Books on Bifurcation Theory

Yu. A. Kuznetsov, Elements of Applied Bifurcation Theory Springer, 2004

H. Kielhöfer, Bifurcation Theory (An introduction with applications to PDE), Springer, 2012

M. Golubitsky, D.G. Schaeffer, Singularities and Groups in Bifurcation Theory, Springer, 1985

M. Haragus, G. Iooss, Local Bifurcations, Center Manifolds and Normal Forms in Infinite-Dimensional Dynamical Systems, Springer, 2011

The Aron conveyer belt

J.L. Aron, Dynamics of acquired immunity boosted by exposure to infection, Math. Biosc. (1983) 64: 249–259

M.V. Barbarossa, G. Röst, Immuno-epidemiology of a population structured by immune status: a mathematical study of waning immunity and immune system boosting, J. Math. Biol. (2015) 71: 1737–1770

The key idea of Aron is to restart the "time to return of susceptibility" clock when reinfection occurs before the individual is susceptible again. Or, in other words, boosting delays the return of susceptibility. In terms of the conveyer belt picture we have

so individuals jump back to the starting point when boosted. Let's represent the position on the immunity conveyer belt by time on an immunity clock. Individuals return to the class of susceptibles when the clock strikes τ. Whenever boosting occurs, time is reset to zero.

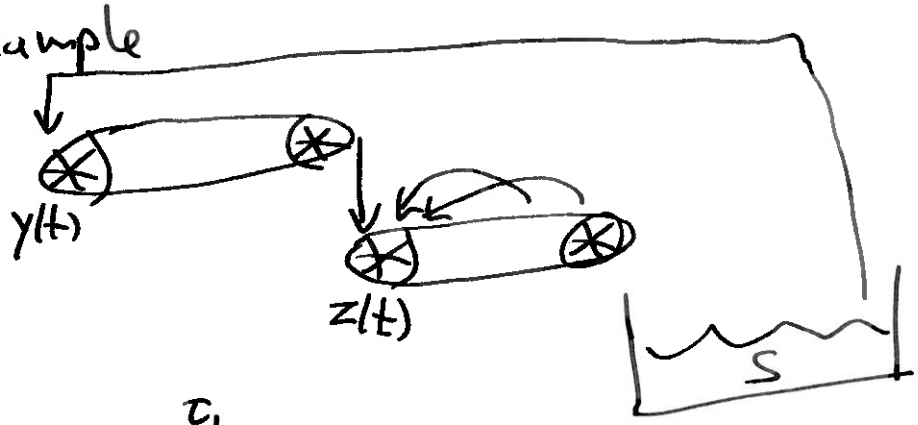
Let $z(t) = \dfrac{\text{number}}{\text{unit of time}}$ of individuals for which at time t the immunity clock shows zero. Let $h(t)$ denote the inflow from outside (for instance, of individuals that reached the end of their infectious period). As before, $F(t)$ denotes the f-o-i at time t. We postulate that boosting of individuals with immunity clock time σ, $0 \le \sigma \le \bar{\tau}$, at time t occurs with probability per unit of time

$$\nu(\sigma)\, F(t)$$

Then

$$z(t) = h(t) + F(t) \int_0^{\bar{\tau}} \nu(\sigma)\, z(t-\sigma)\, e^{-\int_0^{\sigma} \nu(\eta) F(t-\sigma+\eta)\, d\eta}\, d\sigma$$

We now combine this idea with the model formulation of the preceding example



$$y(t) = \int_0^{\tau_1} A(\tau)\, y(t-\tau)\, d\tau \left(N - \int_0^{\tau_1} y(t-\tau)\, d\tau - \int_0^{\bar{\tau}} z(t-\sigma)\, e^{-\int_0^{\sigma} \nu(\eta) F(t-\sigma+\eta)\, d\eta}\, d\sigma \right)$$

$$z(t) = y(t-\tau_1) + \int_0^{\tau_1} A(\tau)\, y(t-\tau)\, d\tau \int_0^{\bar{\tau}} \nu(\sigma)\, z(t-\sigma)\, e^{-\int_0^{\sigma} \nu(\eta) F(t-\sigma+\eta)\, d\eta}\, d\sigma$$

This system has, as far as I know, not been analysed. But see Section 8.5 in the book of H. Inaba, see P5.1. and L. Yang, Y. Nakata, Note on the uniqueness of an endemic equilibrium of an epidemic model with boosting of immunity J. Biol. Syst. (2021) 29 (02) 291–302

Increasing disease as a consequence of reducing transmission

In Aron-inspired models one often assumes, as we did in the preceding example, that boosting does not lead to infectiousness. Implicitly we also assume that it does not lead to illness. Following

R. Águas, G. Gonçalves, M.G.M. Gomes, Pertussis: increasing disease as a consequence of reducing transmission, The Lancet Infectious Diseases (2006) 6 (2) 112-117

A.N. Swart, M. Tomasi, M. Kretzschmar, A.H. Havelaar, O. Diekmann, The protective effects of temporary immunity under imposed infection pressure, Epidemics (2012) 4:43-47

we now illustrate a phenomenon that at first may seem counterintuitive.

Assume that an individual is either

S susceptible
P fully protected
Q partially "

Let the $\boxed{\text{f-o-i } F}$ be a given constant. So we consider F as a parameter. (The motivation to do so derives from foodborne diseases caused by bacteria like Campylobacter or Salmonella, that grow in animal reservoirs and are transmitted to humans via meat.) The diagram

$$\begin{tikzcd}
S \arrow[r, "F", "\text{(illness)}"'] & P \arrow[r, shift left, "\alpha"] & Q \arrow[l, shift left, "F'"] \arrow[ll, bend left, "\gamma"] \arrow[l, "\text{no illness}"']
\end{tikzcd}$$

summarizes our assumptions. (Note that we assume that the transitions are instantaneous.)

Let $\begin{pmatrix} s \\ p \\ q \end{pmatrix}(a) :=$ probability that an individual of age a has i-state $\begin{pmatrix} S \\ P \\ Q \end{pmatrix}$ given survival till at least age a

Assume that all newborns have i-state S.

Then

$$\frac{d}{da}\begin{pmatrix} s \\ p \\ q \end{pmatrix} = \begin{pmatrix} -F & 0 & \gamma \\ F & -\alpha & F \\ 0 & \alpha & -(F+\gamma) \end{pmatrix}\begin{pmatrix} s \\ p \\ q \end{pmatrix}$$

$$\begin{pmatrix} s \\ p \\ q \end{pmatrix}(0) = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$$

By computing eigenvalues and eigenvectors (which is easy since one of the eigenvalues is zero) one obtains the solution as an explicit expression in the parameters F, α, γ and the variable a.

We assume that infection is harmless in the sense that the $\boxed{\text{survival probability}}$ till age a

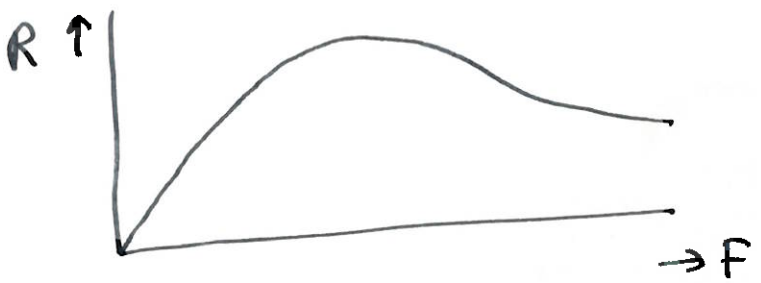
$$\mathcal{F}(a)$$

is not affected. Then the $\boxed{\text{expected}}$ number of infections that a newborn will suffer from during its entire life is given by

$$R = F \int_0^\infty s(a)\,\mathcal{F}(a)\,da$$

(please keep in mind that $s(a)$ depends on F, even though we do not express this in the notation).

The graph



shows that an increase in the f-o-i F may lead to a decrease in disease burden! The explanation is that frequent boosting keeps the protection level high while not leading to illness.

For general $\mathcal{F}(a)$ one needs to compute R numerically, but for

$$\mathcal{F}(a) = e^{-\frac{a}{a_e}} \qquad \text{and} \qquad \mathcal{F}(a) = \mathbb{1}_{[0,a_e]}$$

with a_e = life expectancy, one can derive analytically that

$$\lim_{a_e \to \infty} \frac{R}{a_e} = \frac{\alpha\gamma F}{(\alpha+F)(\gamma+F)}$$

and next notice that, clearly, the right hand side has a maximum somewhere in $(0,\infty)$. One can understand the meaning of the right hand side by arguing as follows. For large a_e, the fact that a newborn individual is susceptible has some, but not much, impact. According to first step analysis, the expected time T needed to make a transition from P to S satisfies

$$T = \frac{1}{\alpha} + \frac{\gamma}{\gamma+F}\,\frac{1}{\gamma+F} + \frac{F}{\gamma+F}\left(\frac{1}{\gamma+F} + T\right)$$

Hence

$$T = \frac{\alpha+\gamma+F}{\alpha\gamma}$$

The expected time needed for a roundtrip $S \to S$ is

$$\frac{1}{F} + T = \frac{(\alpha+F)(\gamma+F)}{\alpha\gamma F}$$

Thus we see that R is, roughly, the expected number of $S \to S$ roundtrips made during life. And the dependence on F can be understood as resulting from the competition between "short" roundtrips $P \rightleftarrows Q$ and "long" roundtrips $S \to P \to Q$.

In the paper by Swart e.a. data for Campylobacter are analysed and the situation in developing countries and industrialized countries is contrasted.

The reinfection threshold

M.G.M. Gomes, L.J. White, G.F. Medley, Infection, reinfection and vaccination under suboptimal immune protection: epidemiological perspectives, J. Theor. Biol. (2004) 228: 539–549
G. Katriel, Epidemics with partial immunity to reinfection, Math. Biosc. (2010) 228: 153–159

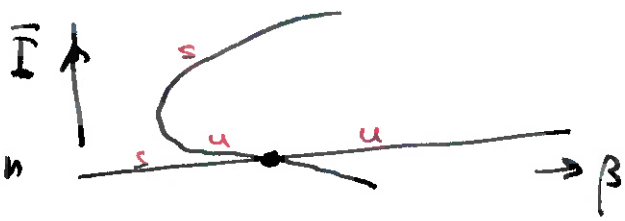
$$\dot{S} = -\beta I S$$
$$\dot{I} = \beta I S - \alpha I + \varepsilon \beta I Q \qquad S + I + Q = N$$
$$\dot{Q} = \alpha I - \varepsilon \beta I Q$$

Observation: If $R_0 = \frac{\beta N}{\alpha} > 1$ a virgin population can experience an outbreak when the pathogen is introduced. When also $\varepsilon \frac{\beta N}{\alpha} > 1$, the (I, Q)-system (with $S = 0$) is of SIS-type, cf. P5.7, and has an endemic steady state.

In the vaccination story (P3.2, 3.3) we had ε_1 like the ε above, but also ε_2 as a modification factor for infectiousness. If we want to introduce such a

parameter in the present setting, we need to split the I category into first time infected individuals and reinfected individuals. The latter have β replaced by $\varepsilon_2\beta$ but possibly also a different α (reinfection may be asymptomatic and therefore not be treated, leading to a lower value of α). In such situations

backward bifurcation



may occur, with the consequence that elimination of the pathogen may not be achieved by bringing R_0 to below one. See Section 4.1.5 SISI Model with Bistability in J. Müller, C. Kuttler, Methods and Models in Mathematical Biology, Springer 2015

D. Greenhalgh, O. Diekmann, M. de Jong, Subcritical endemic steady states in mathematical models for animal infections with incomplete immunity, Math. Biosc. (2000) 165: 1–25

Also see Chapter 8, "Variable susceptibility, Reinfection and Immunity" of the book by H. Inaba, cf. Ps.1, for the Kermack-McKendrick Reinfection Model and much more.

Preliminary conclusion: there exist many variants of "partial immunity" and it seems to be difficult to follow a top down approach by formulating one general model that encompasses all these variants. The following thought experiment illustrates the difficulty.

Situation I : half of the population is fully susceptible, the other half is completely protected

Situation II : for the entire population, the susceptibility is reduced to half of the base line value

Let w be the cumulative f-o-i over a certain period of time. How many cases do we expect during this period? P6.8

Situation I : $\frac{1}{2}(1-e^{-w})N + \frac{1}{2}0$

Situation II : $(1-e^{-\frac{1}{2}w})N$

So even though the first order term in the Taylor expansion for $w \to 0$ is the same, these numbers are $\boxed{\text{not}}$ the same. It matters whether we describe partial immunity by way of a probability distribution over the two i-states "fully susceptible" and "completely protected" or by way of a probability distribution of the parameter describing the reduction of susceptibility.

A two-phase within host model

The description in terms of an immunity clock, that is reset whenever boosting occurs, is very phenomenological. As a first step towards a more realistic description of immune status, we might introduce a one-dimensional quantity y that we interpret as serum antibody level. In an infection episode, interaction between the pathogen and the immune system leads to a rise of y. In a subsequent waning episode, y gradually declines. The simplest description assumes exponential decay:

$$\frac{dy}{dt} = -wy$$

But how do we describe the dynamics during the infection episode? And in particular: what marks the end of an infection episode?

If we postulate

$$\frac{db}{dt} = \mu_0 b - cy \qquad b(0) = b_0$$

$$\frac{dy}{dt} = \mu_1 y \qquad y(0) = y_0$$

where b is a measure of pathogen load (e.g., antigen concentration), we ignore that the rate at which b decreases due to antibody activity should depend on b. The great advantage of this deliberate simplification is that, provided $\mu_1 > \mu_0$, the pathogen load is brought down to zero in a finite time window. So the start of an infection episode is marked by b jumping from zero to b_0, with b_0 determined by the dose

of pathogen that enters the host, while the end of an infection episode is marked by b reaching zero again.

At the start of an infection episode, y has a certain value, say y_0. At the end y has another, higher, value y_1. If we ignore the duration of the infection episode, boosting amounts to a jump of the y variable from y_0 to y_1. As we shall see, the map $y_0 \mapsto y_1$ contains far more information than the simple resetting of an immunity clock.

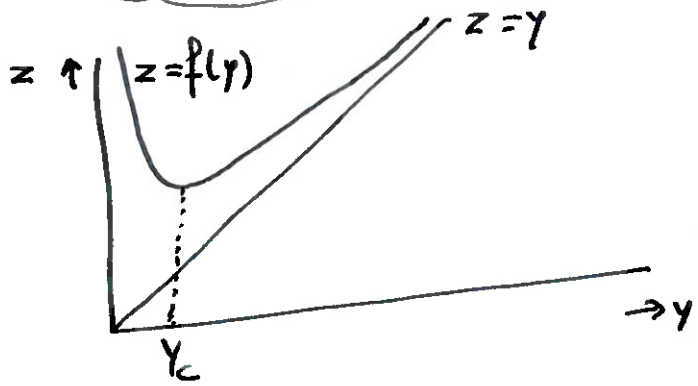
The ODE system for (b,y) provided with the initial condition $(b(0), y(0)) = (b_0, y_0)$ can be solved explicitly. Next the equation $b(t_1) = 0$ can be solved to determine the length t_1 of the infection episode. Thus we find

$$y_1 = y(t_1) = f(y_0)$$

with

$$f(y) = y\left(1 + \frac{(\mu_1 - \mu_0) b_0}{c y_0}\right)^{\frac{\mu_1}{\mu_1 - \mu_0}}$$

remove



From the graph we deduce that, for given dose b_0 and given parameters μ_0, μ_1 and c, there are two values of y_0 that yield the same outcome y_1. One corresponds to a small jump (so to a mild infection, or no infection at all, just boosting) and one corresponding to a big jump, so to a severe infection. There is a critical antibody level y_c separating mild from severe. For $y_0 > y_c$

the magnitude of the jump hardly depends on the exact value of Y_0, but for $Y_0 < Y_c$ there is a rather sensitive dependence: ~~an~~ minor differences in Y_0 may lead to big differences in Y_1.

In [W.F. de Graaf, M. Kretzschmar, P. Teunis, O. Diekmann, A two-phase within host model for immune response and its application to serological profiles of pertussis, Epidemics (2014) 9: 1–7] time course data of IgG against pertussis toxin in serum of 121 patients are used to estimate parameters via MCMC. This leads to a prediction of Y_c. In another, totally unrelated, study the relation between initial IgG PT levels and occurrence of symptoms upon infection was used to determine Y_c. The agreement is surprisingly good. It seems that this very caricatural within-host model does capture some features of the interaction of pathogen and immune system reasonably well.

Waning and Boosting

O. Diekmann, W.F. de Graaf, M.E.E. Kretzschmar, P.F.M. Teunis
Waning and boosting: on the dynamics of immune status
J. Math. Biol. (2018) 77: 2023–2048
R. Rudnicki, M. Tyran-Kamińska, Piecewise Deterministic Processes in Biological Models, SpringerBriefs, 2017
K. Pichór, R. Rudnicki, Dynamics of antibody levels: asymptotic properties, Math. Meth. Appl. Sci (2020) 43: 10490–10499
E. Franco e.a., see P 3.10

At the end of the preceding section we mentioned longitudinal data concerning serological pertussis profiles. The present section relates, in principle, to cross-sectional data.

Let waning be described by the ODE

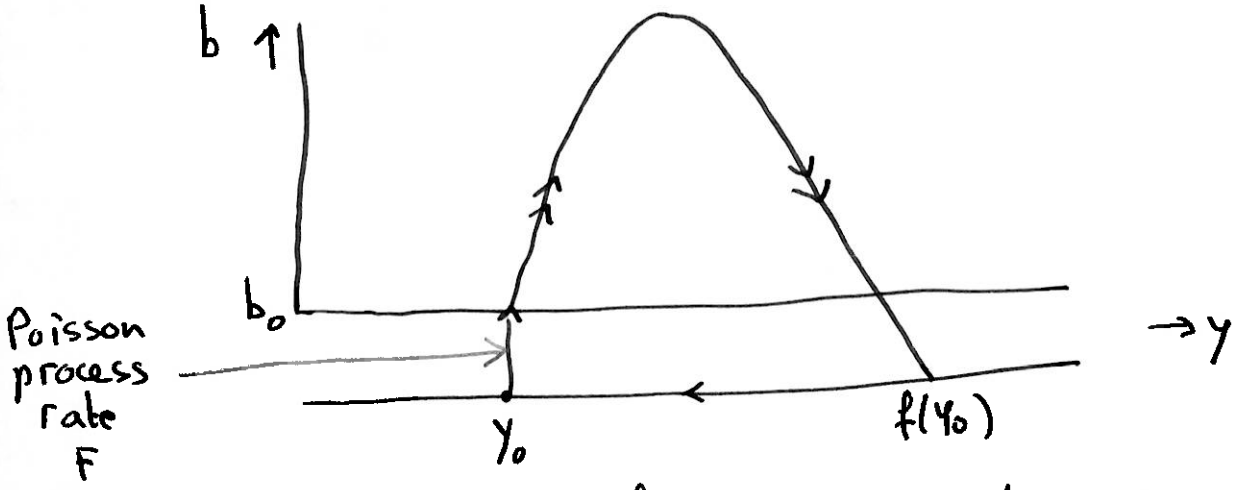
$$\boxed{\frac{dy}{dt} = g(y)}$$

(so earlier we chose $g(y) = -wy$) for the decline of y in between encounters with the pathogen. Let such encounters occur at rate $\boxed{F}$. So F is the constant force of infection and is here considered as a parameter (to formulate a feedback consistency condition for F one needs to make assumptions about infectiousness and these involve the introduction of additional parameters). We assume that, on the time scale set by g and F, the time it takes the immune system to clear an infection is negligible. Or, in other words, we assume that the boosting map f, that sends the immune status just before the infection to the immune status $f(y)$ just after clearance of the pathogen, acts instantaneously.

The three ingredients g, F and f define a Piecewise Deterministic Markov Process (PDMP). The only randomness is in the hitting times of the Poisson process with rate F.

Key question: if we let the process run for a long time, will the distribution of immune status converge to a stable distribution?

[Since feedback via F is ignored, the stable distribution describes the distribution in a population of identical individuals. But note that here we assume that these individuals are immortal. When we want to include demographic turnover, we also need to specify the (distribution of) the immune status at birth and the stable population distribution will be a bit different.]



If the distribution of y at time t is described by the density $n(t,\cdot) \in L_1(0,\infty)$, the evolution of n is governed by the PDE

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial y}(gn) = -Fn + Sn$$

see picture on P 7.2

where

$$(S\phi)(y) = \begin{cases} 0 & y < f(y_c) \\ -F\phi(f_-^{-1}(y))\dfrac{1}{f'(f_-^{-1}(y))} + F\phi(f_+^{-1}(y))\dfrac{1}{f'(f_+^{-1}(y))} & \end{cases}$$

with f_-^{-1} the inverse of f taking values less than y_c

f_+^{-1} " " bigger "

So note that the PDE has a nonlocal term (in this case a term with a transformed argument). This is a general feature in the context of structured population models. Below we shall sketch how this PDE can be derived. But first we want to indicate how the PDE relates to the RE formalism.

<u>Exercise</u> Check that $\int^{\infty} \left[-F\,n(t,y) + (Sn(t,\cdot))(y)\right] dy = 0$ exactly as to be expected ~~by~~ on account of the interpretation. Convince yourself that accordingly we should have

$$R_0 = 1 \;,\; r = 0$$

If we drop the Sn term in the equation, we can solve the PDE by integration along characteristics and explicitly define a semigroup of solution operators $T_0(t)$. This semigroup has infinitesimal generator

$$A_0\phi = -(g\phi)' - F\phi$$

with domain $D(A_0)$ defined appropriately. The full PDE corresponds to the abstract ODE

$$\frac{dn}{dt} = A_0 n + Bn$$

for the function $t \mapsto n(t)$ taking values in $L_1(0,\infty)$. Here

$$B\phi = S\phi$$

describes birth/reappearance, while the A_0 part describes movement in the i-state space and death/disappearance. The variation-of-constants formula yields an integral equation for n:

$$n(t) = T_0(t)n_0 + \int_0^t T_0(t-\tau)Bn(\tau)\,d\tau$$

But we prefer to write

$$\boxed{n(t) = \int_{-\infty}^{t} T_0(t-\tau)Bn(\tau)\,d\tau}$$

i.e., to assume that the process started in the infinite past. If we apply B to both sides, we obtain an integral equation for Bn:

$$\boxed{Bn(t) = \int_{-\infty}^{t} BT_0(t-\tau)Bn(\tau)\,d\tau}$$

Note that the equation for n becomes an explicit expression once Bn is known!

We would like to write this equation in the form of the first equation on P3.9, so to put

$$\Omega = (0, \infty)$$

$$b(t,y) = (B\,n(t))(y)$$

$$b(t,y) = \int_0^\infty \int_\Omega A(\tau, y, \eta)\, b(t-\tau, \eta)\, d\eta\, d\tau$$

But there is a regularity issue: we cannot, in this case, work with a kernel A that is a function, we need to make use of measures. Therefore we now extend the formalism. But first we introduce

Notation

$$T(y) := \int_{y_c}^{y} \frac{d\eta}{g(\eta)}$$

$$\pi(t, y_0) := T^{-1}(t + T(y_0))$$

Note: $\pi(t, y_0)$ is the solution of $\frac{dy}{dt} = g(y)$ at time t when $y(0) = y_0$. For later use we also observe that

$$\frac{\partial \pi}{\partial y}(t,y) = \frac{\partial \pi}{\partial t}(t,y)\,\frac{1}{g(y)} = \frac{g(\pi(t,y))}{g(y)}$$

To indicate that operators act on the space of Borel measures on Ω, we equip them with a $\wedge$. In particular

$$(\hat{T}_0(t)m)(\omega) = e^{-ft}\, m(\pi(-t,\omega))$$

$$(\hat{B}m)(\omega) = f\, m(f^{-1}(\omega))$$

<u>Exercise</u> Check that

$$(\hat{B}\,\hat{T}_0(t)\,m)(\omega) = \int_\Omega \hat{A}(t,\omega,\eta)\, m(d\eta)$$

when we define

$$\hat{A}(t,\omega,\eta) = F e^{-Ft}\, \delta_{f(\pi(t,\eta))}(\omega)$$

The RE now reads

$$\hat{b}(t,\omega) = \int_0^\infty \int_\Omega \hat{A}(\tau,\omega,\eta)\, \hat{b}(t-\tau, d\eta)\, d\tau$$

The corresponding NGO is given by

$$(\hat{K}_0 \Psi)(\omega) = \int_\Omega \left(\int_0^\infty \hat{A}(\tau,\omega,\eta)\, d\tau \right) \Psi(d\eta)$$

In the papers mentioned on P 7.3 it is shown that, under some conditions, $\hat{K}_0$ has a unique fixed point and that this fixed point has a density. By inverting $\hat{B}$ one computes a corresponding stationary distribution. This distribution too has a density. Under some additional conditions one can prove that this stationary distribution is attracting, so deserves to be called "stable". Again we refer to the papers mentioned on P 7.3.

<u>Exercise</u> Let AC denote the subspace of absolutely continuous (with respect to the Lebesgue measure) measures and define $D : AC \to L_1$ as the map that assigns to an absolutely continuous measure the corresponding

density. Show that

$$T_0(t) = D\,\hat{T}_0(t)\,D^{-1}$$

is given explicitly by

$$(T_0(t)\phi)(y) = e^{-Ft}\,\frac{g(\pi(-t,y))}{g(y)}\,\phi(\pi(-t,y))$$

Next derive that formally

$$A_0\phi = \lim_{t\downarrow 0}\frac{1}{t}\left(T_0(t)\phi-\phi\right) = -\frac{\partial}{\partial y}(g\phi) - F\phi$$

Also show that $S = D\hat{B}D^{-1}$

<u>Exercise</u> Prove that $\tau \mapsto \pi(t-\tau, f(\pi(\tau,y)))$ is, for given $y\in\Omega$ and $t>0$, an increasing function on $[0,t]$ if $f'(z)\,g(z) < g(f(z))$, $\forall z\in\Omega$.

[See Lemma 4.5 in Diekmann e.a., P7.3; this result can be used to prove that the part of the distribution corresponding to at least one jump has a density even if we start with a measure that does not have a density. So under this condition there is some regularizing effect.]

<u>Conclusion</u>. In principle one can try to relate the stable distribution to cross-sectional data in order to estimate g, F and f. But to do this properly, one should also pay attention to the immune status of newborn individuals and to the stable age distribution.