Transmission dynamics of infectious diseases on transportation networks

Abstract of Ph.D. Thesis

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Introduction

Delay differential equations have numerous applications in science and engineering. They arise from the mathematical modeling of time-dependent processes where the evolution of the system is not only determined by the present state of the process, but it also depends on certain past states. These equations are different from ordinary differential equations, as the derivative of the unknown function at any time is given by the values of the function at present and prior times. In most applications of delay equations, the delayed feedback function is given explicitly. In this Ph.D. dissertation we propose various models from population dynamics and epidemiology, where the delay terms in the model equations arise as the solution of another dynamical system. The general form of initial value problems for nonautonomous functional differential equations with such dynamically defined delayed feedback function will also be considered in this work. We obtain the usual existence, uniqueness and continuous dependence result for the solution, and show some other, biologically relevant properties. The results derived for the general framework enable us to analyze the model equations coming from biological applications, and in particular, they also provide a powerful tool to investigate some questions of major public health concern, such as the spatial spread of infectious diseases.

The thesis is based on the following publications of the author:

- D. H. Knipl and G. Röst, *Multiregional SIR model with infection during transportation*, Biomath 1 (2012), 1209255 `http://dx.doi.org/10.11145/j.biomath.2012.09.255`
- D. H. Knipl, *Fundamental properties of differential equations with dynamically defined delayed feedback*, Electron. J. Qual. Theory Differ. Equ. No. 17 (2013) pp. 1–18. `http://www.math.u-szeged.hu/ejqtde/p1883.pdf`
- D. H. Knipl, G. Röst and J. Wu, *Epidemic Spread and Variation of Peak Times in Connected Regions Due to Travel-Related Infections — Dynamics of an Antigravity-Type Delay Differential Model*, SIAM J. Appl. Dyn. Syst. 12(4) (2013) pp. 1722—1762. `http://epubs.siam.org/doi/abs/10.1137/130914127`
- D. H. Knipl and G. Röst, *Backward bifurcation in SIVS model with immigration of non-infectives*, Biomath 2 (2013), 1312051 `http://dx.doi.org/10.11145/j.biomath.2013.12.051`

Differential equations with dynamically defined delay term

We consider the initial value problem for the nonautonomous functional differential equation

$$\begin{aligned} x'(t) &= \mathcal{F}(t, x_t), \\ x_\sigma &= \varphi, \end{aligned} \tag{2.1}$$

where $x\colon \mathbb{R} \to \mathbb{R}^n$, $n \in \mathbb{Z}_+$, $t, \sigma \in \mathbb{R}$ and $t \geq \sigma$. For $\tau > 0$, we define our phase space $C = C([-\tau, 0], \mathbb{R}^n)$ as the Banach space of continuous functions from $[-\tau, 0]$ to $\mathbb{R}^n$, equipped with the usual supremum norm $||\cdot||$. Let $\varphi \in C$ be the state of the system at σ. For the segment we use the notation $x_t \in C$, where $x_t(\theta) = x(t+\theta)$ for $\theta \in [-\tau, 0]$. Let $\mathcal{F}\colon \mathbb{R} \times C \to \mathbb{R}^n$ and let $\mathcal{F}$ have the special form $\mathcal{F}(t, \phi) = f(t, \phi(0)) + W(t, \phi(-\tau))$ for $\phi \in C$, $f\colon \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$, $W\colon \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$.

We use the notation $|v|_j$ for the Euclidean norm of any vector $v \in \mathbb{R}^j$ for $j \in \mathbb{Z}_+$. We define a Lipschitz condition as follows. For $j, l \in \mathbb{Z}_+$, we say that a function $F\colon \mathbb{R} \times \mathbb{R}^j \to \mathbb{R}^l$ satisfies the Lipschitz condition (Lip) on each bounded subset of $\mathbb{R} \times \mathbb{R}^j$ if:

(Lip) For all a, $b \in \mathbb{R}$ and $M > 0$, there is a $K(a, b, M) > 0$ such that:

$$|F(t, x_1) - F(t, x_2)|_l \leq K|x_1 - x_2|_j, \ a \leq t \leq b, \ |x_1|_j, |x_2|_j \leq M.$$

We assume that $f\colon \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}^n$ is continuous and satisfies (Lip) on each bounded subset of $\mathbb{R} \times \mathbb{R}^n$. For the definition of W, we make the following preparations. For any $s_0 \in \mathbb{R}$ and $y_* \in \mathbb{R}^m$, $m \in \mathbb{Z}_+$, we consider the initial value problem

$$\begin{aligned} y'(s) &= g(s, y(s)), \\ y(s_0) &= y_*, \end{aligned} \tag{2.2}$$

where $y\colon \mathbb{R} \to \mathbb{R}^m$, $s, s_0 \in \mathbb{R}$, $s \geq s_0$, $g\colon \mathbb{R} \times \mathbb{R}^m \to \mathbb{R}^m$, g is continuous on $\mathbb{R} \times \mathbb{R}^m$ and satisfies the Lipschitz condition (Lip) on each bounded subset of $\mathbb{R} \times \mathbb{R}^m$. The Picard–Lindelöf theorem (see Chapter II, Theorem 1.1 and Chapter V, Theorem 2.1 in [5]) states that there exists a unique solution $y(s; s_0, y_*)$ of (2.2) on the interval $[s_0, s_0 + \alpha]$ for some $\alpha > 0$, and the solution continuously depends on the initial data. We make the following additional assumption:

$(\star)$ For every s_0 and y_*, the solution $y(s; s_0, y_*)$ of (2.2) exists for τ units of time, i.e., on $[s_0, s_0 + \tau]$.

Remark 2.1. The reader may notice that $(\star)$ is equivalent to the following assumption: For every s_0 and y_* the solution $y(s; s_0, y_*)$ exists for all $s \geq s_0$.

Remark 2.2. If we assume that a global Lipschitz condition $(gLip)$ holds for g, that is, the Lipschitz constant for g in (Lip) can be chosen independently of a, b and M, then for any s_0 and y_* the solution of (2.2) exists for all $s \geq s_0$, thus also for τ units of time.

Now we are ready for the definition of W. For $h\colon \mathbb{R}\times\mathbb{R}^n\to\mathbb{R}^m$ and $k\colon \mathbb{R}\times\mathbb{R}^m\to\mathbb{R}^n$, let us assume that h and k are continuous and satisfy the Lipschitz condition (Lip). For simplicity, we use the notation $y_{s_0,v}(s)=y(s;s_0,h(s_0,v))$ for the unique solution of system (2.2) in the case $y_*=h(s_0,v)$, $v\in\mathbb{R}^n$. We define $W\colon \mathbb{R}\times\mathbb{R}^n\to\mathbb{R}^n$ as

$$W(s,v)=k(s,y_{s-\tau,v}(s))=k(s,y(s;s-\tau,h(s-\tau,v))).$$

A Lipschitz condition (Lip^C) is satisfied for $\mathcal{F}$ on each bounded subset of $\mathbb{R}\times C$ if:

(Lip^C) For all a, $b\in\mathbb{R}$ and $M>0$, there is a $K(a,b,M)>0$ such that:

$$|f(t,\phi)-f(t,\psi)|_n\le K||\phi-\psi||,\ a\le t\le b,\ ||\phi||,||\psi||\le M.$$

Before we arrive to an existence–uniqueness theorem on system (2.1), we obtain two simple results. In the proof of the theorem we follow [12].

Proposition 2.3. *$\mathcal{F}$ is continuous on $\mathbb{R}\times C$.*

Lemma 2.5. *$\mathcal{F}$ satisfies the Lipschitz condition (Lip^C) on each bounded subset of $\mathbb{R}\times C$.*

Theorem 2.7. *Let $\sigma\in\mathbb{R}$, $M>0$. There exists $A>0$, depending only on M such that if $\phi\in C=C([-\tau,0],\mathbb{R}^n)$ satisfies $||\phi||\le M$, then there exists a unique solution $x(t)=x(t;\sigma,\phi)$ of (2.1), defined on $[\sigma-\tau,\sigma+A]$. In addition, if K is the Lipschitz constant for $\mathcal{F}$ corresponding to $[\sigma,\sigma+A]$ and M, then*

$$\max_{\sigma-\tau\le\eta\le\sigma+A}|x(\eta;\sigma,\phi)-x(\eta;\sigma,\psi)|_n\le||\phi-\psi||e^{KA}\ \textit{for any}\ ||\phi||,||\psi||\le M.$$

Assuming stronger conditions on f, g, h and k yields a more general result.

Remark 2.8. If f, g, h and k satisfy condition $(gLip)$, then we do not need to make any restrictions on A in Theorem 2.7. More precisely, its statements hold for any $A>0$. In this case, the solution exists for every $t\ge\sigma$ and the inequality

$$||x_t(\phi)-x_t(\psi)||\le||\phi-\psi||e^{K(t-\sigma)}$$

holds for all $t\ge\sigma$.

Most functional differential equations that arise in population dynamics or epidemiology deal only with nonnegative quantities. Therefore it is important to see what conditions ensure that nonnegative initial data give rise to nonnegative solution.

Proposition 2.9. *Suppose that* $h\colon \mathbb{R}\times\mathbb{R}^n\to\mathbb{R}^m$ *and* $k\colon \mathbb{R}\times\mathbb{R}^m\to\mathbb{R}^n$ *map nonnegative vectors to nonnegative vectors for each* $t\in\mathbb{R}$*, moreover assume that*

$$\forall i,t,\forall u\in\mathbb{R}^n_+:\ \ u_i=0\Rightarrow f_i(t,u)\geq 0,$$
$$\forall j,s,\forall w\in\mathbb{R}^m_+:\ \ w_j=0\Rightarrow g_j(s,w)\geq 0.$$

Then for nonnegative initial data the solution of system (2.1) preserves non-negativity, i.e., $x(t)\geq 0$ *for all* $t\geq\sigma$ *where it is defined.*

A delay model for the spread of pandemics between connected regions

We formulate a dynamic model to properly describe the temporal evolution of an epidemics in two regions connected by long distance travel, such as intercontinental flights. Based on the risk assessment guideline of the European Centre for Disease Prevention and Control (ECDC) ([4]), which confirmed that on-board transmission of infectious diseases (e.g., influenza) was possible in flights even with a duration of less than eight hours, we assume that the time needed to complete transportation is not negligible, and we incorporate the possibility into the model that individuals may contract the disease while traveling. The well-known SEAIR (susceptible–exposed–asymptomatic infected–infected–recovered) model is used as a basic epidemic model building block in the regions and also during travel. In the model we distinguish local residents from visitors to account for differences in individuals' mixing behavior.

Let $\tau>0$ denote the average time required to complete a one-way trip. We divide the population in each region into 10 compartments, according to individuals' disease state and residential status (resident versus visitor of the current region, denoted by upper index $m\in\{r,v\}$). Lower index $j\in\{1,2\}$ specifies the region. By means of similar characterization, 10 classes are distinguished for individuals during travel: lower index-pair (j,k), $j,k\in\{1,2\}, j\neq k$, indicates that the individual is traveling from region j to k, and upper index $m\in\{r,v\}$ is used to denote the individual's residential status in the region he/she has just left. All variables and model parameters are listed in the table after the bibliography. Assuming standard incidence, the nonlinear force of infection terms arise as

$$F_j^r(t)=\frac{1}{N_j(t)}\left(\beta_j^{rr}(I_j^r(t)+\rho A_j^r(t))+\beta_j^{vr}(I_j^v(t)+\rho A_j^v(t))\right),$$
$$F_j^v(t)=\frac{1}{N_j(t)}\left(\beta_j^{rv}(I_j^r(t)+\rho A_j^r(t))+\beta_j^{vv}(I_j^v(t)+\rho A_j^v(t))\right),$$
$$F_{j,k}^T(\theta;t_*)=\frac{\beta^T}{n_{j,k}(\theta;t_*)}(i_{j,k}^r(\theta;t_*)+i_{j,k}^v(\theta;t_*)+\rho(a_{j,k}^r(\theta;t_*)+a_{j,k}^v(\theta;t_*))),$$

and the following system of differential equations describes disease transmission in region j, $j \in \{1,2\}$, where $t \geq 0$ denotes time:

$$
\begin{cases}
\dot{S}_j^r(t) = \Lambda_j - S_j^r(t)F_j^r(t) - (d_j^r + \alpha_j)S_j^r(t) + s_{k,j}^v(\tau; t-\tau), \\
\dot{E}_j^r(t) = S_j^r(t)F_j^r(t) - (d_j^r + \mu_{_E} + \alpha_j)E_j^r(t) + e_{k,j}^v(\tau; t-\tau), \\
\dot{A}_j^r(t) = (1-p)\mu_{_E}E_j^r(t) - (d_j^r + \alpha_j + \mu_A)A_j^r(t) + a_{k,j}^v(\tau; t-\tau), \\
\dot{I}_j^r(t) = p\mu_{_E}E_j^r(t) - (d_j^r + \alpha_j + \delta + \mu_I)I_j^r(t) + i_{k,j}^v(\tau; t-\tau), \\
\dot{R}_j^r(t) = \mu_I I_j^r(t) + \mu_A A_j^r(t) - (d_j^r + \alpha_j)R_j^r(t) + r_{k,j}^v(\tau; t-\tau), \\
\\
\dot{S}_j^v(t) = -S_j^v(t)F_j^v(t) - (d_j^v + \gamma_j)S_j^v(t) + s_{k,j}^r(\tau; t-\tau), \\
\dot{E}_j^v(t) = S_j^v(t)F_j^v(t) - (d_j^v + \mu_{_E} + \gamma_j)E_j^v(t) + e_{k,j}^r(\tau; t-\tau), \\
\dot{A}_j^v(t) = (1-p)\mu_{_E}E_j^v(t) - (d_j^v + \gamma_j + \mu_A)A_j^v(t) + a_{k,j}^r(\tau; t-\tau), \\
\dot{I}_j^v(t) = p\mu_{_E}E_j^v(t) - (d_j^v + \gamma_j + \delta + \mu_I)I_j^v(t) + i_{k,j}^r(\tau; t-\tau), \\
\dot{R}_j^v(t) = \mu_I I_j^v(t) + \mu_A A_j^v(t) - (d_j^v + \gamma_j)R_j^v(t) + r_{k,j}^r(\tau; t-\tau).
\end{cases}
\tag{L}
$$

For each given $t_* \geq 0$, the evolution of the densities of individuals with respect to θ are described by the following system (T), where $\theta \in [0, \tau]$ denotes the time elapsed since the beginning of the travel which was initiated at time t_*:

$$
\begin{cases}
\dfrac{\mathrm{d}}{\mathrm{d}\theta}s_{j,k}^r(\theta; t_*) = -s_{j,k}^r(\theta; t_*)F_{j,k}^T(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}e_{j,k}^r(\theta; t_*) = s_{j,k}^r(\theta; t_*)F_{j,k}^T(\theta; t_*) - \mu_{_E}^T e_{j,k}^r(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}a_{j,k}^r(\theta; t_*) = (1-p)\mu_{_E}^T e_{j,k}^r(\theta; t_*) - \mu_{_A}^T a_{j,k}^r(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}i_{j,k}^r(\theta; t_*) = p\mu_{_E}^T e_{j,k}^r(\theta; t_*) - \mu_I^T i_{j,k}^r(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}r_{j,k}^r(\theta; t_*) = \mu_{_A}^T a_{j,k}^r(\theta; t_*) + \mu_I^T i_{j,k}^r(\theta; t_*), \\
\\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}s_{j,k}^v(\theta; t_*) = -s_{j,k}^v(\theta; t_*)F_{j,k}^T(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}e_{j,k}^v(\theta; t_*) = s_{j,k}^v(\theta; t_*)F_{j,k}^T(\theta; t_*) - \mu_{_E}^T e_{j,k}^v(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}a_{j,k}^v(\theta; t_*) = (1-p)\mu_{_E}^T e_{j,k}^v(\theta; t_*) - \mu_{_A}^T a_{j,k}^v(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}i_{j,k}^v(\theta; t_*) = p\mu_{_E}^T e_{j,k}^v(\theta; t_*) - \mu_I^T i_{j,k}^v(\theta; t_*), \\
\dfrac{\mathrm{d}}{\mathrm{d}\theta}r_{j,k}^v(\theta; t_*) = \mu_{_A}^T a_{j,k}^v(\theta; t_*) + \mu_I^T i_{j,k}^v(\theta; t_*),
\end{cases}
\tag{T}
$$

where $j, k \in \{1,2\}, j \neq k$. The initial values for system (T) at $\theta = 0$ are determined by the rates at which individuals start their travels from one region to the other at time t_*.

The terms $s^m_{k,j}(\tau;t-\tau)$, $e^m_{k,j}(\tau;t-\tau)$, $a^m_{k,j}(\tau;t-\tau)$, $i^m_{k,j}(\tau;t-\tau)$, $r^m_{k,j}(\tau;t-\tau)$ in system (L) give the inflow of individuals arriving from region k to compartments S^n_j, E^n_j, A^n_j, I^n_j, R^n_j, $j,k \in \{1,2\}$, $j \neq k$, $m,n \in \{r,v\}, m \neq n$, respectively, at time t.

It is possible to show that systems (L) and (T) can be written in closed forms as systems (2.1) and (2.2), respectively, with their right hand sides independent of t and s (note that θ corresponds to s in terms of the notations of chapter "Differential equations with dynamically defined delay term"). The phase space for the model can be defined as $C_+ = C([-\tau,0],\mathbb{R}^{20}_+)$. We refer to the results of the previous chapter to obtain the following statements.

Proposition 3.1. *For any initial data $\Phi \in C_+$, the solution of system (L) is nonnegative where it exists. System (T) preserves non-negativity for nonnegative initial values.*

Proposition 3.3. *For any fixed t_* and initial data, there exists a unique solution of system (T) on $[0,\infty)$.*

Theorem 3.4. *For any initial data $\Phi \in C_+$, there exists a unique solution of system (L) defined on $[-\tau,\infty)$.*

The next propositions state some other biologically relevant results on the global behavior and boundedness of the solution. We recall that δ denotes disease-induced mortality.

Proposition 3.6. *If $\delta = 0$ then the total populations $(N^r_1(t), N^v_1(t), N^r_2(t), N^v_2(t))$ converge to a unique positive equilibrium, which is denoted by $(\hat{N}^r_1, \hat{N}^v_1, \hat{N}^r_2, \hat{N}^v_2)$.*

Proposition 3.7. *Solutions of system (L) are bounded.*

The basic reproduction number $(\mathcal{R}_0)$ is a central quantity in epidemiology as it determines the average number of secondary infections caused by a typical infected individual during the period of infectiousness, who was introduced into a completely susceptible population. This number is defined as the dominant eigenvalue of the next generation matrix, as introduced in [2, 3]. We apply some modifications on the model setup as we neglect the transition from exposed to infected, and from infected to recovered classes during travel, i.e., we assume that $\mu^T_{_E} = \mu^T_{_A} = \mu^T_{_I} = 0$. This hypothesis allows us to calculate the basic reproduction number explicitly. In the sequel we denote by $(\bar{L})$ the special case of (L) with $\mu^T_{_E} = \mu^T_{_A} = \mu^T_{_I} = 0$.

We construct the next generation matrix $\mathcal{N}$ for system $(\bar{L})$ as we divide all exposed individuals into four groups: residents of region 1 (E^r_1), visitors of region 1 (E^v_1), residents of region 2 (E^r_2) and visitors of region 2 (E^v_2). We denote the number of new infections

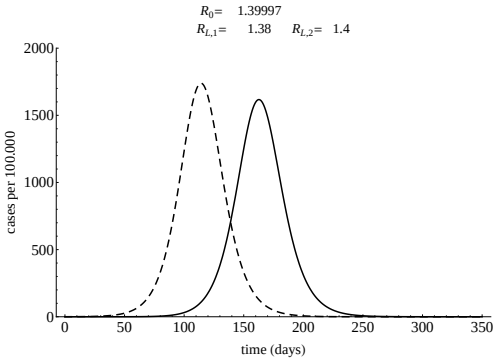

Figure 3.12: Epidemic curves of Canada (region 1, solid curve, peak time: day 160) and Mexico (region 2, dashed curve, peak time: day 117) when peak times were fitted to the real morbidity data of the first wave of the 2009 H1N1 and day 0 corresponds to December the 31st 2008. We ignore demography and set $\mathcal{R}_{L,1} = 1.38$, $\mathcal{R}_{L,2} = 1.4$, $\tau = 0.25$, $\gamma_1^{-1} = \gamma_2^{-1} = 15$, $\beta^T = 20$, $\mu_E^{-1} = 1.4$, $\mu_I^{-1} = 2.7$, $\mu_A^{-1} = 4.1$, $p = 0.6$, $\rho = 0.1$.

among individuals of region k with residential status n generated by an exposed individual of region j with residential status m by $R_{j,k}^{m,n}$, where $j, k \in \{1, 2\}, m, n \in \{r, v\}$. Then $\mathcal{N} \in \mathbb{R}^{4\times 4}$ has the form

$$\mathcal{N} = \begin{pmatrix} R_{11}^{rr} & R_{11}^{vr} & R_{21}^{rr} & R_{21}^{vr} \\ R_{11}^{rv} & R_{11}^{vv} & R_{21}^{rv} & R_{21}^{vv} \\ R_{12}^{rr} & R_{12}^{vr} & R_{22}^{rr} & R_{22}^{vr} \\ R_{12}^{rv} & R_{12}^{vv} & R_{22}^{rv} & R_{22}^{vv} \end{pmatrix}.$$

We define two possible ways of reproduction (the birth of new infection):

(i) a susceptible moves to exposed class while being in a region;

(ii) an exposed individual, who was susceptible before travel, arrives to a region upon completing a trip.

We can obtain the elements of $\mathcal{N}$ by biological reasoning, i.e., by following a typical infected individual during the infectious period, and using our definition of reproduction. It is possible to show that the positive equilibrium $(\hat{N}_1^r, \hat{N}_1^v, \hat{N}_2^r, \hat{N}_2^v)$, which is globally attracting by Proposition 3.6 for $\delta = 0$, works as the unique disease free steady state of system $(\bar{L})$. The following stability result can be obtained in terms of the reproduction number.

Proposition 3.11. *The disease free equilibrium of system* $(\bar{L})$ *is asymptotically stable if* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$.

We parametrize our model for the 2009 A(H1N1) pandemic influenza and use real demographic and air travel data for the numerical simulations. To understand the role

of the different characteristics of the regions played in the propagation of the disease, three distinct origin–destination pairs are considered for the regions. To illustrate the applicability of our approach, we fit the model to the first wave of the 2009 A(H1N1)v pandemic in Canada and Mexico. Travel rates were derived from [6], and we used the public reports of the Mexican Social Security Institute ([10]), the WHO Global Influenza Virological Surveillance ([15]) and the Public Health Agency of Canada ([11]) to estimate historical peak times (day 117–123 in Mexico and day 155–162 in Canada with day 0 corresponding to December 31, 2008). For the simulations we set the local reproduction numbers to ensure that the peak times of the epidemic curves fit the real morbidity data. The result can be seen in Figure 3.12, where $\mathcal{R}_{L,1} = 1.38$ (Canada) and $\mathcal{R}_{L,2} = 1.4$ (Mexico).

Epidemic models with travel related infection

Two further models are presented to describe disease propagation in connected regions. First, an SIR (susceptible–infected–recovered) epidemic model for the spread of infection in and between two regions is investigated, which incorporates the possibility of an entry screening procedure initiated for travelers upon arrival to a region. Such an intervention technique, among other prevention strategies like partial or full airport closure, is considered to be a potential tool in epidemic prevention and control. The model setup gives rise to a situation where the dimension of the system for disease spread in the regions differs from the dimension of the system during travel.

As another example, we also present a model for disease transmission in a population of individuals who travel between r regions. We consider a general transportation network, and we account for the fact that trips between different regions may have different durations. Henceforth a system of autonomous equations with *multiple* delays is formulated to describe the spread of infection in the regions, where each delay term is described via the solution of another differential system for the disease dynamics during travel. Multiple delays in the model setup necessitate the extension of the general framework elaborated in chapter "Differential equations with dynamically defined delay term". In each region and also during the travel from one territory to another, the SIR model is used as a basic model building block. The typical assumptions of standard incidence and mass action incidence on the type of disease transmission are replaced by considering a general infection term, and we give conditions on the infection term for the existence of solutions in the model.

Backward bifurcation in SIVS model with immigration of non-infectives

This chapter concerns with an SIVS (susceptible–infected–vaccinated–susceptible) disease transmission model with travel related inflow of individuals (e.g., immigration). The model is an extension of the works [1, 7, 8], where an epidemic model with vaccination of susceptible individuals in a single population were considered. In our model we incorporate the possibility of immigration of susceptible and vaccinated individuals into the population, the general vaccination model with immigration of non-infected individuals can be described by the system

$$\begin{aligned}\dot{S}(t) =&\Lambda(N(t)) - \beta(N(t))S(t)I(t) - (\mu+\phi)S(t) + \gamma I(t) + \theta V(t) + \eta,\\ \dot{I}(t) =&\beta(N(t))S(t)I(t) + \sigma\beta(N(t))V(t)I(t) - (\mu+\gamma)I(t),\\ \dot{V}(t) =&\phi S(t) - \sigma\beta(N(t))V(t)I(t) - (\mu+\theta)V(t) + \omega,\end{aligned} \tag{5.4}$$

where $S(t)$, $I(t)$, $V(t)$ and $N(t)$ denote the number of susceptible, infected, vaccinated individuals and the total population, respectively, at time t. Λ represents the birth function into the susceptible class and μ is the natural death rate in each class. Disease transmission is modeled by the infection term $\beta(N)SI$, ϕ and γ stand for the vaccination rate of susceptible individuals and the recovery rate of infected individuals. It is assumed that vaccination loses effect at rate θ, moreover $0 \leq \sigma \leq 1$ is introduced to model the phenomenon that vaccination may reduce but not completely eliminate susceptibility to infection. We assume that immigration of susceptible and vaccinated individuals occur with constant rates η and ω, respectively. For the dynamics in the total population $N(t)$ we obtain the equation

$$\dot{N}(t) = \Lambda(N(t)) - \mu N(t) + \eta + \omega.$$

The following proposition gives conditions for the existence of a single positive steady state of N.

Proposition 5.1. *If for the birth function Λ it holds that $\Lambda(0) = 0$, $\Lambda'(0) > \mu$ and there exists an $x_* > 0$ such that $\Lambda'(x_*) < \mu$, moreover $\Lambda'(x) > 0$ and $\Lambda''(x) < 0$ for all $x > 0$, then for any $\eta, \omega \geq 0$ there exists a unique positive solution of $\Lambda(x) = \mu x - \eta - \omega$.*

By defining the population carrying capacity $K = K(\Lambda, \mu, \eta, \omega)$ as the unique solution of $\Lambda(x) = \mu x - \eta - \omega$, it follows from standard arguments that the total population converges to the carrying capacity. Using that $S(t) = N(t) - I(t) - V(t)$ and $\lim_{t\to\infty} N(t) = K$ we can rewrite equations $(5.4)_2$ and $(5.4)_3$, and find that system (5.4) is asymptotically autonomous with the limiting system

$$\begin{aligned}\dot{I}(t) =&\beta(K - I(t) - (1-\sigma)V(t))I(t) - (\mu+\gamma)I(t),\\ \dot{V}(t) =&\phi(K - I(t)) - \sigma\beta V(t)I(t) - (\mu+\theta+\phi)V(t) + \omega,\end{aligned} \tag{5.6}$$

where $\beta = \beta(K)$. In what follows we focus on the mathematical analysis of system (5.6), then we use the theory of asymptotically autonomous systems ([9, 13, 14]) to obtain information on the long-term behavior of solutions of (5.4).

The existence and uniqueness of solutions of system (5.6) follows from fundamental results for ODEs ([5]). We also obtain non-negativity and boundedness for solutions.

Proposition 5.2. *If for initial values $I(0)$ and $V(0)$ it holds that $0 \leq I(0), V(0), I(0) + V(0) \leq K$, then $0 \leq I(t), V(t), I(t) + V(t) \leq K$ is satisfied for all $t > 0$.*

The basic reproduction number can be defined as

$$\begin{aligned}\mathcal{R}_0 &= \frac{\beta(K - (1-\sigma)\bar{V})}{\mu + \gamma} \\ &= \frac{\beta}{\mu + \gamma}\left(\frac{K(\mu + \theta + \sigma\phi)}{\mu + \theta + \phi} - \frac{(1-\sigma)\omega}{\mu + \theta + \phi}\right),\end{aligned}$$

where $\bar{V} = \frac{\phi K + \omega}{\mu + \theta + \phi}$ is the unique disease free equilibrium. For its stability the following result holds:

Proposition 5.3. *The disease free equilibrium of system (5.6) is asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The problem of finding endemic (positive) equilibrium $(\hat{I}, \hat{V})$ for system (5.6) leads to the formula

$$\hat{V} = \frac{\beta(K - \hat{I}) - (\mu + \gamma)}{\beta(1 - \sigma)}$$

for $\hat{V}$ and the second order equation

$$A\hat{I}^2 + B\hat{I} + C = 0 \tag{5.11}$$

for $\hat{I}$, where

$$\begin{aligned}A =& \sigma\beta, \\ B =& (\mu + \theta + \sigma\phi) + \sigma(\mu + \gamma) - \sigma\beta K, \\ C =& \frac{(\mu + \gamma)(\mu + \theta + \phi)}{\beta} - (\mu + \theta + \sigma\phi)K + (1 - \sigma)\omega.\end{aligned}$$

We introduce the notations

$$\breve{I}_1 = \frac{-B - \sqrt{B^2 - 4AC}}{2A}, \qquad \breve{I}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

for the two roots of the steady-state equation (5.11). It is possible to show that under certain conditions, there is an interval for values of $\mathcal{R}_0$ to the left of one where both roots are positive. This phenomenon, called backward bifurcation, is in contrary to the usual scenario of forward transcritical bifurcation, when only the disease free equilibrium exists for $\mathcal{R}_0 < 1$. However, as pointed out in the following proposition, the coexistence of multiple positive steady states for $\mathcal{R}_0 > 1$ is impossible in both bifurcation situations.

Proposition 5.4. *If* $\mathcal{R}_0 > 1$ *then there exists a unique positive equilibrium* $\hat{I} = \frac{-B+\sqrt{B^2-4AC}}{2A}$.

We now characterize the conditions for the existence of backward and forward bifurcations.

Theorem 5.5. *If the condition*

$$\frac{(1-\sigma)\omega}{K} > \frac{(\theta+\mu+\sigma\phi)^2 - \sigma(\mu+\gamma)(1-\sigma)\phi}{(\theta+\mu+\sigma\phi)+\sigma(\mu+\gamma)} \tag{5.13}$$

holds then there is a backward bifurcation at $\mathcal{R}_0 = 1$.

Theorem 5.6. *If condition (5.13) does not hold, then system (5.6) undergoes a forward bifurcation at* $\mathcal{R}_0 = 1$. *In this case there is no endemic equilibrium for* $\mathcal{R}_0 \in [0, 1]$.

Let $\mathcal{R}_c$ denote the critical value of the reproduction number, which corresponds to the left endpoint of the interval to the left of one where multiple positive steady states exist. $\mathcal{R}_c$ is defined as

$$\mathcal{R}_c = \frac{x - U + 2\sqrt{UW}}{(\mu+\gamma)\sigma} \cdot \frac{U}{\mu+\theta+\phi}, \tag{5.16}$$

where we let

$$\begin{aligned} U &= (\theta+\mu+\sigma\phi) - \frac{(1-\sigma)\omega}{K}, \\ x &= \frac{(1-\sigma)\omega}{K} + \sigma(\mu+\gamma), \\ W &= -x + \sigma\frac{(\gamma+\mu)(\mu+\phi+\theta)}{U}. \end{aligned}$$

In what follows we precisely describe the number of endemic equilibria and their local stability for values of $\mathcal{R}_0$ on $[0, \infty)$.

Proposition 5.7. *Assume that there is a backward bifurcation at* $\mathcal{R}_0 = 1$. *With* $\mathcal{R}_c$ *defined in (5.16), only the disease free equilibrium exists if* $\mathcal{R}_0 < \mathcal{R}_c$, *a positive equilibrium emerges at* $\mathcal{R}_0 = \mathcal{R}_c$, *and on* $(\mathcal{R}_c, 1)$ *there exist two distinct endemic equilibria. There also exists a positive equilibrium at* $\mathcal{R}_0 = 1$.

Theorem 5.8. *The endemic equilibrium* $(\hat{I}, \hat{V})$ *for which* $\hat{I} = \breve{I}_2$ *is locally asymptotically stable where it exists: on* $\mathcal{R}_0 \in (1, \infty)$, *and also on* $\mathcal{R}_0 \in (\mathcal{R}_c, 1]$ *in case there is a backward bifurcation at* $\mathcal{R}_0 = 1$. *The endemic equilibrium* $(\hat{I}, \hat{V})$ *for which* $\hat{I} = \breve{I}_1$ *is unstable where it exists: on* $\mathcal{R}_0 \in (\mathcal{R}_c, 1)$ *in case there is a backward bifurcation at* $\mathcal{R}_0 = 1$.

The following theorem concerns with the global behavior of solutions. The results were obtained by making use of the Dulac criterion and the Poincaré–Bendixson theorem.

Theorem 5.9. *If there exists no endemic equilibrium, that is, if $\mathcal{R}_0 < 1$ in case of a forward bifurcation and if $\mathcal{R}_0 < \mathcal{R}_c$ in case of a backward bifurcation, then every solution converges to the disease free equilibrium. For $\mathcal{R}_0 > 1$, the unique endemic equilibrium is globally attracting. If there is a backward bifurcation at $\mathcal{R}_0 = 1$ then on $(\mathcal{R}_c, 1)$ there is no globally attracting equilibrium, though every solution approaches an equilibrium.*

We are interested in the impact of the immigration parameters η and ω on the structure of the bifurcation curve. As pointed out below, regions can be characterized in the parameter space where for any values of the immigration parameters the system experiences a backward or forward bifurcation, respectively. Nevertheless, under certain conditions modifying the value of ω and η has a significant effect on the dynamics: critical values ω_c and η_c can be defined such that the bifurcation behavior at $\mathcal{R}_0 = 1$ changes from forward to backward when we increase ω through ω_c and/or we decrease η through η_c. However, in some cases ω can be chosen so that, independently from the value of η, backward bifurcation is impossible.

Proposition 5.10. *If $(\theta + \mu + \sigma\phi)^2 < \sigma(\mu + \gamma)(1 - \sigma)\phi$, then for all η and ω there is a backward bifurcation at $\mathcal{R}_0 = 1$.*

Proposition 5.11. *If $\omega = 0$, then there is a backward bifurcation at $\mathcal{R}_0 = 1$ if and only if $(\theta + \mu + \sigma\phi)^2 < \sigma(\mu + \gamma)(1 - \sigma)\phi$. This also means that in this case η has absolutely no effect on the direction of the bifurcation.*

The results of the following two propositions were obtained as we chose the general form $\Lambda(x) = \frac{x}{c+dx}$ for the birth function, where for parameters c and d it holds that $0 < c < 1/\mu$ and $d > 0$. It is not hard to see that, with this definition, all the conditions made in Proposition 5.1 for Λ are satisfied.

Proposition 5.12. *Assume that $(\theta + \mu + \sigma\phi)^2 \geq \sigma(\mu + \gamma)(1 - \sigma)\phi$ holds. If the condition*

$$(\theta + \mu + \sigma\phi)\,(\theta + \sigma\mu + \sigma\phi) < \sigma(1 - \sigma)(\mu + \gamma)(\mu + \phi)$$

is satisfied, then for any η there is an ω_c such that for any $\omega \in (\omega_c, \infty)$ there is a backward bifurcation at $\mathcal{R}_0 = 1$, and for any $\omega \in [0, \omega_c]$ there is a forward bifurcation at $\mathcal{R}_0 = 1$. In case the above condition does not hold, then for any η and ω there is a forward bifurcation at $\mathcal{R}_0 = 1$.

Proposition 5.13. *Assume that $(\theta + \mu + \sigma\phi)^2 \geq \sigma(\mu + \gamma)(1 - \sigma)\phi$ holds, and fix ω. If ω is such that*

$$\frac{(1 - \sigma)\omega}{K(\mu, 0, \omega)} > \frac{(\theta + \mu + \sigma\phi)^2 - \sigma(\mu + \gamma)(1 - \sigma)\phi}{(\theta + \mu + \sigma\phi) + \sigma(\mu + \gamma)},$$

then there exists $\eta_c > 0$ such that there is a backward bifurcation at $\mathcal{R}_0 = 1$ for $\eta < \eta_c$, and the system undergoes a forward bifurcation for $\eta \geq \eta_c$. If the above inequality does not hold then there is a forward bifurcation at $\mathcal{R}_0 = 1$.

Last we draw some conclusions on the global behavior of the original model (5.4) by means of our results on system (5.6) and the theory of asymptotically autonomous systems.

Theorem 5.17. *All nonnegative solutions of (5.4) converge to an equilibrium. In particular, if $\mathcal{R}_0 > 1$, then the endemic equilibrium is globally asymptotically stable. If there is a forward bifurcation for (5.6) and $\mathcal{R}_0 \leq 1$, or there is a backward bifurcation for (5.6) and $\mathcal{R}_0 < \mathcal{R}_c$, then the disease free equilibrium is globally asymptotically stable.*

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Variables and key model parameters			
F_j^r, F_j^v	Force of infection of residents and visitors in region j	Λ_j	Recruitment term in region j
$F_{j,k}^T$	Force of infection during travel from region j to region k	d_j^r, d_j^v	Natural death rate of residents and visitors of region j
S_j^r, E_j^r, A_j^r,	Susceptible, exposed, asymptomatic, symptomatic	δ	Disease-induced death rate
I_j^r, R_j^r	infected and recovered residents in region j	$\beta_j^{m,n}$	Transmission rate between an infected individual
S_j^v, E_j^v, A_j^v,	Susceptible, exposed, asymptomatic, symptomatic		with residential status 'm' and a susceptible individual
I_j^v, R_j^v	infected and recovered visitors in region j		with residential status 'n' in region j
N_j^r, N_j^v, N_j	Total population size of residents, visitors and	β^T	Transmission rate during the travel
	all individuals in region j	α_j	Traveling rate of residents of region j to region k
$s_{j,k}^r$, $e_{j,k}^r$, $a_{j,k}^r$,	Density of susceptible, exposed, asymptomatic,	γ_j	Inverse of duration of visitors' stay in region j
$i_{j,k}^r$, $r_{j,k}^r$	symptomatic infected and recovered individuals	τ	Duration of travel between the regions
	during the travel from j to k (traveling to visit k)	p	Probability of developing symptoms
$s_{j,k}^v$, $e_{j,k}^v$, $a_{j,k}^v$,	Density of susceptible, exposed, asymptomatic,	ρ	Reduction of infectiousness of asymptotic infecteds
$i_{j,k}^v$, $r_{j,k}^v$	symptomatic infected and recovered individuals during	μ_E, μ_E^T	Reciprocal of the length of the incubation period
	the travel from j to k (returning to k from visiting j)		in the regions and during the travel
$n_{j,k}^r$, $n_{j,k}^v$, $n_{j,k}$	Total density of residents, visitors and	μ_A, μ_A^T,	Recovery rate of asymptomatic and symptomatic
	all individuals during the travel from j to k	μ_I, μ_I^T	infecteds in the regions and during the travel

Table : Variables and parameters of the SEAIR model (j, $k \in \{1,2\}$, $j \neq k$, $m, n \in \{r, v\}$). In the table, "density" means the density with respect to the time elapsed since the start of travel.