

## Heterogeneity

Two types of individuals, e.g., male-female  
host-vector

$$\frac{\partial S_i}{\partial t} = - F_i S_i \quad i=1,2$$

$$F_i(t) = \int_0^\infty \left\{ A_{ii}(t) \left[ -\frac{\partial S_i}{\partial t}(t-\tau) \right] + A_{i2}(t) \left[ -\frac{\partial S_2}{\partial t}(t-\tau) \right] \right\} d\tau$$

$$S_i(t) := \frac{S_i(0)}{N_i} - \int_0^\infty \left\{ N_i A_{ii}(t) [1 - S_i(t-\tau)] + N_2 A_{i2}(t) [1 - S_2(t-\tau)] \right\} d\tau$$

$$S_i(t) = e^{-\int_0^t F_i(\tau) d\tau}$$

Linearization  $z = \begin{pmatrix} 1 - S_1 \\ 1 - S_2 \end{pmatrix}$ , remove h.o.t. in  $z$

$$z(t) = \int_0^\infty B(\tau) z(t-\tau) d\tau \quad B = \begin{pmatrix} N_1 A_{11} & N_2 A_{12} \\ N_1 A_{21} & N_2 A_{22} \end{pmatrix}$$

Ansatz:  $z(t) = e^{\lambda t} \psi \Rightarrow \psi = K_\lambda \psi$

with

$$K_\lambda := \int_0^\infty e^{-\lambda \tau} B(\tau) d\tau$$

NGM  $K_0$   $R_0 :=$  spectral radius of  $K_0$

$\textcircled{r}$  is the unique real root of "spectral radius  $K_\lambda = 1$ "  
 $\text{sign}(R_0 - 1) = \text{sign } r$

assume that the positive operator  $K_0$  is irreducible

## Final size equation

$$S_i(\infty) = e^{-\left(K_0 \begin{pmatrix} 1 - S_1(\infty) \\ 1 - S_2(\infty) \end{pmatrix}\right)};$$

A solution should satisfy  $0 \leq S_i(\infty) \leq 1$

The solution  $S_i(\infty) = 1$ ,  $i=1,2$ , is called the trivial solution.

### Theorem

For  $R_0 \leq 1$ , the final size equation has no nontrivial solution.

For  $R_0 > 1$ , it has exactly one nontrivial solution.

A first example of a submodel for A:

Let the index correspond to vaccination status. More precisely: type 1 individuals are not vaccinated  
type 2 individuals are vaccinated

Assume that individuals have on average  $c$  contacts per unit of time and that contacts occur at random in the sense that the three types of contacts occur in the proportions

$$\left(\frac{N_1}{N}\right)^2 : 2 \frac{N_1 N_2}{N^2} : \left(\frac{N_2}{N}\right)^2$$

with  $N = N_1 + N_2$ . Let  $b(\tau)$  denote the probability of transmission when a type 1 susceptible individual has contact with a type 1 infected individual that was infected time  $\tau$  ago. Let vaccination reduce the susceptibility by a factor  $\varepsilon_1$  and the infectiousness by a factor  $\varepsilon_2$ . Assume that the time course pattern of infectiousness is not changed by ~~vaccination~~ being vaccinated. (Note that while reduced illness is of major importance for an individual, it is irrelevant

for transmission at the p-level.)

(P3.3)

Then

$$A(\tau) = \frac{c}{N} b(\tau) \begin{pmatrix} 1 & \varepsilon_2 \\ \varepsilon_1 & \varepsilon_1 \varepsilon_2 \end{pmatrix}$$

and

$$B(\tau) = \frac{c}{N} b(\tau) \begin{pmatrix} N_1 & \varepsilon_2 N_2 \\ \varepsilon_1 N_1 & \varepsilon_1 \varepsilon_2 N_2 \end{pmatrix}$$

Note that  $\begin{pmatrix} N_1 & \varepsilon_2 N_2 \\ \varepsilon_1 N_1 & \varepsilon_1 \varepsilon_2 N_2 \end{pmatrix} = \begin{pmatrix} 1 & \\ \varepsilon_1 & \end{pmatrix} \begin{pmatrix} N_1 & \varepsilon_2 N_2 \\ & \end{pmatrix}$

has eigenvector  $\begin{pmatrix} 1 \\ \varepsilon_1 \end{pmatrix}$  with eigenvalue  $N_1 + \varepsilon_1 \varepsilon_2 N_2$

Without vaccination we have  $N_2 = 0, N_1 = N$  and

$$R_0 = c \int_0^\infty b(\tau) d\tau$$

With vaccination

$$\begin{aligned} \tilde{R}_0 &= c \int_0^\infty b(\tau) d\tau \left( \frac{N_1}{N} + \varepsilon_1 \varepsilon_2 \frac{N_2}{N} \right) \\ &= R_0 \left( \frac{N_1}{N} + \varepsilon_1 \varepsilon_2 \frac{N_2}{N} \right) \end{aligned}$$

So if  $N_2 = fN$  then

$$\tilde{R}_0 = R_0 (1 - f + \varepsilon_1 \varepsilon_2 f)$$

which is smaller than one provided

$$f > \frac{1 - \frac{1}{R_0}}{1 - \varepsilon_1 \varepsilon_2}$$

Side remark: since the  $\tau$ -dependence comes in as a scalar factor, the eigenvectors positive of  $K_>$  and  $K_0$  are the same. P 3.4

In the recent preprint medRxiv

[doi.org/10.1101/2021.12.13.21267725](https://doi.org/10.1101/2021.12.13.21267725)

Vaccine breakthrough and the invasion dynamics of SARS-CoV-2 variants

C.M. Saad-Roy, S.A. Levin, J.R. Gog, J. Farrar, C.E. Wagner, C.J.E. Metcalf, B.T. Grenfell

There is also attention for non-random mixing in the sense that "due to underlying spatial or social heterogeneities", the three types of contacts occur in the proportions

$$\left(\frac{N_1}{N}\right)^2 : 2\kappa \frac{N_1 N_2}{N^2} : \left(\frac{N_2}{N}\right)^2$$

with  $\kappa < 1$ . By a scaling factor

$$1 + 2(\kappa-1) \frac{N_1 N_2}{N^2} = 1 + 2(\kappa-1)f(1-f)$$

we achieve that the overall number of contacts per unit of time remains the same.

General Remark When the aim is to determine the effect of a mechanism (like in this case assortative contact structure) by comparing models, gauging is often a nontrivial issue.

A second example: Let the index correspond to a contact intensity level, in the sense that type  $i$  individuals have on average  $c_i$  contacts per unit of time. Assume that a fraction

P 3.5

$$\frac{c_j N_j}{c_1 N_1 + c_2 N_2}$$

of the contacts of any individual is with individuals of type  $j$  (this is called proportionate mixing or weighted random mixing). We assume that the disease status has no influence on the contact process. In particular, if a type  $i$  individual is involved in a contact, it is with probability  $S_i/N_i$  susceptible. These modeling considerations lead to

$$A_{ij}(\tau) = \frac{c_i c_j}{c_1 N_1 + c_2 N_2} b(\tau) \quad i, j = 1, 2$$

Note that there is correlation between the susceptibility and the infectiousness of an individual, but that, concerning the likeliness of a contact between two individuals, the two types have an independent influence (in the preceding example this was the case at first, but no longer when we introduced  $\kappa < 1$ ).

Exercise i) Show that  $K_0$  has eigenvector  $\begin{pmatrix} c_1 \\ c_2 \end{pmatrix}$  with corresponding eigenvalue  $\lambda$

$$R_0 = \int_0^\infty b(\tau) d\tau \quad \frac{c_1^2 N_1 + c_2^2 N_2}{c_1 N_1 + c_2 N_2}$$

ii) Interpret the second factor in the expression for  $R_0$  as

$$\text{mean} + \frac{\text{variance}}{\text{mean}}$$

of the distribution of  $c$  in the population

iii) Show that also  $K_\lambda$  has eigenvector  $\begin{pmatrix} c_1 \\ c_2 \end{pmatrix}$  P3.6

iv) When  $N_1 \ll N_2$  and  $c_1 \gg c_2$  we might say that type 1 individuals form a core group of super-spreaders. Check that the proportions of the two types are

$N_1 : N_2$  among all individuals

$c_1 N_1 : c_2 N_2$  among the incidence in the initial phase of an outbreak

$c_1^2 N_1 : c_2^2 N_2$  among the infectors during the initial phase

v) Show that

$$\frac{\partial R_0}{\partial c_2} < 0 \quad \text{if} \quad \frac{N_2}{N_1} < \frac{c_1}{c_2} \left( \frac{c_1}{c_2} - 2 \right)$$

The, at first counter intuitive, conclusion is that  $R_0$  may decrease even though a subgroup increases its contact rate. Identify the mechanism underlying this phenomenon.

vi) Show that

$$s_1(t) = e^{-c_1 \int_0^\infty b(\tau) w(t-\tau) d\tau}$$

with

$$w(t) := \frac{c_1 N_1}{c_1 N_1 + c_2 N_2} (1 - s_1(t)) + \frac{c_2 N_2}{c_1 N_1 + c_2 N_2} (1 - s_2(t))$$

Rewrite as a nonlinear RE for the scalar function  $w$  and derive the sort-of-final-size equation

$$w(\omega) = \frac{c_1 N_1}{c_1 N_1 + c_2 N_2} \left( 1 - e^{-c_1 \int_0^\infty b(\tau) d\tau w(\omega)} \right) + \frac{c_2 N_2}{c_1 N_1 + c_2 N_2} \underbrace{\left( 1 - e^{-c_2 \int_0^\infty b(\tau) d\tau w(\omega)} \right)}_{\text{Final size}}$$

vii) Consider three situations

(P3.7)

1.  $c_1 = c = c_2$
2.  $c_1 = c, c_2 = 0$
3.  $c_1 = 0, c_2 = c$

Show that in all three cases

$$R_0 = c \int_0^\infty b(x) dx - R_0 w(\omega)$$

$$w(\omega) = 1 - e^{-\omega}$$

Define the overall final size as  $s(\omega)$  with

$$s(\omega) := \frac{s_1(\omega)N_1 + s_2(\omega)N_2}{N_1 + N_2}$$

$(1 - w(\omega))$

Show that

$$1. s(\omega) = 1 - w(\omega) \quad 2. s(\omega) = \frac{N_1}{N_1 + N_2} (1 - w(\omega)) \quad 3. s(\omega) = \frac{N_2}{N_1 + N_2}$$

Conclude that heterogeneity disrupts the monotone relationship between  $R_0$  and final size. In particular, a small group of superspreaders has a large impact on  $R_0$  but, due to its smallness, not necessarily a large impact on final size.

### General Formalism

trait/type  $x \in \mathcal{S}$  with  $\mathcal{S}$  a measurable space (e.g., a Borel subset of  $\mathbb{R}^n$ ). Note that  $\mathcal{S}$  can be finite (or countable), the formalism captures both discrete and continuous settings).

The population distribution is described by a measure  $\Phi$  on  $\mathcal{S}$ , with  $\Phi(\mathcal{S}) = 1$ .

The population size is  $N$ . The number of individuals with trait in  $\omega \subset \mathcal{S}$  is  $N \Phi(\omega)$ .

Example:  $\mathcal{S}$  consists of two points labelled 1 and 2 and

$$N = N_1 + N_2, \Phi_1 = \frac{N_1}{N_1 + N_2}, \Phi_2 = \frac{N_2}{N_1 + N_2}$$

Example  $\mathcal{S} = (0, \infty)$ ,  $\Phi$  is the Gamma Distribution with mean 1 and parameter  $p$  or, in other "words",  $\Phi$  has density  $x \mapsto \frac{p^p}{\Gamma(p)} x^{p-1} e^{-px}$

Apart from  $N$  and  $\Phi$  we need just one model ingredient:

$A(\tau, x, \xi) =$  the expected contribution to the force of infection on an individual with trait  $x$  of an individual with trait  $\xi$  that became infected  $\tau$  units of time ago

Here  $A: \mathbb{R}_+ \times \mathcal{S} \times \mathcal{S} \rightarrow \mathbb{R}_+$  is measurable, non-negative and integrable over  $\mathbb{R}_+ \times \mathcal{S}$  with respect to  $(\tau, \xi)$ . We represent  $S(t, \omega)$ , the number of susceptible individuals at time  $t$  with trait in  $\omega$ , by

$$S(t, \omega) = N \int_{\omega} s(t, x) \Phi(dx)$$

where  $s(t, x)$  can be interpreted as the probability that an individual with trait  $x$  is susceptible at time  $t$ . We assume that

$$\frac{\partial s}{\partial t}(t, x) = -F(t, x)s(t, x)$$

with  $F$  the force-of-infection given by

$$F(t, x) = \int_0^\infty \int_{\mathcal{S}} A(\tau, x, \xi) \left[ -N \frac{\partial s}{\partial t}(t-\tau, \xi) \right] \Phi(d\xi) d\tau$$

Integrating  $F$  with respect to time over  $(-\infty, t]$  we find

$$s(t, x) = e^{-N \int_0^\infty \int_{\mathcal{S}} A(\tau, x, \xi) [1 - s(t-\tau, \xi)] \Phi(d\xi) d\tau}$$

Putting  $y(t, x) = 1 - s(t, x)$ , assuming that  $y$  is small (in a sense not yet specified), and ignoring higher order terms, we deduce the linearized equation

$$y(t, x) = N \int_0^\infty \int_{\mathcal{S}} A(\tau, x, \xi) y(t-\tau, \xi) \Phi(d\xi) d\tau$$

and next, using  $y(t, x) = e^{-\lambda t} \Psi(x)$  as an Ansatz, the nonlinear eigenvalue problem

$$\Psi = K_\lambda \Psi$$

with  $(K_\lambda \Psi)(x) := \int_{\mathcal{S}} k_\lambda(x, \xi) \Psi(\xi) \Phi(d\xi)$

$$k_\lambda(x, \xi) := N \int_0^\infty A(\tau, x, \xi) e^{-\lambda \tau} d\tau$$

We call  $K_\lambda$  the Next Generation Operator (abbreviated to NGO) and its spectral radius  $R_\lambda$  the Basic Reproduction Number. But on which space do these operators act?

Often  $\mathcal{S}$  is a nice subset of  $\mathbb{R}^n$  and the operators act on  $L_1(\mathcal{S}; \text{Lebesgue measure})$ . But here we describe the population distribution over the trait space by  $\Phi$  and do the disease related bookkeeping in terms of fractions, in particular the fraction  $s(t, x)$  of individuals of trait  $x$  that are susceptible at time  $t$ . Accordingly it makes sense to work with the space

$$\mathcal{Y} = \{ \Psi : \Psi \text{ is a bounded measurable function } \mathcal{S} \rightarrow \mathbb{R} \}$$

with norm

$$\|\Psi\| = \sup_{x \in \mathcal{S}} |\Psi(x)|$$

If  $\sup_{x, \xi \in \mathbb{R}} k_0(x, \xi)$  is bounded,  $K_0$  maps  $\mathcal{Y}$  into  $\mathcal{Y}$ . If

P 3.10

$$\int_{\mathbb{R}} |k_0(x_1, \xi) - k_0(x_2, \xi)| \Phi(d\xi) \rightarrow 0 \text{ when } |x_1 - x_2| \rightarrow 0$$

the range of  $K_0$  consists of continuous functions and we may restrict  $K_0$  to  $C(\mathbb{R})$ . If we strengthen this condition to

$$\forall \varepsilon > 0 \exists \delta > 0 \text{ such that } \int_{\mathbb{R}} |k_0(x_1, \xi) - k_0(x_2, \xi)| \Phi(d\xi) < \varepsilon \text{ whenever } |x_1 - x_2| < \delta$$

we can apply Arzela-Ascoli to deduce that  $K_0$  is compact. This is crucial for applying the Krein-Rutman Theorem, the Banach space version of Perron-Frobenius. Here we do not elaborate these aspects (see E. Franco, O. Diekemann, M. Gyllenberg, Modelling physiologically structured populations: renewal equations and partial differential equations, arXiv: 2201.05323 v1, for a detailed elaboration in a slightly different setting, viz. the space of measures on  $\mathbb{R}$  with  $L_1(\mathbb{R}) \cong$  subspace of absolutely continuous measures). Instead we shall soon focus on separable measures. Instead we shall soon focus on separable measures. In mathematical terms, the case of mixing or, in mathematical terms, the case of one-dimensional range. This will allow us to derive explicit expressions and criteria.

As before, the Malthusian parameter  $r$  is defined

as the unique real root of "spectral radius  $K_\lambda = 1$ ".

The final size equation now reads

$$s(\infty, x) = e^{-[K_0(1-s(\infty, \cdot))](x)}$$

and the theorem of P 3.2 holds, since the proof carries over more or less verbatim, provided  $\mathbb{R}$  is compact

and  $K_0$  is irreducible (for instance in the strong sense that a power of  $K_0$  maps every nontrivial nonnegative function to a strictly positive function). (P 3.11)

Example inspired by

L. Almeida, P-A. Bliman, G. Nadin, B. Perthame, N. Vauchelet  
 Final size and convergence rate for an epidemic in heterogeneous populations, M3AS (2021) 31 : 1021 - 1051

H.R. Thieme, Spectral bound and reproduction number for infinite-dimensional population structure and time heterogeneity, SIAM J. Appl. Math. (2009) 70 : 188 - 211

Let  $\Omega \subset \mathbb{R}^n$  be open, bounded, with smooth boundary. Think of  $\Omega$  as a spatial domain but assume that susceptible individuals do not move. Once infected, however, individuals embark on a random walk as described by individuals change their diffusion. (For rabies it is known that foxes change their behaviour and start wandering when infected. See A.P. Dobson, The population biology of parasite-induced changes in host behavior, Quart. Rev. Biol. (1988) 63 : 139 - 165 for a survey.) As an  $\infty$ -dim compartmental model we may assume

$$\frac{\partial S}{\partial t}(t, x) = -\beta I(t, x)S(t, x)$$

$$\frac{\partial I}{\partial t}(t, x) = \beta I(t, x)S(t, x) - \alpha I(t, x) + (\Delta I)(t, x)$$

with no-flux boundary conditions for  $I$  at  $\partial\Omega$ .

Let  $T(t)$  denote the semigroup on  $L_1(\Omega)$  generated by  $G = -\alpha \text{Id} + \Delta_{b.c.}$ . Note that  $T(t)\delta_\xi$ , with  $\delta_\xi$  the unit Dirac mass concentrated in  $\xi$ , is well-defined even though  $\delta_\xi$  does not belong to  $L_1(\Omega)$ .

Define  $A(\tau, x, \xi) = \beta \left( T(\tau) \delta_\xi \right)(x)$

P3.12

Recall that  $\int_0^\infty T(\tau) d\tau = -G^{-1}$  since for  $\alpha > 0$  the semigroup decays exponentially.

Assume that  $\Phi$  has density  $\phi_0$ .

$$\text{Then } (K_0 \psi)(x) = \beta N \int_{\Omega} (-G^{-1} \delta_\xi)(x) \psi(\xi) \phi_0(\xi) d\xi$$

$$= \beta N (-G^{-1} \psi \phi)(x)$$

Note that  $u = -G^{-1} \psi \phi$  is by definition the solution of  $\Delta u - \alpha u = -\psi \phi$  with no-flux boundary conditions for  $u$  at  $\partial \Omega$

The final size equation is obtained from the equation at the bottom of P3.10 by using this specification of  $K_0$ .

Next week we shall investigate the simplifications that are possible in case of separable mixing

$$A(\tau, x, \xi) = a(x) g(\tau, \xi)$$

In a next step we shall assume

$$g(\tau, \xi) = b(\tau) c(\xi)$$

$\Omega = (0, \infty)$ , and  $a(\xi) = \xi$ ,  $\Phi$  is a Gamma Distribution, in order to study the Herd Immunity Threshold (HIT)