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## "Asymptotically Autonomous Epidemic Models"

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# ASYMPTOTICALLY AUTONOMOUS EPIDEMIC MODELS

BY

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# Asymptotically autonomous epidemic models

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**ABSTRACT.** Differential equation systems modeling the spread of infectious diseases are considered which can be rewritten as smaller asymptotically autonomous systems with limiting systems that are easier to handle than the original ones. Using recently developed techniques, it is shown that the asymptotic dynamics of the original systems are the same as the ones of the reduced systems, namely convergence to the disease-free or an endemic equilibrium. The models describe non-lethal sexually transmitted diseases. The first model considers a complex dependence of the incidence on the numbers of susceptible, infective, and removed individuals caused by change of behavior according to the perceived risk. The second model adds multiple strains of the infective agent with total cross-immunity. The third model considers a standard incidence, but a distributed length of the removal period.

KEY WORDS. Epidemic models, endemic equilibrium, complex incidence, multiple strains, cross-immunity, distributed removal period, differential equations, dynamical systems, asymptotically autonomous equations, asymptotic behavior, omega-limit sets.

AMS Subject Classification: 34D05, 45M05, 58F12, 92D30

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## 1. Introduction

Sometimes mathematical models in epidemiology can be formulated as systems of autonomous differential equations that can be rewritten as smaller asymptotically autonomous systems with a limit system that is considerably easier to handle than the original one. Under which conditions do the solutions of the original complicated system have the same asymptotic behavior as those of the easy limit system?

A model of the sort above has been considered by *Blythe, Cooke, Castillo-Chavez* (preprint), for the spread of a sexually transmitted disease. As they assume that individuals may change their behavior according to their perceived risk of being infected, the incidence in their model is an unspecific function of the numbers of susceptible, infective, and recovered individuals. They conjecture that, under a quite general assumption for the incidence function, the disease dynamics converge towards an equilibrium. Their conjecture is based on the fact that their three-dimensional system of autonomous ordinary differential equations has a two-dimensional limit system for which periodic orbits can be ruled out. The theory available so far (in particular *Markus*, 1956) was not sufficient to provide a rigorous proof, however, because their assumption (unless replaced by a much more restrictive one) does not imply the existence of a unique endemic equilibrium that, in addition, is locally asymptotically stable. This state of affairs (which also occurs in ecologic models) motivated us to revisit the theory of asymptotically autonomous differential equations and, more generally, semiflows. *Thieme* (1992, to appear) presents sufficient conditions for the large-time behavior of solutions of asymptotically autonomous systems to be the same as the large-time behavior of solutions of their limit systems. (See Section 3 for a summary.) Examples illustrate that this is not necessarily the case in general. In particular, a Poincaré-Bendixson type trichotomy holds for planar asymptotically autonomous ordinary differential equations which we will use in Section 3 of this paper to prove the above-mentioned conjecture in *Blythe* et al. (preprint). To illustrate the range of application, in Section 4 we incorporate multiple strains of infectious agents which induce total cross-immunity (see *Saunders*, 1981, and *Bremermann, Thieme*, 1989). In Section 5 we show convergence towards equilibrium for an epidemic model where the incidence depends on the number of susceptibles and infectives in a more standard way, but where the immunity period is arbitrarily distributed leading to an asymptotically autonomous integro-differential equation. The limit equation has been considered by *Stech* and *Williams* (1981) and is quite peculiar because convergence towards an equilibrium does neither follow from planar ODE theory (it is an infinite-dimensional problem), neither via a Lyapunov function, nor via monotonicity methods, but via a transformation to an integro-differential equation that is handled by frequency domain methods (see *Londen*, 1975, and *Gripenberg, Londen, Staffans*, 1990, Chapter 17). Asymptotically autonomous differential equations where the limit system has a Lyapunov function have been considered by *Artstein* (1976)

in the case of ordinary, and by *Ball* (1978) in the case of partial differential equations.

The reader who is just interested in the epidemiological contents may skip Section 2 and read Sections 3, 4 and 5 up to the formulation of the main results.

## 2. Asymptotically autonomous differential equations and semiflows

*L. Markus* (1956) published an often quoted (and sometimes misquoted) paper on asymptotically autonomous differential systems where he considers ordinary differential equations

$$\dot{x} = f(t,x), \tag{2.1}$$

$$\dot{y} = g(y), \tag{2.2}$$

in $\mathbf{R}^n$. Equation (2.1) is called *asymptotically autonomous* — with *limit equation* (2.2) — if

$$f(t,x) \to g(x), \quad t \to \infty, \quad \text{locally uniformly in } x \in \mathbf{R}^n,$$

i.e., for $x$ in any compact subset of $\mathbf{R}^n$. For simplicity we assume that $f(t,x), g(x)$ are continuous functions and locally Lipschitz in $x$. The $\omega$-limit set $\omega(t_0,x_0)$ of a forward bounded solution $x$ to (2.1), satisfying $x(t_0) = x_0$, is defined in the usual way:

$$y \in \omega(t_0,x_0) \iff y = \lim_{j\to\infty} x(t_j) \text{ for some sequence } t_j \to \infty \ (j \to \infty).$$

*Thieme* (1992, to appear) extends the Poincaré-Bendixson type dichotomy proved by *Markus* (1956, Theorem 7) to the following Poincaré-Bendixson type trichotomy:

**Theorem 2.1.** *Let $n = 2$ and $\omega$ be the $\omega$-limit set of a forward bounded solution $x$ of the asymptotically autonomous equation (2.1). Assume that there exists a neighborhood of $\omega$ which contains at most finitely many equilibria of (2.2). Then the following trichotomy holds:*

*(i) $\omega$ consists of an equilibrium of (2.2).*

*(ii) $\omega$ is the union of periodic orbits of (2.2) and possibly of centers of (2.2) that are surrounded by periodic orbits of (2.2) lying in $\omega$.*

*(iii) $\omega$ contains equilibria of (2.2) that are cyclically chained to each other in $\omega$ by orbits of (2.2).*

In the third possibility, the $\omega$-limit set contains homoclinic orbits (phase unigons) connecting one equilibrium to itself and/or phase polygons with finitely many sides (connecting equilibria) all of which are traversed in the same direction. More precisely we have finitely many equilibria $e_1, \ldots, e_m$ of (2.2) in $\omega$ and functions $y_j : \mathbf{R} \to \omega, j = 1, \ldots, m$, that solve (2.2) for all $t \in \mathbf{R}$ such that the following holds:

For $j = 1, \ldots, m$, $y_j(t) \to e_j$ for $t \to -\infty$.
For $j = 1, \ldots, m-1$, $y_j(t) \to e_{j+1}$ for $t \to \infty$.
$y_m(t) \to e_1$ for $t \to \infty$.
If $m = 1$, then $y_1(t) \to e_1$ for $t \to \pm\infty$ (homoclinic orbit).

Under the assumption that the solution $x$ of (2.1) does not intersect itself and under a slightly different assumption of asymptotic autonomy, *Klebanov* (preprint, Theorem 3.1) gives a more precise description of the $\omega$-limit set of $x$ than the one in Theorem 2.1. Firstly, centers do not occur in possibility (ii) and, in possibility (iii), every point in $\omega$ that is not an equilibrium of (2.2) lies on an orbit connecting two equilibria of (2.2).

In the applications to come, we have not been able to show that the respective solutions to (2.1) do not intersect themselves. The existence of cyclic orbit connections of equilibria in possibility (iii) is crucial for the Dulac (or divergence) criterion to rule out possibilities (ii) and (iii) such that convergence towards an equilibrium follows (see *Hahn*, 1967, e.g.):

**Corollary 2.2.** *Let $X$ be a subset of $\mathbf{R}^2$ such that any equilibrium of (2.2) in $X$ is the only equilibrium in a sufficiently small neighborhood. Further assume that there exist a subset $Y$ of $\mathbf{R}^2$ and an open simply connected subset $D$ of $\mathbf{R}^2$ with the following properties:*

- *Every bounded forward orbit of (2.1) in $X$ has its $\omega$-limit set in $Y$.*
- *All possible periodic orbits of (2.2) in $Y$ and the closures of all possible orbits of (2.2) that chain equilibria of (2.2) cyclically in $Y$ are contained in $D$.*
- *$g$ is continuously differentiable on $D$ and there is a real-valued continuously differentiable function $\rho$ on $D$ such that the divergence of $\rho g$,*

$$\nabla \cdot (\rho g)(x_1, x_2) = \frac{\partial}{\partial x_1}(\rho g_1)(x_1, x_2) + \frac{\partial}{\partial x_2}(\rho g_2)(x_1, x_2),$$

*is either strictly positive almost everywhere on $D$ or strictly negative almost everywhere on $D$.*

*Then every bounded forward solution of (2.2) in $X$ and every bounded forward solution of (2.1) in $X$ converges towards an equilibrium of (2.2) as time tends to infinity.*

If the solution $x(t)$ to (2.1) satisfying $x(t_0) = x_0$ is denoted by $\Phi(t, t_0, x_0)$ and the solution $y(s)$ of (2.2) satisfying $y(0) = y_0$ is denoted by $\Theta(s, y_0)$, then $\Phi$ is an asymptotically

autonomous semiflow with autonomous limit semiflow $\Theta$ in the following sense:

$$\Phi(t_j + s_j, t_j, x_j) \to \Theta(s, x), \quad j \to \infty, \tag{2.3}$$

for any three sequences $t_j \to \infty, s_j \to s, x_j \to x$ with elements $x, x_j \in \mathbf{R}^n, 0 \le s, s_j < \infty$.

We now consider abstract continuous semiflows, i.e., continuous mappings $\Phi : \Delta \times X \to X$, where $\Delta = \{(t,s); t_0 \le s \le t < \infty\}$ and $X, d$ is a metric space, such that

$$\Phi(t, s, \Phi(s, r, x)) = \Phi(t, r, x), \quad t \ge s \ge r \ge t_0,$$
$$\Phi(s, s, x) = x, \qquad s \ge t_0,\ x \in X.$$

Further we consider continuous autonomous semiflows, i.e., continuous mappings $\Theta : [0, \infty) \times X \to X$ satisfying

$$\Theta(t, \Theta(s, x)) = \Theta(t + s, x), \quad t, s \ge 0$$
$$\Theta(0, x) = x, \qquad x \in X.$$

For simplicity we have implicitly assumed that the semiflows are defined for all forward times.

In the following we assume that $\Phi$ is an *asymptotically autonomous semiflow* with *limit semiflow* $\Theta$, i.e., that (2.3) holds.

We recall that a subset $M$ of $X$ is called *forward invariant* under $\Phi$ (or forward $\Phi$-invariant) if and only if $\Phi(t, s, x) \in M$ whenever $t \ge s \ge t_0, x \in M$. Forward $\Theta$-invariance is defined analogously. $M$ is called $\Theta$-*invariant* if and only if $M$ is forward $\Theta$-invariant and for any $x \in M, t > 0$, there is some $y \in M$ such that $x = \Theta(t, y)$.

Let a point $(s, x)$, $t_0 \le s < \infty, x \in X$, have a pre-compact *(forward) orbit*

$$\{\Phi(t, s, x); t \ge s\}.$$

Then the $\omega$-$\Phi$-limit set of $(s, x)$, $\omega_\Phi(s, x)$, is defined by

$$\omega_\Phi(s, x) = \bigcap_{\tau \ge s} \overline{\{\Phi(t, s, x); t \ge \tau\}}.$$

In other words, $y$ is an element of $\omega_\Phi(s, x)$ if there is a sequence $s \le t_j \to \infty$, $j \to \infty$, such that $\Phi(t_j, s, x) \to y$, $j \to \infty$. We have shown in *Thieme* (1992, Theorem 2.5) that the $\omega$-$\Phi$-limit set of a pre-compact forward orbit is non-empty, compact, connected and attracts the orbit and, most importantly, is invariant under the limit semiflow $\Theta$.

We recall that a $\Theta$-*equilibrium* (or *fixed point*) is an element $e \in X$ such that $\Theta(t, e) = e$ for all $t \ge 0$.

If $\omega_\Phi(s,x) = \{e\}$, then $e$ is a $\Theta$-equilibrium and $\Phi(t,s,x) \to e$ for $t \to \infty$, and we say that the (forward) $\Phi$-orbit of $(s,x)$ converges to $e$.

The basin of attraction (or stable set) of a $\Theta$-equilibrium $e$ is denoted by

$$W_s(e) = \{x \in X; \Theta(t,x) \to e, t \to \infty\}.$$

*Thieme* (1992, Theorem 4.1) shows the following infinite-dimensional version of *Markus*'s Theorem 2 (1956).

**Theorem 2.3.** *Let $e \in X$ be a locally asymptotically stable equilibrium of $\Theta$. Then every pre-compact forward $\Phi$-orbit whose $\omega$-$\Phi$-limit set intersects its basin of attraction $W_s(e)$ converges to $e$.*

We mention that *Thieme* (1992, Corollary 4.3) also considers the situation where all forward orbits of the limit semiflow are attracted by more than one equilibrium. A condition is given under which the same holds for all forward orbits of the asymptotically autonomous semiflow. In order not to introduce too much terminology we only mention a special case.

**Theorem 2.4.** *Let $e_1, e_2 \in X$ be two different equilibria of $\Theta$. Assume that $X$ is the disjoint union of two sets $X_1, X_2$ which are both forward invariant under $\Theta$. Further assume that, for $j = 1,2$, $e_j \in X_j$ and that every pre-compact forward $\Theta$-orbit starting in $X_j$ converges towards $e_j$ and that $e_2$ is locally stable for $\Theta$ and that $e_1$ is locally stable for the restriction of $\Theta$ to $X_1$. Then every pre-compact forward $\Phi$-orbit converges to either $e_1$ or $e_2$.*

*Proof:* We first show that, for $j = 1,2$, $e_j$ is an isolated compact $\Theta$-invariant set. See *Thieme* (1992), for the terminology. It is sufficient to show it for $e_1$. Assume that $\{e_1\}$ is not an isolated compact $\Theta$-invariant set, i.e., that any open neighborhood $U$ of $e_1$ contains a compact $\Theta$-invariant set $M_U$ that is different from $\{e_1\}$. Choosing $U$ small enough we can assume that $e_2 \notin U$. Hence $M_U \subseteq X_1$. Otherwise there would be an orbit starting in $M_U$ that converges towards $e_2$. This orbit would leave $U$ and in particular $M_U$ violating the invariance of $M_U$. Let $x \in M_U, x \neq e_1$. As $M_U$ is compact, there is a full orbit through $x$ in $M_U$ whose $\alpha$-limit set $\alpha$ is compact, non-empty, invariant and contained in $M_U \subseteq X_1$. As $e_1$ is locally stable for the restriction of $\Theta$ to $X_1$, $e_1 \notin \alpha$. As $\alpha$ is non-empty and invariant and is contained in $X_1$, there is an element in $X_1$ whose forward orbit is not attracted to $e_1$, a contradiction.

Secondly the two equilibria cannot be chained to each other in a cyclic way because $e_2$ is locally stable such that there is no orbit connecting $e_2$ to $e_1$. Hence the assumptions of

Corollary 4.3 in *Thieme* (1992) are satisfied and any pre-compact forward $\Phi$-orbit converges towards a $\Theta$-equilibrium, i.e., towards either $e_1$ or $e_2$.

Theorem 2.4 does not specify the domains of attraction of the equilibria $e_1$ and $e_2$ for the asymptotically autonomous semiflow. We add a condition that trivially guarantees that they are the same as for the limit semiflow.

**Theorem 2.5.** *Let $e_1, e_2 \in X$ be two different equilibria of $\Theta$. Assume that $X$ is the disjoint union of a closed set $X_1$ and an open set $X_2$ which are both forward invariant under $\Theta$ and $\Phi$. Further assume that, for $j = 1, 2$, $e_j \in X_j$ and that every pre-compact $\Theta$-orbit starting in $X_j$ converges towards $e_j$ and that $e_2$ is locally stable for $\Theta$ and that $e_1$ is locally stable for the restriction of $\Theta$ to $X_1$. Further assume that $e_1$ is a weak repeller for the semiflow $\Phi$, i.e., no forward $\Phi$-orbit starting in $X_2$ converges to $e_2$. Then, for $j = 1, 2$, every pre-compact forward $\Phi$-orbit starting in $X_j$ converges to $e_j$.*

*Proof:* By Theorem 2.4, pre-compact forward orbits of $\Phi$ converge towards either $e_1$ or $e_2$. As $X_1$ is closed and forward invariant under $\Phi$, any orbit starting in $X_1$ converges towards $e_1$. As $e_1$ is a weak repeller for $X_1$, any orbit starting in $X_2$ converges towards $e_2$.

The proofs in *Thieme* (1992, to appear) rely on proving Butler-McGehee type lemmas for asymptotically autonomous semi-flows. We mention that the Butler-McGehee lemma has been used earlier in as similar way for a chemostat model by *Butler* and *Wolkowitz* (1985). We further mention that Theorem 2.4 and 2.5 also hold when, instead of equilibria, isolated compact $\Theta$-invariant sets are considered.

## 3. A model for sexually transmitted diseases with risk-behavior change

Following *Blythe* et al. (preprint), we consider an $S - I - R - S$ model with a general nonlinear incidence:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - J - \mu S + \rho R, \\
\frac{dI}{dt} &= J - (\gamma + \mu) I, \\
\frac{dR}{dt} &= \gamma I - (\rho + \mu) R, \\
J &= G(S, I, R, N)\, I, \\
N &= S + I + R.
\end{aligned}
\tag{3.1}
$$

$N$ denotes the size of the epidemiologically relevant part of the population, i.e., for sexually transmitted diseases, the sexually active population. As usually, $S, I, R$ denote the numbers of susceptible, infective, and recovered individuals respectively in the relevant part of the population. $J$ denotes the incidence, i.e., the temporal rate of new infections. For simplicity we assume that the function $G$, which describes the dependence of the incidence on the number of susceptible, infective, and recovered individuals and on the total size of the relevant population, is a continuously differentiable and non-negative function of $(S, I, R, N)$ for non-negative $S, I, R$ and strictly positive $N$. The function $G$ has been chosen to have a general form because we assume that individuals have knowledge about the epidemiological state of the population and adjust their behavior according to the perceived risk of being infected. This may lead to quite a complicated functional relationship. See *Blythe* et al. (preprint) for more epidemiological background. There seems to be some redundancy in the function $G$ because one variable could be replaced by the others. The purpose of this redundancy will become apparent later. We require that there are no infections if there are no susceptible, i.e.,

$$G(0, I, R, N) = 0. \tag{3.2}$$

$\Lambda$ is the rate at which individuals are recruited into the epidemiologically relevant part of the population; they enter the susceptible class. $\frac{1}{\mu}$ is the average sojourn time of individuals in the relevant part. Here we assume that both the recruitment rate and the mean sojourn time are not affected by the disease. $\frac{1}{\gamma}$ is the mean length of the infectious period under the condition that the relevant part of the population is not left. $\frac{1}{\rho}$ is the mean length of the immunity period of recovered individuals under the condition that the relevant part of the population is not left. All parameters are assumed to be strictly positive except $\rho$ that may also be 0.

Adding the differential equations in (3.1) we realize that

$$\frac{dN}{dt} = \Lambda - \mu N.$$

Standard arguments provide that solutions starting from non-negative initial data, $N(0) > 0$, are defined and non-negative for all forward times. $N$ is bounded, strictly positive, and bounded away from 0. Further the set

$$N = S + I + R = \frac{\Lambda}{\mu} =: N^* \tag{3.3}$$

is forward invariant and attracts all non-negative solutions in forward time.

The system (3.1) always has the disease-free equilibrium

$$S^\circ = N^*, I^\circ = 0, R^\circ = 0. \tag{3.4}$$

Any endemic equilibrium $S^*, I^*, R^*$ (where $I^*$ is strictly positive) satisfies

$$G(S^*, I^*, R^*, N^*) = \gamma + \mu, \quad S^* + I^* + R^* = N^*, \quad R^* = I^* \frac{\gamma}{\rho + \mu}.$$

Hence $I^*$ satisfies

$$G\Big(N^* - (1+q)I^*, I^*, qI^*, N^*\Big) = \gamma + \mu, \quad 0 < I^* < N^*, \tag{3.5}$$

with

$$q = \frac{\gamma}{\rho + \mu}. \tag{3.6}$$

The autonomous system (3.1) can be rewritten as an asymptotically autonomous planar system:

$$\begin{aligned} \frac{dI}{dt} &= I\Big(G(N - I - R, I, R, N) - \gamma - \mu\Big), \\ \frac{dR}{dt} &= \gamma I - (\rho + \mu)R. \end{aligned} \tag{3.7}$$

where

$$N(t) = N^* + (N(0) - N^*)e^{-\mu t}.$$

(3.7) has the planar limit system

$$\begin{aligned} \frac{dI}{dt} &= I\Big(G(N^* - I - R, I, R, N^*) - \gamma - \mu\Big), \\ \frac{dR}{dt} &= \gamma I - (\rho + \mu)R. \end{aligned} \tag{3.8}$$

We make the following assumption

$$\left(\frac{\partial G}{\partial S} - \frac{\partial G}{\partial I}\right)(S, I, R, N^*) \geq 0, \quad S, I, R \geq 0, S + I + R = N^*. \tag{3.9}$$

**Theorem 3.1.** *Let (3.2), (3.9) and $G(N^*, 0, 0, N^*) \neq \gamma + \mu$ hold and $G(S, I, R, N^*)$ be an analytic function of $(S, I, R)$ with $0 < S, I, R < N^*$. Then any solution to (3.1) starting from non-negative initial data with $N(0) = S(0) + I(0) + R(0) > 0$ converges towards the disease-free equilibrium $(0, 0)$ or towards an endemic equilibrium.*

The exclusion of $G(N^*, 0, 0, N^*) = \gamma + \mu$ is somewhat annoying. This case can also be handled, but requires some additional technical conditions we do not want to go into here,

the more so as, for specific $G$, it can often be dealt with by simple ad hoc considerations. The analyticity assumption for $G$ is to guarantee that (3.5) has only finitely many solutions $I^*, 0 < I^* < N^*$, and can be replaced by assuming just the latter. The rest of this section is devoted to the

*Proof of Theorem 3.1:* We want to apply Corollary 2.2.

We first notice that any $\omega$-limit set of a solution to (3.7) in $X = \{(I,R); I,R \geq 0\}$ is contained in the region

$$Y = \{(I,R); 0 \leq I,R, I+R \leq N^*\}.$$

Equilibria of (3.8) in $Y$ either coincide with the disease-free equilibrium $(0,0)$ or are contained in the region

$$\check{Y} = \{(I,R); I,R > 0, I+R < N^*\}.$$

Recall $G(0,I,R,N) = 0$. By the analyticity assumption for $G$, the left hand side of (3.5) is an analytic function of $0 < I^* < N^*$. Hence (3.5) has either only finitely many solutions with $0 \leq I^* \leq N^*$, or every $I^*$ between 0 and $N^*$ is a solution. The second contradicts $G(0,I,R,N) = 0$. Hence there are only finitely many equilibria of (3.8) in $\check{Y}$ and, since $\check{Y}$ is open, they are also isolated among all equilibria of (3.8) in $\mathbf{R}^2$. It follows from $G(N^*,0,0,N^*) \neq \gamma + \mu$ that $(0,0)$ is also isolated among the equilibria of (3.8) in $\mathbf{R}^2$.

Next we realize that any non-trivial periodic orbit of (3.8) in $Y$ lies in

$$D = \{(I,R); 0 < I,R < N^*\}.$$

This follows from the fact that the axis $I = 0$ is invariant under (3.8) and cannot contain a non-trivial periodic orbit. It follows from the $R$ equation in (3.8), that $R$ is strictly positive, once $I$ is strictly positive. As $I + R \leq N^*$, we have $I, R < N^*$.

Equally, any cyclic chain in $X$ must lie in $D$. First of all, we notice that the disease-free equilibrium $(0,0)$ cannot be part of a cyclic chain of (3.8). Any homoclinic orbit connecting $(0,0)$ to itself in $X$ would lie in $D$. This orbit would tend to $(0,0)$ for $t \to \pm\infty$ which is ruled out by $G(N^*,0,0,N^*) \neq \gamma + \mu$. If $(0,0)$ were part of a cyclic chain in $X$, but not connected to itself by a homoclinic orbit, there would be two orbits converging to $(0,0)$, one for $t \to -\infty$, the other for $t \to \infty$. Both orbits would connect $(0,0)$ to equilibria of (3.8) in $D$. By a similar reasoning as for periodic orbits, the connecting orbits lie in $D$ as well. Again, this cannot happen because $G(N^*,0,0,N^*) \neq \gamma + \mu$.

We now choose

$$\rho(I,R) = \frac{1}{IR}$$

on the open simply connected bounded set $D$. If $g$ denotes the right hand side of (3.8), we have

$$\begin{aligned}\nabla \cdot (\rho g)(I,R) =& \frac{1}{R}\frac{\partial}{\partial I}G(N^* - I - R, I, R) + \frac{\partial}{\partial R}\frac{\gamma}{R} \\ =& \frac{1}{R}\left(-\frac{\partial}{\partial S}G(N^* - I - R, I, R) + \frac{\partial}{\partial I}G(S, I, R)_{|S=N^*-I-R}\right) - \frac{\gamma}{R^2} \\ <& 0.\end{aligned}$$

Our claim now follows from Corollary 2.2.

*Blythe et al.* (preprint) conjecture that the assumptions of Theorem 3.1 are compatible with the existence of multiple endemic equilibria. An (mathematically, though not epidemiologically satisfying) example is given by

$$G(S, I, R, N) = \beta RS/N^2.$$

(If one absolutely want so, one can give the interpretation that a large proportion of recovered individuals may encourage contacts because it creates the impression that contacts may be relatively safe under the present circumstances and that the disease may be easily cured.) Obviously $G$ satisfies the assumptions of Theorem 3.1. The equation for endemic equilibria takes the form

$$R^*\left(N^* - R^*(1 + \frac{\rho+\mu}{\gamma})\right)/N^{*2} = \frac{\gamma+\mu}{\beta}.$$

Setting $\kappa = \frac{R^*}{N^*}\left(1 + \frac{\rho+\mu}{\gamma}\right)$ we have

$$\kappa(1-\kappa) = \frac{(\gamma+\mu)(\rho+\gamma+\mu)}{\gamma\beta} =: \sigma.$$

The left hand side has the maximum $1/4$ , so we can conclude that there is no endemic equilibrium if $\sigma > 1/4$, exactly one endemic equilibrium if $\sigma = 1/4$ and exactly two endemic equilibria if $\sigma < 1/4$.

## 4. Incorporating multiple infective strains with cross-immunity

We now assume that there are different strains of the infective agent which induce (permanent or temporary) complete cross-immunity, i.e., somebody that is infected by one strain cannot be super-infected by another strain and somebody that is immune to one

strain is also immune to all the others. (Compare *Saunders*, 1981, and *Bremermann, Thieme*, 1989.) For other models with complete or partial cross-immunity we refer to *Castillo-Chavez* et al. (1989), *Dwyer, Levin, Buttel* (1990), and the literature mentioned there.)

Let the number of different strains be $n$ and $I_j$ denote the number of individuals infected with strain number $j$ and $R_j$ be the individuals that have recovered from infection with strain $j$ and are now (temporarily or permanently) immune to all strains. The model (3.1) is modified as follows:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \mu S - \kappa \sum_{j=1}^{n} \beta_j I_j + \sum_{j=1}^{n} \rho_j R_j, \\
\frac{dI_j}{dt} &= \kappa \beta_j I_j - (\gamma_j + \mu) I_j, \\
\frac{dR_j}{dt} &= \gamma_j I_j - (\rho_j + \mu) R, \\
\kappa &= K(S, I_1, \ldots, I_n, R_1, \ldots R_n, N), \\
N &= S + \sum_{j=1}^{n} (I_j + R_j).
\end{aligned} \tag{4.1}
$$

We have now made explicit the constant rates $\beta_j$ at which the contact of a susceptible individual with a strain-$j$-infective individual actually leads to an infection. $\kappa$ gives the number of contacts of all susceptible individuals at a given time. The assumption that $\kappa$ is independent of $j$ means that contacts do not discriminate between strains. The dependence of $\kappa$ on $I_1, \ldots, I_n$ and $R_1, \ldots, R_n$ means that the contact numbers may depend on how people adjust their contact behavior according to information on the strain distribution.

Adding the differential equations in (4.1) we again find that

$$\frac{dN}{dt} = \Lambda - \mu N$$

and

$$N(t) \to N^* := \frac{\Lambda}{\mu}, \quad t \to \infty.$$

Set

$$\sigma_j = \frac{\mu + \gamma_j}{\beta_j}. \tag{4.2}$$

If the number of contacts $\kappa$ is constant, then $\kappa/\sigma_j$ is the replacement ratio of strain $j$, i.e., the total number of secondary cases produced by one individual infected by strain $j$. We assume that the difference of the strains is manifested in

$$\sigma_j \neq \sigma_k, \quad j \neq k.$$

Without loss of generality we assume

$$\sigma_1 < \sigma_2 < \cdots < \sigma_n, \tag{4.3}$$

i.e., the first strain is the one with the highest replacement ratio. Following *Saunders* (1981), we set

$$u_j = \frac{1}{\beta_j} \ln \frac{I_j}{I_j(0)} + \sigma_j t,$$

provided that $I_j(t) > 0$. Notice that $I_j(t) > 0$ or $= 0$ respectively, whenever the same holds for $I_j(0)$. It follows from the definition of $u_j$ and from (4.1) that $(d/dt)u_j = \kappa, u_j(0) = 0$. Then $u_1 = u_j$ follows for all times. Using the definition of $u_j$ this implies

$$\left(\frac{I_j(t)}{I_j(0)}\right)^{1/\beta_j} e^{\sigma_j t} = \left(\frac{I_1(t)}{I_1(0)}\right)^{1/\beta_1} e^{\sigma_1 t},$$

in case that $I_1(0) > 0, I_j(0) > 0$. As $\sigma_1 < \sigma_j$ for $j \neq 1$ and $I_1 \leq N$ is bounded, we have that

$$I_j(t) \to 0, t \to \infty, j > 1,$$

with the convergence to 0 being exponentially fast, provided that $I_1(0) > 0$.

*Hence strains that have a lower basic replacement ratio than other strains die out.*

We now trace the fate of the first strain assuming $I_1(0) > 0$:

$$\begin{aligned} \frac{dI_1}{dt} &= \kappa\beta_1 I_1 - (\gamma_1 + \mu)I_1, \\ \frac{dR_1}{dt} &= \gamma_1 I_1 - (\rho_1 + \mu)R, \\ \kappa &= K(N - I_1 - R_1 - \phi, I_1, \ldots, I_n, R_1, \ldots R_n, N), \end{aligned} \tag{4.4}$$

with $N(t) \to N^*, \phi(t) \to 0, I_j(t) \to 0, R_j(t) \to 0$ for $t \to \infty$, $j = 2, \ldots, n$. Hence (4.4) is a planar asymptotically autonomous system that has (3.8) as limit system with

$$G(S, I_1, R_1, N) = \beta_1 K(S, I_1, 0, \ldots, 0, R_1, 0, \ldots, 0, N), \tag{4.5}$$

and $\gamma = \gamma_1, \rho = \rho_1$. The same proof as in Section 3 now provides the following result.

**Theorem 4.1.** *Let $G$ be defined by (4.5) and let (3.2), (3.9), (4.3), and $G(N^*, 0, 0, N^*) \neq \gamma_1 + \mu$ hold. Further let $G(S, I, R, N^*)$ be an analytic function of $(S, I, R)$ with $0 < S, I, R < N^*$. Then any solution to (4.1) with $I_1(0) > 0$ converges to an equilibrium. Moreover $I_j(t) \to 0$, $R_j(t) \to 0$ for $t \to \infty, j = 2, \ldots, n$.*

# 5. An model with arbitrarily distributed removal period

We consider an epidemic model of $S \to I \to R \to S$ type with a distributed length of the removal period. As usually, $S, I, R$ denote the numbers of susceptible, infective, and removed individuals. We assume that the probability $P$ at which a removed individual returns into the susceptible class is described by a non-increasing function $P(c)$ of the individual's class age $c$, i.e., of the time $c$ that has passed since the moment it was removed from the infective class. In order to take this feature into account we stratify the removed part of the population along its class age, i.e.,

$$R(t) = \int_0^\infty r(t,c)dc.$$

We further assume that the per capita rate of effective contacts $C$ (contacts that lead to an infection in case that they occur between a susceptible and an infective individual) depends on the population size $N$, $N = S + I + R$. The incidence (rate of new infections) is then given by $C(N)S\frac{I}{N}$ with $\frac{I}{N}$ giving the chance that a random contact actually occurs with an infective individual. Moreover we suppose some vital dynamics in the form that there is an influx of fresh susceptibles into the populations and individuals die at a fixed per capita rate.

## 5.1. The model. Main result

Let $c_\infty \in (0, \infty]$ be the maximum time span individuals can stay in the removed class, in particular

$$P(c) > 0,\ 0 \le c < c_\infty; \quad P(c) = 0,\ c > c_\infty.$$

Let $\mu$ be the per capita death rate and

$$Q(c) = e^{-\mu c}P(c) \tag{5.1}$$

be the probability to be still in the removed class and alive, provided one has entered this class $c$ time units before. After these preliminaries we can formulate our model as follows:

$$N = S + I + R,$$

$$\frac{dN}{dt} = \Lambda - \mu N,$$

$$\frac{dI}{dt} = C(N)S\frac{I}{N} - (\gamma + \mu)I,$$

$$R(t) = \int_0^{c_\infty} r(t,c)dc, \tag{5.2}$$

$$r(t,c) = \left\{ \begin{array}{ll} \gamma Q(c) I(t-c) & , \ t - t_0 > c \\ \frac{Q(c)}{Q(c-t+t_0)} r_0(c - t + t_0) & , \ c > t - t_0 \end{array} \right\}, \quad 0 \leq c < c_\infty,$$

for $t > t_0$, and

$$N(t_0) = N_0, \ I(t_0) = I_0, \ r(t_0, c) = r_0(c) \text{ for } 0 \leq c < c_\infty.$$

$\Lambda > 0$ denotes a constant influx rate of fresh susceptibles, whereas $\mu$ represents the per capita mortality rate and $\frac{1}{\gamma}$ the mean length of the infective period. The $r$ equation can be explained as follows: If $t - t_0 > c$, removed individuals with class age $c$ at time $t$ are individuals that have been removed from the infective class at time $t - c$, at rate $\gamma$; they are still in the removed class (and alive), with probability $Q(c)$. If $t - t_0 < c$, removed individuals with class age $c$ at time $t$ were already in the removed class before time $t_0$; at time $t_0$ they had a class age $c - t + t_0$. They are still in the removed class with the conditional probability $\frac{Q(c)}{Q(c-t+t_0)}$.

$N$ can be expressed in terms of $\Lambda$ and the initial data:

$$\begin{aligned} N(t) &= N(t_0)e^{-\mu(t-t_0)} + N^* \left(1 - e^{-\mu(t-t_0)}\right), \\ N^* &= \frac{\Lambda}{\mu}. \end{aligned} \tag{5.3}$$

Further the first equation in (5.2) can be used to eliminate $S$:

$$\frac{dI}{dt} = C(N)\frac{I}{N}\left(N - I - \int_0^{c_\infty} r(t,c)dc\right) - (\gamma+\mu)I,$$

$$r(t,c) = \left\{ \begin{array}{ll} \gamma Q(c) I(t-c) & ,t-t_0 > c \\ \frac{Q(c)}{Q(c-t+t_0)} r_0(c-t+t_0) & ,c > t-t_0 \end{array} \right\}, \quad 0 \le c < c_\infty, \tag{5.4}$$

for $t > t_0$, and

$$I(t_0) = I_0,\ r(t_0,c) = r_0(c).$$

Substituting the expression for $r$ into the equation for $I$, (5.4) can be reduced to an integro-differential equation in $I$:

$$\frac{dI}{dt} = \frac{C(N)}{N}\left(N - I - \gamma\int_0^{t-t_0} Q(c)I(t-c)dc + R_0\right)I - (\gamma+\mu)I, \qquad t > t_0, \tag{5.5}$$

with

$$I(t_0) = I_0,\ R_0(t) = \int_0^{c_\infty} \frac{Q(c+t-t_0)}{Q(c)} r_0(c)dc. \tag{5.6}$$

$R_0(t)$ gives the number of removed individuals at time $t$ that have stayed in this class since time $t_0$. Notice that $R_0$ is a non-increasing function of $t$ as $Q(c)$ is decreasing in $c$. It follows from a standard contraction principle argument that (5.5), (5.6) — and so (5.4) — has unique non-negative solutions $I, r$ with $r(t,\cdot) \in L^1_+[0,c_\infty)$ for initial data $I_0 \ge 0, r_0 \in L^1_+[0,c_\infty)$. $L^1_+[0,c_\infty)$ denotes the cone of non-negative integrable functions on $[0,c_\infty)$. Using the Gronwall inequality, one can show that the solutions depend continuously on $I_0, r_0$. Further, by (5.3),

$$N(t) \to N^* = \frac{\Lambda}{\mu}, \quad t \to \infty. \tag{5.7}$$

This guarantees that the solutions exist for all positive times and are bounded. Moreover there is a constant $\hat{N} > 0$ such that, for any solution of (5.5), we have

$$I(t) + \int_0^{c_\infty} r(t,c)dc \le \hat{N} \tag{5.8}$$

for sufficiently large times $t$. For later use we notice that

$$|R_0(t)| \le e^{-\mu(t-t_0)} \int_0^{c_\infty} r_0(c)dc \to 0, \quad t \to \infty, \tag{5.9}$$

for $r_0 \in L^1_+[0, c_\infty)$. After these preparations we formulate our main result.

**Theorem 5.1.** *Let $C(N^*) > \gamma + \mu$ and let the frequency condition*

$$1 + \gamma \int_0^\infty \cos(\nu s) Q(s) ds > 0 \quad \text{for all } \nu > 0 \tag{5.10}$$

*be satisfied. Then the following hold for solutions of (5.2):*

*a) If $I(t_0) = 0$, then $I(t), R(t) \to 0$ for $t \to \infty$.*

*b) If $I(t_0) > 0$, then $I(t) \to I^*, R(t) \to S^*, S(t) \to S^*$ for $t \to \infty$, where*

$$S^* = \frac{\gamma + \mu}{C(N^*)} N^*, \quad I^* = \frac{N^* - S^*}{1 + \gamma Q^*}, \quad R^* = \gamma Q^* I^*, \quad Q^* = \int_0^{c_\infty} Q(c)dc. \tag{5.11}$$

Part a) also holds without $C(N^*) > \gamma + \mu$ and (5.10). The rest of this section is devoted to the proof of Theorem 5.1.

## 5.2. Representation as an asymptotically autonomous semiflow

Uniqueness of solutions and their continuous dependence on initial data imply that the solutions $I, r$ to (5.4) induce a (non-autonomous) semiflow $\Phi$ on $X = [0, \infty) \times L^1_+[0, c_\infty)$,

$$\Phi(t, t_0, (I_0, r_0)) = (I(t), r(t, \cdot)).$$

Standard differential inequalities imply that $\Phi$ is continuous and asymptotically autonomous with the limit-semiflow $\Theta$ being given by $\Theta(t, (I_0, r_0)) = (I(t), r(t, \cdot))$ with $I$ solving

$$\frac{dI}{dt} = \frac{C(N^*)}{N^*} \left( N^* - I - \gamma \int_0^t Q(c) I(t-c) dc + \tilde{R}_0 \right) I - (\gamma + \mu) I,$$

$$\tilde{R}_0(t) = \int_0^{c_\infty} \frac{Q(c+t)}{Q(c)} r_0(c) dc,$$

$$r(t,c) = \begin{cases} \gamma Q(c) I(t-c) & , t > c \\ \frac{Q(c)}{Q(c-t)} r_0(c-t) & , c > t \end{cases}, \quad t > 0, \tag{5.12}$$

$$I(0) = I_0, r(0, \cdot) = r_0.$$

### 5.3. Compactness properties of the semiflow

Let $B \subseteq X_+$ be a bounded set such that, for all $b = (I_0, r_0) \in B$, the solutions $I_b$ to (5.5) are bounded on $[t_0, \infty)$ uniformly for $b \in B$. It follows from (5.5) that

$$\left|\frac{dI_b}{dt}\right| \leq \tilde{N} \quad \text{on } [t_0, \infty)$$

with a constant $\tilde{N} \in (0, \infty)$ that can be chosen independently of $b$. Consider the family $f_{t,b}$ of integrable functions defined by

$$f_{t,b}(c) = \left\{ \begin{array}{cc} \gamma Q(c) I_b(t-c) & , t - t_0 > c \\ 0 & , c > t - t_0 \end{array} \right\}, \quad t > t_0.$$

The usual criterion for compactness of sets in $L^1$ (see *Yosida* 1968, X.1, e.g.) implies that $\{f_{t,b}; t \geq t_0, b \in B\}$ is a pre-compact set in $L^1[0, c_\infty)$. Recall that $Q(c+h) \leq Q(c)e^{-\mu h}$ by (5.1). This implies that, for any measure of non-compactness, $\Gamma$, we have

$$\Gamma(\{\Phi(t, t_0, b); t \geq s, b \in B\}) \leq e^{-\mu(s-t_0)} \sup_{(I_0, r_0) \in B} \int_0^{c_\infty} r_0(c)dc$$

for all $s \geq t_0$. This implies that the $\omega$-$\Phi$-limit set of $\{t_0\} \times B$,

$$\omega_\Phi(\{t_0\} \times B) = \bigcap_{s \geq t_0} \overline{\{\Phi(t, t_0, b); t \geq s, b \in B\}}$$

is non-empty and compact. Estimate (5.8) implies that all forward orbits are bounded and thus have compact closure by the preceeding consideration. Since, by (5.8), there exists a bounded set $B$ to which all solutions are attracted, the compact set $\omega_\Phi(\{t_0\} \times B)$ attracts all $\Phi$-orbits. Similar we find a compact attractor for all $\Theta$-orbits.

### 5.4. Analysis of the limit-equation

Apparently (5.12) has an endemic equilibrium $S^*, I^*, r^*(c)$ with $I^* > 0$ if and only if

$$\frac{C(N^*)}{\gamma + \mu} > 1,$$

where $S^*, I^*$ are given by (5.11) and

$$r^*(c) = \gamma Q(c) I^*.$$

The asymptotic behavior of solutions to (5.12) can be studied following *Stech&Williams* (1981). We introduce

$$z(t) = \ln I(t) - \ln I^*$$

and obtain the following *Stieltjes* integral equation for $z$:

$$\frac{dz}{dt} = -\int_0^t g(z(t-s)d\psi(s) + z_0(t)$$

with

$$g(z) = e^z - 1, \quad \psi(0) = 0,$$

$$\psi(s) = \frac{C(N^*)}{N^*} I^* \left(1 + \gamma \int_0^s Q(c)dc\right),$$

$$z_0(t) = \frac{C(N^*)}{N^*} \left(R_0(t) + \gamma I^* \int_t^\infty Q(c)dc\right).$$

The same analysis as in *Stech&Williams* (1981) — based on *Londen* (1975) — provides convergence of solutions towards the endemic equilibrium provided the frequency condition (5.10) holds. Note that the moment condition $\int_0^{c_\infty} cQ(c)dc < \infty$ is automatically satisfied by (5.1) and the fact that $P$ is non-increasing.

**Theorem 5.2.** *Let $C(N^*) > \gamma + \mu$ and (5.10) hold and $I(0) > 0$. Then, for any solution to (5.12), $I(t) \to I^*, R(t) \to R^*$ for $t \to \infty$. Moreover the endemic equilibrium is locally asymptotically stable.*

The local asymptotic stability under the assumptions of Theorem 5.2 does not follow immediately from *Stech, Williams* (1981). They (*Stech, Williams*, 1981, Section 4) rather show that the endemic equilibrium is locally asymptotically stable if

$$\lambda + \frac{C(N\infty)I^*}{N^*} \left(1 + \gamma \int_0^{c_\infty} e^{-\lambda c} Q(c)dc\right) \neq 0 \quad \forall \lambda \in \mathbf{C}, \Re\lambda \geq 0. \tag{5.13}$$

Actually (5.10) implies (5.13) by a continuation argument adopted from *Hethcote, Thieme* (1985). Define

$$Q_\xi(c) = \xi Q(c) + (1-\xi)e^{-c}, \quad c \geq 0, 0 \leq \xi \leq 1,$$

and set

$$\phi_\xi(\lambda) = \lambda + \frac{C(N\infty)I^*}{N^*}(1 + \gamma\hat{Q}_\xi(\lambda))$$

with $\hat{Q}_\xi$ denoting the *Laplace transform* of $Q_\xi$. Recall that $Q(c) = 0$, $c > c_\infty$. Apparently

$$\hat{Q}_0(\lambda) = \frac{1}{1+\lambda} = \frac{1+\bar{\lambda}}{|1+\lambda|^2}.$$

In particular $\phi_0(\lambda) \neq 0$ if $\Re\lambda \geq 0$. Assume that (5.13) is violated, i.e. $\phi_1(\lambda) = 0$ for some $\lambda$ with $\Re\lambda \geq 0$. If $\Re\lambda = 0$, (5.10) is violated as well, so we can assume that $\Re\lambda > 0$. By *Rouché's* theorem, the zeros $\lambda$ of $\phi_\xi$ depend continuously on $\xi$ at least as long as their real parts are larger than $-\mu$. Observe that $|Q_\xi(\lambda)| \to 0$ uniformly in $\xi \in [0,1]$, if $\Re\lambda + |\Im\lambda| \to \infty$, by the *Riemann&Lebesgue* Lemma. So, as $\phi_1$ has a zero $\lambda$ with positive real part, but $\phi_0$ has no zero with non-negative real part, there must exist some $\xi \in (0,1]$ such that $\phi_\xi(\lambda) = 0$ for some $\lambda$ with $\Re\lambda = 0$. This implies

$$1 + \xi\gamma \int_0^{c_\infty} \cos(\nu c) Q(c) dc + \frac{1-\xi}{1+\nu} = 0$$

with $\nu = \Im\lambda$. As $0 < \xi \leq 1$, this contradicts (5.10).

### 5.5. Convergence towards the endemic equilibrium

The autonomous convergence result stated in Theorem 5.2 is inherited by the asymptotically autonomous system (5.4), as Theorem 5.1 follows from the subsequent

**Theorem 5.3.** *Let $C(N^*) > \gamma + \mu$ and $Q$ satisfy the frequency condition (5.10). Then, for any solution to (5.4), the following hold:*

*a) If $I(t_0) > 0$, then $I(t) \to I^*, R(t) \to R^*$, for $t \to \infty$.*

*b) If $I(t_0) = 0$, then $I(t) \to 0, R(t) \to 0$ for $t \to \infty$.*

*Proof:* b) is immediate. In order to see a) we want to apply Corollary 2.5. Let $X = [0,\infty) \times L^1_+[0,\infty)$, $X_1 = \{0\} \times L^1_+[0,\infty)$, and $X_2 = (0,\infty) \times L^1_+[0,\infty)$. Then $X_1$ and $X_2$ are forward invariant under $\Theta$ and $\Phi$, $X_1$ is closed and $X_2$ is open in $X$. By the results by *Stech, Williams* (1981), see Theorem 5.2, the equilibrium $e_2 = (I^*, r^*)$ attracts every $\Theta$-orbit starting in $X_2$ and $e_1 = (0,0)$ attracts every $\Theta$-orbit starting in $X_1$. Moreover $e_2$ is locally stable and $e_1$ is locally stable for the restriction of $\Theta$ to $X_1$. Recall that, for $I(0) = 0$, $R(t) = \tilde{R}_0(t)$ is non-increasing. Further every $\Phi$-orbit is pre-compact in $X$ by the compactness considerations in Subsection 5.3. Finally $e_1$ is a weak repeller for $X_2$: Assume that there is a solution starting in $X_2$ that converges to $e_1$. As $I_1(0) > 0$, $I_1(t) > 0$ for all $t \geq 0$. It follows from (5.5) and $C(N^*) > \gamma + \mu$ that

$$\liminf_{t\to\infty} \frac{d}{dt} \ln I_1(t) > 0,$$

which implies that $I_1(t)$ finally exhibits exponential increase, a contradiction. Thus all assumptions of Corollary 2.5 are satisfied and our assertion follows.

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