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Studying the recovery procedure for the time-dependent transmission rate(s) in epidemic models

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Abstract Determining the time-dependent transmission function that exactly reproduces disease incidence data can yield useful information about disease outbreaks, including a range potential values for the recovery rate of the disease and could offer a method to test the "school year" hypothesis (seasonality) for disease transmission. Recently two procedures have been developed to recover the time-dependent transmission function, $\beta(t)$, for classical disease models given the disease incidence data. We first review the $\beta(t)$ recovery procedures and give the resulting formulas, using both methods, for the susceptible-infected-recovered (SIR) and susceptible-exposed-infected-recovered (SEIR) models. We present a modification of one procedure, which is then shown to be identical to the other. Second, we explore several technical issues that appear when implementing the procedure for the SIR model; these are important when generating the time-dependent transmission function for real-world disease data. Third, we extend the recovery method to heterogeneous populations modeled with a certain SIR-type model with multiple time-dependent transmission functions. Finally, we apply the $\beta(t)$ recovery procedure to data from the 2002–2003 influenza season and for the six seasons from 2002–2003 through 2007–2008, for both one population class and for two age classes. We discuss the consequences of the technical conditions of the procedure applied to the influenza data. We show that the method is robust in the heterogeneous cases, producing comparable results under two different hypotheses. We perform a frequency analysis, which shows a dominant 1-year period for the multi-year influenza transmission function(s).

Keywords Epidemic models · Time-dependent transmission rate · Recovery procedure · Heterogeneous population disease model · Seasonality · Separability

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1 Introduction

While the recovery rate of a disease can be measured in a controlled laboratory setting and these values used to estimate the value during the actual disease outbreak, the same is not true for the transmission rate. The transmission rate is known to be difficult to measure due to its dependence on the probability of transmission between individuals and social contact rates. On the other hand, there is a wealth of information that could be extracted regarding disease transmission and recovery if the time-dependent transmission function were known. For example, it would be possible to test hypotheses such as whether the school year causes increased disease incidence due to increased contacts among children.

The classical Kermack–McKendrick model for disease outbreaks (Kermack and McKendrick 1927) (see also Brauer et al. 2008; Keeling and Rohani 2008; Murray 2002) considers a population split into three compartments: the susceptible individuals S, the infected individuals I, and the recovered individuals R. The model is commonly called the susceptible-infected-recovered (SIR) model. The model contains two parameters which may be time-dependent: the transmission rate β and the recovery rate ν. The model equations are

$$S'(t) = -\beta(t)S(t)I(t) \tag{1}$$

$$I'(t) = \beta(t)S(t)I(t) - \nu(t)I(t) \tag{2}$$

$$R'(t) = \nu(t)I(t). \tag{3}$$

We assume that S, I, and R are the fraction of the population in each class and in this case $\beta(t)$ and $\nu(t)$ have units time^{-1}. The dependence of the parameters β and ν on time, reflects some external forces that influence the course of the disease outbreak, for example changes in the environment (seasonality) or changes in contact rates. Throughout this paper we assume that the recovery rate ν is a constant and our goal is to recover the time-dependent transmission rate $\beta(t)$ given time series data on the number of infected individuals.

Many approaches have been used to determine, as accurately as possible, the parameter values in epidemic models that best fit the disease data. One must first determine the functional form of the time-dependent transmission rate, $\beta(t)$. Using the fact that outbreaks of diseases such as influenza and measles are periodic, researchers often assume a sinusoidal functional form, as in Bailey (1975) (see also Keeling and Rohani 2008). Another approach is to separate the dependence of the transmission function on environmental factors from the dependence on contact rates. For example, Ponciano and Capistrán (2011) study SIR-type models with a sinusoidal function for the environmental forcing and different disease incidence rates.

If a functional form can be decided on for a model, the second step is to numerically determine the corresponding parameter values. These can be determined by a search through the parameter space via the Nelder–Mead simplex method (Lagarias et al. 1998), as done in Mkhatshwa and Mummert (2011) using MATLAB's fminsearch

program, or using more sophisticated techniques. Capistrán et al. (2009) demonstrate how to determine model parameters by forming and numerically solving an appropriate constrained optimization problem with the (continuous ordinary differential equation) model as a constraint.

Two recent papers, Pollicott et al. (2012) and Hadeler (2011), have presented procedures to recover the time-dependent transmission function $\beta(t)$ from reported incidence data for standard SIR-type disease models. These procedures do not assume any a priori form for $\beta(t)$, instead, they recover the time-dependent transmission function which exactly reproduces the incidence data.

The classical SIR model, and all models presented in both Pollicott et al. (2012) and Hadeler (2011), describe homogeneous populations. Due to social stratifications, more realistic models consider heterogeneous populations, for example by splitting the population into age classes. We extend the $\beta(t)$ recovery procedure to SIR-type compartment models with multiple classes and thus multiple time-dependent transmission functions.

The paper is organized as follows. In Sect. 2 we review the procedures presented by Pollicott et al. (2012) and Hadeler (2011). We provide a modification of the first procedure, which is seen to be identical to the second. The necessary conditions for the recovery procedure, when applied to the SIR model, are also discussed in Sect. 2. Section 3 extends the procedure to certain SIR-type models for heterogeneous populations. We provide two different hypotheses and the corresponding necessary conditions for the recovery procedure. We apply the method to influenza data for both homogeneous and heterogeneous populations in Sect. 4, using both hypotheses. Our discussion and conclusions follow in Sect. 5.

2 Review of previous methods

We review the procedures presented by Pollicott et al. (2012), called here the PWW procedure, and Hadeler (2011), called here the H procedure. The procedures produce the same $\beta(t)$ through different techniques, as is mentioned in both Pollicott et al. (2012) and Hadeler (2011). Another verification that the two methods produce the same $\beta(t)$ is provided in Hadeler (2012).

We give the $\beta(t)$ formula corresponding to the classical SIR and the susceptible-exposed-infected-recovered (SEIR, Eqs. (6)–(9) below) models for each of the two procedures. In both procedures, we assume that the incidence data, $I(t)$, is known for all t in some time interval. This can be achieved by interpolating the infection data as described in Pollicott et al. (2012). When computing $\beta(t)$ for an SIR model, the first derivative of the incidence data is required. When computing $\beta(t)$ for an SEIR model, both the first and the second derivatives are required. We assume that the incidence data function $I(t)$ is sufficiently differentiable for the model.

Although both procedures compute the same time dependent transmission function, one potential disadvantage of the PWW procedure is that it requires higher derivatives of the infection function in order to verify the $\beta(t)$ formula. Hadeler (2011) mentions the requirement of fewer derivatives as a reason to prefer his approach.

Both $\beta(t)$ recovery procedures can be extended to models with multiple infected classes as long as the infected classes have the same transmission rate. An example

of such a model, is the model developed by Mkhatshwa and Mummert (2011) to study super-spreading events in the SARS outbreak. In this model, a super-spreading individual transmits more virus because he or she remains out of the removed class (quarantine or isolation) longer than regular infected individuals, that is, he or she has the same transmission rate but a different recovery rate than regular infected individuals do.

2.1 The modified PWW procedure

The idea behind the procedure of Pollicott et al. (2012) for an SIR-type model is to use the differential equation for $I(t)$, which corresponds to the known incidence data, to solve for $S(t)$. Then substitute this expression and its derivative into the differential equation for $S(t)$. This results in a differential equation for $\beta(t)$. Solving this companion differential equation, gives the time-dependent transmission function. In general, one works from the equation of the last compartment before the recovered class, $R(t)$, "up the system" through the equation for $S'(t)$ to generate a companion differential equation that can be solved.

We present a modification of the PWW procedure, which simplifies the calculation of $\beta(t)$.

Theorem 1 *For the classical SIR model given by Eqs.* (1)–(3)*, the time-dependent transmission function is*

$$\beta(t) = \frac{g(t)}{I(t)\big(S(0) - \int_0^t g(s)\,ds\big)}, \quad \textit{where } g(t) = I'(t) + vI(t).$$

Proof Solve Equation (2) for S to find that

$$S(t) = \frac{I'(t) + vI(t)}{\beta(t)I(t)}. \tag{4}$$

Set the numerator and denominator to be functions $g(t)$ and $h(t)$, respectively.

Differentiate $S(t) = g(t)/h(t)$, with respect to t, and set this equal to the right-hand side of Eq. (1), which in terms of functions $g(t)$ and $h(t)$ is $h(t)\big(-g(t)/h(t)\big)$. Simplifying this equality results in the Bernoulli differential equation in variable $h(t)$

$$\big(-g(t)\big)h'(t) + \big(g'(t)\big)h(t) = \big(-g(t)\big)h^2(t).$$

This differential equation can be solved analytically by first making the substitution $x(t) = 1/h(t)$, which yields the differential equation

$$x'(t) + \big(g'(t)/g(t)\big)x(t) = -1, \tag{5}$$

and then by solving this new differential equation using the method of variation of parameters (integrating factor). The solution is

$$x(t) = e^{-\int_0^t g'(s)/g(s)\,ds}\left[\frac{1}{h(0)} - \int_0^t e^{\int_0^s g'(\sigma)/g(\sigma)\,d\sigma}\,ds\right]$$

which can be simplified by noting that $e^{\int_0^t g'(s)/g(s)\,ds} = g(t)/g(0)$.

Finally, recalling that $\beta(t)I(t) = h(t) = 1/x(t)$ and that $S(0) = g(0)/h(0)$, we find the expression given above for $\beta(t)$. □

The PWW procedure presented in Pollicott et al. (2012) uses the technique above to determine and solve a Bernoulli differential equation for the parameter $\beta(t)$ directly. This leads to a seemingly more complicated, yet equivalent, expression for $\beta(t)$. Using the expression for $\beta(t)$ presented (Pollicott et al. 2012), one must know or guess, a priori, the value of $\beta(0)$. For the expression presented above, one must know instead $S(0)$. From Eq. (4), we see that these two are not independent; knowing the value of one gives the value of the other. Hadeler (2012) discusses some difficulties with guessing and using the value of $\beta(0)$ or $S(0)$ and recommends instead using a weighted average of the infection data.

There are conditions which must be satisfied to ensure that the recovered $\beta(t)$ is well-defined and positive. We discuss these below in Sect. 2.3.

The procedure presented here to recover $\beta(t)$, which is a modification of the PWW procedure, can be extended to a broad class of SIR-type compartment models. Pollicott et al. (2012) discuss how to extend their procedure to the SIR model with waning immunity and the SIR model with a time-dependent indirect transmission rate, among others. We present here the generated $\beta(t)$ for the SEIR model with vital rates using the simplified procedure.

The SEIR model with vital rates is given by the equations

$$S'(t) = \delta - \beta(t)S(t)I(t) - \delta S(t) \tag{6}$$
$$E'(t) = \beta(t)S(t)I(t) - \alpha E(t) - \delta E(t) \tag{7}$$
$$I'(t) = \alpha E(t) - \nu I(t) - \delta I(t) \tag{8}$$
$$R'(t) = \nu I(t) - \delta R(t), \tag{9}$$

where δ (time^{-1}) is the demographic birth and death rates, and $1/\alpha$ (time) is the latency period.

Theorem 2 *For the SEIR model with vital rates the time-dependent transmission function is*

$$\beta(t) = \frac{h(t)e^{\delta t}}{I(t)\left(S(0) + \int_0^t e^{\delta s}(\delta - h(s))\,ds\right)}$$

where

$$h(t) = g'(t) + (\alpha + \delta)g(t) \quad \textit{and } g(t) = \frac{I'(t) + (\nu + \delta)I(t)}{\alpha}.$$

To extend the modified PWW procedure to the SEIR model, solve the differential equation of $I(t)$ for $E(t)$. Plug this expression and its derivative into the differential equation for $E(t)$ and solve for $S(t)$. Use the expression for $S(t)$ in the equation for $S'(t)$, create a companion differential equation, and solve for $\beta(t)$.

2.2 The H procedure

Hadeler (2011) demonstrates how to recover $\beta(t)$ in a different manner for the classical SIR model. The main idea of the H procedure is to analytically solve differential equations where some of the functions are known (because the infection data is known). The equation to integrate is created by adding together some of the equations of the system. The goal is to eventually solve for $S(t)$ in terms of the known functions and also solve for $S(t)$ another way (as in Eq. (4)). Equate the two expressions and solve for $\beta(t)$.

We demonstrate the H procedure using the classical SIR model. Though Hadeler (2011) presents the method with a more involved SIR-type model that includes a loss of immunity term and other time-dependent parameters, we use the classical SIR model, Eqs. (1)–(3), in order to directly compare the PWW procedure and the H procedure.

Technique Begin by adding $S'(t) + I'(t) = -\nu I(t)$. Note that, because the infection data is known, the right-hand side of this equation, $-\nu I(t)$, is a known function. Solve this differential equation and find $S(t)$;

$$S(t) = S(0) + I(0) - \int_0^t \nu I(s)\, ds - I(t).$$

Solve for $S(t)$ in Eq. (2) and equate the two expressions for $S(t)$.

$$S(0) + I(0) - \int_0^t \nu I(s)\, ds - I(t) = \frac{I'(t) + \nu I(t)}{\beta(t) I(t)}.$$

Solving for $\beta(t)$ yields

$$\beta(t) = \frac{I'(t) + \nu I(t)}{I(t)\left(S(0) + I(0) - \int_0^t \nu I(s)\, ds - I(t)\right)}.$$

This expression for $\beta(t)$ is presented as Corollary 2 in Hadeler (2011).

The $\beta(t)$ computed using the H procedure is exactly that computed using the modified PWW procedure presented in Theorem 1, which is seen by noting that

$I(0) - \int_0^t \nu I(s)\,ds - I(t) = -\int_0^t \nu I(s) + I'(t)\,ds = -\int_0^t g(s)\,ds$. Hadeler (2012) demonstrates directly that the PWW and H procedures produce the same $\beta(t)$, without using the modification of the PWW procedure shown here.

The H procedure to recover $\beta(t)$ can be extended to a broad class of SIR-type compartment models. Hadeler (2011) discusses how to use his procedure in a discrete time setting, in a stochastic setting, and assuming an specific exit distribution from the infected class.

2.2.1 Extending the H procedure to the SEIR model

We demonstrate how to extend the H procedure the SEIR model given by Eqs. (6)–(9), which is not shown in Hadeler (2011).

The technique is as follows. Add $S'(t) + E'(t) + I'(t)$ and solve for $S(t) + E(t)$ in terms of the known function $I(t)$. Solve for $E(t)$ in the equation for $I'(t)$, and take the derivative. Use this to solve for $S(t)$ in the equation for $E'(t)$. Add the resulting $S(t)$ and $E(t)$, and equate the sum with the previously determined $S(t) + E(t)$ equation. Solve for $\beta(t)$ to find

$$\beta(t) = \frac{h(t)e^{\delta t}}{I(t)\big(S(0) + E(0) + I(0) + \int_0^t e^{\delta t}(\delta - \nu I)\,ds - e^{\delta t}(I(t) + g(t))\big)},$$

where $g(t)$ and $h(t)$ are as defined previously. Again, this can be shown to be exactly the formula for $\beta(t)$ recovered using the modified PWW procedure by noting that

$$-\int_0^t e^{\delta s} h(s)\,ds = I(0) + g(0) - e^{\delta t}(I(t) + g(t)) - \int_0^t e^{\delta s}\nu I(s)\,ds$$

and that $g(0) = E(0)$.

2.3 Necessary conditions

For the classical SIR model, there are two conditions that must be satisfied to guarantee a well-defined and positive time-dependent transmission function $\beta(t)$.

Condition 1: $I'(t) + \nu I(t) > 0$, for all t;
Condition 2: $S(0) - \int_0^t g(s)\,ds > 0$, for all t.

In Pollicott et al. (2012) these conditions are also called Conditions 1 and 2; Hadeler (2011) discusses these conditions, but does not name them specifically.

Condition 1 guarantees that the resulting $\beta(t)$ is positive. If Condition 1 fails then mathematically the procedure does recover a function $\beta(t)$ that exactly reproduces the infection data; however, the function will be negative at some times, which does not make biological sense. Condition 2 guarantees that $\beta(t)$ is well-defined. If Condition 2 is satisfied up to some time and then fails, the procedure will reconstruct the time-dependent transmission function up until this time and not beyond it.

Not only do these conditions need to be satisfied mathematically to have a well-defined and positive $\beta(t)$, they should be satisfied as part of their interpretations in the SIR model. Condition 1 is the numerator of an expression for the number of susceptible individuals, and so should be greater than zero. The expression in Condition 2 is larger than the number of individuals who remain in the susceptible class at time t, and so should also be positive for all t.

When applying the $\beta(t)$ recovery procedure to disease infection data, the model parameters ν and $S(0)$ need to be estimated. (Note that this implies that there is not one unique $\beta(t)$ that will recreate the infection data; there are infinitely many such $\beta(t)$.) The choice of the two parameters cannot be made independently due to the fact that ν is influential in both Conditions 1 and 2. If ν is increased, then Condition 1 is more likely to be satisfied, and at the same time Condition 2 is less likely to be satisfied, and vice versa. The initial number of susceptible individuals, $S(0)$, appears only in Condition 2. If $S(0)$ is increased, then Condition 2 is more likely to satisfied; if $S(0)$ is decreased, then Condition 2 is less likely to be satisfied. See Sect. 4.1 where we explore these conditions for a verifiable example.

When applying the procedure to infection data, we assume that $S(0)$ is known; it can be determined from the initial number of infected individuals. In Sect. 4.2, the necessary conditions are used to determine a range for the recovery rate, ν days^{-1}.

3 Extending the $\beta(t)$ recovery procedure to models for heterogenous populations

We extend the $\beta(t)$ recovery procedure(s) to SIR-type compartment models for heterogeneous populations with two population classes, for example a population split into two age classes, one corresponding to adults and one corresponding to children. We demonstrate the $\beta(t)$ recovery procedure assuming that the length of the disease outbreak is short compared with the time required to "grow up" from the child class into the adult class. Thus there is no movement from one class to another. With two classes, there is a possibility of four different transmission rates within and between the two groups, and two different recovery rates. The system of differential equations now has six equations:

$$S_1'(t) = -\beta_{11}(t)S_1I_1 - \beta_{12}(t)S_1I_2 \tag{10}$$
$$I_1'(t) = \beta_{11}(t)S_1I_1 + \beta_{12}(t)S_1I_2 - \nu_1(t)I_1 \tag{11}$$
$$R_1'(t) = \nu_1(t)I_1 \tag{12}$$
$$S_2'(t) = -\beta_{21}(t)S_2I_1 - \beta_{22}(t)S_2I_2 \tag{13}$$
$$I_2'(t) = \beta_{21}(t)S_2I_1 + \beta_{22}(t)S_2I_2 - \nu_2(t)I_2 \tag{14}$$
$$R_2'(t) = \nu_2(t)I_2 \tag{15}$$

The transmission rate from infected class I_j to susceptible class S_i is denoted $\beta_{ij}(t)$ time^{-1}, where $i, j = 1, 2$. We assume that the two recovery rates are constant and equal, $\nu_1(t) = \nu_2(t) = \nu$ time^{-1}.

Theorem 3 *For the SIR model for two population classes given in Eqs.* (10)–(15)*, the time-dependent transmission functions satisfy the system of equations*

$$\beta_{11}(t)I_1(t) + \beta_{12}(t)I_2(t) = \frac{g_1(t)}{S_1(0) - \int_0^t g_1(s)\,ds}$$
$$\beta_{21}(t)I_1(t) + \beta_{22}(t)I_2(t) = \frac{g_2(t)}{S_2(0) - \int_0^t g_2(s)\,ds}$$

where

$$g_1(t) = I_1'(t) + \nu I_1(t) \text{ and } g_2(t) = I_2'(t) + \nu I_2(t).$$

Proof Solve Equation (11) for $S_1(t)$ and plug this into Eq. (10). Form a companion differential equation for $h(t) = \beta_{11}(t)I_1(t) + \beta_{12}I_2(t)$ and solve to find the first equation. To find the second equation, repeat the above steps for the second class using Eqs. (13) and (14). □

Extending the $\beta(t)$ recovery procedure to more than two populations can be done similarly. For more than two populations, one may find the matrix notation presented in Hadeler (2012) more convenient to use.

For two populations, assume that the incidence data functions, $I_1(t)$ and $I_2(t)$, are known. If additional information is known about the disease spread then it may be possible to solve for the $\beta_{ij}(t)$ completely. For example, one could assume that $\beta_1(t) = \beta_{11}(t) = \beta_{12}(t) = \beta_{21}(t)$ and $\beta_2(t) = \beta_{22}(t)$. If Population 1 is the adults and Population 2 is the children, then this condition means that the disease spread is different between adults and among the two classes than among the children only. In this case, the two time-dependent transmission functions, $\beta_1(t)$ and $\beta_2(t)$, can be uniquely determined. In Sect. 4, this assumption is called A1.

A second method to reduce from four transmission functions to two, is to assume that each of the transmission functions β_{ij} has the form $b_i c_j$, that is to assume that the transmission matrix $[\beta_{ij}]_{i,j=1,2}$ is separable (has proportionate mixing). (See Hethcote 1996.) In this case, the number of contacts between individuals in two different groups is assumed to be proportional to the activity levels and sizes of the groups. In particular, the "infectivities", c_j, of each group are the same ($c_j(t) \equiv 1$) and only the "susceptibilities", b_i, of the groups are different. This assumption, called A2 in Sect. 4, simplifies the time-dependent transmission functions to the form $\beta_{ij}(t) = b_i(t)$. Hadeler (2012) gives the details of this case for heterogeneous SIR models with n populations.

We note that making any a priori assumption on the form of the four time-dependent transmission functions is likely to cause the model to be less accurate than other simpler models, such as the classical SIR model.

Corollary 1 (Assumption A1) *Assuming that* $\beta_1(t) = \beta_{11}(t) = \beta_{12}(t) = \beta_{21}(t)$ *and* $\beta_2(t) = \beta_{22}(t)$ *the time-dependent transmission functions are*

$$\beta_1(t) = \frac{g_1(t)}{\big(I_1(t) + I_2(t)\big)\big(S_1(0) - \int_0^t g_1(s)\, ds\big)} \tag{16}$$

$$\beta_2(t) = \frac{g_2(t)}{I_2(t)\big(S_2(0) - \int_0^t g_2(s)\, ds\big)} - \frac{\beta_1(t) I_1(t)}{I_2(t)} \tag{17}$$

(Assumption A2) *Assuming that* $b_1(t) = \beta_{11}(t) = \beta_{12}(t)$ *and that* $b_2(t) = \beta_{21}(t) = \beta_{22}(t)$ *the time-dependent transmission (susceptibility) functions are*

$$b_1(t) = \frac{g_1(t)}{\big(I_1(t) + I_2(t)\big)\big(S_1(0) - \int_0^t g_1(s)\, ds\big)} \tag{18}$$

$$b_2(t) = \frac{g_2(t)}{\big(I_1(t) + I_2(t)\big)\big(S_2(0) - \int_0^t g_2(s)\, ds\big)} \tag{19}$$

Notice that $\beta_1(t) = b_1(t)$, meaning that one of the two transmission functions is the same under the different assumptions A1 and A2. Only the transmission functions $\beta_2(t)$ and $b_2(t)$ are different.

3.1 Necessary conditions

For the SIR model for two populations under either assumption A1 or A2 from Corollary 1, there are four conditions that must be satisfied to guarantee well-defined and positive transmission functions. These are the natural extensions of Conditions 1 and 2 for the classical SIR model (see Sect. 2.3).

Condition 1*(a): $I_1'(t) + \nu I_1(t) > 0$, for all t
Condition 1*(b): $I_2'(t) + \nu I_2(t) > 0$, for all t
Condition 2*(a): $S_1(0) - \int_0^t g_1(s)\, ds > 0$, for all t.
Condition 2*(b): $S_2(0) - \int_0^t g_2(s)\, ds > 0$, for all t.

Under assumption A1, the resulting time-dependent transmission functions $\beta_1(t)$ and $\beta_2(t)$ are dependent (see Eq. 17). The requires an additional necessary condition for a well-defined and positive function $\beta_2(t)$.

$$\text{Condition 3*:}\quad \frac{g_2(t)}{I_2(t)\big(S_2(0) - \int_0^t g_2(s)\, ds\big)} > \frac{\beta_1(t) I_1(t)}{I_2(t)}, \quad \text{for all } t$$

To reconstruct the two time-dependent transmission functions, the model parameters ν, $S_1(0)$, and $S_2(0)$ need to be estimated. The relationship between these three parameters and the resulting transmission function is more complicated than in the case of the classical SIR model. We explore these conditions in a verifiable example in Sect. 4.1.

Again, when applying the procedure to infection data we assume that $S_1(0)$ and $S_2(0)$ are known, and the necessary conditions are used to determine a range for the recovery rate, ν days^{-1} (see Sect. 4.2).

4 Applying the recovery procedure

In this section we demonstrate the $\beta(t)$ recovery procedure in a verifiable case. We also apply the procedure to influenza data from 2002–2003 and to the six seasons from 2003–2003 through 2007–2008. In the heterogeneous case, we consider two populations and examine the two assumptions

- Assumption A1: $\beta_1(t) = \beta_{11}(t) = \beta_{12}(t) = \beta_{21}(t)$ and $\beta_2(t) = \beta_{22}(t)$
- Assumption A2: $b_1(t) = \beta_{11}(t) = \beta_{12}(t)$ and $b_2(t) = \beta_{21}(t) = \beta_{22}(t)$

4.1 A verifiable example

The goal of demonstrating the recovery procedure for verifiable data is twofold. First, we demonstrate that the procedure does indeed generate the time-dependent transmission function(s) that recreate the infection data, and second, we examine the effect of varying the "unknown" model parameters on the resulting $\beta(t)$ function(s). (See also Pollicott et al. 2012).

4.1.1 Homogeneous population

We demonstrate the recovery procedure in the case of a homogeneous population and the classical SIR model. We generate the infection data by solving the SIR model with $\beta(t) = \cos(3t)+1.2\,\text{time}^{-1}$, $\nu = 1/3\,\text{time}^{-1}$, $S(0) = 0.8$, $I(0) = 0.01$, $R(0) = 0.19$ from $t = 0$ to $t = 20$. The infection curve of the SIR model is sampled every 0.5 time units. The collected infection data is interpolated using a spline, and this continuous and differentiable representation of the infection data is used in the $\beta(t)$ recovery procedure as the infection function $I(t)$.

The time-dependent transmission function is generated and the SIR model solved with this generated $\beta(t)$, with $\nu = 1/3$ and $S(0) = 0.8$. The sampled infection data along with the reconstructed $I(t)$ solution curve are shown in Fig. 1a. Figure 1b, c shows the original and generated $\beta(t)$ functions on time interval $t = 0$ to $t = 20$ and $t = 0$ to $t = 4$, respectively. We provide the second time interval in order to show that the generated $\beta(t)$ is not exactly the original one due to the culmination of small numerical error, which is not obvious from the longer time interval.

We examine the effect of changing the recovery rate ν on the resulting $\beta(t)$ while holding $S(0) = 0.8$. For Condition 1, when ν is greater than or equal to $0.97 * (1/3)$, the condition is satisfied on the interval $t = 0$ to $t = 20$. For $\nu = 0.96 * (1/3)$ (and smaller) Condition 1 is not satisfied on the interval. As ν decreases from $0.97 * (1/3)$, the time when Condition 1 fails decreases. Figure 2a shows the time when Condition 1 fails as a function of the recovery rate ν.

We find that for ν less than or equal to $1.07 * (1/3)$, Condition 2 is satisfied on time interval $t = 0$ to $t = 20$, while for $\nu = 1.08 * (1/3)$ (and larger) Condition 2 is not satisfied on the interval. As ν increases from $1.07 * (1/3)$, the time when Condition 2 fails decreases. Figure 2b shows the time when Condition 2 fails as a function of the recovery rate ν.

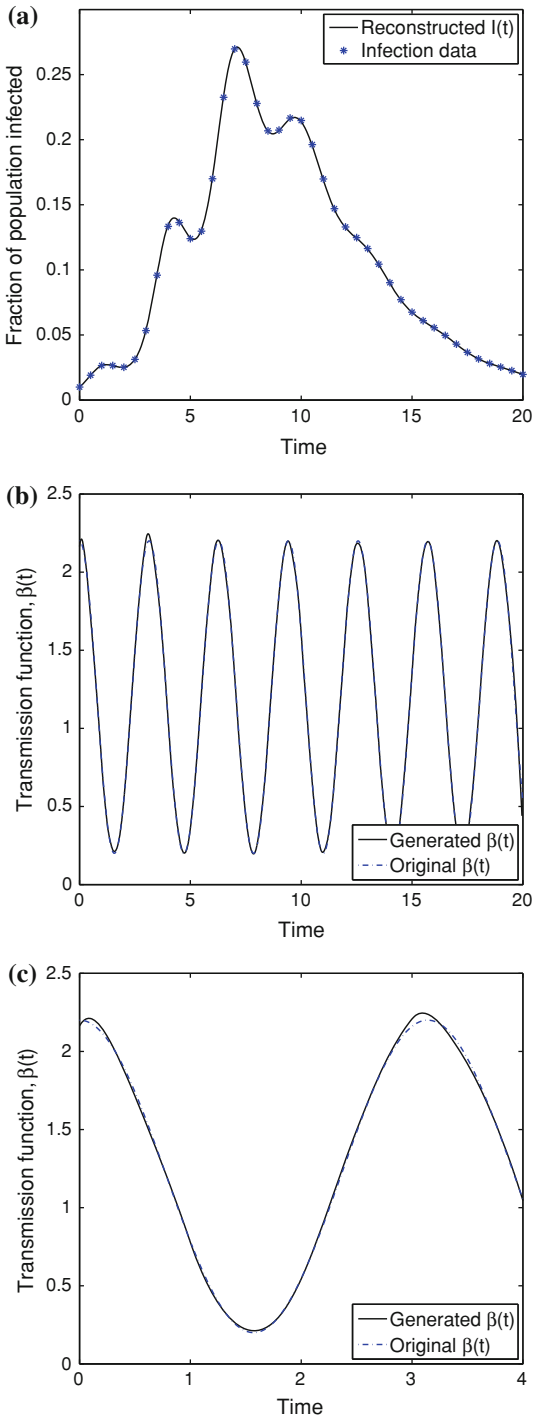


Fig. 1 Simulated data, homogeneous population. **a** The sampled infection data and the reconstructed $I(t)$ solution curve. **b** The original and generated $\beta(t)$ from $t = 0$ to $t = 20$. **c** The original and generated $\beta(t)$ from $t = 0$ to $t = 4$

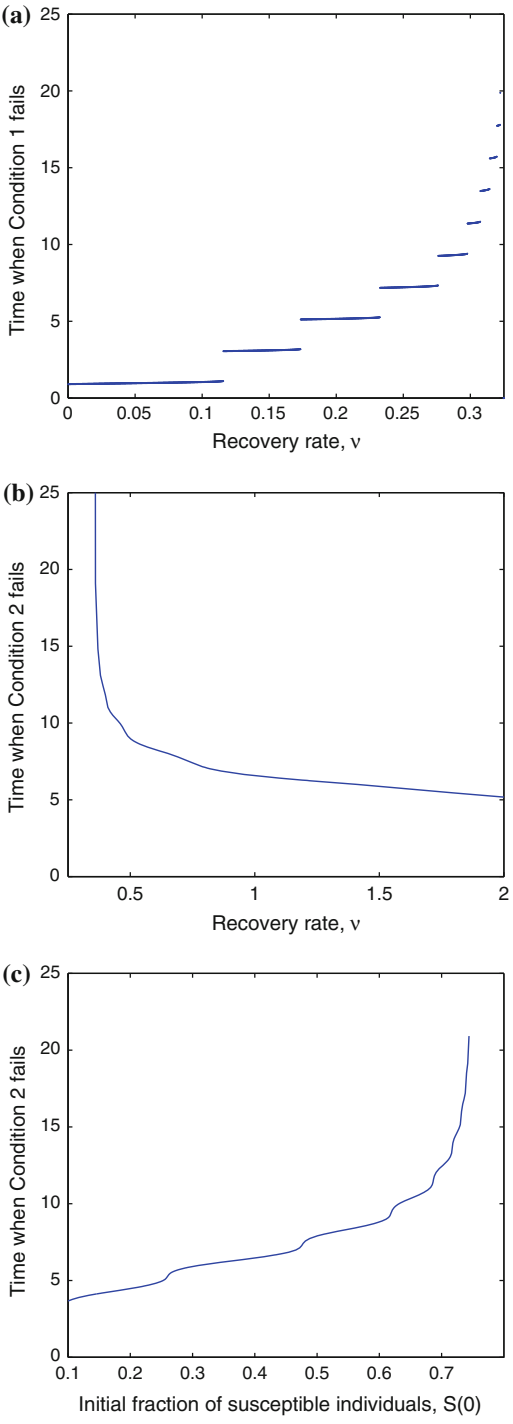


Fig. 2 Simulated data, homogeneous population. **a** Time to failure of Condition 1 as a function of ν for fixed $S(0)$. **b** Time to failure of Condition 2 as a function of ν for fixed $S(0)$. **c** Time to failure of Condition 2 as a function of $S(0)$ for fixed ν

We conclude that for $S(0) = 0.8$, the recover rate must be in the interval $0.97 * (1/3) \leq \mu \leq 1.07 * (1/3)$ for the resulting $\beta(t)$ to be well-defined and positive in the interval $t = 0$ to $t = 20$.

Now we examine the effect of changing the initial number of susceptible individuals $S(0)$ on the resulting $\beta(t)$ while holding $\nu = 1/3$. First, note that $S(0)$ is limited in size by the relation that $1 = S(0) + I(0) + R(0)$, and the requirement that S, I, and R must be non-negative. This leads us to the initial restriction $0 \leq S(0) < 1.25 * (0.8) = 1$.

We find that for $S(0)$ larger than or equal to $0.93 * (0.8)$, Condition 2 is satisfied on the interval $t = 0$ to $t = 20$. For $S(0) = 0.92 * (0.8)$ (and smaller) Condition 2 is not satisfied on the interval. As $S(0)$ decreases from $0.92 * (0.8)$, the time when Condition 2 fails decreases. Figure 2c shows the time when Condition 2 fails as a function of the initial number of infected individuals $S(0)$.

We conclude that for $\nu = 1/3$, the initial number of susceptible individuals must be in the interval $0.93 * (0.8) \leq S(0) \leq 1.25 * (0.8)$ for the resulting $\beta(t)$ to be well-defined and positive in the interval $t = 0$ to $t = 20$.

Finally, we demonstrate the effect of changing ν and $S(0)$ in their allowable ranges on the resulting $\beta(t)$ function. Figure 3a shows the resulting transmission functions for different allowable values of ν while fixing $S(0) = 0.8$; increasing ν results in a higher $\beta(t)$ function. Figure 3b shows the resulting transmission functions for different allowable values of $S(0)$ while fixing $\nu = 1/3$; increasing $S(0)$ results in a lower $\beta(t)$.

4.1.2 Heterogeneous population

We demonstrate the recovery procedure in the case of a heterogeneous population with two time-dependent transmission functions under assumption A1 (a similar exploration could be done for assumption A2). We assume that Population 1 is 75 % and Population 2 is 25 % of the total population. The infection data is generated by solving the SIR model for two populations with $\beta_1(t) = 0.75 * (\cos(3t) + 1.2)$ time^{-1}, $\beta_2(t) = 0.25 * (\cos(3(t + \pi/2) + 1.2))$, time^{-1} $\nu = 1/3$ time^{-1}, $S_1(0) = 0.75 * 0.8$, $S_2(0) = 0.25 * 0.8$, $I_1(0) = 0.75 * 0.01$, $I_2(0) = 0.25 * 0.01$, $R_1(0) = 0.75 * 0.19$, and $R_2(0) = 0.25 * 0.19$. The infection curves of the SIR model are sampled every 0.5 time units. The collected infection data sets were interpolated using a spline, and these continuous and differentiable representation of the infection data were used in the $\beta(t)$ recovery procedure as the infection functions $I_1(t)$ and $I_2(t)$. Figure 4a verifies that the reconstruction procedure generates the $I_1(t)$ and $I_2(t)$ functions; the figure shows the sampled infection data and the reconstructed $I(t)$ solution curves for both populations. Figure 4b shows the original and generated $\beta_1(t)$ and $\beta_2(t)$ functions.

Figure 5a, b shows the resulting transmission functions for different allowable values of ν while fixing the initial number of susceptible individuals to their original values; increasing ν results in a higher $\beta_1(t)$ and a lower $\beta_2(t)$. Figure 6a, b shows the resulting transmission functions for different allowable values of $S_1(0)$ while fixing $\nu = 1/3$ and $S_2(0) = 0.25 * 0.8$; increasing $S_1(0)$ results in a lower $\beta_1(t)$ and a higher $\beta_2(t)$. The value of $S_2(0)$ only effects the transmission function $\beta_2(t)$. Figure 6c shows the resulting transmission function for different allowable values of $S_2(0)$ while fixing $\nu = 1/3$ and $S_1(0) = 0.75 * 0.8$; increasing $S_2(0)$ results in a lower $\beta_2(t)$.

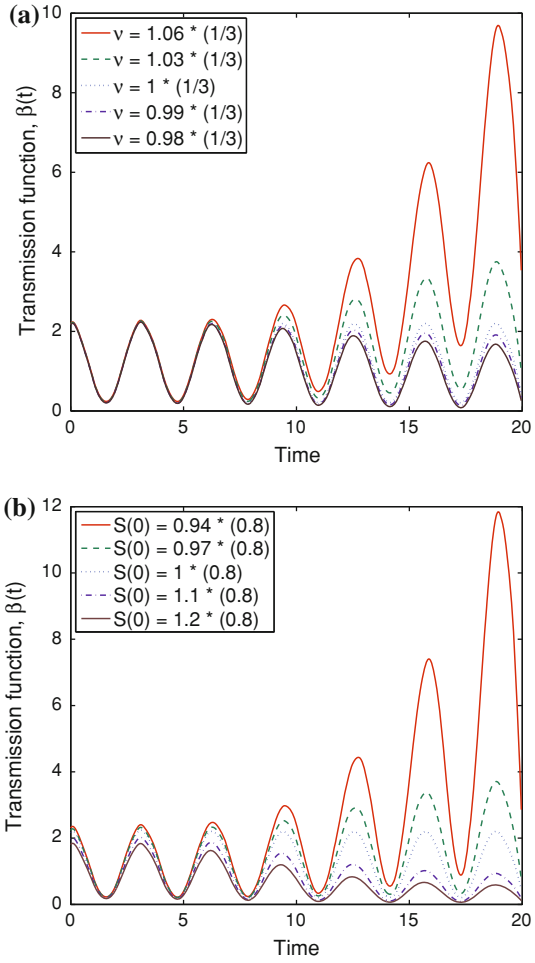


Fig. 3 Simulated data, homogeneous population. Effect of variations in model parameters on the generated time-dependent transmission function $\beta(t)$. **a** Effect of variations in ν for fixed $S(0)$. **b** Effect of variations in $S(0)$ for fixed ν

4.2 Influenza data

In this section we apply the $\beta(t)$ recovery procedure to 2002–2003 influenza data. The number of influenza-like illnesses reported to the U.S. Center for Disease Control and Prevention[1] is used as the base for the number of infected individuals. These numbers were then scaled by 1/.4 for adults (25^+ years) and 1/.56 for children (0–24 years) to account for individuals who are infected but do not seek health care (Biggerstaff and Balluz 2011).

We normalize the total population size to 1, assuming that the size of the U.S. population is 287, 000, 000, which was the approximate reported U.S. population in

[1] http://www.cdc.gov/flu/weekly/ussurvdata.htm; accessed October 26, 2011.

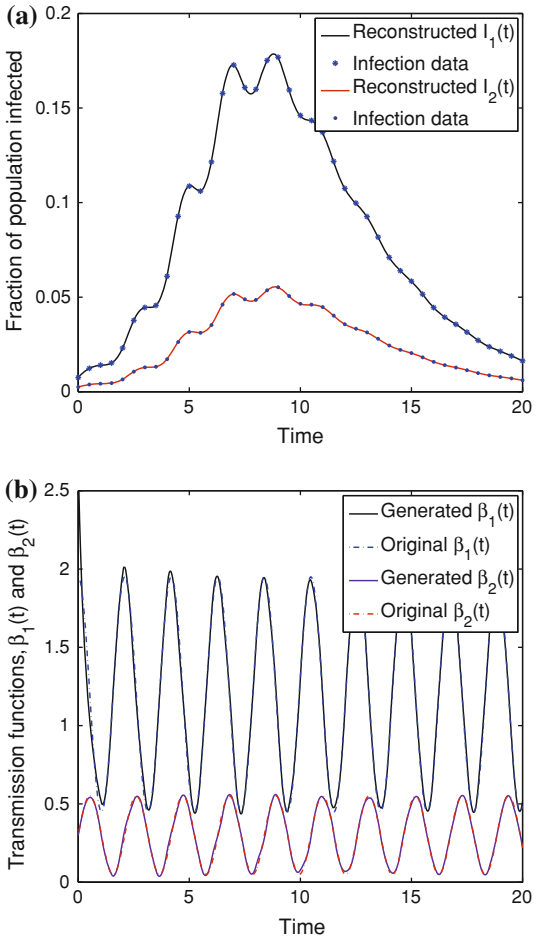


Fig. 4 Simulated data, heterogeneous population. **a** The sampled infection data and the reconstructed $I_1(t)$ and $I_2(t)$ solution curves. **b** The original and generated $\beta_1(t)$; the original and generated $\beta_2(t)$ from $t = 0$ to $t = 20$

July of 2002.[2] We assume that 65 % of the US population is adult, 25^+ years, and the remaining 35 % are youth, 0–24 years.[3] We set the initial percentage infected in each class to be the percentage infected according to the data. Finally, we assume that there are no individuals in the recovered class(es) at time 0.

We assume that the initial number of susceptible individuals is known; it is the total population less the initial number of infected individual. Therefore, we do not explore the effect of changing the initial number of susceptible individuals for the actual flu data.

[2] http://www.census.gov/population/estimates/state/st-99-1.txt; accessed October 26, 2011.

[3] Estimated for 2000; http://censtats.census.gov/data/US/01000.eps; accessed October 26, 2011.

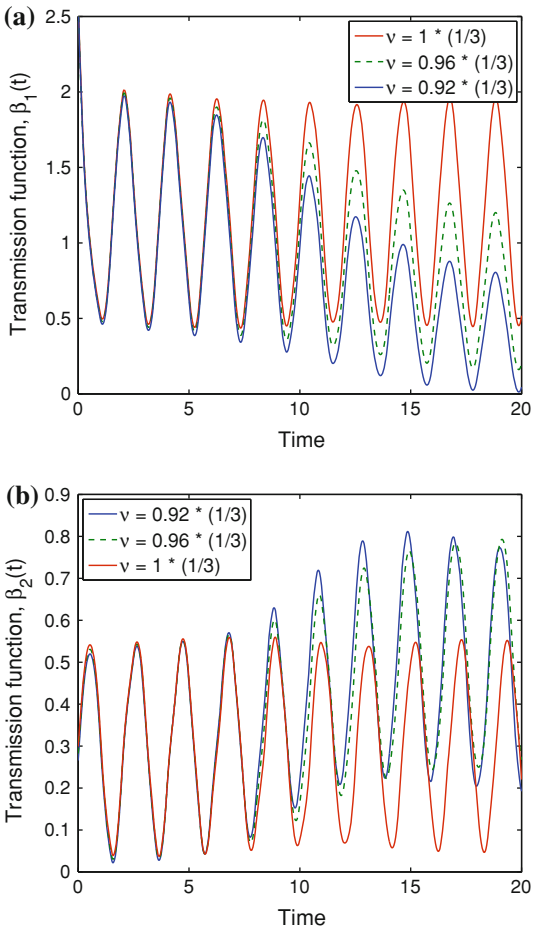


Fig. 5 Simulated data, heterogeneous population. Effect of variations in model parameter ν on the generated time-dependent transmission functions $\beta_1(t)$ and $\beta_2(t)$ for fixed $S_1(0)$ and $S_2(0)$. **a** Effect on $\beta_1(t)$. **b** Effect on $\beta_2(t)$

4.2.1 Homogeneous population

We begin by assuming that all infected individuals are in one population class and that the disease spread can be modeled by the classical SIR model. The infection data was interpolated using a spline and this continuous and differentiable representation of the infection data was used in the $\beta(t)$ recovery procedure.

We find that the recovery rate ν must be in the range $\nu = 0.08$ days^{-1} to 52.00 days^{-1} to have well-defined and positive transmission function. This corresponds to a recovery time between 0.02 and 12.50 days.

Figure 7 shows the resulting transmission function for different allowable values of ν corresponding to recovery times of 3, 4, 5, 6, and 7 days. Increasing ν results in a higher $\beta(t)$.

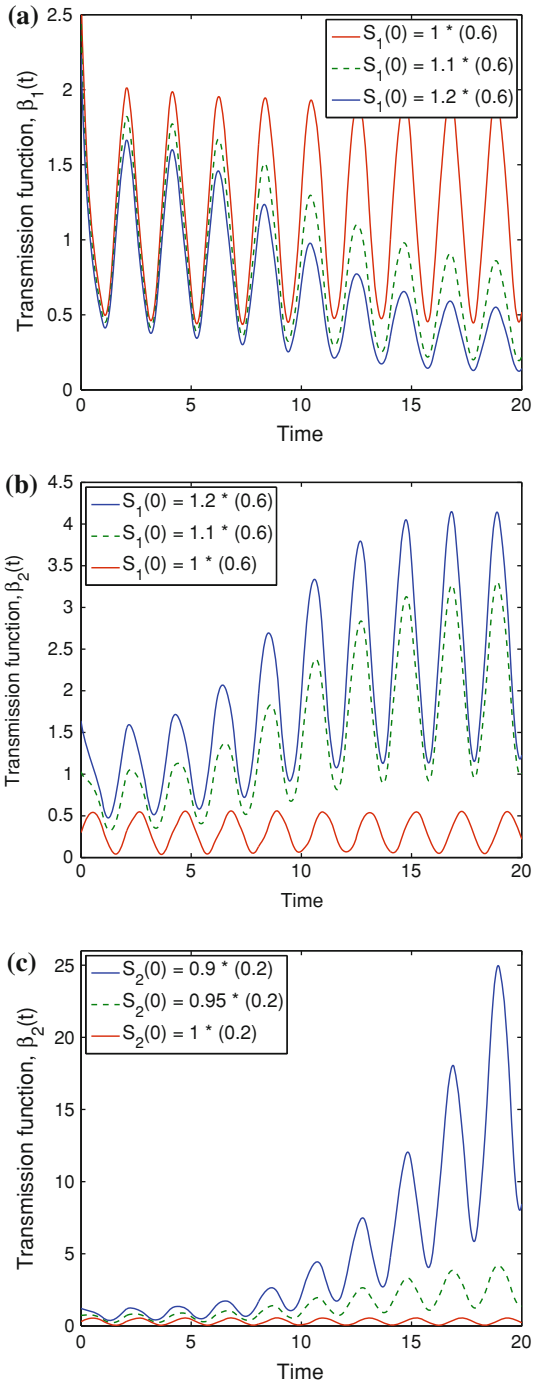


Fig. 6 Simulated data, heterogeneous population. Effect of variations in model parameters on the generated time-dependent transmission functions $\beta_1(t)$ and $\beta_2(t)$ for fixed ν. **a** Effect of variations in $S_1(0)$ on $\beta_1(t)$ for fixed $S_2(0)$. **b** Effect of variations in $S_1(0)$ on $\beta_2(t)$ for fixed $S_2(0)$. **c** Effect of variations in $S_2(0)$ on $\beta_2(t)$ for fixed $S_1(0)$

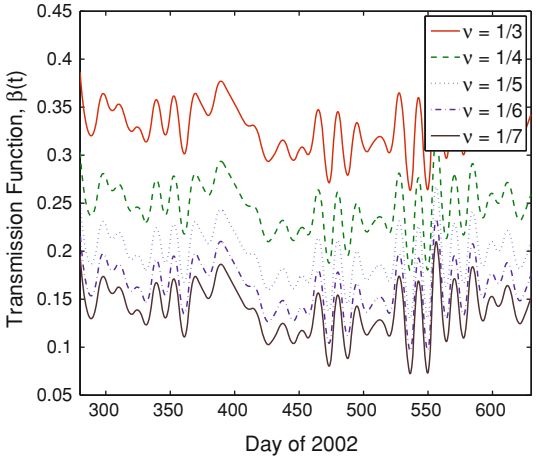


Fig. 7 2002–2003 influenza data, homogeneous population. Effect of variations in model parameter ν on the generated time-dependent transmission function $\beta(t)$ for fixed $S(0)$

4.2.2 Heterogeneous population

Now we assume that the 2002–2003 influenza outbreak can be modeled by the SIR model for two populations with two transmission functions. We assume that the adults are Population 1 and the youth are Population 2. The infection data was interpolated using a spline and the two continuous and differentiable representations of the infection data were used in the $\beta(t)$ recovery procedure.

Under assumption A1, we find that the recovery rate ν must be in the range $\nu = 0.10$ days^{-1} to $\nu = 18.00$ days^{-1} to have well-defined and positive transmission functions. This corresponds to a recovery time in the range 0.06 days to 10.00 days.

Figure 8a, b shows the resulting transmission functions for different allowable values of ν corresponding to recovery times of 3, 4, 5, 6, and 7 days, under assumption A1. Increasing ν results in a higher $\beta_1(t)$ and $\beta_2(t)$.

Under assumption A2, we find that the recovery rate ν must be in the range $\nu = 0.10$ days^{-1} to $\nu = 13.92$ days^{-1} to have well-defined and positive transmission functions. This corresponds to a recovery time in the range 0.07 days to 10.00 days.

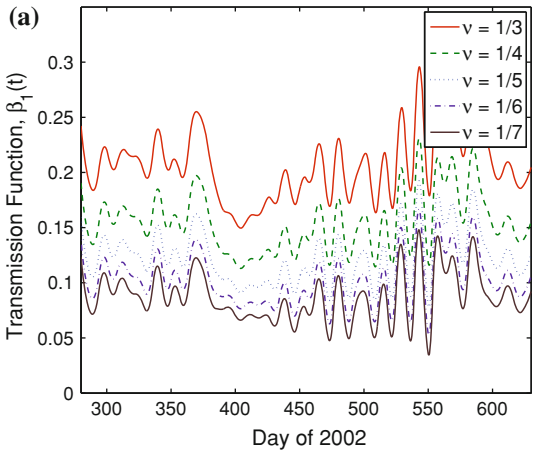
Figure 9 shows the generated $\beta_2(t)$ and $b_2(t)$ using assumptions A1 and A2, respectively, for the heterogeneous SIR model with $\nu = 1/5$ days^{-1}.

4.2.3 Multiple years

We examine the $\beta(t)$ recovery procedure for the six flu seasons, 2002–2003 through 2007–2008. We assume that the size of the U.S. population is the approximate average U.S. population from 2002–2008; that is, 295,850,000.[4]

We begin by assuming that all infected individuals are in one population class and that the disease spread for the entire six flu seasons can be modeled by the classical SIR model. The infection data was interpolated using a spline and this continuous and differentiable representation of the infection data was used in the $\beta(t)$ recovery

[4] http://www.census.gov/population/estimates/state/st-99-1.txt; accessed October 26, 2011.



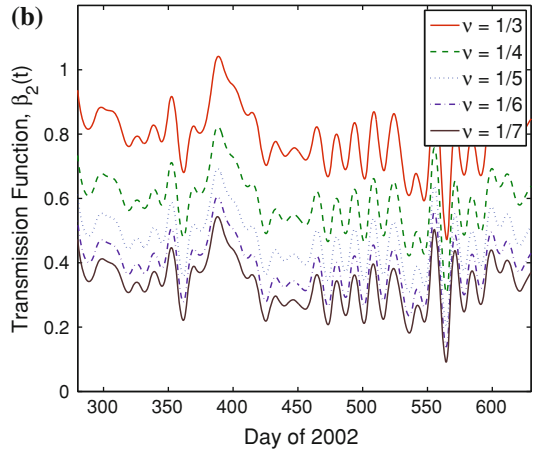


Fig. 8 2002–2003 influenza data, heterogeneous population, under assumption A1. Effect of variations in model parameter ν on the generated time-dependent transmission functions $\beta_1(t)$ and $\beta_2(t)$ for fixed $S_1(0)$ and $S_2(0)$. **a** Effect on $\beta_1(t)$. **b** Effect on $\beta_2(t)$

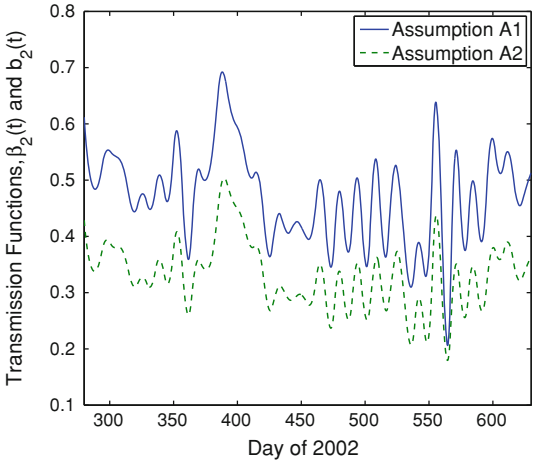


Fig. 9 2002–2003 influenza data, heterogeneous population. Comparison of the generated time-dependent transmission functions $\beta_2(t)$ and $b_2(t)$ under assumptions A1 and A2, with $\nu = 1/5$ days^{-1}

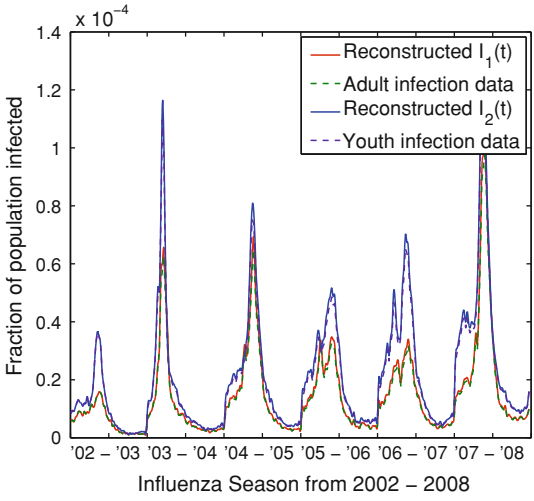


Fig. 10 2002–2003 through 2007–2008 influenza data, heterogeneous population. The adult (25^+ years) and youth (0–24 years) scaled influenza-like-illness data and the reconstructed $I_1(t)$ and $I_2(t)$ solution curves, under assumption A1, with $\nu = 1/5$ days^{-1}

procedure. We find that ν must be in the range $\nu = 0.13$ days^{-1} up to $\nu = 13.18$ days^{-1}. This corresponds to a recovery time in the range 0.08 days to 7.69 days.

Now we assume that the six influenza seasons can be modeled by the SIR model for two populations with two transmission functions. The infection data was interpolated using a spline and the two continuous and differentiable representations of the infection data were used in the $\beta(t)$ recovery procedure.

Under assumption A1, we find that the recovery rate ν must be in the range $\nu = 0.14$ days^{-1} to $\nu = 7.69$ days^{-1} to have well-defined and positive transmission functions. This corresponds to a recovery time in the range 0.13 days to 7.14 days. Under assumption A2, we find that the recovery rate ν must be in the exact same range as under assumption A1.

Figure 10 shows the scaled influenza-like-illness data for the adult and youth populations along with the reconstructed infection curves $I_1(t)$ and $I_2(t)$, with $\nu = 1/5$ days^{-1}, under assumption A1. A comparison of the time dependent transmission functions reconstructed using different allowable values of ν corresponding to recovery times of 3, 4, 5, 6, and 7 days, under assumption A1, are in Fig. 11a, b, respectively. Increasing ν results in a higher $\beta_1(t)$ and $\beta_2(t)$.

Figure 12 shows the generated $\beta_2(t)$ and $b_2(t)$ using assumptions A1 and A2, respectively, for the heterogeneous SIR model with $\nu = 1/5$ days^{-1} for the 2002–2003 through 2007–2008 influenza seasons.

4.2.4 Frequency analysis

We apply frequency analysis via the Fourier transform to the recovered $\beta(t)$, for the homogeneous SIR model and the $\beta_1(t)$ and $\beta_2(t)$ for the heterogeneous SIR model under assumption A1, for the multi-year influenza data from the 2002–2003 season through the 2007–2008 season, using $\nu = 1/5$ days^{-1}. Figure 13 shows the normalized spectrum for the generated time-dependent transmission function $\beta_1(t)$, in the heterogeneous case; the spectra for $\beta(t)$ in the homogeneous cases and $\beta_2(t)$ in

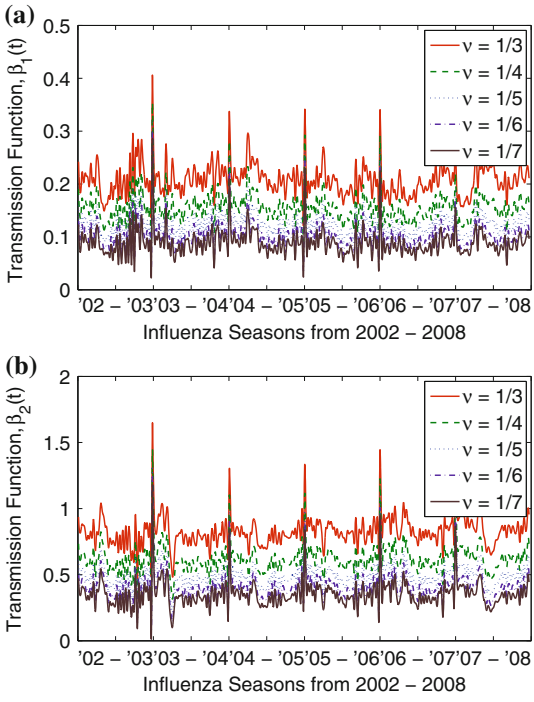


Fig. 11 2002–2003 through 2007–2008 influenza data, heterogeneous population, under assumption A1. Effect of variations in model parameter ν on the generated time-dependent transmission functions $\beta_1(t)$ and $\beta_2(t)$ for fixed $S_1(0)$ and $S_2(0)$. **a** Effect on $\beta_1(t)$. **b** Effect on $\beta_2(t)$

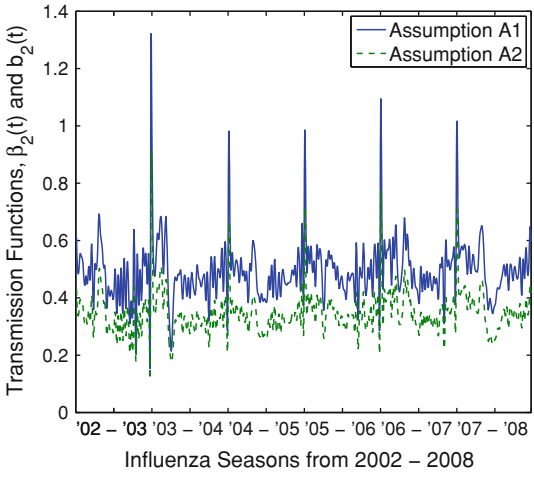


Fig. 12 2002–2003 through 2007–2008 influenza data, heterogeneous population. Comparison of the generated time-dependent transmission functions $\beta_2(t)$ and $b_2(t)$ under assumptions A1 and A2, with $\nu = 1/5$ days^{-1}

the heterogeneous case are similar. The dominant frequency component of $\beta_1(t)$ is at 0.00275 per day, meaning that the length of one complete flu cycle is 1/0.00275 = 363.63 days, approximately one year. The same dominant period appears for both $\beta(t)$ and $\beta_2(t)$.

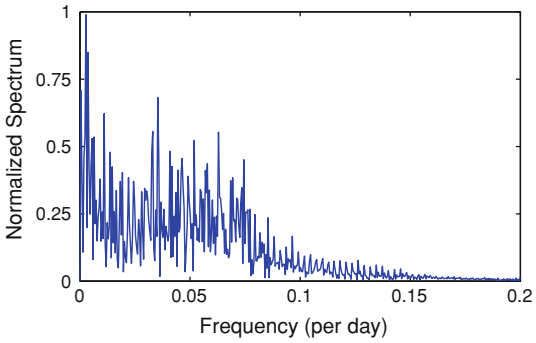


Fig. 13 2002–2003 through 2007–2008 influenza data, heterogeneous population, under assumption A1. Frequency transform of the generated time-dependent transmission function $\beta_1(t)$, with $\nu = 1/5$ days^{-1}, showing the dominant frequency component (normalized modulus)

5 Discussion

In this paper we have reviewed the two recent procedures for recovering the time-dependent transmission function, $\beta(t)$, for SIR-type compartment models. Using a modification of the PWW procedure, the two procedures are shown to produce exactly the same function $\beta(t)$. We have investigated the necessary conditions to ensure a well-defined and positive $\beta(t)$ for the classical SIR model. The recovery procedure was extended to certain SIR-type models for heterogeneous populations. The procedure was demonstrated for a verifiable example for both a single and a multiple population model. Finally, the procedure was applied to homogeneous and heterogeneous influenza data from the 2002–2003 flu season and for the six flu seasons from 2002–2003 through 2007–2008. Two assumptions were considered in order to apply the procedure to the heterogenous population model.

In the verifiable example in Sect. 4.1, the range of feasible ν values is very small and contains the "known" value of ν. The same is true for the interval of allowable $S(0)$ values. While the specific intervals found here apply only to the scenario described above, we conjecture that the same would be true when dealing with real-world data. If the data can indeed be modeled with a given model, then the calculated range of allowable ν values should contain the actual value.

Individuals who are infected with influenza are infectious (shed virus) starting around the second day after exposure and for up to 8 days (Carrat et al. 2008). In other words, infected individuals have a recovery time of 8 or fewer days. All of the situations explored in this paper result in an allowable range of ν values that overlaps this region (see Table 1). We conclude that none of the models considered here are unreasonable models for the influenza data. If one of the models were to produce a range of recovery times corresponding to, say, 3 or fewer days, then we would conclude that the given model is not appropriate for the data.

We note that the allowable range of ν values for the three situations homogeneous, heterogeneous (two age classes) under assumption A1, and heterogeneous (two age classes) under A2 are approximately the same when considering just one flu season or when considering the six seasons together (Table 1). We believe that this demonstrates the robustness of the procedure and the soundness of SIR-type models for modeling influenza.

Table 1 Comparison of the allowable range of recovery times, $1/\nu$ days, determined by the recovery procedure for the time-dependent transmission rate(s)

Influenza season SIR model type, assumption	Recovery time $1/\nu$ days
2002–2003	
Homogeneous	$0.02 \leq 1/\nu \leq 12.50$
Heterogeneous, A1	$0.06 \leq 1/\nu \leq 10.00$
Heterogeneous, A2	$0.07 \leq 1/\nu \leq 10.00$
2002–2003 through 2007–2008	
Homogeneous	$0.08 \leq 1/\nu \leq 7.69$
Heterogeneous, A1	$0.13 \leq 1/\nu \leq 7.14$
Heterogeneous, A2	$0.13 \leq 1/\nu \leq 7.14$

It is interesting to note that the general shape of the transmission function curves remain the same even with differing ν. This is true for both the verifiable example and the influenza example, and for both the homogeneous and heterogeneous models. We conjecture that the relationship between the shape of the transmission function(s) and the disease dynamics gives important information about the transmissibility of the disease over the course of the disease outbreak and we believe that this opens a new area of study that should be explored.

In the case of a heterogeneous population, the time-dependent transmission functions $\beta_1(t)$ and $b_1(t)$ are the same regardless of the assumption of A1 or A2. We provide Figs. 9 and 12 to compare the resulting $\beta_2(t)$ and $b_2(t)$ with $\nu = 1/5$ days^{-1}, for the single and multiple flu seasons, respectively. Note that the resulting transmission functions have the same general shape. Again, we believe that this provides important information about the transmission dynamics. It seems to not be important, for this particular outbreak, which assumption is used. Assumptions A1 and A2 produce similar $\beta_2(t)$ and $b_2(t)$ (and similar allowable ν ranges).

We believe that the reconstructed $\beta(t)$ functions for influenza can help determine specific effects on transmissibility. For example, the $\beta(t)$ recovery procedure gives a new way to test the "school year" hypothesis (seasonality). Flu experts believe that the typical structure of a flu season can be accounted for by increased social contacts among children during the school year. Reconstructing the exact time-dependent transmission function for data will allow one to examine whether there is a drop in the transmission rate over the summer months.

In Pollicott et al. (2012), frequency analysis is applied to the recovered time-dependent transmission function, $\beta(t)$, for the SEIR model applied to multi-year prevaccination UK measles data. Measles are believed to conform to the "school year" hypothesis (Grassly and Fraser 2006; Keeling and Rohani 2008) and their resulting $\beta(t)$ confirms this hypothesis. They find that the resulting $\beta(t)$ for measles shows dominate spectral peaks with 1- and 1/3-year periods, concluding that measles transmission is driven by school contacts. (There were three major school breaks during these years.) This demonstrates a second method to use the reconstructed time-dependent transmission function(s) to test the "school year" hypothesis.

There are many avenues of exploration left open regarding the $\beta(t)$ recovery procedure for epidemic models. We have noted a few above and list a few more here. First, the procedure has been applied to several SIR-type compartment models, some here and others in Pollicott et al. (2012) and Hadeler (2011). The procedure should be explored for more models, including for heterogenous populations. General conditions should be found for which classes of models the procedure applies to and which it does not. Second, we have provided graphs on the time to failure of Conditions 1 and 2 for the verifiable example using the SIR model (Fig. 2). The resulting "time to failure" graphs are intriguing and deserve further study. And third, further work needs to be done with real-world infection data. For example, we believe that the method can be applied to influenza data and the resulting time-dependent transmission functions can help determine which, if any, seasons conform to the "school year" hypothesis.

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