \Delta | R > t) = \mathbb{P}(R > \Delta)$$

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R must follow exponential distribution!

From infection duration to recovery rates

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$\Delta \ll 1$

R random variable: time to recovery for infected hosts

R has exponential distribution

$$\mathbb{P}(R > \Delta) = e^{-\gamma\Delta} \quad \text{for} \quad \gamma = -\ln \mathbb{P}(R > 1)$$

From infection duration to recovery rates

recovery γ

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$$\frac{I(t+\Delta)-I(t)}{\Delta} = -\gamma I(t) = -\underbrace{(\gamma + \cdots + \gamma)}_{I(t) \text{ times}}$$

rate γ = expected number of recovery events between time t and $t + \Delta$

$$\frac{1}{\Delta}\mathbb{P}(t < R < t + \Delta | R > t) = \frac{1}{\Delta}\frac{\int_t^{t+\Delta} \gamma e^{-\gamma x} dx}{e^{-\gamma t}} \approx \gamma \qquad \Delta \ll 1$$

frequency of instantaneous recovery events given exponential distribution

"hazard function" or "intensity of recovery"

From infection duration to recovery rates

recovery γ

susceptible humans S

infectious humans I

$$\frac{I(t+\Delta)-I(t)}{\Delta} = -\gamma I(t) = -\underbrace{(\gamma + \cdots + \gamma)}_{I(t) \text{ times}}$$

γ = intensity of recovery

Which data can be used to get a numerical value for γ ?

From infection duration to recovery rates

recovery γ

susceptible humans S

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time to recovery = infection duration

R has exponential distribution: $\mathbb{E}(R) = \frac{1}{\gamma}$

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From infection duration to recovery rates

recovery γ

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$$\frac{I(t+\Delta)-I(t)}{\Delta} = -\gamma I(t) = -\underbrace{(\gamma + \cdots + \gamma)}_{I(t) \text{ times}}$$

γ = intensity of recovery = $\frac{1}{\text{average infection duration}}$

Which data can be used to get a numerical value for γ ?

time to recovery = infection duration

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Practical: Numerical values for parameters

Infection duration

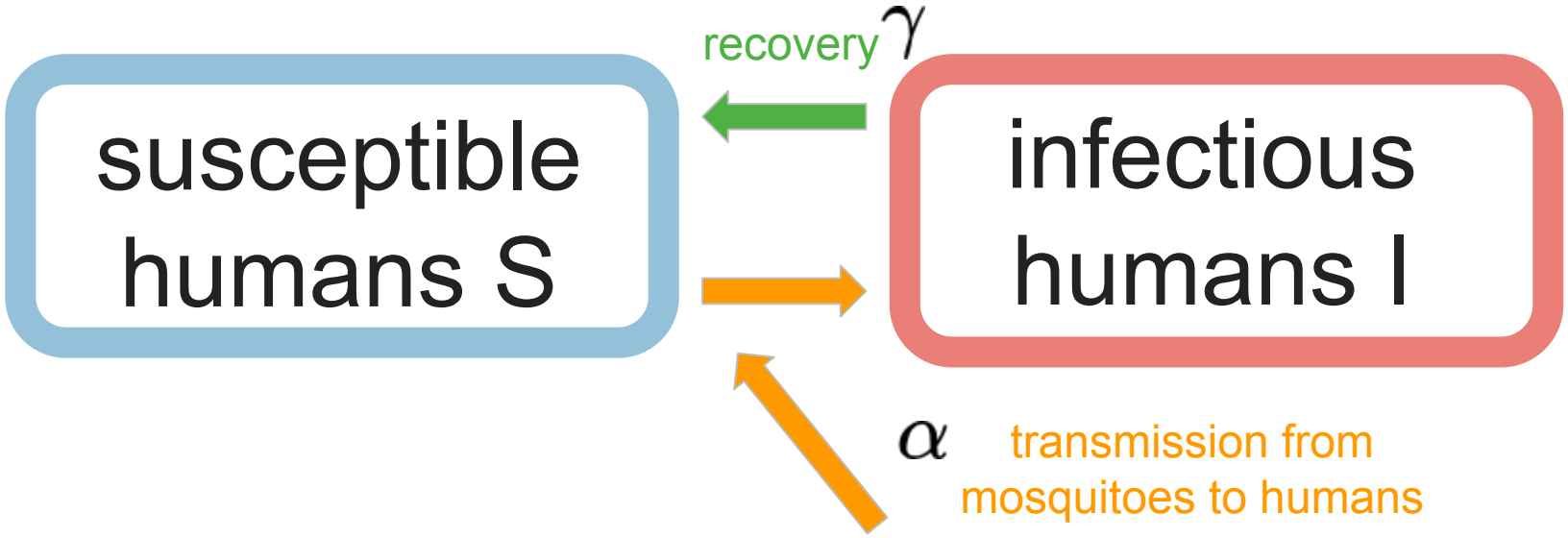
- Download the paper:

Chitnis et al.: *Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model*, Bull Math Bio 2008

- Discuss difference between our simplified Ross-McDonald model and equations 1a) - 1g) in the paper

- Search in the appendix A for possible values of **infection duration** in human hosts

Malaria transmission model with vector control



α_1 α_2

α = biting rate x probability of transmission

host seeking
number of bites mosquitoes can make
number of bites human can receive

infectiousness of pathogen strain
parasite sporozoite load

entomological inoculation rate (EIR): EIR = HBR x PfSR

Practical: Numerical values for parameters

Biting rates and infection probability

- Download the paper:

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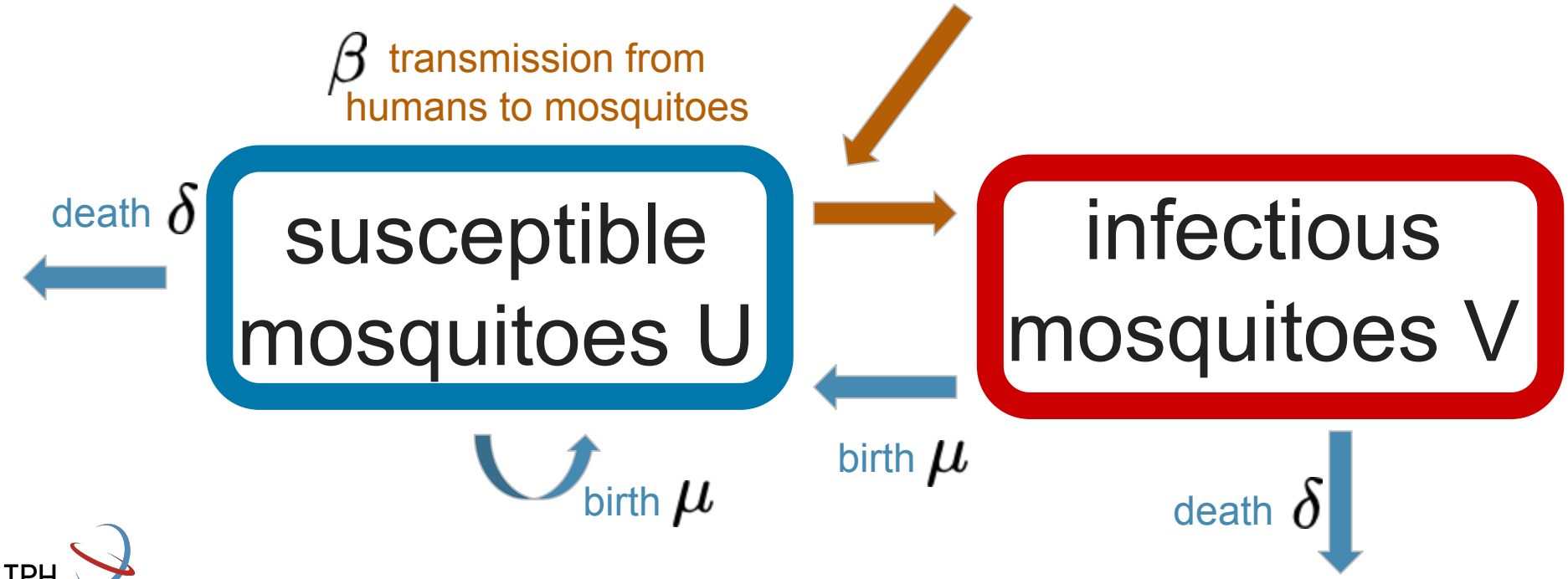
- Search in the table 2&3 (baseline high) possible values of **biting rates** and **probability** of infection

Malaria transmission model with vector control



Practical: Numerical values for parameters

Mosquito life cycle and infections to humans

- Download the paper:

Chitnis et al.: *Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model*, Bull Math Bio 2008

- Search in the table 2&3 (baseline high) possible values of **mosquito birth and death rates** and **probability** of infection from humans to mosquitoes

Practical 6d: Simulate with numerical values!

parameter	description	value	unit
gamma	reciprocal of untreated infection duration		1/day
alpha_1	biting rate within gonotrophic cycle		1/day
alpha_2	probability of transmission to humans		1
delta_1	density-independent mosquito mortality rate		1/day
delta_2	density-dependent mosquito mortality rate		1/mosquito 1/day
mu	per capita mosquito birth rate		1/day
beta	probability of transmission to mosquitoes		1

Practical 6d: Simulate with numerical values!

parameter	description	value	unit
gamma	reciprocal of untreated infection duration	1/285	1/day
alpha_1	biting rate within gonotrophic cycle	0.5	1/day
alpha_2	probability of transmission to humans	0.022	1
delta_1	density-independent mosquito mortality rate	0.033	1/day
delta_2	density-dependent mosquito mortality rate	0.00002	1/mosquito 1/day
mu	per capita mosquito birth rate	0.13	1/day
beta	probability of transmission to mosquitoes	0.48	1

Practical 6d: Simulate with numerical values!

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mu	per capita mosquito birth rate	0.13	1/day
beta	probability of transmission to mosquitoes	0.48	1

```
H=5000; I0=1; V0=8; VectorHumanRatio=5; finalT=1*365
x0 <- c(S=H-I0,I=I0,U=H*VectorHumanRatio-V0,V=V0)##initial condition
timesteps<-seq(0,finalT,1)##time unit in days
alpha1<- 0.5; alpha2<-0.022; alpha=alpha1*alpha2; delta1=0.033; delta2=2*10^-05
delta=delta1+H*VectorHumanRatio*delta2
parms <- c(alpha=alpha, gamma=1/285,beta=0.48, mu=0.13,delta=0.13)
results<-ode(x0,timesteps,RossMcDonald.model,parms)%>%
  as.data.frame
```

Practical 6d: Simulate with numerical values!

parameter	description	value	unit
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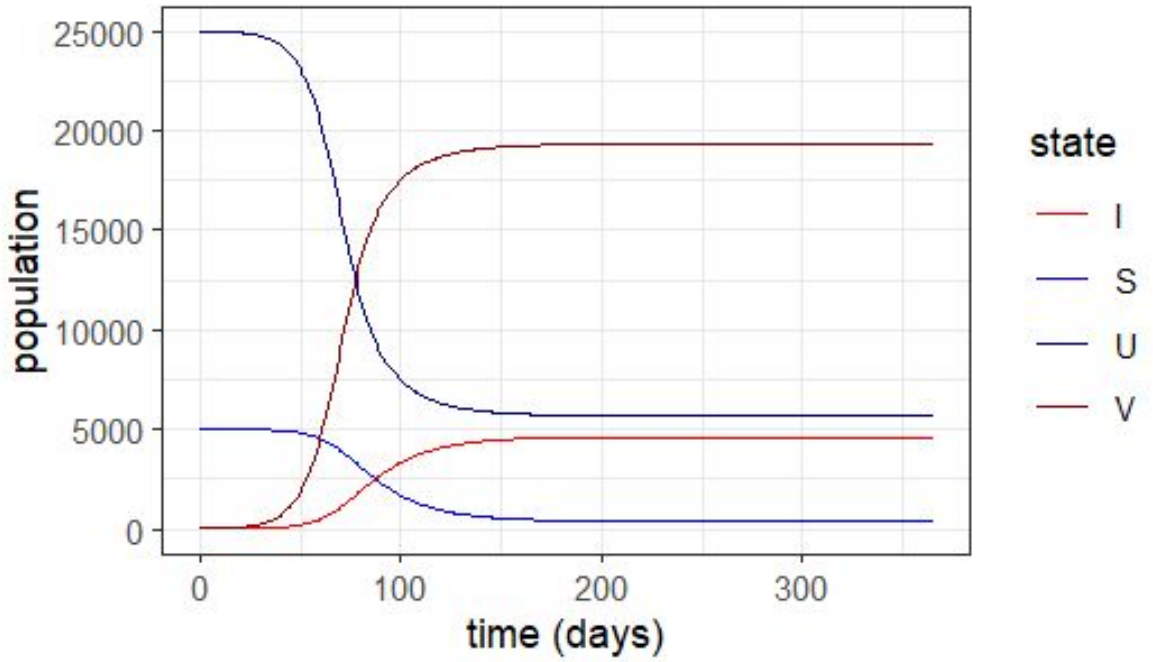
delta_2	density-dependent mosquito mortality rate	0.00002	1/mosquito 1/day
mu	per capita mosquito birth rate	0.1	
beta	probability of transmission to mosquitoes	0.4	



Key takeaway points:

- ordinary differential equations are **memory-less**
- **time to event** in compartment (e.g. recovery) is interpreted as **exponentially distributed** random variable
- **rate** of such event is reciprocal of expected value, such that numerical values for rates can be derived from **average duration** data (e.g. infection, life,...)

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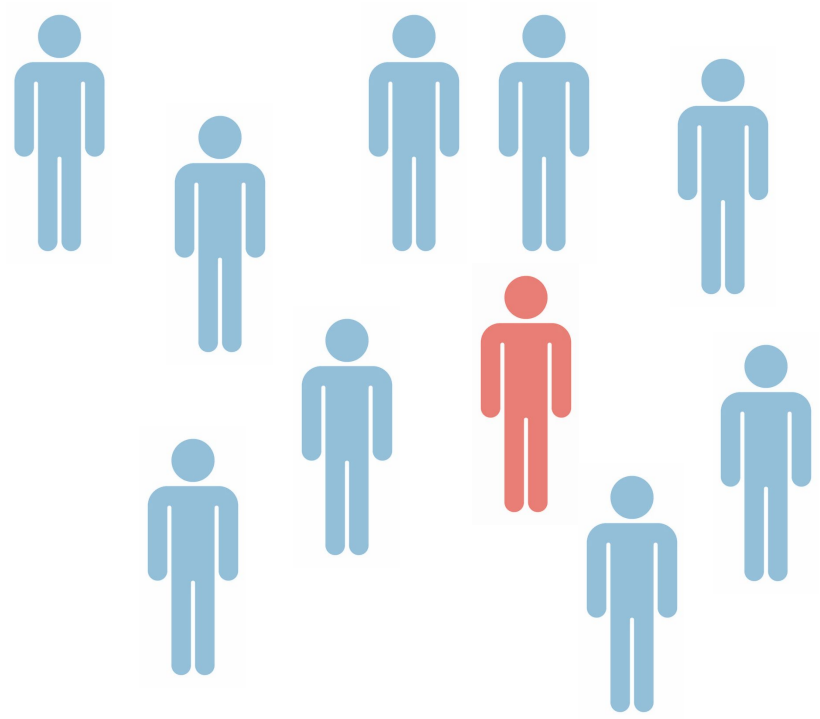
2 - RO

Snapshots of disease prevalence

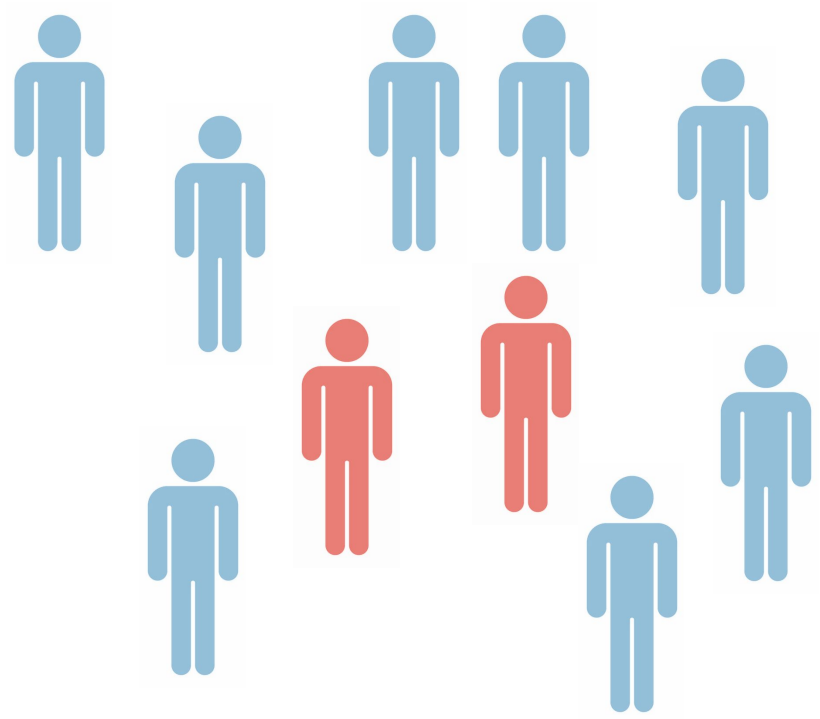


healthy: 9

sick: 1

day: 0

Snapshots of disease prevalence

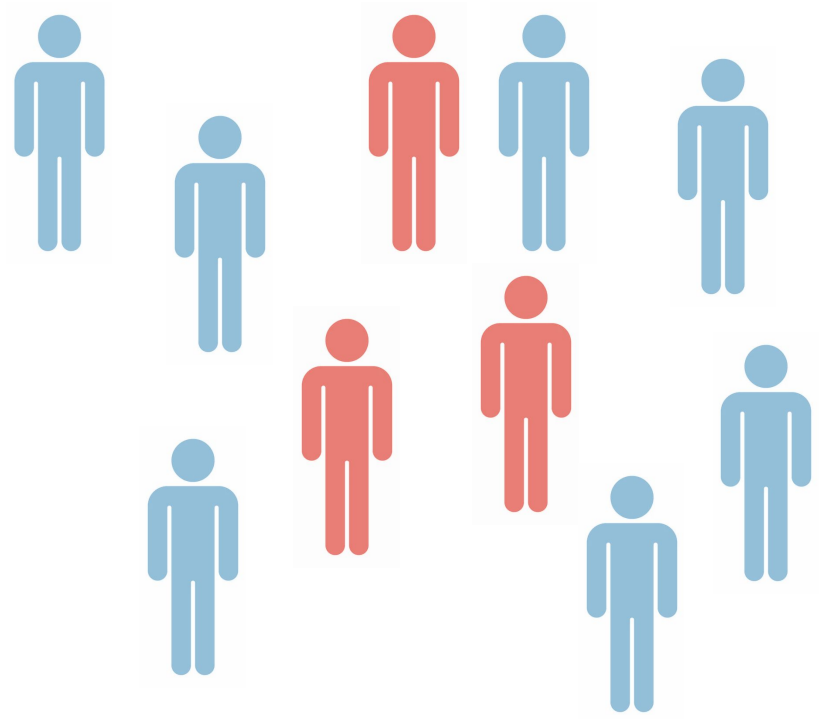


healthy: 8

sick: 2

day: 1

Snapshots of disease prevalence

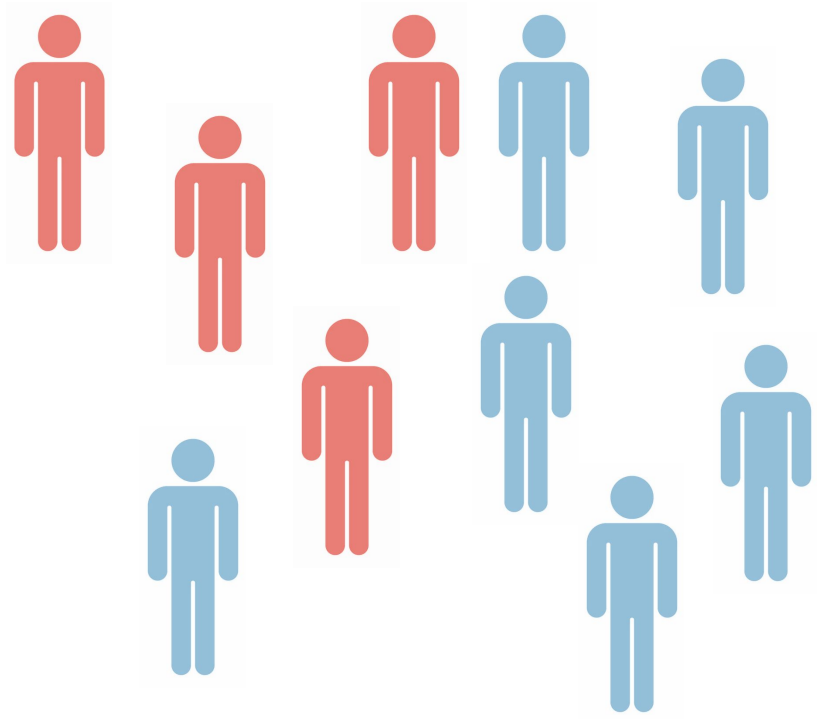


healthy: 7

sick: 3

day: 2

Snapshots of disease prevalence

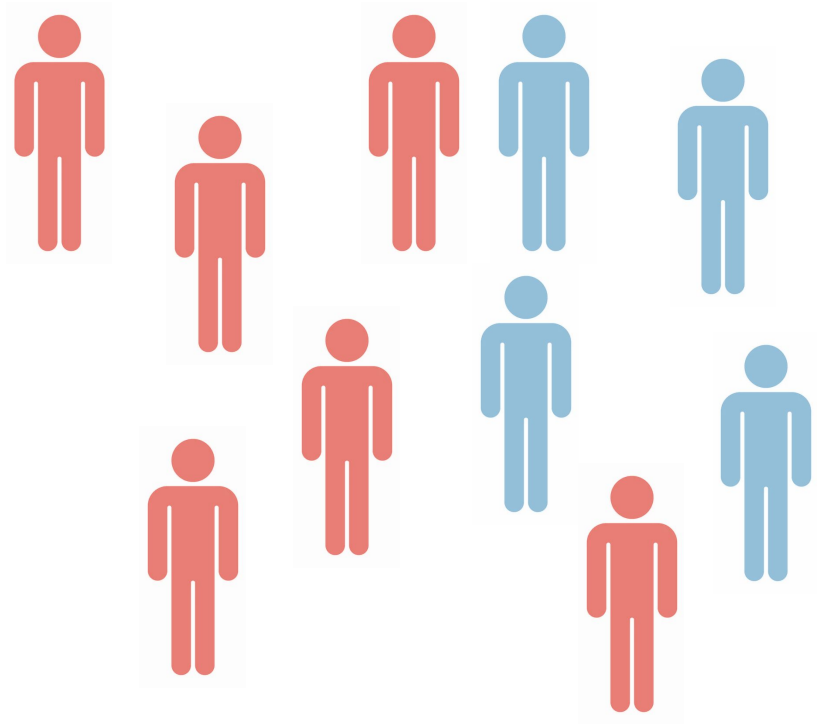


healthy: 6

sick: 4

day: 3

Snapshots of disease prevalence

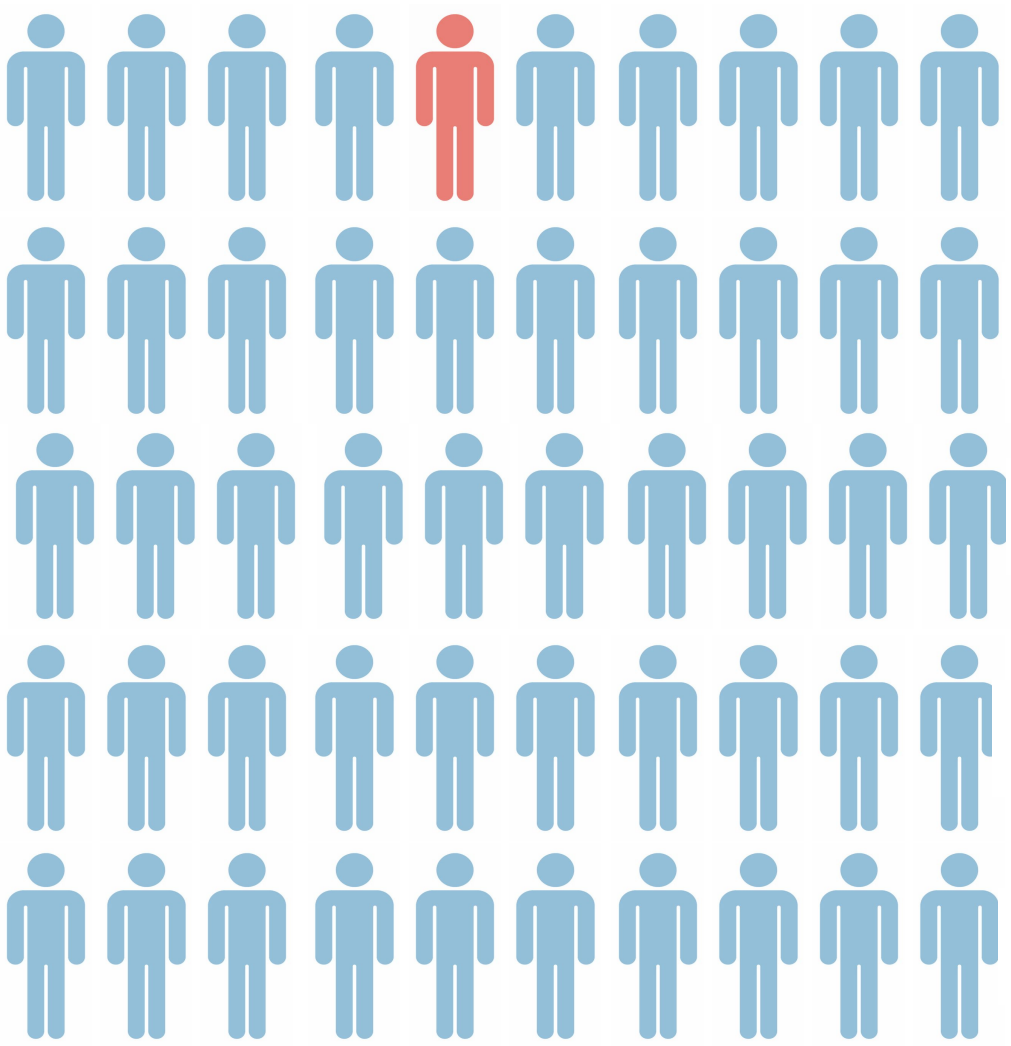


healthy: 4

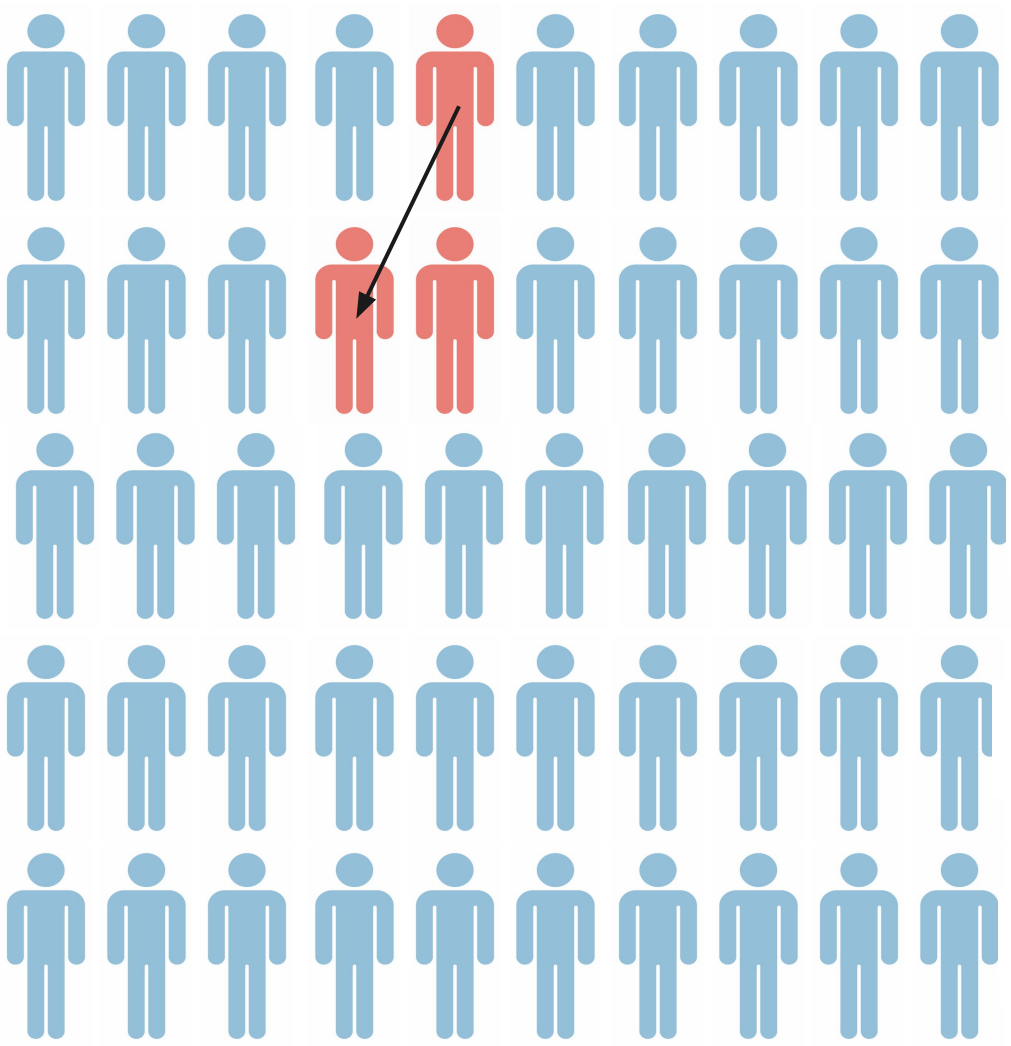
sick: 6

day: 4

Generations



Generations



day: 0

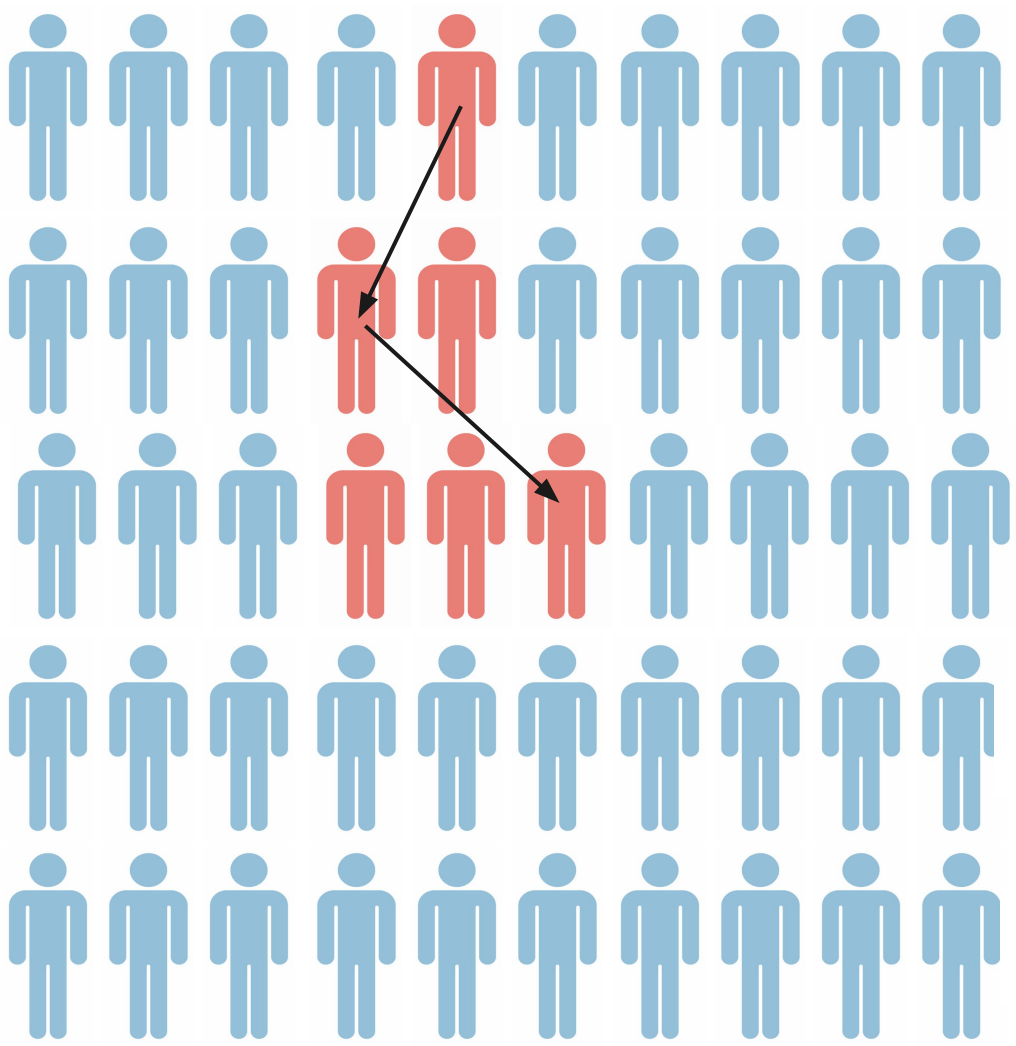
day: 1 new infection: +1

day: 2

day: 3

day: 4

Generations



day: 0

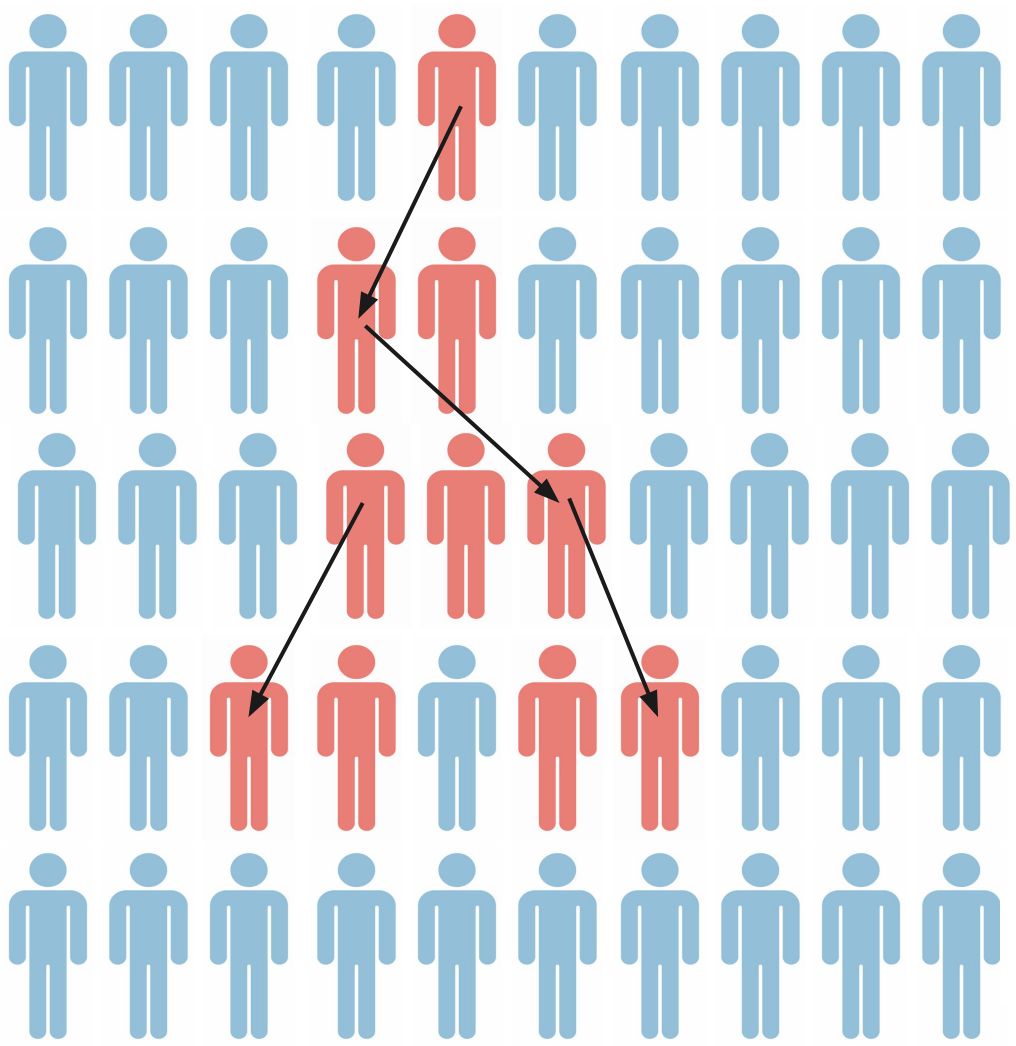
day: 1 new infection: +1

day: 2 new infection: +1

day: 3

day: 4

Generations



day: 0

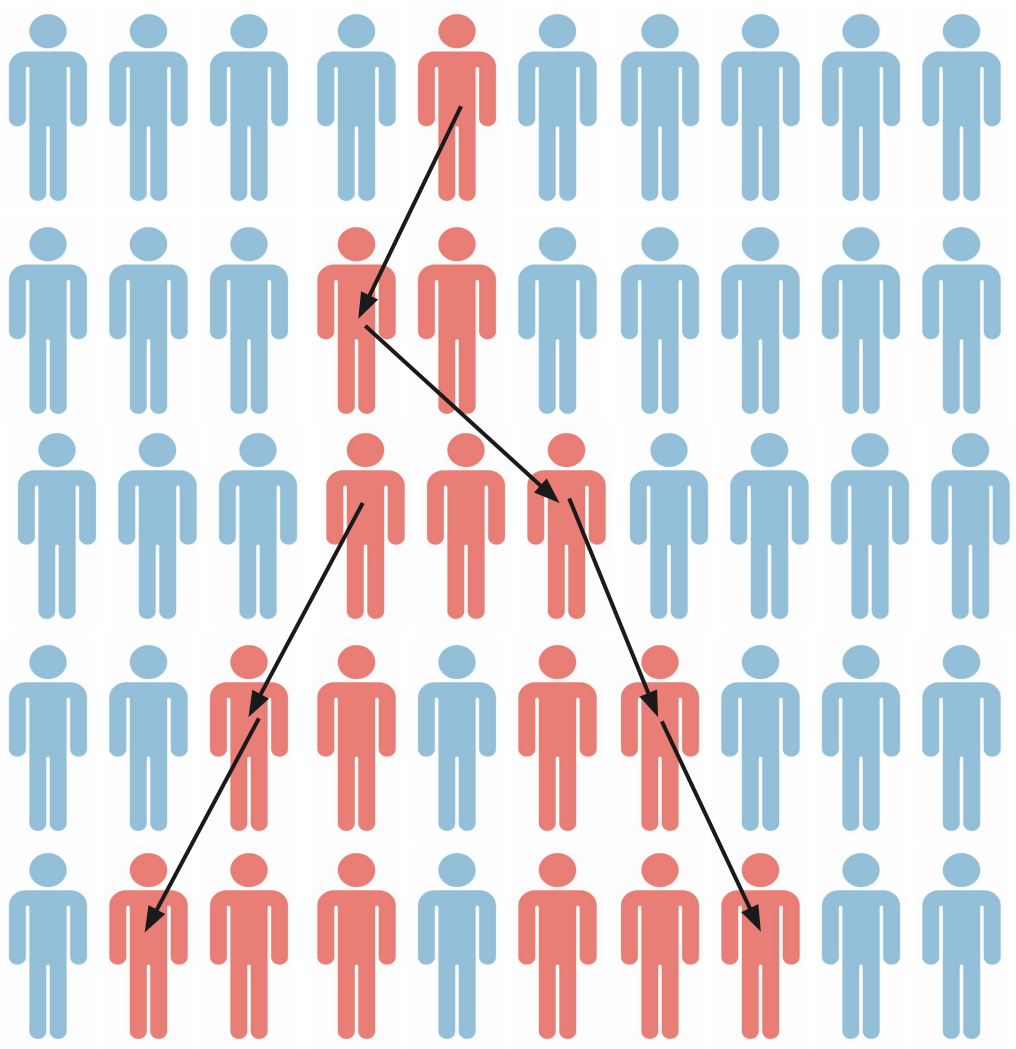
day: 1 new infection: +1

day: 2 new infection: +1

day: 3 new infection: +2 recovery: -1

day: 4

Generations



day: 0

day: 1 new infection: +1

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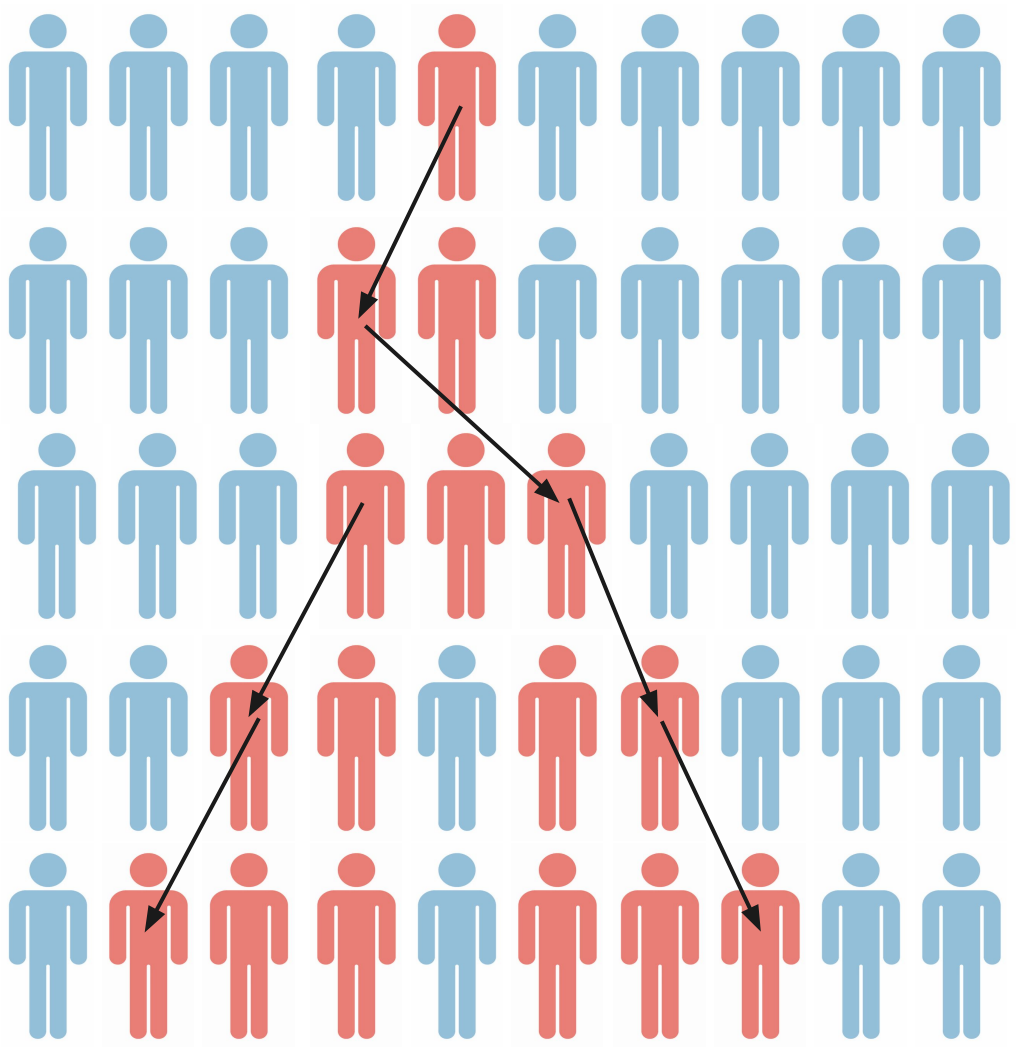
day: 4 new infection: +2

Generations



day: 0

growth rate r:
per capita **change in number of new cases** per unit of time
r= (1+1+2-1+2)/4/10=0.125

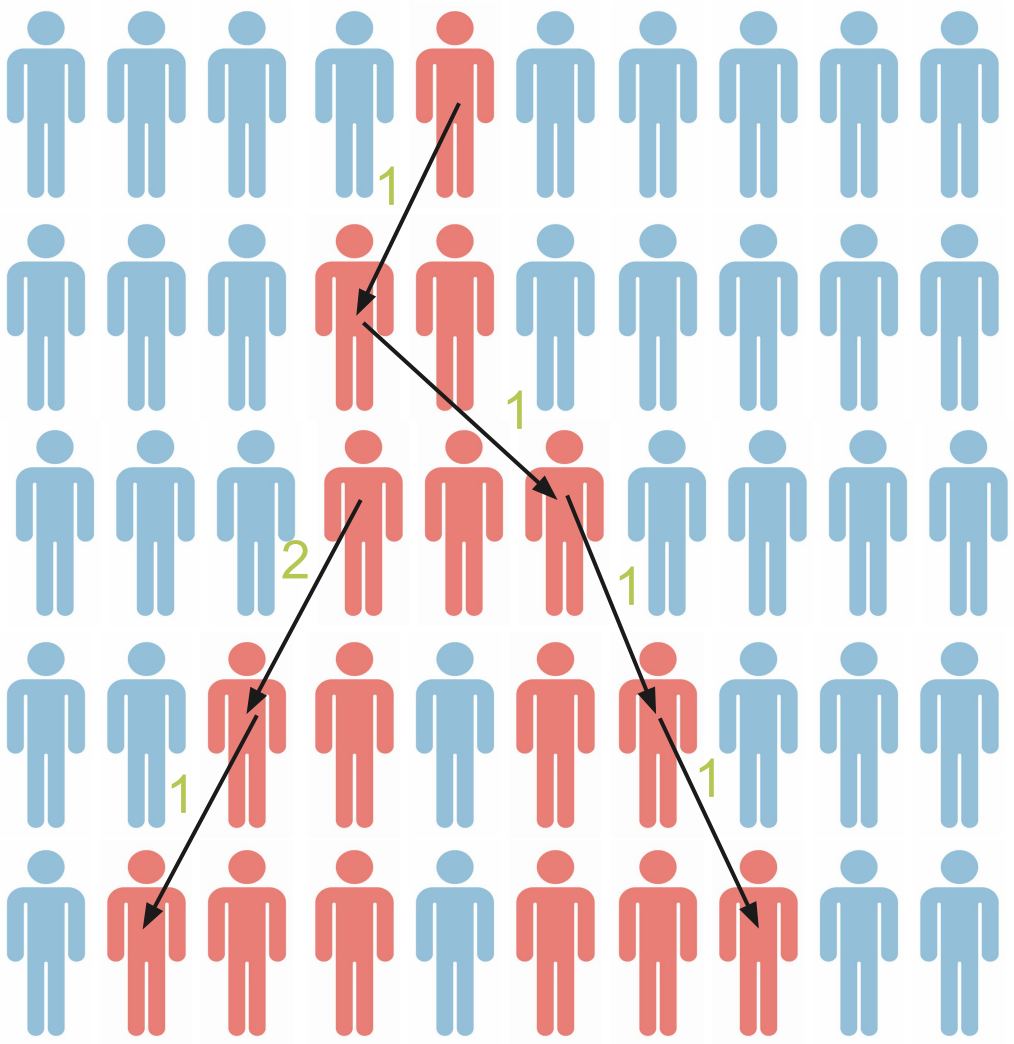
day: 1 new infection: +1

day: 2 new infection: +1

day: 3 new infection: +2 recovery: -1

day: 4 new infection: +2

Generations



day: 0

day: 1 new infection: +1

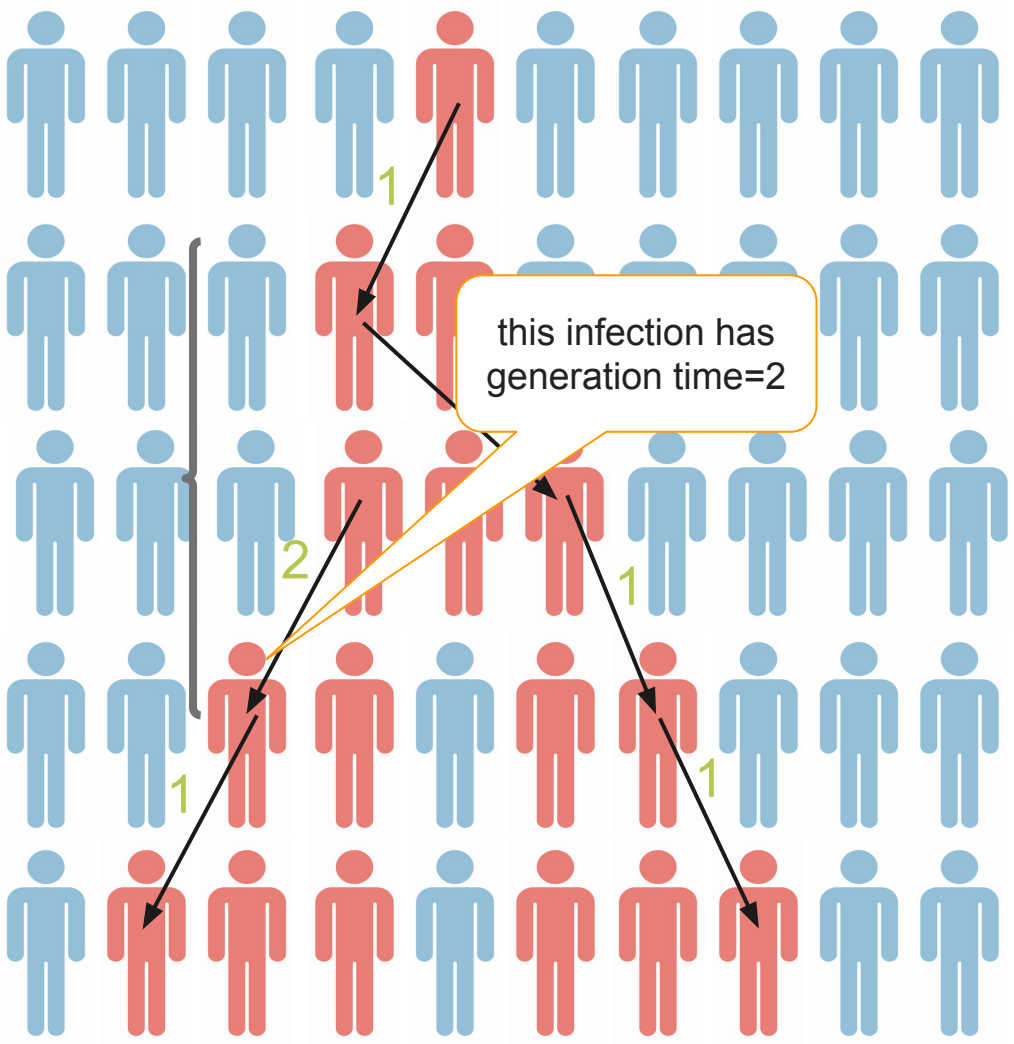
day: 2 new infection: +1

day: 3 new infection: +2 recovery: -1

day: 4 new infection: +2

generation time T:
mean duration between time of infection of a secondary infectee and the time of infection of its primary infector
T= (1+1+2+1+1+1)/6=1.16

Generations



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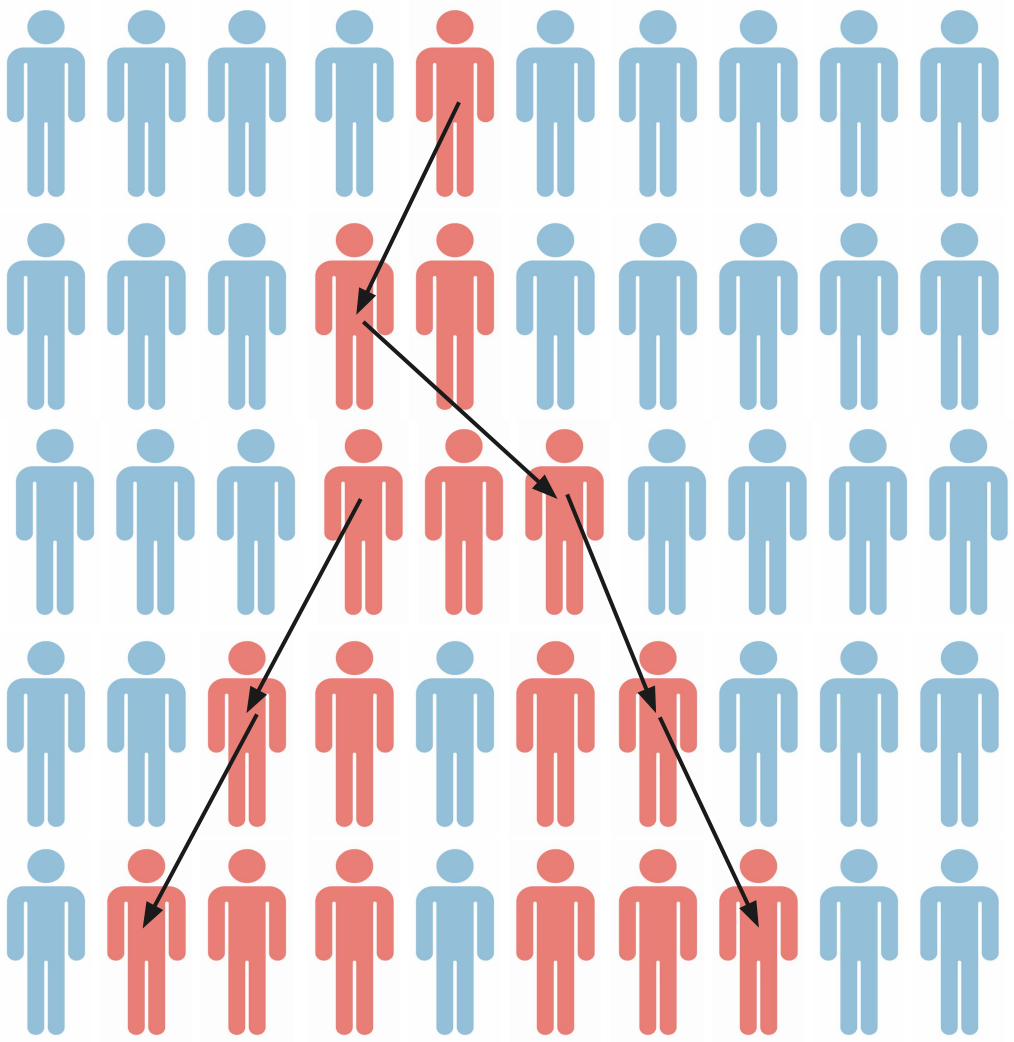
Basic reproduction number



secondary infections caused by each host, average: 6/5>1

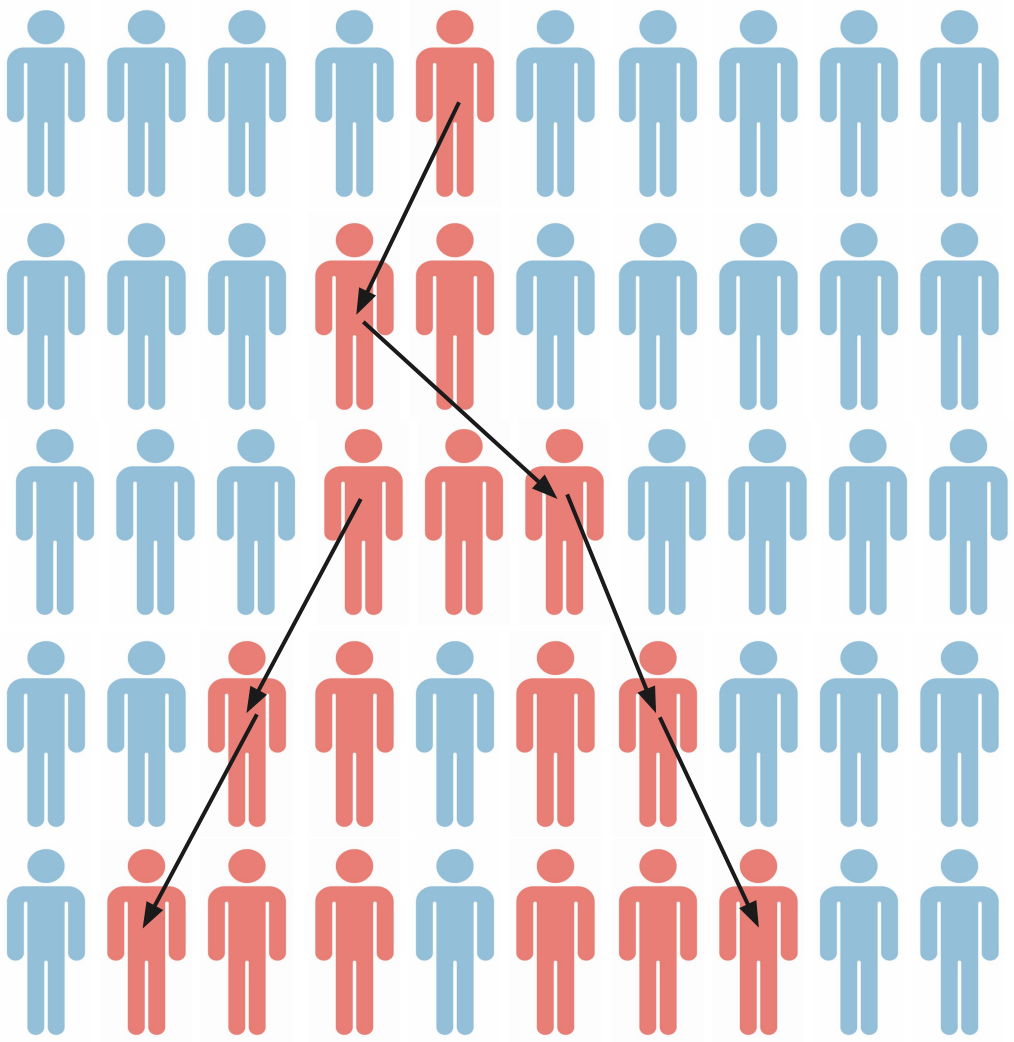
basic reproduction number $\mathcal{R}_0$:

"expected number of secondary infections that arise from a typical primary case during its entire period of infectiousness in a completely susceptible population"

$$\mathcal{R}_0 > 1$$

initial outbreak will result in full-scale epidemic!

Basic reproduction number



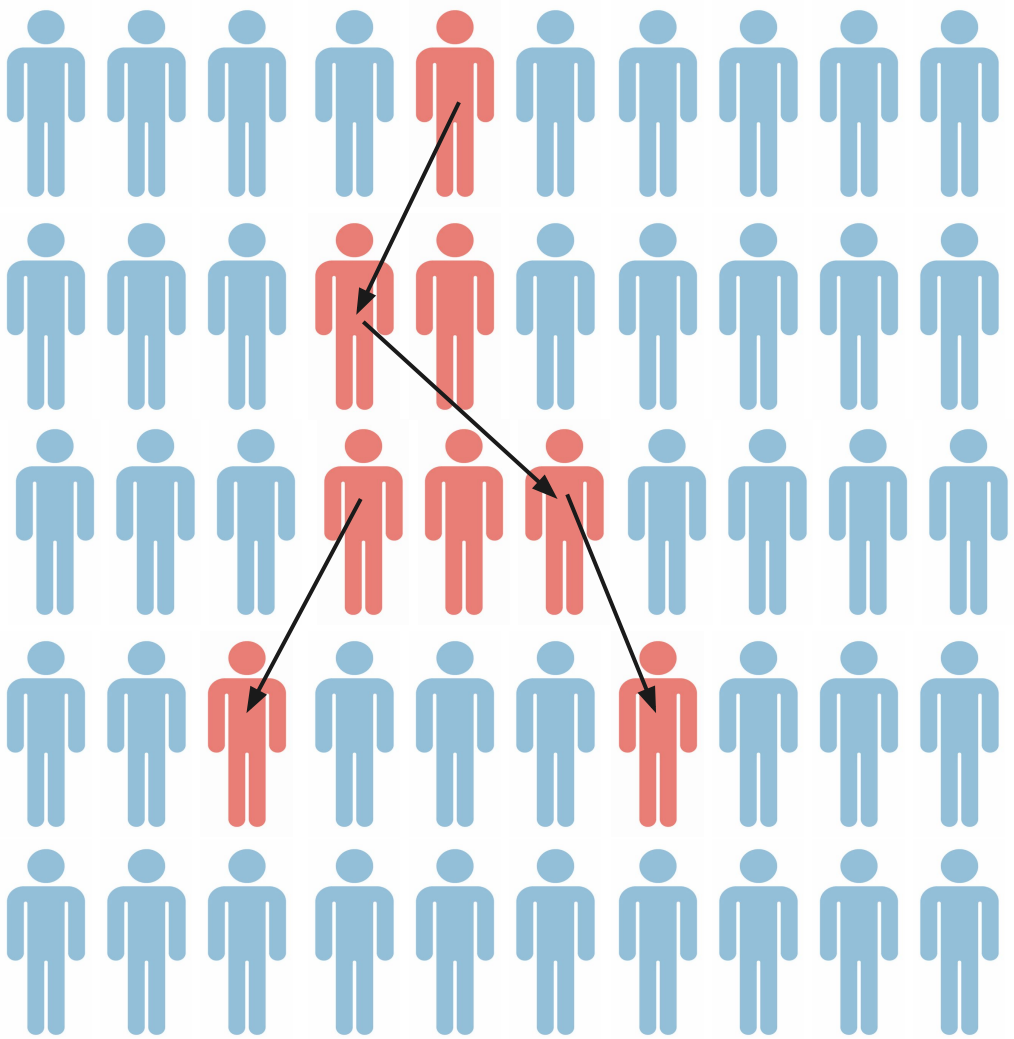
basic reproduction number $\mathcal{R}_0$:

"expected number of secondary infections that arise from a typical primary case during its entire period of infectiousness in a completely susceptible population"

$$\mathcal{R}_0 = 1 + rT$$

$$\mathcal{R}_0 = 1 + 0.125 \times 1.16 = 1.1458$$

Basic reproduction number



secondary infections caused by each host, average: 4/5<1

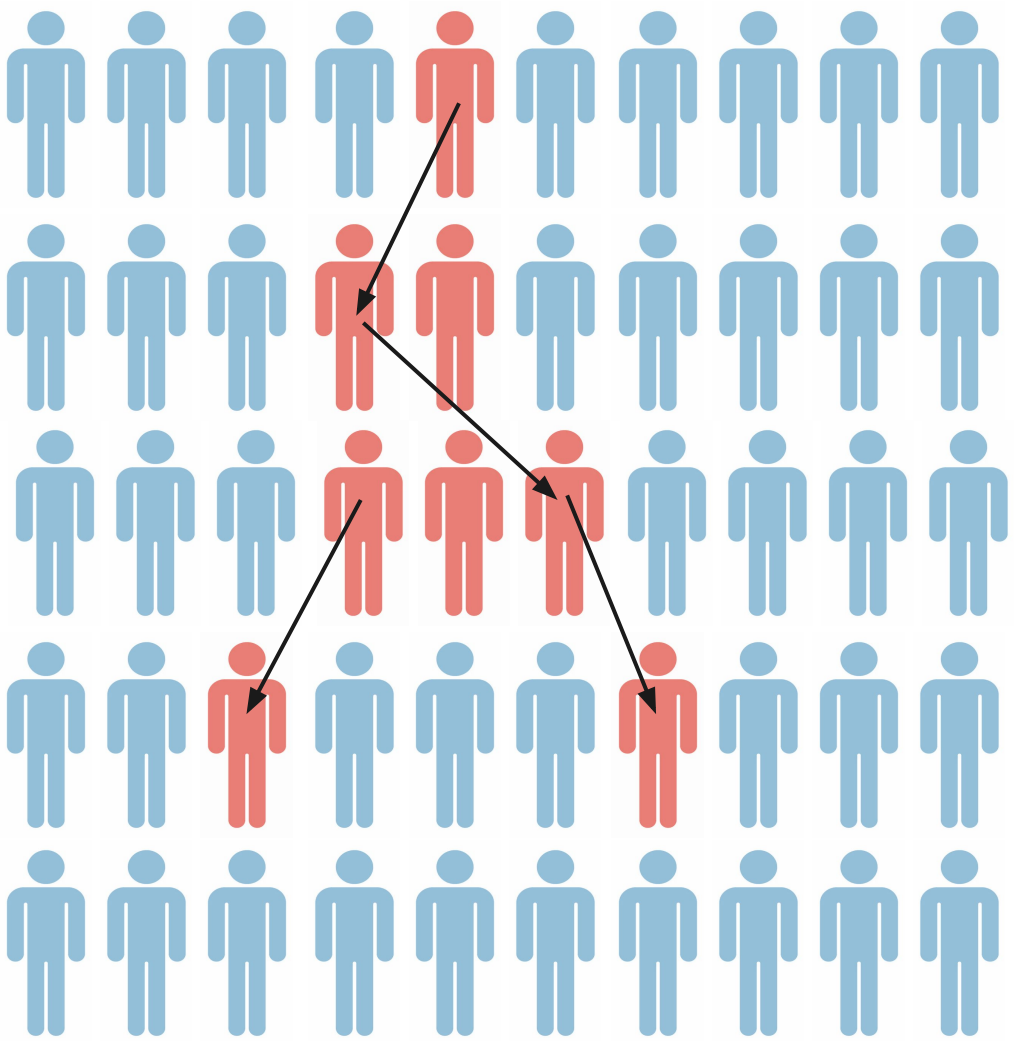
basic reproduction number $\mathcal{R}_0$:

"expected number of secondary infections that arise from a typical primary case during its entire period of infectiousness in a completely susceptible population"

$$\mathcal{R}_0 < 1$$

initial outbreak quickly dies out!

Basic reproduction number

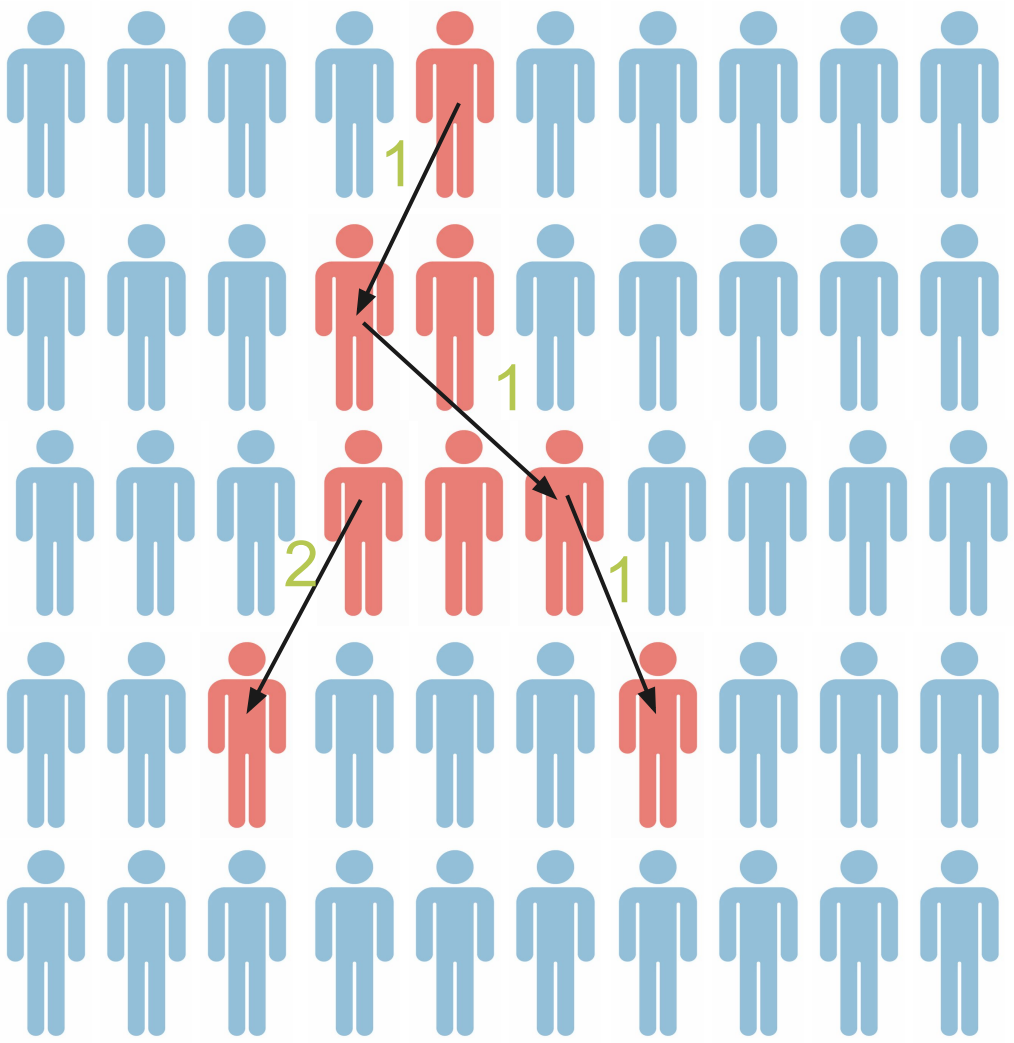


0 2 1 1 0

secondary infections caused by each host, average: 4/5<1

Calculate growth rate r and generation time T based on this observation!

Basic reproduction number



secondary infections caused by each host, average: 4/5<1

Calculate growth rate r and generation time T based on this observation!

r=(1+1-3+2-2)/4/10=-1/40

T=(1+1+2+1)/4=5/4

$$\mathcal{R}_0 = 1 + rT$$ =0.96875

Lotka-Euler equation and basic reproduction number

$n(a)$ rate of new infection at generation time *a*

$b(t) = \int_{a \geq 0} b(t-a) n(a) da$ "renewal equation for new infections"

$b(t) = b(t-a) e^{ra}$ exponential growth with rate *r*

$$b(t) = \int_{a \geq 0} b(t) e^{-ra} n(a) da$$

$$1 = \int_{a \geq 0} e^{-ra} n(a) da$$ "Lotka-Euler equation"

$\mathcal{R}_0 = \int_{a \geq 0} n(a) da$ total number of secondary infections from a host with generation times *a*

generation time = infection duration probability distribution: $g(a) = \frac{n(a)}{\mathcal{R}_0}$

from Lotka-Euler: $\frac{1}{\mathcal{R}_0} = \int_{a \geq 0} e^{-ra} g(a) da$

Lotka-Euler equation and basic reproduction number

from Lotka-Euler: $\frac{1}{\mathcal{R}_0} = \int_{a \geq 0} e^{-ra} g(a) da$

$M_f(z) = \int_{a \geq 0} e^{za} f(a) da$ "moment-generating function of probability distribution f"

$$\mathcal{R}_0 = \frac{1}{M_g(-r)}$$

Now back to **ODE models**: we have seen that from the **memory-less property of time to recovery** it follows that infection duration must be exponentially distributed with intensity: $\gamma = 1/T$

$$g(a) = \gamma e^{-\gamma a}$$

$$M_g(z) = \frac{\gamma}{\gamma - z}$$

$$\mathcal{R}_0 = \frac{\gamma + r}{\gamma} = 1 + \frac{r}{\gamma} = 1 + rT$$

Lotka-Euler equation and basic reproduction number

from Lotka-Euler: $\frac{1}{\mathcal{R}_0} = \int_{a \geq 0} e^{-ra} g(a) da$

$M_f(z) = \int_{a \geq 0} e^{za} f(a) da$ "moment-generating function of probability distribution f"

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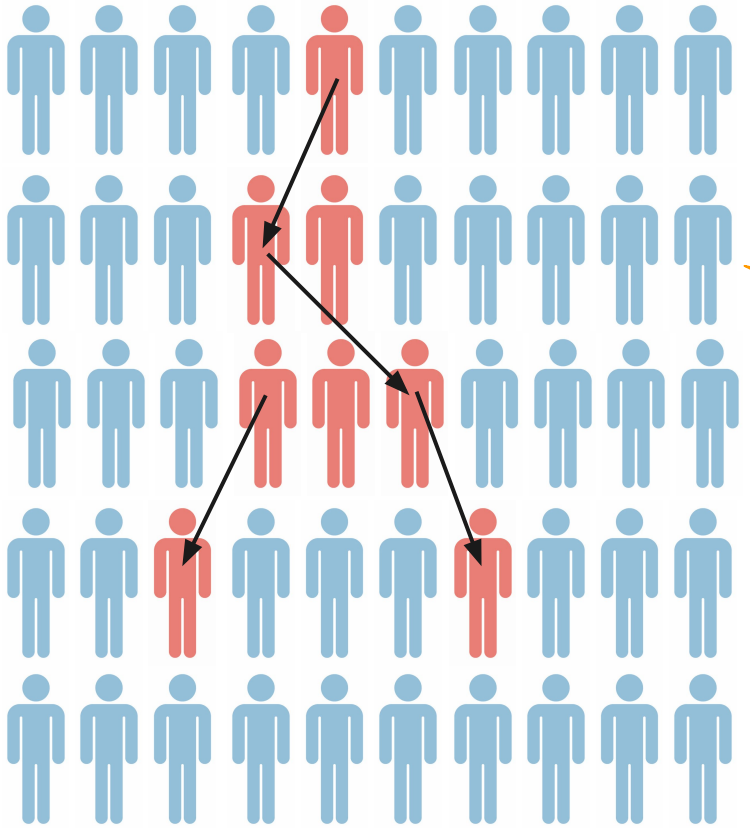
$$M_g(z) = \frac{\gamma}{\gamma - z}$$

Poisson counting process defined as counting process with exponentially distributed time to next event (=recovery); Poisson process has mean b
gamma+r is rate of new infections

$$\mathcal{R}_0 = \frac{\gamma + r}{\gamma} = \frac{\beta}{\gamma}$$

Linearization of differential equations

Let's be a bit more precise



basic reproduction number:

"expected number of secondary infections that arise from a typical primary case during its entire period of infectiousness in a completely susceptible population"

This population is not completely susceptible any more!
Depletion of susceptible!

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$

linearize at the disease-free equilibrium!

Linearization of differential equations

$$\left.\begin{aligned}\frac{dS}{dt} &= -\beta S \frac{I}{N} \\ \frac{dI}{dt} &= \beta S \frac{I}{N} - \gamma I\end{aligned}\right\}$$ **linearize** at the disease free-equilibrium!

$$X = \begin{bmatrix} S \\ I \end{bmatrix} \quad f(X) = \begin{bmatrix} -\beta X_1 \frac{X_2}{N} \\ \beta X_1 \frac{X_2}{N} - \gamma X_2 \end{bmatrix} \quad \left.\frac{dX}{dt} = f(X)\right\}$$ **non-linear differential equation**

$$(Df)(X) = \left(\partial_{X_j} f(X)^i\right)_{i,j=1,2}$$ Jacobian of vector field *f*

$$\left.\frac{dX}{dt} = (Df)(X)\right\}$$ **linear differential equation**

Linearization of differential equations

Find the disease-free equilibrium (DFE) of the SIR system!
Linearize the SIR system at the DFE!

$$X = \begin{bmatrix} S \\ I \end{bmatrix} \quad f(X) = \begin{bmatrix} -\beta X_1 \frac{X_2}{N} \\ \beta X_1 \frac{X_2}{N} - \gamma X_2 \end{bmatrix} \quad (Df)(X) = \left(\partial_{X_j} f(X)^i\right)_{i,j=1,2}$$

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$$\frac{dX}{dt} = f(X) = 0 \Rightarrow \quad X^* = \begin{bmatrix} S^* \\ 0 \end{bmatrix} \qquad S^* = N \text{ w.l.o.g.}$$

$$(Df)(X^*) = \begin{bmatrix} -\beta \times 0 & -\beta \frac{S^*}{N} \\ \beta \times 0 - 0 & \beta \frac{S^*}{N} - \gamma \end{bmatrix}$$

Linearization of differential equations

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Linearize the SIR system at the DFE!

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$$(Df)(X^*) = \begin{bmatrix} -\beta \times 0 & -\beta \frac{S^*}{N} \\ \beta \times 0 - 0 & \beta \frac{S^*}{N} - \gamma \end{bmatrix}$$

This is the only part that contributes to changes in infections!
If it is positive, then epidemic increases!!

$$\beta > \gamma \Leftrightarrow \frac{\beta}{\gamma} > 1$$

Next generation matrix theory

- **linearized system** (depletion of susceptibles are not taken into consideration at the beginning of an epidemic)
- **disease-free equilibrium** (we are only interested whether a single infected host is able to invade the population of susceptibles)
- **only infectious** compartments are considered for **epidemic growth** condition
- **decomposition** into inflow to/ outflow from infectious compartments

Next generation matrix theory

0. Calculate disease-free equilibrium $\frac{dX}{dt} = f(X) = 0$

1. Determine infectious compartments

2. Decompose inflow and outflow for infectious compartments $f = \mathbb{F} - \mathbb{V}$

3. Linearize inflow and outflow at disease-free equilibrium

$$(Df)(X^*) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} + \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

$F = \partial_j \mathbb{F}^i(X^*)$ $V = \partial_j \mathbb{V}^i(X^*)$

F non-negative
F(i,j) rate at which infected individuals in compartment j produce new infections in compartment i

4. Next-generation matrix FV^{-1}

5. Spectral radius $\rho(A) = \max\{|\lambda_i|$

6. $\mathcal{R}_0 = \rho(FV^{-1})$

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V non-singular
V^{-1}(i,j) average time individual spends in compartment j during its lifetime

4. Next-generation matrix FV^{-1}

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4. Next-generation matrix FV^{-1}

FV^{-1}(i,j) expected number of new infections in compartment i produced by the infected individual originally introduced into compartment j

5. Spectral radius $\rho(A) = \max\{|\lambda_i|; A\lambda_i = \lambda_i a_i\}$

6. $\mathcal{R}_0 = \rho(FV^{-1})$

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Next generation matrix theory

Where does the spectral radius come from?

$M := FV^{-1}$ next generation matrix

$M(X^*) : \mathbb{R}^m \to \mathbb{R}^m$ bounded operator with $||M|| = \max_{i,j} M_{ij}$

After *k* generations, infected population in compartment *i* is: $\sum_j M_{ij}^k$

Per-generation growth factor of infections is: $||M^k||^{\frac{1}{k}}$

Long-term growth factor of infections: $\lim_{k\to\infty} ||M^k||^{\frac{1}{k}} = \rho(M)$

$\rho(M)$ is calculated by maximum of the modulus of eigenvalues of M

$\rho(M) < ||M||$ spectral radius is **lower bound** for any matrix norm

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think of binary tree size: 2^k
growth factor: 2

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spectral radius

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R0 for vector-host model with next-generation matrix

$$\frac{dS}{dt}(t) = -\alpha \frac{V(t)}{H} S(t) + \gamma I(t)$$

$$\frac{dI}{dt}(t) = \alpha \frac{V(t)}{H} S(t) - \gamma I(t)$$

$$\frac{dU}{dt}(t) = -\beta \frac{I(t)}{H} U(t) + \mu M - \delta U(t)$$

$$\frac{dV}{dt}(t) = \beta \frac{I(t)}{H} U(t) - \delta V(t)$$

1. Define infectious compartments: $X = \begin{bmatrix} I \\ V \end{bmatrix}$

2. Decompose inflow and outflow for infectious compartments:

$$\mathbb{F} = \begin{pmatrix} \alpha S \frac{V}{H} \\ \beta U \frac{I}{H} \end{pmatrix} \qquad \mathbb{V} = \begin{pmatrix} \gamma I \\ \delta V \end{pmatrix}$$

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3. Linearize inflow and outflow at disease-free equilibrium, calculate Jacobian matrix:

$$\frac{\partial \mathbb{F}}{\partial X} = \begin{bmatrix} 0 & \alpha S^* \frac{1}{H} \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \alpha \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} \qquad \frac{\partial \mathbb{V}}{\partial X} = \begin{bmatrix} \gamma & 0 \\ 0 & \delta \end{bmatrix}$$

4. Calculate next-generation matrix, spectral radius of NGM:

$$\left(\frac{\partial \mathbb{V}}{\partial X}\right)^{-1} = \begin{bmatrix} \gamma^{-1} & 0 \\ 0 & \delta^{-1} \end{bmatrix}$$

$$\mathcal{R}_0 = \rho\left(\frac{\partial \mathbb{F}}{\partial X}\left(\frac{\partial \mathbb{V}}{\partial X}\right)^{-1}\right)$$

Diekmann-Heesterbeek-Metz 1990:
Next Generation Matrix

R0 for vector-host model with next-generation matrix

$$\frac{\partial \mathbb{F}}{\partial X} = \begin{bmatrix} 0 & \alpha S^* \frac{1}{H} \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \qquad \frac{\partial \mathbb{V}}{\partial X} = \begin{bmatrix} \gamma & 0 \\ 0 & \delta \end{bmatrix}$$

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Let's do the $\mathcal{R}_0$ maths!

R0 for vector-host model with next-generation matrix

$$\frac{\partial \mathbb{F}}{\partial X} = \begin{bmatrix} 0 & \alpha S^* \frac{1}{H} \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \qquad \frac{\partial \mathbb{V}}{\partial X} = \begin{bmatrix} \gamma & 0 \\ 0 & \delta \end{bmatrix}$$

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$$\frac{\partial \mathbb{F}}{\partial X}\left(\frac{\partial \mathbb{V}}{\partial X}\right)^{-1} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \begin{bmatrix} \gamma^{-1} & 0 \\ 0 & \delta^{-1} \end{bmatrix} = \begin{bmatrix} 0 & \frac{\alpha}{\delta} \\ \frac{\beta}{\gamma} \frac{M}{H} & 0 \end{bmatrix}$$

Next Generation Matrix

R0 for vector-host model with next-generation matrix

$$\frac{\partial \mathbb{F}}{\partial X} = \begin{bmatrix} 0 & \alpha S^* \frac{1}{H} \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \qquad \frac{\partial \mathbb{V}}{\partial X} = \begin{bmatrix} \gamma & 0 \\ 0 & \delta \end{bmatrix}$$

4. Calculate next-generation matrix, spectral radius of NGM:

$$\left(\frac{\partial \mathbb{V}}{\partial X}\right)^{-1} = \begin{bmatrix} \gamma^{-1} & 0 \\ 0 & \delta^{-1} \end{bmatrix}$$

$$\frac{\partial \mathbb{F}}{\partial X}\left(\frac{\partial \mathbb{V}}{\partial X}\right)^{-1} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \begin{bmatrix} \gamma^{-1} & 0 \\ 0 & \delta^{-1} \end{bmatrix} = \begin{bmatrix} 0 & \frac{\alpha}{\delta} \\ \frac{\beta}{\gamma} \frac{M}{H} & 0 \end{bmatrix}$$

Next Generation Matrix

Characteristic polynomial for eigenvalues

$$\det\left(\begin{bmatrix} 0 & \frac{\alpha}{\delta} \\ \frac{\beta}{\gamma} \frac{M}{H} & 0 \end{bmatrix} - \lambda \mathbb{I}\right) = 0$$

R0 for vector-host model with next-generation matrix

$$\frac{\partial \mathbb{F}}{\partial X} = \begin{bmatrix} 0 & \alpha S^* \frac{1}{H} \\ \beta U^* \frac{1}{H} & 0 \end{bmatrix} = \begin{bmatrix} 0 & \alpha \\ \beta \frac{M}{H} & 0 \end{bmatrix} \qquad \frac{\partial \mathbb{V}}{\partial X} = \begin{bmatrix} \gamma & 0 \\ 0 & \delta \end{bmatrix}$$

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Next Generation Matrix

Eigenvalues

$$\lambda_{1/2} = \pm \sqrt{\frac{\alpha}{\gamma} \frac{\beta}{\delta} \frac{M}{H}}$$

Characteristic polynomial for eigenvalues

$$\det\left(\begin{bmatrix} 0 & \frac{\alpha}{\delta} \\ \frac{\beta}{\gamma} \frac{M}{H} & 0 \end{bmatrix} - \lambda \mathbb{I}\right) = 0$$

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Next Generation Matrix

Eigenvalues

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Characteristic polynomial for eigenvalues

$$\det\left(\begin{bmatrix} 0 & \frac{\alpha}{\delta} \\ \frac{\beta}{\gamma} \frac{M}{H} & 0 \end{bmatrix} - \lambda \mathbb{I}\right) = 0$$

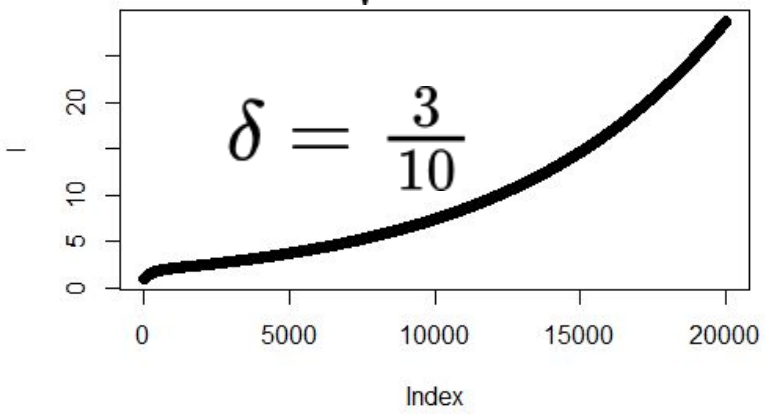
Spectral radius

$$\mathcal{R}_0 = \max |\lambda_i| = \sqrt{\frac{\alpha}{\gamma} \frac{\beta}{\delta} \frac{M}{H}}$$

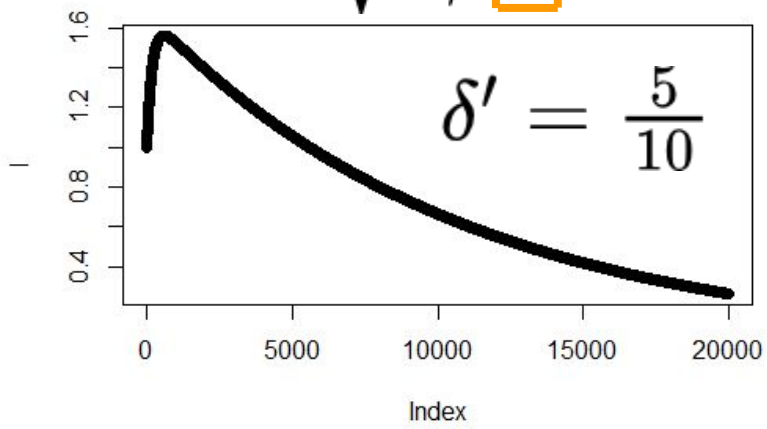
R0 for vector-host model with next-generation matrix

Mosquito Theorem:
vector control is a sufficient condition for malaria elimination in humans

$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}K} > 1$$



$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta'}K} < 1$$



$$\frac{K}{\delta'} = \frac{K}{\delta}\frac{3}{5} < \frac{K}{\delta}$$

ratio of vectors to hosts

$$\mathcal{R}_0 = \max|\lambda_i| = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}\frac{M}{H}}$$

R0 for vector-host model with next-generation matrix

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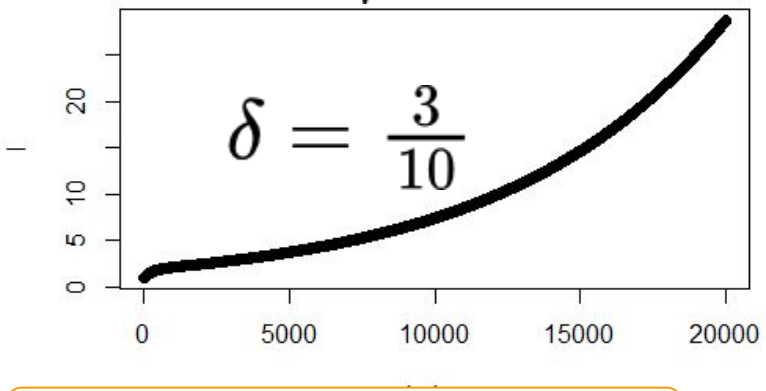

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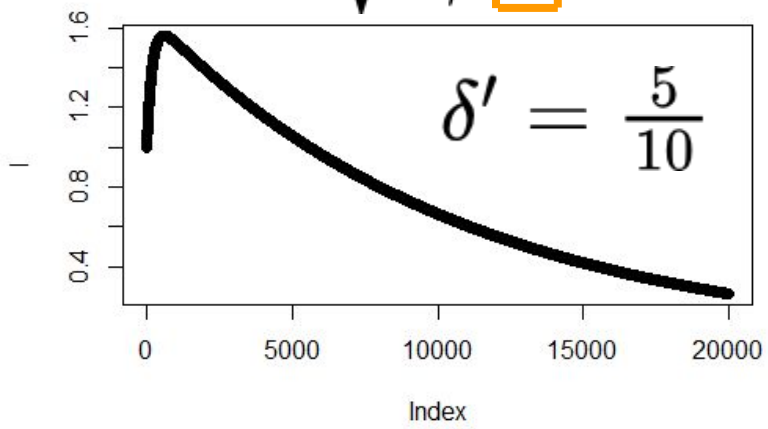

$$\frac{K}{\delta'} = \frac{K}{\delta}\frac{3}{5} < \frac{K}{\delta}$$

Clara Champagne's course:

$$R_0 = \frac{m\,a^2 bc\,e^{-gv}}{rg}$$

ratio of vectors to hosts

$$\mathcal{R}_0 = \max|\lambda_i| = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}\frac{M}{H}}$$

R0 for vector-host model with next-generation matrix

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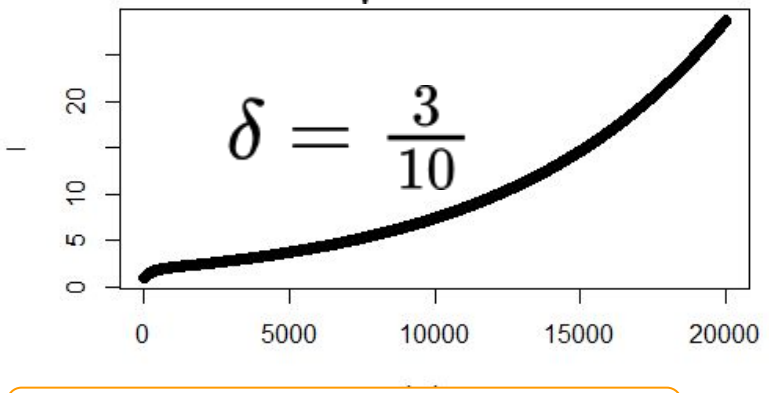

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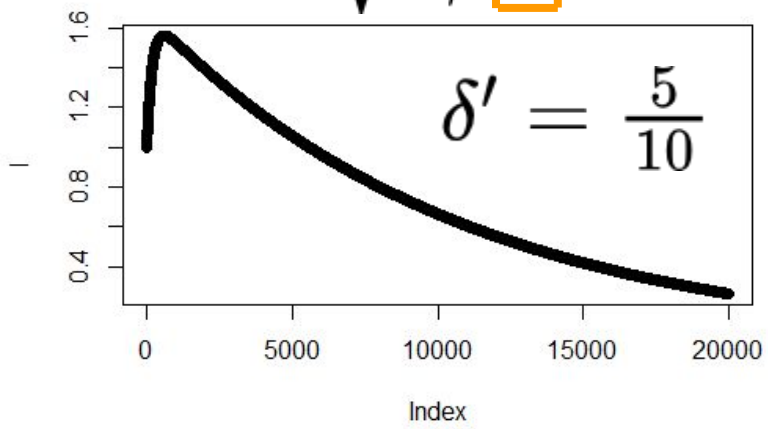

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Clara Champagne's course:

$$R_0 = \frac{m\,a^2bc\,e^{-gv}}{rg}$$

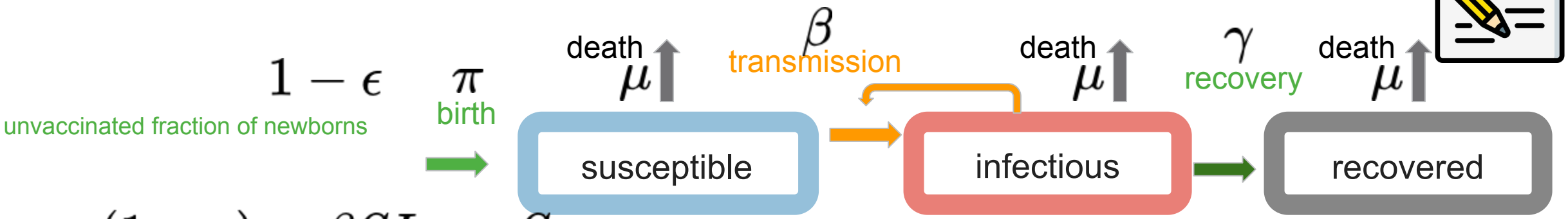
recovery/death

transmission

ratio of vectors to hosts

$$\mathcal{R}_0 = \max|\lambda_i| = \sqrt{\begin{matrix}\alpha & \beta \\ \gamma & \delta\end{matrix}\frac{M}{H}}$$

R0 for SIR model with newborn vaccination

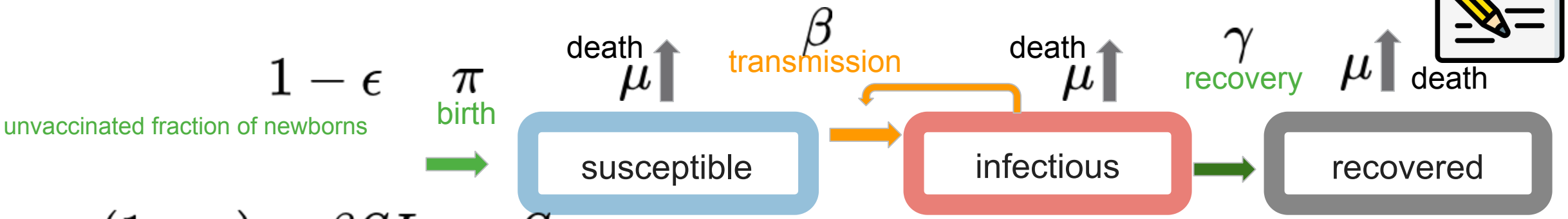


$$\frac{dS}{dt} = \pi(1-\epsilon) - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

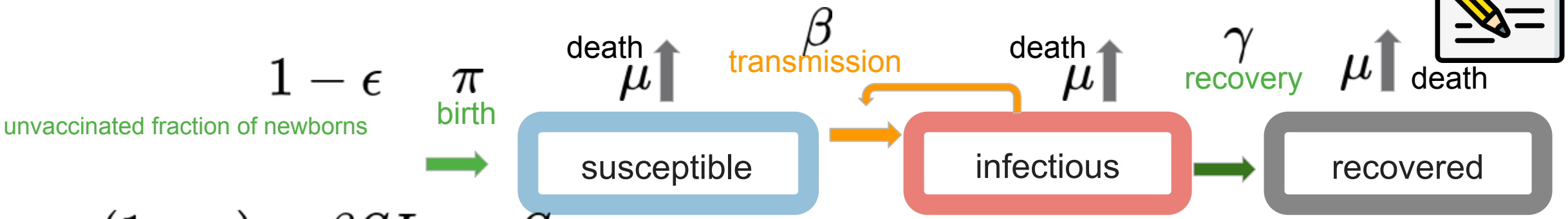
R0 for SIR model with newborn vaccination



$$\frac{dS}{dt} = \pi(1-\epsilon) - \beta SI - \mu S$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

1. DFE: $S^* = (1-\epsilon)\frac{\pi}{\mu}S_0, I = R = 0$
2. Infectious compartment & decomposition: $\mathbb{F} = \beta SI$ $\mathbb{V} = (\gamma+\mu)I$
3. Linearization at DFE $F = (1-\epsilon)\frac{\pi}{\mu}\beta \quad V = \gamma+\mu$
4. Next-generation matrix $FV^{-1} = (1-\epsilon)\frac{\pi}{\mu}\frac{\beta}{\gamma+\mu}$
5. Spectral radius $\mathcal{R}_0^\epsilon = (1-\epsilon)\frac{\pi}{\mu}\frac{\beta}{\gamma+\mu} = (1-\epsilon)\mathcal{R}_0$

R0 for SIR model with newborn vaccination



$$\frac{dS}{dt} = \pi(1-\epsilon) - \beta SI - \mu S$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

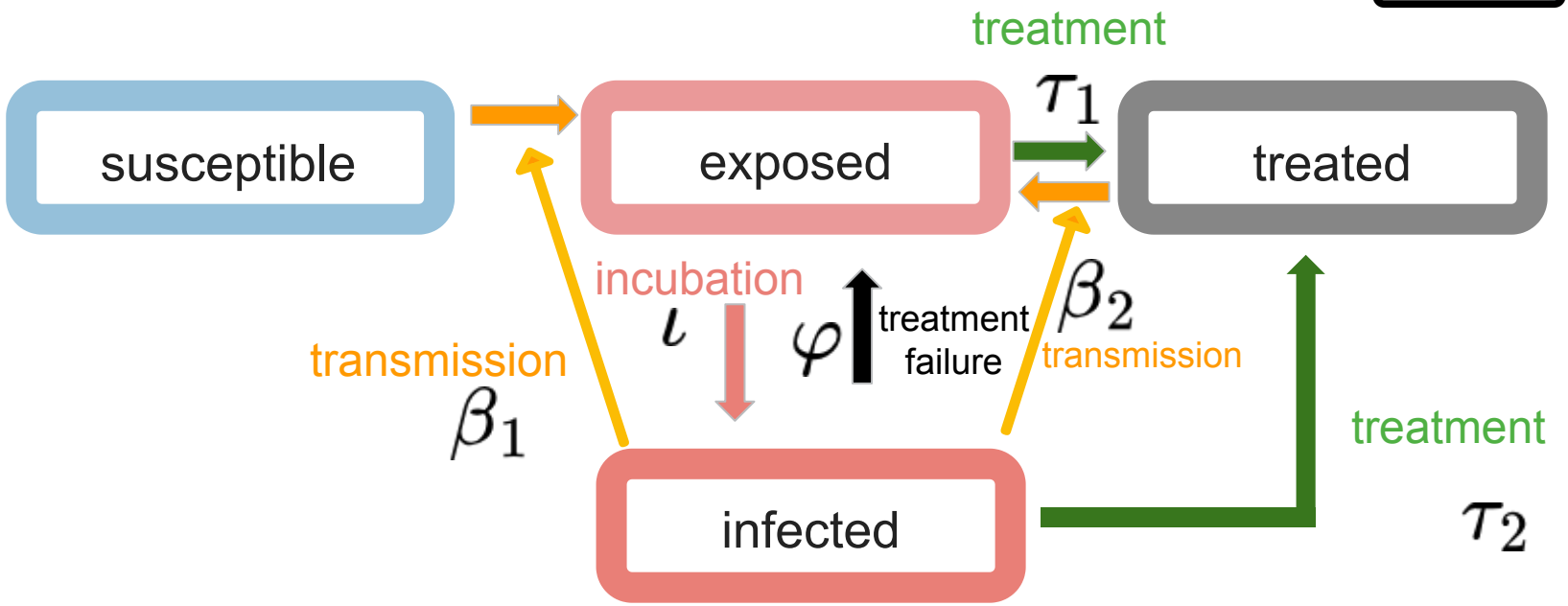
Increasing the vaccination coverage of newborns will control disease spread

$$\mathcal{R}_0^\epsilon = (1-\epsilon)\frac{\pi}{\mu}\frac{\beta}{\gamma+\mu} = (1-\epsilon)\mathcal{R}_0$$

Required vaccination coverage to control disease spread

$$\mathcal{R}_0^\epsilon < 1 \Leftrightarrow \epsilon > 1 - \frac{1}{\mathcal{R}_0}$$

R0 for SEI with treatment failure



R0 for SEI with treatment failure

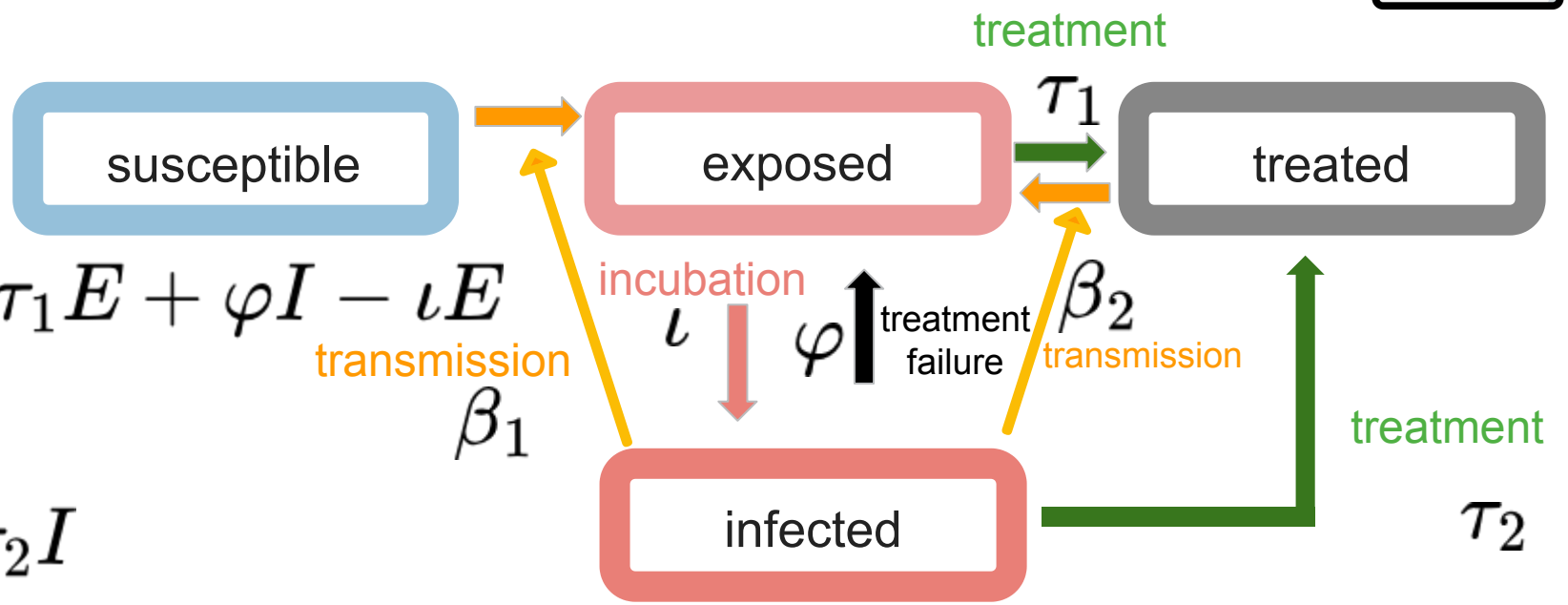
Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

$$\frac{dI}{dt} = \iota E - \varphi I - \tau_2 I$$

$$\frac{dT}{dt} = -\beta_2 T \frac{I}{N} + \tau_1 E + \tau_2 I$$



R0 for SEI with treatment failure

Tuberculosis

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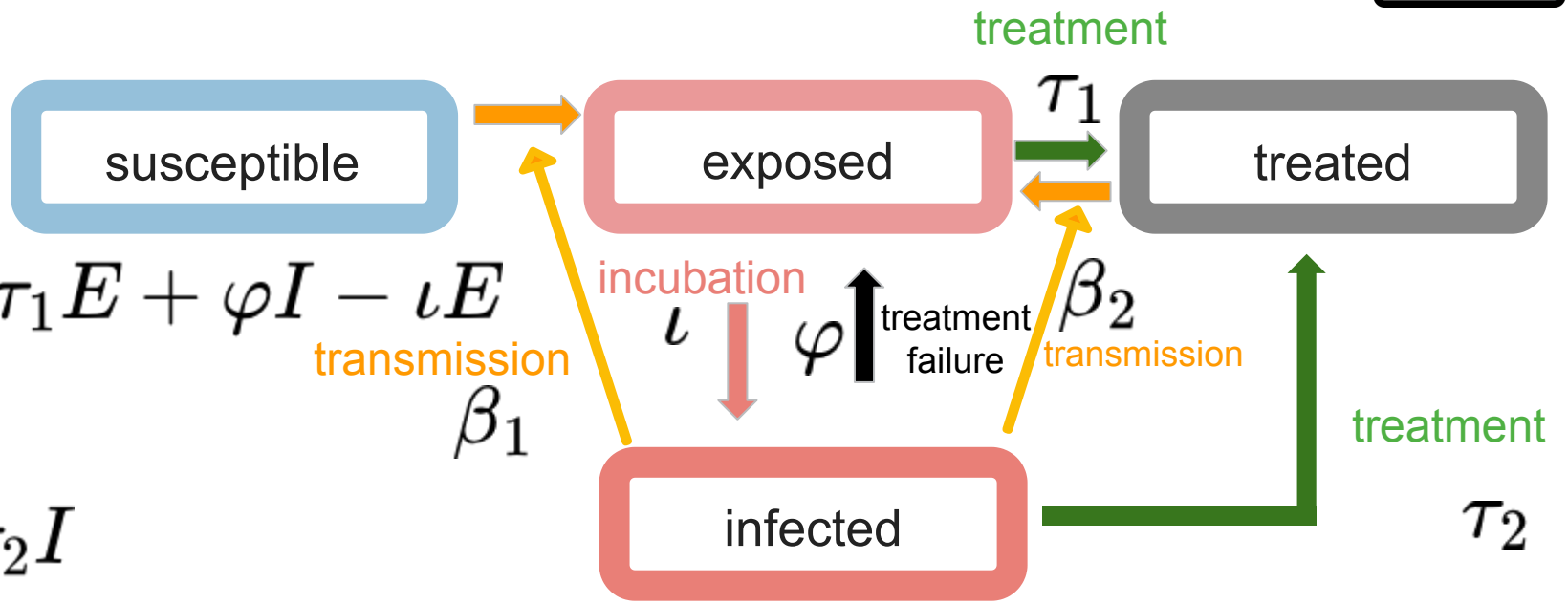

Calculate **basic reproduction number** following the steps:

1. Disease-free equilibrium
2. Infectious compartments & decomposition
3. Linearization
4. Next-generation matrix
5. Spectral radius

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

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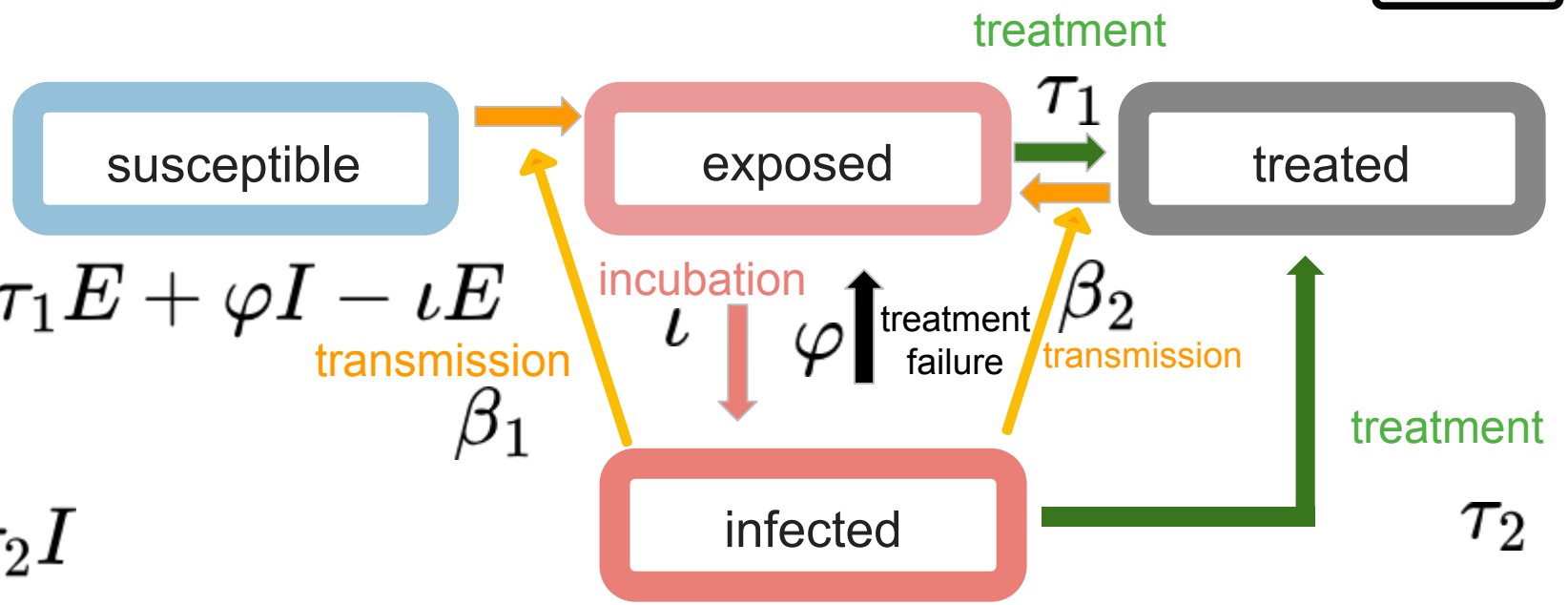

1. Disease-free equilibrium

$$S^* = S(0), E = I = T = 0$$

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

$$\frac{dI}{dt} = \iota E - \varphi I - \tau_2 I$$

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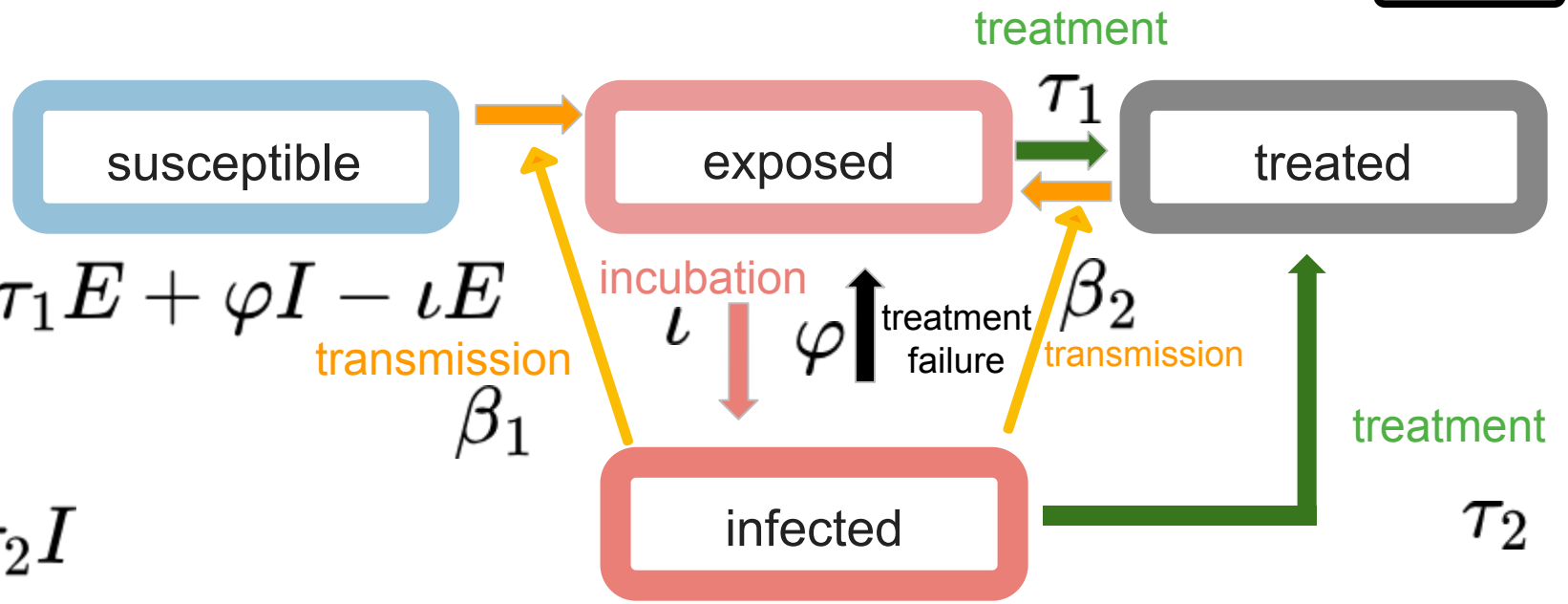

2. Infectious compartments & decomposition

E, I are infectious compartments incubation and treatment failure **are not** considered to be new infections

$$\mathbb{F} = \begin{bmatrix} \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} \\ 0 \end{bmatrix} \quad \mathbb{V} = \begin{bmatrix} \tau_1 E - \varphi I + \iota E \\ -\iota E + \varphi I + \tau_2 I \end{bmatrix}$$

$$\frac{dX}{dt} = f(X) = \mathbb{F}(X) - \mathbb{V}(X)$$

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

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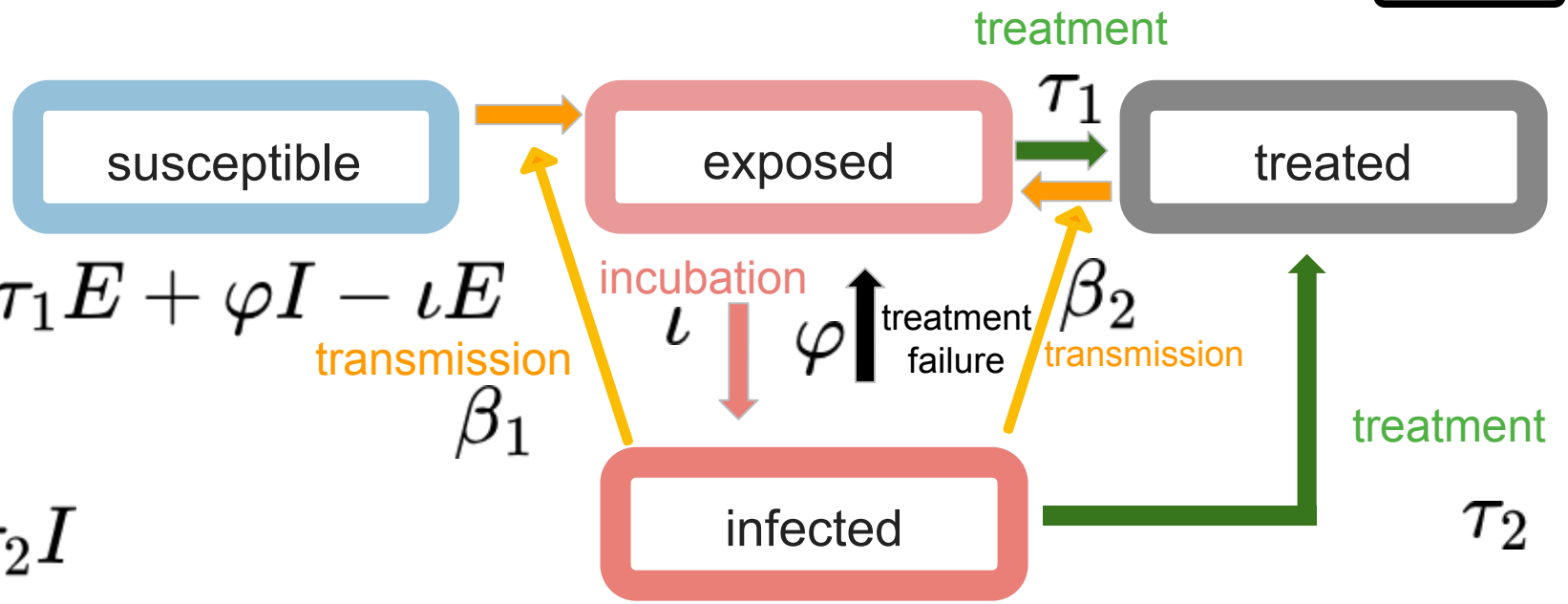

3. Linearization at DFE

$$F = \begin{bmatrix} 0 & \beta_1 \\ 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} \tau_1 + \iota & -\varphi \\ -\iota & \varphi + \tau_2 \end{bmatrix}$$

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

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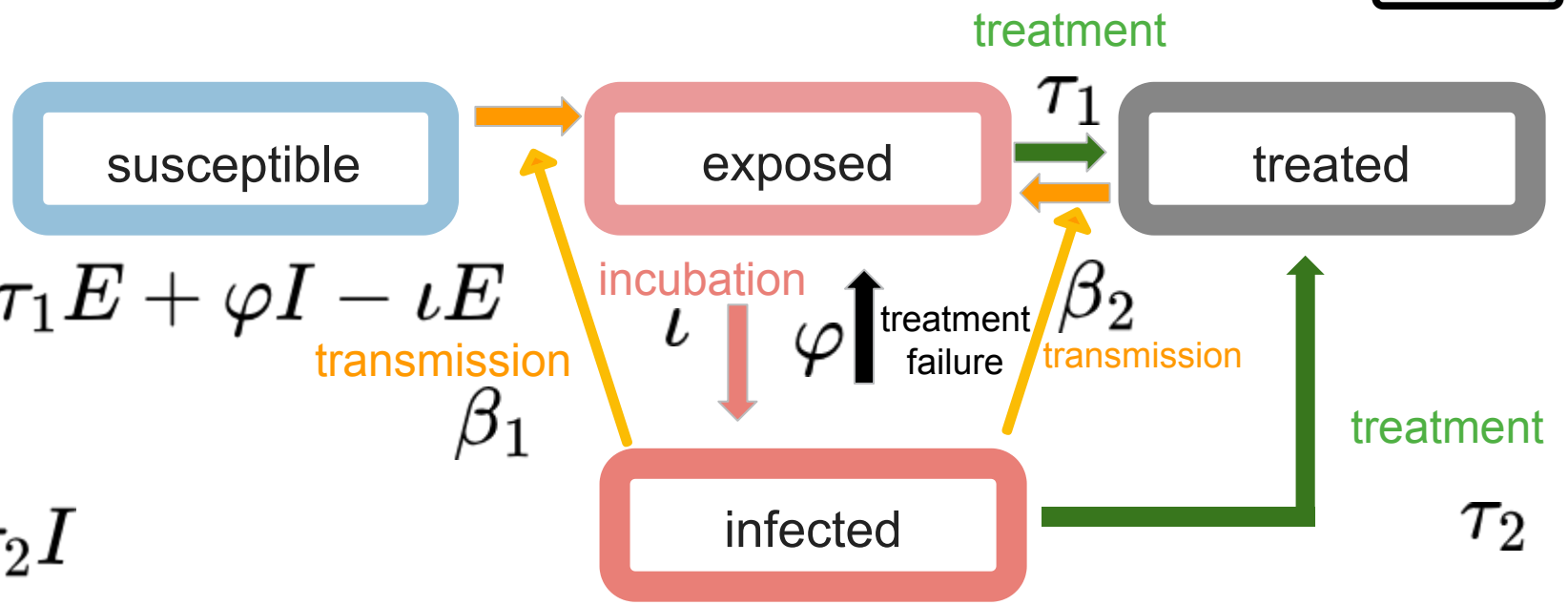

4. Next-generation matrix

$$F = \begin{bmatrix} 0 & \beta_1 \\ 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} \tau_1 + \iota & -\varphi \\ -\iota & \varphi + \tau_2 \end{bmatrix} \quad V^{-1} = \frac{1}{(\tau+\iota)(\varphi+\tau_2)-\iota\varphi} \begin{bmatrix} \varphi + \tau_2 & \varphi \\ \iota & \tau_1 + \iota \end{bmatrix}$$

$$M = FV^{-1} = \frac{1}{(\tau+\iota)(\varphi+\tau_2)-\iota\varphi} \begin{bmatrix} \iota\beta_1 & (\tau_1 + \iota)\beta_1 \\ 0 & 0 \end{bmatrix}$$

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

$$\frac{dI}{dt} = \iota E - \varphi I - \tau_2 I$$

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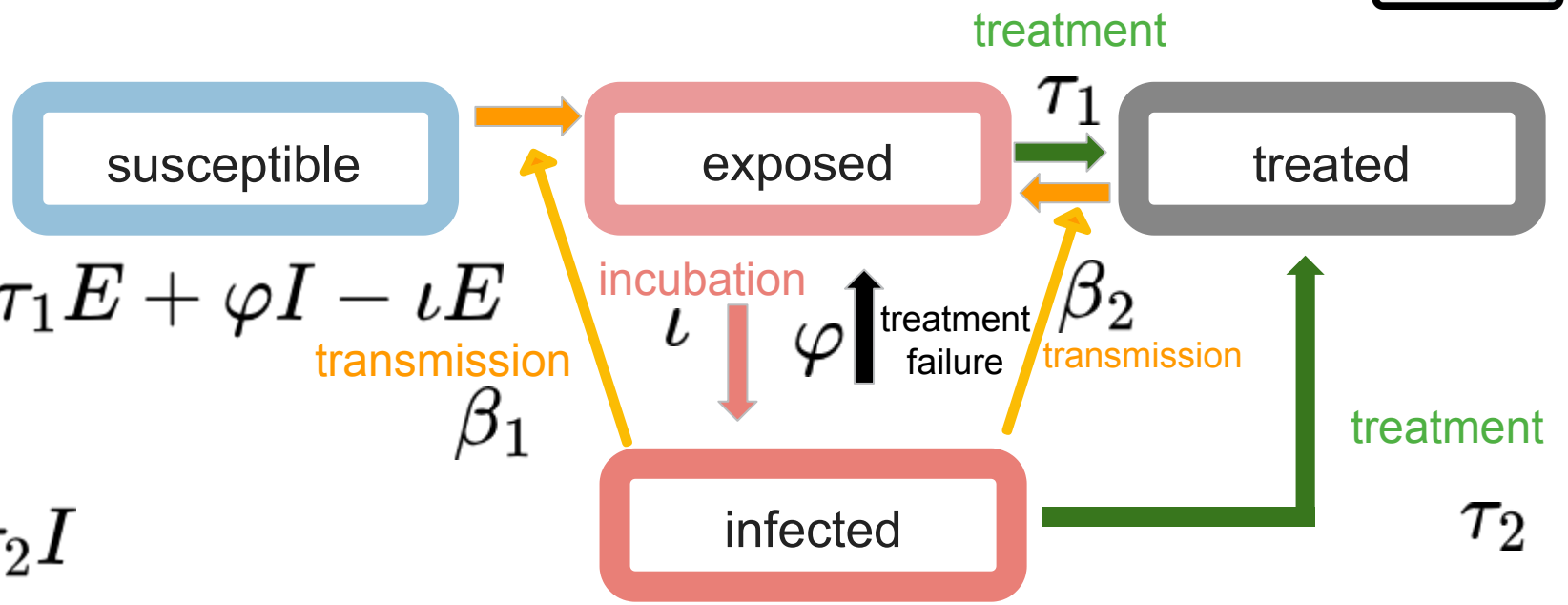

5. Basic reproduction number

$$\mathcal{R}_0 = \frac{\iota\beta_1}{(\tau+\iota)(\varphi+\tau_2)-\iota\varphi}$$

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

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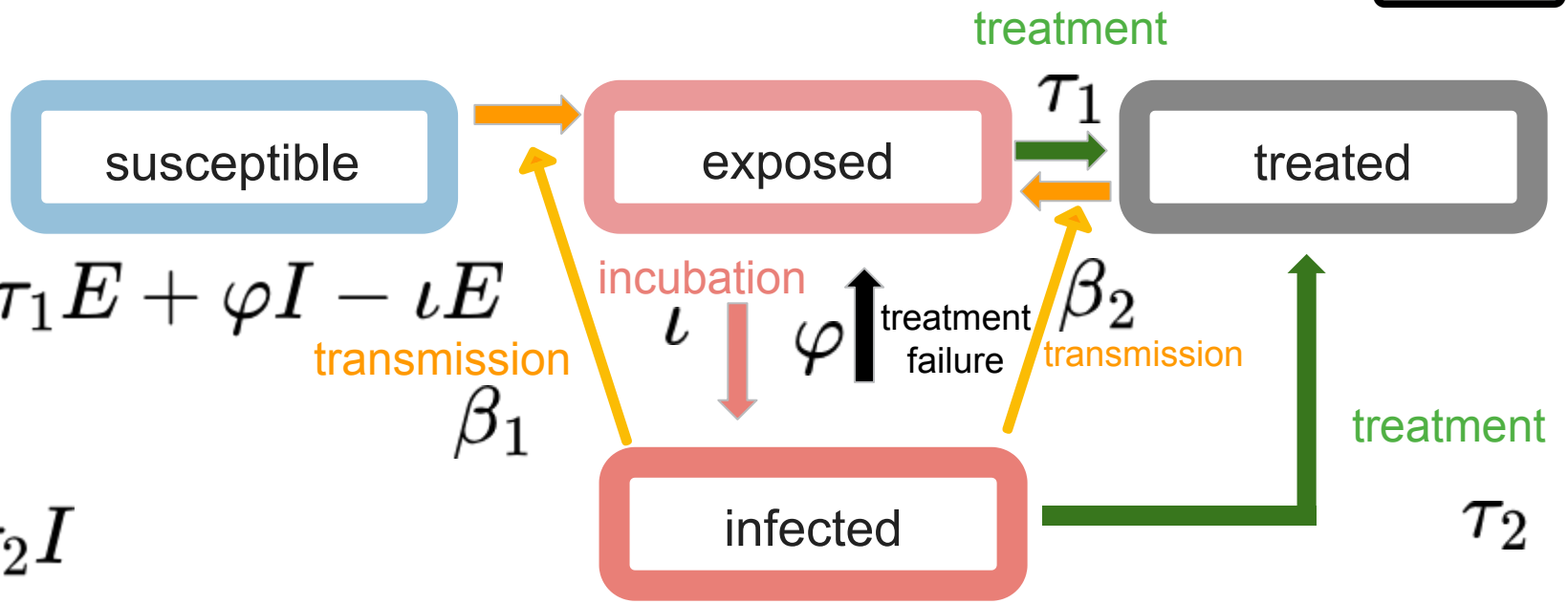

E, I are infectious compartments **both** incubation and treatment failure **are** considered to be new infections

$$\mathbb{F} = \begin{bmatrix} \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} + \varphi I \\ \iota E \end{bmatrix} \qquad \mathbb{V} = \begin{bmatrix} \tau_1 E + \iota E \\ \tau_2 I + \varphi I \end{bmatrix}$$

Decomposition is not unique!

Swiss TPH

R0 for SEI with treatment failure

Tuberculosis

$$\frac{dS}{dt} = -\beta_1 S \frac{I}{N}$$

$$\frac{dE}{dt} = \beta_1 S \frac{I}{N} + \beta_2 T \frac{I}{N} - \tau_1 E + \varphi I - \iota E$$

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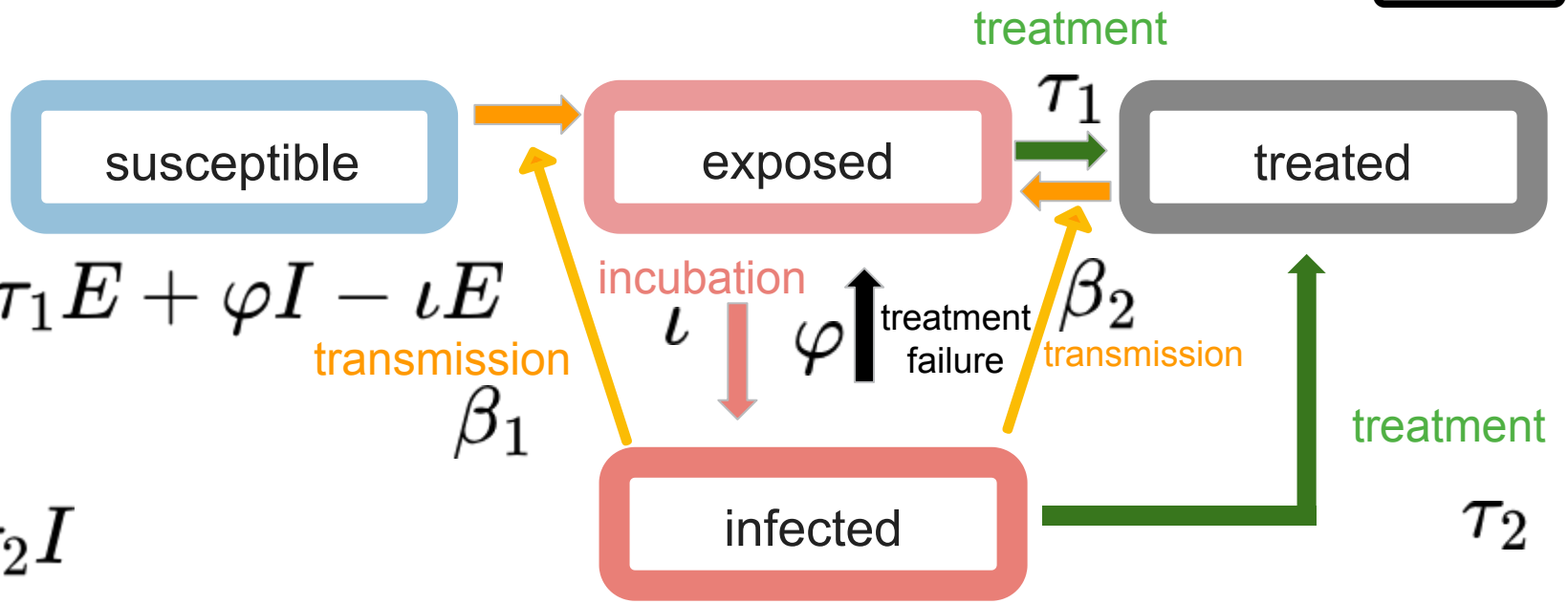

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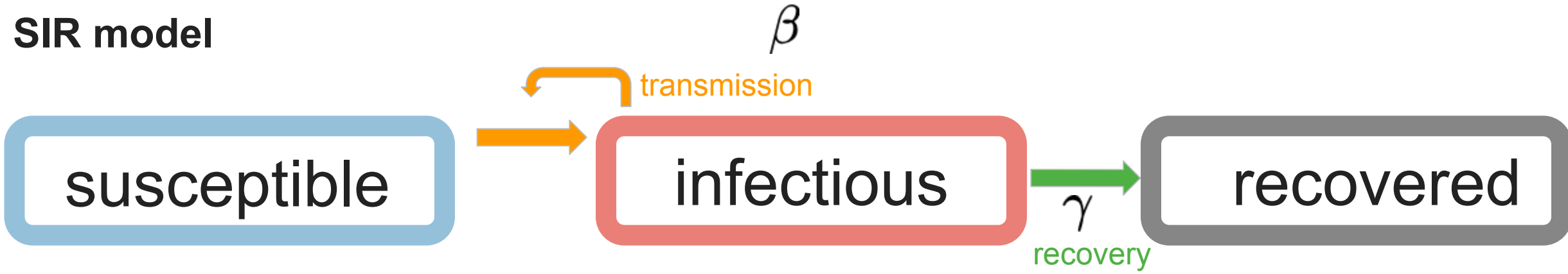
Assignment: Calculate basic reproduction number in this case and compare!

R0 and the final epidemic size

SIR model



$$\left.\begin{aligned}\frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \\ S + I + R &= 1\end{aligned}\right\} \Rightarrow$$

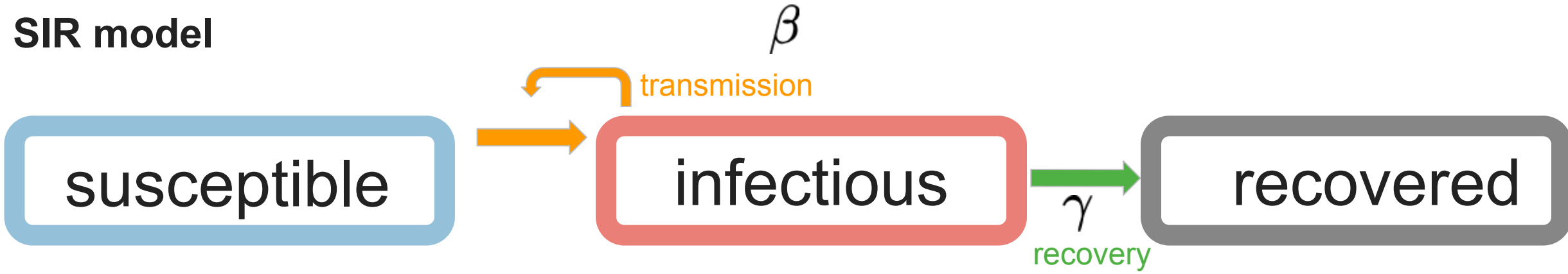
final epidemic size

How many hosts had been infected (and recovered) during the course of the epidemic?

$$I(\infty) = 0 \qquad R(\infty) = ?$$

R0 and the final epidemic size

SIR model

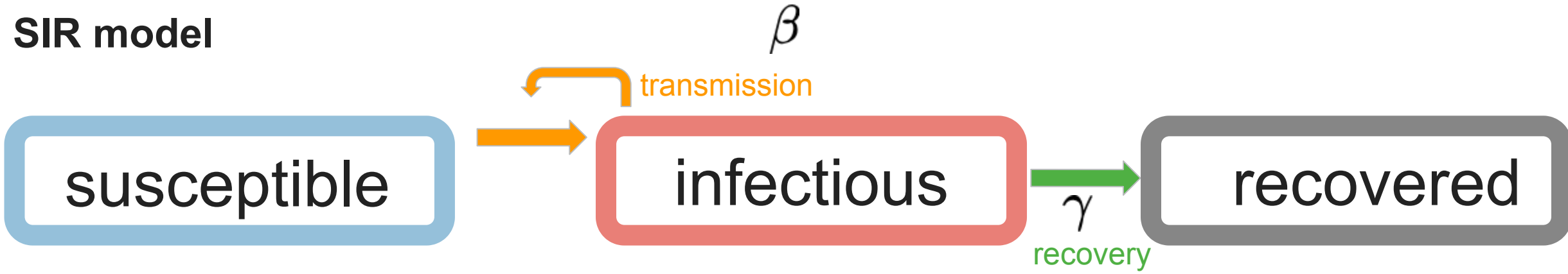


$$\left.\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \\ S + I + R &= 1 \end{aligned}\right\} \Rightarrow \quad \frac{dI}{dS} = \frac{\beta SI - \gamma I}{-\beta SI} = -1 + \frac{\gamma}{\beta}\frac{1}{S}$$

$$dI = -dS + \frac{\gamma}{\beta}\frac{dS}{S} = -dS + \frac{\gamma}{\beta} d\log S$$

R0 and the final epidemic size

SIR model



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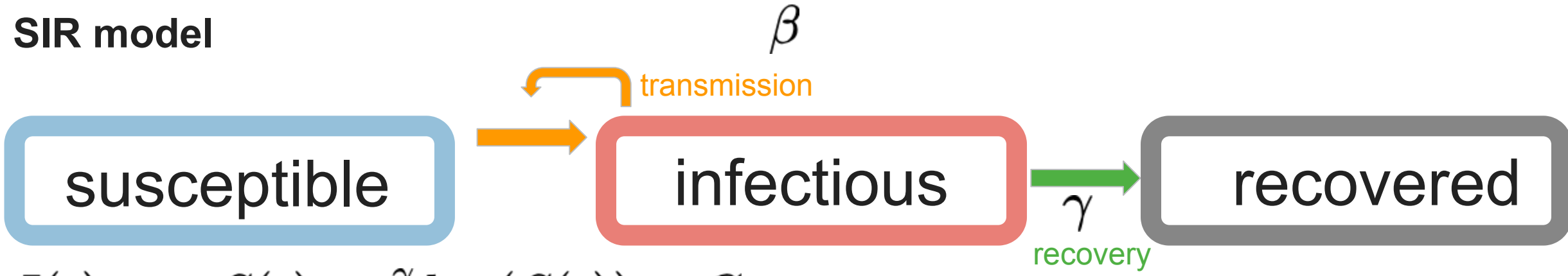
$$dI = -dS + \frac{\gamma}{\beta}\frac{dS}{S} = -dS + \frac{\gamma}{\beta} d\log S$$

$$I(t) = -S(t) + \frac{\gamma}{\beta}\log(S(t)) + C$$

R0 and the final epidemic size

SIR model



$$I(t) = -S(t) + \frac{\gamma}{\beta}\log(S(t)) + C \qquad t \geq 0$$

$$I(0) \approx 0$$
$$S(0) = 1$$
$$I(\infty) = 0$$

$$-S(\infty) + \frac{\gamma}{\beta}\log(S(\infty))) = -S(0) + \frac{\gamma}{\beta}\log(S(0))$$

$$\log S(\infty) = \frac{\beta}{\gamma}(S(\infty) - 1)$$

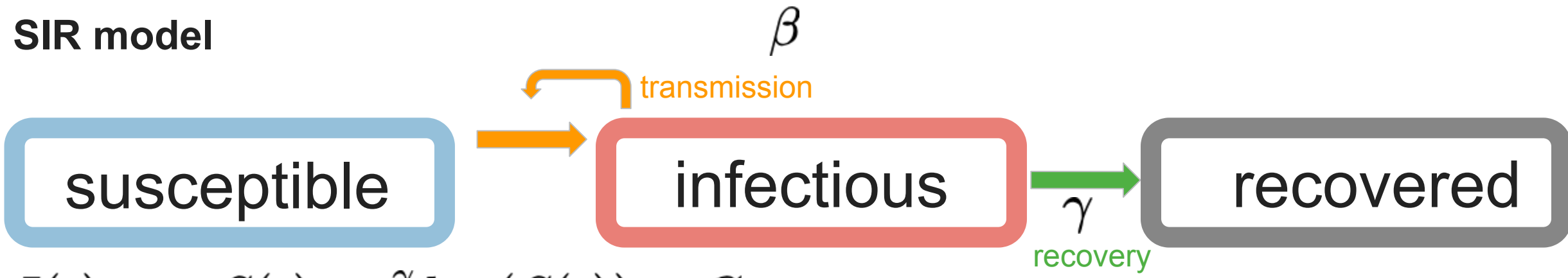
$$S(\infty) = e^{-\frac{\beta}{\gamma}(1-S(\infty))}$$

final epidemic size

$$R(\infty) = 1 - e^{-\frac{\beta}{\gamma}R(\infty)}$$

R0 and the final epidemic size

SIR model



$$I(t) = -S(t) + \frac{\gamma}{\beta}\log(S(t)) + C \qquad t \geq 0$$

$$I(0) \approx 0$$
$$S(0) = 1$$
$$I(\infty) = 0$$

$$-S(\infty) + \frac{\gamma}{\beta}\log(S(\infty))) = -S(0) + \frac{\gamma}{\beta}\log(S(0))$$

$$\log S(\infty) = \frac{\beta}{\gamma}(S(\infty) - 1)$$

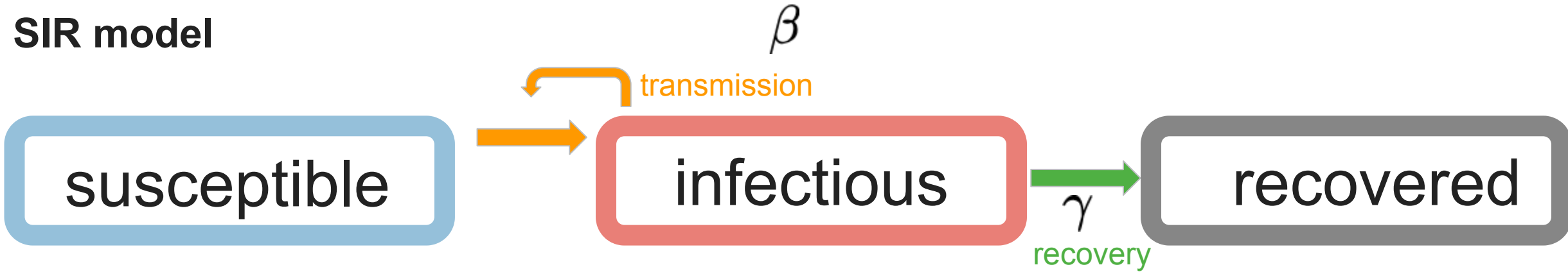
$$S(\infty) = e^{-\frac{\beta}{\gamma}(1-S(\infty))}$$

final epidemic size depends on R0!

$$R(\infty) = 1 - e^{-\mathcal{R}_0 R(\infty)}$$

R0 and the final epidemic size

SIR model



Assignment: Calculate final epidemic size as a function of basic reproduction number using R !

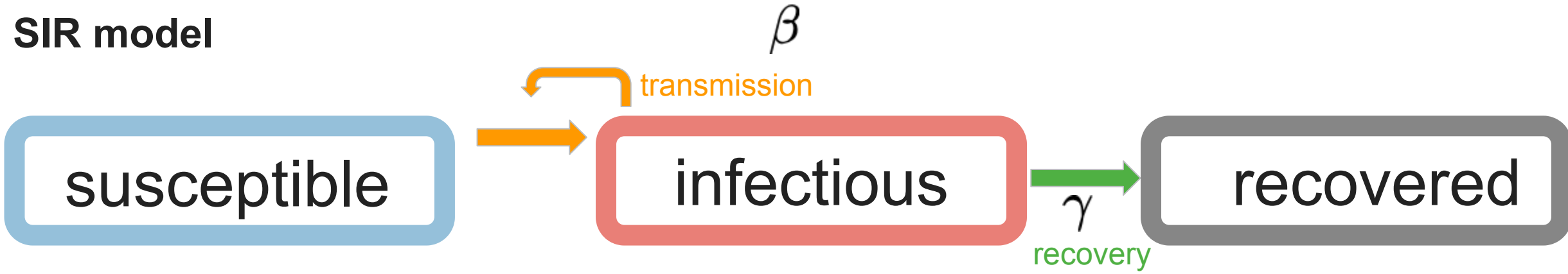
```
f<-function(x,y){x-1+exp(-y*x)}
FES<-function(R0)uniroot(function(x)f(x,R0),c(0.001,1))[[1]]
FES(3)
```

final epidemic size, R0>1

$$R(\infty) = 1 - e^{-\mathcal{R}_0 R(\infty)}$$

R0 and the final epidemic size

SIR model



Assume a case-fatality ratio of 5%!

With the Rwandan population in 2020, how many deaths would have occurred in total during the uncontrolled epidemic?

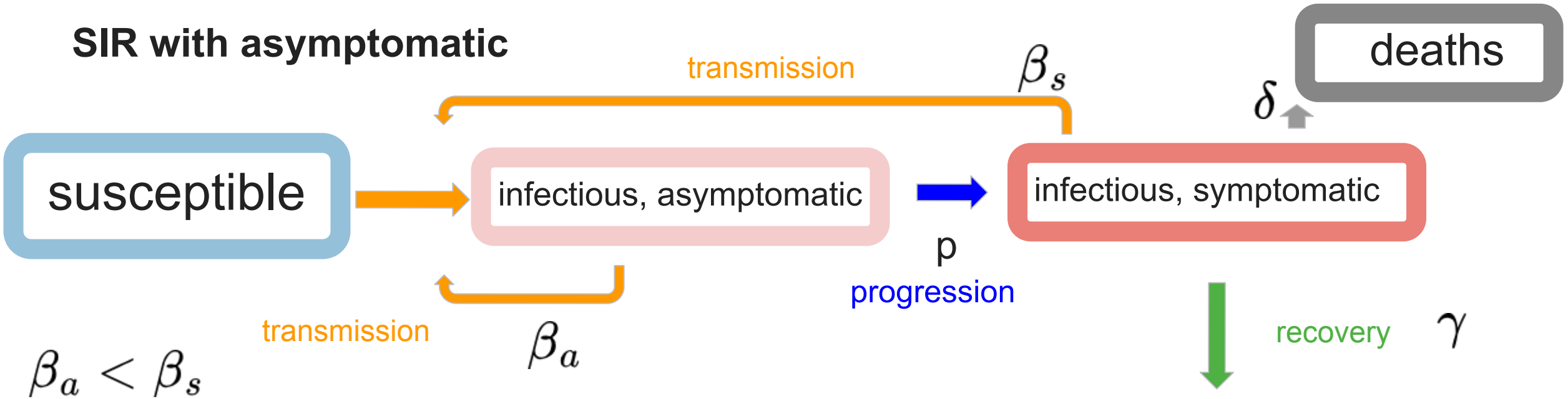
```
sapply(c(1.2,2,3),FES)*14*10^6*0.05
```

Key takeaway points:

- R0 can be derived as an approximation from **growth rate** and **generation time** data
- R0 is a **threshold** summarizing model parameters providing information whether a small outbreak will become an epidemic
- **next-generation matrix** method allows to calculate R0 for more complex models
- R0 is an important **performance indicator** in public health (e.g. vector control, vaccination, final epidemic size)

More examples for next-generation matrix calculations

SIR with asymptomatic



$\beta_a < \beta_s$

asymptomatic are less infectious

$$\mathbb{F} = \begin{bmatrix} \beta_a S \frac{I_a}{N} + \beta_s S \frac{I_s}{N} \\ pI_a \end{bmatrix} \quad \mathbb{V} = \begin{bmatrix} p\beta_a \\ (\gamma+\delta) I_s \end{bmatrix}$$

recovered

$$F = \begin{bmatrix} \beta_a & \beta_s \\ p & 0 \end{bmatrix} \quad V = \begin{bmatrix} p & 0 \\ 0 & \gamma+\delta \end{bmatrix} \quad FV^{-1} = \begin{bmatrix} \frac{\beta_a}{p} & \frac{\beta_s}{\gamma+\delta} \\ 1 & 0 \end{bmatrix}$$

$$\left(\frac{\beta_a}{p} - \lambda\right)(-\lambda) - \frac{\beta_s}{\gamma+\delta} = 0$$

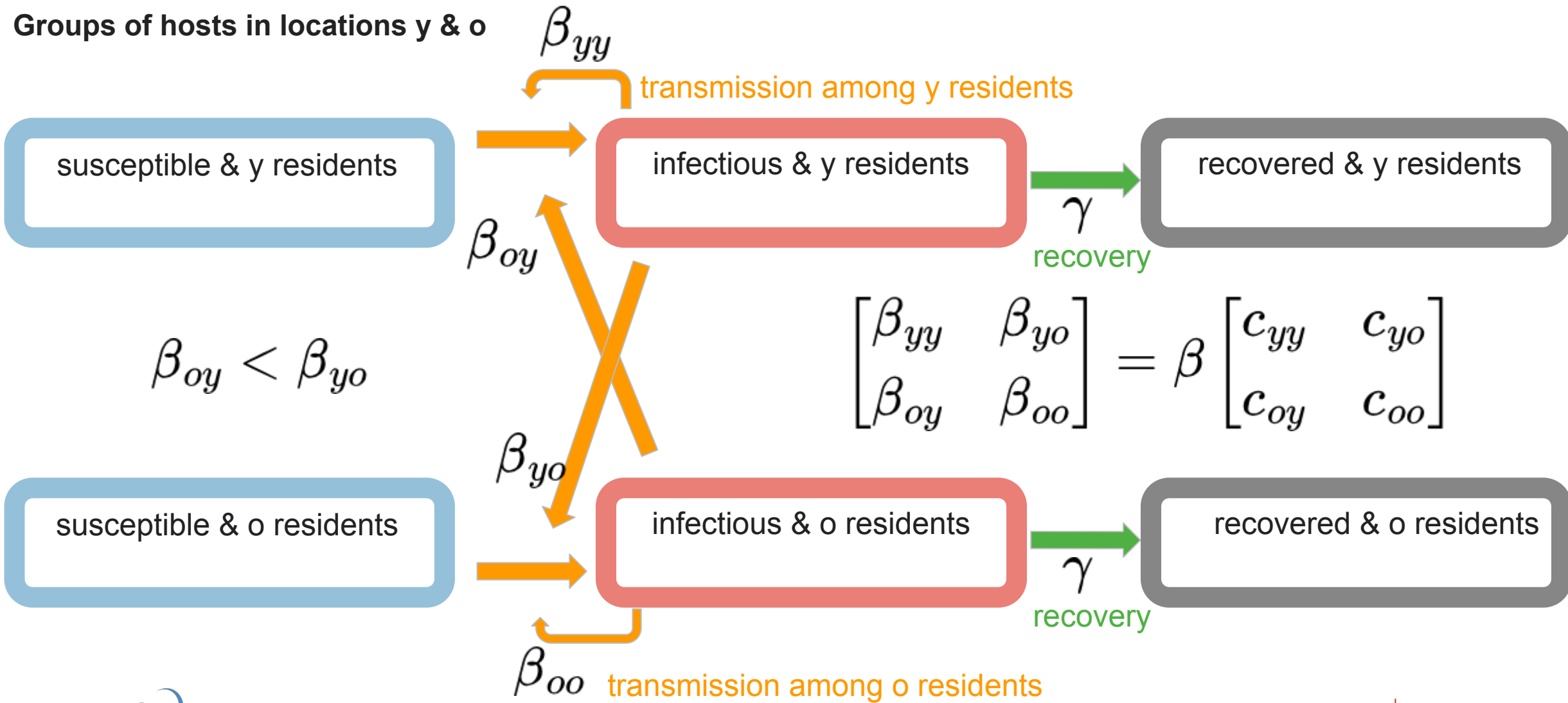
$$\lambda^2 - \lambda\frac{\beta_a}{p} - \frac{\beta_s}{\gamma+\delta} = 0$$

$$\mathcal{R}_0 = \frac{\beta_a}{2p} + \sqrt{\frac{\beta_a^2}{4p^2} + \frac{\beta_s}{\gamma+\delta}}$$

Swiss TPH

More examples for next-generation matrix calculations

Groups of hosts in locations y & o

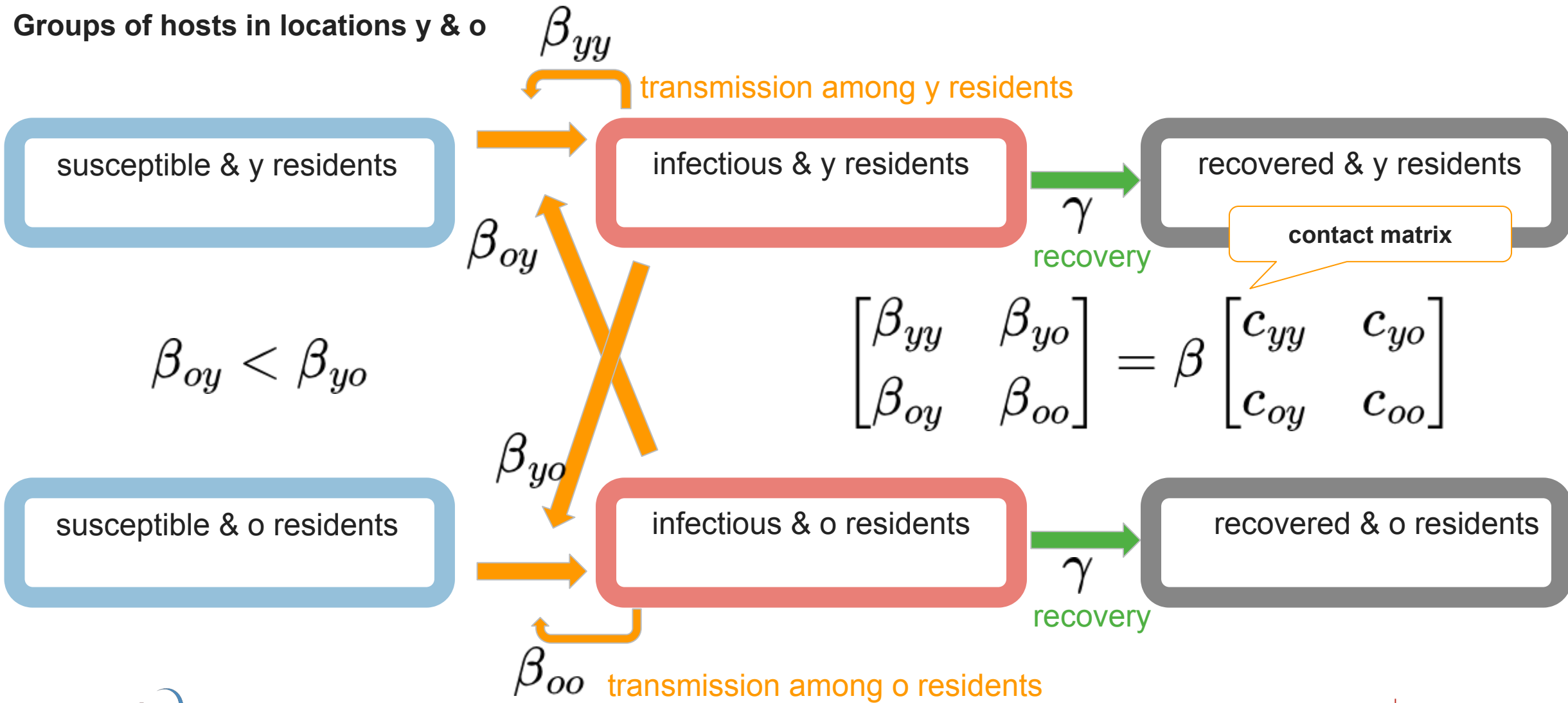


$$\beta_{oy} < \beta_{yo}$$

$$\begin{bmatrix} \beta_{yy} & \beta_{yo} \\ \beta_{oy} & \beta_{oo} \end{bmatrix} = \beta \begin{bmatrix} c_{yy} & c_{yo} \\ c_{oy} & c_{oo} \end{bmatrix}$$

More examples for next-generation matrix calculations

Groups of hosts in locations y & o



More examples for next-generation matrix calculations

$$\mathbb{F} = \begin{bmatrix} \beta \frac{S^y}{N} \sum_i c_{iy} I^i \\ \beta \frac{S^o}{N} \sum_i c_{io} I^i \end{bmatrix} \qquad \mathbb{V} = \begin{bmatrix} \gamma I^y \\ \gamma I^o \end{bmatrix}$$

$$F = \beta \left(\frac{(S^i)^*}{N} c_{ji} \right)_{i,j} \qquad V = \begin{bmatrix} \gamma & 0 \\ 0 & \gamma \end{bmatrix} \qquad V^{-1} = \begin{bmatrix} \gamma^{-1} & 0 \\ 0 & \gamma^{-1} \end{bmatrix}$$

assuming that (S^y)^*=(S^o)^*=N/2

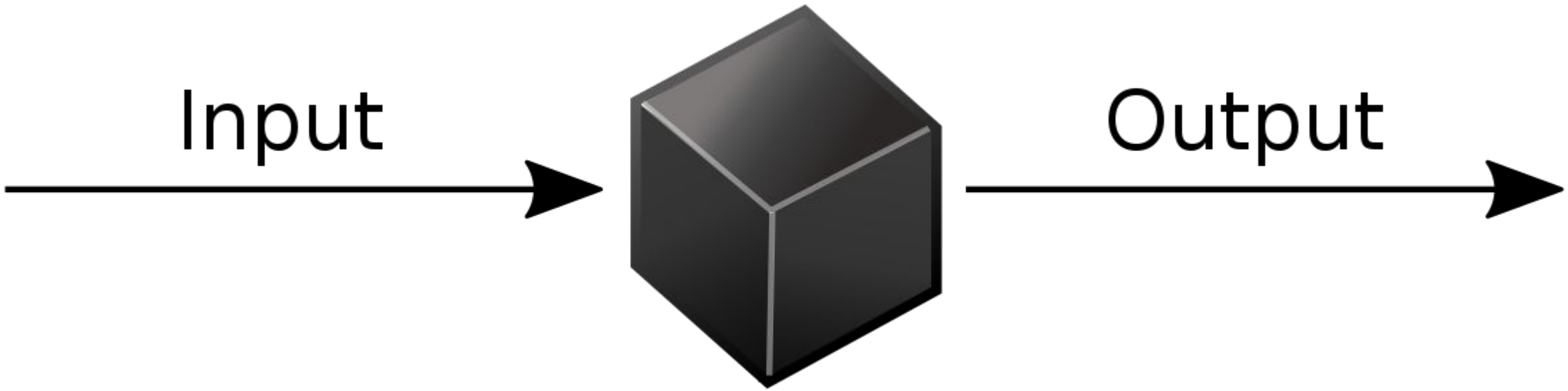
spectral radius of contact matrix

$$\mathcal{R}_0 = \frac{1}{2} \frac{\beta}{\gamma} \rho(C^T) = \frac{1}{2} \frac{\beta}{\gamma} \rho(C)$$

Swiss TPH

3 - Sensitivity analysis

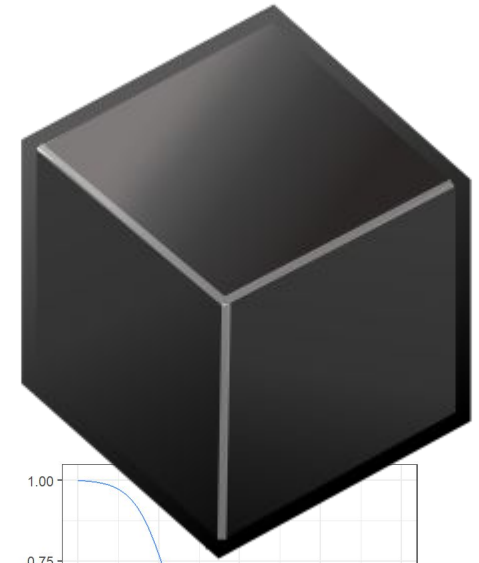
Sensitivity analysis



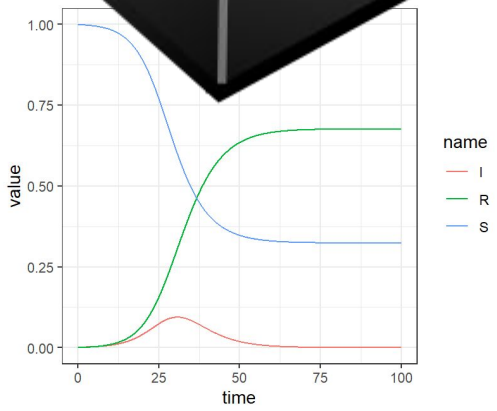
Sensitivity analysis

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

Input



Output



Swiss TPH

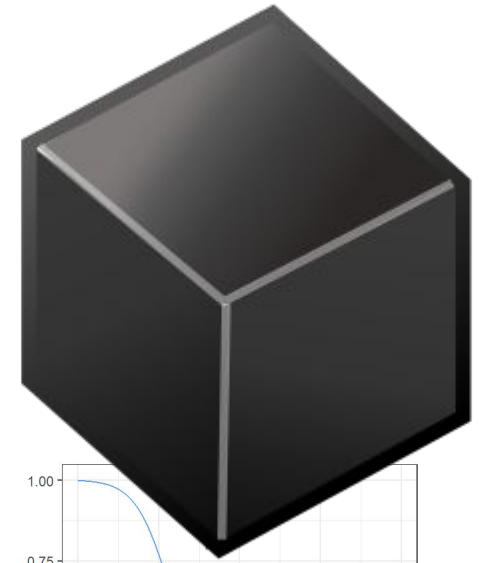
Sensitivity analysis

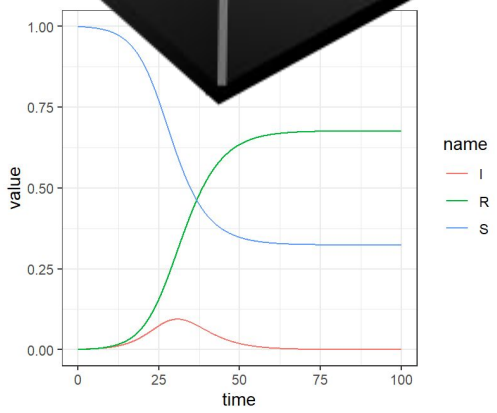
$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

$$\beta = 0.5$$

Input

$$\gamma = 0.3$$





$$\mathcal{R}_0 = \frac{5}{3}$$
$$R(\infty) = 0.68$$

Output

$$\max_{t \geq 0}(I(t)) = 0.09 = \hat{I}$$
$$\operatorname{argmin}_{t \geq 0}\{I(t) = \hat{I}\} = 30.78 \text{ days}$$

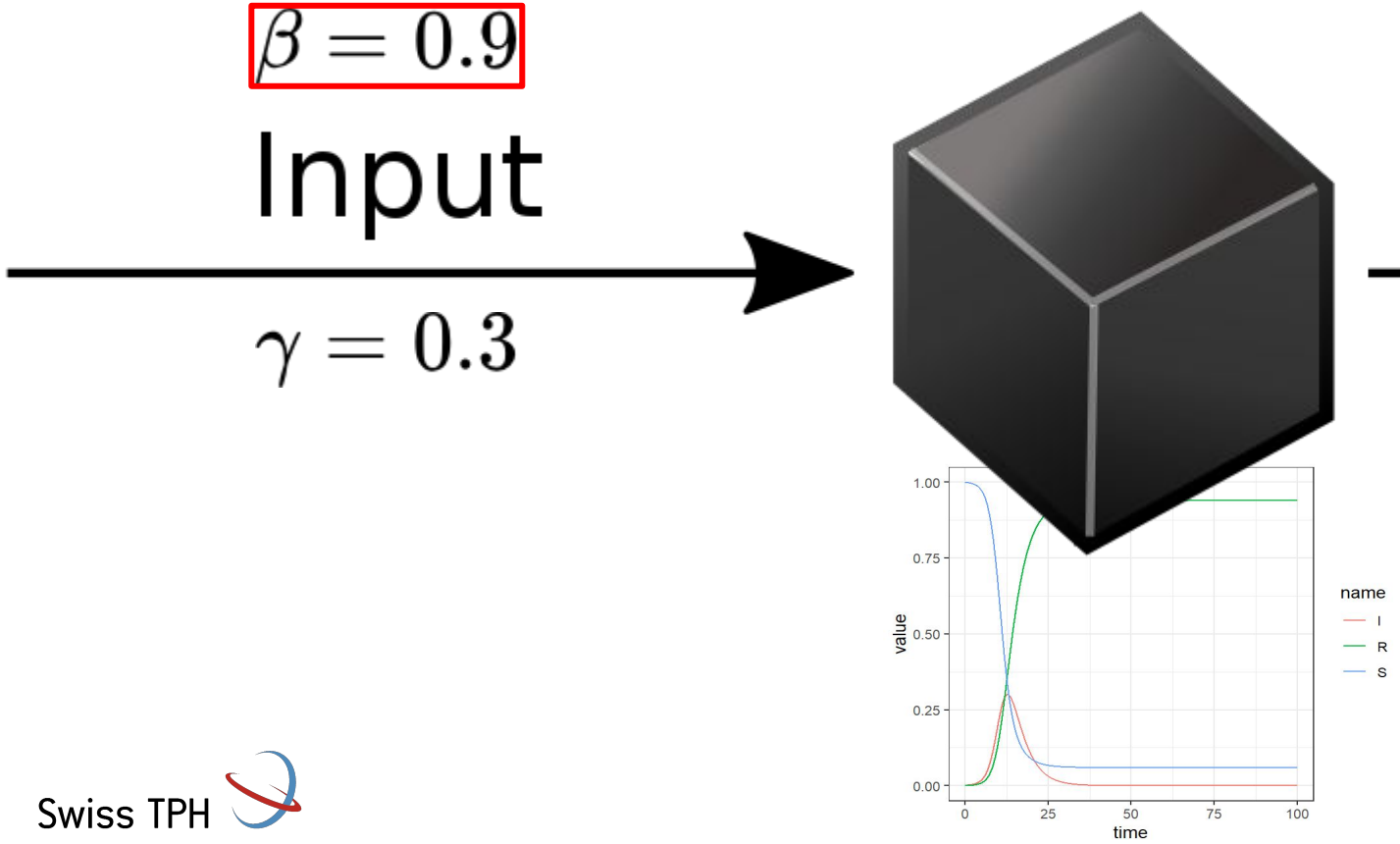
Sensitivity analysis

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

$\beta = 0.9$

Input

$\gamma = 0.3$



$\mathcal{R}_0 = 3$

$R(\infty) = 0.94$

Output

$\max_{t \geq 0}()I(t)) = 0.3 = \hat{I}$

$\text{argmin}_{t \geq 0}\{I(t) = \hat{I}\} = 12.78 \text{ days}$

Sensitivity analysis

Important questions after we have built our model:

- how do small **variations** in input values **influence** model output? [gradient]
- is there a general (e.g. linear) **trend** between input and output? [regression]
- if we consider **input values as random**, how do output values depend on them? [Sobol]
- how are the **input parameters interacting** between each other towards the output? [Sobol]

Sensitivity analysis

Why should we care about sensitivity?

- remove redundant parts of model
- fix insensitive parameters of model
- calibration should focus on sensitive parameters first

Local sensitivity analysis

Gradients

Local sensitivity index of output Q w.r.t. parameter p:

$$\chi_p^Q := \frac{\partial Q}{\partial p}\frac{p}{Q} \approx \frac{\frac{\partial Q}{Q}}{\frac{\partial p}{p}}$$

% change in output

% change in input

$$\chi_\gamma^{\mathcal{R}_0} := \frac{\partial \mathcal{R}_0}{\partial \gamma}\frac{\gamma}{\mathcal{R}_0} = -\beta\gamma^{-2}\frac{\gamma}{\frac{\beta}{\gamma}} = -1$$

for 1 % increase in recovery rate, we have 1% decrease in R0

$$\chi_\beta^{\mathcal{R}_0} := \frac{\partial \mathcal{R}_0}{\partial \beta}\frac{\beta}{\mathcal{R}_0} = \gamma^{-1}\frac{\beta}{\frac{\beta}{\gamma}} = \gamma^{-1}\gamma = 1$$

for 1 % increase in transmission rate, we have 1% increase in R0

Local sensitivity analysis

Gradients

Local sensitivity index of output Q w.r.t. parameter p:

$$\chi_p^Q := \frac{\partial Q}{\partial p}\frac{p}{Q} \approx \frac{\frac{\partial Q}{Q}}{\frac{\partial p}{p}}$$

% change in output

% change in input

$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}K}$$

$$\chi_\beta^{\mathcal{R}_0} := \frac{\partial \mathcal{R}_0}{\partial \beta}\frac{\beta}{\mathcal{R}_0} =$$

Local sensitivity analysis

Gradients

Local sensitivity index of output Q w.r.t. parameter p:

$$\chi_p^Q := \frac{\partial Q}{\partial p}\frac{p}{Q} \approx \frac{\frac{\partial Q}{Q}}{\frac{\partial p}{p}}$$

% change in output

% change in input

$$\mathcal{R}_0 = \sqrt{\frac{\alpha}{\gamma}\frac{\beta}{\delta}K}$$

$$\chi_\beta^{\mathcal{R}_0} := \frac{\partial \mathcal{R}_0}{\partial \beta}\frac{\beta}{\mathcal{R}_0} = \frac{1}{2}$$

Local sensitivity analysis

Gradients

Local sensitivity index of output Q w.r.t. parameter p:

$$\chi_p^Q := \frac{\partial Q}{\partial p}\frac{p}{Q} \approx \frac{\frac{\partial Q}{Q}}{\frac{\partial p}{p}}$$

% change in output

% change in input

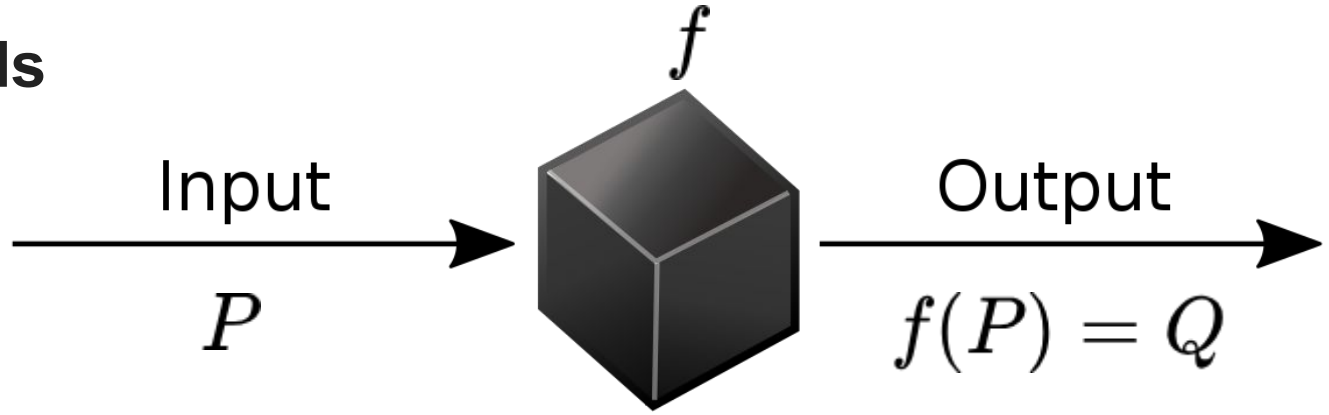
$$R(\infty) = 1 - e^{-\mathcal{R}_0 R(\infty)}$$

$\chi_\beta^{R(\infty)}$ = Use automated differentiation for the root function of $x \mapsto 1 - e^{-\mathcal{R}_0 x} - x$

Global sensitivity analysis

Variance-based methods

- model as black box



- decompose variance in output based on variance in input

$$f_0(P) = \mathbb{E}(f(P))$$ — average effect on output

$$f_i(P_i) = \mathbb{E}(f(P)|P_i) - \mathbb{E}(f(P))$$ — main effect on output by varying P_i

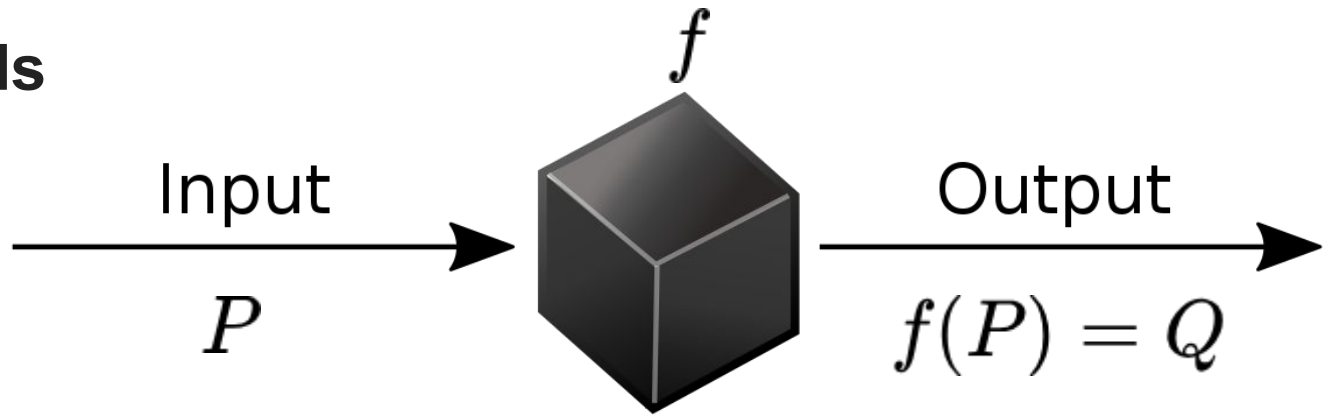
$$f_{ij}(P_i, P_j) = \mathbb{E}(f(P)|P_i, P_j) - f_0 - f_i - f_j$$ — main effect on output by varying P_i and P_j

$$f(P) = f_0 + \sum_i f_i(P_i) + \sum_{i,j} f_{ij}(P_i, P_j) + \cdots$$ — orthogonal decomposition

Global sensitivity analysis

Variance-based methods

- model as black box



- decompose **variance** in output based on variance in input

$$f(P) = f_0 + \sum_i f_i(P_i) + \sum_{i,j} f_{ij}(P_i, P_j) + \dots$$

$$\mathrm{Var}(X) = \mathbb{E}((X - \mathbb{E}(X))^2)$$

$$\mathrm{Var}(f(P)) = \sum_i V_i + \sum_{i<j} V_i V_j + \dots$$

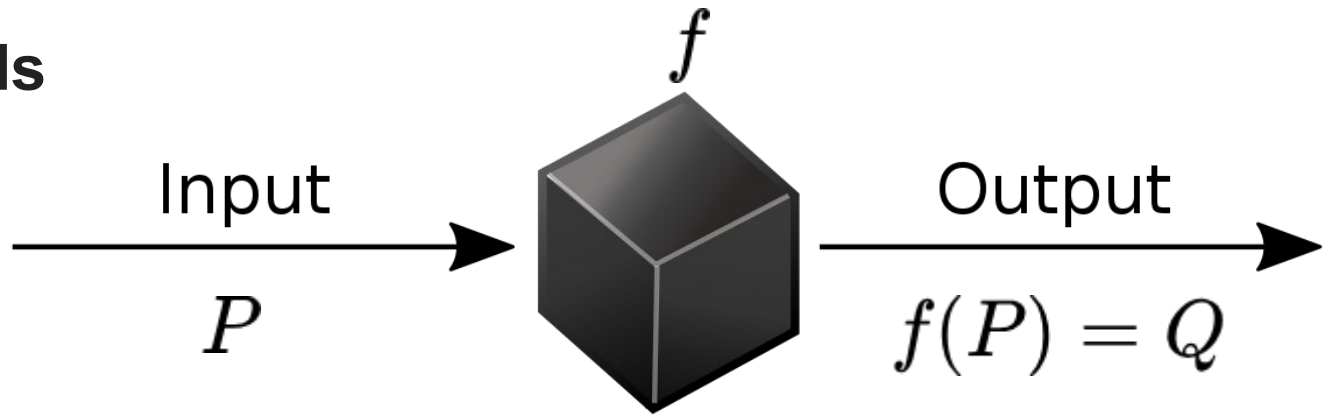
$$V_i = \mathrm{Var}(f_i(P_i)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i))$$

$$V_{ij} = \mathrm{Var}(f_{ij}(P_i, P_j)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i, P_j)) - V_i - V_j$$

Global sensitivity analysis

Variance-based methods

- model as black box



- decompose **variance** in output based on variance in input

$$f(P) = f_0 + \sum_i f_i(P_i) + \sum_{i,j} f_{ij}(P_i, P_j) + \dots$$

$$\mathrm{Var}(X) = \mathbb{E}((X - \mathbb{E}(X))^2)$$

$$\mathrm{Var}(f(P)) = \sum_i V_i + \sum_{i<j} V_i V_j + \dots$$

$$\mathrm{ar}(\mathbb{E}(f(P)|P_i))$$

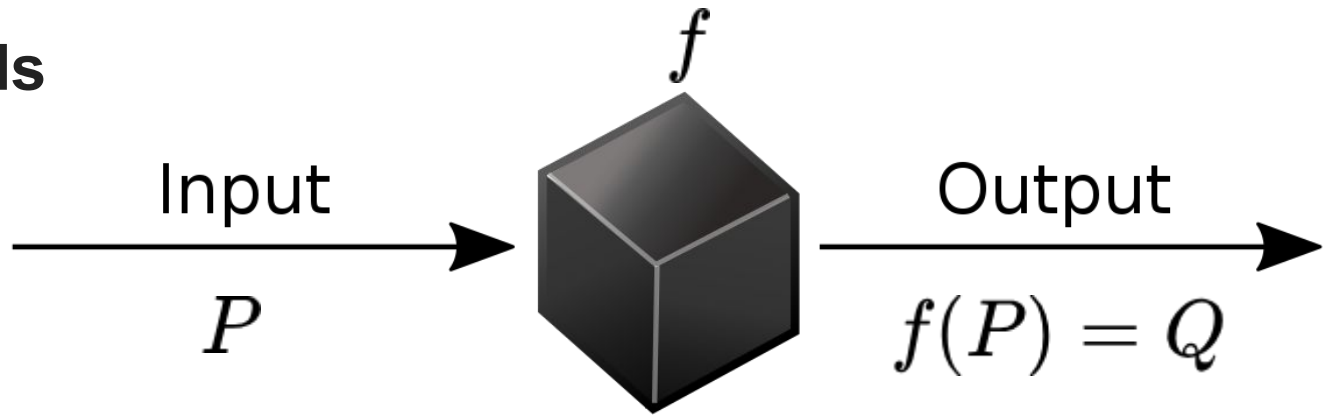
interaction between P_i and P_j

$$V_{ij} = \mathrm{Var}(f_{ij}(P_i, P_j)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i, P_j)) - V_i - V_j$$

Global sensitivity analysis

Variance-based methods

- model as black box



- decompose **variance** in output based on variance in input

$$V_i = \mathrm{Var}(f_i(P_i)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i))$$

$$V_{ij} = \mathrm{Var}(f_{ij}(P_i, P_j)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i, P_j)) - V_i - V_j$$

$$S_i = \frac{V_i}{\mathrm{Var}(f(P))}$$ **first-order Sobol index**

relative contribution of from P_i to the total variance of the output

Global sensitivity analysis

Variance-based methods

$$V_i = \mathrm{Var}(f_i(P_i)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i))$$

$$S_i = \frac{V_i}{\mathrm{Var}(f(P))}$$ **first-order Sobol index**

- need to sample from P_i
- two independent sample sets of size N from parameter distribution A, B
- conditional probability:
- estimator for V_i:

$$\hat{V}_i = \frac{1}{N} \sum_j f(B)_j (f(\underbrace{A_B^i}_{\text{conditional probability}})_j - f(A)_j))$$

A_B^i: i column of B into A

Global sensitivity analysis

Variance-based methods

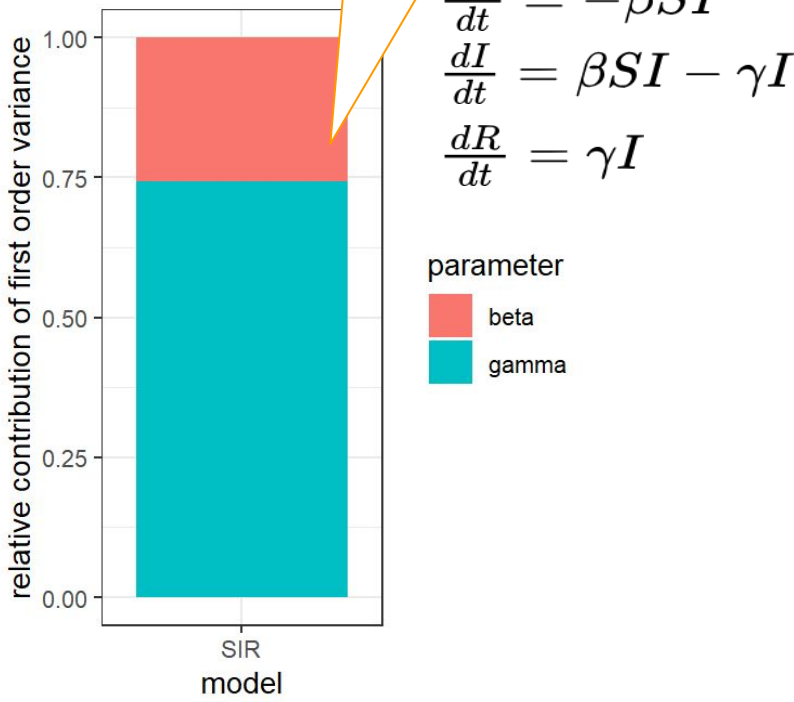
$$V_i = \mathrm{Var}(f_i(P_i)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i))$$

$$S_i = \frac{V_i}{\mathrm{Var}(f(P))}$$ **first-order Sobol index**

$$\hat{V}_i = \frac{1}{N}\sum_j f(B)_j(f(A_B^i)_j - f(A)_j))$$

Need to fix lower/upper bounds for parameter sampling here: 0.1-0.3

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$



Use the `sobolSalt` function in the R package `sensitivity` with f(P)= infection peak for the SIR model!

Download the AIDM2.R script from the webpage!

Global sensitivity analysis

Variance-based methods

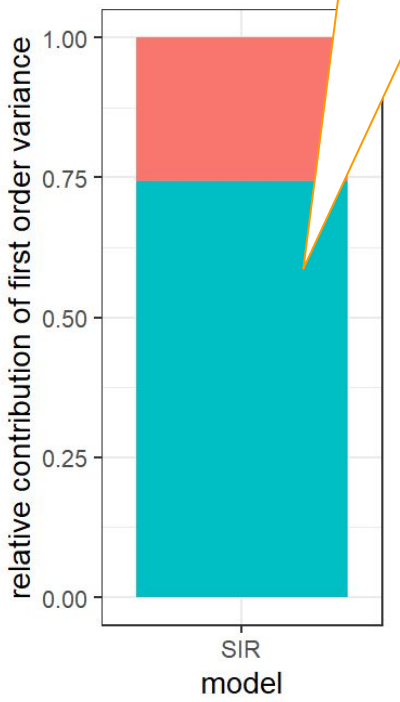
$$V_i = \mathrm{Var}(f_i(P_i)) = \mathrm{Var}(\mathbb{E}(f(P)|P_i))$$

$$S_i = \frac{V_i}{\mathrm{Var}(f(P))}$$ **first-order Sobol index**

$$\hat{V}_i = \frac{1}{N}\sum_j f(B)_j(f(A_B^i)_j - f(A)_j))$$

Contribution to peak of infection is dominated by recovery rate

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$



Use the `sobolSalt` function in the R package `sensitivity` with f(P)= infection peak for the SIR model!

Download the AIDM2.R script from the webpage!

AIDM_02.R

Global sensitivity analysis

Variance-based methods

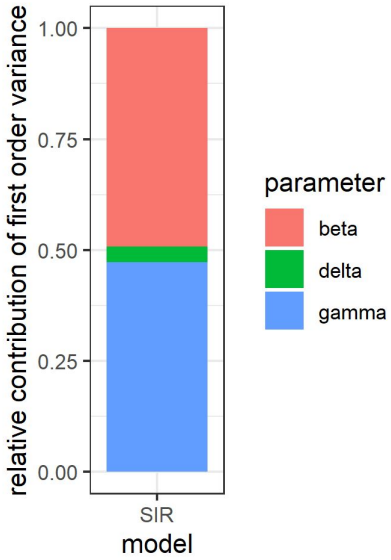
$$S_i = \frac{V_i}{\mathrm{Var}(f(P))}$$ **first-order Sobol index**

Use the `sobolSalt` function in the R package `sensitivity` with f(P)= infection peak for the model!

Adapt the **AIDM_02.R** script for an SIR model with virulence (death from disease)!

Virulence = mortality due to the infectious disease

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \delta I$$
$$\frac{dR}{dt} = \gamma I$$



Global sensitivity analysis

Variance-based methods

Use the `sobolSalt` function in the R package `sensitivity` with f(P)= endemic equilibrium for the malaria model!

Adapt the script in AIDM_02.R!

Sensitivity vs. Uncertainty

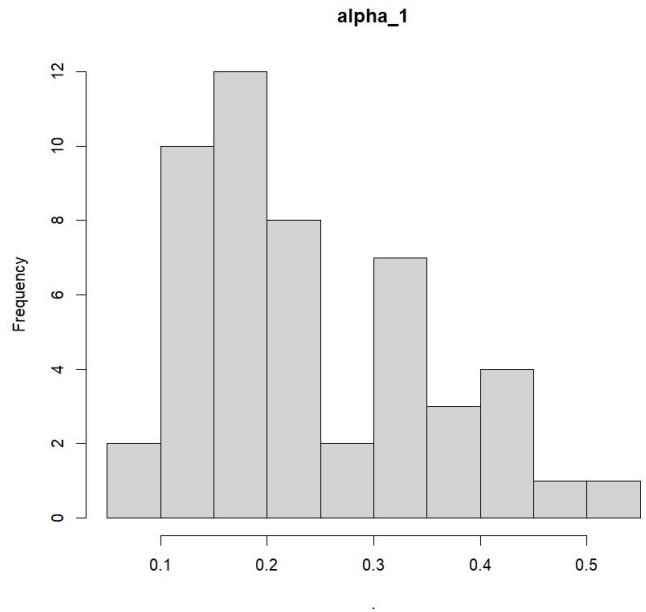
Forward-propagation of uncertainty

- Parameters usually carry **uncertainty**, i.e. the numeric value for simulation is drawn randomly from probability distribution

- Assume that the biting rate ***alpha_1*** follows a Gamma probability distribution with shape=5, scale=0.05 and simulate 500 trajectories:

```
alpha1_500<-rgamma(n=500,shape=5,scale=0.05)
```

How **uncertain is the prevalence** at the endemic equilibrium given parameter uncertainty?



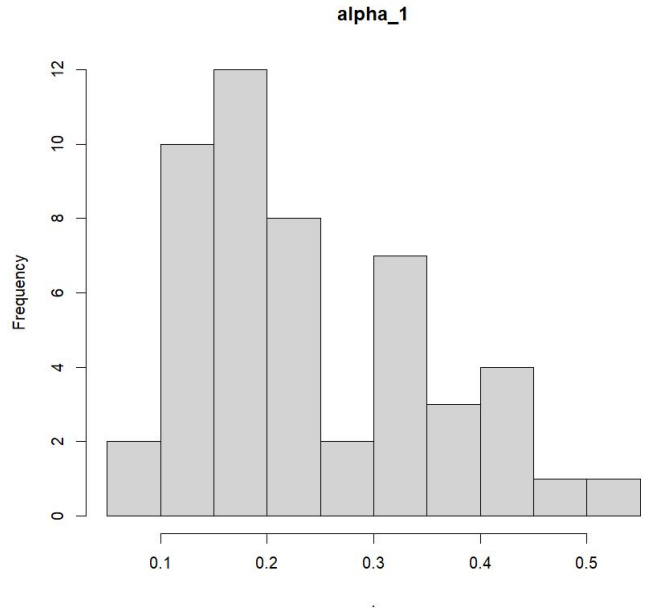
Forward-propagation of uncertainty

How **uncertain is the prevalence** at the endemic equilibrium of our malaria model given parameter uncertainty?

- Write a function

```
runRM<-function(alpha1){...
results$prevalence<-results$I/H
return(results)}
```

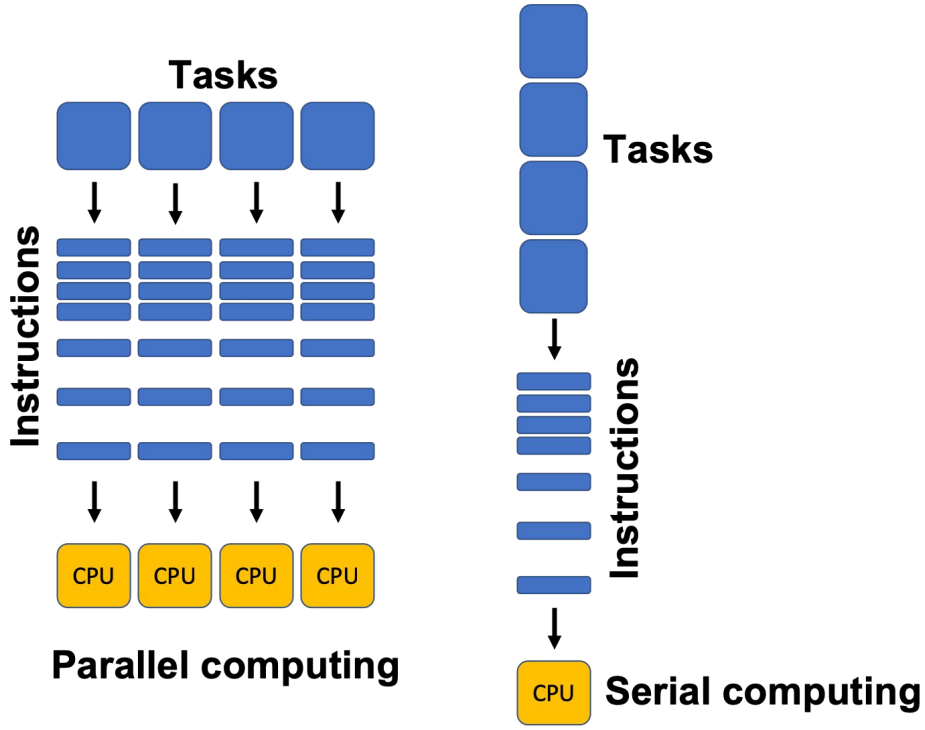
- Use `lapply(alpha1_500,runRM)` in R
- See the AIDM2.R script from the webpage!



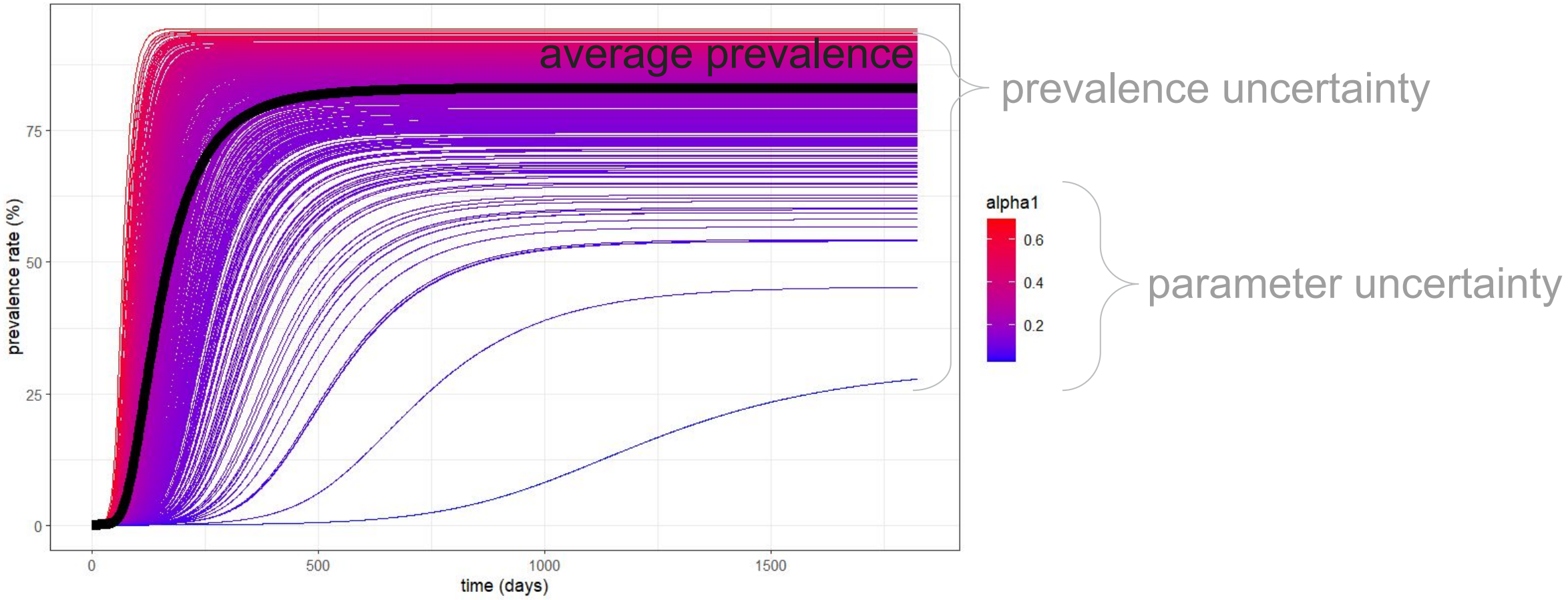
Forward-propagation of uncertainty

- Is `lapply(alpha1_500,runRM)` in R too slow?
- Parallelize!

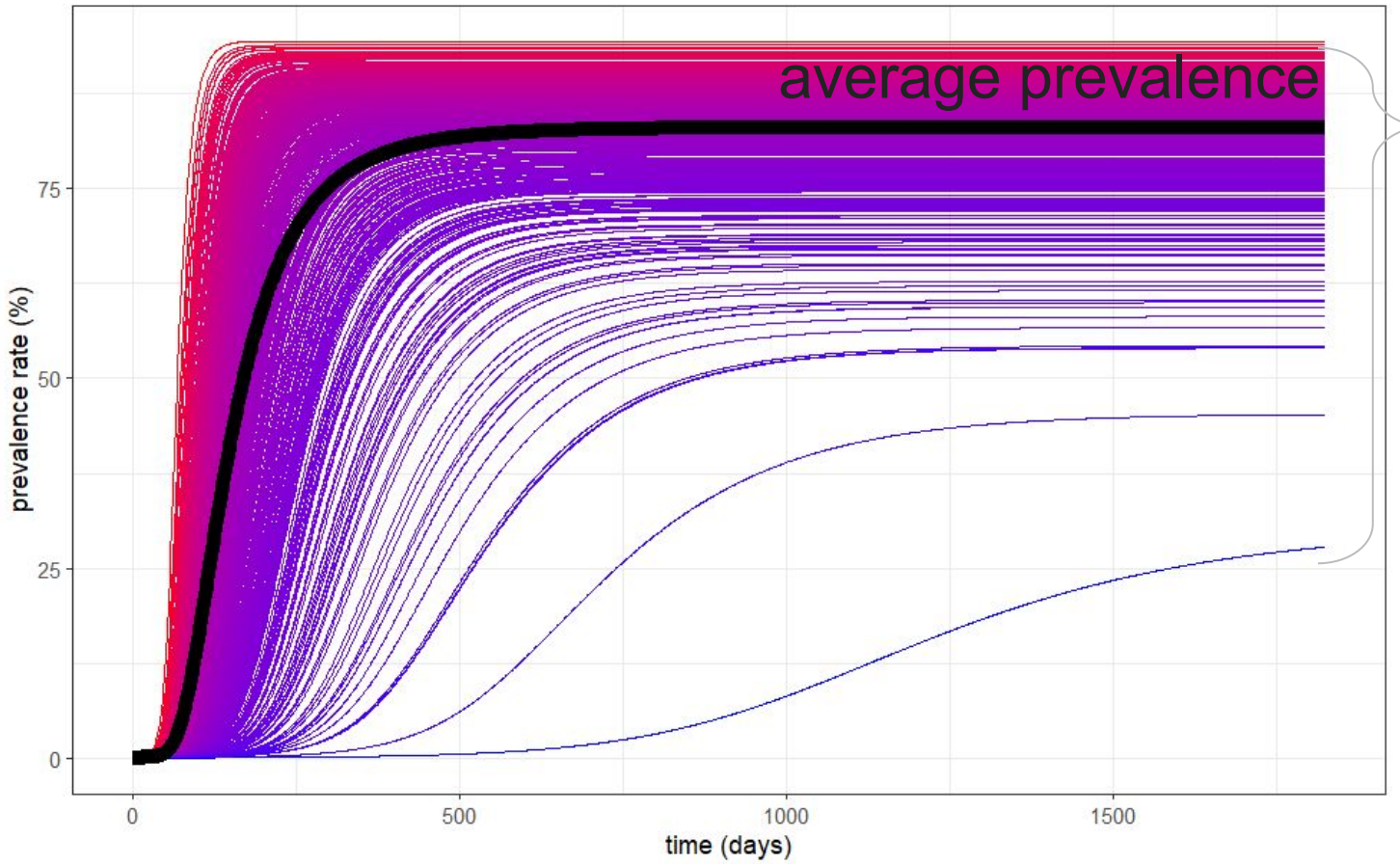
```
library(foreach)
library(doParallel)

n_cores <- detectCores()
cluster <- makeCluster(n_cores - 1)
registerDoParallel(cluster)
n_iterations <- length(alpha1)
results <- list()
results <- foreach(i = 1:n_iterations) %dopar% {
  results[i] <- runRM(alpha1[i])
}
stopCluster(cl = cluster)
for(i in 1:n_iterations){
  results[[i]]$alpha1<-alpha1[i]
  results[[i]]$iter<-i
}
results<-bind_rows(results)
```



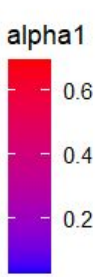
Forward-propagation of uncertainty



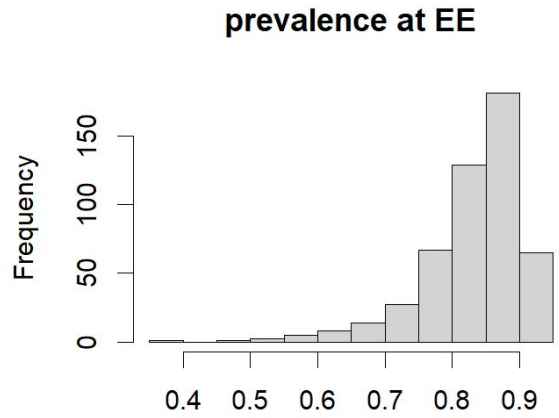
Forward-propagation of uncertainty



prevalence uncertainty



parameter uncertainty



Key takeaway points:

- sensitivity analysis is an **important step in the design** of a model, it allows to understand the input-to-output relationship and interactions

- **gradient-based** sensitivity analysis considers small variations in parameter space

- **global sensitivity** analysis considers the relationship between variance of inputs and outputs

- **forward propagation of uncertainty** is important to illustrate the effect of parameter uncertainty on performance indicators of disease models

Swiss TPH

4 - Curve fitting

Influenza outbreak in a boarding school

date	in bed	convalescent	total
1978-01-22	3	0	763
1978-01-23	8	0	763
1978-01-24	26	0	763
1978-01-25	76	0	763
1978-01-26	225	9	763
1978-01-27	298	17	763
1978-01-28	258	105	763
1978-01-29	233	162	763

Main assumptions

- time series of **symptomatic cases** and **convalescent hosts**
- closed population
- well-mixed
- immunity upon recovery

Visualize the data

- install the R package **`outbreaks`**
- visualize with **`ggplot2`** the data frame influenza_england_1978 as points

Visualize the data

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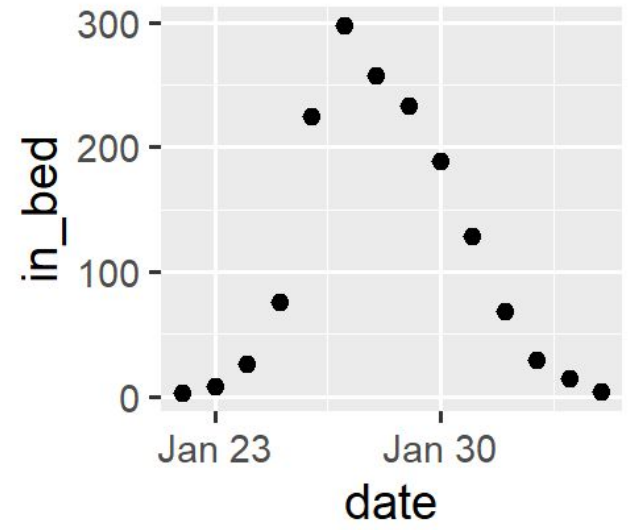
- visualize with **`ggplot2`** the data frame influenza_england_1978 as points

```
library(outbreaks)
##add time column to data from outbreaks package
influenza_england_1978_school<-influenza_england_1978_school%>%
  mutate(time=row_number(),
         total=763)
##plot the data
ggplot(influenza_england_1978_school)+
  geom_point(aes(x=date,y=in_bed))
```



Visualize the data

- solve the ODE system with **`deSolve`** in R with $\beta = 1.1$ and $\gamma = 0.5$
- plot the solution curve on top of the data points

$$\frac{dS}{dt} = -\beta I \frac{S}{N}$$
$$\frac{dI}{dt} = \beta I \frac{S}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

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```
SIR.model<-function(time,state,parms){
  with(as.list(c(state,parms)), {
    beta=parms[1]; gamma=parms[2];
    S=state[1]; I=state[2];R=state[3];N=S+I+R
    dS= - beta*I*S/N
    dI= beta*I*S/N - gamma*I
    dR= gamma*I
    return(list(c(dS,dI,dR)))
  })
}

time.points<-seq(0,nrow(influenza_england_1978_school),0.01)
initial.condition<-c(S=762,I=1,R=0)
parameters<-c(beta=1.1,gamma=0.5)

as.data.frame(ode(initial.condition,time.points,SIR.model,parameters))->solution_SIR

##lets plot the model output on top of the data
ggplot(merge(solution_SIR,influenza_england_1978_school))+
  geom_line(aes(x=time,y=I),color="darkgreen")+
  geom_point(aes(x=time,y=in_bed))
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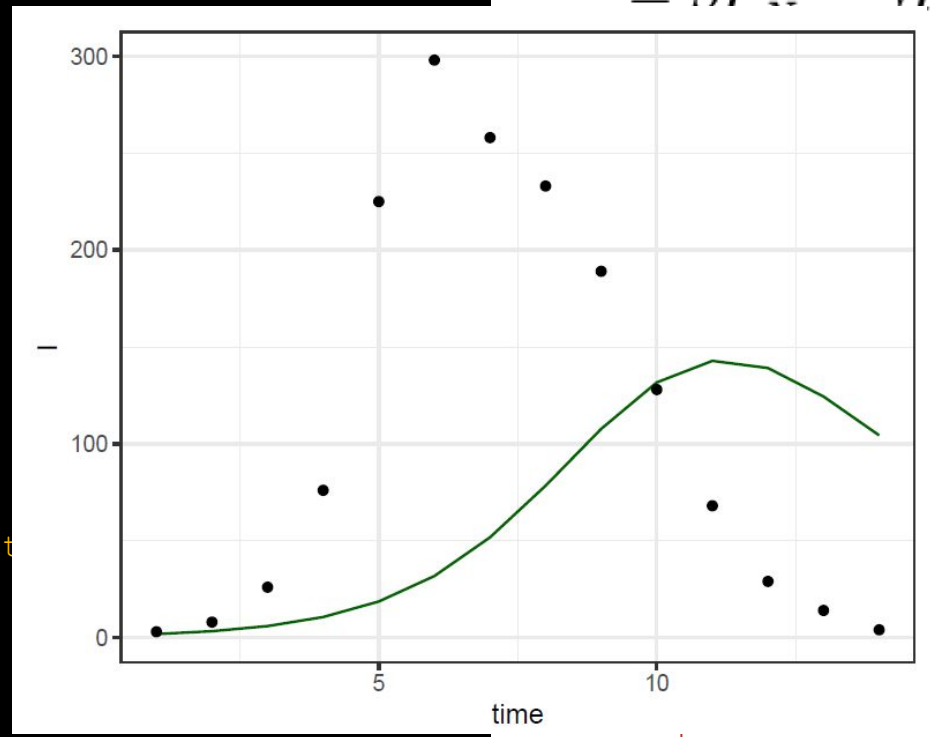


Fitting the curve

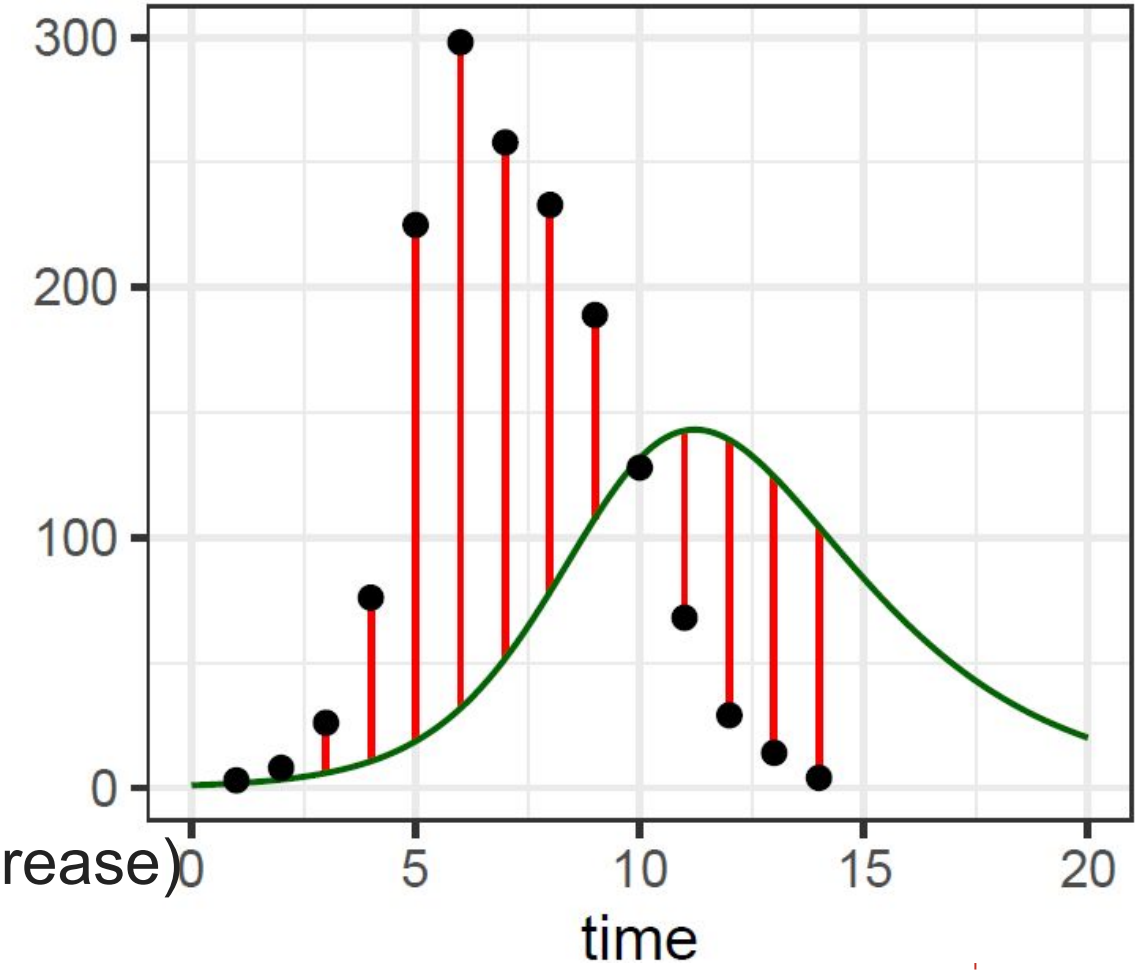
Define error function between model output and data

$$\text{error}(\beta, \gamma) = \sum_{t=1}^{14} |I(t, \beta, \gamma) - d(t)|^2$$

$$\text{error}(\beta, \gamma) = \sum_{t=1}^{14} w_t |I(t, \beta, \gamma) - d(t)|^2$$

$$\sum_{t=1}^{14} w_t = 1$$

weighted error: certain time points in the data are more important (e.g. exponential increase)



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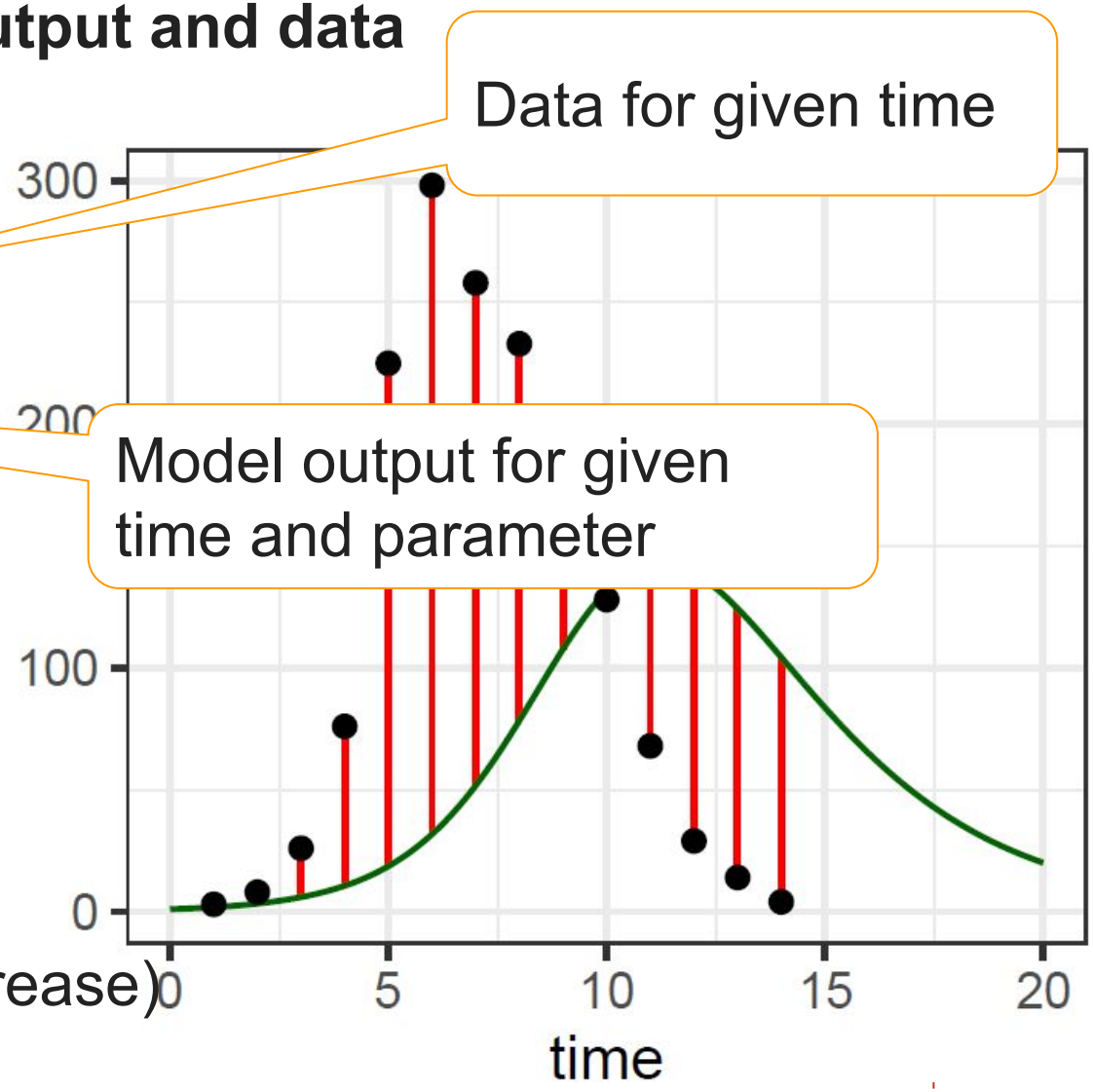
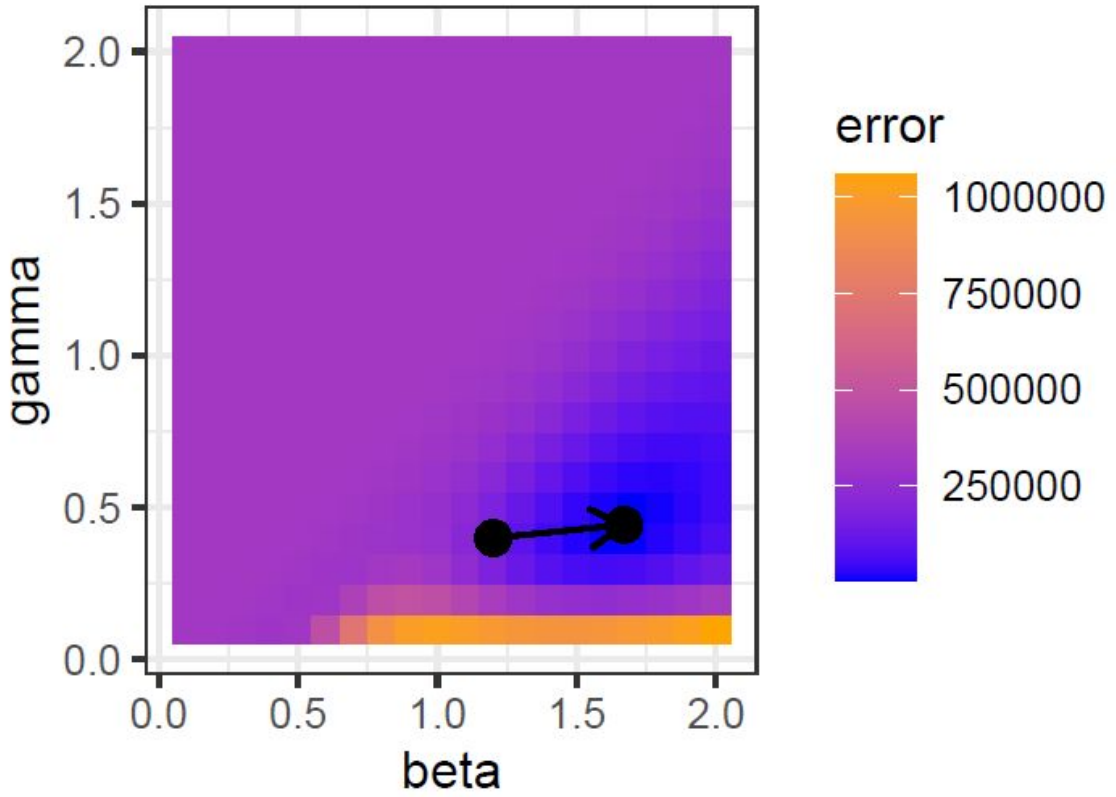
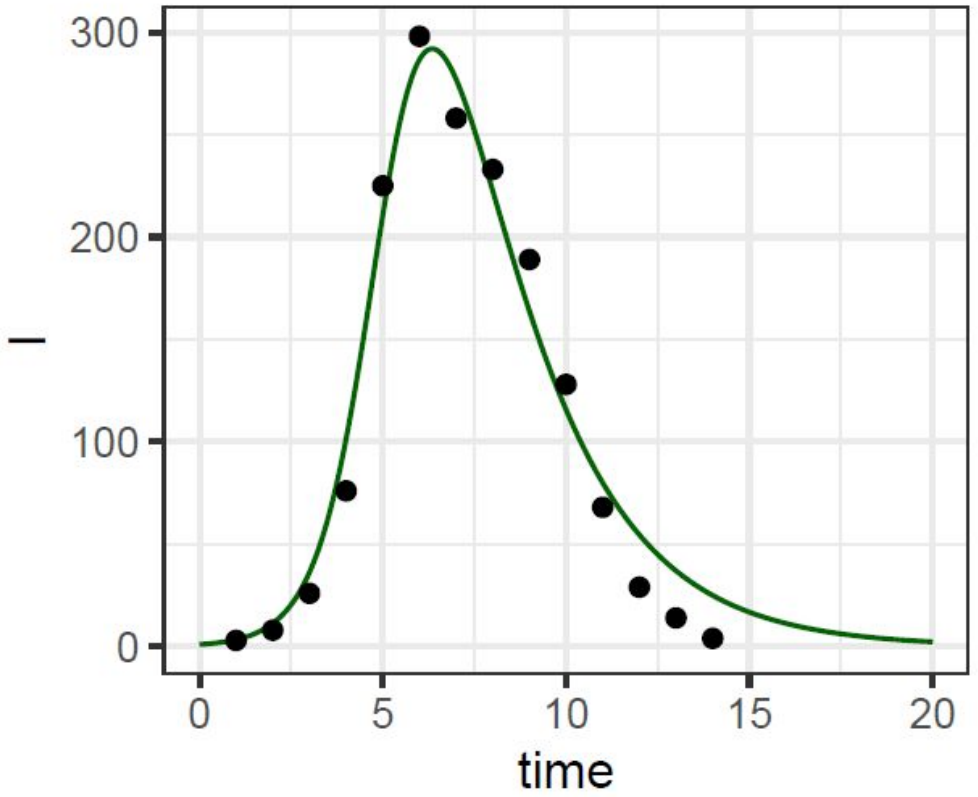


Fitting the curve

Minimizing the error

- error function depends on model parameters
- “best” parameters are those for which error is minimal





Fitting the curve

Optimizing with Gauss-Newton

- residual $r_i := d(i) - I(i, \beta)$
- least square is loss function $S : \beta \mapsto \sum_{i=1}^{14} r_i^2$
- Gauss-Newton gradient equation:

$$\frac{\partial S}{\partial \beta} = 2 \sum_i r_i \frac{\partial r_i}{\partial \beta} = -2 \sum_i r_i \frac{\partial I(i,\beta)}{\partial \beta} = 0$$

- Taylor expansion at β^k

$$I(i, \beta) = I(i, \beta^k) + \frac{\partial I(i,\beta^k)}{\partial \beta}(\beta - \beta^k)$$

- plug this into gradient equation, solve for β to obtain β^{k+1}

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Gauss-Newton will give you only a local minimum!

- plug this into gradient equation, solve for β to obtain β^{k+1}

Fitting the curve

Optimizing with Gauss-Newton

$$\sum_i r_i(\beta)\frac{\partial I^i}{\partial \beta}(\beta) = 0$$

local minimum condition

$k = 0$ w.l.o.g. pick a start value β_0

$$I(i,\beta) = I(i,\beta^k) + \frac{\partial I(i,\beta^k)}{\partial \beta}(\beta - \beta^k)$$

$$\sum_i \left\{ d_i - \left(I^i(\beta_0) + \frac{\partial I^i}{\partial \beta}(\beta_0)(\beta - \beta_0) \right) \right\} \frac{\partial I^i}{\partial \beta}(\beta) = 0 \qquad J := \frac{\partial I}{\partial \beta}$$

$$J^T J\beta = J^T J\beta_0 - J^T r_i(\beta_0)$$

$$\beta = \beta_0 - (J^T J)^{-1} J^T r_i(\beta_0)$$

$$\beta_1 := \beta$$

iterate until gradient is very close to zero

Fitting the curve

Optimizing with Gauss-Newton in R

- use the function **`optim`** in the R package **`stats`**
- build a residual sum of squares function by running he ODE model and comparing its output to the data

```
##residual sum of squares
rss<-function(parameters){
  time.points<-seq(0,20,0.1);
initial.condition<-c(S=762,I=1,R=0)
  ode(initial.condition,time.points,SIR.model,parameters)%>%
    as.data.frame->solution_SIR

solution_SIR<-merge(solution_SIR,influenza_england_1978_school)
  RSS<-sum((solution_SIR$I-solution_SIR$in_bed)^2)
  return(RSS)
}
```

Fitting the curve

Optimizing with Gauss-Newton in R

- assume β and γ are bounded between 0 and 2
- pick your favourite start value for β and γ
- use the **`optim`** function with the "L-BFGS-B" method and provide **`par`**, **`lower`** and **`upper`** arguments

starting value

bound

bound

quasi-Newton method using also Hessian

```
##optimize residual sum of squares over parameter space
start<-c(1.2, 0.4)#initial value
##run newton method for optimization
opt.param <- optim(par=start,rss,method = "L-BFGS-B",lower = c(0,0),upper = c(2,2),hessian
=TRUE,control = list(parscale = c(10^-4,10^-4),factr=1))$par
```

Fitting the curve

```
##let's simulate the optimal solution
ode(initial.condition,time.points,SIR.model,opt.param)%>%
  as.data.frame->solution_SIR_optim

##lets plot the model output on top of the data
ggplot(merge(solution_SIR_optim,influenza_england_1978_school))+
  geom_line(aes(x=time,y=I),color="darkgreen")+
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```

Fitting the curve

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```
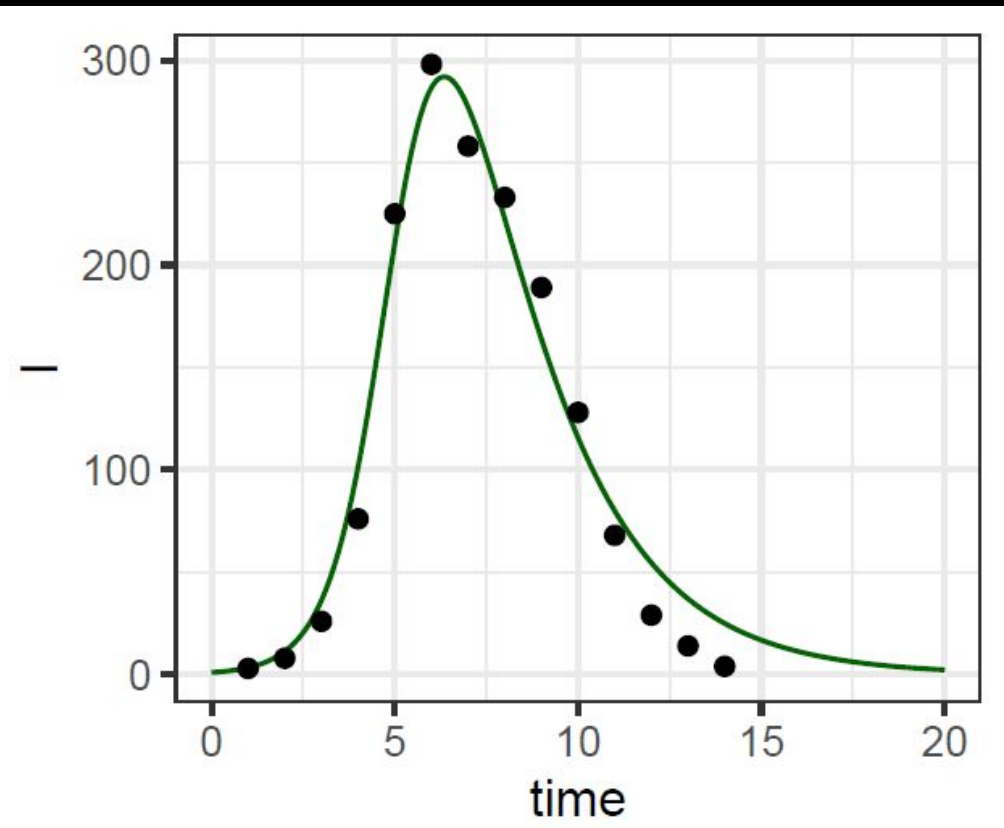



Is fitting the curve sufficient for the model to be informative?

Possible issues:

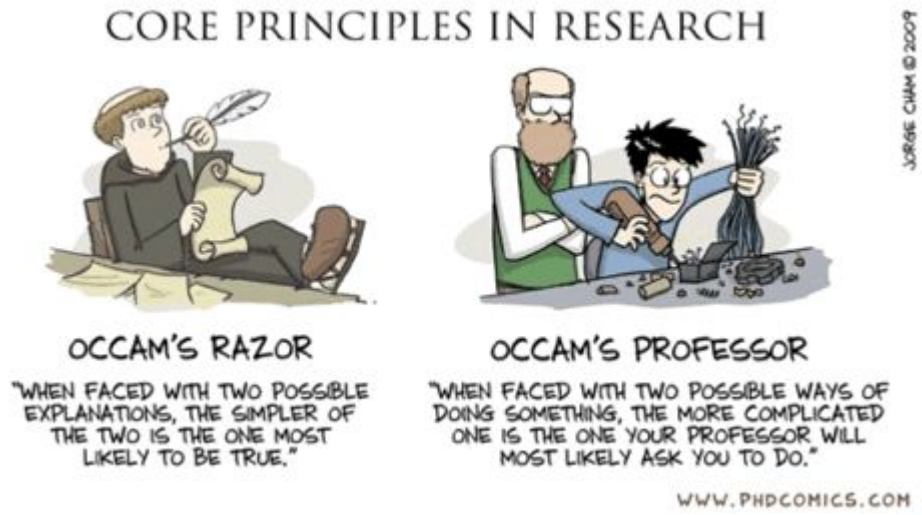
- influenza incubation period, spatial structure of school: **model misspecification**
- **prior knowledge** about clearance rate: narrow down bounds
- data recording has **measurement errors**: need statistical estimator
- **uncertainty** of parameters : credible intervals
- optimal solution not unique : **identifiability**

What is a good model?

Parsimony: explain data with model with as few as possible parameters

- Occam's razor:

  "It is futile to do with more things that which can be done with fewer."



- which model should we prefer?
- model selection with Akaike Information Criterion (AIC):

  $$AIC = number\ of\ parameters - log\ maximum\ likelihood$$

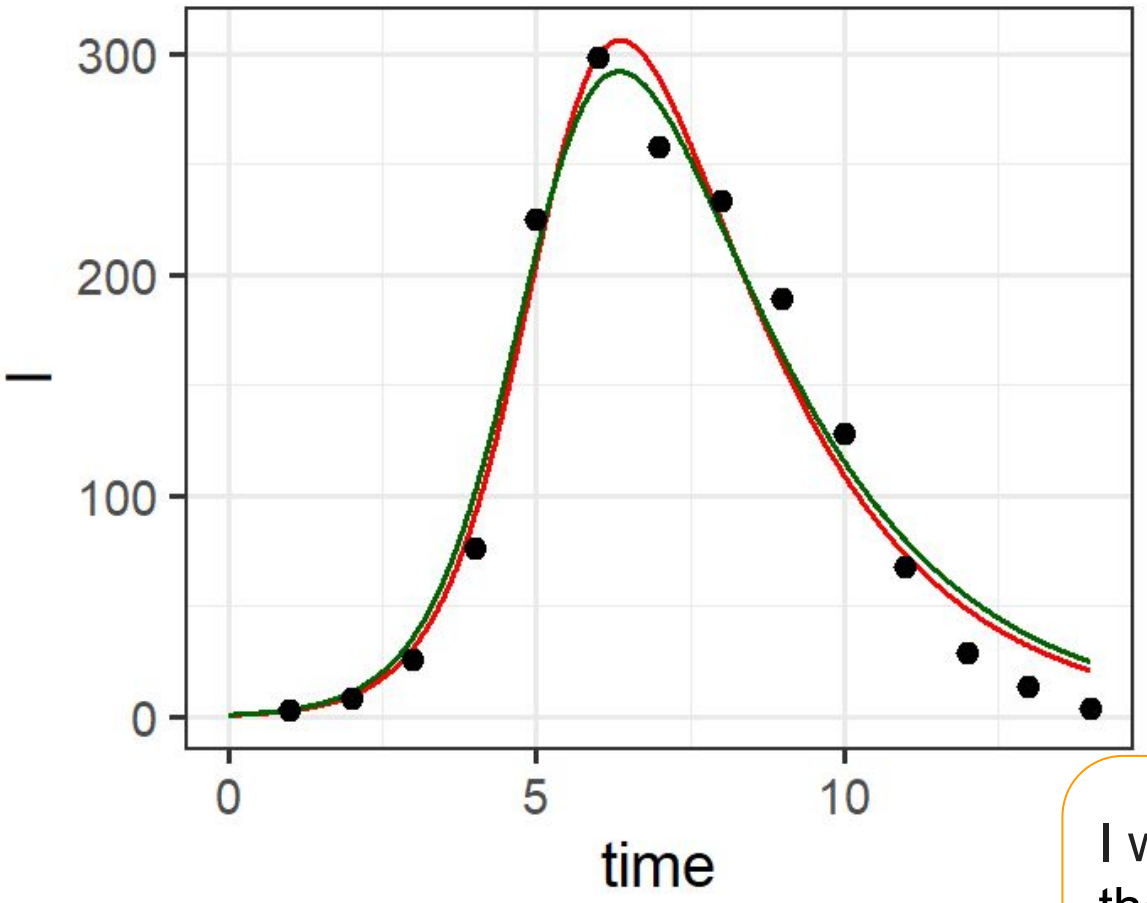
- model with smaller AIC is the better model

What is a good model?

- add an exposed but not yet infectious compartment E to the SIR model
- write α for the inverse incubation period (the rate from E to I)
- find minimal residual sum of squares solution for parameters α, β, γ w.r.t. influenza data
- would you recommend Occam to rather use the SEIR model?

William of Occam, XIVth century

What is a good model?



AIC for SIR

```
2-log(rss(opt.param))=-6.3
```

```
3-log(rss1(opt.param1)=-5.3
```

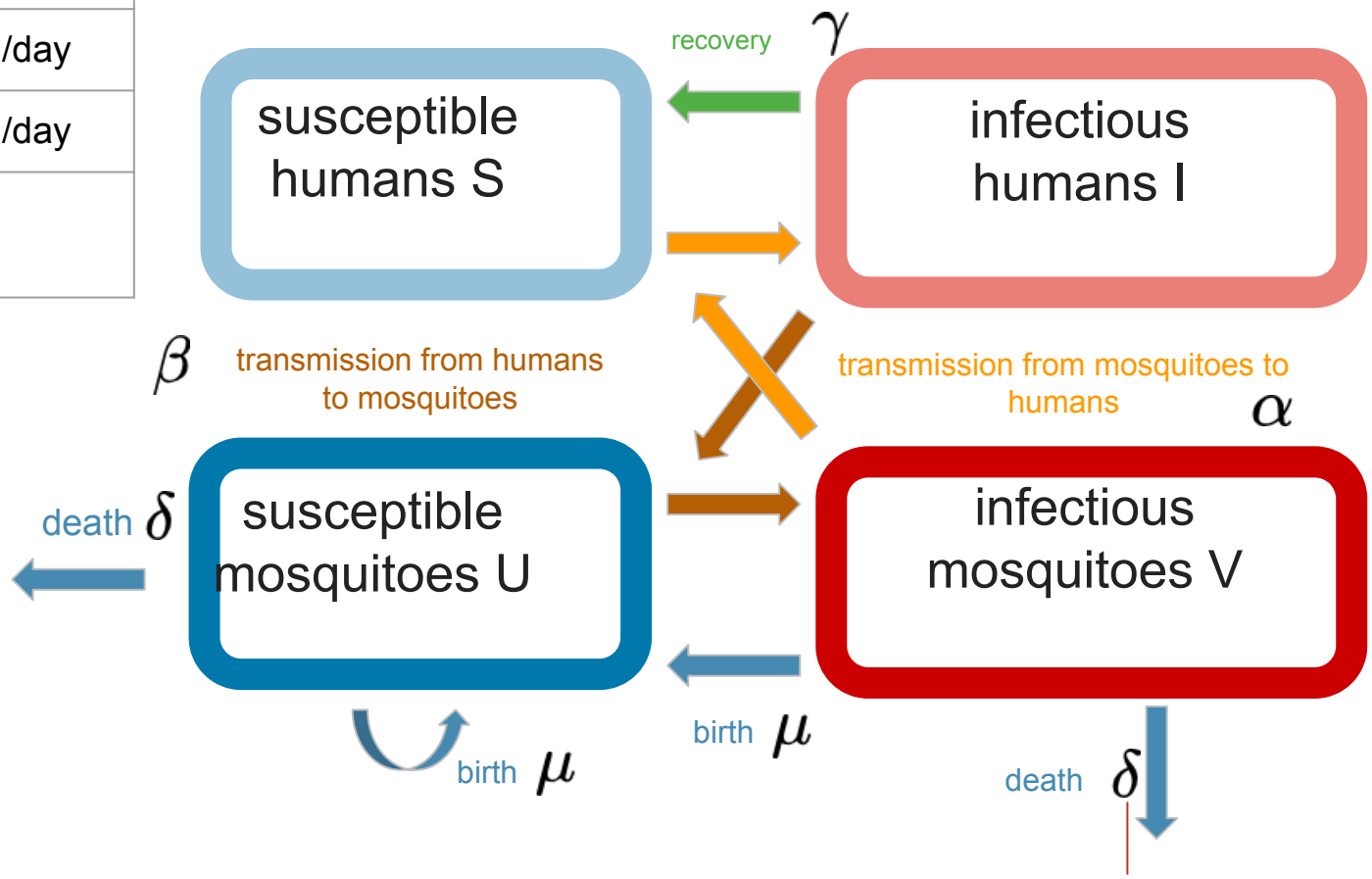
AIC for SEIR

I would **choose the SIR** model, the additional parameter for SEIR does not justify the marginal decrease in error!

William of Occam, XIVth century

Fitting the curve for the Ross-McDonald model

parameter	description	value	unit
gamma	reciprocal of untreated infection duration	1/285	1/day
alpha_1	biting rate within gonotrophic cycle	0.5	1/day
alpha_2	probability of transmission to humans	?	1
delta	mosquito mortality rate	0.13	1/day
mu	per capita mosquito birth rate	0.13	1/day
beta	probability of transmission to mosquitoes	?	1



prevalence at endemic equilibrium=0.35
alpha_2=?
beta=?

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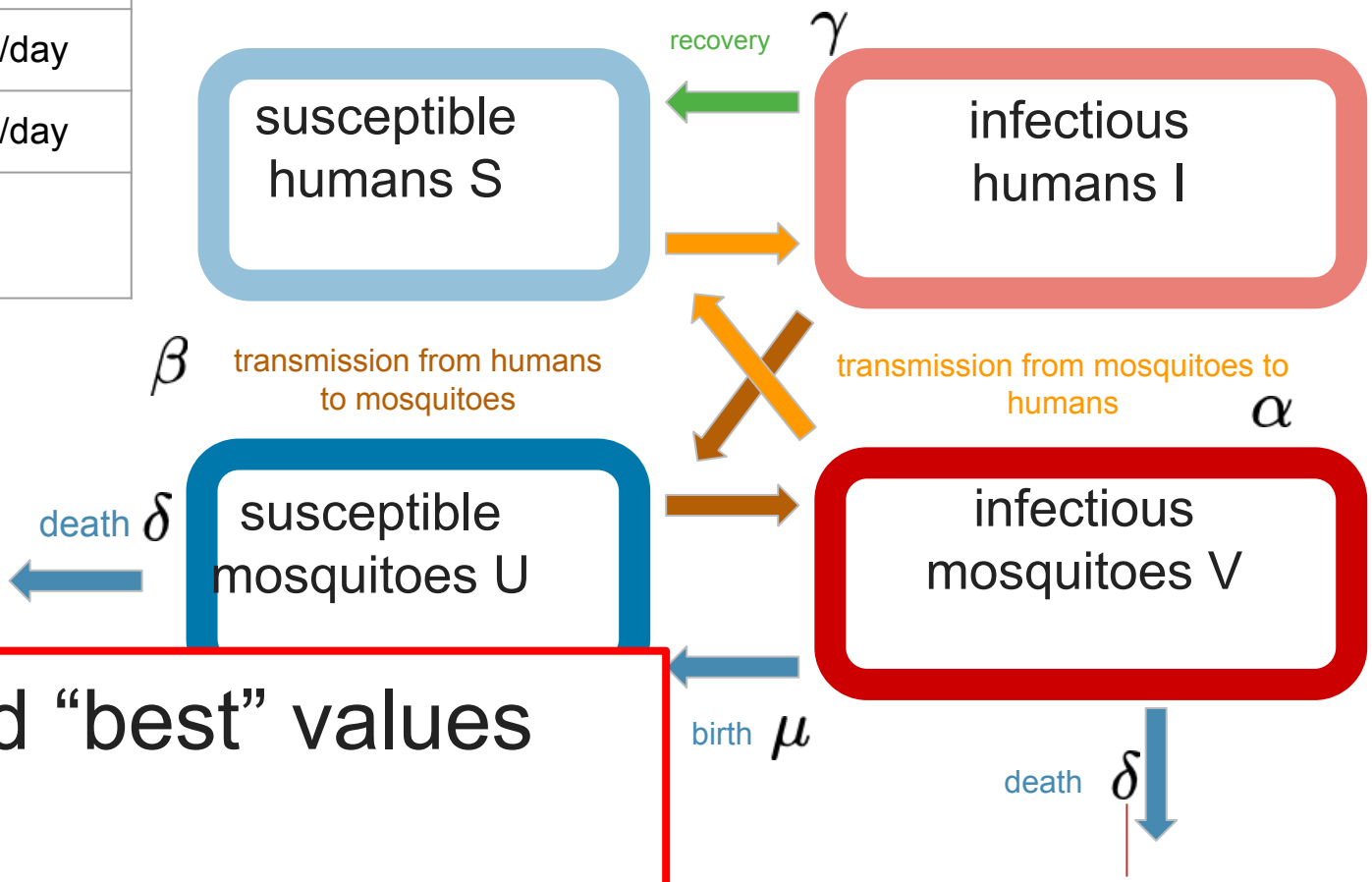

prevalence at endemic equilibrium=0.35
alpha_2=?
beta=?

Use `optim` in R and find "best" values for alpha_2 & beta!

Sw

Fitting the curve for the Ross-McDonald model

parameter	description	value	unit
gamma	reciprocal of untreated infection duration	1/285	1/day
alpha_1	biting rate within gonotrophic cycle	0.5	1/day
alpha_2	probability of transmission to humans	?	1

```
H=5000; I0=1; V0=8; VectorHumanRatio=5; finalT=8*365
x0 <-c(S=H-I0,I=I0,U=H*VectorHumanRatio-V0,V=V0)
time.points<-seq(0,finalT,1)


RSS.RM<-function(parameters){
parms<-c(alpha=0.5*parameters[1],gamma=1/285,beta=parameters[2],
mu=0.13,delta=0.13)
…

return(rss)
}
```

Fitting the curve for the Ross-McDonald model

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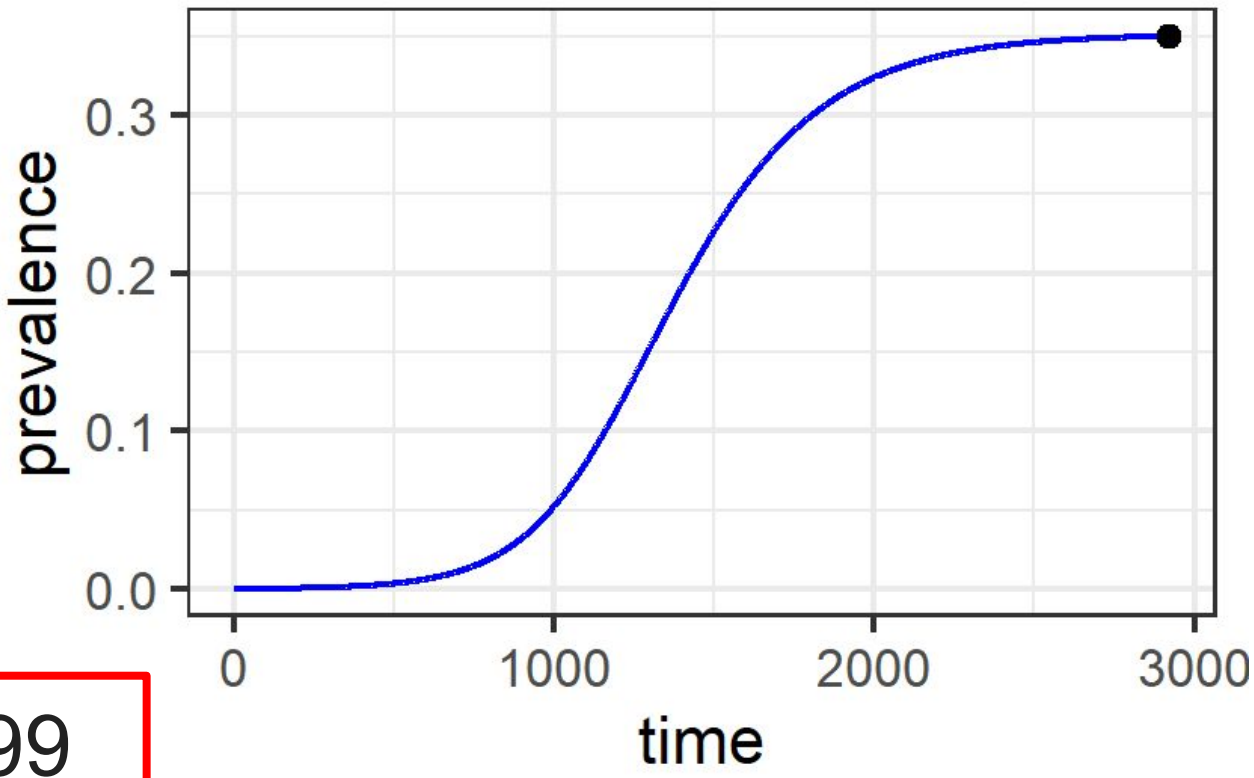


prevalence at endemic equilibrium=0.35
alpha_2=?
beta=?

alpha_2=0.001697, beta=0.2999

Key takeaway points:

- curve fitting assumes that **observations are without measurement error,** and that consecutive observations are **independent**

- use optimization to identify **optimal parameter sets** such that the residual **error** between observations and model outputs **minimal**

- **parsimony** is an epistemological method: “of two competing theories, the simpler one is preferred”

- **parsimony** is **quantified** by information criteria: how much better is the data explained by a model if we add additional parameters to it?

Swiss TPH

5 - Statistical inference

Three paradigms of statistical inference

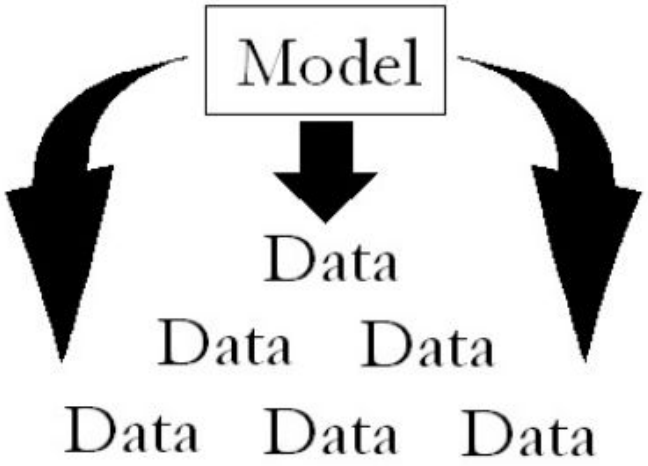
the model is fixed,
the data is random

the model is random,
the data is fixed

frequentist

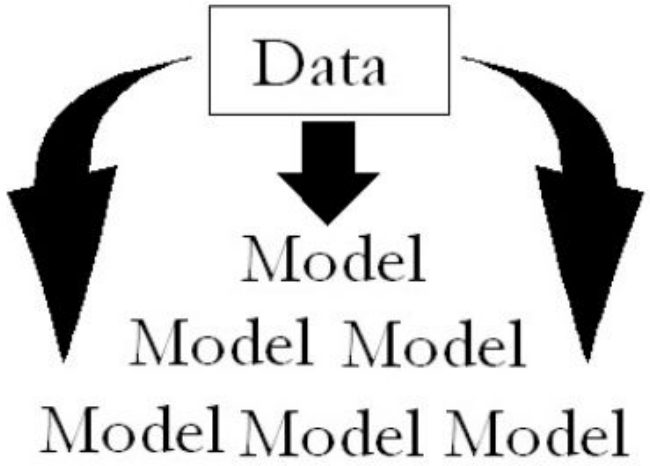
Bayesian

Three paradigms of statistical inference



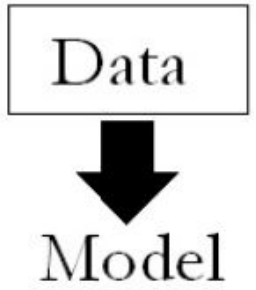
frequentist

Can we **reproduce data** by sampling from statistical population for a **given model parameter**?



Bayesian

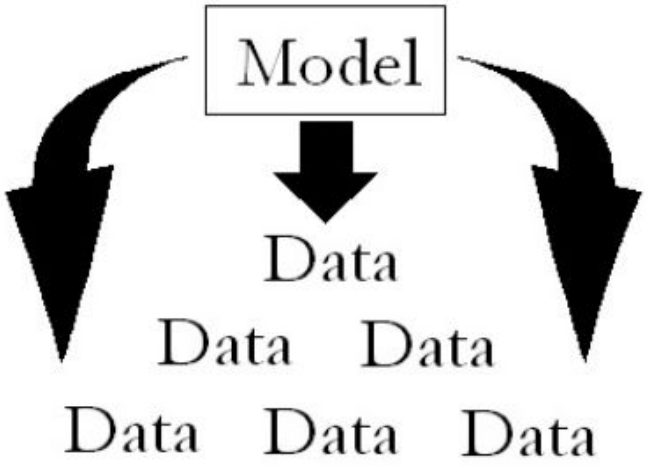
Given the data, what is the **most plausible** probability distribution of **model parameters**?



likelihoodist

Measure **evidence** from data by likelihood function!

Three paradigms of statistical inference



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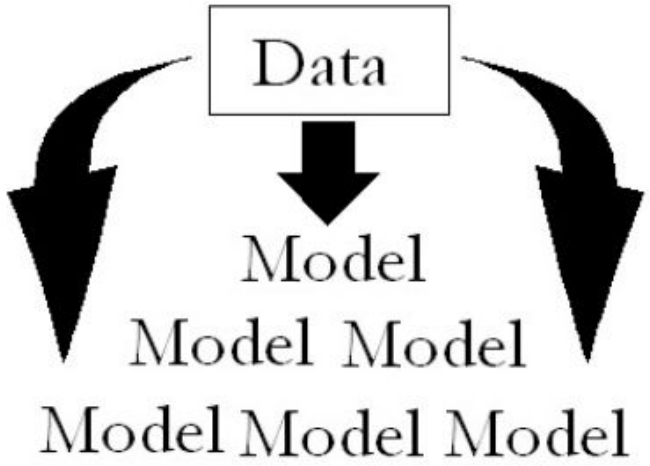

Bayesian

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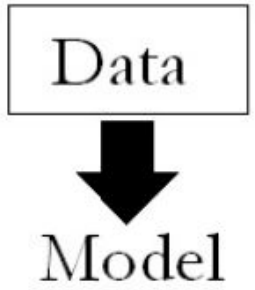
posterior distribution

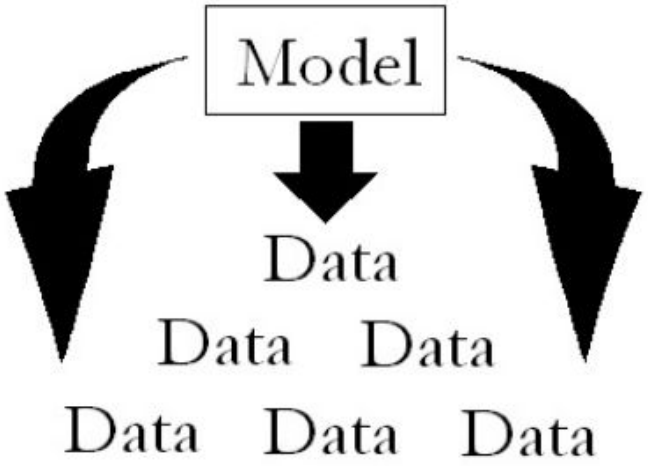


likelihoodist

Measure **evidence** from data by likelihood function!

maximum likelihood

Three paradigms of statistical inference



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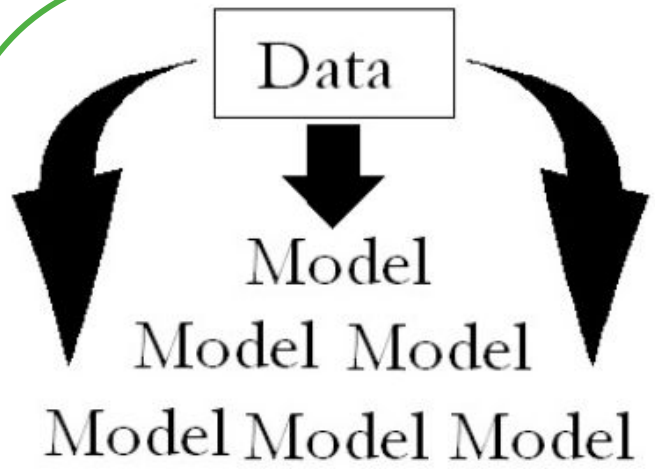

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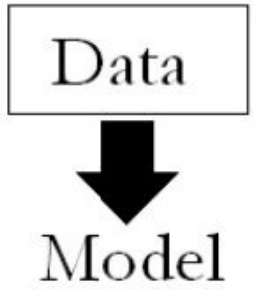


likelihoodist

Measure **evidence** from data by likelihood function!

maximum likelihood

Maximum likelihood

- **data** is considered **random sample** from unknown statistical population
- **maximum likelihood**: find probability distributions which is most likely to generate such samples
- parameterized distribution $f_\theta(.)$ for θ in parameter space Θ
- observed data sample $X \in \mathbb{R}^d$: **likelihood** $L : \theta \mapsto f_\theta(X)$
- **goal: find** $\hat{\theta}(X) = \text{argmax}_\theta L(\theta)$
- $\hat{\theta}$ maximum likelihood estimator which is random variable $\hat{\theta} : \mathbb{R}^d \to \Theta$

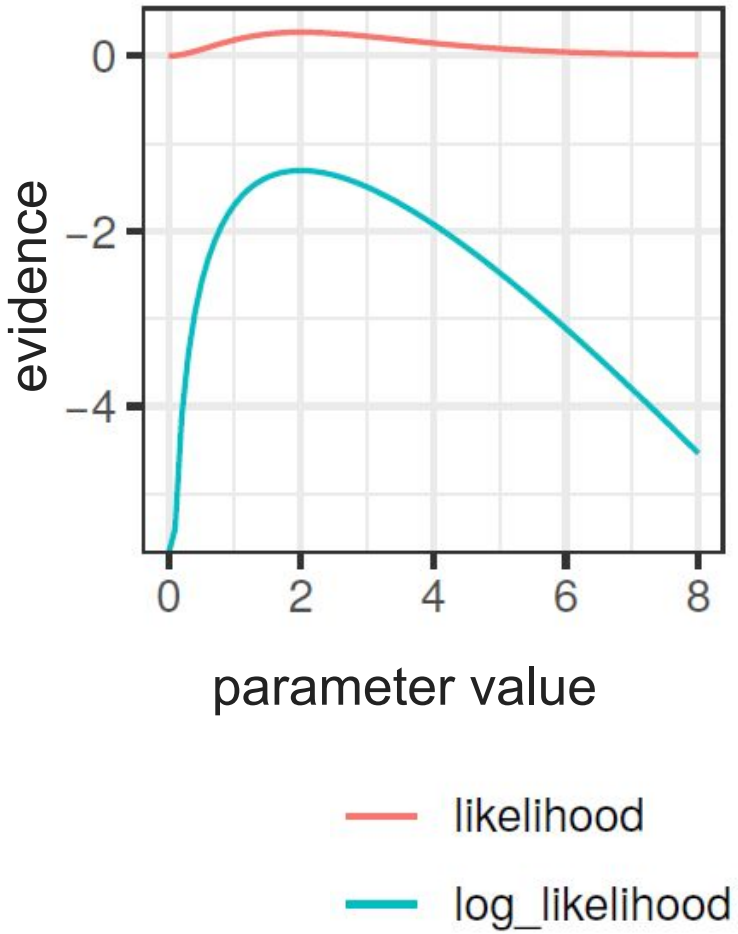
Maximum likelihood

- likelihood is often log-transformed

$$\ell = \log L$$

- solve $\frac{\partial \ell}{\partial \theta} = 0$

- check whether Hessian $\frac{\partial^2 \ell}{\partial \theta^2}$ is negative definite, concave



Maximum likelihood

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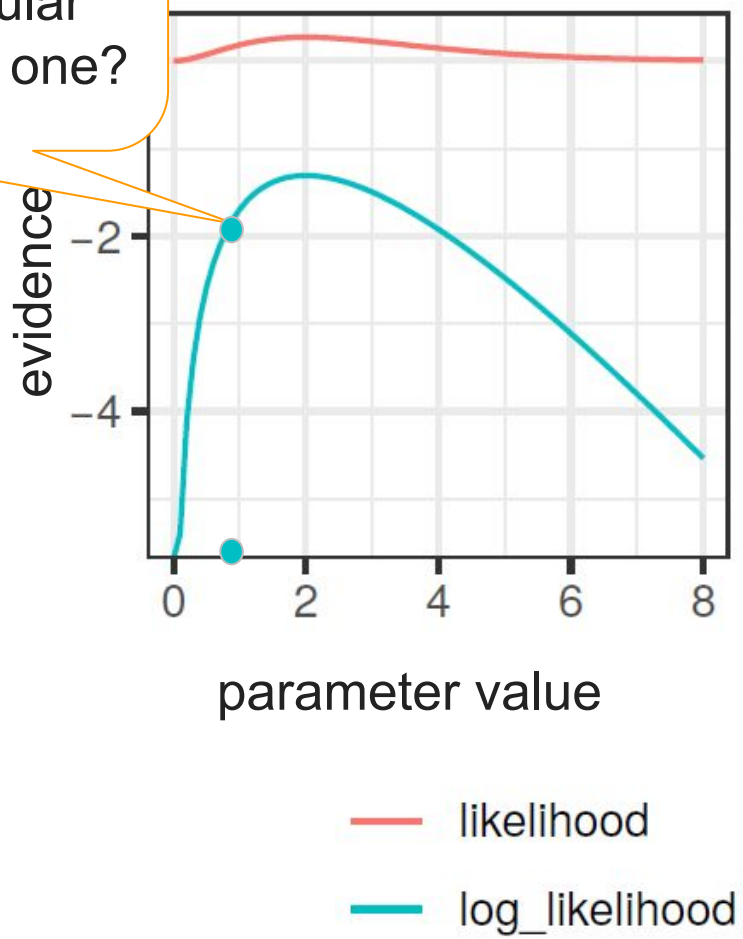
$$\ell = \log L$$

- solve $\frac{\partial \ell}{\partial \theta} = 0$

- check whether Hessian $\frac{\partial^2 \ell}{\partial \theta^2}$ is negative definite, concave

Given data, what is the evidence that our model evaluated for this particular parameter to be the good one?



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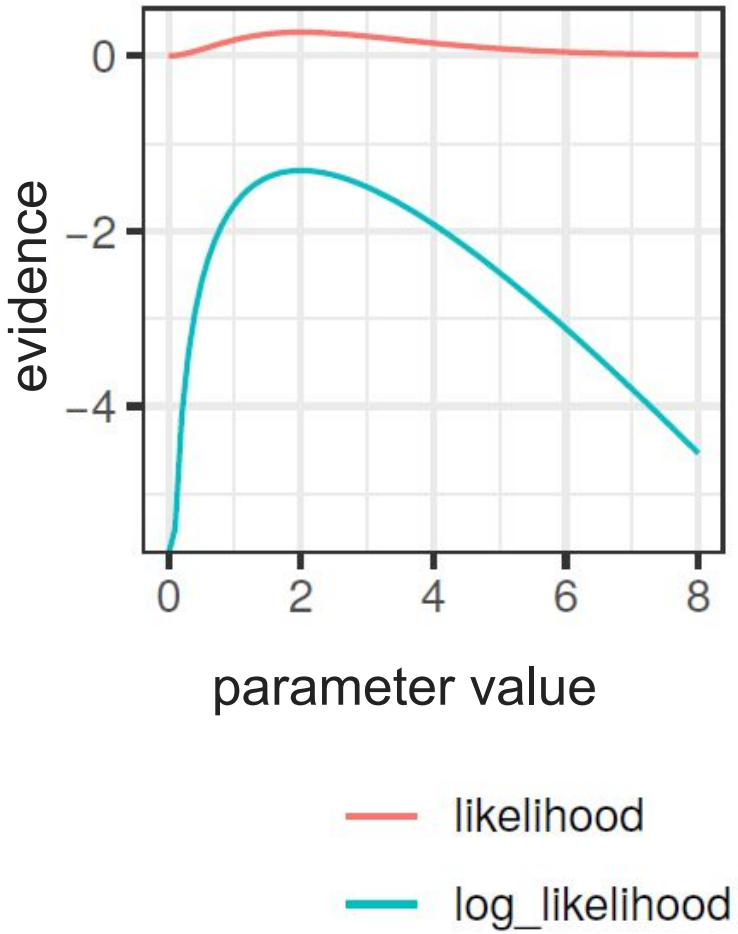
- solve $\frac{\partial \ell}{\partial \theta} = 0$

- check whether Hessian $\frac{\partial^2 \ell}{\partial \theta^2}$ is negative definite, concave

- When does **minimizing the residual sum of squares** correspond to **maximum likelihood**?



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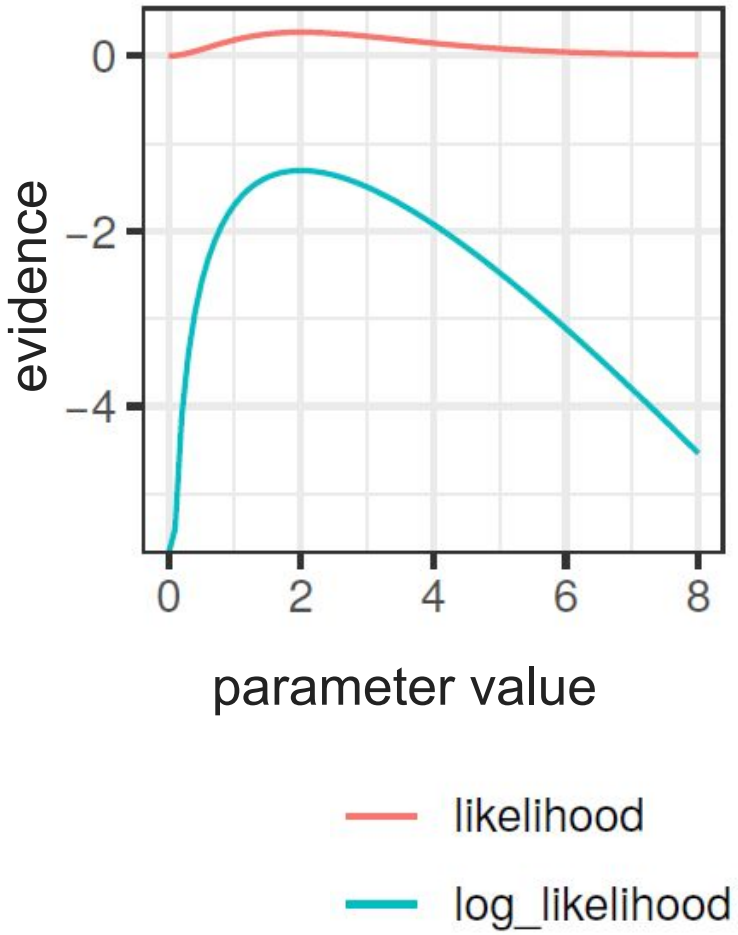
Only if $f_\theta(.)$ is Gaussian!



Maximum log-likelihood estimator

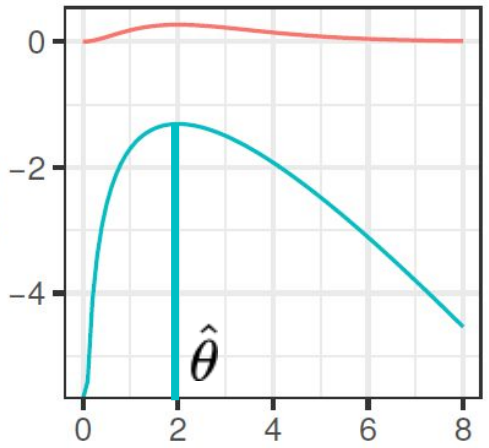
- maximum log likelihood estimator $\hat{\theta}$ depends on sample of size d
- **consistent** estimator:

  with more samples, estimator converges towards true value:

$$\forall \epsilon > 0 : \lim_{d \to \infty} \mathbb{P}(|\hat{\theta}^d - \theta_0| > \epsilon) = 0$$

- **efficient** estimator: $\mathrm{Var}(\hat{\theta}(X))$ as small as possible
- **Cramér-Rao** bound: $\mathrm{Var}(\hat{\theta}(X)) \geq \left[-d\, \mathbb{E}\left(\frac{\partial^2 \ell}{\partial \theta^2}(\theta, X|\theta) \right) \right]^{-1}$
- **curvature**: $\mathrm{Var}\left(\frac{\partial}{\partial \theta} \log f_\theta \right) = -\mathbb{E} \frac{\partial^2}{\partial \theta^2} \log f_\theta$

Fisher information



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Fisher information

"variance of the score is the curvature of the log-likelihood function"

Maximum log-likelihood estimator - example

- Gaussian likelihood with parameter θ

$$f(x,\theta) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(x-\theta)^2}{2\,\sigma^2}\right) \qquad \sigma \text{ fixed}$$

- observations: X_1=7, X_2=8
- calculate maximum likelihood estimator $\hat{\theta}$

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$$f_\theta((7,8)) = \mathbb{P}(7,8|\theta) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(7-\theta)^2}{2\,\sigma^2}\right) \times \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(8-\theta)^2}{2\sigma^2}\right)$$

$$\ell(\theta) = 2\log\left(\frac{1}{\sigma\sqrt{2\pi}}\right) - \frac{(7-\theta)^2}{2\ \sigma^2} - \frac{(8-\theta)^2}{2\,\sigma^2} \qquad \frac{\partial \ell}{\partial \theta} = \frac{1}{2\sigma^2}(7+8-2\theta) = 0$$

$$\hat{\theta} = \frac{7+8}{2}$$

Maximum log-likelihood estimator - example

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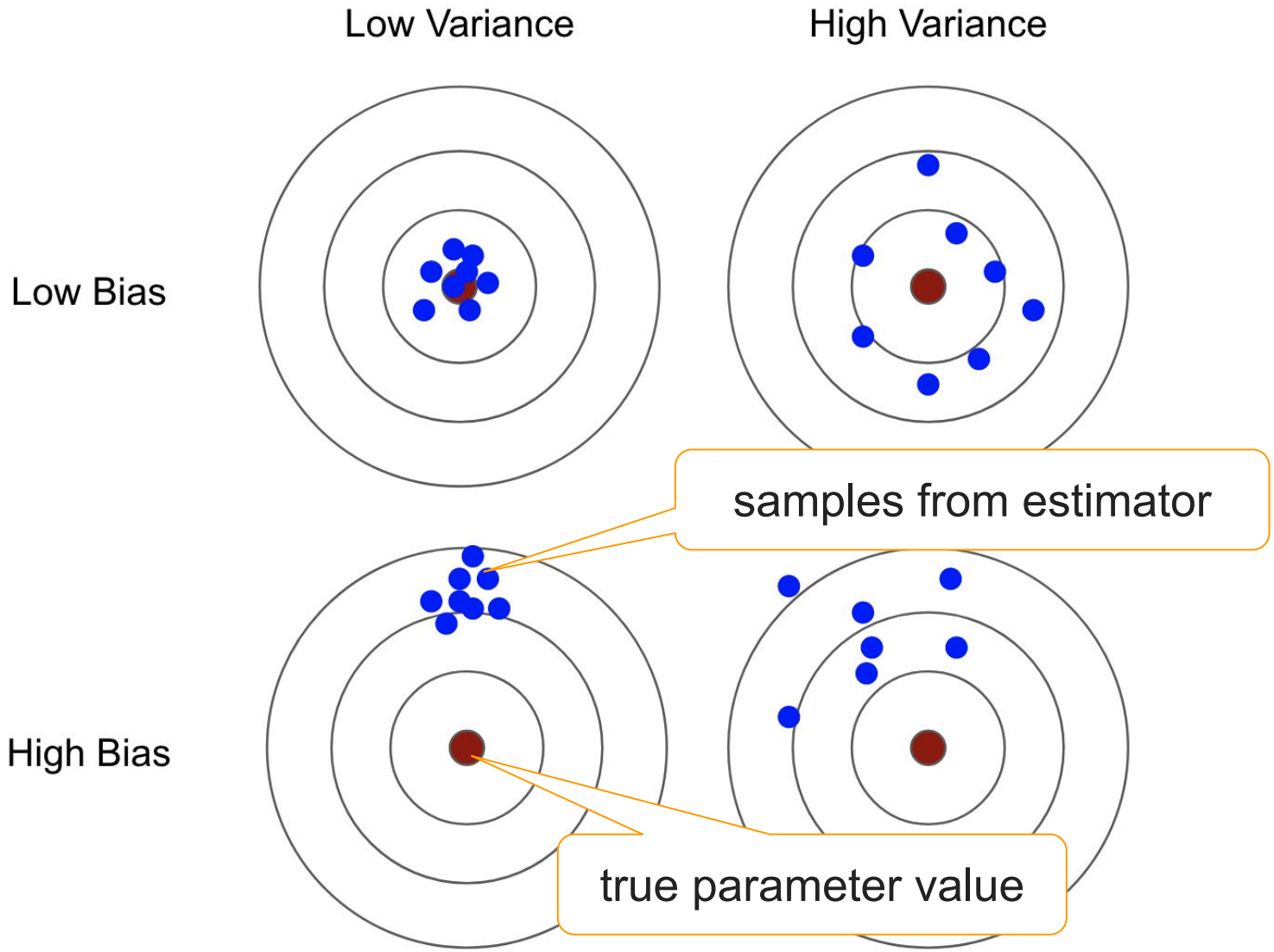
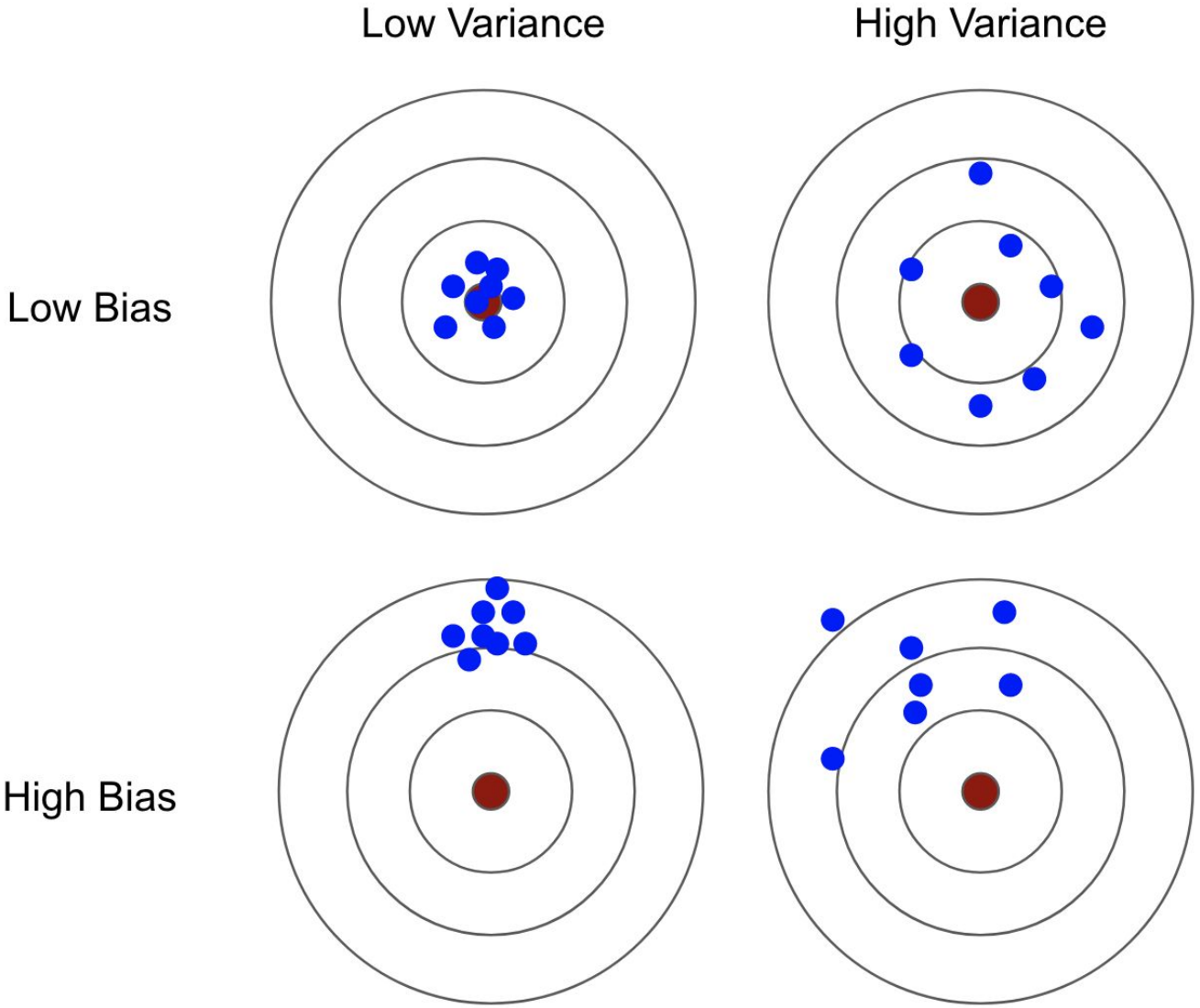
Variance-bias trade-off for estimators

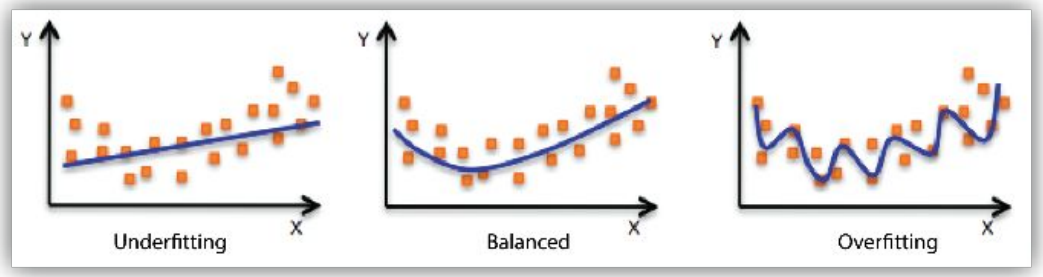


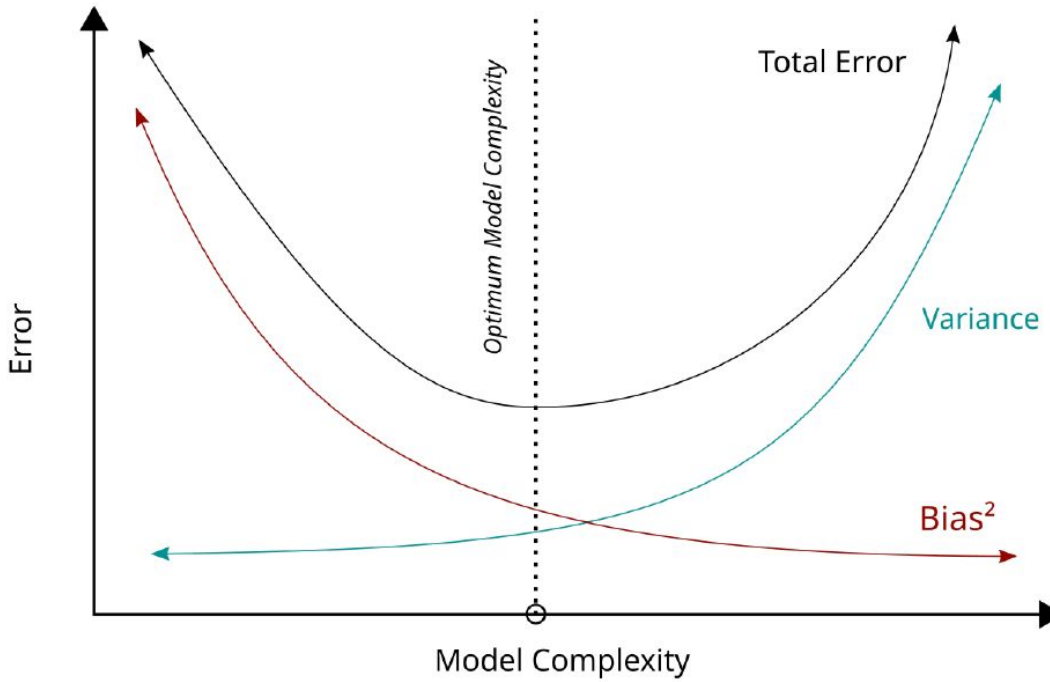
$$\mathrm{bias}(\hat{\theta}) = \mathbb{E}_{X,\theta}(\hat{\theta} - \theta)$$

$$\mathrm{Var}(\hat{\theta}) = \mathbb{E}_{X,\theta}(\hat{\theta} - \mathbb{E}_{X,\theta}(\hat{\theta}))^2$$

Variance-bias trade-off for estimators







Maximum log-likelihood for prevalence

Let's go back to our SIR model

$$\frac{dS}{dt} = -\beta I \frac{S}{N}$$
$$\frac{dI}{dt} = \beta I \frac{S}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

$$X = [X_1, \ldots, X_{14}]$$

observations of hosts in bed

$$\theta = (\beta, \gamma)$$

model parameters

$$I(1, \theta), \ldots, I(14, \theta)$$

numerical solutions for given parameter

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$$f_\theta(X) = \sum_{i=1}^{14} \binom{N}{X_i} \left(\frac{I(i,\theta)}{N}\right)^{X_i} \left(1 - \frac{I(i,\theta)}{N}\right)^{N-X_i}$$

binomial likelihood function with N=763

$$I(1,\theta), \ldots, I(14,\theta)$$

numerical solutions for given parameter

`AIDM_04.R`

Use `optim` in R to find **maximum likelihood estimator** for this particular data!

Maximum log-likelihood for prevalence

$$f_\theta(X) = \sum_{i=1}^{14} \binom{N}{X_i} \left(\frac{I(i,\theta)}{N}\right)^{X_i} \left(1 - \frac{I(i,\theta)}{N}\right)^{N-X_i}$$

```
####log likelihood for prevalence in SIR model
loglikelihood_binom <- function(parameters =c(beta =1.1,gamma=1/3)){
  ## simulate prevalence , per time point , calculate binomial log likelihood

as.data.frame(ode(initial.condition,time.points,SIR.model,parameters))->solution_SIR
  merge(solution_SIR,
        influenza_england_1978_school)%>%
    mutate(beta=parameters[1],gamma=parameters[2])%>%
    mutate(loglikelihood=dbinom(in_bed,size=763,prob=I/763,log=T))%>%
    summarize(loglikelihood=sum(loglikelihood))->df
    return(df$loglikelihood)
}
```

Maximum log-likelihood for prevalence

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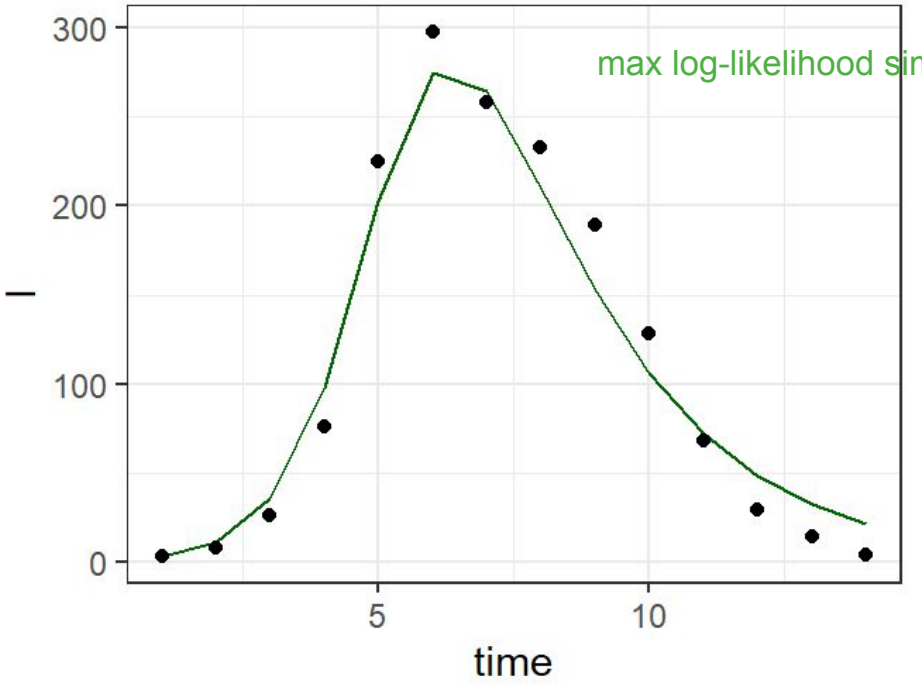


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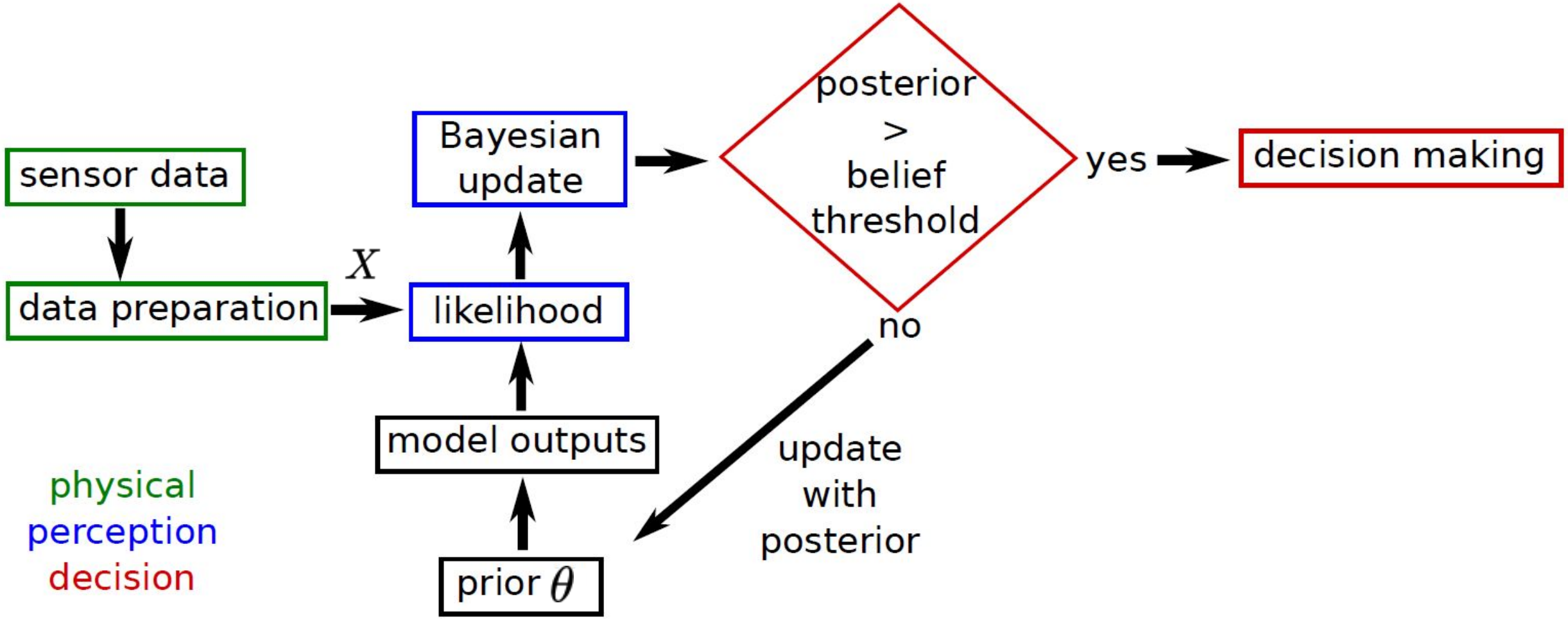
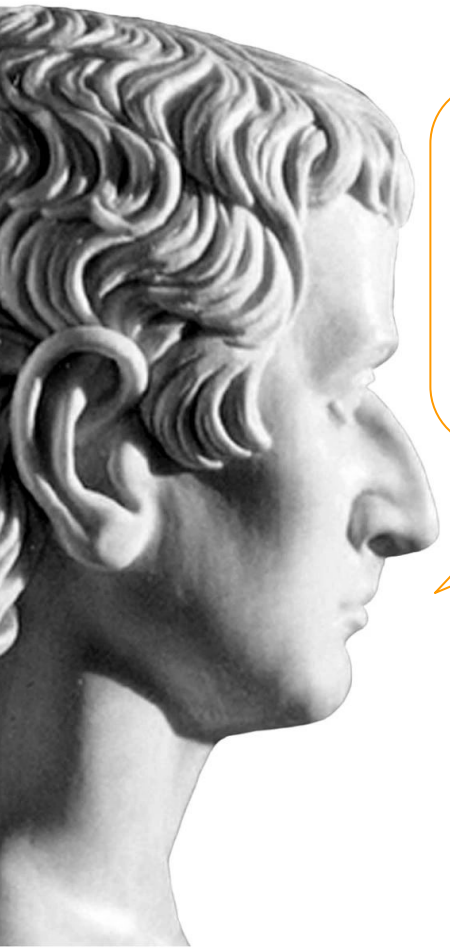
Bayesian inference system



Bayesian updating

knowledge about the parameter **before** having seen the data

knowledge about the parameter **after** having seen the data



the model is random, the data is fixed

θ

X

prior

posterior

$\mathbb{P}(\theta)$

$\mathbb{P}(\theta|X)$

$\mathbb{P}(X|\theta)$

likelihood

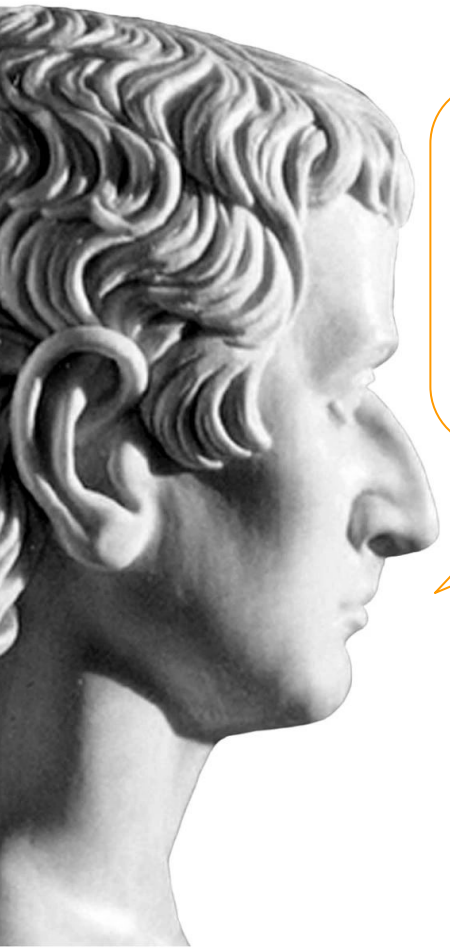
$$\mathbb{P}(\theta|X) > \mathbb{P}(\theta)$$

data evidence increase our belief in parameter hypothesis

Bayesian updating

knowledge about the parameter **before** having seen the data

knowledge about the parameter **after** having seen the data



the model is random, the data is fixed

θ

X

prior $\mathbb{P}(\theta)$

likelihood $\mathbb{P}(X|\theta)$

posterior $\mathbb{P}(\theta|X)$

Bayesian theorem

$$\mathbb{P}(\theta|X) = \frac{1}{\mathbb{P}(X)}\mathbb{P}(X|\theta)\mathbb{P}(\theta) = C\mathbb{P}(X|\theta)\mathbb{P}(\theta)$$

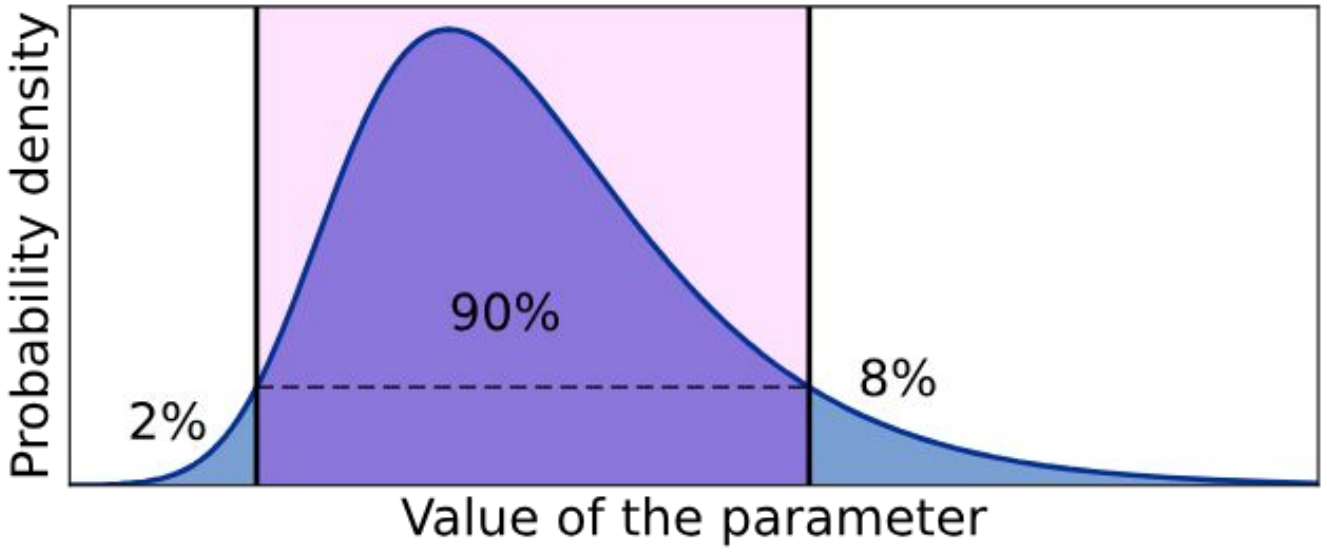
marginal likelihood

$$\mathbb{P}(X) = \int \mathbb{P}(X|\theta)\mathbb{P}(\theta)d\theta$$

integration might be costly!

Uncertainty from Bayesian posterior: credible intervals

- lower and upper bound such that posterior probability that unknown parameter falls within is $X = 95, 90, 89, 75\%$
- depends on prior, not unique...
- **highest density**: region such that density function is highest with probability $X\%$
- **equal-tailed**: e.g. 75% CI: 12.5th and 87.5th percentile, transformation invariant



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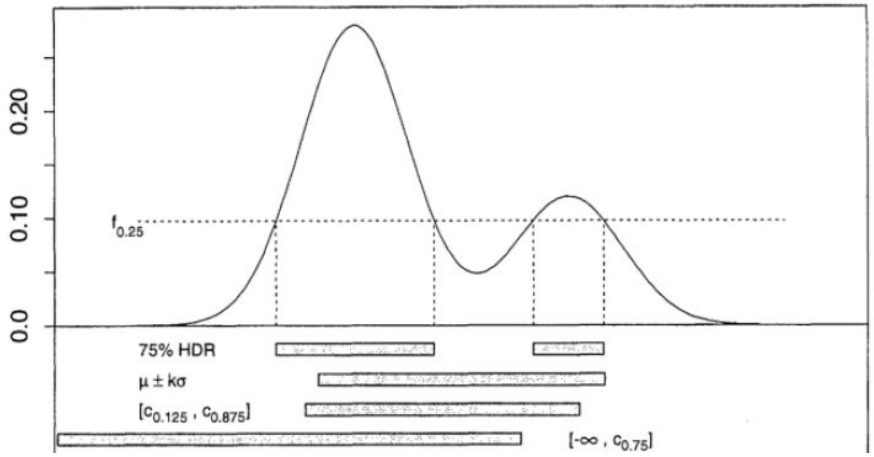

Law of large numbers

- Given independent, identically distributed random variables $X_1, \ldots X_d$, then

$$\lim_{d \to \infty} \frac{1}{d} \sum_i X_i = \mathbb{E}(X_1)$$

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- **weak law**: convergence in probability; $\lim_{d\to\infty} \mathbb{P}(|\frac{1}{d}\sum_i X_i - \mathbb{E}(X_1)| < \epsilon) = 1$
- **strong law**: almost sure convergence
- Proof: assume finite variance, we know $\mathbb{E}(\frac{1}{d}\sum_i X_i) = \mathbb{E}(X_1)$ and $\mathrm{Var}(\frac{1}{d}\sum_i X_i) = \frac{1}{d^2}\sum_i \mathrm{Var}(X_i)$

  Chebyshev's inequality $\mathbb{P}(|X - \mathbb{E}(X)| \geq \epsilon) \leq \frac{\mathrm{Var}(X)}{\epsilon^2}$ used for $X = \frac{1}{d}\sum_i X_i$:

$$\mathbb{P}(|\frac{1}{d}\sum_i X_i - \mathbb{E}(X_1)| < \epsilon) \geq 1 - \frac{\sigma^2}{d\epsilon^2}$$

Monte Carlo integration

- Bayesian posterior: need to calculate integral for marginal likelihood function:

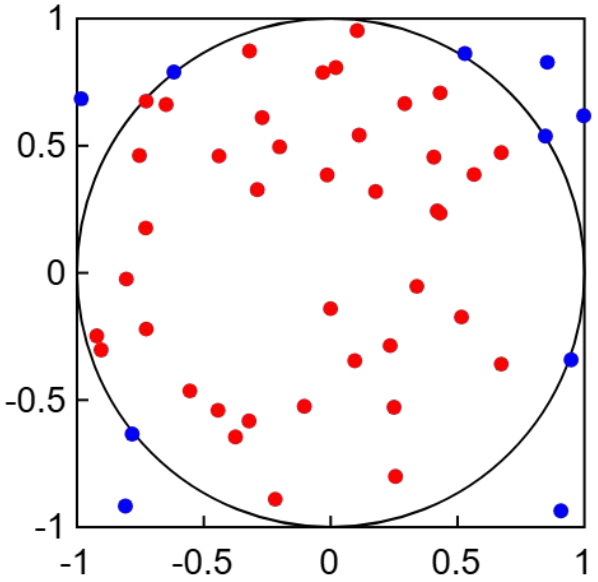
$$f(\theta) = \mathbb{P}(X|\theta)\mathbb{P}(\theta)$$

- **numeric** integration: difficult in higher dimensions
- **Monte Carlo**: sample function values **randomly**: $f(\omega_i)$
- **Monte Carlo estimator**:

$$I_N = \frac{1}{N}\sum_{i=1}^{N} f(\omega_i)$$

- strong **Law of Large Numbers:**

$$\lim_{N\to\infty} I_N = \int f(\theta)d\theta, a.s.$$



$$f(\omega_i) = \mathbb{1}_{|x|<1}(\omega_i)$$

$$\lim_{N\to\infty} I_N = \pi$$

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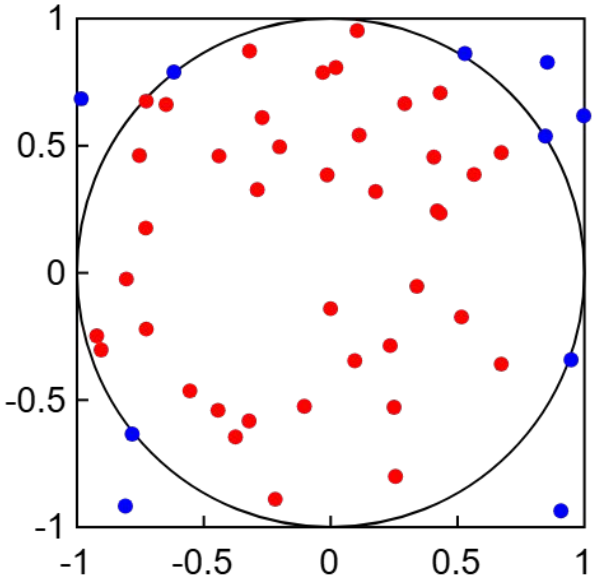

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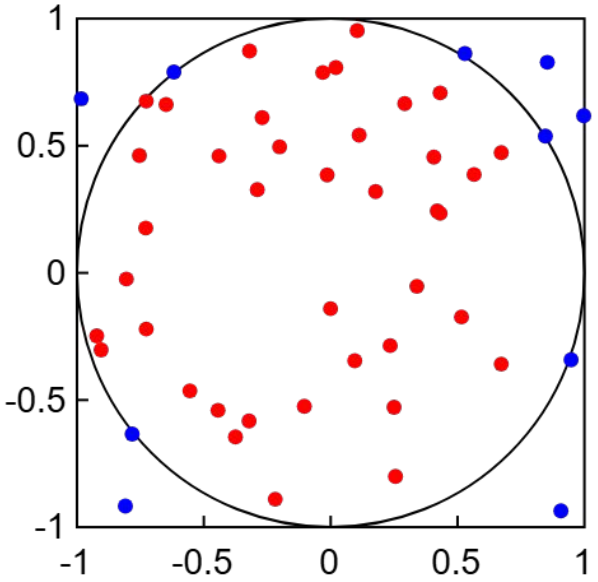
Monte Carlo estimator depends on **prior** $\mathbb{P}(\theta)$

Monte Carlo estimator is **independent** from dimension or parameter space



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Monte Carlo integration: variance and error

- sample variance $\mathrm{Var}(f) = \frac{1}{N-1}\sum_i (f(\omega_i) - I_N)^2 = \sigma_N^2$
- sample variance of integral: $\mathrm{Var}(I_N) = \frac{1}{N}\sigma_N^2$
- if $\{\sigma_N^2\}$ bounded, then convergence: Law of Large Numbers
- Central Limit Theorem:

$$\frac{I_N - \int f(\theta)d\theta}{\sqrt{\sigma_N^2/N}} \xrightarrow{\text{proba}} \mathcal{N}(0,1)$$

- Monte Carlo error estimate: $I_N \pm 1.96\sqrt{\sigma_N^2/N}$

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variance of Monte Carlo integral decrease with increasing sample size

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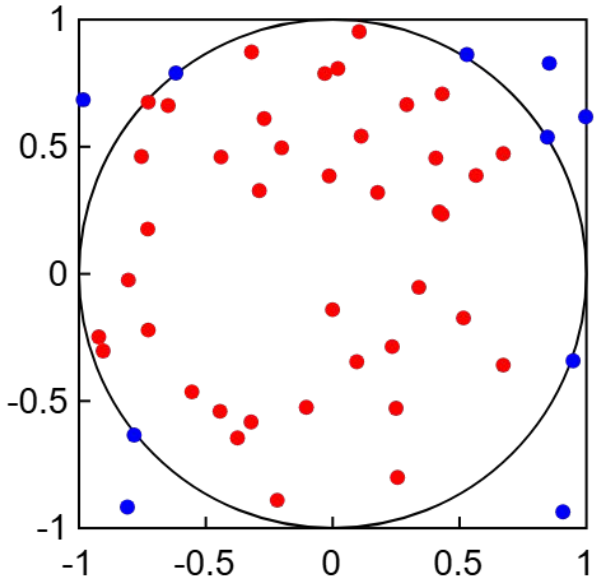
- Central Limit Theorem:

In order to decrease Monte Carlo error by factor 10, you need to increase sample number by factor 100!

- Monte Carlo error estimate: $I_N \pm 1.96\sqrt{\sigma_N^2/N}$

Monte Carlo integration: example



- sample randomly N points in the square
- calculate the fraction of points that fall within the circle
- use $$\text{Ratio} = \frac{\text{Area of circle}}{\text{Area of square}} = \frac{\pi r^2}{4r^2} = \frac{\pi}{4}$$
- calculate area of circle by multiplying fraction of points within circle by 4

AIDM_05.R

Implement in R!

Monte Carlo integration: example for marginal likelihood

- sample N points uniformly distributed in the interval [1.2,2] for **beta** and [0.2,0.6] for **gamma**
- calculate Monte Carlo estimator for marginal likelihood of the SIR model with

$$f(\theta) = \mathbb{P}(X|\theta)\mathbb{P}(\theta)$$

- use $\theta = (\beta, \gamma)$

posterior distribution

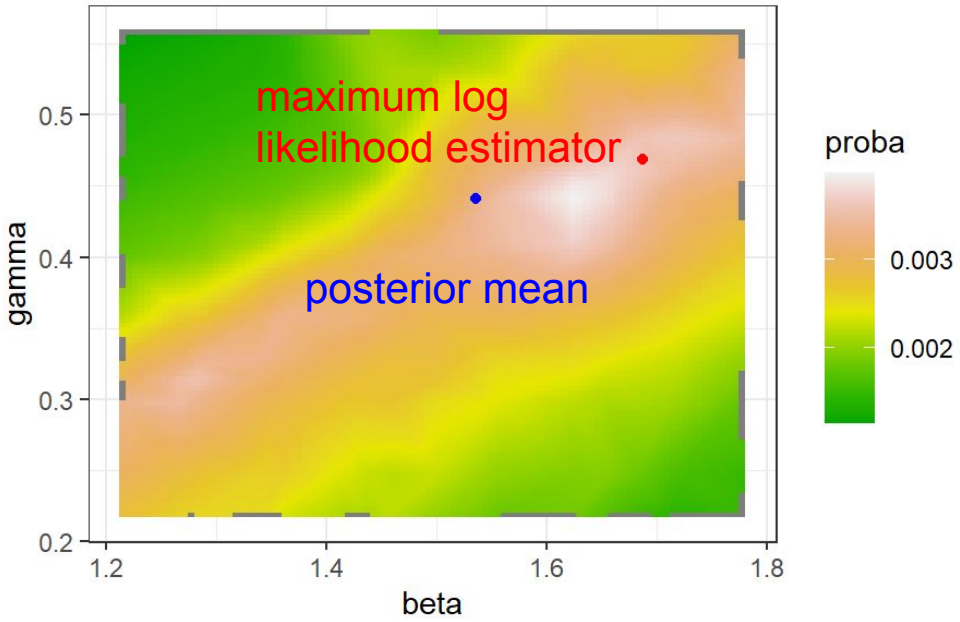
$$\mathbb{P}(\theta|X) = \frac{1}{\mathbb{P}(X)}\mathbb{P}(X|\theta)\mathbb{P}(\theta)$$

Monte Carlo integral

Implement in R!

AIDM_05.R

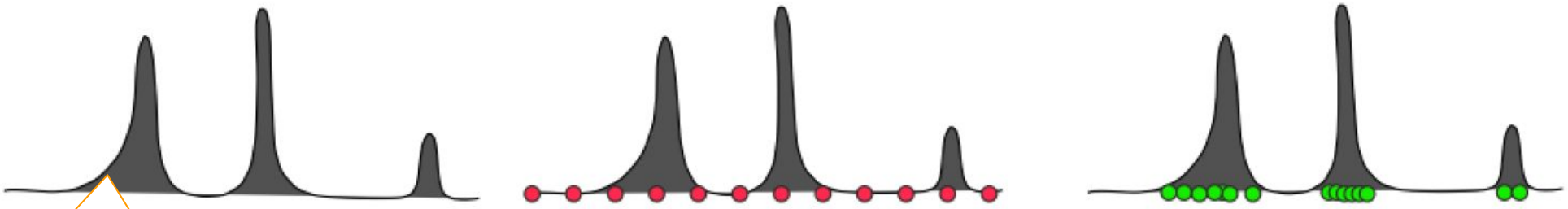
posterior probability distribution



Monte Carlo integration: importance sampling

importance sampling uses proposal distribution q to sample more important parameter regions more often

$$\int f(\theta)d\theta = \int \mathbb{P}(X|\theta)\mathbb{P}(\theta)d\theta = \int \mathbb{P}(X|\theta)\underbrace{\frac{\mathbb{P}(\theta)}{q(\theta)}}_{\text{importance weight}}\underbrace{q(\theta)}_{\text{sampling probability}}d\theta$$



target distribution = prior

Uniform distribution

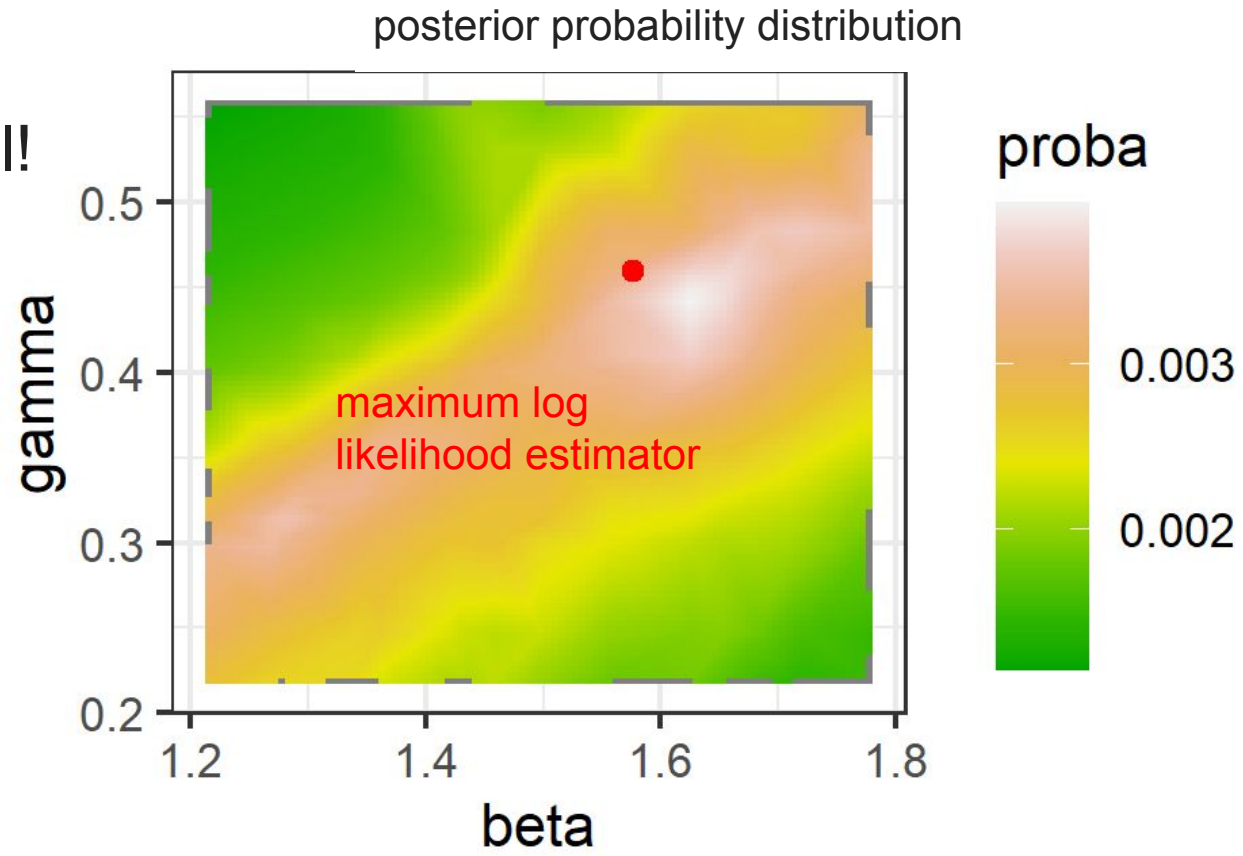
Importance sampling

Monte Carlo integration: importance sampling

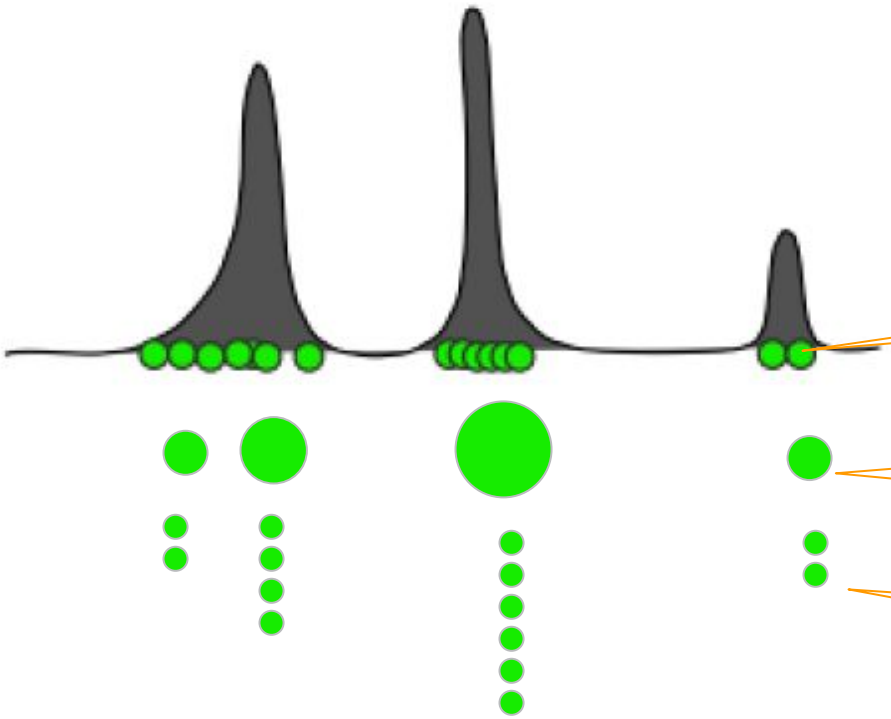
importance sampling uses proposal distribution q to sample more important parameter regions more often

AIDM_05.R

Implement in R with truncated normal distribution as proposal!



Monte Carlo integration: sampling importance resampling



1.Sampling (Importance Sampling): draw samples from proposal distribution. $\omega_1, \ldots, \omega_N \sim q$

2. Weights: proportional to how likely sample is under the target distribution $W_i = \frac{\mathbb{P}(\omega_i)}{q(\omega_i)}$

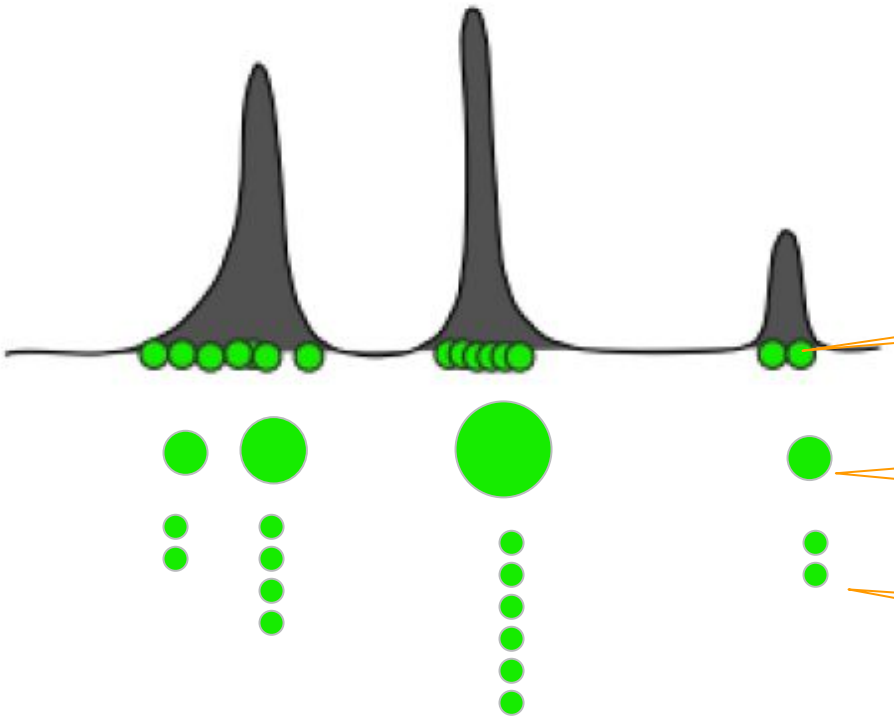
3. Resampling: resample with replacement using the weights $\hat{\omega}_1, \ldots, \hat{\omega}_k \sim \{\omega_1, \ldots, \omega_N\}$ $\tilde{W}_i = \frac{W_i}{\sum_i W_i}$

$$\int f(\theta) d\theta = \int \mathbb{P}(X|\theta)\mathbb{P}(\theta) d\theta$$

Use samples from resampling step to calculate Monte Carlo integral estimator!

Swiss TPH

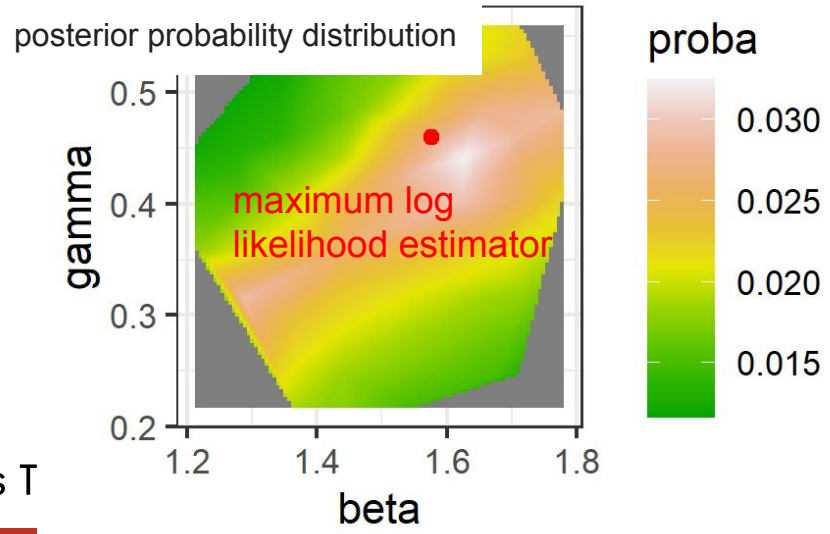
Monte Carlo integration: sampling importance resampling



1.Sampling (Importance Sampling): draw samples from proposal distribution. $\omega_1, \ldots, \omega_N \sim q$

2. Weights: proportional to how likely sample is under the target distribution $W_i = \frac{\mathbb{P}(\omega_i)}{q(\omega_i)}$

3. Resampling: resample with replacement using the weights $\hat{\omega}_1, \ldots, \hat{\omega}_k \sim \{\omega_1, \ldots, \omega_N\}$ $\tilde{W}_i = \frac{W_i}{\sum_i W_i}$



AIDM_05.R

Implement in R with truncated normal distribution as proposal and resample 50 times!

Key takeaway points:

- **paradigms of inference** distinguish whether model parameter is fixed, and data random, or parameter random and data fixed
- **maximum log likelihood** approach is an alternative to curve fitting, taking also into consideration parameter uncertainty
- **Bayesian inference** allows to improve prior knowledge on parameters by comparing model outputs with data
- **Monte Carlo integration** is a (not always) efficient way to calculate high-dimensional integrals for Bayesian posterior

Swiss TPH

Modeling malaria transmission and drug resistance at the population level

Christian Selinger & Monica Golumbeanu

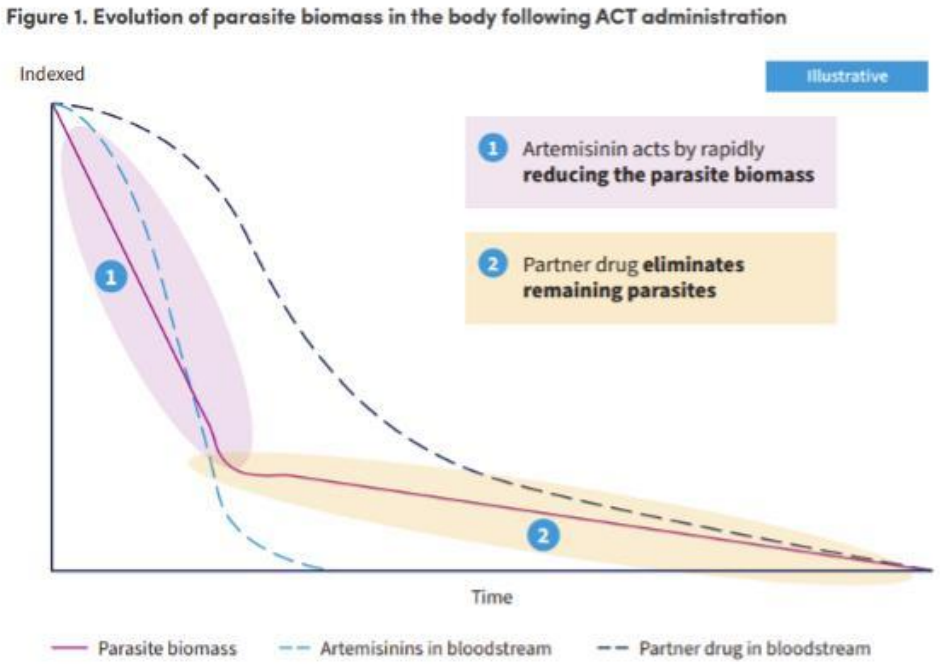
How antimalarial combination therapy works

Rapid Parasite Clearance (Artemisinin Component)

- The artemisinin derivative (e.g., artesunate, artemether, or dihydroartemisinin) acts quickly, significantly reducing the parasite load within the first 24-48 hours.

Sustained Killing Effect (Partner Drug)

- Since **artemisinin clears most but not all parasites**, a longer-acting partner drug (e.g., lumefantrine, amodiaquine, mefloquine, piperaquine) eliminates the remaining parasites over several days.
- The **partner drug has a longer half-life**, preventing reinfection and reducing the risk of **recrudescence (treatment failure due to surviving parasites).**

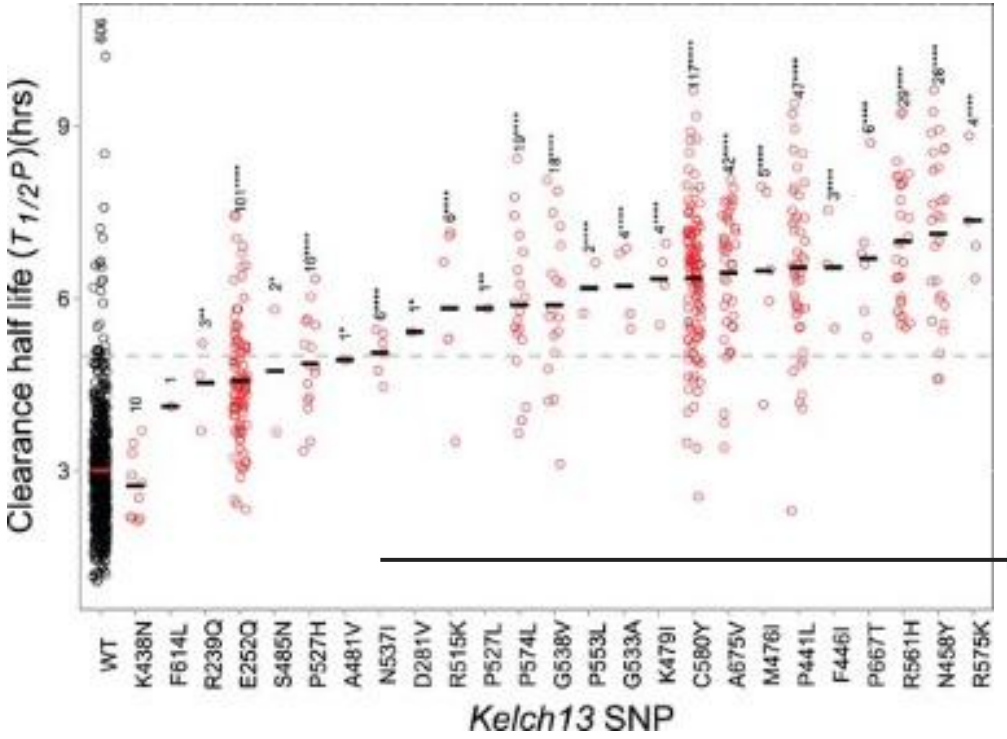


https://www.mmv.org/malaria/symptoms-and-treatments/about-artemisinin-and-ACTs

Different levels of antimalarial resistance are present in a population

- Over time, parasites naturally undergo mutations which allow them to **evolve** and, under right conditions (selective pressure), they **evade the effects of antimalarial treatments**, making them less effective.

- **Antimalarial resistance** is when *malaria parasites* (like *Plasmodium falciparum*) **no longer respond effectively to antimalarial drugs** that previously worked to treat the infection.



Delay in parasite clearance across parasite genotypes

https://academic.oup.com/mbe/article/34/1/131/2680802

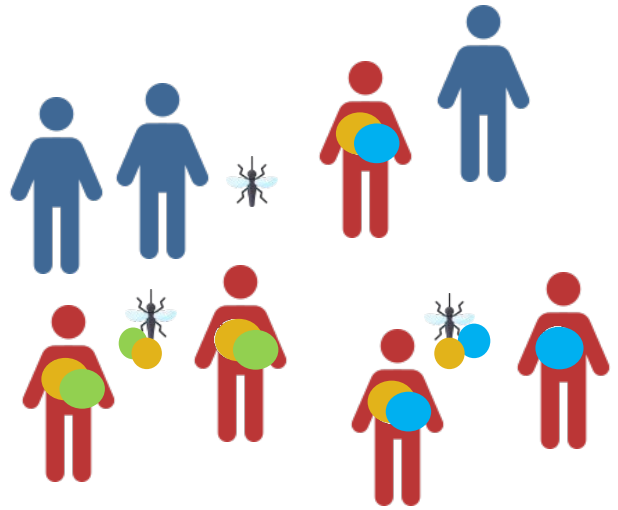
What drives the spread of antimalarial resistance in a population?

Drug pressure: treating infections kills sensitive parasites but allows resistant ones to survive and multiply.

Fitness cost/advantage: in the absence of drugs, resistant parasites may spread more slowly (or even be outcompeted)

Transmission dynamics: infected humans pass parasites to mosquitoes, which infect other humans

Human movement & mosquito migration: Spread of resistant parasites geographically



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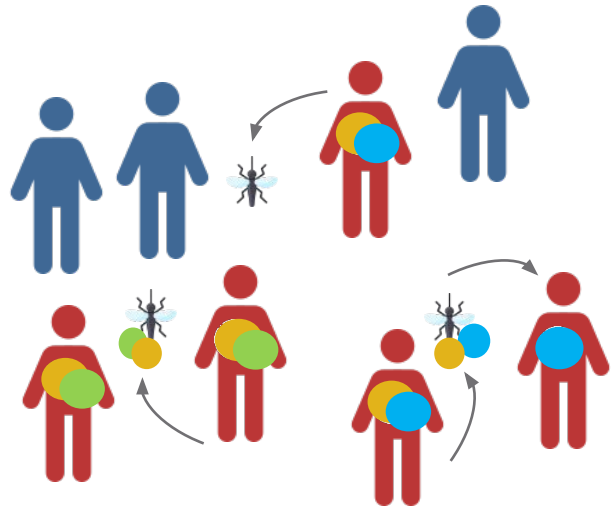
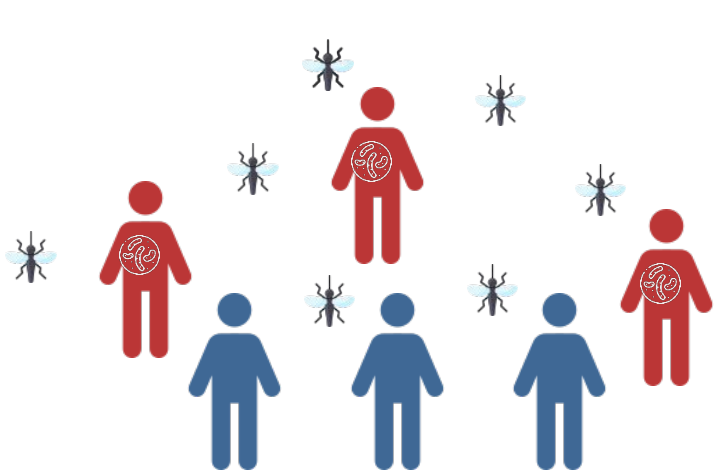
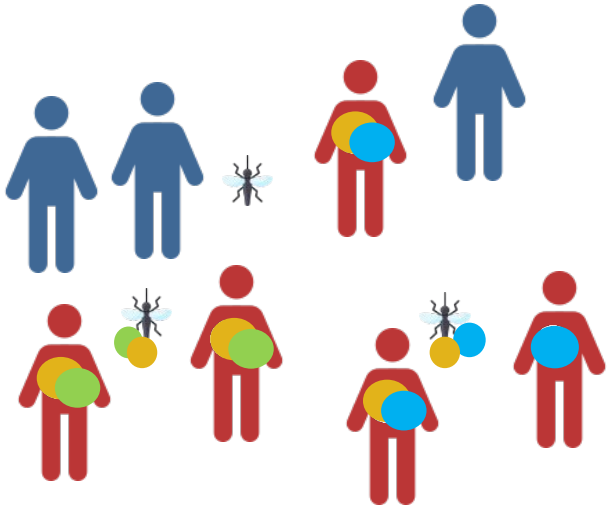
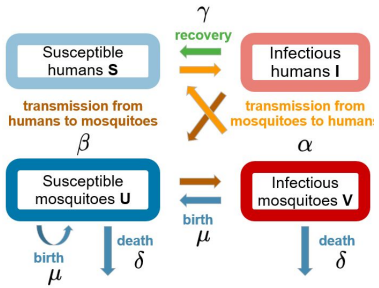


Integrating malaria transmission dynamics with parasite genetics



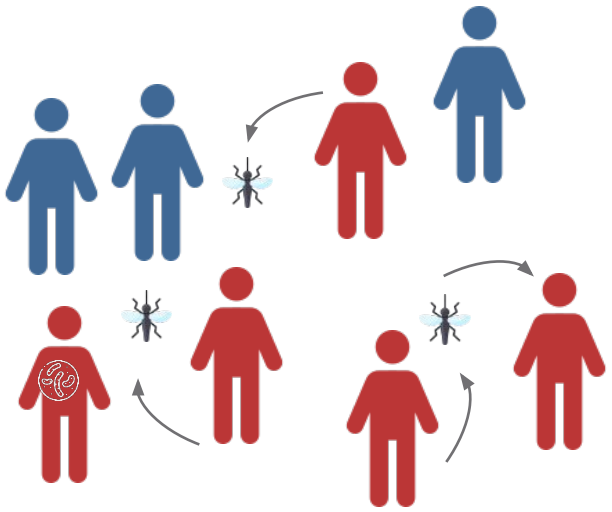


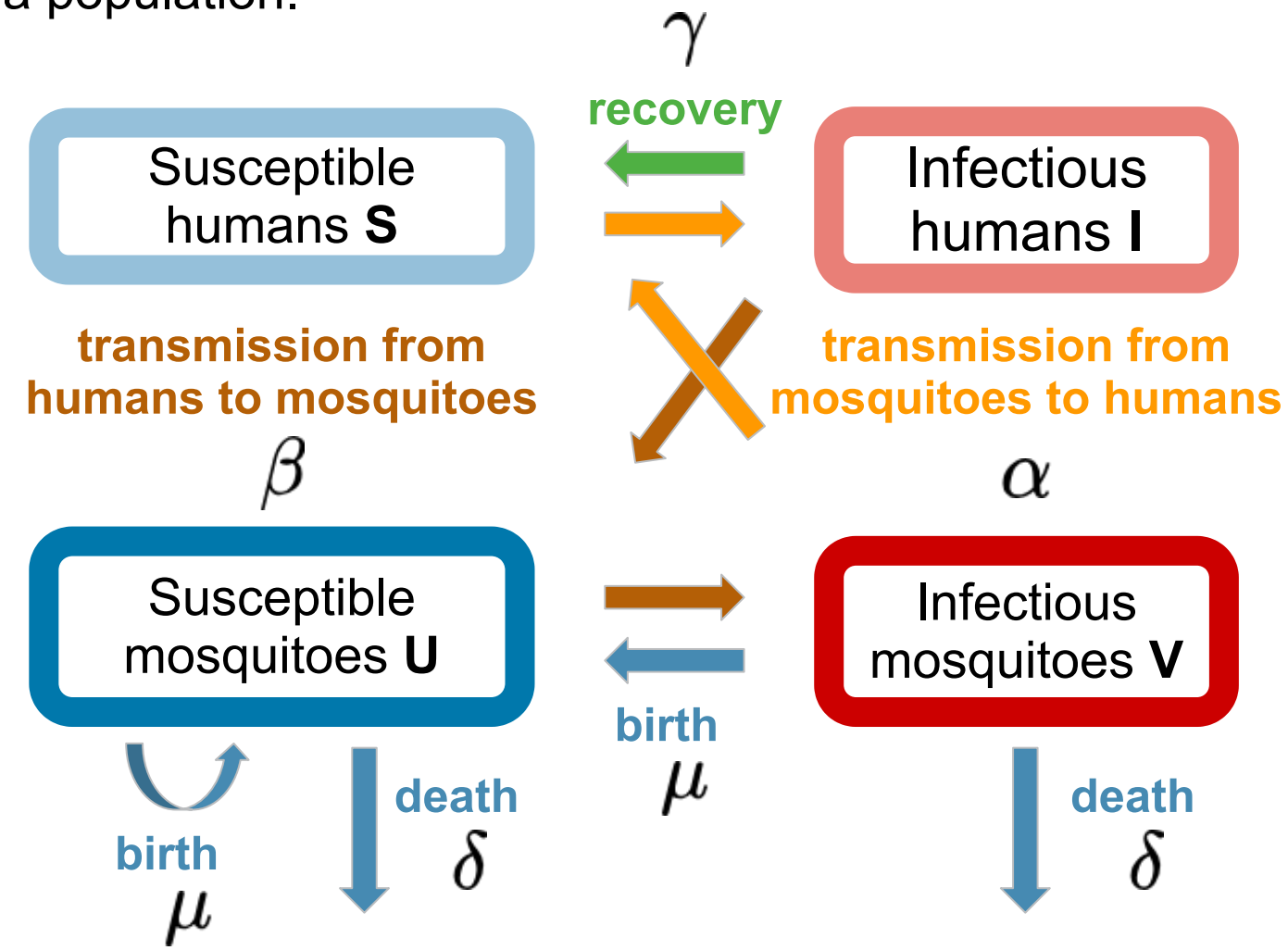


Malaria transmission dynamics models

Malaria transmission dynamics model

A **malaria transmission model** is a mathematical framework used to simulate and analyze how malaria spreads in a population.





Swiss TPH

Malaria transmission dynamics model

Model equations:

$$\frac{dS}{dt}(t) = -\alpha\frac{V(t)}{H}S(t) + \gamma I(t)$$

$$\frac{dI}{dt}(t) = \alpha\frac{V(t)}{H}S(t) - \gamma I(t)$$

$$\frac{dU}{dt}(t) = -\beta\frac{I(t)}{H}U(t) + \mu M - \delta U(t)$$

$$\frac{dV}{dt}(t) = \beta\frac{I(t)}{H}U(t) - \delta V(t)$$

Assumptions:

- Constant mosquito population size:

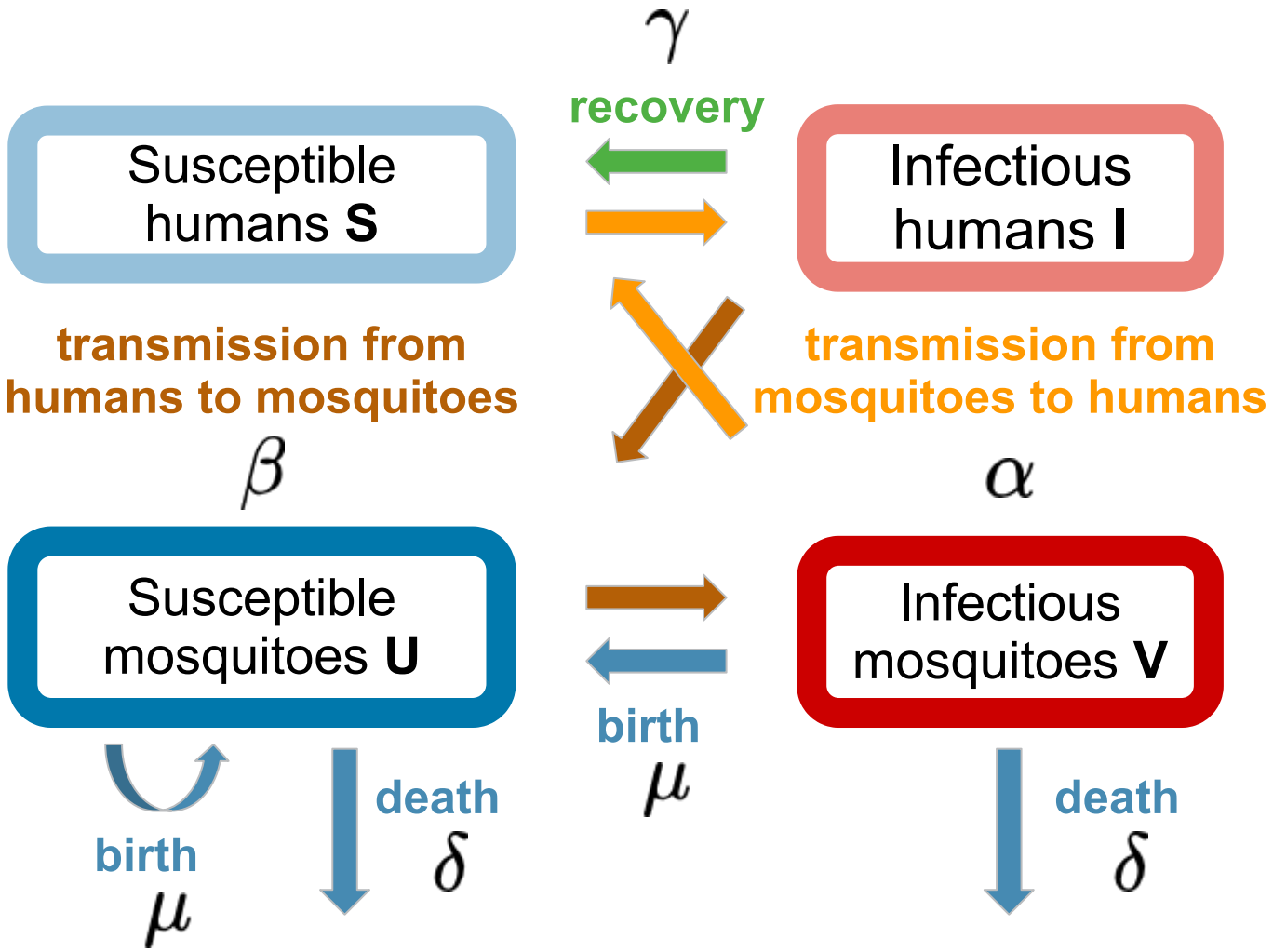
  $M = U(0) + V(0)$

- Birth and death rates are equal:

  $\mu = \delta$

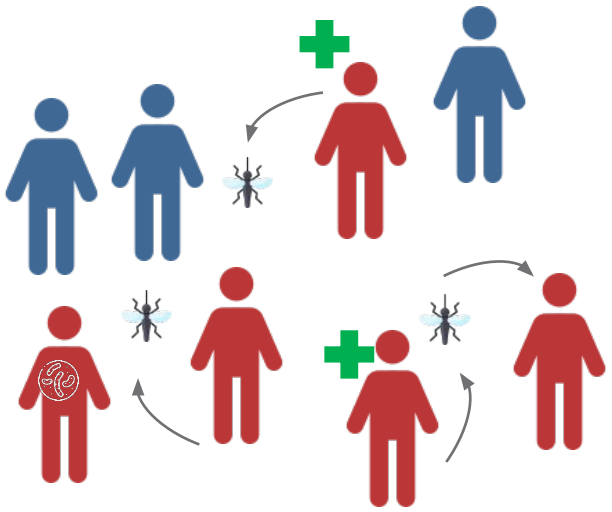
- Constant human population size

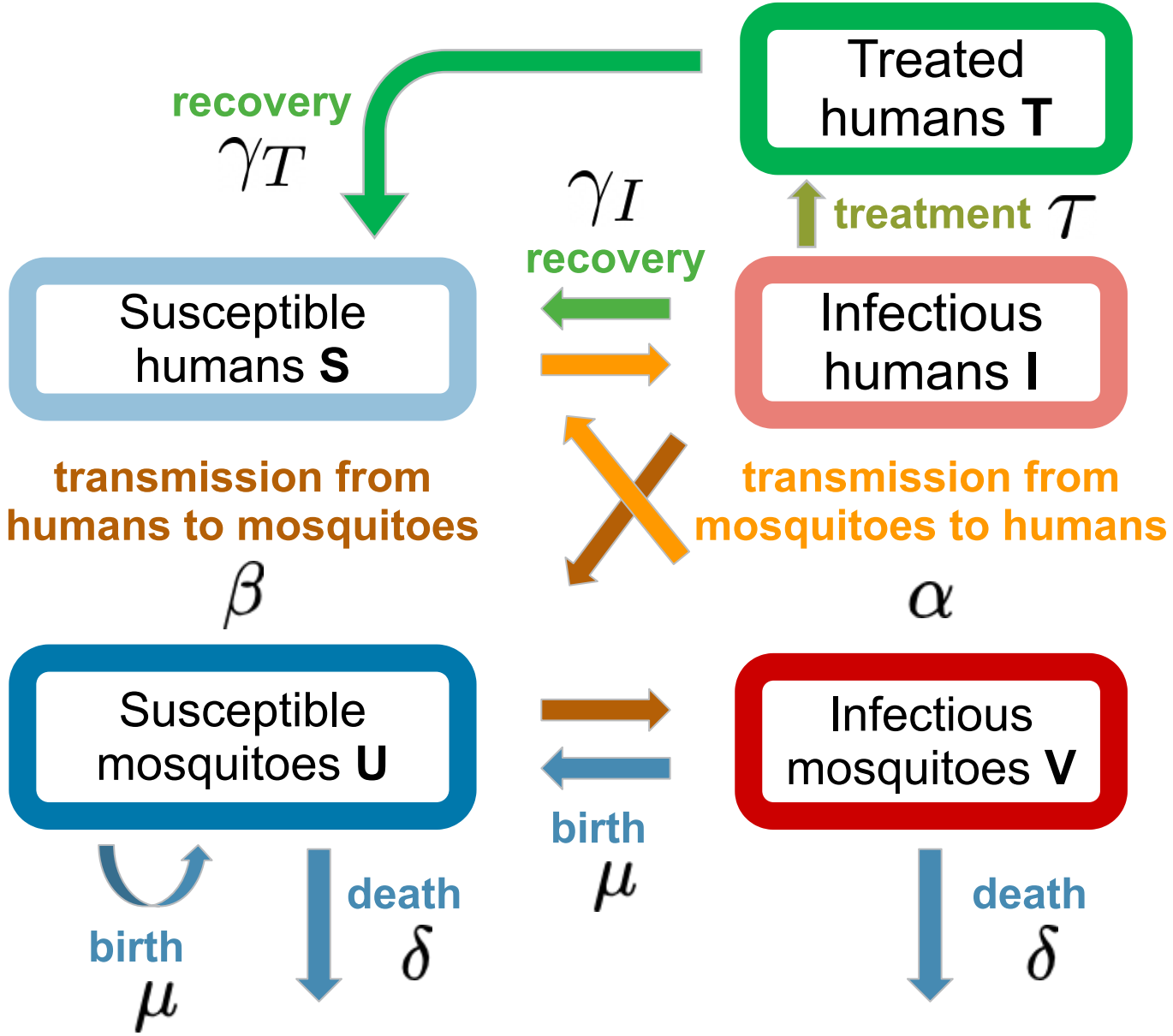
  $H = S(0) + I(0)$



Swiss TPH

Malaria transmission dynamics model with treatment

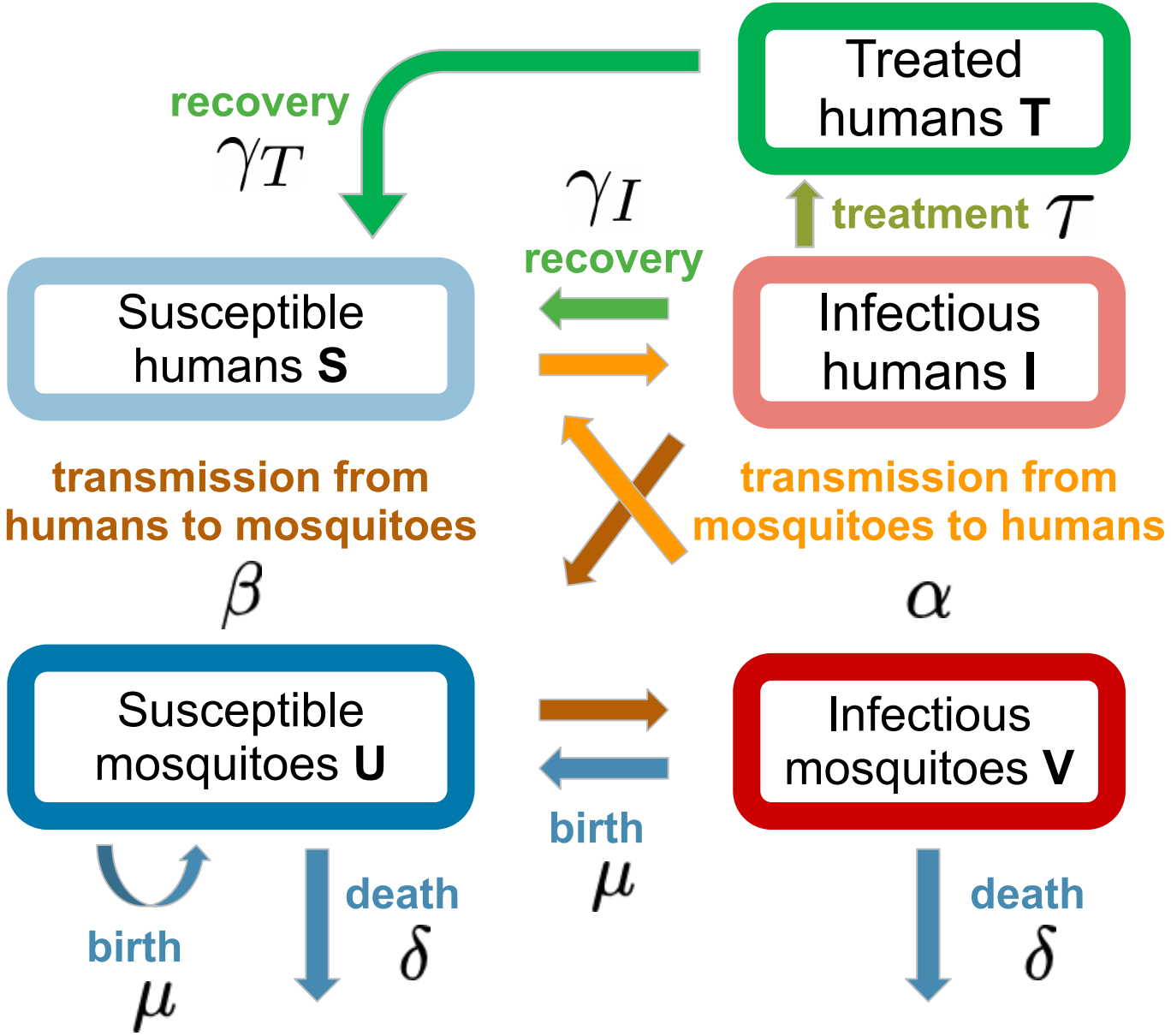




Swiss TPH

Malaria transmission dynamics model with treatment

$$\frac{dS}{dt} = -\alpha S\frac{V}{H} + \gamma_I I + \gamma_T T$$
$$\frac{dI}{dt} = \alpha S\frac{V}{H} - \tau I$$
$$\frac{dT}{dt} = \tau I - \gamma_T T$$
$$\frac{dU}{dt} = -\beta U\frac{I}{H} + \mu(U+V) - \delta U$$
$$\frac{dV}{dt} = \beta U\frac{I}{H} - \delta V$$



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- Birth and death rates are equal:

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  $H = S(0) + I(0)$

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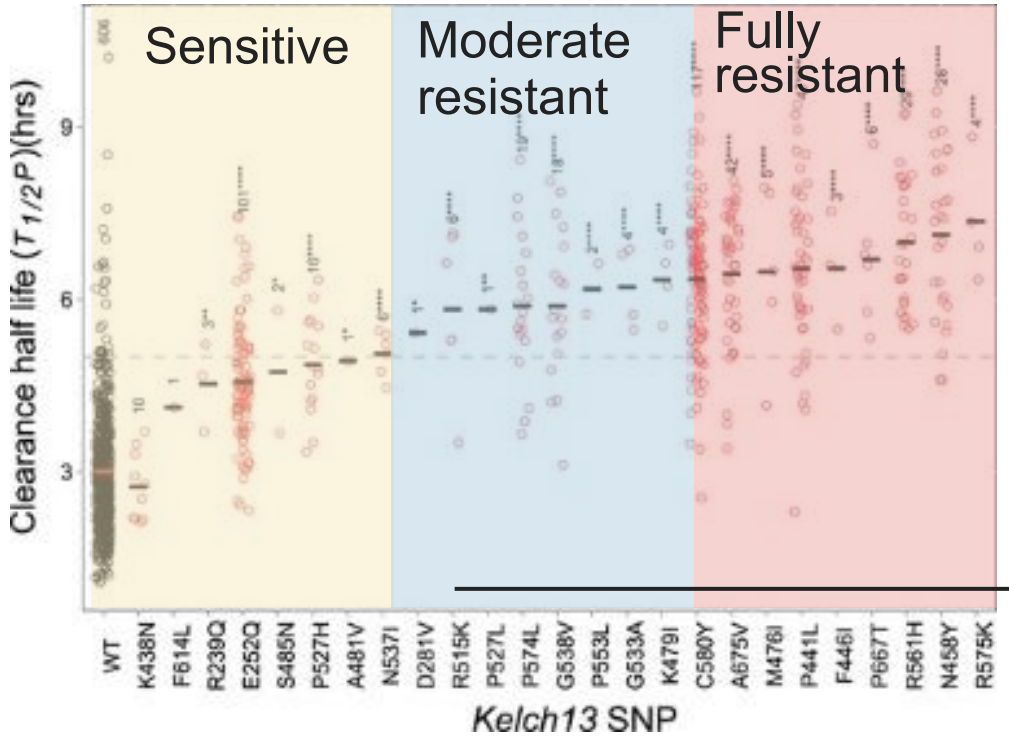
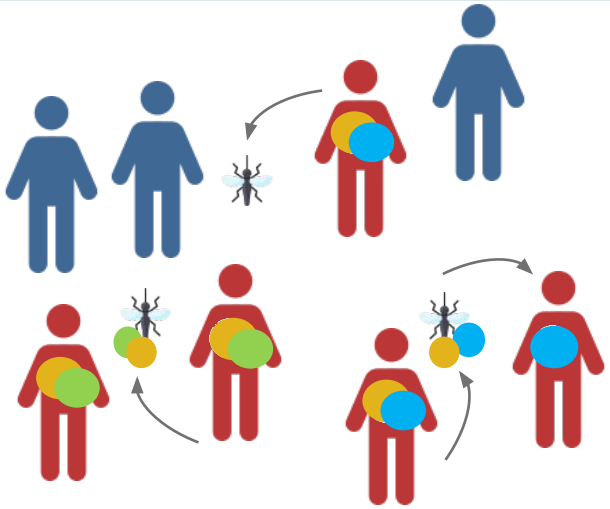


Varying drug failure rates across parasite genotypes

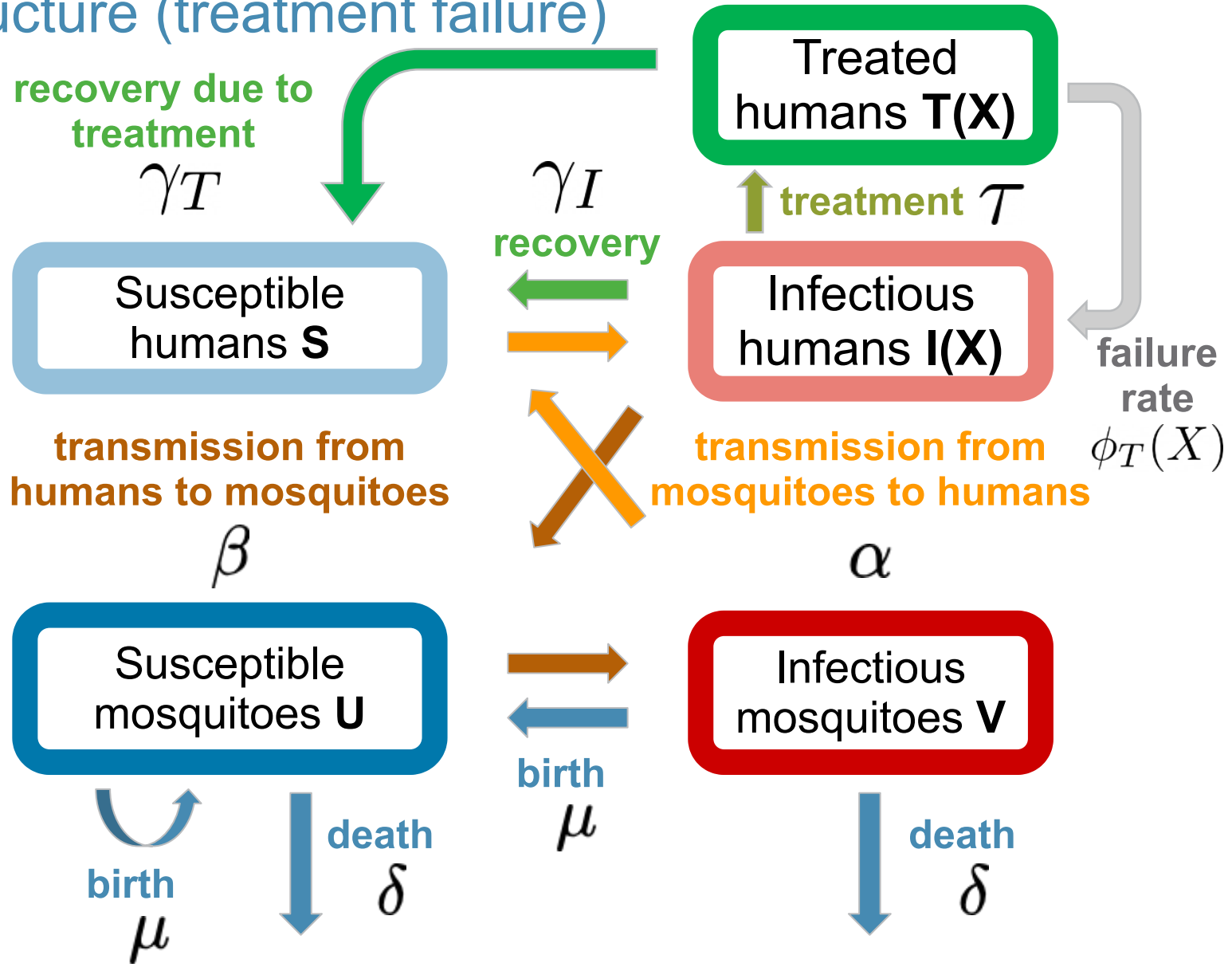
Delay in parasite clearance across parasite genotypes

Malaria transmission dynamics model with treatment and parasite genotype structure (treatment failure)

Humans are infected with parasites with **different genotypes** at frequencies f_X (different levels of treatment failure) → infected humans **I(X)**



Each parasite genotype has associated a **treatment failure rate** $\phi_T(X)$



Swiss TPH

Malaria transmission dynamics model with treatment and parasite genotype structure (treatment failure)

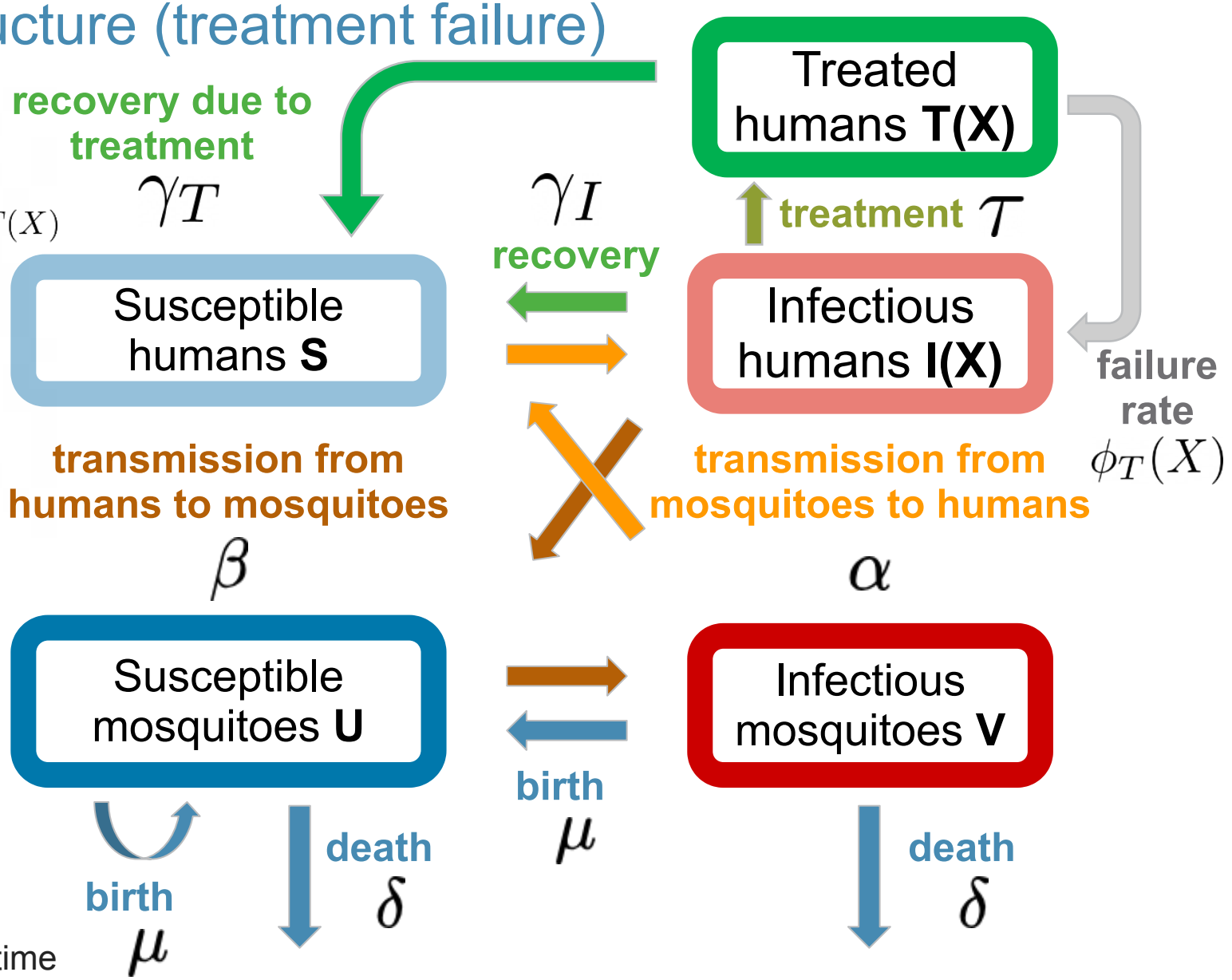
$$\frac{dS}{dt} = -\alpha S\frac{V}{H} + \gamma_I \sum_X I(X) + \gamma_T \sum_X T(X)$$

$$\frac{dI(X)}{dt} = \alpha S\frac{V}{H} f_X - \tau I(X) - \gamma_I I(X) + \phi_T(X)T(X)$$

$$\frac{dT(X)}{dt} = \tau I(X) - \gamma_T T(X) - \phi_T(X)T(X)$$

$$\frac{dU}{dt} = -\beta U \sum_X \frac{I(X)}{H} + \mu(U+V) - \delta U$$

$$\frac{dV}{dt} = \beta U \sum_X \frac{I(X)}{H} - \delta V$$



Assumptions:

- Constant mosquito population size:

  $M = U(0) + V(0)$

- Birth and death rates are equal:

  $\mu = \delta$

- Constant human population size

  $H = S(0) + I(0)$

- Genotype frequencies f_X are constant in time

Malaria transmission dynamics model with treatment and parasite genotype structure (treatment failure)

AIDM_RMresist.R

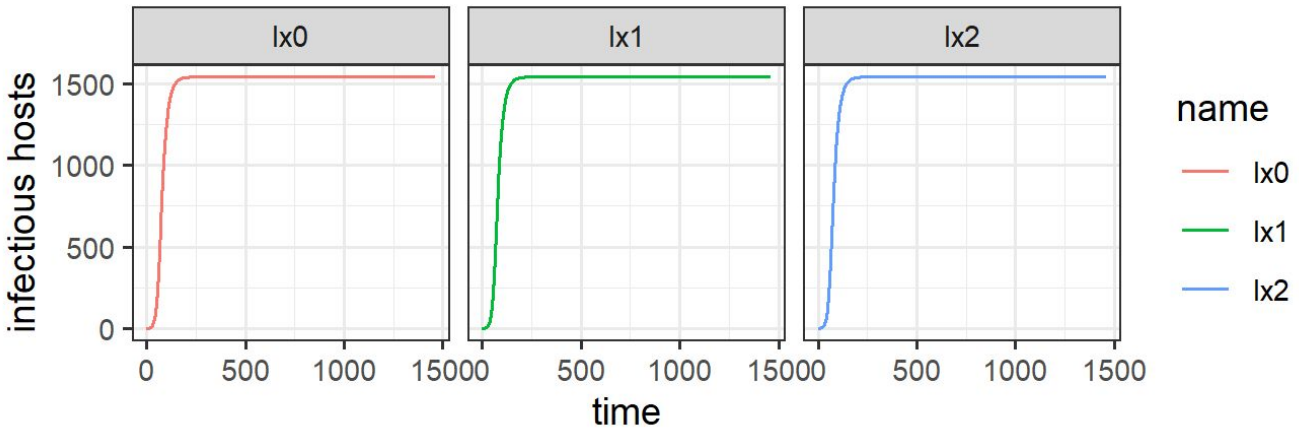
```
H=5000;V0=8; VectorHumanRatio=5; finalT=4*365
x0 <- c(S=H-3,Ix0=1,Ix1=1,Ix2=1,Treatx0=0,Treatx1=0,Treatx2=0,
        U=H*VectorHumanRatio-V0,V=V0)##initial condition
time.points<-seq(0,finalT,1)##time unit in days

parms<-c(
alpha=0.5*0.022,
gammaI=1/285,
gammaT=1/30,
phiTx0=0,phiTx1=1/15,phiTx2=1/5,##failure rate
tau=0,
beta=0.48, mu=0.13, delta=0.13,
fx0=1/3,fx1=1/3,fx2=1/3
)
```

Initial condition with one infection per genotype.

Failure rates for different genotype = phenotype!

Same probability to acquire any genotype during transmission



treatment rate = 0
coexistence of 3 genotypes (no fitness cost for resistant genotypes x1 & x2!)

Malaria transmission dynamics model with treatment and parasite genotype structure (treatment failure)

AIDM_RMresist.R

```
H=5000;V0=8; VectorHumanRatio=5; finalT=4*365
x0 <- c(S=H-3,Ix0=1,Ix1=1,Ix2=1,Treatx0=0,Treatx1=0,Treatx2=0,
        U=H*VectorHumanRatio-V0,V=V0)##initial condition
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parms<-c(
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gammaT=1/30,
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tau=0,
beta=0.48, mu=0.13, delta=0.13,
fx0=1/3,fx1=1/3,fx2=1/3
)
```
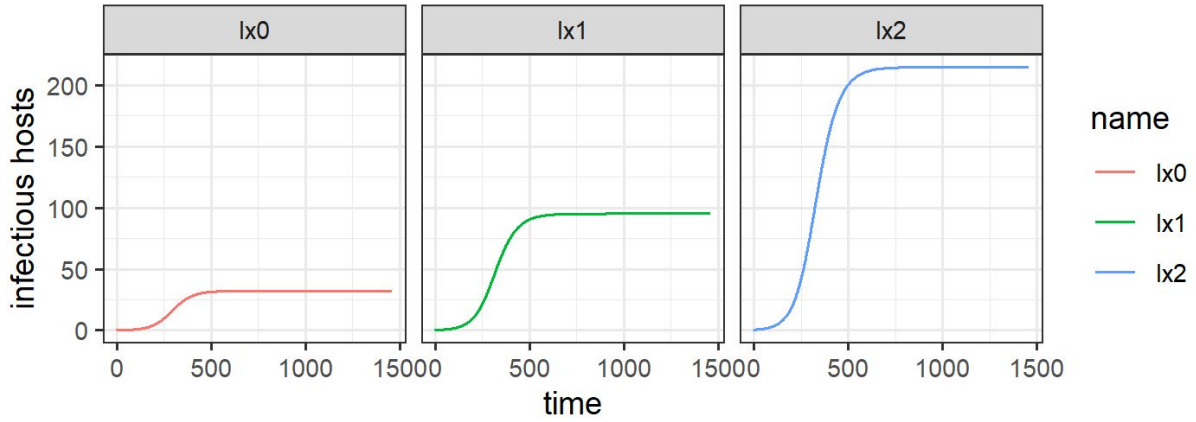

Initial condition with one infection per genotype.

Failure rates for different genotype = phenotype!

Same probability to acquire any genotype during transmission



treatment rate = 0.4
coexistence of 3 genotypes, fitness advantage for resistant types x1, x2

Malaria transmission dynamics model with treatment and parasite genotype structure (treatment failure)

AIDM_RMresist.R

```
H=5000;V0=8; VectorHumanRatio=5; finalT=4*365
x0 <- c(S=H-3,Ix0=1,Ix1=1,Ix2=1,Treatx0=0,Treatx1=0,Treatx2=0,
        U=H*VectorHumanRatio-V0,V=V0)##initial condition
time.points<-seq(0,finalT,1)##time unit in days

parms<-c(
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gammaT=1/30,
phiTx0=0,phiTx1=1/15,phiTx2=1/5,##failure rate
tau=0,
beta=0.48, mu=0.13, delta=0.13,
fx0=1/3,fx1=1/3,fx2=1/3
)
```
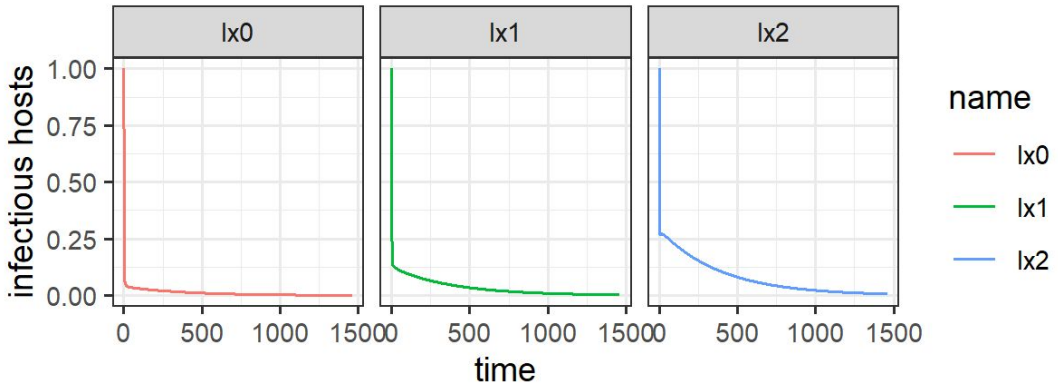

Initial condition with one infection per genotype.

Failure rates for different genotype = phenotype!

Same probability to acquire any genotype during transmission



treatment rate = 0.8
all three genotypes are eliminated