

# Mathematical Epidemiology of Infectious Diseases

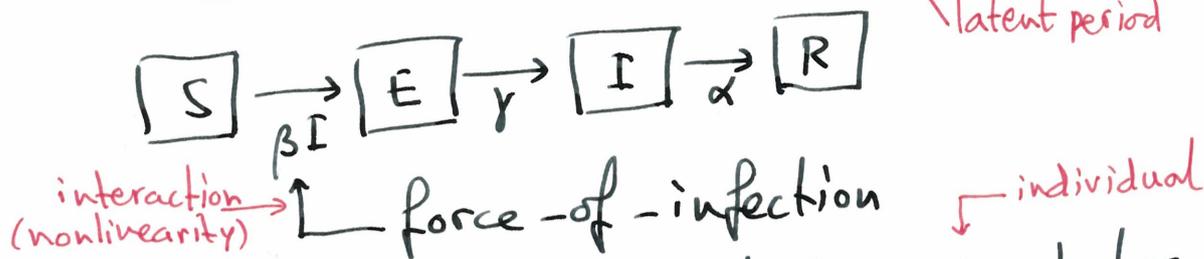
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## 1. Kermack-McKendrick 1927

Epidemic Outbreak:

no demographic turnover of host  
no loss of immunity

### 1.1 SEIR (susceptible, exposed, infectious, removed)



Markov: sojourn times are exponentially distributed

expected time in E:  $\frac{1}{\gamma}$

expected time in I:  $\frac{1}{\alpha}$

Note: stochastic at i-level, deterministic at p-level

$$\dot{S} = -\beta IS$$

$$\dot{E} = \beta IS - \gamma E$$

$$\dot{I} = \gamma E - \alpha I$$

$$\dot{R} = \alpha I$$

Disease free  
steady states

$$(N, 0, 0)$$

with

$N$  arbitrary

# Linearization

$$x = \begin{pmatrix} E \\ I \end{pmatrix} \quad \frac{dx}{dt} = Mx \quad M = \begin{pmatrix} -\gamma & \beta N \\ \gamma & -\alpha \end{pmatrix}$$

Side-remark:  $M$  is POD (positive-off-diagonal) also known as "Metzler" which is equivalent to  $e^{tM} \geq 0$

Decomposition:  $M = \overset{\substack{\uparrow \\ \text{transmission}}}{T} + \overset{\substack{\uparrow \\ \text{transition}}}{\Sigma}$

$$T = \begin{pmatrix} 0 & \beta N \\ 0 & 0 \end{pmatrix} \quad \Sigma = \begin{pmatrix} -\gamma & 0 \\ \gamma & -\alpha \end{pmatrix}$$

$$\int_0^\infty e^{\tau \Sigma} d\tau = -\Sigma^{-1} = \begin{pmatrix} \frac{1}{\gamma} & 0 \\ \frac{1}{\alpha} & \frac{1}{\alpha} \end{pmatrix}$$

Interpretation:  $(-\Sigma^{-1})_{ij}$  = expected future time spend in state  $i$  when presently in state  $j$

## NGM Next Generation Matrix

$$-T \Sigma^{-1} = \begin{pmatrix} \frac{\beta N}{\alpha} & \frac{\beta N}{\alpha} \\ 0 & 0 \end{pmatrix}$$

element  $ij$  gives the expected number of future cases with  $i$ -state "at birth"  $i$  caused by an individual presently in state  $j$

The NGM is a positive matrix (meaning that all entries are non-negative).

Basic Reproduction Number denoted by

$$R_0$$

is the spectral radius of the NGM which, by Perron-Frobenius theory, is the dominant eigenvalue (meaning that  $|\lambda| \leq R_0$  for all  $\lambda \in \sigma(\text{NGM})$ ) and has a corresponding positive eigenvector.

Interpretation:  $R_0$  is the expected number of secondary cases per primary case

Now note that in the present situation the range of  $T$  is spanned by  $\begin{pmatrix} 1 \\ 0 \end{pmatrix}$ . It follows that the NGM has only one non-zero eigenvalue, given by

$$R_0 = \frac{\beta N}{\alpha}$$

(as one can more directly derive from the interpretation).

First conclusion: Ignoring that the susceptible population decreases due to the infection ( $\approx$  linearization) and adopting a generation perspective, we find that the pathogen prevalence increases when  $R_0 = \frac{\beta N}{\alpha} > 1$  and decreases when  $R_0 = \frac{\beta N}{\alpha} < 1$ . We say that  $R_0$  has threshold value one.

The linearized dynamics in real time is governed by the eigenvalues of  $M$ . Now note that

$$Mx = \lambda x \iff -T(\Sigma - \lambda I)^{-1}y = y$$
$$\uparrow$$
$$x = (\Sigma - \lambda I)^{-1}y$$

Using once more that the range of  $T$  is spanned by (i) we obtain the characteristic equation

$$\frac{r\beta N}{(\alpha + \lambda)(\gamma + \lambda)} = 1$$

As a function of real  $\lambda$ , the left hand side is monotone decreasing and equal to  $R_0 = \frac{\beta N}{\alpha}$  for  $\lambda = 0$ . The Malthusian parameter  $r$  is the largest real root and is given explicitly by

$$r = \frac{-(\alpha + \gamma) + \sqrt{(\alpha - \gamma)^2 + 4\gamma\beta N}}{2}$$

By the observation above we find

$$\text{sign}(R_0 - 1) = \text{sign } r$$

and conclude that there is consistency: pathogen prevalence increases in real time iff it increases on a generation basis. Note, however, that  $R_0$  does not depend on  $\gamma$  while (as an easy calculation shows)  $r$  increases with  $\gamma$ . Readers are encouraged to pinpoint the reason! (We shall get back to this later, in more generality.)

Conclusion of the analysis of the linearized equations: if a pathogen is introduced into a "virgin" host population, its prevalence will initially grow exponentially at rate  $r > 0$  when  $R_0 > 1$

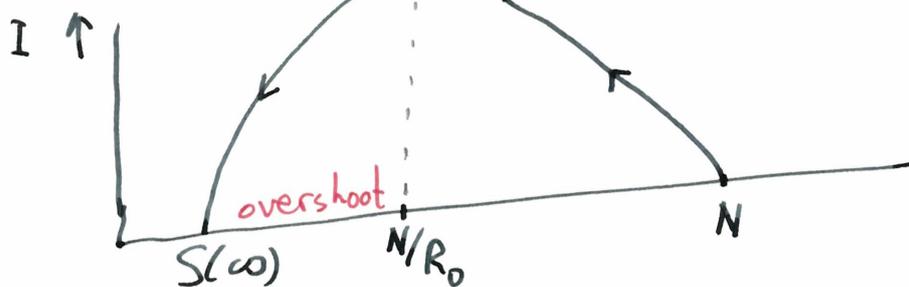
Question: what happens next?

By formally taking the limit  $\gamma \rightarrow \infty$  we simplify SEIR to SIR

1.5

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \alpha I = (\beta S - \alpha) I$$



Cumulative force of infection

$$w(t) = \beta \int_{-\infty}^t I(\tau) d\tau \rightarrow S$$

$\Rightarrow$

$$S(t) = N e^{-w(t)}$$

Also

$$\frac{d}{dt} [S + I] = -\alpha I = -\frac{\alpha}{\beta} \frac{dw}{dt} \Rightarrow S + I + \frac{\alpha}{\beta} w = \text{constant} = N$$

$$\Rightarrow \frac{dw}{dt} = \beta I = \beta (N - S - \frac{\alpha}{\beta} w) = \beta N (1 - e^{-w}) - \alpha w$$

$$w(-\infty) = 0 \quad \beta N (1 - e^{-w(\infty)}) = \alpha w(\infty)$$

Exercise Show that the SEIR system can be reduced to

$$\frac{dw}{dt} = \beta I$$

$$\frac{dI}{dt} = \gamma N (1 - e^{-w}) - (\alpha + \gamma) I - \frac{\alpha \gamma}{\beta} w$$

and that the equation for  $w(\infty)$  is exactly the same as for the SIR system

## 1.2 The Renewal Equation

1.6

It is a persistent misconception that the celebrated 1927 paper by Kermack & McKendrick is about compartmental models (everybody quotes the paper, nobody reads the paper...). Their far more general model takes the form of a Renewal Equation (RE).

$$\dot{S}(t) = - \underbrace{F(t)}_{\text{force-of-infection (f-o-i)}} S(t) \Rightarrow S(t) = N e^{-w(t)}$$

$$\text{with } w(t) = \int_{-\infty}^t F(\tau) d\tau$$

incidence = number of new cases per unit of time

constitutive equation:

$$F(t) = \int_0^{\infty} \underbrace{A(\tau)}_{\geq 0} [-\dot{S}(t-\tau)] d\tau$$

one-and-only model ingredient: expected contribution to the f-o-i time  $\tau$  after becoming infected (integrable by assumption)

$$\begin{aligned} \Rightarrow w(t) &= \int_{-\infty}^t F(\sigma) d\sigma = \int_{-\infty}^t \int_0^{\infty} A(\tau) [-\dot{S}(\sigma-\tau)] d\tau d\sigma \\ &= \int_0^{\infty} A(\tau) [N - S(t-\tau)] d\tau \end{aligned}$$

Eliminating  $S$  we obtain

$$w(t) = N \int_0^{\infty} A(\tau) [1 - e^{-w(t-\tau)}] d\tau$$

Equivalently, with

$$s(t) = \frac{S(t)}{N}$$

$$s(t) = e^{-N \int_0^{\infty} A(\tau) [1 - s(t-\tau)] d\tau}$$

To describe the initial phase, we put  $y(t) = 1 - s(t)$ , assume that  $y$  is very small, Taylor expand and ignore h.o.t. (higher order terms). This leads to the linear RE

$$y(t) = N \int_0^{\infty} A(\tau) y(t-\tau) d\tau$$

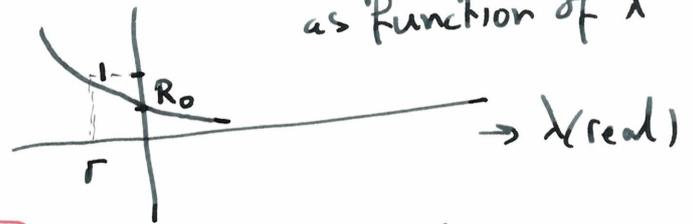
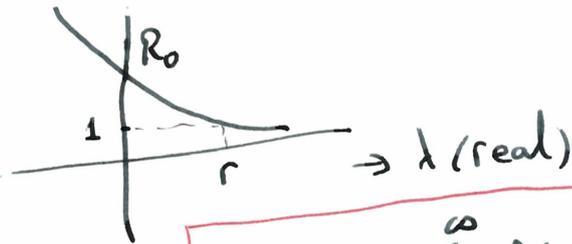
Whenever an equation is linear and translation invariant (note that at the rhs (right hand side) the variable  $t$  only occurs as an argument of  $y$ ), try exponential functions as solution. The Ansatz

$$y(t) = e^{\lambda t}$$

leads to the Euler-Lotka equation

$$1 = N \int_0^{\infty} A(\tau) e^{-\lambda \tau} d\tau$$

graphs of rhs as function of  $\lambda$



Define  $R_0 = N \int_0^{\infty} A(\tau) d\tau$  and define the

Malthusian parameter  $r$  as the unique real root of the Euler-Lotka equation, then

$$\text{sign}(R_0 - 1) = \text{sign } r$$

### 1.3 The final size equation

1.8

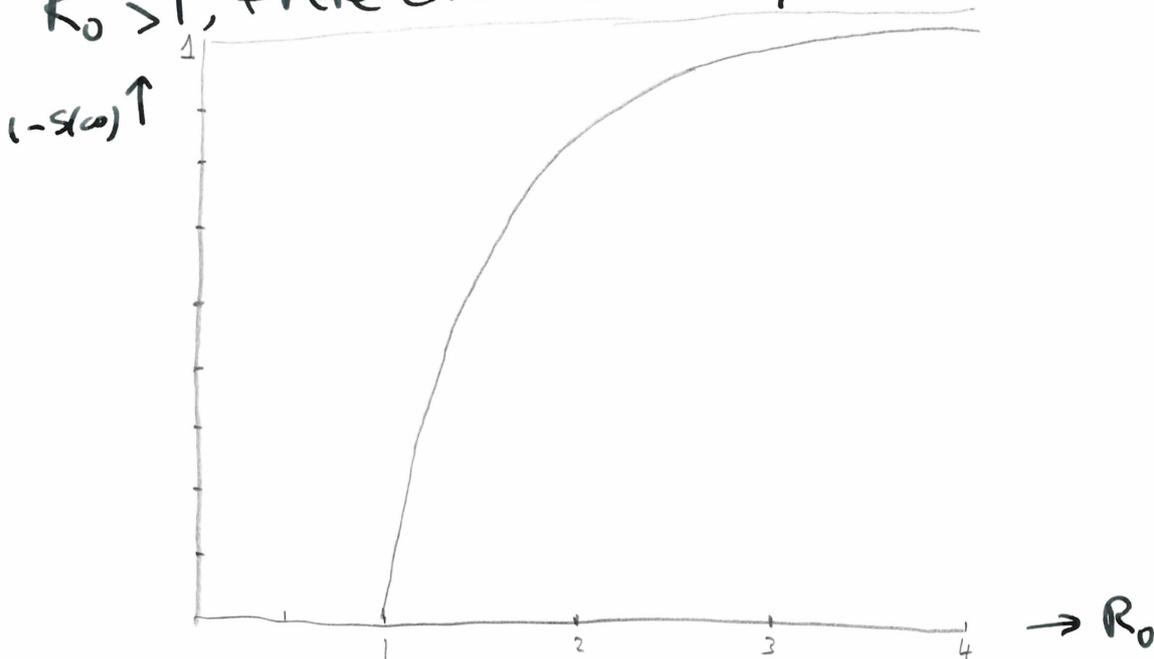
At the end of the outbreak, a fraction  $1 - s(\infty)$  has become infected. Together they generate a total  $f-o-i$

$$(1 - s(\infty)) N \int_0^{\infty} A(t) dt = (1 - s(\infty)) R_0$$

The remaining susceptible fraction  $s(\infty)$  escaped infection. So we can interpret  $s(\infty)$  as the probability to escape. This leads to the consistency condition

$$s(\infty) = e^{-R_0(1 - s(\infty))}$$

which is called the final size equation. If we take the limit  $t \rightarrow \infty$  in the nonlinear RE for  $s(t)$  and use that  $A$  is integrable, we obtain exactly this equation. A simple graphical argument shows that, provided  $R_0 > 1$ , there exists exactly one solution  $s(\infty) \in (0, 1)$ .



Properties:  $s(\infty) < \frac{1}{R_0}$

$\frac{\partial s(\infty)}{\partial R_0} < 0$  {so if we increase  $N$ , the fraction that escapes becomes smaller (due to overshoot)}

$$s(\infty) \sim e^{-R_0} \text{ for } R_0 \rightarrow \infty$$

## 1.4 The relationship between $r$ and $R_0$

1.9

When a new disease emerges, one can (try to) estimate  $r$  from data. A first reason to be interested in  $R_0$ , is that the final size is completely determined by this compound parameter. A second reason is that many control measures, especially those reducing contacts, have a multiplicative effect on  $R_0$  (and consequently the control aim is usually formulated as bringing the value of  $R_0$  to below one). So it is of interest to derive an estimate ~~from~~ of  $R_0$  from an estimate of  $r$ . But to do so, information about how  $A$  depends on  $\tau$  is crucial, as we now demonstrate by way of an example. For SEIR we have

$$R_0 = \frac{r^2}{\alpha\gamma} + \left(1 + \frac{\gamma}{\alpha}\right) \frac{r}{\gamma} + 1$$

If instead we consider the situation in which every individual has a latent period of exactly  $\frac{1}{\gamma}$  and an infectious period of exactly  $\frac{1}{\alpha}$  units of time, so a function



then some straightforward computations yield

$$R_0 = \frac{r}{\alpha} \frac{e^{r/\gamma}}{1 - e^{-r/\alpha}}$$

For more about this issue, search the literature with key words "generation-interval", "serial-interval"

## 1.5 Time discretization

1.10

see O. Diekmann, H.G. Othmer, R. Planqué, M.C.J. Bootsma  
The discrete-time Kermack-McKendrick model: A versatile and computationally attractive framework for modeling epidemics (2021) PNAS 118 (39) e2106332118

Time step corresponds to interval between data points (one day, one week, ...)

Think "multiplicative" (reduction by a factor) and not "additive" (subtraction, like in forward Euler):

$$S(t+1) = S(t) e^{-\hat{F}(t)}$$

$$\hat{F}(t) = \sum_{j=1}^{\infty} A_j [S(t-j) - S(t+1-j)]$$

$$\Rightarrow s(t+1) = e^{-N \sum_{k=1}^{\infty} (1 - s(t-k+1)) A_k} \text{ incidence}$$
$$= s(t) e^{-N \sum_{k=1}^{\infty} (s(t-k) - s(t-k+1)) A_k}$$

initial condition:  $s(0)$  & history of incidence

Linearization:  $y(t+1) = N \sum_{k=1}^{\infty} A_k y(t+1-k)$

$$R_0 = N \sum_{k=1}^{\infty} A_k \quad \text{Euler-Lotka} \quad 1 = N \sum_{k=1}^{\infty} \lambda^{-k} A_k$$

unique real root  $\rho$  and  $\text{sign}(\rho - 1) = \text{sign}(R_0 - 1)$

Final size equation:  $s(\infty) = e^{-R_0(1-s(\infty))}$   
exactly as before

## 1.6 Peak size and timing

How much does the precise form of  $A(t)$  matter? As we saw, it does not matter at all for the final size  $1 - s(\infty)$ , only the summary statistic  $R_0$  matters in this context.

In contrast, when we want to "translate" information about  $r$  into information about  $R_0$ , it matters a lot.

To determine the influence on the timing and the size of the prevalence peak (by way of an example), a comparison was made between the discrete version

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

$$E(t+1) = (1 - e^{-\beta I(t)}) S(t) + (1 - \gamma) E(t)$$

$$I(t+1) = \gamma E(t) + (1 - \alpha) I(t)$$

of the SEIR model and the discrete version of A on page 1.9, with every individual having a latent period of exactly length  $T_E$  and an infectious period of exactly length  $T_I$ . To calibrate the two models we specified  $T_E$ ,  $T_I$  and  $R_0$  (via the multiplicative parameter  $\beta N$ ) and next computed  $\rho$  from the Euler-Lotka equation. For the SEIR version we chose  $\gamma = \frac{1}{T_I}$  and next made sure that the dominant eigenvalue of  $\begin{pmatrix} 1 - \gamma & \beta N \\ \gamma & 1 - \alpha \end{pmatrix}$  is equal to  $\rho$  by the choice

$$\alpha = \frac{(\rho - 1)(\rho - 1 + \gamma)}{\gamma(R_0 - 1) + 1 - \rho}$$

With the choice  $\beta N = \alpha R_0$  we then achieved 1.12  
that the two variants have the same  $R_0$ ,  $\rho$   
and expected length of the latent period.

Numerical computations show (see paper for details):

For fixed periods, the peak is 8-15% higher  
and comes a couple of days earlier  
(the difference is largest when  $T_E$  is large and  
 $T_I$  is small)

Informal "explanation": roughly speaking, the out-  
break reaches its peak when  $S$  is reduced to the  
level corresponding to  $R_0 = 1$ . How many more cases  
occur from then onwards, depends on how many  
already infected individuals there are at this  
instant. For compartmental models, the distribution  
of time until going to "removed" has a <sup>(relatively)</sup> fat tail.  
But when  $R_0$  is the same, so is the final size.  
Hence the "reservoir" size must be smaller for  
compartmental models. And reservoir size correlates  
with peak size.

1.7

## Conclusion

The precise form of  $A(\tau)$  does matter!  
So why do so many modellers choose to work with  
compartmental models? Possible reasons:

- habit, imitation (everybody does)
- RE are unfamiliar (unusual type of delay equ.)
- K-McK 1927 is systematically misquoted
- for RE there are no user friendly tools available

Wishful thinking: the discrete version of Section 1.5  
solves the last problem

## 1.8 Reflection

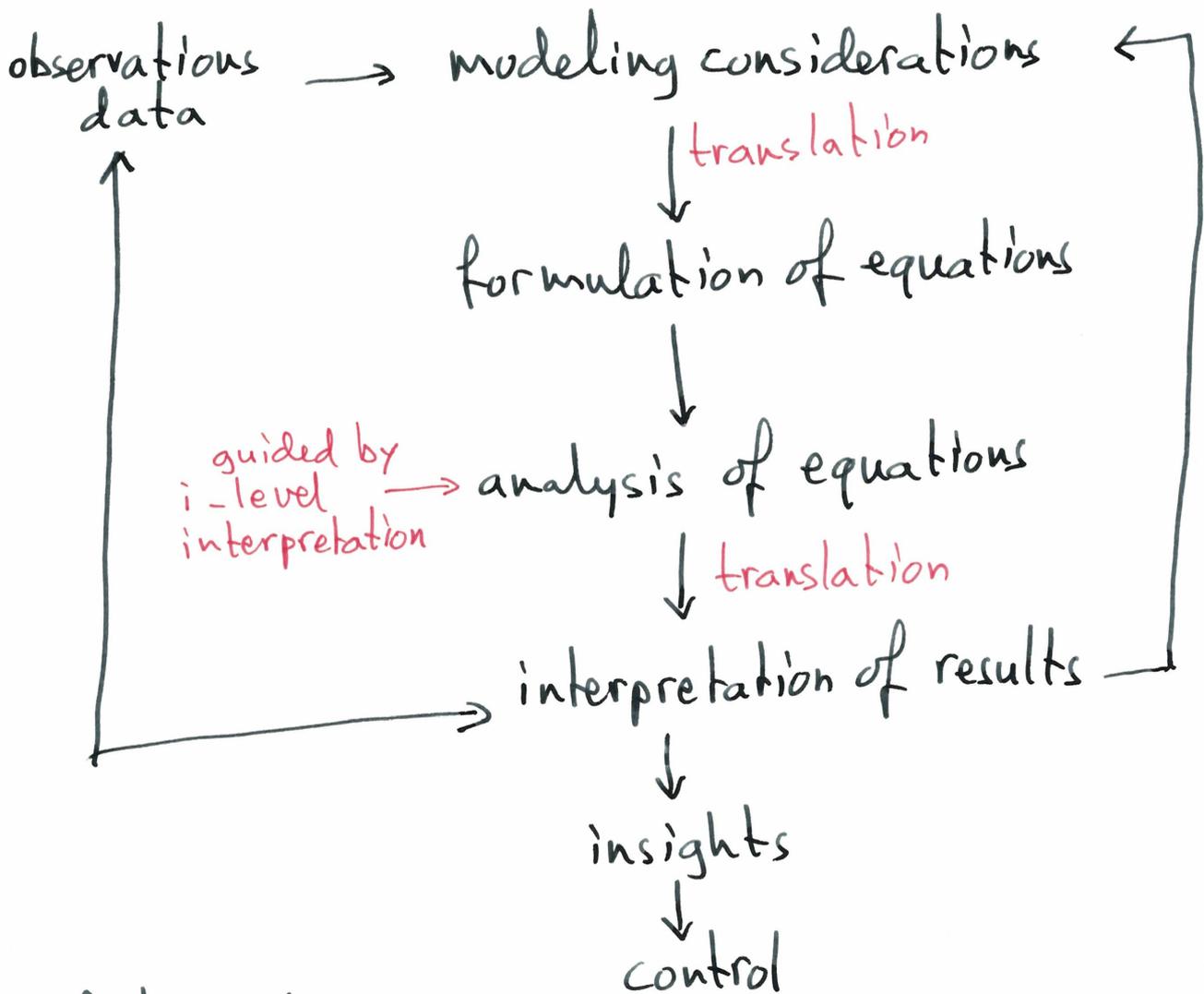
1.13

In the presentation above we ignored

demographic stochasticity

in particular

- i) extinction despite growth potential
- ii) final size in a finite population described by a probability distribution
- iii) large host population limit (law of large numbers, central limit thm.)



For infectious diseases, also statistical analysis of data requires a model to capture the dependence arising from transmission.

It seems that Picasso once said: Art is the lie that helps us to discover the truth. In our context "Art" should be replaced by "A model"