1. compartmental models & RE (one state-at-birth)

$$A(\tau) = U e^{\tau \Sigma} V$$

2. RE & dyn. syst. : A delay equ. is a rule for extending a function of time towards the future on the basis of the (assumed to be) known history.

3. Demographic stochasticity
   i) prob. minor outbreak (branching process)
   ii) distribution of final size

4. Heterogeneity ← next week

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1. $\frac{dS}{dt} = -\underbrace{FS}_{\text{incidence}}$ $\qquad F(t) = \int_0^\infty A(\tau)\, \text{incidence}(t-\tau)\, d\tau$

common

SEIR : $F = \beta I = Ux \qquad U = (0 \;\; \beta) \qquad x = \begin{pmatrix} E \\ I \end{pmatrix}$ ← state at "birth"

$$\frac{dx}{dt} = \Sigma x + FSV \qquad V = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

$$x(t) = \int_{-\infty}^{t} F(\sigma) S(\sigma)\, e^{(t-\sigma)\Sigma} V\, d\sigma = \int_0^\infty F(t-\tau) S(t-\tau)\, e^{\tau\Sigma} V\, d\tau$$

$$\Rightarrow \quad F(t) = Ux(t) = \int_0^\infty \text{incidence}(t-\tau)\, \underbrace{U e^{\tau\Sigma} V}_{A(\tau)}\, d\tau$$

Reference : O. Diekmann, M. Gyllenberg, J. A. J. Metz
Finite dimensional state representation of linear and nonlinear delay systems,
J. Dyn. Diff. Equ. (2018) 30 : 1439 – 1467

Please note:

$$R_0 = N \int_0^\infty A(\tau)\, d\tau = N U (-\Sigma^{-1}) V$$

Euler-Lotka $\quad 1 = N \int_0^\infty A(\tau) e^{-\lambda\tau}\, d\tau = N U (-(\Sigma - \lambda I)^{-1}) V$

and this condition is equivalent to $My = \lambda y$ with $M = \Sigma + T$ and T defined by $Tx = N(Ux)V$

Another example: asymptomatic (index 1) and symptomatic (index 2) infectious ind.

$$\frac{dS}{dt} = -\beta_1 I_1 S - \beta_2 I_2 S$$

$$\frac{dE}{dt} = \beta_1 I_1 S + \beta_2 I_2 S - \gamma E \quad \leftarrow \text{state-at-birth}$$

$$\frac{dI_1}{dt} = \gamma E - \eta I_1 - \alpha_1 I_1$$

$$\frac{dI_2}{dt} = \eta I_1 - \alpha_2 I_2$$

$$\frac{dS}{dt} = -FS \qquad x = \begin{pmatrix} E \\ I_1 \\ I_2 \end{pmatrix} \quad V = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$$

$$\frac{dx}{dt} = \Sigma x + FSV$$

$$U = (0 \ \beta_1 \ \beta_2)$$

$$F = Ux$$

$$A(\tau) = U e^{\tau \Sigma} V$$

<u>Exercise</u> Use the interpretation to show that

$$-\Sigma^{-1} = \begin{pmatrix} \frac{1}{\gamma} & 0 & 0 \\ \frac{1}{\eta+\alpha_1} & \frac{1}{\eta+\alpha_1} & 0 \\ \frac{\eta}{\eta+\alpha_1}\frac{1}{\alpha_2} & \frac{\eta}{\eta+\alpha_1}\frac{1}{\alpha_2} & \frac{1}{\alpha_2} \end{pmatrix}$$

Hint: an asymptomatic individual becomes symptomatic at rate η and is removed at rate α_1. It follows that the individual becomes symptomatic with probability $\frac{\eta}{\eta+\alpha_1}$ and removed with probability $\frac{\alpha_1}{\eta+\alpha_1}$ (please check). This idea is an important component of the Gillespie algorithm for simulation.

<u>Exercise</u> Derive $R_0 = \frac{\beta_1 N}{\eta+\alpha_1} + \frac{\eta}{\eta+\alpha_1}\frac{\beta_2 N}{\alpha_2}$

in two ways: i) by elaborating $R_0 = N\,U(-\Sigma^{-1})V$
ii) directly from the interpretation

An alternative $M = \Sigma + T$ decomposition and the related notion of type-reproduction number

Literature: J.A.P. Heesterbeek, M.G. Roberts
The type-reproduction number T in models for infectious disease control,
Math. Biosc. (2007) 206 : 3–10

H. Inaba, H. Nishiura, The state-reproduction number for a multistate class age structured epidemic system and its application to the asymptomatic transmission model, Math. Biosc. (2008) 216 : 77–89

J.M. Cushing, O. Diekmann, The many guises of R_0 (a didactic note), J. Theor. Biol. (2016) 404 : 295–302

In order to facilitate the computations, we formally take the limit $\gamma \to \infty$ and consider

$$\frac{dS}{dt} = -\beta_1 I_1 S - \beta_2 I_2 S$$

$$\frac{dI_1}{dt} = \beta_1 I_1 S + \beta_2 I_2 S - \eta I_1 - \alpha_1 I_1$$

$$\frac{dI_2}{dt} = \eta I_1 - \alpha_2 I_2$$

In terms of $x = \begin{pmatrix} I_1 \\ I_2 \end{pmatrix}$ the linearization $\frac{dx}{dt} = Mx$ at the steady state $(N,0,0)$ has

$$M = \begin{pmatrix} \beta_1 N - \eta - \alpha_1 & \beta_2 N \\ \eta & -\alpha_2 \end{pmatrix}$$

The transmission-transition decomposition is

$$M = T + \Sigma \text{ with } T = \begin{pmatrix} \beta_1 N & \beta_2 N \\ 0 & 0 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} -\eta-\alpha_1 & 0 \\ \eta & -\alpha_2 \end{pmatrix}$$

It leads to the NGM

$$-T\Sigma^{-1} = \begin{pmatrix} \frac{\beta_1 N}{\eta+\alpha_1} + \frac{\eta}{\eta+\alpha_1}\frac{\beta_2 N}{\alpha_2} & \frac{\beta_2 N}{\alpha_2} \\ 0 & 0 \end{pmatrix}$$

(and thus to) ~~with~~ $R_0 = \frac{\beta_1 N}{\eta+\alpha_1} + \frac{\eta}{\eta+\alpha_1}\frac{\beta_2 N}{\alpha_2}$

as already found above. This reproduction number counts the (expected) number of secondary asymptomatic cases produced per primary asymptomatic case.

Now note that we can only observe symptomatic cases. This leads to the question: can one define a reproduction number that counts the expected number of secondary <u>symptomatic</u> cases produced per primary <u>symptomatic</u> case? And thus to the decomposition

$$M = T + \Sigma \text{ with } T = \begin{pmatrix} 0 & 0 \\ \eta & 0 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} \beta_1 N-\eta-\alpha_1 & \beta_2 N \\ 0 & -\alpha_2 \end{pmatrix}$$

The assumption

$$\frac{\beta_1 N}{\eta+\alpha_1} < 1 \iff \beta_1 N - \eta - \alpha_1 < 0$$

guarantees that $\tau \mapsto e^{\tau\Sigma}$ is integrable. If it would not be satisfied, an asymptomatic individual produces, on average, already more than one additional asymptomatic individual before turning symptomatic or being removed. These in turn ... leading to an avalanche.

For this decomposition we find

$$-T\Sigma^{-1} = \frac{1}{\alpha_2(\eta+\alpha_1-\beta_1 N)}\begin{pmatrix} 0 & 0 \\ \alpha_2\eta & \beta_2 N\eta \end{pmatrix}$$

The range is now spanned by $\begin{pmatrix} 0 \\ 1 \end{pmatrix}$

and the dominant eigenvalue is $\tilde{R}_0 = \frac{\beta_2 N\eta}{\alpha_2(\eta+\alpha_1-\beta_1 N)}$

If control efforts focus on symptomatic individuals, they may reduce β_2 or increase α_2. This leads to a multiplicative reduction of $\tilde{R}_0$ (i.e., multiplication of $\tilde{R}_0$ by a positive number smaller than one). Hence $\tilde{R}_0$ is a good indicator for the effects of this type of control. The key idea of the type reproduction number of Heesterbeek & Roberts is to let the intended control inspire the decomposition of M into Σ and T, while making sure that the eigenvalues of Σ lie in the left half of the complex plane to guarantee the integrability of $\tau \mapsto e^{\tau\Sigma}$.

Important observation: even though in general $R_0 \neq \tilde{R}_0$, it holds that $\operatorname{sign}(R_0 - 1) = \operatorname{sign}(\tilde{R}_0 - 1)$, since both are equal to $\operatorname{sign} r$ with r the Malthusian parameter, i.e., the right-most eigenvalue of M.

Side remark: The following is a more direct derivation of the expression for $\tilde{R}_0$. Consider a new symptomatic case. It is expected to produce $\frac{\beta_2 N}{\alpha_2}$ new asymptomatic cases. Each of these can produce additional asymptomatic cases before becoming symptomatic. Let E be the expected number of (asymptomatic) individuals becoming symptomatic among a focus individual and the additional asymptomatic individuals that it produces directly and indirectly, with reproduction limited to the asymptomatic period. Then, by first step analysis and the Markov property

$$E = \frac{\eta}{\eta+\alpha_1+\beta_1 N} 1 + \frac{\alpha_1}{\eta+\alpha_1+\beta_1 N} 0 + \frac{\beta_1 N}{\eta+\alpha_1+\beta_1 N} 2E$$

$$\Rightarrow E = \frac{\eta}{\eta+\alpha_1-\beta_1 N} \text{ and } \tilde{R}_0 = \frac{\beta_2 N}{\alpha_2} E$$

<u>Exercise</u> The compartmental system

$$\dot{S} = -\beta S I$$
$$\dot{E}_1 = p\beta S I - \gamma_1 E_1$$
$$\dot{E}_2 = (1-p)\beta S I - \gamma_2 E_2$$
$$\dot{I} = -\alpha I + \gamma_1 E_1 + \gamma_2 E_2$$

describes a situation in which two types of individuals occur with distribution $p : 1-p$, characterized by a different exponential distribution of the length of the latent period.

Specify U, V, Σ and compute $A(\tau) = U e^{\tau \Sigma} V$

<u>Hint</u>: interpret "one state-at-birth" in the stochastic sense of being described by one probability distribution.

Show that $R_0 = N \int_0^\infty A(\tau)\,d\tau = \frac{\beta N}{\alpha}$ (hence R_0 does <u>not</u> depend on γ_1, γ_2 and p).

Show that the Malthusian parameter r does depend on γ_1, γ_2 and p.

Show that

$$A(\tau) = p\, A_1(\tau) + (1-p) A_2(\tau)$$

and interpret this expression in terms of an expectation.

<u>Remark</u> We can view $A(\tau)$ as the expected output of infectious material at time τ after the input event of becoming infected. A compartmental model then corresponds to a state-representation of the input-output map. But, unfortunately, within-host dynamics is far more complicated than what is captured by these phenomenological compartmental descriptions

Renewal Equations

1. linear : resolvent & Laplace transform
2. sun-star & twin
3. pseudo-spectral approximation $\Rightarrow$ ODE

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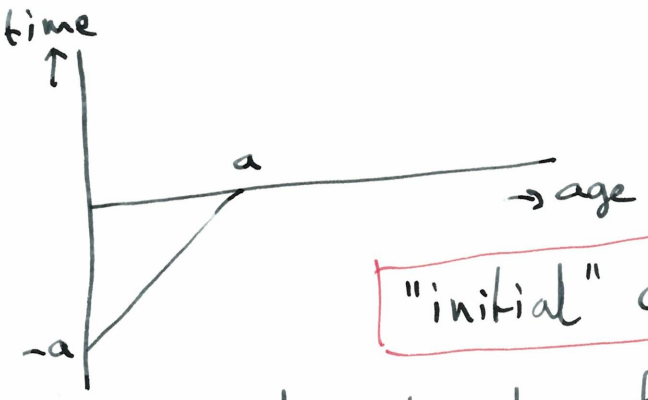
age-structured population dynamics A.J. Lotka (1880-1949)

$$b(t) = \int_0^\infty b(t-a)\,k(a)\,da$$

with $k(a) = \beta(a)\,\mathcal{F}(a)$ where β describes the fertility as a function of age and $\mathcal{F}(a)$ is the probability of surviving till at least age a (here we focus on mothers and daughters, assuming a 1:1 sex ratio)

$$R_0 = \int_0^\infty k(a)\,da \qquad \text{Euler Lotka } 1 = \int_0^\infty e^{-\lambda a} k(a)\,da$$

real root r = Malthusian parameter
= intrinsic rate of natural increase



age distribution has density

$$n(t,a) = b(t-a)\,\mathcal{F}(a)$$

$\boxed{\text{"initial" condition}}$: $b(\theta) = \phi(\theta)$, $\theta \le 0$

$\Rightarrow$ $b = k * b + f$ with

$$f(t) := \int_t^\infty \phi(t-a)\,k(a)\,da = \int_0^\infty \phi(-\sigma)\,k(t+\sigma)\,d\sigma$$

$\boxed{\text{generation expansion}}$ / successive approximation

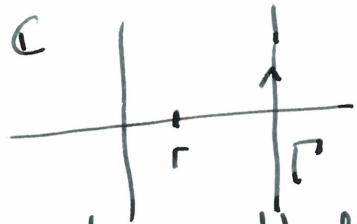
$$b = f + k*b = f + k*f + k^{2*}*f + \cdots$$

$$\Rightarrow \boxed{b = f + \rho * f} \quad \text{with} \quad \rho := \sum_{j=1}^{\infty} k^{j*} \text{ the } \boxed{\text{resolvent}}$$

An alternative representation of the solution is based on the Laplace transform:

$$b = k*b + f \Rightarrow \bar{b} = \bar{k}\bar{b} + \bar{f} \Rightarrow \bar{b} = (1-\bar{k})^{-1}\bar{f}$$

$$\Rightarrow b(t) = \frac{1}{2\pi i}\int_{\Gamma} e^{zt}\,(1-\bar{k}(z))^{-1}\,\bar{f}(z)\,dz$$



$$\Rightarrow \boxed{b(t) = C(\phi)\,e^{rt} + o(e^{rt})} \quad t \to \infty$$

For entropy methods, see B. Perthame, Transport Equations in Biology, Springer, 2007

W. Feller, On the integral equation of renewal theory Ann. Math. Statist. (1941) 12(3): 243–267

Also see Chapter XI of Vol. 2 of ~~his~~ Feller's book.

G. Gripenberg, S-O Londen, O. Staffans, Volterra Integral and Functional Equations, CUP, 1990

The epidemic model leads to the nonlinear equation

$$F(t) = N\int_0^{\infty} A(\tau)\,F(t-\tau)\,e^{-\int_{-\infty}^{t-\tau} F(\sigma)\,d\sigma}\,d\tau$$

for the f-o-i F. The dynamical systems perspective works as follows:

i) assign an "initial" condition $F(\theta) = \phi(\theta)$, $\theta \le 0$

ii) solve the equation to define $F(t)$ for $t \geq 0$ P2.9

iii) translate along the extended function, i.e., update the history to

$$F_t(\theta) := F(t+\theta) \quad , \theta \leq 0$$

So the state-space consists of functions of θ while ~~and~~ t denotes the time at which we consider the state.

<u>Exercise</u> Define $S(t)\phi = F_t$. Check that formally $S(0) = I$ and ~~that~~ $S(t+s) = S(t)S(s)$, $t,s \geq 0$

<u>Hint</u> Use that in ii) above the <u>unique</u> solution is constructed and that we can write the equation as

$$F(t) = N\int_0^\infty A(\tau) F_t(-\tau) e^{-\int_\tau^\infty F_t(-\eta)d\eta} d\tau$$

to make the <u>translation invariance</u> explicit.

<u>Questions</u> What space of functions of θ do we choose as state space? Can we prove the principle of linearized stability? Can we construct stable- unstable- and center manifolds? Can we prove the Hopf bifurcation theorem?

Both b and F are rates. They yield numbers (respectively, subpopulation sizes and probabilities) upon integration. So it is natural to work with L_1. Here we restrict to the case of <u>finite delay</u>, see O. Diekmann, M. Gyllenberg, Equations with infinite delay: Blending the abstract and the concrete, J. Diff. Equa. (2012) 252: 819-851 for the technically more demanding case of infinite delay.

A very good thing about L_1 is that translation is continuous, which makes the semigroup of operators defined by translation along a constructed solution strongly continuous. A very bad thing about L_1 is that point evaluation (in particular in the right end point of the interval, where the rule for extension provides the value) is not well-defined.
See for an extensive discussion

O. Diekmann, S.M. Verduyn Lunel, Twin semigroups and delay equations, J. Diff. Equa. (2021) 286: 332–410

O. Diekmann, Ph. Getto, M. Gyllenberg, Stability and bifurcation analysis of Volterra functional equations in the light of suns and stars, SIAM J. Math. Anal. (2007) 39: 1023–1069

Conclusion: by using duality and a Gelfand-Pettis type of integral, the standard local stability and bifurcation results can be established.
Remark: for an alternative approach based on integrated semigroups, see

P. Magal, S. Ruan, Theory and Applications of Abstract Semilinear Cauchy Problems, Springer, 2018

But how about numerical bifurcation tools?
See O. Diekmann, F. Scarabel, R. Vermiglio, Numerical bifurcation analysis of renewal equations via pseudospectral approximation, J. Comp. Appl. Math. (2021) 397: 113611

F. Scarabel, D. Breda, O. Diekmann, M. Gyllenberg, R. Vermiglio Numerical bifurcation analysis of physiologically structured population models via pseudospectral approximation, Vietnam J. Math. (2021) 49: 37–67

Demographic Stochasticity

O. Diekmann, J.A.P. Heesterbeek, T. Britton
Mathematical Tools for Understanding Infectious Disease Dynamics, PUP, 2013

- probability of a minor outbreak: Sections 1.2.2 & 3.3
- final size distribution: Sections 1.3.4 & 3.5.2, see in particular Fig. 3.7, p. 68 & figure below

T. Britton, E. Pardoux (eds.)
Stochastic Epidemic Models with Inference
Springer, LNM vol. 2255, 2019