

Modeling and Estimation of Infectious Diseases in a Population with Heterogeneous Dynamic Immunity

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Modeling and Estimation of Infectious Diseases in a Population with Heterogeneous Dynamic Immunity*

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Abstract

The paper presents a model for the evolution of an infectious disease in a population with individual-specific immunity. The immune state of an individual varies with time according to its own dynamics, depending on whether the individual is infected or not. The model involves a system of size-structured (first order) PDEs that capture both the dynamics of the immune states and the transition between compartments consisting of infected, susceptible, etc. individuals. Due to the unavailability of precise data about the immune states of the individuals, the main focus in the paper is on developing a technique for set-membership estimations of aggregated quantities of interest. The technique involves solving specific optimization problems for the underlying PDE system and is developed up to a numerical method. Results of numerical simulations are presented for a benchmark model of SIS-type, potentially applicable to diseases like influenza and to various sexually transmitted diseases.

Keywords: mathematical epidemiology, immunoepidemiology, immune status, heterogeneous SIS-models, size-structured systems, set-membership estimations

MSC Classification: 92D30, 93E10, 35F10, 49K20

1 Introduction

Ever since the seminal work by Kermack and McKendrick [14] compartmental models, such as *SIR*- or *SIS*-models, play a prominent role in mathematical epidemiology. The idea behind such models is to divide the population into several groups such as susceptibles (S), infectives (I), recovered (R), etc., and to study the interactions between these groups and in particular the transition of individuals from one group into another.

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It is obvious that the immune system of individuals plays an important role in this process by counteracting the pathogen inside the body. The exact understanding of how this process works and the modelling of in-host dynamics is the aim of immunology. An introduction to this discipline may be found in [20]. In an epidemiological context immunology is important because the state of the immune system influences, for example, the susceptibility, infectivity, and recovery of individuals. The combination of these two disciplines, sometimes referred to as “immunoepidemiology” ([5, 11, 19]), is therefore a natural consequence. One way to achieve this is to model the within-host dynamics of the pathogen and couple this with an epidemiological model by assuming that the state of within-host dynamics influences the transmission of the pathogen between hosts. This approach has led to a number of contributions, e.g. [1, 3, 7, 9, 10].

We will instead focus on the influence on the epidemiological dynamics of the waning and boosting of the immune response towards a disease. A short explanation of why the immune response increases and decreases depending on exposure to a pathogen can, for example, be found in [5]. One approach to capture the waning of immunity towards a disease is to introduce additional subclasses of, for example, recovered individuals (e.g. [12, 22]) or individuals with waning immunity from vaccination (e.g. [18, 21]). This approach has the advantage that the dynamics are still described by an ODE model, however these ODE systems can become large if many compartments are added. Another approach is to assume that the recovered population is structured with respect to the immune status of the individuals. This approach retains the low-dimensionality of the equations, however at the cost of introducing a PDE into the system (e.g. [6]). Such systems can also be formulated to include boosting of the immune system for the recovered population as well ([5]). Other approaches to model the boosting of the immune system during the infective period leads to models with multiple structured populations ([19]). We will study dynamical systems in which every sub-population is structured with respect to the host immunity. An example of such a model can be found in [26].

In this paper we present a model for the evolution of the susceptible and infected subpopulations (*SIS*-model) in which the immunity of individuals has its own dynamics, depending on whether the individual is susceptible or infected. The model involves a system of first order PDEs (of the type of the so-called size-structured systems), which is similar to (but different from) [26]. It could be interpreted in terms of an influenza infection, but similar models may be appropriate to simulate sexually transmitted diseases [4]. In [26] it is argued that this framework can also be used to model microparasite infections.

To numerically simulate heterogeneous models such as the one developed here, the initial distribution of the population along the possible immunity states has to be known. However, precise information about this distribution is not available in practice. Therefore, we develop a method to estimate the dynamics of the disease under uncertain initial conditions, based

on available data only. It builds on the general approach of set-membership estimation under deterministic uncertainty (see e.g. [15, 16, 17]).

The paper is organised as follows. In Section 2 we introduce a benchmark *SIS*-model with heterogeneous immunity, which consists of a pair of size-structured first order PDEs. In Section 3 we begin the investigation of this model by studying its steady state distributions. In Section 4 we present a more general class of models (including *SIR*-models, for example), and develop the appropriate set-membership estimation technique. This allows us to estimate the evolution of the disease without complete knowledge of its initial state. Finally, in Section 5 we apply this technique to the benchmark model to gain additional insights about the steady states found in Section 3 and to study how differences in the initial distribution influence the short term and long term behaviour of the disease.

2 The heterogeneous *SIS* model

In the model below we consider a closed population of fixed size, a part of which is infected by influenza. Each individual has an immunity level characterized by a number $\omega \in [0, 1]$: the larger is ω , the higher is the immunity of an individual. The level of immunity has its own dynamics. If an individual is susceptible (that is, not infected, in the present context) in a time interval $[\tau, \theta)$, then her immunity level obeys the equation

$$\dot{\omega}(t) = d(\omega(t)), \quad \omega(\tau) = \omega_\tau, \quad t \in [\tau, \theta), \quad (1)$$

where ω_τ is the immunity level at time τ and $d(\omega)$ is the velocity of decrease of immunity at immune state ω . Thus, $d : [0, 1] \rightarrow (-\infty, 0]$.

Similarly, $e : [0, 1] \rightarrow [0, \infty)$ represents the velocity of increase of immunity of infected individuals: the dynamics of the immune state of an individual which is infected in $[\theta, \eta)$ is described by the equation

$$\dot{\omega}(t) = e(\omega(t)), \quad \omega(\theta) = \omega_\theta, \quad t \in [\theta, \eta). \quad (2)$$

Of course, if a susceptible individual becomes infected at time θ , then the dynamics of her immune level switches from (1) to (2), then switches back to (1) at the time of recovery. In the long run such switchings may happen several time. Notice that the dynamics of the immune state is not individual-specific – the laws (1) and (2) apply to each individual.

In order to ensure existence and uniqueness of the solutions of the above ODEs, and invariance of the interval $[0, 1]$ (which is required in order to make the model meaningful) we assume that d and e are continuously differentiable and $d(0) = e(1) = 0$. This resembles the assumption that the interval $[0, 1]$ contains all possible immune states.

Now, we describe the model of the evolution of the susceptible and the infected subpopulations, beginning with some notations. The numbers $S(t, \omega)$ and $I(t, \omega)$ represent the sizes of the susceptible/infected subpopulations of immunity state ω at time t . The susceptibility of a susceptible individual depends on the immunity state and is denoted by $p(\omega) \geq 0$. The infectivity of an infected individual may also depend on the immunity state and is denoted by $q(\omega) \geq 0$. The recovery rate of an infected individual of immunity state ω is denoted by $\delta(\omega) \geq 0$. Finally, $\sigma(t) \geq 0$ is the strength of infection or effective contact rate. It is reasonably assumed to depend on time in order to capture possible seasonal changes or other time-dependent effects.

Notice that the total population size can be represented as

$$N(t) = \int_0^1 [S(t, \omega) + I(t, \omega)] d\omega.$$

In the model below it will be assumed that the total population size remains constant, therefore one may normalize it to $N(t) = 1$. Then under the assumption of proportional mixing (see e.g. [8]), the incidence rate takes the form

$$\frac{\int_0^1 q(\zeta)I(t, \zeta) d\zeta}{N(t)} = \int_0^1 q(\zeta)I(t, \zeta) d\zeta. \quad (3)$$

The evolution of the susceptible/infected individuals, regarding the changes of the immunity state, is described by the equations

$$\begin{aligned} \frac{\partial}{\partial t} S(t, \omega) + \frac{\partial}{\partial \omega} (d(\omega)S(t, \omega)) &= -\sigma(t)p(\omega) \int_0^1 q(\zeta)I(t, \zeta) d\zeta S(t, \omega) + \delta(\omega)I(t, \omega), \\ \frac{\partial}{\partial t} I(t, \omega) + \frac{\partial}{\partial \omega} (e(\omega)I(t, \omega)) &= \sigma(t)p(\omega) \int_0^1 q(\zeta)I(t, \zeta) d\zeta S(t, \omega) - \delta(\omega)I(t, \omega), \end{aligned} \quad (4)$$

complemented with the initial conditions

$$S(0, \omega) = S^0(\omega), \quad I(0, \omega) = I^0(\omega), \quad \omega \in [0, 1], \quad (5)$$

and the boundary (zero-flux) conditions

$$d(1)S(t, 1) = 0, \quad e(0)I(t, 0) = 0, \quad t \geq 0. \quad (6)$$

In our case we will fulfil the zero-flux conditions by assuming that $d(1) = e(0) = 0$, which is not principally necessary, but is reasonable and makes the analysis technically simpler (see Remark 3 in Section 4.1). For simplicity, the data $p, q, \delta, \sigma, S^0, I^0$ are assumed to be continuous functions

(although this assumption can be easily relaxed – only measurability and boundedness suffice). Also it is reasonably assumed that $d(\omega) < 0$ and $e(\omega) > 0$ for $\omega \in (0, 1)$ (strict loss/gain of immunity if not-perfect/missing), and that $p(0) > 0$, $q(0) > 0$. Due to the normalization of the population size we have to assume also that $\int_0^1 [S^0(\omega) + I^0(\omega)] d\omega = 1$.

Equations (4) have a clear micro-foundation: they can be derived (like in physics) by calculating what amount of individuals will enter/leave immunity state interval $[\omega, \omega + \Delta\omega]$ in a time horizon $[t, t + \Delta t]$, and then pass to a limit with Δt and $\Delta\omega$. This kind of size-structured systems are widely used in mathematical biology, while in the context of epidemiology we may refer to [19, 26].

The exact definition of the notion of solution of equations (4)–(6) will be given in Section 4.

Remark 1. In the above model we assumed in advance (by taking $N(t) = 1$) that the population has constant size. Notice that equations (4) together with the zero-flux conditions (6) and the natural condition $d(0) = e(1) = 0$ keep the size of the population constant (= 1).

Remark 2. The assumption that there is no in/out flow of population is somewhat restrictive. In fact, in- and out-flows of equal amounts of individuals is implicitly included in the model, provided that the flows have the same ω -distributions as the existing population, hence have no effect on S and I . Moreover, the model (4)–(6) can be easily enhanced to include out-flows due to mortality (also additional mortality caused by infection) and migration, and in-flows of new-borns and immigrants, having heterogeneous immunity states. This is just a matter of adding new terms in equations (4) and replacing the incidence rate with the left term in (3) in order to take into account a possible change of the population size.

3 Steady states

In this section we investigate the steady states of the benchmark system (4) in the case of time-invariant strength of infection $\sigma(t) = \sigma$. Steady states are important in the study of asymptotic behaviour and give valuable information, in general. Although we are, due to the complexity of the model, not able to completely describe the steady states or asymptotic behaviour analytically, the calculations here are the basis for a numerical analysis of the steady states which will be carried out in Section 5.

We formally drop the time dependence of the functions $S(t, \omega)$ and $I(t, \omega)$. This yields (denoting

differentiation with respect to ω by '))

$$\begin{aligned} (d(\omega)S(\omega))' &= -\sigma p(\omega) \int_0^1 q(\zeta)I(\zeta) d\zeta S(\omega) + \delta(\omega)I(\omega), \\ (e(\omega)I(\omega))' &= \sigma p(\omega) \int_0^1 q(\zeta)I(\zeta) d\zeta S(\omega) - \delta(\omega)I(\omega). \end{aligned} \tag{7}$$

Note that we have $(d(\omega)S(\omega) + e(\omega)I(\omega))' = 0$ which implies

$$d(\omega)S(\omega) + e(\omega)I(\omega) = \kappa = \text{const.} \tag{8}$$

From the zero-flux conditions (6) and the assumption $d(0) = e(1) = 0$ we obtain that $\kappa = 0$.

3.1 Disease free steady states

First, we look for disease free steady states of (7), i.e. solutions with $I(\omega) \equiv 0$. Under this condition (8) becomes $d(\omega)S(\omega) = 0$ which implies $S(\omega) = 0$ for $\omega \in (0, 1)$. Since $\int_0^1 S(\omega) d\omega = 1$ we get that $S(\omega) = a\delta_0(\omega) + (1-a)\delta_0(\omega-1)$ for $a \in [0, 1]$ and where $\delta_0(\omega)$ is the Dirac-delta. In particular, the only disease free steady state that fulfils the zero-flux condition $d(1)S(1) = 0$ is $S(\omega) = \delta_0(\omega)$.

3.2 Endemic steady states

Now, we consider the solutions of the steady state system (7), where $I(\omega)$ is not zero almost everywhere. We furthermore restrict ourselves to solutions where both $S(\omega)$ and $I(\omega)$ are non-negative. For this analysis we fix an $\omega^* \in (0, 1)$. Furthermore, for $\theta \in (0, \infty)$ we define the three functions

$$g(\theta) = \frac{\theta}{\int_0^1 q(\omega) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} d\zeta} d\omega}, \tag{9}$$

$$I_\theta(\omega) = g(\theta) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} d\zeta}, \tag{10}$$

$$S_\theta(\omega) = -\frac{e(\omega)}{d(\omega)} I_\theta(\omega). \tag{11}$$

First, assume that $(S^*(\omega), I^*(\omega))$ solves (7) and is non-negative. Define

$$\theta^* = \int_0^1 q(\omega) I^*(\omega) d\omega. \tag{12}$$

Using (7) and (8) it is easy to show for $\omega \in (0, 1)$ that $I^*(\omega)$ fulfils

$$I^{*'}(\omega) = -\left(\frac{\sigma p(\omega)\theta^*}{d(\omega)} + \frac{\delta(\omega) + e'(\omega)}{e(\omega)} \right) I^*(\omega).$$

From this we see that for $\omega \in (0, 1)$ we can write

$$I^*(\omega) = I^*(\omega^*) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta^*}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} d\zeta}. \quad (13)$$

Multiplying this equation by $q(\omega)$ and integrating over $(0, 1)$ yields

$$\theta^* = I^*(\omega^*) \int_0^1 q(\omega) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta^*}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} d\zeta} d\omega,$$

which is equivalent to $I^*(\omega^*) = g(\theta^*)$. Plugging this into (13) we see that $I^*(\omega) = I_{\theta^*}(\omega)$, and using (8), that $S^*(\omega) = S_{\theta^*}(\omega)$. Note that because the solution is assumed to be non-negative and that $I^*(\omega)$ is not identically zero, we get that $\theta^* > 0$.

Now conversely assume that $\theta > 0$. Then it is obvious that I_{θ} and S_{θ} are both non-negative, as $g(\theta) > 0$. Due to our definition of $g(\theta)$ it is easy to see that $\int_0^1 q(\omega) I_{\theta}(\omega) d\omega = \theta$. Using this, by a simple differentiation of (10) we obtain that for $\omega \in (0, 1)$

$$I'_{\theta}(\omega) = -\frac{\sigma p(\omega) \int_0^1 q(\zeta) I_{\theta}(\zeta) d\zeta}{d(\omega)} I_{\theta}(\omega) - \frac{\delta(\omega) + e'(\omega)}{e(\omega)} I_{\theta}(\omega). \quad (14)$$

Multiplying (11) with $\frac{d(\omega)}{e(\omega)}$ and plugging the result into (14), then multiplying by $e(\omega)$ yields

$$(e(\omega) I_{\theta}(\omega))' = \sigma p(\omega) \int_0^1 q(\zeta) I_{\theta}(\zeta) d\zeta S_{\theta}(\omega) - \delta(\omega) I_{\theta}(\omega).$$

Consequently, $(S_{\theta}(\omega), I_{\theta}(\omega))$ solves (7) on the open interval $(0, 1)$. Thus, we have proven the following theorem.

Theorem 1. *Choose $\omega^* \in (0, 1)$. Let $g(\theta)$, $I_{\theta}(\omega)$ and $S_{\theta}(\omega)$ be defined as in (9), (10) and (11) respectively.*

- *If $\theta > 0$, then $(S_{\theta}(\omega), I_{\theta}(\omega))$ solves (7) for all $\omega \in (0, 1)$.*
- *If $(S^*(\omega), I^*(\omega))$ solves (7), define θ^* as in (12). Then $\theta^* > 0$ and $(S^*(\omega), I^*(\omega)) = (S_{\theta^*}(\omega), I_{\theta^*}(\omega))$ for all $\omega \in (0, 1)$.*

This theorem shows that there is a one-to-one correspondence between non-negative solutions of (7) on $(0, 1)$ and positive numbers θ . In general the total population N in these solutions

is not 1, as is assumed in our case. We are therefore now looking for solutions for which this condition is fulfilled. Using (10) and (11) this yields

$$\begin{aligned}
1 &= \int_0^1 I_\theta(\omega) + S_\theta(\omega) \, d\omega \\
&= \int_0^1 g(\theta) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} \, d\zeta} - \frac{e(\omega)}{d(\omega)} g(\theta) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} \, d\zeta} \, d\omega \\
&= g(\theta) \int_0^1 \left(1 - \frac{e(\omega)}{d(\omega)}\right) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} \, d\zeta} \, d\omega.
\end{aligned}$$

Using (9) we see that for $\theta \in (0, \infty)$ this is equivalent to

$$r(\theta) = 0,$$

where $r(\theta)$ is defined as

$$r(\theta) = \int_0^1 \left(\left(1 - \frac{e(\omega)}{d(\omega)}\right) \theta - q(\omega) \right) e^{-\int_{\omega^*}^{\omega} \frac{\sigma p(\zeta)\theta}{d(\zeta)} + \frac{\delta(\zeta)+e'(\zeta)}{e(\zeta)} \, d\zeta} \, d\omega. \quad (15)$$

We see that $r(0) < 0$ (possibly $-\infty$) and $r(\theta) > 0$ (again possibly infinite) for any θ bigger than $\sup_{\omega \in [0,1]} q(\omega) =: Q$. Therefore any solution of the equation $r(\theta) = 0$ must lie in the interval $(0, Q)$. With this notation we arrive at the following corollary.

Corollary 1. *The system (7) has a solution that fulfils the zero-flux condition, is non-negative, and fulfils $N = 1$ if and only if the function $r(\theta)$ has a root $\theta^* \in (0, Q)$. In this case the solution is given by $(S_{\theta^*}, I_{\theta^*})$. This solution is unique if and only if this root is unique.*

We note that one can show that $r(\theta)$ is continuous on the set where it is bounded. The question of the existence of a solution to $r(\theta) = 0$ is therefore closely connected to the question of where $r(\theta)$ is bounded. This however, cannot be answered in general and depends on the particular choice of parameter functions. The same applies to the uniqueness.

In epidemiological models it is common that one can define an indicator λ such that if λ is below a certain threshold there exists no endemic steady state, and there exists a unique steady state if λ is above this threshold. In the current context, such an indicator could be the number of roots of $r(\theta)$ in $[0, Q]$. It is an open question to obtain an indicator of similar kind as the basic reproduction number.

4 Set-membership estimation

In order to calculate a solution of system (4) one needs to know the initial distributions of the susceptible and infected subpopulations along the heterogeneity ω , that is, $S(0, \omega)$ and $I(0, \omega)$. However, this information is usually not available in detail. We may assume that the total number of susceptible and infected individuals at time 0, that is, the quantities $S(0) = \int_0^1 S(0, \omega) d\omega$ and $I(0) = \int_0^1 I(0, \omega) d\omega$, are known. We may also have additional information about the initial distributions, for example point-wise constraints of the form $u(\omega) := (S(0, \omega), I(0, \omega)) \in [\phi_1(\omega), \phi_2(\omega)]$ where ϕ_1 and ϕ_2 are known functions. More generally, we summarize the available information about the initial data as $u(\cdot) \in \mathcal{U}$, where \mathcal{U} is a closed, convex and bounded subset of $L_\infty := L_\infty([0, 1] \mapsto \mathbb{R}_+^n)$. Below in this section we will formulate the problem of set-membership estimation of the aggregated state of the system, $y(t) := \left(\int_0^1 S(t, \omega) d\omega, \int_0^1 I(t, \omega) d\omega \right)$, based on the information $u(\cdot) \in \mathcal{U}$ about the initial data and the systems dynamics. Moreover, a computational tool for finding (approximating) the set-membership estimation will be provided. This will be done in a more general framework, including other (also higher dimensional) models of interest in epidemiology and beyond.

4.1 Formulation of the general model

Below $x : [0, T] \times [0, 1] \rightarrow \mathbb{R}^n$ will be viewed as a distributed state function and $y : [0, T] \rightarrow \mathbb{R}^m$ – as an aggregated state function, with their dynamics given by the equations

$$\frac{\partial}{\partial t} x(t, \omega) + \frac{\partial}{\partial \omega} (A(\omega)x(t, \omega)) = f(t, \omega, x(t, \omega), y(t)), \quad x(0, \omega) = u(\omega), \quad (16)$$

$$y(t) = \int_0^1 g(t, \omega, x(t, \omega)) d\omega. \quad (17)$$

The following assumptions will be standing in this section. The function $f : [0, T] \times [0, 1] \times \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n$ is differentiable in x and y , the derivatives f_x and f_y and f itself are measurable in (t, ω) , locally essentially bounded, and locally Lipschitz continuous in (x, y) uniformly in (t, ω) . The function $g : [0, T] \times [0, 1] \times \mathbb{R}^n \rightarrow \mathbb{R}^m$ is differentiable in x , the derivative g_x and the function g itself are measurable in ω and continuous in t , locally essentially bounded, and locally Lipschitz continuous in x uniformly in (t, ω) . Moreover, $f(t, \omega, x, y) \geq -cx$, $g(t, \omega, x) \geq 0$, where $c \geq 0$ is a constant and the inequalities (understood component-wise) hold for every (t, ω) and every $x \geq 0$ and $y \geq 0$. The matrix function $A : [0, 1] \rightarrow \mathbb{R}^n \times \mathbb{R}^n$ is diagonal with continuously differentiable diagonal elements $a_i(\omega)$, $a_i(0) = a_i(1) = 0$ and $a_i(\omega) \neq 0$ for $\omega \in (0, 1)$.

Remark 3. The assumptions about f and g are fulfilled in our model (4) with $x = (S, I)$ and $y(t)$ as in the beginning of the present section. Moreover, there we have $A = \text{diag}(d, e)$ and

the assumptions about A are fulfilled if d and e are as assumed in Section 2. We stress that the additional assumption $d(1) = e(0) = 0$ made there provides one way to satisfy the zero-flux conditions (6). In this case equations (16), (17) require only initial conditions to produce a unique solution (see below). If $d(1) \neq 0$ and/or $e(0) \neq 0$, then the zero-flux conditions must be ensured by adding the boundary conditions $S(t, 1) = 0$ and/or $I(t, 0) = 0$ (see, e.g., the more general consideration in [2]). The approach below is still applicable, but the calculations become more cumbersome.

As it will be seen below, a solution of (16), (17) is uniquely defined by the initial condition

$$x(0, \omega) = u(\omega), \quad \omega \in [0, 1], \quad (18)$$

where $u : [0, 1] \mapsto \mathbb{R}_+^n$ is a measurable and bounded function.

The notion of solution of system (16)–(18) can be defined in several ways, but for the considered problem the method of characteristics seem to be most natural. Let for $i = 1, \dots, n$ the function $\omega_i : [0, T] \times [0, 1] \rightarrow [0, 1]$ be defined as the unique solution of the initial value problem

$$\frac{\partial}{\partial t} \omega_i(t, \rho) = a_i(\omega_i(t, \rho)), \quad \omega_i(0, \rho) = \rho,$$

where ρ is regarded as a parameter for ω_i . Due to the assumptions about $a_i(\omega)$, the mapping $(t, \rho) \mapsto (t, \omega_i(t, \rho))$ is a diffeomorphism of $[0, T] \times [0, 1]$ onto itself. Its inverse has the form $(t, \omega) \mapsto (t, \rho_i(t, \omega))$, where ρ_i is continuously differentiable and satisfies $\omega_i(t, \rho_i(t, \omega)) = \omega$ and $\rho_i(t, \omega_i(t, \rho)) = \rho$.

As a motivation for the definition below we assume that x is a continuously differentiable solution of (16)–(18). Denote $z_i(t, \rho) = x_i(t, \omega_i(t, \rho))$, thus $x_i(t, \omega) = z_i(t, \rho_i(t, \omega))$. Then

$$\begin{aligned} \frac{d}{dt} z_i(t, \rho) &= \frac{\partial}{\partial t} x_i(t, \omega_i(t, \rho)) + a_i(\omega_i(t, \rho)) \frac{\partial}{\partial \omega} x_i(t, \omega_i(t, \rho)), \\ z_i(0, \rho) &= x_i(0, \omega_i(0, \rho)) = x_i(0, \rho) = u(\rho), \end{aligned}$$

hence

$$\frac{d}{dt} z_i(t, \rho) = f_i(t, \omega_i(t, \rho), x(t, \omega_i(t, \rho)), y(t)) - a_i'(\omega_i(t, \rho)) z_i(t, \rho). \quad (19)$$

$$z_i(0, \rho) = u(\rho). \quad (20)$$

The above equations motivate the following definition (cf. [2]).

Definition 1. The pair of functions $x : [0, T] \times [0, 1] \rightarrow \mathbb{R}^n$ and $y : [0, T] \rightarrow \mathbb{R}^m$ is a solution of system (16)–(18) if x has the representation $x_i(t, \omega_i(t, \rho)) = z_i(t, \rho)$, $t \in [0, T]$, $\rho \in [0, 1]$, where $z_i(t, \rho)$ is measurable in ρ and absolutely continuous in t for a.e. ρ , and (19), (20), (17) are satisfied almost everywhere.

The definition is correct and x is a measurable function due to the measurability of z and the fact that $(t, \rho) \mapsto (t, \omega_i(t, \rho))$ is a diffeomorphism. For the same reason the functions $x_j(t, \omega_i(t, \rho)) = z_j(t, \rho_j(t, \omega_i(t, \rho)))$ in the right-hand side of (19) are well defined and measurable. A solution x does not need to be differentiable. It may even be discontinuous in each of the directions t and ω , but x_i is absolutely continuous along almost every characteristic line $(t, \omega_i(t))$.

Lemma 1. *If (x, y) is a solution of (16)–(18) then the mappings*

$$[0, T] \ni t \mapsto x(t, \cdot) \in L_1(0, 1) \quad \text{and} \quad [0, T] \ni t \mapsto y(t)$$

are continuous.

Proof. The second claim follows from the first due to the Lipschitz continuity of g in x and the boundedness of x . Let us prove the first claim. For every $i = 1, \dots, n$ and for a.e. $t, \tau \in [0, 1]$ we have, by change of the variable $\omega = \omega_i(t, \rho)$

$$\begin{aligned} & \int_0^1 |x_i(t, \omega) - x_i(\tau, \omega)| \, d\omega = \int_0^1 |x_i(t, \omega_i(t, \rho)) - x_i(\tau, \omega_i(t, \rho))| \frac{\partial}{\partial \rho} \omega_i(t, \rho) \, d\rho \\ & \leq \int_0^1 [|x_i(t, \omega_i(t, \rho)) - x_i(\tau, \omega_i(t, \rho))| + |x_i(\tau, \omega_i(t, \rho)) - x_i(\tau, \omega_i(\tau, \rho))|] \frac{\partial}{\partial \rho} \omega_i(t, \rho) \, d\rho \\ & = \int_0^1 |z_i(t, \rho) - z_i(\tau, \rho)| \frac{\partial}{\partial \rho} \omega_i(t, \rho) \, d\rho + \int_0^1 |x_i(\tau, \omega) - x_i(\tau, \omega_i(\tau, \rho_i(t, \omega)))| \, d\omega \\ & \leq c_1 |t - \tau| + \int_0^1 |x_i(\tau, \omega) - x_i(\tau, \omega + \varepsilon(\omega, t, \tau))| \, d\omega, \end{aligned}$$

where $|\varepsilon(\omega, t, \tau)| \leq c_2 |t - \tau|$ (c_1 and c_2 are appropriate constants). It is a standard fact from the analysis (a consequence from Lousin's theorem, for example) that the second term converges to zero when $t \rightarrow \tau$. \square

Existence and uniqueness of a solution can be proved by a fixed point argument similarly as in [2]. Although in some respects the problem in that paper is more general than the one considered here, the additional assumption $a_i > 0$ is made in [2], which is not fulfilled even for our heterogeneous SIS model. The existence proof for (16)–(18), however, requires only a minor modification.

4.2 The set-estimation problem

As explained at the beginning of the section, the initial data $u(\omega)$ is not assumed to be exactly known. Instead, we assume that the only information about $u(\cdot)$ is that $u \in \mathcal{U}$, where \mathcal{U} is a given bounded, closed and convex subset of L_∞ . Every element $u \in \mathcal{U}$ will be considered as a

possible realization of the uncertainty in the initial data. Let our task be to obtain information about a part of the components of the aggregated state y at a given time, say $t = T$. That is, we wish to estimate the projection $\text{pr}_L y(T)$ on a given subspace $L \subset \mathbb{R}^m$.

Every $u \in \mathcal{U}$ generates a unique solution $(x[u], y[u])$ of (16)–(18). Denote

$$\mathcal{R}(T) := \{y[u](T) : u \in \mathcal{U}\}.$$

That is, $\mathcal{R}(T)$ is the set of all aggregated states $y(T)$ that result from some possible realization of the uncertainty, $u \in \mathcal{U}$. In this sense, $\mathcal{R}(T)$ is the exact (meaning *minimal*) set-membership estimation of the aggregated state at time T . Thus the object of our interest is the set $\mathcal{R}_L(T) := \text{pr}_L \mathcal{R}(T)$. Below we adapt a well-known method for obtaining estimates

$$\mathcal{E}(T) \supset \mathcal{R}_L(T).$$

Even more, the method allows to obtain outer approximations of arbitrary accuracy to the convex hull $\text{co } \mathcal{R}(T)$.

For a fixed $l \in L$ we consider the problem of maximization of

$$J_l(u) := \langle l, y[u](T) \rangle \tag{21}$$

on the set \mathcal{U} , where $\langle \cdot, \cdot \rangle$ denotes the scalar product in \mathbb{R}^m . Notice that J is bounded on \mathcal{U} (see Lemma 2 in the Appendix). Without caring about existence of a solution of problem (21), we observe that if (u_l, y_l) is an ε -solution (in the sense that $J_l^\varepsilon := J_l(u_l) \geq \sup_{\mathcal{U}} J_l - \varepsilon$), then

$$\text{co } \mathcal{R}(T) \subset \{y : \langle l, y \rangle \leq J_l^\varepsilon + \varepsilon\}.$$

Repeating the same for a mesh $\{l_i\}$ in the unit sphere on L , we obtain the set-membership estimation

$$\text{co } \mathcal{R}_L(T) \subset \mathcal{E}(T) := \bigcap_i \{y : \langle l_i, y \rangle \leq J_{l_i}^\varepsilon + \varepsilon\},$$

which is the intersection of a finite number of (affine) half-spaces. Furthermore, if ε is small enough and the mesh $\{l_i\}$ is dense enough in the unit sphere in L , the estimation $\mathcal{E}(T)$ provides an arbitrarily fine outer approximation (in Hausdorff sense) to the convex hull of $\mathcal{R}_L(T)$. Notice also that $\text{co } \{y_{l_i}\}$ provides an inner approximation to $\text{co } \mathcal{R}_L(T)$.

The main issue in the above set-estimation approach is to solve problem (21). For this, one can apply the standard gradient projection method. In order to implement it, one needs to calculate the derivative of $J(u)$ and perform projections on \mathcal{U} . In the next subsection we focus on the first issue, while the implementation of the gradient projection method is standard and will only be briefly discussed.

4.3 Solving the set-estimation problem

Recall that f_x, f_y, g_x denote the respective derivatives of f and g . Furthermore, let $*$ denote transposition. Given $u \in \mathcal{U}$ and the corresponding solution $(x, y) := (x[u], y[u])$, consider the following *adjoint system*

$$\begin{aligned} \left(\frac{\partial}{\partial t} + A(\omega) \frac{\partial}{\partial \omega} \right) \lambda(t, \omega) &= -f_x(t, \omega, x(t, \omega), y(t)) \lambda(t, \omega) - g_x(t, \omega, x(t, \omega)) \nu(t) \\ \lambda(T, \omega) &= -g_x(T, \omega, x(T, \omega)) \nu(T), \\ \nu(t) &= \int_0^1 f_y(t, \omega, x(t, \omega), y(t)) \lambda(t, \omega) d\omega \end{aligned} \tag{22}$$

with respect to $\lambda : [0, T] \times [0, 1] \mapsto \mathbb{R}^n$ and $\nu : [0, T] \mapsto \mathbb{R}^m$. This system has the same structure as (16)–(18) (and is linear), therefore the solution is understood in the same way, with the same characteristic functions ω_i . Thus a solution of (22) exists and is unique.

Theorem 2. *The functional $J_l : L_\infty \mapsto \mathbb{R}$ is Fréchet differentiable. Its derivative has an L_∞ representation, namely for every $u \in \mathcal{U}$*

$$J'_l(u)(\cdot) = -\lambda(0, \cdot),$$

where λ is defined by the adjoint system (22). More precisely, for every $u \in \mathcal{U}$ there are constants c and $\eta > 0$ such that

$$|J(u + v) - J(u) - \langle J'(u), u - v \rangle| \leq c \|v\|_{L_\infty(\Omega)}^2 \quad \text{for every } v \in L_\infty(\Omega) \text{ with } \|v\| \leq \eta,$$

where $\langle \cdot, \cdot \rangle$ is the scalar product in $L_2(\Omega)$.

The proof of this theorem uses similar arguments as [23, Proposition 1]. However, the latter concerns a system of a form similar to (19)–(20), but much simpler. There, the characteristic functions $\omega_i(t, \rho)$ are the same for each i , which is a substantial simplification, although mainly technical. Therefore, we sketch the proof of Theorem 2 in the Appendix.

The numerical solving of problem (21) is organized as follows. First we discretize the equations (16), (17) similarly as in the recent paper [25], passing in this way to a mathematical programming problem. Due to certain symmetry properties of the discretization scheme used (the Heun scheme for time discretization combined with the trapezoidal rule for integration), solving the discretized system obtained by the same scheme applied to the adjoint system (22) allows to calculate the derivative of the objective function similarly as in Theorem 2. Then we apply the standard gradient projection method for mathematical programming.

We also mention that in order to obtain a good approximation of the set-membership estimation $\mathcal{E}(T)$ it is necessary to solve problem (21) for many unit vectors l in the subspace of interest, L . Moreover, estimations $\mathcal{E}(T_i)$ at a discrete mesh $\{T_i\}$ of time instances may be wished. Naturally, the obtained (approximate) maximizer u for given $T = T_i$ and l can be used as initial guess for neighboring instances T_j and vectors l , which makes the overall estimation procedure tractable on a commercial PC. The critical dimension for the implementability of the method is that of the space L (not the dimensions n and m , which can be much larger). Practically, the number of aggregated states y_j of interest (that is, $\dim(L)$) may vary from 1 to 3.

5 Numerical analysis

In this section we apply the results from Section 4 to calculate set membership estimations for the benchmark system (4). According to Lemma 2 in the Appendix, the mapping $u \rightarrow (S[u](t), I([u](t)))$ is continuous in L_∞ . Then due to the convexity of \mathcal{U} , the exact set-estimation $\mathcal{R}(t)$ is a connected set. Hence, its projection on the I -subspace is an interval, $[I_{\min}(t), I_{\max}(t)]$. Due to the relation $S(t) = 1 - I(t)$ we obtain that

$$\mathcal{R}(t) = \{(S, I) \in \mathbb{R}^2 : S = 1 - I, I \in [I_{\min}(t), I_{\max}(t)]\}. \quad (23)$$

Thus, in order to calculate the estimation $\mathcal{R}(t)$ it suffices to solve problem (21) for only two vectors l_1 and l_2 given by the positive and negative I -axis.

First, we use the method described at the end of Section 4 and demonstrate how this can be used to analyze the steady states of the benchmark system numerically. The actual functional parameters for a given disease are hard to obtain (see discussion in Section 6), therefore to illustrate the method we take parameters of simple form (that fulfill all the assumptions), where the force of infection and the recovery rate are of a magnitude appropriate for modeling influenza (see e.g. [13]):

- $\sigma = 2.5$
- $p(\omega) = 1 - \omega$,
- $q(\omega) = 2p(\omega)$,
- $\delta(\omega) = 2\omega$,
- $d(\omega) = -0.015\omega(1 - \omega)$,
- $e(\omega) = 0.15\omega(1 - \omega)$.

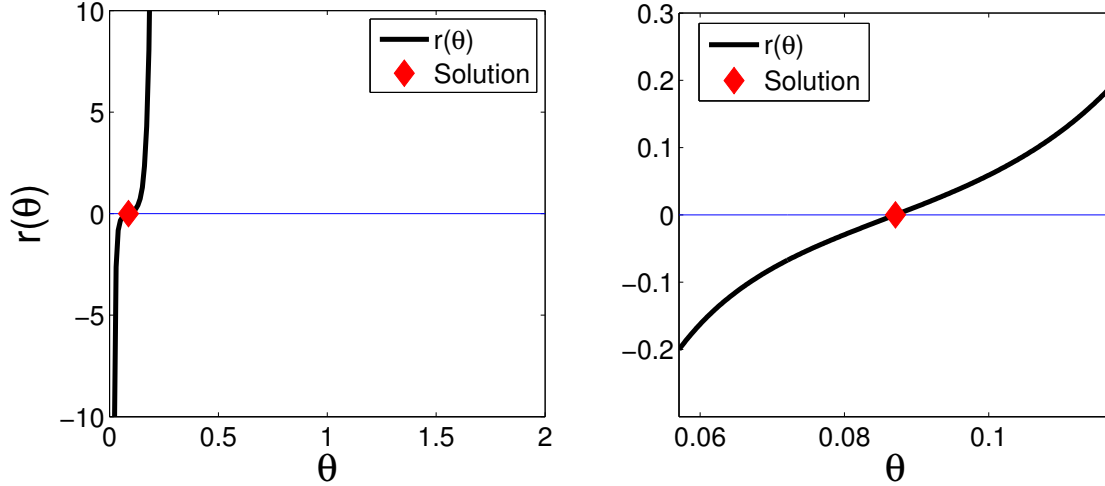


Figure 1: On the left we see the function $r(\theta)$ plotted over the interval $[0, Q]$. Note that the function is not bounded on the whole interval, but is continuous whenever it is bounded. On the right we show the behaviour of $r(\theta)$ near its root. We see that it is strictly monotonically increasing there. In particular, $r(\theta)$ has a unique root given by $\theta^* \approx 0.08707$.

Using these parameters we can calculate the function $r(\theta)$ as described at the end of Section 3. In Figure 1 we show the function $r(\theta)$ over the interval $[0, Q]$. Note that $Q = 2$ in our case. From this calculation we can conclude that $r(\theta)$ has a unique root. Hence, a steady state exists and it is unique. Having calculated the root θ^* we can then calculate the steady state solution $(S_{\theta^*}, I_{\theta^*})$. We show this in Figure 2, where we compare the steady state solution with the solution to system (4) at $t = 200$, where the components of $u(\omega)$ are given by the functions $u_1(\omega) = e^{-2\omega} - e^{-2}$ and $u_2(\omega) = e^{2\omega} - 1$, scaled so that $\int_0^1 u(\omega) d\omega = (0.9, 0.1)$.

Note that while an order of magnitude apart, the shapes of the steady states for S and I are identical. This is explained by equation (8) (with $\kappa = 0$) which yields $S(\omega) = -\frac{e(\omega)}{d(\omega)}I(\omega)$. In our case $\frac{-e(\omega)}{d(\omega)} = 10$ from which it follows that the shapes are identical. This is of course a result of our simple choice of parameters and in general this will not be the case.

We will use the steady states we found to describe the set \mathcal{U} of possible initial distributions. Namely, we set $\phi(\omega) = (S_{\theta^*}(\omega), I_{\theta^*}(\omega))$ and define

$$\mathcal{U} = \left\{ u \in L_\infty : \int_0^1 u(\omega) d\omega = \int_0^1 \phi(\omega) d\omega, u(\omega) \in [0.5\phi(\omega), 1.5\phi(\omega)] \right\}.$$

Thus, we assume that the prevalence $I(t) = \int_0^1 I(t, \omega) d\omega$ of the disease is initially as we would expect in a steady state, but we allow uncertainty in the actual distribution of the immune level among the population. That the particular initial condition becomes largely irrelevant for t this

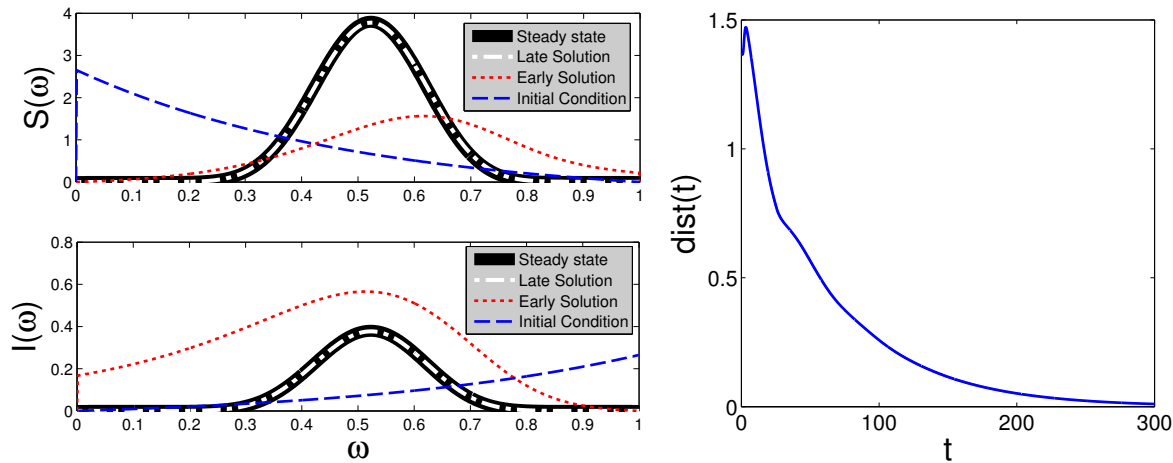


Figure 2: We see for both the susceptible and infected population the theoretical steady states $S_{\theta^*}(\omega)$ and $I_{\theta^*}(\omega)$ given by the thick black line. The dashed white lines show $S(300, \omega)$ and $I(300, \omega)$ respectively, where S and I were calculated from system (4) using an exponential initial condition. We also show the initial conditions and the solution at the earlier point $t = 20$. On the right we plot $\text{dist}(t) = \|(S_{\theta^*}(\omega), I_{\theta^*}(\omega)) - (S(t, \omega), I(t, \omega))\|_{L_1}$ to show that the solution does indeed converge towards the steady state.

large can be seen in Figure 3. There we use the set-membership estimation technique developed in Section 4 to calculate the maximum and minimum value the prevalence $I(t)$ may achieve. We see that the prevalence converges to a single value independent of the initial condition.

We see that with these calculations we can analyse the asymptotic behaviour of the aggregated variables of system (4). Using the function $r(\theta)$ we can determine existence and uniqueness of an endemic steady state solution and using the set-membership estimation we can conclude that this steady state is globally asymptotically stable for all initial data $u(\cdot) \in \mathcal{U}$.

If we significantly decrease the force of infection by taking $\sigma = 0.25$, we find that we can no longer find a root of $r(\theta)$, and numerical calculations yield that $r(\theta)$ is either plus or minus infinity on the interval $[0, Q]$. In Figure 4 we see that the solution does indeed converge to the disease free steady state we described in Section 3.

We now calculate solutions to system (4) with periodic $\sigma(t)$. We take all parameters as in the previous subsection, but change σ to $\sigma(t) = 2.5(1 + \sin(\frac{4\pi}{100}t)/100)$. The results can be seen in Figure 5. Similar to the case with constant σ the maximal and minimal prevalence converge towards each other. However, they now converge to a periodic solution that oscillates in accordance with the function $\sigma(t)$. In Figure 6 we show the results if the sinus term is

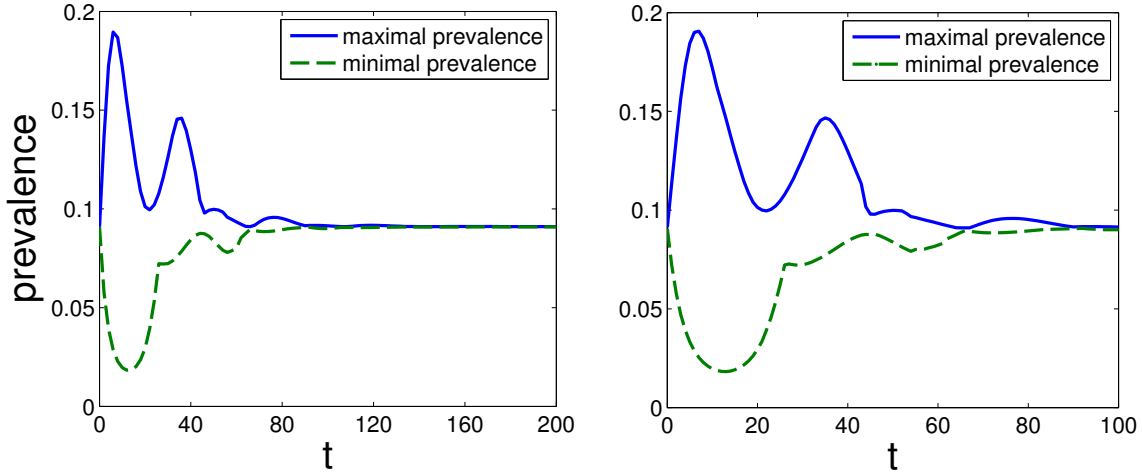


Figure 3: Set-membership estimation of the prevalence $I(t)$. Note that while for small t the prevalence can take significantly different values for different initial conditions, for large t both the maximum and the minimum converge to the same value. On the right we show in more detail the interval where the maximum and minimum differ significantly.

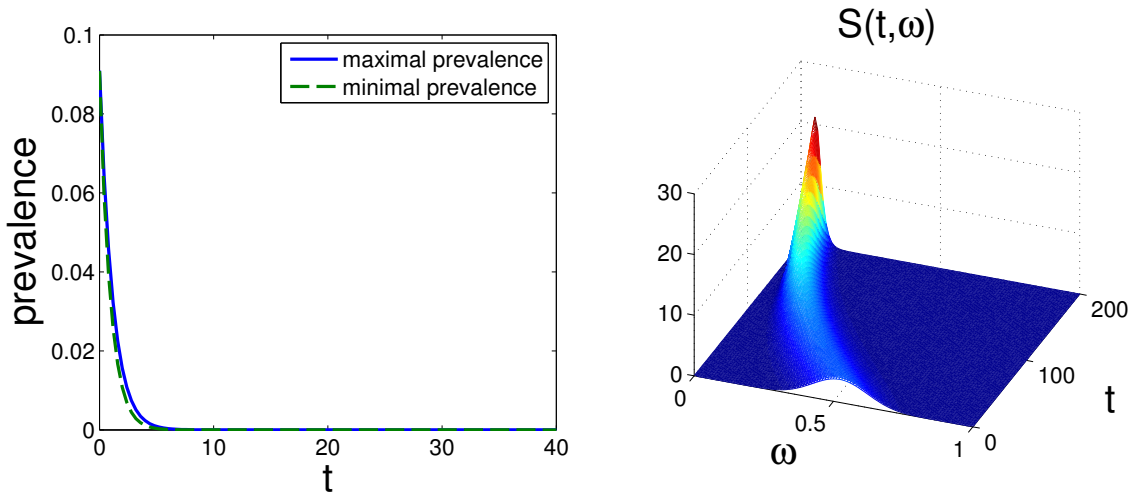


Figure 4: On the left we show the set-membership estimation of the prevalence for $\sigma = 0.25$. It can be seen that the disease dies out. On the right we show the solution $S(t, \omega)$ with initial condition $u(\omega) = \phi(\omega)$. We see that the function does indeed tend towards a Dirac delta at $\omega = 0$.

dampened less and we take $\sigma(t) = 2.5(1 + \sin(\frac{4\pi}{100}t)/10)$. Qualitatively, we see the same behaviour as before, but with more pronounced oscillations. Overall we see that periodic behaviour, which

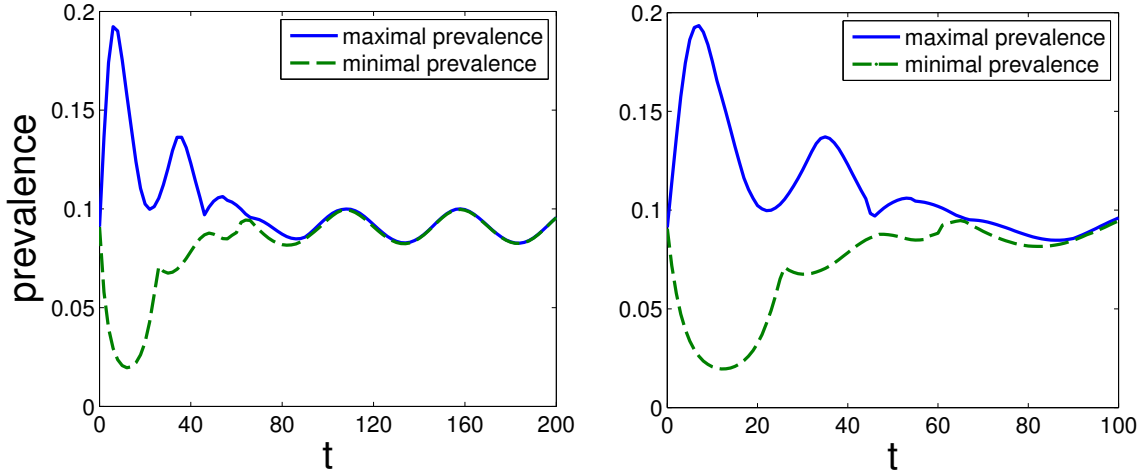


Figure 5: Set-estimation of the prevalence for the system with $\sigma(t) = 2.5(1 + \sin(\frac{4\pi}{100}t)/100)$. The prevalence $I(t)$ converges to a periodic solution.

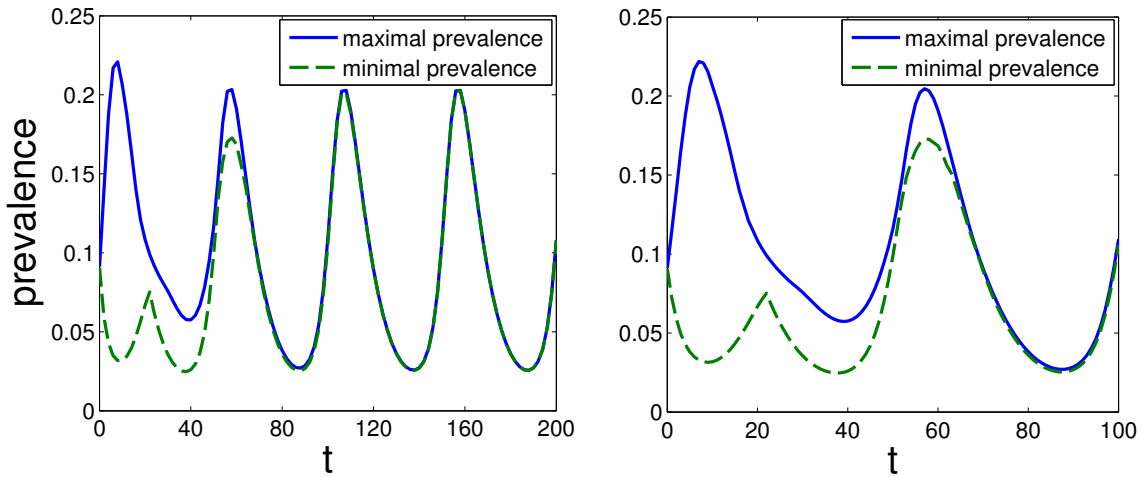


Figure 6: Set-estimation of the prevalence for the system with $\sigma(t) = 2.5(1 + \sin(\frac{4\pi}{100}t)/10)$. The prevalence $I(t)$ converges again to a periodic solution, but with more pronounced oscillations.

is commonly observed in various diseases, is readily reproduced by this model.

In conclusion, using the techniques developed we are able to estimate the evolution of the disease under uncertain information and to numerically describe the asymptotic behaviour of the system (4) for initial conditions $u \in \mathcal{U}$. In particular we see that while the long term behaviour may be independent of the initial condition u , the short term behaviour may change significantly for

different u . For example, events that decrease the immunity of the population may lead to a temporary outbreak of the disease, or an intervention that is aimed at increasing the immunity will only have temporary benefits. Using set-estimation we can gain information about possible outcomes of such events and actions.

6 Conclusions

In this paper we present a model for the evolution of an infectious disease in a population where the individuals have different immunity and their immune states vary with the time according to its own dynamics. We propose a set-membership estimation procedure based on the available information about the initial distribution of the population along the possible immune states. The rest of the parameters of the model are assumed known. However, this is usually not the case: many of the parameters may be uncertain and changing with the time – the rates of losing/gaining immunity, d and e , the strength of infection, σ , etc. The approach in this paper can be enhanced correspondingly, with the difference that the auxiliary optimization problems that are involved in the set-membership estimations will become more complex, still being tractable by standard methods in the optimal control theory of size structured systems (see e.g. [24]). Such an enhancement could be a topic of further research.

Appendix

Lemma 2. *There exists a constant C such that for every $u_1, u_2 \in \mathcal{U}$ and for the corresponding solutions $(x[u_1], y[u_1])$ and $(x[u_2], y[u_2])$ of system (16)–(18) it holds that*

$$\|x[u_1] - x[u_2]\|_{L_\infty} + \|y[u_1] - y[u_2]\|_C \leq C\|u_1 - u_2\|_{L_\infty}.$$

Proof According to the definition of a solution, $x_i[u_j](t, \omega) = z_i[u_j](t, \rho_i(t, \omega))$, where $z_i[u_j]$ together with $y[u_j]$ satisfy equations (19)–(20) with $u = u_j$, $j = 1, 2$. Then it is straightforward that

$$\|x[u_1] - x[u_2]\|_{L_\infty} = \|\Delta z\|_{L_\infty},$$

where $\Delta z_i(t, \rho) = z_i[u_1](t, \rho) - z_i[u_2](t, \rho)$, $\Delta z = (\Delta z_1, \dots, \Delta z_n)$.

Let $\Theta \subset [0, 1]$ be of full measure and such that the functions $z_i[u_j](\cdot, \rho)$ are absolutely continuous for every $\rho \in \Theta$. Then

$$\|\Delta z\|_{L_\infty} = \sup_{t \in [0, T]} \overline{\Delta z}(t),$$

where $\overline{\Delta z}(t) := \max_{i=1, \dots, n} \sup_{\rho \in \Theta} |\Delta z_i(t, \rho)|$ is a Lipschitz continuous function due to the uniform Lipschitz continuity of $\Delta z_i(\cdot, \rho)$. From the assumptions about the data of the system, equation (17) and equation (19), we successively obtain that

$$|y[u_1](t) - y[u_2](t)| \leq c_1 \overline{\Delta z}(t),$$

$$\begin{aligned} \overline{\Delta z}(t) &\leq \|u_1 - u_2\|_{L_\infty} + \int_0^t (c_2 \overline{\Delta z}(s) + c_3 |y[u_1](s) - y[u_2](s)|) ds \\ &\leq \|u_1 - u_2\|_{L_\infty} + \int_0^t c_4 \overline{\Delta z}(s) ds, \end{aligned}$$

where c_1, \dots, c_4 are appropriate constants. The claim of the lemma follows from Grönwall's inequality. \square

Proof of Theorem 2. Let $u \in \mathcal{U}$ and let $\tilde{u} \in L_\infty(0, 1)$. Denote $\varepsilon := \|\tilde{u} - u\|_\infty$, which will be presumably a "small" number. We denote by (x, y) and (\tilde{x}, \tilde{y}) the corresponding solutions of (16)–(18). Also we denote by z_i and \tilde{z}_i the corresponding z -functions from the definition of solution, so that $x_i(t, \omega_i(t, \rho)) = z_i(t, \rho)$, similarly for \tilde{z}_i . Further, $\Delta u := \tilde{u} - u$, $\Delta x := \tilde{x} - x$, $\Delta y := \tilde{y} - y$, and $\Delta z := \tilde{z} - z$. Then using (19), Lemma 2 and some standard calculus we obtain that the following equations are fulfilled:

$$\begin{aligned} \frac{d}{dt} \Delta z_i(t, \rho) &= f_{ix}(t, \omega_i(t, \rho)) \Delta x(t, \omega_i(t, \rho)) + f_{iy}(t, \omega_i(t, \rho)) \Delta y(t) - a'(\omega_i(t, \rho)) \Delta z_i(t, \rho) + o(\varepsilon), \\ \Delta z_i(0, \rho) &= \Delta u_i(\rho), \\ \Delta y(t) &= \int_0^1 g_x(t, \omega, x(t, \omega)) \Delta x(t, \omega) d\omega + o(\varepsilon), \end{aligned}$$

where the superscripts x and y denote differentiation with respect to x and y , the prime in a' denotes differentiation in ω , the missing arguments of f_{ix} and f_{iy} are obviously $x(t, \omega_i(t, \rho))$, $y(t)$, and $o(\varepsilon)$ is any function of ε (possibly depending on t and ρ), such that $o(\varepsilon)/\varepsilon \rightarrow 0$ (uniformly in t, ρ) when $\varepsilon \rightarrow 0$. We mention that the second equation above holds due to $z_i(0, \rho) = x_i(0, \omega_i(0, \rho)) = x_i(0, \rho) = u_i(\rho)$.

Now we consider the adjoint system (22) and denote by $\zeta_i(t, \rho) = \lambda_i(t, \omega_i(t, \rho))$ the function corresponding to λ in Definition 1. Thus

$$\begin{aligned} \frac{d}{dt} \zeta_i(t, \rho) &= -f_{x_i}(t, \omega_i(t, \rho))^* \lambda(t, \omega_i(t, \rho)) - g_{x_i}(t, \omega_i(t, \rho), x(t, \omega_i(t, \rho)))^* \nu(t), \\ \zeta_i(T, \rho) &= -g_{x_i}(T, \omega_i(T, \rho), x(T, \omega_i(T, \rho)))^* l, \\ \nu(t) &= \int_0^1 f_{y_i}(t, \omega, x(t, \omega), y(t))^* \lambda(t, \omega) d\omega. \end{aligned}$$

Using the second last equation and changing the variable $\omega = \omega_i(t, \rho)$, we represent

$$\begin{aligned}
J_l(\tilde{u}) - J_l(u) &= \langle l, \Delta y(T) \rangle = \int_0^1 \langle l, g_x(T, \omega, x(T, \omega)) \Delta x(T, \omega) \rangle d\omega + o(\varepsilon) \\
&= \int_0^1 \sum_{i=1}^n \Delta x_i(T, \omega_i(T, \rho)) g_{x_i}(T, \omega_i(T, \rho), x(T, \omega_i(T, \rho)))^* l \frac{\partial}{\partial \rho} \omega_i(T, \rho) d\rho + o(\varepsilon) \\
&= - \sum_{i=1}^n \int_0^1 \Delta z_i(T, \rho) \zeta_i(T, \rho) \frac{\partial}{\partial \rho} \omega_i(T, \rho) d\rho + o(\varepsilon). \tag{24}
\end{aligned}$$

Now, we rework the following expression integrating by parts:

$$\begin{aligned}
&\sum_{i=1}^n \int_0^T \int_0^1 \frac{d}{dt} \Delta z_i(t, \rho) \zeta_i(t, \rho) \frac{\partial}{\partial \rho} \omega_i(t, \rho) d\rho dt \\
&= \sum_{i=1}^n \int_0^1 \Delta z_i(T, \rho) \zeta_i(T, \rho) \frac{\partial}{\partial \rho} \omega_i(T, \rho) d\rho - \sum_{i=1}^n \int_0^1 \Delta z_i(0, \rho) \zeta_i(0, \rho) \frac{\partial}{\partial \rho} \omega_i(0, \rho) d\rho \\
&\quad - \sum_{i=1}^n \int_0^T \int_0^1 \Delta z_i(t, \rho) \left[\frac{d}{dt} \zeta_i(t, \rho) \frac{\partial}{\partial \rho} \omega_i(t, \rho) + \zeta_i(t, \rho) \frac{\partial}{\partial t} \frac{\partial}{\partial \rho} \omega_i(t, \rho) \right] d\rho dt.
\end{aligned}$$

Then we use the relation (24) and the identities

$$\begin{aligned}
\Delta z_i(0, \rho) &= \Delta u_i(\rho), \quad \zeta_i(0, \rho) = \zeta_i(0, \rho_i(0, \rho)) = \lambda_i(0, \rho), \\
\frac{\partial}{\partial \rho} \omega_i(0, \rho) &= 1, \quad \frac{\partial}{\partial t} \frac{\partial}{\partial \rho} \omega_i(t, \rho) = a'(\omega_i(t, \rho)) \frac{\partial}{\partial \rho} \omega_i(t, \rho)
\end{aligned}$$

to obtain the representation

$$J_l(\tilde{u}) - J_l(u) = \sum_{i=1}^n \int_0^1 \Delta z_i(0, \rho) \zeta_i(0, \rho) d\rho + \Delta + o(\varepsilon) = - \int_0^1 \langle \lambda(0, \rho), \Delta u(\rho) \rangle d\rho + \Delta + o(\varepsilon), \tag{25}$$

where

$$\begin{aligned}
\Delta &:= - \sum_{i=1}^n \int_0^T \int_0^1 \frac{d}{dt} \Delta z_i(t, \rho) \zeta_i(t, \rho) \frac{\partial}{\partial \rho} \omega_i(t, \rho) d\rho dt \\
&\quad - \sum_{i=1}^n \int_0^T \int_0^1 \Delta z_i(t, \rho) \left[\frac{d}{dt} \zeta_i(t, \rho) + \zeta_i(t, \rho) a'(\omega_i(t, \rho)) \right] \frac{\partial}{\partial \rho} \omega_i(t, \rho) d\rho dt.
\end{aligned}$$

After substituting the expressions for $\frac{d}{dt} \Delta z_i(t, \rho)$, $\frac{d}{dt} \zeta_i(t, \rho)$, obtained in the beginning of the proof, changing back the variable $\rho = \omega_i(t, \omega)$, and using the equations for Δy and ν , it is a matter of simple algebra to obtain that $\Delta = o(\varepsilon)$. Then from (25)

$$J_l(\tilde{u}) - J_l(u) = - \int_0^1 \langle \lambda(0, \omega), \tilde{u}(\omega) - u(\omega) \rangle d\rho + o(\|\tilde{u} - u\|_\infty),$$

which implies the claim of the theorem. \square

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