Including Demographic Turnover

Recall the SIR equations from P1.5. The modification

$$\frac{dS}{dt} = -\beta S I + B - \mu S$$

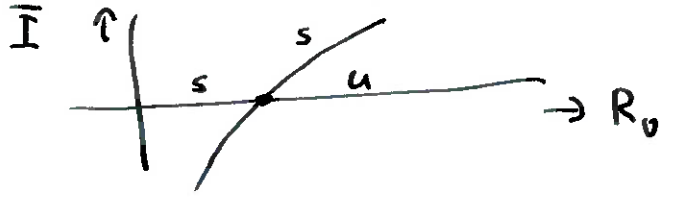
$$\frac{dI}{dt} = \beta S I - \alpha I - \mu I$$

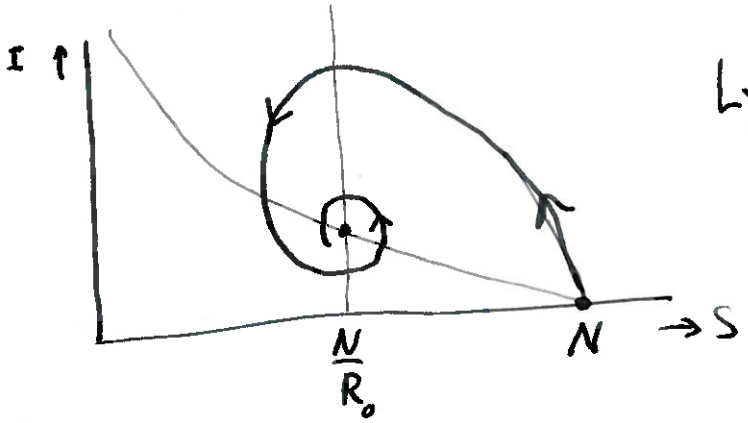
takes into account that individuals live for an exponentially distributed, with parameter μ, amount of time and that newborns enter the population at rate B and are susceptible. The total population is given by

$$N = \frac{B}{\mu}$$

(side remark: if "material" is flowing into a container at rate B and the average sojourn time is $\frac{1}{\mu}$, the contents is the product of these two quantities; in more complicated situations this trivial observation is often helpful to interpret (and check!) explicit expressions; see Exercise 4.11 in the DHB book)

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





Lyapunov function

$$V(S,I) = S - \bar{S}\ln S + I - \bar{I}\ln I$$

$\Rightarrow$ global stability

Transmission has time scale $\frac{1}{\alpha}$

Demographic turnover has time scale $\frac{1}{\mu}$

Often $\varepsilon = \frac{\mu}{\alpha}$ is a small parameter

See H. Jardón-Kojakhmetov, C. Kuehn, A. Pugliese, M. Sensi, A geometrix analysis of the SIR, SIRS and SIRWS epidemiological models, Nonlinear Analysis: Real World Applications (2021) 58: 103220 Also see M. Wechselberger, Geometric Singular Perturbation theory Beyond the standard form, Springer 2020

In that case orbits come very close to the S-axis and demographic stochasticity may very well lead to extinction of the pathogen. This was indeed observed for measles on Iceland (as opposed to measles in New York). See books by Cliff and Haggett and papers by Bryan Grenfell and co-workers. It led to the still somewhat mysterious notion of "critical community size", see Section 4.7 of DHB.

Exercise Check that the mean age $\bar{a}$ of newly infected individuals is given by

$$\bar{a} = \frac{1}{\mu + \bar{F}} = \frac{1}{\mu + \beta \bar{I}} = \frac{\bar{S}}{B} = \frac{1}{\mu R_0}$$

This formula allows you to estimate R_0 from an observed $\bar{a}$ and μ.

Exercise To represent vaccination shortly after birth, we replace B by $(1-f)B$ and assume that $\varepsilon_1, \varepsilon_2 = 0$, with $\varepsilon_1, \varepsilon_2$ as introduced on P32,3.3. Check that elimination of the pathogen requires

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

Exercise Read (for instance on Wikipedia) about Rubella/Rubéole and the risk for a developing fetus of a pregnant woman who contracts rubella. Combine the last two exercises to reflect on the ~~danger~~ dangers when vaccination is gradually introduced. See T. Panagiotopoulos, I. Antoniadou, E. Valassi-Adam, Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. British Medical Journal (1999) 319: 1462-1466.

Exercise Consider a host population in which pathogen strain 1 is in steady state. Let, for instance by mutation, strain 2 enter the population. Assume complete cross-immunity. Show that the number of individuals infected by strain 2 will increase iff $R_0^2 > R_0^1$. Often this observation leads to the "conclusion" that pathogens maximise their basic reproduction ratio. But a better way of summarising the essence is to say that pathogens minimise the resource level $\bar{S} = N/R_0$, see O. Diekmann, A beginners guide to adaptive dynamics, Banach Center Publications (2004) 63: 47-86
S. Lion, J.A.J. Metz, Beyond R_0 maximisation: on pathogen evolution and environmental dimensions. Trends in Ecology and Evolution (2018) 33: 75-90

Exercise Many species of wild animal give birth only during a short period of the year. A caricatural description is to assume that at integer values of time t a fixed quantity is added to the pool of susceptibles. Formulate a hybrid (i.e., combining continuous-time and discrete-time features) model along these lines and analyse it. See Exercise 4.14 in DHB and see M.G. Roberts, R.R. Kao, The dynamics of an infectious disease in a population with birth pulses. Math. Biosc. (1998) 149: 23-36 (motivated by tuberculosis in possums)

F.M. Hilker, T.A. Sun, L.J.S. Allen, F.M. Hamelin
Separate seasons of infection and reproduction can lead to multi-year population cycles, J. Theor. Biol. (2020) 489: 110158
for somewhat different models in the same spirit.

Regulation

Next consider the situation that the host population grows exponentially in the absence of the host. What does happen when we introduce a pathogen? Does

i) the pathogen go extinct?
ii) the pathogen population grow, but at a slower rate than the host?
iii) the pathogen population grow at the same rate (possibly reduced relative to *before* the introduction) as the host?
iv) the pathogen stop the host population growth?
v) the pathogen drive the host population to extinction? (thus delving its own grave)

But what does host population growth mean? When numbers grow, does the density increase as well? For instance, think of an expanding city.
In the context of epidemic models, the key question is whether the number of contacts per unit of time per individual increases? What is your guess for a STD (Sexually Transmitted Disease)? Motivated by this example, we here assume that this number remains constant. When we assume that infectious individuals do not reproduce and that, at the end of the infectious period, death occurs with probability $1-f$, we are led to consider

$$\frac{dS}{dt} = bS + bR - \mu S - \gamma \frac{SI}{N}$$

$$\frac{dI}{dt} = -\mu I + \gamma \frac{SI}{N} - \alpha I$$

$$\frac{dR}{dt} = -\mu R + f\alpha I$$

where $N = S + I + R$ and where we assume that $b > \mu$. Here γ is the product of the number of contacts per unit of time per individual and the probability that transmission occurs when a susceptible and an infectious individual have contact. Note that the system is first (degree) homogeneous, making exponential solutions possible. By introducing the fractions

$$y = \frac{I}{N}, \quad z = \frac{R}{N}$$

we can decouple into the two-dimensional system

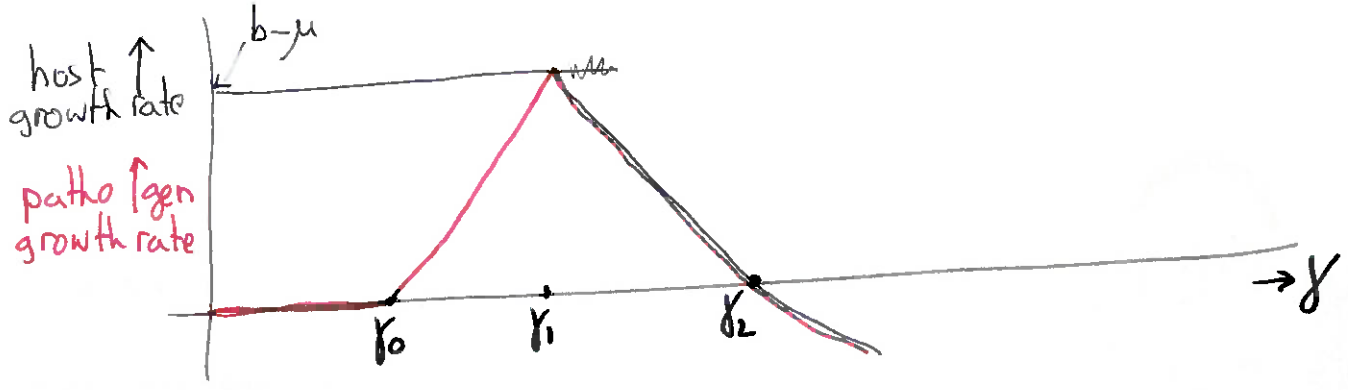
$$\dot{y} = y\{\gamma(1-y-z) - \alpha + \alpha(1-f)y + b(y-1)\}$$

$$\dot{z} = y(f\alpha + (1-f)\alpha z) - bz(1-y)$$

and a scalar equation

$$\dot{N} = \{b - \mu - (b + \alpha(1-f)y\}N$$

for the total population size. Analysis leads to the diagram



At $\gamma_0 = \alpha+\mu$ we have $R_0 = \frac{\gamma}{\alpha+\mu} = 1$

For γ between γ_0 and γ_1, the pathogen grows at rate $\gamma-\alpha-\mu$ while the host grows at the larger rate $b-\mu$, resulting in the "dilution" effect that $S = N$.

For $\gamma = \gamma_1$ we have $\gamma-\alpha-\mu = b-\mu$ so $\gamma_1 = b+\alpha$.

For $\gamma > \gamma_1$ both populations grow (or decrease, for $\gamma > \gamma_2$) at the rate $b-\mu-(b+\alpha(1-f)\bar{y})$ where $\bar{y} = \bar{y}(\gamma)$ is the y-component of the nontrivial steady state of the two-dimensional system. Whether or not γ_2 exists, i.e., whether or not this rate decreases to below zero, depends on whether

$$\frac{\alpha}{\alpha+\mu} f \frac{b}{\mu}$$

exceeds one (then γ_2 does not exist) or is below one (then $\gamma_2 < \infty$)

Note that this expression can be interpreted as the expected number of offspring (in the true = demographic sense) of an individual that is itself infected right at birth. The analysis underlying the diagram can be found in the elaboration of Exercise 4.24 in DHB.

The extinction for $\gamma > \gamma_2$ leads to the question: how reasonable is it to assume a given number of contacts per unit of time per individual when the population becomes really small? When we replace $\gamma \frac{SI}{N}$ by

$$\gamma C(N) \frac{SI}{N}$$

with $C(N) > 0$, C nondecreasing, $C(N) \sim N$ for $N \downarrow 0$ and $C(N) \to$ constant for $N \to \infty$, we "bridge the gap" between the incidence terms

$$\beta SI \quad \text{and} \quad \gamma \frac{SI}{N}$$

In this setting, the region $\gamma > \gamma_2$ is characterized by a steady state coexistence of host and pathogen. So the host population growth is stopped, but the host is not driven to extinction. See Exercise 4.25 in DHB and see O. Diekmann, M. Kretzschmar, Patterns in the effects of infectious diseases on population growth, J. Math. Biol. (1991) 29:539–570

In the latter paper a second parameter measures the influence of the disease on the fertility of the hosts. This may lead to bistability: either the population grows exponentially or it oscillates periodically with large amplitude.

A submodel for the contact rate

When contacts have a non-negligible duration, there is automatically an upper bound for the number of contacts per unit of time per individual. Here we take this situation as our starting point, but next take a limit in which contact duration becomes negligible. The aim is to provide a somewhat mechanistic derivation of an explicit expression for the function $C(N)$ introduced on the preceding page. This derivation is based on

J. M. P. Heesterbeek, J. A. J. Metz, The saturating contact rate in marriage and epidemic models, J. Math. Biol. (1993) 31:529–539

and can also be found in Section 12.2 of DHB. Two equivalent characterizations of $C(N)$ are

- $C(N)$ is the fraction of individuals that, at any given moment of time, is engaged in a contact
- $C(N)$ is the fraction of time that an individual is involved in a contact with another individual, given that the population size equals N

(here we assume that an individual can only be involved in one contact at a given time) See DHB Exercise 12.2.

Because pairs consist of two individuals, there are

$$\tfrac{1}{2} N C(N) \quad \text{pairs}$$

If pair formation is not at all influenced by the S–I distinction, a fraction

$$2\,\frac{SI}{N^2}$$

of these pairs is of S–I type.

So there are

$$\tfrac{1}{2} N C(N)\, 2\,\frac{SI}{N^2} = C(N)\frac{SI}{N}$$

pairs of S–I type. Transmission can, by assumption, only happen in such a pair.

Let the pair formation/dissolution process be described by

$$\dot{X} = -\rho X^2 + 2\sigma P$$

$$\dot{P} = \tfrac{1}{2}\rho X^2 - \sigma P$$

where X represents the singles and P the pairs. Note that $N = X + 2P$ is constant. The steady state

$$\bar{X} = \frac{\sqrt{1+4\nu N} - 1}{2\nu} \qquad \bar{P} = \frac{1 + 2\nu N - \sqrt{1+4\nu N}}{4\nu}$$

is globally stable. Here $\boxed{\nu = \frac{\rho}{\sigma}}$.

We now put

$$C(N) = \frac{2\bar{P}}{N} = \frac{1 + 2\nu N - \sqrt{1+4\nu N}}{2\nu N} = \frac{2\nu N}{1 + 2\nu N + \sqrt{1+4\nu N}}$$

In this "derivation" we ignored that an S-I pair becomes an I-I pair after transmission. This is reasonable if the rate of transmission within a pair is small relative to ρ and σ since then S and I change only slowly at the time scale at which X and P equilibrate. In more technical terms: we make a quasi-steady-state approximation.

Realistic Survival Probability

If no infectious disease is circulating, we observe the **stable age distribution**

$$S(t,a) = B\,\mathcal{F}(a)$$

where $\mathcal{F}(a)$ is the probability that an individual stays alive for at least a units of time. (Note that $N = B\int_0^\infty \mathcal{F}(a)\,da$ and that $\int_0^\infty \mathcal{F}(a)\,da = -\int_0^\infty a\,\mathcal{F}\,|da) =$ **life expectancy**; now recall the side remark on P 8.1). The equations introduced on P 8.1 implicitly assume that

$$\mathcal{F}(a) = e^{-\mu a}$$

For human populations in modern times, this is at blatant variance with the facts! The aim of the present section is to formulate a RE that incorporates both a general survival probability $\mathcal{F}$ and a general infectiousness specification $A = A(\tau)$.

When an infectious disease is circulating and the disease leads to permanent immunity while in no way influencing the survival probability, we have

$$S(t,a) = B\,\mathcal{F}(a)\,e^{-\int_0^a F\,(t-a+\sigma)\,d\sigma}$$

where F is the f-o-i. Note that here we use the age a only to know how long an individual is exposed to the f-o-i and **not** to describe the contact structure (this we will do below). In particular, the f-o-i is **not** age-specific.

If we interpret $A(\tau)$ as the expected contribution to the f-o-i of an individual that was infected τ units of time ago, given survival, we need to specify the expected contribution as

$$\frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)} A(\tau)$$

when the individual has age a at the moment of becoming infected. Since

$$\text{incidence} = F(t) \int_0^\infty S(t,a)\, da$$

this leads to the RE

$$F(t) = \int_0^\infty F(t-\tau) \int_0^\infty S(t-\tau, a) \frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)}\, da\, A(\tau)\, d\tau$$

Note that the last equation on the preceding page expresses S explicitly in terms of the model ingredients B and $\mathcal{F}$ and past values of F.

This RE for F always has the disease-free steady state $F = 0$. A nontrivial steady state $\bar{F}$ should satisfy

$$1 = B \int_0^\infty \int_0^\infty e^{-\bar{F}a} \mathcal{F}(a+\tau)\, da\, A(\tau)\, d\tau$$

The right-hand side is a monotonically decreasing function of $\bar{F}$, converging to zero for $\bar{F} \to \infty$. So if we assume that the value at $\bar{F} = 0$, which we denote by R_0 since

$$R_0 = B \int_0^\infty \int_0^\infty \mathcal{F}(a+\tau)\, da\, A(\tau)\, d\tau$$

$$= \text{expected number of secondary cases per primary case in a fully susceptible population}$$

[Indeed, the age distribution of cases is the stable age distribution $B\mathcal{F}(a)$ and an individual of age a is expected to contribute $\frac{\mathcal{F}(a+\tau)}{\mathcal{F}(a)}A(\tau)$ to the f-o-i]

exceeds one, there exists precisely one steady endemic f-o-i $\bar{F}$. And if $R_0 < 1$, no such endemic state exists.

The Principle of Exchange of Stability guarantees that the endemic steady state is stable for R_0 slightly greater than one. In

D. Breda, O. Diekmann, W. F. de Graaf, A. Pugliese, R. Vermiglio On the formulation of epidemic models (an appraisal of Kermack and McKendrick), J. Biol. Dyn. (2012) 6 (suppl. 2): 103-117

the RE is linearized at the endemic steady state and a characteristic equation is derived. For the special case $\mathcal{F}(a) = e^{-\mu a}$ it can be shown that, for any non-negative and integrable function A, all roots of this characteristic equation have negative real part. An analysis of the characteristic equation with general $\mathcal{F}(a)$ is, so far, elusive.

Preliminary conclusion: to formulate a model with general $\mathcal{F}$ and general A is straightforward. To provide a pen and paper analysis of such a general model is a challenge.

Now recall the time discretization described on P1.10. Here, following the supplementary material of the paper mentioned on that page, we introduce a similar discretization for a model incorporating demographic turnover.

Let $p(a) :=$ the probability of survival from age $a-1$ to age a

$$\mathcal{F}(a) := p(a)p(a-1)\cdots p(1) \text{ for } a \geq 1, \quad \mathcal{F}(0) := 1$$

Let M be the maximal age (in the sense that $p(M+1)=0$ while $p(a)>0$ for $a \leq M$). Assume that the number of births in one unit of time is a constant, denoted by B. In the absence of the pathogen, the dynamics are described by

$$X(t+1,a+1) = p(a+1)\,X(t,a) \qquad a = 0,1,\cdots,M-1$$

where $X(t,a)$ is the number of individuals of age a at time t, with $X(t,0) = B$ for all t. It follows that X assumes the stable distribution

$$X(t,a) = B\,\mathcal{F}(a)$$

Next, consider the situation in which the pathogen is present. Let $X_1(t,a)$ be the number of susceptible individuals of age a at time t, with $X_1(t,0) = B$ for all t (so we exclude that individuals become infected in the time interval in which they are born). The update rule for X_1 is

$$X_1(t+1,a+1) = p(a+1)\,e^{-\hat{F}(t)}\,X_1(t,a)$$

with $\hat{F}(t)$ the age-independent cumulative f-o-i over $(t,t+1]$. So here we assume that "survival" and "not becoming infected" are independent.

Let $X_2(t,a)$ denote the age-specific incidence at time t, i.e.,

$$X_2(t+1,a+1) = p(a+1)\left(1 - e^{-\hat{F}(t)}\right) X_1(t,a)$$

for $j \geq 3$ we specify

$$X_j(t+1, a+1) = p(a+1) X_{j-1}(t,a)$$

in order to have a bookkeeping scheme in which the survivors of past incidence are represented. The upper bound for the index j relates to the upper bound of the support of the discretized version of $A(\tau)$. More precisely, we specify

$$\hat{F}(t) = \sum_{j=1}^{m} A_j \sum_{a=j}^{M} X_{j+1}(t,a)$$

Taken together the last four equations constitute a first order system of recurrence equations. Alternatively we can write

$$\hat{F}(t) = B \sum_{j=1}^{m} A_j \sum_{a=j}^{M} \mathcal{F}(a) \left(e^{-\sum_{k=0}^{a-j-1} \hat{F}(t-a+k)} - e^{-\sum_{k=0}^{a-j} \hat{F}(t-a+k)} \right)$$

which is a higher order recurrence relation for the scalar quantity $\hat{F}$.

We conclude that a numerical implementation of a model with general $\mathcal{F}$ and general A is straightforward.

Please see E. Messina, M. Pezzella, A. Vecchio, Positive numerical approximation of integro-differential epidemic model Axioms (2022) 11(2) 69

for very recent work on numerical methods for the epidemic outbreak model.

Age-specific contact structure

For humans, age is among the most relevant (for disease transmission) forms of heterogeneity. It correlates with many aspects of social behaviour, notably sexual activity. In addition, public health administration often distinguishes individuals on the basis of age (to begin with when it concerns the vaccination of young children). In the results of a large-scale quantitative sociological study of age structured contact patterns are reported.

J. Mossong e.a., Social contacts and mixing patterns relevant to the spread of infectious diseases, PLoS Med 5(3) e74 (2008)

Let now $F(t,a)$ denote the age-specific f-o-i. Then

$$S(t,a) = B\,\mathcal{F}(a)\, e^{-\int_0^a F(t-a+\sigma,\sigma)\,d\sigma}$$

Let the model ingredient $c(a,\alpha)$ describe the contact structure. Perhaps assume that

$$c(a,\alpha) = c(\alpha,a)$$

(if you come to think about asymmetric contacts between parents and their children, you will realise that this is an assumption and not a self-evident requirement).

Let $A(\tau,a)$ describe the infectiousness of an individual that was infected τ units of time ago while having age a, given survival. Then

$$F(t,a) = \int_0^\infty \int_0^\infty F(t-\tau,\sigma)\, S(t-\tau,\sigma)\, c(a,a+\tau)\, \frac{\mathcal{F}(\sigma+\tau)}{\mathcal{F}(\sigma)}\, A(\tau,\sigma)\,d\sigma\,d\tau$$

By inserting the expression for S we obtain an abstract RE, where "abstract" means that the unknown function of time

takes values in a space of functions of age.
As far as I know, the problem in this form has so far not been studied. In pioneering work triggered by HIV, D. Greenhalgh and H. Inaba studied a SIR variant in the late 80s early 90s of the last century, see Chapter 6 of Inaba's book, P5.1.

When one assumes that

$$c(a,\alpha) = \sum_{k=1}^{n} f_k(a)\, g_k(\alpha)$$

for certain sets of functions $\{f_k\}$ and $\{g_k\}$, with possibly $f=g$ in order to make c symmetric, the right hand side of the equation for F has, as a function of age, finite dimensional range. A frequently used method is to discretize age by forming intervals which together cover the relevant part of the age axis and to discretize c accordingly (this means that a function of two continuous variables is replaced by a matrix). More precisely let $\{I_i\}$ be a collection of intervals with $I_i \cap I_j = \emptyset$ when $i \neq j$ and $\bigcup_{i=1}^{n} I_i = \mathbb{R}_+$. Require

$$c(a,\alpha) = c_{ij} \quad \text{for } a \in I_i \text{ and } \alpha \in I_j$$

Then $$c(a,\alpha) = \sum_{k,l} c_{kl}\, \mathbb{1}_k(a)\, \mathbb{1}_l(\alpha) = \sum_k \mathbb{1}_k(a) \sum_l c_{kl}\, \mathbb{1}_l(\alpha)$$

In such a situation R_0 is the dominant eigenvalue of a matrix and a steady state is completely determined by finitely many real numbers.
For more general theory see the book by Inaba and see
K. Okuwa, H. Inaba, T. Kuniya, An age-structured epidemic model with boosting and waning of immune status, Math. Biosc. Eng. (2021) 18(5): 5207–5236
This reference is misplaced. It should appear on P6.1, Aron conveyer belt
X-Z Li, J. Yang, M. Martchev, Age Structured Epidemic Modeling, Springer, 2020
and the references given there.
A time discretization can be formulated along the lines of P8.12–8.13 with F now a function of both time and age.