Next generation matrix methods and sensitivity analysis of the reproduction number

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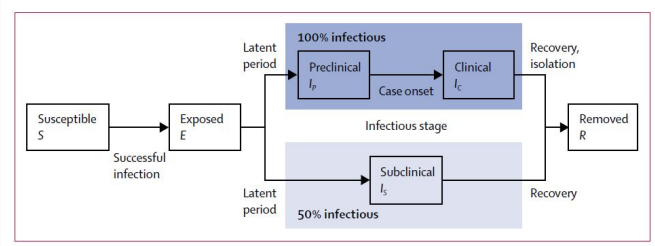
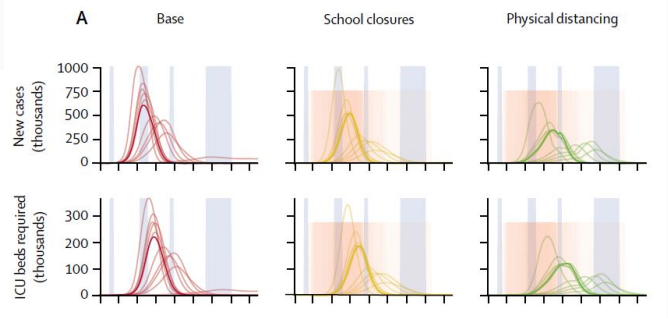
Role of mathematical models in epidemiology

- **Models** are **simple representation of complex phenomena**. Mathematical models use algebraic formulae and symbols to describe parameters of interest.
- Models are able to make **projections** and **explore hypothesis that are not possible otherwise**. Such as **vaccination plans**, **implementation of non-pharmaceutical interventions**. Study the seasonality of a disease, the impact of the emergence of a new variant of concern and project **disease burden**.
- **If the model fails to behave according to our understanding of the subject**, then it probably means that some **assumptions are either wrong or insufficient**

Source: Davies et. al. 2020



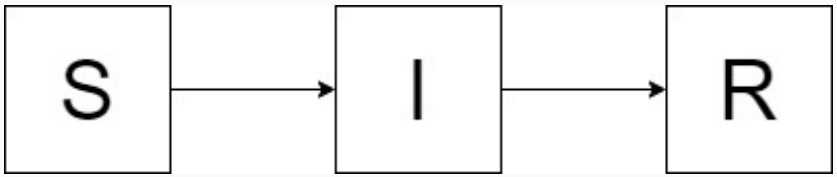


Compartmental models

- **The population is split between the compartments** and individuals move between them;
- The most common framework to develop such models are ordinary differential equations;

SIR model

- The SIR model partitions the population in the **susceptible**, **infected** and **recovered** groups;
- It is often used to model infectious diseases that are **transmitted from human to human**;
- Recovery confers long lasting protection against infection;



SIR model

ODE system

$$\begin{cases} S'(t) = -\beta \frac{I(t)}{N} S(t) \\ I'(t) = \beta \frac{I(t)}{N} S(t) - \gamma I(t) \\ R'(t) = \gamma I(t) \end{cases}$$

Population is constant $S' + I' + R' = 0$ and the initial conditions are such that $S_0 + I_0 + R_0 = N$.

Steady state

The disease free steady state is given by

$$(S_{dfe}, I_{dfe}, R_{dfe}) = (N, 0, 0).$$

Parameters

- $\beta > 0$ is the transmission rate;
- $\gamma > 0$ is the recovery rate;
- N is the number of individuals in the population;

Force of infection

$$\lambda(t) = \beta \frac{I(t)}{N}$$

It represents the rate at which susceptible individuals become infected.

SIR model

Let's look again at the differential equations for S and I

$$\begin{cases} S'(t) = -\underbrace{\beta \frac{I(t)}{N} S(t)}_{incidence} \\ I'(t) = \underbrace{\beta \frac{I(t)}{N} S(t)}_{incidence} - \gamma I(t) \end{cases}$$

The **flux going from $S \to I$ must correspond to the incidence of infection**. We can further interpret this term

$$incidence = S * \underbrace{C}_{contact\ rate} * \underbrace{I/N}_{fraction\ of\ I} * \underbrace{p}_{probability\ of\ transmission}$$

where $\beta = C * p, C > 0, 0 < p \leq 1$.

SIR model

SIR in R

```
# SIR equations
SIR ← function(t, y, parms) {          # time, variable, params

  with(as.list(c(y, parms)),{
    # Change in Susceptibles
    dS ← - beta * S * (I/N)            # S'

    # Change in Infecteds
    dI ← beta * S * (I/N) - gamma * I  # I'

    dR ← gamma * I                     # R'

    return(list(c(dS, dI,dR)))
  })
}
```

SIR model

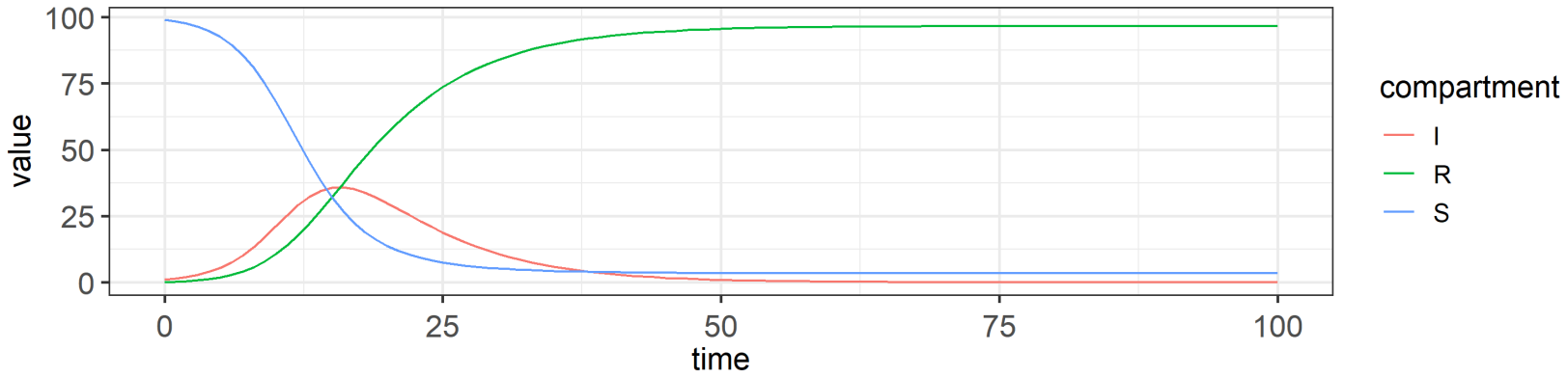
Parameters

```
beta=0.5  # transmission rate
gamma=1/7 # recovery rate (7 days infectious period)

N=100     # Total population
I0=1      # Initial number of infected
S0=N-I0   # Initial number of susceptibles
R0=0      # Initial number of recovered

init ← c(S=S0,I=I0,R=R0)                    # initial conditions
parameters ← c(beta=beta,gamma=gamma,N=N)    # parameters
time ← seq(0,100)                           # time grid (100 days)
```

SIR model

Simulation

```
out←ode(y=init,times=time,SIR,parms=parameters)  # ODE solver
out.df←as.data.frame(out)                        # transform output into a data.frame
out.df %>%                                       # plot the results
  pivot_longer(-time) %>%
  ggplot()+
  geom_line(aes(x=time,y=value,color=name))+
  labs(color="compartment")+
  theme_bw(base_size = 14) + theme(axis.text.x=element_text(size=14, angle=0, vjust=0.
                                   axis.text.y=element_text(size=14),
                                   plot.title=element_text(size=14))
```



Exercise 1: playing with the model

1. Perform simulations using different values for β and γ.
2. What happens when to the final number of recovered (day 100) if we decrease β? What if we increase γ?
3. How does changing β impact the results? What about γ?
4. Is there a set of parameters β and γ such that an outbreak does not occur?

SIR model

Let's revisit the equation for the infected

$$I' = I(\beta \frac{S}{N} - \gamma)$$

From the previous equation we can make the following remark:

- I is **increasing** when $\frac{\beta}{\gamma}\frac{S}{N} > 1$
- I is **constant** when $\frac{\beta}{\gamma}\frac{S}{N} = 1$
- I is **decreasing** when $\frac{\beta}{\gamma}\frac{S}{N} < 1$

At the start of the epidemic $S \approx N$, an outbreak occurs if

$$\frac{\beta}{\gamma} = R_0 > 1,$$

where R_0 is the average number of infections caused by an infected individual in a population that is fully susceptible. If $R_0 < 1$ then the **number of infected will decrease** with each generation and **the disease will eventually die out**.

The reproduction number

"The reproduction number is arguably the most important quantity in infectious disease epidemilogy"

Source: Diekmann et. al. 2009

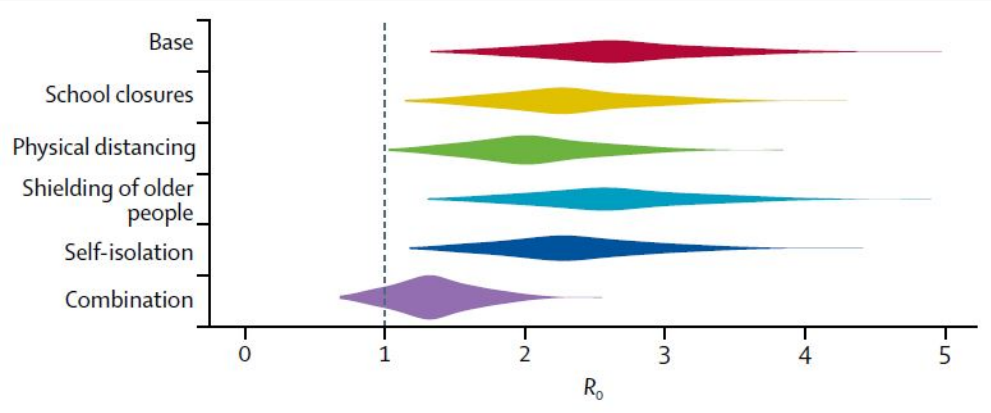
- **The reproduction number is characterized by the pathogen and population in which it spreads**;
- From the reproduction number we can obtain the herd immunity threshold, in the setting of an SIR epidemic. This represents the proportion of susceptible individuals required to be immunized in order to eventually eradicate the infection $(R_0 < 1)$;
- It is also used to obtain the final attack rate (or final size of an epidemic);
- During COVID-19 it was often utilized to design proper non-pharmaceutical interventions (NPIs). In the context of our example, if $R_0 = 3.5$ we would need a decrease of 71.4% in contacts in order to obtain an $R_0 = 1$

The reproduction number

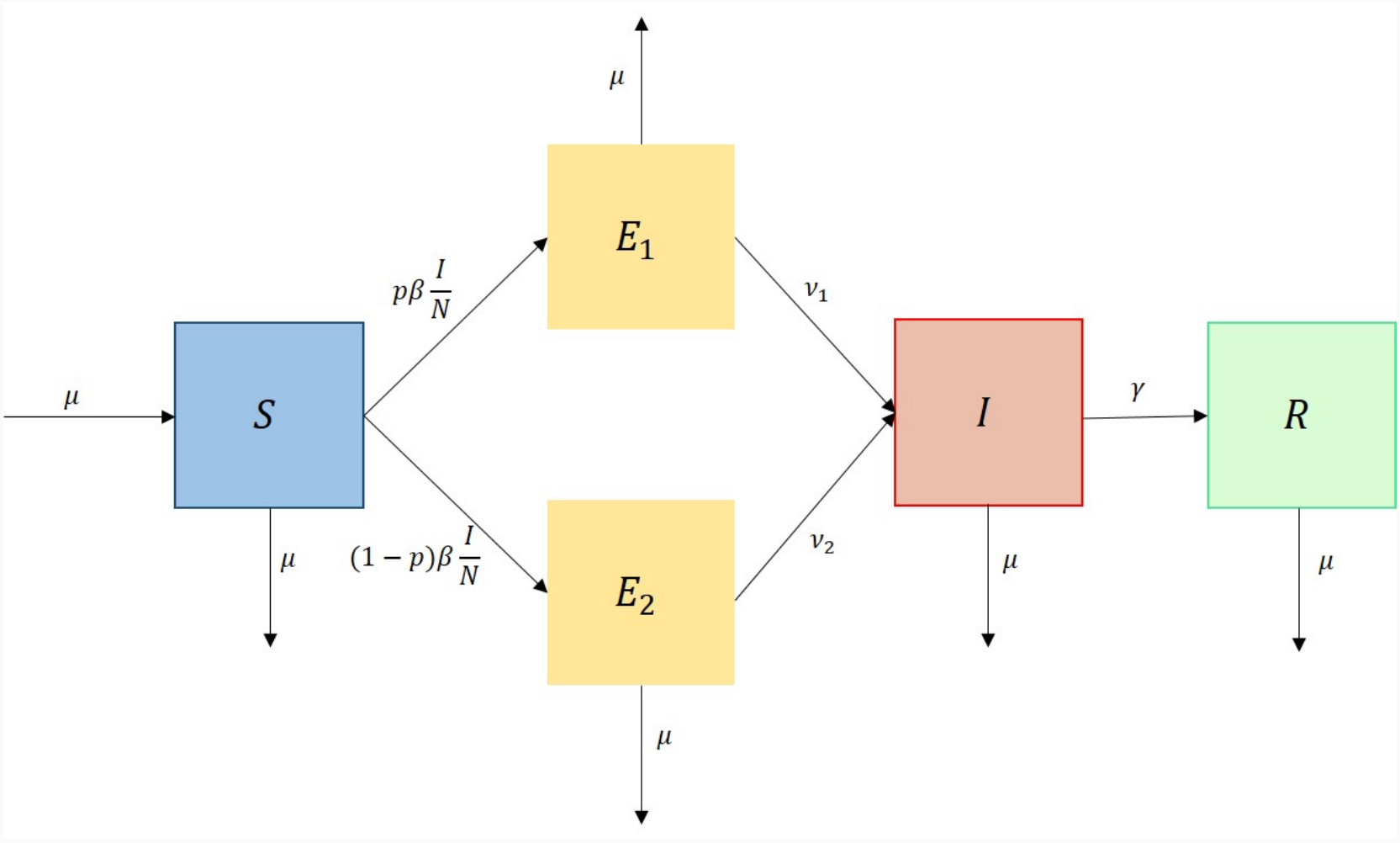
- The reproduction number treats the infection process as a demographic process, i.e. consecutive "generations" of infected individuals;
- R_0 is the interpreted as the expected number of offspring (in the epidemiological sense) of a typical individual in a fully susceptible population;
- If the number of "newborns" increases with each generation, this indicates a an epidemic growth, with growth factor R_0.

Can we obtain a general way to compute the R_0 for any compartmental model?

Source: Davies et. al. 2020



SEIR model with two latent stages



SEIR model with two latent stages

ODE system

$$\begin{cases} S' = \mu N - \beta \frac{SI}{N} - \mu S \\ E_1' = p\beta \frac{SI}{N} - (\nu_1 + \mu) E_1 \\ E_2' = (1-p)\beta \frac{SI}{N} - (\nu_2 + \mu) E_2 \\ I' = \nu_1 E_1 + \nu_2 E_2 - (\gamma + \mu) I \\ R' = \gamma I - \mu R \end{cases}$$

Population is constant $S' + E_1' + E_2' + I' + R' = 0$ and the initial conditions are such that $S^0 + E_1^0 + E_2^0 + I^0 + R^0 = N$.

Parameters

- $\mu > 0$ birth/death rate;
- $0 < p \leq 1$ probability a new infected starting at E_1
- $\beta > 0$ is the transmission rate;
- $\nu_1 > 0$ is the rate of leaving E_1;
- $\nu_2 > 0$ is the rate of leaving E_2;
- $\gamma > 0$ is the recovery rate;
- N is the number of individuals in the population;

Steady state

The disease free steady state is given by

$$(S^*, E_1^*, E_2^*, I^*, R^*) = (N, 0, 0, 0, 0).$$

SEIR model with two latent stages

Step 1.

- Linearized subsystem of infected

$$\begin{cases} E_1' = p\beta I - (\nu_1 + \mu)E_1 \\ E_2' = (1-p)\beta I - (\nu_2 + \mu)E_2 \\ I' = \nu_1 E_1 + \nu_2 E_2 - (\gamma + \mu)I \end{cases}$$

From an **epidemiological point of view**, the **linearization** around the infection-free steady state $(S^*, E_1^*, E_2^*, I^*, R^*) = (N, 0, 0, 0, 0)$ reflects, through the R_0, the **potential of the initial spread of the infection** in a fully susceptible population. We assume that the initial change in the susceptible is negligible.

This is the starting point to compute R_0. The system can now be written as

$$x' = Jx,$$

where J is the Jacobian matrix obtained from the linearization for the original system, $x = [E_1, E_2, I]^\intercal$.

SEIR model with two latent stages

Step 2.

- Write J in the form

$$J = T + \Sigma$$

where T contains the **rates associated with the creation of infections** and Σ the **transition rates describing changes in state** (including removal by death or immunity). In our example we have

$$T = \begin{pmatrix} 0 & 0 & p\beta \\ 0 & 0 & (1-p)\beta \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$\Sigma = \begin{pmatrix} -(\nu_1 + \mu) & 0 & 0 \\ 0 & -(\nu_2 + \mu) & 0 \\ \nu_1 & \nu_2 & -(\gamma + \mu) \end{pmatrix}$$

SEIR model with two latent stages

Step 3.

- Compute

$$\mathbf{K_L} = -T\Sigma^{-1}$$

$\mathbf{K_L}$ represents the next generation matrix with large domain. The ijth entry of $\mathbf{K_L}$ is the **expected number of offspring** with *state-at-infection* i produced by an individual currently in state j throughout its entire infected life.

The reproduction number R_0 is given by

$$R_0 = \rho(\mathbf{K_L})$$

which corresponds to the maximum eigenvalue in absolute value of $\mathbf{K_L}$. Note that Σ^{-1} exists as long as recovery/death processes exist.

SEIR model with two latent stages

Step 4. (optional)

- We have

$$\mathbf{K_L} = -T\Sigma^{-1} = \begin{pmatrix} \frac{p\beta\nu_1}{(\nu_1+\mu)(\gamma+\mu)} & \frac{p\beta\nu_2}{(\nu_2+\mu)(\gamma+\mu)} & \frac{p\beta}{\gamma+\mu} \\ \frac{(1-p)\beta\nu_1}{(\nu_1+\mu)(\gamma+\mu)} & \frac{(1-p)p\beta\nu_2}{(\nu_2+\mu)(\gamma+\mu)} & \frac{(1-p)\beta}{\gamma+\mu} \\ 0 & 0 & 0 \end{pmatrix}$$

We can further write $\mathbf{K_L}$ in a block matrix

$$\mathbf{K_L} = \begin{pmatrix} \mathbf{K} & A \\ 0 & 0 \end{pmatrix}$$

where

$$\mathbf{K} = \begin{pmatrix} \frac{p\beta\nu_1}{(\nu_1+\mu)(\gamma+\mu)} & \frac{p\beta\nu_2}{(\nu_2+\mu)(\gamma+\mu)} \\ \frac{(1-p)\beta\nu_1}{(\nu_1+\mu)(\gamma+\mu)} & \frac{(1-p)p\beta\nu_2}{(\nu_2+\mu)(\gamma+\mu)} \end{pmatrix}$$

We can show that the set of eigenvalues of $\mathbf{K_L}$ are those of $\mathbf{K}$ plus a 0.

SEIR model with two latent stages

Let's take a closer look at $\mathbf{K}$

$$\mathbf{K} = \begin{pmatrix} \overbrace{\frac{\nu_1}{\mu+\nu_1}\frac{\beta}{\gamma+\mu}p}^{(E_1,E_1)} & \overbrace{\frac{\nu_2}{\mu+\nu_2}\frac{\beta}{\gamma+\mu}p}^{(E_1,E_2)} \\ \underbrace{\frac{\nu_1}{\mu+\nu_1}\frac{\beta}{\gamma+\mu}(1-p)}_{(E_2,E_1)} & \underbrace{\frac{\nu_2}{\mu+\nu_2}\frac{\beta}{\gamma+\mu}(1-p)}_{(E_2,E_2)} \end{pmatrix}$$

we have

$$K_{11} = \underbrace{\frac{\nu_1}{\mu+\nu_1}}_{probability\ to\ survive\ E_1} * \underbrace{\frac{\beta}{\gamma+\mu}}_{infections\ produced} * \underbrace{p}_{p\ will\ become\ E_1}.$$

Thus K_{11} is the average number of infections with *state-at-infection* E_1 that will eventually be produced by an individual currently in E_1.

This interpretation enables the **construction** of the next generation matrix $\mathbf{K}$ **purely from epidemiological reasoning**.

SEIR model with two latent stages

Step 5. (optional)

Since $\mathbf{K}$ is a 2×2 matrix we can easily compute $\rho(\mathbf{K})$. Let's use the following results from linear Algebra:

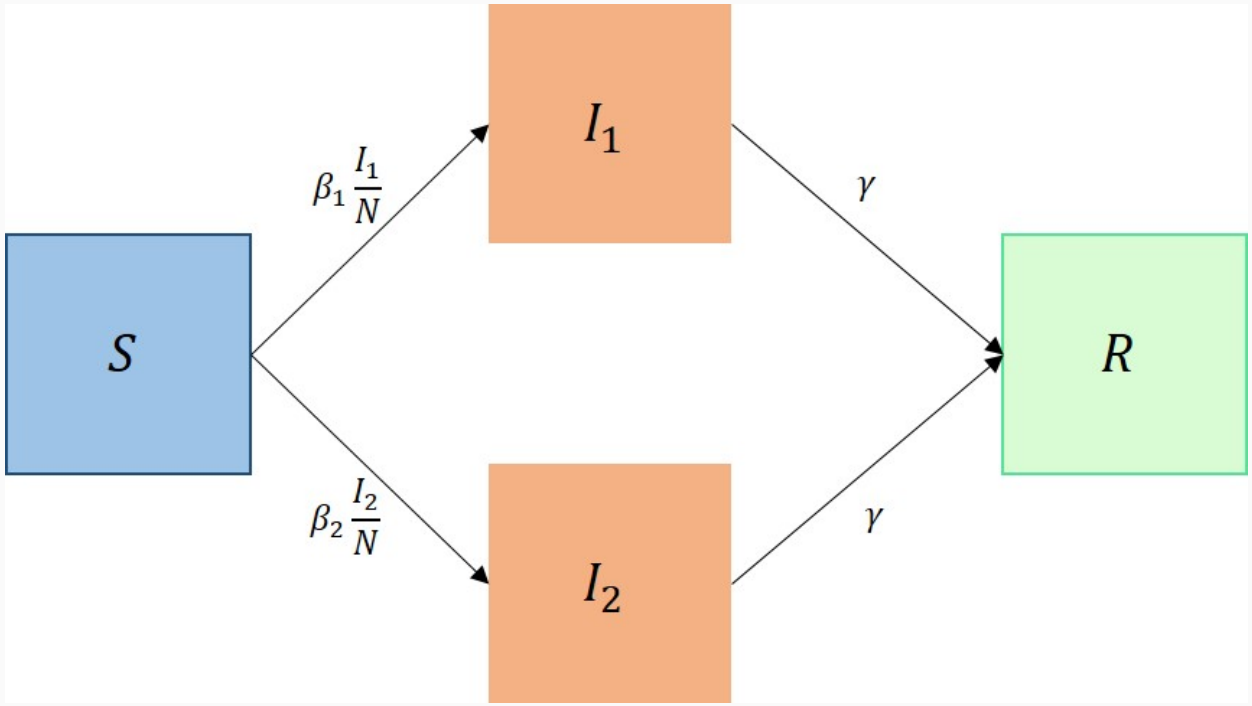
1. The determinant of $\mathbf{K}$ is the product of its eigenvalues;
2. The trace of $\mathbf{K}$ (sum of the diagonal elements) is the sum of its eigenvalues;

We can easily see that $det(\mathbf{K}) = 0$, hence 0 must be an eigenvalue. Hence

$$R_0 = \rho(\mathbf{K}) = tr(\mathbf{K}) = \left(\frac{p\nu_1}{\nu_1 + \mu} + \frac{(1-p)\nu_2}{\nu_2 + \mu} \right) \frac{\beta}{\gamma + \mu}.$$

Exercise 2

Compute the reproduction number of the following model:



In this setting two pathogens exist that compete for the same susceptible pool. Individuals infected by strain i, $i = 1, 2$ can only produce infections of type i. Recovery rate is the same for both strains.

Solution

ODE system

$$\begin{cases} S' = -\left(\beta_1 \frac{I_1}{N} + \beta_2 \frac{I_2}{N}\right) S \\ I_1' = \beta_1 \frac{I_1}{N} S - \gamma I_1 \\ I_2' = \beta_2 \frac{I_2}{N} S - \gamma I_2 \\ R' = \gamma (I_1 + I_2) \end{cases}$$

Population is constant $S' + I_1' + I_2' + R' = 0$ and the initial conditions are such that $S^0 + I_1^0 + I_2^0 + R^0 = N$.

Steady state

The disease free steady state is given by

$$(S^*, I_1^*, I_2^*, R^*) = (N, 0, 0, 0).$$

Parameters

- $\beta_1 > 0$ is the transmission rate for infection of type 1;
- $\beta_2 > 0$ is the transmission rate for infection of type 2;
- $\gamma > 0$ is the recovery rate;
- N is the number of individuals in the population;

Solution

- Linearized subsystem of infected

$$\begin{cases} I_1' = (\beta_1 - \gamma) I_1 \\ I_2' = (\beta_2 - \gamma) I_2 \end{cases}$$

- T and Σ^{-1}

$$T = \begin{pmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{pmatrix} \qquad -\Sigma^{-1} = \begin{pmatrix} \frac{1}{\gamma} & 0 \\ 0 & \frac{1}{\gamma} \end{pmatrix}$$

- Next generation matrix

$$\mathbf{K} = \begin{pmatrix} \frac{\beta_1}{\gamma} & 0 \\ 0 & \frac{\beta_2}{\gamma} \end{pmatrix}$$

- Reproduction number

$$R_0 = \max\left(\left\{\frac{\beta_1}{\gamma}, \frac{\beta_2}{\gamma}\right\}\right)$$

Exercise 3

1. Implement the previous model in *R*;
2. Run simulations for different values of β_1 and β_2;
3. Compute R_0 for each scenario;
4. Compute the curve for $\frac{I_1}{I_1+I_2}$, which corresponds the proportion of infections of type 1.
5. What can you conclude?

Solution

- Two strain SIR model implementation

```
# SIIR equations
SIIR ← function(t, y, parms) {          # time, variable, params

  with(as.list(c(y, parms)),{

    dS ← - (beta_1 * (I_1/N) + beta_2 * (I_2/N)) * S # S'

    dI_1 ←  beta_1 * (I_1/N) * S - gamma * I_1  # I_1'

    dI_2 ←  beta_2 * (I_2/N) * S - gamma * I_2  # I_1'

    dR ← gamma * (I_1+I_2)                    # R'

    return(list(c(dS,dI_1,dI_2,dR)))
  })
}
```

Solution

- Two strain SIR model parameters and R_0

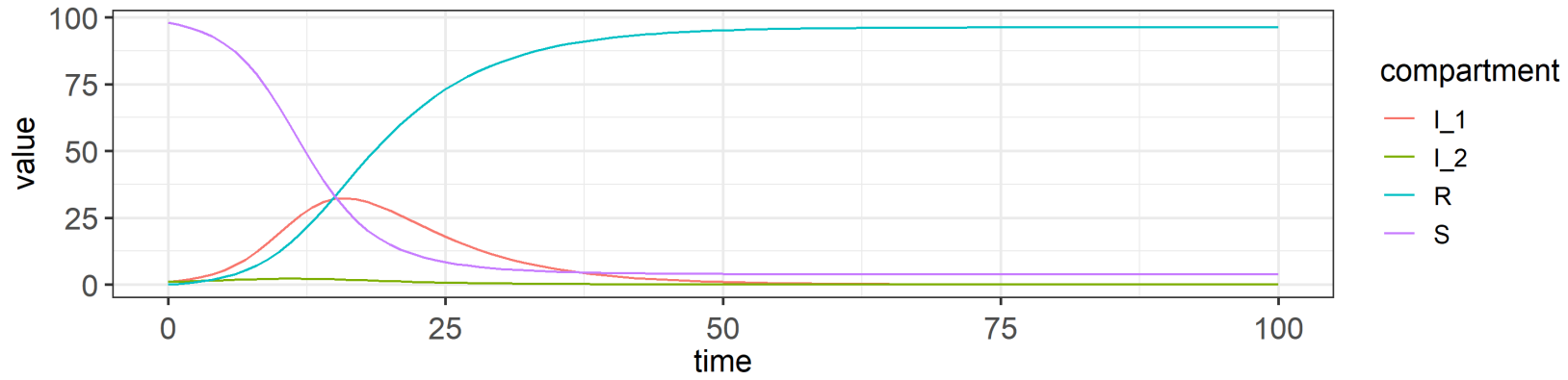
```
beta_1=0.5  # transmission rate of type 1
beta_2=0.25  # transmission rate of type 2
gamma=1/7 # recovery rate (7 days infectious period)

N=100     # Total population
I0_1=1           # Initial number of infected
I0_2=1           # Initial number of infected
S0=N-I0_1-I0_2   # Initial number of susceptibles
R0=0             # Initial number of recovered

R_0=max(beta_1/gamma,beta_2/gamma)

init ← c(S=S0,I_1=I0_1,I_2=I0_2,R=R0)                          # initial conditions
parameters ← c(beta_1=beta_1,beta_2=beta_2,gamma=gamma,N=N)     # parameters
time ← seq(0,100)                                              # time grid (100 days)

R_0
```

```
## [1] 3.5
```

Solution

- Simulations

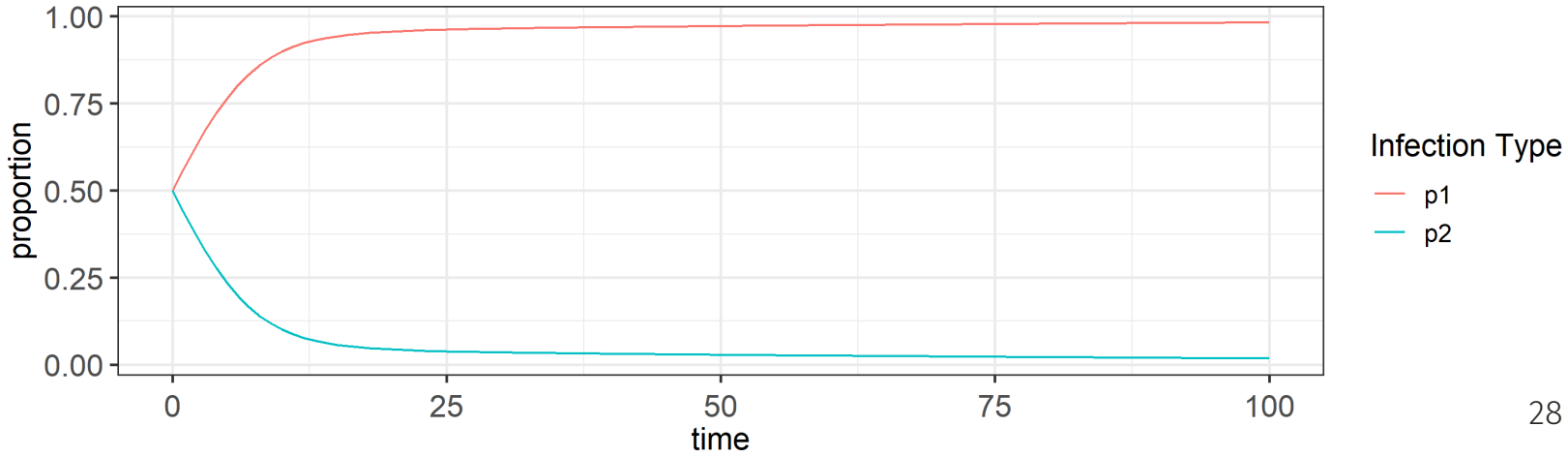
```
out←ode(y=init,times=time,SIIR,parms=parameters)  # ODE solver
out.df←as.data.frame(out)                         # transform output into a data.frame
out.df %>%                                        # plot the results
  pivot_longer(-time) %>%
  ggplot()+
  geom_line(aes(x=time,y=value,color=name))+
  labs(color="compartment")+
  theme_bw(base_size = 14) + theme(axis.text.x=element_text(size=14, angle=0, vjust=0.
                                   axis.text.y=element_text(size=14),
                                   plot.title=element_text(size=14))
```



Solution

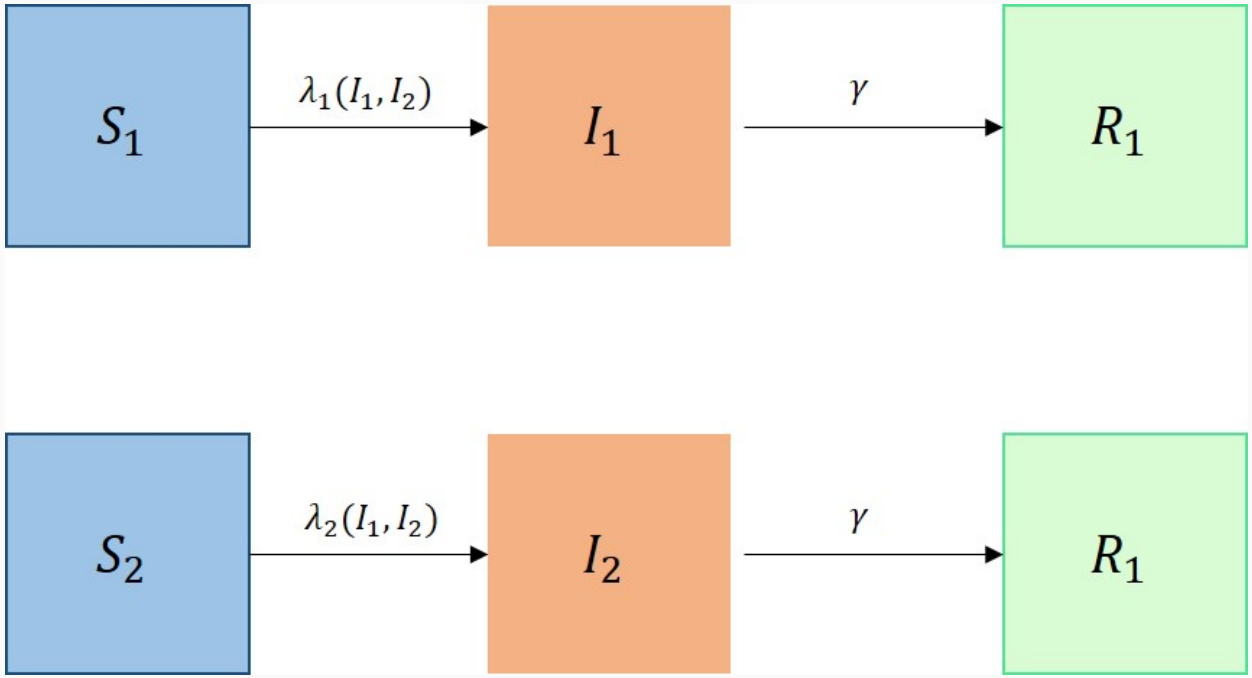
- Computing $\frac{I_1}{I_1+I_2}$

```
out.df %>%
  mutate(p1=I_1/(I_1+I_2)) %>%
  ggplot()+
  geom_line(aes(x=time,y=p1,color="p1"))+
  geom_line(aes(x=time,y=1-p1,color="p2"))+
  labs(y="proportion",x="time")+
  labs(color="Infection Type")+
  theme_bw(base_size = 14) + theme(axis.text.x=element_text(size=14, angle=0, vjust=0.
                                   axis.text.y=element_text(size=14),
                                   plot.title=element_text(size=14))
```



Heterogenous SIR model

Consider that individuals are **fundamentally different** according to some discrete categories, e.g. sex and age. These **differences will be manifested in all states the epidemiological life of an individual**.



Heterogenous SIR model

ODE system

$$\begin{cases} S_1'(t) = -\lambda_1(t) S_1(t) \\ S_2'(t) = -\lambda_2(t) S_2(t) \\ I_1'(t) = \lambda_1(t) S(t) - \gamma I_1(t) \\ I_2'(t) = \lambda_2(t) S(t) - \gamma I_2(t) \\ R_1'(t) = \gamma I_1(t) \\ R_2'(t) = \gamma I_2(t) \end{cases}$$

Steady state

The disease free steady state is given by

$$(S_1^*, S_2^*, I_1^*, I_2^*, R_1^*, R_2^*) = (N_1, N_2, 0, 0, 0, 0).$$

Force of infection

$$\lambda_i(t) = \beta_{i1} \frac{I_1(t)}{N_1} + \beta_{i2} \frac{I_2(t)}{N_2}, \, i = 1, 2$$

Parameters

- $\beta_{ij} > 0$ is the transmission rate between groups i and j, $i, j = 1, 2$
- $\gamma > 0$ is the recovery rate;
- N_1 is the number of individuals in population group 1;
- N_2 is the number of individuals in population group 2;

Heterogenous SIR model

We've seen previously that $\beta = C * p$,

$$\beta_{ij} = a_i C_{ij} h_j$$

- a_i is the susceptibility parameter associated with group i, i.e. it measures **how likely** it is for someone in group i to be **infected given an infectious contact**;
- h_j is the infectivity parameter associated with group j, i.e. it measures **how likely** it is for someone in group j to transmit the infection given a contact with a susceptible individual;
- C_{ij} is the average number of contacts per unit of time. The reciprocity of contacts gives us

$$C_{ij} N_i = C_{ji} N_j$$

i.e. the total number of contacts that group i has with j must equal those of j with i. This helps use simplify the next generation matrix.

Heterogeneous SIR model

The next generation matrix for this model is given by:

$$\mathbf{K} = \frac{1}{\gamma}\begin{pmatrix} \overbrace{a_1 C_{11} h_1}^{\beta_{11}} & a_1 C_{21} h_2 \\ a_2 C_{12} h_1 & a_2 C_{22} h_2 \end{pmatrix}$$

If $C_{ij} = c$ (homogeneous mixing), $i, j = 1, 2$ then we can obtain R_0 by noting that the $det(\mathbf{K}) = 0$, hence

$$R_0 = tr(\mathbf{K}) = \frac{c}{\gamma}(a_1 h_1 + a_2 h_2)$$

This is not often the case...

In the case where homogeneous mixing cannot be assumed, we can use numerical techniques to obtain R_0, especially for matrices with high dimensions.

Heterogeneous SIR model

R code

```
# Go to https://lwillem.shinyapps.io/socrates_comix/

C_file=read.csv(file="PORTUGAL_SCM.csv") # Portugal 2020 CoMiX contacts (all waves)
C=as.matrix(C_file)             # transform to matrix (2 age groups 0-30, 30+)
a = diag(c(1,1),nrow=2,ncol=2)  # matrix with the susceptibility profile
h = diag(c(1,1),nrow=2,ncol=2)  # matrix with the infectivity profile
gamma=1                         # recovery rate

K=(1/gamma)*(a %*% t(C )%*% h)               # compute the next generation matrix
rownames(K)=c("infectee_0-29","infectee_30+");colnames(K)=c("infector_0-29","infector_
```

```
##                infector_0-29 infector_30+
## infectee_0-29       5.838249     2.249822
## infectee_30+        5.579954     3.470077
```

```
R_0=max(abs(eigen(K)$values));R_0
```

```
## [1] 8.389931
```

Sensitivity analysis

- $\mathbf{K}$ **has constant entries**. The **parameters of the model are not time dependent**.
- In reality, the epidemiological landscape changes quickly.
- Public health interventions, changes in behaviour, new variants.

Sensitivity analysis enables us to understand how potential **perturbations to epidemiological parameters affects outcomes of interest**. Consider the R_0 obtained for the SIR model:

$$R_0 = \frac{\beta}{\gamma} = \beta D$$

where D stands for the average duration of the infectious period $D = \frac{1}{\gamma}$. The sensitivities of $R_0(\beta, D)$ w.r.t β and D are given by

$$\frac{\partial R_0}{\partial \beta} = D \qquad \frac{\partial R_0}{\partial D} = \beta$$

Sensitivity analysis

Sensitivity of the reproduction number

When we can't obtain an explicit analytic expression for R_0 we can compute the sensitivities of R_0 with respect to entries of $\mathbf{K}$ using the right and left eigenvector associated with R_0. We need the following considerations:

- K is primitive (all entries positive if raised to sufficiently high powers);
- K is diagonalizable (does it have distinct eigenvalues?);

Let $\mathbf{w}$ and $\mathbf{v}$ be the right and left eigenvector associated with R_0, if $\langle \mathbf{v}, \mathbf{w} \rangle = 1$ then

$$\frac{\partial R_0}{\partial k_{ij}} = v_i w_j, \quad i, j = 1, \ldots, M$$

where v_i and w_j correspond to the ith and jth entry of $\mathbf{v}$ and $\mathbf{w}$, respectively. k_{ij} is the ijth entry of the $M \times M$ next generation matrix $\mathbf{K}$. Sensitivities can be summarised in the sensitivity matrix $\mathcal{S}$

$$\mathcal{S} = \mathbf{v}\mathbf{w}^\mathsf{T}$$

Sensitivity analysis

Sensitivity of the reproduction number

A first order Taylor expansion reads

$$R_0^{\Delta k_{ij}} \approx R_0 + \Delta k_{ij} \underbrace{\frac{\partial R_0}{\partial k_{ij}}}_{sensitivity}$$

Hence we can interpret sensitivities as the slope of the expected change in R_0 given a absolute perturbation of k_{ij} of magnitude Δk_{ij}.

Sensitivity analysis

R code

```
R = eigen(K)
  colnames(R$vectors)=c("dominant",as.character(seq(2,ncol(R$vectors))))
  if(all(R$vectors[,1]<0)){
    R$vectors[,1]=R$vectors[,1]*-1 # make sure the dominant right eigenvalue is positi
  }

  norm=T
  if(norm==T){
    R$vectors[,1]=R$vectors[,1]/sum(R$vectors[,1]) # normalize such that ||w|| = 1
  }

# calculate the left eigenvectors constrained on <v_i,w_i> = 1 and <v_i,w_j> = 0, for
L=eigen(t(K))
  colnames(L$vectors)=c("dominant",as.character(seq(2,ncol(L$vectors))))

  for (i in seq(1,ncol(L$vectors))) {
    L$vectors[,i]=L$vectors[,i]/as.numeric((t(L$vectors[,i])%*%R$vectors[,i]))
  }
  eigens=list(values=R$values,w=R$vectors,v=L$vectors)
```

Sensitivity analysis

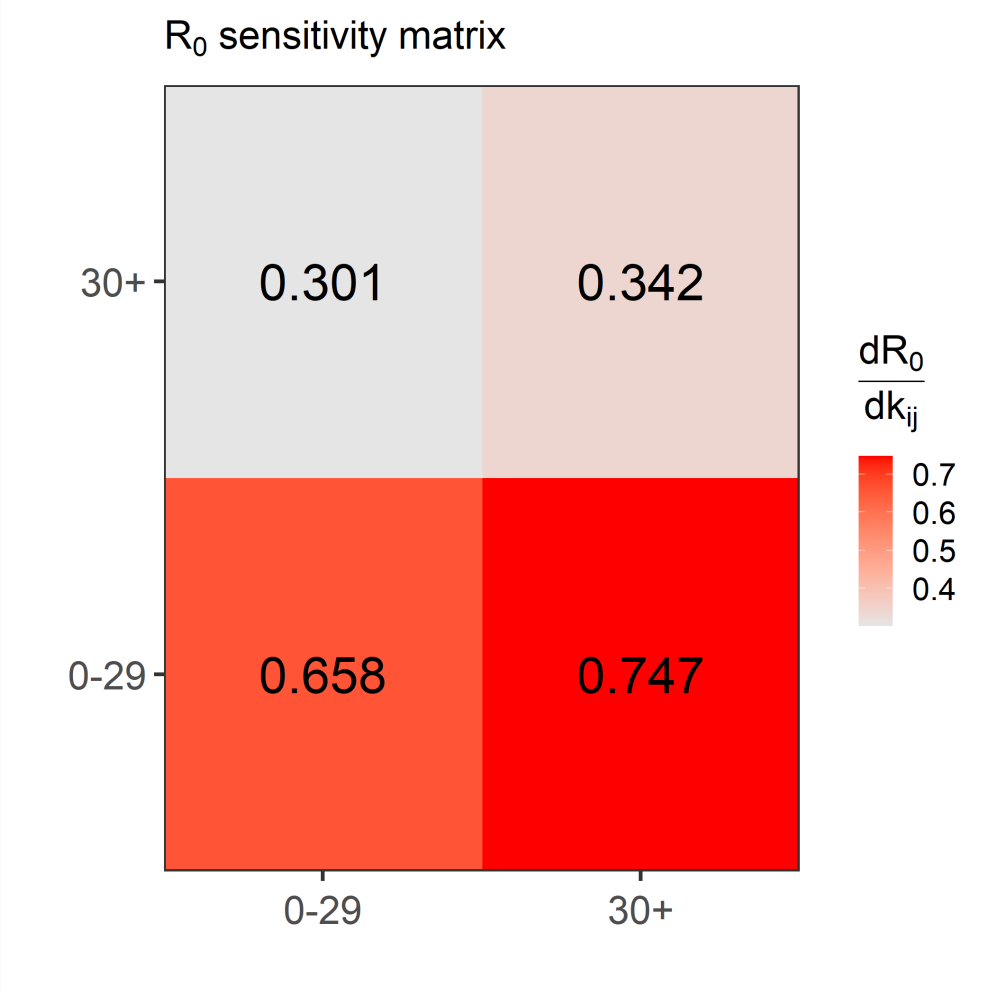
R code

```
sens=eigens$v[,"dominant"] %*% t(eigens$w[,"dominant"]) # vw^T
  colnames(sens) ← colnames(K)
  rownames(sens) ← rownames(K)

sens
```

```
##                infector_0-29 infector_30+
## infectee_0-29      0.6584796    0.7468282
## infectee_30+       0.3011190    0.3415204
```

Sensitivity analysis

Sensitivity matrix



Sensitivity analysis

Elasticity of the reproduction number

Changes to R_0 given a proportional perturbation in an entry obtain via the elasticity

$$e_{ij} = \frac{k_{ij}}{R_0} \frac{\partial R_0}{\partial k_{ij}},$$

Elasticity measures proportional sensitivity. Matrix E summarises the elasticities of R_0:

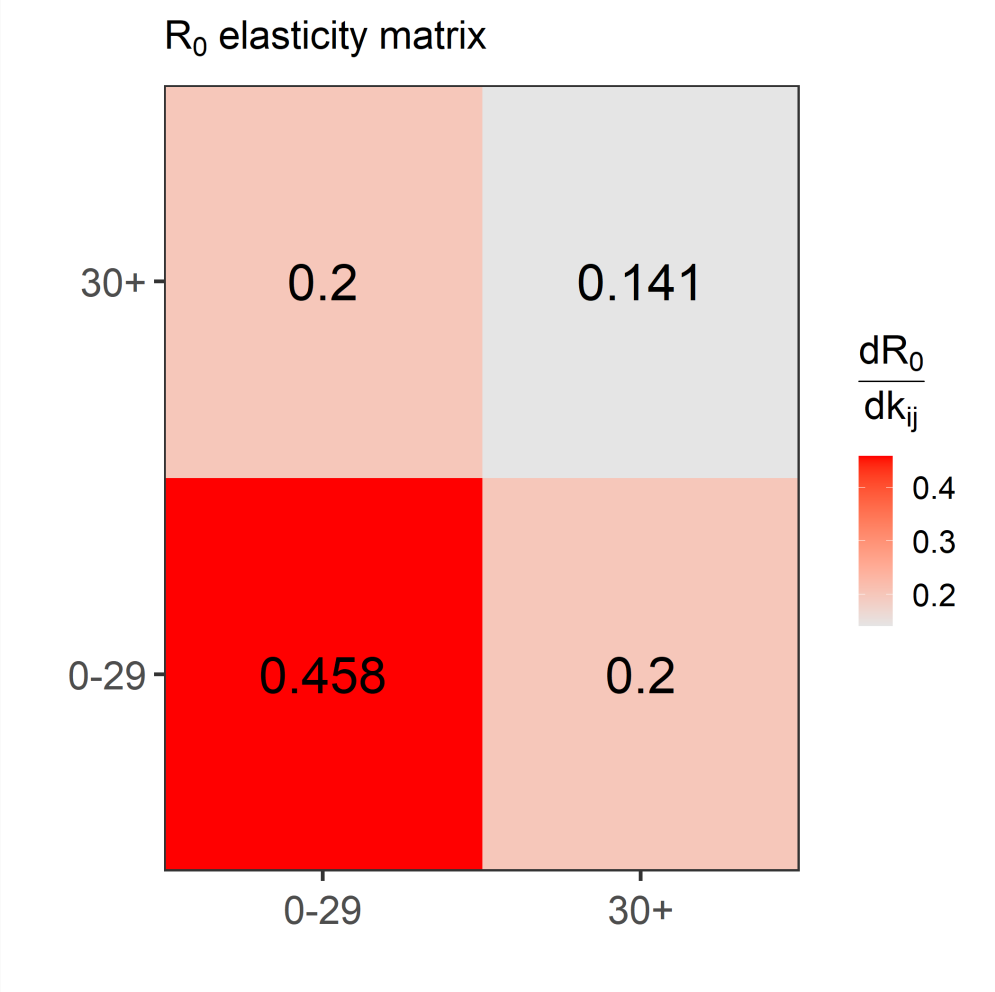
$$E = \frac{1}{R_0} S \odot K$$

Elasticities e_{ij} have the following property as a result of Euler's theorem on homogeneous functions:

$$\sum_{i,j} e_{R_0}(k_{ij}) = 1$$

Sensitivity analysis

R code for the elasticity matrix



What more can we learn from the NGM?

- The right eigenvector $\mathbf{w}$ can be interpreted as the **relative incidence** (after many generations) as long as $||\mathbf{w}|| = 1$.

Let's illustrate this result with the exercise about the two strain SIR model. We had

$$\mathbf{K} = \begin{pmatrix} \frac{\beta_1}{\gamma} & 0 \\ 0 & \frac{\beta_2}{\gamma} \end{pmatrix}$$

which has eigenvectors $\mathbf{w_1} = [1\ 0]^\intercal$ and $\mathbf{w_2} = [0\ 1]^\intercal$. This means that when $\frac{\beta_1}{\gamma} > \frac{\beta_2}{\gamma}$ **eventually all infections will be of type** 1, and the opposite if $\frac{\beta_1}{\gamma} < \frac{\beta_2}{\gamma}$. Just as we saw in our numerical exercise.

- The column sum of the $\mathbf{K}$ can be interpreted as the **expected number of infections created by an individual in group** j throughout his infectious life;

This result is obtained directly from the interpretation of the entries of $\mathbf{K}$. Let $k_j = \sum_i k_{ij}$, we have

$$\min\{\mathbf{k_1}, \ldots, \mathbf{k_M}\} \leq R_0 \leq \max\{\mathbf{k_1}, \ldots, \mathbf{k_M}\},$$

Sensitivity analysis

The **cumulative elasticity** of group j is given by

$$e_j = \sum_{i=1}^{M} \frac{k_{ij}}{R_0} v_i w_j = \sum_{i=1}^{M} e_{ij} = v_j w_j.$$

The sum of cumulative elasticities is also 1. These elasticities represent the **proportional contribution** of the transmission characteristics of each group towards the global growth factor given by R_0.

In the works

- Sensitivity of lower-level parameters (e.g. $\frac{\partial R_0}{\partial a_i}$, the sensitivity of R_0 with respect to the susceptibility parameter of group i);
- Sensitivity of the relative incidence $(\mathbf{w})$;
- Combined sensitivity of the growth factor (R_0) and infection distribution $(\mathbf{w})$;

Exercise 4

- Try and replicate the sensitivity analysis for the heterogeneous SIR model using a higher dimension social contact matrix (more age groups) obtained from https://lwillem.shinyapps.io/socrates_comix/
- Consider different assumptions for the susceptibility and infectivity profile (parameters a_i and h_j)
- What is the reproduction number?
- What is the expected distribution of infections between groups?
- What is the group that infects the most?
- What is the group that contributes most towards the growth factor R_0?

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